Editorial

Ticagrelor and heart surgery controversy: we may have better antiplatelet options

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Submitted Oct 11, 2016. Accepted for publication Oct 21, 2016.
doi: 10.21037/jtd.2016.11.26
View this article at: http://dx.doi.org/10.21037/jtd.2016.11.26

The unmet medical need

Despite advanced techniques and favorable clinical outcomes, the optimal antiplatelet strategy following coronary artery bypass grafting (CABG) is an unsolved mystery. Development of novel antiplatelet agents is pivotal for the management of patients with clinically evident coronary atherothrombosis in general, and those requiring CABG in particular. In contrast to the percutaneous coronary interventions, and stent implantations where aggressive antiplatelet strategies are conventional, the protection over CABG is a matter of considerable controversy with regard to the choice of optimal agent(s), potential dose adjustment, duration of therapy, and, most importantly, need for discontinuation during surgery (1,2). These uncertainties cannot be ignored since CABG remains the preferred treatment in patients with complex multivessel coronary artery disease (3). Indeed, CABG is more efficacious than coronary interventions with drug-eluting stents in patients with multivessel disease, reducing the risk of mortality [risk ratio (RR): 0.70, 95% confidence interval (CI): 0.57–0.87] (4), especially in diabetics by about a third (RR 0.67; 95% CI, 0.52–0.86) (5), including long-term for over 4 years survival (RR: 0.73; 95% CI, 0.62–0.86) (6).

Ticagrelor

Ticagrelor (formely known as AZD6140) is a first-in-class reversible antiplatelet agent chemically known as a cyclopentyltriazolopyrimidine, with distinguishing properties from that of thienopyridines ticlopidine, clopidogrel, or prasugrel (7). Importantly, unlike thienopyridines, ticagrelor does not require metabolic activation and has a dual mode of action that encompasses inhibition of both P2Y12 receptor and equilibrative nucleoside transporter 1 (8). Such dual mechanism increases adenosine plasma concentration in ACS patients (8), potentially augmenting the antiplatelet potency, and contributing to cardiac protection such as vasodilation and increases in coronary blood flow (9). However, if the adenosine hypothesis of ticagrelor action is valid, then few negative considerations should be kept in mind as well. Among those is the fact that adenosine *per se* never improved mortality in any clinical trial, challenging PLATO trial death benefit, but cause early vasoconstriction supporting ticagrelor "early death paradox" post-PCI picked up by the FDA reviewers (10), and matching well with lack of any ticagrelor advantage in the PLATO-angiographic substudy (11). Recently, Gherli R, and colleagues reported preoperative risks of continued ticagrelor with or without aspirin during CABG (12). In short, among 2,482 patients from the E-CABG registry, the study cohort included 786 consecutive patients with ACS. One-to-one propensity score matching provided 215 pairs, whose baseline and operative covariates had a standardized difference of less than 10%. Preoperative use of ticagrelor was associated with a similar risk of bleeding according to the bleeding classifications, but the incidence of platelet transfusion was higher in the ticagrelor group. Compared with those receiving aspirin alone, continuing ticagrelor up to the time of surgery or discontinuing its use less than 2 days before surgery was associated with a 3.5 times higher risk of platelet transfusion. The paper concludes that among patients undergoing CABG, the use of preoperative ticagrelor with or without aspirin compared with aspirin alone was associated with

more platelet transfusion but similar degree of bleeding; but in patients receiving ticagrelor 1 day before or up until surgery, there was an increased rate of severe bleeding. The paper provides important contribution confirming some of the already available evidence. However, there are at least two major shortcomings which are obvious to unbiased readership. First, currently there are more than dozen of bleeding classifications with at least some clinical validation in numerous trials and registries (TIMI, GUSTO, BARC), including PLATO-bleeding scale introduced specifically for ticagrelor bleeding risk assessment. The authors applied anecdotal E-CABG and UDPB scores limiting the transparency of the bleeding rates comparison. The other obvious limitation is lack of any cardiovascular, and deaths rates outcome data reported in this paper. Indeed, mortality, myocardial infarction, stroke comparisons should be easily available in the registry, and should be mandatory reported in the abstract for any valid clinical message. Moreover, the FDA-generated evidence from PLATO clearly does not support ticagrelor use during CABG (10).

