Rivaraxaban a basso dosaggio e aspirina nella prevenzione di eventi trombotici arteriosi e venosi in pazienti con arteriopatia periferica sintomatica sottoposta a rivascolarizzazione

Sub-analisi del trial VOYAGER PAD

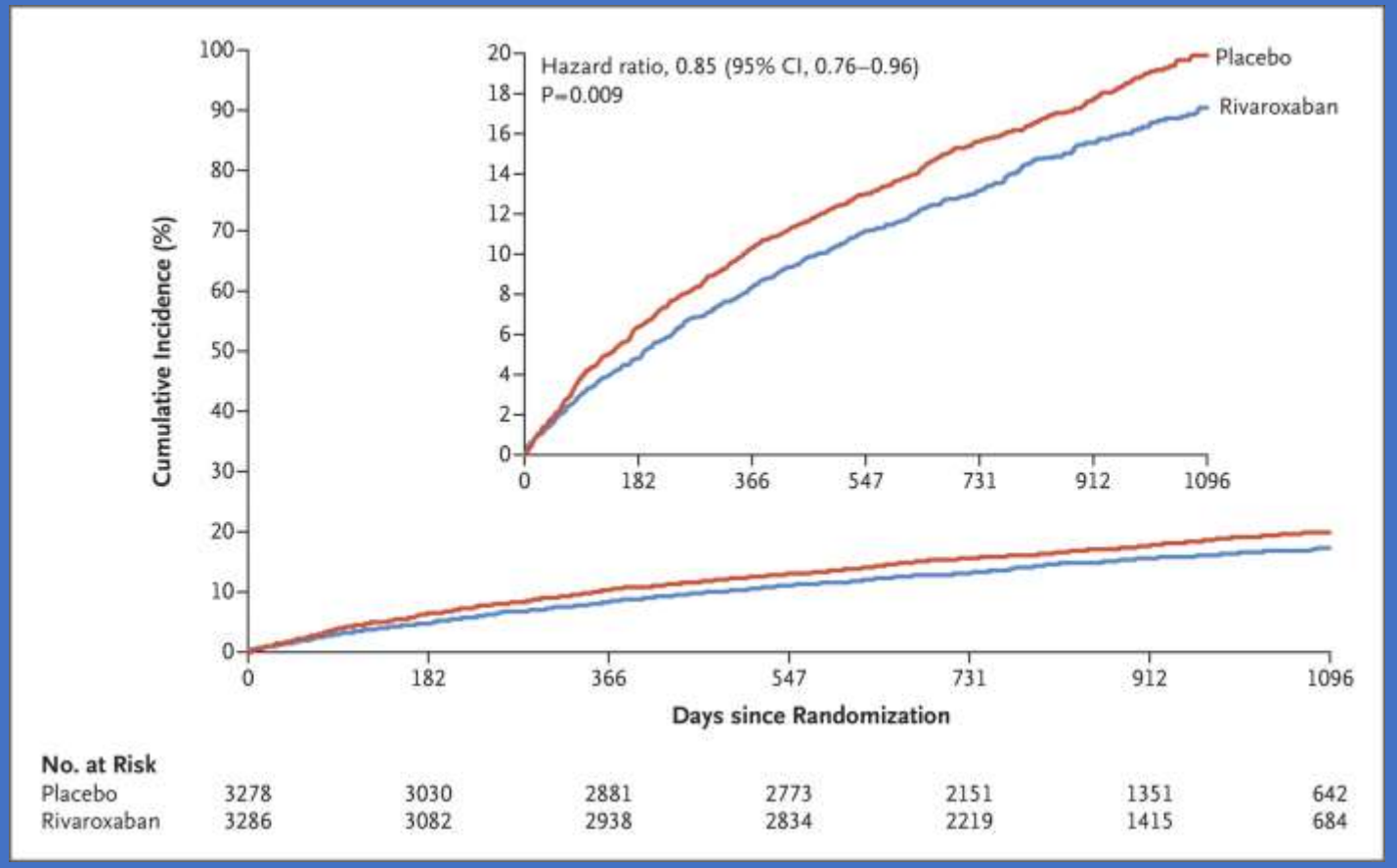
Background

- Arterial and venous events occur frequently in symptomatic peripheral artery disease patients after revascularization.
- More than one hemostatic pathway is involved in atherosclerotic vessel thrombotic events.
- Rivaroxaban added to aspirin reduces first and subsequent arterial and venous thrombotic events.
- Total event analysis enhances understanding of treatment impact on full burden of thrombotic risk.

