



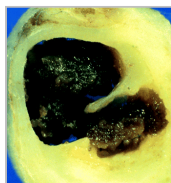
Reduction in Acute Limb Ischemia with Rivaroxaban versus Placebo in Peripheral Artery Disease after Lower Extremity Revascularization: Insights from VOYAGER PAD

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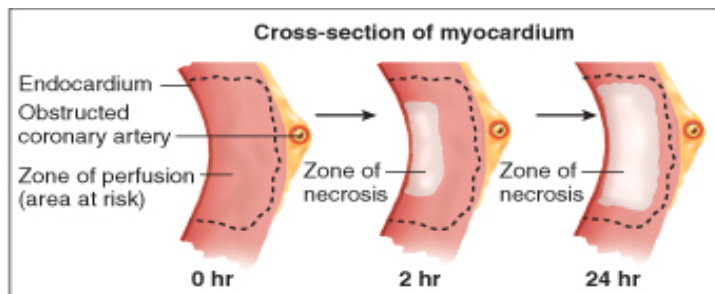
*European Society of Cardiology Virtual Congress 2020
Late-Breaking Science
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Background

ST elevation myocardial infarction



- Acute thrombotic occlusion of an artery threatening tissue loss
- **“Time Is Muscle”**
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication

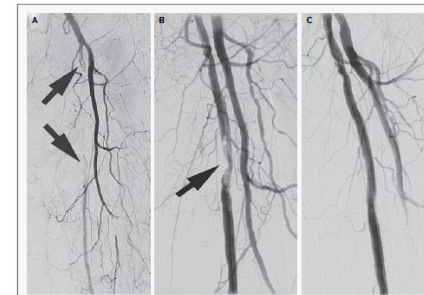


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- **Mortality at 1 year 8.1%¹**
- **Recurrent MACE at 1 year 3.4%¹**
- **HF at 1 year 7.4%¹**

1. Zeymer et al. EORP EU STEMI Registry 2019

Acute limb ischemia (ALI)



- Acute thrombotic occlusion of an artery threatening tissue loss
- **“Time Is Muscle”**
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication

