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RESEARCH LETTER

Low-dose rivaroxaban and aspirin among patients with peripheral artery disease: a meta-analysis of the COMPASS and VOYAGER trials

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Aims Peripheral artery disease (PAD) patients suffer a high risk of major cardiovascular (CV) events, with atherothrombo-embolism as the underlying pathophysiologic mechanism. Recently, two large randomized clinical trials evaluated the efficacy and safety of low-dose rivaroxaban twice daily plus aspirin in stable PAD outpatients and those immediately after peripheral revascularization. We sought to determine if the effects of low-dose rivaroxaban and aspirin compared to aspirin alone are consistent across this broad spectrum of PAD patients.

Methods and results We conducted a random-effects meta-analysis of the COMPASS and VOYAGER randomized trials among 11 560 PAD patients (4996 from COMPASS and 6564 from VOYAGER) in the primary analysis and 9332 (2768 from COMPASS and 6564 from VOYAGER) with lower extremity (LE)-PAD in the secondary analysis. The hazard ratio (HR) for the composite of CV death, myocardial infarction, ischaemic stroke, acute limb ischaemia, or major vascular amputation was 0.79 (95% confidence interval, CI: 0.65–0.95) comparing low-dose rivaroxaban plus aspirin to aspirin alone. While the risk of major bleeding was increased with low-dose rivaroxaban plus aspirin compared to aspirin alone [HR: 1.51 (95% CI: 1.22–1.87)], there was no significant increase in severe bleeding [HR: 1.18 (95% CI: 0.79–1.76)]. Similar effects were observed in the subset with symptomatic LE-PAD.

Conclusions Among PAD patients, low-dose rivaroxaban plus aspirin is superior to aspirin alone in reducing CV and limb outcomes including acute limb ischaemia and major vascular amputation. This reduction is offset by a relative increase in major bleeding, but not by an excess of fatal or critical organ bleeding. The consistency of findings of these trials

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supports the use of combination low-dose rivaroxaban plus aspirin in PAD patients across a broad spectrum of disease.

Keywords Rivaroxaban • Peripheral artery disease • Meta-analysis

Introduction

Globally more than 200 million people suffer from peripheral artery disease (PAD), and the incidence is rising due to advancing age, high rates of smoking in certain regions of the world, and the rising incidence of type 2 diabetes.[1] PAD patients have wide-spread atherosclerosis and suffer a high risk of major cardiovascular (CV) events, with atherothrombosis as the underlying pathophysiologic mechanism.[2,3] The mainstay of medical therapy for PAD patients is risk factor modification including smoking reduction/cessation, treatment of diabetes, LDL cholesterol lowering, and optimal blood pressure control; and for PAD patients with intermittent claudication a walking programme is recommended.[4] In stable PAD patients, Class 1 guidelines recommend use of a single antiplatelet agent with either aspirin or clopidogrel, with mixed recommendations for antithrombotic management after lower extremity (LE) revascularization.[4,5] These guidelines also recommend against the use of long-term oral anticoagulation with moderate or high-intensity warfarin used with or without antiplatelet therapy, due to the unacceptably high risk of serious bleeding.[4,5]

Recently, two large randomized clinical trials have been completed in which a large number of PAD patients were randomized to receive low-dose Factor Xa inhibitor, rivaroxaban (2.5 mg twice daily) vs. placebo on a background of antiplatelet therapy. The COMPASS trial enrolled patients with stable PAD from a clinic setting[6] and the VOYAGER trial enrolled patients shortly after a technically successful LE revascularization.[7] Each trial individually showed a significant reduction in their primary CV outcomes and reported an increase in major but not severe bleeding. We sought to determine if the effects of low-dose rivaroxaban plus aspirin compared to aspirin alone are consistent across the whole spectrum of PAD patients.

Methods

Both clinical trials were multicentre, randomized double-blind, placebo-controlled, and compared low-dose rivaroxaban 2.5 mg twice daily to placebo on a background of antiplatelet therapy. Both trials received central and local research ethics board approvals and adjudicated primary endpoint components and have been previously published.[8,9] Briefly, COMPASS was a multicentre, double-blind, randomized, placebo-controlled trial that enrolled 27 395 patients with coronary artery disease (CAD) and/or PAD, and compared three treatment arms: the combination of rivaroxaban 2.5 mg twice daily plus aspirin or rivaroxaban 5 mg twice daily (with aspirin placebo), vs. aspirin alone (with rivaroxaban placebo), for the prevention of CV death, myocardial infarction (MI), or stroke. The principal safety outcome was a modified version of International Society of Thrombosis and Hemostasis (ISTH) major bleeding.[10] In total, 7470 PAD patients were enrolled into COMPASS, and included patients with symptomatic LE-PAD (history of aorto-femoral bypass surgery, lower limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac or infrainguinal arteries); limb or foot amputation for arterial vascular disease; intermittent claudication with an ankle brachial index (ABI) of less than 0.90 or a peripheral artery stenosis (≥50%) documented by angiography or duplex ultrasound, carotid artery disease, or asymptomatic PAD defined as CAD with a low ABI at baseline. The details of inclusion criteria, exclusion criteria, adjudication process, and definitions of outcomes have been previously published.[8] The trial was stopped early for efficacy following a recommendation by the independent Data and Safety Monitoring Board, and the PAD patients were followed for a median of 21 months [interquartile range (IQR): 15–28 months].[10] For this meta-analysis, we include 4996 patients from COMPASS with any PAD and the subset of 2768 patients with symptomatic LE-PAD who were randomized to the rivaroxaban 2.5 mg twice daily plus aspirin as compared to those randomized to the aspirin alone arm[11] (*Figure 1*).

