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ORIGINAL ARTICLE
Coronary artery disease

Long-term treatment with the combination of rivaroxaban and aspirin in patients with chronic coronary or peripheral artery disease: outcomes during the open label extension of the COMPASS trial

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Aims To describe outcomes of patients with chronic coronary artery disease (CAD) and/or peripheral artery disease (PAD) enrolled in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) randomized trial who were treated with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily during long-term open-label extension (LTOLE).

Methods and results Of the 27 395 patients enrolled in COMPASS, 12 964 (mean age at baseline 67.2 years) from 455 sites in 32 countries were enrolled in LTOLE and treated with the combination of rivaroxaban and aspirin for a median of 374 additional days (range 1–1191 days). During LTOLE, the incident events per 100 patient years were as follows: for the primary outcome [cardiovascular death, stroke, or myocardial infarction (MI)] 2.35 [95% confidence interval (CI) 2.11–2.61], mortality 1.87 (1.65–2.10), stroke 0.62 (0.50–0.76), and MI 1.02 (0.86–1.19), with CIs that overlapped those seen during the randomized treatment phase with the combination of rivaroxaban and aspirin. The incidence rates for major and minor bleeding were 1.01 (0.86–1.19) and 2.49 (2.24–2.75), compared with 1.67 (1.48–1.87) and 5.11 (95% CI 4.77–5.47), respectively, during the randomized treatment phase with the combination.

Conclusion In patients with chronic CAD and/or PAD, extended combination treatment for a median of 1 year and a maximum of 3 years was associated with incidence rates for efficacy and bleeding that were similar to or lower than those seen during the randomized treatment phase, without any new safety signals.

Keywords Coronary artery disease • Peripheral artery disease • Aspirin • Rivaroxaban

Introduction

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial demonstrated that the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily compared with aspirin 100 mg once daily reduced the risk of stroke, myocardial infarction (MI), or cardiovascular (CV) death and all-cause mortality in patients with chronic coronary artery disease (CAD) and/or peripheral artery disease (PAD).[1–4] The benefits of the combination were evident at the time of the first formal interim analysis,[5] and prompted the Data Safety and Monitoring Board (DSMB) to recommend discontinuation of the antithrombotic arms of the study.

Based on the benefits demonstrated with the combination of rivaroxaban and aspirin during randomized treatment, the study sponsor, Bayer AG, made available rivaroxaban 2.5 mg twice daily in combination with aspirin 75–100 mg once daily to all COMPASS sites that agreed to participate as part of a long-term open-label extension (LTOLE). Open-label combination treatment would continue to be provided to patients at sites that agreed to participate until the combination was approved by regulatory authorities in their country for the treatment of chronic CAD or PAD or for a maximum of 3 years from the start of LTOLE, whichever occurred first. Treatment could be initiated as soon as regulators and ethics committees approved the LTOLE protocol amendment and the drug was available at the site. During LTOLE, patients were followed every 6 months to evaluate adherence and safety, and to collect clinical outcomes, including stroke, MI, and mortality.

This report describes the outcomes of patients during the time that they were enrolled in LTOLE and received treatment with the combination of rivaroxaban and aspirin, as well as outcomes of patients who were assigned the combination of rivaroxaban and aspirin during the randomized treatment period.

Methods

Study design

COMPASS was a multicentre, international, double-blind, double-dummy, randomized trial that enrolled patients with chronic CAD or PAD.[6] The study protocol for the main trial and for the LTOLE was approved by relevant institutional review boards and all patients provided written informed consent.

The trial enrolled randomized 27 395 patients to receive rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg once daily. Additionally, using a 3 × 2 partial factorial design, the trial randomized 17 598 patients not taking a proton pump inhibitor at baseline to receive pantoprazole 40 mg once daily or a placebo. On 6 February 2017, after a mean follow-up of 23 months, the DSMB recommended discontinuation of the antithrombotic arms of the trial after observing a clear benefit in favour of the combination of rivaroxaban and aspirin compared with aspirin. Rivaroxaban 5 mg twice daily did not significantly reduce the primary outcome compared with aspirin.

