VOYAGER PAD
Efficacy and Safety of Rivaroxaban in Patients with PAD undergoing Revascularization with and without Coronary Artery Disease

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CPC Clinical Research
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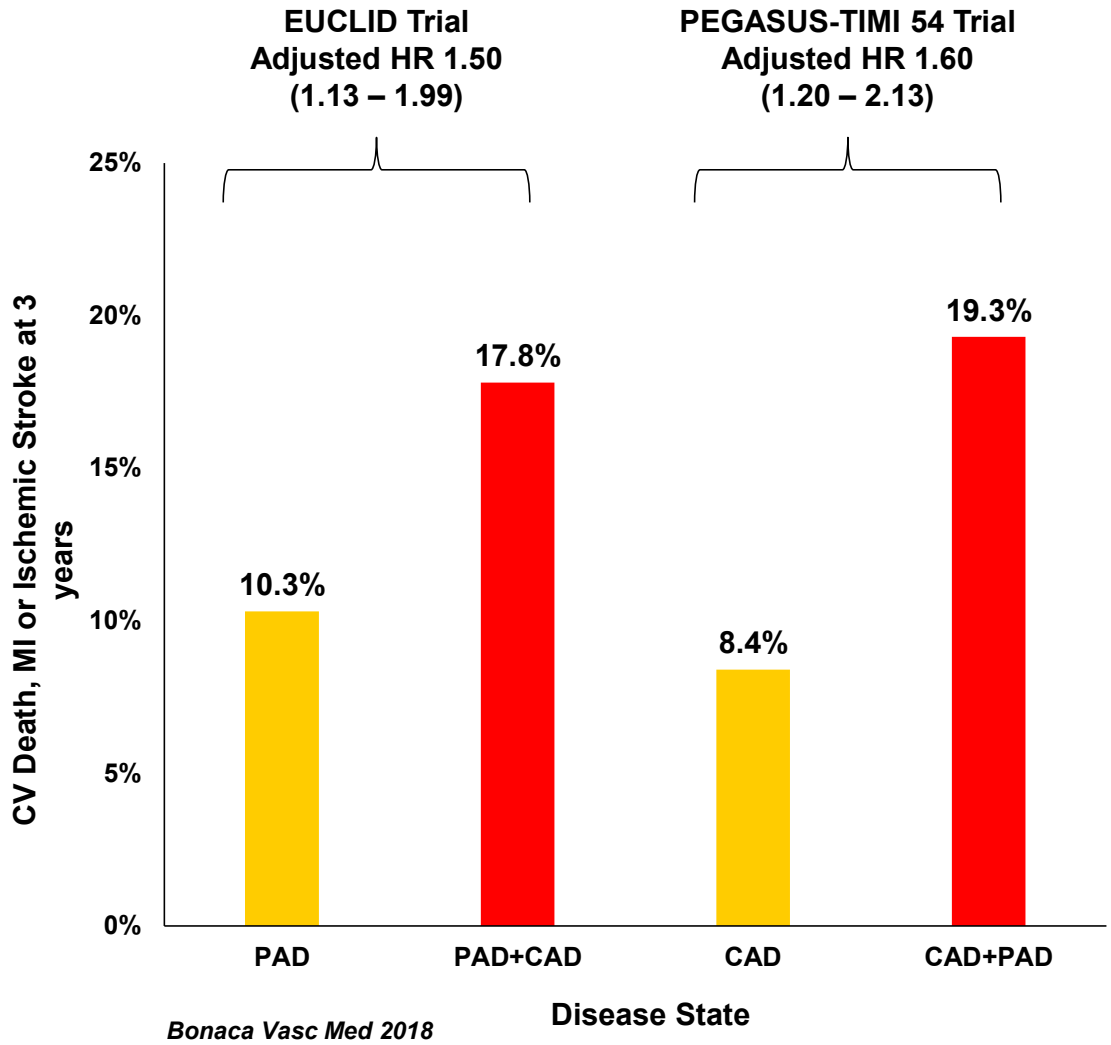
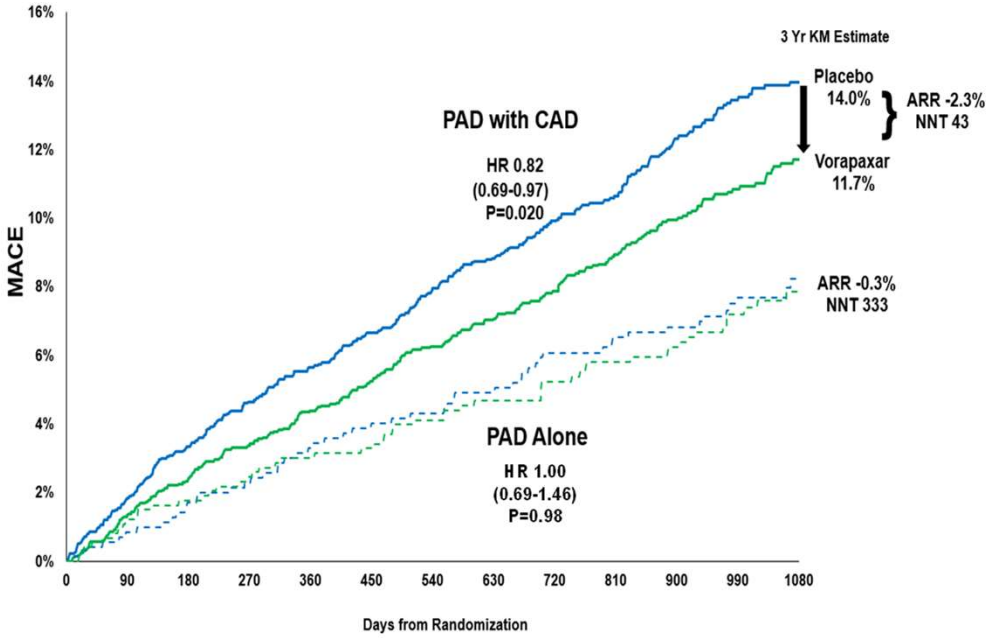
Concomitant CAD Increases MACE Risk in PAD



