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REVIEW

Comparison of Aspirin and Rivaroxaban Plus Aspirin in the Management of Stable Coronary Artery Disease or Peripheral Artery Disease: A Systematic Review of Randomized Controlled Trials

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Introduction: Low-dose aspirin or clopidogrel, statins, renin–angiotensin system inhibitors, and beta blockers are the cornerstone therapy for cardiovascular prevention in patients with coronary heart disease. Using only single-antiplatelet therapy for secondary prevention in patients with stable coronary artery disease (SCAD) and/or peripheral artery disease (PAD) has a significant risk of recurrent thrombotic complications.

Objective: This systematic review aimed to compare aspirin alone and its combination with rivaroxaban for secondary cardiovascular prevention in patients with SCAD and/or PAD.

Methods: The literature search was conducted on PubMed, ClinicalTrials.gov, Cochrane Library, and Google Scholar for articles published from November 2011 to September 2021. An advanced search strategy was used to retrieve relevant studies related to aspirin and/or rivaroxaban use for secondary cardiovascular prevention in patients with SCAD and/or PAD. Records identified from the databases were extracted using a data-abstraction format prepared in Microsoft Excel. Studies' methodological quality was assessed using the Cochrane risk-of-bias tool for randomized trials. This systematic review is registered in PROSPERO (CRD42022306598) and was prepared based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Results: A total of five randomized controlled trials (RCTs) with 33,959 participants were included for final analysis. These studies showed that rivaroxaban with aspirin was more effective than the standard therapy of aspirin alone in the prevention of secondary cardiovascular events (major adverse cardiovascular events (MACEs) and/or major adverse limb events (MALEs), but the combination increased major bleeding.

Conclusion: The combination of rivaroxaban with aspirin is more effective than aspirin alone in the prevention of both MACEs and MALEs in patients with stable CAD and/or PAD. However, the combination treatment is associated with increased of major bleeding. Therefore, the combination of rivaroxaban and aspirin is superior to monotherapy in the management of patients with a high risk of developing MACEs and MALEs.

Keywords: rivaroxaban, aspirin, stable coronary artery disease, peripheral artery disease

Introduction

Atherosclerosis is responsible for pathophysiology of coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular/carotid artery disease.[1,2] CAD and PAD share a common pathogenesis and associated risk factors (eg, smoking, dyslipidemia, hypertension, and diabetes mellitus).[3] They are characterized by a diseased endothelium, low-grade inflammation, lipid accumulation, and plaque formation within the intima of the vessel wall.[4] Plaque rupture or erosion can provoke superimposed atherothrombosis and subsequent vessel occlusion, leading to cardiovascular events, including myocardial infarction (MI), stroke, limb ischemia, and cardiovascular death.[5] Patients with CAD

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and/or PAD are at high risk of major adverse cardiovascular events (MACEs; MI, stroke, cardiac death)[6] and/or major adverse limb events (MALEs; limb ischemia, amputation, arterial revascularization).[7]

Recommendations for prevention of these events include lifestyle modifications (eg, exercise, healthy diet, smoking cessation), and drug therapy by aspirin or clopidogrel, statins, angiotensin-converting enzyme inhibitors, and beta blockers.[8] Despite these prevention strategies, MACEs and MALEs continue to pose a considerable burden, and CAD remains the leading cause of death worldwide.[6] For secondary prevention, aspirin results in lowering the risk of MACEs and cardiovascular death by 19% and 9%, respectively, compared with placebo therapy.[9] Using single-antiplatelet therapy for secondary prevention in patients with stable CAD (SCAD) and/or PAD is associated with a significant risk of recurrent thrombotic complications.[8] Although the combination of warfarin and aspirin is associated with an improvement in cardiovascular outcomes compared with antiplatelet therapy alone, there is an increase in major bleeding events. In addition, vitamin K antagonists have unpredictable responses due to drug–drug and food–drug interactions, which necessitate routine coagulation monitoring and dose adjustments.[10] Novel oral anticoagulants, such as rivaroxaban, can reduce some limitations of traditional anticoagulants. Pathology studies have shown that exposure of plaque contents to circulating blood as a result of erosion or rupture events stimulates the activation of platelets and the coagulation cascade, which results in the formation of clots. Therefore, therapeutic targeting with antiplatelet and antithrombotic therapy has the potential to more effectively treat both of these conditions than antiplatelet agents alone, which in turn eventually decreases complications like MACEs.[1,11] The combination of rivaroxaban with an antiplatelet agent has a synergistic effect on the inhibition of factor-induced platelet aggregation.[12] The US Food and Drug Administration (FDA) has recently approved rivaroxaban 2.5 mg twice daily for the prevention of recurrent MACEs in patients with SCAD and PAD.[13] However, the risk–benefit profile of low-dose rivaroxaban when used with antiplatelet therapy (aspirin or P2Y12 inhibitor) versus antiplatelet alone in these patients is not completely understood. This systematic review thus, compares the therapeutic efficacy and safety of aspirin alone and its combination with rivaroxaban for secondary cardiovascular prevention in adult patients with CAD and/or PAD.

