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

Rupert M. Bauersachs, MD, Michael Szarek, Marianne Brodmann, MD, Ivan Gudz, MD, Eike Sebastian Debus, MD, PhD, Mark R. Nehler, MD, Sonia S. Anand, MD, Manesh R. Patel, MD, Connie N. Hess, MD, MHS, Warren H. Capell, MD, Kevin Rodgers, MD, Eva Muehlhofer, MD, Lloyd P. Haskell, MD, MBA, Scott D. Berkowitz, MD, William R. Hiatt, MD, Marc P. Bonaca, MD, MPH

on behalf of the VOYAGER PAD Investigators

Scientific Sessions of the ACC's 70th Annual Scientific Session
May 15-17, 2021, in Atlanta, Georgia
17634

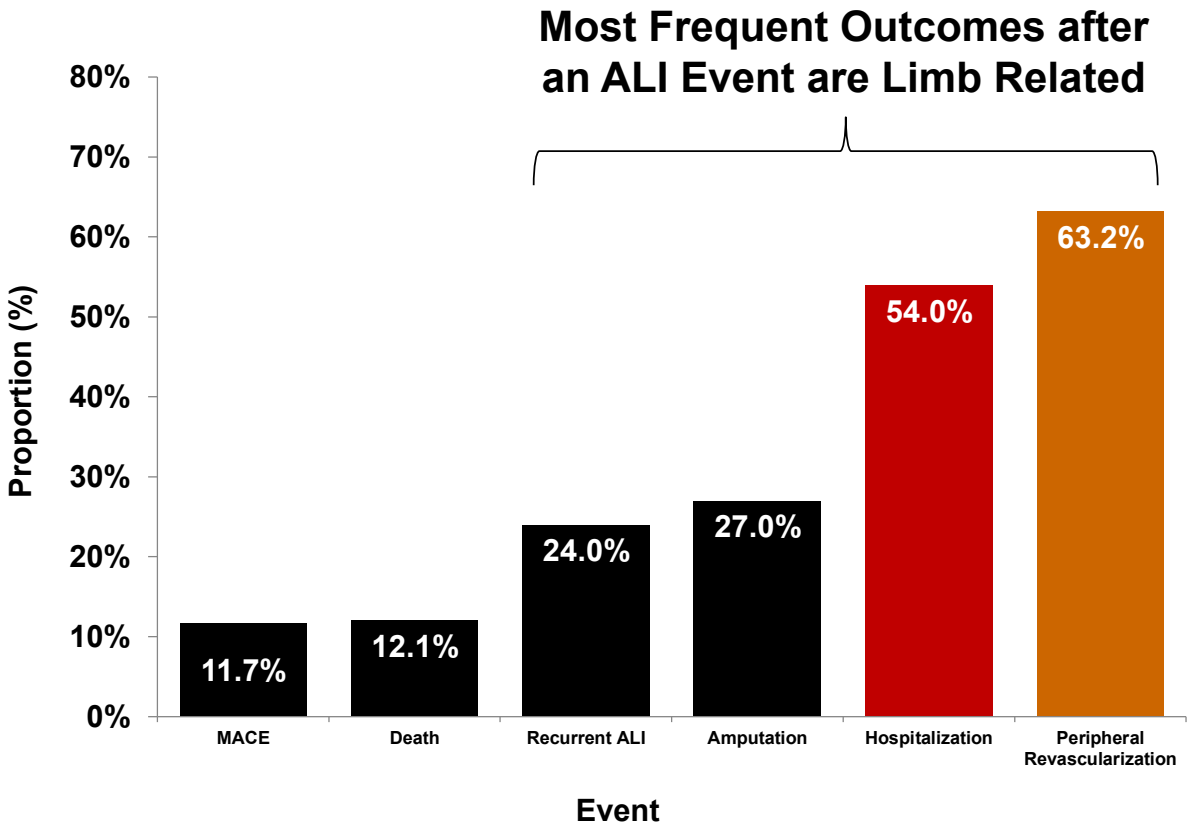
Disclosures

- VOYAGER PAD funded through a grant from Bayer to CPC Clinical Research
- Other research grants to CPC Clinical Research from Arca, Amgen, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk

