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ORIGINAL INVESTIGATIONS

Rivaroxaban Plus Aspirin in Patients With Vascular Disease and Renal Dysfunction

From the COMPASS Trial

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ABSTRACT

BACKGROUND Chronic kidney disease is associated with an increased risk of both bleeding and ischemic cardiovascular events.

OBJECTIVE The purpose of this study was to determine the balance of risks and benefits from the dual pathway antithrombotic regimen (rivaroxaban 2.5 mg twice daily [bd] plus aspirin, compared with aspirin) in vascular patients with or without moderate renal dysfunction.

METHODS This was a secondary analysis of the COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS) trial involving 27,395 patients with chronic coronary or peripheral artery disease.

RESULTS In COMPASS, 21,111 patients had an estimated glomerular filtration rate (GFR) at baseline of ≥60 ml/min, 6,276 had a GRF of <60 ml/min. Both the primary efficacy outcome (cardiovascular death, myocardial infarction, or stroke) and major bleeding were more frequent in those with renal dysfunction, and the frequency of these outcome events was inversely related to GFR. However, the primary outcome was consistently reduced with rivaroxaban 2.5 mg bd plus aspirin, irrespective of GFR category (GFR ≥60 ml/min, 3.5% rivaroxaban plus aspirin, 4.5% aspirin alone, hazard ratio [HR]: 0.76, 95% confidence interval [CI]: 0.64 to 0.90; GFR <60 ml/min, 6.4% rivaroxaban plus aspirin, 8.4% aspirin alone, HR: 0.75; 95% CI: 0.60 to 0.94). Major bleeding was more frequent with rivaroxaban 2.5 mg plus aspirin versus aspirin alone in those with GFR ≥60 ml/min (2.9% rivaroxaban plus aspirin, 1.6% aspirin alone, HR: 1.81; 95% CI: 1.44 to 2.28) and similarly in those with GFR <60 ml/min (3.9% rivaroxaban plus aspirin, 2.7% aspirin alone, HR: 1.47, 95% CI: 1.05 to 2.07).

CONCLUSIONS The benefits of the dual pathway COMPASS regimen (rivaroxaban 2.5 mg bd plus aspirin), versus aspirin alone, are preserved in patients with moderate renal dysfunction without evidence of an excess hazard of bleeding. (J Am Coll Cardiol 2019;73:2243–50) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ASA = acetyl salicylic acid

CAD = coronary artery disease

GFR = glomerular filtration rate

MI = myocardial infarction

Chronic kidney disease increases the risk of both thromboembolism and bleeding (1–7). Prior studies have investigated the effectiveness of treating patients with varying degrees of renal impairment and antithrombotic agents (8,9) and with non-vitamin K antagonist oral anticoagulants compared with warfarin among patients with atrial fibrillation (10–17). Full anticoagulation, even without acetylsalicylic acid (ASA, or aspirin), increases bleeding risks in the presence of renal dysfunction (4–7). Higher age and the prevalent comorbidities associated with vascular disease also increase both bleeding risks and adverse cardiovascular outcomes. Non-vitamin K antagonist oral anticoagulants vary in their extent of renal excretion, with 25% to 80% of the drug excreted unchanged in the urine (15–17). Hence, the balance of risk versus benefit for antithrombotic combinations may be altered in the presence of renal dysfunction.

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In the COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS) trial, we hypothesized that one-quarter of the full anticoagulant dose of rivaroxaban (2.5 mg twice daily [bd]) and ASA together, or one-half dose of rivaroxaban alone (5 mg bd) would be superior to ASA alone for the prevention of major vascular events in patients with chronic vascular disease (18). In the COMPASS trial overall, rivaroxaban 2.5 mg bd plus aspirin, compared with aspirin alone, reduced cardiovascular outcomes and increased major bleeding in patients with stable atherosclerotic vascular disease (19–21). In contrast rivaroxaban 5 mg twice daily did not reduce cardiovascular outcomes and increased major bleeding (19).

