Circulation

ORIGINAL RESEARCH ARTICLE

Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes Mellitus and Cardiovascular Disease

Insights From the COMPASS Trial

Editorial, see p 1855

BACKGROUND: Patients with established coronary artery disease or peripheral artery disease often have diabetes mellitus. These patients are at high risk of future vascular events.

METHODS: In a prespecified analysis of the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies), we compared the effects of rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily) versus placebo plus aspirin in patients with diabetes mellitus versus without diabetes mellitus in preventing major vascular events. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points included all-cause mortality and all major vascular events (cardiovascular death, myocardial infarction, stroke, or major adverse limb events, including amputation). The primary safety end point was a modification of the International Society on Thrombosis and Haemostasis criteria for major bleeding.

RESULTS: There were 10 341 patients with diabetes mellitus and 17 054 without diabetes mellitus in the overall trial. A consistent and similar relative risk reduction was seen for benefit of rivaroxaban plus aspirin (n=9152) versus placebo plus aspirin (n=9126) in patients both with (n=6922) and without (n=11 356) diabetes mellitus for the primary efficacy end point (hazard ratio, 0.74, P=0.002; and hazard ratio, 0.77, P=0.005, respectively, $P_{interaction}$=0.77) and all-cause mortality (hazard ratio, 0.81, P=0.05; and hazard ratio, 0.84, P=0.09, respectively; $P_{interaction}$=0.82). However, although the absolute risk reductions appeared numerically larger in patients with versus without diabetes mellitus, both subgroups derived similar benefit (2.3% versus 1.4% for the primary efficacy end point at 3 years, Gail-Simon qualitative $P_{interaction}$<0.0001; 1.9% versus 0.6% for all-cause mortality, $P_{interaction}$=0.02; 2.7% versus 1.7% for major vascular events, $P_{interaction}$<0.0001). Because the bleeding hazards were similar among patients with and without diabetes mellitus, the prespecified net benefit for rivaroxaban appeared particularly favorable in the patients with diabetes mellitus (2.7% versus 1.0%; Gail-Simon qualitative $P_{interaction}$=0.001).

CONCLUSIONS: In stable atherosclerosis, the combination of aspirin plus rivaroxaban 2.5 mg twice daily provided a similar relative degree of benefit on coronary, cerebrovascular, and peripheral end points in patients with and without diabetes mellitus. Given their higher baseline risk, the absolute benefits appeared larger in those with diabetes mellitus, including a 3-fold greater reduction in all-cause mortality.

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Key Words: anticoagulants ■ coronary artery disease ■ diabetes mellitus ■ peripheral artery disease ■ platelet aggregation inhibitors

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ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- In a prespecified analysis, COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) Diabetes compared low-dose rivaroxaban (2.5 mg twice daily) plus aspirin versus placebo plus aspirin in 6922 patients with stable coronary or peripheral artery disease and diabetes mellitus.
- Although there was a consistent and similar relative risk reduction with rivaroxaban plus aspirin versus placebo plus aspirin in patients both with and without diabetes mellitus for the primary efficacy end point and all-cause mortality, notably, the absolute risk reductions appeared larger in patients with diabetes mellitus, including a 3-fold greater reduction in mortality.
- There appeared to be a larger absolute net clinical benefit in those with diabetes mellitus.

What Are the Clinical Implications?

- In patients with stable atherosclerosis and diabetes mellitus without an indication for dual antiplatelet therapy such as recent stenting or recent acute coronary syndromes, the addition of low-dose rivaroxaban to aspirin provides substantial reductions in ischemic events, including a significant reduction in all-cause mortality, with absolute risk reductions that appeared larger in those with versus without diabetes mellitus.
- Non-fatal major bleeding was increased similarly in those with versus without diabetes mellitus.
- In patients at acceptable bleeding risk, the addition of low-dose rivaroxaban to aspirin should be considered in the secondary prevention regimen of patients with atherosclerosis and diabetes mellitus.

Diabetes mellitus is a commonly occurring major risk amplifier in patients with established atherosclerosis.[1–4] In particular, those with polyvascular disease, a marker of significant clinical atherosclerotic burden, and concomitant diabetes mellitus, which frequently coexist, constitute a very high-risk group of patients subject to coronary, cerebral, and peripheral ischemic events.[1,5,6] Lipid-lowering therapies and glycemia-modifying drugs can help attenuate this risk.[7–18] Despite effective control of other risk factors, diabetes mellitus still contributes to a prothrombotic state and residual cardiovascular risk.[19] Antiplatelet therapy, including dual antiplatelet therapy, has been established as effective across a wide variety of stable atherosclerotic patients, with some suggestion of heightened benefit in those with diabetes mellitus at baseline.[20–29]

More recently, a strategy of dual pathway antithrombotic therapy with an antiplatelet and a reduced-dose anticoagulant has been tested and shown to be effective.[30–38] The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) demonstrated that aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus rivaroxaban placebo for the reduction of ischemic events in 27 395 patients with coronary artery disease or peripheral artery disease. A significant reduction in cardiovascular death was seen with dual pathway inhibition, as well as lower all-cause mortality.

In the present prespecified analysis of COMPASS, we analyzed the results of rivaroxaban plus aspirin versus aspirin alone in the subgroups of patients with or without diabetes mellitus at baseline.

METHODS

The data that support the findings of this study may be made available from the corresponding author on reasonable request. The design and results of the overall COMPASS trial have been previously published. In brief, COMPASS was a multicenter, double-blind, randomized, placebo-controlled trial of 27 395 patients with a history of coronary artery disease or peripheral artery disease. Patients were randomized to aspirin plus rivaroxaban placebo, rivaroxaban (5 mg twice daily) plus aspirin placebo, or double antithrombotic therapy with aspirin plus rivaroxaban 2.5 mg twice daily. The primary outcome was cardiovascular death, myocardial infarction (MI), or stroke. Secondary end points included all-cause mortality and major adverse limb events. We also analyzed all major ischemic vascular events (cardiovascular death, MI, stroke, and major adverse limb events, including amputation). The primary safety end point was a modification of the International Society on Thrombosis and Haemostasis criteria for major bleeding. The prespecified net clinical benefit was defined as MI, stroke, cardiovascular death, or bleeding leading to death or symptomatic bleeding into a critical organ. The protocol was approved by the relevant health authorities and institutional review boards. Written informed consent was required from all participants.

