Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

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Summary

Background Patients with peripheral artery disease have an increased risk of cardiovascular morbidity and mortality. Antiplatelet agents are widely used to reduce these complications.

Methods This was a multicentre, double-blind, randomised placebo-controlled trial for which patients were recruited at 602 hospitals, clinics, or community practices from 33 countries across six continents. Eligible patients had a history of peripheral artery disease of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease), of the carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or coronary artery disease with an ankle–brachial index of less than 0·90. After a 30-day run-in period, patients were randomly assigned (1:1:1) to receive oral rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or to aspirin once a day (100 mg and rivaroxaban placebo twice a day). Randomisation was computer generated. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. The primary outcome was cardiovascular death, myocardial infarction or stroke; the primary peripheral artery disease outcome was major adverse limb events including major amputation. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings Between March 12, 2013, and May 10, 2016, we enrolled 7470 patients with peripheral artery disease from 558 centres. The combination of rivaroxaban plus aspirin compared with aspirin alone reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (126 [5%] of 2492 *vs* 174 [7%] of 2504; hazard ratio [HR] 0·72, 95% CI 0·57–0·90, p=0·0047), and major adverse limb events including major amputation (32 [1%] *vs* 60 [2%]; HR 0·54 95% CI 0·35–0·82, p=0·0037). Rivaroxaban 5 mg twice a day compared with aspirin alone did not significantly reduce the composite endpoint (149 [6%] of 2474 *vs* 174 [7%] of 2504; HR 0·86, 95% CI 0·69–1·08, p=0·19), but reduced major adverse limb events including major amputation (40 [2%] *vs* 60 [2%]; HR 0·67, 95% CI 0·45–1·00, p=0·05). The median duration of treatment was 21 months. The use of the rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (77 [3%] of 2492 *vs* 48 [2%] of 2504; HR 1·61, 95% CI 1·12–2·31, p=0·0089), which was mainly gastrointestinal. Similarly, 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).

Interpretation Low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events when compared with aspirin alone. Although major bleeding was increased, fatal or critical organ bleeding was not. This combination therapy represents an important advance in the management of patients with peripheral artery disease. Rivaroxaban alone did not significantly reduce major adverse cardiovascular events compared with asprin alone, but reduced major adverse limb events and increased major bleeding.

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Introduction

Patients with carotid artery disease or with peripheral artery disease of the lower extremities are at high risk for major adverse cardiovascular events,[1–3] and patients with peripheral artery disease of the lower extremities are also at high risk for major adverse limb events such as severe limb ischaemia and amputation.[4] In addition to smoking cessation and exercise, statins, angiotensin converting enzyme (ACE) inhibitors, and antiplatelet agents (aspirin or a P2Y12 inhibitor) are used to reduce vascular complications.[4–6] Anticoagulant therapies have not been shown to be superior to antiplatelet therapy in peripheral artery disease and have unacceptably high rates of major bleeding.[7] Specifically, high intensity (international

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See Online for appendix

Research in context

Evidence before this study

Patients with peripheral artery disease are at high risk for major cardiovascular and limb events. The mainstay of treatment for patients with peripheral artery disease includes use of a single antiplatelet agent daily to prevent major adverse cardiovascular events. Other antithrombotic regimens have been tested in patients with peripheral artery disease including vitamin K antagonists and newer antiplatelet agents including P2Y12 antagonists used alone or in combination with aspirin, but none have been shown to be superior to antiplatelet therapy alone.

Added value of this study

The peripheral artery disease analysis of the COMPASS trial shows that use of low-dose rivaroxaban twice a day, together with aspirin 100 mg once a day, reduces cardiovascular death, myocardial infarction, stroke, and acute limb ischaemia and amputation, compared with aspirin alone. Although there is an increase in bleeding leading to more hospital admissions, there is no excess of fatal bleeding, intracranial bleeding, or bleeding into critical organs. Thus, the net clinical benefit favours the use of low-dose rivaroxaban plus aspirin.

Implications of all the available evidence

The combination of low dose rivaroxaban twice a day with aspirin could replace aspirin alone as standard of care in patients with stable peripheral artery disease who are not at high risk for bleeding.

normalised ratio [INR] of 3–4·5) and moderate intensity warfarin (INR 2–3) used with aspirin does not reduce major adverse cardiovascular events but does increase the risk of life-threatening bleeding, including intracranial haemorrhage.[7,8] Furthermore, ticagrelor was not superior to clopidogrel in reducing major adverse cardiovascular events or major adverse limb events in patients with peripheral artery disease.[9] Dual antiplatelet therapy is not consistently superior to single antiplatelet therapy in reducing major adverse cardiovascular events or major adverse limb events in patients with peripheral artery disease.[10,11] Vorapaxar, a platelet receptor modulator, did not reduce major adverse cardiovascular events in patients with peripheral artery disease but acute limb ischaemia was significantly reduced, and there was an increase in moderate and severe bleeding.[12]

Rivaroxaban, an oral factor Xa inhibitor, is effective in treating venous thromboembolism,[13] and has been shown to prevent thromboembolic events in atrial fibrillation.[14] Low dose rivaroxaban prevents venous thromboembolism after orthopaedic surgery,[15] and the Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS-2) trial[16] showed that low-dose rivaroxaban (2·5 mg twice a day) used in addition to dual antiplatelet therapy reduced major adverse cardiovascular events in patients with acute coronary syndromes, although rivaroxaban alone (5 mg twice a day) increased major, intracranial, and fatal bleeds. In the COMPASS trial,[17] we sought to identify whether a low dose of rivaroxaban given twice a day when used with aspirin or without aspirin, was more effective than aspirin alone in reducing major adverse cardiovascular events and major adverse limb events in patients with peripheral artery disease.

Methods

Study design and participants

The design of COMPASS has been previously published.[17] COMPASS was a multicentre, double-blind, randomised, placebo-controlled trial comparing low-dose rivaroxaban with aspirin or rivaroxaban alone (with aspirin placebo) versus aspirin alone (with rivaroxaban placebo) for prevention of cardiovascular death, myocardial infarction, and stroke in patients with coronary artery disease or peripheral artery disease who were receiving other proven therapies. Patients with a need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, oral anticoagulant therapy, strong inhibitors of CYP 3A4, strong inducers of CYP 3A4, or other medication with known interactions with rivaroxaban were excluded from the trial.[17] Patients were enrolled from 602 hospitals, clinics, or community practices in 33 countries across six continents (appendix). To be eligible for trial inclusion, patients with peripheral artery disease were required to have one of the following: aorto-femoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularisation of the iliac, or infrainguinal arteries; or limb or foot amputation for arterial vascular disease; or intermittent claudication and one or more of either an ankle brachial index (ABI) of less than 0·90 or a peripheral artery stenosis (≥50%) documented by angiography or duplex ultrasound; or carotid revascularisation or asymptomatic carotid artery stenosis of at least 50% diagnosed by duplex ultrasound or angiography. Because ABI was measured in all trial participants at baseline, patients enrolled with coronary artery disease who had an ABI of less than 0·90 were included in the overall peripheral artery disease cohort. The ABI was calculated by the ratio of the highest limb systolic blood pressure over the highest brachial systolic blood pressure and Doppler measurements were not required. All peripheral artery disease definitions used in COMPASS are found in the appendix.

