ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

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ABSTRACT

BACKGROUND

We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS

In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

RESULTS

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=−4.126), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424.)

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DESPITE THE USE OF EFFECTIVE SECOND-ary prevention strategies, 5 to 10% of patients with cardiovascular disease have recurrent events each year.[1] When used for secondary prevention, aspirin results in a 19% lower risk of major adverse cardiovascular events and a 9% lower risk of cardiovascular death than placebo.[2] Long-term treatment with a vitamin K antagonist, alone or in combination with aspirin, is superior to aspirin for secondary prevention after acute myocardial infarction but is associated with more bleeding, including intracranial bleeding.[3] Thus, anticoagulation has generally not been recommended for patients in this context.

Rivaroxaban is a selective direct factor Xa inhibitor that is used to prevent and treat venous thromboembolism[4-6] and to prevent stroke or systemic embolism in atrial fibrillation.[7] Among patients with an acute coronary syndrome, the risk of cardiovascular death, stroke, or myocardial infarction was lower with rivaroxaban (2.5 mg or 5 mg twice daily) than with placebo, and mortality was lower with the dose of 2.5 mg twice daily than with placebo.[8] However, the risk of major bleeding was higher with rivaroxaban (at either dose) than with placebo. We designed the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial to test the hypothesis that rivaroxaban in combination with aspirin or given alone is more effective than aspirin alone in preventing recurrent cardiovascular events, with acceptable safety, in patients with stable atherosclerotic vascular disease.

METHODS

TRIAL CONDUCT

The COMPASS trial, conducted at 602 centers in 33 countries, is a double-blind, double-dummy, randomized trial using a 3-by-2 partial factorial design and involving patients with a history of stable atherosclerotic vascular disease.[9] In one randomized comparison (now completed and reported here), rivaroxaban with or without aspirin was compared with aspirin alone. In the other randomized comparison (still ongoing), pantoprazole is being compared with placebo in patients participating in the trial who are not receiving a proton-pump inhibitor. For an overview of the study design, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial sponsor is Bayer. The steering committee, comprising Population Health Research Institute (PHRI) investigators, study leaders in each country, and Bayer representatives, was responsible for the development of the protocol, which is available at NEJM.org, and for the conduct and oversight of the study. The protocol was approved by the relevant health authorities and institutional review boards. A list of participating investigators and committee members is provided in the Supplementary Appendix. All the data analyses were independently performed at PHRI. The first author vouches for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

ELIGIBILITY

Patients were eligible if they provided written informed consent and met the criteria for coronary artery disease, peripheral arterial disease, or both (see the Supplementary Appendix). Patients with coronary artery disease who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [GFR] <60 ml per minute, heart failure, or nonlacunar ischemic stroke ≥1 month earlier). Exclusion criteria were a high bleeding risk; a recent stroke or previous hemorrhagic or lacunar stroke; severe heart failure; advanced stable kidney disease (estimated GFR <15 ml per minute); the use of dual antiplatelet therapy, anticoagulation, or other antithrombotic therapy; and noncardiovascular conditions deemed by the investigator to be associated with a poor prognosis. In addition, patients receiving a proton-pump inhibitor were not eligible for the pantoprazole randomization. Written informed consent was obtained from all the participants.

RANDOMIZATION AND FOLLOW-UP

Eligible participants (except those who underwent randomization 4 to 14 days after coronary-artery bypass graft [CABG] surgery) entered a run-in phase during which they received a rivaroxaban-matched placebo twice daily and aspirin at a dose of 100 mg once daily. The purpose of the run-in phase was to identify participants who were unwilling or unable to adhere to the trial regimen, who had adverse events, or who were otherwise

not suitable for randomization. Patients who underwent randomization 4 to 14 days after CABG surgery were not required to participate in the run-in phase because thrombotic graft occlusion is most common during the first few weeks after surgery and we sought to enroll such patients promptly.

Participants who adhered to the assigned regimen and who did not have adverse events, as well as those enrolled 4 to 14 days after CABG surgery, were randomly assigned in a 1:1:1 ratio to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily) with an aspirin-matched placebo once daily, or aspirin (100 mg once daily) with a rivaroxaban-matched placebo twice daily, stratified according to center and the use of proton-pump inhibitor therapy at the time of randomization. Study aspirin was enteric-coated. Patients who were eligible for the proton-pump inhibitor randomization were also randomly assigned in a 1:1 ratio to receive pantoprazole (40 mg once daily) or matched placebo. After randomization, participants were seen at 1 and 6 months and then at 6-month intervals.

OUTCOMES

The primary efficacy outcome for the randomized comparison of rivaroxaban with or without aspirin versus aspirin alone was the composite of cardiovascular death, stroke, or myocardial infarction. The main safety outcome was a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding and included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay). Unlike the ISTH criteria,[10] we considered all bleeding that led to presentation to an acute care facility or hospitalization as major.