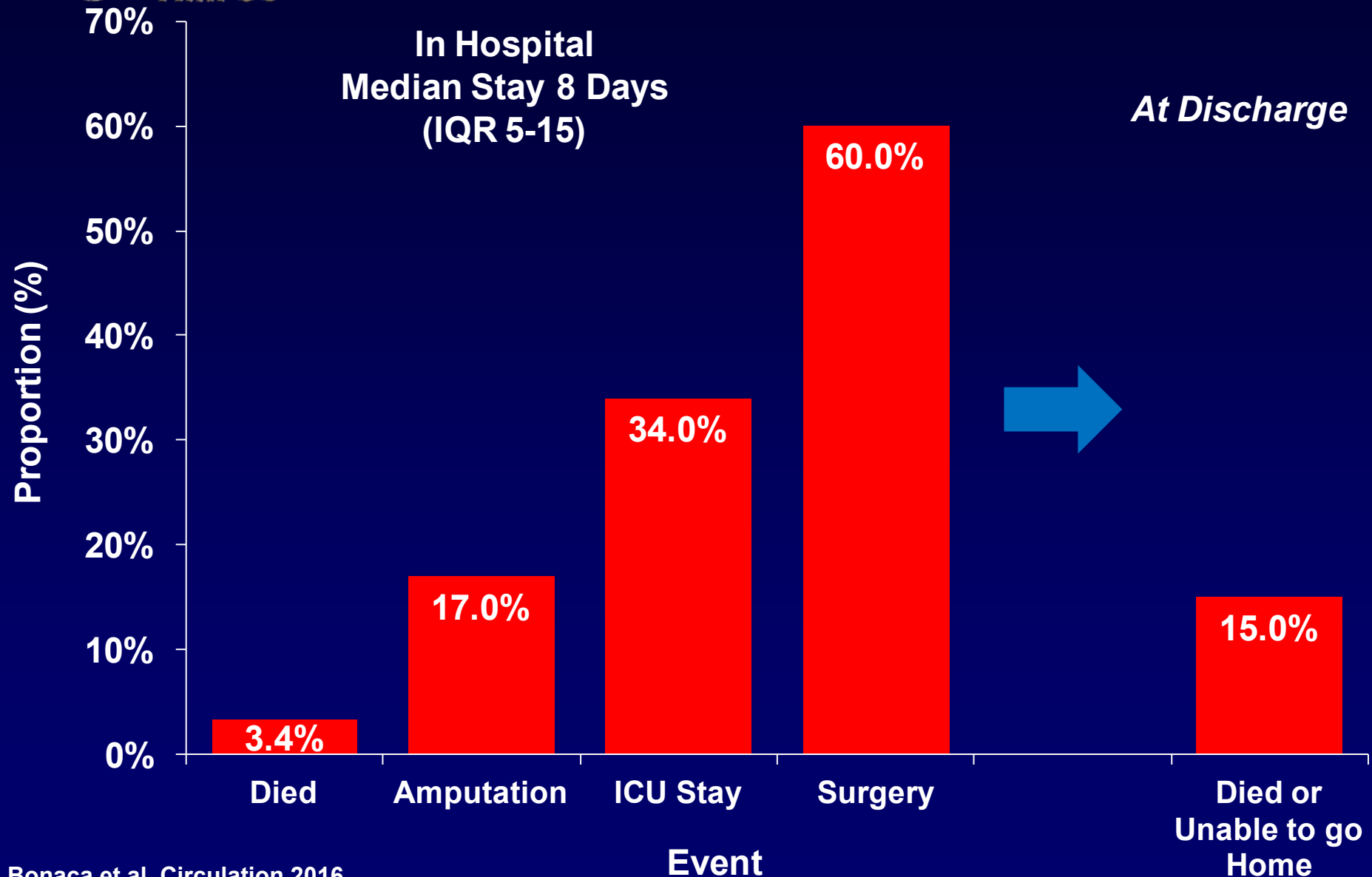


0 Hour → 24 Hour

- **Mortality at 1 year 12.1%²**
- **MACE 11.7%, Recurrent ALI 24% (1 yr)²**
- **Amputation at 1-year 27%²**