Patients with a high risk of bleeding, stroke within 1 month, a history of haemorrhagic or lacunar stroke, severe heart failure with a known ejection fraction of less than 30%, or estimated glomerular filtration rate of less than 15 mL/min were excluded. Detailed exclusion criteria have been published.[17] The protocol was approved

by health authorities and institutional review boards in all participating countries and written informed consent was obtained from all participants.

Randomisation and masking

Patients were randomly assigned in a 1:1:1 ratio to receive either low-dose rivaroxaban with aspirin, rivaroxaban alone, or aspirin alone stratified by centre and use of proton-pump inhibitor (PPI). A computer-generated randomisation schedule was generated by the Population Health Research Institute. Each treatment group was double dummy, and the patient, investigators, and central study staff were masked to treatment allocation. Patients who were not already taking a PPI were also randomly assigned to receive pantoprazole or an equivalent placebo. This component of the trial is continuing, and is not reported in this Article.

Procedures

Eligible patients entered a 30-day run-in phase during which time they received rivaroxaban placebo twice a day and aspirin 100 mg once a day, both administered orally. After the run-in period, participants who adhered to the assigned regimen and who did not have any adverse events, were randomly assigned to receive either rivaroxaban 2·5 mg twice a day with aspirin 100 mg once a day, rivaroxaban 5 mg twice a day (with aspirin placebo once a day), or aspirin 100 mg once a day (with rivaroxaban placebo twice a day). At the randomisation visit, patients were assessed for eligibility, adherence to run-in medications, had physical measurements taken including blood pressure and ankle brachial index, and answered questionnaires to obtain data on the participants' health and quality of life. Participants were seen at 1 and 6 months after randomisation and 6 month intervals thereafter. Patients were assessed at follow-up visits to record outcomes and adverse events, and to enhance adherence. Additional follow-up visits were done via telephone at 3 and 9 months.

Outcomes

The primary cardiovascular efficacy outcome was the composite of cardiovascular death, myocardial infarction or stroke. Peripheral artery disease outcomes were prespecified and included: acute limb ischaemia, chronic limb ischaemia, and amputation (appendix). Acute limb ischaemia was defined as limb threatening ischaemia with evidence of acute arterial obstruction by radiological criteria or a new pulse deficit leading to an intervention (ie, surgery, thrombolysis, peripheral angioplasty, or amputation) within 30 days of symptoms onset. All cases of reported acute limb ischaemia were verified using a diagnostic algorithm developed for use in COMPASS, and an adjudicator reviewed the event if the diagnostic algorithm did not confirm the event. Chronic limb ischaemia was defined as severe limb ischaemia leading to a vascular intervention. Major amputation was defined as amputations due to a vascular event above the forefoot, or

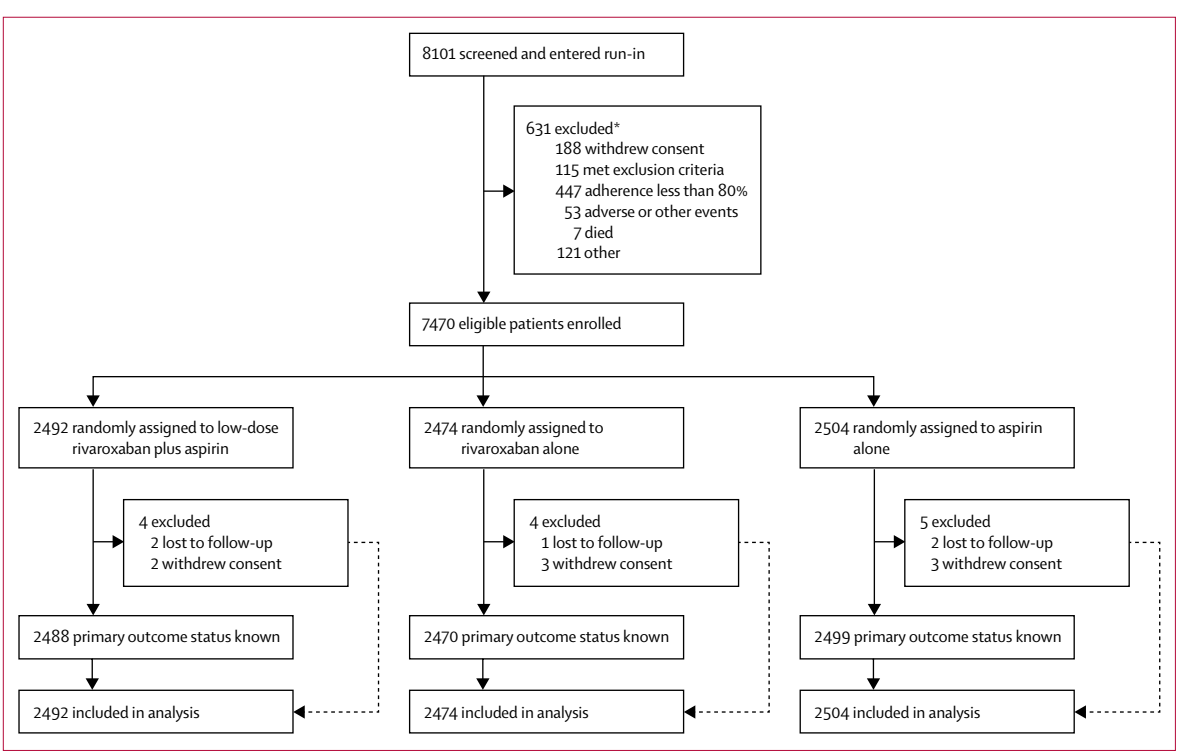

Figure 1: **Trial profile of participants with peripheral artery disease**
*Some participants had more than one reason for exclusion after the run-in period.

