Infections Deaths in the PLATO Trial

Victor Serebruany1 Jean-Francois Tanguay2

1 Department of Neurology, Johns Hopkins University, Baltimore, Maryland, United States
2 Interventional Cardiology, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada

TH Open 2021;5:e503–e506.

Address for correspondence Victor Serebruany, MD, PhD, Department of Neurology, Johns Hopkins University School of Medicine, 14110 Rover Mill Road, West Friendship, MD 21794, United States (e-mail: vserebr1@jhmi.edu; heartdrug@aol.com).

Introduction

The relations between infections, hemostasis, and potency of antithrombotic therapy are intertwined but important, especially after utilization of current aggressive dual antiplatelet strategies following coronary revascularization. Indeed, such complex interventions per se often require use of numerous devices into and out of the arterial circulation, and these procedures may cause bacteremia2 or even septicemia.3 Since already established shortcomings following clopidogrel may include impaired wound healing and increased postsurgery infections,4,5 more powerful ...
Table 1 FDA analyses of infections and sepsis-related deaths in PLATO

| Infection                | Ticagrelor | Clopidogrel |
|--------------------------|------------|-------------|
| Upper respiratory        | 947 (10.25%) | 882 (9.6%) |
| Lungs                    | 233 (2.52%) | 245 (2.67%) |
| Urinary tract            | 184 (2.0%)  | 161 (1.8%)  |
| Viral                    | 466 (5.05%) | 415 (4.52%) |
| Bacterial                | 506 (5.48%) | 492 (5.36%) |
| Any infection            | 1,488 (16.11%) | 1,438 (15.65%) |
| Fever                    | 331 (3.58%)  | 318 (3.46%)  |
| Sepsis-related deaths    | 7 (0.1%)     | 23 (0.2%)    |

Abbreviation: FDA, Food and Drug Administration.

antiplatelet strategies could present even greater risks. The mechanism responsible for such harmful association is probably indirect and involves weakening of platelet–neutrophil–endothelial cross-talk necessary to combat infections, and/or keep inflammation from spreading. However, the comparative risks of infections including sepsis among adverse events in such patients have not been identified. The first alarming signal that potent long-term antiplatelet therapy may cause excess of infections that was observed in the prasugrel arm of TRITON-TIMI 38 trial.6 Consistently, ticagrelor in PLATO caused more infections but surprisingly less sepsis-related deaths (SRD) than clopidogrel.7 The details of the Food and Drug Administration (FDA) review7 are outlined in Table 1.

The data outlined in the Table 1 strongly suggest that more profound platelet inhibition with ticagrelor causes a slightly greater risk for infections than after clopidogrel. Such observation may be related to the fact that ticagrelor PLATO regimen was more potent. However, how could the reduction of SRD reported after ticagrelor therapy be reconciled? With details unavailable for public these numbers should be independently verified, despite some preliminary attempts to explain this paradox.8-10 We recently gained access to the detailed FDA-issued dataset of 938 PLATO deaths which has been matched with local patient-level data from sites controlled by the sponsor revealing that actual existence, the precise dates, and the proper causes of some deaths in PLATO were inaccurately reported in favor of ticagrelor.11 Moreover, there is a massive discrepancy between primary death causes reported to the FDA, and those utilized by the PLATO Investigators for numerous secondary overoptimistic reports published in top journals for over a decade.12 Examining cancer deaths revealed that many clopidogrel events were misreported in PLATO favoring ticagrelor as well.13 Here, we disclose verified deaths from pneumonia and sepsis in PLATO, examining their reporting patterns and validity.