Between 6 February 2017 and 18 July 2017, all patients attended a close-out visit where they were informed of the results of the antithrombotic randomization and were told to stop the rivaroxaban and aspirin trial medications and switch to non-study low-dose aspirin at a dose of 75–100 mg once daily. Patients were also informed that there might be the opportunity to participate in the LTOLE study once regulatory and ethics approvals were obtained and the drug was available at the site.

Eligibility

All patients enrolled in COMPASS who completed follow-up until the end of the antithrombotic randomization (irrespective of randomized treatment allocation or whether they continued randomized treatment until the final visit) and who continued to meet the COMPASS inclusion and exclusion criteria[6] (see the Supplementary material online, *Table S1*) were eligible to participate in LTOLE. If a patient was (i) attending a site that declined to participate in LTOLE, (ii) declined to participate, or (iii) no longer met the eligibility criteria for COMPASS, they were

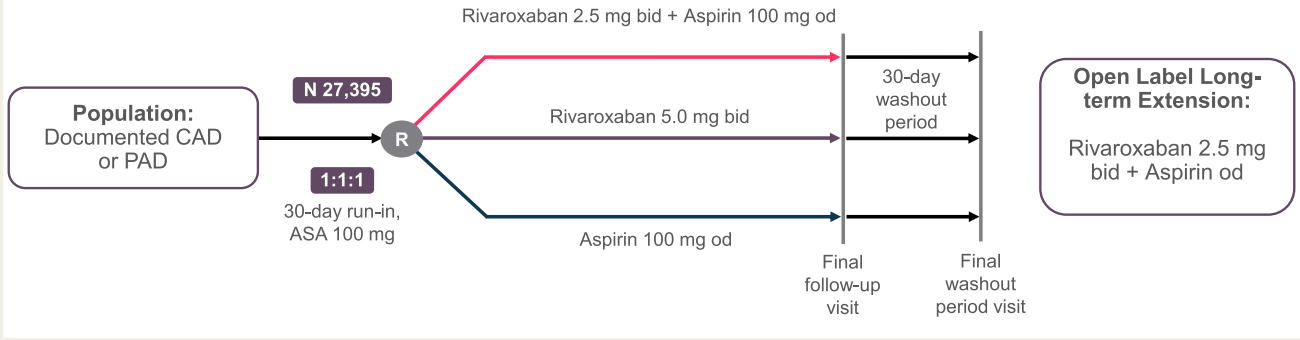

Figure 1 Study schematic.