	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)
Mean age, years	67·9 (8·45)	67·8 (8·49)	67·8 (8·47)
Sex			
Female	718 (29%)	674 (27%)	717 (29%)
Male	1774 (71%)	1800 (73%)	1787 (71%)
Mean body-mass index, kg/m²	28·3 (5·0)	28·4 (4·8)	28·4 (5·0)
Blood pressure			
Mean systolic blood pressure, mm Hg	138·9 (18·5)	138·6 (18·3)	138·6 (18·2)
Mean diastolic blood pressure, mm Hg	77·7 (10·1)	77·5 (10·2)	77·8 (10·3)
Smoking status			
Current	682 (27·4)	685 (27·7)	685 (27·4)
Former	1147 (46)	1154 (46·6)	1143 (45·6)
Never	663 (26·6)	635 (25·7)	676 (27)
Risk factors for PAD			
Median total cholesterol, mmol/L	4·2 (3·6–5·0)	4·2 (3·6–5·0)	4·2 (3·6–5·0)
Hypertension	1966 (78·9)	1939 (78·4)	2017 (80·6)
Diabetes	1100 (44·1)	1083 (43·8)	1104 (44·1)
History of CAD	1656 (66·5)	1609 (65)	1641 (65·5)
History of stroke	171 (6·9)	177 (7·2)	154 (6·2)
History of PAD			
Previous aorta-femoral or lower extremity bypass surgery, PTA of iliac, or infrainguinal artery	668 (26·8)	703 (28·4)	674 (26·9)
History of intermittent claudication and ABI <0·90 or substantial peripheral arterial stenosis ≥50%	1142 (45·8)	1120 (45·3)	1140 (45·5)
Previous limb or foot amputation	116 (4·7)	107 (4·3)	112 (4·5)
Symptomatic PAD of lower extremities*	1409 (56·5)	1361 (55·0)	1359 (54·3)
Carotid artery disease†	617 (24·8)	622 (25·1)	680 (27·2)
Symptomatic PAD‡	2026 (81·3)	1983 (80·1)	2039 (81·4)
CAD and ABI <0·90§	466 (18·7)	491 (19·8)	465 (18·6)
ABI			
Normal ≥0·90	1226 (49·2)	1187 (48)	1191 (47·6)
0·70–0·90	979 (39·3)	949 (38·4)	984 (39·3)
≤0·70	211 (8·5)	268 (10·8)	249 (9·9)
eGFR <60 mL/min	688 (27·6)	681 (27·5)	706 (28·2)
Medications			
Antiplatelet	2185 (87·7)	2123 (85·8)	2187 (87·3)
Lipid lowering	2088 (83·8)	2074 (83·8)	2074 (82·8)
ACE-I or ARB	1715 (68·8)	1757 (71)	1765 (70·5)
β blocker	1477 (59·3)	1479 (59·8)	1485 (59·3)
Non-study PPI use	826 (33·1)	812 (32·8)	815 (32·5)

Data are mean (SD), n (%), or median (IQR). PAD=peripheral artery disease. CAD=coronary artery disease. PTA=percutaneous transluminal angioplasty. ABI=ankle brachial index. eGFR=estimated glomerular filtration rate. ACE-I=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. PPI=proton-pump inhibitor. *Defined as intermittent claudication with ABI <0·90 or stenosis of ≥50%; or previous aorta-femoral or lower extremity bypass surgery, percutaneous transluminal angioplasty of iliac or infrainguinal arteries, or limb or foot amputation for arterial vascular disease. †Defined as previous carotid endarterectomy or stent or asymptomatic carotid artery stenosis of ≥50%. ‡Symptomatic PAD is the sum of symptomatic PAD of lower extremities and carotid artery disease. §Asymptomatic PAD of lower extremities.

Table 1: **Baseline characteristics**

defined as minor amputation if involving the forefoot and digits. Key composite outcomes for peripheral artery disease were major adverse limb events (defined as the development of acute or chronic limb ischaemia over the course of the trial follow-up, including any additional major amputations due to a vascular event that was not included in acute or chronic limb ischaemia), the composite of major adverse cardiovascular events and major adverse limb events, and the composite of major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke) and major adverse limb events including major amputations.

The primary safety outcome was major bleeding and we used a modification of the International Society on Thrombosis and Hemostasis (ISTH) criteria for major bleeding, defined as the composite of bleeding that was fatal, symptomatic bleeding into a critical organ, surgical site requiring reoperation, or requiring hospitalisation (including presentation to an acute care facility without an overnight stay). The net clinical benefit outcome for the overall trial was prespecified as cardiovascular death, myocardial infarction, stroke, or fatal or critical bleeding. For peripheral artery disease, we also examined the net clinical benefit of major adverse cardiovascular events or major adverse limb events including major amputation offset by fatal or critical organ bleeds.

Statistical analysis

The overall trial was designed to have at least 90% power to detect a 20% relative risk reduction of major adverse cardiovascular events in each of the rivaroxaban treatment groups compared with aspirin. The overall trial, which enrolled 27 395 participants, was an event-driven trial that was planned to be continued until at least 2200 participants had a confirmed primary outcome event.

The peripheral artery disease analysis was a pre-specified subgroup with no specific plan to adjust for multiple testing. Adjustments for multiple testing were only done for the main study. The peripheral artery disease outcome definitions were specified in advance and we verified events using an algorithm and, when needed, adjudication by a vascular disease expert physician. All outcomes that occurred after randomisation and before the recommendation of the data and safety monitoring board to stop the trial on Feb 6, 2017, were included in the analysis. At this time the only information divulged to the members of the peripheral artery disease sub-committee was information included in the press release by the company that the overall results on the primary outcome were clearly favourable. No information on any subgroups or numerical details of results were shared with the peripheral artery disease committee who finalised the analysis plan without any knowledge of the results in the peripheral artery disease subgroup or information from individual patients. Each of the two rivaroxaban-based regimens were compared with the aspirin control group. We did these two comparisons using two separate stratified log-rank tests. Analysis of outcomes were based on Kaplan-Meier estimates of cumulative risk over time. We estimated hazard ratios (HR), relative risk reduction and corresponding 95% CIs using two separate stratified Cox

	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)	Low-dose rivaroxaban plus aspirin versus aspirin alone		Rivaroxaban alone versus aspirin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Primary and secondary outcomes							
Cardiovascular death, stroke, myocardial infarction*	126 (5%)	149 (6%)	174 (7%)	0·72 (0·57–0·90)	0·0047	0·86 (0·69–1·08)	0·19
Coronary heart disease death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	115 (5%)	147 (6%)	169 (7%)	0·68 (0·53–0·86)	0·0011	0·88 (0·70–1·10)	0·25
Cardiovascular death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	142 (6%)	168 (7%)	198 (8%)	0·71 (0·57–0·88)	0·0019	0·86 (0·70–1·05)	0·14
Myocardial infarction	51 (2%)	56 (2%)	67 (3%)	0·76 (0·53–1·09)	..	0·84 (0·59–1·20)	..
Stroke	25 (1%)	43 (2%)	47 (2%)	0·54 (0·33–0·87)	..	0·93 (0·61–1·40)	..
Cardiovascular death	64 (3%)	66 (3%)	78 (3%)	0·82 (0·59–1·14)	..	0·86 (0·62–1·19)	..
Death	129 (5%)	134 (5%)	142 (6%)	0·91 (0·72–1·16)	..	0·95 (0·75–1·20)	..
Prespecified limb outcomes							
Acute limb ischaemia‡	19 (1%)	19 (1%)	34 (1%)	0·56 (0·32–0·99)	0·042	0·57 (0·32–1·00)	0·046
Chronic limb ischaemia‡	16 (1%)	18 (1%)	24 (1%)	0·67 (0·35–1·26)	0·21	0·76 (0·41–1·40)	0·37
Major adverse limb event‡	30 (1%)	35 (1%)	56 (2%)	0·54 (0·35–0·84)	0·0054	0·63 (0·41–0·96)	0·032
All vascular amputations	11 (<1%)	17 (1%)	28 (1%)	0·40 (0·20–0·79)	0·0069	0·61 (0·33–1·11)	0·10
Major amputation‡	5 (<1%)	8 (<1%)	17 (1%)	0·30 (0·11–0·80)	0·011	0·46 (0·20–1·08)	0·068
Major adverse limb event plus major amputation§	32 (1%)	40 (2%)	60 (2%)	0·54 (0·35–0·82)	0·0037	0·67 (0·45–1·00)	0·046
Key composite outcomes for PAD							
Cardiovascular death, stroke, myocardial infarction or major adverse limb event	155 (6%)	184 (7%)	222 (9%)	0·69 (0·56–0·85)	0·0004	0·83 (0·68–1·01)	0·065
Cardiovascular death, stroke, myocardial infarction or major adverse limb event including major amputation	157 (6%)	188 (8%)	225 (9%)	0·69 (0·56–0·85)	0·0003	0·84 (0·69–1·02)	0·077