Three secondary efficacy outcomes were specified: the composite of ischemic stroke, myocardial infarction, acute limb ischemia, or death from coronary heart disease; the composite of ischemic stroke, myocardial infarction, acute limb ischemia, or cardiovascular death; and death from any cause. Tertiary efficacy outcomes included individual components of the primary and secondary outcomes, as well as hospitalization for cardiovascular causes, revascularization, limb amputation, stent thrombosis, angina, heart failure, venous thromboembolism, resuscitated cardiac arrest, and a new diagnosis of cancer. The net-clinical-benefit outcome was the composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ. The main outcome for the pantoprazole versus placebo randomization was upper gastrointestinal complications.[9] Event definitions and a full list of prespecified events included in this report are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We planned on enrolling 27,400 participants. As an event-driven trial, with an expected control-group event rate of 3.3 per 100 person-years, it was designed to continue until at least 2200 participants had a confirmed primary efficacy outcome, thereby providing 90% power to detect a 20% lower risk in each of the two comparisons of rivaroxaban versus aspirin.

An independent data and safety monitoring board monitored the study, with formal stopping guidelines for efficacy and nonformal guidelines for safety. Two formal interim analyses of efficacy were planned, when 50% and 75% of primary efficacy events had occurred. A modified Haybittle–Peto rule was used, which required a difference of 4 SD at the first interim analysis that was consistent over a period of 3 months, and a consistent difference of 3 SD at the second interim analysis (see the Supplementary Appendix).

All the outcome events in all randomly assigned patients that occurred between randomization and the date of stopping the trial were included in the analysis, according to the intention-to-treat principle. Comparisons between each of the rivaroxaban-based groups and the common aspirin control group were performed with the use of two separate log-rank tests stratified according to treatment with a proton-pump inhibitor (not randomly assigned to a proton-pump inhibitor, pantoprazole at a dose of 40 mg once daily, or a pantoprazole-matched placebo once daily). 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%[11] (see the Supplementary Appendix). However, an early stop of both antithrombotic treatment groups for efficacy had not been anticipated, and therefore a strategy for

formal testing of secondary outcomes at the interim analysis was not prespecified.

Kaplan–Meier estimates of the cumulative risk were used to evaluate the timing of event occurrences in the three antithrombotic treatment groups. Hazard ratios and corresponding 95% confidence intervals were obtained from stratified Cox proportional-hazards models. The assumptions of the Cox models were verified with plots of log of negative log of the survival function against the log of time. All reported P values are two-sided.

RESULTS

PARTICIPANTS

From March 2013 through May 2016, a total of 27,395 persons who successfully completed the run-in phase or who were enrolled 4 to 14 days after CABG surgery were randomly assigned to rivaroxaban plus aspirin, rivaroxaban, or aspirin (Fig. S1 in the Supplementary Appendix). A total of 2320 participants did not successfully complete the run-in phase and were excluded.

Baseline characteristics are presented in Table 1. The mean age of participants was 68.2 years, and 22.0% were women. Lipid-lowering agents were used by 89.8%, and angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers by 71.2%. The mean systolic blood pressure was 136 mm Hg, the mean diastolic blood pressure 78 mm Hg, and the mean total cholesterol level 4.2 mmol per liter (162 mg per deciliter). A total of 90.6% of the participants had a history of coronary artery disease, and 27.3% had a history of peripheral arterial disease.

EARLY TERMINATION, FOLLOW-UP, AND ADHERENCE

At the first formal interim analysis for efficacy (50% of planned events), the independent data and safety monitoring board recommended early termination of the randomized comparison of rivaroxaban with or without aspirin versus aspirin alone on February 6, 2017, having observed a consistent difference in the primary efficacy outcome in favor of rivaroxaban plus aspirin ($z=-4.592$).

The z statistic for the comparison of rivaroxaban plus aspirin versus aspirin alone was larger than the prespecified 4 SD, but the z statistic for the comparison of rivaroxaban alone versus aspirin alone had not met this criterion ($z=-2.44$).

Because there was a statistically significant effect for both comparisons, the data and safety monitoring board recommended stopping the rivaroxaban and aspirin groups of the trial.

Follow-up for the comparison of pantoprazole versus placebo continued and is ongoing. Vital status was available for 27,331 participants (99.8%) to February 6, 2017, and the mean duration of follow-up of these participants was 23 months (maximum duration, 47 months). At the final visit for this component of the trial, the percentage of participants who had permanently discontinued study treatment was 16.5% in the rivaroxaban-plus-aspirin group, 17.0% in the rivaroxaban-alone group, and 15.7% in the aspirin-alone group.

