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Safety and Efficacy of Rivaroxaban-Aspirin Combination Compared to Aspirin Monotherapy on Lower Peripheral Artery Disease after Revascularization: Systematic Review and Meta-analyses

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Abstract

Introduction. Currently, single antiplatelet treatments using aspirin or clopidogrel are recommended for post-revascularization peripheral artery disease (PAD) patients. However, a recent study suggested that a combination of rivaroxaban and aspirin was more favorable to use. We conducted a systematic review to determine the efficacy and safety of rivaroxaban and aspirin combination compared to aspirin alone.
Method. A systematic review conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol. Search using keywords was conducted on Cochrane, PubMed, Scopus, EBSCOHost, and Google Scholar. Inclusion and exclusion criteria were applied. Selected studies were appraised using the Cochrane risk of bias tool v.2 for inclusion. The studies included were extracted for characteristics and outcomes. Outcomes were analyzed qualitatively and quantitatively. We used a fixed- or random-effect model to determine the pooled ratio per appropriate. A 95% confidence interval and p-value of 0.05 and below were used as indicators of statistical significance.
Results. Two multicentered, randomized controlled studies were included after searching. They were appraised with a low risk of bias. Both studies showed greater primary effectivity outcomes in the combination group and improvements in major bleeding risk. The quantitative analysis found lower PAD complications rate (OR = 0.79; 95% CI = 0.66–0.95), which included myocardial infarction, stroke, cardiovascular death, and acute limb ischemia. The combination group provided lesser primary (OR = 1.32; 95% CI = 1.06–1.67) and secondary (OR = 1.47; 95% CI = 1.19–1.84) safety outcomes.
Conclusion. A combination of rivaroxaban and aspirin provided better clinical outcomes in post-revascularization PAD patients. However, this combination should be used carefully as this yields a more significant risk of bleeding in the population.

Keywords: aspirin, efficacy, peripheral artery disease, Revascularization, rivaroxaban

Introduction

Peripheral artery disease (PAD) is one of the most common causes of disability worldwide. PAD is a vascular condition caused by inhibition of the bloodstream towards the upper or lower limb due to blood vessel narrowing or the formation of atherosclerosis. PAD was acquired by 200 million people worldwide, increasing numbers. PAD is commonly asymptomatic in early stages, which could progress to complications such as gangrene, which leads to amputation. Therefore, early identification and prompt treatment are essential.[1]

Treatment of PAD is focused on preventing narrowing and clotting of vessels, hence reducing fatal conditions such as stroke and myocardial infarction.[2,3] Revascularization is a surgical method to return perfusion toward the ischemic area. Single antiplatelet treatments using aspirin or clopidogrel are currently advised by guidelines to be administered in post-revascularization patients in order to reduce the risk of myocardial infarction and stroke and to improve vascular patency.[4,5] However, there were several post-revascularization bleeding risks due to single antiplatelet treatment.[6] Therefore, special attention towards post-revascularization pharmacology treatment and the bleeding risk are urgently needed.

A newer study found that adding rivaroxaban to aspirin as an anti-thrombocyte yielded a greater effect than aspirin single therapy. Rivaroxaban, which serves as an anticoagulant, could reduce the risk of ischemia, including limb side effects due to PAD. In terms of safety, a combination of rivaroxaban and aspirin was deemed not significantly different compared to a combination of placebo and aspirin.[7] However, there was a suspicion of higher bleeding risk due to hemostasis mechanisms. Therefore, we conducted a systematic review to determine a comparison between the rivaroxaban-aspirin combination and aspirin monotherapy for post-revascularization PAD patients. Information acquired from this study was expected to improve clinical care for post-revascularization PAD patients.