Data are n (%) unless otherwise indicated. HR=hazard ratio. PAD=peripheral artery disease. *Prespecified primary outcome of the overall trial. †Prespecified secondary outcomes of the overall trial. ‡Prespecified PAD outcomes. §An additional 11 major amputations of a vascular cause were done that were unlinked to acute or chronic limb ischaemia, two in the low-dose rivaroxaban plus aspirin group, five in the rivaroxaban alone group, and four in the aspirin alone group.

Table 2: **Efficacy of rivaroxaban compared with aspirin in patients with peripheral artery disease**

proportional hazards models. We verified linearity and proportionality of the hazard ratios. We examined treatment effects in subgroups of patients with peripheral artery disease including by location of disease and by key baseline characteristics.

An independent data and safety monitoring board monitored the overall study with formal stopping guidelines for efficacy and non-formal guidelines for safety. Details are provided elsewhere.[17,18] This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Role of the funding source

The study was designed by the Steering Committee and the sponsor, Bayer AG. Site management, data collection, and data analysis were coordinated at the Population Health Research Institute, which is affiliated with Hamilton Health Sciences and McMaster University in ON, Canada. The authors had full access to the data and take responsibility for the results.

Results

Between March 12, 2013, and May 10, 2016, 27 395 patients were enrolled into the overall COMPASS trial. The planned original sample size for COMPASS was 19 500 patients of which we planned to enrol at least 5000 patients with peripheral artery disease (25% of the total). However the sample size was increased due to slower than expected recruitment and a lower than expected aggregate event rate of the primary outcome, 6048 participants with symptomatic peripheral artery disease were enrolled and an additional 1422 patients enrolled with coronary artery disease who had an ABI of less than 0·90 at baseline were included in the peripheral artery disease cohort before the working group became aware of the trial results, for a total of 7470 patients with peripheral artery disease.

The independent data and safety monitoring board recommended early termination of the rivaroxaban and aspirin portion of the overall study on Feb 6, 2017, having observed a reduction in the primary outcome in favour of the low-dose rivaroxaban plus aspirin group, which met their formal efficacy stopping guidelines criteria. All events that occurred by this date are included in the analysis. 8101 patients with peripheral artery disease were screened and entered the run-in portion of the study (figure 1). Of the 7470 patients classified as having peripheral artery disease, 6048 met the inclusion criteria for symptomatic peripheral artery disease, including 4129 (55%) with symptomatic peripheral artery disease of the lower extremities, and 1919 (26%) who had previous carotid revascularisation

For the **press release** see http://news.bayer.com/baynews/baynews.nsf/id/Phase-III-COMPASS-study-Bayers-Rivaroxaban-Patients-Coronary-Peripheral-Artery-Disease-Shows?OpenDocument&sessionID=1507028346

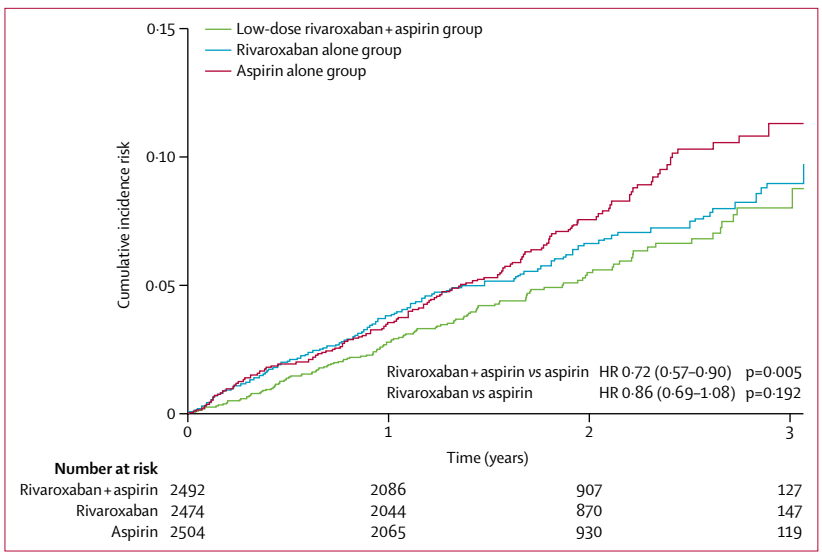

Figure 2: **Cumulative incidence of the primary efficacy outcome**

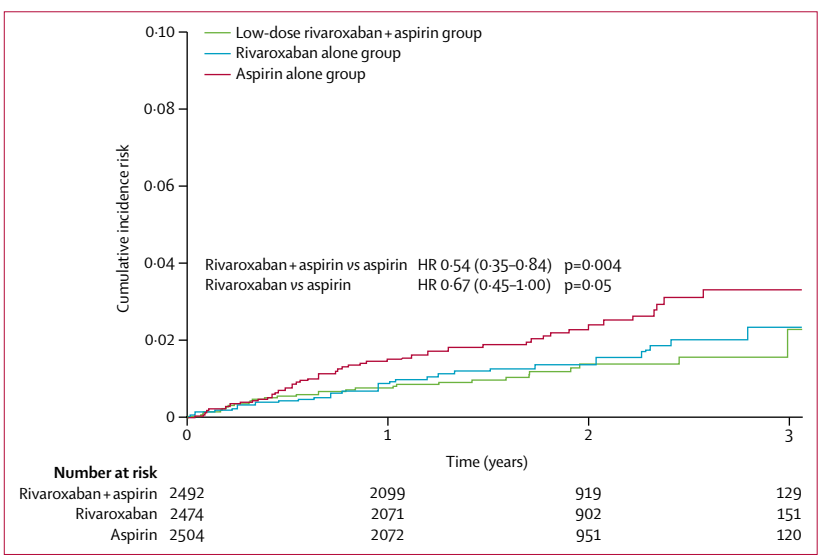

Figure 3: **Cumulative incidence of individual components of major adverse limb events including major amputation**

or carotid stenosis of at least 50%. An additional 1422 patients (20%) who met the trial inclusion criteria for coronary artery disease who had an ABI of less than 0·90 were included and designated as having asymptomatic peripheral artery disease. 7457 patients (>99%) had complete follow-up (figure 1). The median duration of the follow-up was 21 months. At the final follow up visit, 392 (17%) of 2345 participants randomly assigned to rivaroxaban plus aspirin, 418 (18%) of 2322 participants assigned to rivaroxaban alone, and 378 (16%) of 2343 participants assigned to aspirin alone were permanently off study drug. Efficacy and safety outcomes are presented per 100 patient-years of follow-up in the appendix.

