

# **Rivaroxaban plus Aspirin versus Aspirin Alone After Endovascular Revascularization for Symptomatic PAD: Insights from VOYAGER PAD**

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VOYAGER PAD Investigators**

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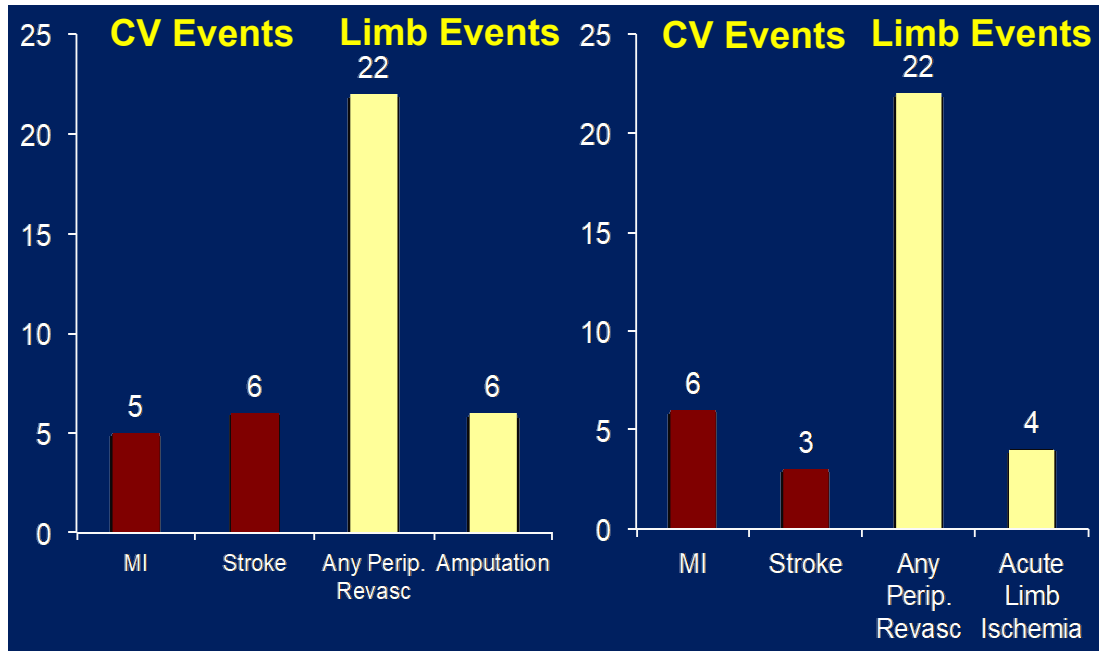
# Disclosures

- **Research Grants:** Amgen, Bayer, HeartFlow, Janssen, Novartis, NHLBI, Phillips
- **Advisory Board:** Bayer, Janssen, HeartFlow

