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

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Summary

Background Coronary artery disease is a major cause of morbidity and mortality worldwide, and is a consequence of acute thrombotic events involving activation of platelets and coagulation proteins. Factor Xa inhibitors and aspirin each reduce thrombotic events but have not yet been tested in combination or against each other in patients with stable coronary artery disease.

Methods In this multicentre, double-blind, randomised, placebo-controlled, outpatient trial, patients with stable coronary artery disease or peripheral artery disease were recruited at 602 hospitals, clinics, or community centres in 33 countries. This paper reports on patients with coronary artery disease. Eligible patients with coronary artery disease had to have had a myocardial infarction in the past 20 years, multi-vessel coronary artery disease, history of stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel coronary artery bypass graft surgery. After a 30-day run in period, patients were randomly assigned (1:1:1) to receive rivaroxaban (2·5 mg orally twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg orally twice a day), or aspirin alone (100 mg orally once a day). Randomisation was computer generated. Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. The primary outcome of the COMPASS trial was the occurrence of myocardial infarction, stroke, or cardiovascular death. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Findings Between March 12, 2013, and May 10, 2016, 27 395 patients were enrolled to the COMPASS trial, of whom 24 824 patients had stable coronary artery disease from 558 centres. The combination of rivaroxaban plus aspirin reduced the primary outcome more than aspirin alone (347 [4%] of 8313 *vs* 460 [6%] of 8261; hazard ratio [HR] 0·74, 95% CI 0·65–0·86, p<0·0001). By comparison, treatment with rivaroxaban alone did not significantly improve the primary outcome when compared with treatment with aspirin alone (411 [5%] of 8250 *vs* 460 [6%] of 8261; HR 0·89, 95% CI 0·78–1·02, p=0·094). Combined rivaroxaban plus aspirin treatment resulted in more major bleeds than treatment with aspirin alone (263 [3%] of 8313 *vs* 158 [2%] of 8261; HR 1·66, 95% CI 1·37–2·03, p<0·0001), and similarly, more bleeds were seen in the rivaroxaban alone group than in the aspirin alone group (236 [3%] of 8250 *vs* 158 [2%] of 8261; HR 1·51, 95% CI 1·23–1·84, p<0·0001). The most common site of major bleeding was gastrointestinal, occurring in 130 [2%] patients who received combined rivaroxaban plus aspirin, in 84 [1%] patients who received rivaroxaban alone, and in 61 [1%] patients who received aspirin alone. Rivaroxaban plus aspirin reduced mortality when compared with aspirin alone (262 [3%] of 8313 *vs* 339 [4%] of 8261; HR 0·77, 95% CI 0·65–0·90, p=0·0012).

Interpretation In patients with stable coronary artery disease, addition of rivaroxaban to aspirin lowered major vascular events, but increased major bleeding. There was no significant increase in intracranial bleeding or other critical organ bleeding. There was also a significant net benefit in favour of rivaroxaban plus aspirin and deaths were reduced by 23%. Thus, addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from coronary artery disease worldwide.

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Introduction

Coronary artery disease is a global medical problem and a leading cause of morbidity and mortality.[1] Patients with coronary artery disease are at risk for myocardial infarction, ischaemic stroke, and cardiovascular death. The underlying pathophysiology of these events in patients with atherosclerosis is rupture or erosion of an atherosclerotic plaque which exposes the sub-endothelial matrix to circulating blood.[2] This activates both platelet aggregation and the coagulation cascade, which leads to

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See Online for appendix

Research in context

Evidence before this study

Stable coronary artery disease is a serious health problem globally. The effects of Factor Xa inhibitor drugs in patients with coronary artery disease have been studied with both apixaban and rivaroxaban. Higher dose anticoagulation with apixaban was not effective after acute coronary syndrome and caused too much bleeding. Lower doses of rivaroxaban, 2·5 mg and 5 mg twice a day, reduced vascular events in the ATLAS 2 study, when given as an additional treatment to mostly dual antiplatelet therapy in patients after acute coronary syndrome. The 2·5 mg dose reduced vascular events and mortality and had less bleeding than the 5 mg dose. This led to approval in many countries and provided the impetus to study rivaroxaban in patients with stable coronary artery disease.

Added value of this study

The COMPASS trial has now shown that in patients with stable coronary artery disease, most of whom are many years from either myocardial infarction or a revascularisation procedure, rivaroxaban 2·5 mg given twice a day in combination with aspirin 100 mg once a day reduces major vascular events by 26% and reduces death by 24%. Rivaroxaban increased major bleeding by 69%, but there was no significant increase in either intracranial or fatal bleeding. Results were consistent across a variety of patient subgroups. Thus, COMPASS has extended the positive results of ATLAS 2, showing that addition of rivaroxaban to aspirin is effective with an acceptable bleeding risk that mostly involves the gastrointestinal tract. However, COMPASS enrolled a large population of stable patients with coronary artery disease, almost all of whom were remote from recent events such as surgery or stent procedures, which provides more generalisable evidence than ATLAS 2.

Implications of all the available evidence

Addition of rivaroxaban to aspirin treatment in patients with stable coronary artery disease at almost any stage of their disease has the potential to substantially reduce morbidity and mortality of a high-risk population.

an occlusive thrombus in the artery.[3] Aspirin irreversibly blocks the formation of thromboxane A2, which reduces platelet aggregation, and is widely used for the prevention of ischaemic events in patients with coronary artery disease, because randomised trials have shown a reduction in the risk of vascular events by about 20%.[3]

Vitamin K antagonists such as warfarin inhibit (or prevent) the function of the vitamin K-dependent coagulation proteins and the formation of thrombin. Vitamin K antagonists also lower cardiovascular events after myocardial infarction, although their use is limited by the potential for excessive bleeding.[4] Combined therapy with vitamin K antagonists and aspirin has also been assessed, and has shown additional benefit against recurrent myocardial infarction and death compared with aspirin alone; however, clinical uptake has been restricted by increased serious bleeding, including intracranial haemorrhage.[4] Factor Xa inhibitors provide more specific competitive inhibition of coagulation proteins with improved or similar efficacy to warfarin, and lower rates of intracranial bleeding.[5–8] Although conceptually attractive, experience with combined use of a factor Xa inhibitor and an antiplatelet agent has had mixed results.[9,10] In patients with acute coronary syndrome, a dose of 5 mg twice a day of the factor Xa inhibitor apixaban showed no reduction in thrombotic events when combined with antiplatelet therapy; and increased fatal and intracranial bleeding compared with placebo.[9] On the other hand, in the ATLAS 2 trial,[10] lower doses of rivaroxaban were tested in patients on antiplatelet therapy (mostly dual antiplatelet therapy in the first year of follow-up and mostly aspirin thereafter). Rivaroxaban reduced the risk of major ischaemic events, and particularly the lowest dose of rivaroxaban (2·5 mg twice a day) when added to antiplatelet therapy, reduced the composite outcome of stroke, myocardial infarction, and cardiovascular death and also reduced overall mortality, with a moderately increased risk of haemorrhage. The higher dose of rivaroxaban tested (5 mg twice a day) when added to antiplatelet therapy increased bleeding, with higher risk of fatal bleeding than the lower dose.

In stable coronary artery disease, trials of dual antiplatelet therapy have provided inconsistent results. Addition of clopidogrel to aspirin in stable coronary artery disease did not substantially reduce major vascular events.[11] By contrast, the addition of ticagrelor to aspirin in chronic stable coronary artery disease, 1–3 years after acute coronary syndrome reduced major vascular events, but increased bleeding and did not significantly reduce mortality.[12] Thus, there is a need to improve current approaches to antithrombotic therapy for stable coronary artery disease.

There have been no studies of a factor Xa inhibitor in patients with stable coronary artery disease, most of whom receive single antiplatelet therapy. The addition of a low dose of a factor Xa inhibitor to single antiplatelet therapy in these patients has the potential to substantially reduce vascular events, especially if this can be achieved with an acceptable increase of bleeding. It is also possible that a strategy of using a moderate dose of factor Xa inhibitor alone could be superior to antiplatelet therapy. In the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial, we hypothesised that low-dose rivaroxaban and aspirin together, or a higher dose of rivaroxaban alone, would be superior to aspirin alone for the prevention of major vascular events in patients with stable vascular disease.[13,14]

The present paper reports trial results for patients with coronary artery disease in the COMPASS trial.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled trial was done in 602 centres in 33 countries. Details of the study protocol have been published.[13] The main results for the whole study population have been published.[14] Ethics approval was obtained from local data safety and monitoring boards, which approved the study protocol.