The trial was stopped early at the recommendation of the independent data and safety monitoring board because of the overwhelming efficacy of the rivaroxaban plus aspirin arm versus aspirin alone. This analysis focuses on the 18 278 patients in those 2 study groups and compares the outcomes in those with and those without diabetes mellitus according to the case history at baseline.

Statistical Analysis

Analyses were conducted according to the intention-to-treat principle. We compared baseline characteristics of patients with and without diabetes mellitus at baseline using Wilcoxon 2-sample tests for continuous variables and Pearson χ^2 tests for categorical variables. Survival analyses were based on the time to a first event. Kaplan-Meier risks at 36 months were calculated. We used stratified Cox proportional hazards regression models to estimate hazard ratios (HRs) and corresponding 95% CIs to compare the effects of antithrombotic regimens in patients with and without diabetes mellitus. Significance was tested with the use of stratified log-rank

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Table 1. Baseline Characteristics of Patients With and Without Diabetes Mellitus at Baseline Randomized to Rivaroxaban Plus Aspirin or to Placebo Plus Aspirin

Characteristic	No Diabetes Mellitus (n=11 356)	Diabetes Mellitus (n=6922)	*P* Value
Age, y	69.0±7.7	67.0±8.2	<0.0001
Female	2370 (20.9)	1678 (24.2)	<0.0001
Body mass index, kg/m^2	27.7±4.3	29.3±5.2	<0.0001
Systolic blood pressure, mm Hg	135±18	136±17	<0.0001
Diastolic blood pressure, mm Hg	78±10	77±10	0.01
Total cholesterol, mmol/L	4.2±1.0	4.2±1.1	<0.0001
Tobacco use			
Never	3602 (31.7)	2223 (32.1)	0.58
Former	5456 (48.0)	3081 (44.5)	<0.0001
Current	2298 (20.2)	1618 (23.4)	<0.0001
Hypertension	8089 (71.2)	5695 (82.3)	<0.0001
Previous stroke	343 (3.0)	343 (5.0)	<0.0001
Previous myocardial infarction)	7220 (63.6)	4155 (60.0)	<0.0001
Heart failure	2328 (20.5)	1614 (23.3)	<0.0001
Coronary artery disease	10 491 (92.4)	6083 (87.9)	<0.0001
Peripheral artery disease	2792 (24.6)	2204 (31.8)	<0.0001
Estimated glomerular filtration rate, mL/min			
<30	64 (0.6)	99 (1.4)	<0.0001
30–<60	2357 (20.8)	1648 (23.8)	<0.0001
≥60	8932 (78.7)	5174 (74.8)	<0.0001
Race			
White	7647 (67.3)	3708 (53.6)	<0.0001
Black	68 (0.6)	100 (1.4)	<0.0001
Asian	1507 (13.3)	1341 (19.4)	<0.0001
Other	2134 (18.8)	1773 (25.6)	<0.0001
Geographic region			
North America	1616 (14.2)	997 (14.4)	0.75
South America	2274 (20.0)	1834 (26.5)	<0.0001
Western Europe, Israel, Australia, or South Africa	4037 (35.5)	1673 (24.2)	<0.0001
Eastern Europe	2032 (17.9)	1179 (17.0)	0.14
Asia-Pacific	1397 (12.3)	1239 (17.9)	<0.0001
Medication			
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	7836 (69.0)	5101 (73.7)	<0.0001
Calcium-channel blocker	2800 (24.7)	2095 (30.3)	<0.0001
Diuretic	3010 (26.5)	2463 (35.6)	<0.0001
β-Blocker	7917 (69.7)	4866 (70.3)	0.41
Lipid-lowering agent	10 322 (90.9)	6075 (87.8)	<0.0001
Nonsteroidal anti-inflammatory drug	578 (5.1)	426 (6.2)	0.002
Hypoglycemic agent	35 (0.3)	5691 (82.2)	<0.0001
Nontrial proton pump inhibitor	4120 (36.3)	2412 (34.8)	0.05

For continuous variables, values are mean±SD; for categorical variables, n (%) is shown. *P* value is from the Wilcoxon 2-sample test for continuous variables and Pearson χ^2 test for categorical variables.

tests. The assumption of the proportional hazards was verified by use of the plots of the log of the negative log of survival function against the log of time. Interaction between the effect of treatment with rivaroxaban/aspirin and diabetes mellitus status was tested in a stratified Cox model fitted to all patients. The Gail-Simon test for qualitative interactions was used to test for interaction of absolute risk reduction, with the null hypothesis that not all of the subgroup reductions

favored rivaroxaban plus aspirin. All reported *P* values are 2 sided. No adjustments were made for multiple subgroup or end-point comparisons; therefore, all results presented herein should be viewed as hypothesis generating. Analyses were performed with SAS software for Linux, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 27 395 randomized patients with stable atherosclerosis in COMPASS, 10 341 had diabetes mellitus at enrollment and 17 054 did not. A total of 18 278 patients were randomized to the combination of rivaroxaban and aspirin or aspirin alone in the COMPASS trial. Of these, 6922 had diabetes mellitus at baseline and 11 356 did not have diabetes mellitus. Baseline characteristics of those with and without diabetes mellitus from the entire trial are shown in Table I in the Data Supplement, and those from the rivaroxaban plus aspirin and placebo plus aspirin arms are shown in Table 1. Those with diabetes mellitus were significantly younger and more likely female; it is not surprising that there were several other significant differences between the 2 groups. Table II in the Data Supplement shows the baseline characteristics in the rivaroxaban plus aspirin and rivaroxaban plus placebo arms in those with diabetes mellitus, and Table III in the Data Supplement provides this information for those without diabetes mellitus.

The primary efficacy end point for aspirin plus low-dose rivaroxaban versus aspirin plus rivaroxaban placebo in those with and without diabetes mellitus is shown in Figure 1. Table 2 provides several efficacy and safety comparisons. There was a consistent and similar relative risk reduction for benefit of rivaroxaban plus aspirin versus aspirin alone in patients with and without diabetes mellitus for the primary efficacy end point and the secondary end points, including mortality (Figure 2). However, because of their higher baseline risk, although the absolute risk reductions appeared larger in patients with versus without diabetes mellitus, both subgroups derived similar benefit (Kaplan-Meier event rates, 2.3% versus 1.4% for the primary end point at 3 years, Gail-Simon qualitative $P_{interaction}$<0.0001; 1.9% versus 0.6% for all-cause mortality, $P_{interaction}$= 0.02); the respective number needed to treat for 3 years was 44 versus 73 and 54 versus 167.