Method

A systematic review conducted based on the protocol established by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol.[8] York University registered This study on PROSPERO with registration number CRD42022356214. Studies were searched from Cochrane, PubMed, EBSCOHost, Scopus, and Google Scholar. We used keywords (("rivaroxaban"[MeSH Terms] OR rivaroxaban [Text Word]) AND ("aspirin"[MeSH Terms] OR aspirin [Text Word]) AND ("peripheral arterial disease"[MeSH Terms] OR peripheral arterial disease [Text Word]) AND ("revascularization" [MeSH Terms] OR Revascularization [Text Word])) in PubMed which enable medical sub-heading (MeSH) terms and (("rivaroxaban" OR "Xarelto") AND ("aspirin" OR "acetylsalicylic acid" OR "ASA") AND ("peripheral arterial disease" OR "PAD") AND ("revascularization")) in other databases.

We omitted duplicated studies and applied criteria to filter studies. Inclusion criteria were applied as follows: (1) randomized-controlled trials; (2) post-revascularization lower PAD patients; (3) intervention group of rivaroxaban and aspirin combination; (4) control group of aspirin monotherapy; (5) outcome of clinical outcomes and complications such as acute ischemic, limb amputation, myocardial infarction, ischemic stroke, and mortality due to cardiovascular disease.

In addition, the following exclusion criteria were applied: (1) no full text available; (2) single-armed studies; (3) language other than English.

Studies met the criteria were appraised using the Cochrane risk of bias critical appraisal tool (Cochrane RoB 2.0) for a decision on inclusion.[9] Included studies were extracted for information such as authors, study location, patients' characteristics, information on given interventions, and measured outcomes (myocardial infarction, amputation, ischemic stroke, cardiovascular death, and others). Comparison of efficacy and safety was analyzed qualitatively with output of odds ratio (OR), hazard ratio (HR), risk ratio (RR), or any relevant output with a p-value of 0.05 and below considered statistically significant. In addition, a 95% confidence interval was considered for statistical significance. Quantitative analysis was conducted using RevMan 5.4.[10]. Heterogeneity analysis was conducted using the Cochrane or Higgins test with an I^2 value of 50% and greater or a p-value of 0.05 or lesser, considered as heterogeneously distributed data. Heterogenous data was analyzed using a random-effect model, whereas homogenously distributed data was analyzed using a fixed-effect model.[11].

Results

Thorough searching and selection resulted in two final studies (Figure 1). Critical appraisal using RoB2 on those studies showed that those studies have a low risk of bias and thus could be included in this study (Figure 2). Two studies were randomized-controlled studies with trial names COMPASS and VOYAGER PAD.[7,12]

Both studies have similar evenly distributed characteristics (Table 1). COMPASS and VOYAGER PAD studies showed a significantly greater reduction of acute limb ischemia risk in the rivaroxaban and aspirin group than in aspirin alone. Both studies presented greater primary effectivity outcomes in the rivaroxaban and aspirin arms. The COMPASS study explained significant differences in major adverse limb events, whereas the VOYAGER PAD study succeeded in explaining the improvement of secondary effectivity outcome. However, both studies showed significant improvements in major bleeding risk, while the COMPASS study stated that there was also a significant improvement in minor bleeding risk (Table 2).[7,12]

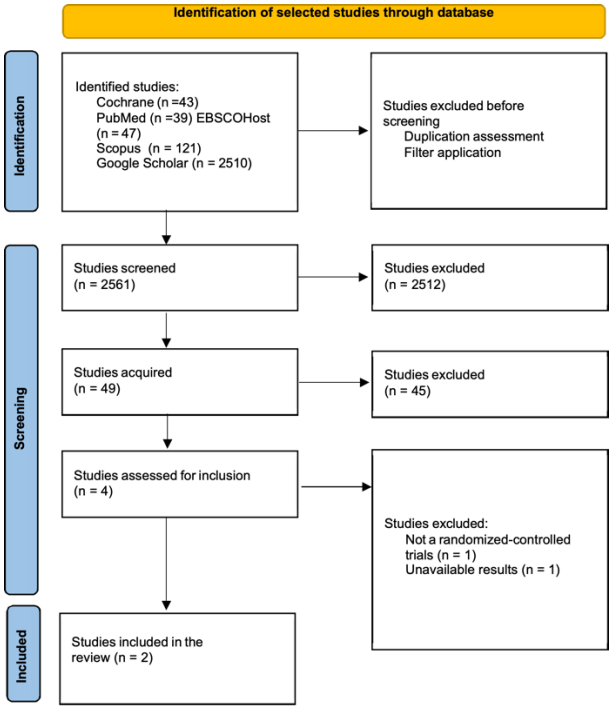

Figure 1. Literature search using PRISMA flow.