PRIMARY EFFICACY OUTCOME

A primary outcome event of cardiovascular death, stroke, or myocardial infarction occurred in 379 patients (4.1%) who were assigned to rivaroxaban plus aspirin, 448 (4.9%) who were assigned to rivaroxaban alone, and 496 (5.4%) who were assigned to aspirin alone (Table 2 and Fig. 1). For the comparison of rivaroxaban (2.5 mg twice daily) plus aspirin with aspirin alone, the hazard ratio for the primary outcome was 0.76 (95% confidence interval [CI], 0.66 to 0.86; P<0.001; $z=-4.126$). For the comparison of rivaroxaban (5 mg twice daily) alone with aspirin alone, the hazard ratio was 0.90 (95% CI, 0.79 to 1.03; P=0.12; $z=-1.575$).

SECONDARY EFFICACY OUTCOMES

The secondary composite outcome of ischemic stroke, myocardial infarction, acute limb ischemia, or death from coronary heart disease occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (329 patients [3.6%] vs. 450 patients [4.9%]; hazard ratio, 0.72; 95% CI, 0.63 to 0.83; P<0.001) (Table 2). The secondary outcome of ischemic stroke, myocardial infarction, acute limb ischemia, or cardiovascular death also occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (389 patients [4.3%] vs. 516 patients [5.7%]; hazard ratio, 0.74; 95% CI, 0.65 to 0.85; P<0.001). There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01). The threshold P value us-

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Age — yr	68.3±7.9	68.2±7.9	68.2±8.0
Female sex — no. (%)	2059 (22.5)	1972 (21.6)	1989 (21.8)
Body-mass index†	28.3±4.8	28.3±4.6	28.4±4.7
Blood pressure — mm Hg			
Systolic	136±17	136±18	136±18
Diastolic	77±10	78±10	78±10
Cholesterol — mmol/liter	4.2±1.1	4.2±1.1	4.2±1.1
Tobacco use — no. (%)	1944 (21.2)	1951 (21.4)	1972 (21.6)
Hypertension — no. (%)	6907 (75.5)	6848 (75.1)	6877 (75.4)
Diabetes — no. (%)	3448 (37.7)	3419 (37.5)	3474 (38.1)
Previous stroke — no. (%)	351 (3.8)	346 (3.8)	335 (3.7)
Previous myocardial infarction — no. (%)	5654 (61.8)	5653 (62.0)	5721 (62.7)
Heart failure — no. (%)	1963 (21.4)	1960 (21.5)	1979 (21.7)
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)
Peripheral arterial disease — no. (%)§	2492 (27.2)	2474 (27.1)	2504 (27.4)
Estimated GFR — no. (%)¶			
<30 ml/min	77 (0.8)	80 (0.9)	86 (0.9)
30 to <60 ml/min	1977 (21.6)	2028 (22.2)	2028 (22.2)
≥60 ml/min	7094 (77.5)	7005 (76.8)	7012 (76.8)
Race — no. (%)‖			
White	5673 (62.0)	5672 (62.2)	5682 (62.3)
Black	76 (0.8)	94 (1.0)	92 (1.0)
Asian	1451 (15.9)	1421 (15.6)	1397 (15.3)
Other	1952 (21.3)	1930 (21.2)	1955 (21.4)
Geographic region — no. (%)			
North America	1304 (14.2)	1305 (14.3)	1309 (14.3)
South America	2054 (22.4)	2036 (22.3)	2054 (22.5)
Western Europe, Israel, Australia, or South Africa	2855 (31.2)	2845 (31.2)	2855 (31.3)
Eastern Europe	1607 (17.6)	1612 (17.7)	1604 (17.6)
Asia–Pacific	1332 (14.6)	1319 (14.5)	1304 (14.3)
Medication — no. (%)			
ACE inhibitor or ARB	6475 (70.7)	6581 (72.2)	6462 (70.8)
Calcium-channel blocker	2413 (26.4)	2374 (26.0)	2482 (27.2)
Diuretic	2727 (29.8)	2666 (29.2)	2746 (30.1)
Beta-blocker	6389 (69.8)	6401 (70.2)	6394 (70.1)
Lipid-lowering agent	8239 (90.0)	8204 (90.0)	8158 (89.4)
NSAID	531 (5.8)	466 (5.1)	473 (5.2)
Nontrial PPI	3268 (35.7)	3266 (35.8)	3264 (35.8)