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

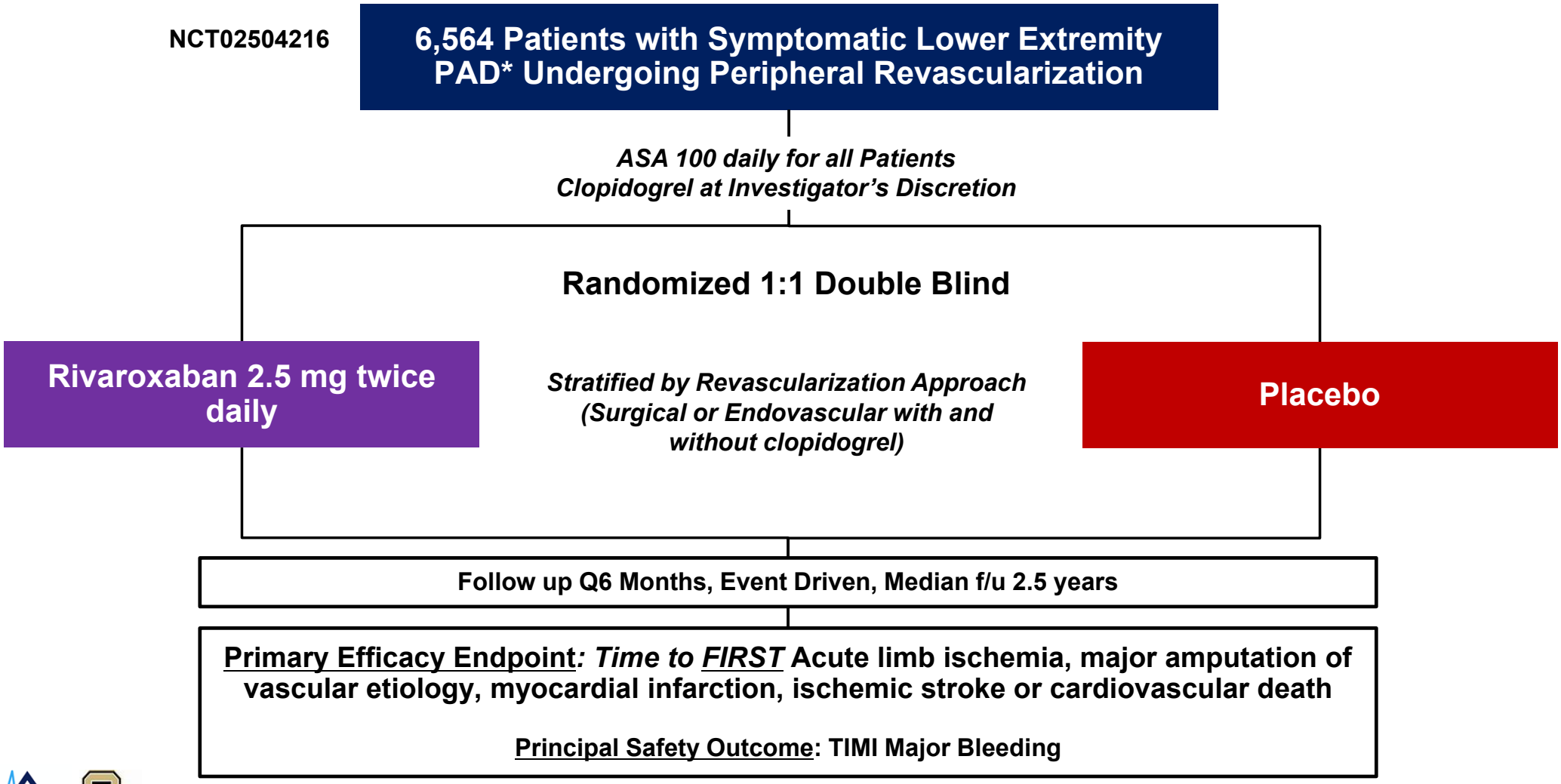
After Acute Limb Ischemia Outcomes are poor and Repeat Revascularizations are frequently required