VOYAGER PAD

6564 patients with PAD who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin.

Characteristic	Rivaroxaban (N=3286)	Placebo (N=3278)
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)



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Prevention of arterial and venous thrombotic events in symptomatic peripheral arterial disease patients after lower extremity revascularization in the VOYAGER PAD trial: Dual anticoagulant/antiplatelet regimen vs antiplatelet therapy alone

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AIMS AND METHODS

- **Objectives:** Assess total arterial and venous thrombotic burden after LER for symptomatic PAD and effect of low-dose anticoagulation added to low-dose antiplatelet therapy.
- **Methods:** VOYAGER PAD randomized 6564 symptomatic PAD patients undergoing LER to rivaroxaban 2.5 mg twice-daily or placebo on aspirin background. Marginal proportional-hazards models used to generate treatment hazard ratios and associated 95% CIs for first and total events; non-thrombotic deaths treated as competing terminal events. Incidence rates calculated as number of events per 100 patient-years follow-up.

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Categories of total arterial and venous thrombotic events

Event	Placebo N = 3278	Rivaroxaban N = 3286	Total N = 6564
Total thrombotic events	772	600	1372
Arterial events	725 (93.9)	574 (95.7)	1299 (94.7)
Acute limb ischemia	306 (42.2)	202 (35.2)	508 (39.1)
Major amputation for vascular causes	133 (18.3)	117 (20.4)	250 (19.2)
Non-fatal myocardial infarction	170 (23.4)	152 (26.5)	322 (24.8)
Non-fatal ischemic stroke	86 (11.9)	75 (13.1)	161 (12.4)
Fatal myocardial infarction or stroke	30 (4.1)	28 (4.9)	58 (4.5)
Venous events	47 (6.1)	26 (4.4)	73 (5.3)
Non-fatal venous thromboembolic event*	41 (87.2)	25 (96.1)	66 (90.4)
Fatal pulmonary embolism or other fatal thromboembolic event	6 (12.8)	1 (3.8)	7 (9.6)

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Baseline and procedural characteristics of participants by type of thrombotic event

Characteristics at Randomization	(A) No Event (n = 5635; 86%)	(B) One Arterial or Venous (n = 645; 10%)	(C) Multiple Arterial or Venous Event (n = 284; 4%)	p-value	
				(A) vs. (B) + (C)	(B) vs. (C)
Baseline characteristics					
Coronary artery disease, %	30.6	38.9	33.1	<.0001	n.s.
Diabetes mellitus, %	38.9	47.3	46.1	<.0001	n.s.
eGFR<60 ml/min/1.73 m^2	19.7	23.7	22.2	.01	n.s.
BMI, kg/m^2	26.0 (23.3–29.1)	26.0 (23.0–29.1)	25.7 (23.2–28.3)	n.s.	n.s.
History of Cancer, %	4.9	7.1	4.6	n.s.	n.s.
Medications					
Statin, %	79.8	83.3	75.7	n.s.	.009
Clopidogrel, %	51.1	47.6	45.1	.02	n.s.
PAD & Procedural characteristics					
Prior peripheral artery disease history					
History of claudication, %	95.7	94.4	93.3	.03	n.s.
History of revascularization, %	34.4	42.2	43.3	<.0001	n.s.
History of amputation, %	5.3	9.3	10.6	<.0001	n.s.
Ankle Brachial Index, Median (IQR)	0.56 (0.43–0.67)	0.53 (0.40–0.65)	0.51 (0.38–0.63)	<.0001	n.s.
Type of revascularization					
Surgical, %	32.1	39.1	43.3	<.0001	n.s.
Endovascular or hybrid, %	67.9	60.9	56.7		
Days from procedure to randomization, median (IQR)	5 (2–7)	5 (3–7)	5 (3–8)	<.0001	n.s.
Target lesion length					n.s.
Short (<5 cm), %	23.4	18.8	15.5	<.0001	
Intermediate (5 to <15 cm), %	40.7	35.5	32.0		
Long (≥15 cm), %	32.7	42.8	47.5	<.0001	n.s.
Atherectomy, %	4.8	4.8	2.8	n.s.	n.s.