This report examines the safety and efficacy of reduced dose anticoagulation (rivaroxaban) in combination with aspirin in the COMPASS trial (the "dual pathway COMPASS regimen") (22), versus ASA alone in patients who are in sinus rhythm but at increased vascular risk. As rivaroxaban 5 mg bd without ASA did not reduce cardiovascular outcomes, the focus of this paper is on the comparison between the dual-pathway COMPASS regimen and ASA.

METHODS

POPULATION. COMPASS was a multicenter, double-blind, randomized, placebo-controlled trial comparing rivaroxaban 2.5 mg bid with ASA in combination or rivaroxaban 5 mg bid (with ASA placebo) versus ASA alone (with rivaroxaban placebo) for prevention of cardiovascular death, myocardial infarction (MI), or stroke (major adverse cardiovascular events) in patients with coronary artery disease (CAD) or peripheral artery disease and markers of increased vascular risk. The doses selected for the COMPASS trial were based on prior dose ranging studies and the ATLAS-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis In Myocardial Infarction 51) trial (18,19). The details of inclusion and exclusion criteria have been published previously (18,19).

Patients included in the COMPASS trial had chronic "stable" CAD and/or peripheral artery disease (18). For CAD patients age younger than 65 years, additional risk factors were required, and these comprised documented atherosclerosis or revascularization involving at least 2 vascular beds, or at least 2 additional risk factors. The additional risk factors included a glomerular filtration rate (GFR) <60 ml/min (but those with a GRF <15 ml/min were excluded); hence, the population was enriched for moderately severe renal dysfunction.

OUTCOMES. The pre-specified primary outcome of the trial was the composite of cardiovascular death, stroke, or MI; in this report, the individual endpoints are also reported and strokes are categorized as hemorrhagic or ischemic/unknown. The safety outcomes were major bleeding (by modified International Society on Thrombosis and Haemostasis criteria), fatal bleeding, and intracranial bleeding (18,19).

Patients in the COMPASS trial were categorized by severity of chronic renal disease according to the estimated (CKD-Epi) GFR <60 and ≥60 ml/min and the relation between renal dysfunction and outcomes was also investigated as a continuous function of GFR.

STATISTICAL METHODS. Analyses were conducted according to the intention-to-treat principle. Annualized event rates were calculated as number of patients with an outcome per total number of patient-years of follow-up. Event rates were calculated within the deciles of estimated glomerular filtration rate (eGFR) and displayed in a plot along with a parametric cubic spline smoothing function. Survival analyses were based on the time to a first event. Stratified Cox proportional hazards regression models were used to compare the effects of antithrombotic regimens within categories of eGFR. Significance was tested using stratified log-rank tests. Interaction between the effect of treatment with rivaroxaban/aspirin and eGFR was tested in a stratified Cox model fit to all patients. All reported p values are 2-sided.

Analyses were performed using SAS software for Linux, version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

From the overall COMPASS population (n = 27,395), 21,111 patients had an estimated GFR at baseline ≥60 ml/min, and 6,276 had a GFR <60 ml/min. For those with a reduced GFR, baseline characteristics differed, including older age and a greater prevalence of diabetes, hypertension, peripheral artery disease, and stroke, but the rates of coronary artery disease and prior MI were similar (**Table 1**). Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, lipid-lowering agents, nonsteroidal anti-inflammatory drugs, and nontrial proton pump inhibitors were similar, but diuretic agents and calcium-channel blockers were more frequent in those with a reduced GRF (**Table 1**).

Considering the primary efficacy outcome of COMPASS (cardiovascular death, MI, or stroke) this composite was more frequent in those with renal dysfunction and the frequency was inversely related to GFR (**Central Illustration**). Cardiovascular deaths and MIs also increased in frequency with reduced GFR (**Table 2**).