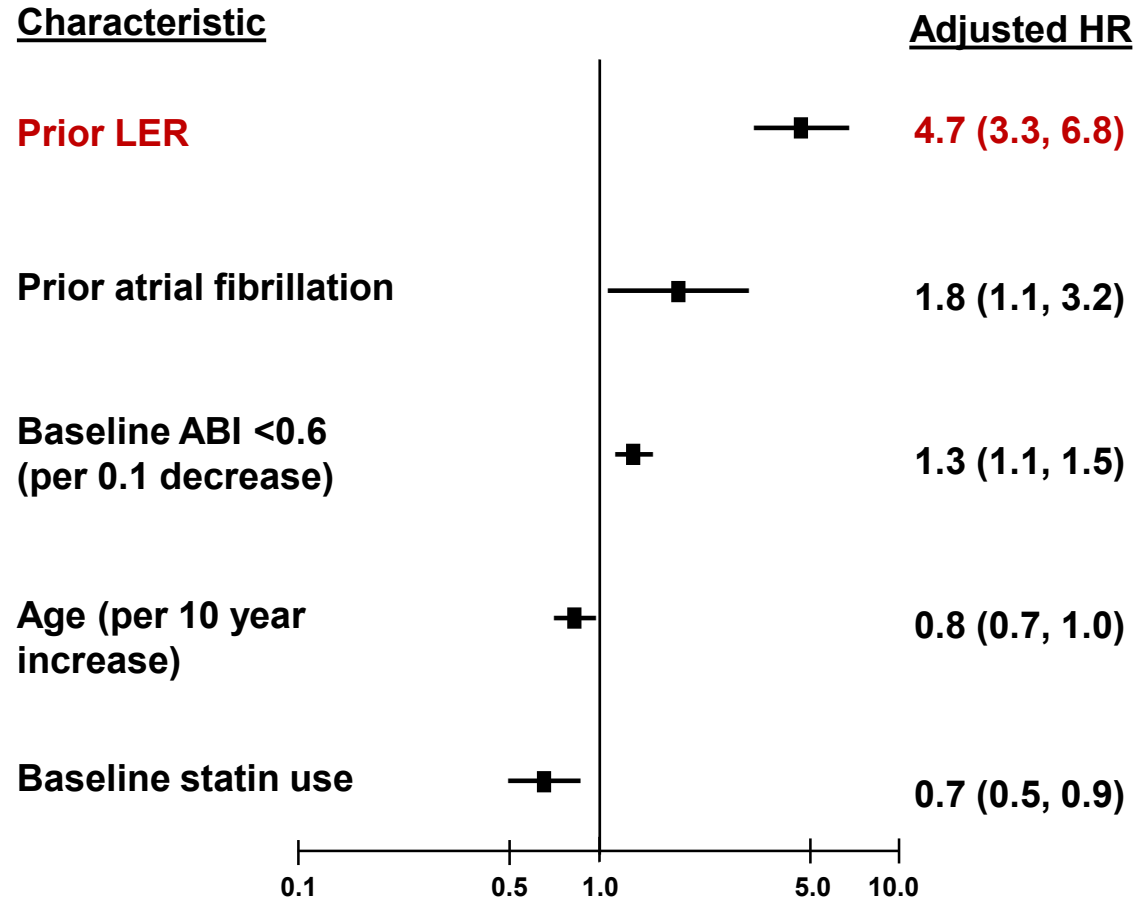
2. Bonaca et al. Circulation 2016

Outcomes at First Presentation with ALI

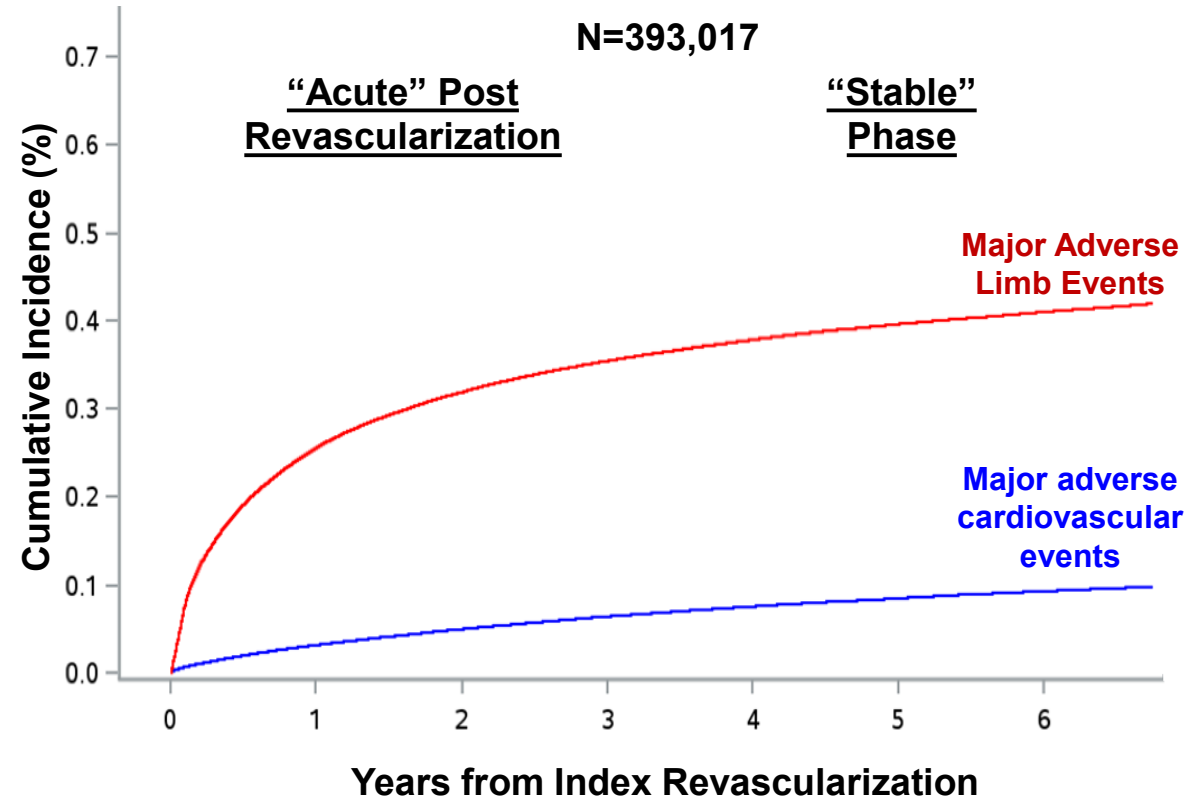


Lower extremity revascularization (LER) is associated with ALI

Factors Associated with ALI



Ischemic Risk in Patients Undergoing LER



An affiliate of:



VOYAGER PAD Trial Design

NCT02504216

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

ASA 100 daily for all Patients
Clopidogrel at Investigator's Discretion (up to 6 months)

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 28 Months

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

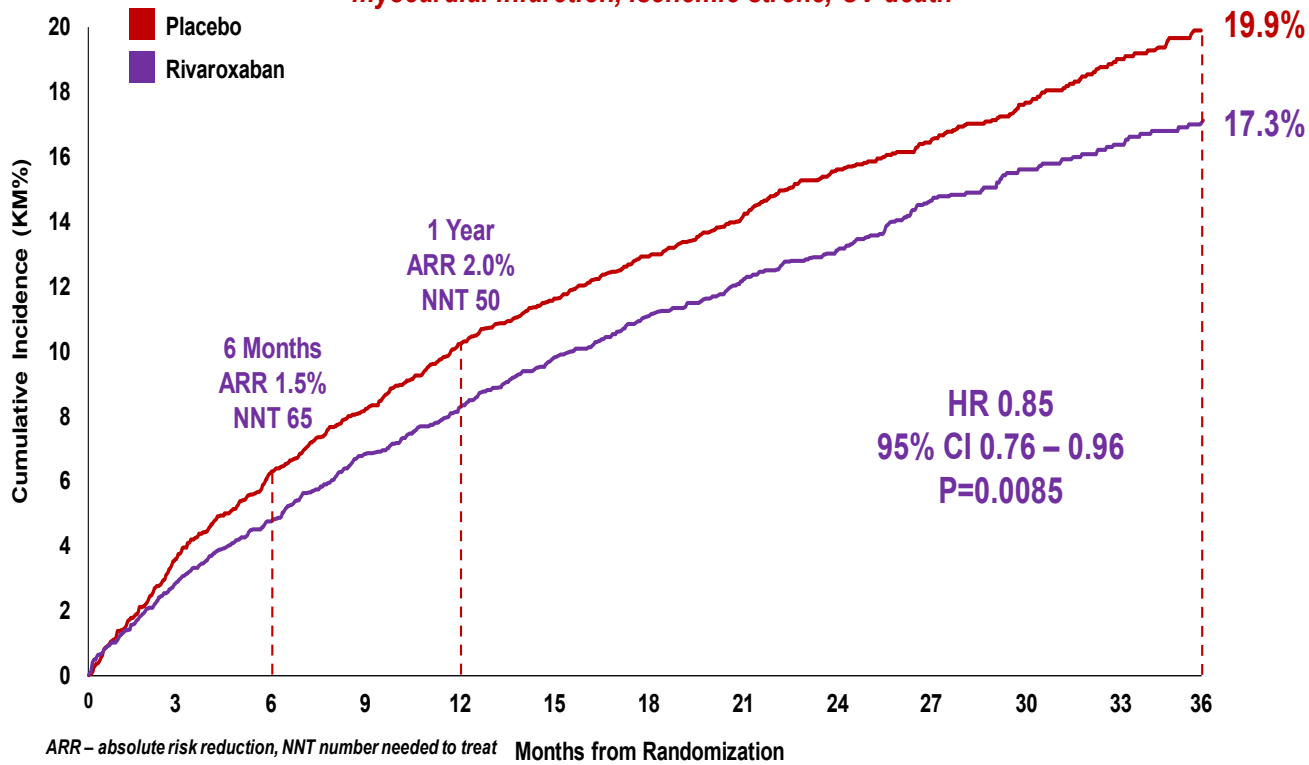
Principal Safety Outcome: TIMI Major Bleeding

