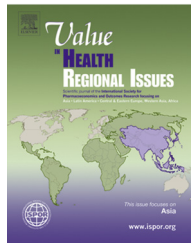
VALUE IN HEALTH REGIONAL ISSUES 6C (2015) 22–32

Available online at www.sciencedirect.com

ScienceDirect

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



Efficacy and Safety of Thrombin-Receptor Antagonist (Atopaxar and Vorapaxar) in Patients with Acute Coronary Syndrome or Coronary Artery Disease—A Meta-Analysis of Randomized Controlled Trials

Lan Gao, PhD[1,2], *Fei-Li Zhao, PhD, MPH*[3], *Shu-Chuen Li, PhD, MBA*[1,*]

[1]*School of Biomedical Sciences and Pharmacy, The University of Newcastle, Newcastle, Callaghan, NSW, Australia;* [2]*Deakin Health Economics, Population Health Strategic Research Centre, Faculty of Health, Deakin University, Melbourne, VIC, Australia;* [3]*Access and Public Affair, Pfizer Australia, Sydney, NSW, Australia*

ABSTRACT

Background: Meta-analysis for the efficacy and safety data of thrombin-receptor antagonist (TRA) based on patients with acute coronary syndrome (ACS) or coronary artery disease (CAD) and indirect comparisons between TRAs were not available. **Objectives:** We intended to synthesize the primary end points based on different patient populations (ACS or CAD) as well as perform indirect comparison between two newly invented antiplatelet agents atopaxar and vorapaxar. **Methods:** A literature search was performed in MEDLINE, Embase, and Cochrane Library. Incidences of major adverse cardiovascular events (MACEs) and bleeding events according to thrombolysis in myocardial infarction were selected as primary outcomes, whereas adverse effects were considered as secondary outcomes. Corresponding results were synthesized using Revman 5.1 according to ACS or CAD cohorts. **Results:** Among the seven included randomized controlled trials, the efficacy end points in the TRA treatment group were favorable compared with placebo. Specifically, the odds ratio (OR) of MACEs was 0.80 (95% confidence interval [CI] 0.52–1.22) for patients with ACS and 0.74 (95% CI 0.53–1.05) for the cohort with CAD. The events of bleeding were unanimously superior in the placebo arm for both cohorts. The indirect comparison showed a superior trend in favor of atopaxar over vorapaxar in occurrences of MACEs (OR 0.93; 95% CI 0.38–1.32), myocardial infarction (OR 0.52; 95% CI 0.13– 0.95), and cardiovascular death (OR 0.82; 95% CI 0.12–4.24) and caused less incidence of bleeding. **Conclusions:** Besides being more effective than placebo in improving the incidence of MACEs but with a higher risk of bleeding, TRAs may exert different effects in patients with ACS and CAD. Indirect comparisons also suggested that atopaxar might be better than vorapaxar in lowering the incidence of MACEs, myocardial infarction, and cardiovascular death and at the same time with lower risks of bleeding.

Keywords: acute coronary syndrome, coronary artery disease, meta-analysis, randomized controlled trials, thrombin-receptor antagonist.

Introduction

Antiplatelet regimens such as aspirin and P2Y12 antagonist clopidogrel with demonstrated desirable effect in inhibiting platelet activation are recommended for patients with acute coronary syndrome (ACS) and coronary artery disease (CAD) [1–3]. Disappointingly, all these agents fail to deactivate thrombin receptors, which could be the most powerful receptors to mobilize platelets. Consequently, even with the deactivation of the P2Y12 adenosine diphosphate ADP receptor and TxA2-related activation pathways, platelets can still exert their role via the stimulation of thrombin receptors, leading to the aggregation of platelets and subsequent thrombosis [4].

The advent of competitive protease-activated receptor antagonists might be a promising option to block thrombin-induced platelet aggregation [5]. The newly invented atopaxar and vorapaxar could be regarded as representatives of this family. Thrombin-receptor antagonist (TRA) is a potent blocker of thrombin-mediated platelet activation without interfering with thrombin-mediated cleavage of fibrinogen [6].

The efficacy and safety of these two agents have been investigated in several clinical trials in different patient cohorts. However, probably partially because of the limited sample size and insufficient follow-up, the conclusions are inconsistent across studies. In fact, a meta-analysis addressing the efficacy and safety of atopaxar and vorapaxar was reported recently by Capodanno et al. [7]. In this meta-analysis, patients with CAD or non–ST-segment elevation ACS with or without planned percutaneous coronary intervention or a history of atherosclerosis (including ischemic stroke, myocardial infarction [MI], and peripheral artery

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to:* Shu-Chuen Li, MS 108, Medical Sciences Building, The University of Newcastle, Callaghan, NSW, Australia 2308.

