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FDA PLATO deaths list challenges aspirin dose–ticagrelor interaction

Victor Serebruany[1,*], Jean-Francois Tanguay[2]

[1] *Department of Neurology, Johns Hopkins University, Baltimore, MD 21794, USA*

[2] *Montreal Heart Institute, Université de Montréal, Montreal, QC H1B, Canada*

*Correspondence: vserebr1@jhmi.edu; heartdrug@aol.com (Victor Serebruany)

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Ticagrelor was compared to clopidogrel in the PLATO trial, which randomized 18,624 patients with ACS to either ticagrelor (180 mg loading dose plus 90 mg twice daily maintenance dose) or clopidogrel (300–600 mg loading dose plus 75 mg once daily maintenance dose) both on top of aspirin [1]. Ticagrelor leads to a significant reduction in the primary endpoint (a composite of death from vascular causes, myocardial infarction, or stroke) compared to clopidogrel (9.8% vs. 11.7%, 95% confidence interval (CI): 0.77–0.92, $p < 0.001$) [1]. However, the PLATO-US data were completely inversed when all primary efficacy endpoint components were better for clopidogrel [2] (See Fig. 1 for details).

The controversy surrounded this observation led to multiple *post-hoc* analyses, which generated a questionable hypothesis that higher daily aspirin dose of 300–325 mg in the US (53.6%) compared to the rest of the world (1.7%) was the exclusive key factor (out of 37 variables explored) to explain the geographical interaction of the reason why ticagrelor was harmful in the US trial population [2]. In the ticagrelor-aspirin $\geq$300 mg/daily cohort, all-cause (HR = 1.27; 95% CI: 0.84–1.93, $p = 0.26$) and cardiovascular mortality (HR = 1.39; 95% CI: 0.87–2.2, $p = 0.17$) were still higher after ticagrelor but not significantly as presented by the FDA reviewers [2, 3]. Not only the ticagrelor-aspirin interaction did not reach significance, but the data were obtained from a very small subgroup, in a highly post-randomization fashion with non prespecified analyses as well as multiple confounding problems with plausibility, and no biological sense [3]. Among other limitations the FDA reviewers noted sensitivity to reclassification of small numbers of cases regarding loading versus maintenance aspirin dosing, and the distribution of events in high-dose aspirin observed outside of the USA [2–4]. In short, the FDA documents clearly suggest that aspirin dosing does not fully explain the disparate PLATO results. In addition, the Advisory Committee members found no evidence to establish such link, uniformly rejecting the hypothesis that aspirin dose affects the heterogeneity of outcomes in PLATO [4].

Moreover, a highly significant diabetic-aspirin interaction in PLATO has later challenged the ticagrelor-high dose aspirin hypothesis [5]. In fact, diabetics (regardless of treatment arm) had a highly significant reduction in major adverse cardiovascular events, all-cause mortality, and vascular mortality if they received higher aspirin doses >300 mg ($p <$ 0.0001 for all interactions) [2, 5]. Importantly, in patients treated with early (within 24 hours) percutaneous coronary intervention (PCI), ticagrelor significantly increased all-cause mortality (30 day: HR = 1.89; 95% CI: 1.26–2.81, $p =$ 0.002) compared to clopidogrel [2, 3]. The strong ticagrelor-early PCI interaction was the major reason for the FDA primary efficacy reviewer to state that "ticagrelor should not be approved in the US until this interaction is refuted" [2]. Despite such obvious shortcomings and uncertainties, the lower aspirin dose concept driven from PLATO-US controversy was enforced, and is currently implemented in the European [6], Canadian [7] and US [8] guidelines. We have been seeking reevaluation of the overall PLATO endpoint differences, especially focusing on mortality, driven from sponsor-monitored sites versus outcomes observed by independent Contract Research Organization (CRO) for a decade [4].