Methods

Protocol and Reporting

This systematic review is registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42022306598) and was conducted based on PRISMA guidelines.

Data Source and Search Strategy

The review was undertaken by searching relevant articles published between November 2011 and September 2021 in PubMed, ClinicalTrials.gov, Cochrane Library, and Google Scholar. In addition, reference lists of included articles were evaluated for possible inclusion in the review. The systematic search was conducted using the following keywords: [(rivaroxaban OR Xarelto OR factor Xa inhibitors) AND (aspirin OR acetylsalicylic acid) AND (coronary artery disease OR stable coronary artery disease OR peripheral artery disease OR vascular diseases OR cardiovascular diseases OR peripheral arterial diseases OR arterial occlusive diseases)].

Study Selection and Eligibility Criteria

All clinical trials reporting on the safety and efficacy of rivaroxaban plus aspirin or aspirin alone in adult patients with CAD or PAD were included in the review. Furthermore, only studies published in English were included. However, the review did not include case reports, observational studies, case series, case–control studies, letters to the editor, author perspectives, review articles, abstract proceedings, or expert comments.

Data Extraction

All studies obtained from the databases were exported to Endnote version 8 software and the duplicates removed. The titles and abstracts of studies retrieved using the search strategy and those from additional sources were screened to identify studies that satisfied the inclusion criteria. These studies were screened and assessed by reading the full text of

potentially eligible studies. Data were extracted using a Microsoft Excel spreadsheet containing data related to study characteristics (first author, publication year, sample size, country, study duration, population characteristics, and sample size) and the results (efficacy and safety outcomes).

Quality Assessment and Risk of Bias

The quality of the studies was assessed using the Cochrane risk-of-bias tool for randomized trials.[14] It is structured into six sets of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Within each domain, a series of questions helps to elicit information on features of the trial that are relevant to the risk of bias. A proposed judgment about the risk of bias arising from each domain is generated by an algorithm, based on answers to the signaling questions. Judgment can be at "low" or "high" risk of bias, or can indicate "some concerns."

Outcome Measurements

The primary outcome was the first occurrence of MACEs ie, a composite of cardiovascular death, MI, or stroke and/or MALEs that included major amputation, limb ischemia, and arterial revascularization over the course of a trial. The safety outcome was major bleeding, defined as a composite of bleeding that was fatal, symptomatic bleeding into a critical organ, surgical site requiring reoperation, or requiring hospitalization (including presentation to an acute care facility without an overnight stay) according to the International Society on Thrombosis and Hemostasis (ISTH) criteria.[15]

Results

Literature Identification and Search Findings

A total of 85 studies were identified from various databases. After the removal of duplicates and nonrelevant articles by title, 43 articles were selected to be evaluated further based on their abstracts. Full-text screening was then performed on 13 studies, and seven were excluded due to ineligibility (eg, different primary end point of interest, an absence of full article). Finally, five randomized controlled trials (RCTs) studies were included in this review (Figure 1).

