ATLAS, NEJM 2012 Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Background

Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose rivaroxaban might improve cardiovascular outcomes inpatients with a recent acute coronary syndrome.

Methods

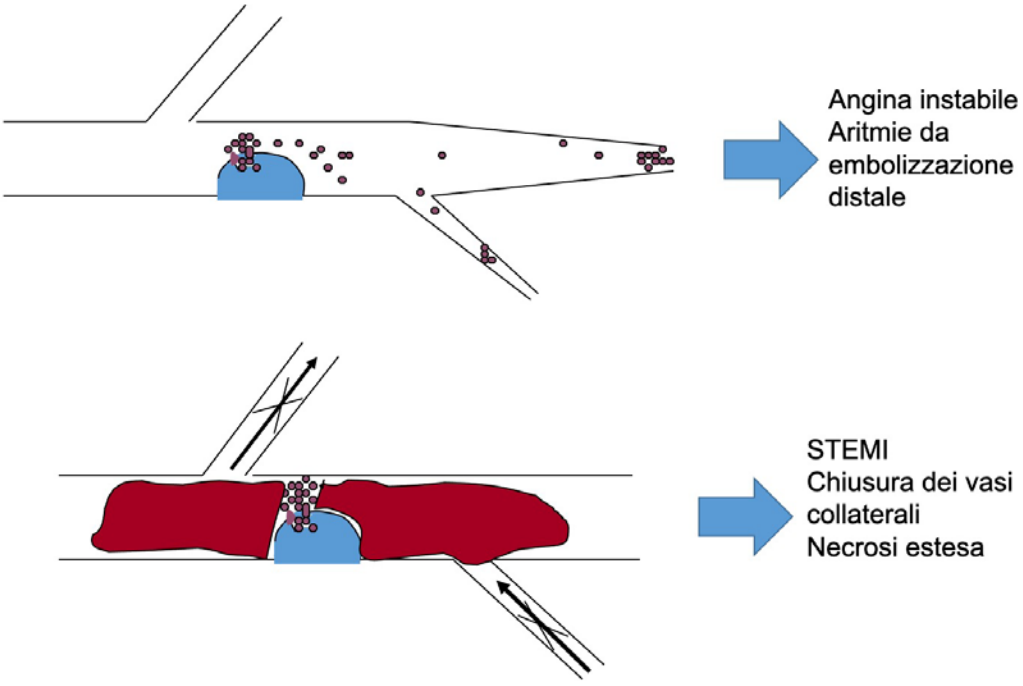
In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

The median time from the index event to randomization was 4.7 days (interquartile range, 3.2 to 6.0). Background therapy included the intended use of a thienopyridine in 93% of the patients, and the mean duration of treatment with a thienopyridine was 13.3 months.

No difference in the use of, aspirin, statin, beta-blockers, Ace-inhibitors, calcuim channel blockers between groups

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Rivaroxaban		Placebo (N=5176)
	2.5 mg Twice Daily (N=5174)	5 mg Twice Daily (N=5176)	
Age			
Mean — yr	61.8±9.2	61.9±9.0	61.5±9.4
≥65 yr — no. (%)	1905 (36.8)	1921 (37.1)	1835 (35.5)
≥75 yr — no. (%)	466 (9.0)	441 (8.5)	498 (9.6)
Male sex — no. (%)	3875 (74.9)	3843 (74.2)	3882 (75.0)
Race — no. (%)†			
White	3798 (73.4)	3815 (73.7)	3796 (73.3)
Black	34 (0.7)	34 (0.7)	39 (0.8)
Asian	1099 (21.2)	1055 (20.4)	1075 (20.8)
Other	243 (4.7)	272 (5.3)	266 (5.1)
Weight — kg			
Median	78.0	78.0	78.0
Interquartile range	68.0–90.0	68.0–88.0	68.0–88.5
Creatinine clearance — ml/min‡			
Median	85.1	84.8	85.6
Interquartile range	68.3–105.0	68.5–104.7	68.1–105.1
Medical history — no. (%)			
Previous myocardial infarction	1363 (26.3)	1403 (27.1)	1415 (27.3)
Hypertension	3470 (67.1)	3499 (67.6)	3494 (67.5)
Diabetes	1669 (32.3)	1648 (31.8)	1647 (31.8)
Hypercholesterolemia	2498 (48.3)	2544 (49.1)	2496 (48.2)
Index diagnosis — no. (%)			
STEMI	2601 (50.3)	2584 (49.9)	2632 (50.9)
NSTEMI	1321 (25.5)	1335 (25.8)	1323 (25.6)
Unstable angina	1252 (24.2)	1257 (24.3)	1221 (23.6)
PCI or CABG for index event — no. (%)	3138 (60.6)	3123 (60.3)	3126 (60.4)