*PAD defined as:
- Ischemic symptoms
(functional limitation, rest pain or ischemic ulceration) AND
- Imaging evidence of occlusion AND
- Abnormal ABI/TBI

VOYAGER PAD Primary Results

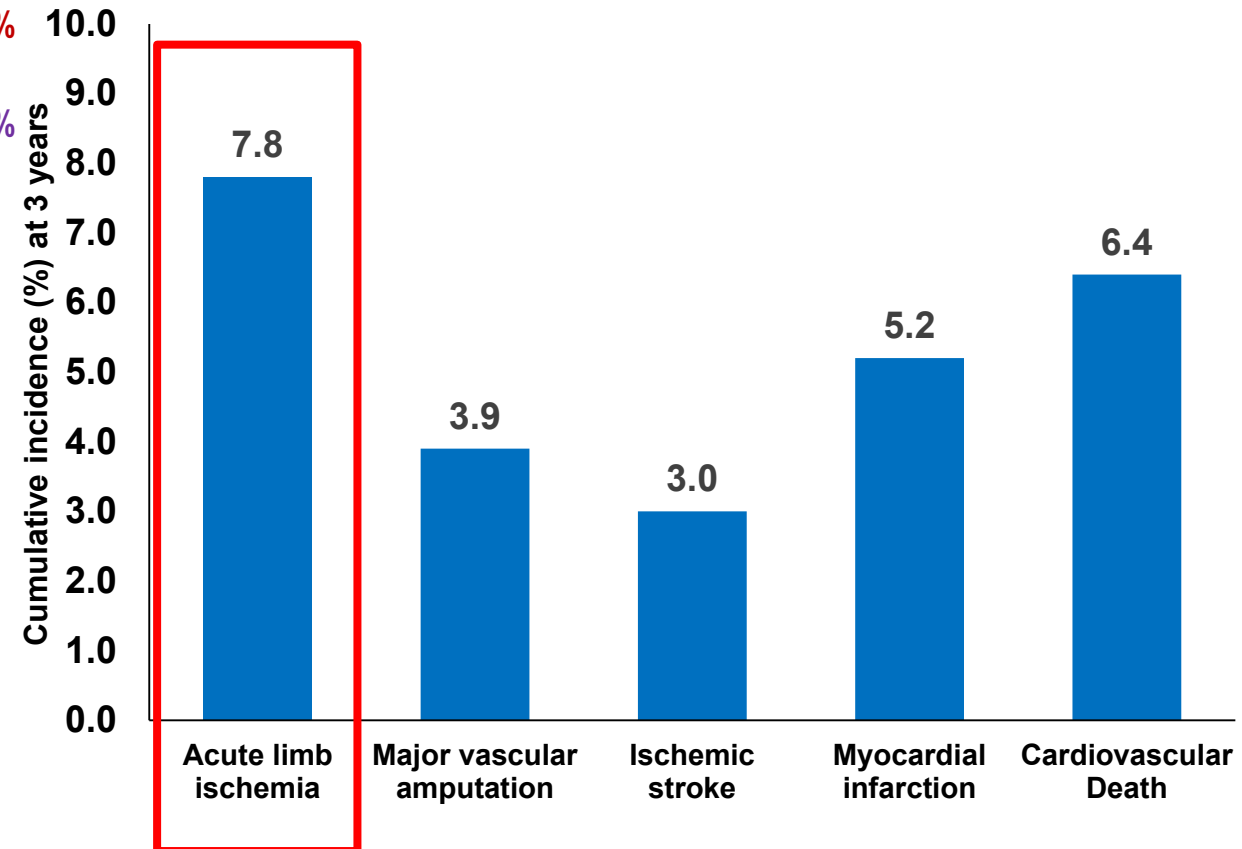
Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



Primary Endpoint Components in Placebo Patients

On background aspirin, statin (81%), and clopidogrel (59%)



Objectives

In PAD patients undergoing lower extremity revascularization (LER) for ischemic symptoms:

- To understand the natural history and clinical correlates of ALI
- To evaluate the effect of **rivaroxaban 2.5 mg twice daily plus low dose aspirin** versus **low dose aspirin alone** on ALI after LER
- To evaluate whether the efficacy of this strategy for ALI is consistent with regard to timing, background therapy, type of revascularization, and patient characteristics

Methods

- **ALI prospectively ascertained and independently adjudicated by a blinded committee using an established definition**
- **ALI defined as sudden worsening of limb perfusion requiring hospitalization and:**
 - **New pulse deficit with associated rest pain, pallor, paresthesia, or paralysis,**
AND EITHER
 - **Confirmation of arterial obstruction (imaging, hemodynamics, intraprocedural findings, pathologic evaluation) OR**
 - **Treatment with thrombolysis, thrombectomy, or urgent revascularization**
- **Prespecified secondary analysis of VOYAGER PAD**
- **Effect of rivaroxaban estimated with Cox proportional hazards model stratified according to LER type and clopidogrel use**