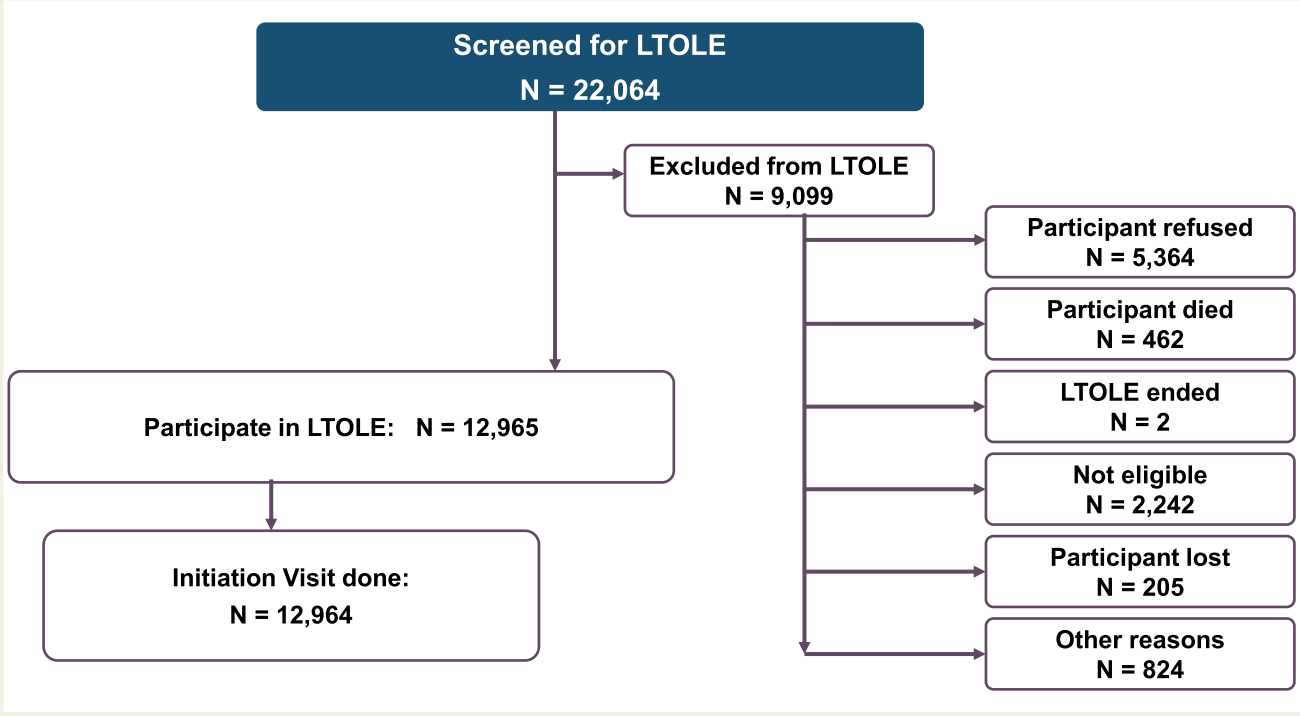

Figure 2 Patient flow diagram for long-term open-label extension entry.

discontinued from further follow-up at 30 days after their final rivaroxaban/aspirin visit (i.e. the 30-day washout visit), their final pantoprazole visit (for those participating in the pantoprazole randomization), or their LTOLE screening visit (where they either declined participation or were determined to no longer be eligible), whichever occurred last. It was recommended that these patients continue standard-of-care non-study antithrombotic treatments. All LTOLE participants received rivaroxaban 2.5 mg twice daily in combination with aspirin 75–100 mg once daily. If a patient discontinued one or both LTOLE study treatments, they discontinued follow-up in LTOLE.

Study cohorts

We analysed two patient cohorts. The first cohort included patients enrolled in LTOLE (n = 12 964), from the start to the end of LTOLE. The second cohort included patients who were randomized to receive the combination of rivaroxaban and aspirin (n = 9 152), from the start to the end of randomized treatment who served as a comparator group.

Outcomes

The primary efficacy outcome was a composite of stroke, MI, or CV death. The main safety outcome was modified International Society on Thrombosis and Haemostasis (ISTH) major bleeding, and included fatal bleeding, symptomatic bleeding in a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization (including presentation to an acute care facility without overnight stay).[6]

From the start of the COMPASS trial until completion of randomized treatment, outcomes were collected on standardized event forms with supporting documentation and were processed using a computer-programmed algorithm. A central adjudication committee further reviewed and adjudicated all events not confirmed by the algorithm. Apart

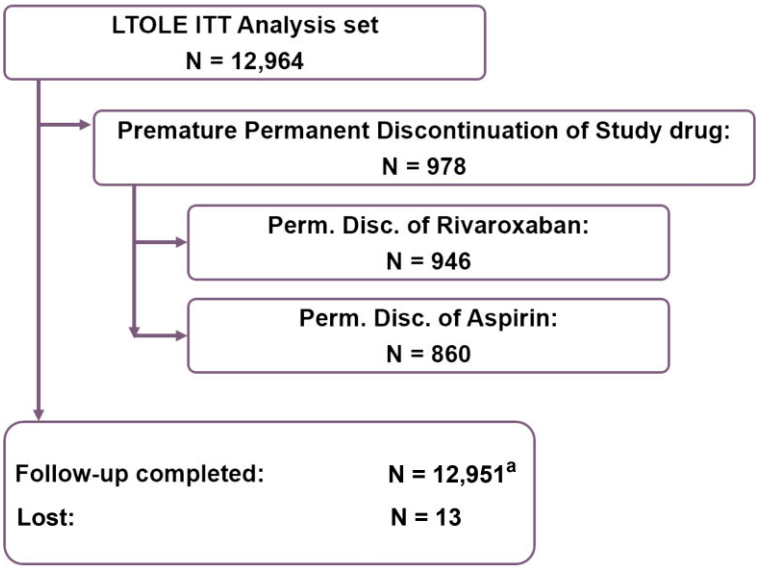

Figure 3 Patient disposition during long-term open-label extension.
[a]Includes 18 patients who refused further follow up; their most recent visit was counted as their final visit.

from a brief period of overlap between the pantoprazole vs. placebo randomized evaluation and the start of LTOLE (during which events were still being collected on the standardized event forms), events during LTOLE were collected on streamlined event forms and did not undergo adjudication.