* Plus–minus values are means ±SD. There were no significant differences among the three randomized groups. Participants in the rivaroxaban-plus-aspirin group received 2.5 mg of rivaroxaban twice daily and 100 mg of aspirin once daily. Participants in the rivaroxaban-alone group received 5 mg of rivaroxaban twice daily and an aspirin-matched placebo once daily. Participants in the aspirin-alone group received 100 mg of aspirin once daily and a rivaroxaban-matched placebo twice daily. To convert cholesterol values to milligrams per deciliter, divide by 0.02586. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, NSAID nonsteroidal antiinflammatory drug, and PPI proton-pump inhibitor.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Shown are patients with a history of coronary artery disease irrespective of whether it met the inclusion criteria for the trial.
§ Shown are patients with a history of peripheral arterial disease irrespective of whether it met the inclusion criteria for the trial.
¶ The GFR was calculated by means of the Chronic Kidney Disease Epidemiology Collaboration formula. Data on GFR were missing for four patients in the rivaroxaban-plus-aspirin group and four in the rivaroxaban-alone group.
‖ Race was reported by the patient.

ing the Hochberg procedure for each of the above comparisons was 0.0025. For the regimen of rivaroxaban alone as compared with aspirin alone, because no significant effect was seen for the primary composite outcome, formal testing of the secondary outcomes was not performed.

BLEEDING AND OTHER ADVERSE EVENTS

Major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001) (Table 3), mainly owing to a difference in bleeding that led to presentation to an acute care facility or hospitalization. Most of the excess major bleeding was into the gastrointestinal tract, with no significant between-group difference in the rate of fatal bleeding, intracranial bleeding, or symptomatic bleeding into a critical organ. The rate of major bleeding as defined by the ISTH criteria (the composite of fatal bleeding, bleeding into a critical organ, bleeding requiring ≥2 units of transfusion within 48 hours, and bleeding associated with a decrease in the hemoglobin level of ≥2 g per deciliter) was significantly greater with rivaroxaban plus aspirin than with aspirin alone.

Major bleeding events occurred in more patients in the rivaroxaban-alone group than in the aspirin-alone group (255 patients [2.8%] vs. 170 patients [1.9%]; hazard ratio, 1.51; 95% CI, 1.25 to 1.84; P<0.001) (Table 3). The excess major bleeding included symptomatic bleeding into a critical organ and bleeding that led to hospitalization.

Serious adverse events were reported in 721 patients (7.9%) assigned to rivaroxaban plus aspirin, 702 (7.7%) assigned to rivaroxaban alone, and 662 (7.3%) assigned to aspirin alone. Details of serious adverse events according to system organ class are shown in Table S2 in the Supplementary Appendix.

NET CLINICAL BENEFIT

The risk of the composite net-clinical-benefit outcome of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ was lower with rivaroxaban plus aspirin than with aspirin alone (431 patients [4.7%] vs. 534 patients [5.9%]; hazard ratio, 0.80; 95% CI, 0.70 to 0.91; P<0.001) (Table 3). The risk of the net-clinical-benefit outcome was not significantly lower with rivaroxaban alone than with aspirin alone.

SUBGROUP ANALYSES

The effects of rivaroxaban plus aspirin as compared with aspirin alone on the primary outcome (Fig. 2) and on major bleeding (Fig. S2 in the Supplementary Appendix) were consistent among subgroups that were defined according to age, sex, geographic region, race or ethnic group, body weight, renal function, and history of cardiovascular risk factors (tobacco use, hypertension, diabetes, or dyslipidemia). Results in participants who met the eligibility criteria for coronary artery disease and in those who met the eligibility criteria for peripheral arterial disease were also consistent and are being reported separately.[12,13]

DISCUSSION

Among patients with stable atherosclerotic vascular disease, a high proportion of whom were receiving proven secondary prevention therapies, the rate of the primary outcome (a composite of cardiovascular death, stroke, or myocardial infarction) was lower by 24% with rivaroxaban (2.5 mg twice daily) plus aspirin than with aspirin alone (4.1% vs. 5.4%), but the rate of major bleeding was higher by 70% (3.1% vs. 1.9%). The rate of the net-clinical-benefit outcome was lower by 20% with rivaroxaban plus aspirin than with aspirin alone (4.7% vs. 5.9%). The comparison of rivaroxaban (5 mg twice daily) alone with aspirin alone did not show a significant difference in the primary outcome or the net-clinical-benefit outcome, but the rate of major bleeding was higher with rivaroxaban alone.

