

Efficacy and safety of vorapaxar for the prevention of adverse cardiac events in patients with coronary artery disease: a meta-analysis

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Background: Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Vorapaxar, a protease-activated receptor-1 (PAR-1) antagonist, is a novel antiplatelet agent that may provide us a new way in antithrombotic therapy. Several studies had been conducted to evaluate the efficacy of vorapaxar in the treatment of CAD, but the results were inconsistent. Here a meta-analysis was made to assess the efficacy and safety of vorapaxar in reducing adverse cardiac events in patients with CAD.

Methods: A comprehensive literature search was conducted. The primary efficacy endpoint was the major adverse cardiac events, which was defined as a composite of cardiovascular death, myocardial infarction (MI), stroke, urgent coronary revascularization, or recurrent ischemia with rehospitalization. The primary safety endpoint was the composite of major or minor bleeding events. Pooled effects were measured by odds ratios (ORs) with 95% confidence intervals (CIs). A random-effect or fixed model was used in this meta-analysis.

Results: Totally, 31,388 patients from four randomized controlled trials (RCTs) were included in this meta-analysis. Patients who took vorapaxar combined with standard dual anti-platelet therapy (aspirin and thienopyridine) showed a lower incidence in major adverse cardiac events (OR, 0.86, 95% CI: 0.75–0.99, P=0.03), MI (OR, 0.79, 95% CI: 0.67–0.95, P=0.01) and ischemic stroke (OR, 0.72, 95% CI: 0.58–0.89, P=0.003) than those who only took placebo instead. But there was no significant reduction in cardiovascular death (OR, 0.95, 95% CI: 0.82–1.09, P=0.45). Nevertheless, the vorapaxar group were associated with a higher risk of bleeding events (P<0.001).

Conclusions: The result of this meta-analysis indicated that adding vorapaxar to the standard dual anti-platelet therapy may be efficient in reducing the incidence of major adverse cardiac events at the cost of increasing risk of bleeding events.

Keywords: Coronary artery disease (CAD); efficacy; safety; vorapaxar

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Introduction

As a consequence of the rapid modernization of the developing world, coronary artery disease (CAD) has become a leading cause of morbidity and mortality worldwide with a prevalence that reaches pandemic levels (1). The thrombosis caused by platelet activation in CAD patients may lead to the ischemia cardiovascular and cerebrovascular events. The standard dual anti-platelet therapy (aspirin combined with thienopyridine) can effectively decrease the incidences of these adverse clinical events and is widely used as a secondary prevention strategy in CAD patients (2). However, quite a number of patients who have already received standard dual anti-platelet therapy even still suffer from recurrent ischemic cardiovascular and cerebrovascular events. To further reduce these adverse events, novel anti-platelet agents are needed (3).

Protease-activated receptor-1 (PAR-1) is an important receptor which mediates the activation of platelet in a different pathway with thromboxane A₂ and P2Y₁₂ receptor. It plays a non-ignorable role in the process of platelet activation under the standard dual anti-platelet therapy (4). Vorapaxar is the first PAR-1 antagonist approved by the U.S. Food and Drug Administration for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) and peripheral artery disease, without a previous stroke or transient ischemic attack (5). In recent years, several randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of vorapaxar in the treatment of CAD. However, the results were not consistent (6). Some studies found that vorapaxar was helpful in reducing the ischemic risk in patients with atherothrombotic processes (6). However, several other studies did not show any efficacy outcomes but an increasing risk of bleeding events (7-9). Therefore, the efficacy and safety of vorapaxar in reducing the incidence of adverse cardiovascular and cerebrovascular events should be systematically evaluated. Here in this study, we performed a meta-analysis of eligible studies to assess the efficacy and safety of vorapaxar in CAD patients.

Methods

Study search strategy

Relevant studies were identified from PubMed, Scopus, Cochrane Library and Embase using the following terms: vorapaxar, CAD, coronary heart disease and SCH530348.

The retrieval time restricted from January 1st, 2008 to November 1st, 2015. Articles were limited to English-language studies. The included participants were patients with CAD who did not receive urgent percutaneous coronary intervention (PCI). If the same patient population was included in other studies, only the most recent study was considered in this meta-analysis.

