International Journal of Cardiology 215 (2016) 273–276

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Continued vorapaxar versus withdrawed clopidogrel both on top of low dose aspirin in patients undergoing heart surgery: A call for randomized trial

Victor L. Serebruany [a,*], Moo Hyun Kim [b], Elena Golukhova [c], Yury Pya [d], Makhabbat Bekbossynova [d], Marco Cattaneo [e], Thomas A. Marciniak [f,1]

[a] Johns Hopkins University, Baltimore, MD, USA
[b] Clinical Trials Unit, Dong-A University, Busan, South Korea
[c] Bakoulev Center for Cardiovascular Surgery, Moscow, Russia
[d] National Research Cardiac Surgery Center, Astana, Kazakhstan
[e] University of Milan, Milan, Italy
[f] FDA, Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 11 April 2016
Accepted 13 April 2016
Available online 17 April 2016

Keywords:
Vorapaxar
Heart surgery
Clinical outcomes
Mortality
Efficacy
Bleeding
Clinical trials

ABSTRACT

Despite advanced techniques and improved clinical outcomes, the optimal antiplatelet strategy following coronary artery bypass grafting (CABG) is an unsolved mystery. Vorapaxar, a novel platelet thrombin receptor (PAR-1/4) blocker, is currently approved for post-myocardial infarction and peripheral artery disease indications on top of clopidogrel or/and aspirin. We here summarize the outcomes in patients after CABG for justification of a future vorapaxar trial. We comprehended the CABG outcomes after vorapaxar yielded from TRACER, TRA2P trials, and affiliated FDA reviews. The verified evidence suggests that composite of death, myocardial infarction and stroke occurred in 2.2% of vorapaxar vs. 8.1% placebo in TRA2P. These data were similar to the endpoint differences (5.9% after vorapaxar vs. 8.3% for placebo) in TRACER. The mortality reduction also consistently suggests vorapaxar advantage (1.7% vs. 2.5% in TRA2P, and 1.7% vs. 3.9% in TRACER). Notably, the post-CABG bleeding risks after vorapaxar were only slightly, but not significantly higher. Moreover, the bleeding disadvantage in the experimental arm was most likely related to overtreatment since majority of patients in both TRACER and TRA2P received triple antiplatelet therapy with aspirin, clopidogrel on top of vorapaxar. Overall, the FDA-confirmed evidence advocate for the future vorapaxar post-CABG outcome-driven trial. The head-to-head trial testing dual therapy with continued over CABG vorapaxar versus withdrawed clopidogrel, both on top of low dose aspirin is warranted. We conclude that the primary outcomes including mortality were consistently better for heart surgery patients after vorapaxar, while the excess of bleeding was mild. Continuing vorapaxar during CABG may be superior to currently recommended withdrawal antiplatelet strategies, and should be tested in an adequately powered randomized outcome-driven trial.

1. Introduction

Development of novel antiplatelet agents is pivotal for the management of patients with clinically evident coronary atherothrombosis in general, and those requiring heart surgery (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 to 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].

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 [7]. The drug Phase III

* Corresponding author at: HeartDrug™ Research Laboratories, Johns Hopkins University, Osler Medical Building, 7600 Osler Drive, Suite 307, Towson, MD 21204, USA.
E-mail address: vserebr1@jhmi.edu (V.L. Serebruany).
[1] Retired..

http://dx.doi.org/10.1016/j.ijcard.2016.04.124
0167-5273/

Table 1
Bleeding and efficacy rates in the TRA2P indicated population for 21 days post-CABG.

Variable/arm	Placebo (n = 199)	Vorapaxar (n = 177)
Bleeding		
GUSTO (severe and moderate)	12.1%	15.8%
TIMI (major + minor)	9.1%	10.2%
TIMI major	7.0%	7.9%
Intracranial	0.5%	0
Primary endpoint[a]	8.1%	2.2%
Deaths	2.5%	1.7%

[a] Excluding 115 placebo and 92 vorapaxar patients with primary endpoints prior to CABG.

program included two large outcome trials in patients with acute and chronic coronary atherothrombosis, namely Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes (TRACER) [8], and Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Arteriosclerosis (TRA 2P-TIMI 50) [9]. Both trials underwent comprehensive FDA reviews, which revealed some surprising and encouraging findings with regard to outcomes in post- CABG-cohorts [10]. Herein, the efficacy and safety of vorapaxar related to CABG are briefly reviewed with a focus on the perspectives and obstacles for an outcome-driven heart surgery trial.