The primary efficacy outcome was reduced in those randomized to rivaroxaban plus aspirin compared with aspirin alone (**Central Illustration**) with a consistent hazard ratio (HR) in those with GFR ≥60 ml/min (GFR ≥60 ml/min, 3.5% rivaroxaban plus aspirin, 4.5% aspirin alone; HR: 0.76; 95% confidence interval [CI]: 0.64 to 0.90; and those with GFR <60 ml/min (6.4% rivaroxaban plus aspirin, 8.4% aspirin alone, HR: 0.75; 95% CI: 0.60 to 0.94) (**Figure 1**). Considering those with more marked renal dysfunction (GFR <30 ml/min; n = 243) the HRs were consistent (HR: 0.73; 95% CI: 0.28 to 1.91) (Online Table 1). Tests for subgroup interaction by the categories of renal function were not significant for the primary efficacy outcomes and for the primary safety (bleeding) analysis (**Table 2**).

The rates of stroke of any cause were reduced for the rivaroxaban 2.5 mg bd plus aspirin group versus aspirin for those with GFR ≥60 ml/min (0.9% and 1.3%, respectively; HR: 0.67; 95% CI: 0.48 to 0.92) and GFR <60 ml/min (1.0% and 2.3%, respectively; HR: 0.42; 95% CI: 0.25 to 0.70). There were very few strokes among the 243 patients with a GFR <30 ml/min (none in the rivaroxaban treatments and 3 in the aspirin-only arm) (Online Table 1). Ischemic or uncertain strokes were also reduced for those treated with rivaroxaban 2.5 mg bd plus aspirin versus aspirin alone with GFR <60 ml/min (0.7% and 2.2%, respectively, HR: 0.31; 95% CI: 0.17 to 0.57) and for GFR ≥60 ml/min (0.8% and 1.2%, respectively, HR: 0.62; 95% CI: 0.44 to 0.87). There were no patients with ischemic or uncertain strokes with GFR <30 ml/min in the rivaroxaban plus aspirin treatment group, and 3 in the aspirin-only group (Online Table 1).

Cardiovascular death was reduced for the rivaroxaban 2.5 mg bd plus aspirin group versus aspirin for those with GFR ≥60 ml/min (1.3% and 1.7%, respectively, HR: 0.73; 95% CI: 0.56 to 0.96) and for GFR <60 ml/min (3.5% and 3.9%, respectively, HR: 0.88; 95% CI: 0.64 to 1.20).

The consistency of treatment effects for the efficacy outcomes by GFR status is given in the **Central Illustration** for rivaroxaban 2.5 mg bd plus aspirin versus aspirin. Throughout the range in GFR, the rivaroxaban 2.5 mg plus aspirin patients had consistently lower primary efficacy outcomes. Tests for statistical interactions were not significant (**Table 2**).

