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.

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

Deepak L. Bhatt, MD, MPH
John W. Eikelboom, MBBS
Stuart J. Connolly, MD
P. Gabriel Steg, MD
Sonia S. Anand, MD
Subodh Verma, MD, PhD
Kelley R.H. Branch, MD
Jeffrey Probstfield, MD
Jackie Bosch, PhD
Olga Shestakovska, MSc
Michael Szarek, PhD
Aldo Pietro Maggioni, MD
Petr Widimský, MD
Alvaro Avezum, MD
Rafael Diaz, MD
Basil S. Lewis, MD
Scott D. Berkowitz, MD
Keith A.A. Fox, MBChB
Lars Ryden, MD
Salim Yusuf, DPhil
On behalf of the COMPASS Steering Committee and Investigators*

*A complete list of COMPASS Steering Committee and Investigators is provided in the Appendix.

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

Sources of Funding, see page 1852

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

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

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.

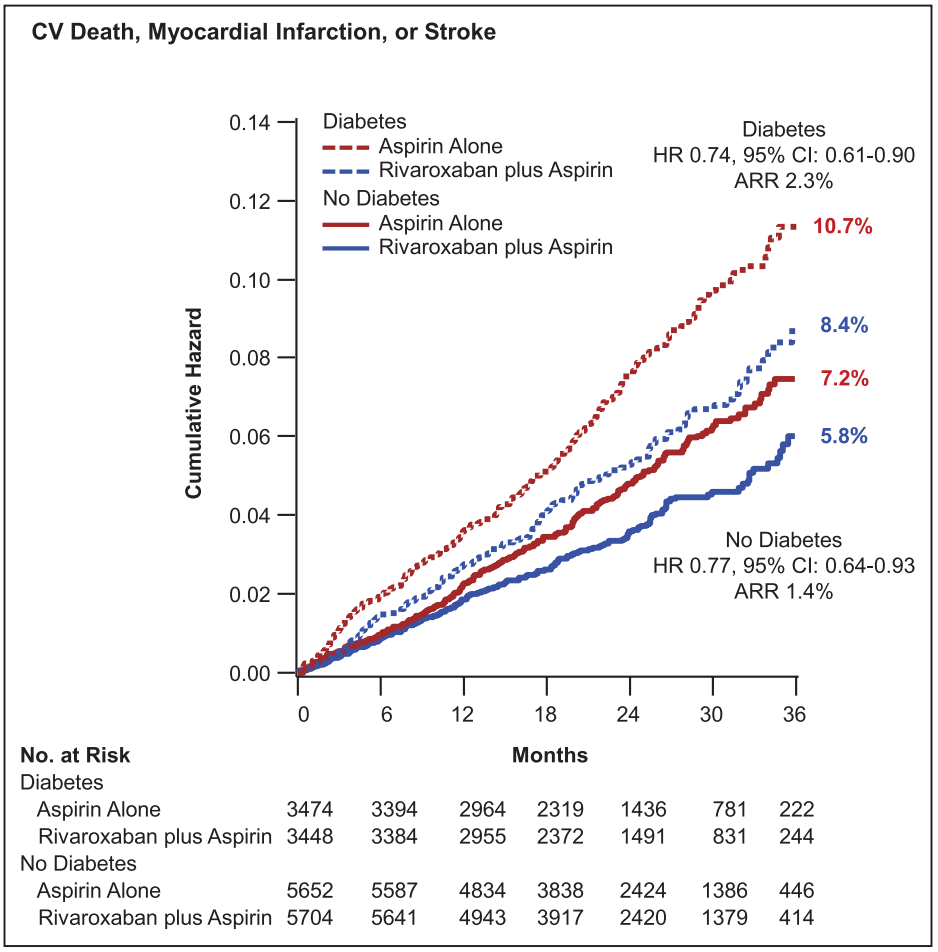

Figure 1. Cardiovascular death, myocardial infarction, or stroke.
Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The primary end point of cardiovascular death, myocardial infarction, or stroke is shown. 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,

