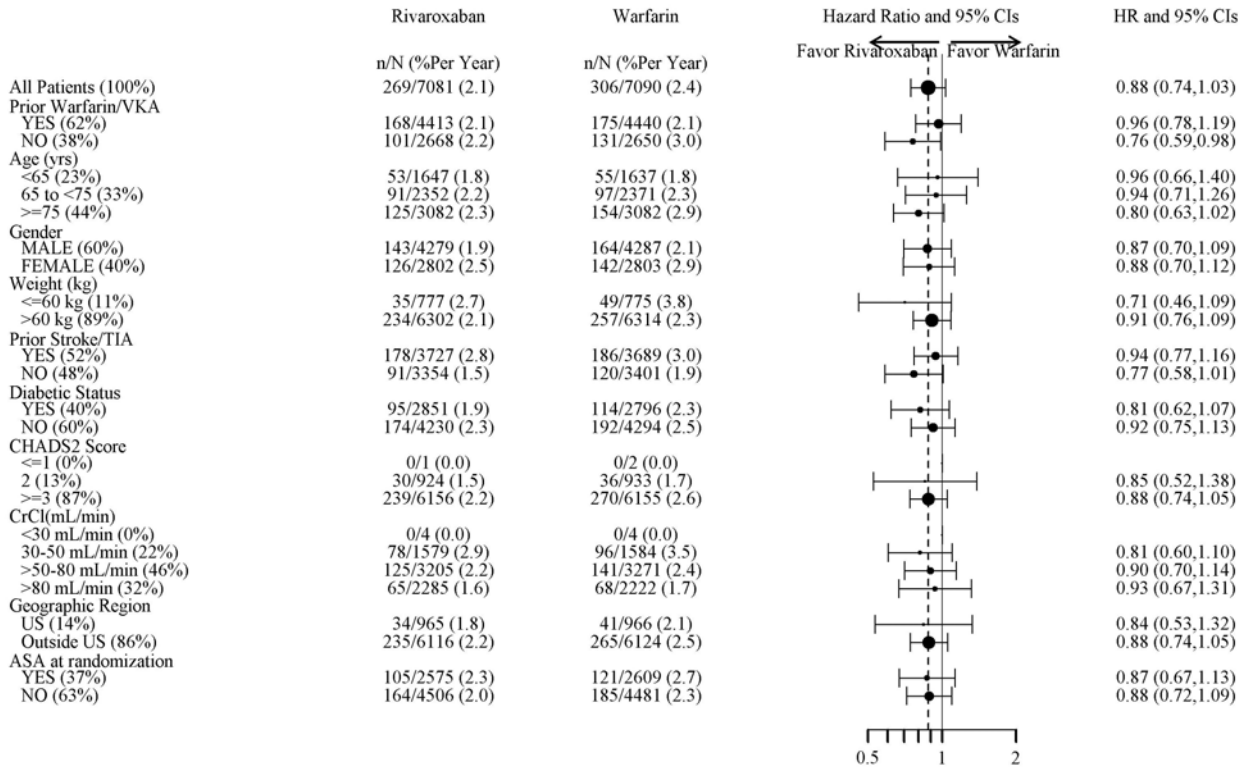
Figure 6 shows the risk of stroke or non-CNS systemic embolism across major subgroups.

Figure 6: Risk of Stroke or Non-CNS Systemic Embolism by Baseline Characteristics in ROCKET AF* (Intent-to-Treat Population)



* Data are shown for all randomized patients followed to site notification that the study would end.
Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

The efficacy of XARELTO was generally consistent across major subgroups.

The protocol for ROCKET AF did not stipulate anticoagulation after study drug discontinuation, but warfarin patients who completed the study were generally maintained on warfarin. XARELTO patients were generally switched to warfarin without a period of coadministration of warfarin and XARELTO, so that they were not adequately anticoagulated after stopping XARELTO until attaining a therapeutic INR. During the 28 days following the end of the study, there were 22 strokes in the 4637 patients taking XARELTO vs. 6 in the 4691 patients taking warfarin.

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of XARELTO for preventing post-cardioversion stroke and systemic embolism is unknown.

