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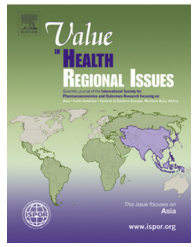

Efficacy and Safety of Thrombin-Receptor Antagonist (Atopaxar and Vorapaxar) in Patients with Acute Coronary Syndrome or Coronary Artery Disease—A Meta-Analysis of Randomized Controlled Trials

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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.

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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.

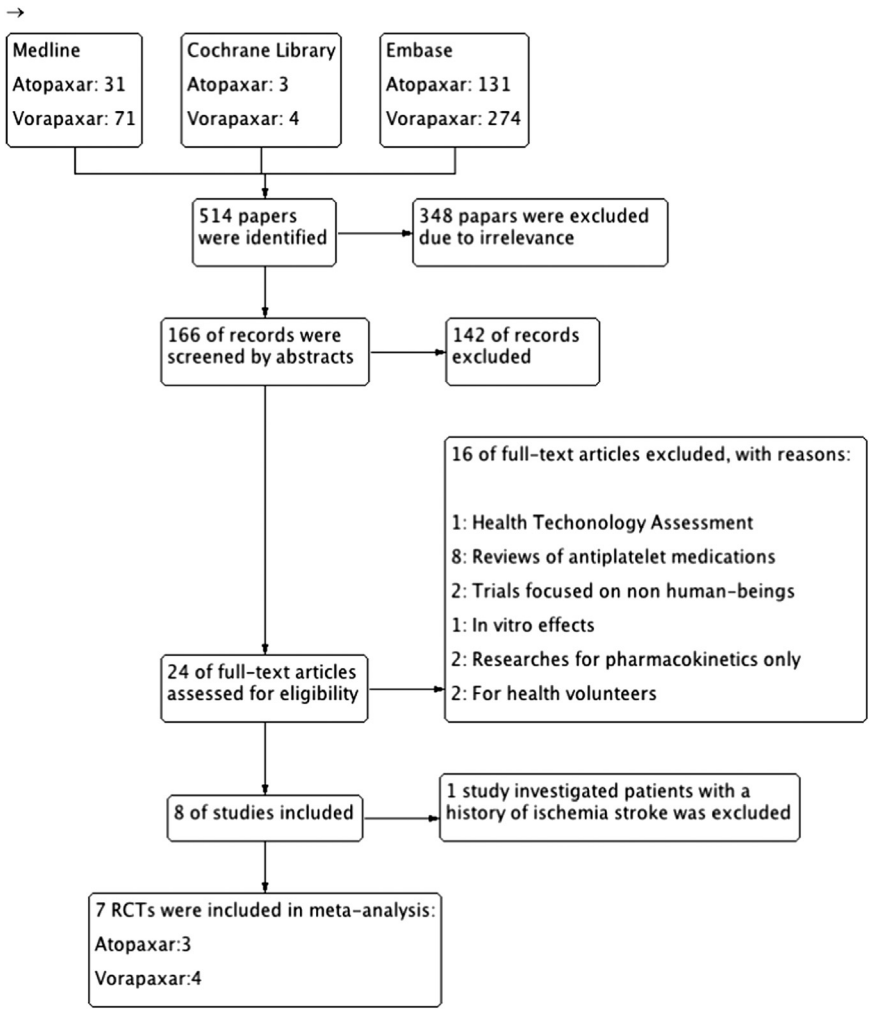

Fig. 1 – Study selection process. RCT, randomized controlled trial.

Acute Coronary Syndrome

Description

There were four RCTs that recruited patients with a diagnosis of ACS [28,29,31,32]. Three of the studies included patients with acute symptoms of newly onset coronary ischemia under similar diagnosis criteria (new ST-segment depression of >0.1 mv or transient ST-segment elevation of <30 minutes of >0.1 mV in at least two contiguous leads; elevated levels of cardiac troponin I/T or creatine kinase MB within 24 hours before enrolment). Only one study had the time period extended to 72 hours. Moreover, different loading doses were arranged for participants after the randomization. Specifically, for atopaxar, the loading dose was 400 mg in two studies [28,31]; for vorapaxar, the loading dose was 20/40 mg [29] or 40 mg [32]. The treatment duration varied from 12 weeks to more than a year (Table 1).

Efficacy End Points

Generally, efficacy end points in the TRA treatment group showed a favorable trend when compared with placebo. For instance, the OR of MACEs was 0.80 (95% CI 0.52–1.22), with medium heterogeneity detected. In terms of ORs for MI and stroke, the pooled effects still favored TRA (OR 0.51, 95% CI 0.25–1.05, and 0.80, 95% CI 0.59–1.08, respectively). When considering recurrent ischemia, however, TRA was inferior to placebo, with an OR of 1.27 (95% CI 0.78–2.05). Where applicable, we synthesized the studies reporting events of CV death, MI, or stroke. The heterogeneity of these variables ranged from low to medium. Our syntheses showed that with respect to CV death, TRA and placebo displayed equivalent efficacies (OR 1.00; 95% CI 0.82–1.22). In contrast, the incidence of CV death, MI, or stroke was lower in the TRA-treated group, with an OR of 0.88 (95% CI 0.77–1.00) without heterogeneity (Fig. 2).

