Reductions in Total Ischemic Events with Rivaroxaban in Patients with Symptomatic PAD after Revascularization: The VOYAGER PAD Trial

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on behalf of the VOYAGER PAD Investigators

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Disclosures

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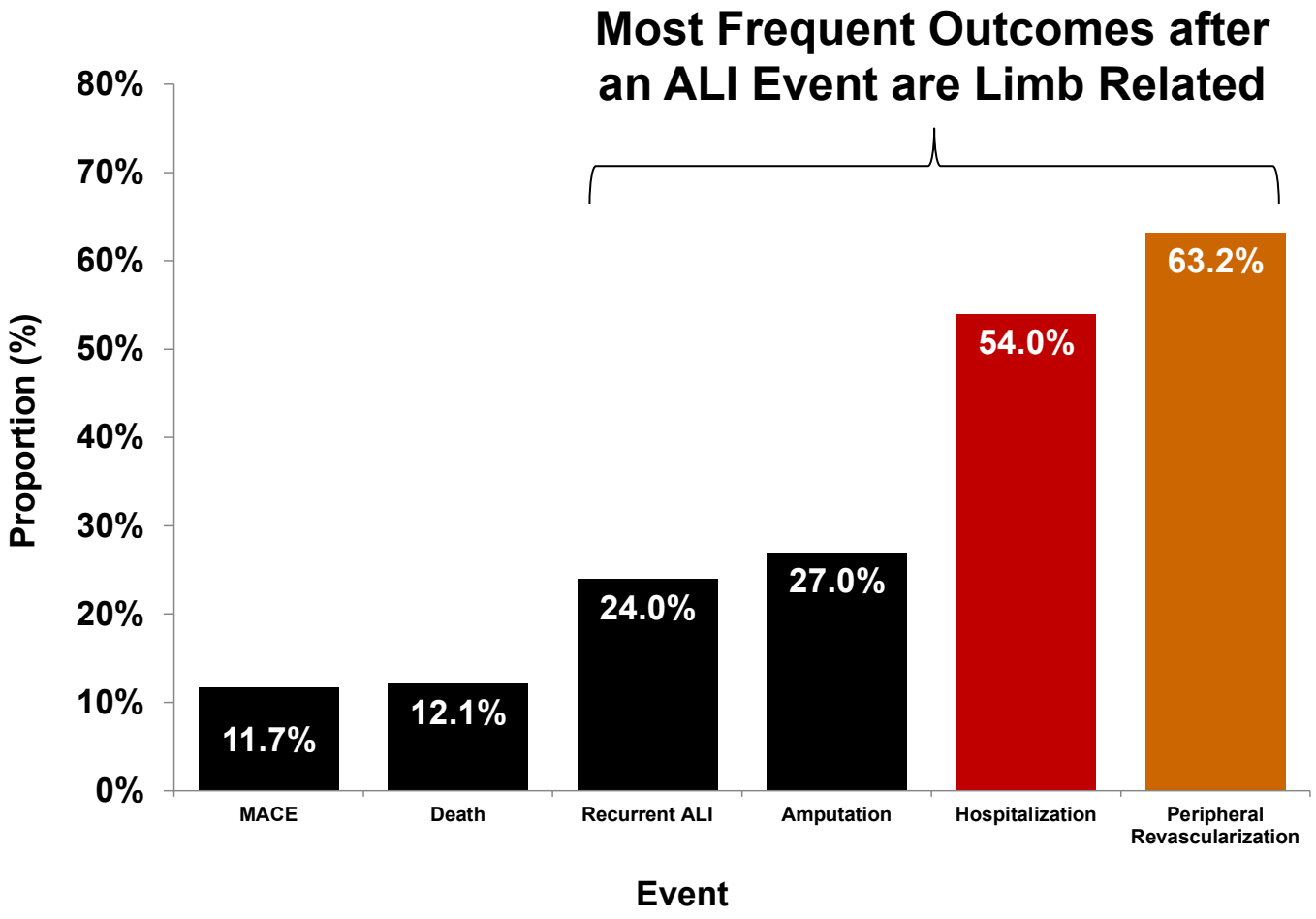
After Lower Extremity Revascularization there is a 4-Fold Risk of Acute Limb Ischemia

After Acute Limb Ischemia Outcomes are poor and Repeat Revascularizations are frequently required

	HR for ALI
TRA2P-TIMI 50 PAD Bonaca et al. Circulation 2016	**HR 3.60** (2.10 – 6.18) P<0.001
PEGASUS-TIMI 54 PAD Bonaca et al. JACC 2016	Adjusted **HR 3.76** (2.26 – 6.25) p<0.001
EUCLID Jones et al. Circulation 2016	Adjusted **HR 4.23** (2.86 – 6.25) p<0.001



Bonaca et al. Circulation 2016

VOYAGER PAD Design

NCT02504216

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg twice daily

Stratified by Revascularization Approach (Surgical or Endovascular with and without clopidogrel)

Placebo

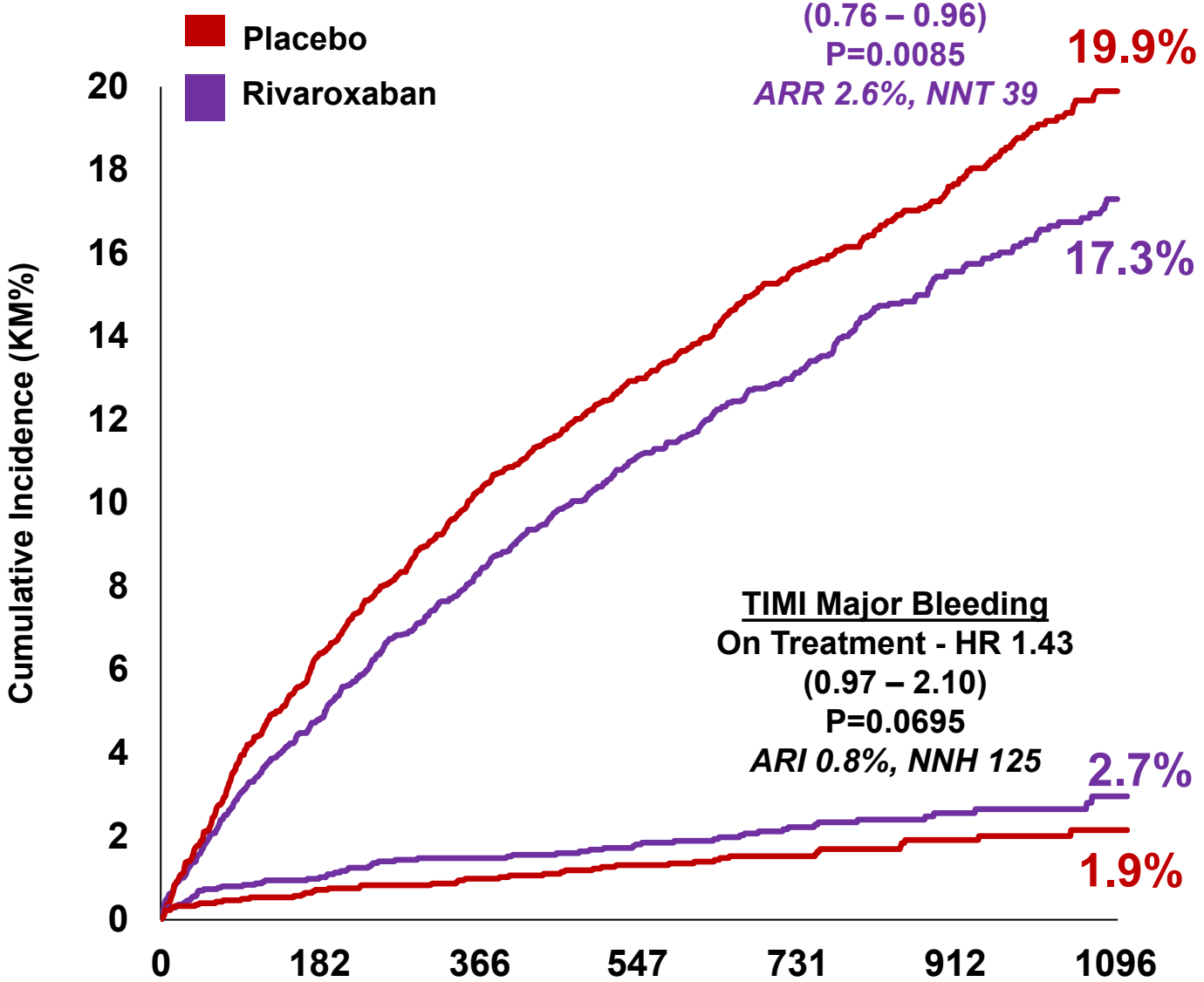
Follow up Q6 Months, Event Driven, Median f/u 2.5 years