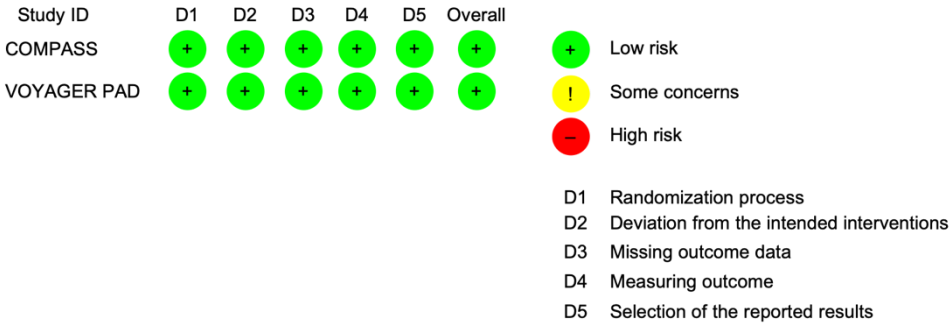

Figure 2. Critical appraisal of selected studies.[9]

Table 1. Characteristics of selected studies.[7,12]

Studies	COMPASS[12]		VOYAGER PAD[7]	
Therapies	**R+A**	**A**	**R+A**	**A**
Subject size	2492	2504	3286	3278
Mean age (year)	67.9	67.8	67.0±9	67.0±9
Women (%)	29	29	25.8	26.1
Systolic blood pressure (mmHg)	138.9±18.5	138.6±18.2		
Diastolic blood pressure (mmHg)	77.7±10.1	77.8±10.3		
Body mass index (kg/m^2)	28.3±5.0	28.4±5.0	26.0±4.3	26.0±4.3
Symptomatic PAD (%)	81.3	81.4		
Symptomatic lower extremity PAD (%)	56.5	54.3		
Risk factors and comorbidities				
Hypertension (%)	78.9	80.6	81.7	81.1
Dyslipidemia (%)			60	60
Smoking (%)	27.4	27.4	34.9	34.5
Diabetes mellitus (%)	44.1	44.1	40	40.1
GFR <60 mL/minute/1.73 m^2 (%)	18.7	18.6	20.1	31
Coronary artery disease (%)	18.7	18.6	32	31
Myocardial infarct (%)			11.1	10.6
Carotid artery disease (%)	24.8	27.2	8.6	8.9
Stroke (%)	6.9	6.2		
History of PAD				
Ankle-brachial index				
Mean			0.56±0.19	0.56±0.19
Normal (≥0.9) (%)	49.2	47.6		
0.7-0.9 (%)	39.3	39.3		
≤0.7 (%)	8.5	9.9		
History of the femoral aorta or lower extremity bypass, iliac or infrainguinal artery percutaneous transluminal angioplasty (%)	26.8	26.9		
History of intermittent claudication (%)	45.8	45.5	95.3	95.7
History of limb amputation (%)	4.7	4.5	5.9	6
History of acute limb ischemia (%)			30.4	29.6
Medication history				
Statin (%)	83.8	82.8	79.4	80.6
ACE inhibitor or ARB (%)	68.8	70.5	63.8	62.9
Antiplatelet (%)	87.7	87.3	99.1	99.1
Beta-blocker (%)	59.3	59.3		
Proton pump inhibitor (%)	33.1	32.5		

Abbreviations: R + A = Rivaroxaban with aspirin; A = Aspirin monotherapy; PAD = peripheral artery disease; GFR = glomerular filtration rate; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

Table 2. Outcome of selected studies.[7,12]

