Circulation

ORIGINAL RESEARCH ARTICLE

Stroke Outcomes in the COMPASS Trial

Mukul Sharma, MD, MSc et al

BACKGROUND: Strokes were significantly reduced by the combination of rivaroxaban plus aspirin in comparison with aspirin in the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies). We present detailed analyses of stroke by type, predictors, and antithrombotic effects in key subgroups.

METHODS: Participants had stable coronary artery or peripheral artery disease and were randomly assigned to receive aspirin 100 mg once daily (n=9126), rivaroxaban 5 mg twice daily (n=9117), or rivaroxaban 2.5 mg twice daily plus aspirin (n=9152). Patients who required anticoagulation or had a stroke within 1 month, previous lacunar stroke, or intracerebral hemorrhage were excluded.

RESULTS: During a mean follow-up of 23 months, fewer patients had strokes in the rivaroxaban plus aspirin group than in the aspirin group (83 [0.9% per year] versus 142 [1.6% per year]; hazard ratio [HR], 0.58; 95% CI, 0.44–0.76; *P*<0.0001). Ischemic/uncertain strokes were reduced by nearly half (68 [0.7% per year] versus 132 [1.4% per year]; HR, 0.51; 95% CI, 0.38–0.68; *P*<0.0001) by the combination in comparison with aspirin. No significant difference was noted in the occurrence of stroke in the rivaroxaban alone group in comparison with aspirin: annualized rate of 0.7% (HR, 0.82; 95% CI, 0.65–1.05). The occurrence of fatal and disabling stroke (modified Rankin Scale, 3–6) was decreased by the combination (32 [0.3% per year] versus 55 [0.6% per year]; HR, 0.58; 95% CI, 0.37–0.89; *P*=0.01). Independent predictors of stroke were prior stroke, hypertension, systolic blood pressure at baseline, age, diabetes mellitus, and Asian ethnicity. Prior stroke was the strongest predictor of incident stroke (HR, 3.63; 95% CI, 2.65–4.97; *P*<0.0001) and was associated with a 3.4% per year rate of stroke recurrence on aspirin. The effect of the combination in comparison with aspirin was consistent across subgroups with high stroke risk, including those with prior stroke.

CONCLUSIONS: Low-dose rivaroxaban plus aspirin is an important new antithrombotic option for primary and secondary stroke prevention in patients with clinical atherosclerosis.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01776424.

The full author list is available on page 1144.

Key Words: aspirin ■ atherosclerosis ■ prevention and control ■ randomized controlled trial ■ rivaroxaban ■ stroke

Sources of Funding, see page 1144

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- The combination of rivaroxaban 2.5 mg twice daily with aspirin 100 mg prevented stroke and disabling stroke better than aspirin in patients without atrial fibrillation with stable vascular disease without increasing the risk of hemorrhagic stroke.
- The effect was consistent across subgroups of baseline risk and particularly marked in those with a history of previous stroke.

What Are the Clinical Implications?

- Patients with coronary artery or peripheral artery disease and no recent events have a more efficacious treatment than aspirin to prevent stroke.
- This raises the hypothesis that combining anticoagulant and antiplatelet therapy may be better than either alone for stroke prevention.

Stroke is a leading cause of death and of disability-adjusted years of life lost.[1] Most strokes (77%) are first-ever strokes, underscoring the importance of effective primary prevention strategies.[2] Individuals with atherosclerosis have an increased risk of stroke,[3,4] and aspirin (along with blood pressure lowering and statin therapy) is recommended for cardiovascular prevention. However, aspirin produces only a 12% reduction in the risk of major vascular events (myocardial infarction, stroke, or vascular death) when used for primary prevention, and a 19% risk reduction when used for secondary prevention.[5] A more effective antithrombotic strategy for the prevention of major vascular events in patients with atherosclerosis has been an important unmet need.

The COMPASS trial (Cardiovascular Outcomes for People using Anticoagulation Strategies) tested rivaroxaban given alone or in combination with aspirin as an alternative to aspirin monotherapy for the prevention of vascular events in patients with stable coronary artery or peripheral artery disease.[6] The study was stopped after the independent data and safety monitoring board found clear evidence of benefit of the combination of rivaroxaban and aspirin. The main results have been reported and included a brief summary of the effect on strokes.[7] Here we report detailed information on stroke, including disability, independent predictors of stroke, and the effects of the combination of low-dose rivaroxaban and aspirin in comparison with aspirin according to risk status.

METHODS

Patients and Study Design

The COMPASS trial design, analysis plan, and main results have been previously published.[6,7] Requests for data access will be considered by the COMPASS Publications Committee on an individual basis beginning 4 years after publication of the main results.[7] COMPASS was a randomized, double-blind, double-dummy trial comparing rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, and rivaroxaban 5 mg twice daily with aspirin 100 mg once daily for the prevention of cardiovascular death, myocardial infarction, or stroke in patients with stable coronary artery disease or peripheral artery disease (including asymptomatic carotid artery stenosis ≥50% or previous carotid revascularization). In a partial factorial design, participants not already taking a proton pump inhibitor were also randomly assigned to receive pantoprazole or placebo. The study was approved by an institutional review board at each site, and all participants gave informed consent before study procedures.

Eligible patients had stable coronary artery disease, peripheral artery disease, or both.[2] Major exclusion criteria included high bleeding risk as defined by the investigator, severe heart failure, advanced kidney disease (estimated glomerular filtration rate <15 mL/min), or a requirement for dual antiplatelet therapy, anticoagulation (eg, atrial fibrillation), or other antithrombotic therapy. Patients were excluded if there was an ischemic stroke within 1 month, prior hemorrhagic stroke, or symptomatic lacunar stroke, because these groups were believed to have an increased risk of intracranial hemorrhage. Patients with asymptomatic lacunar infarcts detected by brain imaging were otherwise eligible.

Participants were recruited from 602 sites from 33 countries.[6] At the first planned formal interim analysis, the independent data-monitoring committee recommended termination of the rivaroxaban and aspirin arms of the study for clear evidence of benefit.[7]

Randomization and Masking

Participants were randomly assigned in a 1:1:1 ratio to receive low-dose rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone stratified by center and use of a proton pump inhibitor by using a central web-based system. A computer-generated randomization schedule was generated by the Population Health Research Institute. Participants, investigators, and study staff were blinded to treatment allocation, and each treatment group was double dummy.

Procedures

Stroke was defined as the presence of acute focal neurological deficit thought to be of vascular origin with signs and symptoms lasting ≥24 hours or to time of death. On the basis of neuroimaging or autopsy, strokes were further classified as ischemic stroke, hemorrhagic stroke (consisting of primary intracerebral/intraparenchymal brain hemorrhage or subarachnoid hemorrhage), or uncertain type of stroke (in the absence of relevant brain imaging or autopsy). Hemorrhagic stroke did not include hemorrhagic transformation of cerebral infarct, posttraumatic intracerebral hemorrhage, hemorrhage into a tumor, or hemorrhage into a vascular malformation. Subdural and epidural hematomas were not counted as strokes but as major bleeds. Transient ischemic attack was defined as an acute focal neurological deficit of vascular origin with signs and symptoms lasting <24 hours, irrespective of the presence of acute ischemia

by neuroimaging, but was not systematically collected. All strokes were adjudicated centrally by using a 2-tier process: first, by an automated algorithm that checked that key criteria for stroke were met; and second, by a stroke expert, if the algorithm did not confirm the event. All hemorrhagic strokes were adjudicated by a stroke expert. Adjudicators were unaware of treatment assignment.