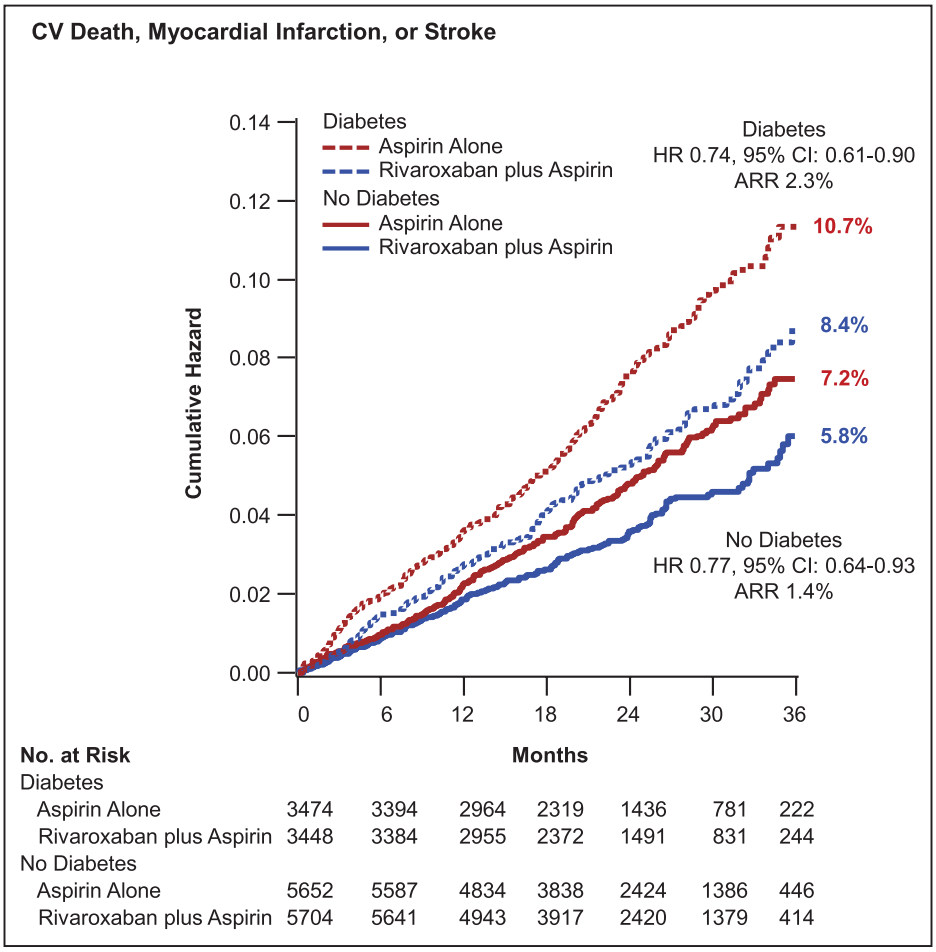

Figure 1. Cardiovascular death, myocardial infarction, or stroke.
Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The primary end point of cardiovascular death, myocardial infarction, or stroke is shown. Percentages are Kaplan-Meier risks at 3 years. ARR indicates absolute risk reduction; and HR, hazard ratio.

Table 2. Outcomes in Patients With and Without Diabetes Mellitus for Rivaroxaban Plus Aspirin Versus Placebo Plus Aspirin

	Rivaroxaban Plus Aspirin (n=9152)		Placebo Plus Aspirin (n=9126)		Rivaroxaban Plus Aspirin vs Placebo Plus Aspirin		
	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	Hazard Ratios (95% CIs)	*P* Value	*P* Value for Interaction*
Efficacy outcomes							
Cardiovascular death, stroke, or myocardial infarction							0.77
No diabetes mellitus at baseline	200/5704 (3.5)	5.8	257/5652 (4.5)	7.2	0.77 (0.64–0.93)	0.005	
Diabetes mellitus at baseline	179/3448 (5.2)	8.4	239/3474 (6.9)	10.7	0.74 (0.61–0.90)	0.002	
Death resulting from any cause							0.82
No diabetes mellitus at baseline	166/5704 (2.9)	5.1	197/5652 (3.5)	5.7	0.84 (0.68–1.03)	0.09	
Diabetes mellitus at baseline	147/3448 (4.3)	6.8	181/3474 (5.2)	8.6	0.81 (0.65–1.00)	0.05	
Cardiovascular death							0.92
No diabetes mellitus at baseline	83/5704 (1.5)	2.7	104/5652 (1.8)	2.9	0.79 (0.59–1.06)	0.11	
Diabetes mellitus at baseline	77/3448 (2.2)	3.5	99/3474 (2.8)	4.9	0.77 (0.58–1.04)	0.09	
Stroke							0.56
No diabetes mellitus at baseline	37/5704 (0.6)	1.4	69/5652 (1.2)	2.0	0.53 (0.36–0.79)	0.002	
Diabetes mellitus at baseline	46/3448 (1.3)	2.2	73/3474 (2.1)	3.6	0.63 (0.43–0.90)	0.01	
Ischemic or uncertain stroke							0.56
No diabetes mellitus at baseline	29/5704 (0.5)	1.2	62/5652 (1.1)	1.7	0.46 (0.30–0.72)	0.0005	
Diabetes mellitus at baseline	39/3448 (1.1)	1.9	70/3474 (2.0)	3.5	0.55 (0.37–0.82)	0.003	
Myocardial infarction							0.43
No diabetes mellitus at baseline	100/5704 (1.8)	2.8	107/5652 (1.9)	2.9	0.93 (0.71–1.22)	0.59	
Diabetes mellitus at baseline	78/3448 (2.3)	3.7	98/3474 (2.8)	4.0	0.79 (0.59–1.06)	0.12	
Major adverse limb events							0.27
No diabetes mellitus at baseline	12/5704 (0.2)	0.3	30/5652 (0.5)	0.8	0.40 (0.20–0.78)	0.005	
Diabetes mellitus at baseline	22/3448 (0.6)	1.2	34/3474 (1.0)	1.6	0.65 (0.38–1.11)	0.11	
Total vascular amputation							0.84
No diabetes mellitus at baseline	3/5704 (<0.1)	0.06	7/5652 (0.1)	0.2	0.43 (0.11–1.65)	0.20	
Diabetes mellitus at baseline	12/3448 (0.3)	0.5	24/3474 (0.7)	1.2	0.50 (0.25–1.00)	0.04	
Cardiovascular death, stroke, myocardial infarction, major adverse limb events, or major vascular amputation							0.88
No diabetes mellitus at baseline	212/5704 (3.7)	6.1	282/5652 (5.0)	7.8	0.74 (0.62–0.89)	0.001	
Diabetes mellitus at baseline	201/3448 (5.8)	9.4	272/3474 (7.8)	12.1	0.73 (0.61–0.88)	0.0007	
Safety outcomes							
Major bleeding							0.97
No diabetes mellitus at baseline	178/5704 (3.1)	4.4	105/5652 (1.9)	3.2	1.69 (1.33–2.15)	<0.0001	
Diabetes mellitus at baseline	110/3448 (3.2)	4.5	65/3474 (1.9)	3.4	1.70 (1.25–2.31)	0.0006	
Intracranial major bleeding							0.44
No diabetes mellitus at baseline	17/5704 (0.3)	0.4	17/5652 (0.3)	0.7	0.99 (0.51–1.95)	0.98	
Diabetes mellitus at baseline	11/3448 (0.3)	0.4	7/3474 (0.2)	0.4	1.57 (0.61–4.05)	0.35	
Fatal bleeding							0.87
No diabetes mellitus at baseline	10/5704 (0.2)	0.4	7/5652 (0.1)	0.2	1.43 (0.55–3.77)	0.46	
Diabetes mellitus at baseline	5/3448 (0.1)	0.2	3/3474 (<0.1)	0.2	1.66 (0.40–6.93)	0.48	
Net clinical benefit outcomes							
Cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ							0.78
No diabetes mellitus at baseline	227/5704 (4.0)	6.6	276/5652 (4.9)	7.6	0.81 (0.68–0.97)	0.02	