Safety End Points

All the included studies adopted the incidence of bleeding as their safety end point. The severity of bleeding was classified according to TIMI (major, minor, minimal, or non-TIMI bleeding) [34]. In addition, all the RCTs used a clinical evaluation committee to adjudicate the bleeding event to avoid potential bias.

Except for minimal bleeding (OR 0.89; 95% CI 0.53–1.47), events of any TIMI bleeding, major bleeding, minor bleeding, and non-TIMI bleeding were disappointingly higher in TRA-managed patients, with ORs of 1.47 (95% CI 1.33–1.62), 1.55 (95% CI 1.25–1.93), 1.59 (95% CI 1.20–2.11), and 1.37 (95% CI 1.24–1.51), respectively, without heterogeneities (Fig. 3).

Three RCTs presented the incidence of adverse events [28,29,31]. Not surprisingly, the incidence of adverse events was lower in the placebo group, with an OR of 1.13 (95% CI 0.78–1.62) (see Appendix in Supplemental Materials).

Table 1 – Characteristics of included studies.

Study ID	Study drug	Country	Randomization	Methodology quality			Treatment and follow-up
				Blindness	Concealment	ITT	
Acute coronary syndrome							
Goto et al. (2010) [28]	Atopaxar	Japan	Not clear	Not clear	Not clear	Yes	12 and 4 wk
O'Donoghue et al. (2011) [31]	Atopaxar	22 countries 184 sites	Interactive voice response system	Double blinding	Adequate	Yes	12 and 4 wk
Goto et al. (2010) [29]	Vorapaxar	Japan	Not clear	Not clear	Not clear	Yes	60 and 0 d
Tricoci et al. (2012) [32]	Vorapaxar	37 countries 818 sites	24-h automated voice response system	Double blinding	Adequate	Yes	≥1 y
Coronary artery disease							
Goto et al. (2010) [28]	Atopaxar	Japan	Not clear	Not clear	Not clear	Yes	24 and 4 wk
Wiviott et al. (2011) [33]	Atopaxar	11 countries 136 sites	Not clear	Double blinding	Adequate	Yes	24 and 4 wk
Becker et al. (2009) [27]	Vorapaxar	USA	Interactive voice response system	Double blinding	Adequate	Yes	60 and 30 d
Morrow et al. (2012) [30]*	Vorapaxar	32 countries 1032 sites	Central computerized system	Double blinding	Adequate	Yes	24–36 mo

Two studies also presented results regarding hepatic function [28,31]. The OR of pooled events of alanine transaminase levels beyond 3 times of the upper limit of normal was 2.58 (95% CI 0.41–16.17) compared with placebo, indicating that the number of patients with abnormal liver function treated by TRA was higher. Goto et al. [29] also reported the number of patients with abnormal hepatic function (3 of 14 in the placebo group and 7 of 71 in the TRA group), although the definition of abnormal hepatic disorder in that study was not specified (see Appendix in Supplemental Materials).

Subgroup Analyses

The three dose levels of atopaxar used in the studies exerted different effects on the incidence of MACEs and any bleeding classified by TIMI. Surprisingly, the lowest dose (50 mg) had the most preferable profile in both MACEs and bleeding in terms of ORs (0.64, 95% CI 0.28–1.47, and 0.80, 95% CI 0.43–1.51, respectively), whereas the other two higher doses were inferior to placebo in both variables (ORs were 1.24, 95% CI 0.61–2.51, and 1.25, 95% CI 0.70–2.20, and 1.04, 95% CI 0.50–2.20, and 1.02, 95% CI 0.49–2.12, respectively). All syntheses reported low to medium heterogeneity.

Only one RCT took different doses of vorapaxar into considerations (1 and 2.5 mg) [29], and the other just administered 2.5 mg to patients with ACS [32]. Hence, only this higher dose (2.5 mg) was synthesized in subgroup analysis. The results showed that events of bleeding based on TIMI criteria were higher in vorapaxar-treated patients than in placebo-treated patients (ORs 1.49; 95% CI 1.35–1.65; $I^2 = 0\%$) (see Appendix in Supplemental Materials).

Coronary Artery Disease

Description

Four RCTs were included in this meta-analysis [27,28,30,33], with treatment period varying from 60 days to 24 months. In

Table 1 – *continued*.