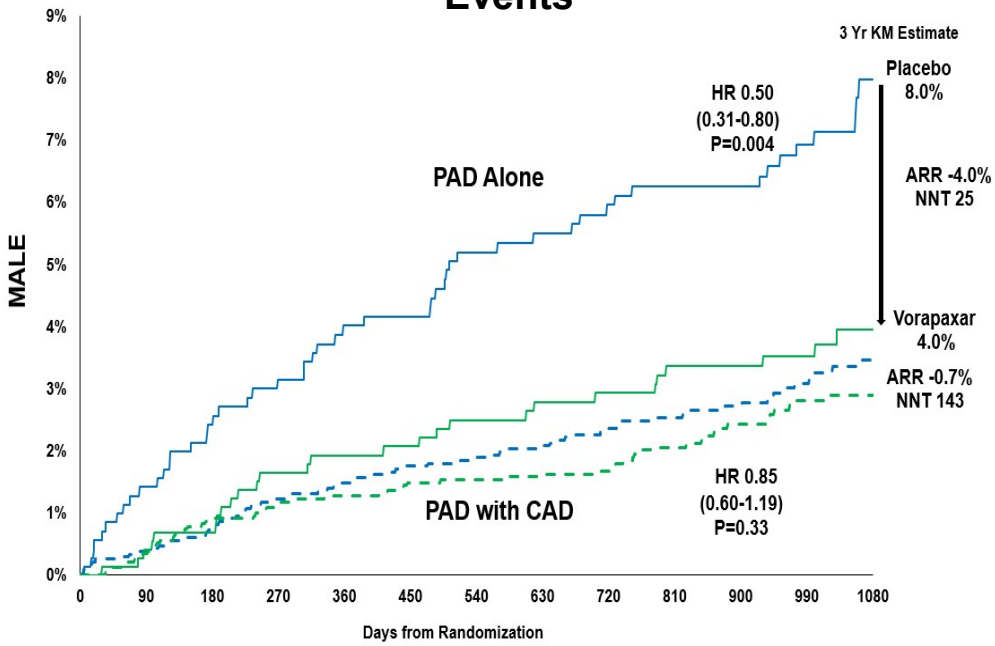
Bonaca Vasc Med 2018

Effect of Vorpaxar in Patients in PAD for MACE and Major Adverse Limb Events by CAD Status