Patients were eligible for the COMPASS trial if they met the criteria for coronary artery disease, peripheral arterial disease, or both. To be enrolled with a diagnosis of coronary artery disease, patients had to have either myocardial infarction within 20 years, multi-vessel coronary artery disease, history of stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel coronary artery bypass graft surgery. Multi-vessel coronary artery disease was defined as stenosis of at least 50% of diameter in two or more coronary arteries, confirmed by coronary angiography, by non-invasive imaging, or by stress studies suggesting substantial ischaemia in two or more coronary artery territories. Patients also needed to be aged at least 65 years, to have documented atherosclerosis or revascularisation in an additional vascular bed (carotid or peripheral), or needed to have at least two of the following risk factors: current smoker or quit within 1 year of randomisation, diabetes mellitus, estimated glomerular filtration rate (eGFR) of less than 60 mL/min, heart failure, or non-lacunar ischaemic stroke at least 1 month before randomisation. Some patients who were enrolled on the basis of specific inclusion criteria for peripheral arterial disease also had coronary artery disease present that did not necessarily meet the strict criteria for coronary artery disease stated above, but were still included in the analysis. Patients with coronary artery disease could also meet inclusion criteria if they had received coronary artery bypass surgery within 4–14 days, when at least 24 h had passed since the removal of chest tubes, and at least 12 h after last administration of any anticoagulant.

Key exclusion criteria included high risk of bleeding, stroke within 1 month, any history of haemorrhagic or lacunar stroke, severe heart failure with a known ejection fraction of less than 30%, eGFR of less than 15 mL/min, and the need for dual-antiplatelet therapy or for any non-aspirin antiplatelet therapy. All participants were required to provide written informed consent.

Randomisation and masking

Patients were randomly assigned to receive low-dose rivaroxaban plus aspirin, rivaroxaban alone (with aspirin placebo), or aspirin alone (with rivaroxaban placebo) in a 1:1:1 ratio. We used a central internet web-based randomisation for the allocation of participants to receive one of the three antithrombotic therapy treatments in a double-blind manner. A computer-generated randomisation schedule was generated by the Population Health Research Institute and used to allocate participants to treatment. Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. In a partial factorial design, patients not already receiving a proton-pump inhibitor were also randomly assigned to receive double-blind pantoprazole or matching placebo. The purpose of this factorial assessment was to identify if pantoprazole would reduce upper gastrointestinal complications (this part of the study is ongoing).

Procedures

Eligible and consenting patients entered a 30-day run-in period during which time they received placebo (twice a day) and aspirin (100 mg once a day). Patients with recent coronary artery bypass surgery did not enter the run-in phase but were immediately randomly assigned to treatment. Patients who had more than 80% adherence to treatment during the run-in phase and who continued to consent were then allocated to study drug of either low-dose rivaroxaban (2·5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg twice a day plus aspirin placebo once a day), or aspirin alone (100 mg once a day plus rivaroxaban placebo twice a day). Patients continued with study medication until study termination or until it was discontinued because of the occurrence of an adverse event. Patients also continued to receive all other prescribed medication. After the first treatment, participants were seen at 1 and 6 months, and then at 6 month intervals, at which time a general medical assessment was done.

Outcomes

The primary efficacy outcome was a composite consisting of the first occurrence of stroke, myocardial infarction, or cardiovascular death. The third universal definition of myocardial infarction was used.[15] There were three planned secondary outcomes which, for the overall analysis, were planned to be tested in a predefined sequence. These secondary outcomes were a composite of coronary heart disease death, myocardial infarction, ischaemic stroke, or acute limb ischaemia; occurrence of myocardial infarction, ischaemic stroke, cardiovascular death, or acute limb ischaemia; and overall mortality.

The primary safety outcome was major bleeding defined as fatal bleeding, symptomatic bleeding into a critical organ or area, surgical site bleeding leading to reoperation, or bleeding leading to hospital visit or admission. Symptomatic bleeding into a critical organ or area included intracranial, intraspinal, intraocular, retroperitoneal, adrenal, intra-articular, pericardial, or intramuscular (with compartment syndrome bleeding), or bleeding into the respiratory tract, liver, pancreas, or kidney. To assess net clinical benefit, we planned to assess the effect of treatment

on overall mortality and on a net clinical benefit composite outcome consisting of stroke, myocardial infarction, cardiovascular death, fatal bleeding, and symptomatic bleeding into a critical organ or area.

Statistical analysis

We planned to enrol 27 400 patients, of which the expected event rate in the control group was 3·2% per year. The overall study had 90% power to detect a 20% relative risk reduction for the two comparisons of low-dose rivaroxaban plus aspirin or rivaroxaban alone compared with aspirin. No specific sample size was calculated in advance for the subgroup of individuals with coronary artery disease, but given that the coronary artery disease population was expected to be about 85–90% of the trial population, statistical power to detect a 20% relative risk reduction was expected to be greater than 80%.

All analysis was done on the intention-to-treat population, defined as all patients randomly assigned to treatment regardless of whether they received or continued study medication. To address multiplicity related to testing two primary and six secondary hypotheses, we planned to use a mixture gatekeeping procedure based on the Hochberg test to control the familywise error rate of 5%. However, an early stop of both antithrombotic treatment groups for efficacy had not been anticipated, and therefore we did not prespecify a strategy for formal testing of secondary outcomes at the interim analysis. We did not specify provisions to address multiple testing for subgroups such as patients with coronary artery disease. Analysis of these outcomes were based on Kaplan-Meier estimates of cumulative incidence. We estimated the hazard ratio (HR) and 95% CI on the basis of stratified (three-level proton-pump inhibitor use) Cox proportional hazard models. The assumptions of the Cox models were verified by visually assessing the standard plots of the log of the negative log of Kaplan-Meier estimates of the survival function versus the log of time, and further by confirming that no time–treatment interaction existed when a time–treatment interaction term was included in the Cox model. Landmark analyses[16] for efficacy, safety, net clinical benefit and total mortality were done for three time periods: from randomisation to 1 year, from 1 to 2 years, and from 2 years until the end of the trial. Patients at risk of the outcome in each of the landmark windows were patients known to be alive at the beginning of the landmark window and who had not previously had the outcome event of interest before the landmark point.

An independent data safety monitoring board monitored the study with two formal interim analyses of efficacy planned when 50% and 75% of primary efficacy outcomes had accrued. For the first efficacy analysis, a modified Haybittle-Peto rule was used requiring benefits exceeding four standard deviations with the primary outcome which was to be consistently observed over 3 months. At the time of the first interim analysis on Feb 6, 2017, the data and safety monitoring board recommended that the study be stopped because of the clear evidence of efficacy meeting the pre-defined statistical monitoring boundaries. Plans were then made to complete final study visits. Analyses presented include all events in all patients randomly assigned to treatment that had occurred until Feb 6, 2017, when the recommendation to terminate the study by the data and safety monitoring board was made. This trial is registered with

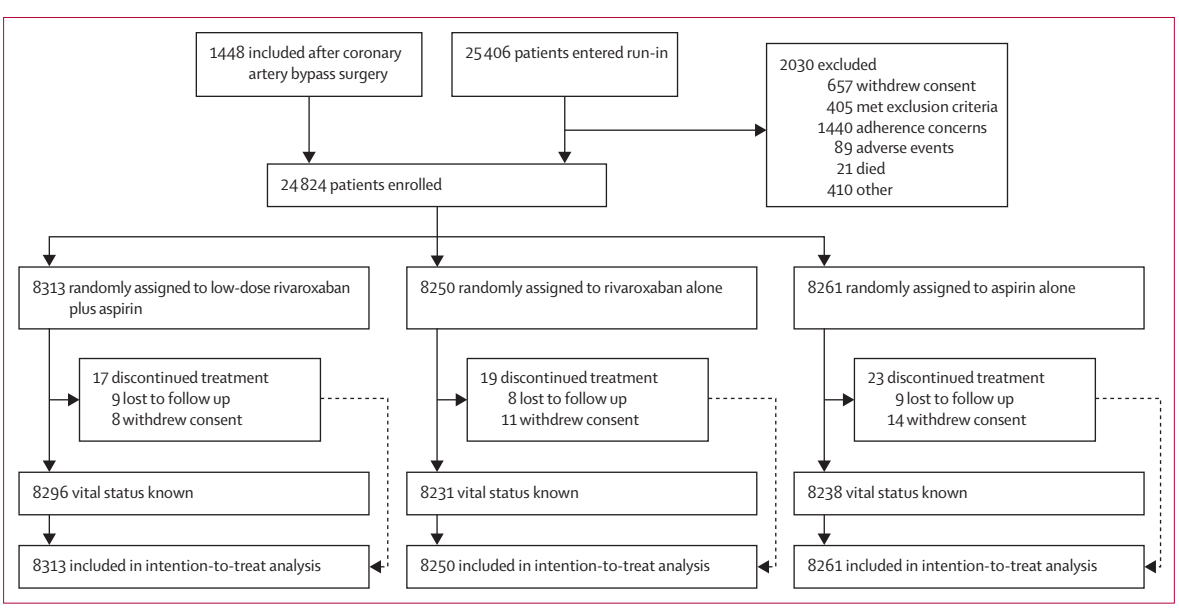


Figure 1: **Trial profile**
*Some participants had more than one reason for exclusion after the run-in period.