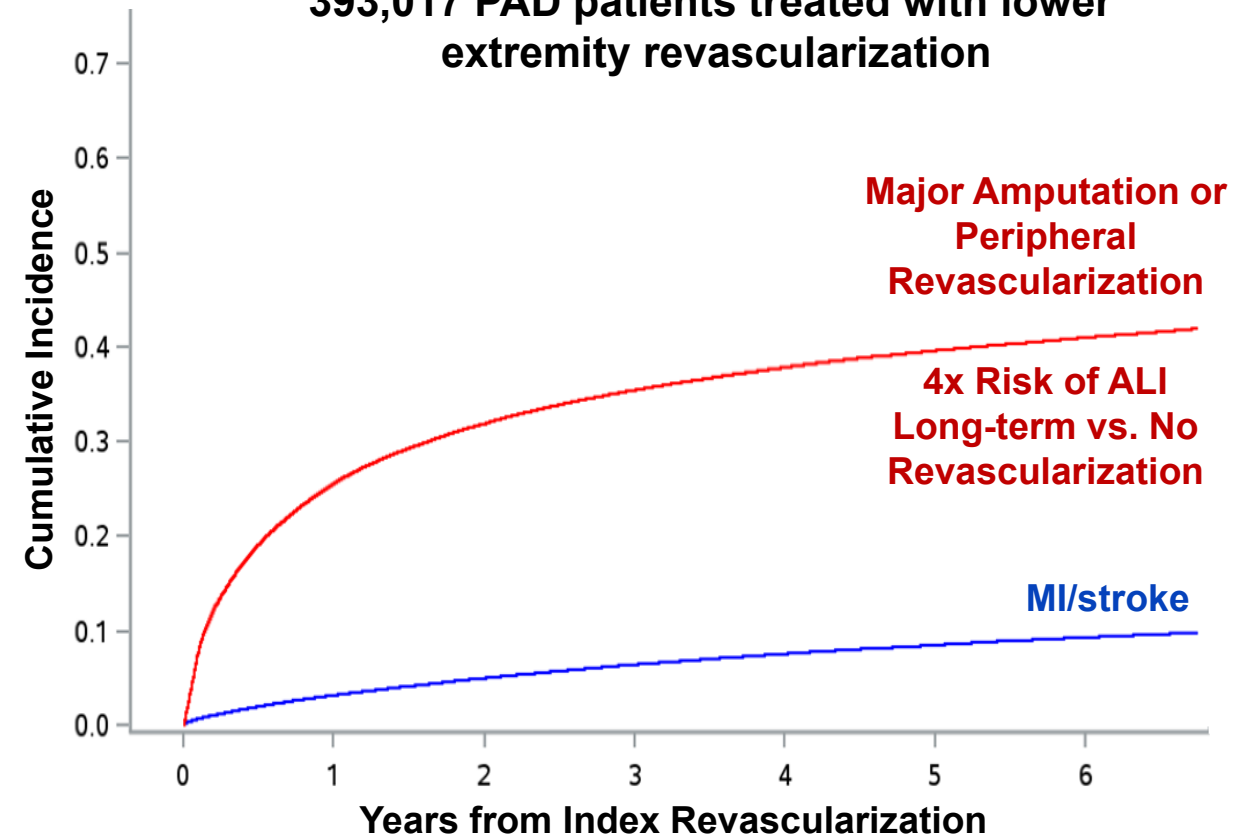
# Peripheral Artery Disease (PAD) and Risk of Arterial Thrombosis

4 Year Events in REACH Registry

3 Year Events in TRA2P-TIMI 50



393,017 PAD patients treated with lower extremity revascularization



# Background

Although dual antiplatelet therapy (DAPT) is often used following endovascular LER, this strategy is not supported by any class 1A PAD guideline recommendations.

- Class IIB recommendation for dual antiplatelet therapy for endovascular and surgical procedures (ACC/AHA and ESC)
- Class IIA with C level of evidence for endovascular procedures (ESC)
- Use of dual antiplatelet therapy is discouraged by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.

**Hence, despite the high risk, there is no agreed upon proven antithrombotic strategy that has demonstrated efficacy for reducing major adverse limb and cardiovascular events after endovascular revascularization for symptomatic peripheral artery disease**