14.2 Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

EINSTEIN Deep Vein Thrombosis and EINSTEIN Pulmonary Embolism Studies

XARELTO for the treatment of DVT and/or PE was studied in EINSTEIN DVT [NCT00440193] and EINSTEIN PE [NCT00439777], multi-national, open-label, non-inferiority studies comparing XARELTO (at an initial dose of 15 mg twice daily with food for the first three weeks, followed by XARELTO 20 mg once daily with food) to enoxaparin 1 mg/kg twice daily for at least five days with VKA and then continued with VKA only after the target INR (2.0-3.0) was reached. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent and patients with creatinine clearance <30 mL/min, significant liver disease, or active bleeding were excluded from the studies. The intended treatment duration was 3, 6, or 12 months based on investigator's assessment prior to randomization.

A total of 8281 (3449 in EINSTEIN DVT and 4832 in EINSTEIN PE) patients were randomized and followed on study treatment for a mean of 208 days in the XARELTO group and 204 days in the enoxaparin/VKA group. The mean age was approximately 57 years. The population was 55% male, 70% Caucasian, 9% Asian and about 3% Black. About 73% and 92% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies, respectively, received initial parenteral anticoagulant treatment for a median duration of 2 days. Enoxaparin/VKA-treated patients in the EINSTEIN DVT and EINSTEIN PE studies received initial parenteral anticoagulant treatment for a median duration of 8 days. Aspirin was taken as on treatment concomitant antithrombotic medication by approximately 12% of patients in both treatment groups. Patients randomized to VKA had an unadjusted mean percentage of time in the INR target range of 2.0 to 3.0 of 58% in EINSTEIN DVT study and 60% in EINSTEIN PE study, with the lower values occurring during the first month of the study.

In the EINSTEIN DVT and EINSTEIN PE studies, 49% of patients had an idiopathic DVT/PE at baseline. Other risk factors included previous episode of DVT/PE (19%), recent surgery or trauma (18%), immobilization (16%), use of estrogen-containing drug (8%), known thrombophilic conditions (6%), or active cancer (5%).

In the EINSTEIN DVT and EINSTEIN PE studies, XARELTO was demonstrated to be non-inferior to enoxaparin/VKA for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE [EINSTEIN DVT HR (95% CI): 0.68 (0.44, 1.04); EINSTEIN PE HR (95% CI): 1.12 (0.75, 1.68)]. In each study the conclusion of non-inferiority was based on the upper limit of the 95% confidence interval for the hazard ratio being less than 2.0.

Table 11 displays the overall results for the primary composite endpoint and its components for EINSTEIN DVT and EINSTEIN PE studies.

Table 11: Primary Composite Endpoint Results* in EINSTEIN DVT and EINSTEIN PE Studies – Intent-to-Treat Population

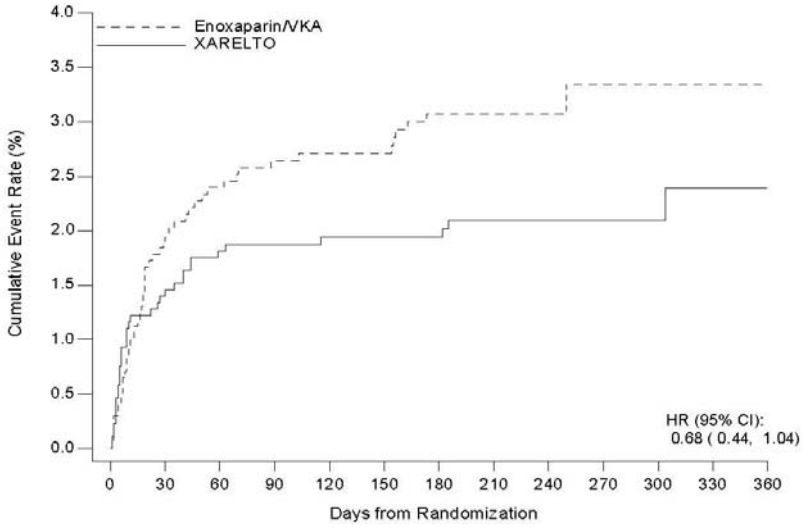
Event	XARELTO 20 mg†	Enoxaparin/VKA†	XARELTO vs. Enoxaparin/VKA Hazard Ratio (95% CI)
EINSTEIN DVT Study	**N=1731 n (%)**	**N=1718 n (%)**	
Primary Composite Endpoint	36 (2.1)	51 (3.0)	0.68 (0.44, 1.04)
Death (PE)	1 (<0.1)	0	
Death (PE cannot be excluded)	3 (0.2)	6 (0.3)	
Symptomatic PE and DVT	1 (<0.1)	0	
Symptomatic recurrent PE only	20 (1.2)	18 (1.0)	
Symptomatic recurrent DVT only	14 (0.8)	28 (1.6)	
EINSTEIN PE Study	**N=2419 n (%)**	**N=2413 n (%)**	
Primary Composite Endpoint	50 (2.1)	44 (1.8)	1.12 (0.75, 1.68)
Death (PE)	3 (0.1)	1 (<0.1)	
Death (PE cannot be excluded)	8 (0.3)	6 (0.2)	
Symptomatic PE and DVT	0	2 (<0.1)	
Symptomatic recurrent PE only	23 (1.0)	20 (0.8)	
Symptomatic recurrent DVT only	18 (0.7)	17 (0.7)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (3, 6 or 12 months) irrespective of the actual treatment duration. If the same patient had several events, the patient may have been counted for several components.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