The modified Rankin Scale (mRS) was obtained on participants with stroke at 7 days or hospital discharge. Scores range from 0, indicating no symptoms or disability, to 6, indicating death, with a score of 3 indicating moderate disability.[8,9] The Standard Assessment of Global Activities in the Elderly is a 16-item assessment with 4-level ordinal response scale that measures cognitive, instrumental, and basic activities of daily living, and functional abilities, as well, and was collected at study entry, at 2 years, and at the last visit.

Statistical Analysis

Analyses were conducted according to the intention-to-treat principle. All reported *P* values are 2-sided. Annualized event rates were calculated as number of participants with an outcome per total number of person-years of follow-up. Event rates were displayed as number of patients with an event per 100 patient-years of follow-up (%/y). Survival analyses were based on the time to a first event. Patients could have >1 event. Stratified Cox proportional hazards regression models were used to compare the effects of antithrombotic regimens on stroke incidence. Significance was tested using stratified log-rank tests. The strata variable was proton pump inhibitor use: not randomized to proton pump inhibitor, randomized to active pantoprazole, randomized to pantoprazole placebo. Relative risk reduction was calculated as 1 minus hazard ratio. Absolute risk reduction and the number-needed-to-treat per year were calculated as the difference of annualized event rates and the reciprocal of this difference, respectively. Baseline predictors of stroke were assessed using univariate and multivariable Cox proportional hazards regression models. Multivariable models were developed as follows: first, selected baseline characteristics were evaluated using univariate models; variables significant at *P*=0.20 for either all stroke, ischemic/uncertain stroke, or hemorrhagic stroke were included in multivariable model 0; next, variables significant at *P*=0.10 in model 0 for either of the 3 outcomes were included in model 1, which was the final model. Finally, the treatment effects of rivaroxaban/aspirin were examined in subgroups of important baseline variables, which were identified in multivariable analysis. Analyses were performed using SAS software for Linux, version 9.4 (SAS Institute Inc). This trial is registered with https://www.clinicaltrials.gov, Unique identifier NCT01776424, and is closed to new participants.

Role of the Funding Source

The study was designed by the Steering Committee, which included representatives from the sponsor, Bayer AG, who collaborated in the study design, reviewed the manuscript, and participated in the decision to publish. Site management, data collection, and analysis were done at the Population Health Research Institute, affiliated with McMaster University and Hamilton Health Sciences in Ontario, Canada. All authors had access to the data and made the final decision to publish.

Table 1. Antithrombotic Treatments and Stroke

Strokes	Rivaroxaban Plus Aspirin (n=9152)		Rivaroxaban Alone (n=9117)		Aspirin Alone (n=9126)		Rivaroxaban Plus Aspirin vs Aspirin Alone		Rivaroxaban Alone vs Aspirin Alone	
	No. of First Events* (%)	Annual Rate,† %/y	No. of First Events* (%)	Annual Rate,† %/y	No. of First Events* (%)	Annual Rate,† %/y	Hazard Ratio‡ (95% CI)	*P* Value	Hazard Ratio‡ (95% CI)	*P* Value
Stroke	83 (0.9)	0.5	117 (1.3)	0.7	142 (1.6)	0.8	0.58 (0.44–0.76)	<0.0001	0.82 (0.65–1.05)	0.12
Ischemic stroke	64 (0.7)	0.4	83 (0.9)	0.5	125 (1.4)	0.7	0.51 (0.38–0.69)	<0.0001	0.66 (0.50–0.88)	0.004
Secondary hemorrhagic transformation	5 (<0.1)	0.03	5 (<0.1)	0.03	14 (0.2)	0.08	0.35 (0.13–0.99)	0.04	0.36 (0.13–0.99)	0.04
Uncertain stroke	4 (<0.1)	0.02	8 (<0.1)	0.05	7 (<0.1)	0.04	0.57 (0.17–1.94)	0.36	1.14 (0.41–3.15)	0.80
Ischemic or uncertain stroke	68 (0.7)	0.4	91 (1.0)	0.5	132 (1.4)	0.8	0.51 (0.38–0.68)	<0.0001	0.69 (0.53–0.90)	0.006
Hemorrhagic stroke	15 (0.2)	0.09	27 (0.3)	0.2	10 (0.1)	0.06	1.49 (0.67–3.31)	0.33	2.70 (1.31–5.58)	0.005
Intracerebral/ intraparenchymal/ intraventricular	13 (0.1)	0.07	23 (0.3)	0.1	6 (<0.1)	0.03	2.15 (0.82–5.66)	0.11	3.83 (1.56–9.42)	0.002
Subarachnoid	2 (<0.1)	0.01	4 (<0.1)	0.02	4 (<0.1)	0.02	0.49 (0.09–2.70)	0.41	1.00 (0.25–4.00)	0.99
Death within 30 days of stroke	11 (0.1)	0.06	19 (0.2)	0.1	13 (0.1)	0.07	0.84 (0.38–1.88)	0.68	1.46 (0.72–2.96)	0.29
Modified Rankin Scale (mRS) at 7 days or discharge										
0–2	51 (0.6)	0.3	67 (0.7)	0.4	90 (1.0)	0.5	0.56 (0.40–0.79)	0.001	0.75 (0.54–1.02)	0.07
3–6	32 (0.3)	0.2	52 (0.6)	0.3	55 (0.6)	0.3	0.58 (0.37–0.89)	0.01	0.95 (0.65–1.38)	0.77

*Percent (%) is the proportion of patients with an outcome.
†Percent per year (%/y) is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have >1 event.
‡Hazard ratios (95% CI) are from the stratified Cox proportional hazards regression models. *P* values are from the stratified log-rank tests.

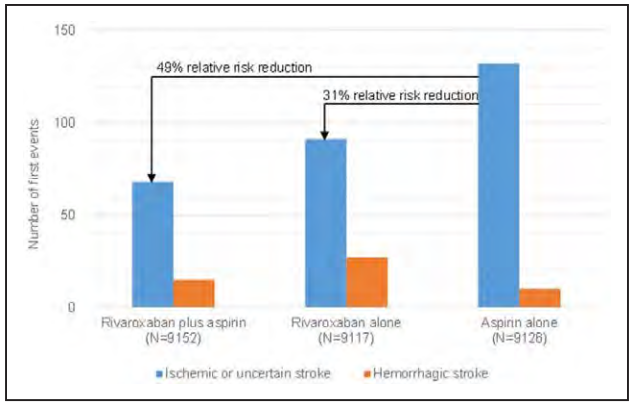

Figure 1. Stroke subtypes by treatment allocation.

RESULTS

The mean age of 27 395 randomly assigned participants was 68.2 years (SD=7.9), 21 375 (78%) were men, 24 824 (91%) had a history of coronary artery disease, 7470 (27%) had peripheral vascular disease, and 1032 (4%) had prior stroke, >1 month before randomization. Of the latter patients, 502 (49%) had peripheral artery disease and 797 (77%) had coronary artery disease. Carotid stenosis ≥50% or previous carotid intervention was present in 1919 (7%) participants. Baseline blood pressure averaged 136/78 mm Hg; 24 601 (90%) were taking a lipid-lowering drug, and 19 518 (71%) were taking an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker.

The mean follow-up was 23 months. The primary efficacy outcome of COMPASS, consisting of the composite of cardiovascular death, myocardial infarction, and stroke, occurred in significantly fewer participants in the rivaroxaban plus aspirin group than in the aspirin group (hazard ratio [HR], 0.76; 95% CI, 0.66–0.86; *P*<0.001).