# 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

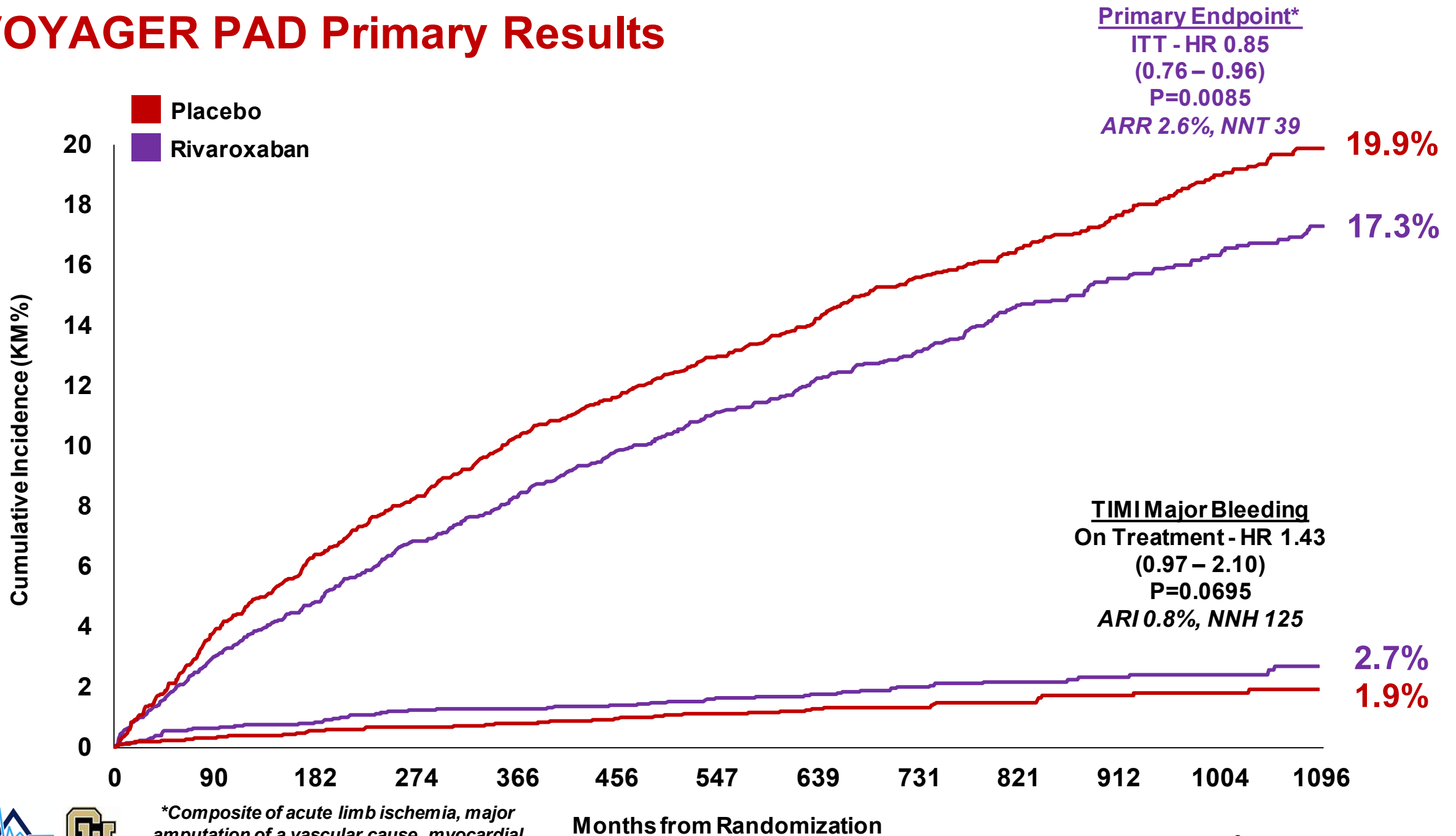
Follow up Q6 Months, Event Driven, Median f/u 28 Months

**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



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



# Objectives and Methods

## Objectives

- To evaluate whether the efficacy and safety of rivaroxaban 2.5 mg twice daily with aspirin vs. aspirin alone is consistent in those stratified to endovascular revascularization including:
  - **Efficacy**
    - *Primary efficacy endpoint and principal safety outcome*
    - *Key secondary efficacy outcomes of **major adverse limb events, including unplanned index limb revascularization** due to the high risk of recurrent procedures in this population*
  - **Safety**
    - Principal safety outcome (on-treatment) of TIMI major bleeding
    - Secondary outcome for safety of ISTH major bleeding
- Outcomes adjudicated by a blinded CEC

# Baseline Characteristics

Characteristic	Endovascular N=4293	Surgical N=2271	P-value
<b>Age &amp; Gender – n (%)</b>			
Mean age – Yrs (SD)	68 (8.6)	66 (8.1)	<0.001
Female	1238 (28.8)	466 (20.5)	<0.001
<b>Medical History – n (%)</b>			
Hypertension	3517 (81.9)	1825 (80.4)	0.134
Diabetes Mellitus	1920 (44.7)	709 (31.2)	<0.001
Hyperlipidemia	2766 (64.4)	1173 (51.7)	<0.001
Chronic Kidney Disease	507 (11.8)	99 (4.4)	<0.001
Current Smoker	1442 (33.6)	837 (36.9)	<0.001
<b>Cardiac Disease – n (%)</b>			
Coronary Artery Disease	1387 (32.3)	680 (29.9)	0.054
Percutaneous Coronary Intervention	645 (15.0)	207 (9.1)	<0.001
Coronary Artery Bypass Graft	384 (8.9)	150 (6.6)	0.001
Heart Failure	320 (7.5)	219 (9.6)	0.003