The results for each peripheral artery disease subgroup for key efficacy and safety outcomes are shown in the appendix. The characteristics of those with peripheral artery disease were well balanced between the three treatment groups (table 1). The mean age was 67·8 years (SD 8·5), 5361 (72%) were men, 5496 (74%) were current or former smokers, and 4906 (66%) also had coronary artery disease.

The primary outcome of cardiovascular death, myocardial infarction, or stroke occurred in 126 (5%) of 2492 patients with peripheral artery disease who received low-dose rivaroxaban plus aspirin and in 174 (7%) of 2504 patients who received aspirin alone. (table 2, figure 2) Low-dose rivaroxaban plus aspirin was superior to aspirin alone (hazard ratio [HR] 0·72, 95% CI 0·57–0·90, p=0·0047). By contrast, the primary outcome in the rivaroxaban alone group was not significantly superior to that seen in the aspirin alone group (149 [6%] of 2474 *vs* 174 [7%] of 2504; HR 0·86, 95% CI 0·69–1·08, p=0·19). A similar pattern was observed for the composite of: coronary heart disease deaths, myocardial infarction, ischaemic stroke, and acute limb ischaemia with the low-dose rivaroxaban plus aspirin group being significantly superior to the aspirin alone group (115 [5%] of 2492 *vs* 169 [7%] of 2504; HR 0·68, 95% CI 0·53–0·86, p=0·0011) and the rivoroxaban alone group showing no difference to the aspirin alone group (147 [6%] of 2474 *vs* 169 [7%] of 2504; HR 0·88, 95% CI 0·70–1·10, p=0·25). The combined outcome of cardiovascular death, myocardial infarction, ischaemic stroke, or acute limb ischaemia was less frequent in the low-dose rivaroxaban plus aspirin group than in the aspirin alone group (142 [6%] of 2492 *vs* 198 [8%] of 2504; HR 0·71, 95% CI 0·57–0·88, p=0·0019), but similar between the rivaroxaban alone and aspirin alone groups (168 [7%] of 2474 *vs* 198 [8%] of 2504; HR 0·86, 95% CI 0·70–1·05, p=0·14; table 2). There was no significant reduction in total mortality in the low-dose rivaroxaban plus aspirin group when compared with the aspirin alone group (HR 0·91, 95% CI 0·72–1·16, p=0·45).

Major adverse limb events were also significantly lower in the low-dose rivaroxaban plus aspirin group compared with the aspirin alone group (30 [1%] of 2492 *vs* 56 [2%] of 2504; HR 0·54, 95% CI 0·35–0·84, p=0·0054). Similarly, major adverse limb events were also significantly lower in the rivaroxaban alone group than in the aspirin alone group (35 [1%] of 2474 *vs* 56 [2%] of 2504; HR 0·63, 95% CI 0·41–0·96, p=0·032). The rate of acute limb ischaemia was also significantly lower in the low-dose rivaroxaban plus aspirin group and the rivaroxaban alone group when compared with the aspirin alone group (table 2). Major amputations were fewer in the low-dose rivaroxaban plus aspirin group when compared with aspirin alone (HR 0·30, 95% CI 0·11–0·80), but no significant reduction was observed for rivaroxaban alone group when compared with the aspirin alone group (HR 0·46, 95% CI 0·20–1·08). Although most major amputations of

	Low-dose rivaroxaban plus aspirin group (n=2492)	Rivaroxaban alone group (n=2474)	Aspirin alone group (n=2504)	Low-dose rivaroxaban plus aspirin versus aspirin alone		Rivaroxaban alone versus asprin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Major bleeding*	77 (3%)	79 (3%)	48 (2%)	1·61 (1·12–2·31)	0·0089	1·68 (1·17–2·40)	0·0043
Fatal bleeding	4 (<1%)	5 (<1%)	3 (<1%)	..	..	..	..
Non-fatal symptomatic intracranial haemorrhage	4 (<1%)	3 (<1%)	8 (<1%)	..	..	..	..
Non-fatal, non-intracranial haemorrhage symptomatic bleeding into a critical organ	13 (1%)	18 (1%)	8 (<1%)	1·55 (0·64–3·74)	0·33	2·15 (0·94–4·96)	0·065
Other major bleeding (surgical site bleeding requiring reoperation or bleeding leading to hospitalisation	56 (2%)	53 (2%)	29 (1%)	1·94 (1·24–3·04)	0·0031	1·86 (1·18–2·92)	0·0064
Fatal or symptomatic bleeding into a critical organ	21 (1%)	26 (1%)	19 (1%)	1·10 (0·59–2·05)	..	1·39 (0·89–3·09)	..
Fatal or symptomatic bleeding into a critical organ or surgical site bleeding leading to re-operation	25 (1%)	29 (1%)	22 (1%)	1·13 (0·64–2·01)	..	1·34 (0·77–2·52)	..
ISTH major bleeding	64 (3%)	53 (2%)	40 (2%)	1·61 (1·08–2·39)	..	1·34 (0·89–2·02)	..
Sites of bleeding							
Gastrointestinal	41 (2%)	26 (1%)	18 (1%)	2·28 (1·31–3·96)	0·0027	1·46 (0·80–2·66)	0·22
Intracranial	5 (<1%)	6 (<1%)	9 (<1%)	0·56 (0·19–1·66)	..	0·68 (0·24–1·91)	..
Genitourinary	3 (<1%)	14 (1%)	2 (<1%)	..	..	..	..
Ocular	7 (<1%)	8 (<1%)	3 (<1%)	..	..	..	..
Skin	5 (<1%)	6 (<1%)	8 (<1%)	..	..	..	..
Respiratory	4 (<1%)	4 (<1%)	0	..	..	..	..
Other	15 (1%)	15 (1%)	10 (<1%)	..	..	..	..
Minor bleeding	198 (8%)	170 (7%)	141 (6%)	1·43 (1·15–1·77)	0·0011	1·23 (0·98–1·54)	0·069
Net benefit							
Cardiovascular death, myocardial infarction, stroke, and critical organ or fatal bleeding†	140 (6%)	168 (7%)	185 (7%)	0·75 (0·60–0·94)	0·011	0·92 (0·75–1·13)	0·43
Cardiovascular death, myocardial infarction, stroke or major adverse limb events, major amputation, or fatal or critical organ bleeding	169 (7%)	207 (8%)	234 (9%)	0·72 (0·59–0·87)	0·0008	0·89 (0·74–1·07)	0·23

Data are n (%) unless otherwise indicated. HR=hazard ratio. ISTH=International Society of Thrombosis and Hemostasis.*Includes four components of prespecified major bleeding definition summarised hierarchically. †Prespecified net clinical benefit outcome.