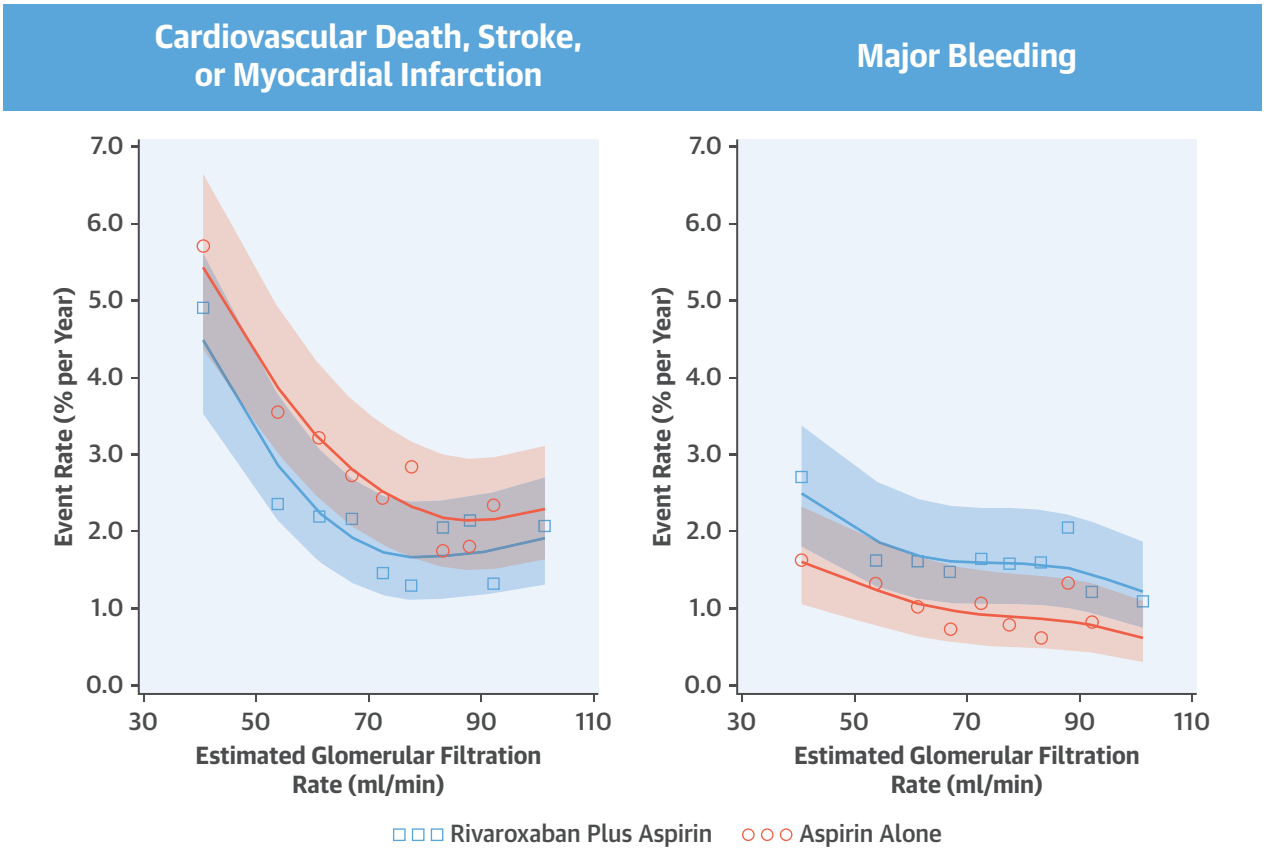
TABLE 1 Baseline Characteristics of Patients by Category of Renal Dysfunction

	eGFR	
	<60 ml/min (n = 6,276)	**≥60 ml/min (n = 21,111)**
Age, yrs	71.7 ± 7.4	67.2 ± 7.8
Female	1,959 (31.2)	4,059 (19.2)
Body mass index, kg/m^2	28.7 ± 4.9	28.2 ± 4.7
Systolic blood pressure, mm Hg	136 ± 18	136 ± 17
Diastolic blood pressure, mm Hg	77 ± 10	78 ± 10
Total cholesterol, mmol/l	4.2 ± 1.1	4.2 ± 1.1
Tobacco use		
Never	2,401 (38.3)	6,352 (30.1)
Former	3,028 (48.2)	9,740 (46.1)
Current	847 (13.5)	5,019 (23.8)
Hypertension	5,175 (82.5)	15,452 (73.2)
Diabetes	2,581 (41.1)	7,757 (36.7)
Previous stroke	329 (5.2)	702 (3.3)
Previous myocardial infarction	3,825 (60.9)	13,199 (62.5)
Heart failure	1,516 (24.2)	4,386 (20.8)
Coronary artery disease	5,561 (88.6)	19,255 (91.2)
Peripheral arterial disease	2,075 (33.1)	5,392 (25.5)
Medication		
ACE inhibitor or ARB	4,660 (74.3)	14,852 (70.4)
Calcium-channel blocker	1,809 (28.8)	5,457 (25.8)
Diuretic agent	2,597 (41.4)	5,538 (26.2)
Beta-blocker	4,537 (72.3)	14,640 (69.3)
Lipid-lowering agent	5,571 (88.8)	19,023 (90.1)
NSAID	358 (5.7)	1,111 (5.3)
Nontrial PPI	2,326 (37.1)	7,467 (35.4)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitors.