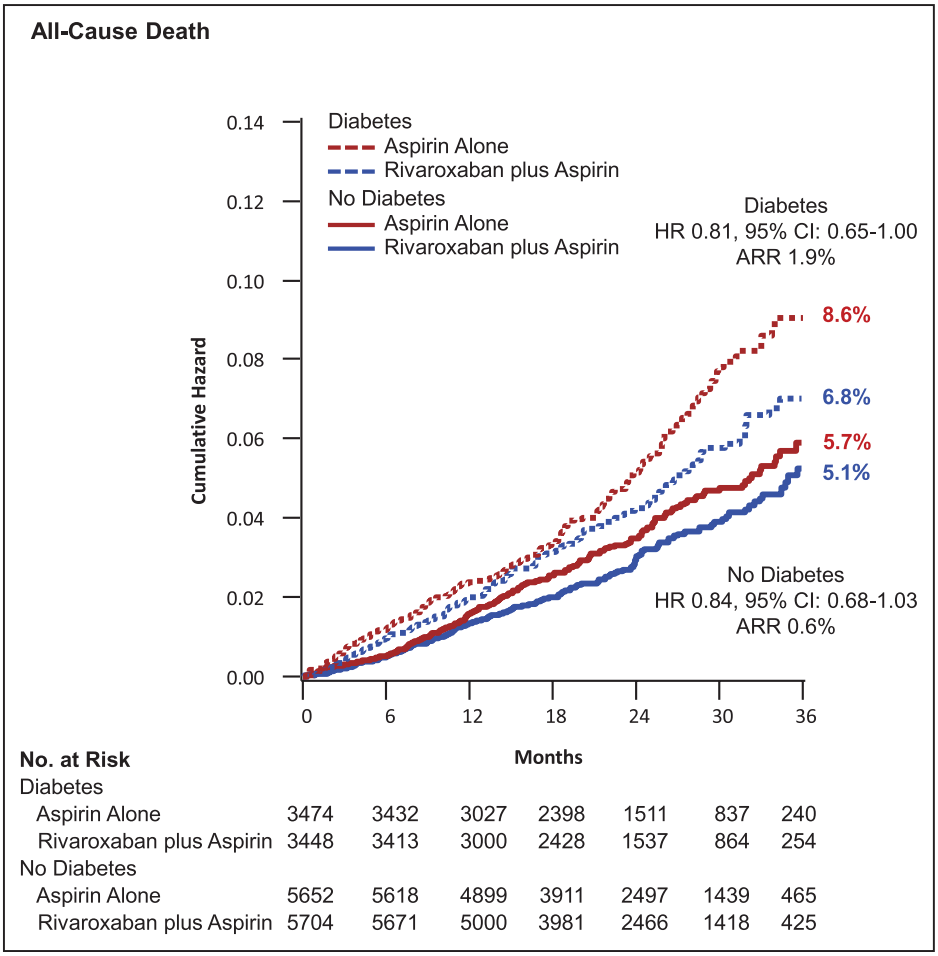

Figure 2. All-cause death.

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.