ClinicalTrials.gov, number NCT01776424, and is closed to new participants.

Role of the funding source

The study was designed by the Steering Committee, which included scientists from the sponsor, Bayer AG, who collaborated in study design, manuscript review and decision to publish. Site management and data collection and analysis were done at the Population Health Research Institute, Hamilton Health Sciences, and McMaster University in Hamilton, ON, Canada. SJC, JWE, JB, and SY had full access to the data and all authors made the final decision to publish.

Results

Patients with coronary artery disease were enrolled at 558 hospitals, outpatient sites, or clinics in 33 countries between March 12, 2013, and May 10, 2016. A total of 27 395 patients successfully completed the run-in or were enrolled 4–14 days after coronary artery bypass surgery, and were randomly assigned to receive low-dose rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone (figure 1). Of the total patients enrolled, 24 824 (91%) had coronary artery disease and were randomised to treatment. Mean duration of follow-up was 1·95 years, follow-up was 99·8% complete. The mean age was 68·3 years (SD 7·8) and 19 792 (80%) were male (table 1). There were 17 028 patients (69%) with history of previous myocardial infarction, 1238 (5%) of which had occurred within 1 year of enrolment, 7234 (29%) between 1 and 5 years and 8520 (34%) beyond 5 years from enrolment. Multi-vessel disease was diagnosed in 15 469 patients (62%). There were 1120 patients with coronary artery disease who developed a need for dual antiplatelet therapy during COMPASS. The investigator had the option to put the patient on the lower dose of rivaroxaban (or matching placebo using blinded therapy) or to discontinue rivaroxaban until dual antiplatelet therapy was no longer clinically required. In the low-dose rivaroxaban plus aspirin treatment group, there were 358 (4%) participants who went on dual antiplatelet therapy during the study; 344 had rivaroxaban discontinued during dual antiplatelet therapy and 14 remained on low-dose rivaroxaban. In the rivaroxaban alone treatment group, 384 (5%) participants went on dual antiplatelet therapy during the study; 369 had rivaroxaban treatment discontinued and 15 remained on low-dose rivaroxaban.

There were 347 (4%) of 8313 patients who had a primary outcome event in the low-dose rivaroxaban plus aspirin group, and 460 (6%) of 8261 patients in the aspirin alone group (HR 0·74, 95% CI 0·65–0·86, p<0·0001; table 2, figure 2). By contrast, participants in the rivaroxaban alone group did not have an improvement in primary outcome compared with aspirin alone (411 [5%] of 8250 *vs* 460 [6%] of 8261; HR 0·89, 95% CI 0·78–1·02, p=0·094). Stroke occurred less frequently in patients in the low-dose rivaroxaban plus aspirin group than in the aspirin alone group (74 [1%] of 8313 *vs* 130 [2%]; HR 0·56, 95% CI 0·42–0·75, p<0·0001), though was not different between the rivaroxaban alone and the aspirin alone groups (105 [1%] of 8250 *vs* 130 [2%] of 8261; HR 0·81, 95% CI 0·62–1·05; p=0·10).

Patients with atrial fibrillation requiring anti-coagulation were excluded from entering the trial. Atrial fibrillation was documented to have occurred during the trial in 121 (1%) of 8313 patients in the low-dose rivaroxaban plus aspirin group, in 123 (1%) of

	Low-dose rivaroxaban plus aspirin (n=8313)	Rivaroxaban alone (n=8250)	Aspirin alone (n= 8261)
Age, years	69 (65–73)	69 (65–73)	69 (65–73)
Sex			
Female	1736 (21%)	1650 (20%)	1646 (20%)
Male	6577 (79%)	6600 (80%)	6615 (80%)
Body-mass index, kg/m²	28·4 (4·7)	28·4 (4·6)	28·5 (4·7)
eGFR, mL/min	73·9 (17·6)	73·8 (17·6)	73·7 (17·9)
Systolic blood pressure, mm Hg	135 (17)	135 (18)	135 (17)
Diastolic blood pressure, mm Hg	77 (10)	77 (10)	78 (10)
Risk factors			
Smoking status			
Current smoker	1679 (20%)	1680 (20%)	1687 (20%)
Former smoker	3944 (47%)	3889 (47%)	3908 (47%)
Diabetes	3043 (37%)	3015 (37%)	3040 (37%)
Hypertension	6280 (76%)	6214 (75%)	6218 (75%)
Peripheral artery disease	1656 (20%)	1609 (20%)	1641 (20%)
Previous myocardial infarction	5654 (68%)	5653 (69%)	5721 (69%)
<1 year	410 (5%)	403 (5%)	425 (5%)
1–2 years	798 (10%)	774 (9%)	769 (9%)
2–5 years	1612 (19%)	1614 (20%)	1667 (20%)
≥5 years	2824 (34%)	2847 (35%)	2849 (35%)
Percutaneous coronary intervention	4971 (60%)	4986 (60%)	4905 (59%)
Previous CABG	2704 (33%)	2555 (31%)	2586 (31%)
Multivessel coronary artery disease	5252 (63%)	5174 (63%)	5043 (61%)
Heart failure	1909 (23%)	1893 (23%)	1912 (23%)
Stroke	279 (3%)	250 (3%)	268 (3%)
Previous treatment			
ACE inhibitor or ARB	5970 (72%)	6059 (73%)	5939 (72%)
Lipid-lowering drug	7667 (92%)	7604 (92%)	7573 (92%)
Calcium channel blocker	2177 (26%)	2136 (26%)	2224 (27%)
β-blocker	6124 (74%)	6143 (75%)	6154 (75%)
Region			
North American	1190 (14%)	1196 (15%)	1197 (15%)
South American	1779 (21%)	1730 (21%)	1747 (21%)
Western European including Australia, Israel, and South Africa	2663 (32%)	2659 (32%)	2653 (32%)
Eastern European	1477 (18%)	1478 (18%)	1487 (18%)
Asia, Pacific and other	1204 (15%)	1187 (14%)	1177 (14%)

Data are median (IQR), mean (SD) or n (%). eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass graft surgery. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker.

