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Verifying Death Reports in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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Background: Excess vascular deaths in the PLATO trial comparing ticagrelor to clopidogrel have been repeatedly challenged by the Food and Drug Administration (FDA) reviewers and academia. Based on the Freedom of Information Act, BuzzFeed won a court order and shared with us the complete list of reported deaths for the ticagrelor FDA New Drug Application (NDA) 22–433. This dataset was matched against local patient-level records from PLATO sites monitored by the sponsor.

Study Question: Whether FDA death data in the PLATO trial matched the local site records.

Study Design: The NDA spreadsheet contains 938 precisely detailed PLATO deaths. We obtained and validated local evidence for 52 deaths among 861 PLATO patients from 14 enrolling sites in 8 countries and matched those with the official NDA dataset submitted to the FDA.

Measures and Outcomes: Existence, precise time, and primary cause of deaths in PLATO.

Results: Discrepant to the NDA document, sites confirmed 2 extra unreported deaths (Poland and Korea) and failed to confirm 4 deaths (Malaysia). Of the remaining 46 deaths, dates were reported correctly for 42 patients, earlier (2 clopidogrel), or later (2 ticagrelor) than the actual occurrence of death. In 12 clopidogrel patients, cause of death was changed to “vascular,” whereas 6 NDA ticagrelor “nonvascular” or “unknown”

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V.S. and BuzzFeed News were under mutual non-disclosure and non-circumvention agreement dated November 6, 2019 which ended June 1, 2020. V.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. T.M. reviewed the FDA-issued spreadsheet, and calculated several numbers. Study concept and design: J.-F.T, T.M., V.S. Obtained funding: BuzzFeed (New York, NY) paid legal fees to file the FOIA complaint, court fees, and external attorneys to obtain PLATO deaths dataset from the FDA. Administrative, technical, or material support: HeartDrug Research LLC (Wilmington, DE).

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deaths were site-reported as of “vascular” origin. Sudden death was incorrectly reported in 4 clopidogrel patients, but omitted in 4 ticagrelor patients directly affecting the primary efficacy PLATO endpoint.

Conclusions: Many deaths were inaccurately reported in PLATO favoring ticagrelor. The full extent of mortality misreporting is currently unclear, while especially worrisome is a mismatch in identifying primary death cause. Because all PLATO events are kept in the cloud electronic Medidata Rave capture system, securing the database content, examining the dataset changes or/and repeated entries, identifying potential interference origin, and assessing full magnitude of the problem are warranted.

Keywords: clinical trial, ticagrelor, clopidogrel, death, mortality

INTRODUCTION

Despite the Food and Drug Administration (FDA’s) controversial decision to approve ticagrelor in 2011,¹ the drug’s use has been expanding around the globe.² Currently, ticagrelor holds a superiority recommendation over clopidogrel for acute coronary syndromes in European,³ Canadian,⁴ and American⁵ guidelines based mostly on the results of the PLATO trial.⁶ However, the advantages of ticagrelor over clopidogrel in PLATO were inconsistent and exhibited “geographical” differences,⁷ the latter depending upon whether or not the sponsor had been involved in site monitoring in certain countries.^{8,9} The second uncertainty following PLATO occurred after the delayed PHILO trial results publication became available.¹⁰ That study was designed to gain regulatory approval of ticagrelor in Japan, matching precisely with the PLATO design. However, there were numerically more cardiovascular and all-cause deaths with ticagrelor in PHILO, similar to the independently monitored PLATO US results, and challenging the ticagrelor mortality benefit reported in the sponsor-controlled PLATO cohort.^{11,12} Lack of ticagrelor mortality benefit observed in PHILO was consistent with other trials justifying independent verification of deaths in PLATO.¹² Recently, data from the large, uniform, US government-run international repository suggested a consistent disproportional excess of mortality associated with ticagrelor when compared with clopidogrel and especially with prasugrel.² Finally, consistent lack of mortality benefit confirmation in all other ticagrelor trials supports the verification of PLATO deaths by the Task Force (Table 1). The above discrepancies led us to seek verification of PLATO deaths despite a decade having passed.