Figures 7 and 8 are plots of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups in EINSTEIN DVT and EINSTEIN PE studies, respectively.

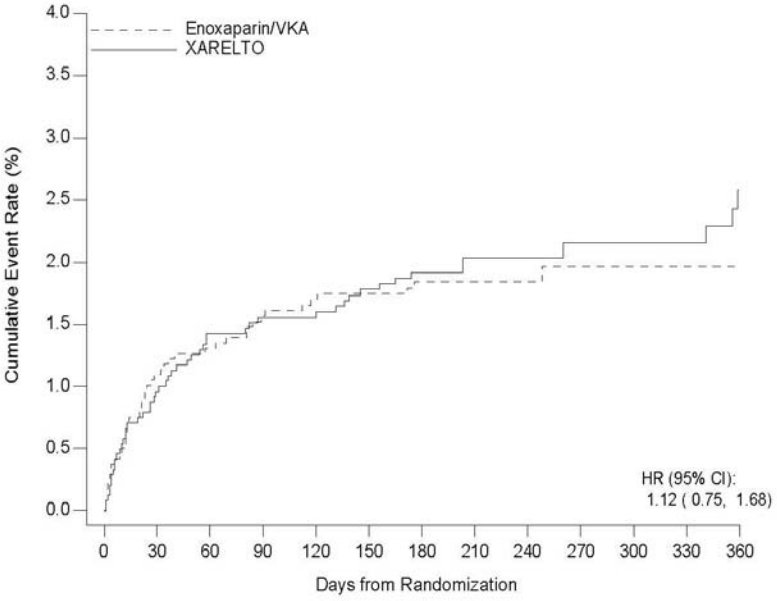
Figure 7: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN DVT Study



Number of Patients at Risk

Enoxaparin/VKA (N= 1718)	1616	1581	1565	1368	1358	1301	380	362	342	325	297	264
XARELTO (N= 1731)	1668	1648	1635	1424	1412	1369	400	369	364	345	309	266

Figure 8: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Intent-to-Treat Population) – EINSTEIN PE Study



Number of Patients at Risk

Enoxaparin/VKA (N= 2413)	2316	2295	2280	2155	2146	2113	835	787	773	746	722	675
XARELTO (N= 2419)	2350	2321	2311	2180	2167	2133	837	794	785	757	725	672

14.3 Reduction in the Risk of Recurrence of DVT and/or PE

EINSTEIN CHOICE Study

XARELTO for reduction in the risk of recurrence of DVT and of PE was evaluated in the EINSTEIN CHOICE study [NCT02064439], a multi-national, double-blind, superiority study comparing XARELTO (10 or 20 mg once daily with food) to 100 mg acetylsalicylic acid (aspirin) once daily in patients who had completed 6 to 12 months of anticoagulant treatment for DVT and/or PE following the acute event. The intended treatment duration in the study was up to 12 months. Patients with an indication for continued therapeutic-dose anticoagulation were excluded.