Table 1: **Baseline characteristics of patients with coronary artery disease**

	Low-dose rivaroxaban plus aspirin (n=8313)	Rivaroxaban alone (n=8250)	Aspirin alone (n=8261)	Low-dose rivaroxaban plus aspirin *vs* aspirin alone		Rivaroxaban alone *vs* aspirin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Myocardial infarction, stroke, or cardiovascular death*	347 (4%)	411 (5%)	460 (6%)	0·74 (0·65–0·86)	<0·0001	0·89 (0·78–1·02)	0·094
Myocardial infarction, ischaemic stroke, coronary heart disease death, or acute limb ischaemia	299 (4%)	357 (4%)	411 (5%)	0·72 (0·62–0·83)	<0·0001	0·87 (0·75–1·00)	0·048
Myocardial infarction, ischaemic stroke, cardiovascular death, or acute limb ischaemia*	349 (4%)	406 (5%)	470 (6%)	0·73 (0·64–0·84)	<0·0001	0·86 (0·76–0·98)	0·029
Death*	262 (3%)	316 (4%)	339 (4%)	0·77 (0·65–0·90)	0·0012	0·93 (0·80–1·09)	0·37
Cardiovascular death*	139 (2%)	175 (2%)	184 (2%)	0·75 (0·60–0·93)	0·010	0·95 (0·77–1·17)	0·63
Non-cardiovascular death	123 (2%)	141 (2%)	155 (2%)	0·79 (0·62–1·00)	0·048	0·91 (0·73–1·15)	0·43
Myocardial infarction	169 (2%)	176 (2%)	195 (2%)	0·86 (0·70–1·05)	0·15	0·90 (0·74–1·11)	0·33
Myocardial infarction or sudden cardiac death†	234 (3%)	273 (3%)	273 (3%)	0·85 (0·71–1·01)	0·065	1·00 (0·85–1·18)	1·00
Myocardial infarction, coronary heart disease death, sudden death, resuscitated cardiac arrest, or unstable angina*†	264 (3%)	314 (4%)	314 (4%)	0·83 (0·71–0·98)	0·028	1·00(0·86–1·17)	1·00
Stroke*	74 (1%)	105 (1%)	130 (2%)	0·56 (0·42–0·75)	<0·0001	0·81 (0·62–1·05)	0·10
Ischaemic stroke or unspecified site	60 (1%)	79 (1%)	120 (2%)	0·50 (0·36–0·67)	<0·0001	0·66 (0·50–0·87)	0·0037
Haemorrhagic stroke	14 (<1%)	27 (<1%)	10 (<1%)	1·39 (0·62–3·32)	0·43	2·70 (1·31–5·59)	0·0051
Heart failure	178 (2%)	174 (2%)	182 (2%)	0·97 (0·79–1·19)	0·78	0·96 (0·78–1·18)	0·66
Admission to hospital	2369 (29%)	2374 (29%)	2402 (29%)	0·98 (0·92–1·04)	0·46	0·99 (0·94–1·05)	0·71
Cardiovascular cause	1189 (14%)	1205 (15%)	1270 (15%)	0·92 (0·85–1·00)	0·046	0·95 (0·87–1·02)	0·16
Non-cardiovascular cause	1552 (19%)	1506 (18%)	1481 (18%)	1·05 (0·98–1·13)	0·18	1·02 (0·95–1·10)	0·52
Coronary revascularisation	530 (6%)	527 (6%)	553 (7%)	0·95 (0·84–1·07)	0·39	0·95 (0·85–1·07)	0·43
Stent thrombosis	50 (1%)	50 (1%)	46 (1%)	1·08 (0·72–1·61)	0·71	1·09 (0·73–1·62)	0·68

Data are n (%) or HR (95% CI). The top row shows the primary outcome and the next three rows show the secondary outcomes in sequence. HR=hazard ratio. *For these comparisons rivaroxaban plus aspirin is statistically superior to rivaroxaban alone. †Indicates a post-hoc analysis.

Table 2: **Efficacy outcomes for patients with coronary artery disease**

8250 patients in the rivaroxaban alone group, and in 121 (1%) of 8261 patients in the aspirin alone group. Only five (7%) of 74 strokes that occurred in the low-dose rivaroxaban plus aspirin group occurred in patients who developed atrial fibrillation during the trial compared with nine (7%) of 130 strokes that occurred in patients in the aspirin alone group and eight (8%) of 105 strokes that occurred were in patients in the rivaroxaban alone group.

There were significant reductions in all three secondary outcomes in the low-dose rivaroxaban plus aspirin group compared with aspirin. For the composite of myocardial infarction, ischaemic stroke, coronary heart disease death, or acute limb ischaemia, the reduction was 28% (299 [4%] of 8313 *vs* 411 [5%] of 8261; HR 0·72, 95% CI 0·62–0·83, p<0·0001) and for the composite of myocardial infarction, ischaemic stroke, cardiovascular death, or acute limb ischaemia the reduction was 27% (349 [4%] *vs* 470 [6%]; HR 0·73, 95% CI 0·64–0·84; p<0·0001). 262 patients (3%) in the low-dose rivaroxaban plus aspirin group died and 339 patients (4%) of patients in the aspirin alone group (HR 0·77, 95% CI 0·65–0·90, p=0·0012). 316 patients (4%) in the rivaroxaban alone group died compared with 339 patients (4%) in the aspirin alone group (HR 0·93, 0·80–1·09, p=0·37).

Major bleeding occurred in 263 (3%) of 8313 patients in the low-dose rivaroxaban plus aspirin group and in 158 (2%) of 8261 patients in the aspirin alone group (HR 1·66, 95% CI 1·37–2·03, p<0·0001; table 3, figure 2). Patients in the rivaroxaban alone group had increased major bleeding compared with patients in the aspirin alone group (236 [3%] of 8250 *vs* 158 [2%] of 8261; HR 1·51, 95% CI 1·23–1·84, p<0·0001). There was a statistically significant increase in intracranial bleeding with rivaroxaban alone compared to aspirin alone (43 [1%] *vs* 23 [<1%]; HR 1·87, 95% CI 1·13–3·11). The most common site of major bleeding in patients receiving rivaroxaban plus aspirin was the gastrointestinal tract. Gastrointestinal major bleeding was increased by rivaroxaban plus aspirin compared with aspirin alone

(HR 2·13, 95% CI 1·57–2·88). Intracranial and fatal bleeding were not significantly different between the rivaroxaban plus aspirin group and the aspirin alone group. A post-hoc landmark analysis examined the effects of treatment during year 1, year 2, and beyond year 2 (figure 3). This analysis suggests that the risk of bleeding from addition of rivaroxaban to aspirin decreases after the first year, whereas the reduction in the primary outcome remains relatively constant throughout all timepoints.

In an exploratory analysis to identify whether there was an effect on coronary events, we analysed the composite outcome of coronary heart disease death, myocardial infarction, sudden cardiac death, or resuscitated cardiac arrest. Compared with aspirin, there was a reduction in coronary events in the low-dose rivaroxaban plus aspirin group (HR 0·82, 95% CI 0·69–0·97).

We prospectively defined a net clinical benefit outcome that consisted of the primary efficacy outcomes of stroke, myocardial infarction, or cardiovascular death as well as more severe bleeding which included fatal bleeding and symptomatic bleeding into a critical organ or area. This composite outcome occurred in 392 (5%) of 8313 patients in the low-dose rivaroxaban plus aspirin group and in 494 (6%) of 8261 patients in the aspirin alone group (HR 0·78, 95% CI 0·69–0·90, p=0·0003). For the addition of rivaroxaban to aspirin, the number needed to treat for the mean study duration of 1·9 years to prevent occurrence of one of the primary outcomes was 72 and the number needed to harm for fatal or symptomatic bleeding into a critical organ was 471. The number needed to prevent a death was 105 when compared with the aspirin alone group.

The addition of low-dose rivaroxaban to aspirin resulted in an improvement in the primary efficacy outcome both in patients with a previous myocardial infarction (HR 0·74, 95% CI 0·63–0·88) and those without previous myocardial infarction (0·76, 0·58–0·98, $p_{interaction}$=0·91; figure 4). Patients receiving all guideline-mandated secondary prevention strategies (non-smokers receiving β-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs) had similar benefits from rivaroxaban plus aspirin compared with those not doing so. We did a post-hoc analysis on a group of patients who had more stable clinical symptoms, defined as those without either myocardial infarction or who had not received any revascularisation procedure in the 2 years before enrolment (n=18 207). These patients had a similar benefit from adding rivaroxaban to aspirin as those who had one of these events in the past 2 years.

The trials in myocardial infartion (TIMI) secondary prevention risk score is a validated method to assign risk of major vascular events. Patients at lower and higher risk of these vascular events had similar relative benefits from addition of rivaroxaban to aspirin. However, the higher risk patients had a greater reduction in the composite primary outcome (2·1 events per 100 patients) than the intermediate (1·0 events per 100 patients) and lower risk patients (0·8 events per 100 patients). There was a significant interaction in the effects among those with previous coronary artery bypass surgery compared with patients who had not had this procedure when treated with low-dose rivaroxaban plus aspirin versus aspirin alone.

With increased age, there was a smaller reduction in the primary outcome and a larger increase in major bleeding, when low-dose rivaroxaban was added to aspirin treatment. However, the interactions were not significant in any of the primary efficacy, primary safety, or net benefit analyses.

