VOYAGER PAD
Efficacy and Safety of Rivaroxaban in Patients with PAD undergoing Recurrent Lower Extremity Revascularization

CIRSE
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University of Colorado Anschutz Medical Campus

CPC Clinical Research

An Academic Research Organization Affiliated with the University of Colorado School of Medicine

Disclosures

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PAD Patients with Prior Revascularization are at 4-Fold Risk of Acute Limb Ischemia

TRA2P-TIMI 50 PAD

Characteristic	Adjusted HR for ALI
Prior Peripheral Revascularization	HR 3.60 (2.10 – 6.18) P<0.001
ABI ≤ 0.5	HR 2.86 (1.81 – 4.51)
ABI ≥ 1.3	HR 2.71 (1.09 – 6.72)
Current Smoking	HR 2.17 (1.01 – 4.67) P=0.046

Bonaca et al. Circulation 2016

PEGASUS-TIMI 54 PAD

Prior revascularization
Adjusted HR for ALI 3.76
(2.26 – 6.25)
p<0.001

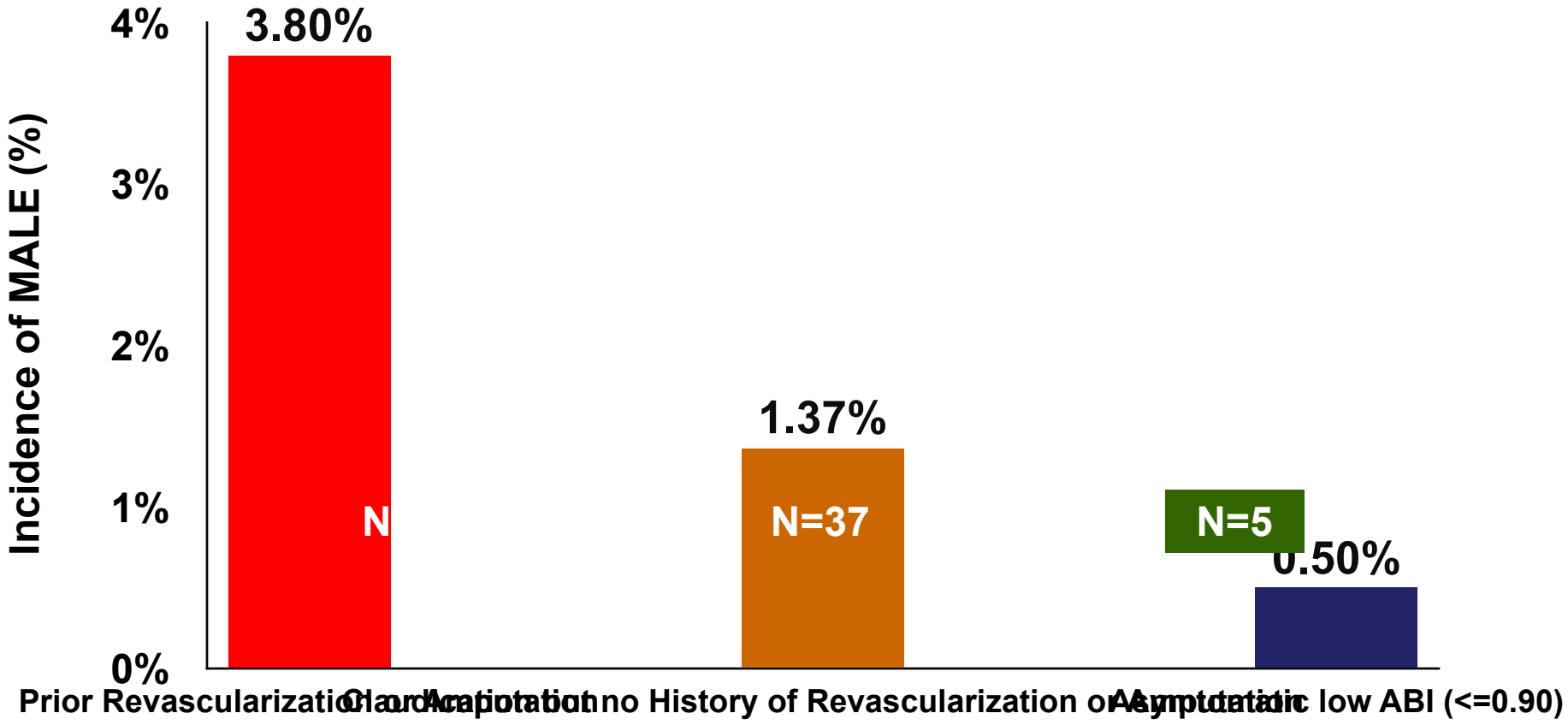
Bonaca et al. JACC 2016

EUCLID

Prior revascularization
Adjusted HR for ALI 4.23
(2.86 – 6.25)
p<0.001

Jones et al. Circulation 2016

Heterogeneity in Risk of Major Adverse Limb Events by Severity of Limb Disease



Bonaca MP, Creager MA. JACC 2018

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

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

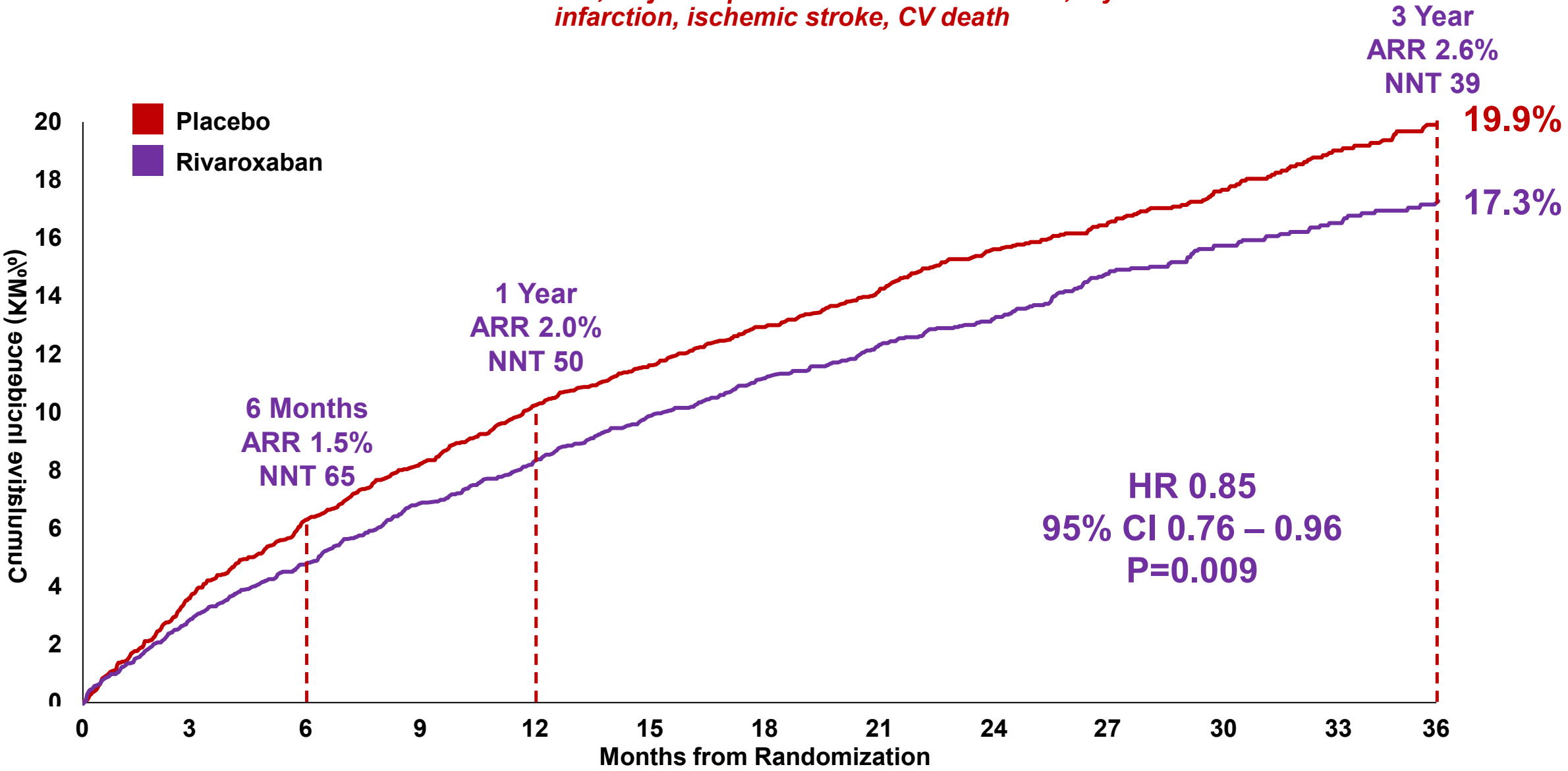
Principal Safety Outcome: TIMI Major Bleeding