Studies	**COMPASS**[12]			**VOYAGER PAD**[7]		
Therapies	**R+A**	**A**	**p**	**R+A**	**A**	**p**
Primary efficacy outcome	6.30	8.99	0.0047	15.46	17.82	0.009
Myocardial infarct (%)	2.05	2.68		3.99	4.52	
Stroke (%)	1.00	1.88	0.018	2.16	2.5	
Cardiovascular death (%)	2.57	3.12		6.06	5.31	
Acute limb ischemia (%)	0.76	1.36	0.042	4.72	6.93	0.017
Chronic limb ischemia (%)	0.64	0.96				
Major adverse limb events (%)	1.20	2.24	0.0037			
Amputation due to vascular cause (%)	0.44	1.12	0.0069	3.14	3.51	3.51
Major amputation (%)	0.20	0.68	0.011			
Secondary efficacy outcome						
Death (all) (%)	5.18	5.67		9.77	9.06	0.34
Hospitalization due to coronary/peripheral thrombosis (%)				7.97	10.86	<0.001
Revascularization (%)				17.77	19.98	0.03
Venous thromboembolism (%)				0.76	1.25	
Primary safety outcome						
Major bleeding (%)	3.09	1.92	0.0089	1.9	1.35	0.07
Intracranial bleeding (%)	0.16	0.32		0.4	0.52	
Fatal bleeding (%)	0.16	0.12		0.18	0.18	
Secondary safety outcome						
ISTH major bleeding (%)	2.57	1.6	0.0089	4.3	3.08	0.007
BARC major bleeding (%)				2.86	2.25	0.1
Minor bleeding (%)	7.95	5.63	0.0011			
Bleeding location	1.65	0.72	0.0027			
Gastrointestinal (%)	0.2	0.36	0.56			
Intracranial (%)	0.12	0.08				
Urogenital (%)	0.28	0.12				
Ocular (%)	0.2	0.72				
Cutaneous (%)	0.16	0.32				
Respiration (%)	0.6	0				
Others (%)		0.4				

Abbreviations: R + A = Rivaroxaban with aspirin; A = Aspirin monotherapy; ISTH = International Society on Thrombosis and Haemostasis; BARC = Bleeding Academic Research Consortium

The quantitative analysis found that there was a better primary effectivity outcome in the rivaroxaban and aspirin group compared to aspirin alone, presented with a lower PAD complication rate (OR=0.79; 95% CI=0.66–0.95). This number was derived from subgroup analysis of myocardial infarction, stroke, cardiovascular death, and acute limb ischemia. However, there was no difference in secondary effectivity outcome between groups (OR=0.63; 95% CI=0.29–1.40) which can be seen in Figure 3.[7,12]

The combination of aspirin and rivaroxaban showed lesser safety compared to aspirin alone based on primary safety outcome (OR=1.32; 95% CI=1.05–1.67). Subgroup analysis showed no significant safety differences between aspects of the primary safety outcome. Analysis of secondary safety outcome showed that the combination of aspirin and rivaroxaban showed lesser safety (OR=1.47; 95% CI=1.19–1.84), which also could be seen in Figure 3.[7,12]