Methods

Based on the Freedom of Information Act, BuzzFeed filed a legal complaint in U.S. Federal Court, won an expedited order, and shared with us the complete PLATO death list submitted to the FDA by the ticagrelor sponsor. The FDA 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 exit. Each event contains whether the death cause was vascular (code 11), nonvascular (code 12), or unknown (code 97). There were 14 subcodes for vascular, 9 subcodes for nonvascular deaths, and universal code “99” which applied for “other” causes. Among infections, the spreadsheet contains primary deaths’ codes for pneumonia (12–2) and SRD (12–8) only. Most of the data were controlled and reported by PLATO sponsor, with the exception of the United States, Russia, Georgia, and most (sites 5101–5106) of Ukraine. The entire United States was monitored by ReSearch Pharmaceutical Services, (Wort Washington, Pennsylvania, United States; http://www.rpsweb.com). All Russian, Georgian, and most Ukrainian sites were monitored by Evidence CRP, now Worldwide Clinical Trials, (Morrisville, North Carolina, United States; http://wwctrials.com/). The FDA-issued list contains 18 precisely detailed pneumonia deaths and 30 SRD. We have local verified records on four of such deaths (two each for pneumonia and SRD) among 861 PLATO patients from 14 enrolling sites in eight countries and matched those with what was reported to the FDA. We also assessed the reporting pattern of deaths from infections issued by the FDA just scrolling down column “S” for the nonvascular death causes.

Results

Among 18 FDA-reported pneumonia deaths in PLATO, those attributed to ticagrelor (n = 10) were numerically more than after clopidogrel (n = 8). We matched two PLATO patients with the local site data (one ticagrelor and one clopidogrel). Both cases were reported correctly. With regard to SRD verification in two clopidogrel cases, both primary death causes were reported incorrectly. As reported by site the primary cause of death of one clopidogrel patient was multi-organ failure (nonvascular subcode 9) but not SRD (subcode 8). Another patient is of significant interest since sepsis was among the secondary diagnoses. However, site reported respiratory failure (nonvascular subcode 1) as a primary death cause but not sepsis. Of the remaining 21 clopidogrel SRD, 6 were reported as three separate pairs repeating previous in list patient record suggesting last minute addition of incorrect cases. In contrast, four ticagrelor SRD has been accompanied by very close clopidogrel SRD entry in a pattern to “compensate” or maintain ticagrelor sepsis advantage. See Table 2 for details.

The surprising and highly unusual pattern of three pairs of close or next in line clopidogrel patients marked as SRD can be easily detected by just scrolling down Excel list column “S” among fatalities in Brazil and India. Repeated placement in pairs of subcode 8 (SRD) for 6 clopidogrel patients could indicate database manipulation or/and last-minute modifications to artificially worsen clopidogrel infection risks. Interestingly, patients in between: on line 77 received...
ticagrelor but patient on line 87 was on clopidogrel. However, that particular patient reported on line 87 experienced a cardiogenic shock, the "precious" vascular cause of death potentially contributing to PLATO primary efficacy outcome, and next in line 88 deceased clopidogrel patient was reported as SRD.

**Impression**

The main finding of this report suggests that ticagrelor is not better than clopidogrel with regard to risks of infections and affiliated deaths. Aside from possible misreporting, and unsubstantiated claims that ticagrelor could prevent SRD in PLATO, the drug per se probably do not cause direct inflammation effect but could negatively contribute via excessive chronic platelet inhibition when used in full-dose long term. Assessing infections signal after ticagrelor was tricky because of more infections, but over three times, less SRD than after clopidogrel were reported in PLATO. In contrast to the balanced and mildly concerned FDA report, the secondary PLATO publications overoptimistically present the infections data as somewhat a protective effect of ticagrelor.\(^8\text{-}^{10,14\text{-}16}\) Aside from reduction in ischemic cardiovascular events, the explanations for the mortality benefits of ticagrelor by suggesting pleiotropic effects\(^17\text{-}^{19}\) cannot be sustained since PLATO deaths benefit has been never achieved in later ticagrelor trials, making any extravagant explanation(s) meritless.

Long-term dual antiplatelet therapy may be associated with the unexpected but fatal complications including bleeding, infections, and SRD. This is especially alarming since modern antiplatelet strategies are often used off-label with regard to treatment duration. Also, randomized evidence suggests that most vascular benefits emerge early after coronary stenting but most complications including bleeding or/and infections grow over time of exposure. Unfortunately, we will not be able to intelligently assess the real rates of infections after dual antiplatelet therapy since the trials design do not measure such adverse events. However, more recent trials suggested that shorter antiplatelet strategies decrease bleeding risks without increased mortality.