	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



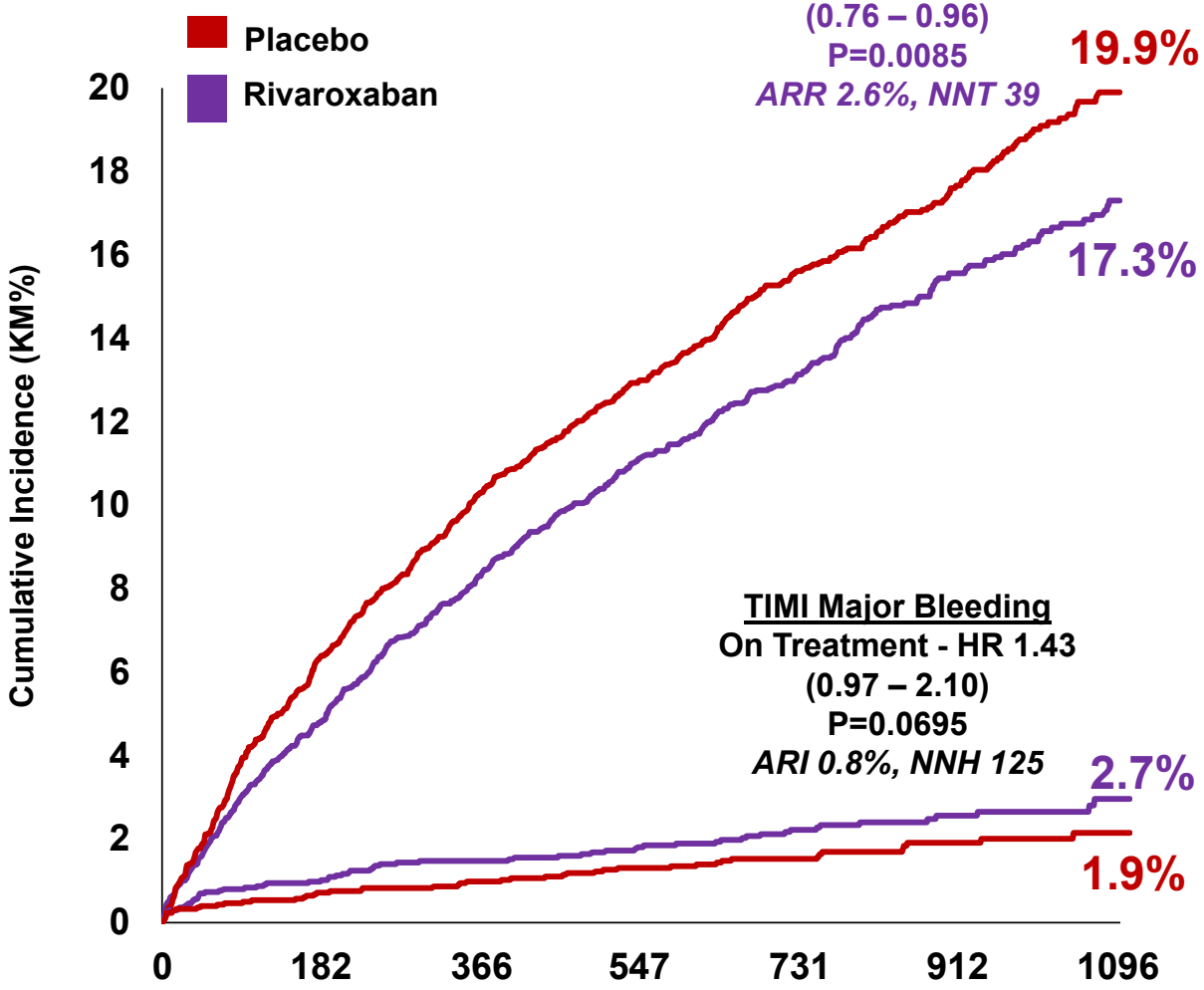
Bonaca et al. Circulation 2016

VOYAGER PAD Design

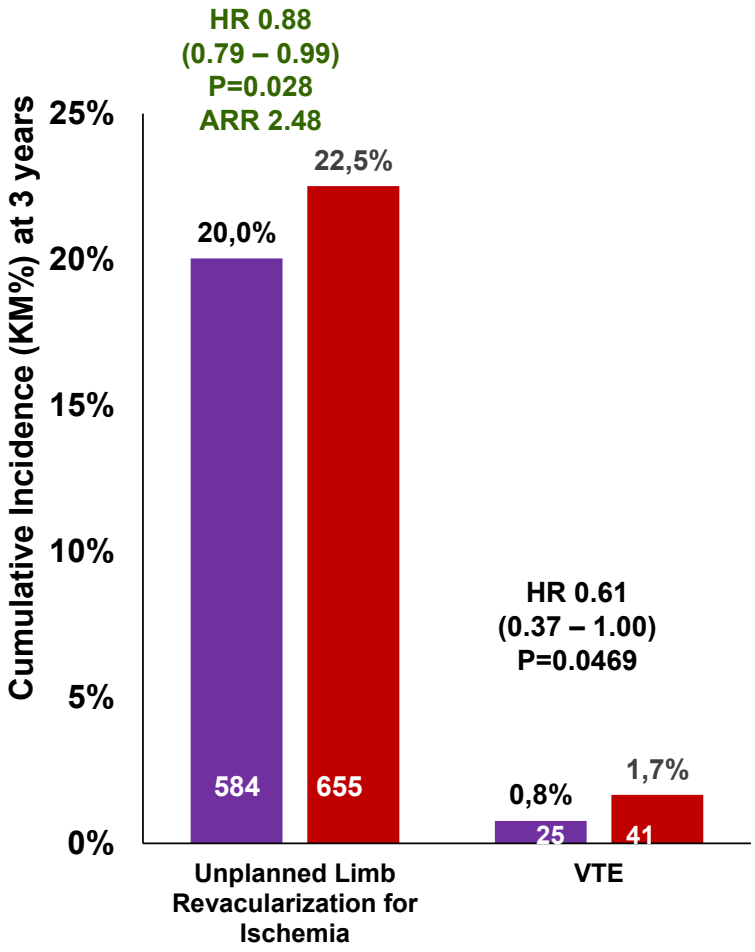


Capell WH, Bonaca MP, Nehler MR…Hiatt WR. AHJ 2018
Bonaca MP…Hiatt WR NEJM 2020

VOYAGER PAD Primary Results



Secondary Vascular Outcomes



