

Superior early periprocedural efficacy of prasugrel over ticagrelor in patients after stenting

Victor L. Serebruany¹, Elena Z. Golukhova², Naida I. Bulaeva²

¹ Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

² Bakoulev Center for Cardiovascular Surgery, Academy of Medical Sciences, Moscow, Russia

The optimal choice of antiplatelet agent for secondary prevention of vascular events represents an unsolved critical medical issue. Among oral P2Y₁₂ inhibitors, clopidogrel, prasugrel, or ticagrelor are broadly available; however, the lack of any definite outcome-driven randomized comparative evidence results in variability of preferences and confusion with prescription patterns. Moreover, randomized data are challenged by trial heterogeneity, massive drug discontinuations, and incomplete follow-ups.¹ Importantly, beyond early poststent protection after acute coronary syndromes so obvious for prasugrel, one agent, ticagrelor, consistently claims mortality benefit despite the controversial PLATO trial results² and skeptical Food and Drug Administration (FDA) reviews.^{3,4} Since such benefit was never confirmed by any further ticagrelor trials, any attempts to match the outcomes are important. We will here compare the early benefits of prasugrel in the TRITON trial⁵ versus ticagrelor in the PLATO trial,² keeping in mind the striking differences in the timing of benefit (immediate for prasugrel versus delayed for ticagrelor).

Triaging 3 components of the combined efficacy endpoint in TRITON suggests that the difference between the 2 arms was driven by the rates of nonfatal myocardial infarction, favoring prasugrel over clopidogrel (475 and 620 events, respectively).⁵ In contrast, mortality was identical (prasugrel, 154 vs clopidogrel, 155 patients) when for each cardiovascular death prevented by prasugrel (133 vs 150 cases), one additional fatal bleeding occurred (21 vs 5 events), as correctly reflected in the accompanying editorial.⁶ Therapy with both agents was associated with the equal distribution of strokes (prasugrel, 61 vs clopidogrel, 60). The FDA-generated **TABLE 1** clearly indicates that the mortality benefit from using prasugrel in TRITON was limited

to patients with ST-segment elevation myocardial infarction (STEMI).⁷

There was a small but consistent trend (30 fatalities) towards more deaths in the experimental TRITON arm among patients with non-STEMI, in contrast to the obvious prasugrel advantage in the STEMI cohort. Importantly, the survival rate for the second myocardial infarction (MI) in TRITON was much higher than previously reported,⁸ clearly reflecting that not all MIs in TRITON “were born equal.” Considering that most efficacy endpoints in TRITON occurred during the first 3 days after the initial qualifying event, many periprocedural events and/or “enzymatic bombs” were included. In fact, TRITON revealed an increase of 41.7% in the rate of nonfatal MI when compared with the highest reported rate in the previous clopidogrel trials. This finding is alarming and requires further clarification and better comprehension.

One may suggest that the striking differences in the rates of nonfatal MI may be attributed to the patient selection and severity of initial ischemic burden. This is especially challenging, because TRITON patients were treated better than those enrolled in the earlier clopidogrel trials on statins, hypertension control, and others. Only later, after a comprehensive FDA review,⁷ the cause of such discrepancy was clearly solved. The sponsor after the trial switched to a more liberal MI definition expanding the event count. Applying a more inclusive MI definition explains the increased rate of nonfatal MI, which was also confirmed by the FDA-generated evidence of the delay of MI adjudication in TRITON.⁹ Such definition manipulation would never happen after TRITON, since the universal definition of MI¹⁰ became mandatory for all future trials on acute coronary syndrom. In contrast to TRITON with increased numbers of MI, these numbers

Correspondence to:

Victor L. Serebruany, MD, PhD,
Johns Hopkins University,
Osler Medical Building,
7600 Osler Drive, Suite 307, Towson,
Maryland, 21204, United States,
phone: +1-410-274-2405,
email: vserebr1@jhmi.edu

Received: August 25, 2017.

Accepted: August 28, 2017.

Published online:

November 30, 2017.

Conflict of interest: VLS is listed as an inventor, and received compensation for the U.S. Patent Application P-17 232 “Method for treating vascular diseases with prasugrel” assigned to Lilly. He received funding for research studies with both clopidogrel and prasugrel, and consulting fees from ticagrelor manufacturer.

Pol Arch Intern Med. 2017;

127 (11): 720-721

doi:10.20452/pamw.4158

Copyright by Medycyna Praktyczna,

Kraków 2017

TABLE 1 Site-reported first event types in the TRITON trial

Event	UA/NSTEMI			STEMI		
	Clopidogrel	Prasugrel	Δ	Clopidogrel	Prasugrel	Δ
MI	235	175	60	62	48	14
Stroke	43	43	0	24	22	2
Death	83	113	-30	58	49	9

Abbreviations: MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

in PLATO (ticagrelor, 504 vs clopidogrel, 593 events) appear very reasonable,^{2,3} and the main problem was in applying “creative” event adjudication when only clopidogrel-generated MIs were counted, while the additional events that occurred in the ticagrelor arm were omitted.¹¹

This issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*) features an elegant small study¹² suggesting that guided early prasugrel administration may decrease periprocedural myocardial injury during percutaneous coronary intervention (PCI) in patients after stenting. Most importantly, the observation of this interesting phenomenon matches ideally with the TRITON trial results, but the clinical utility of these data is still unclear and definitely requires a much larger, better randomized study, with uniformed platelet biomarker assessment, long follow-up, and a careful mandatory collection of clinical events. The authors are absolutely correct by recommending repeated platelet testing for a better definition and validation of the clinical utility of prasugrel to prevent early periprocedural events.¹² Interestingly, the discussed study fully supports the FDA-generated prasugrel reviews of TRITON. Since early “enzymatic bombs” are so common in patients with classic STEMI, it is important to compare the outcomes of prasugrel versus ticagrelor in this highest-risk cohort. As regards mortality, the comparative STEMI survival curves in TRITON versus PLATO are shown in Supplementary material (*Figure S1*).

There are 3 remarkable facts that can be revealed from mortality comparisons between the 2 trials. First, despite consistently claiming “mortality benefit,” the STEMI death rate after ticagrelor (4.90%) was substantially higher than fatalities after prasugrel (3.28%). This finding is alarming since prasugrel is not marketed as a life-saver, but shows a mortality reduction of 33% in TRITON compared with ticagrelor in the cohort at highest risk of STEMI in PLATO. Second, it is very confusing why the rate of deaths from clopidogrel differs so much between TRITON and PLATO. This is especially controversial since clopidogrel was underdosed (just 300 mg loading dose) in TRITON, but not in PLATO, where pretreatment and higher loading doses were allowed. It would be reasonable to expect more deaths after prasugrel than after ticagrelor within the similar cohorts with classic STEMI. Finally, the entire mortality pattern over time looks so different

between prasugrel and ticagrelor. While the benefit of prasugrel was almost entirely front loaded, ticagrelor surprisingly exhibited mortality reduction very late in the trial. Such a trend was never seen with any antiplatelet agent, and raises the eyebrows that something “fishy” happened in PLATO. In fact, an inverted immediate benefit was first picked up in the FDA reviews, generating a term “ticagrelor early PCI death paradox,”^{3,4} revealing that early after PCI more ticagrelor than clopidogrel patients died in PLATO. These data were lately confirmed by the official PLATO angiographic substudy,¹³ denying any early benefit of ticagrelor on blood flow and thrombolysis in myocardial infarction flow grades.

In short, we are currently clueless as to a direct comparative impact of prasugrel versus ticagrelor on preventing early periprocedural occlusions after PCI. Ironically, it is likely that we will not know these precise data in the future as well, since no large outcome-driven studies are planned for comparisons between prasugrel and ticagrelor. However, the available body of evidence, verified by the FDA secondary reviews, indicates that prasugrel should be the drug of choice to block periprocedural enzymatic flushes early after stenting.

Supplementary material Supplementary material is available with the article at www.pamw.pl.

REFERENCES

- Marciniak TA, Cherepanov V, Golukhova E, et al. Drug discontinuation and follow-up rates in oral antithrombotic trials. *JAMA Intern Med.* 2016; 176: 257-259.
- Wallentin L, Becker RC, Budaj A, et al; the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009; 361: 1045-1057.
- The FDA ticagrelor secondary review. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220192.pdf>. Accessed August 21, 2017.
- The FDA ticagrelor review of complete response. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000TOC.cfm. Accessed August 21, 2017.
- Wiviott SD, Braunwald E, McCabe CH, et al; the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007; 357: 2001-2015.
- Bhatt DL. Intensifying platelet inhibition – navigating between Scylla and Charybdis. *N Engl J Med.* 2007; 357: 2078-2081.
- Prasugrel Secondary Review. <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-00-FDA.htm>. Accessed August 21, 2017.
- Serebruany VL. Excess rates of nonfatal myocardial infarction in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel (preventing clinical events or chasing enzymatic ghosts?). *Am J Cardiol.* 2008; 101: 1364-1366.
- Serebruany VL. Delays of event adjudication in the TRITON trial. *Cardiology.* 2010; 115: 217-220.
- Thygesen K, Alpert JS, White HD; the Joint ESC/ACCF/AHA/WHF Task Force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. *Eur Heart J.* 2007; 28: 2525-2538.
- Serebruany VL, Atar D. Central adjudication of myocardial infarction in outcome-driven clinical trials—common patterns in TRITON, RECORD, and PLATO? *Thromb Haemost.* 2012; 108: 412-414.
- Tomaniak M, Koltowski L, Kochman J, et al. Can prasugrel decrease the extent of periprocedural myocardial injury during elective percutaneous coronary intervention? *Pol Arch Intern Med.* 2017; 127: 730-740.
- Kunadian V, James SK, Wojdyla DM, et al. Angiographic outcomes in the PLATO trial (Platelet Inhibition and Patient Outcomes). *JACC Cardiovasc Interv.* 2013; 6: 671-683.