Primary Efficacy Endpoint*: Time to FIRST* Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

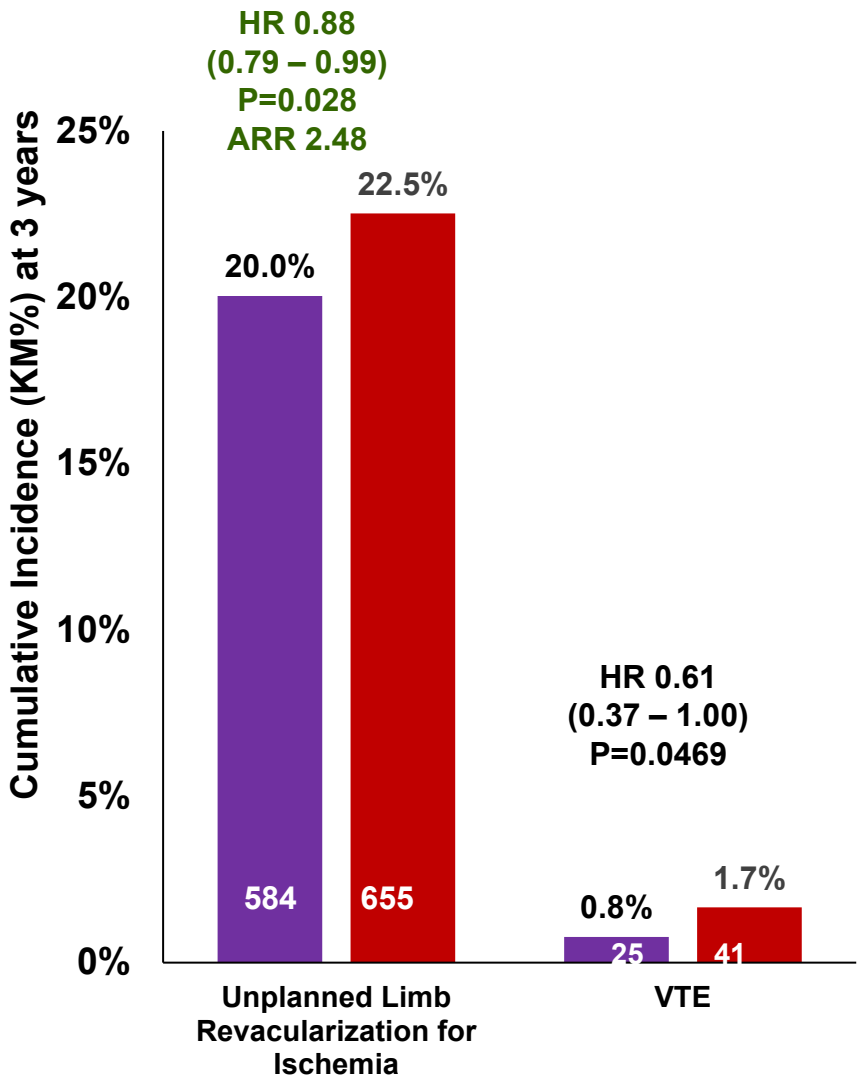
Principal Safety Outcome: TIMI Major Bleeding

Capell WH, Bonaca MP, Nehler MR…Hiatt WR. AHJ 2018
Bonaca MP…Hiatt WR NEJM 2020

VOYAGER PAD Primary Results



Secondary Vascular Outcomes



*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death

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VOYAGER PAD

VOYAGER PAD

- 1 in 5 patients undergoing LER experienced a ***first*** adverse limb or cardiovascular event inspite of aspirin in all patients, statins in 80% and clopidogrel in half of the patients.
- The addition of rivaroxaban 2.5 mg twice daily reduced first events by app. 15% (NNT of 39 to prevent a ***first*** event at 3 years).
- The rate of total (first and potentially subsequent) events after LER and the effect of rivaroxaban on reduction of total events is unknown

Objectives

- In a pre-specified analysis to investigate the number of first and total events in PAD patients undergoing LER.
- To evaluate the composition of events including all limb and cardiovascular events
- To evaluate the efficacy of rivaroxaban on first and total events.

Methods

- **Patients:**
  - **Qualifying patients had symptomatic PAD defined by abnormal ankle-brachial index (ABI) ≤ 0.80 or toe-brachial index (TBI) ≤ 0.60 (in those without a prior history of LER) with an anatomy of occlusive disease distal to the external iliac artery**

- **Efficacy:**
  - **Primary composite (ITT) of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke or CV death**
  - **Prespecified categories of Vascular events included subsequent LER and venous thromboembolic events**

- **Outcomes adjudicated by a blinded CEC***

- **Marginal proportional hazards model**
  - **allowing for the possibility of multiple vascular events within a given participant**
  - **non-vascular death as a competing terminal event**

* Peripheral revascularizations and venous thromboembolism were reported by investigators blinded to treatment assignment

Baseline Characteristics of Participants by Number of Vascular Events

	(A) No Events (n=4263; 65%)	(B) One Event (n=1209; 18%)	(C) Multiple Events (n=1092; 17%)	p-value (A) vs. (B) + (C)	p-value (B) vs. (C)
Coronary artery disease	29.3	35.2	35.9	<0.0001	n.s.
Diabetes mellitus	37.3	45.2	45.2	<0.0001	n.s.
eGFR<60 ml/min/1.73m²	19.2	22.2	21.8	0.008	n.s.
Prior revascularization	30.2	40.8	50.7	<0.0001	<0.0001
Qualifying revascularization				0.0007	n.s.
Endovascular	65.3	68.4	70.5		
Surgical	34.7	31.6	29.5		
≥15 cm target lesion	30.8	36.3	45.9	<0.0001	<0.0001
Atherectomy	3.4	5.5	9.2	<0.0001	0.0007
Randomized to rivaroxaban	50.8	51.4	45.7	n.s.	0.007
Medications					
Statin	78.7	82.4	82.2	0.0005	n.s.
Clopidogrel	49.5	51.0	53.7	0.03	n.s.