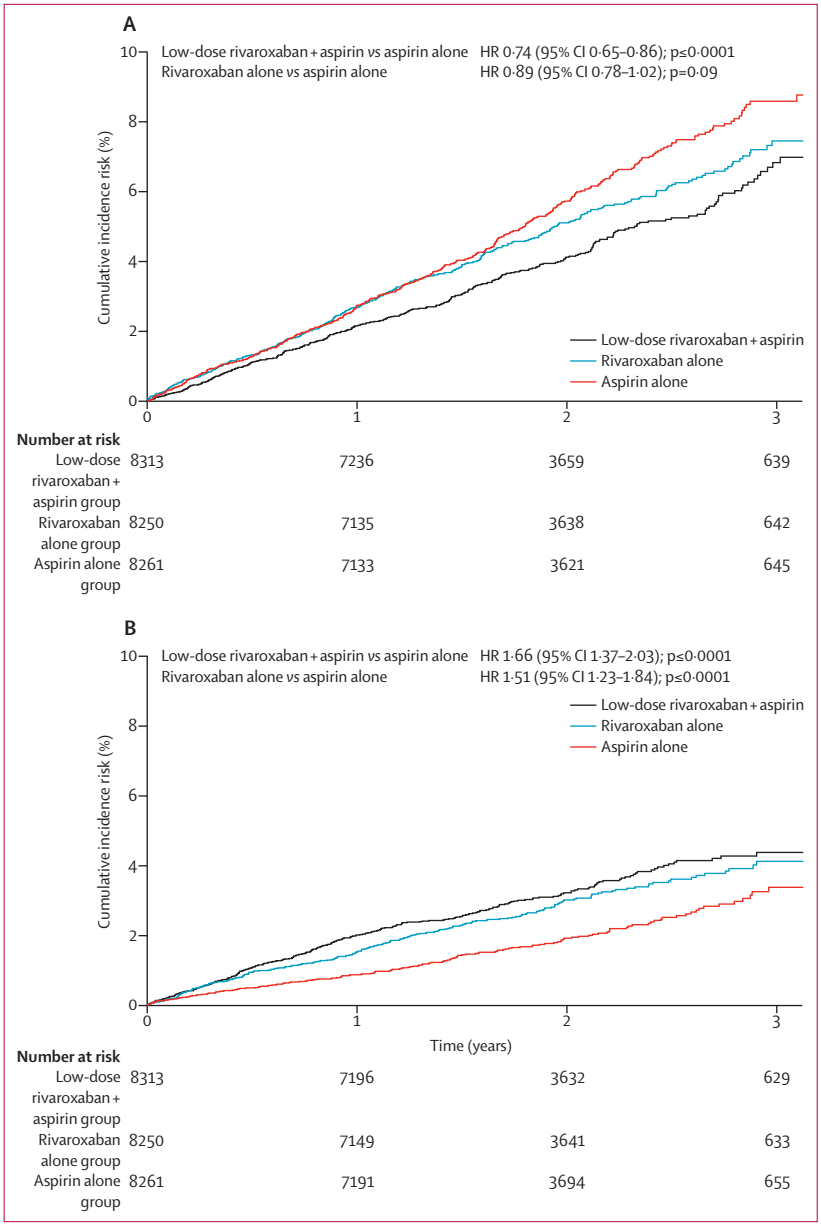


Figure 2: **Primary efficacy and safety outcomes**
Graphs represent (A) primary efficacy outcomes and (B) safety outcomes. HR=hazard ratio.

	Low-dose rivaroxaban plus aspirin (n=8313)	Rivaroxaban alone (n=8250)	Aspirin alone (n=8261)	Low-dose rivaroxaban plus aspirin *vs* aspirin alone		Rivaroxaban alone *vs* aspirin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Major bleeding	263 (3%)	236 (3%)	158 (2%)	1·66 (1·37–2·03)	<0·0001	1·51 (1·23–1·84)	<0·0001
Fatal bleeding*	14 (<1%)	12 (<1%)	9 (<1%)	1·55 (0·67–3·58)	0·30	1·33 (0·56–3·16)	0·51
Non-fatal symptomatic ICH*	19 (<1%)	32 (<1%)	19 (<1%)	0·99 (0·52–1·87)	0·98	1·69 (0·96–2·99)	0·065
Non-fatal, non-ICH, symptomatic bleeding into critical organ*	36 (<1%)	42 (1%)	25 (<1%)	1·42 (0·85–2·36)	0·18	1·70 (1·04–2·79)	0·033
Other major bleeding*	194 (2%)	150 (2%)	105 (1%)	1·85 (1·46–2·34)	<0·0001	1·44 (1·12–1·84)	0·0041
Fatal bleeding or symptomatic ICH	33 (<1%)	44 (1%)	28 (<1%)	1·17 (0·71–1·93)	0·54	1·58 (0·98–2·53)	0·058
Fatal bleeding or symptomatic bleeding into critical organ or surgical site bleeding requiring reoperation	76 (1%)	101 (1%)	58 (1%)	1·30 (0·92–1·83)	0·13	1·75 (1·27–2·42)	0·0006
ISTH major bleeding	186 (2%)	164 (2%)	105 (1%)	1·77 (1·39–2·24)	<0·0001	1·57 (1·23–2·01)	0·0003
GUSTO							
Severe or life-threatening†	30 (<1%)	43 (1%)	28 (<1%)	1·06 (0·63–1·78)	0·82	1·54 (0·96–2·48)	0·073
Moderate‡	76 (1%)	60 (1%)	37 (<1%)	2·04 (1·38–3·03)	0·0003	1·63 (1·08–2·45)	0·019
Transfusion within 48 h of bleeding	79 (1%)	61 (1%)	41 (1%)	1·92 (1·31–2·80)	0·0006	1·49 (1·01–2·22)	0·045
Minor bleeding	775 (9%)	688 (8%)	454 (6%)	1·74 (1·55–1·95)	<0·0001	1·55 (1·38–1·75)	<0·0001
Site of major bleeding							
Gastrointestinal	130 (2%)	84 (1%)	61 (1%)	2·13 (1·57–2·88)	<0·0001	1·38 (0·99–1·92)	0·053
Intracranial	26 (<1%)	43 (1%)	23 (<1%)	1·12 (0·64–1·96)	0·69	1·87 (1·13–3·11)	0·013
Skin or injection site	25 (<1%)	27 (<1%)	10 (<1%)	2·47 (1·19–5·14)	0·012	2·71 (1·31–5·60)	0·0050
Urinary	13 (<1%)	25 (<1%)	21 (<1%)	0·61 (0·31–1·23)	0·16	1·19 (0·67–2·13)	0·55
Cardiovascular death, stroke, myocardial infarction, fatal bleeding or symptomatic bleeding into a critical organ	392 (5%)	462 (6%)	494 (6%)	0·78 (0·69–0·90)	0·0003	0·94 (0·82–1·06)	0·31

Data are n (%) or HR (95% CI). HR=hazard ratio. ICH=intracranial haemorrhage. ISTH=International Society of Thrombosis and Hemostasis. GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries. *If a participant had more than one major bleed, only the most serious bleed is counted in these analyses. †Defined as intracerebral or treated with inotropic drug. ‡Defined as other bleed requiring a transfusion.