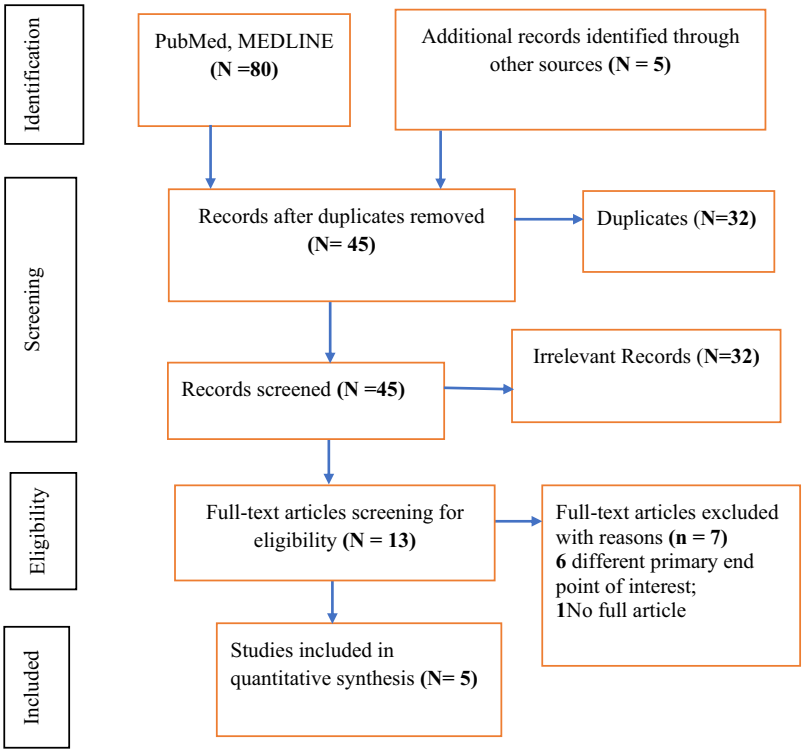

Figure 1 PRISMA flow diagram for study selection.

Characteristics of Included RCTs

Data were obtained from 33,959 (male 26,235, female 7724) patients that had been collected from many countries with different races across six continents. The mean age of the study participants was around 68 years. The collected trials were published between 2018 and 2021. Apart from one study, all of them were multinational RCTs. The smallest and largest sample sizes were 1086 and 27,395, respectively. Follow-up duration ranged from approximately 19 to 36 months (Table 1).

Three trials evaluated a combination of rivaroxaban with aspirin, aspirin only (placebo plus aspirin), and rivaroxaban alone in patients with stable CAD or PAD. The other two trials presented their data by comparing the combination of rivaroxaban and aspirin with aspirin alone. Aspirin (81–325 mg) was utilized in all studies. The dose of rivaroxaban was 2.5 mg twice daily when used alone or in combination with aspirin (Table 1).

Individual Study Results

Combination of Rivaroxaban and Aspirin and Prevention of MACEs and/or MALEs

Of the 33,959 patients, 12,438 received rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day). The remaining 12,438 and 9117 received aspirin 100 mg once a day and rivaroxaban 5 mg twice a day, respectively. Four trials evaluated combinations of rivaroxaban and aspirin vs aspirin alone (placebo plus aspirin). Three RCTs compared rivaroxaban and aspirin with rivaroxaban and rivaroxaban alone in patients with stable CAD or PAD. Of the trials,[16–20] one examined patients with or without a history of mild to moderate heart failure, ie, a prespecified subgroup analysis included 5902 patients with heart failure (21.5%) of the total (27,395) trial population. These trials reported the incidence of the primary efficacy outcome in composite cardiovascular death, MI, or stroke prevention in the rivaroxaban and aspirin group was significantly lower than the aspirin-only group in participants with heart failure (108 patients [5.5%] versus 157 patients [7.9%], HR 0.68, 95% CI 0.53–0.86] and those without heart failure [3.8% versus 4.7%, HR 0.79, 95% CI 0.68–0.93; p=0.28]).[17]

Similarly, the other trial examined those patients with and without diabetes mellitus in preventing MACEs, ie, a prespecified subgroup analysis included 6922 patients with diabetes mellitus (38%) of the total (18,278) trial population, and the composite primary efficacy end point of cardiovascular death, MI, stroke, and MALE prevention in the rivaroxaban and aspirin group was significantly lower than the placebo plus aspirin group in participants with diabetes mellitus (201 patients [5.8%] versus 272 patients [7.8%], HR 0.73 95% CI 0.61–0.88; p=0.0007). Furthermore, a similar relative risk reduction was apparent for the benefit of rivaroxaban plus aspirin versus placebo plus aspirin in patients both with and without diabetes mellitus, although there was a larger absolute net clinical benefit in those with diabetes mellitus.[16]