CENTRAL ILLUSTRATION **Rivaroxaban Plus Aspirin in Renal Dysfunction**



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Rates of COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS) primary efficacy outcome (cardiovascular death, stroke, or myocardial infarction; **left**) and major bleeding **(right)** according to estimated glomerular filtration rate (eGFR) (with 95% confidence interval). To define the relation between the severity of renal dysfunction (as estimated by eGFR), a continuous plot is provided over the range of eGFR in the COMPASS study for the primary outcome and for bleeding. Throughout the range in eGFR, rivaroxaban plus aspirin demonstrates fewer primary outcome events than aspirin plus placebo (cardiovascular death, stroke, or myocardial infarction, **left**) but consistently more bleeding **(right)**. The **lines** (aspirin: **red**, rivaroxaban: **blue**) show the relation between event rates and eGFR; **cross-hatched areas** show 95% CI bounds (aspirin: **red**, rivaroxaban: **blue**).

Major bleeding was more frequent with reduced renal function, irrespective of treatment strategy (Central Illustration).

Considering the randomized treatments, major bleeding was more frequent in those randomized to rivaroxaban 2.5 mg plus aspirin versus aspirin alone in those with GFR ≥60 ml/min (2.9% rivaroxaban plus aspirin 1.6% aspirin, HR: 1.81; 95% CI: 1.44 to 2.28) and in those with GFR <60 ml/min (3.9% rivaroxaban plus aspirin, 2.7% aspirin, HR: 1.47; 95% CI: 1.05 to 2.07). Major bleeds were too few to calculate a reliable hazard ratio for those with a GRF <30 ml/min (3 on aspirin alone and 1 with rivaroxaban 2.5 mg bd plus aspirin [Online Table 1]). Although bleeding rates were higher for those with renal dysfunction, irrespective of treatment strategy (Table 2), the absolute difference in rates of major bleeding was similar for those with GRF <60 ml/min (0.7% per annum) compared with GRF ≥60 ml/min (0.7% per annum) (Figure 1).

The consistency of the impact of the randomized treatment on major bleeding according to renal dysfunction is indicated in the Central Illustration. Throughout the range in GFR, the rivaroxaban 2.5 mg plus aspirin patients had consistently higher rates of major bleeding, with no evidence of a divergence of the curves with lower GFR (Central Illustration). The interaction terms were nonsignificant. The consistency of treatment effects according to GFR ≥60 or <60 ml/min is given in Figure 1.

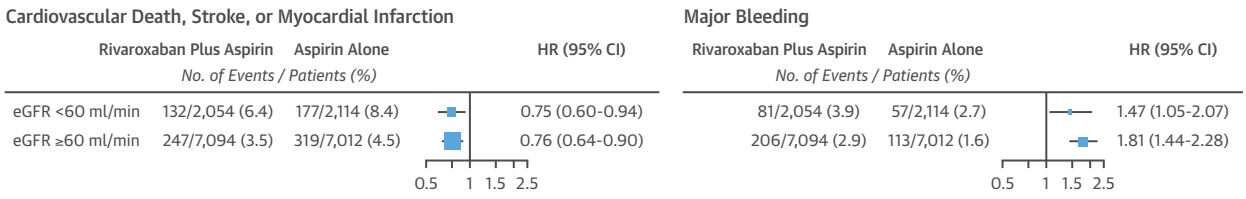
TABLE 2 Effect of Antithrombotic Therapies on COMPASS Efficacy and Safety Outcomes by Category of Renal Dysfunction <60 and ≥60 ml/min