The unremarkable and probably correct reporting of pneumonia deaths but possible increase of clopidogrel SRD count in PLATO was no surprise to the Task Force since changes of death dates, and especially their causes were already well-documented and previously reported.\(^11\) What is puzzling are the observation of three pairs of clopidogrel SRD in Brazil and India justifying complete reassessment of PLATO deaths. Such mis-reporting of data or error in late process of submission could not be detected by the independent researchers or scientific executive committee. Furthermore, the FDA could pick-up such evidence without an independent new monitoring of all deaths in PLATO. The observation that such rare fatal outcomes as SRD are reported in pairs is highly questionable. Indeed, SRD were reported as a primary cause of death in less than 3.2% PLATO fatalities making these 3 pairs of clopidogrel unusual and very unlikely. Such particular pattern of death reporting is very similar to cancer misreporting in PLATO when clopidogrel deaths were also entered in pairs.\(^1\) The FDA-issued dataset entries for questionable sepsis deaths in PLATO trial suggest a play of chance. The numbers are simply way too large-scale world-wide clinical trial to access the difference of our abilities to draw definite conclusions. In fact, within any large-scale world-wide clinical trial to access the difference of 8 versus 10 fatal pneumonia events is challenging, and may represent a play of chance. The numbers are simply too small to make any qualifying statements. The SRD misreporting will not necessarily change the direction of PLATO trial.

---

**Table 2** FDA-issued dataset entries for questionable sepsis deaths in PLATO trial

| ENTR | Country     | Age | ETN           | Gender | STUDYDY | TRTRTXT | NVASSCLS |
|------|-------------|-----|---------------|--------|---------|---------|----------|
| 22   | Argentina   | 57  | E1016xxx2DE   | Female | 37      | Clopidogrel | 8        |
| 24   | Argentina   | 71  | E1016xxx4DE   | Male   | 8       | Ticagrelor | 8        |
| 76   | Brazil      | 59  | E1422xxx1DE   | Male   | 52      | Clopidogrel | 8        |
| 78   | Brazil      | 77  | E1425xxx11DE  | Female | 147     | Clopidogrel | 8        |
| 86   | Brazil      | 64  | E1427xxx6DE   | Female | 56      | Clopidogrel | 8        |
| 88   | Brazil      | 75  | E1427xxx5DE   | Male   | 34      | Clopidogrel | 8        |
| 193  | Czech       | 67  | E1804xxx9DE   | Female | 69      | Ticagrelor | 8        |
| 195  | Czech       | 62  | E1805xxx4DE   | Female | 51      | Clopidogrel | 8        |
| 436  | India       | 74  | E2717xxx37DE  | Female | 198     | Clopidogrel | 8        |
| 440  | India       | 74  | E2719xxx8DE   | Female | 83      | Clopidogrel | 8        |
| 467  | Indonesia   | 52  | E2805xxx1DE   | Female | 131     | Ticagrelor | 8        |
| 468  | Israel      | 70  | E2901xxx79DE  | Female | 169     | Clopidogrel | 8        |
| 650  | Poland      | 73  | E3625xxx45DE  | Female | 242     | Ticagrelor | 8        |
| 651  | Poland      | 71  | E3625xxx72DE  | Female | 17      | Clopidogrel | 8        |

Abbreviations: ENTR, patient number among 938 reported PLATO deaths, goes in alphabetical order from Argentina to the United States, ending with 2 last deaths from Ukraine after monitoring switch from CRO to the sponsor; ETN, event tracking number; FDA, Food and Drug Administration; STUDYDY, Study days; TRTRTXT, randomization treatment text; NVASSCLS, subclassification of nonvascular death code.\(^12\)
results evaluation since numerous issues gave been already reported.\textsuperscript{11–13} Together with the FDA, we are currently implementing the joint status report in civil case number 21–572 based on the Freedom of Information Act in Washington, District of Columbia, District Court focusing on PLATO late event adjudication and some submission NDA 022433 evidence.