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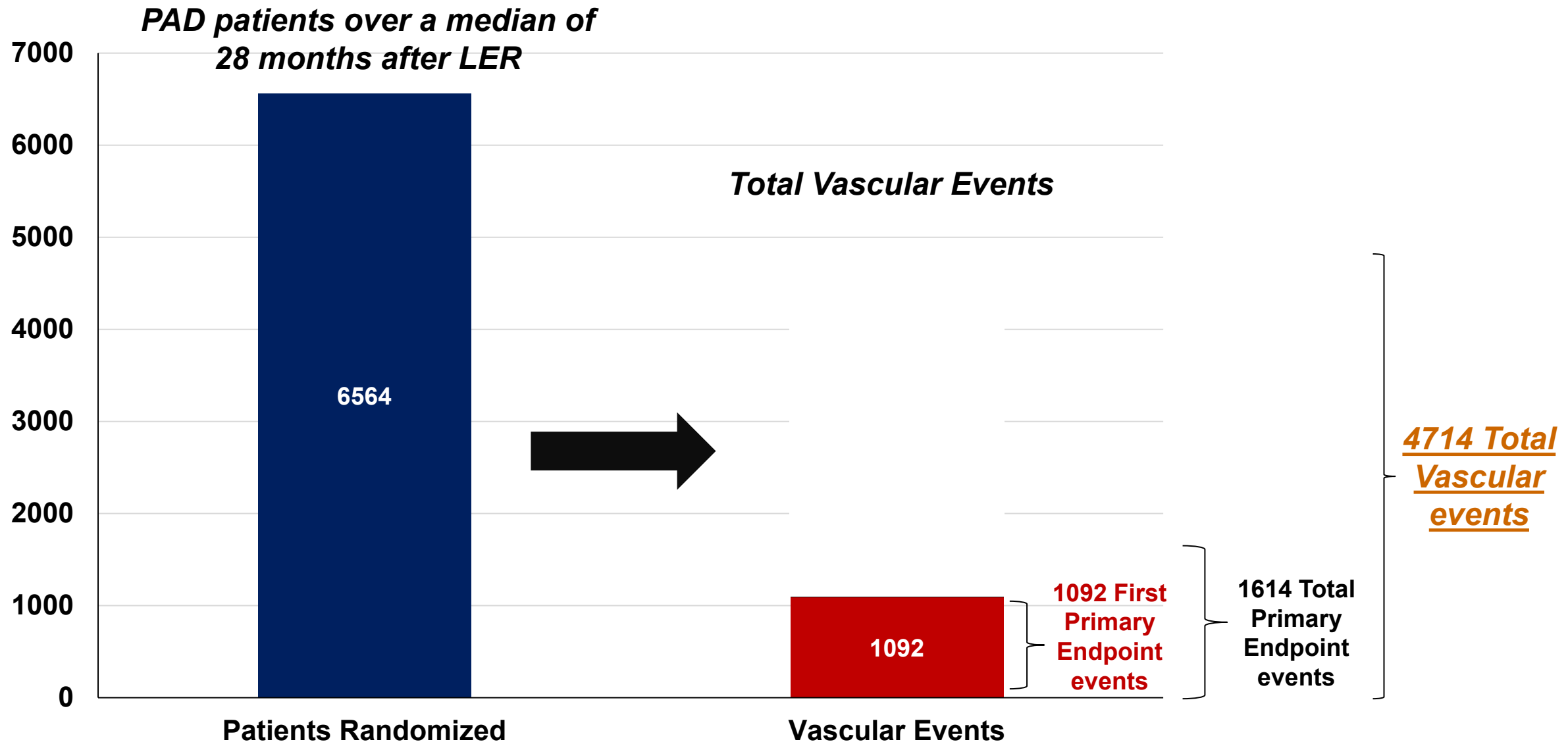
Symptomatic PAD after LER - First and Total Vascular Events



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Categories of Total Events

Event	Rivaroxaban (n = 3286)	Placebo (n = 3278)	Total (n = 6564)
Total Vascular	**2186**	**2528**	**4714**
Primary endpoint events	**745**	**869**	**1614**
Other Vascular events	**1441**	**1659**	**3100**
Non-vascular death	122	123	245