Statistical analyses

We report baseline characteristics (collected at the time of randomization) in patients enrolled in LTOLE, in patients who received rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily during randomized treatment, and in patients not enrolled in LTOLE. For patients enrolled in LTOLE, we also report treatments (non-antithrombotic and antithrombotic) received in the interval between the final rivaroxaban/aspirin visit and LTOLE enrolment.

We report outcomes as the number of subjects with an event per 100 patient years of follow-up (incidence rates). We also report incidence rates in the following pre-specified subgroups—CAD (yes/no), PAD (yes/no), and both CAD and PAD (yes/no)—and in additional subgroups according to the presence or absence of a previously defined high-risk feature (these high-risk groups were identified in analyses completed after the end of randomized treatment)[7]: polyvascular disease (yes/no), diabetes (yes/no), chronic kidney disease (yes/no), and mild or moderate heart failure (yes/no). We also report incidence rates in patients with 0, 1, 2, or 3 or 4 of these high-risk features.

We did not perform formal statistical comparisons of baseline characteristics or event rates. All analyses were performed using SAS (version 9.4).

Study management and sponsor

The COMPASS trial and its LTOLE were coordinated by the Population Health Research Institute, Hamilton Health Sciences, and McMaster University in Hamilton, Canada, and were overseen by a steering committee that included representatives of the study sponsor. The study was sponsored by Bayer AG. The COMPASS study is registered at www.clinicaltrials.gov (NCT01776424). The data that support the findings of this study are available from the corresponding author (JWE) upon reasonable request.

Results

Figure 1 demonstrates the overall study design. Of the 27 395 patients enrolled in COMPASS from 602 sites in 33 countries, 12 964 patients from 455 sites in 32 countries were enrolled in LTOLE. Supplementary material online, *Table S2*, presents LTOLE enrolment by country and *Figure 2* presents a flow diagram for entry into LTOLE. Of the 12 964 patients who entered the LTOLE, 946 (7.3%) permanently discontinued rivaroxaban and 860 (6.6%) permanently discontinued aspirin (*Figure 3*).

The first patient was enrolled in COMPASS on 12 March 2013, and the last follow-up for randomized antithrombotic treatment was 18 July 2017. The first patient was enrolled in LTOLE on 9 January 2018, and the last visit occurred on 15 June 2021. The mean duration of follow-up in LTOLE was 427.6 days (SD 205.2) and median was 374 days (IQR 295–574 days; range 1–1191 days).

Table 1 presents the baseline characteristics at the time of entry into the COMPASS trial of the 12 964 patients enrolled in LTOLE, the 9 152 patients randomized to receive the combination of rivaroxaban and aspirin, and the 14 431 patients not enrolled in LTOLE.

Table 2 summarizes antithrombotic therapies received between the end of randomized rivaroxaban and aspirin treatment and the commencement of LTOLE in patients who participated in LTOLE. During this period, 94.3% received aspirin, 5.3% received clopidogrel, and <1% received another antiplatelet drug or an anticoagulant.

Table 1 Baseline characteristics at entry into the COMPASS trial of patients treated with the combination of rivaroxaban and aspirin during long-term open-label extension, during randomized evaluation, and patients not enrolled in long-term open-label extension