There were 291 participants who had ischemic/uncertain strokes (1.0% of the study population), 52 (0.2%) hemorrhagic strokes (42 intraparenchymal/intracerebral hemorrhages and 10 subarachnoid hemorrhages), but this distribution varied importantly between treatment groups (see below). Mortality within 30 days of stroke occurred in 43 participants and did not differ significantly by treatment group (Table 1). Details of systemic hemorrhage type and fatal hemorrhage by treatment group has been previously reported.[7]

Effects of Antithrombotic Treatment Assignment on Stroke Incidence and Severity

Stroke occurred at an annualized rate of 0.8% in the aspirin alone group and was reduced to 0.5% in the rivaroxaban plus aspirin group (HR, 0.58; 95% CI, 0.44–0.76; *P*<0.0001). No significant difference was noted in the occurrence of stroke in the rivaroxaban alone group in comparison with aspirin: annualized rate of 0.7% (HR, 0.82; 95% CI, 0.65–1.05) (Table 1). The annualized rate of ischemic/uncertain stroke among participants assigned aspirin alone was 0.8% per year; ischemic/uncertain strokes were reduced by nearly half (HR, 0.51; 95% CI, 0.38–0.68; *P*<0.0001) by rivaroxaban plus aspirin in comparison with aspirin alone (Table 1, Figures 1 and 2A). The effect of rivaroxaban alone versus aspirin on ischemic/uncertain strokes was similarly substantial (HR, 0.69; 95% CI, 0.53–0.90; *P*=0.006). Hemorrhagic transformation of ischemic stroke was reduced in both rivaroxaban arms in comparison with aspirin monotherapy, occurring in 5 participants assigned rivaroxaban plus aspirin (HR, 0.35; 95% CI, 0.13–0.99), 5 participants assigned rivaroxaban alone (HR, 0.36; 95% CI, 0.13–0.99), and 14 participants assigned aspirin alone.

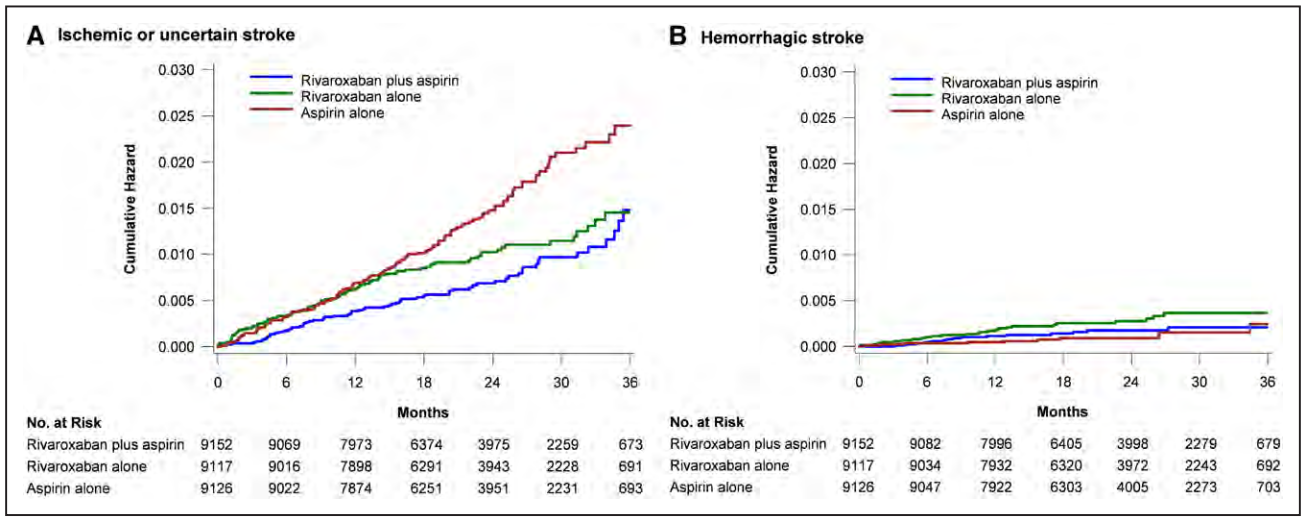

Figure 2. Incidence rates of stroke according to treatment group.
A, Ischemic or uncertain stroke. **B**, Hemorrhagic stroke.

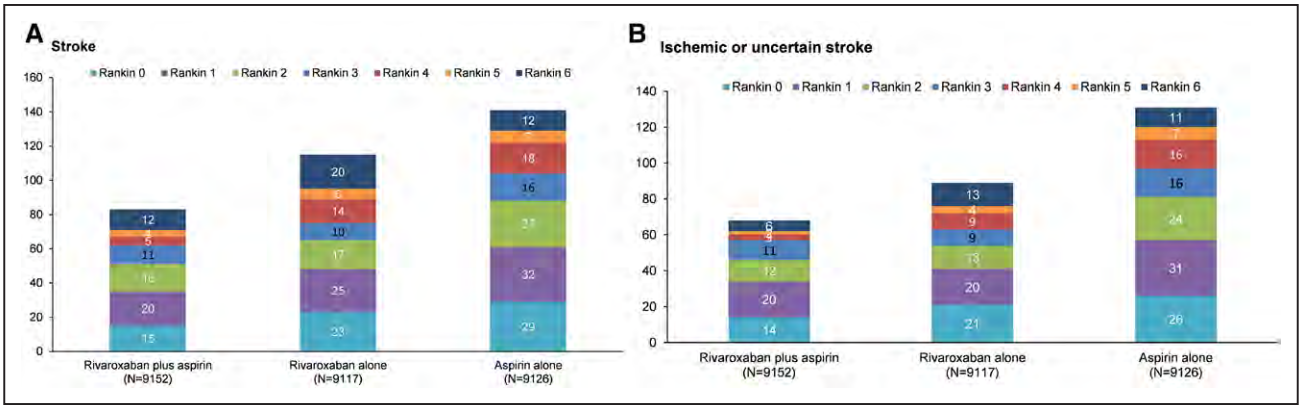

Figure 3. Distribution of the mRS scores of stroke and ischemic/uncertain stroke.
A, Stroke. **B**, Ischemic/uncertain stroke. The mRS scores of first events are shown. First strokes with missing mRS are not presented. mRS indicates modified Rankin Scale.

The incidence of hemorrhagic stroke was significantly increased by rivaroxaban alone in comparison with aspirin alone (27 versus 10; HR, 2.70; 95% CI, 1.31–5.58; *P*=0.005) but not by rivaroxaban plus aspirin versus aspirin alone (15 versus 10; HR, 1.49; 95% CI, 0.67–3.31; *P*=0.33) (Table 1). Kaplan-Meier plots did not demonstrate a higher early risk of hemorrhagic stroke following the initiation of rivaroxaban (Figure 2B).

The modified Rankin Scale (mRS) scores at day 7 or hospital discharge were similarly distributed for participants assigned aspirin alone and those assigned rivaroxaban plus aspirin (Table 1, Figure 3). The annualized rate of disabling or fatal stroke (mRS, 3–6) was 0.3% on aspirin alone and was reduced to 0.2% on rivaroxaban plus aspirin (HR, 0.58; 95% CI, 0.37–0.89; *P*=0.01). Participants assigned to rivaroxaban alone and aspirin alone had a similar rate of disabling or fatal stroke (mRS, 3–6) of 0.3% per year.

Standard Assessment of Global Activities in the Elderly scores were available at randomization for 339 participants among the 342 participants with stroke (99%) and at the final visit for 236 (69%). Mean Standard Assessment of Global Activities in the Elderly scores in participants experiencing a stroke increased between baseline and final visit in all 3 treatment allocations, but there was no significant difference according to antithrombotic treatment (Table 2).