The VOYAGER PAD trial was a double blind placebo controlled trial of 6564 patients with symptomatic LE-PAD who were randomized within 10 days following peripheral revascularization to the combination of rivaroxaban 2.5 mg twice daily and aspirin or to aspirin alone, with or without concomitant clopidogrel.[9] Eligible patients were at least 50 years old and had documented symptomatic LE-PAD including symptoms, anatomic evidence of disease distal to the external iliac artery, and ABI ≤0.80 or toe brachial index (TBI) ≤0.60 for patients with no prior history of revascularization or ABI ≤0.85 or TBI ≤0.65 for patients with prior history of revascularization. Patients were eligible after a technically successful revascularization for symptomatic PAD and could begin study drug up to 10 days. Patients were excluded if they were clinically unstable, at increased bleeding risk, or needed prohibited concomitant medications including long-term clopidogrel (i.e. >6 months). Patients were stratified by index revascularization procedure type (endovascular including the combination of endovascular and surgical vs. open surgical) and clopidogrel use. The principal safety outcome in VOYAGER was TIMI major bleeding, with ISTH major bleeding as secondary safety outcome. The median follow-up period was 28 months (IQR: 22 to 34 months).

Outcomes

The five-point composite of CV death, MI, ischaemic stroke, acute limb ischaemia, or major amputation of a vascular cause was used as the primary efficacy outcome. The secondary efficacy outcome composites included: CV death, MI, ischaemic stroke [major adverse cardiovascular events (MACE)], and separately major adverse limb events (MALE) defined as acute limb ischaemia or major vascular amputation. The primary safety outcome for this analysis was ISTH major bleeding (which was the secondary safety outcome in each trial), and we also separately examined severe bleeding defined as fatal or symptomatic bleeding into a critical organ (including intracranial haemorrhage).[12] These outcomes were evaluated in the total PAD population (primary analysis), and separately for only those patients with symptomatic LE-PAD (secondary analysis) (*Figure 1*). We also explored the sources of heterogeneity by harmonizing definitions between the two trials as much as possible.

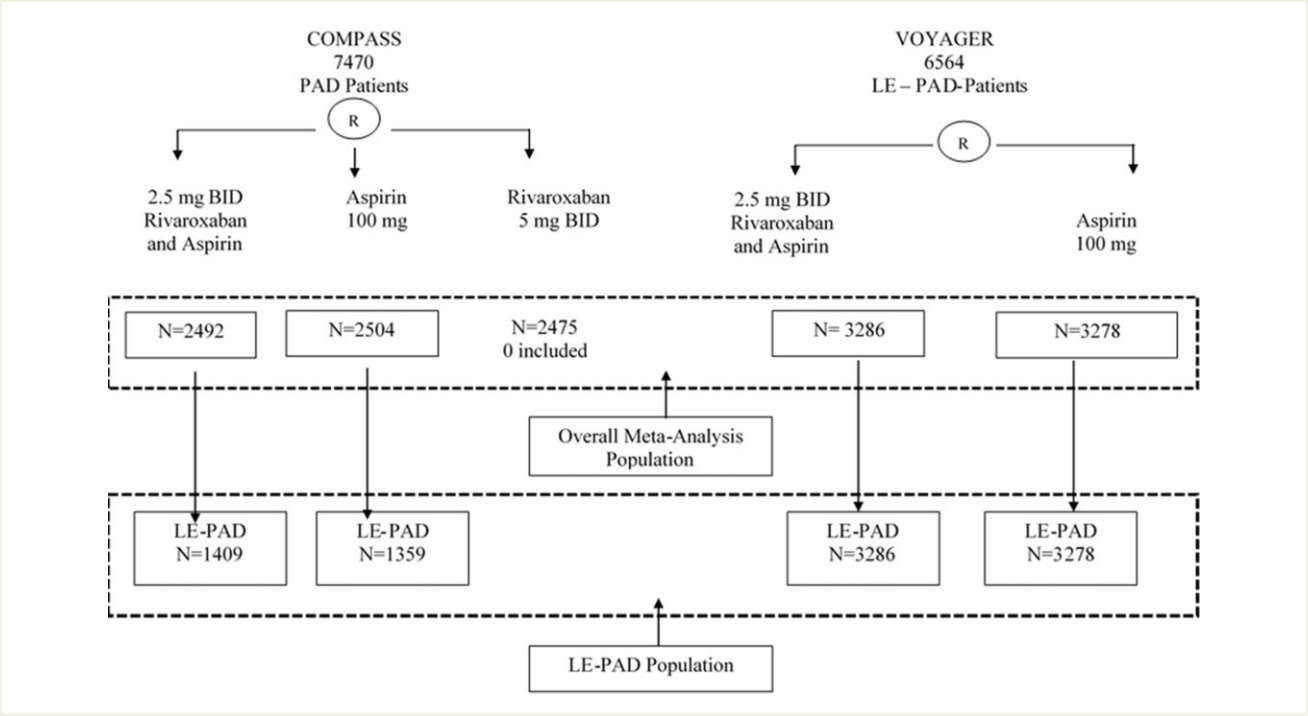

Figure 1 Flow chart trial populations.