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

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***

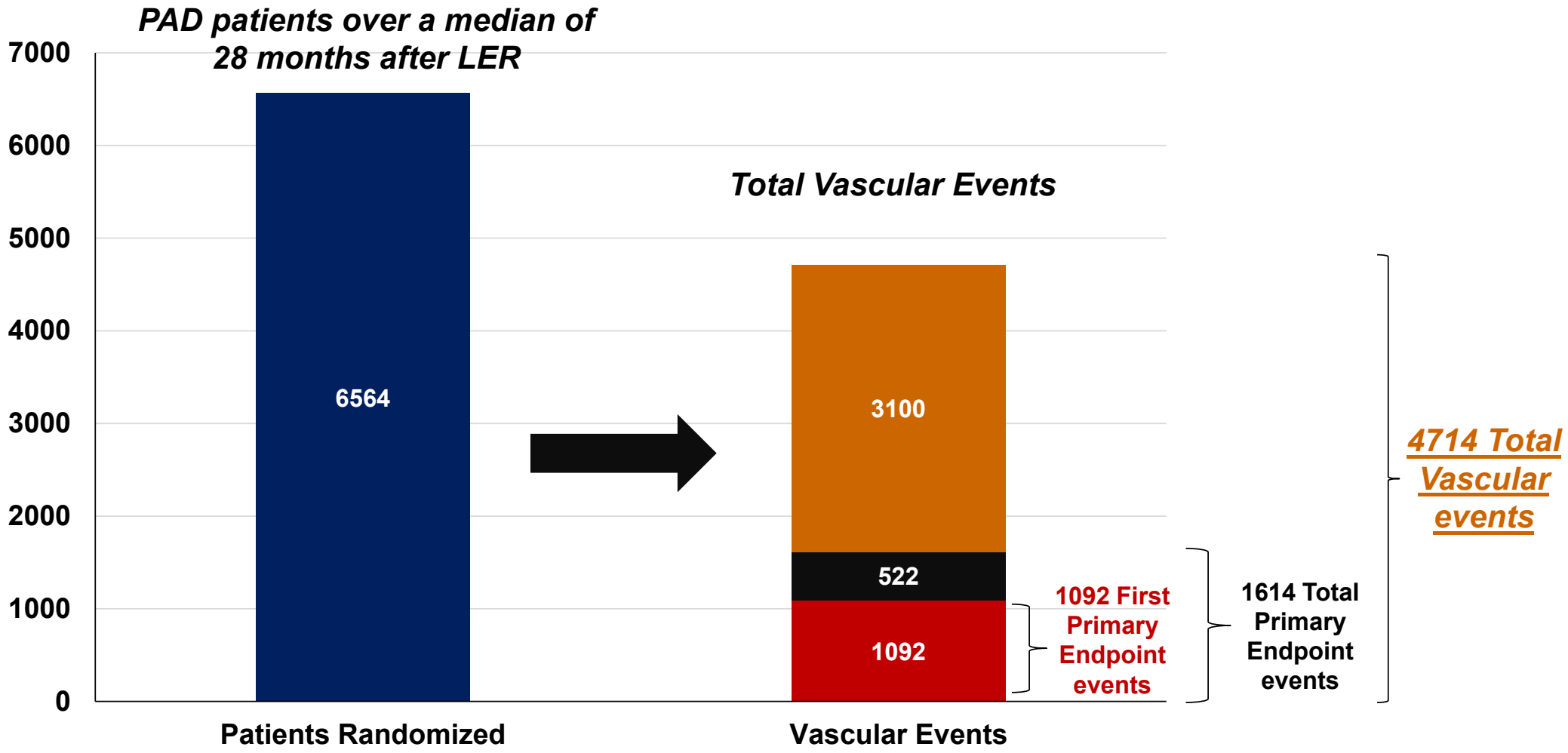
- **Marginal proportional hazards model**
  - **allowing for the possibility of multiple vascular events within a given participant**
  - **non-vascular death as a competing terminal event**