Table 3: **Adverse events**

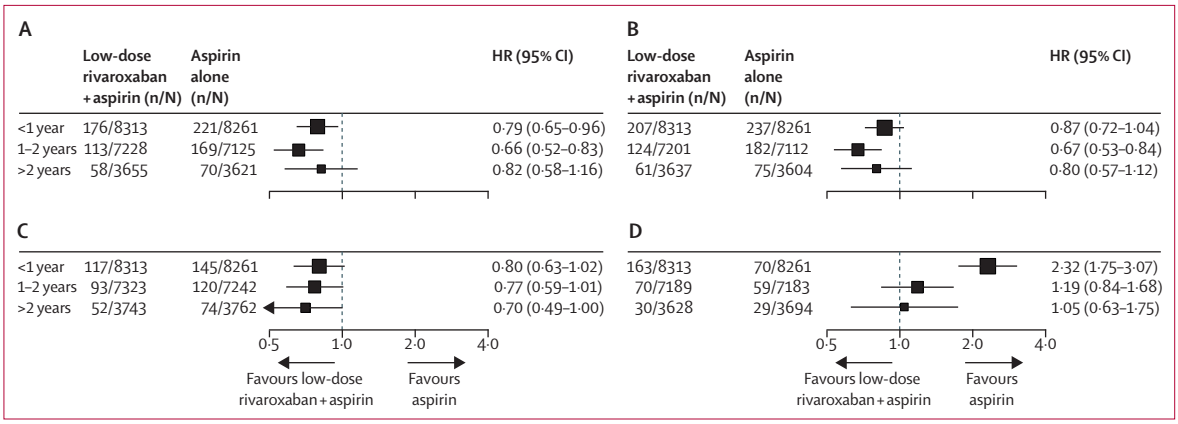


Figure 3: **Landmark analysis**

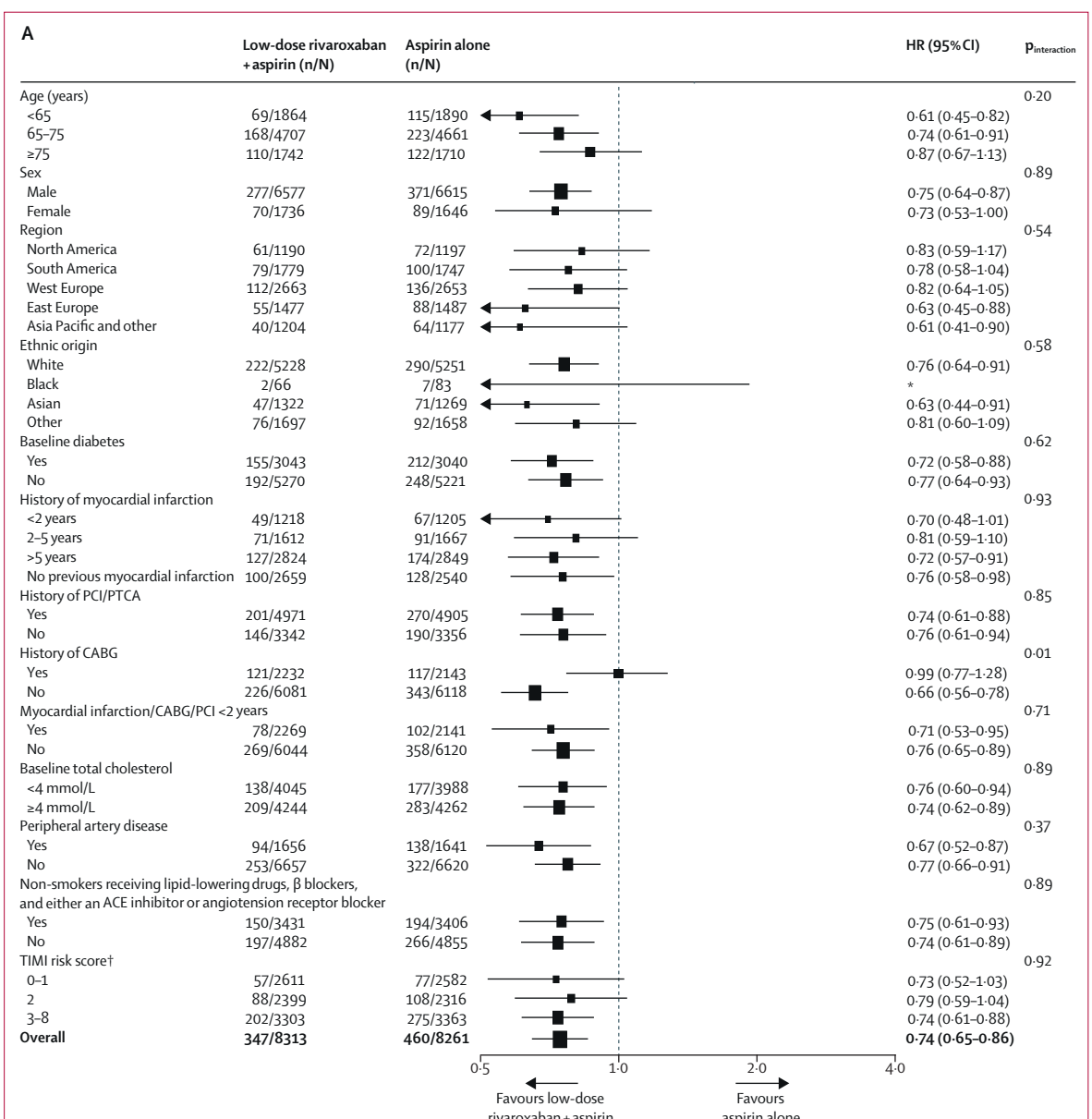
Analysis of (A) primary efficacy outcome, (B) net clinical benefit, (C) all-cause death, and (D) major bleeding. HR=hazard ratio.

Discussion

In patients with stable coronary artery disease who were well treated both with interventional and medical treatments, addition of low-dose rivaroxaban to aspirin reduced major vascular events by 26%, including stroke by 44% and mortality by 23%. Rivaroxaban alone did not reduce the primary outcome compared with aspirin alone, and increased intracranial bleeding. Addition of low-dose rivaroxaban to aspirin increased bleeding. Most of this increase was in gastrointestinal bleeding; there was no

statistically significant increase in either fatal bleeding or intracerebral bleeding. The net benefit, measured either by a composite outcome or by death, favoured addition of low-dose rivaroxaban to aspirin treatment.

Ischaemic events in patients with coronary artery disease are usually caused by an occlusive thrombosis that is a consequence of activation of platelets and the coagulation cascade. Both anticoagulation therapy alone and antiplatelet therapy alone (with aspirin) reduce mortality after myocardial infarction.[3,4] Combining anticoagulation therapy with warfarin and aspirin after myocardial infarction reduced vascular events compared with aspirin alone, but substantially increased intracranial and other bleeding.[4] With the common use of coronary interventions and with increased use of combinations of antiplatelet drugs—eg, aspirin and P2Y12 inhibitors—interest in anticoagulant therapy for coronary artery disease waned until the introduction of the factor Xa inhibitors. These drugs provide effective anticoagulation in various conditions with reduced risk of fatal and intracranial bleeding compared with warfarin. Two of these factor Xa inhibitors have been assessed in patients with acute coronary syndrome. In the APPRAISE-2 trial,[9] a dose of apixaban used in atrial fibrillation (5 mg twice a day) was added to dual antiplatelet therapy and resulted in more bleeding



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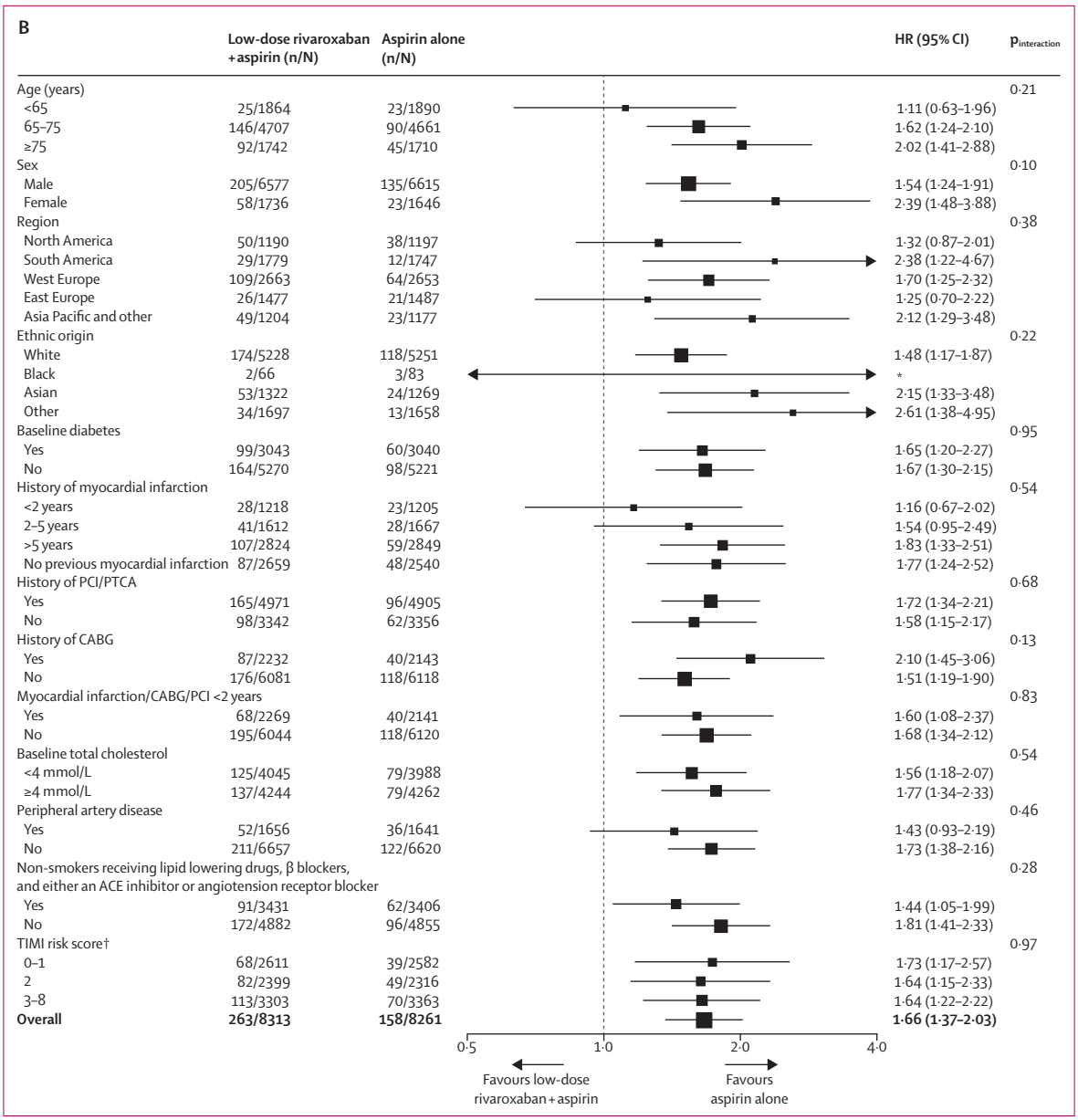