Baseline Predictors of Stroke and Effect in Subgroups

Age, systolic and diastolic blood pressure, total cholesterol, history of hypertension, diabetes mellitus, prior stroke, heart failure, peripheral artery disease, lower estimated glomerular filtration rate, and Asian ethnicity were predictive of stroke on univariate analysis (Table I in the online-only Data Supplement). Carotid stenosis ≥50% or previous carotid revascularization was predictive of ischemic/uncertain stroke.

Independent predictors of stroke were age, systolic blood pressure at baseline, history of hypertension, diabetes mellitus, prior stroke, and Asian ethnicity (Table 3). Of these, prior stroke was the strongest predictor (HR, 3.63; 95% CI, 2.65–4.97; *P*<0.0001). Risk factors for ischemic/uncertain stroke were age, systolic blood pressure, total cholesterol, history of hypertension, diabetes mellitus, prior stroke, peripheral artery disease, and Asian ethnicity. Hemorrhagic stroke was associated with systolic

Table 2. mRS and SAGE Scores Among Participants With Stroke

Scores	Rivaroxaban Plus Aspirin (n=9152)		Rivaroxaban Alone (n=9117)		Aspirin Alone (n=9126)		Rivaroxaban Plus Aspirin vs Aspirin Alone		Rivaroxaban Alone vs Aspirin Alone	
	No. of Patients	Mean±SD	No. of Patients	Mean±SD	No. of Patients	Mean±SD	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value*
SAGE score										
Baseline	83	2.9±3.4	115	2.7±3.8	141	3.3±5.0	–0.4 (–1.6 to 0.9)	0.94	–0.6 (–1.7 to 0.6)	0.30
Final visit	57	5.4±6.1	76	5.2±5.7	101	4.5±5.8	0.9 (–1.0 to 2.9)	0.32	0.7 (–1.0 to 2.4)	0.20
Change between baseline and final visit	57	2.3±5.8	75	2.9±4.2	101	1.6±5.0	0.7 (–1.1 to 2.4)	0.54	1.2 (–0.2 to 2.6)	0.01
mRS score										
At 7 days or discharge	83	2.4±2.0	115	2.6±2.1	141	2.2±1.9	0.2 (–0.4 to 0.7)	0.66	0.3 (–0.1 to 0.8)	0.29

mRS indicates modified Rankin Scale; and SAGE, Standard Assessment of Global Activities in the Elderly.
**P* values are from the Wilcoxon rank-sum tests.

Table 3. Independent Predictors of Stroke, Multivariable Analysis

Predictors of Stroke	No. of Patients (% of Cohort)	Stroke			Ischemic or uncertain stroke			Hemorrhagic stroke		
		Annual Rate, * %/y	Adjusted Hazard Ratio† (95% CI)	*P* Value	Annual Rate, * %/y	Adjusted Hazard Ratio† (95% CI)	*P* Value	Annual Rate, * %/y	Adjusted Hazard Ratio† (95% CI)	*P* Value
Age				0.001			0.0003			0.29
<65 y	6517 (23.8)	0.8	Ref. group		0.7	Ref. group		0.08	Ref. group	
65–74 y	15 183 (55.4)	0.5	0.81 (0.60–1.08)		0.4	0.71 (0.52–0.96)		0.1	1.71 (0.76–3.83)	
≥75 y	5695 (20.8)	0.9	1.31 (0.95–1.80)		0.8	1.22 (0.87–1.72)		0.1	2.10 (0.82–5.36)	
Systolic blood pressure				0.0002			0.002			0.04
≤120 mm Hg	5493 (20.1)	0.4	Ref. group		0.4	Ref. group		0.05	Ref. group	
121–139 mm Hg	10 964 (40.0)	0.6	1.46 (1.03–2.08)		0.5	1.38 (0.95–2.02)		0.09	1.98 (0.74–5.30)	
≥140 mm Hg	10 936 (39.9)	0.8	1.98 (1.41–2.80)		0.7	1.84 (1.27–2.66)		0.1	3.13 (1.20–8.19)	
Total cholesterol				0.23			0.06			0.36
<5.2 mmol/L	22 998 (84.1)	0.6	Ref. group		0.5	Ref. group		0.1	Ref. group	
5.2–6.2 mmol/L	3043 (11.1)	0.8	1.23 (0.90–1.68)		0.8	1.37 (0.99–1.90)		0.05	0.49 (0.15–1.57)	
>6.2 mmol/L	1298 (4.8)	0.9	1.34 (0.86–2.08)		0.9	1.49 (0.95–2.35)		0.04	0.43 (0.06–3.13)	
Tobacco use				0.94			0.42			0.002
Never	8757 (32.0)	0.7	Ref. group		0.6	Ref. group		0.04	Ref. group	
Former	12 771 (46.6)	0.6	1.01 (0.79–1.29)		0.5	0.88 (0.68–1.14)		0.1	2.68 (1.17–6.15)	
Current	5867 (21.4)	0.7	1.06 (0.76–1.46)		0.5	0.80 (0.56–1.15)		0.2	5.32 (2.12–3.34)	
Hypertension				0.02			0.02			0.60
No	6763 (24.7)	0.4	Ref. group		0.3	Ref. group		0.08	Ref. group	
Yes	20 632 (75.3)	0.7	1.43 (1.07–1.92)		0.6	1.49 (1.07–2.06)		0.1	1.20 (0.61–2.37)	
Diabetes mellitus				0.007			0.001			0.50
No	17 054 (62.3)	0.5	Ref. group		0.4	Ref. group		0.1	Ref. group	
Yes	10 341 (37.7)	0.8	1.35 (1.09–1.69)		0.8	1.49 (1.17–1.89)		0.09	0.82 (0.45–1.47)	
Previous stroke				<0.0001			<0.0001			0.02
No	26 363 (96.2)	0.6	Ref. group		0.5	Ref. group		0.09	Ref. group	
Yes	1032 (3.8)	2.6	3.63 (2.65–4.97)		2.4	3.75 (2.69–5.23)		0.3	3.12 (1.22–7.98)	
Peripheral artery disease				0.12			0.02			0.20
No	19 925 (72.7)	0.6	Ref. group		0.5	Ref. group		0.1	Ref. group	
Yes	7470 (27.3)	0.9	1.20 (0.95–1.52)		0.8	1.33 (1.04–1.71)		0.07	0.63 (0.31–1.28	
Race				0.003			0.06			0.02
White	17 027 (62.2)	0.6	Ref. group		0.5	Ref. group		0.08	Ref. group	
Black	262 (1.0)	0.2	0.31 (0.04–2.21)		0.2	0.33 (0.05–2.39)		0	-	
Asian	4269 (15.6)	1.0	1.59 (1.22–2.08)		0.8	1.44 (1.07–1.93)		0.2	2.61 (1.43–4.97)	
Other	5837 (21.3)	0.7	1.03 (0.78–1.37)		0.6	1.01 (0.75–1.37)		0.08	1.13 (0.51–2.51)	

Ref. group indicates reference group.

*Percent per year (%/y) is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have >1 event.

†Hazard ratios (95% CI) and *P* values are from the multivariable Cox proportional hazards regression models. Participants with average systolic blood pressure 139.5 mm Hg are included in the ≥140 mm Hg category.

blood pressure, tobacco use, prior stroke, and Asian ethnicity. We examined the effects of treatment assignment on the outcome of stroke in subgroups identified as predictors of stroke occurrence during the trial (Figure 4). Consistent effects were seen across all relevant subgroups with no significant treatment interactions.