* 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/1.73m^2	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.

Symptomatic PAD after LER - First and Total Vascular Events



CPC Clinical Research

VOYAGER PAD

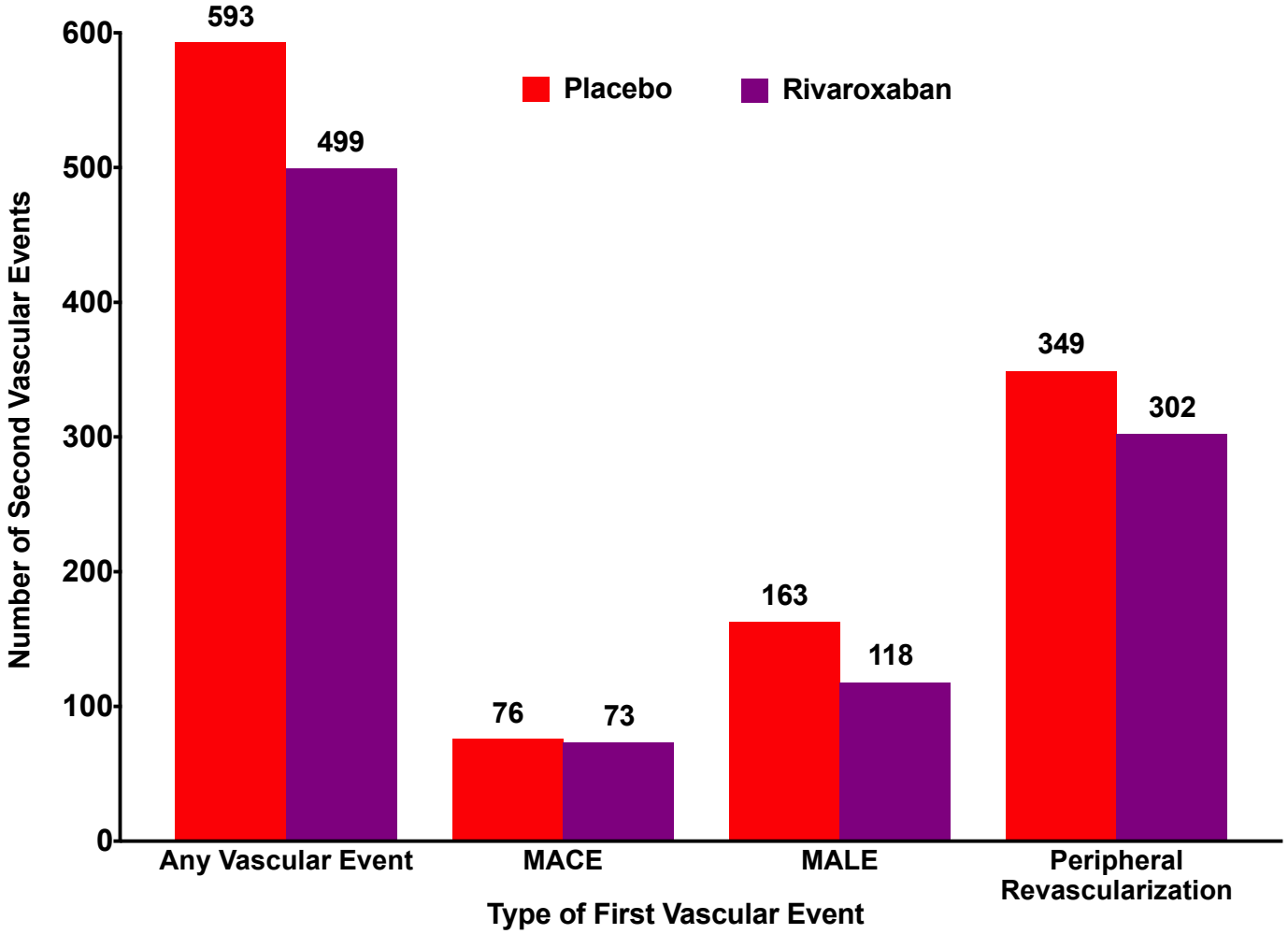
Categories of Total Events

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

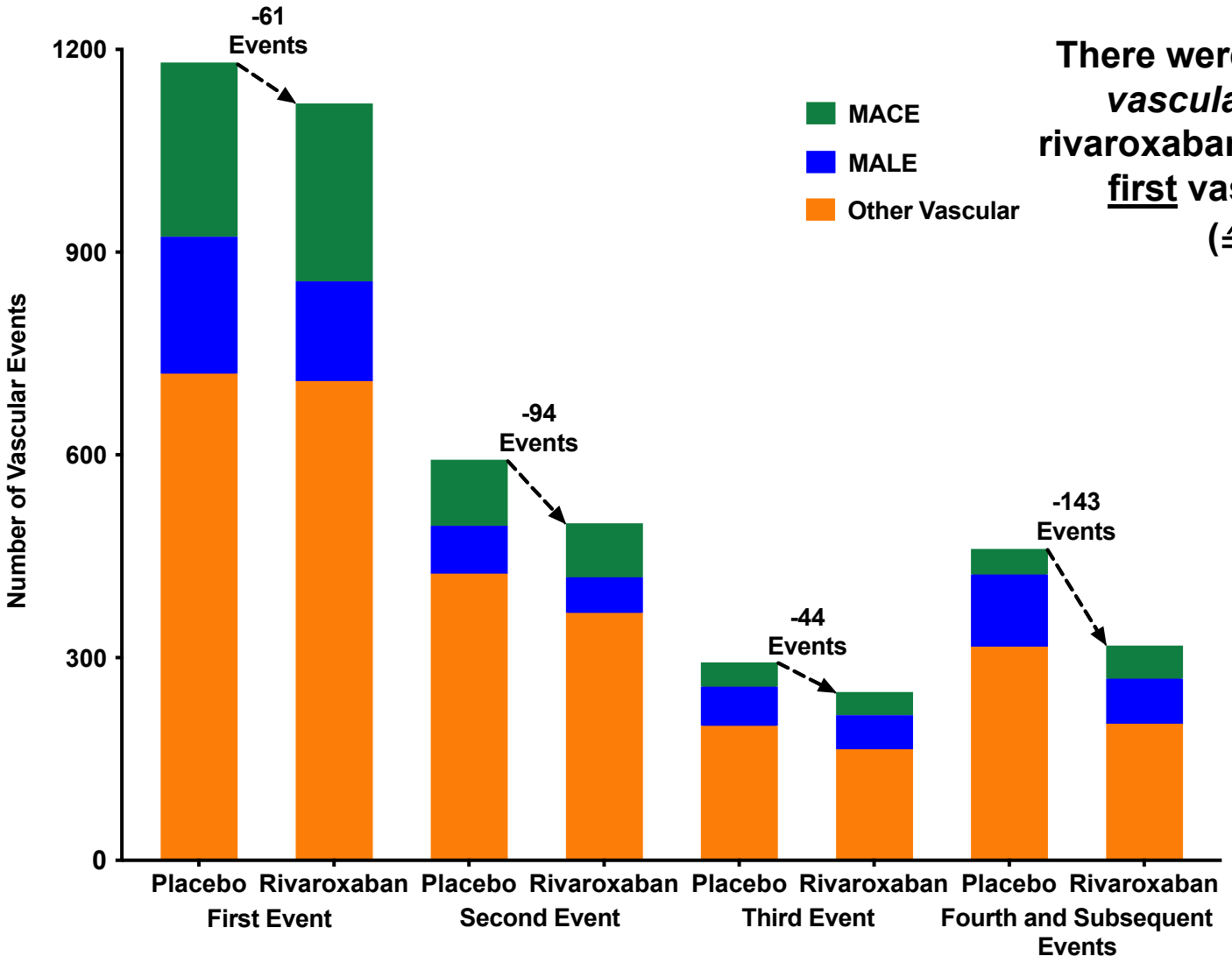
Second Vascular Event by Type of First Non-fatal Vascular Event