	Rivaroxaban Plus Aspirin (n = 9,152)		Aspirin Alone (n = 9,126)		Rivaroxaban Plus Aspirin Versus Aspirin Alone		
	No. of First Events/Patients (%)	Annual Rate, %/yr	No. of First Events/Patients (%)	Annual Rate, %/yr	HR (95% CI)	p Value	p Value For Interaction
Efficacy outcomes							
Cardiovascular death, stroke, or myocardial infarction							0.95
eGFR <60 ml/min	132/2,054 (6.4)	3.4	177/2,114 (8.4)	4.5	0.75 (0.60–0.94)	0.01	
eGFR ≥60 ml/min	247/7,094 (3.5)	1.8	319/7,012 (4.5)	2.4	0.76 (0.64–0.90)	0.001	
Cardiovascular death							0.41
eGFR <60 ml/min	71/2,054 (3.5)	1.8	83/2,114 (3.9)	2.1	0.88 (0.64–1.20)	0.41	
eGFR ≥60 ml/min	89/7,094 (1.3)	0.7	120/7,012 (1.7)	0.9	0.73 (0.56–0.96)	0.02	
Stroke							0.13
eGFR <60 ml/min	20/2,054 (1.0)	0.5	49/2,114 (2.3)	1.2	0.42 (0.25–0.70)	0.0007	
eGFR ≥60 ml/min	63/7,094 (0.9)	0.5	93/7,012 (1.3)	0.7	0.67 (0.48–0.92)	0.01	
Ischemic or uncertain stroke							0.05
eGFR <60 ml/min	14/2,054 (0.7)	0.4	46/2,114 (2.2)	1.2	0.31 (0.17–0.57)	<0.0001	
eGFR ≥60 ml/min	54/7,094 (0.8)	0.4	86/7,012 (1.2)	0.6	0.62 (0.44–0.87)	0.005	
Hemorrhagic stroke							0.58
eGFR <60 ml/min	6/2,054 (0.3)	0.2	3/2,114 (0.1)	0.07	2.01 (0.50–8.06)	0.31	
eGFR ≥60 ml/min	9/7,094 (0.1)	0.07	7/7,012 (<0.1)	0.05	1.26 (0.47–3.39)	0.64	
Myocardial infarction							0.28
eGFR <60 ml/min	53/2,054 (2.6)	1.4	73/2,114 (3.5)	1.8	0.73 (0.51–1.04)	0.08	
eGFR ≥60 ml/min	125/7,094 (1.8)	0.9	132/7,012 (1.9)	1.0	0.93 (0.73–1.19)	0.57	
Safety outcomes							
Major bleeding							0.30
eGFR <60 ml/min	81/2,054 (3.9)	2.1	57/2,114 (2.7)	1.4	1.47 (1.05–2.07)	0.02	
eGFR ≥60 ml/min	206/7,094 (2.9)	1.5	113/7,012 (1.6)	0.8	1.81 (1.44–2.28)	<0.0001	
Fatal bleeding							0.79
eGFR <60 ml/min	5/2,054 (0.2)	0.1	4/2,114 (0.2)	0.1	1.25 (0.34–4.67)	0.74	
eGFR ≥60 ml/min	10/7,094 (0.1)	0.07	6/7,012 (<0.1)	0.04	1.63 (0.59–4.48)	0.34	
Symptomatic bleeding into critical organ							0.73
eGFR <60 ml/min	25/2,054 (1.2)	0.6	17/2,114 (0.8)	0.4	1.50 (0.81–2.77)	0.20	
eGFR ≥60 ml/min	48/7,094 (0.7)	0.4	36/7,012 (0.5)	0.3	1.32 (0.85–2.03)	0.21	
Fatal bleeding, symptomatic bleeding into critical organ, or surgical site bleeding requiring reoperation							0.50
eGFR <60 ml/min	31/2,054 (1.5)	0.8	20/2,114 (0.9)	0.5	1.59 (0.90–2.78)	0.10	
eGFR ≥60 ml/min	56/7,094 (0.8)	0.4	44/7,012 (0.6)	0.3	1.25 (0.85–1.86)	0.26	
Symptomatic bleeding into critical organ or surgical site bleeding requiring reoperation							0.45
eGFR <60 ml/min	31/2,054 (1.5)	0.8	19/2,114 (0.9)	0.5	1.67 (0.94–2.96)	0.07	
eGFR ≥60 ml/min	53/7,094 (0.7)	0.4	41/7,012 (0.6)	0.3	1.27 (0.85–1.92)	0.24	
Bleeding leading to hospitalization							0.12
eGFR <60 ml/min	72/2,054 (3.5)	1.9	53/2,114 (2.5)	1.3	1.41 (0.99–2.00)	0.06	
eGFR ≥60 ml/min	186/7,094 (2.6)	1.4	94/7,012 (1.3)	0.7	1.97 (1.54–2.52)	<0.0001	
Major intracranial bleeding							0.41
eGFR <60 ml/min	11/2,054 (0.5)	0.3	7/2,114 (0.3)	0.2	1.59 (0.62–4.10)	0.33	
eGFR ≥60 ml/min	17/7,094 (0.2)	0.1	17/7,012 (0.2)	0.1	0.98 (0.50–1.92)	0.95	
Net clinical benefit outcomes							
Cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ							0.89
eGFR <60 ml/min	147/2,054 (7.2)	3.8	188/2,114 (8.9)	4.8	0.79 (0.64–0.98)	0.03	
eGFR ≥60 ml/min	284/7,094 (4.0)	2.1	346/7,012 (4.9)	2.6	0.81 (0.69–0.94)	0.007	