Various antithrombotic regimens have been tested as alternatives to aspirin for long-term cardiovascular prevention. Trials of vitamin K antagonists involving patients with stable cardiovascular disease showed a reduction in the risk of subsequent cardiovascular events,[3] but there was no benefit in patients with peripheral arterial disease,[14] and there was a significant increase in bleeding, including intracranial bleeding.[3,14] Among patients with stable cardiovascular disease, those who received clopidogrel had a lower risk of major adverse cardiovascular events than those who received aspirin, but there was no significant difference in the risk of cardiovascular death or death from any cause.[15] Among patients with symptomatic stable cardiovascular disease or multiple risk factors, the combination of clopidogrel and aspirin did not result in a significantly lower rate of major adverse cardio-

Table 2. Efficacy Outcomes.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001	0.90 (0.79–1.03)	0.12
Secondary outcomes‡							
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63–0.83)	<0.001	0.88 (0.77–1.01)	0.06
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65–0.85)	<0.001	0.88 (0.77–0.99)	0.04
Death from any cause	313 (3.4)	366 (4.0)	378 (4.1)	0.82 (0.71–0.96)	0.01	0.97 (0.84–1.12)	0.67
Other outcomes§							
CV death	160 (1.7)	195 (2.1)	203 (2.2)	0.78 (0.64–0.96)	0.02	0.96 (0.79–1.17)	0.69
Non-CV death	153 (1.7)	171 (1.9)	175 (1.9)	0.87 (0.70–1.08)	0.20	0.98 (0.79–1.21)	0.84
Death from CHD	86 (0.9)	128 (1.4)	117 (1.3)	0.73 (0.55–0.96)	0.03	1.09 (0.85–1.41)	0.48
Stroke¶	83 (0.9)	117 (1.3)	142 (1.6)	0.58 (0.44–0.76)	<0.001	0.82 (0.65–1.05)	0.12
Ischemic or uncertain type	68 (0.7)	91 (1.0)	132 (1.4)	0.51 (0.38–0.68)	<0.001	0.69 (0.53–0.90)	0.006
Hemorrhagic	15 (0.2)	27 (0.3)	10 (0.1)	1.49 (0.67–3.31)	0.33	2.70 (1.31–5.58)	0.005
Myocardial infarction	178 (1.9)	182 (2.0)	205 (2.2)	0.86 (0.70–1.05)	0.14	0.89 (0.73–1.08)	0.24
Heart failure	197 (2.2)	191 (2.1)	192 (2.1)	1.02 (0.84–1.24)	0.84	0.99 (0.81–1.21)	0.95
Venous thromboembolism	25 (0.3)	36 (0.4)	41 (0.4)	0.61 (0.37–1.00)	0.05	0.88 (0.56–1.38)	0.58
Hospitalization							
For CV causes	1303 (14.2)	1317 (14.4)	1394 (15.3)	0.92 (0.86–1.00)	0.04	0.94 (0.87–1.01)	0.11
For non-CV causes	1701 (18.6)	1649 (18.1)	1624 (17.8)	1.05 (0.98–1.13)	0.14	1.02 (0.95–1.09)	0.54

* ALI denotes acute limb ischemia, CHD coronary heart disease, CI confidence interval, and CV cardiovascular.
† Only P values for the primary outcome are confirmatory.
‡ For details on statistical testing of secondary outcomes, see the Supplementary Appendix.
§ There was no adjustment for the testing of these outcomes.
¶ One participant in the rivaroxaban-alone group had more than one type of stroke. A total of 26 of the 392 participants who were reported to have atrial fibrillation had a stroke: 7 participants in the rivaroxaban-plus-aspirin group, 8 participants in the rivaroxaban-alone group, and 11 participants in the aspirin-alone group.

vascular events or death from any cause than aspirin alone.[16] Among patients who had had myocardial infarction 1 to 3 years previously, the combination of ticagrelor and aspirin resulted in a lower rate of major adverse cardiovascular events and a higher rate of major bleeding than aspirin alone, and there was no significant between-group difference in mortality.[17] Among patients with stable peripheral arterial disease, ticagrelor did not result in a significantly lower rate of major adverse cardiovascular events than clopidogrel.[18] Among patients with stable cardiovascular disease who were receiving single or

dual antiplatelet therapy, vorapaxar resulted in a lower rate of major adverse cardiovascular events and a higher rate of moderate or severe bleeding than placebo, with no significant between-group difference in mortality.[19]

The potential benefit of rivaroxaban in patients with cardiovascular disease was previously evaluated in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial. This trial tested rivaroxaban on a background of single or dual antiplatelet thera-

Figure 1. Cumulative Incidence of the Primary Efficacy Outcome among Participants Receiving Rivaroxaban plus Aspirin, Rivaroxaban Alone, or Aspirin Alone.

Participants in the rivaroxaban-plus-aspirin group received 2.5 mg of rivaroxaban twice daily and 100 mg of aspirin once daily. Participants in the rivaroxaban-alone group received 5 mg of rivaroxaban twice daily and an aspirin-matched placebo once daily. Participants in the aspirin-alone group received 100 mg of aspirin once daily and a rivaroxaban-matched placebo twice daily. The inset shows the same data on an expanded y axis.

py in patients with a recent acute coronary syndrome. Rivaroxaban at a dose of 2.5 mg twice daily or 5 mg twice daily resulted in a lower rate of major adverse cardiovascular events than placebo, and the dose of 2.5 mg twice daily resulted in lower mortality,[8] findings consistent with the COMPASS results. The mean duration of rivaroxaban treatment in the ATLAS ACS 2–TIMI 51 trial was 13.3 months, whereas persons enrolled in the COMPASS trial who had a history of myocardial infarction were enrolled a mean of 7.1 years after the acute event and continued to receive treatment for a mean of 23 months.