Characteristic	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily		
	During LTOLE ($n = 12964$)	During randomized treatment ($n = 9152$)	Patients not enrolled in LTOLE ($n = 14431$)
Age (years), mean (SD)	67.2 (7.8)	68.2 (7.9)	69.1 (8.0)
Female sex, *n* (%)	2879 (22.2%)	2059 (22.5%)	3138 (21.7%)
Cholesterol (mmol/L), mean (SD)	4.19 (1.07)	4.19 (1.08)	4.19 (1.06)
Tobacco use, *n* (%)	2878 (22.2%)	1944 (21.2%)	2990 (20.7%)
Hypertension, *n* (%)	9575 (73.9%)	6907 (75.5%)	11072 (76.7%)
CAD, *n* (%)	11753 (90.7%)	8313 (90.8%)	13072 (90.6%)
Prior MI, *n* (%)	8324 (64.2%)	5654 (61.8%)	8703 (60.3%)
PAD, *n* (%)	3421 (26.4%)	2492 (27.2%)	4053 (28.1%)
Prior stroke, *n* (%)	441 (3.4%)	351 (3.8%)	595 (4.1%)
BMI (kg/m^2), mean (SD)	28.6 (4.6)	28.3 (4.8)	28.1 (4.8)
Systolic blood pressure (mmHg), mean (SD)	134.9 (17.0)	135.5 (17.5)	136.1 (18.0)
Diastolic blood pressure (mmHg), mean (SD)	77.6 (9.7)	77.4 (9.9)	77.5 (10.2)
eGFR (mL/min/1.73 m^2), mean (SD)	74.7 (17.2)	73.9 (17.9)	73.0 (18.6)
<30	63 (0.5%)	77 (0.8%)	180 (1.2%)
30 to ≤60	2641 (20.4%)	1977 (21.6%)	3393 (23.5%)
≥60	10260 (79.1%)	7094 (77.5%)	10851 (75.2%)
Ethnicity, *n* (%)			
White or Caucasian	8691 (67.0%)	5673 (62.0%)	8337 (57.8%)
Black/African American	115 (0.9%)	76 (0.8%)	146 (1.0%)
Asian	1147 (8.8%)	1451 (15.8%)	3122 (21.6%)
Other	3011 (23.2%)	1952 (21.3%)	8337 (57.8%)
Cancer	737 (5.7%)	596 (6.5%)	998 (6.9%)
CV risk categories			
Polyvascular disease, *n* (%)	2796 (21.6%)	6204 (22.6%)	3415 (23.6%)
Heart failure, *n* (%)	3074 (23.7%)	1963 (21.4%)	2825 (19.6%)
[a]Chronic kidney disease, *n* (%)	2704 (20.9%)	2054 (22.4%)	3573 (24.8%)
Diabetes, *n* (%)	4502 (34.7%)	3448 (37.7%)	5847 (40.5%)

CAD, coronary artery disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; Hg, mercury; m^2, square meter; LTOLE, long-term open-label extension; MI, myocardial infarction; min, minute; PAD, peripheral artery disease; and SD, standard deviation.
[a]Chronic kidney disease is defined as eGFR <60 mL/min/1.73 m^2

Table 3 presents outcomes in patients treated with the combination of rivaroxaban and aspirin during LTOLE as well as incidence rates during randomized evaluation of the combination. The number of patients with a primary outcome event during LTOLE was 353, with a rate of 2.35 [95% confidence interval (CI) 2.11–2.61] per 100 patient years, which was similar to the incidence rates observed during the randomized evaluation of the combination of rivaroxaban and aspirin (379 patients with a primary outcome event rate of 2.18 (95% CI 1.97–2.41) per 100 patient years]. Compared with the incidence rates during randomized treatment, the incidence rates for mortality, stroke, and severe limb ischaema were similar, with overlapping confidence intervals, where a incidence rates for hospitalization appeared to be lower, with CIs that did not overlap with those during randomized treatment.

Table 4 presents incidence rates in key subgroups of patients treated with the combination of rivaroxaban and aspirin during LTOLE compared with during randomized treatment. In general, the findings in subgroups were consistent in those seen during the randomized evaluation, with numerically higher absolute event rates in those at higher baseline risk (CAD plus PAD, polyvascular disease, heart failure, chronic kidney disease, or diabetes).