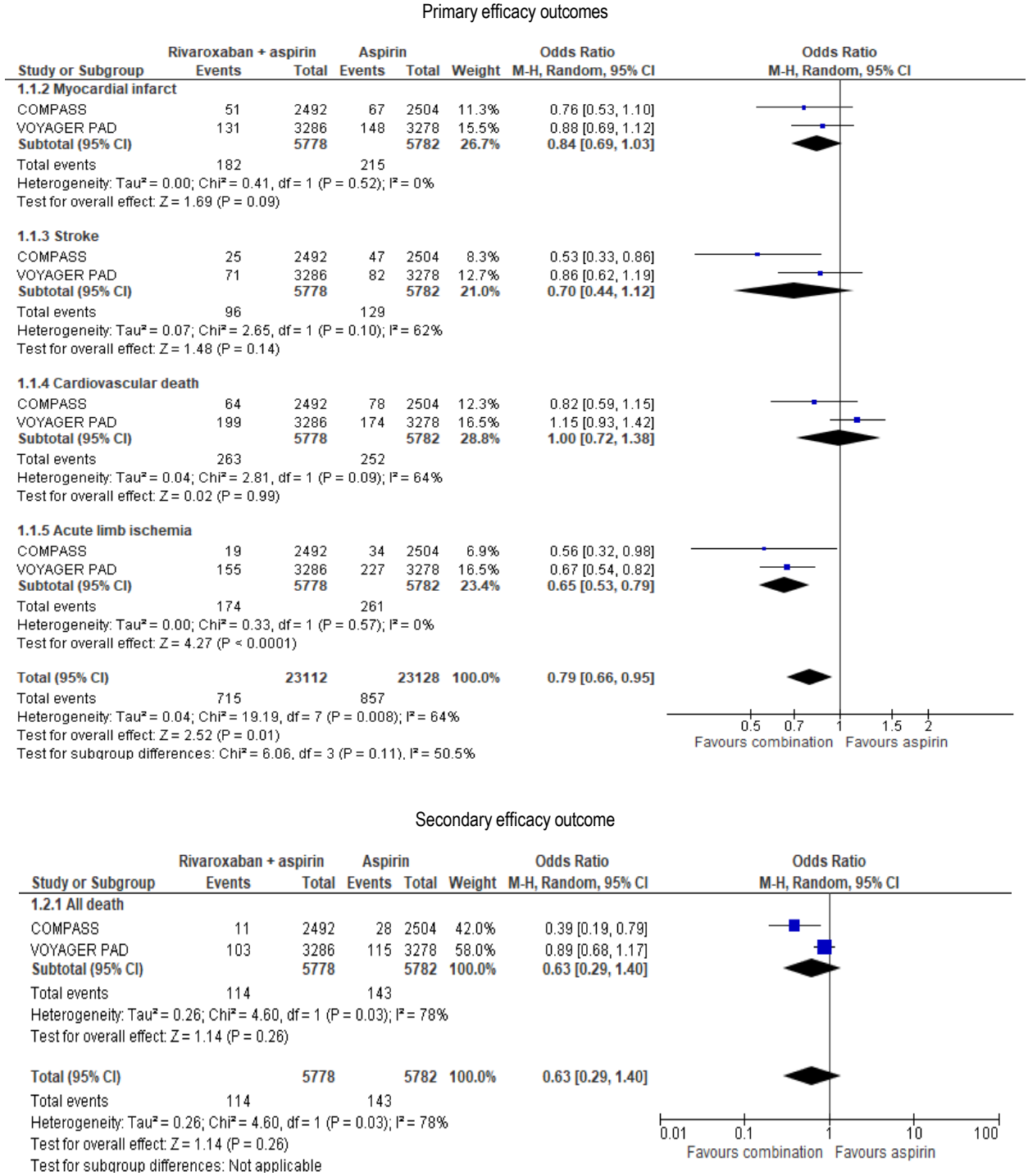

Figure 3. Quantitative analysis on the efficacy of selected studies.[7,12]