Another study done on patients with stable peripheral or carotid artery disease reported that combination therapy represented an important advance in the management of patients with PAD. Rivaroxaban plus aspirin compared with aspirin only reduced the composite end point of cardiovascular death, MI, or stroke (126 [5%] of 2492 vs 174 [7%] of 2504, HR 0.72, 95% CI 0.57–0.90, p=0.0047), and MALEs, including major amputation (32 [1%] vs 60 [2%], HR 0.54, 95% CI 0.35–0.82, p=0.0037).[13] The trial concluded that rivaroxaban in combination with aspirin was effective for the prevention of cardiovascular events in Chinese patients with stable CAD and PAD.

The main efficacy end-effect events occurred at 1.5%/year in the combination of rivaroxaban and aspirin group, 3.7%/year in the rivaroxaban-only group, and 2.5%/year in the aspirin-alone group. A total of 6564 patients had undergone randomization, approximately two-thirds were treated with an endovascular procedure (65%), and a third had been treated surgically (35%). A total of 1533 patients (23%) had undergone index revascularization for critical limb ischemia. Overwhelming efficacy of rivaroxaban plus aspirin in the prevention of MACEs and MALEs was indicated in all the five trials.[16–20]

Combination of Rivaroxaban and Aspirin and Risk of Major Bleeding

Safety outcomes followed a similar pattern to that seen in the five trials. Anand et al[17] reported that there was a relative increase in major bleeding in the low-dose rivaroxaban plus aspirin group in comparison with the aspirin-only group, [77 patients [3%] versus 48 patients [2%], HR 1.61, 95% CI 1.12–2.31; p=0.0089]. Similarly, the rivaroxaban 5 mg BID regimen showed more major bleeding (79 patients [3%] versus 48 patients [2%], HR 1.68, 95% CI 1.17–2.40; p=0.0043).[19] The finding of another trial also showed that there was a significant increase in major bleeding with the dual-pathway

Table 1 Characteristics and summary of RCTs included in the systematic review

	Country	Sample size (total)	Intervention (rivaroxaban plus aspirin), n	Control		Follow-up duration (months)	Efficacy outcomes	Safety outcomes
				Rivaroxaban alone, n	Aspirin alone, n			
Anand et al 2018[19]	Multinational	7470	2492	2474	2504	21	Rivaroxaban plus aspirin vs aspirin alone: reduced • MALEs = 126 [5%] of 2492 vs 174 [7%] of 2504; HR 0.72, 95% CI 0.57–0.90, p=0.0047 • MALEs= (32 [1%] vs 60 [2%]; HR 0.54 95% CI 0.35–0.82, p=0.0037)	Major bleeding • Rivaroxaban plus aspirin vs aspirin increased MB= [(77 [3%] of 2492 vs 48 [2%] of 2504; HR 1.61, 95% CI 1.12–2.31, p=0.0089)] • Major bleeding occurred in 79 (3%) of 2474 patients with rivaroxaban 5 mg and in 48 (2%) of 2504 in the aspirin-alone group (HR 1.68, 95% CI 1.17–2.40; p=0.0043).
Bhatt et al 2020[16]	Multinational	18,278	9152		9126	36	MACEs and MALEs: • Rivaroxaban plus aspirin vs aspirin = 201/3448 (5.8%) vs 272/3474 (7.8%): HR 0.73, 95% CI 0.61–0.88, p=0.0007	Intracranial bleeding: • Rivaroxaban plus aspirin 5/3448 (0.1%) vs placebo plus aspirin 3/3474 (<0.1%): HR 1.66, 95% CI 0.40–6.93
Liang et al 2021[18]	China	1086	366	365	355	19	Main efficacy end-effect event occurrence: • Rivaroxaban and aspirin 1.5%/year • Rivaroxaban 3.7%/year • Aspirin 2.5%/year	Incidence of primary safety end-point occurrence: • Rivaroxaban and aspirin 1.0% • Rivaroxaban 1.6% • Aspirin 1.2%, differences not statistically significant (p>0.05)
Branch et al 2019[17]	Multinational	5902	1963	1960	1979	30	• Rivaroxaban and aspirin compared to aspirin alone in prevention of MACEs: 5.5% versus 7.9%, HR 0.68, 95% CI 0.53–0.86 • Rivaroxaban alone 124/1960 (6.3%)	Major bleeding: • Rivaroxaban and aspirin 49/1963 (2.5%) • Aspirin alone 36/1979 (1.8%), HR 1.36, 95% CI 0.88–2.09 • Rivaroxaban alone 56/1960 (2.9%)
Bonaca et al 2020[20]	Multinational	6564	3286		3278	30	• Composite MACEs and MALEs occurred in 508 patients in the rivaroxaban group and 584 patients in the placebo group. • 17.3% events in rivaroxaban group vs 19.9% in the placebo group, HR 0.85, 95% CI 0.76–0.96, p=0.009.	Major bleeding based on TIMI classification occurred in 62 patients in the rivaroxaban group and 44 in the placebo group (HR 1.43, 95% CI 0.97–2.10, p=0.07)