Inclusion criteria

Eligible studies should meet all the following criteria: (I) only RCTs were considered; (II) participants should be patients with CAD and did not receive urgent PCI; (III) comparison should be made between two groups: vorapaxar group (vorapaxar + dual anti-platelet therapy) and placebo group (placebo + dual anti-platelet therapy); (IV) articles should report the efficacy and safety outcomes of vorapaxar. Meeting abstracts, case reports, editorials and reviews were excluded.

Data extraction and assessment

Two investigators independently extracted data from the included studies. Data extraction included the first author's surname, publication year, region, demographic data, target population, treatment protocol, follow-up period, efficacy outcomes and safety outcomes. Disagreement was dissolved by discussion between the two investigators.

The primary efficacy outcome in this study was major adverse cardiovascular events (MACE) which was defined as a composite of cardiovascular death, MI, stroke, urgent coronary revascularization and recurrent ischemia with rehospitalization. The primary safety outcomes included thrombolysis in myocardial infarction (TIMI) major or minor bleeding and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or moderate bleeding. The definition of bleeding events was shown in *Table 1*.

The quality of the studies was evaluated with the Jadad assessment scale. The grading is mainly based on the generation of the randomization, the application of the double-blind method and the instruction of the loss to follow-up (10). The full mark is 5 points. If the article is marked as 3 points or higher, it would be considered to be of high quality. The Cochrane Collaboration's tool was also used to assess the risk of bias about the included studies. Random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential threats to

Table 1 Definition of bleeding events

Classification	Severity	Criteria
TIMI	Major	Intracranial or overt bleeding with a drop in hemoglobin of ≥ 5 g/dL or hematocrit drop $\geq 15\%$
	Minor	Spontaneous gross hematuria, spontaneous hematemesis, observed bleeding associated with a fall in hemoglobin ≥ 3 g/dL but a hematocrit drop $\leq 15\%$
GUSTO	Severe	Fatal or intracerebral bleeding, or bleeding resulting in substantial hemodynamic compromise requiring treatment
	Moderate	Bleeding requiring transfusion

TIMI, thrombolysis in myocardial infarction; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries.

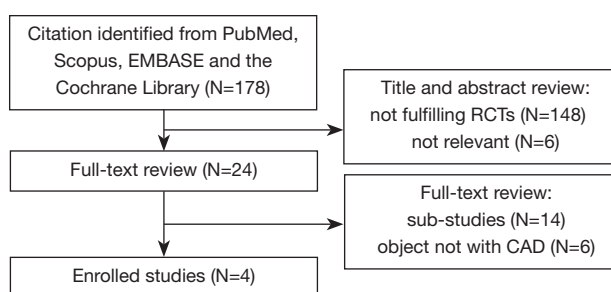


Figure 1 The flow chart of the literature search process. CAD, coronary artery disease.

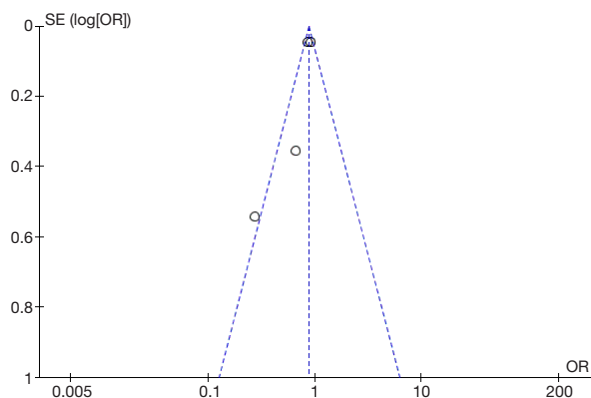


Figure 2 Funnel plot of this meta-analysis.

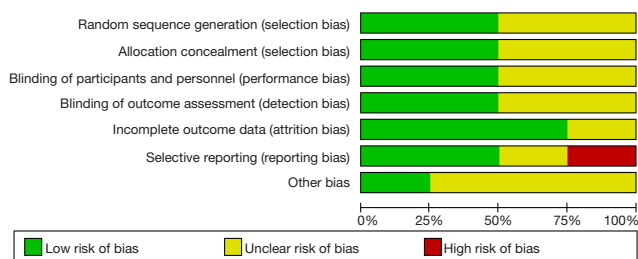


Figure 3 Risk of bias graph.

validity are the judge entries. These two scales have revealed that the studies included here are qualified.