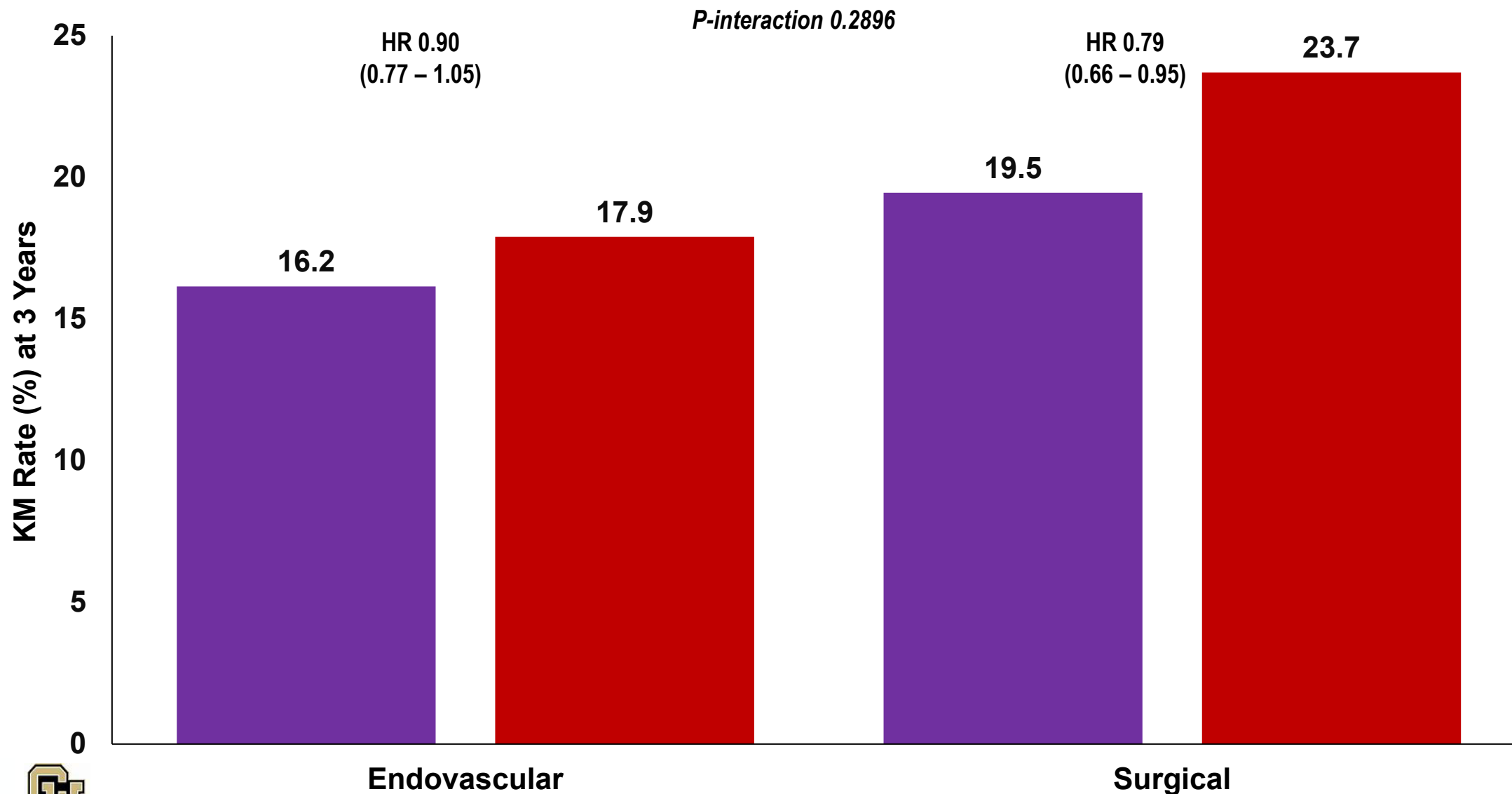
<b>Baseline Medications</b>	<b>Endovascular N=4293</b>	<b>Surgical N=2271</b>	<b>P-value</b>
<b>Medication – n/N (%)</b>			
<b>Aspirin (Non-Study)</b>	<b>2951 (68.7)</b>	<b>1317 (58.0)</b>	<b>0.056</b>
<b>Clopidogrel at Randomization</b>	<b>2964 (69.0)</b>	<b>349 (15.4)</b>	<b>&lt;0.001</b>
<b>Dual Anti-Platelet Therapy</b>	<b>2299 (53.6)</b>	<b>268 (11.8)</b>	<b>&lt;0.001</b>
<b>Beta-Blocker</b>	<b>1876 (43.7)</b>	<b>917 (40.4)</b>	<b>0.010</b>
<b>Statin</b>	<b>3509 (81.7)</b>	<b>1740 (76.6)</b>	<b>&lt;0.001</b>
<b>ACE Inhibitor / ARB</b>	<b>2806 (65.4)</b>	<b>1353 (59.6)</b>	<b>&lt;0.001</b>