MACE



Major Adverse Limb Events



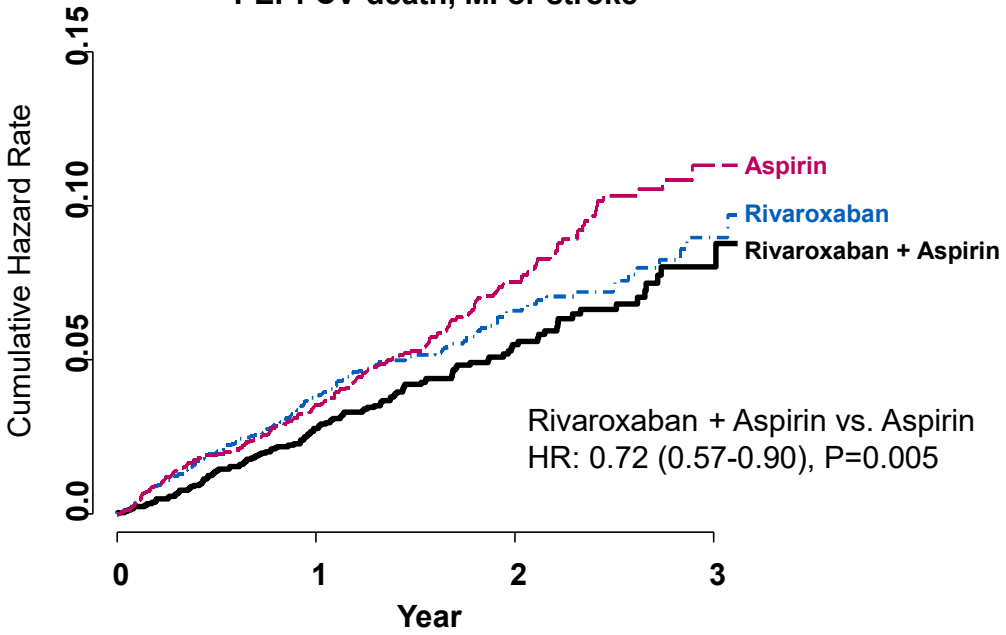
Qamar A…Bonaca MP. Vascular Medicine 2019

Rivaroxaban and MACE in Stable CAD

COMPASS

Population selected for PAD or CAD with enrichment

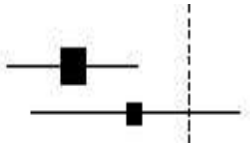
PEP: CV death, MI or stroke



Rivaroxaban + Aspirin vs. Aspirin
HR: 0.72 (0.57-0.90), P=0.005

Concomitant CAD 65%

CAD		
Yes	111/1656 (7%)	168/1641 (10%)
No	46/836 (6%)	57/863 (7%)