(*Continued*)

Table 2. Continued

	Rivaroxaban Plus Aspirin (n=9152)		Placebo Plus Aspirin (n=9126)		Rivaroxaban Plus Aspirin vs Placebo Plus Aspirin		
	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	Hazard Ratios (95% CIs)	*P* Value	*P* Value for Interaction*
Diabetes mellitus at baseline	204/3448 (5.9)	9.1	258/3474 (7.4)	11.8	0.78 (0.65–0.94)	0.01	
Cardiovascular death, stroke, myocardial infarction, or major bleeding							0.25
No diabetes mellitus at baseline	360/5704 (6.3)	3.4	341/5652 (6.0)	3.2	1.05 (0.91–1.22)	0.50	
Diabetes mellitus at baseline	269/3448 (7.8)	4.2	291/3474 (8.4)	4.5	0.93 (0.78–1.09)	0.36	

Percent is the proportion of patients with an outcome. Hazard ratios (95% CIs) are from the stratified Cox proportional hazards regression models fit in the respective subgroup. *P* values are from the stratified log-rank test.

*Test of interaction of relative risk reduction (Cox regression).

In an evaluation of the totality of ischemic events (cardiovascular death, stroke, MI, major adverse limb events, or major vascular amputation) at 3 years, those without diabetes mellitus at baseline had a significant reduction to 6.1% from 7.8% (HR, 0.74 [95% CI, 0.62–0.89]; *P*=0.001) with dual pathway antithrombotic therapy; in those with diabetes mellitus, the corresponding rates were 9.4% and 12.1% (HR, 0.73 [95% CI, 0.61–0.88]; *P*=0.0007; Table 2). Although the HRs were similar, the absolute risk reductions were 1.7% and 2.7%, respectively (Gail-Simon qualitative $P_{interaction}$<0.0001; Figure 3). The respective number needed to treat for 3 years was 60 versus 38.

As in the trial overall, there was a significant increase in major bleeding with the dual pathway regimen in the subgroups with and without diabetes mellitus,

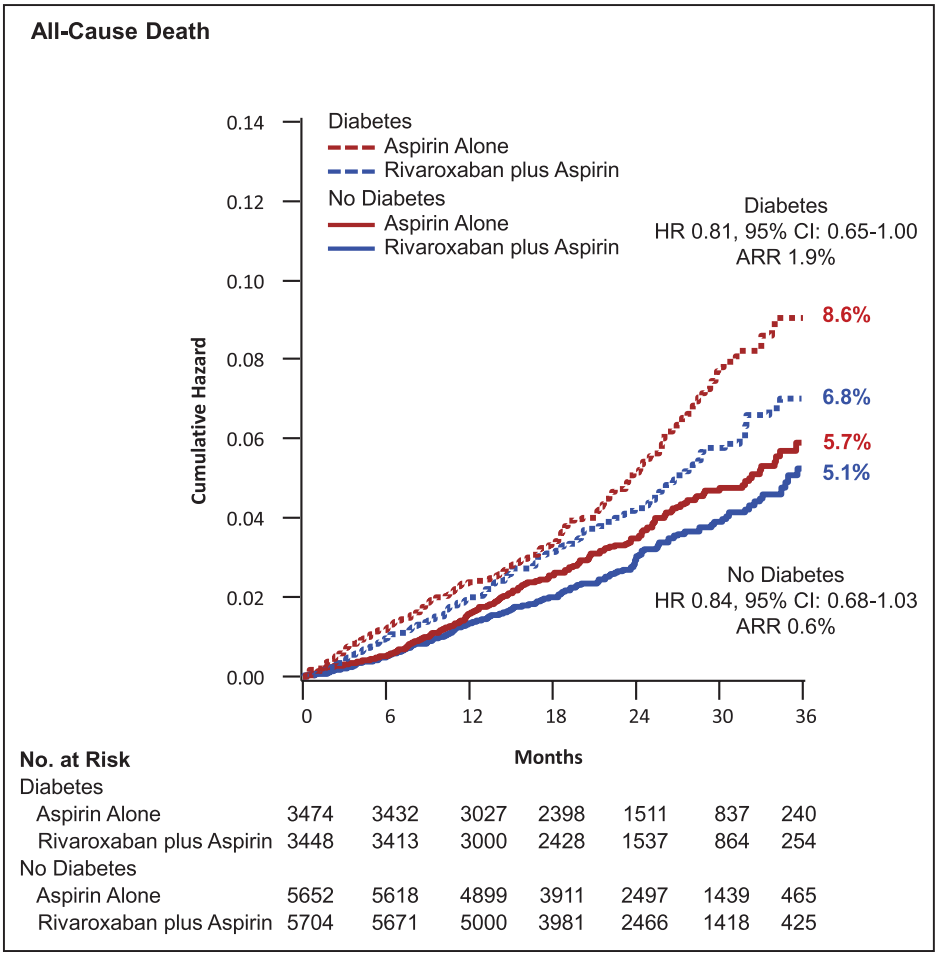

Figure 2. All-cause death.

Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The secondary end point of all-cause death is shown. Percentages are Kaplan-Meier risks at 3 years. ARR indicates absolute risk reduction; and HR, hazard ratio.

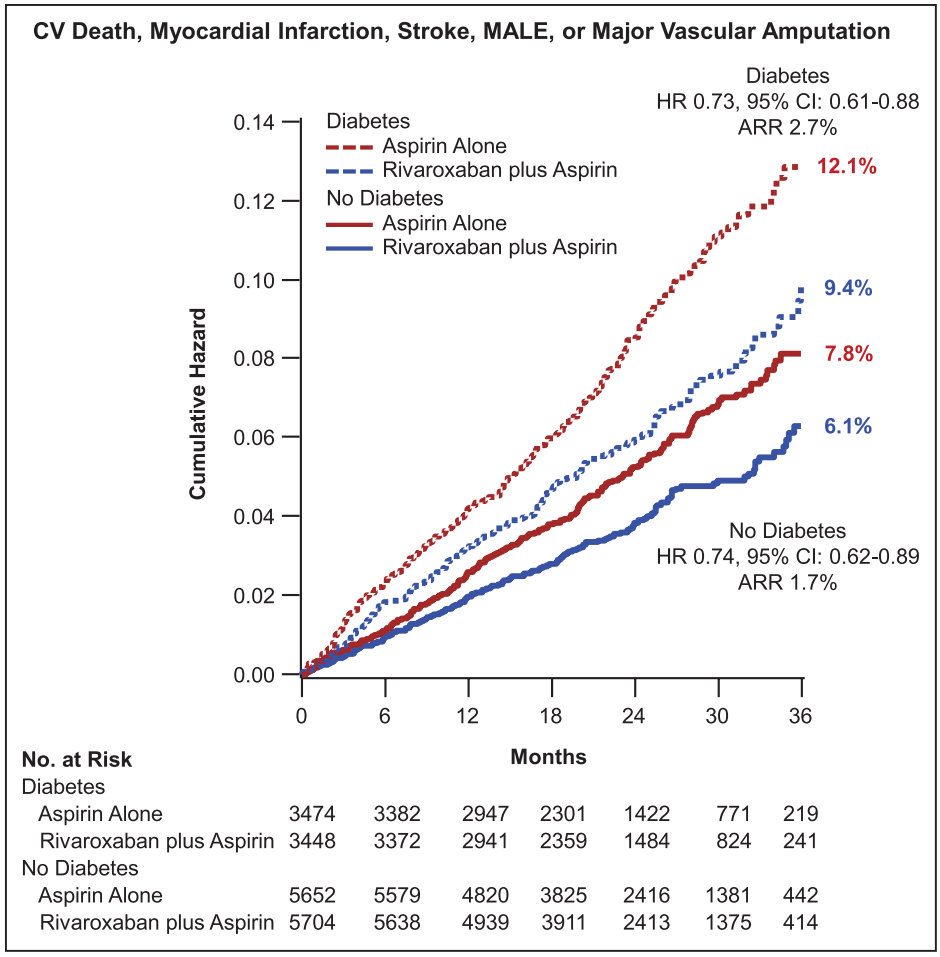

Figure 3. Major vascular events.
Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The expanded end point of all major vascular events (cardiovascular death, myocardial infarction, stroke, or major adverse limb events [MALEs], including amputation) is shown. Percentages are Kaplan-Meier risks at 3 years. ARR indicates absolute risk reduction; and HR, hazard ratio.

with a similar degree of risk increase. In those without diabetes mellitus, major bleeding was increased at 3 years to 4.4% from 3.2% (HR 1.69 [95% CI, 1.33–2.15]; $P<0.0001$). In those with diabetes mellitus, major bleeding was increased at 3 years to 4.5% from 3.4% (HR, 1.69 [95% CI, 1.33–2.15]; $P=0.0006$, $P_{interaction}=0.97$). There were no significant increases in intracranial or fatal bleeding. The absolute net clinical benefit for dual pathway inhibition with our prespecified definition was numerically greater (2.7% versus 1.0%) in those with versus those without diabetes mellitus, although both subgroups derived similar benefit (Gail-Simon qualitative $P_{interaction}=0.001$; Figure 4). In a nonprespecified post hoc analysis, major bleeding was combined with the primary efficacy end point, and this resulted in no significant difference between treatment arms in either those with or without diabetes mellitus (Table 2). There was no significant interaction with randomization to proton pump inhibitor versus placebo on the increased risk of major bleeding with rivaroxaban in the patients with diabetes mellitus (Table IV in the Data Supplement).

Results were similar in those with diabetes mellitus treated with medications versus those with diabetes mellitus but not receiving diabetes mellitus medications at baseline (Table 3). Consistent results were also seen in the patients with diabetes mellitus with or without a history of ischemic events (MI, unstable angina, stroke, transient ischemic attack) and with or without a history of revascularization (percutaneous coronary intervention, coronary artery bypass grafting, peripheral artery intervention, peripheral artery bypass surgery; Table 4).

DISCUSSION

This prespecified analysis of COMPASS shows that patients with stable atherosclerosis with concomitant diabetes mellitus have similar relative but, because of their more dismal prognosis, numerically greater absolute risk reductions in ischemic events than those without diabetes mellitus. This greater absolute efficacy occurs without any incremental increase in major bleeding complications in those with versus those without diabetes mellitus.