Abbreviations: TIMI, Thrombolysis in Myocardial Infarction; hazard ratio; CI,MALES, major adverse limb events; MACEs, major adverse cardiovascular events.

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regimen, but reported no significant increases in intracranial or fatal bleeding.[16] The study from China revealed that incidence of primary safety end-point occurrence was 1.0% in the rivaroxaban and aspirin combination group and 1.6% and 1.2% in the rivaroxaban-alone and aspirin-alone groups, respectively, but the differences were not statistically significant ($p>0.05$).[18] Branch et al[17] also had similar findings to these trials. Major bleeding was high in the combination group (49/1963 [2.5%]) in comparison with the aspirin-alone group (36/1979 [1.8%], HR 1.36, 95% CI 0.88–2.09) in participants with heart failure, but major bleeding was increased in the rivaroxaban-alone group (56/1960 [2.9%]).[17] In another study, ISTH major bleeding occurred in 140 patients in the rivaroxaban with aspirin group compared with 100 patients in the aspirin plus placebo group (5.94% and 4.06%, HR 1.42, 95% CI 1.10–1.84; $p=0.007$).[20]

Quality Assessment of RCTs

According to the Cochrane risk-of-bias tool for randomized trials, two trials showed low risk, while three raised some concern about risk of bias. The overall quality rating was considered moderate (Table 2).

Discussion

This systematic review identified five RCTs that compared rivaroxaban with aspirin versus aspirin alone in patients with stable CAD. These five trials demonstrated the combination of rivaroxaban and aspirin compared with aspirin alone produced superior relative risk reductions in MACEs, but the combination caused a greater increase in major bleeding. The addition of rivaroxaban (2.5 or 5 mg twice daily) to low-dose aspirin (81–325 mg) was utilized in all studies vs antiplatelet therapy (low-dose aspirin).[21] The evidence supports the choice of a daily dose of 81–100 mg for the prevention of arterial thromboembolism in all high-risk patients. This recommendation is based on low doses of aspirin being enough to suppress thromboxane-dependent platelet activation.[22,23]

Branch et al[15] indicated that the combination of rivaroxaban and aspirin compared with aspirin alone is superior in relative risk reduction of MACEs, but the combination was linked with an increase in major bleeding (2.5% vs 1.8%). Again, rivaroxaban alone was inferior in reducing MACEs when compared with the combination of rivaroxaban with aspirin and also les effective in reducing major bleeding. A combination of rivaroxaban with aspirin was also tested in the ATLAS ACS 2 trial, in which patients were enrolled early after acute coronary syndrome, treated with either dual-antiplatelet therapy (93%), or aspirin (7%), and randomized to rivaroxaban 2.5 mg BID and 5 mg BID.[24] This study demonstrated significant reductions in MACEs and all-cause mortality with low-dose rivaroxaban 2.5 mg BID, as well as an increase in major bleeding.