Doses (mg) and no. of ITT population		Characteristics of participants							
		Age (y), mean ± SD or IT or M*	Male (%)	Weight (kg)	DM (%)	HT (%)	Aspirin (%)	Previous PCI	PCI in study period
Placebo	61	64.5 ± 9.8	82	66.0 ± 12.2	27.9	73.8	100	7	90.2
50	54	65.4 ± 8.0	87	63.5 ± 12.3	40.7	77.8	96.3	13	85.2
100	65	66.3 ± 8.5	80	63.8 ± 12.5	32.3	81.5	96.9	13	83.1
200	61	63.8 ± 8.9	73.8	65.3 ± 14.4	36.1	75.4	98.4	12	90.2
Placebo	142	62.1 ± 9.14	66.9	NA	20.7	71.4	97.8	In total	NA
50	156	60.7 ± 9.16	71.2		24.5	70.3	96.1	259	
100	157	61.6 ± 9.46	72.0		21.0	68.2	94.2		
200	148	62.3 ± 10.38	63.5		23.0	73.0	94.5		
Placebo	21	65 ± 11	76	67 ± 12	52	81	100	NA	100
1.0	37	Active	Active	Active	Active	Active	Active		Active
2.5	34	64 ± 9	80	65 ± 10	52	75	100		100
Placebo	6471	58–72	71.8	70–92	31.4	71.0	96.9	1531	57.4
2.5	7473	58–71	72.0	70–93	31.5	70.1	96.4	1559	58.1
Placebo	66	65.4 ± 7.2	83.3	66.3 ± 11.8	95.5	80.3	100	55	NA
50	63	66.8 ± 7.5	92.1	65.6 ± 9.2	95.2	79.4	100	52	
100	66	66.7 ± 7.4	89.4	66.4 ± 10.4	93.9	78.8	100	53	
200	68	67.1 ± 6.8	85.3	67.2 ± 9.6	94.1	88.2	100	60	
Placebo	176	63	76	86	63	NA	95	62	NA
50	182	64	75	90	71		90	63	
100	174	62	75	90	64		95	62	
200	186	64	78	89	69		91	66	
Placebo	151	62.7 ± 9.3	85	90.16±18.7	32	NA	98	68	151
0.5	136	Active	Active	Active	Active		Active	208	136
1.0	139	64.5 ± 9.8	74	89.2±19.2	36		99		139
2.5	138								138
Placebo	13224	53–69	76.2	NA	25.5	68.4	81.2–98.1	8620†	NA
2.5	13225	53–69	76.0		25.4	69.0	80.7–98.1	8641†	

IT, interquartile range; M, median; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention.

* This study enrolled all the patients with a history of atherosclerosis (including a spontaneous MI or ischemia stroke or peripheral artery disease). Patients with any previous coronary artery disease and previous coronary revascularization accounted for 78.1% and 65.3% and 78.4% and 65.2% in the vorapaxar and placebo group, respectively.

† These figures included patients who underwent coronary-artery bypass grafting (CABG) [27].

terms of doses, atopaxar was administered as 50, 100, and 200 mg in two studies, while vorapaxar was administered at 0.5, 1.0, and 2.5 mg in one study [27] and at 2.5 mg in the other RCT [33]. Of the four studies, three included only patients diagnosed with CAD, while the other also enrolled patients with ischemia, stroke, or peripheral artery disease [33]. Patients with previous CAD, however, accounted for the largest proportion of participants (>78% in each group). It is also worth mentioning that except for patients in one study [27], subjects in the other three RCTs did not undergo percutaneous coronary intervention during the study period. This intervention might alter the prognosis of patients because it was observed that early invasive approach compared with a conservative approach in high-risk patients with non–ST-segment elevation MI can improve clinical outcomes with a decrease in in-hospital death and recurrent MI [35] (Table 1).

Efficacy End Points

Overall, TRA-treated patients enjoyed a better profile in all the efficacy end points. Particularly, the number of MACEs (OR 0.74; 95% CI 0.53–1.05), CV deaths, MIs, or strokes (OR 0.86; 95% CI 0.79–0.94; MI: OR 0.82; 95% CI 0.74–0.92; stroke: OR 0.97; 95% CI 0.83–1.14), CV deaths (OR 0.89; 95% CI 0.76–1.05), and recurrent ischemias (OR 0.36; 95% CI 0.15–0.86) were all lower than in the placebo-treated group. One study by Goto et al. [28] observed, however, that during their 24-week treatment plus 4-week follow-up period, the only MACE reported was recurrent ischemia