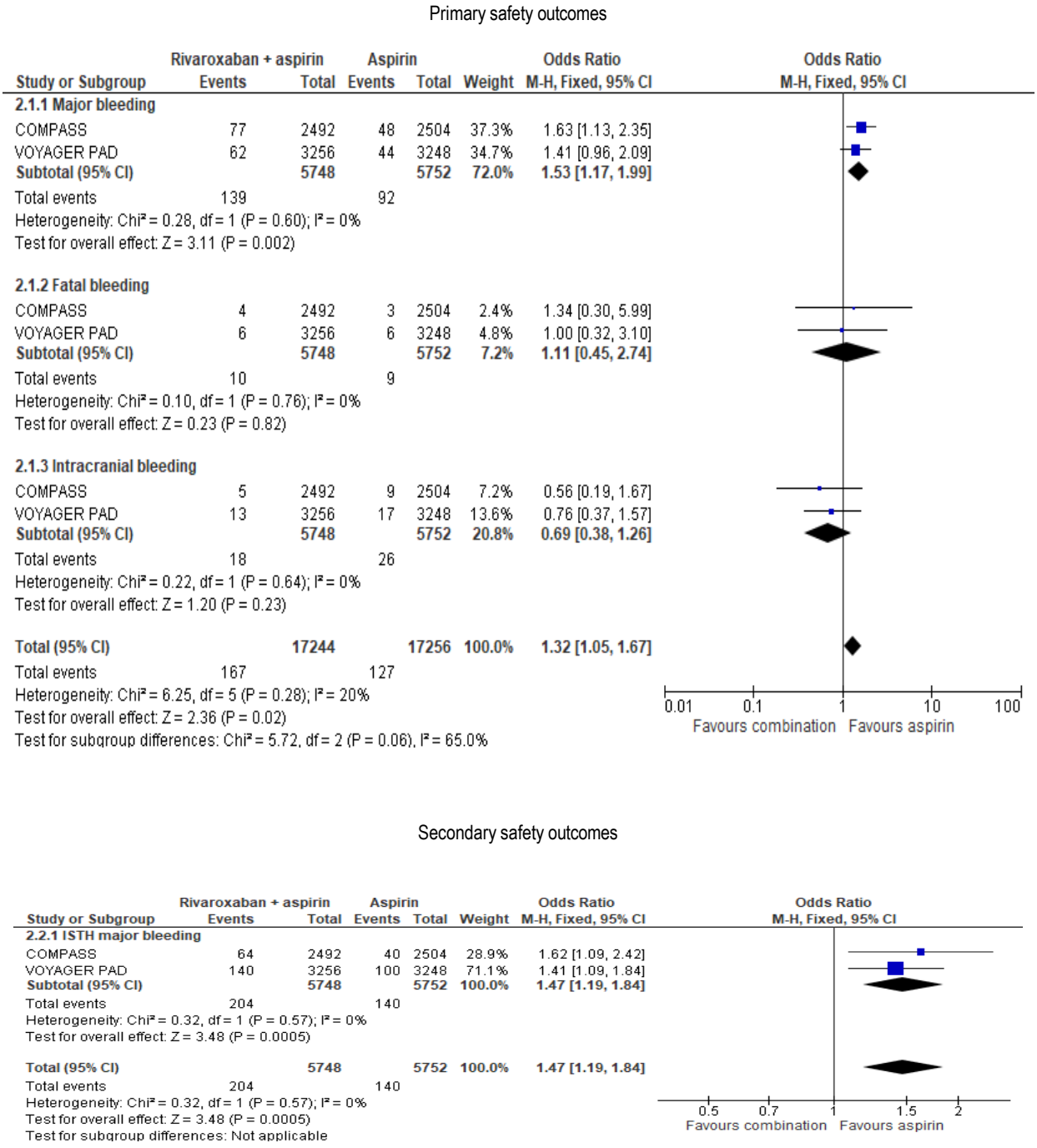

Figure 4. Quantitative analysis on safety of selected studies.[7,12]

Discussion

A combination of aspirin and rivaroxaban was more effective compared to aspirin monotherapy.[7,12] This finding was relatively new compared to the current application, which recommended either aspirin or clopidogrel monotherapy for PAD without considering clinical conditions. (12) More intensive treatment, such as dual antiplatelet of aspirin and P2Y12 inhibitor, such as clopidogrel, has class IIb recommendation.[13,14] However, several studies showed no benefit of dual antiplatelet treatment for post-revascularization PAD.[13–15] A CASPAR study enrolled 851 patients, treating post-revascularization PAD with aspirin 75–100 mg daily and clopidogrel 75 mg daily showed no difference in risk of occlusion, index-graft revascularization, amputation, and death. Compared to aspirin monotherapy after 24 months of observation. The same study stated that there was an elevation of bleeding risk in the combination group compared to the monotherapy group.[16]