* Investigator-reported; not subject to adjudication by independent committee

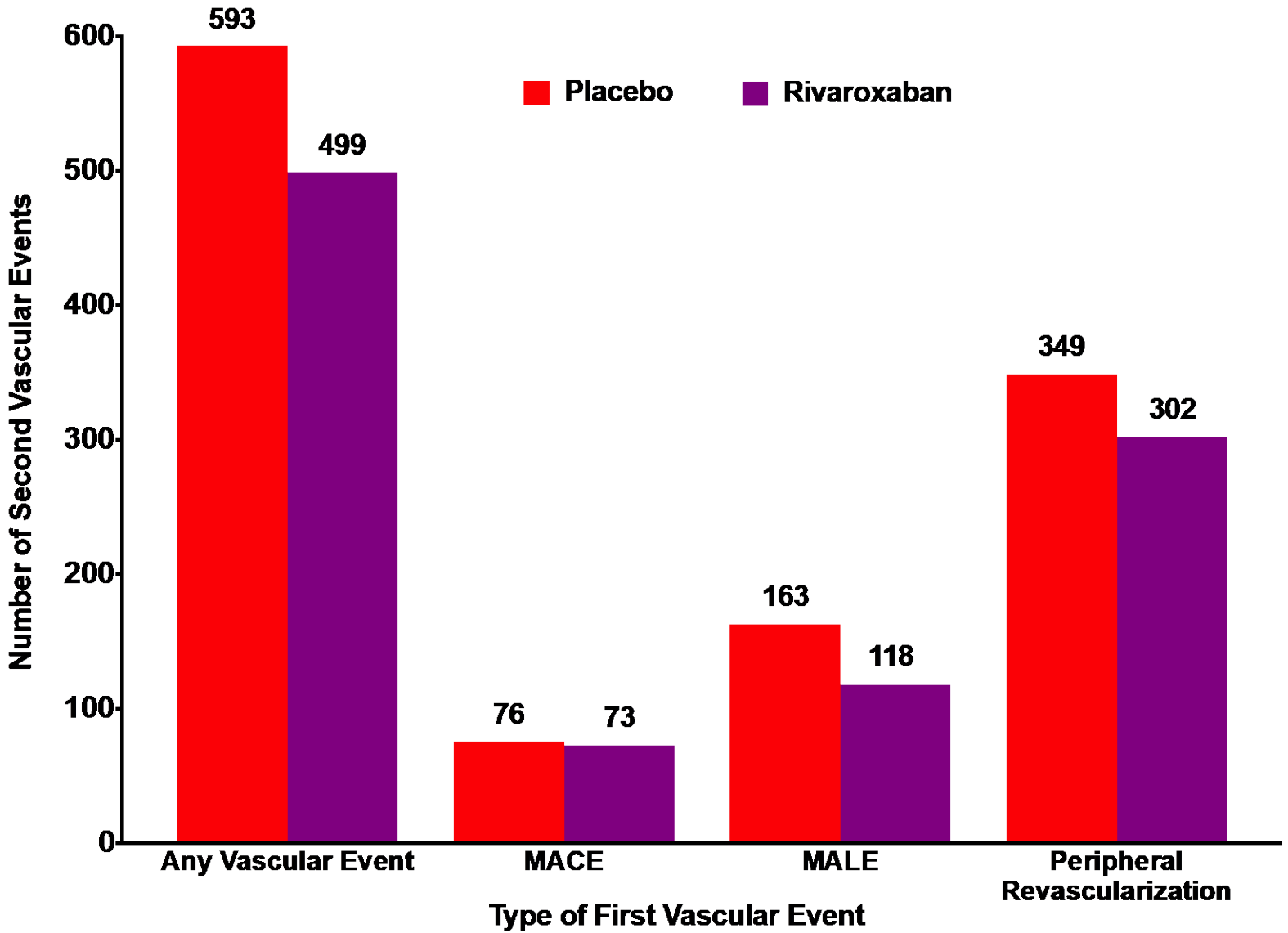
Categories of Total Events

Event	Rivaroxaban (n = 3286)	Placebo (n = 3278)	Total (n = 6564)
Total Vascular	**2186**	**2528**	**4714**
Primary endpoint events	**745**	**869**	**1614**
Acute limb ischemia	*202*	*306*	*508*
Major amputation for vascular causes	*117*	*133*	*250*
Non-fatal myocardial infarction	*152*	*170*	*322*
Non-fatal ischemic stroke	*75*	*86*	*161*
Cardiovascular Death	*199*	*174*	*373*
Other Vascular events	**1441**	**1659**	**3100**
Peripheral revascularization*	*1416*	*1618*	*3034*
Venous thromboembolic event*	*25*	*41*	*66*
Non-vascular death	122	123	245

* Investigator-reported; not subject to adjudication by independent committee

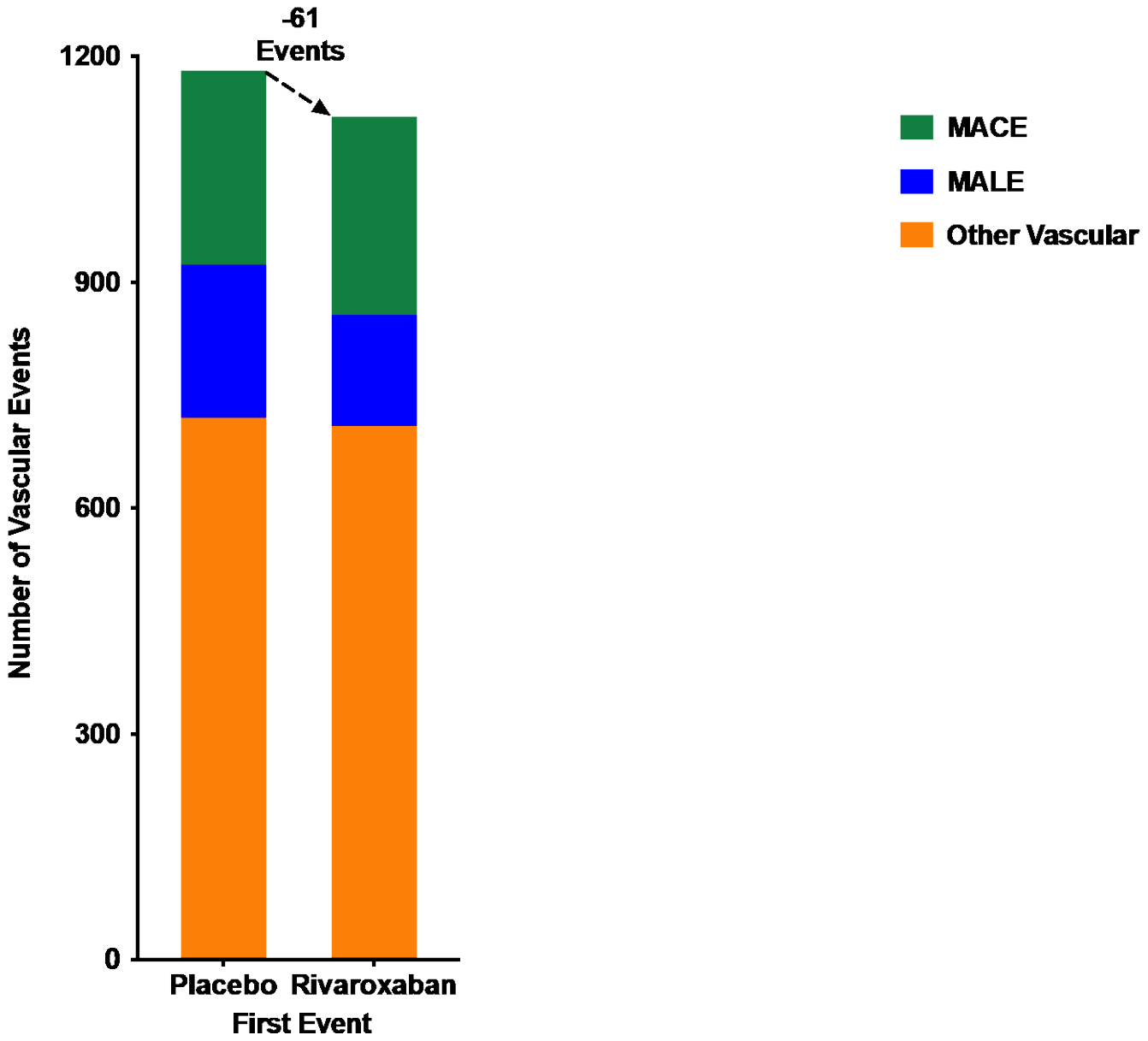
Second Vascular Event by Type of First Non-fatal Vascular Event

60% of second events were in patients who had a first peripheral revascularization



MACE = major adverse cardiovascular event; MALE = major adverse limb event.