Table 5 presents bleeding incidence rates with the combination of rivaroxaban and aspirin during LTOLE compared with during randomized evaluation. The number of patients with major bleeding during LTOLE was 152, with an incidence rate of 1.01 (95% CI 0.86–1.19) per 100 patient years, whereas the number of patients with major bleeding during randomized evaluation of the combination of rivaroxaban and aspirin was 288, with an incidence rate of

Table 2 Antithrombotic therapies after completion of randomized antithrombotic treatment and prior to start of long-term open-label extension, and concomitant therapies at the time of long-term open-label extension start

Treatments	Patients enrolled in LTOLE (n = 12 964)
Antithrombotic therapies prior to LTOLE enrolment	
Antiplatelet	
Aspirin	12 228 (94.3%)
Clopidogrel	682 (5.3%)
Prasugrel	27 (0.2%)
Ticagrelor	38 (0.3%)
Ticlopidine	25 (0.2%)
Dipyridamole	25 (0.2%)
Other	47 (0.4%)
Anticoagulant	
Parenteral	54 (0.4%)
Rivaroxaban (non-study)	110 (0.8%)
Apixaban	14 (0.1%)
Dabigatran	14 (0.1%)
Vitamin K antagonist	24 (0.2%)
Other	12 (<0.1%)
Non-antithrombotic therapies at time of LTOLE enrolment	
Proton pump inhibitor (non-study)	3938 (30.4%)
NSAID	578 (4.5%)
ACE inhibitor/ARB	9661 (74.5%)
Alpha blocker or another vasodilator	1671 (12.9%)
Diuretic	3936 (30.4%)
Lipid-lowering agent	11 732 (90.5%)
Calcium channel blocker	3608 (27.8%)
Beta blocker	9095 (70.2%)
Hypoglycaemic agent	4146 (32.0%)
Selective serotonin reuptake inhibitor	533 (4.1%)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LTOLE, long-term open-label extension; and NSAID, non-steroidal anti-inflammatory drug.

Table 3 Efficacy outcomes in patients treated with the combination of rivaroxaban and aspirin during long-term open-label extension or during randomized evaluation

	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily			
	During LTOLE (N = 12 964)[a]		During randomized treatment (N = 9152)[b]	
Outcome	n	N/100 p-yrs	N	N/100 p-yrs
Primary				
CV death, stroke, MI	353	2.35 (2.11–2.61)	379	2.18 (1.97–2.41)
Mortality	282	1.87 (1.65–2.10)	313	1.78 (1.58–1.98)
CV death	166	1.10 (0.94–1.28)	160	0.91 (0.77–1.06)
Non-CV death	116	0.77 (0.63–0.92)	153	0.87 (0.74–1.02)
Stroke	94	0.62 (0.50–0.76)	83	0.47 (0.38–0.59)
MI	153	1.02 (0.86–1.19)	178	1.02 (0.88–1.18)
Severe limb ischaemia	21	0.14 (0.09–0.21)	22	0.12 (0.08–0.19)
Hospitalization	1664	11.83 (11.27–12.41)	2600	17.76 (17.09–18.46)

CI, confidence interval; CV, cardiovascular; LTOLE, long-term open-label extension; MI, myocardial infarction; and p-yrs, patient years.
[a]N/100 p-yrs: incidence rate estimated as number of subjects with incident events divided by the cumulative at-risk time in the reference population, where a subject is no longer at risk once an incident event has occurred.
[b]Patients randomized to the combination of rivaroxaban and aspirin are also represented in the LTOLE population.

Table 4 Events per 100 patient years for cardiovascular death, stroke, or myocardial infarction in key subgroups of patients treated with the combination of rivaroxaban and aspirin during long-term open-label extension and during randomized evaluation