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

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

Primary Endpoint

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



ARR – absolute risk reduction, NNT number needed to treat

Bonaca MP…Hiatt WR et al. NEJM 2020;382:1994–2004
Bonaca MP et al. Presented at ACC 2020. Slides available at
www.clinicaltrialresults.org/Slides/ACC%202020/Bonaca_VOYAGER-PAD.pptx

VOYAGER PAD

Hypotheses

Symptomatic PAD patients undergoing *recurrent* lower extremity revascularization (prior LER) versus those undergoing *first* LER:

- **Will have a higher rate of acute limb ischemia**
- **Will derive even greater benefits with a rivaroxaban plus aspirin strategy versus aspirin alone, particularly for acute limb ischemia**

Methods

- The presence of known prior LER was reported by investigators at baseline and was defined as any history of endovascular, hybrid or surgical LER

- Primary outcome is composite of acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, CV death

- COX model with interaction terms to assess for heterogeneity of efficacy and safety of rivaroxaban by prior LER status

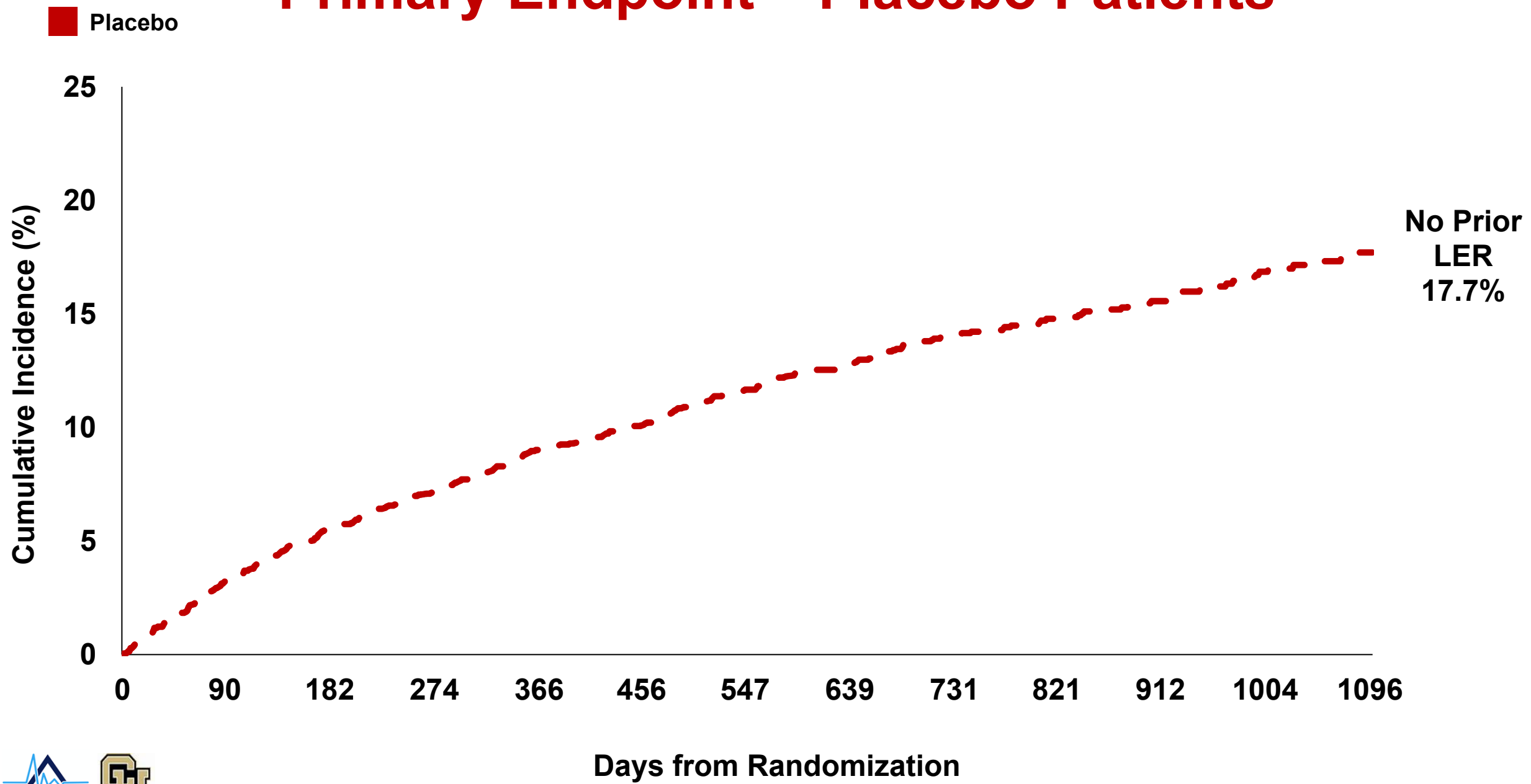
Baseline Characteristics

Baseline Characteristics	No Prior LER N=4226	Prior LER N=2336	P-value
Median age, median (IQR) – yr	67 (61 – 73)	67 (61 – 73)	0.74
Female no. (%)	26	25	0.46
White Caucasian no. (%)	81	80	<0.001
Hypertension (%)	79	86	<0.001
Diabetes Mellitus (%)	35	51	0.066
Hyperlipidemia (%)	54	71	<0.001
Current smoking (%)	35	33	<0.001
eGFR < 60 ml/min.1.73m^2	19	22	0.0259
Coronary artery disease (%)	28	38	<0.001
Carotid stenosis ≥ 50% (%)	6	11	<0.001
History of heart failure (%)	8	8	0.42