First and Subsequent Vascular Events



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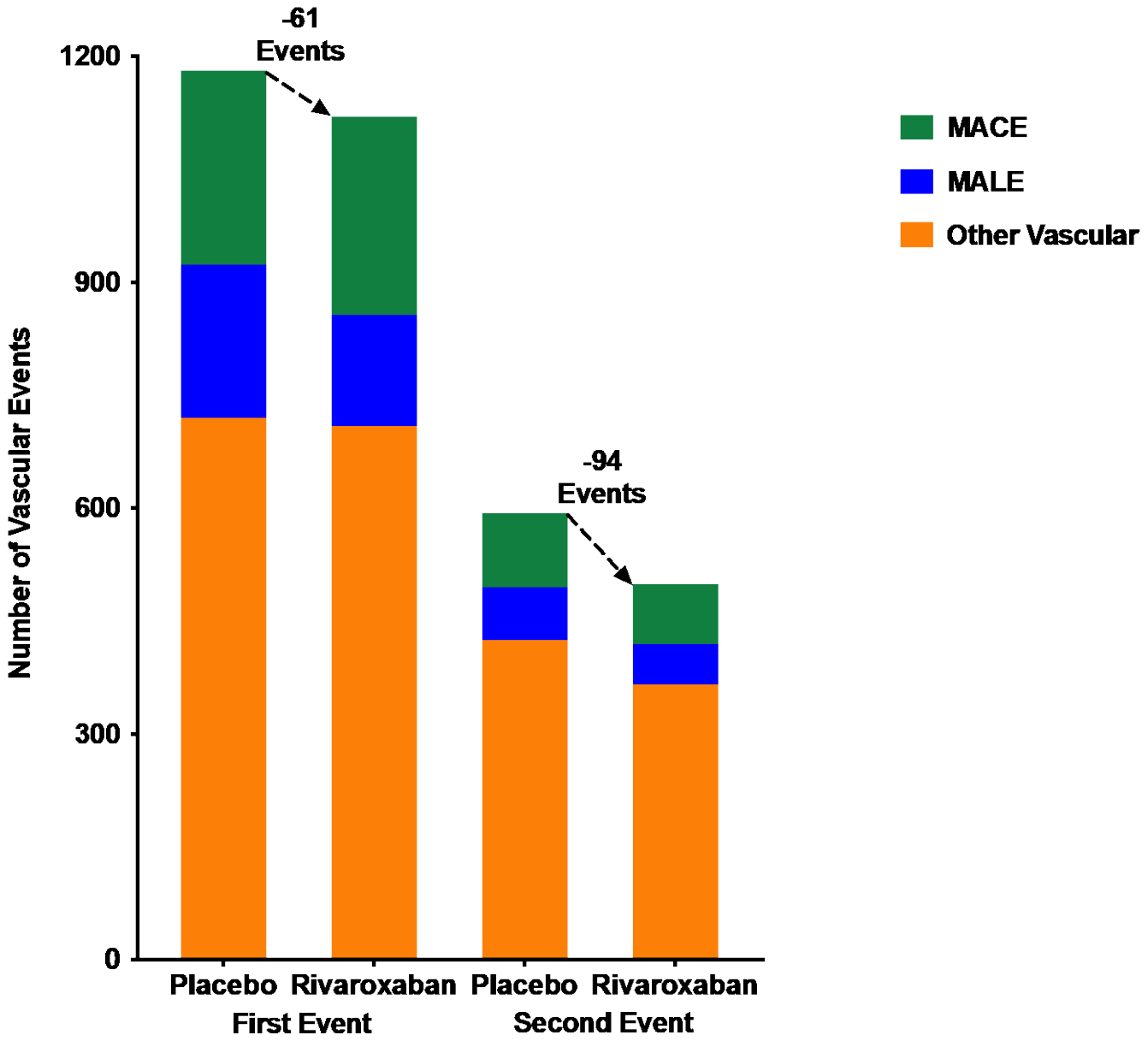
First and Subsequent Vascular Events



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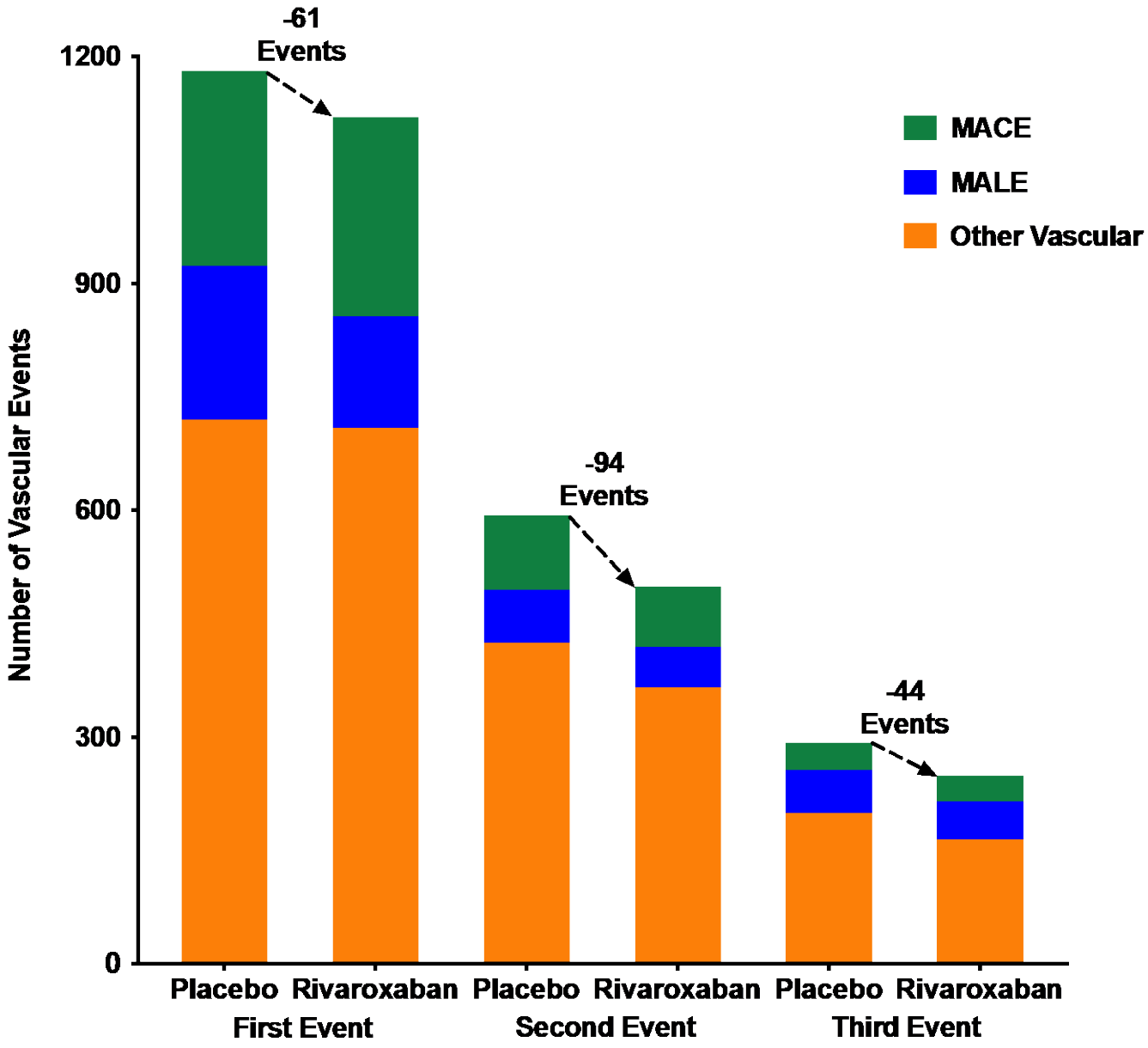