Baseline Characteristics

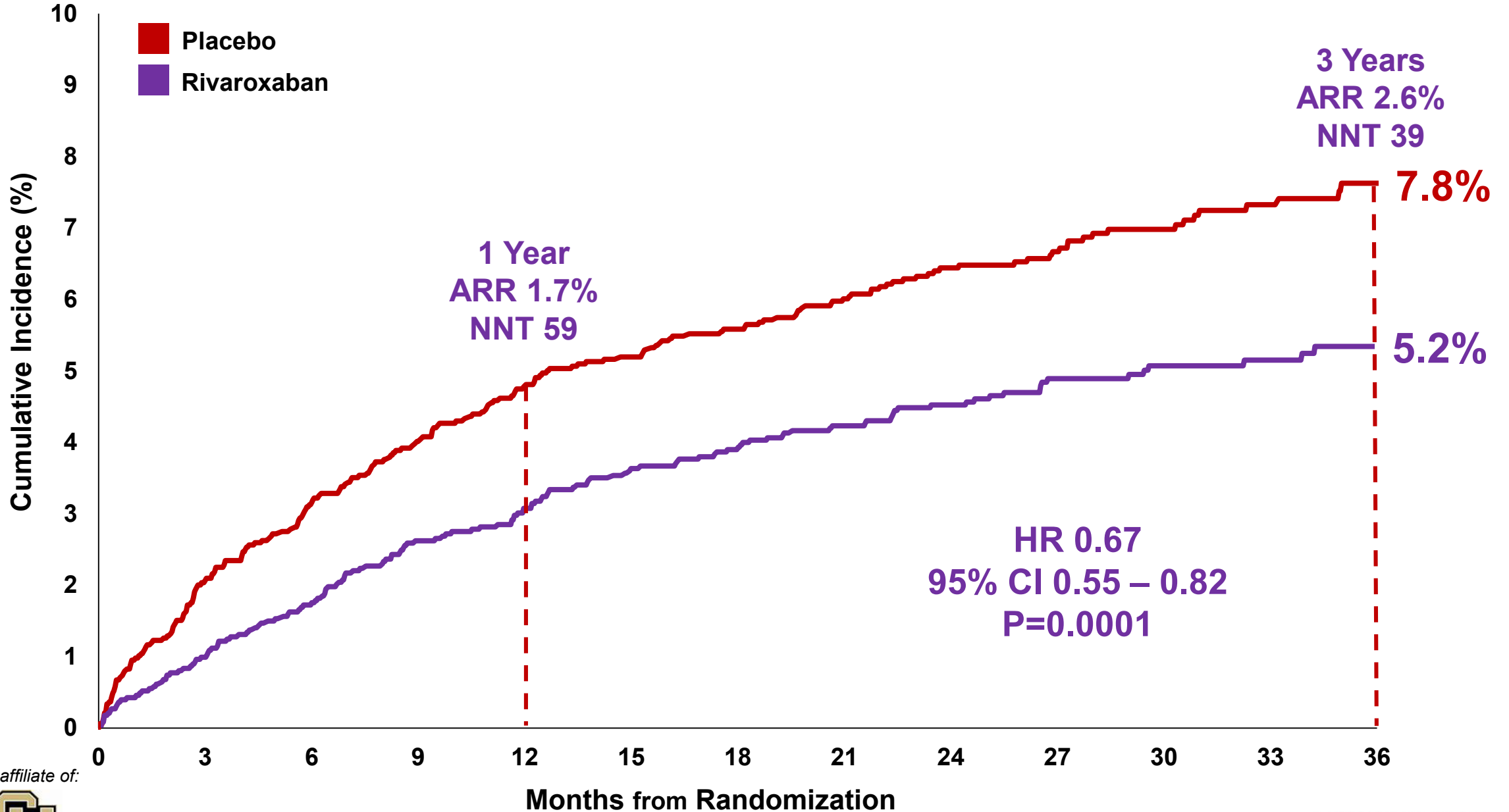
382 patients with 1st ALI by efficacy cut-off date, total 508 ALI events (126 recurrent ALI)

Characteristic at Randomization	With ALI N=382 %	Without ALI N=6182 %	P-value
Age, years median (IQR)	65 (59-71)	67 (61-73)	<0.01
Female	25	26	0.86
Caucasian	88	80	<0.01
Hypertension	79	82	0.28
Diabetes mellitus	32	41	<0.01
Hyperlipidemia	56	60	0.07
Current smoking	44	34	<0.01
eGFR < 60 ml/min/1.73m ²	16	20	0.04
Coronary artery disease	29	32	0.36
Baseline clopidogrel use	54	60	<0.01
Baseline statin use	75	80	0.02