We finally gained access to the detailed dataset of 938 PLATO deaths reported to the FDA. Those records were matched with original local patient-level data from sites controlled by the sponsor revealing that actual existence, precise dates and proper causes of some deaths in PLATO were inaccurately reported in favor of ticagrelor [9]. Moreover, for the first time we gained access to deaths dependent on the monitoring source. Somehow per country deaths on ticagrelor and clopidogrel were never disclosed to public, despite the fact that PLATO Investigators acknowledged "geographical" differences in trial outcomes [10]. The CRO's reported outcomes from USA, Russia, Georgia, and most of Ukraine, while sites in other 39 countries were monitored by the sponsor. Such method used in the PLATO trial [10] led to death reporting from combined "North America" mixing true unbiased US data monitored by CRO with heavily misreported outcomes in Canada [9] which were controlled by the sponsor. We compare if there were any differences in aspirin doses when deaths were reported by the sponsor versus independent CRO's. The details are outlined in the Table 1.

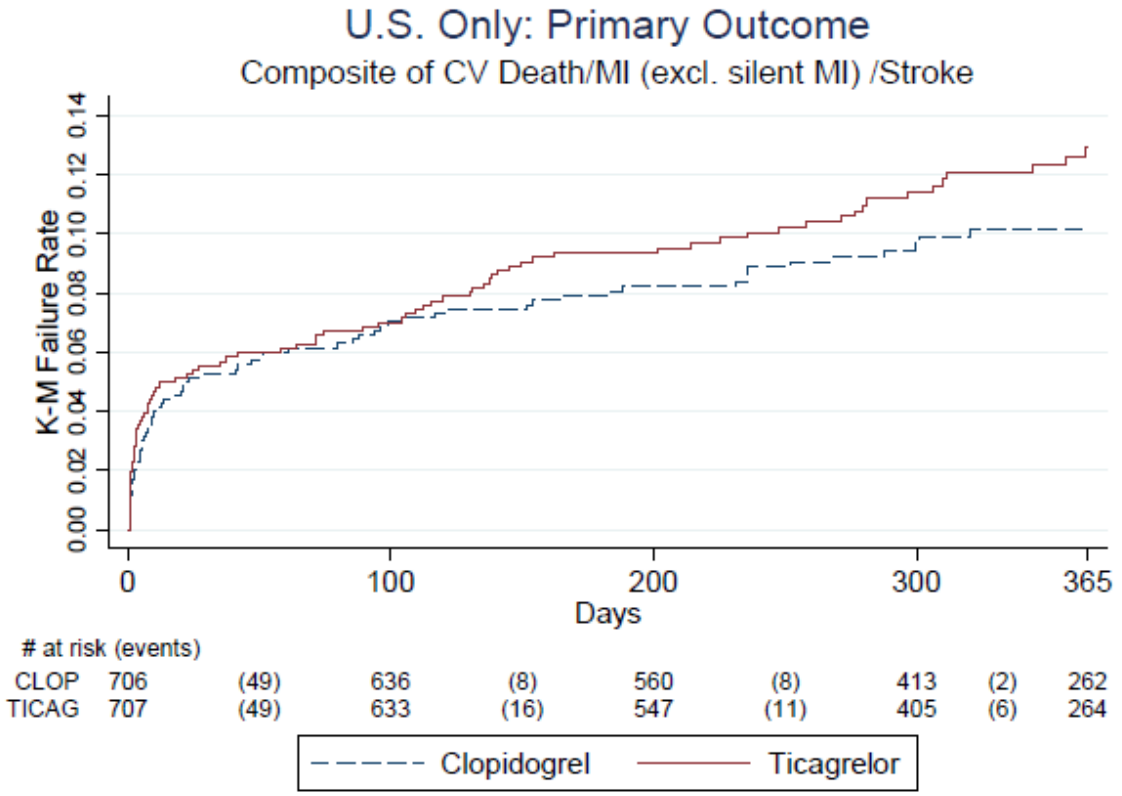

Fig. 1. PLATO outcomes in the USA. No early benefit of ticagrelor and growing over time superiority of clopidogrel. Source: R. Fiorentino, Clinical reviewer.