Because the benefit-risk assessment favored the 10 mg dose versus aspirin compared to the 20 mg dose versus aspirin, only the data concerning the 10 mg dose is discussed below.

A total of 2275 patients were randomized and followed on study treatment for a mean of 290 days for the XARELTO and aspirin treatment groups. The mean age was approximately 59 years. The population was 56% male, 70% Caucasian, 14% Asian and 3% Black. In the EINSTEIN CHOICE study, 51% of patients had DVT only, 33% had PE only, and 16% had PE and DVT combined. Other risk factors included idiopathic VTE (43%), previous episode of DVT/PE (17%), recent surgery or trauma (12%), prolonged immobilization (10%), use of estrogen containing drugs (5%), known thrombophilic conditions (6%), Factor V Leiden gene mutation (4%), or active cancer (3%).

In the EINSTEIN CHOICE study, XARELTO 10 mg was demonstrated to be superior to aspirin 100 mg for the primary composite endpoint of time to first occurrence of recurrent DVT or non-fatal or fatal PE.

Table 12 displays the overall results for the primary composite endpoint and its components.

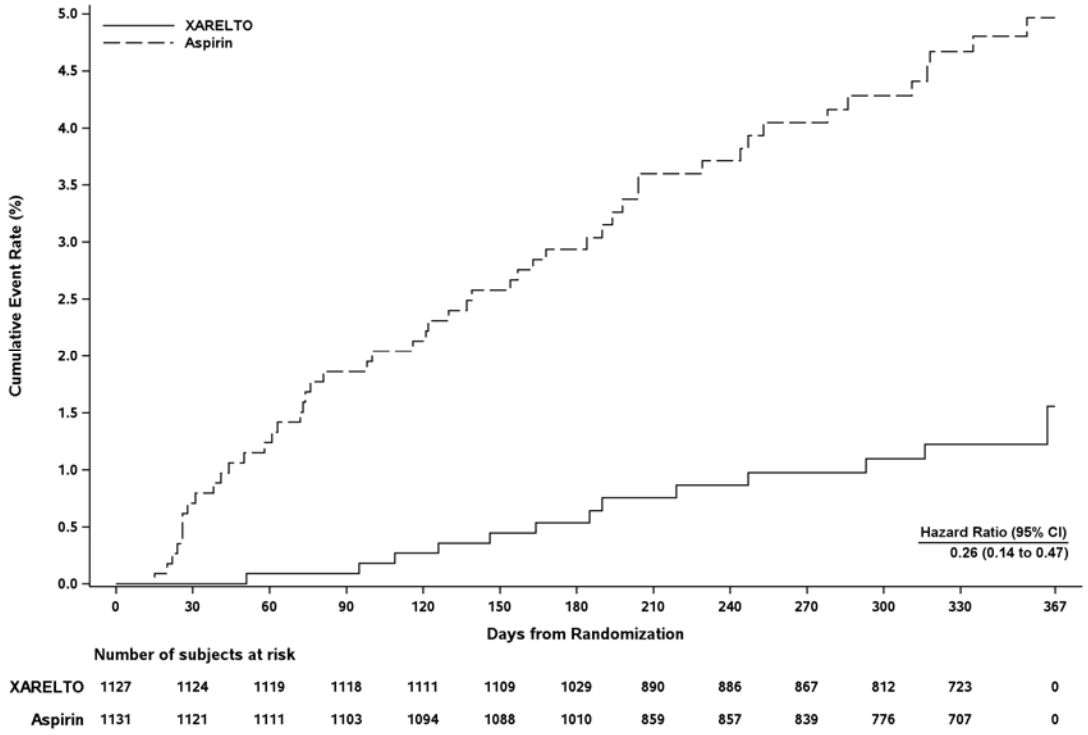
Table 12: Primary Composite Endpoint and its Components Results* in EINSTEIN CHOICE Study – Full Analysis Set

Event	XARELTO 10 mg N=1,127 n (%)	Acetylsalicylic Acid (Aspirin) 100 mg N=1,131 n (%)	XARELTO 10 mg vs. Aspirin 100 mg Hazard Ratio (95% CI)
Primary Composite Endpoint	13 (1.2)	50 (4.4)	0.26 (0.14, 0.47) p<0.0001
Symptomatic recurrent DVT	8 (0.7)	29 (2.6)	
Symptomatic recurrent PE	5 (0.4)	19 (1.7)	
Death (PE)	0	1 (<0.1)	
Death (PE cannot be excluded)	0	1 (<0.1)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (12 months) irrespective of the actual treatment duration. The individual component of the primary endpoint represents the first occurrence of the event.