Participants With Prior Stroke: Relative and Absolute Reductions by Antithrombotic Treatment

Considering the 1032 participants with prior stroke, the rate of ischemic/unknown stroke averaged 3.4% per year among aspirin-assigned patients and was reduced

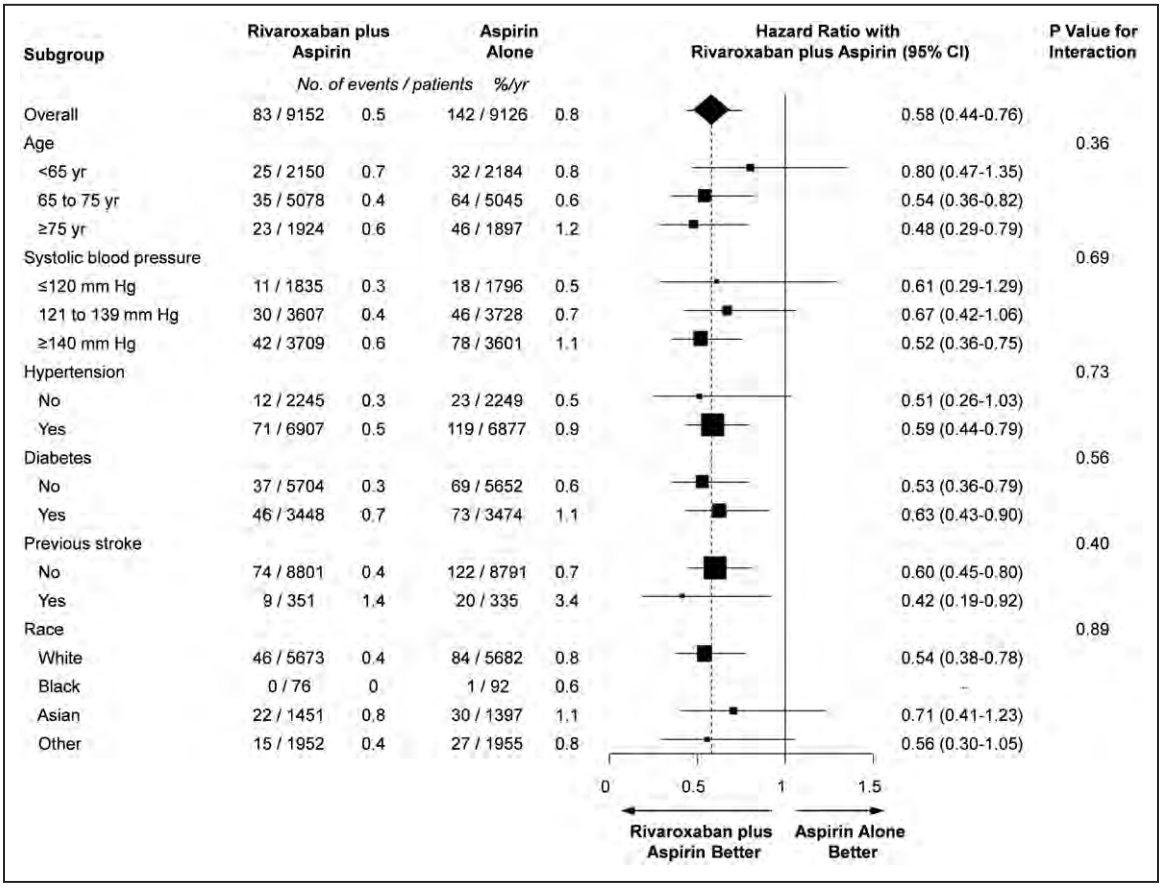

Figure 4. Relative risk of stroke for the comparison of rivaroxaban plus aspirin versus aspirin alone, in subgroups of selected baseline characteristics.

by 67% with rivaroxaban plus aspirin (HR, 0.33; 95% CI, 0.14–0.77; *P*=0.01; interaction *P*=0.28). The absolute stroke reduction in these participants was 2.3% per year with rivaroxaban plus aspirin (number needed to treat for 1 year, 43) (Table 4). The annualized rate of the composite outcome of cardiovascular death, stroke, or myocardial infarction in those with prior stroke was 6.6% in those assigned to aspirin and was reduced to 3.7% in those assigned to aspirin and rivaroxaban (HR, 0.57; 95% CI, 0.34–0.96; *P*=0.04; interaction *P*=0.27; number needed to treat for 1 year, 36). No significant reduction was observed in the occurrence of ischemic/uncertain stroke in participants with prior stroke assigned rivaroxaban alone in comparison with aspirin (HR, 0.79; 95% CI, 0.41–1.52; *P*=0.47). Similarly, no significant difference was noted in the composite outcome of cardiovascular death, stroke, or myocardial infarction with rivaroxaban alone in those with prior stroke (Table 4).

Participants with a prior stroke had a higher annualized rate of hemorrhagic stroke of 0.3% compared with 0.09% for those without prior stroke (HR, 3.12; 95% CI, 1.22–7.98; *P*=0.02). The total number of hemorrhagic strokes was small in the population with prior stroke (rivaroxaban plus aspirin=2, rivaroxaban alone=3, aspirin alone=0) (Table 4). The absence of hemorrhagic stroke in participants assigned aspirin precluded testing of interaction by previous stroke status for this outcome.

Major bleeding was not significantly increased in individuals with previous stroke, occurring at an annualized rate of 1.5% in comparison with 1.4% in those without a history of previous stroke (HR, 1.06; 95% CI, 0.72–1.56; *P*=0.76; interaction *P*=0.19).

High-Risk Patients Without Prior Stroke

To define the effects of the study treatments for the primary prevention of stroke across a gradient of stroke risk, analyses were conducted in participants without a history of stroke (Table 5). Excluding those high-risk patients with prior stroke, independent risk factors for stroke included age (≥75 versus <65 years; HR, 1.71; 95% CI, 1.20–2.44), systolic blood pressure at entry (≥140 versus ≤120 mm Hg; HR, 1.66; 95% CI, 1.16–2.37), and history of hypertension (HR, 1.36; 95% CI, 1.01–1.84), history of diabetes mellitus (HR, 1.46; 95% CI, 1.15–1.84), and Asian ethnicity (HR, 1.69; 95% CI, 1.27–2.25). In those without prior stroke, smoking and Asian ethnicity were independent predictors of hemorrhagic stroke, but total cholesterol, history of hypertension, and baseline blood pressure were not predictive of hemorrhage.

Table 4. Effect of Rivaroxaban Among Participants With or Without Previous Stroke