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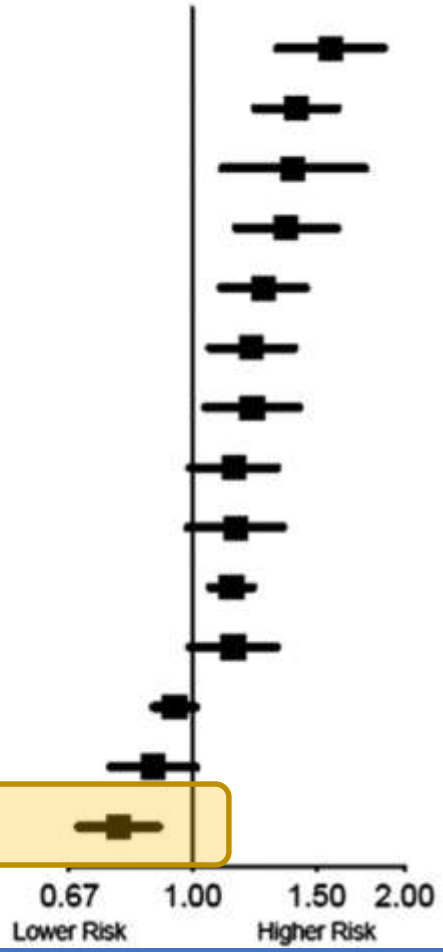
Independent determinants of total thrombotic events

Characteristic	HR (95% CI)	p-value
Prior surgical revascularization	1.57 (1.32, 1.87)	<0.0001
Target lesion ≥ 15 cm	1.40 (1.23, 1.60)	<0.0001
Prior amputation	1.39 (1.10, 1.76)	0.0051
Indication for index revascularization = CLI	1.36 (1.16, 1.60)	0.0002
History of diabetes	1.26 (1.10, 1.45)	0.0008
History of CAD	1.22 (1.06, 1.39)	0.0050
Surgical index revascularization	1.22 (1.05, 1.41)	0.01
Prior endovascular procedure	1.15 (1.00, 1.32)	0.06
eGFR <60 mL/min	1.15 (0.99, 1.34)	0.07
Index ABI, 0.19 decrease	1.14 (1.06, 1.22)	0.0002
Current smoker	1.14 (1.00, 1.31)	0.06
Systolic BP, 16 mmHg increase	0.95 (0.88, 1.01)	0.10
History of hypertension	0.88 (0.77, 1.01)	0.07
Rivaroxaban treatment	0.79 (0.69, 0.90)	0.0003