The efficacy of the rivaroxaban and aspirin combination is best explained by concepts of coagulation and thrombocytes' activation and aggregation, which are principles of artery thrombosis. Thrombosis on PAD involves a significant risk of major arterial thrombosis, such as acute limb ischemia.[17,18] This event involves three important phases, which account for the interaction between red blood cells and blood vessel walls in order to create hemostasis and occlusive PAD. The first phase includes thrombocyte adhesion and activation, accounting for GPIIbIIIa, von Willebrand factor, GPIb, GPIaIIa, and collagen. Phase two is initiated by changing prothrombin to thrombin with the help of factor Xa. Thrombin activates fibrinogen into fibrin, which initiates coagulation. The third phase is fibrin degeneration, which is assisted by

plasmin. Fibrin is broken into fibrin degeneration products. Rivaroxaban is aimed at the second phase, whereas aspirin is aimed at the first phase; thus, a combination between them is supposed to reduce post-revascularization PAD complications and improve its efficacy.[19]

Other authors have confirmed these findings. A study by Bonaca et al. showed that a combination of rivaroxaban and aspirin could reduce acute limb ischemia, unplanned index limb revascularization, amputation, and cardiovascular death in the first and third-year post-revascularization with a hazard ratio of 0.76 (95% CI = 0.62–0.95) and 0.84 (95% CI = 0.71–1.00), respectively.[20] Cohort study by Hess et al. showed that a combination of rivaroxaban and aspirin could reduce venous thromboembolism, which could not be reduced by usage of clopidogrel (HR = 0.61; 95% CI = 0.37–0.998 vs. HR = 0.69; 95% CI = 0.32– 1.48). (41) A Study by Berkowitz et al. showed a significant 23% reduction of thrombosis in the combination group. In a study by Bauersachs et al., they found that the combination of rivaroxaban and aspirin significantly reduced vascular complications by 14%.[21] Jurk et al. found that combination therapy significantly reduced tissue factors, which accounted for the reduction of thrombocyte reactivity in post-revascularization PAD patients.[22]

However, the confounding factors should be addressed. A study by Hess et al. mentioned that excessive weight and being an older age significantly affected the incidence of venous thromboembolism with a hazard ratio of 3.04 (95% CI = 1.09–8.43) and 1.81 (95% CI = 1.06–3.11), respectively.[23] Another study by Hess et al., women are more at risk for unplanned index limb revascularization (HR = 1.18; 95% CI = 1.00-1.40), and women are more likely to withdraw from treatment plans (HR = 1.13; 95% CI = 1.03–1.25).[24] Whereas, hypertension and previous amputation history did not account for the increased risk of venous thromboembolism, according to the study.[23]

In perspective of safety, combinations of aspirin and rivaroxaban have a higher risk of bleeding compared to aspirin monotherapy. This was also confirmed by another study by Gibson et al. on acute coronary syndrome patients, which stated that a combination of aspirin and rivaroxaban significantly reduced atherothrombotic events but increased the risk of bleeding. However, the same study stated that the risk of TIMI major bleeding was considered low (1.5%).[20] Another study by Liang et al., which was conducted in acute coronary syndrome or PAD patients, found that the administration of rivaroxaban and aspirin combination increased the risk of bleeding in both men and women.[25] A review by Anand et al. found that there were seven bleedings occurred for each 1,000 post-revascularization PAD patients treated with rivaroxaban and aspirin and one fatal bleeding or critical organ bleeding for every 1,000 patients.[26] Therefore, the benefits of this combination were considered over the risk.

This is a systematic review of randomized, multicentered, controlled trials that discussed new aspects of post-revascularization PAD treatment. However, this review was restricted to the number of studies analyzed. Therefore, we recommended that more high-quality studies be conducted to make subgroup analysis of this field possible. Quantitative analysis on more detailed primary
outcome, secondary outcome, and safety should be made to ease clinicians in decision-making and patient care.

Conclusions

A combination of rivaroxaban and aspirin was proven more effective in treating post-revascularization PAD patients compared to aspirin monotherapy but yielded a larger bleeding risk; it should be used with caution in patients with low-to-medium bleeding risk.

Disclosure

The authors declare no conflict of interest.

Role of authors

Conceptualization RET DP, Data curation RET, Formal analysis RET, Funding acquisition RET, Investigation RET DP, Methodology RET DP, Project administration RET DP, Resources RET, Software RET, Supervision DP, Validation RET DP, Visualization RET, Writing original draft preparation RET, Writing review and editing RET DP.

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