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



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

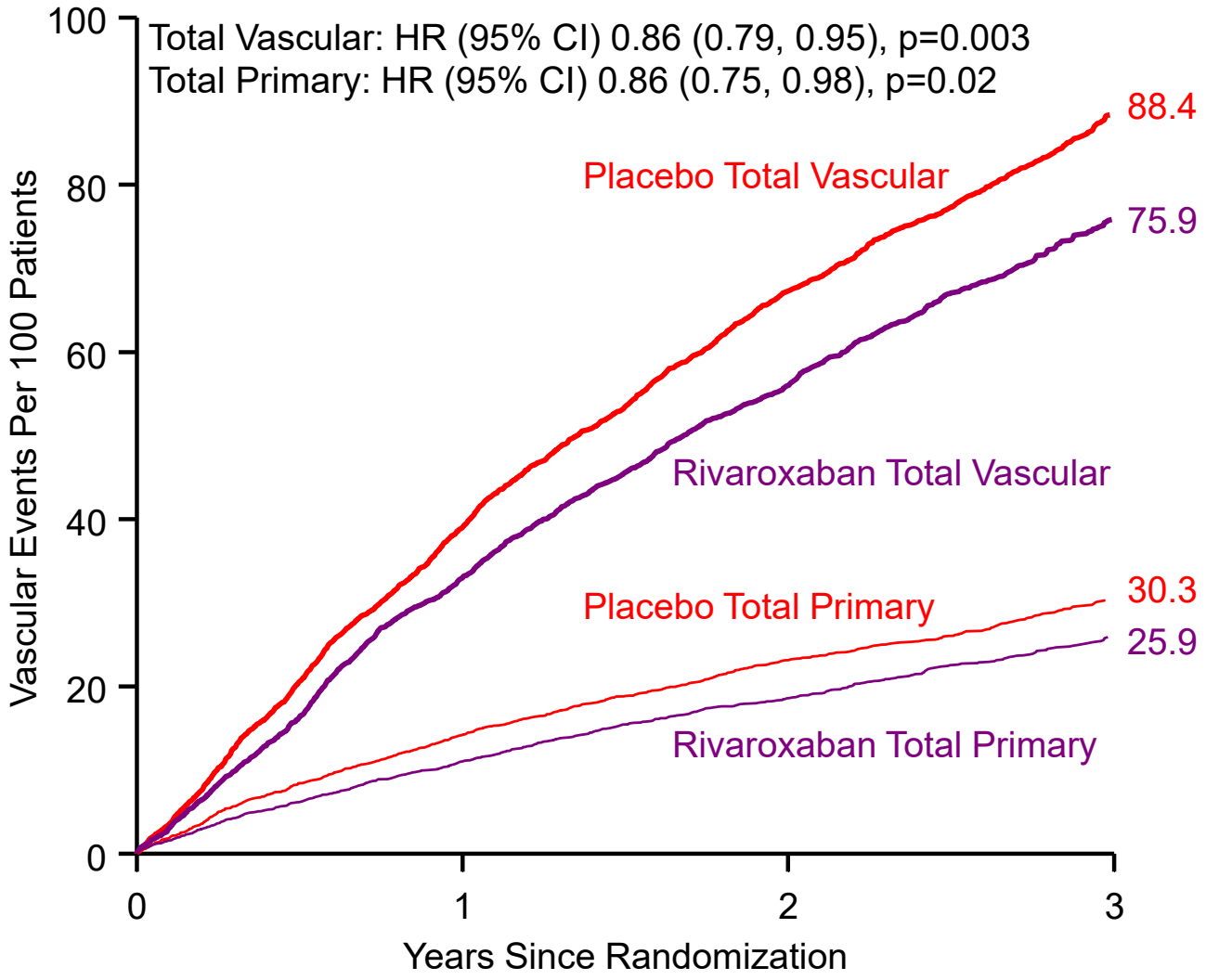
First and Subsequent Vascular Events



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

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

Accrual of Events per 100 Patients



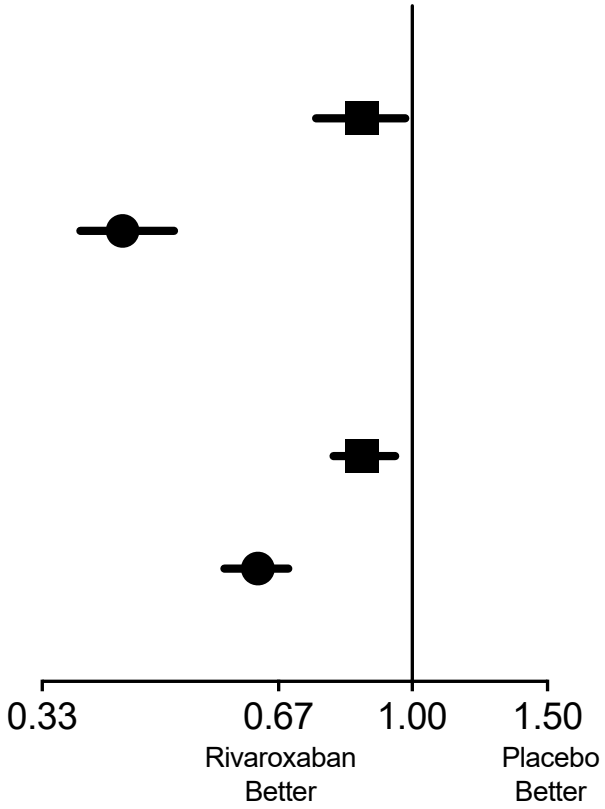
CPC Clinical Research