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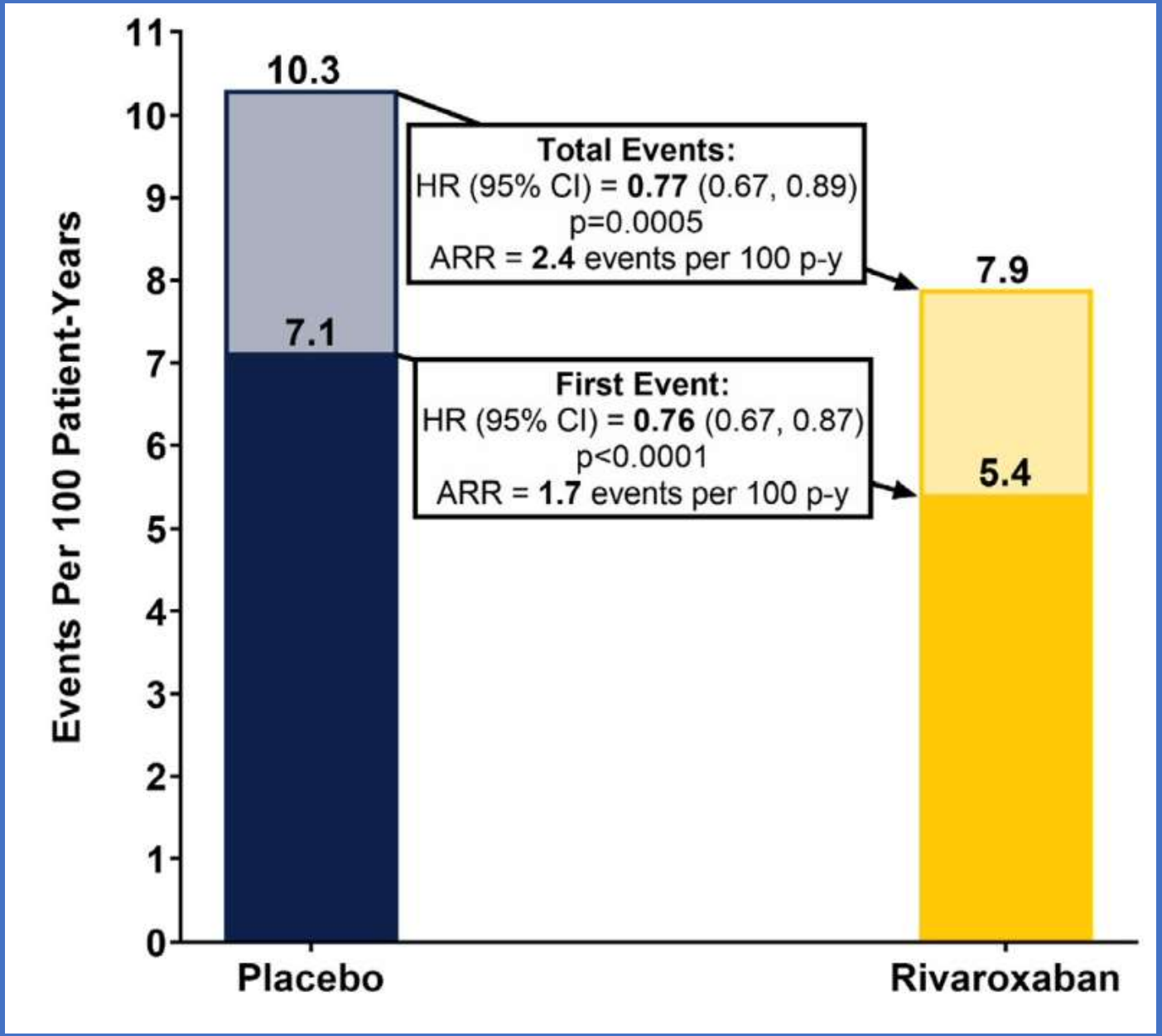
First and total arterial and venous thrombotic events, per 100 patient-years