ATLAS, NEJM 2012 Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Results

Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P = 0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P = 0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P = 0.03). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P = 0.002) and from any cause (2.9% vs. 4.5%, P = 0.002), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P = 0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P = 0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P = 0.04).

Conclusions

In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer Healthcare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)

Table 2. Kaplan–Meier Estimates and Hazard Ratios for Efficacy and Safety End Points.*

End Point	Rivaroxaban			Placebo (N=5113)
	2.5 mg Twice Daily (N=5114)	5 mg Twice Daily (N=5115)	Combined (N=10,229)	
Efficacy				
			number (percent)	
Death from cardiovascular causes, myocardial infarction, or stroke — primary end point	313 (9.1)	313 (8.8)	626 (8.9)	376 (10.7)
Death from cardiovascular causes	94 (2.7)	132 (4.0)	226 (3.3)	143 (4.1)
Myocardial infarction	205 (6.1)	179 (4.9)	384 (5.5)	229 (6.6)
Stroke				
Any	46 (1.4)	54 (1.7)	100 (1.6)	41 (1.2)
Ischemic	30 (1.0)	35 (0.9)	65 (0.9)	34 (1.0)
Death from any cause, myocardial infarction, or stroke — secondary end point	320 (9.3)	321 (9.1)	641 (9.2)	386 (11.0)
Death from any cause	103 (2.9)	142 (4.4)	245 (3.7)	153 (4.5)
Stent thrombosis	47 (2.2)	51 (2.3)	98 (2.3)	72 (2.9)
	(N=5115)	(N=5110)	(N=10,225)	(N=5125)
Safety				
TIMI major bleeding not associated with CABG	65 (1.8)	82 (2.4)	147 (2.1)	19 (0.6)
TIMI minor bleeding	32 (0.9)	49 (1.6)	81 (1.3)	20 (0.5)
TIMI bleeding requiring medical attention	492 (12.9)	637 (16.2)	1129 (14.5)	282 (7.5)
Intracranial hemorrhage	14 (0.4)	18 (0.7)	32 (0.6)	5 (0.2)
Fatal bleeding	6 (0.1)	15 (0.4)	21 (0.3)	9 (0.2)

COMPASS, NEJM 2017 Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

BACKGROUND

We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS

In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease 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). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Age — yr	68.3±7.9	68.2±7.9	68.2±8.0
Female sex — no. (%)	2059 (22.5)	1972 (21.6)	1989 (21.8)
Body-mass index†	28.3±4.8	28.3±4.6	28.4±4.7
Blood pressure — mm Hg			
Systolic	136±17	136±18	136±18
Diastolic	77±10	78±10	78±10
Cholesterol — mmol/liter	4.2±1.1	4.2±1.1	4.2±1.1
Tobacco use — no. (%)	1944 (21.2)	1951 (21.4)	1972 (21.6)
Hypertension — no. (%)	6907 (75.5)	6848 (75.1)	6877 (75.4)
Diabetes — no. (%)	3448 (37.7)	3419 (37.5)	3474 (38.1)
Previous stroke — no. (%)	351 (3.8)	346 (3.8)	335 (3.7)
Previous myocardial infarction — no. (%)	5654 (61.8)	5653 (62.0)	5721 (62.7)
Heart failure — no. (%)	1963 (21.4)	1960 (21.5)	1979 (21.7)