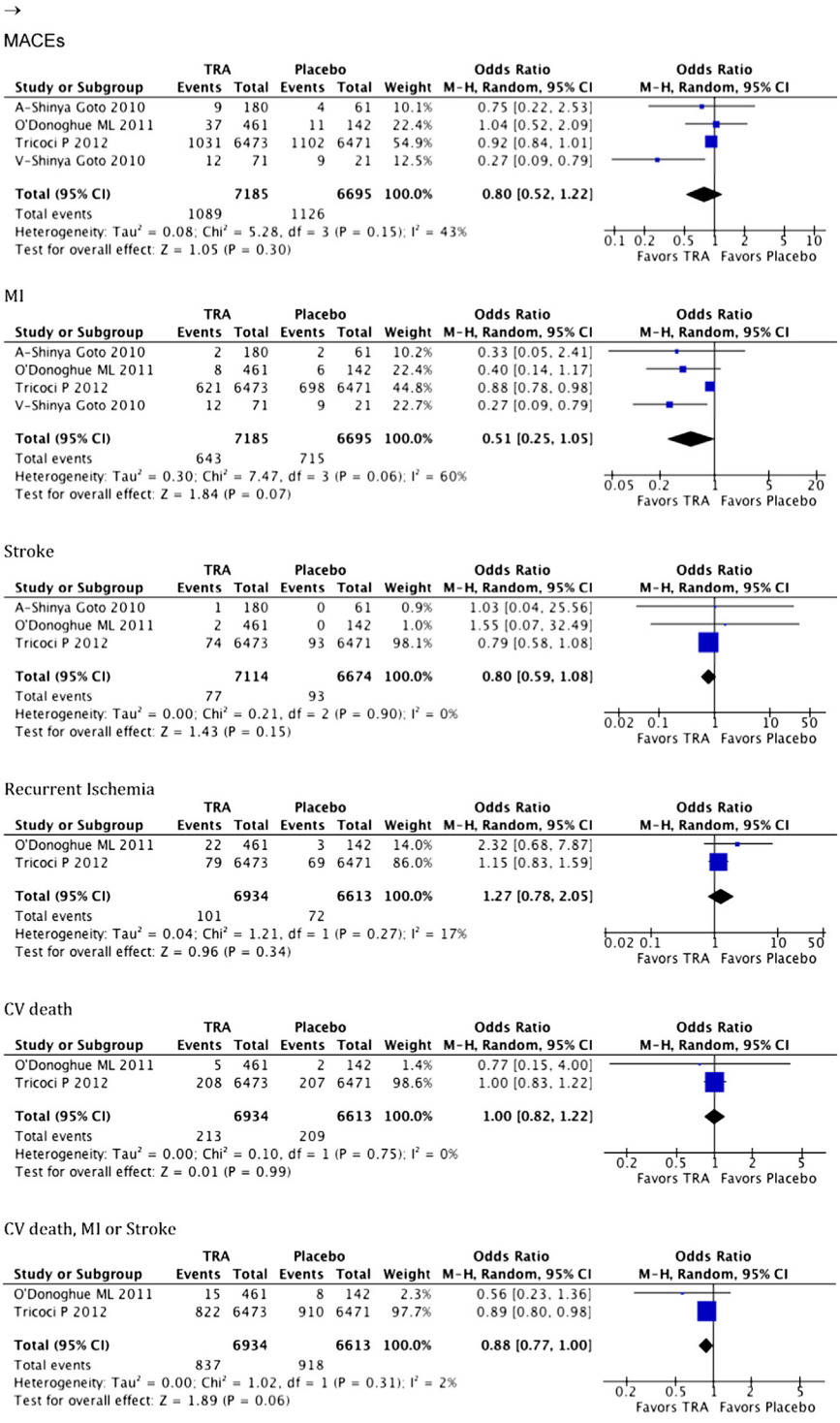

Fig. 2 – Pooled efficacy effects (TRA vs placebo) for patients with ACS. ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; TRA, thrombin-receptor antagonist.

events without the incidence of CV death, MI, or stroke in both arms. Hence, this study was not included in the synthesis pertaining to these variables.

With respect to heterogeneity, except for the pooled effects of MACEs ($P = 0.24$; $I^2 = 28\%$), all the other variables did not show any heterogeneity, indicating the consistency in results across studies (Fig. 4).

Safety End Points

In contrast to efficacy end points, the events of bleeding classified by TIMI were superior in the placebo arm. For instance, the ORs of any TIMI bleeding, major bleeding, and minor bleeding were 1.48 (95% CI 1.37–1.59), 1.45 (95% CI 1.21–1.73), and 1.19 (95% CI 0.39–3.68), respectively, without heterogeneity detected. Because no