<b>Geography</b>		<b>P-value</b>
<b>Region – n/N (%)</b>		<b>&lt;0.001</b>
<b>North America</b>	<b>542 (12.6)</b>	<b>152 (6.7)</b>
<b>Western Europe</b>	<b>1324 (30.8)</b>	<b>502 (22.1)</b>
<b>Eastern Europe</b>	<b>1316 (30.7)</b>	<b>1283 (56.5)</b>
<b>Asia Pacific</b>	<b>787 (18.3)</b>	<b>174 (7.7)</b>
<b>South America</b>	<b>324 (7.5)</b>	<b>160 (7.0)</b>

<b>PAD and Procedural Characteristics</b>	<b>Endovascular N=4293</b>	<b>Surgical N=2271</b>	<b>P-value</b>
<b>PAD Severity</b>			
<b>ABI at Screening, Mean (SD)</b>	<b>0.57 (0.18)</b>	<b>0.47 (0.19)</b>	<b>&lt;0.001</b>
<b>ABI at 1 Mth Post-Procedure, Mean (SD)</b>	<b>0.93 (0.18)</b>	<b>0.87 (0.21)</b>	<b>&lt;0.001</b>
<b>Critical Limb Ischemia – n/N (%)</b>	<b>837 (19.5)</b>	<b>696 (30.7)</b>	<b>&lt;0.001</b>
<b>Prior Amputation – n (%)</b>			
<b>Prior Major Amputation</b>	<b>40 (0.9)</b>	<b>25 (1.1)</b>	<b>0.514</b>
<b>Prior Minor Amputation</b>	<b>202 (4.7)</b>	<b>84 (3.7)</b>	<b>0.065</b>
<b>History of Prior Limb Revascularization – n (%)</b>			
<b>Peripheral PTA</b>	<b>1510 (35.2)</b>	<b>398 (17.5)</b>	<b>&lt;0.001</b>
<b>Surgical Bypass</b>	<b>283 (6.6)</b>	<b>379 (16.7)</b>	<b>&lt;0.001</b>
<b>Initiation of Study Drug, Mean Days (SD)</b>	<b>4.5 (2.8)</b>	<b>6 (2.5)</b>	<b>&lt;0.001</b>
<b>Target Lesion Length (cm)</b>			
<b>≥ 15</b>	<b>1263 (30.3)</b>	<b>989 (45.5)</b>	<b>&lt;0.05</b>
<b>5 – &lt; 15</b>	<b>1799 (43.1)</b>	<b>814 (37.4)</b>	<b>&lt;0.05</b>
<b>&lt; 5</b>	<b>1111 (26.6)</b>	<b>373 (17.1)</b>	<b>&lt;0.05</b>