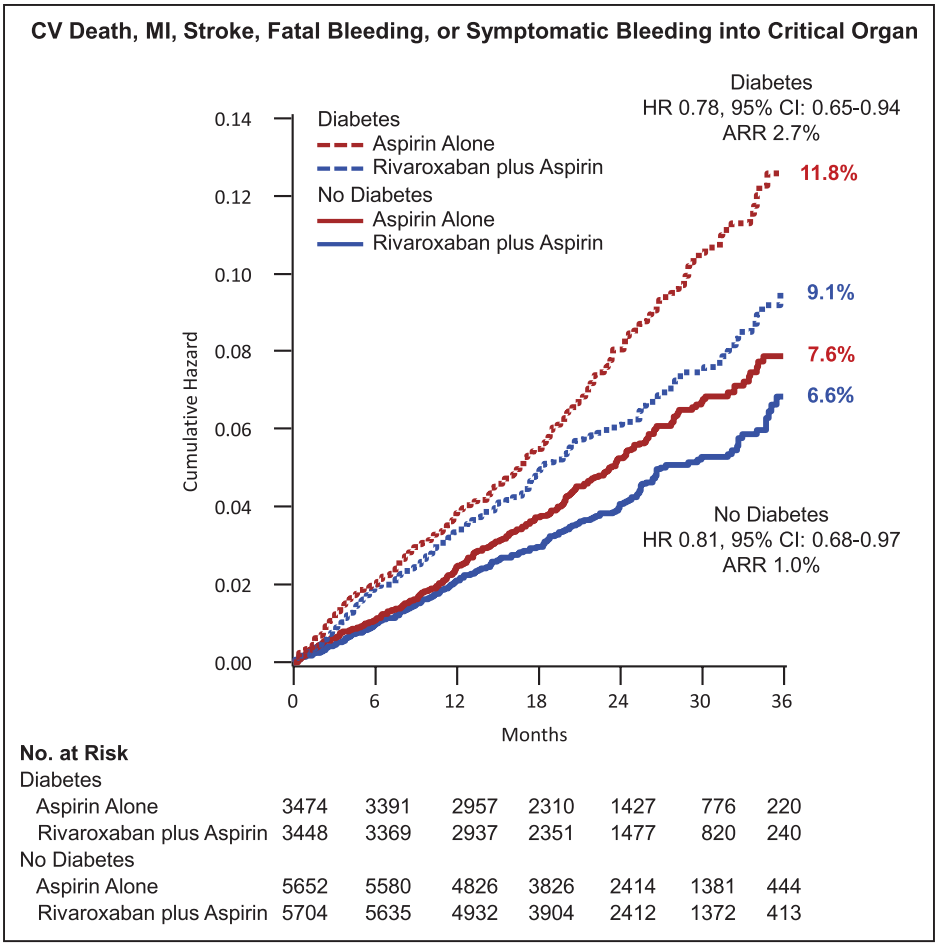

Figure 4. Net clinical benefit.
Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The net clinical benefit outcome (cardiovascular death, myocardial infarction [MI], stroke, fatal bleeding, or symptomatic bleeding into a critical organ) is shown. Percentages are Kaplan-Meier risks at 3 years. ARR indicates absolute risk reduction; and HR, hazard ratio.

Thus, the net clinical benefit for irreversible outcomes appears greater in those with versus those without diabetes mellitus. This finding makes the use of dual pathway inhibition with aspirin plus low-dose rivaroxaban particularly attractive in this high-risk population.

Patients with atherosclerosis and diabetes mellitus are a very high-risk group. Despite several advances in different therapeutic areas such as lipid, blood pressure, and glycemic control, patients with diabetes mellitus continue to have high rates of recurrent ischemic events. The population of patients with diabetes mellitus studied in COMPASS represents a very broad representation of secondary prevention, including patients with coronary artery disease, peripheral artery disease, and carotid disease. Patients had prior ischemic events or stable atherosclerosis without such a history. Patients with a history of revascularization and those without prior revascularization were enrolled in COMPASS, and all these subgroups appeared to have a consistent benefit in the overall trial and in the patients with diabetes mellitus. This latter observation does distinguish these results from the multiple trials of dual antiplatelet therapy that also show significant benefit and suggest greater absolute risk reductions in those with diabetes mellitus but that have not demonstrated convincing benefit in as diverse a group of patients with atherosclerosis outside of those with prior ischemic events or prior stenting. It is worth noting, however, that ischemic event rates in patients with diabetes mellitus in COMPASS treated with aspirin plus low-dose rivaroxaban were still higher than the rate in those without diabetes mellitus treated with placebo. Thus, there is further room for residual risk reduction.

In the setting of diabetic primary prevention, aspirin has been found to be superior to placebo, even in the contemporary era, although predictably bleeding was increased.[39] However, with careful patient selection, there are patients with diabetes mellitus without evident atherosclerosis who have a favorable net clinical benefit.[40–42] Now, in the secondary prevention of patients with diabetes mellitus, it is also clear that intensifying the antithrombotic regimen beyond aspirin alone is warranted in patients who are at an acceptable risk of bleeding. Examination of the prespecified definition of net clinical

Table 3. Outcomes in Patients With Diabetes Mellitus (Untreated and Treated With Hypoglycemic Agents) and Without Diabetes Mellitus for Rivaroxaban Plus Aspirin Versus Placebo Plus Aspirin