Percent (%) is the proportion of patients with an outcome. Percent per year (%/yr) is the rate per 100 patient-years of follow-up. Hazard ratios (HR) (95% confidence intervals [CIs]) are from the stratified Cox proportional hazards regression models fit in the respective subgroup. p values are from the stratified log-rank test.

eGFR = estimated glomerular filtration rate.

FIGURE 1 Treatment Effects According to the Category of Renal Dysfunction (eGFR <60 and ≥60 ml/min)



The COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS) primary efficacy outcome (cardiovascular death, stroke, or myocardial infarction; **left**) is consistently and significantly less frequent with rivaroxaban plus aspirin compared with aspirin plus placebo. Conversely, rivaroxaban plus aspirin compared with aspirin plus placebo shows more bleeding **(right)**, but there is no evidence that the excess in bleeding is more marked in those with estimated glomerular filtration rate (eGFR) <60 ml/min. CI = confidence interval; HR = hazard ratio.

Fatal bleeds were rare in the treatment groups and of similar frequency in those with GFR ≥60 ml/min (rivaroxaban plus aspirin <0.1% per annum, aspirin alone <0.1% per annum), and for GRF <60 ml/min (rivaroxaban plus aspirin 0.1% per annum, aspirin alone 0.1% per annum). There were similar results for intracranial bleeds in those with GFR ≥60 ml/min (rivaroxaban plus aspirin 0.2% per annum, aspirin 0.2% per annum) and GFR <60 ml/min (rivaroxaban plus aspirin 0.3% per annum, aspirin 0.2% per annum) (Table 2).

Symptomatic bleeding into a critical organ occurred with a frequency of 0.3% per annum with ASA (GFR ≥60 ml/min), and 0.4% per annum with ASA (GFR <60 ml/min) (Table 2). This compares with 0.4% per annum with rivaroxaban plus aspirin (GFR ≥60 ml/min), and 0.6% per annum with rivaroxaban and aspirin (GFR <60 ml/min) (Table 2).

Net clinical benefit, comprising cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into critical organ, demonstrated consistent findings for those with GRF ≥60 ml/min (HR: 0.81; 95% CI: 0.69 to 0.94) and <60 ml/min (HR: 0.79; 95% CI: 0.64 to 0.98) for rivaroxaban 2.5 mg bd plus aspirin versus aspirin alone. Given the higher event rates in those with renal dysfunction (but similar HR for the treatment effect), the absolute difference in favor of the combined rivaroxaban strategy compared with aspirin alone was numerically greater among those with GFR <60 ml/min (1.0% per annum) compared with 0.5% per annum for GFR ≥60 ml/min.