METHODS

Lately, based on the US Freedom of Information Act, BuzzFeed news filed a legal complaint in a US federal

court (Figure 1), won an expedited order, and shared with us the complete PLATO death list submitted by the ticagrelor New Drug Application (NDA) 22-433 sponsor. We matched the NDA dataset with the medical records or/and vital registries provided by several PLATO sites monitored by the sponsor. The NDA spreadsheet contains 938 PLATO deaths with trial identification numbers, country, enrolling site, patient age, gender, treatment assignments, discontinuations, outcome codes, dates, and precise causes of trial entry and exit. We obtained data for 861 PLATO patients including 52 deaths from 14 enrolling sites in 8 countries and matched those with the NDA dataset.

RESULTS

Overall, we were able to obtain patient-level local data from 14 PLATO sites in 8 countries (Canada, Hungary, Israel, Malaysia, Mexico, Norway, Poland, and South Korea). Principal investigators from Israel and Malaysia cooperated, but were not able to retrieve original trial clinical records. The Malaysian PLATO team, however, provided detailed personal recollections and confirmed affidavits from principal investigator and research coordinator regarding site deaths. We received death details from a high recruiting Polish site including clinical notes and Powszechny Elektroniczny System Ewidencji Ludności national registry transcripts.

Most PLATO deaths match precisely between the original site records and the NDA-reported events. Indeed, most causes and timings of deaths were reported and transferred correctly. But not all reports match. First, there was a discrepancy between the published PLATO death counts⁵ and the numbers of fatalities reported by NDA 22-433. These differences are outlined in Table 2. It is actually positive that the NDA dataset reported all deaths rather than just those used for intend to treat analyses. The reduction in death counts from the NDA to the published data⁵ seems reasonable, although

Table 1. Justification for independent verification of deaths in PLATO.

PLATO fact	Comment
Discrepancy in mortality between Phase II and Phase III trials	In contrast to PLATO, earlier studies (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs clopidogrel in non-STsegment Elevation myocardial infarction and Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs clopidogrel in non-STsegment Elevation myocardial infarction-2) run by the Thrombolysis in Myocardial Infarction group exhibit more deaths with ticagrelor.
Extraordinary high death rate after clopidogrel therapy	All-cause mortality (5.9%) was extremely high. This happened despite 46% of patients were pretreated with clopidogrel, excessive incomplete follow-up (14.7%), and PLATO's relatively short duration (median 10.5 mo).
Average death rates and inversed outcomes in the USA	The US mortality was 3.22% for clopidogrel, same as in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (3.2%), but 3.84% in US for ticagrelor.
Delayed timing of ticagrelor mortality "benefit"	Lack of early, but massive delayed (after 2–3 mo) ticagrelor mortality prevention unseen for any antiplatelet drug in any Acute Coronary Syndrome (ACS) trial.
High proportion of vascular deaths	Excess proportion of deaths from vascular causes (89%) in clopidogrel arm.
Mismatch between myocardial infarction (MI) and death rates	The corresponding MI rate in clopidogrel arm (6.9%) is realistic, but contradicts unreasonably high (5.1%) risk of vascular deaths.
Prevention of unusual causes of deaths by any antiplatelet agent	Reduction of sudden death (n = 17), heart failure (n = 11), arrhythmia (n = 8), and sepsis (n = 16) fatalities by ticagrelor
Late change of trial monitoring control	Thrombolysis in Myocardial Infarction group has been preplanned to run PLATO, but instead, ticagrelor sponsor did that.
East European "paradox" in outcomes	Poland (0.69; 0.53–0.90) and Hungary (0.59; 0.40–0.86) yielded the narrowest hazard ratio for outcomes among all countries. These 2 countries combined account for 21% of enrolled patients, but yielded 46% of events favoring ticagrelor.
Description of deceased clopidogrel patient who later developed nonfatal bleeding in the NDA 22–433 review	May represent unintentional error or broken uncovered pattern of fraud
Similarity with rosuvastatin in Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin	Similar dissociation between average MI rates and high mortality in control arms for both trials with astronomical names.

slightly disproportional favoring ticagrelor, and may represent a legitimate attempt to remove extra fatalities because of the complicated nature of the trial design. For example, the analysis period in PLATO was strictly limited to 12 months. We observed several cases for which the patient was still receiving a study drug within the active trial frame and experienced an adverse outcome which was properly not counted. Also, unusual but not incorrect was the decision to include the bleeding deaths not related to trauma as a component of the primary endpoint.