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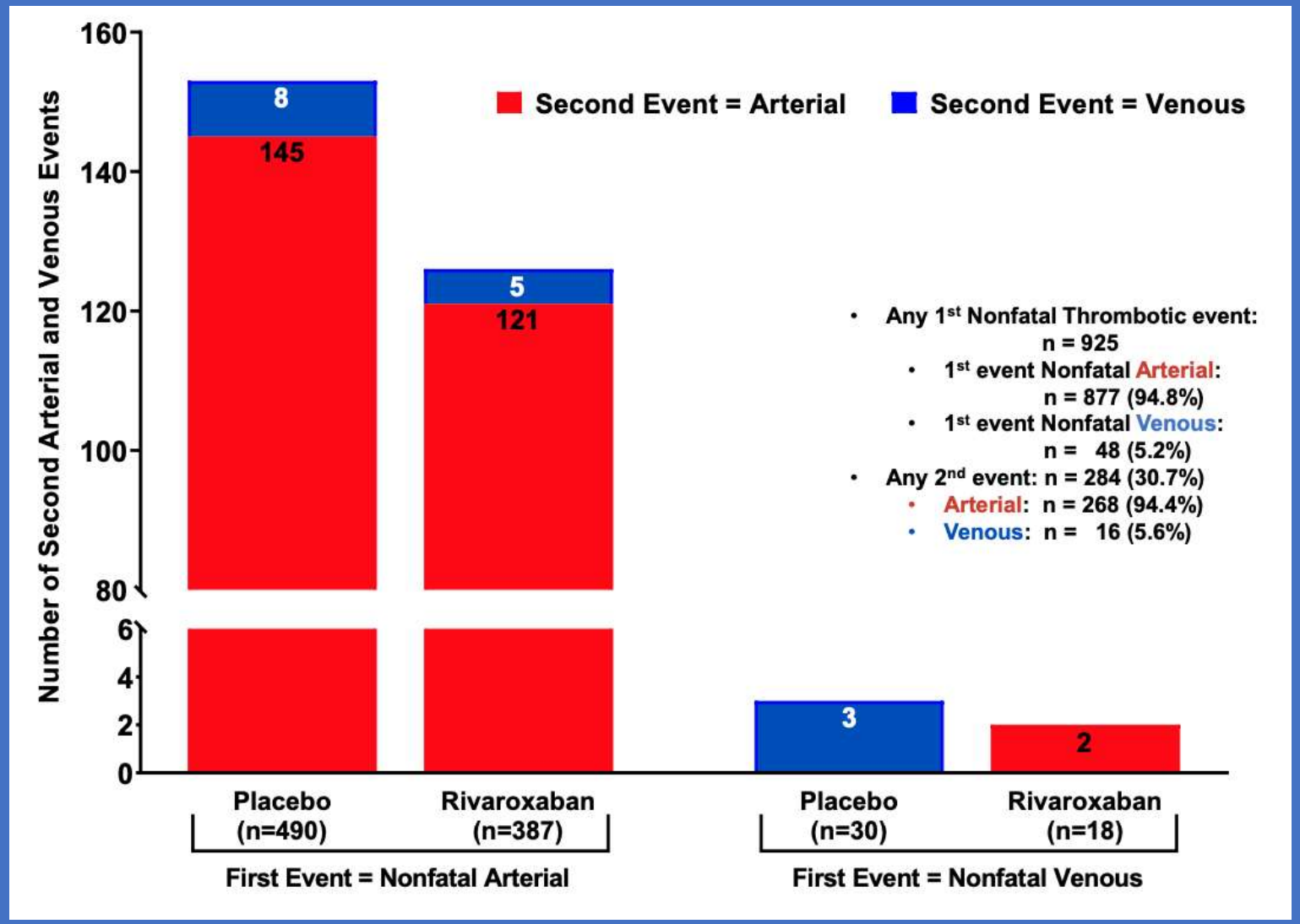
Second Arterial and Venous Thrombotic Events by Type of First Nonfatal Event