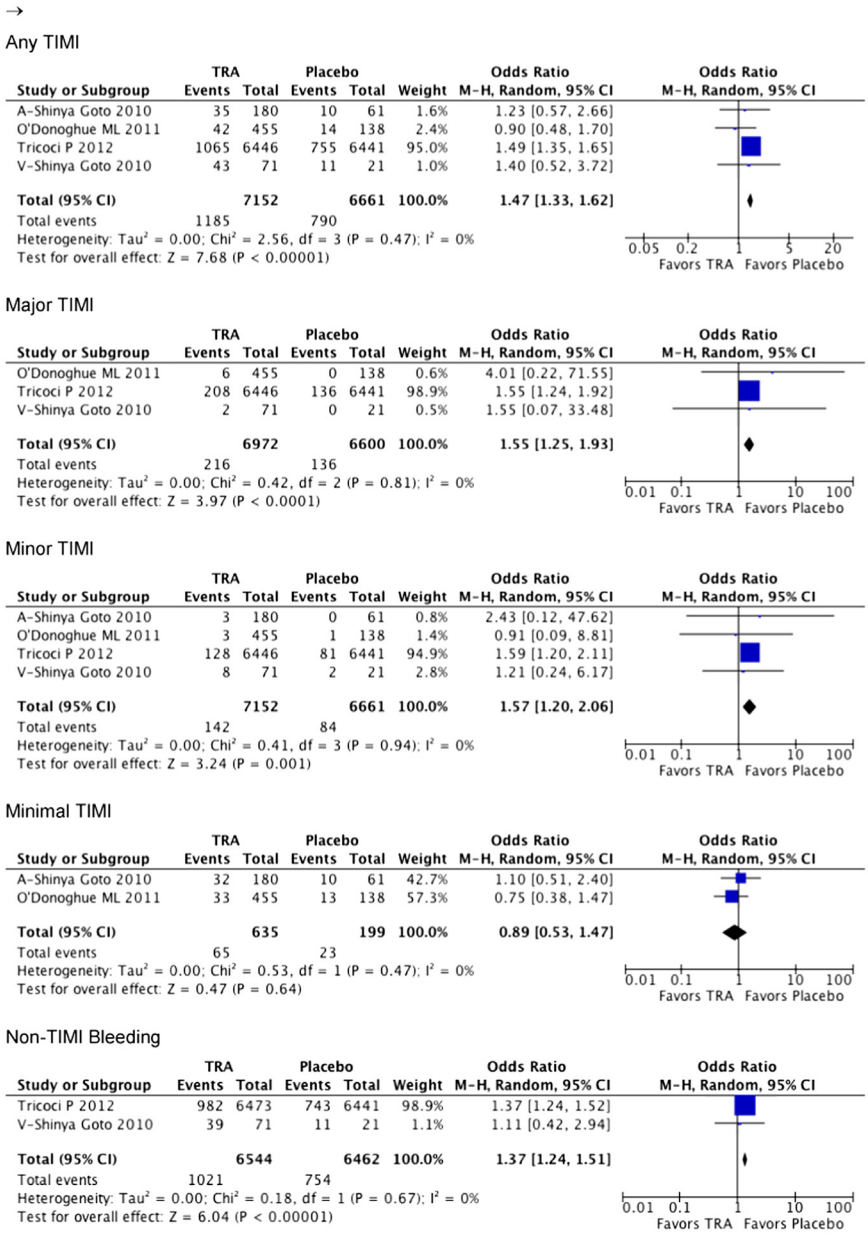

Fig. 3 – Pooled safety effects (TRA vs placebo) for patients with ACS. ACS, acute coronary syndrome; CI, confidence interval; TIMI, thrombolysis in myocardial infarction; TRA, thrombin-receptor antagonist.

major bleeding events were reported in one study, this study was not included in this synthesis [28] (Fig. 5).

Hepatic function was reported in two studies [28,33], with alanine transaminase and enzymes aspartate transaminase levels in both TRA-treated patients significantly higher than in patients treated with placebo. Specifically, the pooled ORs for patients whose liver function parameters exceeded 3 times the upper limit of normal level were 9.66 (95% CI 1.30–71.59) in case of ALT and 6.80 (95% CI 0.91–51.01) in case of AST, both without heterogeneities (see Appendix in Supplemental Materials).

Subgroup Analysis

For atopaxar, with dose escalation, there was an upward trend in the pooled effects of ORs for MACEs (ranged from 0.29 [95% CI 0.09–0.97] to 0.59 [95% CI 0.23–1.56] with doses of 50–200 mg). In line with the efficacy end point, bleeding events based on the TIMI classification showed that placebo was more preferable than TRA. Specifically, all the three doses of atopaxar were inferior to placebo (ORs varied from 1.56 [95% CI 0.79–3.07] to 2.24 [95% CI 1.18–4.25]). The highest dose of atopaxar (200 mg) generated the most effective outcome in MACEs but was accompanied with the most bleeding incidence.

When it comes to vorapaxar, only the 2.5-mg dose was explored in terms of events of TIMI bleeding by both studies. Unfortunately, the incidence of bleeding was still higher in the TRA-administered group, with an OR of 1.48 (95% CI 1.37–1.60) (see Appendix in Supplemental Materials).

Risk-Benefit Analysis

As a result, for the ACS cohort, total averted CV events were 459.87 with an excess of 438.82 bleeding episodes per 10,000 treated, which suggested that benefits of TRA outweighed risks.