Statistical analysis

The efficacy analysis was conducted in all randomized patients regardless of whether they received study treatment following an intention-to-treat principle, considering outcomes that occurred from randomization to the end of the study period. The safety analysis was conducted in the safety population considering only outcomes that occurred during the on-treatment period of the study. For each outcome of each trial, crude percentages and annualized rates and the natural log of the hazard ratios (HRs) estimated by the Cox proportional-hazards model were calculated. To estimate the average effect of rivaroxaban plus aspirin vs. aspirin alone, using study level data, a random effects model was used with estimates pooled using the generic inverse variance method considering the natural log of the HR estimates and the DerSimonian and Laird estimator for τ^2 with no correction for the 95% confidence interval's (CI's).[13] The heterogeneity of treatment effects was evaluated by the inconsistency index (I^2), with heterogeneity of 25% as low, 50% as moderate, and 75% as high heterogeneity respectively.[14] The number of events prevented or caused per 1000 patients treated for 1 year was calculated by subtracting the annualized event rate of the treatment group from the control or placebo group and multiplying this number by 10.[15] All analyses were performed in R using the *meta* package.

Results

Baseline characteristics

The baseline characteristics of each trial are shown in *Table 1*. All patients had PAD and the average age and proportion of women in the COMPASS and VOYAGER trials were similar, but there were some important differences. The COMPASS patients were more likely to have concomitant CAD compared to the VOYAGER patients (66% vs. 31%), whereas the VOYAGER patients had more severe PAD than COMPASS patients (Fontaine Class III or IV—32% vs. 3%, respectively). In both trials, PAD patients were well treated with >80% use of lipid-lowering agents and more than two-thirds on angiotensin-converting enzyme/angiotensin receptor blocker's (ACE/ARB's) at baseline. In addition, the COMPASS trial protocol did not allow concomitant use of any additional platelet aggregation inhibitor, while the VOYAGER trial allowed a short course of clopidogrel up to 6 months after endovascular intervention, which was used in approximately 50% of the post-revascularization patients for a median duration of 29.0 days.

Efficacy

For the combined PAD patients of COMPASS and VOYAGER, *Figure 2A* depicts the individual trial point estimates and the combined meta-analysis estimate and confidence intervals are shown for the composite of CV death, MI, ischaemic stroke, acute limb ischaemia, and major vascular amputation (MACE or MALE). Individual components of the primary outcome are also found in the Supplementary material online, *Figures*. In each trial, a statistically significant reduction in the primary composite outcome was seen in those treated with rivaroxaban plus aspirin compared to those treated with aspirin only. The pooled analysis indicated a 21% reduction in the primary composite outcome (HR: 0.79; 95% CI: 0.65–0.95), with moderate heterogeneity observed; $I^2 = 59.7\%$, $P = 0.11$. More specifically, using the combined annualized event rates, the absolute risk reduction was 1.20%/year, which can be interpreted as prevention of 12 MACE or MALE events per 1000 patients treated for a year.

Table 1 Baseline characteristics

	COMPASS PAD	COMPASS symptomatic LE-PAD	VOYAGER
Number	4996	2768	6564
Female, *n* (%)	1435 (28.7)	813 (29.4)	1704 (25.9)
Age, median (IQR)	68 (63, 74)	67 (61, 73)	67 (61, 73)
PAD history			
ABI, median (IQR)	0.90 (0.81, 1.06)	0.92 (0.81, 1.06)	0.56 (0.42, 0.67)
Claudication (%)	2282 (45.7)	1985 (71.7)	4368 (66.5)
Prior amputation (%)	228 (4.6)	214 (7.7)	390 (5.9)
Prior PTA or revascularization surgery (%)	1342 (26.9)	1139 (41.1)	2336 (35.6)
History of critical limb ischaemia (Fontaine III or IV) (%)	139 (2.8)	119 (4.3)	2088 (31.8)
Current smokers (%)	1367 (27.4)	863 (31.2)	2279 (34.7)
Diabetes (%)	2204 (44.1)	1308 (47.3)	2623 (40.0)
Concomitant coronary artery disease (%)	3297 (66.0)	1498 (54.1)	2067 (31.5)
Renal insufficiency (%) (eGFR < 60 mL/min)	1394 (27.9)	754 (27.2)	1327 (20.2)
Heart failure history (%)	937 (1.1)	458 (16.5)	539 (8.2)
Lipid-lowering agent (%)	4162 (83.3)	2175 (78.6)	5249 (80.0)
ACE or ARB use at baseline (%)	3480 (69.7)	1848 (66.8)	4159 (63.4)
Clopidogrel use at randomization (%)[a]	0	0	3282 (50)

[a]Exclusion criteria in COMPASS trial.
ABI, ankle brachial index; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LE, lower extremity; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty.