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without reducing ischaemic events. By contrast, in the ATLAS 2 trial,[10] two reduced doses of rivaroxaban were tested after acute coronary syndrome, with 93% of patients receiving dual antiplatelet therapy for the first year. These relatively low doses of rivaroxaban lowered the frequency of vascular events by 16% compared with placebo. However, rivaroxaban, when given 5 mg twice a day, increased TIMI score of major bleeding from 0·6% to 2·1%.[10] The lowest dose of rivaroxaban tested (2·5 mg twice a day) significantly reduced cardiovascular and total deaths, but increased major bleeding compared with placebo (HR 3·46, 95% CI 2·08–5·77, p<0·001).[10] However, significantly fewer individuals had fatal bleeding at the lowest rivaroxaban dose than at the higher dose. These positive findings with rivaroxaban 2·5 mg twice a day in the ATLAS-2 trial provided the impetus for the COMPASS study, which has now confirmed the efficacy of rivaroxaban 2·5 mg twice a day when added to antiplatelet therapy in patients with coronary artery disease.

The ATLAS 2 and COMPASS trials are complementary, but also differ in some respects. Both studies included patients with coronary artery disease, but patients in the COMPASS trial were in the chronic stable phase of their disease and followed up for 1·95 years, whereas ATLAS-2 enrolled patients after acute coronary syndrome and they

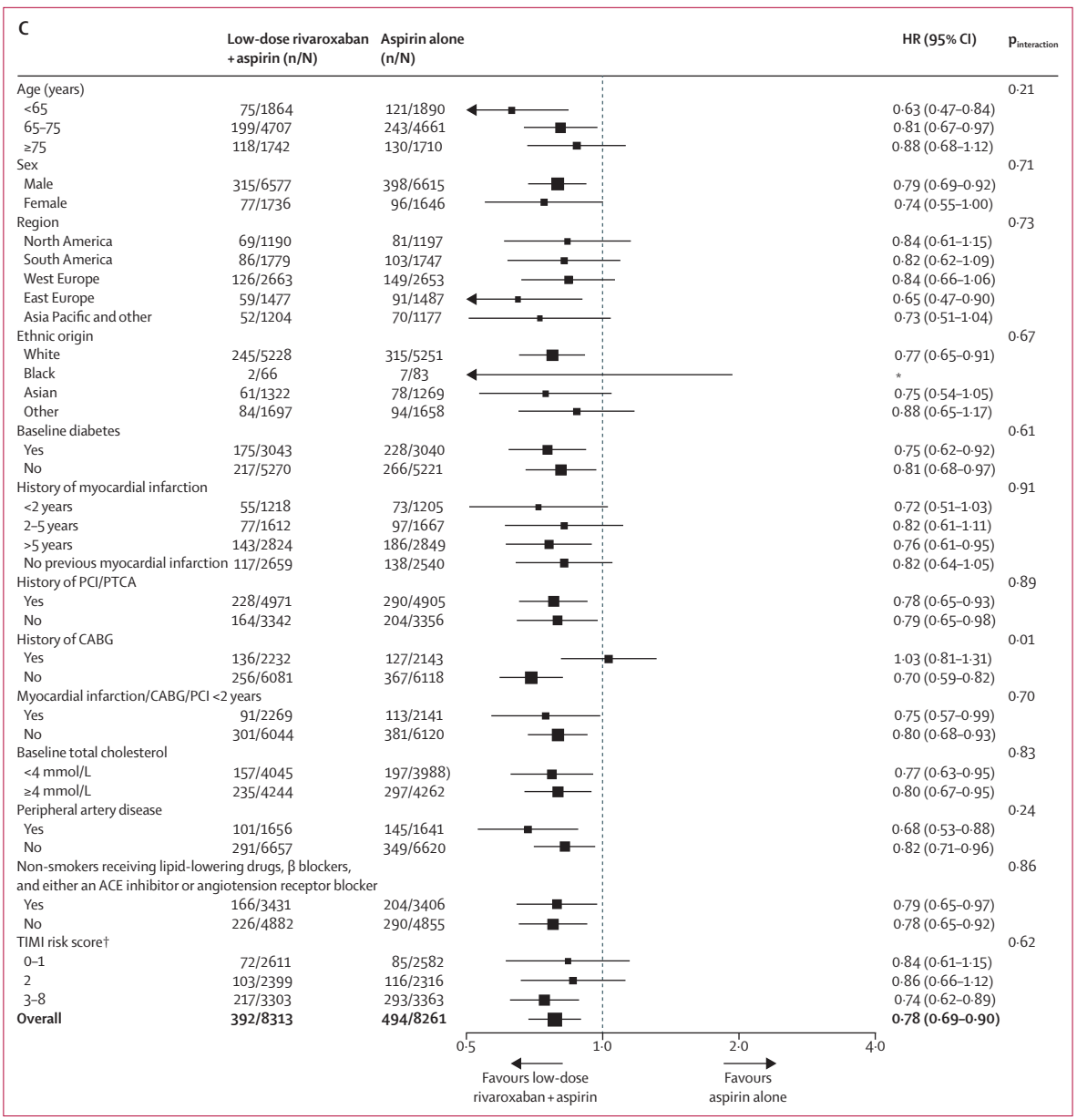

Figure 4: **Subgroup analyses**

Subgroup analyses are shown for (A) the primary outcome, (B) major bleeding, and (C) net clinical benefit. PCI=percutaneous coronary intervention. PTCA=percutaneous transluminal coronary angioplasty. CABG=coronary artery bypass graft surgery. CAD=coronary artery disease. ACE=angiotensin-converting enzyme. TIMI=trials in myocardial infartion *Values too small to estimate. †TIMI risk score gives one point each to the following criteria: current smoker, heart failure, diabetes, CABG surgery, stroke, hypertension, age >75 years, estimated glomerular filtration rate <60 mL/min.

were followed up for a mean of 13 months. In COMPASS, low-dose rivaroxaban was added to less intensive (single) antiplatelet therapy; however, in ATLAS 2, most patients received dual antiplatelet therapy in their first year in combination with rivaroxaban. There are important similarities in the results of the two studies. In both studies, addition of low-dose rivaroxaban to antiplatelet therapy reduced the composite of major vascular events and reduced mortality. In both studies there were more modest reductions in clinical myocardial infarction compared with the effects on other vascular outcomes. The two studies appeared to differ in the degree of stroke reduction. In ATLAS-2 there was a small non-significant reduction in ischaemic stroke (HR 0·89, 95% CI 0·55–1·45) but an increase in haemorrhagic stroke (16 patients in the low-dose rivaroxaban plus antiplatelet group *vs* seven in patients only receiving antiplatelet therapy with rivaroxaban placebo) that offset each other, resulting in a non-significant excess in total stroke (HR 1·24, 95% CI 0·86–1·78). The relative reduction

in ischaemic or unspecified stroke with low-dose rivaroxaban added to aspirin compared with aspirin alone in COMPASS in patients with coronary artery disease is 50% (HR 0·50; 95% CI 0·36–0·67) and the increase in haemorrhagic stroke was not significant, resulting in a substantial reduction in total strokes with rivaroxaban during the stable phase of coronary artery disease. The lesser increase in haemorrhagic stroke with low-dose rivaroxaban plus aspirin in COMPASS, compared with low-dose rivaroxaban plus antiplatelet therapy in ATLAS 2, is likely to be because it was added to a single antiplatelet therapy rather than to a dual antiplatelet therapy.