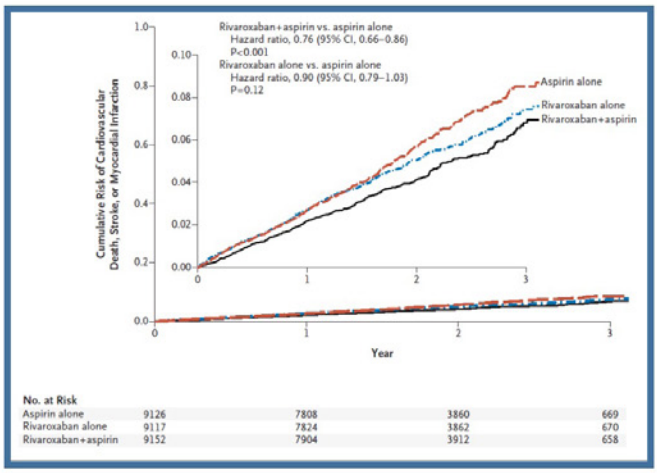
COMPASS, NEJM 2017 Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

RESULTS

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=−4.126), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424.)



COMPASS, NEJM 2017

Table 3. Bleeding Events and Net Clinical Benefit.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001	1.47 (1.16–1.87)	0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40	1.59 (1.00–2.53)	0.05
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09	1.58 (1.13–2.19)	0.006
Major bleeding according to ISTH criteria	206 (2.3)	175 (1.9)	116 (1.3)	1.78 (1.41–2.23)	<0.001	1.52 (1.20–1.92)	<0.001
Transfusion within 48 hr after bleeding	87 (1.0)	66 (0.7)	44 (0.5)	1.97 (1.37–2.83)	<0.001	1.50 (1.03–2.20)	0.03
Minor bleeding	838 (9.2)	741 (8.1)	503 (5.5)	1.70 (1.52–1.90)	<0.001	1.50 (1.34–1.68)	<0.001
Site of major bleeding							
Gastrointestinal	140 (1.5)	91 (1.0)	65 (0.7)	2.15 (1.60–2.89)	<0.001	1.40 (1.02–1.93)	0.04
Intracranial	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
Skin or injection site	28 (0.3)	28 (0.3)	12 (0.1)	2.31 (1.18–4.54)	0.01	2.34 (1.19–4.60)	0.01
Urinary	13 (0.1)	30 (0.3)	21 (0.2)	0.61 (0.31–1.23)	0.16	1.43 (0.82–2.50)	0.20
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001	0.94 (0.84–1.07)	0.36

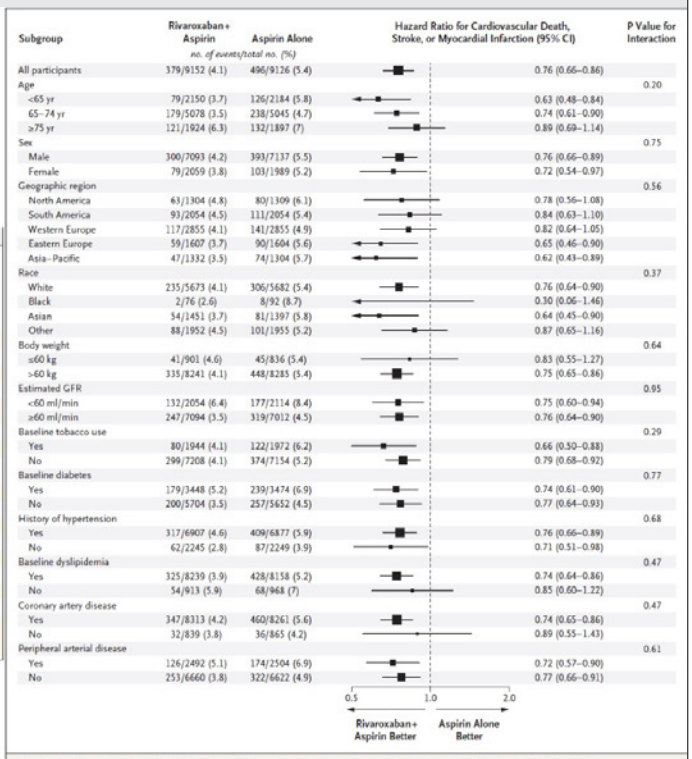


Figure 2. Subgroup Analyses for the Primary Outcome for the Comparison of Rivaroxaban plus Aspirin with Aspirin Alone.