The definition of major bleeding in the COMPASS trial was based on the ISTH definition, which includes fatal bleeding, symptomatic bleeding into a critical area or organ, bleeding causing a decrease in the hemoglobin level of 2 g or more per deciliter, or bleeding that led to transfusion of 2 or more units of whole blood or

red cells. However, the definition used in the COMPASS trial, which had been adopted in response to a request from regulators, differed from the ISTH definition in that it did not take into account whether bleeding was associated with a decrease in the hemoglobin level or with blood transfusion, and it included any bleeding that led to hospitalization with or without an overnight stay, thus including events that would not be considered major bleeding in other trials. Although there was also a significant increase in the rate of major bleeding with rivaroxaban with the use of the ISTH scale, there were approximately one third fewer major bleeding events with this definition than with the use of the modified ISTH definition. Our definition of net clinical benefit balanced the lower risk of cardiovascular death, stroke, or myocardial infarction against the most serious bleeding events and showed a significant benefit of combination therapy.

Table 3. Bleeding Events and Net Clinical Benefit.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001	1.47 (1.16–1.87)	0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40	1.59 (1.00–2.53)	0.05
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09	1.58 (1.13–2.19)	0.006
Major bleeding according to ISTH criteria	206 (2.3)	175 (1.9)	116 (1.3)	1.78 (1.41–2.23)	<0.001	1.52 (1.20–1.92)	<0.001
Transfusion within 48 hr after bleeding	87 (1.0)	66 (0.7)	44 (0.5)	1.97 (1.37–2.83)	<0.001	1.50 (1.03–2.20)	0.03
Minor bleeding	838 (9.2)	741 (8.1)	503 (5.5)	1.70 (1.52–1.90)	<0.001	1.50 (1.34–1.68)	<0.001
Site of major bleeding							
Gastrointestinal	140 (1.5)	91 (1.0)	65 (0.7)	2.15 (1.60–2.89)	<0.001	1.40 (1.02–1.93)	0.04
Intracranial	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
Skin or injection site	28 (0.3)	28 (0.3)	12 (0.1)	2.31 (1.18–4.54)	0.01	2.34 (1.19–4.60)	0.01
Urinary	13 (0.1)	30 (0.3)	21 (0.2)	0.61 (0.31–1.23)	0.16	1.43 (0.82–2.50)	0.20
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001	0.94 (0.84–1.07)	0.36