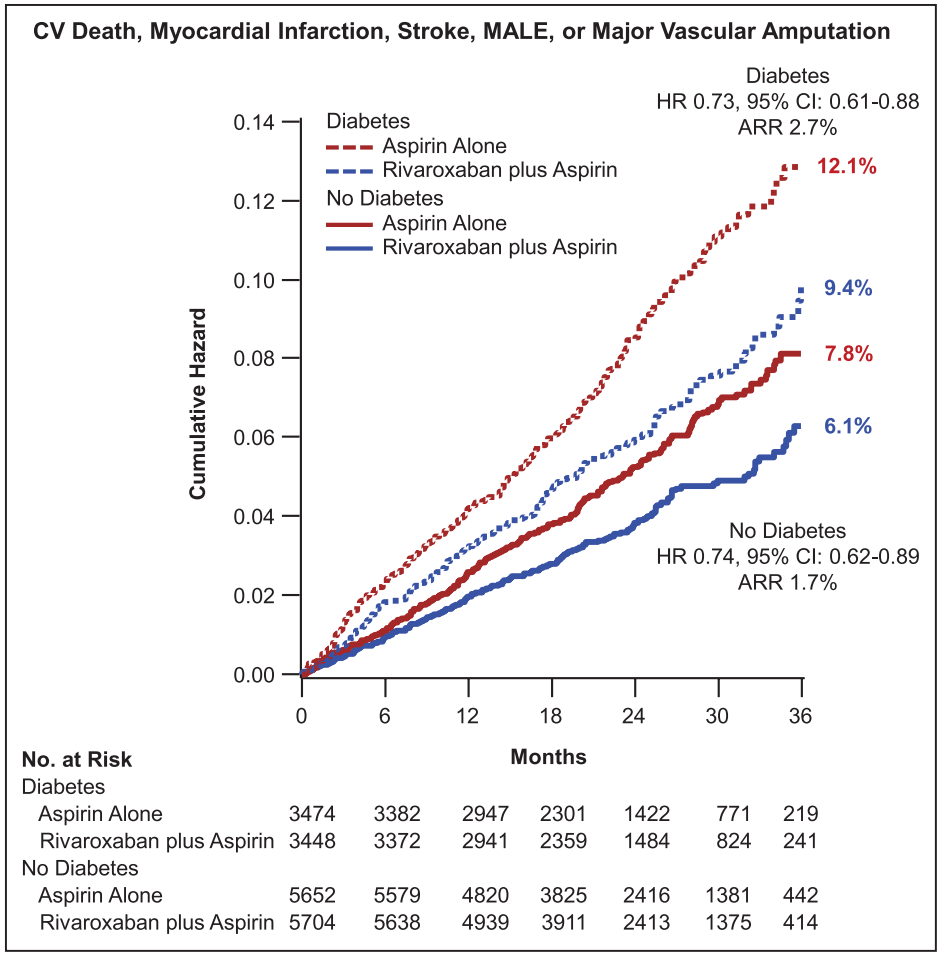

Figure 3. Major vascular events.
Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The expanded end point of all major vascular events (cardiovascular death, myocardial infarction, stroke, or major adverse 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.