# Primary Endpoint by Endovascular vs. Surgical

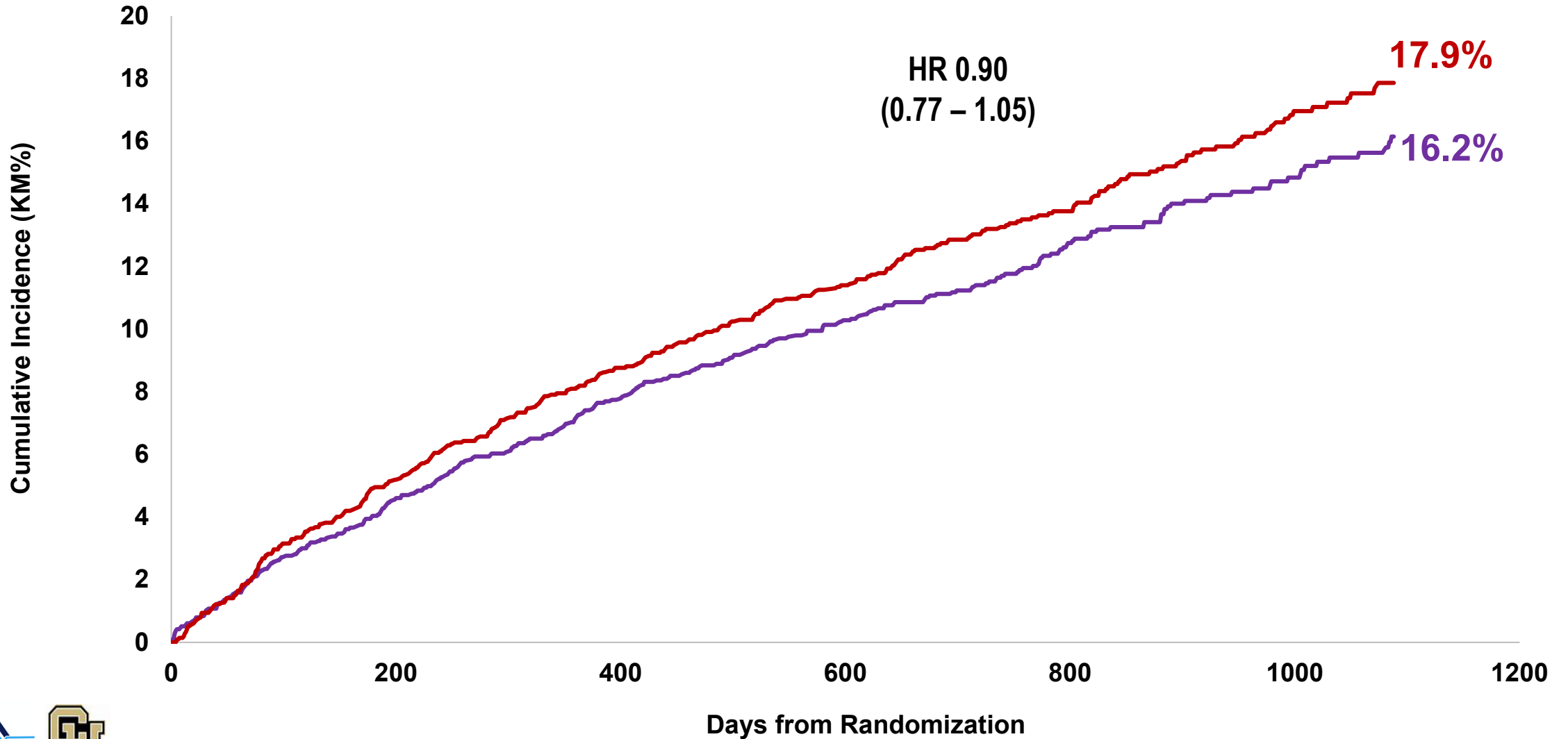
Placebo  
Rivaroxaban



■ Placebo  
■ Rivaroxaban

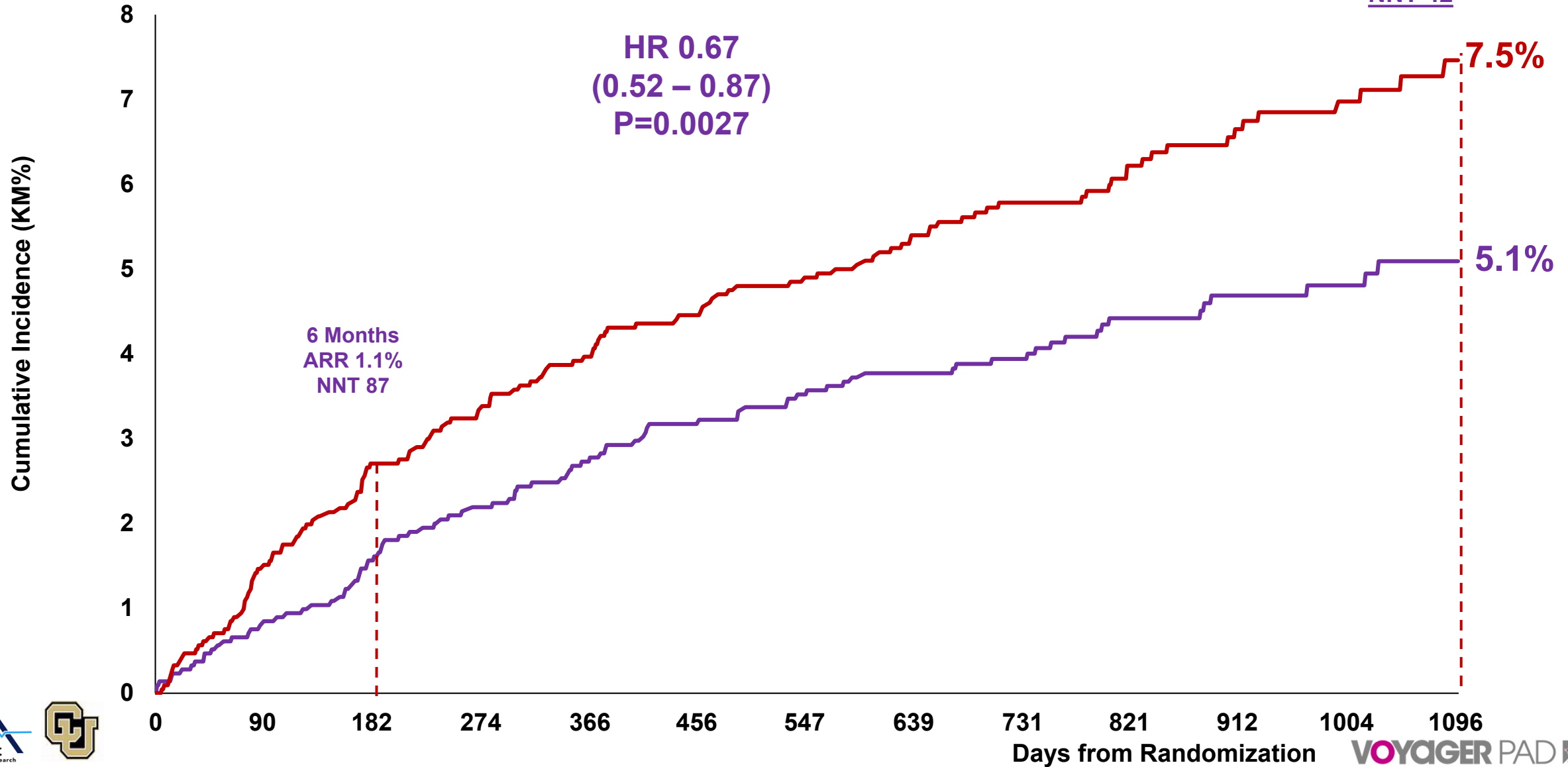