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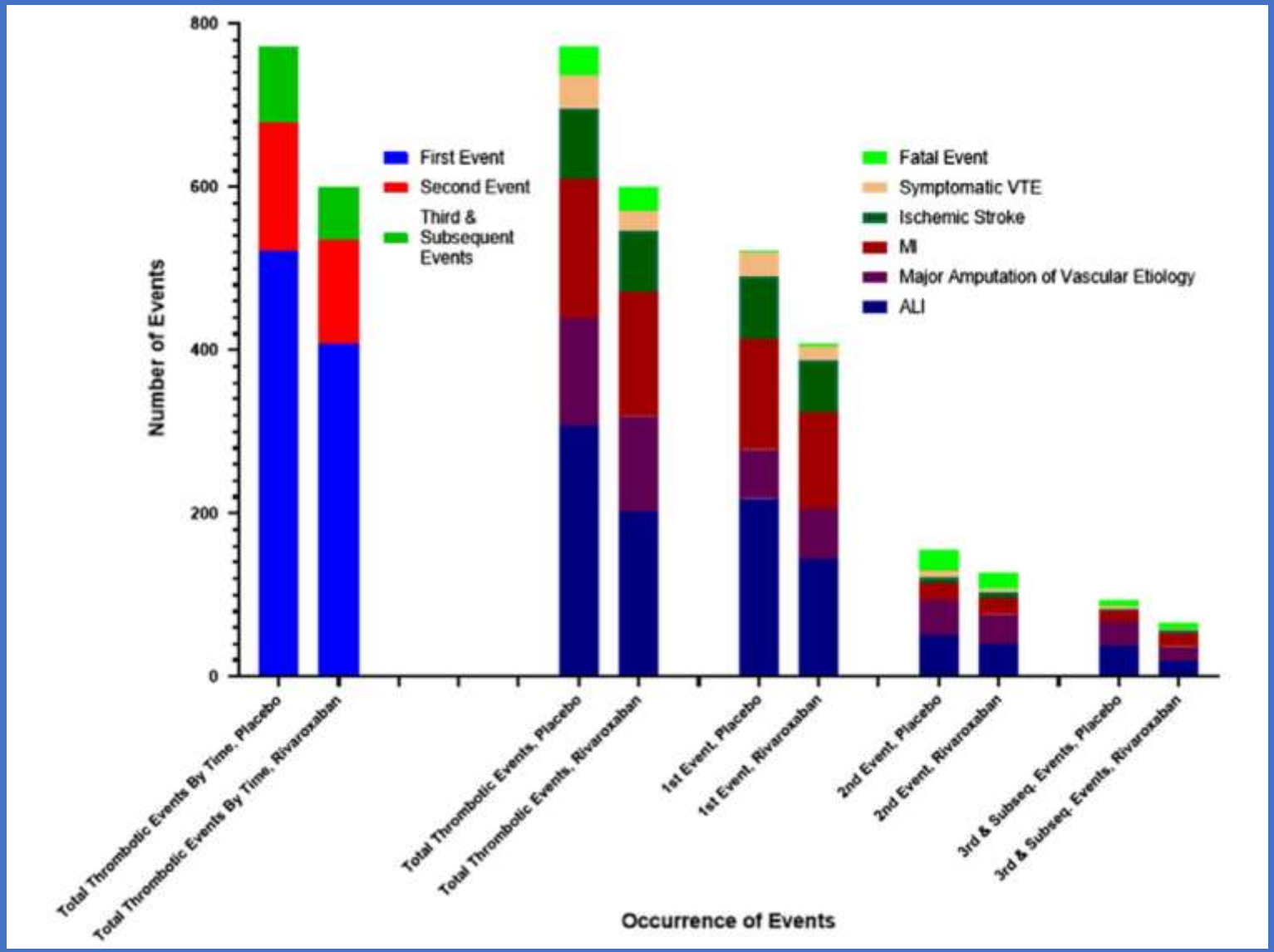
Distribution of total (first and subsequent) arterial and venous thrombotic events