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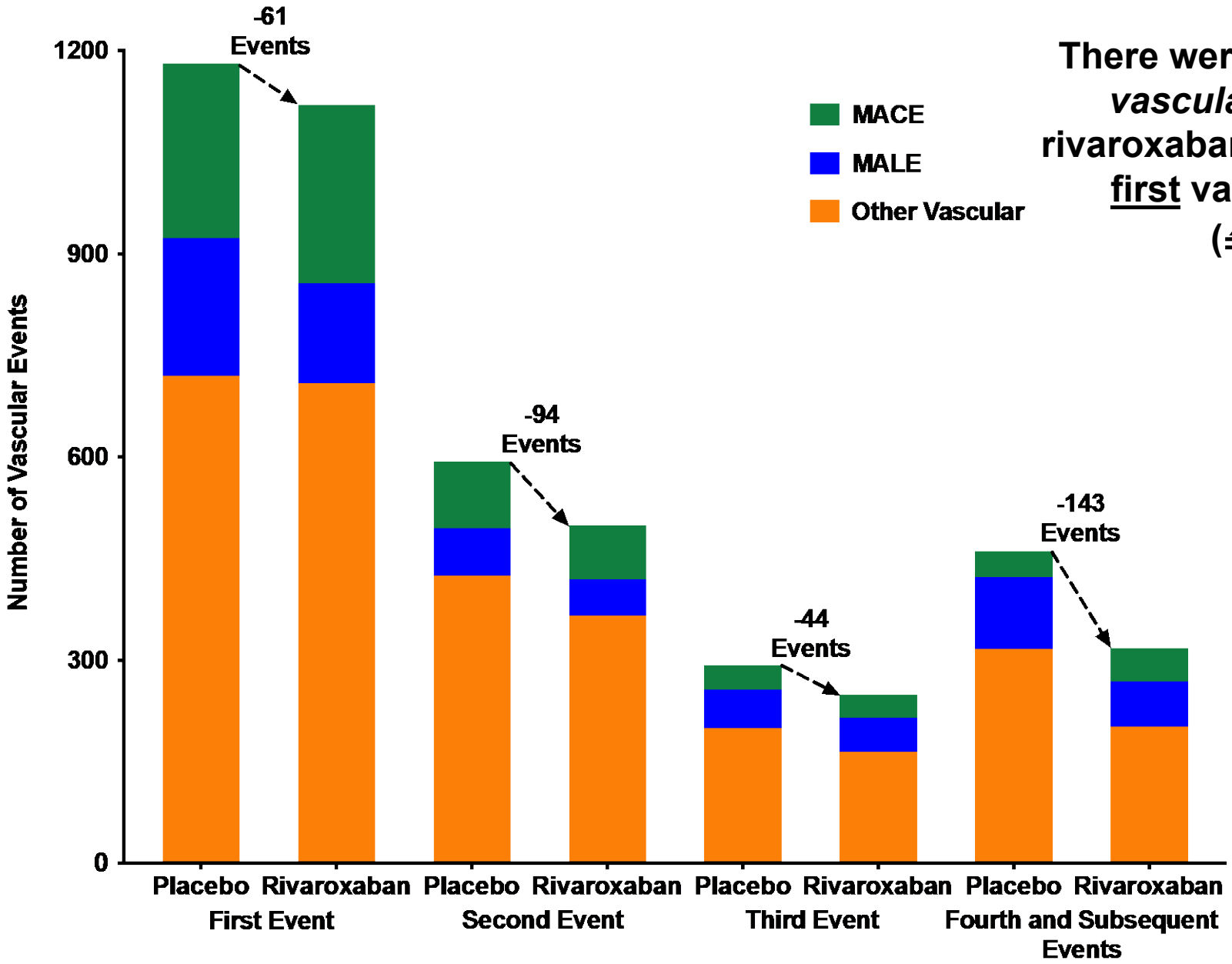
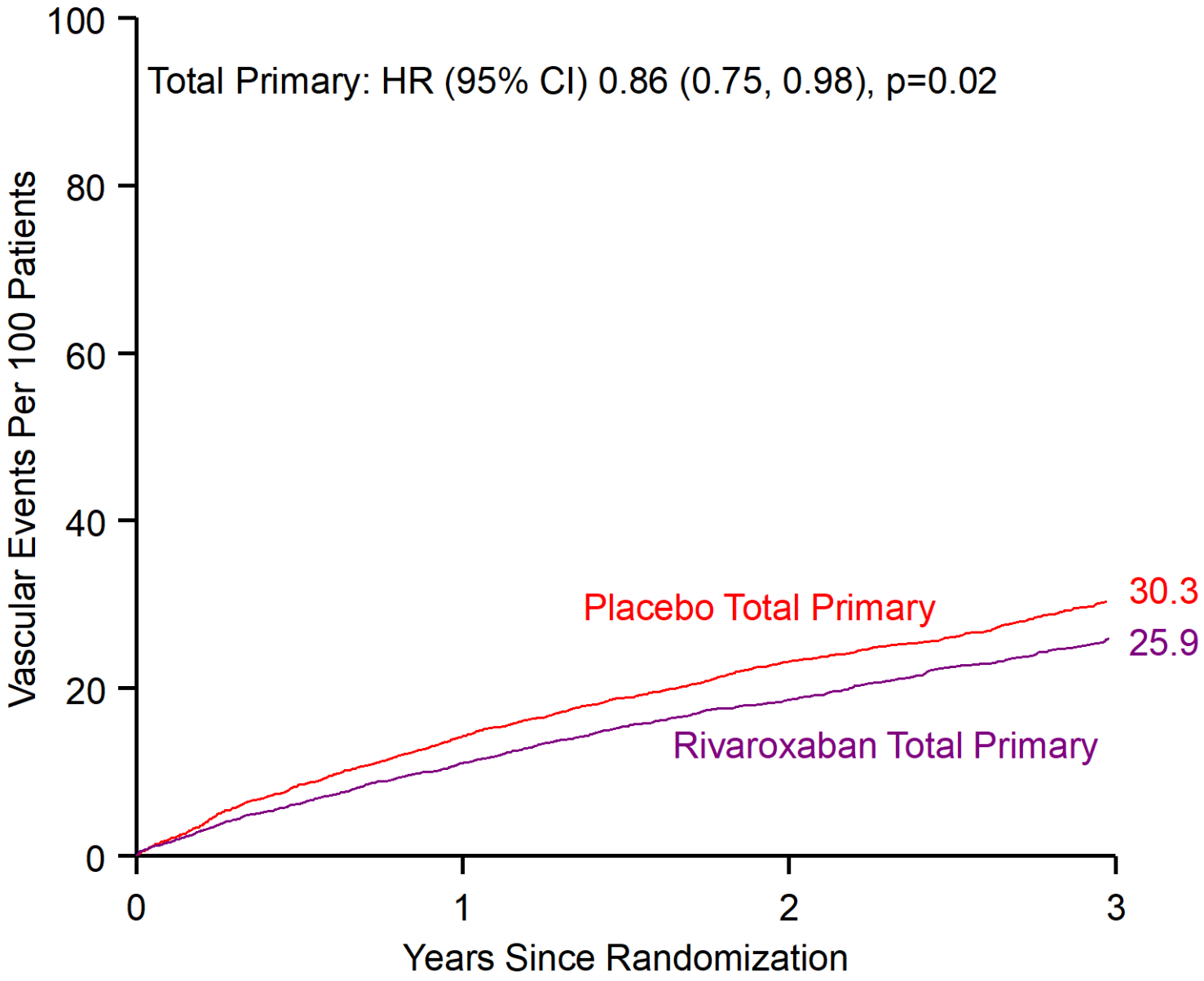