MACE alone: CV death, MI, ischaemic stroke

In *Figure 2B*, the individual trial point estimates, and the combined meta-analysis estimates and confidence intervals are shown for MACE alone. Examining each trial separately, in the COMPASS trial a 27% risk reduction was observed, $P = 0.007$, whereas in VOYAGER a 3% risk reduction was observed, $P = 0.73$. The pooled analysis shows a non-significant 15% reduction (HR: 0.85; 95% CI: 0.65–1.13), with high heterogeneity at 75.8%; $P = 0.04$.

MALE: acute limb ischaemia or major vascular amputation

In *Figure 2C*, the individual trial estimates and combined pooled estimate for MALE are shown. The individual trials, as well as the pooled analysis, showed a large and "significant 32% reduction" (HR: 0.68; 95% CI: 0.52–0.90; $P = 0.007$) with combination rivaroxaban plus aspirin compared to aspirin alone. The heterogeneity was moderate at 33%, $P = 0.22$.

Safety

ISTH major bleeding

In *Figure 2D*, the individual trial estimates and the pooled analysis estimates are shown for ISTH major bleeding. In each trial, patients treated with rivaroxaban plus aspirin compared to those treated with aspirin alone had a statistically significant increase in ISTH major bleeding. The pooled HR was 1.51 (95% CI: 1.22–1.87); $P = 0.0002$ with no heterogeneity observed. The absolute risk increase was 0.6%/year, which translates into six patients experiencing major bleeding per 1000 patients treated with rivaroxaban plus aspirin compared to aspirin alone over a year. Severe bleeding (fatal or critical organ) was not significantly higher in the rivaroxaban plus aspirin arm compared to aspirin alone (0.5%/year vs. 0.4%/year; $P = 0.43$), and no difference in intracranial haemorrhage was observed (0.2%/year vs. 0.2%/year; $P = 0.38$) (Supplementary material online, *Figures*).

For the secondary population of symptomatic LE-PAD

A total of 9332 patients with symptomatic LE-PAD were combined. There was a significant 19% reduction in the primary composite outcome (HR: 0.81; 95% CI: 0.68–0.96; $P = 0.01$). The absolute risk reduction was 1.28%/year, which translates into the prevention of 13 events per 1000 patients treated for 1 year (*Figure 2E*). For the MACE composite, a 28% reduction was observed in the COMPASS trial and a 3% in VOYAGER, with a summary hazard ratio of 0.86 (0.65–1.15; $P = 0.30$) (*Figure 2F*). For the outcome of MALE defined as acute limb ischaemia or major vascular amputation, the pooled summary estimate was a significant 17% reduction (HR: 0.73; 95% CI: 0.61–0.86; $P = 0.0002$) (*Figure 2G*). The ISTH major bleeding was increased in a similar proportion as seen in the overall population [HR: 1.60; 95% CI: 0.12–2.29; $P = 0.01$] (*Figure 2H*), and no excess of severe bleeding was observed (Supplementary material online, *Figures*). Generally, lower heterogeneity for the 5-point primary outcome was observed for the symptomatic LE-PAD population compared to the overall data.

Exploratory analysis

We evaluated the impact of removing of CV deaths, not due to MI or ischaemic stroke from the five-point primary composite endpoint, and observed that the effect of rivaroxaban plus aspirin compared to aspirin alone was of greater magnitude and significance of [HR = 0.73 (95% CI: 0.64–0.83; $P < 0.0001$)], with substantially lower heterogeneity; $I^2 = 6.3\%$, $P = 0.30$ (*Figure 3A*). This greater precision and reduced