	Rivaroxaban Plus Aspirin (n=9152)		Placebo Plus Aspirin (n=9126)		Rivaroxaban Plus Aspirin vs Placebo Plus Aspirin		
	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	Hazard Ratios (95% CIs)	*P* Value	*P* Value for Interaction*
Efficacy outcomes							
Cardiovascular death, stroke, or myocardial infarction							0.94
No diabetes mellitus at baseline	200/5704 (3.5)	5.8	257/5652 (4.5)	7.2	0.77 (0.64–0.93)	0.005	
Diabetes mellitus and treated	146/2820 (5.2)	8.2	197/2871 (6.9)	10.8	0.73 (0.59–0.91)	0.004	
Diabetes mellitus and not treated	33/628 (5.3)	9.1	42/603 (7.0)	10.4	0.78 (0.50–1.24)	0.29	
Death resulting from any cause							0.75
No diabetes mellitus at baseline	166/5704 (2.9)	5.1	197/5652 (3.5)	5.7	0.84 (0.68–1.03)	0.09	
Diabetes mellitus and treated	119/2820 (4.2)	6.7	141/2871 (4.9)	8.1	0.84 (0.66–1.07)	0.17	
Diabetes mellitus and not treated	28/628 (4.5)	7.1	40/603 (6.6)	10.9	0.69 (0.43–1.13)	0.14	
Cardiovascular death							0.67
No diabetes mellitus at baseline	83/5704 (1.5)	2.7	104/5652 (1.8)	2.9	0.79 (0.59–1.06)	0.11	
Diabetes mellitus and treated	64/2820 (2.3)	3.6	77/2871 (2.7)	4.6	0.83 (0.59–1.15)	0.26	
Diabetes mellitus and not treated	13/628 (2.1)	3.1	22/603 (3.6)	5.9	0.60 (0.30–1.19)	0.14	
Stroke							0.66
No diabetes mellitus at baseline	37/5704 (0.6)	1.4	69/5652 (1.2)	2.0	0.53 (0.36–0.79)	0.002	
Diabetes mellitus and treated	41/2820 (1.5)	2.1	62/2871 (2.2)	3.8	0.66 (0.44–0.98)	0.04	
Diabetes mellitus and not treated	5/628 (0.8)	2.2	11/603 (1.8)	2.5	0.44 (0.15–1.26)	0.12	
Ischemic or uncertain stroke							0.59
No diabetes mellitus at baseline	29/5704 (0.5)	1.2	62/5652 (1.1)	1.7	0.46 (0.30–0.72)	0.0005	
Diabetes mellitus and treated	35/2820 (1.2)	1.9	59/2871 (2.1)	3.7	0.59 (0.39–0.90)	0.01	
Diabetes mellitus and not treated	4/628 (0.6)	2.1	11/603 (1.8)	2.5	0.35 (0.11–1.09)	0.06	
Myocardial infarction							0.41
No diabetes mellitus at baseline	100/5704 (1.8)	2.8	107/5652 (1.9)	2.9	0.93 (0.71–1.22)	0.59	
Diabetes mellitus and treated	60/2820 (2.1)	3.5	82/2871 (2.9)	4.0	0.73 (0.52–1.01)	0.06	
Diabetes mellitus and not treated	18/628 (2.9)	4.3	16/603 (2.7)	3.7	1.13 (0.57–2.21)	0.73	
Major adverse limb events							0.49
No diabetes mellitus at baseline	12/5704 (0.2)	0.3	30/5652 (0.5)	0.8	0.40 (0.20–0.78)	0.005	
Diabetes mellitus and treated	20/2820 (0.7)	1.3	32/2871 (1.1)	1.8	0.63 (0.36–1.10)	0.10	
Diabetes mellitus and not treated	2/628 (0.3)	0.8	2/603 (0.3)	0.6	0.96 (0.14–6.85)	0.97	
Total vascular amputation							0.77
No diabetes mellitus at baseline	3/5704 (<0.1)	0.06	7/5652 (0.1)	0.2	0.43 (0.11–1.65)	0.20	
Diabetes mellitus and treated	10/2820 (0.4)	0.4	22/2871 (0.8)	1.3	0.46 (0.22–0.97)	0.04	
Diabetes mellitus and not treated	2/628 (0.3)	0.6	2/603 (0.3)	0.8	1.04 (0.15–7.36)	0.97	
Cardiovascular death, stroke, myocardial infarction, major adverse limb events, or major vascular amputation							0.97
No diabetes mellitus at baseline	212/5704 (3.7)	6.1	282/5652 (5.0)	7.8	0.74 (0.62–0.89)	0.001	
Diabetes mellitus and treated	166/2820 (5.9)	9.3	227/2871 (7.9)	12.2	0.72 (0.59–0.88)	0.001	
Diabetes mellitus and not treated	35/628 (5.6)	9.9	45/603 (7.5)	11.2	0.77 (0.50–1.20)	0.25	
Safety outcomes							
Major bleeding							0.90
No diabetes mellitus at baseline	178/5704 (3.1)	4.4	105/5652 (1.9)	3.2	1.69 (1.33–2.15)	<0.0001	
Diabetes mellitus and treated	95/2820 (3.4)	4.8	58/2871 (2.0)	3.8	1.66 (1.20–2.30)	0.002	

(*Continued*)

Table 3. Continued

	Rivaroxaban Plus Aspirin (n=9152)		Placebo Plus Aspirin (n=9126)		Rivaroxaban Plus Aspirin vs Placebo Plus Aspirin		
	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	Hazard Ratios (95% CIs)	*P* Value	*P* Value for Interaction*
Diabetes mellitus and not treated	15/628 (2.4)	3.3	7/603 (1.2)	1.6	2.14 (0.87–5.26)	0.09	
Intracranial major bleeding							0.70
No diabetes mellitus at baseline	17/5704 (0.3)	0.4	17/5652 (0.3)	0.7	0.99 (0.51–1.95)	0.98	
Diabetes mellitus and treated	10/2820 (0.4)	0.5	6/2871 (0.2)	0.5	1.67 (0.61–4.59)	0.32	
Diabetes mellitus and not treated	1/628 (0.2)	0.2	1/603 (0.2)	0.2	1.02 (0.06–16.3)	0.99	
Fatal bleeding							0.93
No diabetes mellitus at baseline	10/5704 (0.2)	0.4	7/5652 (0.1)	0.2	1.43 (0.55–3.77)	0.46	
Diabetes mellitus and treated	3/2820 (0.1)	0.1	3/2871 (0.1)	0.2	1.00 (0.20–4.97)	0.99	
Diabetes mellitus and not treated	2/628 (0.3)	0.6	0/603 (0)	0	-	-	
Net clinical benefit outcomes							
Cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ							0.84
No diabetes mellitus at baseline	227/5704 (4.0)	6.6	276/5652 (4.9)	7.6	0.81 (0.68–0.97)	0.02	
Diabetes mellitus and treated	169/2820 (6.0)	9.1	210/2871 (7.3)	11.9	0.80 (0.65–0.98)	0.03	
Diabetes mellitus and not treated	35/628 (5.6)	9.4	48/603 (8.0)	11.5	0.72 (0.46–1.11)	0.14	
Cardiovascular death, stroke, myocardial infarction, or major bleeding							0.51
No diabetes mellitus at baseline	360/5704 (6.3)	3.4	341/5652 (6.0)	3.2	1.05 (0.91–1.22)	0.50	
Diabetes mellitus and treated	224/2820 (7.9)	4.3	242/2871 (8.4)	4.6	0.93 (0.78–1.12)	0.44	
Diabetes mellitus and not treated	45/628 (7.2)	3.9	49/603 (8.1)	4.3	0.92 (0.61–1.38)	0.69	

Percent is the proportion of patients with an outcome. Hazard ratios (95% CIs) are from the stratified Cox proportional hazards regression models fit in the respective subgroup. *P* values are from the stratified log-rank test.