* ICH denotes intracranial hemorrhage, and ISTH International Society on Thrombosis and Haemostasis.
† If a participant had more than one event of major bleeding, only the most serious bleeding event was counted in these analyses.
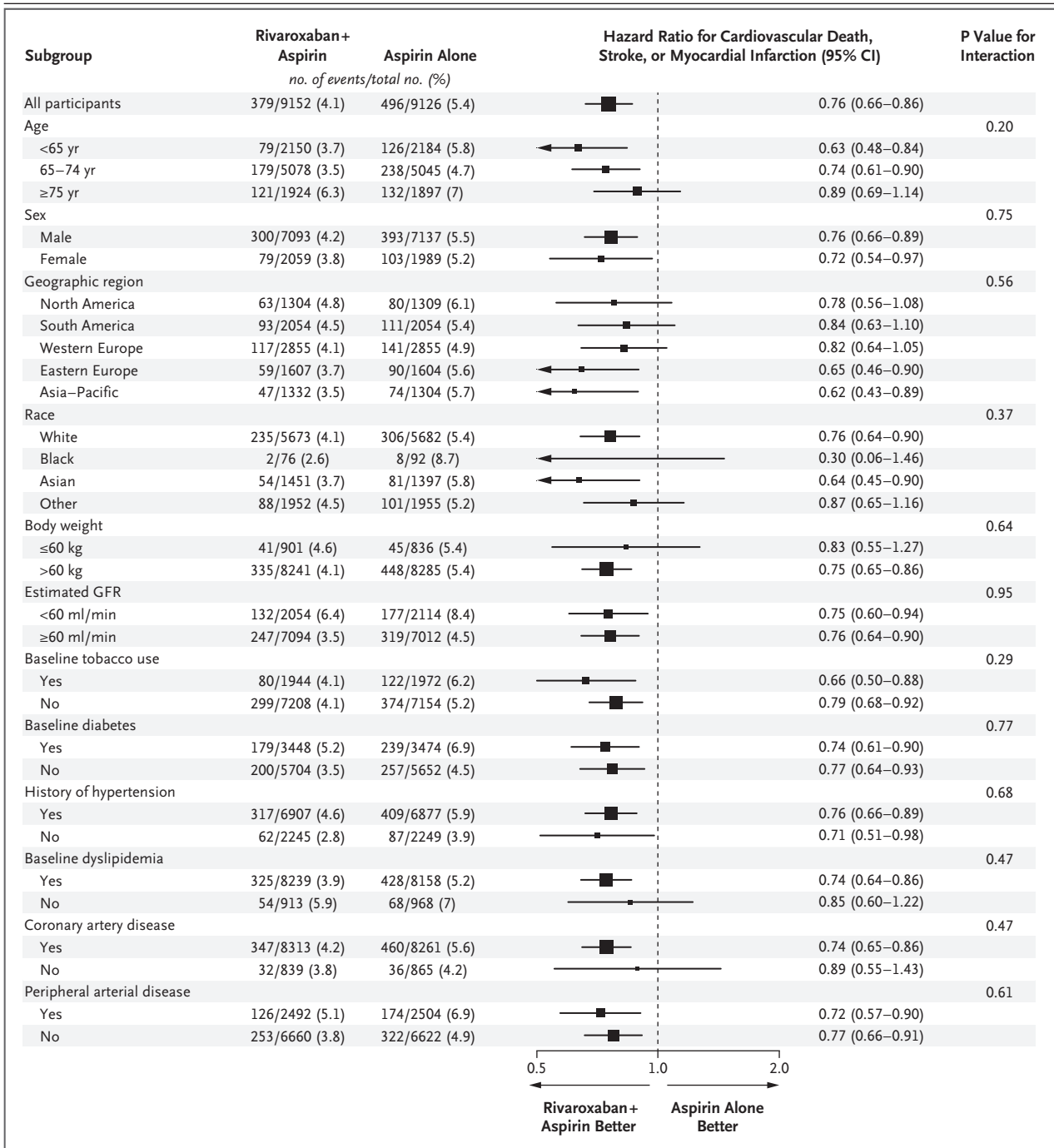
Subgroup	Rivaroxaban+ Aspirin	Aspirin Alone	Hazard Ratio for Cardiovascular Death, Stroke, or Myocardial Infarction (95% CI)		P Value for Interaction
	no. of events/total no. (%)				
All participants	379/9152 (4.1)	496/9126 (5.4)		0.76 (0.66–0.86)	
Age					0.20
<65 yr	79/2150 (3.7)	126/2184 (5.8)		0.63 (0.48–0.84)	
65–74 yr	179/5078 (3.5)	238/5045 (4.7)		0.74 (0.61–0.90)	
≥75 yr	121/1924 (6.3)	132/1897 (7)		0.89 (0.69–1.14)	
Sex					0.75
Male	300/7093 (4.2)	393/7137 (5.5)		0.76 (0.66–0.89)	
Female	79/2059 (3.8)	103/1989 (5.2)		0.72 (0.54–0.97)	
Geographic region					0.56
North America	63/1304 (4.8)	80/1309 (6.1)		0.78 (0.56–1.08)	
South America	93/2054 (4.5)	111/2054 (5.4)		0.84 (0.63–1.10)	
Western Europe	117/2855 (4.1)	141/2855 (4.9)		0.82 (0.64–1.05)	
Eastern Europe	59/1607 (3.7)	90/1604 (5.6)		0.65 (0.46–0.90)	
Asia–Pacific	47/1332 (3.5)	74/1304 (5.7)		0.62 (0.43–0.89)	
Race					0.37
White	235/5673 (4.1)	306/5682 (5.4)		0.76 (0.64–0.90)	
Black	2/76 (2.6)	8/92 (8.7)		0.30 (0.06–1.46)	
Asian	54/1451 (3.7)	81/1397 (5.8)		0.64 (0.45–0.90)	
Other	88/1952 (4.5)	101/1955 (5.2)		0.87 (0.65–1.16)	
Body weight					0.64
≤60 kg	41/901 (4.6)	45/836 (5.4)		0.83 (0.55–1.27)	
>60 kg	335/8241 (4.1)	448/8285 (5.4)		0.75 (0.65–0.86)	
Estimated GFR					0.95
<60 ml/min	132/2054 (6.4)	177/2114 (8.4)		0.75 (0.60–0.94)	
≥60 ml/min	247/7094 (3.5)	319/7012 (4.5)		0.76 (0.64–0.90)	
Baseline tobacco use					0.29
Yes	80/1944 (4.1)	122/1972 (6.2)		0.66 (0.50–0.88)	
No	299/7208 (4.1)	374/7154 (5.2)		0.79 (0.68–0.92)	
Baseline diabetes					0.77
Yes	179/3448 (5.2)	239/3474 (6.9)		0.74 (0.61–0.90)	
No	200/5704 (3.5)	257/5652 (4.5)		0.77 (0.64–0.93)	
History of hypertension					0.68
Yes	317/6907 (4.6)	409/6877 (5.9)		0.76 (0.66–0.89)	
No	62/2245 (2.8)	87/2249 (3.9)		0.71 (0.51–0.98)	
Baseline dyslipidemia					0.47
Yes	325/8239 (3.9)	428/8158 (5.2)		0.74 (0.64–0.86)	
No	54/913 (5.9)	68/968 (7)		0.85 (0.60–1.22)	
Coronary artery disease					0.47
Yes	347/8313 (4.2)	460/8261 (5.6)		0.74 (0.65–0.86)	
No	32/839 (3.8)	36/865 (4.2)		0.89 (0.55–1.43)	
Peripheral arterial disease					0.61
Yes	126/2492 (5.1)	174/2504 (6.9)		0.72 (0.57–0.90)	
No	253/6660 (3.8)	322/6622 (4.9)		0.77 (0.66–0.91)	

```
         0.5          1.0          2.0
     Rivaroxaban+        Aspirin Alone
     Aspirin Better         Better
```