Figure 9 is a plot of the time from randomization to the occurrence of the first primary efficacy endpoint event in the two treatment groups.

Figure 9: Time to First Occurrence of the Composite of Recurrent DVT or Non-fatal or Fatal PE by Treatment Group (Full Analysis Set) – EINSTEIN CHOICE Study



14.4 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE, Controlled, Double-blind, Randomized Study of BAY 59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip or Knee Replacement (RECORD 1, 2, and 3) [NCT00329628, NCT00332020, NCT00361894] studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared XARELTO 10 mg once daily starting at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age [± standard deviation (SD)] was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min, or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (± SD) to active XARELTO and enoxaparin was 33.3 ± 7.0 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 13.

Table 13: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 1			RECORD 2		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**	**XARELTO 10 mg once daily**	**Enoxaparin† 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N=1513**	**N=1473**		**N=834**	**N=835**	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2.0%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non-fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	**N=1600**	**N=1587**		**N=928**	**N=929**	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	**N=2103**	**N=2119**		**N=1178**	**N=1179**	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

* Relative Risk Reduction; CI = confidence interval
† Includes the placebo-controlled period of RECORD 2
‡ Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared XARELTO 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active XARELTO and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3.0 days, respectively. The efficacy data are provided in Table 14.

Table 14: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N=813**	**N=871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N=895**	**N=917**	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p = 0.024
Number of Patients	**N=1206**	**N=1226**	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* Relative Risk Reduction; CI = confidence interval

† Proximal DVT, nonfatal PE or VTE-related death

14.5 Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD

The evidence for the efficacy and safety of XARELTO for the reduction in the risk of stroke, myocardial infarction, or cardiovascular death in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) was derived from the double-blind Cardiovascular OutcoMes for People using Anticoagulation StrategieS trial (COMPASS) [NCT10776424]. A total of 27,395 patients were evenly randomized to rivaroxaban 2.5 mg orally twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg orally twice daily alone, or aspirin 100 mg once daily alone. Because the 5 mg dose alone was not superior to aspirin alone, only the data concerning the 2.5 mg dose plus aspirin are discussed below.

Patients with established CAD or PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] <60 mL per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Patients with PAD were either symptomatic with ankle brachial index <0.90 or had asymptomatic carotid artery stenosis ≥50%, a previous carotid revascularization procedure, or established ischemic disease of one or both lower extremities. Patients were excluded for use of dual antiplatelet, other non-aspirin antiplatelet, or oral anticoagulant therapies, ischemic, non-lacunar stroke within 1 month, hemorrhagic or lacunar stroke at any time, or eGFR <15 mL/min. *[see Warnings and Precautions (5.2)]*.

The mean age was 68 years and 21% of the subject population were ≥75 years. Of the included patients, 91% had CAD, 27% had PAD, and 18% had both CAD and PAD. Of the patients with CAD, 69% had prior MI, 60% had prior percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/ percutaneous coronary intervention (PCI), and 26% had history of coronary artery bypass grafting (CABG) prior to study. Of the patients with PAD, 49% had intermittent claudication, 27% had peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty, 26% had asymptomatic carotid artery stenosis > 50%, and 4% had limb or foot amputation for arterial vascular disease.

The mean duration of follow-up was 23 months. Relative to aspirin alone, XARELTO plus aspirin reduced the rate of the primary composite outcome of stroke, myocardial infarction or cardiovascular death. The benefit was observed early with a constant treatment effect over the entire treatment period (see Table 15 and Figure 11).