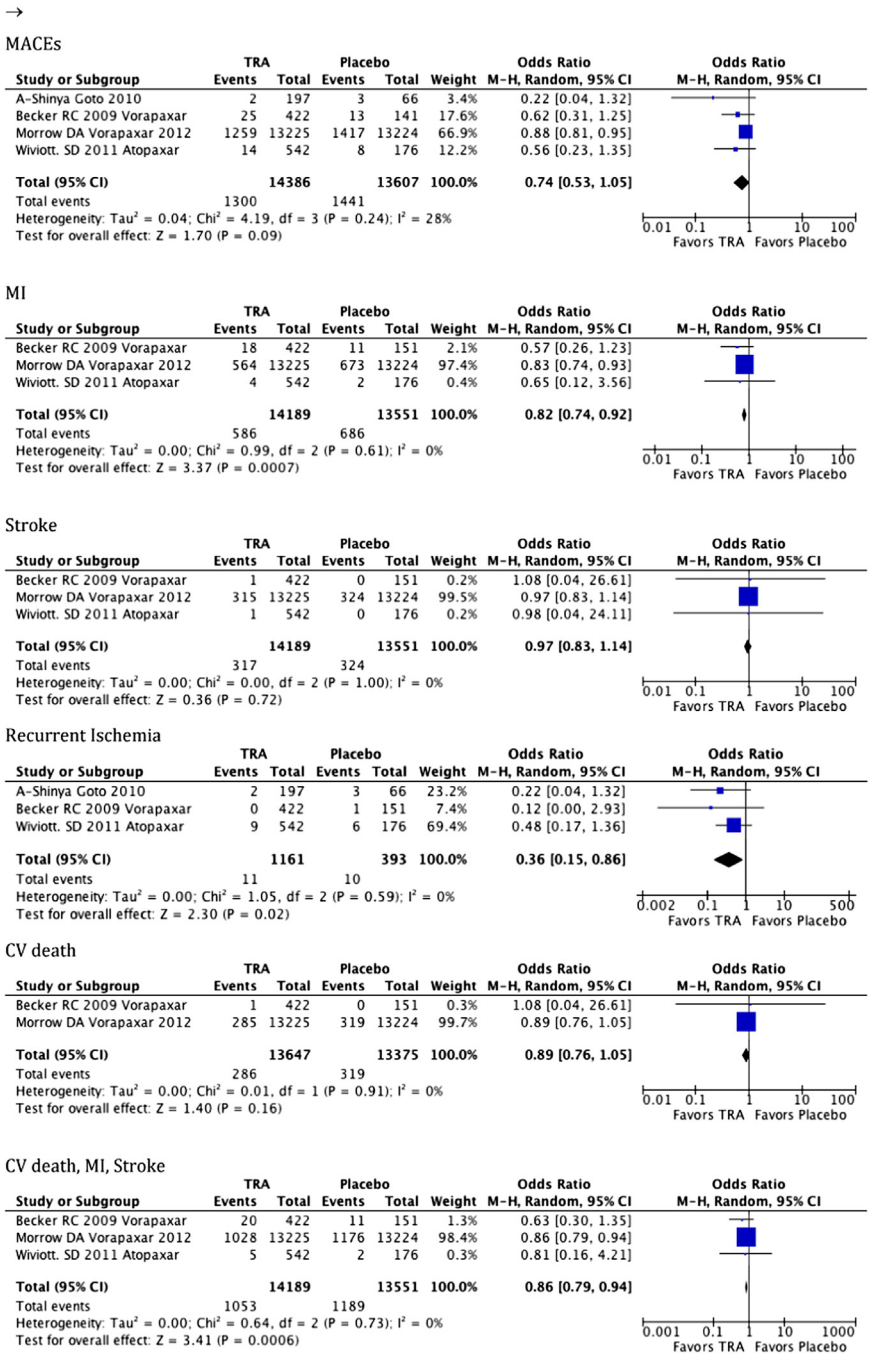

Fig. 4 – Pooled efficacy effects (TRA vs placebo) for patients with CAD. CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; TRA, thrombin-receptor antagonist.

For the CAD cohort, total averted CV events were 279.36 with an excess of 384.52 bleeding episodes per 10,000 treated. So, for the latter cohort, the administration of TRA would result in excess bleeding risk, and its use may need to be justified.

Indirect Comparisons between Atopaxar and Vorapaxar

The indirect comparison showed a superior trend in favor of atopaxar over vorapaxar in the occurrences of any MACEs (ORs 0.93; 95% CI 0.38–1.32), MIs (ORs 0.52; 95% CI 0.13–0.95), and CV deaths (ORs 0.82; 95% CI 0.12–4.24). Nevertheless, in terms of the incidence of stroke and recurrent ischemia events, atopaxar appears inferior to vorapaxar, with ORs of 1.26 (95% CI 0.15–7.73) and 1.55 (95% CI 0.02–21.93), respectively. Most importantly, atopaxar incurred less bleeding incidence as defined by any TIMI (ORs 0.69; 95% CI 0.29–2.78) than did vorapaxar (Table 2).