Participants	Rivaroxaban Plus Aspirin (n=9152)		Rivaroxaban Alone (n=9117)		Aspirin Alone (n=9126)		Rivaroxaban Plus Aspirin vs Aspirin Alone			Rivaroxaban Alone vs Aspirin Alone		
	No. of First Events/ Patients	Annual Rate, * %/y	No. of First Events/ Patients	Annual Rate, * %/y	No. of First Events/ Patients	Annual Rate, * %/y	Hazard Ratio† (95% CI)	*P* Value	*P* Value for Interaction	Hazard Ratio† (95% CI)	*P* Value	*P* Value for Interaction
Stroke									0.40			0.86
No previous stroke	74/8801	0.4	99/8771	0.6	122/8791	0.7	0.60 (0.45–0.80)	0.0006		0.81 (0.62–1.06)	0.13	
Previous stroke	9/351	0.7	18/346	2.9	20/335	3.4	0.42 (0.19–0.92)	0.03		0.88 (0.47–1.67)	0.70	
Ischemic or uncertain stroke									0.28			0.71
No previous stroke	61/8801	0.4	75/8771	0.4	112/8791	0.7	0.54 (0.40–0.74)	0.0001		0.67 (0.50–0.90)	0.007	
Previous stroke	7/351	1.1	16/346	2.6	20/335	3.4	0.33 (0.14–0.77)	0.01		0.79 (0.41–1.52)	0.47	
Hemorrhagic stroke									-			-
No previous stroke	13/8801	0.08	24/8771	0.1	10/8791	0.06	1.29 (0.57–2.94)	0.54		2.41 (1.51–5.03)	0.02	
Previous stroke	2/351	0.3	3/346	0.5	0/335	0	-	-		-	-	-
Major bleeding									0.19			0.14
No previous stroke	276/8801	1.7	243/8771	1.5	167/8791	1.0	1.66 (1.37–2.01)	<0.0001		1.47 (1.21–1.79)	0.0001	
Previous stroke	12/351	1.9	12/346	1.9	3/335	0.5	3.79 (1.07–13.4)	0.04		3.84 (1.08–13.6)	0.04	
Minor bleeding									0.05			0.65
No previous stroke	820/8801	5.2	715/8771	4.5	484/8791	3.0	1.73 (1.55–1.94)	<0.0001		1.51 (1.35–1.70)	<0.0001	
Previous stroke	18/351	3.0	26/346	4.3	19/335	3.3	0.91 (0.48–1.73)	0.76		1.39 (0.72–2.34)	0.39	
CV death, stroke, or MI									0.27			0.42
No previous stroke	356/8801	2.1	406/8771	2.4	458/8791	2.8	0.77 (0.67–0.88)	0.0002		0.89 (0.78–1.01)	0.08	
Previous stroke	23/351	3.7	42/346	7.0	38/335	6.5	0.57 (0.34–0.96)	0.04		1.07 (0.69–1.66)	0.77	

CV indicates cardiovascular; and MI, myocardial infarction.
Dashes indicate that the value could not be calculated.
*Percent per year (%/y) is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have >1 event.
†Hazard ratios (95% CI) are from the stratified Cox proportional hazards regression models fit in the respective subgroup. *P* values are from the stratified log-rank tests.

A consistent effect on relative risk was noted across risk strata with a similar relative reduction at all levels of risk, although the absolute benefit was highest in the high-risk group (Table 6).

Risk stratification using these independent predictors resulted in about one-third of participants categorized as high risk for ischemic/uncertain stroke with an absolute stroke rate of 1.3% per year. Treatment with rivaroxaban plus aspirin was associated with a 53% reduction in the annualized rate of ischemic/unknown strokes in high-risk patients (absolute reduction of 0.6% per year; number needed to treat for 1 year, 142) (HR, 0.57; 95% CI, 0.39–0.84; interaction *P*=0.72). Combination treatment did not increase the risk of hemorrhagic stroke in this group (HR, 1.76; 95% CI, 0.59–5.24). High-risk patients assigned rivaroxaban alone experienced a reduction in the occurrence of ischemic/uncertain stroke (HR, 0.51; 95% CI, 0.34–0.77; interaction *P*=0.05) and an increase in hemorrhagic stroke (HR, 3.08; 95% CI, 1.12–8.47; interaction *P*=0.50).

DISCUSSION

The combination of rivaroxaban and aspirin significantly reduced stroke by 42% in comparison with aspirin alone in a population with stable atherosclerotic

Table 5. Independent Predictors of Stroke Among Participants Without Previous Stroke, Multivariable Analysis

Predictors of Stroke	No. of Patients (% of Cohort)	Stroke			Ischemic or Uncertain Stroke			Hemorrhagic Stroke		
		Annual Rate, * %/y	Adjusted Hazard Ratio† (95% CI)	*P* Value	Annual Rate, * %/y	Adjusted Hazard Ratio† (95% CI)	*P* Value	Annual Rate, * %/y	Adjusted Hazard Ratio† (95% CI)	*P* Value
Age				<0.0001			<0.0001			0.44
<65 y	6161 (23.4)	0.6	Ref. group		0.5	Ref. group		0.08	Ref. group	
65–74 y	14715 (55.8)	0.5	0.93 (0.67–1.28)		0.4	0.85 (0.60–1.21)		0.09	1.37 (0.59–3.14)	
≥75 y	5487 (20.8)	0.9	1.71 (1.20–2.44)		0.8	1.66 (1.13–2.43)		0.1	1.86 (0.71–4.89)	
Systolic blood pressure				0.01			0.08			0.11
≤120 mm Hg	5294 (20.1)	0.4	Ref. group		0.4	Ref. group		0.05	Ref. group	
121–139 mm Hg	10579 (40.1)	0.5	1.31 (0.91–1.89)		0.5	1.22 (0.83–1.81)		0.09	1.90 (0.71–5.14)	
≥140 mm Hg	10488 (39.8)	0.7	1.66 (1.16–2.37)		0.6	1.51 (1.03–2.21)		0.1	2.75 (1.04–7.29)	
Total cholesterol				0.11			0.02			0.52
<5.2 mmol/L	22190 (84.3)	0.6	Ref. group		0.5	Ref. group		0.1	Ref. group	
5.2–6.2 mmol/L	2895 (11.0)	0.8	1.32 (0.94–1.85)		0.7	1.48 (1.03–2.11)		0.06	0.57 (0.17–1.84)	
>6.2 mmol/L	1225 (4.7)	0.8	1.47 (0.90–2.39)		0.8	1.66 (1.00–2.74)		0.05	0.50 (0.07–3.67)	
Tobacco use				0.35			0.95			0.003
Never	8403 (31.9)	0.6	Ref. group		0.5	Ref. group		0.04	Ref. group	
Former	12312 (46.7)	0.6	1.09 (0.83–1.43)		0.5	0.96 (0.72–1.28)		0.1	2.76 (1.13–6.76)	
Current	5648 (21.4)	0.6	1.24 (0.91–1.83)		0.5	1.01 (0.69–1.48)		0.2	5.52 (2.06–14.8)	
Hypertension				0.05			0.04			0.70
No	6628 (25.1)	0.4	Ref. group		0.3	Ref. group		0.09	Ref. group	
Yes	19735 (74.9)	0.6	1.36 (1.01–1.84)		0.5	1.41 (1.01–1.98)		0.09	1.15 (0.58–2.28)	
Diabetes mellitus				0.002			0.0002			0.37
No	16540 (62.7)	0.5	Ref. group		0.4	Ref. group		0.1	Ref. group	
Yes	9823 (37.3)	0.8	1.46 (1.15–1.84)		0.7	1.64 (1.27–2.12)		0.08	0.75 (0.40–1.41)	
Peripheral artery disease				0.07			0.02			0.34
No	19395 (72.6)	0.5	Ref. group		0.4	Ref. group		0.1	Ref. group	
Yes	6968 (26.4)	0.7	1.26 (0.98–1.62)		0.7	1.38 (1.05–1.81		0.07	0.70 (0.33–1.46)	
Race				0.001			0.03			0.03
White	16481 (62.5)	0.5	Ref. group		0.4	Ref. group		0.08	Ref. group	
Black	254 (1.0)	0.2	0.35 (0.05–2.52)		0.2	0.38 (0.05–2.73)		0	-	
Asian	4061 (15.4)	0.9	1.69 (1.27–2.25)		0.7	1.54 (1.12–2.11)		0.2	2.57 (1.34–4.92)	
Other	5567 (21.1)	0.6	1.00 (0.73–1.36)		0.5	1.01 (0.72–1.40)		0.06	0.90 (0.37–2.21)	

Ref. group indicates reference group.
Dashes indicate that the value could not be calculated.
*Percent per year (%/y) is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have >1 event.
†Hazard ratios (95% CI) and *P* values are from the multivariable Cox proportional hazards regression models. Participants with average systolic blood pressure 139.5 mm Hg are included in the ≥140 mm Hg category.

peripheral and coronary artery disease. The effect was driven by a 49% relative reduction in ischemic stroke partially offset by a nonsignificant increase in hemorrhagic stroke. Rivaroxaban alone did not significantly reduce stroke, and increased hemorrhagic stroke, making this an unattractive treatment option.