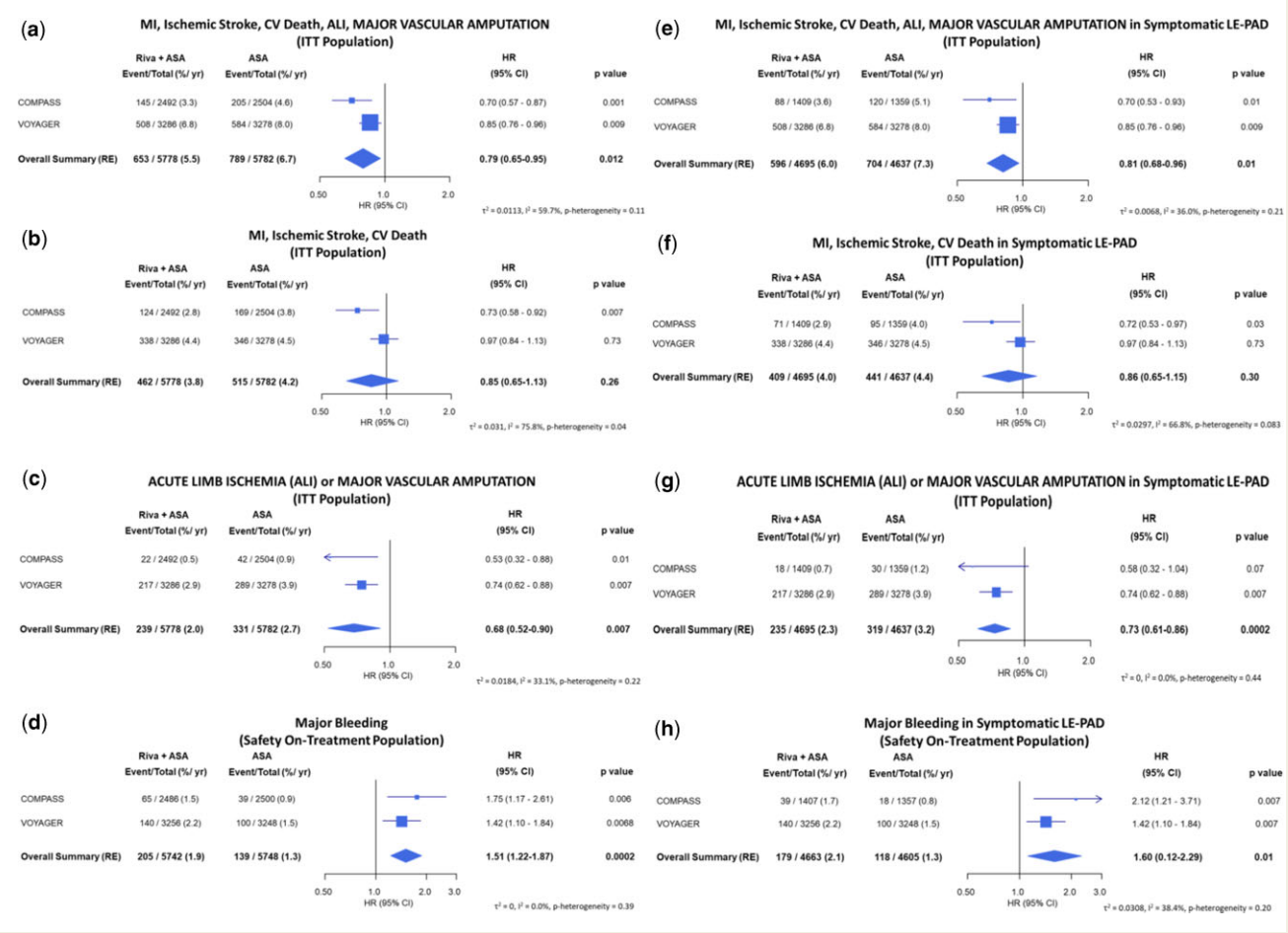

Figure 2 (*A*) Rivaroxaban + Aspirin vs. Aspirin on Primary Composite (MI, ischaemic stroke, CV death, ALI, major vascular amputation) in COMPASS PAD and VOYAGER trials. (*B*) Rivaroxaban + Aspirin vs. Aspirin on MACE (CV death, or ischaemic stroke, or MI) in COMPASS PAD and VOYAGER. (*C*) Rivaroxaban + Aspirin vs. Aspirin on MALE (acute limb ischaemia and major vascular amputation) in COMPASS PAD and VOYAGER. (*D*) Rivaroxaban + Aspirin vs. Aspirin on Major Bleeding in COMPASS PAD and VOYAGER. (*E*) Rivaroxaban + Aspirin vs. Aspirin on Primary Composite (MI, ischaemic stroke, CV death, ALI, major vascular amputation) in symptomatic LE-PAD COMPASS PAD and VOYAGER trials. (*F*) Rivaroxaban + Aspirin vs. Aspirin on MACE (CV death, or ischaemic stroke, or MI) in symptomatic LE-PAD COMPASS PAD and VOYAGER trials. (*G*) Rivaroxaban + Aspirin vs. Aspirin on MALE (acute limb ischaemia and major vascular amputation) in symptomatic LE-PAD COMPASS PAD and VOYAGER trials. (*H*) Rivaroxaban + Aspirin vs. Aspirin on Major Bleeding in symptomatic LE-PAD COMPASS PAD and VOYAGER trials.

heterogeneity were also observed for the secondary MACE outcome with the pooled estimate suggesting a 22% (95% CI: 6–35%) reduction with rivaroxaban plus aspirin compared to aspirin alone, with low heterogeneity (I^2 = 8.9%, P = 0.29) (*Figure 3B*). Similar reductions in heterogeneity were observed among the subset of patients with symptomatic LE-PAD (*Figure 3C* and *D*).