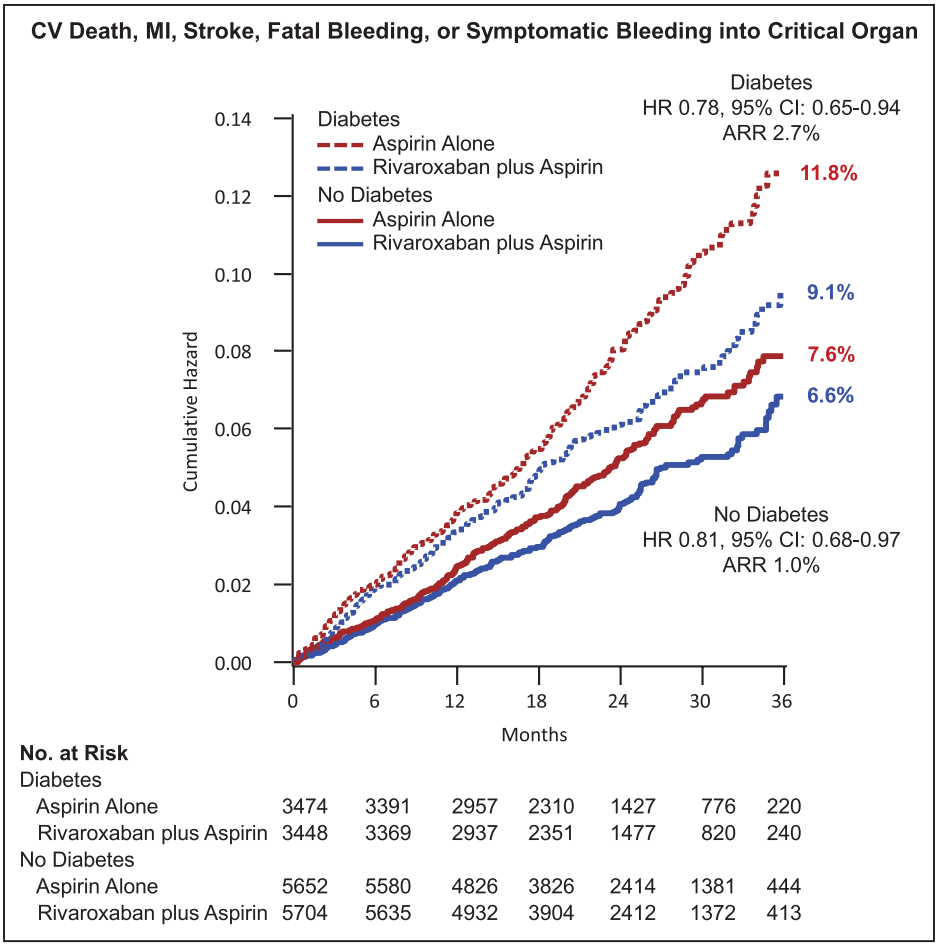

Figure 4. Net clinical benefit.
Kaplan-Meier event curves for patients with and without diabetes mellitus randomized to aspirin plus placebo or aspirin plus low-dose rivaroxaban. The net clinical benefit outcome (cardiovascular death, myocardial infarction [MI], stroke, fatal bleeding, or symptomatic 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

Received February 23, 2020; accepted March 16, 2020.

Guest Editor for this article was Gregory Lip, MD.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

The Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.120.046448.

Correspondence

Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis Street, Boston, MA 02115. Email dlbhattmd@post.harvard.edu

Affiliations

Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School Boston, MA (D.L.B.). Population Health Research Institute, McMaster

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.

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

University and Hamilton Health Sciences, Ontario, Canada (J.W.E., S.J.C., S.S.A., J.B., O.S., S.Y.). Université de Paris and Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, France (P.G.S.). Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Ontario, Canada (S.V.). University of Washington Medical Centre, Seattle (K.R.H.B., J.P.). School of Rehabilitation Science, McMaster University, Hamilton, Ontario, Canada (J.B.). State University of New York, Downstate School of Public Health, Brooklyn (M.S.). ANMCO Research Center, Florence, Italy (A.P.M.). Third Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic (P.W.). Hospital Alemão Oswaldo Cruz, São Paulo, Brazil (A.A.). Estudios Clínicos Latino América, Rosario, Argentina (R.D.). Instituto Cardiovascular de Rosario, Argentina (R.D.). Lady Davis Carmel Medical Centre and the Technion-Israel Institute of Technology, Haifa (B.S.L.). Bayer US LLC, Whippany, NJ (S.D.B.). Centre for Cardiovascular Science, University of Edinburgh, United Kingdom (K.A.A.F.). Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden (L.R.).

Sources of Funding

The COMPASS study was funded by Bayer AG.