DISCUSSION

In accord with previous findings in various clinical settings, including acute coronary syndrome and atrial fibrillation, patients with chronic vascular disease demonstrate higher rates of adverse cardiovascular outcomes and bleeding with renal dysfunction (1,2,7-9,23,24). The key questions addressed in this report are whether the treatment effects observed in patients with preserved renal function, for both safety and efficacy, are consistent with those observed in patients with moderate renal dysfunction. As approximately 30% rivaroxaban is cleared unchanged by the kidneys, the balance between efficacy and safety could be altered in those with renal dysfunction. The findings from this analysis suggest that for both efficacy and safety, the relative treatment effects observed with the dual-pathway COMPASS regimen (rivaroxaban 2.5 mg bd and aspirin), compared with aspirin alone are consistent among those with preserved and those with moderately impaired renal function. The HRs for benefit ranged from 0.76 to 0.73 for the categories of renal dysfunction, and statistical tests for interaction were nonsignificant. Similarly, the HRs for major bleeding did not show statistical heterogeneity. By design, COMPASS did not include patients with an GFR <15 ml/min at the time of randomization, and there were relatively few patients in with an GRF between 15 and 30 ml/min. The cutpoints for GFR of ≥60 and <60 ml/min are provided for comparison with findings of other studies using the same cut points. However, the continuous plots of GFR versus outcomes suggest a consistent pattern of benefit for the dual-pathway COMPASS regimen across the observed range of renal function.

The clinical interpretation of these findings is that the benefits of the dual-pathway COMPASS regimen are maintained, proportionately, in those with moderate renal dysfunction. There is no evidence of an excess hazard of bleeding among those with moderate renal dysfunction and the dual-pathway COMPASS regimen. The absolute treatment effects are numerically greater among those with moderate renal dysfunction where event rates are higher

(1.1% reduction per annum vs. 0.6% reduction per annum with preserved renal dysfunction), and the absolute difference in major bleeding was similar for those with preserved or moderately impaired renal function (0.7% and 0.7% per annum for GRF ≥60 or <60 ml/min, respectively). Thus, the findings suggest that the absolute net treatment benefits are consistent and there is no excess bleeding hazard in those with moderate renal dysfunction.

How do the findings of this study fit with prior investigations of antiplatelet therapy or anticoagulation in the context of renal dysfunction? In the randomized trial of fondaparinux (OASIS 5), the absolute treatment effects were more marked in those with renal dysfunction (9). In the PEGASUS TIMI 54 trial, patients with non-end-stage renal dysfunction on ticagrelor had a better outcome in comparison with those on placebo, but irrespective of renal dysfunction, those on ticagrelor had higher rates of bleeding; corresponding findings have been seen in other trials of antiplatelet therapy (25–27). Although stroke risk and bleeding risks are increased among patients with moderate to severe renal dysfunction in patients with atrial fibrillation, the benefit versus risk of anticoagulation in that population has varied in different studies (12–14,23,24,26). Thus, there remained uncertainty about combined antiplatelet therapy and low-dose anticoagulation in a population with chronic vascular disease (as in the COMPASS study).

STUDY LIMITATIONS. The limitations of this analysis are that there were, by design, few patients included in COMPASS with severe renal dysfunction, and the analysis does not take account of patients with a deterioration in renal function during the course of the study. Nevertheless, the vast majority of patients encountered with chronic vascular disease fall within the spectrum of this analysis.

CONCLUSIONS

The findings of the COMPASS study demonstrate that the effect of the dual-pathway COMPASS regimen (rivaroxaban 2.5 mg bd plus aspirin) versus aspirin alone are preserved in patients with moderate renal dysfunction, and there is no evidence of an excess hazard of bleeding with the COMPASS dual-pathway strategy in those with moderate renal dysfunction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Impaired renal function is associated with a greater risk of cardiovascular events and bleeding during antithrombotic therapy, whether aspirin is given alone or in combination with an anticoagulant.

TRANSLATIONAL OUTLOOK: Further studies are needed to compare this regimen of rivaroxaban plus aspirin with other combinations of antiplatelet and anticoagulant drugs in patients with moderate renal dysfunction and stable atherosclerotic disease.

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KEY WORDS aspirin, atherosclerosis, death, myocardial infarction, rivaroxaban, stroke

APPENDIX For a supplemental table, please see the online version of this paper.