# Endovascular patients

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



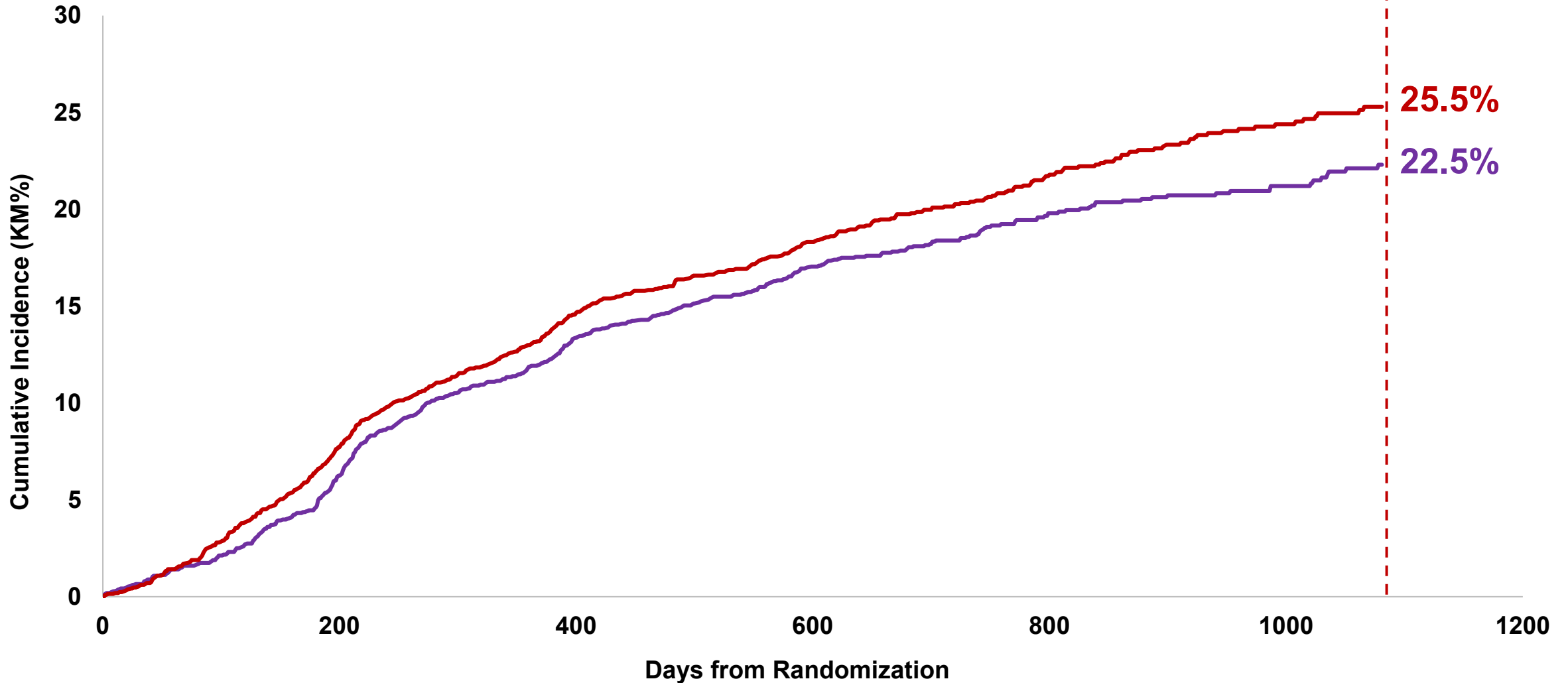
# Endovascular patients - Major Adverse Limb Events