Disclosures

Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, PLx Pharma, and Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org; vice chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Medtelligence/ReachMD (Continuing Medical Education steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and US national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (Continuing Medical Education steering committees); other: *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, and The Medicines Company; royalties: Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site coinvestigator: Biotronik, Boston Scientific, CSI, St Jude Medical (now Abbott), and Svelte; trustee: American College of Cardiology; and unfunded research: FlowCo, Merck, Novo Nordisk, and Takeda. Dr Eikelboom reports consulting fees and/or honoraria from AstraZeneca, Bayer Boehringer-Ingelheim, Bristol-Myer-Squibb, Daiichi-Sankyo, Eli Lilly, Glaxo-Smith-Kline, Pfizer, Janssen, and Sanofi-Aventis and grant support from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Glaxo-Smith-Kline, Pfizer, Janssen, and Sanofi-Aventis. Dr Connolly reports lecture fees and consulting fees from Bristol-Myers Squibb, Pfizer, Portola Pharmaceuticals, Boehringer Ingelheim, Servier, Daiichi Sankyo, and Medtronic. Dr Steg discloses the following relationships: research grant from Amarin, Bayer, Sanofi, and Servier, as well as speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer-Ingelheim, Bristol-Myers-Squibb, Idorsia, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, and Servier. Dr Anand has received speaking and consulting fees from Bayer. Dr Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery and reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group. He is also president of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. Dr Branch has received consulting fees from Bayer, Janssen, and AstraZeneca and research support from Bayer, Astellas, and the National Institutes of Health/National Heart, Lung, and Blood Institute. Dr Bosch received fees for advisory board work for Bayer. Dr Maggioni reports receiving fees for serving as a study committee member from Novartis, Bayer, Fresenius Medical Care, and Cardiorentis. Dr Szarek reports receiving consulting fees from CiVi and Esperion, consulting fees and fees for serving on a data and safety monitoring board from Resverlogix and Baxter, and fees for serving on a steering committee from Regeneron and Sanofi. Dr Widimský reports honoraria and/or advisory board fees from Bayer, AstraZeneca, Phizer, Servier, Medtronic, and Novartis and fees for the COMPASS trial national coordinator role from Bayer. Dr Avezum discloses the following relationships: Population Health Research Institute (for the COMPASS Operations Committee, Publications Committee, Steering Committee, and Brazil national coleader, funded by Bayer), lecture fees from Bayer and Boheringer-Ingelheim, and research funding from Sanofi Aventis. Dr Diaz has received research grants from Sanofi, Eli Lilly, Amgen, Population Heart Research Institute, Duke Clinical Research Institute, Montreal Health Research Coordinating Center, Lepetit Sa, Dalcor, Cirius Therapeutics, and Heart Initiative and speaker fees from Sanofi, AstraZeneca, Eli Lilly, and Amgen. Dr Lewis reports research funding from Bayer Healthcare, MSD, AstraZeneca, Pfizer, and Kowa Pharmaceuticals, as well as consultant fees and honoraria from MSD and Pfizer. Dr Berkowitz is employed as a clinical research physician by Bayer US, LLC. Dr Fox received grants from Bayer/Janssen and AstraZeneca and consulting and honoraria from Bayer/Janssen, Sanofi/Regeneron, and Verseon. Dr Ryden reports research grants from the Swedish Heart-Lung Foundation, The Familjen Erling-Perssons Foundation, private foundations, Amgen, Bayer AG, Boehringer Ingelheim, MSD, and Novo Nordisk, as well as personal fees (consulting) from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi. Dr Yusuf has received grants and honoraria from Bayer, BI, Astra, BMS, and Cadila. The other authors report no conflicts.

APPENDIX

Steering Committee: S. Yusuf, K.A.A. Fox, S. Connolly, J.W. Eikelboom, J. Bosch, V. Aboyans, M. Alings, S. Anand, A. Avezum, D.L. Bhatt, K. Branch, P. Commerford, N. Cook-Bruns, G. Dagenais, A. Dans, R. Diaz, G. Ertl, C. Felix, T. Guzik, R. Hart, M. Hori, A. Kakkar, K. Keltai, M. Keltai, J. Kim, A. Lamy, F. Lanas, B. Lewis, Y. Liang, L. Liu, E. Lonn, P. Lopez-Jaramillo, A. Maggioni, K. Metsarinne, P. Moayyedi, M. O'Donnell, A. Parkhomenko, L. Piegas, N. Pogosova, J. Probstfield, L. Ryden, M. Sharma, P.G. Steg, S. Stoerk, A. Tonkin, C. Torp-Pedersen, J. Varigos, P. Verhamme, D. Vinereanu, P. Widimsky, K. Yusoff, and J. Zhu.

REFERENCES

1. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Röther J, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180–189. doi: 10.1001/jama.295.2.180
2. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–1206. doi: 10.1001/jama.297.11.1197
3. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, Wilson PW, Alberts MJ, D'Agostino R, Liau CS, et al; 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. Cavender MA, Steg PG, Smith SC Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL; REACH Registry Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation*. 2015;132:923–931. doi: 10.1161/CIRCULATIONAHA.114.014796
5. Alberts MJ, Bhatt DL, Mas JL, Ohman EM, Hirsch AT, Röther J, Salette G, Goto S, Smith SC Jr, Liau CS, et al; REduction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J*. 2009;30:2318–2326. doi: 10.1093/eurheartj/ehp355