Early stroke disability (mRS score at 7 days or hospital discharge) was similarly distributed across treatment arms, but the annualized risk of fatal or disabling stroke was lower in participants assigned the combination of rivaroxaban and aspirin. The reduction in stroke occurrence with the combination was consistent across mRS scores, suggesting that the reduced rate of stroke-associated death and disability was attributable to a reduction in the occurrence of stroke rather than an effect on stroke severity or enhanced recovery. Disability as measured by the mRS early after stroke occurrence predicts future resource utilization and costs but imperfectly correlates with long-term disability.[10]

Table 6. Risk Stratification Among Participants Without Previous Stroke

Stratified Risk	Rivaroxaban Plus Aspirin (n=9152)		Rivaroxaban Alone (n=9117)		Aspirin Alone (n=9126)		Rivaroxaban Plus Aspirin vs Aspirin Alone			Rivaroxaban Alone vs Aspirin Alone		
	No. of First Events/ Patients	Annual Rate, %/y	No. of First Events/ Patients	Annual Rate, %/y	No. of First Events/ Patients	Annual Rate, %/y	Hazard Ratio (95% CI)	*P* Value	*P* Value for Interaction	Hazard Ratio (95% CI)	*P* Value	*P* Value for Interaction
Stroke									0.72			0.08
Low to medium risk	32/5839	0.3	52/5847	0.5	50/5852	0.4	0.64 (0.41–1.00)	0.05		1.05 (0.71–1.55)	0.80	
High risk	42/2937	0.7	47/2906	0.8	72/2927	1.3	0.57 (0.39–0.84)	0.004		0.65 (0.45–0.94)	0.02	
Ischemic or uncertain stroke									0.62			0.05
Low to medium risk	25/5838	0.2	39/5856	0.3	42/5844	0.4	0.59 (0.36–0.98)	0.04		0.93 (0.60–1.44)	0.74	
High risk	36/2938	0.6	36/2897	0.7	70/2935	1.3	0.51 (0.34–0.76)	0.001		0.51 (0.34–0.77)	0.001	
Hemorrhagic stroke									0.36			0.50
Low to medium risk	4/5841	0.04	9/5883	0.08	5/5814	0.05	0.79 (0.21–2.96)	0.73		1.81 (0.61–5.41)	0.29	
High risk	9/2935	0.2	15/2870	0.3	5/2965	0.09	1.76 (0.59–5.24)	0.31		3.08 (1.12–8.47)	0.03	

Risk stratification according to tertiles of estimated probability of having an outcome. Variables included in the multivariable prediction model are those shown in Table 5. Low- to medium-risk subgroup includes patients in the first and second tertiles, combined because of the low number of events and no difference in the event rates. The high-risk subgroup includes patients in the third tertile.

The risk reduction for stroke with the combination of rivaroxaban plus aspirin over aspirin was consistent over stroke risk groups with the absolute benefit greatest in those at highest risk.

The most important predictor of the occurrence of stroke was a history of prior stroke, ie, the secondary prevention population. Participants with prior stroke had an almost 5-fold increase in the annualized rate of stroke on aspirin in comparison with those having no history of stroke (3.4% versus 0.7%) despite good blood pressure control and use of statins. The absolute benefit of adding 2.5 mg rivaroxaban twice daily to aspirin was large for secondary stroke prevention: a 2.5% reduction in ischemic stroke and a 3.3% reduction in cardiovascular death, stroke, or myocardial infarction. This subgroup is of particular interest because it was the strongest predictor of stroke, and antithrombotic efficacy tends to be greater in secondary prevention.[5] The average time between prior stroke and trial entry was 5.3 years, and hence, the occurrence of prior stroke identifies individuals with a sustained high risk of vascular events. A history of prior stroke identifies patients with atherosclerosis who have large absolute stroke reductions if treated with rivaroxaban added to aspirin.

Previous trials of combination therapy for stroke prevention have compared clopidogrel and extended-release dipyridamole added to aspirin with aspirin alone or clopidogrel alone.[11–13] The combination of dipyridamole with aspirin did not demonstrate benefit over clopidogrel in the secondary prevention of stroke.[12] The CHANCE trial (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) showed that clopidogrel added to aspirin started within 24 hours of minor stroke or transient ischemic attack reduced stroke occurrence at 90 days,[11,14] but this treatment was not tested for long-term treatment and has not been widely adopted. Clopidogrel added to aspirin in individuals with recent lacunar stroke did not provide increased protection against stroke recurrence and was associated with an increase in bleeding and mortality.[13] Consequently, aspirin remains a widely accepted therapy for secondary stroke prevention.

Stroke etiology is heterogeneous, and the majority of strokes are embolic in origin, arising from arterial or cardiac sources.[15] In atrial fibrillation, rivaroxaban 20 mg (reduced to 15 mg in renal failure) has been shown to be effective for stroke prevention.[16] The observed effects of combination therapy in COMPASS on stroke are consistent with the hypothesis that anticoagulation by inhibition of factor Xa in addition to cyclo-oxygenase inhibition reduces noncardiac embolism into the cerebral circulation better than inhibition of cyclo-oxygenase alone. Factor Xa interacts with protease-activated receptor 1 and 2. Activation of these receptors in the arterial wall has the potential to increase endothelial dysfunction and inflammation.[17] Inhibition of factor Xa by rivaroxaban may reduce stroke in individuals with atherosclerosis through multiple mechanisms. In addition,

platelet inhibition may be necessary to reduce emboli initiated by thrombus formation at sites of endothelial injury. Our findings suggest a synergistic effect of antiplatelet and anticoagulant therapy in the prevention of atherothrombotic events, and are consistent with historical trials of aspirin and heparin in patients with an acute coronary syndrome where combined therapy was superior to either treatment alone.[18] Factor Xa inhibition at rivaroxaban doses of 2.5 mg twice daily appears to be insufficient to significantly increase intracerebral hemorrhage even in the presence of aspirin, whereas doses of 5 mg twice daily are associated with a significant increase in this safety end point.

Limitations include that participants with recent stroke were excluded from COMPASS, and hence, we cannot comment on treatment effects in the early post-stroke period. We did not systematically collect transient ischemic attacks from sites, and it is possible that some strokes were misclassified as transient ischemic attacks, resulting in a reduced number of stroke end points. Imaging for suspected stroke was interpreted at the site and was not centrally reviewed.

In summary, low-dose rivaroxaban plus aspirin is an important new option for efficacious antithrombotic therapy for primary and especially secondary prevention of stroke in patients with atherosclerosis. The absolute risk reduction for secondary prevention is substantial and makes a compelling case favoring the use of 2.5 mg rivaroxaban twice daily plus aspirin in these patients.

ARTICLE INFORMATION

Received May 9, 2018; accepted November 30, 2018.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.118.035864.