In the subset of patients with heart failure at randomization (1694 [10.9%]), reduction in MACEs was amplified, with a 41% relative risk reduction compared with placebo (16.8% to 10.1% for patients with and without heart failure, HR 0.59, 95% CI 0.42–0.81, $p=0.002$).[25] The results of the Branch et al[17] are consistent with Liang et al[16] in patients with CAD for the primary efficacy outcome. MACEs occurred in 1.5%, 3.7%, and 2.5%/year of patients in the rivaroxaban and aspirin groups (rivaroxaban single-use group and aspirin-alone group, respectively). The incidence of major bleeding in the combination therapy was superior to that of a single agent. Comparable to the those two trials, the Anand et al[19]

Table 2 Risk of bias of trials included in the systematic review

First author	Domains					
	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Anand[17]	Low	Low	Low	Low	Low	Low
Bhatt[14]	Low	Low	Low	Low	Low	Low
Liang[16]	Low	Low	Some concern	Low	Low	Low
Branch[15]	Low	Low	Low	Some concern	Low	Low
Bonaca[18]	Low	Low	Low	Some concern	Low	Low

trial in patients with PAD revealed that treatment with low-dose rivaroxaban twice a day plus aspirin once a day reduced MACEs (126 [5%] of 2492 vs aspirin alone 174 [7%] of 2504, HR 0.72, 95% CI 0.57–0.90; p=0.0047) and MALEs, including major amputation (combination of rivaroxaban and aspirin 32 [1%] vs aspirin 60 [2%], HR 0.54 95% CI 0.35–0.82; p=0.0037), with increased bleeding in the combination group. Finding effective and relatively safe antithrombotic regimens for patients with PAD to decrease MACEs and MALEs with an acceptable bleeding profile has been challenging, and **there have been few** large clinical trials in patients with PAD,[26] eg, Anand et al.[19]

Another trial reported that moderate-intensity vitamin K-antagonist therapy with antiplatelet therapy was associated with a substantial increase in life-threatening bleeding and no reduction in MACEs or MALEs.[27] Patients with PAD often have widespread atherosclerosis and an increased risk of atherothrombotic events in multiple vascular territories (ie, coronary, cerebral, and peripheral) and mortality.[28,29] Therefore, combination therapy of rivaroxaban with aspirin represents an important advance in the management of patients with PAD. Rivaroxaban alone does not significantly reduce MACEs compared with aspirin alone, but reduces MALEs and increased major bleeding. Similarly, reports from Bonaca et al,[20] which were done in patients with PAD who had undergone lower-extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes than aspirin alone. However, there was a meaningfully higher rate of the secondary safety outcome of ISTH[15] — major bleeding in the rivaroxaban group. Despite several advances in different therapeutic areas, such as lipids, blood pressure, and glycemic control, patients with diabetes mellitus continue to have high rates of recurrent ischemic events.[30] In the setting of diabetic primary prevention, aspirin has been found to be superior to placebo, even in the contemporary era, although predictably bleeding is increased,[31] similarly to the other trials.[17–20] Bhatt et al[18] pointed out that in patients with diabetes mellitus, rivaroxaban plus aspirin is superior in secondary prevention of cardiovascular death, stroke, MI, MALEs, or major vascular amputation. It is also clear that intensifying the antithrombotic regimen beyond aspirin alone is warranted in patients who are at an acceptable risk of bleeding.

This review has some strengths and limitations. Including a large number of participants with a comparison group and blinding the participants and investigators were the main strengths of the RCTs covered. The limitations were using a limited number of articles and largely heterogeneous data, which might make it difficult to reach strong findings.

Conclusion

The combination of rivaroxaban and aspirin is more effective than aspirin alone in prevention of MACEs and MALEs in patients with stable CAD and/or PAD with comorbidity. However, the combination treatment is associated with an increased risk of major bleeding. Therefore, the combination of rivaroxaban and aspirin is superior to monotherapy in the management of patients with a high risk of developing MACEs and MALEs.

Abbreviations

CAD, coronary artery disease; ISTH, International Society on Thrombosis and Hemostasis; MACEs, major adverse cardiovascular events; MALEs, major adverse limb events; PAD, peripheral artery disease.

Disclosure

The authors report no potential conflicts of interest related to the research, authorship, and/or publication of this article.

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