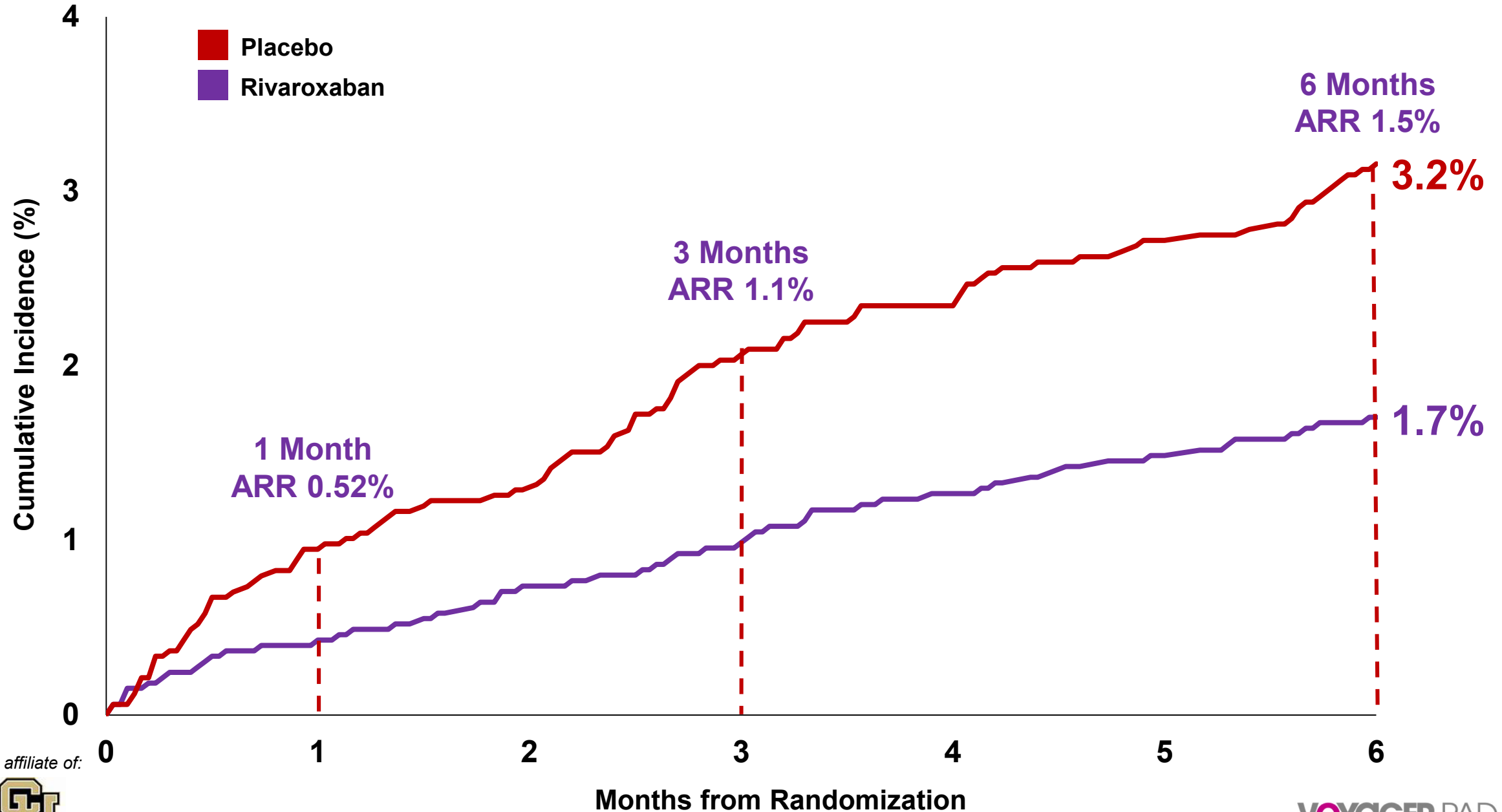
PAD & Procedural Characteristics

	With ALI N=382 %	Without ALI N=6182 %	P-value
<i>Peripheral Artery Disease History</i>			
Prior lower extremity revascularization	48	35	<0.01
Prior amputation	6	6	0.82
ABI at screening, median (IQR)	0.5 (0.4-0.6)	0.6 (0.4-0.7)	<0.01
<i>Indication for Revascularization</i>			
Critical limb ischemia	28	23	0.02
Claudication	72	77	0.02
<i>Type of Revascularization</i>			
Surgical	51	32	<0.01
Endovascular or hybrid	49	68	<0.01