Figure 2. Subgroup Analyses for the Primary Outcome for the Comparison of Rivaroxaban plus Aspirin with Aspirin Alone.

The size of each box is proportional to the number of events. Arrows indicate that the limits of the confidence interval are not shown. The subgroup labeled "Western Europe" also includes participants in Israel, Australia, and South Africa. GFR denotes glomerular filtration rate.

There are a few limitations of the trial that should be considered. First, we did not specifically study patients with a previous stroke. However, of those enrolled, 1032 also had a history of stroke, and the benefits of the combination of rivaroxaban and aspirin in preventing cardiovascular death, stroke, or myocardial infarction were consistent in these patients. Furthermore, the combination of rivaroxaban and aspirin resulted in a lower rate of ischemic stroke than aspirin alone. Second, although the majority of patients were receiving proven secondary prevention therapies, and the blood pressure and total cholesterol levels were serially recorded during the study, we did not specifically record statin use or low-density lipoprotein cholesterol levels at baseline, and the trial protocol did not specifically emphasize aggressive use of secondary prevention therapies to lower blood pressure and cholesterol levels. However, the results were consistent in patients with baseline blood pressure below or above the mean and in those with baseline cholesterol levels below or above the median, supporting the conclusion that the benefits of combination therapy are additive to those of other proven secondary preventive therapies. Third, trials that are stopped early for efficacy may overestimate the treatment effect. However, before the time of stopping, the data and safety monitoring board had observed a progressive increase in benefit of the combination of rivaroxaban and aspirin for more than 1 year. Furthermore, the data reported here include additional events that occurred before the cutoff but were not reported at the time of stopping the study and exclude some events that were refuted during adjudication. It is noteworthy that the results based on events reported by the sites and after adjudication are nearly identical (Table S3 in the Supplementary Appendix).

In conclusion, in patients with stable atherosclerotic vascular disease, we compared three antiplatelet regimens: rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), and aspirin (100 mg once daily). The risk of major adverse cardiovascular events was significantly lower with the combination of rivaroxaban plus aspirin than with aspirin alone, and the risk of major bleeding was significantly higher. Rivaroxaban alone did not result in a significantly lower risk of major adverse cardiovascular events than aspirin alone and resulted in a significantly higher risk of major bleeding.

APPENDIX

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REFERENCES

1. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350-7.

2. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.

3. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. J Am Coll Cardiol 2003;41:Suppl S: 62S-69S.

4. Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty: pooled analysis of four studies. Thromb Haemost 2011;105:444-53.

5. The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.

6. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.

7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883-91.

8. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9-19.

9. Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, design and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial. Can J Cardiol 2017;33:1027-35.

10. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.

11. Brechenmacher T, Xu J, Dmitrienko A, Tamhane AC. A mixture gatekeeping procedure based on the Hommel test for clinical trial applications. J Biopharm Stat 2011;21:748-67.

12. Connolly SJ, Eikelboom JW, Fox KAA, et al. Randomized trial of rivaroxaban in stable coronary artery disease. Lancet (in press).

13. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban in patients with stable peripheral or carotid artery disease: an international randomized, double-blind, placebo-controlled trial. Lancet (in press).

14. The Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med 2007;357:217-27.

15. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.

16. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.

17. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800.

18. Hiatt WR, Fowkes FGR, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med 2017;376:32-40.

19. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012;366:1404-13.

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