Statistical analysis

Meta-analysis review methodology was used for this study. Odds ratio (OR) with 95% confidence interval (CI) was used. P value ≤ 0.10 was considered to be significant for statistical heterogeneity. If P value ≤ 0.10 , a random-effect model was chosen. Otherwise, a fixed-effect model was used instead. The pooled OR was performed for dominant model. All statistical tests were performed with RevMan 5.2.

Results

Eligible studies

A total of 178 potentially eligible studies were identified, and 148 were excluded for not fulfilling inclusion criteria on the basis of RCTs. Twenty-six studies were excluded for other reasons, such as different studies but with the same population. A flow diagram of the trial selection process was given in Figure 1. Funnel plot was shown in Figure 2. The Cochrane Collaboration’s tool was also used (Figure 3).

After the screening, four RCTs (6,11-13) incorporating 31,388 patients met the inclusion criteria and were included in this meta-analysis (Table 2). Of the four studies, sample size ranged from 92 to 17,779 and the study period ranged from 2 to 30 months. No significant difference had been observed in the gender and age distribution between the vorapaxar and placebo group in each study.

Efficacy

Major adverse cardiovascular events (MACE)

Four studies (6,11-13) incorporating 15,864 patients in

Table 2 Main characteristic of all the studies included in the meta-analysis

Studies	Country	Follow-up (month)	Numbers (placebo/vorapaxar)	Age	Patients	+Aspirin (placebo/vorapaxar)	+Thienopyridine (placebo/vorapaxar)	Efficacy outcome	Safety outcome	Jadad score
Becker et al. 2009 (6)	USA	2.0	151/422	≥45	CAD	148/417 (98.01%/98.81%)	146/409 (96.69%/96.92%)	MACE/CD, MI, stroke/CD, MI/CD/MI/stroke/UCR/death	TIMI major or minor bleeding	3
Goto et al. 2010 (11)	Japan	2.0	21/71	≥18	CAD	21/71 (100%/100%)	21/71 (100%/100%)	MACE/CD, MI, stroke/CD, MI/CD/MI/stroke/UCR/death	TIMI major or minor bleeding	3
Tricoci et al. 2012 (12)	England	16.7	6,471/6,473	58–72	ACS	6,272/6,243 (96.92%/96.45%)	5,639/5,668 (87.14%/87.56%)	MACE/CD, MI, stroke/CD, MI/CD/MI/stroke/UCR/death/stent thrombosis	TIMI major or minor bleeding/GUSTO moderate or severe bleeding	4
Scirica et al. 2012 (13)	USA	30.0	8,881/8,898	51–66	MI	8,716/8,732 (98.14%/98.13%)	6,960/6,934 (78.31%/77.93%)	MACE/CD, MI, stroke/CD, MI/CD/MI/Stroke/UCR/death/stent thrombosis	TIMI major or minor bleeding/GUSTO moderate or severe bleeding	4

CAD, coronary artery disease; ACS, acute coronary syndrome; MACE, major adverse cardiac events defined as a composite of cardiovascular death, myocardial infarction, stroke, urgent coronary revascularization and recurrent ischemia with rehospitalization; CD, cardiovascular death; MI, myocardial infarction; UCR, urgent coronary revascularization; TIMI, thrombolysis in myocardial infarction; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries.

vorapaxar group and 15,524 patients in placebo group were included in this analysis. The incidence of MACE was 12.5% (1,983/15,864) in the vorapaxar group while that was 14.0% (2,175/15,524) in the placebo group. There was a significant decrease in the incidence of MACE when adding vorapaxar to the standard dual anti-platelet therapy (OR, 0.86, 95% CI: 0.75–0.99, P=0.03) (Figure 4).

Myocardial infarction (MI)

Four studies (6,11–13) were included in this analysis. The incidence of MI in the vorapaxar group was 6.83% while that was 8.11% in the placebo group. Patients who received the vorapaxar had a lower risk of MI than those received placebo (OR, 0.79, 95% CI: 0.67–0.95, P=0.01) (Figure 5).