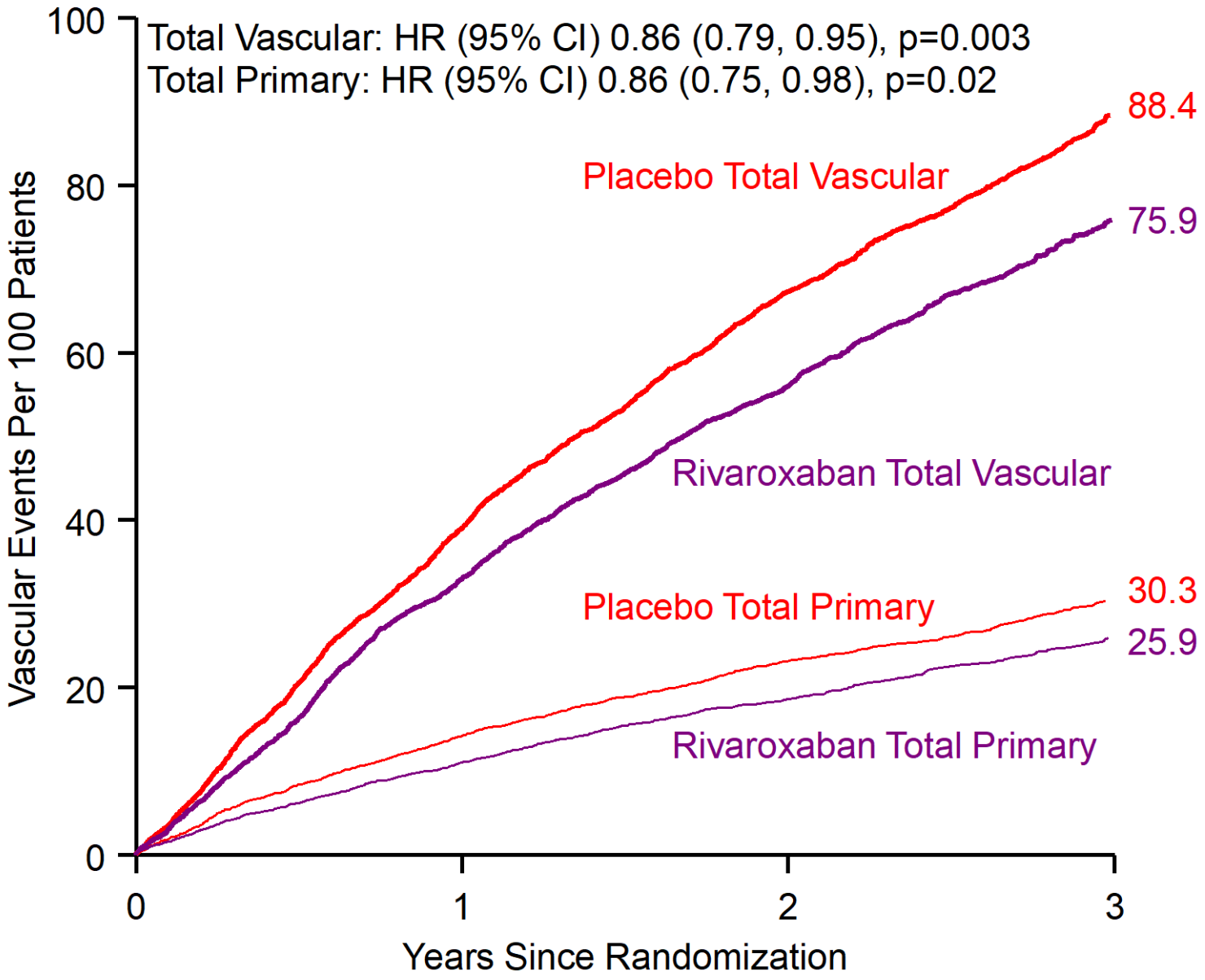
There were *342 fewer* ***total*** *vascular events* with rivaroxaban versus 61 fewer **first** vascular events (≙ 18 %).

MACE = major adverse cardiovascular event; MALE = major adverse limb event.

Accrual of Events per 100 Patients

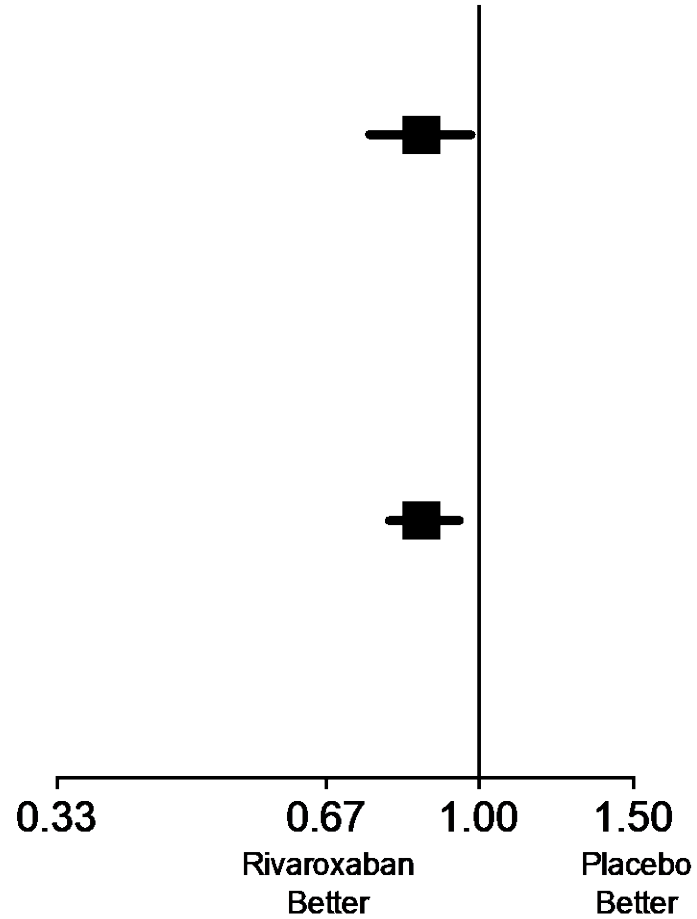


Accrual of Events per 100 Patients



ITT vs. “On-Treatment”