A benefit-risk analysis of the data from COMPASS was performed by comparing the number of CV events (CV deaths, myocardial infarctions and non-hemorrhagic strokes) prevented to the number of fatal or life-threatening bleeding events (fatal bleeds + symptomatic non-fatal bleeds into a critical organ) in the XARELTO plus aspirin group versus the aspirin group. Compared to aspirin alone, during 10,000 patient-years of treatment, XARELTO plus aspirin would be expected to result in 70 fewer CV events and 12 additional life-threatening bleeds, indicating a favorable balance of benefits and risks.

The results in patients with PAD, CAD, and both CAD and PAD were consistent with the overall efficacy and safety results (see Figure 10).

Figure 10 shows the risk of primary efficacy outcome across major subgroups.

Figure 10: Risk of Primary Efficacy Outcome by Baseline Characteristics in COMPASS (Intent-to-Treat Population)

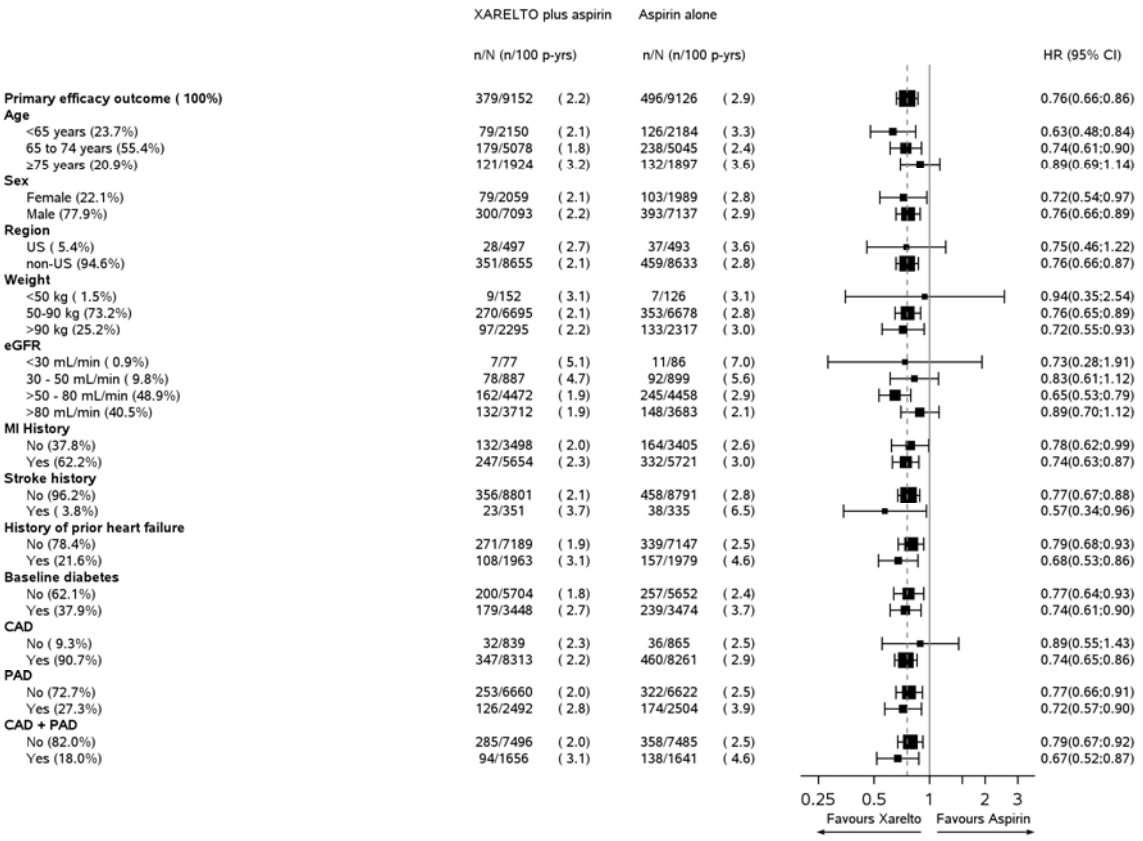


Table 15: Efficacy results from COMPASS study

Study Population	Patients with CAD or PAD*				
	Xarelto plus aspirin† N=9152		Aspirin alone† N=9126		
Event	n (%)	Event Rate (%/year)	n (%)	Event Rate (%/year)	Hazard Ratio (95% CI)‡