Table 3: **Safety outcomes and net benefit for patients with peripheral artery disease**

vascular cause were reported in conjunction with acute or chronic limb ischaemia, two events in the low-dose rivaroxaban plus aspirin group, five in the rivaroxaban alone group, and four in the aspirin group were not. Taken together, compared to aspirin, the combination of rivaroxaban plus aspirin significantly reduced the combination major adverse limb events plus all major amputations of a vascular cause by 46% (HR 0·54, 95% CI 0·35–0·82, p=0·0037) and a reduction of 33% was seen with rivaroxaban alone when compared with aspirin alone (HR 0·67, 95% CI 0·45–1·00, p=0·046; table 2, figure 3).

The composite of major adverse cardiovascular events or major adverse limb events was also significantly lower in the low-dose rivaroxaban plus aspirin group than in the aspirin alone group (155 [6%] of 2492 *vs* 222 [9%] of 2504; HR 0·69, 95% CI 0·56–0·85, p=0·0004) but was not lower in the rivaroxaban alone group than in the aspirin alone group (184 [7%] of 2474 *vs* 222 [9%] of 2504; HR 0·83, 95% CI 0·68–1·01, p=0·065; table 2) Additionally, there were fewer major amputations such that the addition of this outcome reinforced the reductions in major adverse cardiovascular events or major adverse limb events including major amputation leading to a 31% risk reduction with low-dose rivaroxaban plus aspirin versus aspirin alone (p=0·0003; appendix), but there were no significant reductions in this outcome with rivaroxaban alone versus aspirin alone (p=0·077; table 2)

Major bleeding occurred in 77 (3%) of 2492 patients who had low-dose rivaroxaban plus aspirin, 79 (3%) of 2474 patients who had rivaroxaban alone, and in 48 patients (2%) of 2504 who had aspirin alone (table 3). There was a relative increase in major bleeding in the low-dose rivaroxaban plus aspirin group compared with the aspirin alone group (HR 1·61, 95% CI 1·12–2·31, p=0·0089) and also in the rivaroxaban alone group when compared with aspirin alone (HR 1·68, 95% CI 1·17–2·40; p=0·0043). No differences in fatal bleeding or non-fatal intracranial haemorrhages or symptomatic bleeding into a critical organ were observed between any

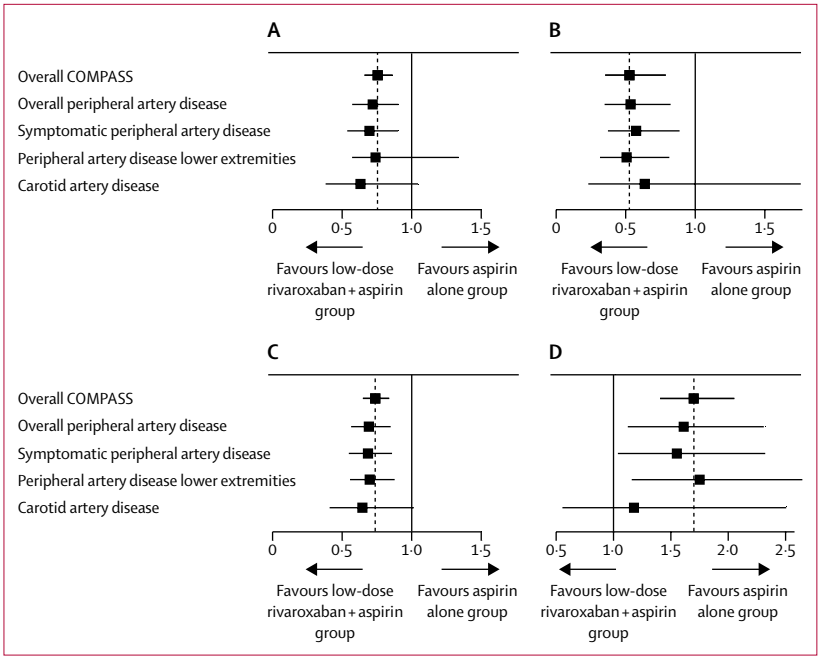

Figure 4: **Analyses of primary and secondary outcomes**
Hazard ratios and 95% CI are shown for all subgroups of patients with peripheral artery disease for major adverse cardiovascular events (A) and major adverse limb events including major amputation (B), major adverse cardiovascular or limb events including major amputation (C) and for major bleeding (D). The dotted line indicates the point estimate for the overall COMPASS trial population (n=27 395).

of the treatment groups. Other major bleeding including surgical site bleeding requiring re-operation or bleeding leading to hospitalisation was significantly increased in patients receiving the low-dose rivaroxaban plus aspirin than in the aspirin alone group (HR 1·94, 95% CI 1·24–3·04, p=0·0031); similarly, this increase was also seen in the rivaroxaban alone group when compared with the asprin alone group (HR 1·86, 95% CI 1·18–2·92, p=0·0064). The most common site of bleeding for all groups was gastrointestinal (table 3).

The prespecified net clinical benefit outcome consisting of cardiovascular death, myocardial infarction, stroke, and fatal or critical organ bleeding occurred in 140 (6%) of 2492 patients with low-dose rivaroxaban plus aspirin and in 185 (7%) of 2504 with aspirin alone (HR 0·75, 95% CI 0·60–0·94, p=0·011) and in 168 (7%) of 2474 patients rivaroxaban alone, which was similar to the aspirin alone group (HR 0·92, 95% CI 0·75–1·13, p=0·43). The net clinical benefit outcome including major adverse cardiovascular events or major adverse limb events including major amputation, or fatal or critical organ bleeding occurred in 169 (7%) rivaroxaban plus aspirin compared to 234 patients (9%) in aspirin alone (HR 0·72, 95% CI 0·59–0·87, p=0·0008). Thus, for every 1000 patients treated 27 major adverse cardiovascular events or major adverse limb events including major amputation would be prevented and one fatal and one critical organ bleed would be caused over a 21-month period. Additional net clinical benefit data are presented in the appendix.

The effects of low-dose rivaraxoban plus aspirin on the efficacy outcomes were consistently better than aspirin alone across various subgroups of peripheral artery disease including that of the lower extremities and carotid artery disease (figure 4). Furthermore, the effects of low-dose rivaroxaban plus aspirin versus aspirin alone on the combined outcome of major adverse cardiovascular events and major adverse limb events including major amputation were consistent in patients with and without diabetes, patients who were current versus former or never smokers, those with lower extremity peripheral artery disease versus other peripheral artery disease, those who had an ABI of less than 0·90 versus ≥0·90, those with symptomatic peripheral artery disease versus patients with coronary artery disease who had an ABI of less than 0·90, and those with and without coronary artery disease. (figure 5)

Discussion

Patients with peripheral artery disease who were enrolled into the COMPASS trial and received the combination of rivaroxaban 2·5 mg twice a day plus aspirin 100 mg a day had fewer major adverse cardiovascular events by 28%, major adverse limb events by 46%, and the composite of major adverse cardiovascular or limb events by 31% compared with the aspirin alone group. Although this combination was associated with an increase in risk of major bleeding, there was no excess in fatal or critical organ bleeds, and the benefit–risk analysis indicates a net benefit. Rivaroxaban 5 mg twice a day, when compared with aspirin alone did not significantly decrease major adverse cardiovascular events, but decreased limb events, and increased major bleeding.