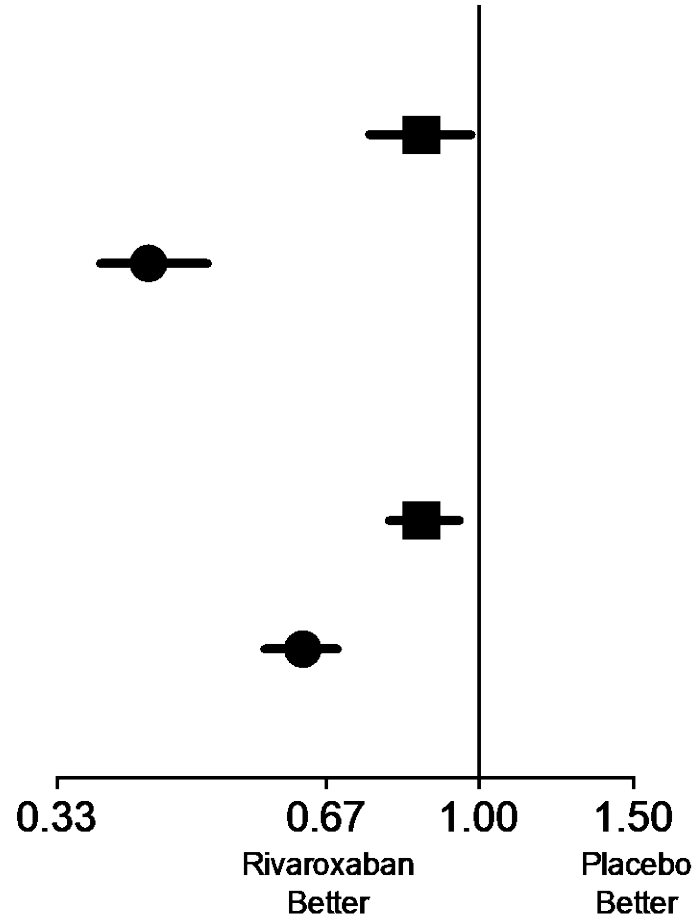
	Treatment HR (95% CI)
Total Primary Endpoint Events	
Intention-to-Treat	0.86 (0.75, 0.98)
Total Vascular Events	
Intention-to-Treat	0.86 (0.79, 0.95)



ITT vs. “On-Treatment”

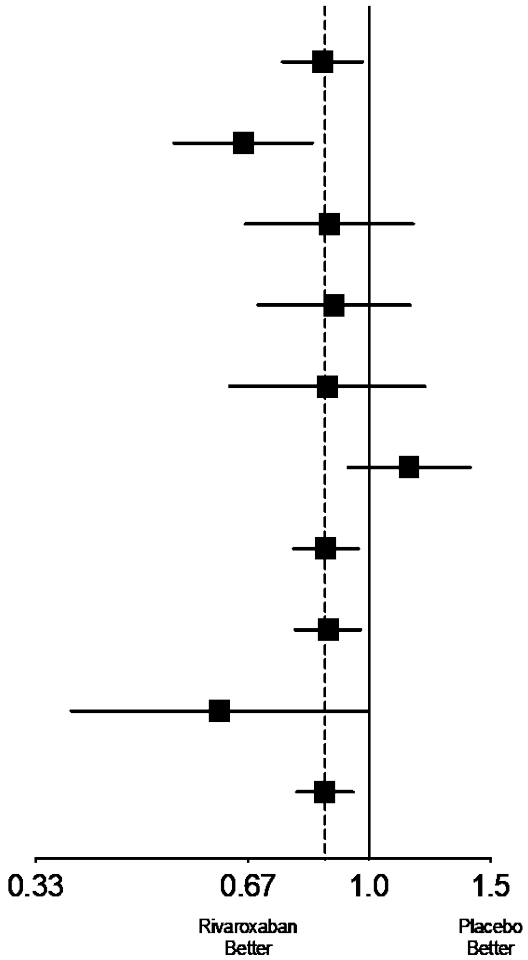
903 of 2186 vascular events in rivaroxaban group occurred after given patient’s last dose

	Treatment HR (95% CI)
Total Primary Endpoint Events	
Intention-to-Treat	0.86 (0.75, 0.98)
Time-Varying Rivaroxaban Exposure	0.42 (0.37, 0.49)
Total Vascular Events	
Intention-to-Treat	0.86 (0.79, 0.95)
Time-Varying Rivaroxaban Exposure	0.63 (0.57, 0.69)



Treatment Effects on Total Vascular Events

	Total Events per 100 Patients*		
	Rivaroxaban (n=3286)	Placebo (n=3278)	HR (95% CI)
Primary endpoint events	**25.9**	**30.3**	**0.86 (0.75, 0.98)**
Acute limb ischemia	6.6	10.2	0.66 (0.52, 0.83)
Major amputation	3.8	4.3	0.88 (0.66, 1.16)
Non-fatal myocardial infarction	5.3	5.7	0.89 (0.69, 1.15)
Non-fatal ischemic stroke	2.6	3.0	0.87 (0.63, 1.20)
Vascular death	7.1	6.5	1.14 (0.93, 1.40)
Other vascular events	**48.5**	**56.5**	**0.87 (0.78, 0.97)**
Peripheral revascularization	47.8	55.0	0.87 (0.78, 0.97)
Venous thromboembolic event	0.7	1.5	0.61 (0.37, 1.00)
All vascular events	**75.9**	**88.4**	**0.86 (0.79, 0.95)**



* 3 years after randomization

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VOYAGER PAD

Summary

- In VOYAGER PAD, among 6,564 randomized there were
  - 4714 total first and subsequent vascular events including
  - 1614 primary endpoint events and 3100 other vascular events

- Rivaroxaban reduced
  - total primary endpoint events (HR 0.86,95% CI 0.75-0.98; p=0.02)
  - total vascular events (HR 0.86,95% CI 0.79-0.95; p=0.003)

- An estimated 4.4 primary and 12.5 vascular events /100 participants were avoided with rivaroxaban over three years.

Conclusions

- **PAD Patients undergoing LER are at high risk of adverse limb and cardiovascular events, with particularly high burden when considering total events inspite of standard available medical therapy**
- **The risk profile in patients with symptomatic PAD is dominantly driven by adverse limb outcomes, particularly after LER, including acute limb ischemia, major vascular amputation and recurrent revascularization.**

- **Rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone reduces first and subsequent adverse limb and cardiovascular events with an even greater total benefit when considering all events.**
- ***Rivaroxaban 2.5 mg twice daily with aspirin should be considered as adjunctive therapy after LER to reduce first and subsequent adverse outcomes***

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Thank you very much for your attention!

Results accepted for Publication at JACC