Benefit to risk analysis

In *Figure 4*, the events prevented per 1000 patients treated are shown for the annualized event rates. Considering the total events prevented and caused in one year, treating 1000 PAD patients with low-dose rivaroxaban plus aspirin compared to aspirin alone prevents 12 major CV or limb events, and causes 6 major bleeds, of which 1 is a fatal or critical organ bleed, and 0 intracranial bleeds are caused. Among patients with symptomatic LE-PAD, treating 1000 patients with low-dose rivaroxaban plus aspirin compared to aspirin alone prevents 13 major CV or limb events, and causes 8 major bleeds, of which 1 is a fatal or critical organ bleed, and 0 intracranial bleeds are caused.

Discussion

This meta-analysis combining the COMPASS and VOYAGER trials shows a consistent and significant reduction of the composite of major adverse cardiac and limb vascular events comparing patients treated with the combination of low-dose rivaroxaban plus aspirin to aspirin alone, across a broad spectrum of PAD patients. While a significant increase in major bleeding is observed, the incidence of fatal or critical organ bleeding is low and non-significant, such that the net clinical benefit remains favourable. The consistency of treatment effects was observed across this broad range of PAD patients (from

Figure 3a: **Fatal/Non-Fatal MI, Fatal/Non-Fatal Ischemic Stroke, ALI, MAJOR VASCULAR AMPUTATION (ITT Population)**

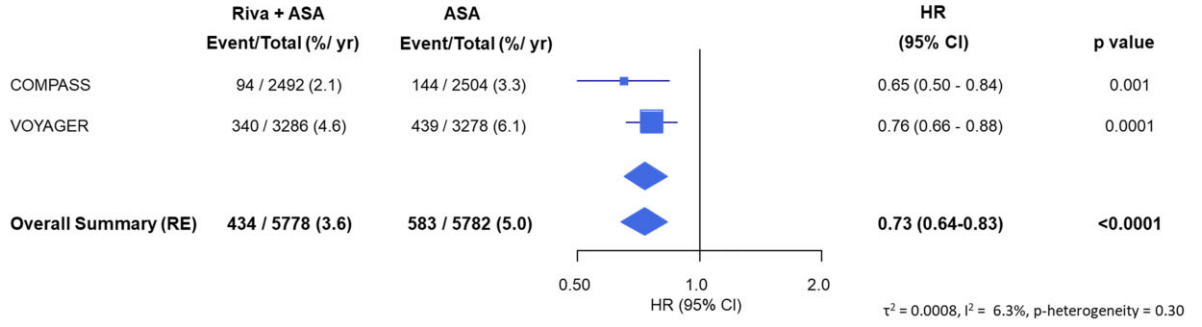

Figure 3b: **Fatal/Non-Fatal MI, Fatal/Non-Fatal Ischemic Stroke (ITT Population)**

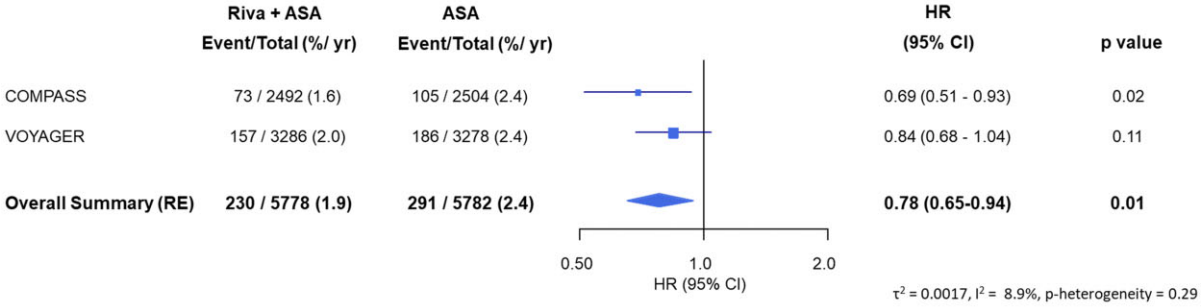

Figure 3c: **Fatal/Non-Fatal MI, Fatal/Non-Fatal Ischemic Stroke, ALI, MAJOR VASCULAR AMPUTATION in Symptomatic LE-PAD (ITT Population)**

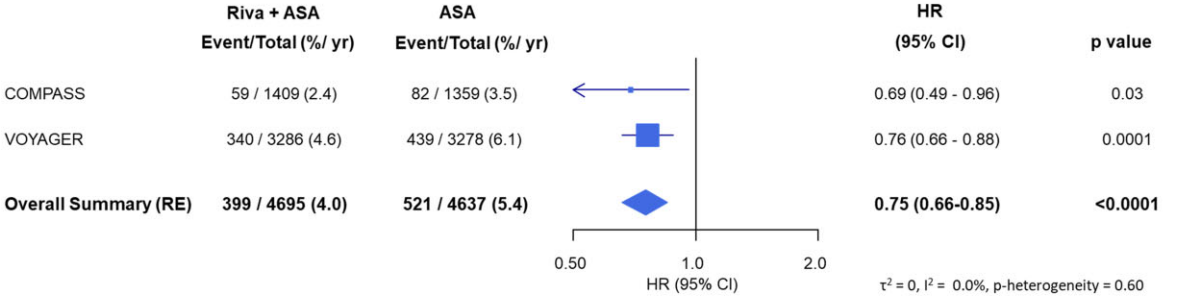

Figure 3d: **Fatal/Non-Fatal MI, Fatal/Non-Fatal Ischemic Stroke in Symptomatic LE-PAD (ITT Population)**