The size of each box is proportional to the number of events. Arrows indicate that the limits of the confidence interval are not shown. The subgroup labeled "Western Europe" also includes participants in Israel, Australia, and South Africa. GFR denotes glomerular filtration rate.

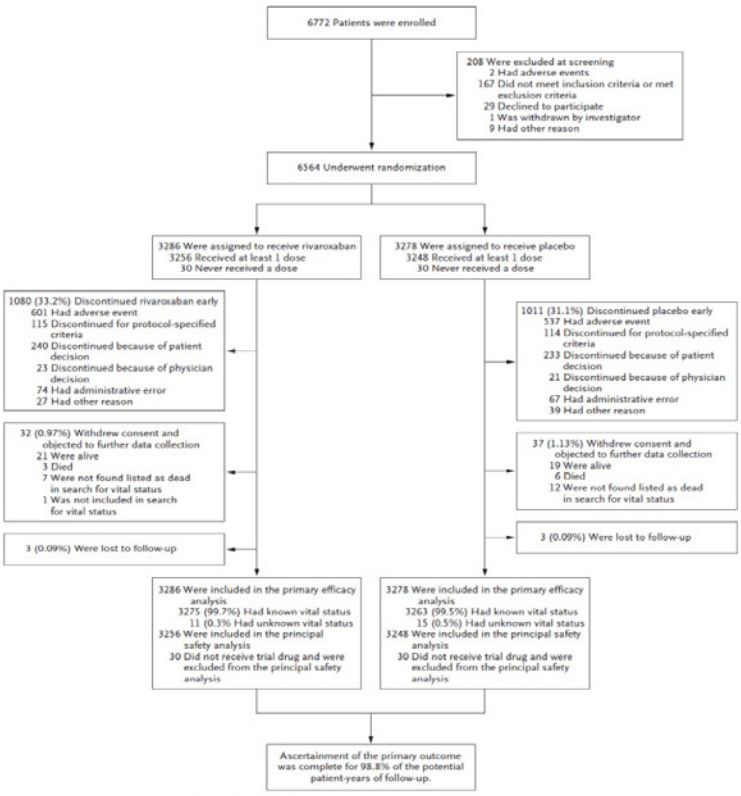
VOYAGER NEJM 2020, Rivaroxaban in Peripheral Artery Disease after Revascularization

BACKGROUND

Patients with peripheral artery disease who have undergone lower-extremity revascularization are at high risk for major adverse limb and cardiovascular events. The efficacy and safety of rivaroxaban in this context are uncertain.

METHODS

In a double-blind trial, patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. The principal safety outcome was major bleeding, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification; major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) was a secondary safety outcome.



VOYAGER NEJM 2020, Rivaroxaban in Peripheral Artery Disease after Revascularization