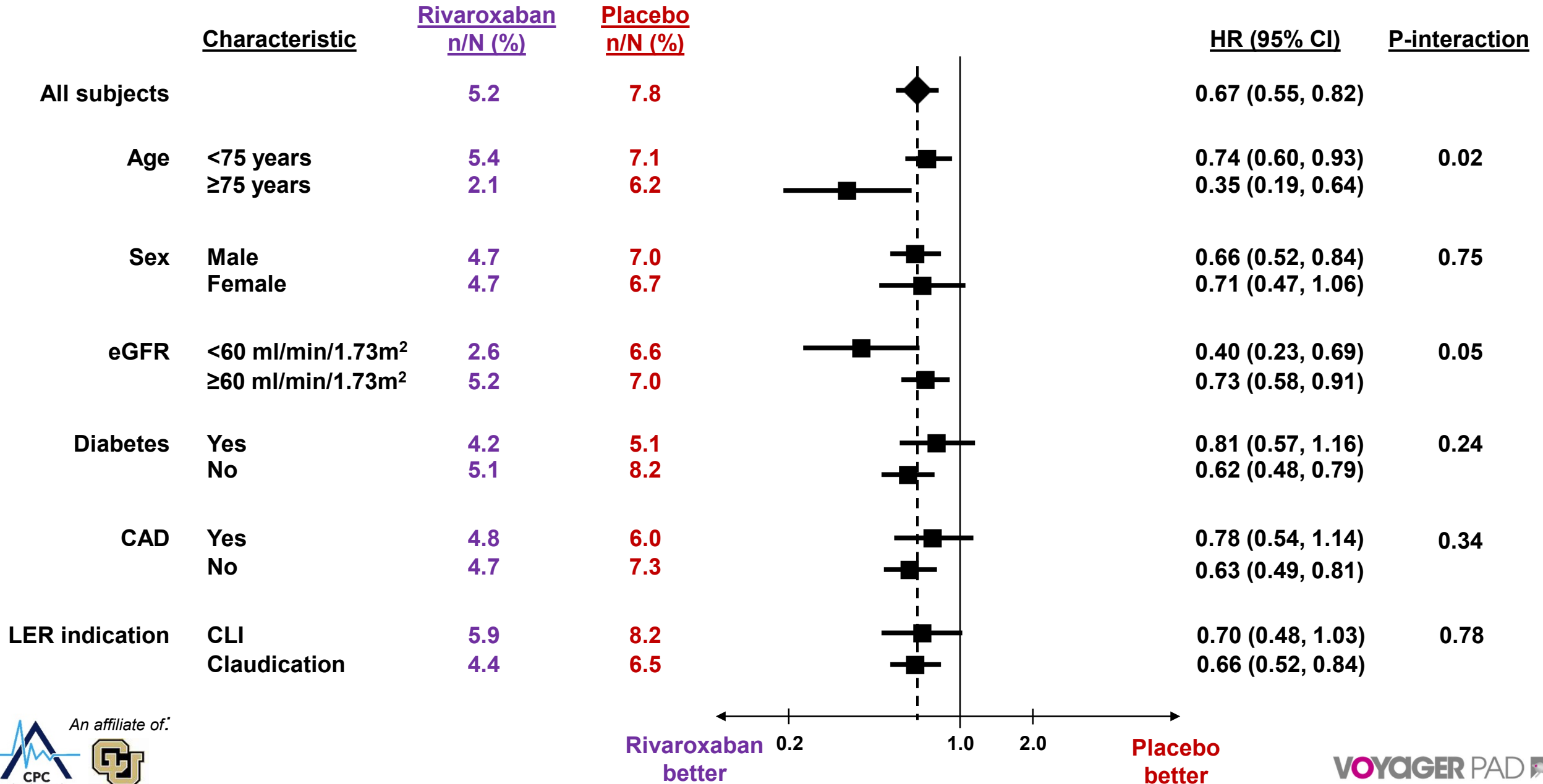
Effect of Rivaroxaban on ALI



Early Acute Limb Ischemia

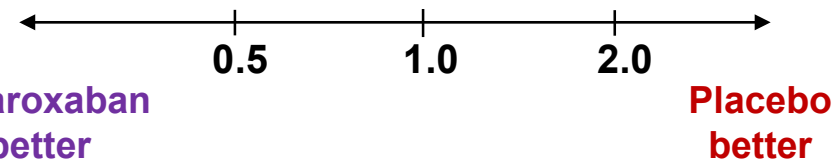


Effect of Rivaroxaban on ALI in Selected Subgroups (1)



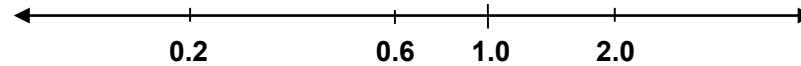
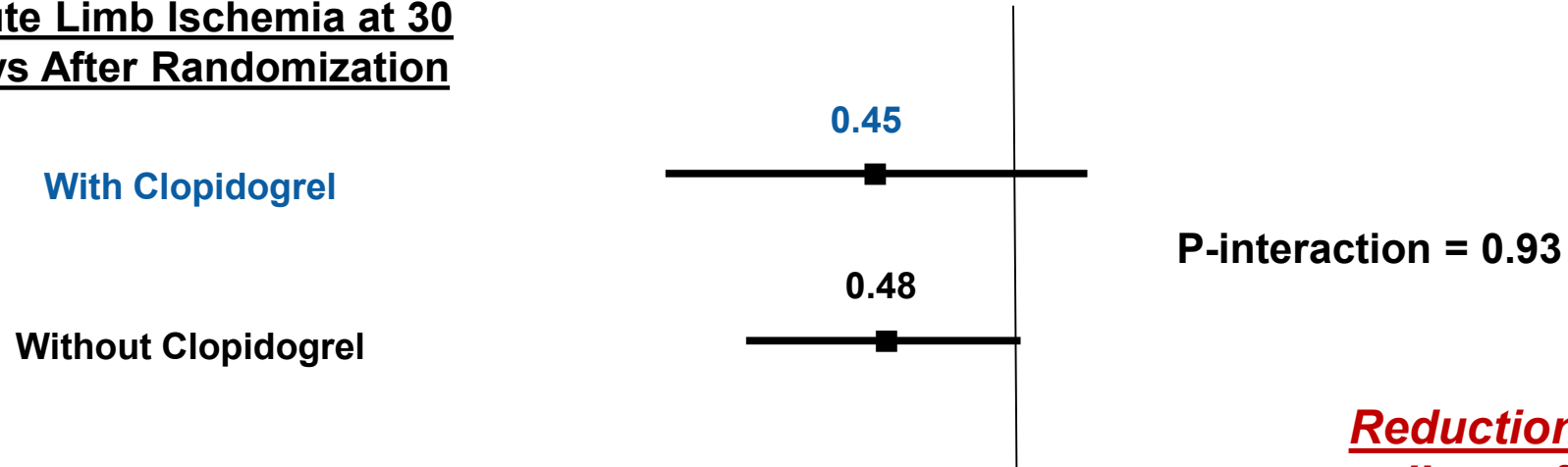
Effect of Rivaroxaban on ALI in Selected Subgroups (2)