The FDA outlook

The agency acknowledged that for all antiplatelet agents a clinically relevant question is what to do with them prior to surgery. Continuing them may lead to procedure-related bleeding while discontinuing them may lead to cardiac events. The FDA conducted the detailed review of the CABG-PLATO cohort, examined bleeding and some cardiac events post-CABG in PLATO. First, the agency was not impressed by the diminished post-CABG bleeding after ticagrelor when compared with clopidogrel, counting six fatal post-CABG bleedings for each agent. Since any potential advantage due to reversibility was not exhibited in PLATO, vascular complications following heart surgery should be under scope of the FDA as well. In PLATO, there were 770 ticagrelor patients, and 814 clopidogrel patients who received CABG. The major bleeding rates were similar between study arms with 619 (80.4%) versus 654 (80.3%), with identical hemorrhagic fatalities (6 deaths each). Moreover, it seems many bleeding risks may be underreported, limiting our proper assessment of risks associated with ticagrelor in post-CABG PLATO cohort. The agency clearly stated that "the risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG" (10). Unfortunately, the FDA did not conduct the detailed review of vascular outcomes specifically in post-CABG patients, however, some data are available. While overall PLATO results advocated for ticagrelor use, the combined early PCI and CABG group show opposite trends. In fact early interventions or surgery resulted in similar cardiovascular events or vascular deaths (3.2% versus 3.3%), moreover, ticagrelor was associated with higher all-cause 30-day mortality (1.9% versus 1.4%) following early PCI or heart surgery. Interestingly, this trend was similar independently from the underlying type of myocardial infarction, when ticagrelor caused slightly worsened results in both non-STEMI and STEMI cohorts in PLATO (10). Finally, the FDA Medical Team Leader expressed reasonable concerns with regard to the PLATO conduct, and integrity when many post-CABG ticagrelor cases were discontinued, questionably adjudicated, or lost in follow up.

Vorapaxar

Vorapaxar is a first-in-class selective, orally active, potent, and competitive protease-activated receptor 1 (PAR-1) antagonist that inhibits thrombin-induced platelet activation (13). The drug phase III program included two large outcome trials in patients with acute and chronic coronary atherothrombosis, namely Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes (TRACER) (14), and Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Arteriosclerosis (TRA 2P-TIMI 50) (15). Both trials underwent comprehensive FDA reviews, which revealed some surprising and encouraging findings with regard to outcomes in post-CABG-cohorts (16). The FDA clearly stated that the bleeding rates were slightly higher, but both the primary endpoint rates and death rates were substantially lower with vorapaxar post-CABG. The results in the two trials appear consistent. The agency concluded that there appears to be no need for vorapaxar interruption during CABG (16).

Impressions

Overall, the FDA reviewers were not particularly impressed by ticagrelor, but emphasize potential benefit of vorapaxar for antithrombotic protection in CABG. This advantage appears to be consistent across the trials with regard to at least three valuable issues. First, the bleeding disadvantage of vorapaxar during CABG was notable, but mild, not

significant, and seems like an acceptable payoff. Second, in contrast to ticagrelor, the rates of primary endpoint events, and mortality were lower after vorapaxar. These differences are truly impressive, although the FDA did not provide any comparative statistics. Finally, and most importantly from the practical standpoint, is the fact that vorapaxar benefit was observed when the drug was not interrupted over CABG. The possibility to avoid discontinuation may drive vorapaxar as an optimal antiplatelet agent for surgery in general, and CABG in particular, and this unique property should not be underestimated and/or lost in transition.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Kai Zhu (Department of Cardiac Surgery, Zhongshan Hospital Fudan University, Shanghai, China).
Conflicts of Interest: Dr. Serebruany is listed as an inventor for the issued US patent "Treating vascular events with statins by inhibiting PAR-1 and PAR-4" (7,842,716) assigned to HeartDrug™ Research; and "Method for treatment of platelet activity with E5555" (USN 61/080,791); assigned to Eisai and HeartDrug™. He 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. He received consultant fees from ticagrelor manufacturer. Others have nothing to disclose.

Comment on: Gherli R, Mariscalco G, Dalén M, *et al.* Safety of preoperative use of ticagrelor with or without aspirin compared with aspirin alone in patients with acute coronary syndromes undergoing coronary artery bypass grafting. JAMA Cardiol 2016. [Epub ahead of print].

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Cite this article as: Serebruany V, Bulaeva N, Golukhova E. Ticagrelor and heart surgery controversy: we may have better antiplatelet options. J Thorac Dis 2016;8(11):3016-3019. doi: 10.21037/jtd.2016.11.26