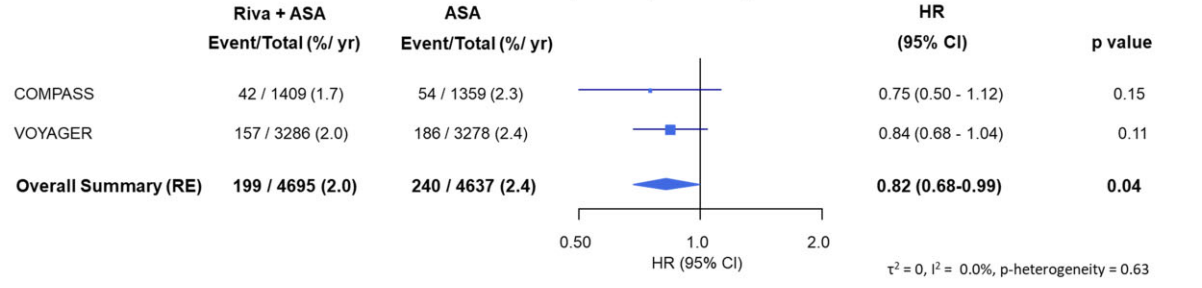

Figure 3 (*A*) Fatal and non-fatal MI, fatal or non-fatal ischaemic stroke, ALI, major vascular amputation in overall COMPASS PAD and VOYAGER trials. (*B*) Fatal and non-fatal MI, fatal or non-fatal ischaemic stroke, in overall COMPASS PAD and VOYAGER trials. (*C*) Fatal and non-fatal MI, fatal or non-fatal ischaemic stroke, ALI, major vascular amputation in symptomatic LE-PAD COMPASS PAD and VOYAGER trials. (*D*) Fatal and non-fatal MI, fatal or non-fatal ischaemic stroke, in symptomatic LE-PAD COMPASS PAD and VOYAGER trials.

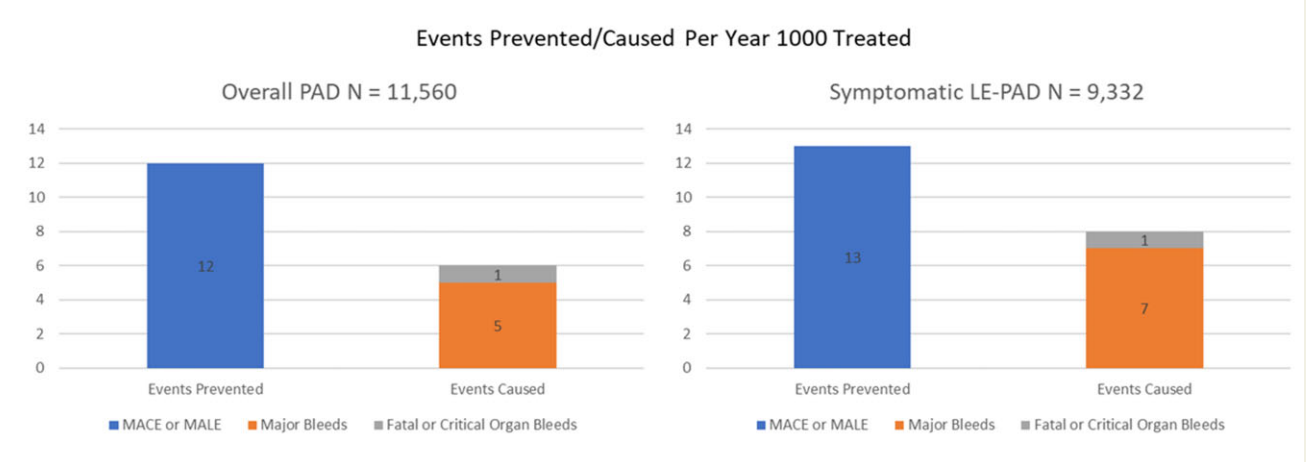

Figure 4 Events prevented/caused per 1000 patients treated with Rivaroxaban + Aspirin vs. Aspirin on MACE or MALE, ISTH major bleeding, fatal or critical organ bleeding, intracranial haemorrhage in combined COMPASS PAD and VOYAGER trials, overall and in symptomatic LE-PAD.

stable outpatients including those with carotid disease, to recently revascularized LE-PAD patients), and is present irrespective of CAD history, severity of PAD, or concomitant clopidogrel use. These data provide robust estimates of net benefit that clinicians can use to guide future decision-making in their management of PAD patients.