These FDA-issued data indicate that CRO's reported deaths numbers are in the opposite direction than PLATO sponsor reported death numbers, and this difference was highly significant. Such observation suggests that the "surprising" results were not PLATO-US outcomes, but those primary events misreported outside US. Lack of such obvious analyses (CRO's versus Sponsor) not conducted by the FDA is unexplained and intriguing. Indeed, there were 39 variables tested to explain PLATO-US phenomenon [2], but surprisingly why such a simple variable was never explored and disclosed to public. Why the deaths distributions by country were never disclosed despite almost 100 of secondary PLATO publications? Releasing such death distributions in the countries monitored by independent CRO's could justify a thorough review of all sponsor-reported trial outcomes. Importantly, ticagrelor inferiority in Russia and Georgia was even stronger than in the US, but this result had nothing to do with the higher aspirin doses. Both Russia and Georgia are governed by European Society of Cardiology ACS recommendations, and aspirin in the daily use of over 100 mg for cardiac indications is not used in both countries. In fact, local pharmacies in both countries are not even offering aspirin in the 325 mg dosage. In the formularies, there are cardio aspirins with 100 mg/pill or "аспирин кардио" for Russia, and "ასპირინი კარდიო" in Georgia (Bayer), or less popular cardiomagnyl by Takeda containing aspirin daily 75 mg dose in both countries. Gaining access to the complete PLATO death dataset issued by the FDA was determinant to explore in depths the reason(s) for possible discrepancies in deaths reporting. With these new data we were able to disclose the striking difference in mortality by each country, and to link this difference to the monitoring source. Excess ticagrelor deaths in the countries with no high-aspirin dose controversy strongly suggest the artificial nature of the existing hypothesis to explain inversed US-PLATO outcomes. The comparison between the FDA records and local patient-level data from sites controlled by the sponsor revealed that actual existence, precise dates and proper causes of some deaths in PLATO were inaccurately reported in favor of ticagrelor [9]. Moreover, there is a massive discrepancy between primary death causes reported to the FDA, and those utilized by the PLATO Investigators for numerous secondary reports published in top journals for over decade [11]. Examining cancer deaths reveled that at least 8 clopidogrel events were misreported in PLATO favoring ticagrelor as well [12].

In summary, dose of aspirin has nothing or very little to do with ticagrelor "benefit". Outcomes misreporting may be much more important. We now know that it is not only the US paradox, but the outcomes in the countries not monitored by the sponsor consistently exhibited ticagrelor inferiority in mortality over clopidogrel. In both Russia and Georgia aspirin is not used at the dose over 100 mg/daily for any cardiac indication, but ticagrelor deaths were higher than in the US.

Table 1. Deaths reported to the FDA by CRO's and Sponsor in PLATO.

Source/Country	Enrolled (n)	High-dose Aspirin (%)	Deaths (Clopidogrel)	Deaths (Ticagrelor)	△ Deaths
CRO:					
United States*	1413	Yes (53.6%)	24	29	5
Russia**	678	None (0%)	19	29	10
Georgia**	519	None (0%)	7	12	5
Ukraine***	163***	None (0%)	6	5	–1
Total	2773	Yes (27.6%)	**56**	**75****	**19**
Sponsor:					
Total	15,851	781 (4.9%)	**462****	**345**	**–117****

*: ReSearch Pharmaceutical Services (Fort Washington, Pennsylvania, USA). **: Evidence CRP, now Worldwide Clinical Trials (Morrisville, North Carolina, USA). ***: CRO (163 patients, 9 deaths); sponsor (6 patients, 2 deaths). ****: $p < 0.001$. △: Delta or difference.

Author contributions

VS wrote the initial draft and analyzed the FDA-issued PLATO deaths dataset. JT made a critical revision and re-assessed the evidence.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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