E-mail: ShuChuen.Li@newcastle.edu.au

2212-1099$36.00 – see front matter

http://dx.doi.org/10.1016/j.vhri.2015.01.003

disease) were included without consideration of the particular diagnosis cohort. The authors concluded that atopaxar and vorapaxar could reduce the composite of death, MI, or stroke as compared with placebo (odds ratio [OR] 0.87; 95% confidence interval [CI] 0.81–0.92) whereas atopaxar and vorapaxar did not differ from placebo in terms of the risk of death (OR 0.99; 95% CI 0.09–1.09) or stroke (OR 0.96; 95% CI 0.84–1.10). Comparison between atopaxar and vorapaxar, however, was not performed in the analysis. Considering that there were differences between these two drugs in terms of terminal half-life, metabolism, concentration that produces 50% inhibition [5], discrepancy in therapeutic effect and safety profile may exist for patients with different diagnosis, which necessitates further ascertainment. Therefore, unlike this published meta-analysis, we intended to synthesize the primary end points based on different patient populations (ACS or CAD) as well as perform indirect comparison between these two newly invented antiplatelet agents. The results from our present study would provide more clinical information when choosing the most appropriate TRA for patients in view of the different prognosis for patients with ACS or CAD.

Methods

Data Sources

An electronic literature search was performed using the following search terms: platelet aggregation inhibitor, antiplatelet, acute coronary syndrome (ACS), coronary artery disease (CAD), cardiovascular disease (CVD), atherosclerosis, atherothrombosis; double-blind, placebo-controlled, randomised trials, RCT, (controlled) clinical trial, with one of the following terms, thrombin-receptor antagonist (TRA), protease-activated-receptor (PAR-1) antagonist, atopaxar (E-5555), vorapaxar (SCH-530348), as extension in Embase, MEDLINE, and Cochrane database from inception to May 15, 2012. In addition, a manual search was carried out from the identified bibliography.

Inclusion Criteria

1. Studies should be reported in English.
2. All participants in the study should be explicitly diagnosed with ACS or CAD (or at least include a subgroup of patients diagnosed with CAD).
3. Double-blind study should contain a placebo-controlled arm, a minimal 20 patients in each group, and be of a duration of 12 weeks.
4. Study should at least present the results regarding the major adverse cardiovascular (CV) events (MACEs) and incidence of bleeding according to thrombolysis in myocardial infarction (TIMI) in each arm.

Data Extraction

Information extracted included study protocol, drug doses, treatment duration, characteristics of participants, randomization and blinding process, and intention-to-treat (ITT) and safety populations. Primary outcomes included the incidence of MACEs (a composite death from CV disease, MI, stroke, recurrent ischemia, or urgent revascularization) and the incidence of bleeding events according to TIMI (major, minor, minimal, or non-TIMI bleeding) (the definition of TIMI bleeding is detailed in the Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.01.003). Secondary outcomes included adverse effects if applicable. Data were extracted according to doses and the combined atopaxar/vorapaxar group (all doses), respectively.

Two reviewers independently conducted the data extraction process. Any discrepancies were resolved via discussion. Only data agreed by the two reviewers were included in the meta-analysis.

Data Analysis

The Revman 5.1 software was used to perform the meta-analysis. Efficacy outcomes were analyzed on the basis of the ITT population, whereas safety outcomes were analyzed on the basis of the safety population. For definition, the *ITT population* is all randomized patients who received at least one dose of study medication and had at least one postbaseline assessment; the *safety population* is all randomized patients who received at least one dose of study medication. To compare the TRA with placebo, we used random effects of the weighted Mantel-Haenszel method to estimate pooled ORs and 95% CIs for each variable according to the ACS or CAD cohort. In addition, because there was no direct head-to-head comparative study of atopaxar and vorapaxar, adjusted indirect comparisons based on the Bucher frequentist method [8] were performed to compare primary efficacy and safety end points between atopaxar and vorapaxar.

Subgroup analyses were also conducted. Heterogeneity was assessed via the I^2 test, which measures the percentage of total variation across studies due to heterogeneity. A percentage of 25%, 50%, and 75% indicates low, medium, and high heterogeneity, respectively [9].

Furthermore, to ascertain whether benefits of TRA administration outweigh risks, a risk-benefit analysis was subsequently conducted to calculate estimated averted CV events versus bleeding events when 10,000 patients were treated by TRA compared with placebo. Specifically, the number of MIs, strokes, recurrent ischemias, CV deaths, and any bleeding events with or without TRA was first calculated. Then, each kind of averted CV events was calculated by multiplying the rate for the placebo group by (1 − risk ratio) derived from our meta-analysis and then by 10,000. The same approach was applied to estimate bleeding events.

Results

The electronic literature search initially yielded 514 articles, with 102 from MEDLINE, 7 from Cochrane Library, and 405 from Embase, respectively. After screening the titles of the identified studies, 348 were excluded because of irrelevance. Subsequently, the remaining 166 articles were checked for eligibility on the basis of abstracts. As a result, 24 articles met predefined inclusion criteria. Sixteen of these retrieved studies, however, were excluded because they were health technology assessment studies [10] or reviews [11–18], were for nonhuman subjects [19,20], investigated in vitro effect [21], carried out testing in healthy volunteers [22,23], or focused on pharmacokinetics only [24,25], leaving 8 randomized controlled trials (RCTs) as potentially eligible. Furthermore, because one study was dedicated to investigate the therapeutic effect of vorapaxar for patients with a history of ischemia stroke [26], it was excluded eventually. In all, seven RCTs were finally included in our meta-analysis [27–33]. The selection and culling process is presented in Figure. 1, whereas characteristics and quality evaluation of the included RCTs are summarized in Table 1. Except for two studies [28,29], all included studies were double-blinded and the method to accomplish randomization was mainly an interactive voice response system.

We subdivided our meta-analysis according to different TRA-administered cohorts (ACS or CAD); thus, the following results were presented.