Stroke, MI or CV death	379 (4.1)	2.2	496 (5.4)	2.9	0.76 (0.66, 0.86)
- Stroke	83 (0.9)	0.5	142 (1.6)	0.8	0.58 (0.44, 0.76)
- MI	178 (1.9)	1.0	205 (2.2)	1.2	0.86 (0.70, 1.05)
- CV death	160 (1.7)	0.9	203 (2.2)	1.2	0.78 (0.64, 0.96)
Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	329 (3.6)	1.9	450 (4.9)	2.6	0.72 (0.63, 0.83)
- Coronary heart disease death§	86 (0.9)	0.5	117 (1.3)	0. 7	0.73 (0.55, 0.96)
- Ischemic stroke	64 (0.7)	0.4	125 (1.4)	0.7	0.51 (0.38, 0.69)
- Acute limb ischemia#	22 (0.2)	0.1	40 (0.4)	0.2	0.55 (0.32, 0.92)
CV death¶, MI, ischemic stroke, acute limb ischemia	389 (4.3)	2.2	516 (5.7)	3.00	0.74 (0.65, 0.85)
All-cause mortality	313 (3.4)	1. 8	378 (4.1)	2.2	0.82 (0.71, 0.96)
Lower extremity amputations for CV reasons	15 (0.2)	<0.1	31 (0.3)	0.2	0.48 (0.26, 0.89)
Patients with PAD					
Acute limb ischemia	19 (0.8)	0.4	34 (1.4)	0.8	0.56 (0.32, 0.99)

* intention to treat analysis set, primary analyses.

† Treatment schedule: XARELTO 2.5 mg twice daily plus aspirin 100 mg once daily, or aspirin 100 mg once daily.

‡ vs. aspirin 100 mg

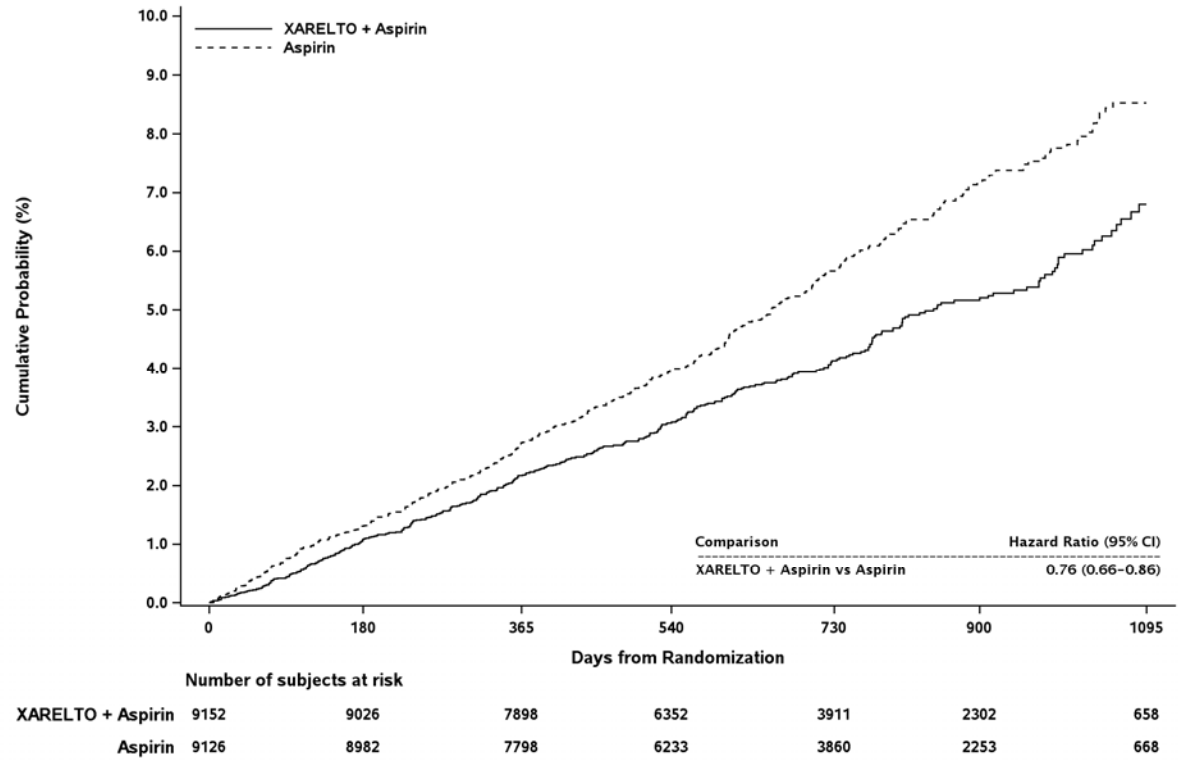
§ Coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure.