Cardiovascular death

Four studies (6,11–13) incorporating 15,864 in vorapaxar group and 15,524 in placebo group were included in this analysis. The incidence of cardiovascular death in the vorapaxar group was 2.26% while that was 2.43% in the placebo group. There was no significant difference among the two groups in the occurrence of cardiovascular death (OR, 0.95, 95% CI: 0.82–1.09, P=0.45) (Figure 6).

Ischemic stroke

Two studies (12,13) incorporating 15,371 patients taking vorapaxar and 15,352 patients taking placebo were included in this analysis. The incidence of ischemic stroke in the vorapaxar group was 0.93% while that was 1.29% in the placebo group. The vorapaxar group showed a lower risk in ischemic stroke than the placebo group (OR, 0.72, 95% CI: 0.58–0.89, P=0.003) (Figure 7).

Other efficacy outcomes

The risk of some other cardiovascular and cerebrovascular events between the two groups had also been assessed. The result had been shown in Table 3. Some positive outcomes had been observed. It indicated that vorapaxar combined with the dual-antiplatelet therapy could lower the risk of cardiovascular death or MI or stroke (OR, 0.84, 95% CI: 0.78–0.90, P=0.01) (Table 3) and cardiovascular death or MI (OR, 0.82, 95% CI: 0.69–0.96, P=0.01) (Table 3).

Safety

TIMI major or minor bleeding

Three studies (6,11,12) incorporating 6,939 in the vorapaxar group and 6,613 in the placebo group were included in

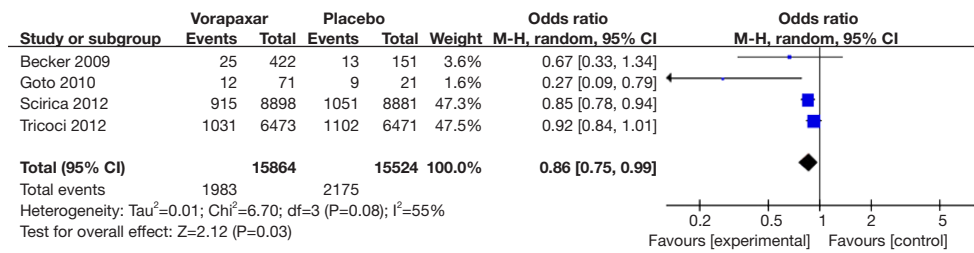


Figure 4 The incidence of MACE in the vorapaxar group was lower than placebo group. CI, confidence interval; MACE, major adverse cardiac events.

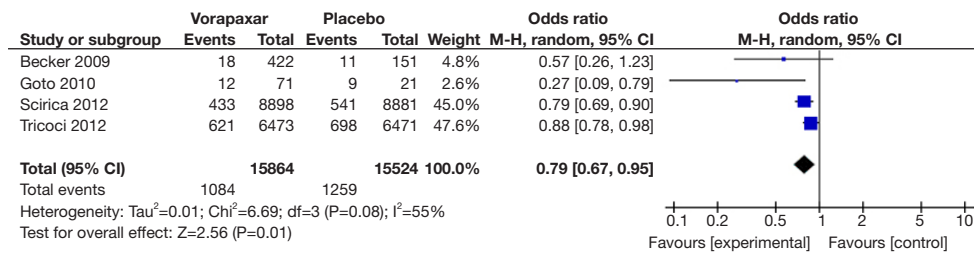


Figure 5 The incidence of MI in the vorapaxar group was lower than placebo group. CI, confidence interval; MI, myocardial infarction.

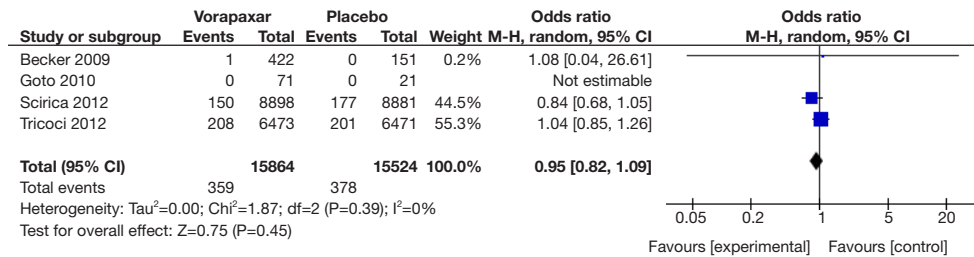


Figure 6 No significant difference in cardiovascular death had been observed between the vorapaxar group and placebo group; CI, confidence interval.