VOYAGER PAD

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)

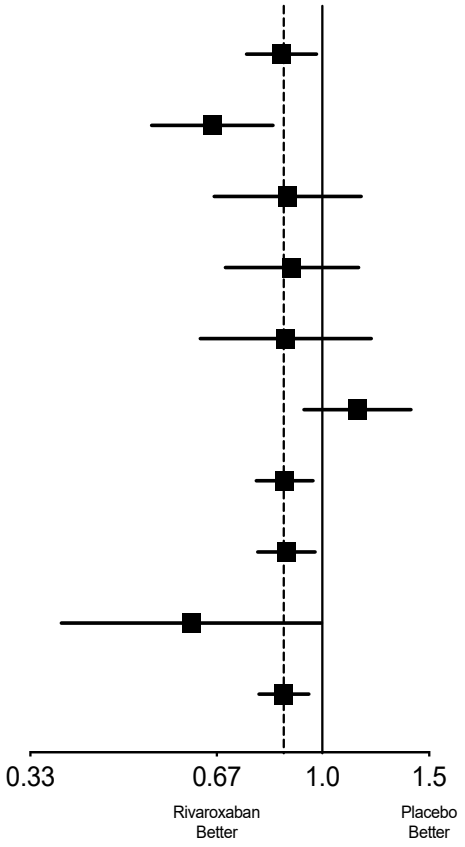


CPC Clinical Research

VOYAGER PAD

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

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***

JACC

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Thank you very much for your attention!

Results accepted for Publication at JACC