Patients with peripheral artery disease often have widespread atherosclerosis and have an increased risk of atherothrombotic events in multiple vascular territories (ie, coronary, cerebral, and peripheral) and mortality.[19,20] Finding effective and relatively safe antithrombotic regimens for patients with peripheral artery disease to decrease major adverse cardiovascular events and major adverse limb events with an acceptable bleeding profile has been challenging, and there have been few large clinical trials that have been done in patients with peripheral artery disease.[21] Moderate intensity vitamin K antagonist therapy with antiplatelet therapy is associated with a substantial increase in life-threatening bleedings, and no reduction in major adverse cardiovascular events or major adverse limb events.[7] Furthermore, single and dual antiplatelet regimens have not conclusively shown reductions in major adverse limb events.[10,20,22,23] Before COMPASS, the most promising therapies for patients with chronic stable peripheral artery disease were clopidogrel which was superior to aspirin to prevent major adverse cardiac events,[24] although the efficacy in preventing limb events was less clear; and the platelet receptor antagonist vorapaxar[12] used together with other antiplatelet drugs. In TRA2P-TIMI 50,[12] although the

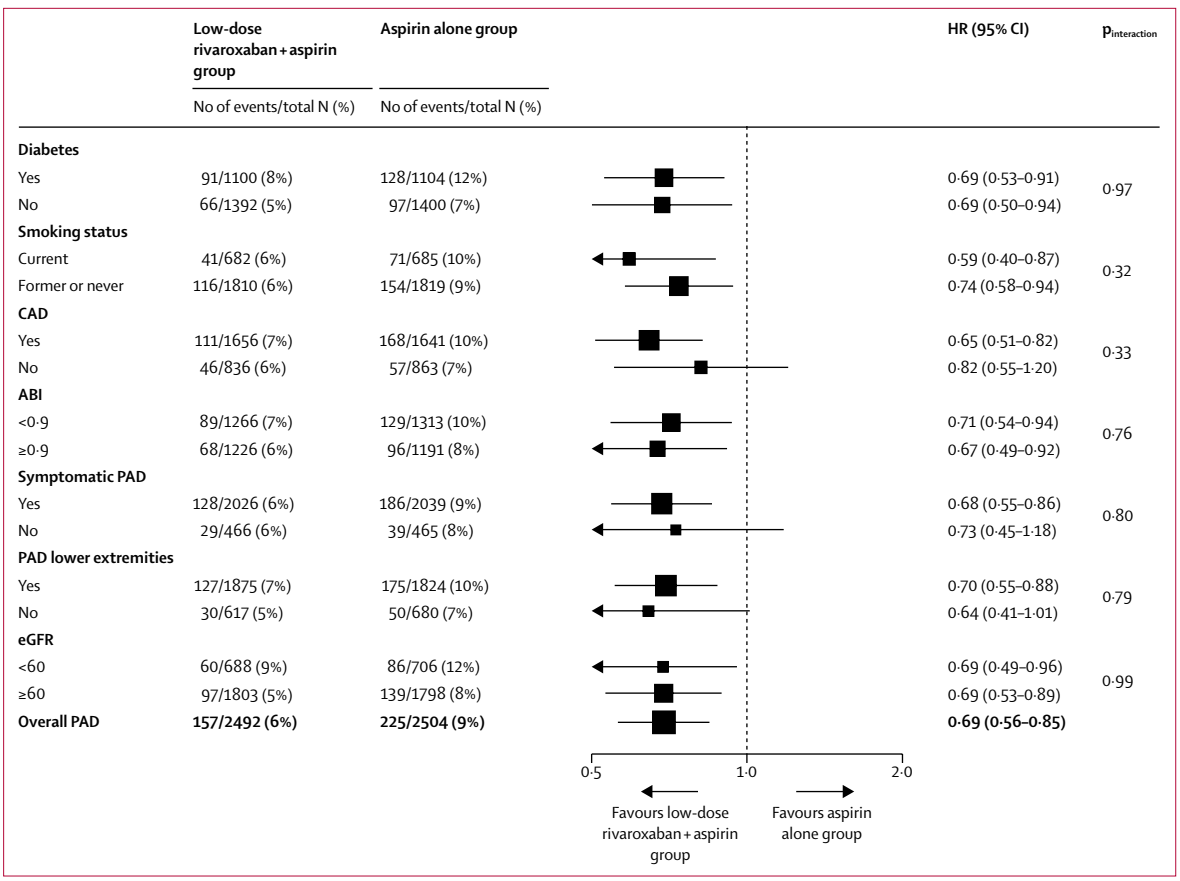

Figure 5: **Subgroup analyses of the COMPASS trial**
Data are hazard ratios and 95% CI.

composite of cardiovascular death, myocardial infarction, and stroke was reduced with vorapaxar in the overall trial, no significant benefit was observed in patients with peripheral artery disease, and there was more moderate or severe bleeding. However, a reduction in acute limb ischaemia and peripheral revascularisation was observed with vorapaxar.

In COMPASS we studied a broad range of patients with peripheral artery disease including those with symptomatic peripheral artery disease of the lower extremities, carotid artery disease and those with coronary artery disease with an ABI of less than 0·90 who were well treated with medical therapy as shown by the high use of statins and ACE inhibitors or angiotensin receptor blockers. The use of proven medical therapies in patients with peripheral artery disease has increased over the past 10 years in clinical trials[7,9] and is likely to contribute to the lower than expected rate of cardiovascular events. This finding emphasises the importance of optimising treatment in the general peripheral artery disease population.[4,25,26] Consistent benefits in the reduction of major adverse cardiovascular events and major adverse limb events occurred with combination of rivaroxaban 2·5 mg plus aspirin compared with aspirin alone but did not occur to the same extent with the rivaroxaban 5 mg twice a day regimen. These results are also consistent with the results of the overall trial, which have been reported separately.[18] Collectively, these results show that in patients with arterial vascular disease, low dose anticoagulants and aspirin have an additive effect. The subgroup of patients with peripheral artery disease but no coronary artery disease was too small to show significance on its own, but the results were directionally consistent with the rest of the patients in the analysis, and the test for heterogeneity was not significant.

In this patient population with stable peripheral artery disease, major adverse limb events (which includes acute and chronic limb ischaemia leading to peripheral artery interventions such as peripheral artery revascularisation and amputation) were reduced by almost half with the combination of low-dose rivaroxaban plus aspirin when compared with aspirin alone. This is an important finding because persistent, severe limb ischaemia threatens limb viability and can lead to amputation, which in turn increases the risk of major adverse cardiovascular events.[19] Furthermore, major amputation is associated with a 50% risk of mortality in the year after

the procedure[27,28] and any therapy that can reduce a patient's risk of developing acute limb ischaemia and major amputation might also reduce their future risk of major adverse cardiovascular events and mortality.[20]

Patients with peripheral artery disease are also at increased risk of bleeding, which is partly explained by their high number of comorbid conditions such as advanced age and renal insufficiency.[7,8,23] In COMPASS, although an increase in major bleeding was observed in both rivaroxaban groups when compared with aspirin alone, there was no excess in fatal or critical organ bleeds, bleeding into a surgical site requiring reoperation, and no excess of major bleeding observed in the peripheral artery disease subgroup compared with the coronary artery disease subgroup.[29] Furthermore, most of the bleedings were gastrointestinal, which rarely leave permanent sequelae. The net clinical benefit in patients with peripheral artery disease, which considers the decrease in major adverse cardiovascular events and the increase in fatal or critical organ bleeding, favours rivaroxaban 2·5 mg plus aspirin compared with aspirin alone, and when major adverse cardiovascular events and major adverse limb events including amputation are combined, the net clinical benefit is similar.