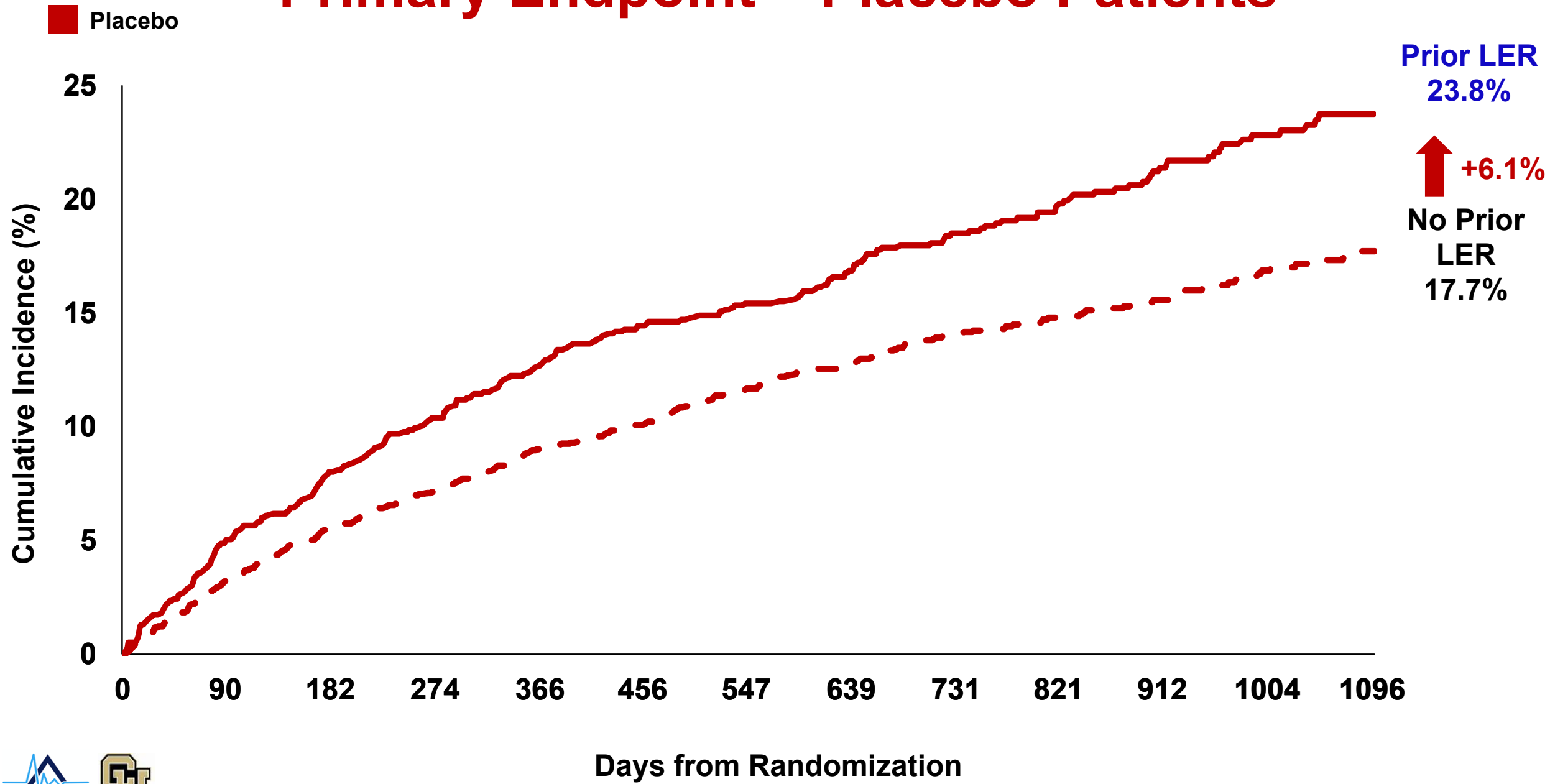
Baseline Characteristics

Baseline Characteristics	No Prior LER N=4226	Prior LER N=2336	P-value
Qualifying revascularization			**<0.001**
Surgical (%)	36	27	
Endovascular (%)	64	73	
Reason for revascularization			**<0.001**
Critical limb ischemia (%)	26	18	
PAD Characteristics			
Prior major amputation (%)	0.7	1.5	0.0026
Prior amputation (%)	5	7	0.0054
Prior bypass (%)	0	28	<0.001
Prior endovascular (%)	0	82	<0.001
ABI (median, IWR)	0.53 (0.40 – 0.65)	0.58 (0.45 – 0.70)	<0.0001
Medications			
Statins	77	85	<0.001
ACE/ARB	61	68	<0.001
Clopidogrel at randomization	47	56	<0.001