6. Gutierrez JA, Scirica BM, Bonaca MP, Steg PG, Mosenzon O, Hirshberg B, Im K, Raz I, Braunwald E, Bhatt DL. Prevalence and outcomes of polyvascular (coronary, peripheral, or cerebrovascular) disease in patients with diabetes mellitus (from the SAVOR-TIMI 53 trial). *Am J Cardiol.* 2019;123:145–152. doi: 10.1016/j.amjcard.2018.09.014
7. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380:11–22. doi: 10.1056/NEJMoa1812792
8. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol.* 2017;5:941–950. doi: 10.1016/S2213-8587(17)30313-3
9. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, Budaj AJ, Diaz R, Goodman SG, Hanotin C, et al; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol.* 2019;7:618–628. doi: 10.1016/S2213-8587(19)30158-5
10. Verma S, Bhatt DL. More CREDENCE for SGLT2 Inhibition. *Circulation.* 2019;140:1448–1450. doi: 10.1161/CIRCULATIONAHA.119.041181
11. Verma S, Poulter NR, Bhatt DL, Bain SC, Buse JB, Leiter LA, Nauck MA, Pratley RE, Zinman B, Ørsted DD, et al. Effects of liraglutide on cardiovascular outcomes in patients with type 2 diabetes mellitus with or without history of myocardial infarction or stroke. *Circulation.* 2018;138:2884–2894. doi: 10.1161/CIRCULATIONAHA.118.034516
12. Verma S, Mazer CD, Bhatt DL. The perils of polyvascular disease in type 2 diabetes. *Lancet Diabetes Endocrinol.* 2018;6:914–916. doi: 10.1016/S2213-8587(18)30311-5
13. Verma S, Bhatt DL, Bain SC, Buse JB, Mann JFE, Marso SP, Nauck MA, Poulter NR, Pratley RE, Zinman B, et al; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Effect of liraglutide on cardiovascular events in patients with type 2 diabetes mellitus and polyvascular disease: results of the LEADER trial. *Circulation.* 2018;137:2179–2183. doi: 10.1161/CIRCULATIONAHA.118.033898
14. Connelly KA, Bhatt DL, Verma S. Can we DECLARE a victory against cardio-renal disease in diabetes? *Cell Metab.* 2018;28:813–815. doi: 10.1016/j.cmet.2018.11.010
15. Verma S, Leiter LA, Latter DA, Bhatt DL. A LEADER in the management of type 2 diabetes and cardiorenal disease. *J Thorac Cardiovasc Surg.* 2020;159:978–984. doi: 10.1016/j.jtcvs.2019.03.134
16. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380:347–357. doi: 10.1056/NEJMoa1812389
17. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2019;393:31–39. doi: 10.1016/S0140-6736(18)32590-X
18. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation.* 2019;139:2022–2031. doi: 10.1161/CIRCULATIONAHA.118.038868
19. Bhatt DL. Antiplatelet therapy following myocardial infarction in patients with diabetes. *JAMA.* 2012;308:921–922. doi: 10.1001/2012.jama.11467
20. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354:1706–1717. doi: 10.1056/NEJMoa060989
21. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, et al; CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol.* 2007;49:1982–1988. doi: 10.1016/j.jacc.2007.03.025
22. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med.* 2015;372:1791–1800. doi: 10.1056/NEJMoa1500857
23. Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, Im K, Murphy SA, Held P, Braunwald E, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol.* 2016;67:2732–2740. doi: 10.1016/j.jacc.2016.03.529
24. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol.* 2016;67:2719–2728. doi: 10.1016/j.jacc.2016.03.524
25. Dalby AJ, Gottlieb S, Cyr DD, Magnus Ohman E, McGuire DK, Ruzyllo W, Bhatt DL, Wiviott SD, Winters KJ, Fox KAA, et al; TRILOGY ACS Investigators. Dual antiplatelet therapy in patients with diabetes and acute coronary syndromes managed without revascularization. *Am Heart J.* 2017;188:156–166. doi: 10.1016/j.ahj.2017.03.015
26. Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee CW, Mauri L, Valgimigli M, Park SJ, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J.* 2016;37:390–399. doi: 10.1093/eurheartj/ehv443
27. Bhatt DL, Fox K, Harrington RA, Leiter LA, Mehta SR, Simon T, Andersson M, Himmelmann A, Ridderstråle W, Held C, et al; THEMIS Steering Committee. Rationale, design and baseline characteristics of the effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients intervention study. *Clin Cardiol.* 2019;42:498–505. doi: 10.1002/clc.23164
28. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med.* 2019;381:1309–1320. doi: 10.1056/NEJMoa1908077
29. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, Held C, Andersson M, Himmelmann A, Ridderstråle W, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet.* 2019;394:1169–1180. doi: 10.1016/S0140-6736(19)31887-2
30. Bosch J, Eikelboom JW, Connolly SJ, Bruns NC, Lanius V, Yuan F, Misselwitz F, Chen E, Diaz R, Alings M, et al. Rationale, design and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. *Can J Cardiol.* 2017;33:1027–1035. doi: 10.1016/j.cjca.2017.06.001
31. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377:1319–1330. doi: 10.1056/NEJMoa1709118
32. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, Metsarinne K, O'Donnell M, Dans AL, Ha JW, et al; COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;391:205–218. doi: 10.1016/S0140-6736(17)32458-3
33. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, Aboyans V, Alings M, Kakkar AK, Keltai K, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;391:219–229. doi: 10.1016/S0140-6736(17)32409-1
34. Anand SS, Eikelboom JW, Dyal L, Bosch J, Neumann C, Widimsky P, Avezum AA, Probstfield J, Cook Bruns N, Fox KAA, et al; COMPASS Trial Investigators. Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial. *J Am Coll Cardiol.* 2019;73:3271–3280. doi: 10.1016/j.jacc.2019.02.079
35. Darmon A, Bhatt DL, Elbez Y, Aboyans V, Anand S, Bosch J, Branch KR, Connolly SJ, Dyal L, Eikelboom JW, et al. External applicability of the COMPASS trial: an analysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Eur Heart J.* 2018;39:750–757a. doi: 10.1093/eurheartj/ehx658
36. Darmon A, Sorbets E, Ducrocq G, Elbez Y, Abtan J, Popovic B, Ohman EM, Röther J, Wilson PF, Montalescot G, et al; REACH Registry Investigators. Association of multiple enrichment criteria with ischemic and bleeding