Conclusion

The pneumonia deaths were reported correctly, while many SRD were misreported in PLATO favoring ticagrelor.

Conflict of Interest

None related to this manuscript. The authors report the following general conflicts: V.S. is listed as an inventor for the issued U.S. patent “Treating vascular events with statins by inhibiting PAR-1 and PAR-4” (7,842,716) assigned to HeartDrug Research; and received compensation for the issued U.S. Patent 11/996,380 “Use of PAR-1/PAR-4 inhibitors for treating and preventing vascular diseases” on prasugrel assigned to Lilly. V.S. received funding for research studies with clopidogrel, and prasugrel; and consultant fees from clopidogrel and ticagrelor manufacturers. J.-F.T. have nothing to declare.

References

1 Kipshidze N, Platonova E, DiNicolantonio JJ, Kuliczkowski W, Serebruany VL. Excessive long-term platelet inhibition with prasugrel or ticagrelor and risk of infection: another hidden danger? Am J Ther 2015;22(02):e22–e27
2 Ramsdale DR, Aziz S, Newall N, Palmer N, Jackson M. Bacteremia following complex percutaneous coronary intervention. J Invasive Cardiol 2004;16(11):632–634
3 Leroy O, Martin E, Prat A, et al. Fatal infection of coronary stent implantation. Cathet Cardiovasc Diagn 1996;39(02):168–170, discussion 171
4 Gross AK, Dunn SP, Feola DJ, et al. Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. J Thromb Thrombolysis 2013;35(02):147–154
5 Blasco-Colmenares E, Perl TM, Guallar E, et al. Aspirin plus clopidogrel and risk of infection after coronary artery bypass surgery. Arch Intern Med 2009;169(08):788–796
6 Center for drug evaluation and research. Application number: 22–307. Assessed September 9, 2020 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022307s000_sumr.pdf
7 The FDA ticagrelor review of complete response. Assessed August 20, 2020 at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000MedR.pdf
8 Varenhorst C, Alström U, Scirica BM, et al. Factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery. J Am Coll Cardiol 2012;60(17):1623–1630
9 Varenhorst C, Alström U, Braun OO, et al. Causes of mortality with ticagrelor compared with clopidogrel in acute coronary syndromes. Heart 2014;100(22):1762–1769
10 Storey RF, James SK, Siegbahn A, et al. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. Platelets 2014;25(07):517–525
11 Serebruany V, Tanguay J-F, Benavides MA, et al. Clinical Trials Outcomes Verification Task Force. Verifying death reports in the platelet inhibition and patient outcomes (PLATO) trial. Am J Ther 2020;27(06):e563–e572
12 Serebruany VL, Tanguay J-F, Marciniak TA. The FDA and PLATO Investigators death lists: call for a match. Int J Clin Pract 2021;75(07):e14105
13 Serebruany V, Tanguay J-F. Misreported cancer deaths in PLATO trial. J Clin Med 2021;10(14):3140
14 Thomas MR, Storey RF. Effect of P2Y12 inhibitors on inflammation and immunity. Thromb Haemost 2015;114(03):490–497
15 Sexton TR, Zhang G, Macaulay TE, et al. Ticagrelor reduces thromboinflammatory markers in patients with pneumonia. JACC Basic Transl Sci 2018;3(04):435–449
16 Omarjee L, Meilhac O, Perrot F, Janin A, Mahe G. Can Ticagrelor be used to prevent sepsis-induced coagulopathy in COVID-19? Clin Immunol 2020;216:108468
17 Ellithi M, Baye J, Wilke RA. CYP2C19 genotype-guided antiplatelet therapy: promises and pitfalls. Pharmacogenomics 2020;21(12):889–897
18 Ait Mokhtar O, Gaubert M, Laine M, et al. Pleiotropic effects of ticagrelor: myth or reality? Arch Cardiovasc Dis 2016;109(8–9):445–448
19 Jeong HS, Kim JH, Hong SJ. Pleiotropic effects of ticagrelor beyond its potent antiplatelet effects contributing to additional clinical benefits. JACC Cardiovasc Interv 2018;11(17):1785