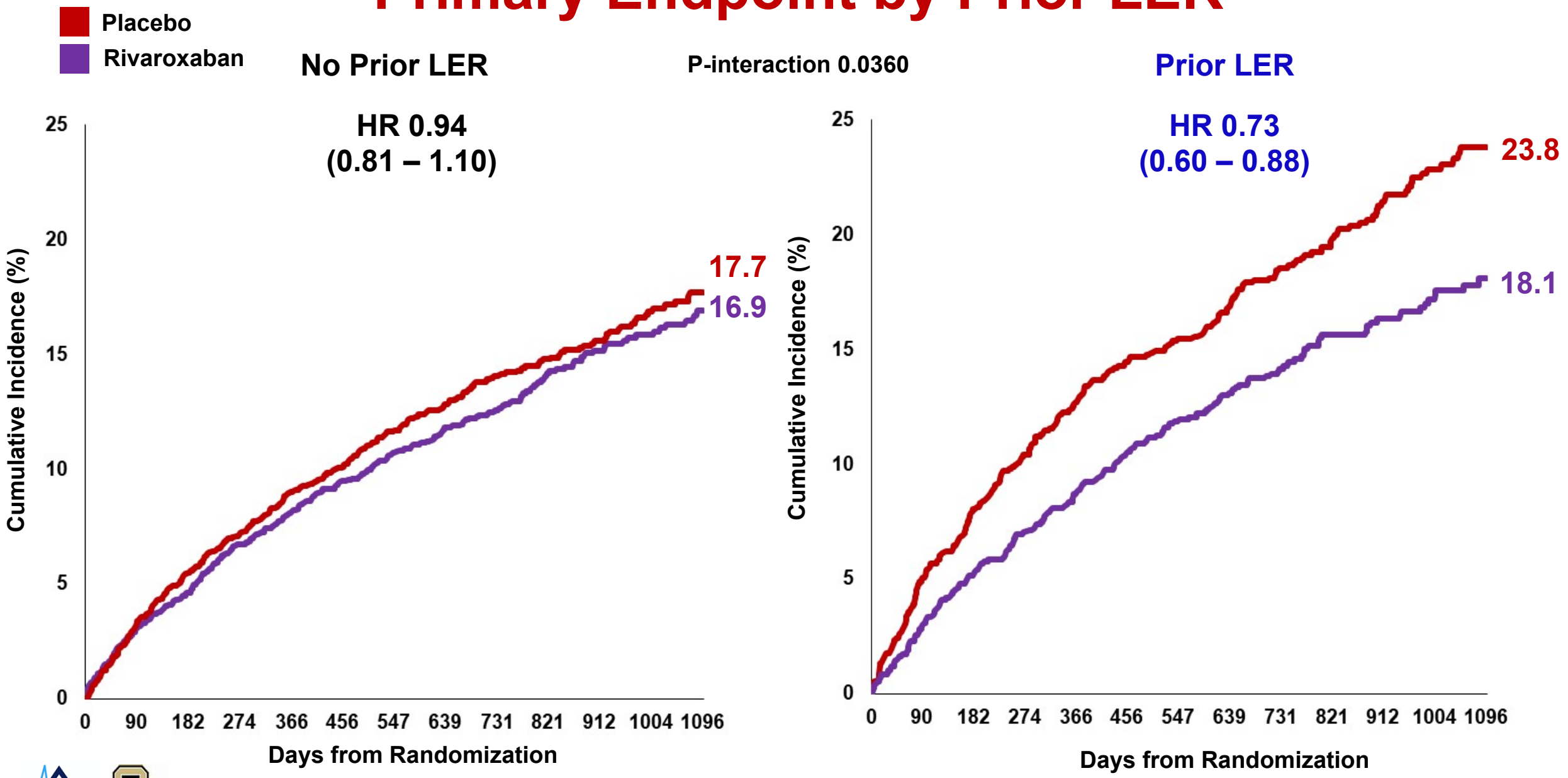
Primary Endpoint – Placebo Patients



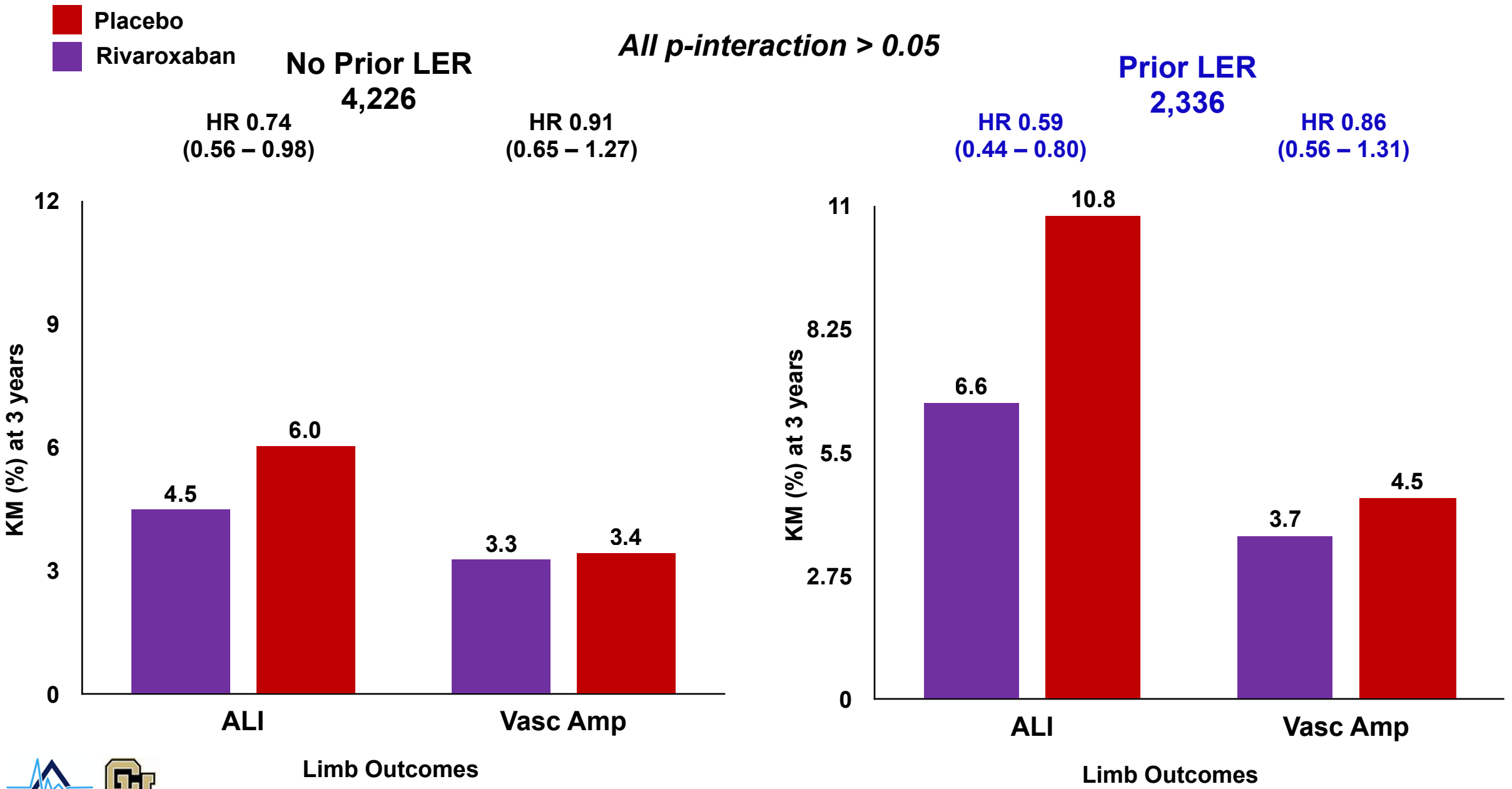
Primary Endpoint – Placebo Patients



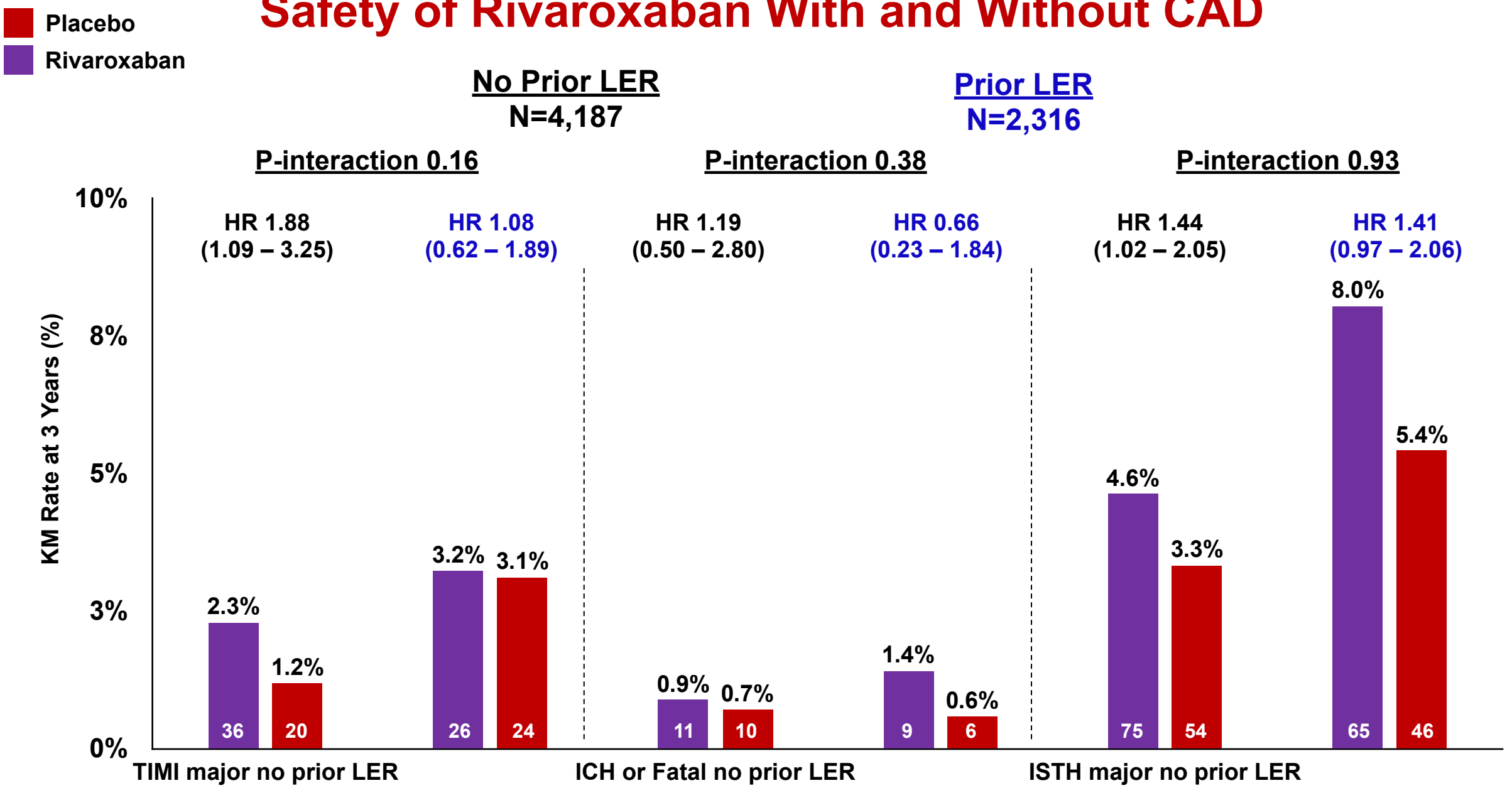
Primary Endpoint by Prior LER



Limb Outcomes with Rivaroxban with and without Prior LER



Safety of Rivaroxaban With and Without CAD



Summary

Symptomatic PAD patients undergoing *recurrent* lower extremity revascularization (prior LER) versus those undergoing *first* LER:

- **Have higher rates of ischemic events, particularly acute limb ischemia**
- **Derive even greater benefit of a rivaroxban plus aspirin versus aspirin alone for the composite of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death with the greatest absolute benefit for acute limb ischemia**

- **The safety of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of prior LER**

Conclusion

- **Prior analyses in stable PAD demonstrate that prior LER is an independent predictor of ALI even late after intervention**

- **The current analysis demonstrates that within this population, those with a multiple revascularizations are at higher risk than those who have undergone a first revascularization only and may derive particularly robust benefit from rivaroxaban plus aspirin versus aspirin alone**

- **These observations further demonstrate the heterogeneity of risk in the PAD population and may assist in clinical risk stratification and therapeutic decision making**