The comparison of NDA-reported ticagrelor versus clopidogrel deaths in different countries is shown in Table 3. The geographic distribution of death rates was remarkably inconsistent in PLATO. Even within Europe, deaths rates varied between 1.95% in Finland

to 4.93% in Germany. Overall, we analyzed data for 52 PLATO deaths from 14 enrolling sites in 8 countries and matched those with the NDA dataset. Discrepancies between local site records and what has been reported in the NDA are outlined below (Tables 4–6). In contrast to the NDA report, sites confirmed 2 additional deaths and failed to confirm 4 deaths (Figure 2). Of the remaining 46 deaths, dates were reported correctly (n = 42), earlier (2 clopidogrel), or later (2 ticagrelor) than actual. In 12 clopidogrel patients cause of death was changed to "vascular," whereas 6 "nonvascular" or "unknown" deaths on ticagrelor were actually of "vascular" origin. Sudden death was incorrectly reported in 4 clopidogrel, but omitted in 4 ticagrelor patients, which was critical for accurate assessment of the primary efficacy PLATO endpoint.

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

BUZZFEED INC.,)
111 East 18th Street, 13th Floor)
New York, NY 10003)
)
Plaintiff,)
)
v.)
)
FOOD AND DRUG ADMINISTRATION,)
10903 New Hampshire Avenue)
Silver Spring, MD 20993)
)
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,)
200 Independence Ave., SW)
Washington, DC 20201)
)
Defendants.)

COMPLAINT

1. Plaintiff BUZZFEED INC. files this Freedom of Information Act suit to force Defendants FOOD AND DRUG ADMINISTRATION and U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES to release records related to the drugs Brilinta and Kengreal.

PARTIES

2. Plaintiff BUZZFEED INC. is a member of the media and made the FOIA requests at issue in this case.
3. Defendant U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (“DHHS”) is a federal agency subject to the Freedom of Information Act, 5 U.S.C. § 552.
4. Defendant FOOD AND DRUG ADMINISTRATION (“FDA”) is a federal agency and component of DHHS and is subject to the Freedom of Information Act, 5 U.S.C. § 552.

FIGURE 1. BuzzFeed complaint on ticagrelor.

DISCUSSION

Missing or incorrect data are concerning for validation of clinical trials.¹³ The major finding of this report is that actual existence, precise dates, and proper causes of

some deaths in PLATO were mismatched between what was sent by the local sites and what was received by the FDA. Several clopidogrel deaths were reported earlier than actual, whereas their causes were switched from “nonvascular” or “unknown” to “vascular.” In

Table 2. Deaths in PLATO by issued source.

Source	Ticagrelor (n)	Clopidogrel (n)	Total (n)
PLATO published	399	506	905
NDA reported	420	518	938

Table 3. Distribution of deaths by country in PLATO.

Country*	Patients enrolled	Deaths; Clopidogrel/ Ticagrelor; (%)†
Argentina	410	40; 21/19; (9.76)
Australia	83	3; 1/2; (3.61)
Austria	143	5; 3/2; (3.50)
Belgium	170	8; 7/1; (4.71)
Brazil	590	62; 41/21; (10.51)
Bulgaria	451	32; 18/14; (7.10)
Canada	401	12; 5/7; (2.99)
China	416	21; 12/9; (5.05)
Czech Republic	1021	41; 22/19; (4.02)
Denmark	382	15; 10/5; (3.93)
Finland	154	3; 3/0; (1.95)
France	422	22; 13/9; (5.21)
Georgia	519	19; 7/12; (3.66)
Germany	1156	57; 27/30; (4.93)
Greece	90	4; 3/1; (4.44)
Hungary	1267	56; 36/20; (4.42)
India	575	52; 31/21; (9.04)
Indonesia	62	14; 8/6; (22.58)
Israel	636	21; 12/9; (3.30)
Italy	625	11; 8/3 (1.76)
Malaysia	56	8; 6/2 (14.29)
Mexico	137	12; 6/6 (8.76)
Netherlands	913	22; 17/5 (2.41)
Norway	159	5; 1/4 (3.14)
Philippines	78	16; 10/6 (23.66)
Poland	2666	104; 51/53; (3.90)
Portugal	152	8; 3/5; (5.26)
Romania	397	22; 14/8 (5.54)
Russia	678	48; 19/29; (7.08)
South Korea	120	4; 3/1; (3.33)
Singapore	64	3; 3/0; (4.69)
Slovakia	336	20; 11/9; (5.95)
South Africa	149	17; 8/9; (11.41)
Spain	314	13; 9/4 (4.14)
Sweden	347	12; 6/6 (3.46)
Switzerland	211	8; 5/3 (3.79)
Taiwan	92	8; 2/6 (8.70)
Thailand	152	32; 19/13 (21.05)
Turkey	51	8; 6/2 (15.69)
United Kingdom	281	14; 9/5 (4.98)
Ukraine	169	13; 8/5 (7.69)
USA	1413	53; 24/29 (3.75)