	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily			
	During LTOLE ($n = 12964$)[a]		During randomized treatment ($n = 9152$)[b]	
Subgroup	***N***	***N*/100 p-yrs (95% CI)**	***N***	***N*/100 p-yrs (95% CI)**
CAD				
Yes	310	2.31 (2.06–2.58)	347	2.17 (1.95–2.41)
No	43	2.71 (1.95–3.65)	32	2.28 (1.56–3.22)
PAD				
Yes	115	2.85 (2.35–2.42)	126	2.82 (2.35–3.36)
No	238	2.17 (1.90–2.46)	253	1.96 (1.72–2.21)
CAD plus PAD				
Yes	72	2.93 (2.29–3.69)	94	3.06 (2.47–3.75)
No	281	2.24 (1.98–2.51)	285	1.99 (1.77–2.24)
Polyvascular disease, *n* (%)				
Yes	90	2.83 (2.28–3.48)	114	3.01 (2.48–3.61)
No	263	2.22 (1.96–2.51)	265	1.95 (1.72–2.20)
Heart failure, *n* (%)				
Yes	108	3.15 (2.59–3.81)	108	3.13 (2.57–3.78)
No	245	2.11 (1.86–2.39)	271	1.94 (1.72–2.19)
Chronic kidney disease, *n* (%)†				
Yes	95	3.03 (2.45–3.70)	132	3.41 (2.85–4.04)
No	258	2.17 (1.91–2.45)	247	1.83 (1.61–2.07)
Diabetes, *n* (%)				
Yes	171	3.26 (2.79–3.79)	179	2.74 (2.35–3.17)
No	182	1.86 (1.60–2.15)	200	1.84 (1.60–2.12)
Polyvascular disease, heart failure, chronic kidney disease, or diabetes				
0	79	1.57 (1.24–1.95)	63	1.10 (0.84–1.40)
1	135	2.26 (1.90–2.68)	155	2.26 (1.92–2.65)
2	97	3.11 (2.53–3.80)	112	3.04 (2.51–3.66)
3 or 4	42	4.67 (3.37–6.31)	49	4.40 (3.26–5.82)

CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; LTOLE, long-term open-label extension; MI, myocardial infarction; and PAD, peripheral artery disease.
[a]*N*/100 p-yrs: incidence rate estimated as number of subjects with incident events divided by the cumulative at-risk time in the reference population, where a subject is no longer at risk once an incident event has occurred.
[b]Patients randomized to the combination of rivaroxaban and aspirin are also represented in the LTOLE population.

1.67 (1.48–1.87) per 100 patient years. A similar pattern was evident for individual components of major bleeding, major sites of bleeding, and minor bleeding.

Table 6 presents the incidence rates of patients according to the treatment to which they were initially allocated. During randomized treatment, patients allocated to receive the combination of rivaroxaban and aspirin had lower incidence rates of CV death, stroke, or MI and higher incidence rates of ISTH modified major bleeding compared with those allocated aspirin. During LTOLE, patients originally allocated to receive the combination of rivaroxaban and aspirin had similar incidence rates of CV death, stroke, or MI and of ISTH major bleeding compared with those originally allocated to receive aspirin.

Discussion

The results of the COMPASS LTOLE study indicate that in patients with chronic CAD and/or PAD, extended treatment with the combination of rivaroxaban 2.5 mg twice daily and aspirin 75–100 mg once daily during an additional median follow-up of 374 days [interquartile range (IQR) 295–574 days; range 1–1191 days] was associated with incidence rates for the composite of CV death, stroke, or MI, major bleeding, and minor bleeding that that were similar to or lower than those seen during the randomized treatment phase. No new safety concerns were identified during long-term treatment.

Bleeding event rates appeared to be lower during LTOLE than during the randomized phase, and hospitalization for bleeding

Table 5 Bleeding outcomes in patients treated with the combination of rivaroxaban and aspirin during long-term open-label extension or during randomized evaluation

	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily			
	During LTOLE ($n = 12964$)[a]		During randomized treatment ($n = 9152$)[b]	
Outcome	***N***	***N*/100 p-yrs**	***N***	***N*/100 p-yrs**
Major modified ISTH	152	1.01 (0.86–1.19)	288	1.67 (1.48–1.87)
Fatal	9	0.06 (0.03–0.11)	15	0.09 (0.05–0.14)
Critical organ bleeding (non-fatal)	40	0.27 (0.19–0.36)	73	0.42 (0.33–0.52)
Requiring reoperation (non-fatal and non-critical organ)	12	<0.1 (0.04–0.14)	15	0.09 (0.05–0.14)
Hospitalization (non-fatal, non-critical organ, not leading to reoperation)	90	0.60 (0.48–0.73)	259	1.50 (1.32–1.69)
Site of major bleeding				
Gastrointestinal	45	0.30 (0.22–0.40)	140	0.80 (0.67–0.95)
Intracranial	16	0.11 (0.06–0.17)	28	0.16 (0.11–0.23)
Minor bleeding	370	2.49 (2.24–2.75)	838	5.11 (4.77–5.47)

ISTH, International Society on Thrombosis and Haemostasis; LTOLE, long-term open-label extension.
[a]*N*/100 p-yrs: incidence rate estimated as number of subjects with incident events divided by the cumulative at-risk time in the reference population, where a subject is no longer at risk once an incident event has occurred.
[b]Patients randomized to the combination of rivaroxaban and aspirin are also represented in the LTOLE.