■ Placebo  
■ Rivaroxaban



# Endovascular Patients Unplanned Index Limb Revascularization

■ Placebo  
■ Rivaroxaban



3 Year  
ARR 3.0%  
NNT 33

25.5%  
22.5%



# Safety Events Endovascular Group

	Rivaroxaban 2.5 mg bid, (N=2135) KM Rate 3-yrs	Placebo (N=2112) KM Rate 3-yrs	HR (95% CI)	P-value (two-sided)
TIMI major bleeding	3.28	2.13	1.60 ( 1.02, 2.51)	0.039
Fatal bleeding	0.16	0.17	1.01 ( 0.20, 5.02)	0.987
Intracranial bleeding	0.80	1.17	0.80 ( 0.36, 1.77)	0.586
TIMI Minor bleeding	2.06	1.30	1.58 (0.92, 2.73)	0.097
ISTH major bleeding	6.90	4.78	1.44 (1.07,1.95)	0.016

# Primary Endpoint with Rivaroxaban in Endovascular Patients by Concomitant Clopidogrel

Primary Endpoint

		Rivaroxaban 2.5 mg bid,  (N=2153) (%)	Placebo  (N=2140) (%)	Hazard Ratio and 95% CI	P value of Interaction
<b>Primary Efficacy Outcome</b>	Clopidogrel Used at Randomization				0.475
	Yes	13.4%	15.4%	0.86 ( 0.71, 1.04)	
	No	15.8%	16.5%	0.97 ( 0.74, 1.27)	
<b>MALE</b>	Clopidogrel Used at Randomization				0.838
	Yes	4.5%	6.6%	0.64 ( 0.50, 0.92)	
	No	4.1%	6.4%	0.74 ( 0.39, 1.03)	



# Safety with Rivaroxaban in Endovascular Patients by Concomitant Clopidogrel

Primary Safety Endpoint

		Rivaroxaban 2.5 mg bid,  (N=2135) (%)	Placebo  (N=2112) (%)	Hazard Ratio and 95% CI	P value of Interaction
<b>TIMI Major Bleeding</b>	Clopidogrel Used at Randomization	2.1%	1.5%	1.39 ( 0.81, 2.40)	0.403
	Yes	2.8%	1.4%	2.10 ( 0.94, 4.68)	
	No				
<b>ISTH Major Bleeding</b>	Clopidogrel Used at Randomization	4.7%	3.6%	1.32 ( 0.92, 1.89)	0.399
	Yes	5.4%	3.3%	1.74 ( 1.01, 2.99)	
	No				

# Summary

- In VOYAGER PAD, patients with PAD undergoing endovascular LER were at high risk of irreversible harm events of the heart, limb and brain with:
  - ~1 in 6 having a first event within 3 years of intervention
  - ~ 1 in 14 having an irreversible limb event within 3 years of intervention
- In patients undergoing endovascular LER, Rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone
  - Significantly reduces a broad range of thrombotic major limb complications including major amputation, acute limb ischemia, and unplanned index limb revascularization at 3 years*
  - Increases bleeding in TIMI major bleeding and a NNH in endovascular patients of ~100, and no increase in fatal bleeding or intracranial hemorrhage*
- The benefits of rivaroxaban 2.5 mg twice daily added to aspirin were not augmented by the concomitant use of clopidogrel

# Implications

- **Symptomatic PAD patients undergoing endovascular revascularization are at very high risk of irreversible harm events of the limb, heart and brain in spite of available medical therapies**
- **A strategy of rivaroxaban 2.5 mg twice daily added to aspirin should be considered in Endovascular treated patients to reduce major adverse limb events and unplanned limb revascularization.**
- **These data provide rationale for acute initiation of rivaroxaban 2.5 mg twice daily added to aspirin after endovascular revascularization (VOYAGER PAD) in addition to long-term use for chronic PAD care (COMPASS)**

# Thank You