*No deaths reported among 16 patients enrolled at a single site in Hong Kong.

†C – clopidogrel; T – ticagrelor; % - overall death rate combined for both drugs.

contrast, few ticagrelor deaths were reported later and some vascular deaths were incorrectly entered in the NDA list as “non-vascular” or “unknown.” Importantly, principal investigators, attending physicians, interventional cardiologists, research coordinators, study nurses, and local sponsor monitors should not be held responsible for data interference because they consistently and sincerely reported true validated events or committed few unintentional errors with the Medidata Rave electronic data capture system entries, which was universally used in PLATO. As expected, there were several unintentional mistakes such as wrong patient name, gender, or erroneous year of enrollment. However, we found no evidence whatsoever that sites per se deliberately reported incorrect mortality data. Without detailed review of local site records, but based exclusively on national vital registries, these PLATO misreporting issues would not have been revealed since all misreported patients were actually deceased. Sooner or later, from different primary cause, but dead making any proper adjudication attempt impossible to achieve considering lack of paper records.

Regarding the discrepancy in total PLATO deaths, the dataset “cleaning” resulted in more removed ticagrelor (n = 21) than clopidogrel (n = 12) deaths. In fact, all deaths within the trial period should be counted although PLATO excluded deaths after “withdrawal of consent”. Importantly, withdrawal of consent or volunteer discontinuations for ticagrelor patients seems to have been quite liberal.¹⁹ The geographical differences in death rates reported in PLATO are wide, although the current dataset is not sufficient to make any definite conclusions. Indeed, within the same continent guided by universal recommendations, Europe yielded very different deaths numbers starting from low rates in Italy (1.8%) or Finland (2.0%); average in Poland (4.0%) or Hungary (4.4%); high in Germany (4.9%), France (5.2%), or Bulgaria (7.1%); to very high in Turkey (15.7%). The Polish ticagrelor benefit “phenomenon” in PLATO is not related to mortality since there were numerically more ticagrelor deaths, but most likely was because of questionable massive MI adjudication exclusively in the clopidogrel arm,^{14,15} which should be explored further. In contrast, deaths reporting from Belgium, Brazil, Denmark, Germany, India, Netherlands, and Turkey are concerning and should be verified. Unfortunately, we were unable to retrieve data from 2 high volume German centers in Wuppertal (281 patients with 20 deaths), and Dortmund (158/7), but authorities may consider reviewing this issue later. In fact, the single center Helios in Wuppertal (Germany) contributed more deaths than Australia, Austria, Belgium, and Finland combined. Other missing information arose in the dataset from Malaysia. In short, a high-

Table 4. Mismatches between site- and NDA-reported death dates in PLATO.