Discussion

Even after strictly adhering to the recommended dual antiplatelet treatment, the incidence of recurrent ischemia events, MIs,

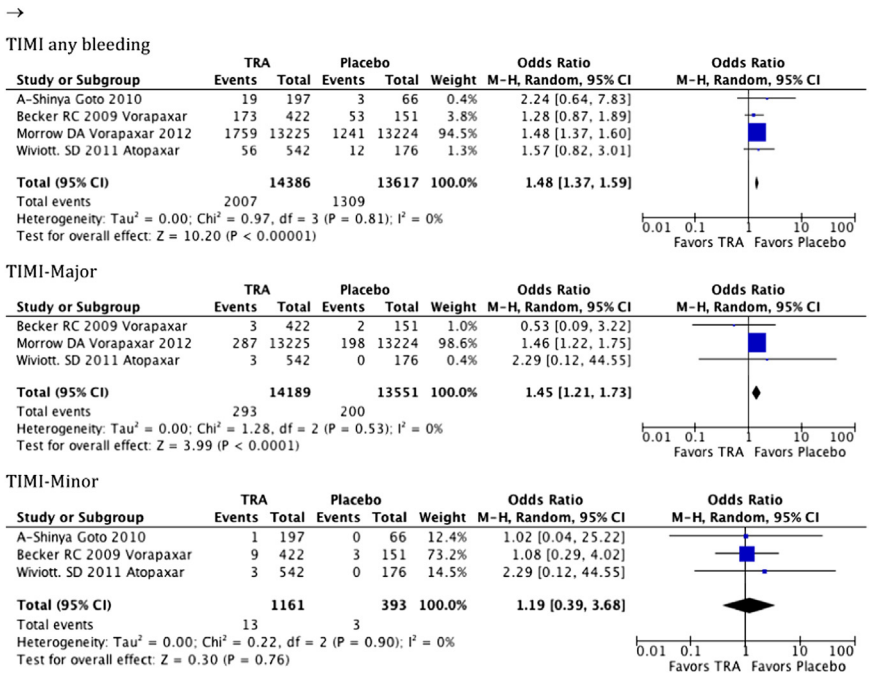

Fig. 5 – Pooled safety effects (TRA vs placebo) for patients with CAD. CAD, coronary artery disease; CI, confidence interval; TIMI, thrombolysis in myocardial infarction; TRA, thrombin-receptor antagonist.

strokes, and CV deaths among patients after being diagnosed with ACS or CAD was still persistently high. The inhibition of protease-activated-receptor 1 by TRA may provide additional benefits in attenuating ischemic events [36,37]. From our meta-analysis, we have several findings that may contribute to ascertaining the clinical position of TRA. First, for patients with ACS, a promising finding from subgroup analyses was that the lowest dose of atopaxar (50 mg) displayed more favorable profiles in MACEs and bleeding events when using placebo as comparator. Second, for patients with CAD, the only subgroup analysis identified that the occurrence of bleeding was not greater in those taking a higher dose of vorapaxar than in those taking a combination of TRAs. Third, the indirect comparison suggested that in terms of efficacy end points, atopaxar might be more preferable than vorapaxar in lowering the occurrence of MACEs, MIs, and CV deaths, but may lead to a higher incidence of stroke and recurrent ischemia events with lower bleeding risk. Last, on comparing to the widely used clopidogrel (for CV events, OR 0.87; 95% CI 0.81–0.94; $P < 0.01$, compared with placebo plus aspirin), results from the meta-analysis showed that these two new drugs were comparable (Table 2).

Clinically speaking, the prognosis of ACS and CAD is divergent. As reported by Alcock et al. [38], patients undergoing percutaneous coronary intervention after a diagnosis of ACS had higher long-term mortality than did those with stable CAD. In addition, for the population with ACS, contemporary interventional and medical management strategies may effectively and specifically counter the adverse prognostic impact of coronary instability and myocardial damage [38]. As a result, the effect of TRA should be analyzed on the basis of different diagnosis. Specific to our study, it was observed that the effect of TRA on primary efficacy (MACEs) and safety (TIMI bleeding) end points was similar for patients with ACS and CAD. Inconsistent with the overall efficacy end points, however, the occurrence of MI and stroke was moderately better in the ACS cohort. In contrast, the effect of improving the incidence of recurrent ischemia was definitely better in the CAD cohort. Furthermore, with respect to atopaxar, pooled effects displayed inconsistent results as to the ACS and CAD cohorts. For atopaxar 50-mg dose, a different effect on the incidence of MACEs was observed for the ACS and CAD population, with better effect achieved in patients with CAD. In contrast, the other two higher doses (100 and 200 mg) showed contradictory results. In the ACS cohort, these two doses were not superior to placebo at all, whereas in the CAD cohort, they demonstrated more desirable effects in MACEs. The possible interpretation for this divergence might be the difference in response to TRA with respect to various cohorts. Furthermore, as indicated in one study, the blood markers of thrombin

Table 2 – Indirect comparison between atopaxar and vorapaxar (ORs , 95% CI)