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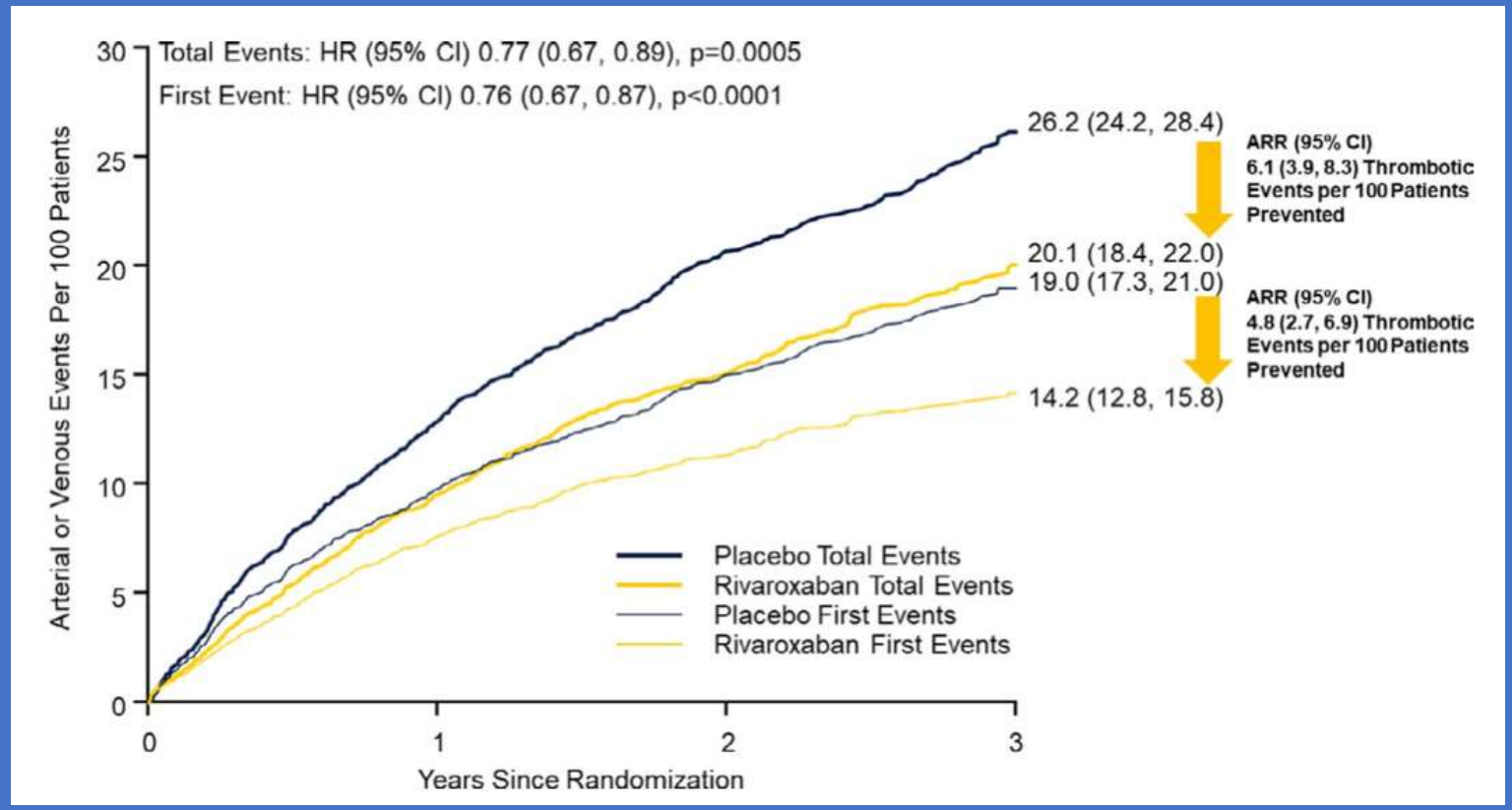
Effect of rivaroxaban on arterial and venous thrombotic events



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Limitations

- Observations are limited to the subpopulation of symptomatic PAD patients who had successfully undergone LER within the previous 10 days.
- VTE was a secondary endpoint in VOYAGER PAD and was investigator-reported, not adjudicated; however, VTE was prospectively ascertained, and this analysis was prespecified.
- Adjusted models accounted for known baseline characteristics but post-randomization variables were not included, so residual confounding may exist.
- Whether study medication was continuously taken throughout or discontinued at some point in the trial is an issue with all therapeutic clinical trials and in practice.
- Discontinuation of the study drug before a patient's first event can impact both time-to-first and recurrent-event analyses, whereas those that occur after a first event would affect only a recurrent-event analysis

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Conclusions

- In an atherosclerotic patient population at heightened thrombotic risk, VOYAGER PAD provides evidence for a broad and persistent benefit of dual pathway inhibition, combining low-dose anticoagulation with low-dose antiplatelet therapy, over antiplatelet therapy alone, to affect both thrombin generation and platelet activation and lead to a reduction in first and subsequent arterial and venous thrombotic events.
- Future clinical trials should continue this focus on a holistic, that is, comprehensive CV outcome assessment, including total arterial and venous thrombotic events, to capture the full spectrum of clinical benefit.
- Judicious modulation of the hemostatic system through more than one path- way appears to provide more benefit than simply ramping up the intensity of inhibition of only one of its integrated components.

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