Country/PLATO ID#	Arm	Death date (site)	Death date (NDA)	Cause of death	Comment
Norway					
34xxxxxx	Ticagrelor	23Dec2008	Jan 21, 2009	Vascular	28-d delayed death reported at the day of last follow-up
34xxxxxx	Ticagrelor	20Apr2007	Apr 27, 2007	Vascular	7-d delayed death
Hungary					
26xxxxxxx	Clopidogrel	03Mar2008	Feb 23, 2008	Nonvascular	10-d earlier death, misreported as vascular and sudden
26xxxxxxx	Clopidogrel	25Sep2008	Apr 4, 2008	Nonvascular	150 d earlier death reported as vascular/sudden, but the patient died after strict 365-d follow-up, and should be excluded
Poland					
36xxxxxx	Unknown	31Aug2007	No report	Vascular	Female patient (PESEL #5609xxxxxxxxxx) not in the NDA list
South Korea					
40xxxxxx	Unknown	02Jun2008	No report	Vascular	Patient "YSY", enrolled May 30,2008, experience sudden death due to cardiac arrest, not in the NDA list

enrolling PLATO site operating in the urban, but remote community hospital setting moved to a new location in 2011, with trial archives entirely missing. Study materials were returned to sponsor. The NDA records indicate 4 deaths (3 on clopidogrel and 1 on ticagrelor) from that site. However, the principal investigator and study nurse repeatedly recalled no follow-up deaths recollection among enrolled patients in PLATO. These data are unconfirmed, but worth mentioning for further exploring.

Our verification efforts revealed that aside from unreported, or wrongly tabulated extra fatalities, which were

not common, the mismatch in the death causes may be a major concern if confirmed in the rest of PLATO patients. In short, several clopidogrel patients were reported in the NDA as "dead" on the exact same day when in reality they experienced a non-fatal event. Such inaccuracy may have led to enhanced overall "vascular mortality reduction" claim, and to an exaggerated ticagrelor "early survival benefit" over clopidogrel so desperately needed to convince interventional cardiologists to switch for ticagrelor. Lately, the ISAR REACT 5, a large randomized trial failed to confirm a ticagrelor benefit in ACS patients when compared with prasugrel¹⁶ so as the POPularAGE

Table 5. Misreported causes of deaths in PLATO.

Country/PLATO ID#	Arm	Death cause (site)	Death cause (NDA)
Canada			
16xxxxxx	Clopidogrel	Nonvascular	Vascular
16xxxxxx	Clopidogrel	Nonvascular	Vascular
16xxxxxx	Ticagrelor	Vascular	Nonvascular
Mexico			
32xxxxxxx	Clopidogrel	Nonvascular	Vascular
Hungary			
26xxxxxxx	Clopidogrel	Nonvascular	Vascular
26xxxxxxx	Ticagrelor	Vascular	Unknown
26xxxxxxx	Clopidogrel	Nonvascular	Vascular
26xxxxxx	Clopidogrel	Nonvascular	Vascular
26xxxxxx	Clopidogrel	Nonvascular	Vascular

Table 6. Misreported deaths codes in PLATO.

Country/PLATO ID#	Arm	Death cause (site)	Death cause (NDA)	Audited cause of death
Canada				
16xxxxxx	Clopidogrel	12-09	11-10	Failure to thrive (not eating, drinking) in nursing home
16xxxxxx	Clopidogrel	12-03	11-05	Lung cancer, never on drug
16xxxxxx	Ticagrelor	11-01	12-01	Cardio-respiratory arrest, sudden death
Norway				
34xxxxxxx	Ticagrelor	11-01	11-02	Sudden death
34xxxxxxx	Clopidogrel	11-10	11-11	Heart failure, but no drug discontinuation as reported
Mexico				
32xxxxxxx	Clopidogrel	12-01	11-02	Respiratory failure, intubation, ventilator, definite pulmonary death
32xxxxxxx	Ticagrelor	11-01	11-10	Sudden death, no heart failure
Hungary				
26xxxxxxx	Clopidogrel	12-01	11-07	Respiratory failure, cancer death
26xxxxxxx	Ticagrelor	11-05	97	Stroke
26xxxxxxx	Clopidogrel	12-07	11-10	Renal failure
26xxxxxx	Ticagrelor	11-01	11-10	Sudden death, tamponade, autopsy confirmed
26xxxxxx	Clopidogrel	11-02	11-01	Myocardial infarction (MI) after possible stent thrombosis
26xxxxxx	Clopidogrel	12-01	12-99	Hypotension, neurological damage due to hypoxia
26xxxxxx	Clopidogrel	12-01	11-01	Respiratory failure
26xxxxxx	Ticagrelor	11-01	11-02	Sudden death
26xxxxxx	Clopidogrel	12-09	11-10	Multiorgan failure (MOF)
26xxxxxx	Clopidogrel	11-02	11-01	MI
Poland				
36xxxxxx	Ticagrelor	11-03	11-99	Unstable angina, not unclear or "other"
South Korea				
40xxxxxx	Clopidogrel	11-02	11-01	Documented MI, no sudden death