*Test of interaction of relative risk reduction (Cox regression).

benefit in COMPASS, consisting of irreversible harms, demonstrated significant benefit for dual pathway inhibition, whereas a post hoc definition of net clinical benefit incorporating all major bleeding did not demonstrate significant benefit. However, although major bleeding is important, it is not appropriate to weight it equivalently to MI, ischemic stroke, amputations, or certainly all-cause mortality.[42]

Limitations of this analysis include that it is a subgroup not specifically powered for efficacy or safety assessments, although the analysis was prespecified. The early stopping of the trial further limits the power of subgroup analysis, although the independent data and safety monitoring board felt that the trial needed to be stopped as a result of overwhelming efficacy, including a reduction in all-cause mortality that echoed a prior trial with this double antithrombotic regimen.[43,44] Nevertheless, sufficient statistical power was present to demonstrate a significant reduction in the primary end point in the overall trial and in those with and without diabetes mellitus, increasing confidence in the subgroup analyses presented herein. Another limitation is that diabetes mellitus was defined only by case history, and duration of diabetes mellitus was not captured in the case report form. Some prior studies of antiplatelet agents have shown a gradient of benefit among those treated with insulin versus oral medications versus diet only; however, insulin treatment was not captured.[45,46]

CONCLUSIONS

Aspirin plus low-dose rivaroxaban reduces major cardiovascular events versus aspirin alone in patients with stable atherosclerosis, regardless of the presence or absence of diabetes mellitus, although the absolute risk reductions are numerically larger in those with diabetes mellitus.

ARTICLE INFORMATION

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Table 4. Effect of Antithrombotic Therapies in Subgroups of Patients With Diabetes Mellitus

	Rivaroxaban Plus Aspirin (n=3448)		Placebo Plus Aspirin (n=3474)		Rivaroxaban Plus Aspirin vs Placebo Plus Aspirin		
	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	First Events/ Patients, n (%)	Kaplan-Meier Risk at 36 mo, %	Hazard Ratios (95% CIs)	*P* Value	*P* Value for Interaction*
Cardiovascular death, stroke, or myocardial infarction							
History of prior ischemic events at baseline							0.85
No	42/937 (4.5)	8.8	57/981 (5.8)	10.1	0.76 (0.51–1.14)	0.18	
Yes	137/2511 (5.5)	8.3	182/2493 (7.3)	11.0	0.73 (0.59–0.91)	0.006	
History of prior revascularization at baseline							0.87
No	58/978 (5.9)	10.0	85/1068 (8.0)	12.8	0.73 (0.52–1.02)	0.06	
Yes	121/2470 (4.9)	7.9	154/2406 (6.4)	9.9	0.75 (0.59–0.95)	0.02	
History of prior ischemic events or revascularization at baseline							0.88
No	18/416 (4.3)	11.0	26/435 (6.0)	12.3	0.71 (0.39–1.30)	0.27	
Yes	161/3032 (5.3)	8.3	213/3039 (7.0)	10.6	0.74 (0.61–0.91)	0.004	
Major bleeding							
History of prior ischemic events at baseline							0.64
No	31/937 (3.3)	4.1	17/981 (1.7)	3.4	1.92 (1.06–3.47)	0.03	
Yes	79/2511 (3.1)	4.6	48/2493 (1.9)	3.5	1.63 (1.14–2.33)	0.007	
History of prior revascularization at baseline							0.39
No	25/978 (2.6)	3.7	20/1068 (1.9)	3.3	1.34 (0.74–2.41)	0.33	
Yes	85/2470 (3.4)	4.7	45/2406 (1.9)	3.4	1.84 (1.28–2.64)	0.001	
History of prior ischemic events or revascularization at baseline							0.33
No	7/416 (1.7)	2.2	7/435 (1.6)	3.9	1.04 (0.36–2.96)	0.94	
Yes	103/3032 (3.4)	4.7	58/3039 (1.9)	3.4	1.78 (1.29–2.46)	0.0004	
Cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ							
History of prior ischemic events at baseline							0.64
No	52/937 (5.5)	9.9	64/981 (6.5)	10.9	0.85 (0.59–1.22)	0.37	
Yes	152/2511 (6.1)	8.8	194/2493 (7.8)	12.1	0.76 (0.62–0.95)	0.01	
History of prior revascularization at baseline							0.97
No	66/978 (6.7)	11.0	90/1068 (8.4)	13.5	0.79 (0.57–1.08)	0.14	
Yes	138/2470 (5.6)	8.5	168/2406 (7.0)	11.1	0.79 (0.63–0.99)	0.04	
History of prior ischemic events or revascularization at baseline							0.83
No	21/416 (5.0)	11.9	29/435 (6.7)	13.0	0.75 (0.43–1.31)	0.31	
Yes	183/3032 (6.0)	9.0	229/3039 (7.5)	11.7	0.79 (0.65–0.96)	0.02	
Cardiovascular death, stroke, myocardial infarction, or major bleeding							
History of prior ischemic events at baseline							0.55
No	69/937 (7.4)	12.4	72/981 (7.3)	12.7	1.01 (0.72–1.40)	0.97	
Yes	200/2511 (8.0)	11.5	219/2493 (8.8)	13.2	0.90 (0.74–1.09)	0.27	
History of prior revascularization at baseline							0.37
No	79/978 (8.1)	13.0	102/1068 (9.6)	15.7	0.83 (0.62–1.11)	0.21	
Yes	190/2470 (7.7)	11.3	189/2406 (7.9)	12.1	0.98 (0.80–1.20)	0.82	
History of prior ischemic events or revascularization at baseline							0.40
No	24/416 (5.8)	13.0	33/435 (7.6)	16.1	0.75 (0.44–1.27)	0.28	
Yes	245/3032 (8.1)	11.8	258/3039 (8.5)	12.8	0.95 (0.80–1.13)	0.55	

Percent is the proportion of patients with an outcome. Hazard ratios (95% CIs) are from the stratified Cox proportional hazards regression models fit in the respective subgroup. *P* values are from the stratified log-rank test.

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