<u>Characteristic</u>	<u>Rivaroxaban</u> <u>n/N (%)</u>	<u>Placebo</u> <u>n/N (%)</u>		<u>HR (95% CI)</u>	<u>P-interaction</u>
Qualifying revascularization					0.74
<i>Surgical</i>	7.4	10.3		0.70 (0.53, 0.93)	
<i>Endovascular</i>	3.4	5.2		0.65 (0.49, 0.87)	



Reduction in Early Acute Limb Ischemia with Rivaroxaban With and Without Clopidogrel

Acute Limb Ischemia at 30 Days After Randomization



Rivaroxaban Better

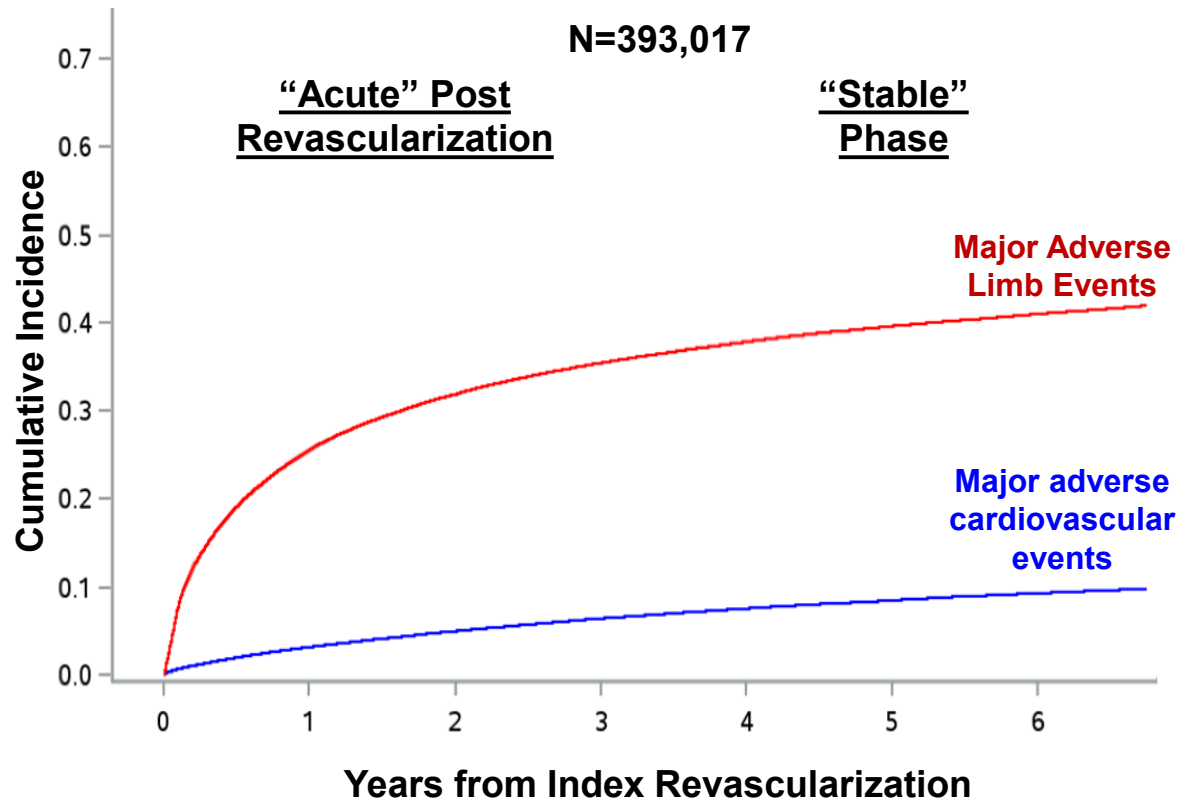
Placebo Better

Summary

- **ALI was the most frequent ischemic event after LER for symptomatic PAD**
- **ALI occurs early after LER, and the risk continues over time including recurrent events**
- **Rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone significantly reduces risk of ALI**
- **This benefit appears early, persists over time, and is consistent in major subgroups *including*:**
 - *Method of revascularization*
 - *Background clopidogrel use*

Conclusions

Risk in Patients Undergoing LER



- **ALI is a major cause of morbidity in PAD patients undergoing LER, particularly early after intervention**
- **Regardless of revascularization approach and background clopidogrel use, rivaroxaban plus aspirin should be considered early after LER to reduce ALI**

MI and ALI with and without CAD

Placebo
Rivaroxaban

HR 0.77
(0.55 – 1.08)
ARR 1.5%

P-interaction 0.33

HR 0.98
(0.70 – 1.35)
ARR 0.5%

P-interaction 0.34

HR 0.78
(0.54 – 1.14)
ARR 1.1%

HR 0.63
(0.49 – 0.81)
ARR 3.1%