For the cause of death main codes: "11" – vascular; "12" – non vascular; "97" – unknown; Vascular subcodes: "1" = sudden death; "2" = myocardial infarction; "3" = unstable angina; "4" = other coronary artery disease; "5" = stroke; "6" = arterial embolism; "7" = pulmonary embolism; "8" = ruptured aortic aneurysm; "9" = aortic dissection; "10" = heart failure; "11" = cardiac arrhythmia; "12" = death from bleeding (not trauma); "13" = endocarditis; "14" = valvular disease; "99" = other. Non-vascular codes: "1" = respiratory failure; "2" = pneumonia; "3" = cancer; "4" = trauma; "5" = suicide; "6" = liver failure; "7" = renal failure; "8" = sepsis; "9" = multiorgan failure; "99" = other.

study against clopidogrel in the elderly.¹⁷ Moreover, comprehensive data from the Swedish SWEDEHEART Registry analyzed over 14,000 elderly patients, and revealed 17% excess death risk (hazard ratio = 1.17; 95% confidence interval, 1.03–1.32) after ticagrelor when compared with clopidogrel.¹⁸

Another challenge in PLATO was the mismatch of death causes whereby "vascular" deaths were over-reported for clopidogrel, whereas underreported for ticagrelor. In fact, such a pattern was anticipated since officially published clopidogrel vascular

deaths over total deaths were very high (89%) in PLATO,⁶ compared with 81% in ISAR-5; 76% in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; 64% in Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin, and 52% in POPularAGE. Interestingly, there were no bleeding deaths after clopidogrel in POPularAGE,¹⁷ which were counted as "vascular" in PLATO. Moreover, in support of overall evidence, the recent ESC 2020 Guidelines

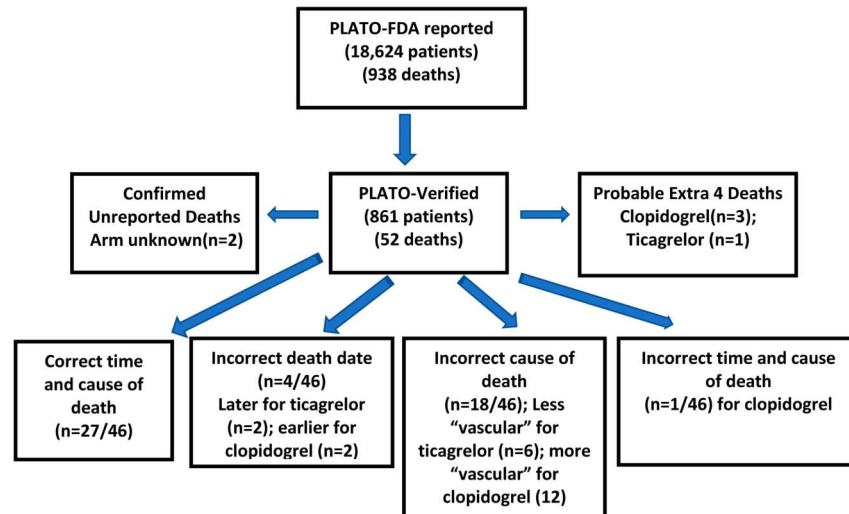


FIGURE 2. PLATO deaths verification algorithm and results.

downgraded ticagrelor and recommend prasugrel in Non ST-elevated-ACS patients undergoing coronary interventions.¹⁹

The intriguing subset of late PLATO deaths (5 clopidogrel and 2 ticagrelor) occurred in nursing homes. These deaths are usually not witnessed, with no autopsy performed. The patients were very sick with an array of comorbid diagnoses such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, anemia, arthritis, hip replacement, constipation, and cancer. Among cardiovascular diseases, heart failure, and arrhythmias are most common. Such patients usually die calmly refusing food and water, with a true cause of death as “failure to thrive.” However, 4 of 5 of nursing home clopidogrel deaths were counted as “vascular” and, despite obvious cause as “cardiac arrest,” no ticagrelor patients were reported as dead from vascular causes. The late nursing home deaths probably represent the “grey zone” for death counts in long-term trials.