Drug	MACEs	MI	Stroke	Recurrent ischemia	CV death	Any TIMI
Atopaxar	0.81 (0.49–1.33)	0.43 (0.19–0.99)*	1.17 (0.19– 7.22)	1.02 (0.21–4.93)	0.77 (0.15–4.00)	1.20 (0.81–1.77)*
Vorapaxar	0.87 (0.77–0.99)*	0.82 (0.71–0.96)*	0.93 (0.81–1.07)	0.66 (0.10–4.45)	0.94 (0.83–1.06)	1.48 (1.39–1.57)*
Atopaxar vs vorapaxar	0.93 (0.38–1.32)	0.52 (0.13–0.95)*	1.26 (0.15– 7.73)	1.55 (0.02–21.93)	0.82 (0.12–4.24)	0.69 (0.29–2.78)

CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; TIMI, thrombolysis in myocardial infarction.
* Significant results.

generation and activity persist beyond the acute phase of ACS in patients receiving aspirin and clopidogrel and could predict an increased likelihood of adverse clinical outcomes [39]. Because the blood level of thrombin in patients with ACS may be varied relative to that in patients with CAD, as the competitor for thrombin to deprive protease-activated receptor, TRA may exert a different effect on these two cohorts possibly owing to dissimilar levels of thrombin. Overall, if our observation that patients with CAD would benefit more than would patients with ACS from TRA treatment could be confirmed by future clinical trials, the cost-effectiveness profile of TRA could be established for distinctive target population. Besides the clinical implication, this would be of significant value for decision makers in formulating clinical guidelines and resource allocation.

Nonetheless, the 95% CI of ORs (pertaining to efficacy end points for both ACS and CAD cohorts with low to median heterogeneities) from our meta-analysis all included one for either direct and indirect comparisons and thus would be interpreted as demonstrating no statistically significant difference compared with placebo. When performing the indirect comparisons, the variance of individual study was combined to estimate the variance for integrated outcomes, leading to a greater variance than in the individual studies. Consequently, the CIs for those outcomes were even larger and showed no statistical significance. For the direct comparisons, this observation of no significance has to be interpreted together with two factors, namely, duration of the trials and intent of the trials. First, the varying duration of the included RCTs primarily accounted for the large variance in the final results. Particularly, the duration for five of the included RCTs varied from 12 weeks to 24 weeks while the other two RCTs lasted for 502 days (median) and 3 years, respectively. Because the MACEs require various time to progress or present (e.g., 1 in 10 patients experienced a major ischemic outcome within 1 year of an ACS even with the dual antiplatelet therapy) [4,40] and long-term medication management is irreplaceable, the short duration of some of our included trials may fail to catch the TRA's benefits in decreasing the incidence for these events [27–29,31,33].

This leads to the second factor about the intent of the included trials. It is well accepted that in clinical setting, when we attempt to evaluate an antiplatelet agent, safety is always the priority concern. Hence, the included studies with a treatment duration of 12 to 24 weeks would provide information to address this concern and probably designed with this as one if not the main objective. As demonstrated in our meta-analysis, the pooled ORs for the primary safety end point (defined as any TIMI) were 1.47 (95% CI 1.33–1.63) and 1.48 (95% CI 1.37–1.59) for patients with ACS and CAD, respectively, when TRA was compared with placebo. Therefore, it is important to determine whether patients can obtain net benefit from the treatments. As a result, the risk-benefit analysis favors the use of TRA in patients with ACS rather than in those with CAD. So for the latter cohort, the administration of TRA would result in excess bleeding risk, and its use may need to be justified.

After satisfying the safety and efficacy demands, another major issue is to determine the cost-effectiveness profile of these specific medications. Because lifetime preventive treatment is needed for patients with a history of ACS or CAD, it is imperative to ascertain the long-term treatment cost-effectiveness for the administration of TRA. With an appropriate modeling method, the efficacy outcomes presented in our study may be extrapolated to evaluate the long-term cost-effectiveness of TRA. Last but not the least, even though future RCTs with a larger number of subjects and longer duration would be the best solution to address the efficacy, safety, and cost-effectiveness profile of TRA, our study could be the best substitution based on the available evidence at the moment.

Inherently, several limitations of our present study should also been noted. First, the treatment durations of included studies varied substantially, ranging from 12 weeks to more than 2 years. It is not uncommon for a patient with ACS or CAD to take antiplatelets for a long term; therefore, the short time period cannot adequately capture differences in MACEs or safety profile attributable to a treatment. However, not all patients with ACS or CAD underwent percutaneous coronary intervention during the study period although percutaneous coronary intervention may alter the prognosis of ACS or CAD to a certain extent.

Conclusions

Our study showed that the two kinds of TRAs might be more effective than placebo in improving the incidence of MACEs but with a higher risk of TIMI bleeding and hepatic disorder. Furthermore, the TRA may exert different effects in patients with ACS or CAD, especially for the occurrence of MIs, strokes, and recurrent ischemias. Results from the indirect comparison showed that atopaxar might be more preferable to vorapaxar but this would need to be confirmed by future head-to-head studies.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2015.01.003 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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