2. Vorapaxar and CABG

The most evidence with regard to heart surgery has been driven from the overall negative TRACER secondary analyses, while in the successful TRA2P, the sample size of CABG cohort was woefully small, and these data are still unpublished. Among 12,944 patients in TRACER, 1312 (10.1%) underwent CABG during index hospitalization, with 78% on vorapaxar at the time of surgery. Compared with placebo CABG patients, vorapaxar-treated patients had a 45% lower rate of the primary endpoint (a composite of death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization during index hospitalization) (HR: 0.55; 95% CI: 0.36 to 0.83; P = 0.005), with a significant interaction (P = 0.012). The CABG-related TIMI major bleeding was numerically higher with vorapaxar, but not significantly (9.7% vs. 7.3%; HR: 1.36; 95% CI: 0.92 to 2.02; P = 0.12), with no excess in fatal bleeding (0% vs. 0.3%) or need for reoperation (4.7% vs. 4.6%) [11]. Importantly, the bleeding in TRACER was artificially exaggerated due to unjustified overtreatment in NSTEMI patients with predominantly triple antiplatelet strategies. The real life clinical scenarios will apply dual strategies with vorapaxar on top of low dose aspirin reducing bleeding disadvantage even further. Moreover, CABG bleeding at 30-days, and at 2 years were reduced in TRACER after transradial (n = 2192) versus transfemoral (n = 4880) approach what is also promising. Overall, 30-day GUSTO moderate/severe and non-CABG TIMI major/minor bleeding occurred less frequently in transradial (0.9% vs. 2.0%, P = 0.001) vs. transfemoral (1.1% vs. 2.5%, P = 0.005) patients. A similar reduction was seen at 2 years (3.3% vs. 4.7%, P = 0.008; 3.3% vs. 4.9%, P < 0.001, respectively) advocating for radial access [12]. The relevance of these data is unclear since patients were not randomized dependent on the PCI assess site, what was done at interventionalist discretion. Importantly, general surgery was also not associated with increased perioperative ischemic or bleeding events after vorapaxar [13].

Table 2
Bleeding and efficacy rates in TRACER for 21 days post-CABG.

Variable/arm	Placebo (n = 953)	Vorapaxar (n = 935)
Bleeding		
GUSTO (severe and moderate)	17.0%	21.1%
TIMI (major + minor)	8.5%	11.1%
TIMI major	8.1%	11.0%
Intracranial	0	0.3%
Primary endpoint[a]	8.3%	5.9%
Deaths	3.9%	1.7%

[a] Excluding 85 placebo and 92 vorapaxar patients with primary endpoints prior to CABG.

Table 3
Advantages and obstacles for vorapaxar CABG trial.

Fact on vorapaxar	Impact	Comment
First-in-class	Pro	Never been tested for CABG indication
Excellent pharmacokinetics	Pro	Consistent exposure after once daily intake
99.8% serum albumin binding	Pro	Excellent bioavailability
10 days half-life elimination	Pro	Steady state over platelet life span
GI and biliary excretion	Pro	Suitable for patients with renal impairment
Delicate platelet inhibition	Pro	Maintaining the "comfort zone"
Low molecular weight	Pro	No known renal or hepatic toxicity issues
Reduction in primary endpoint	Pro	Surprise finding from TRA2P and TRACER
Mortality advantage	Pro	Consistent for post-CABG in both trials
No need for withdrawal	Pro	Major advantage over other antiplatelet agents
Low clinical utilization	Con	Despite approval in May 2014, no sales reported
Trial costs	Con	Very high, large sample size, low event rate

GI—gastrointestinal.

3. The FDA outlook

The FDA conducted the detailed review of both vorapaxar trials [10]. 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. In both vorapaxar clinical trials the protocols recommended continuing vorapaxar despite surgery. The best documented surgical procedures in the trials were CABGs. Therefore, the FDA examined bleeding and cardiac events post-CABG in both vorapaxar trials. To assign CABG-related bleeding, the FDA Medical Team Leader examined bleeding rates post-CABG regardless of treatment arm. The bleeding rates were highest immediately post-CABG but did not appear to return to a low level until about 21 days post-CABG. Hence the Agency counted any bleeding event occurring within 21 days post-CABG as a CABG-related bleeding, similarly for deaths and primary endpoints. About 199 placebo and 177 vorapaxar patients in the TRA2P indicated population had a CABG reported, including after the earliest last follow-up date. In TRACER about 953 placebo and 935 vorapaxar patients had a CABG reported. In both studies the majority of patients had vorapaxar continued until the day of surgery. In TRA2P the 25th percentile was discontinuation 10 days prior and in TRACER 3 days prior. The selected bleeding and efficacy rates for 21 days post-CABG in the TRA2P indicated population in Table 1 and for TRACER in Table 2.

Bleeding rates were slightly higher with vorapaxar post-CABG. Both the primary endpoint rates and death rates were substantially lower with vorapaxar post-CABG. The results in the two studies appear consistent. The Agency concluded that there appears to be strong justification from the trials for continuing vorapaxar despite surgery.

4. Discussion

Despite improved clinical outcomes after heart surgery, improving post-CABG survival is critical, being an obvious unmet medical need. It is still unclear whether adjustment of antiplatelet therapy will impact mortality, however, the initial vorapaxar experience post-CABG is encouraging. Understandably, these data are scarce since among hard