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Rivaroxaban (N=3286)	Placebo (N=3278)
Median age (IQR) — yr	67.0 (61.0–73.0)	67.0 (61.0–73.0)
Female sex — no. (%)	847 (25.8)	857 (26.1)
Median body-mass index (IQR) †	26.0 (23.3–29.1)	26.0 (23.2–29.1)
Race — no. (%)‡		
White	2647 (80.6)	2656 (81.0)
Asian	484 (14.7)	482 (14.7)
Black	84 (2.6)	71 (2.2)
Other	71 (2.2)	69 (2.1)
Geographic region — no. (%)		
North America	347 (10.6)	347 (10.6)
Western Europe	914 (27.8)	912 (27.8)
Eastern Europe	1301 (39.6)	1298 (39.6)
Asia Pacific	481 (14.6)	480 (14.6)
South America	243 (7.4)	241 (7.4)
Risk factors and coexisting conditions — no. (%)		
Hypertension	2684 (81.7)	2658 (81.1)
Hyperlipidemia	1971 (60.0)	1968 (60.0)
Current smoker	1147 (34.9)	1132 (34.5)
Diabetes mellitus	1313 (40.0)	1316 (40.1)
Estimated GFR <60 ml/min/1.73 m^2	661 (20.1)	666 (20.3)
Symptomatic coronary artery disease	1052 (32.0)	1015 (31.0)
Myocardial infarction	365 (11.1)	349 (10.6)
Known carotid artery disease	282 (8.6)	293 (8.9)
Peripheral artery disease–related history		
Median ankle–brachial index (IQR)	0.56 (0.42–0.67)	0.56 (0.42–0.67)
Previous amputation — no. (%)	194 (5.9)	196 (6.0)
History of claudication — no. (%)	3132 (95.3)	3137 (95.7)
History of critical limb ischemia — no. (%)	999 (30.4)	969 (29.6)
Previous peripheral revascularization — no. (%)	1181 (35.9)	1155 (35.2)
Qualifying revascularization — no. (%)		
Performed for claudication	2521 (76.7)	2504 (76.4)
Performed for critical limb ischemia§	762 (23.2)	771 (23.5)
Endovascular	2153 (65.5)	2140 (65.3)
Surgical	1133 (34.5)	1138 (34.7)
Medications — no. (%)		
Statin	2608 (79.4)	2641 (80.6)
ACE inhibitor or ARB	2096 (63.8)	2063 (62.9)
Aspirin at randomization	3256 (99.1)	3248 (99.1)
Clopidogrel at randomization	1658 (50.5)	1655 (50.5)

VOYAGER NEJM 2020, Rivaroxaban in Peripheral Artery Disease after Revascularization

RESULTS

A total of 6564 patients underwent randomization; 3286 were assigned to the rivaroxaban group, and 3278 were assigned to the placebo group. The primary efficacy outcome occurred in 508 patients in the rivaroxaban group and in 584 in the placebo group; the Kaplan–Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85, 95% confidence interval [CI], 0.76 to 0.96; P=0.009). TIMI major bleeding occurred in 62 patients in the rivaroxaban group and in 44 patients in the placebo group (2.65% and 1.87%; hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P=0.07). ISTH major bleeding occurred in 140 patients in the rivaroxaban group, as compared with 100 patients in the placebo group (5.94% and 4.06%; hazard ratio, 1.42; 95% CI, 1.10 to 1.84; P=0.007).

CONCLUSIONS

In patients with peripheral artery disease who had undergone lower-extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone. (Funded by Bayer and Janssen Pharmaceuticals; VOYAGER PAD ClinicalTrials.gov number, NCT02504216.)

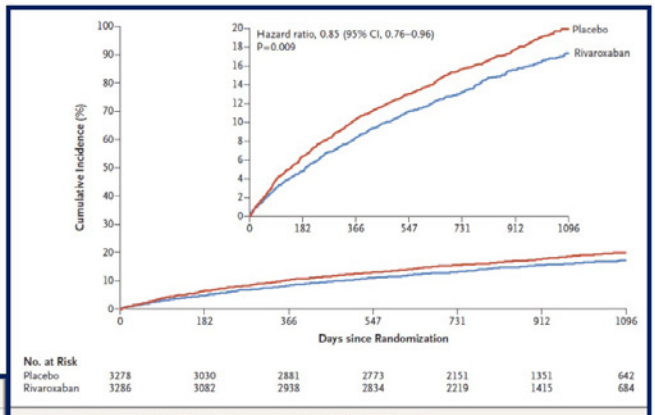


Figure 2. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.
The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. The inset shows the same data on an expanded y axis.

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban (N=3256)		Placebo (N=3248)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K-M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Principal safety outcome: TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87	1.43 (0.97–2.10)	0.07
Intracranial hemorrhage	13 (0.40)	0.60	17 (0.52)	0.90	0.78 (0.38–1.61)	
Fatal bleeding	6 (0.18)	0.21	6 (0.18)	0.21	1.02 (0.33–3.15)	
Intracranial or fatal bleeding	17 (0.52)	0.74	19 (0.58)	0.97	0.91 (0.47–1.76)	
Secondary safety outcomes						
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06	1.42 (1.10–1.84)	0.007
BARC major bleeding†	93 (2.86)	3.86	73 (2.25)	2.92	1.29 (0.95–1.76)	0.10