¶ CV death includes CHD death, or death due to other CV causes or unknown death.

Acute limb ischemia is defined as limb-threatening ischemia leading to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation).

CHD: coronary heart disease, CI: confidence interval; CV: cardiovascular; MI: myocardial infarction

Figure 11: Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in COMPASS



CI: confidence interval

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO (rivaroxaban) Tablets are available in the strengths and packages listed below:

- 2.5 mg tablets are round, light yellow, and film-coated with a triangle pointing down above a "2.5" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:

NDC 50458-577-60	Bottle containing 60 tablets
NDC 50458-577-18	Bottle containing 180 tablets
NDC 50458-577-10	Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 10 mg tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-580-30 Bottle containing 30 tablets

  NDC 50458-580-90 Bottle containing 90 tablets

  NDC 50458-580-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 15 mg tablets are round, red, biconvex film-coated tablets with a triangle pointing down above a "15" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-578-30 Bottle containing 30 tablets

  NDC 50458-578-90 Bottle containing 90 tablets

  NDC 50458-578-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 20 mg tablets are triangle-shaped, dark red film-coated tablets with a triangle pointing down above a "20" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-579-30 Bottle containing 30 tablets

  NDC 50458-579-90 Bottle containing 90 tablets

  NDC 50458-579-89 Bulk bottle containing 1000 tablets

  NDC 50458-579-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- Starter Pack for treatment of deep vein thrombosis and treatment of pulmonary embolism:

  NDC 50458-584-51 30-day starter blister pack containing 51 tablets: 42 tablets of 15 mg and 9 tablets of 20 mg

Store at 25°C (77°F) or room temperature; excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions for Patient Use

- Advise patients to take XARELTO only as directed.
- Remind patients to not discontinue XARELTO without first talking to their healthcare professional.
- Advise patients with atrial fibrillation to take XARELTO once daily with the evening meal.
- Advise patients for initial treatment of DVT and/or PE to take XARELTO 15 mg or 20 mg tablets with food at approximately the same time every day *[see Dosage and Administration (2.1)]*.
- Advise patients who are at a continued risk of recurrent DVT and/or PE after at least 6 months of initial treatment, to take XARELTO 10 mg once daily with or without food *[see Dosage and Administration (2.1)]*.
- Advise patients who cannot swallow the tablet whole to crush XARELTO and combine with a small amount of applesauce followed by food *[see Dosage and Administration (2.5)]*.
- For patients requiring an NG tube or gastric feeding tube, instruct the patient or caregiver to crush the XARELTO tablet and mix it with a small amount of water before administering via the tube *[see Dosage and Administration (2.5)]*.
- If a dose is missed, advise the patient to take XARELTO as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

Bleeding Risks

- Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with XARELTO *[see Warnings and Precautions (5.2)]*.
- If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

Invasive or Surgical Procedures

Instruct patients to inform their healthcare professional that they are taking XARELTO before any invasive procedure (including dental procedures) is scheduled.

Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)]*.

Pregnancy and Pregnancy-Related Hemorrhage

- Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with XARELTO *[see Use in Specific Populations (8.1)]*.
- Advise pregnant women receiving XARELTO to immediately report to their physician any bleeding or symptoms of blood loss *[see Warnings and Precautions (5.7)]*.

Lactation

Advise patients to discuss with their physician the benefits and risks of XARELTO for the mother and for the child if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.2)]*.

Females and Males of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.3)]*.

Product of Germany

Finished Product Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778

or
Bayer AG
51368 Leverkusen, Germany

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560 Licensed from: Bayer HealthCare AG 51368 Leverkusen, Germany

For more information go to www.XARELTO-US.com or call 1-800-526-7736.

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