It is also unclear whether patient-level paper records were available and actively used by PLATO adjudicators, or the decision on death cause was done based exclusively on the changed electronic Clinical Research Forms yielded from the already mismatched NDA dataset. Because the FDA reviewers definitely had no access to PLATO paper records, and used the .pdf files of electronic Clinical Research Form’s, most likely trial adjudicators were in the similar situation, and were unable to determine misreporting discrepancies. Finally, PLATO investigators published over 60 secondary papers explaining and promoting the benefits of ticagrelor in a variety of trial subpopulations linked to trial

outcomes reflected in the NDA dataset. Importantly, the mismatches in cardiovascular origin and precise timing of PLATO deaths are now challenging the scientific validity of such scientific reports. The insight from the present study would have an impact on other pivotal trials. The presented findings implicitly mean that some of the contemporary medical progress based on results from large-scale clinical trials may have methodological and interpretation flaws. Obviously, the current analysis could preclude any more direct involvement of the sponsor to control data flow in such indication-seeking studies. It is currently unclear how the index findings will affect overall PLATO trial results. Fortunately, the entire PLATO database is available in the cloud storage for ongoing investigation which is underway. We are unaware of any other such practices described in the paper concerning other antiplatelet drugs trials, although few things truly matter now. First, the Freedom of Information Act allows to publicly access the very intimate trial data to avoid future inaccuracies or mismatches in reporting. Further research could focus on the role of FDA in PLATO controversy including repeated sabotaged investigations of the Task Force, and woeful failures of site inspections in Hungary. The Task Force will further analyze patterns of cancer and sepsis deaths reporting, and comparison of sponsor versus third party Clinical Research Organization PLATO fatalities.

Limitations

There are obvious limitations to our report worth mentioning. We were able to retrieve and verify data

from only 861 patients, with 52 deaths. So, most PLATO fatalities are still unverified and current numbers may be not high enough to be absolutely compelling to precisely assess the magnitude of the problem. A positive impact is that more PLATO investigators are approaching us to share the death records from their sites, and we expect much larger sample size of PLATO deaths verification in the future. Also, the exact mechanisms of obtaining deaths reports differs among sites, and we assume that the investigators state correctly site-reported outcomes. However, because of the objective dichotomous nature of fatal events (events are clearly yes or no), we are sure that these events were the most appropriate ones to choose for such selective analysis. Although it is impossible to judge at this point what was the real background and the magnitude of the “mismatches” we observed, it is worth disclosing for stimulating a scientific discussion to clarify these uncertainties. It is unclear how the official adjudication applied to the various data sources. For instance, whether the data deposited into the high-level government database adjudicated events or just recorded them? And furthermore, whether it was a different level or degree of adjudication potentially anticipating such discrepancies. That is the entire task of, for example, independent Clinical Endpoint Committees or independent Clinical Adjudication Committees: to verify or to discard proposed endpoint assessments by the principal investigators from the local site. Even if this principle is more prevalent in softer endpoints such as “heart failure” or “myocardial infarctions,” this partly also applies for causes of death. It is also entirely unclear whether other outcomes, especially myocardial infarctions, cancers, infections, and bleeding were correctly reported. It is quite possible that some site records were inaccurate, but we attempted to use at least 2 independent sources to verify local evidence. The differences in record keeping quality heavily depends on participating countries, with the top scores belonging to Mexico and Canada. Since all PLATO events are kept in the cloud-based Medidata Rave electronic data capture system (Medidata Solutions, Inc. New York, NY), a verification based on the data examination in that system may be warranted.

CONCLUSION

Details of some deaths such as causes, precise timing and actual event occurrences were inaccurately reported in PLATO favoring ticagrelor. The extent of mortality mismatch is unclear, and could challenge the

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entire trial validity if confirmed in the overall full dataset. Because all PLATO events are kept in the Medidata Rave electronic capture system, securing the database content, analyses of changes or/and repeated entries, identifying potential interference origin, and assessing the full magnitude of the problem are warranted.

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