Our study has some limitations. First, since the overall COMPASS study was stopped before its planned number of total events, confidence intervals are slightly less precise than those planned for the primary outcomes, secondary outcomes, and subgroup analyses. Second, a third of patients with peripheral artery disease were taking a PPI at the outset of the trial and, of the remaining patients, half were randomly assigned to receive an active PPI and the other half to placebo. If PPIs reduce gastrointestinal bleeds, it is possible that the high use of PPI might have reduced the risk of bleeding in all the treatment groups. This issue can only be clarified after completion of the PPI component of the COMPASS trial. Third, ABI was measured using a sphygmomanometer and palpation of the artery in most individuals (73%) and a Doppler probe was used in only 24% of participants. The use of the Doppler probe is not common in cardiology clinics, especially outside high-income countries. Nevertheless, the simpler approach to measuring ABI is predictive of future major adverse cardiovascular events in previous studies.[30] Furthermore, patients with coronary artery disease who had no known clinical peripheral artery disease but who had an ABI of less than 0·90 were included in the peripheral artery disease cohort. However, most patients who were included in this analysis had clinical evidence of peripheral artery disease and, importantly, the benefits of treatment of low-dose rivaroxaban and aspirin were consistent across all of the peripheral artery disease subgroups.

In conclusion, low-dose rivaroxaban used together with aspirin was more effective than aspirin alone in preventing both major adverse cardiovascular and limb events including major amputation and increased major bleeding, although there was little fatal or critical organ bleeding. Therefore, the combination of rivaroxaban and aspirin represents an important advance in the management of patients with peripheral artery disease.

Contributors

SSA, JB, JWE, SJC, RGH, and SY conceived the study, reviewed the scientific literature, and were responsible for study design, data collection, data analysis, data interpretation, writing, and reviewing the report. DPL contributed to adjudication and data management. SIB oversaw the statistical analysis. All authors above take responsibility for this report. RD, PW, VA, MA, KK, APM, BSL, SS, JZ, PL-J, MO'D, PJC, DV, NP, LR, JDV, TV, AAA, and KB contributed to data collection, data interpretation, and reviewing the report. AKK, KAAF, DLB, FM, and EC contributed to the study design, data interpretation, and reviewed and commented on the manuscript.

Declaration of interests

SSA has received honoraria from Bayer and Novartis. JWE reports grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, during this study as well as for projects outside the submitted work; grants and personal fees from Janssen, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Sanofi-Aventis outside the submitted work. SJC reports grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, during this study as well as for projects outside the submitted work; grants and personal fees from Janssen, AstraZeneca, Portola and Sanofi-Aventis, outside the submitted work. RD reports grants from Population Health Research Institute during the conduct of this study. PW receives occasional speaker honoraria from Bayer and honoraria for the COMPASS trial National Leader role. VA has received honoraria from Bayer, Bristol-Myers Squibb, Pfizer, Novartis, Merck, Sharp & Dohme, outside the submitted work. MA has received consulting fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, and Pfizer. AKK has received personal fees from Bayer AG, Boehringer-Ingelheim, Daiichi Sankyo Europe, Janssen Pharma, Sanofi SA, Armetheon and a grant from Bayer AG. APM reports personal fees from Novartis, Bayer, Cardiorentis, and Fresenius outside the submitted work. BSL reports a grant from Bayer and personal fees from Pfizer/Bristol-Myers Squibb during the conduct of the study. SS reports financial compensation from Bayer AG for work related to the conduct of the study; grants from Servier and Boehringer Ingelheim; grants, personal fees, and non-financial support from Novartis; grants and personal fees from Thermo Fisher; and personal fees from Pfizer outside the submitted work. JZ reports grants from Population Health Research Institute and personal fees from lectures from Bayer and Boehringer Ingelheim outside the submitted work. MO'D received payment from Population Health Research Institute for participant recruitment stipends. PJC was remunerated by Population Health Research Institute for his role as National Leader in South Africa. His department received support from Population Health Research Institute for the conduct of the study. He has also received personal fees from UptoDate outside the submitted work. DV has received grants and honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/ Pfizer, Daiichi Sankyo, and Johnson & Johnson during the conduct of the study; he also received grants and personal fees from Boehringer Ingelheim, Pfizer, Novartis, and Servier outside the submitted work. LR reports grants from Swedish Heart Lung Foundation, Swedish Diabetes Foundation, Amgen, Bayer AG and grants and personal fees from Boehringer Ingelheim, Merck, Sharp & Dohme, and Novo Nordisk outside the submitted work. KAAF reports grants and personal fees from Bayer/Janssen during the conduct of the study; grants and personal fees from AstraZeneca, personal fees from Sanofi/Regeneron and Eli Lilly outside the submitted work. DLB reports personal fees from Population Health Research Institute during the conduct of the study; grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi-Aventis, The Medicines Company, Roche, Pfizer, Forest Laboratories/AstraZeneca, Ischemix, Amgen, Eli Lilly, Chiesi, and Ironwood; other unfunded research collaborations with FlowCo, PLx Pharma, Takeda, Cardiology, Regado Biosciences, and Boston VA Research Institute, Clinical Cardiology, Veterans Administration, St Jude

Medical, Biotronik, Cardax, American College of Cardiology, Boston Scientific, and Merck; personal fees from Duke Clinical Research Institute, Mayo Clinic, Population Health Research Institute, Belvoir Publications, Slack Publications, WebMD, Elsevier, HMP Communications, Harvard Clinical Research Institute, the Journal of the American College of Cardiology, Cleveland Clinic, and Mount Sinai School of Medicine; personal fees and non-financial support from the American College of Cardiology and the Society of Cardiovascular Patient Care; and non-financial support from the American Heart Association outside the submitted work. FM is an employee of Bayer AG, the sponsor of this trial. JDV reports personal fees from Novartis outside the submitted work. TV reports grants and personal fees from Bayer during the conduct of the study; personal fees from Bayer, Pfizer/Bristol-Myers Squibb, Daiichi Sankyo, and Boehringer Ingelheim outside the submitted work. AAA has received honoraria and consulting fees from Boehringer Ingelheim and Pfizer. EC is an employee of Bayer AG, the sponsor of this trial. KB reports grants from Bayer, Astellas, and Janseen outside of the submitted work. RGH has received research support from Bayer AG including personal remuneration for participation in Bayer-sponsored clinical research and on advisory boards. SY has received research grants, honoraria, and travel expenses for lectures from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and AstraZeneca. All other authors declare no competing interests.

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