Table 6 Incidence rates for cardiovascular death, stroke, or myocardial infarction and modified International Society on Thrombosis and Haemostasis major bleeding during randomized treatment and during long-term open-label extension according to original treatment assignment

Event	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily ($n = 4399$)	Rivaroxaban 5 mg twice daily ($n = 4292$)	Aspirin 100 mg once daily ($n = 4273$)
CV death, stroke, or MI			
During randomized treatment	2.27 (2.12, 2.42)	2.71 (2.55, 2.88)	2.98 (2.81, 3.16)
During LTOLE	2.47 (2.06, 2.94)	2.46 (2.04, 2.93)	2.12 (1.73, 2.57)
ISTH modified major bleeding			
During randomized treatment	1.62 (1.45, 1.82)	1.45 (1.28, 1.63)	0.98 (0.84, 1.13)
During LTOLE	0.79 (0.56, 1.07)	1.12 (0.85, 1.45)	1.13 (0.85, 1.47)

during LTOLE was approximately seven-fold lower than hospitalization for CV causes. This pattern was also observed in the REduction of Atherothrombosis for Continued Health (REACH) registry analysis of COMPASS-like patients.[8,9] However, comparison of incidence rates reported during LTOLE study with those during randomized treatment should be interpreted with caution. On the one hand, patients enrolled in LTOLE generally had a more favourable risk profile than those not enrolled in LTOLE, presumably because those who experienced events during randomized treatment were less likely to enter LTOLE. On the other hand, patients who entered LTOLE were several years older than at the time that they were randomized in the COMPASS trial and might therefore be expected to be at higher ischaemic and bleeding risk than during randomized treatment.

The LTOLE study provides additional insights into the pattern of bleeding during treatment with long-term treatment with the combination of rivaroxaban and aspirin. Previous analyses from the randomized treatment period demonstrated that excess bleeding with dual pathway therapy was confined to the first year after starting treatment,[10] a pattern that has also been seen in other trials of antithrombotic therapy.[11] During LTOLE, patients originally randomized to rivaroxaban and aspirin had similar incidence rates for CV death, MI, or stroke and lower incidence rates for modified ISTH major bleeding compared with those during randomized treatment with the combination. However, patients originally randomized to aspirin had lower incidence rates for CV death, stroke, or MI and similar incidence rates for modified ISTH major bleeding during LTOLE. This pattern is consistent with the superior efficacy of the combination of rivaroxaban and aspirin over aspirin, which is accompanied by an early increase in bleeding that is less evident in the long term.

Our analyses have limitations. First, only 47% of the original COMPASS cohort (12964/27395) entered LTOLE, thereby

introducing potential selection and survival biases. Second, patients who entered LTOLE are not directly comparable with those who were originally randomized in the COMPASS trial because the two cohorts are overlapping and patients enrolled in LTOLE are several years older. Third,COMPASS LTOLE did not include a control group. Finally, unlike during the randomized phase of COMPASS, we did not adjudicate outcomes during LTOLE. Although the results were virtually identical with or without adjudication, adjudication refuted 10–15% of the efficacy events reported by the sites because there was insufficient evidence to confirm that they met the definition.[1] Overall bleeding event rates were not affected by adjudication because we did not refute any bleeds (they could only be reclassified). We expect that incidence rates for efficacy were somewhat higher during LTOLE than they would have been had we adjudicated events. Each of these limitations underscores the importance of cautious interpretation of comparisons between treatment groups or follow-up periods.

Conclusions

In conclusion, COMPASS LTOLE demonstrated that among patients who agreed to participate after successfully completing follow-up during the randomized phase, treatment with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily for up to a further 3 years was associated with incidence rates for CV death, stroke, or MI that were similar to those seen during the randomized phase, and with similar or lower incidence rates for bleeding, including gastrointestinal and intracranial bleeding. These data provide further support for guideline recommendations for the long-term use of the combination of rivaroxaban and aspirin in high-risk patients with chronic CAD and/or PAD.[12]

Supplementary material

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