There are notable differences in the trial populations of the COMPASS and VOYAGER trials which likely account for the heterogeneity in effect sizes observed between trials. The COMPASS trial enrolled patients who were more likely to have concomitant CAD and a lower proportion of patients with critical limb ischaemia, whereas VOYAGER patients had the opposite profile by trial design. The presence of CAD is a known effect modifier for the MACE component of the CV endpoint which may explain the larger reduction in MACE observed in the COMPASS trial, as compared to the VOYAGER trial population. Furthermore, 50% of VOYAGER patients were taking concomitant clopidogrel for a limited time period (median duration 29 days after randomization). However, this did not modify the overall efficacy or safety of the combination of rivaroxaban plus aspirin.[9] By statistically combining these two trials, while noting these important differences, we observe consistent treatment effects of low-dose rivaroxaban plus aspirin compared to aspirin alone for the combined outcomes MACE or MALE, and robust effects on MALE alone. When we limited the clinical events most likely linked to athero-thrombo-embolism, i.e. fatal or non-fatal MI and ischaemic stroke (and removed CV deaths due to non-modifiable causes such as congestive heart failure) the observed pooled treatment effect was enhanced and the moderate to high heterogeneity was reduced to low heterogeneity.

Bleeding as defined by ISTH criteria was significantly increased in both trials.[6] Bleeding is expected when antithrombotic therapy is intensified with the addition of an anticoagulant to aspirin. It is reassuring however that in both trials, no significant excess of severe or irreversible harm bleeds such as fatal or critical organ haemorrhage occurred. In both the COMPASS and VOYAGER trials major bleeding was 'front loaded' meaning that the relative increase in major bleeding primarily occurred in the first year after treatment initiation, with no relative increase in bleeding observed thereafter. The relative benefit to risk comparison of events prevented vs. caused on an annualized basis is shown in *Figure 4*.[9]

In the subset of COMPASS symptomatic LE-PAD patients who were more closely matched to the VOYAGER trial population, we observed a similar magnitude reduction in the composite outcome, and the secondary outcomes of MACE or MALE, with lower heterogeneity observed in the pooled estimates. When, causes of CV death not attributable to fatal or non-fatal MI or ischaemic stroke were removed, there was greater magnitude and significance of the reduction observed with rivaroxaban plus aspirin as compared to aspirin alone. Overall, the robust findings of this meta-analysis should assist both cardiologists and vascular specialists who see patients with CAD and PAD, and the vascular practitioners who perform LE revascularization, to initiate low-dose rivaroxaban plus aspirin in their patients, given the reductions in MACE and MALE they will achieve.

The COMPASS and VOYAGER were randomized trials with strict inclusion and exclusion criteria. To determine the impact of these therapies as they are used in clinical practice, the XATOA registry, an international real-world registry of patients with CAD and PAD who are treated with low-dose rivaroxaban plus aspirin has been developed.[16] From this registry, we will learn how the results of large randomized trials such as COMPASS and VOYAGER are translated into practice, including which patients are selected for treatment, their concomitant medications, and the incidence of future vascular and bleeding risks in a real-world population.

Strengths and limitations

The strengths of this analysis include the combination of two large trials of PAD patients in which similar randomized therapies and outcomes were evaluated. In both trials for efficacy, an intention-to-treat analysis was used, and while this may underestimate the treatment effects among patients who adhere to low-dose rivaroxaban plus aspirin long-term, it provides a less biased and conservative estimate of the treatment effect. In parallel, an on-treatment analysis was used to assess safety outcomes. Furthermore, in both trials PAD patients

were well treated with other medical therapies such as statins and ACE/ARB's, thus the effects of combination low-dose rivaroxaban plus aspirin over aspirin alone are observed over and above good medical management of these PAD populations. By combining the COMPASS and VOYAGER trials in a meta-analysis we show the consistency of the low-dose rivaroxaban plus aspirin compared to aspirin alone, and the benefit and risk profile across different types of PAD patients, and for different outcomes, addressing questions frequently asked by clinicians. The summary effects across the primary and secondary efficacy outcomes were moderately to highly heterogeneous, whereas less heterogeneity was observed for the bleeding outcomes. The heterogeneity was reduced substantially when CV death was restricted to fatal or non-fatal MI or ischaemic stroke. Furthermore, it is interesting to note when the COMPASS trial population was limited to symptomatic LE-PAD patients only, and better matched to the VOYAGER PAD population, the heterogeneity for efficacy outcomes also decreased. However, in both examinations of reduced heterogeneity, we recognize that the statistical power was lower due to the lower number of events. The different pattern of point estimates reflects both random error and variation in true effect sizes reflecting differences in the study populations (i.e. type of PAD, proportion with concomitant CAD or critical limb ischaemia, and responsiveness of outcomes linked to athero-thrombo-embolism) between COMPASS and VOYAGER. A future individual patient meta-analysis may help further understand the observed variation.

Conclusions

Among patients with PAD, low-dose rivaroxaban plus aspirin is superior to aspirin alone in reducing CV and limb outcomes including acute limb ischaemia and major vascular amputation. This is offset by an increase in major bleeding, but no excess of severe bleeding. The consistency of findings in these trials support consideration of rivaroxaban in PAD patients across a broad spectrum of disease.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability

The data underlying this article are available in the article and in its online supplementary material. Sonia S. Anand, Leanne Dyal, Michael Szareck, and Marc Bonaca had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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