risks among COMPASS-eligible patients. *J Am Coll Cardiol.* 2019;73:3281–3291. doi: 10.1016/j.jacc.2019.04.046
37. Fox KAA, Eikelboom JW, Anand SS, Bhatt DL, Bosch J, Connolly SJ, Harrington RA, Steg PG, Yusuf S. Anti-thrombotic options for secondary prevention in patients with chronic atherosclerotic vascular disease: what does COMPASS add? *Eur Heart J.* 2019;40:1466–1471. doi: 10.1093/eurheartj/ehy347
38. Boden WE, Bhatt DL. Will COMPASS point to a new direction in thrombotic risk reduction in patients with stable cardiovascular disease? *Circulation*. 2018;138:858–860. doi: 10.1161/CIRCULATIONAHA.118.035405
39. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379:1529–1539.
40. Raber I, McCarthy CP, Vaduganathan M, Bhatt DL, Wood DA, Cleland JGF, Blumenthal RS, McEvoy JW. The rise and fall of aspirin in the primary prevention of cardiovascular disease. *Lancet.* 2019;393:2155–2167. doi: 10.1016/S0140-6736(19)30541-0
41. Abdelaziz HK, Saad M, Pothineni NVK, Megaly M, Potluri R, Saleh M, Kon DLC, Roberts DH, Bhatt DL, Aronow HD, et al. Aspirin for primary prevention of cardiovascular events. *J Am Coll Cardiol.* 2019;73:2915–2929. doi: 10.1016/j.jacc.2019.03.501
42. Steg PG, Bhatt DL. Is there really a benefit to net clinical benefit in testing antithrombotics? *Circulation.* 2018;137:1429–1431. doi: 10.1161/CIRCULATIONAHA.117.033442
43. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;366:9–19. doi: 10.1056/NEJMoa1112277
44. Gibson CM, Chakrabarti AK, Mega J, Bode C, Bassand JP, Verheugt FW, Bhatt DL, Goto S, Cohen M, Mohanavelu S, et al; ATLAS-ACS 2 TIMI 51 Investigators. Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51. *J Am Coll Cardiol.* 2013;62:286–290. doi: 10.1016/j.jacc.2013.03.041
45. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol.* 2002;90:625–628. doi: 10.1016/s0002-9149(02)02567-5
46. Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol.* 2000;35:922–928. doi: 10.1016/s0735-1097(99)00650-6