The addition of an anticoagulant to antiplatelet therapy would be expected to increase bleeding, which we observed in COMPASS. Although adding low-dose rivaroxaban to aspirin resulted in more major bleeding, there was no significant increase in either intracranial or fatal bleeding. Most of the excess in bleeding was gastrointestinal. Both rivaroxaban and aspirin can increase gastrointestinal bleeds and so a further increase with the combination of the two is not surprising. Gastrointestinal bleeding can indeed sometimes be serious, especially in the elderly,[17] so the significant reduction in mortality observed with the addition of low-dose rivaroxaban to aspirin in this trial is reassuring, indicating that the increase in bleeding seen does not offset the benefit of reduction in vascular events. Furthermore, the composite outcome used to measure net clinical benefit, which included both the major vascular events and the more severe bleeds, favoured the addition of rivaroxaban to aspirin in patients with coronary artery disease. Because of the pantaprozole partial factorial randomisation, more patients in COMPASS received a proton-pump inhibitor than would otherwise have received one in usual clinical practice. Although it remains unproven that a proton-pump inhibitor reduces bleeding in patients receiving an anticoagulant, it is possible that the higher rate of proton-pump inhibitor use in COMPASS reduced bleeding rates. Our landmark analysis shows that the increased hazard for bleeding with addition of rivaroxaban to aspirin was much greater in the first year of therapy than in subsequent years, whereas the reduction in major vascular events is consistent over time.

The reduction in cardiovascular mortality was expected and was explained partly by the effects of treatment on myocardial infarction and stroke. There might also have been some sudden deaths related to myocardial ischaemia that were not classified as myocardial infarction. The reduction in non-cardiovascular mortality was not expected and is more difficult to explain. It might be partly due to misclassification of cause of death, but this possibility was minimised by the use of standardised definitions and the use of a combination of a predefined algorithm and adjudication to classify death by cause. A table in the appendix shows details about the causes of both cardiovascular and non-cardiovascular deaths. The patients included in our study had stable coronary artery disease, and were well managed with evidence-based therapies. 82% of patients had received revascularisation procedures, 92% of patients were taking a lipid-lowering agent, 72% were taking an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and 74% were taking a β blocker. About a third of patients had not had a previous myocardial infarction. Of those with a previous myocardial infarction, most had had their myocardial infarction many years before randomisation to treatment. The benefits of addition of low-dose rivaroxaban to aspirin were consistent whether patients were within 2 years of myocardial infarction, 2–5 years after myocardial infarction, beyond 5 years, or never had an infarction.

COMPASS enrolled patients with stable chronic coronary artery disease similar to those assessed in most of the trials of lipid-lowering drugs, or the trials evaluating angiotensin-converting enzyme inhibitors.[18,19] The observation that the benefit of adding rivaroxaban to aspirin was consistent, both in patients with more recent events and in patients with cardiovascular events many years previously, indicates that rivaroxaban will be useful over long periods of treatment. This is strikingly different from what was observed from adding ticagrelor to aspirin in patients 1–3 years after acute coronary syndrome.[20] Patients who had been stable for 1 year or more on single antiplatelet therapy did not appear to benefit from addition of ticagrelor.[20] Similarly, in a subgroup analysis of the CHARISMA trial,[21] patients with previous myocardial infarction, stroke, or symptomatic peripheral artery disease benefited from addition of clopidogrel to aspirin, and the degree of this benefit diminished with duration of time from the ischaemic event. The benefits from the addition of rivaroxaban to aspirin treatment in COMPASS is of the order of magnitude observed with the use of statins or angiotensin-converting enzyme inhibitors for 4–5 years. Landmark analysis of the effects of adding rivaroxaban to aspirin suggests that the risk of increased bleeding from rivaroxaban decreases over time and indicates that long-term therapy will be beneficial. Patients stratified as either low, medium, or high risk for recurrent events using the TIMI risk score had similar relative benefits from rivaroxaban and so the absolute benefits of rivaroxaban increased with increased risk as expected. The use of rivaroxaban alone did not significantly reduce the primary outcome. Rivaroxaban plus aspirin was superior to a higher dose of rivaroxaban alone indicating that intensification of anticoagulation is less effective than low intensity simultaneous inhibition of both coagulation and platelet activity. COMPASS represents a further important step in the systematic progress that has been made over the past three decades in reducing risk of vascular events in patients with coronary artery disease using multiple different approaches. The avoidance of tobacco, and use of statins, angiotensin-converting enzyme inhibitors, and β blockers along with the combination of rivaroxaban and aspirin can be collectively expected to reduce

recurrent events and deaths in patients with coronary artery disease by as much as 80%.[22]

One limitation of our study is that we do not know the reasons why patients were non-adherent during the run-in phase and it might have been helpful to know if any patients were aspirin intolerant. We also did not classify myocardial infarctions occurring during the study according to the specific subtypes, as described in the Third Universal Definition of Myocardial Infarction and this classification might have allowed a more in-depth understanding of the effect of rivaroxaban on this important outcome.

In conclusion, COMPASS shows that addition of low-dose rivaroxaban to aspirin in patients with coronary artery disease, who are being well treated, reduces major vascular events. Although there is an increase in bleeding, this excess risk does not offset the benefits of adding rivaroxaban to aspirin, and addition of rivaroxaban to aspirin results in a significant reduction in mortality. The addition of low-dose rivaroxaban to current evidence-based therapies will be of clinical benefit in a broad group of individuals with coronary artery disease.

Contributors

All of the authors (except LD) served on the Steering Committee and thus were responsible for the design and execution of the study as well as for manuscript review and for decision to publish. LD was responsible for data integrity and for primary data analysis. In addition, SJC, JWE, JB, SSA, and SY were responsible for day to day operations of the coordinating centre. GD, FL, KM, MO'D, ALD, J-WH, ANP, AAA, EL, LL, CT-P, PW, APM, CF, MH, KY, TJG, KRHB, and JDV all served as Country National Leaders with responsibility for site management within their countries. NCB, SDB, DLB, and KAAF were members of the Operations Committee which met frequently to manage ongoing study scientific issues.

Declaration of interests

SJC reports grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, during the conduct of the study, and grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Janssen, AstraZeneca, Portola, and Sanofi Aventis outside the submitted work. JWE reports grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo during the conduct of the study, and grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Janssen, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Sanofi Aventis outside the submitted work. FL reports grants and personal fees from Bayer during the conduct of the study; personal fees from Pfizer; and grants and personal fees from Merck, Sharp & Dohme, Sanofi-Aventis, and Boehringer Ingelheim outside the submitted work. MO'D reports that his institution received grants from Population Health Research Institute/Bayer, during the conduct of the study. ALD reports grants, personal fees, and non-financial support from the Population Health Research Institute during the conduct of the study, and personal fees from Pfizer and Boehringer Ingelheim outside the submitted work. J-WH reports grants from the Population Health Research Institute during the conduct of the study. ANP reports grants and personal fees from Pfizer, Bayer, Janssen, AstraZeneca, Sanofi-Aventis, and Merck, Sharp & Dohme outside the submitted work. AAA reports consultancy fees from Boehringer Ingelheim outside the submitted work. EL reports personal fees from Bayer outside the submitted work. LL reports grants from the Population Health Research Institute during the conduct of the study. CT-P reports grants and personal fees from Bayer during the conduct of the study, and grants from Biotronic outside the submitted work. APM reports personal fees from Novartis, Bayer, Cardiorentis, and Fresenius outside the submitted work. CF reports personal fees from the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada during the conduct of the study. TJG reports personal fees from the Public Health Reasearch Institute during the conduct of the study, and personal fees from Sanofi Aventis outside the submitted work. DLB reports personal fees from the Population Health Research Institute during the conduct of the study, grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, Roche, Pfizer, Forest Laboratories/AstraZeneca, Ischemix, Amgen, Eli Lilly, Chiesi, Ironwood, and The Medicines Company; personal fees from the Mayo Clinic, the Population Health Research Institute, Belvoir Publications, Slack Publications, WebMD, Elsevier, HMP Communications, Harvard Clinical Research Institute, Journal of the American College of Cardiology, Cleveland Clinic, Mount Sinai School of Medicine, Duke Clinical Research Institute; personal fees and non-financial support from the American College of Cardiology and the Society of Cardiovascular Patient Care; non-financial support from the American Heart Association; and non-financial relationships with Medscape Cardiology, Regado Biosciences, Boston VA Research Institute, Veterans Administration, Merck, Clinical Cardiology, St Jude Medical, Biotronik, Cardax, American College of Cardiology, Boston Scientific, FlowCo, PLx Pharma, and Takeda, outside the submitted work. KRHB reports grants from Bayer during the conduct of the study; and advisory board fees from Janssen outside the submitted work. NCB reports employment by Bayer during the conduct of the study. SDB reports employment by Bayer during the conduct of the study. SSA reports personal fees from Bayer and Novartis outside the submitted work. JDV reports personal fees from Novartis outside the submitted work. KAAF reports grants and personal fees from Bayer/Janssen during the conduct of the study, and grants and personal fees from AstraZeneca, personal fees from Sanofi/Regeneron and Eli Lilly outside the submitted work. SY reports grants and personal fees from Bayer during the conduct of the study. All other authors declare no competing interests.

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