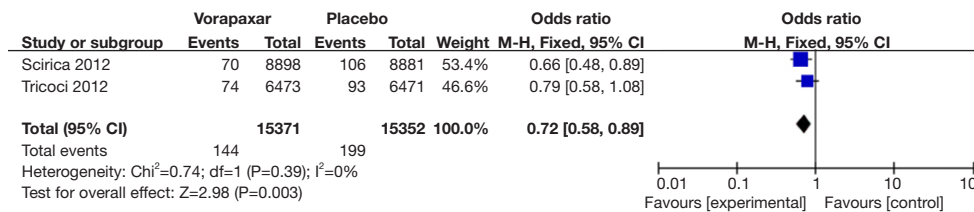


Figure 7 The incidence of ischemic stroke in vorapaxar group was lower than placebo group. CI, confidence interval.

the TIMI major or minor bleeding assessment. Patients who received vorapaxar got a bleeding rate of 5.17% while it was 3.39% in those who received placebo. It indicated that patients receiving vorapaxar had a higher risk in TIMI major or minor bleeding (OR, 1.56, 95% CI: 1.31–1.85, P<0.00001) (Figure 8).

GUSTO moderate and severe bleeding

Another analysis about bleeding assessment was GUSTO moderate and severe bleeding. Two studies (12,13) incorporating 15,344 patients in vorapaxar group and 15,322 patients in placebo group were included in GUSTO moderate and severe bleeding assessment. Similarly, it

Table 3 Other efficacy outcomes of the vorapaxar

Efficacy outcome	Studies	Patients (placebo/vorapaxar)	Model	OR	95% CI	P value
Cardiovascular death/myocardial infarction/stroke	4	15,524/15,864	Random	0.84	0.78-0.90	0.01
Cardiovascular death/myocardial infarction	4	15,524/15,864	Random	0.82	0.69-0.96	0.01
Urgent coronary revascularization	2	15,352/15,371	Fixed	0.95	0.83-1.09	0.47
Any stroke	3	15,503/15,793	Fixed	0.87	0.72-1.05	0.15
Death from any cause	2	15,352/15,371	Fixed	0.99	0.88-1.11	0.89

OR, odds ratio; CI, confidence interval.

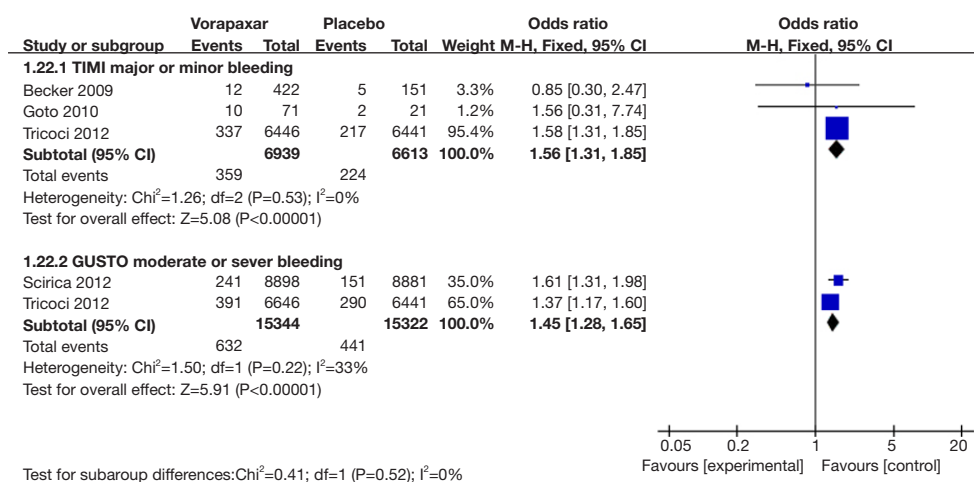


Figure 8 The risk of bleeding in vorapaxar group was higher than placebo group. TIMI, thrombolysis in myocardial infarction; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; CI, confidence interval.

showed that patients who received vorapaxar had a higher risk in GUSTO moderate and severe bleeding with a bleeding rate of 4.1% in contrast to 2.88% (OR, 1.45, 95% CI: 1.28–1.65, $P<0.00001$) (Figure 8).