Authors

Mukul Sharma, MD, MSc; Robert G. Hart, MD; Stuart J. Connolly, MD; Jackie Bosch, MSc, PhD; Olga Shestakovska, MSc; Kelvin K.H. Ng, MBBS; Luciana Catanese, MD; Katalin Keltai, PhD; Victor Aboyans, MD, PhD; Marco Alings, MD, PhD; Jong-Won Ha, MD, PhD; John Varigos, BSc (Hon); Andrew Tonkin, MD, MBBS; Martin O'Donnell, MB, PhD; Deepak L. Bhatt, MD, MPH; Keith Fox, BSc, MBChB; Aldo Maggioni, MD; Scott D. Berkowitz, MD; Nancy Cook Bruns, MD; Salim Yusuf, MBBS, DPhil; John W. Eikelboom, MBBS, MSc

Correspondence

Mukul Sharma, MD, Population Health Research Institute, DBCVSRI C4-1XX, 237 Barton Str E, Hamilton, ON L8L 2X2 Canada. Email mike.sharma@phri.ca

Affiliations

McMaster University/Population Health Research Institute, Hamilton, Canada (M.S., R.G.H., S.J.C., J.B., O.S., K.K.H.N., L.C., S.Y., J.W.E.). Semmelweis University, Budapest, Hungary (K.K.). Dupuytren University Hospital, Limoges, France (V.A.). Amphia Ziekenhuis and Werkgroep Cardiologische centra Nederland, Utrecht, Nederlands (M.A.). Yonsei University College of Medicine, Seoul, Korea (J.-W.H.). Monash University, Clayton, Melbourne, Australia (J.V., A.T.). National University of Ireland, Galway, Ireland (M.O.). Brigham and Women's Hospital, Boston, MA (D.L.B.). University of Edinburgh, Scotland (K.F.). Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy (A.M.). Bayer AG, Wuppertal, Germany (S.D.B., N.C.B.).

Acknowledgments

Author Contributions: Dr Sharma drafted the manuscript, interpreted and analyzed data; Dr Hart was involved in the design of the COMPASS trial, development of the case report forms, the event adjudication plan, adjudicating stroke events (cochairing the event adjudication committee), interpreting the results, and comments on drafting the manuscript; Dr Connolly is study coprincipal investigator and was involved in protocol design, data collection, and manuscript review; Dr Bosch was involved in study design, data collection, data analysis, and interpretation; Dr Shestakovska was involved in statistical analysis and production of tables and graphs; Dr Ng was involved in critical review of the manuscript and adjudication; Dr Catanese was involved with review of the manuscript and adjudication; Dr Keltai, as a member of the Steering Committee, provided input to the design and the execution of the study, reviewed the manuscript, and provided input and approved the final submission; Dr Aboyans was involved in data collection and interpretation; Dr Alings contributed to data collection, data interpretation, and manuscript review; Dr Ha was involved in data collection and interpretation; Dr Varigos contributed by obtaining data and review of the manuscript; Dr Tonkin was involved in data collection and interpretation; Dr O'Donnell was involved in data collection, interpretation, and review of the manuscript; Dr Bhatt was involved in study design, data collection and interpretation, and critical review of the manuscript; Dr Fox was involved in design and analysis of the COMPASS study (Co-Chair) and revisions to the manuscript; Dr Maggioni contributed to study design, data collection, and critical revision of the manuscript; Dr Berkowitz was involved in roles with trial operationalization, data collection, resource support and funding, data interpretation, review of and comment on writing, and decision to publish; Dr Yusuf was involved with design and analysis of the COMPASS study (Steering Committee Co-Chair) and critical review of the manuscript; Dr Eikelboom contributed to the design of the study, the collection of data, and the interpretation of the data and provided critical revisions to the manuscript.

Sources of Funding

None.

Disclosures

Dr Sharma reports grants and personal fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, and Portola during the conduct of this study. Dr Connolly reports grants and personal fees from Bayer and Boehringer Ingelheim. Dr Hart has received research support from Bayer AG including personal remuneration for participation in Bayer-sponsored clinical research and advisory boards 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. Dr Eikelboom 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. Dr O'Donnell reports that his institution received grants from Population Health Research Institute/Bayer during the conduct of the study. Dr Maggioni reports personal fees from Novartis, Bayer, Cardiorentis, and Fresenius outside the submitted work. Dr Bhatt 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, and Duke Clinical Research Institute; personal fees and nonfinancial support from the American College of Cardiology and the Society of Cardiovascular Patient Care; nonfinancial support from the American Heart Association; and nonfinancial 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. Dr Bruns reports employment by Bayer during the conduct of the study. Dr Berkowitz reports employment by Bayer during the conduct of the study. Dr Varigos reports personal fees from Novartis outside the submitted work. Dr Fox reports grants and personal fees from Bayer/Janssen during the conduct of the study, and grants and personal fees from AstraZeneca, and personal fees from Sanofi/Regeneron and Eli Lilly outside the submitted work. Dr Yusuf reports grants and personal fees from Bayer during the conduct of the study.

REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014;383:245–254.
2. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220. doi: 10.1161/CIR.0b013e31823ac046
3. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, Wilson PW, Alberts MJ, D'Agostino R, Liau CS, Mas JL, Röther J, Smith SC Jr, Salette G, Contant CF, Massaro JM, Steg PG; REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304:1350–1357. doi: 10.1001/jama.2010.1322
4. Ducrocq G, Amarenco P, Labreuche J, Alberts MJ, Mas JL, Ohman EM, Goto S, Lavallée P, Bhatt DL, Steg PG. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation*. 2013;127:730–738. doi: 10.1161/CIRCULATIONAHA.112.141572
5. Antithrombotic Trialists' (ATT) Collaboration1, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–1860.
6. Bosch J, Eikelboom JW, Connolly SJ, Bruns NC, Lanius V, Yuan F, Misselwitz F, Chen E, Diaz R, Alings M, Lonn EM, Widimsky P, Hori M, Avezum A, Piegas LS, Bhatt DL, Branch KRH, Probstfield JL, Liang Y, Liu L, Zhu J, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Fox KAA, Kakkar A, Parkhomenko AN, Ertl G, Störk S, Keltai K, Keltai M, Ryden L, Dagenais GR, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Ha JW, Tonkin AM, Varigos JD, Lewis BS, Felix C, Yusoff K, Steg PG, Aboyans V, Metsarinne KP, Anand SS, Hart RG, Lamy A, Moayyedi P, Leong DP, Sharma M, Yusuf S. Rationale, design, and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. *Can J Cardiol*. 2017;33:1027–1035.
7. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Störk S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–1330. doi: 10.1056/NEJMoa1709118
8. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
9. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19:1497–1500.
10. Mittmann N, Seung SJ, Hill MD, Phillips SJ, Hachinski V, Coté R, Buck BH, Mackey A, Gladstone DJ, Howse DC, Shuaib A, Sharma M. Impact of disability status on ischemic stroke costs in Canada in the first year. *Can J Neurol Sci*. 2012;39:793–800.
11. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340
12. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, Vandermaelen C, Voigt T, Weber M, Yoon BW; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–1251. doi: 10.1056/NEJMoa0805002
13. SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med*. 2012;367:817–825.
14. Hankey GJ. Dual antiplatelet therapy in acute transient ischemic attack and minor stroke. *N Engl J Med*. 2013;369:82–83. doi: 10.1056/NEJMe1305127
15. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13:429–438. doi: 10.1016/S1474-4422(13)70310-7
16. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: 10.1056/NEJMoa1009638
17. Spronk HM, de Jong AM, Crijns HJ, Schotten U, Van Gelder IC, Ten Cate H. Pleiotropic effects of factor Xa and thrombin: what to expect from novel anticoagulants. *Cardiovasc Res*. 2014;101:344–351. doi: 10.1093/cvr/cvt343
18. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation*. 2005;112:3855–3867. doi: 10.1161/CIRCULATIONAHA.105.573550