Discussion

The present meta-analysis is consisted of four qualified RCTs (6,11-13) with 31,388 patients enrolled. The vorapaxar group could significantly lower the incidence of MACE, MI and ischemia stroke than the placebo group. But no significant difference of cardiovascular death was observed between the two groups. On the other hand, adding vorapaxar to the standard dual anti-platelet therapy increased the risk of bleeding, including TIMI major or minor bleeding events and GUSTO moderate and severe bleeding events.

In the standard dual anti-platelet therapy of patients with CAD, aspirin and thienopyridine are recommended to be used in combination (14-16). Aspirin is an irreversible

inhibitor of cyclooxygenase-1 that produces a permanent defect in thromboxane A₂-mediated platelet activation (17), while thienopyridine prevents adenosine diphosphate-induced platelet activation and aggregation by irreversibly inhibiting the P2Y₁₂ receptor (17,18). The combining use of these two drugs can effectively reduce thrombosis. However, 12-month risk of recurrent vascular events remains at approximately 10% among CAD patients (19). It suggests that some other mechanisms may also play an important role, such as the thrombin-mediated pathway (20).

Vorapaxar, a novel oral anti-platelet agent, is a competitive, reversible antagonist of PAR-1, which can block thrombin-induced platelet activation. In some phase II studies, vorapaxar had been proved to be a key contributor in the platelet activation, while play a relatively secondary role in hemostasis (21,22). But there was still some phase III (12,23) studies showed that the combining use of three anti-platelet agents (aspirin, clopidogrel and vorapaxar) increased the risk of intracranial hemorrhage.

In the past few years, a series of phase II and phase III studies (6,8,24,25) about vorapaxar had been conducted in different countries, but no consensus conclusion had been made on its efficacy and safety outcomes. Capodanno and his colleagues (26) summarized the relative literatures and conducted a meta-analysis in 2012, which showed that the PAR-1 antagonist may decrease ischemic events in patients with CAD as compared with placebo at the cost of an increased risk of clinically significant bleeding. However, the population enrolled in the meta-analysis was not the same on the basic disease, which might have an impact on the result of the study. In order to comprehensively evaluate the effect of vorapaxar on patients with CAD, we conduct the present updated meta-analysis.

In this pooled analysis, the population in the four included studies (6,11-13) was restricting to the patients with CAD who did not need an urgent PCI, which reduced the confounder caused by the different basic disease. The results concluded from this analysis were similar with some of the studies, indicating that vorapaxar could significantly lower the incidence of MACE (11,13), MI (11-13) and ischemia stroke than the placebo group (13). However, adding vorapaxar to the standard dual anti-platelet therapy did not lower the risk of cardiovascular death and may increase the risk of bleeding events. In this case, clinicians should weigh the pros and cons.

Some limitations should be taken into consideration. Firstly, only four qualified studies were enrolled in this meta-analysis, and two (6,11) of which got small sample sizes as well as rather short follow-up periods. Moreover, no fatal bleeding or intracranial haemorrhage events were evaluated in these two studies. Secondly, because of the limitation of the language, only journals published in Chinese and English have been reviewed. And there was no RCT about vorapaxar published in Chinese literatures. Therefore, all of the studies were in English, which might lead to the language bias. Thirdly, all of the studies evaluated the efficacy and safety outcomes via comparing the combining use of the three anti-platelet agents (aspirin, thienopyridine and vorapaxar) with merely standard dual anti-platelet therapy (aspirin and thienopyridine). There was lack of trials on the effect about using vorapaxar alone, vorapaxar combined with aspirin, vorapaxar combined with thienopyridine. Lastly, the suitable therapeutic dose was still lack of evidence.

Conclusions

Vorapaxar is a novel anti-platelet drug which has a bright

application prospect in patients with CAD. The results of this meta-analysis indicated that the combining use of vorapaxar, aspirin and thienopyridine may reduce the incidence of MI and ischemic stroke. However, it also increases the risk of bleeding events. Further studies are still needed before it is widely used in clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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