Lancet 2018;391:219-229

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

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

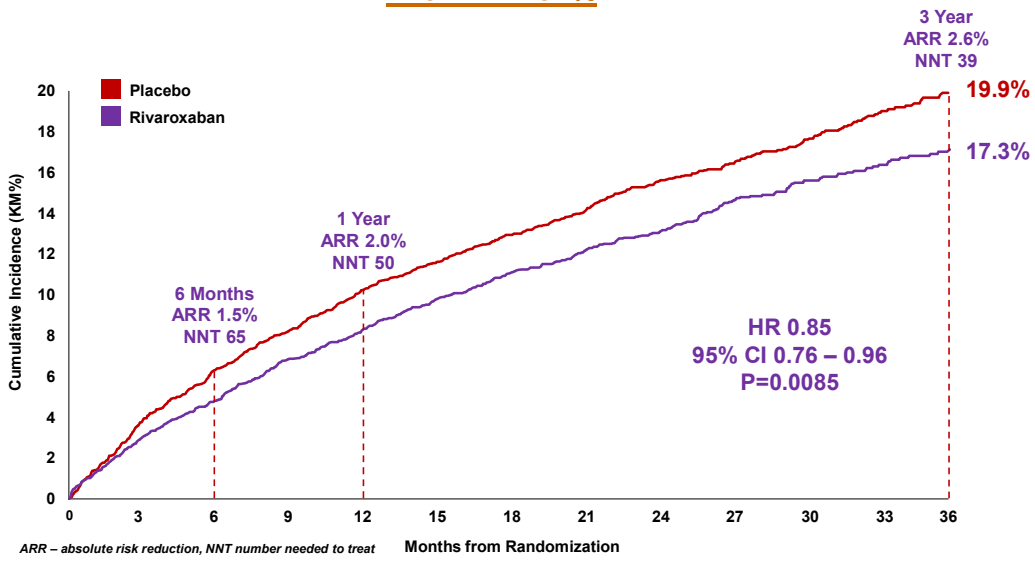
Rivaroxaban Across the Spectrum of PAD

VOYAGER PAD

Population selected for lower extremity symptomatic PAD after revascularization with no enrichment for CV risk

PEP: Acute limb ischemia, major amputation of a vascular etiology, MI, ischemic stroke or CV death

With CAD 32%



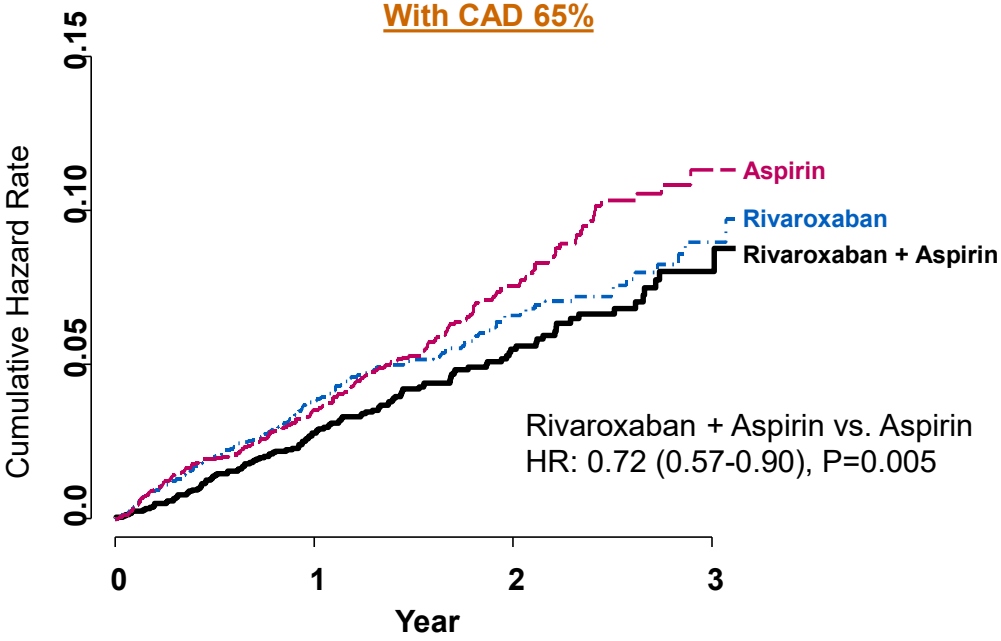
NEJM 2020;382:1994-2004

COMPASS

Population selected for PAD or CAD with enrichment criteria for CV risk

PEP: CV death, MI or stroke

With CAD 65%



Lancet 2018;391:219-229

VOYAGER PAD

Objectives

In PAD patients undergoing LER for ischemic symptoms randomized to rivaroxaban 2.5 mg twice daily plus low dose aspirin versus aspirin alone:

- **To evaluate whether CAD is associated with increased risk of MACE and/or major adverse limb events (MALE) compared to no CAD**
- **To evaluate whether the safety and efficacy of rivaroxaban after lower extremity revascularization is consistent in patients with and without CAD**

Methods

- The presence of known coronary artery disease (with CAD) was reported by investigators at baseline and was defined as any known history including prior MI, coronary revascularization, other stable CAD

- 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 CAD status

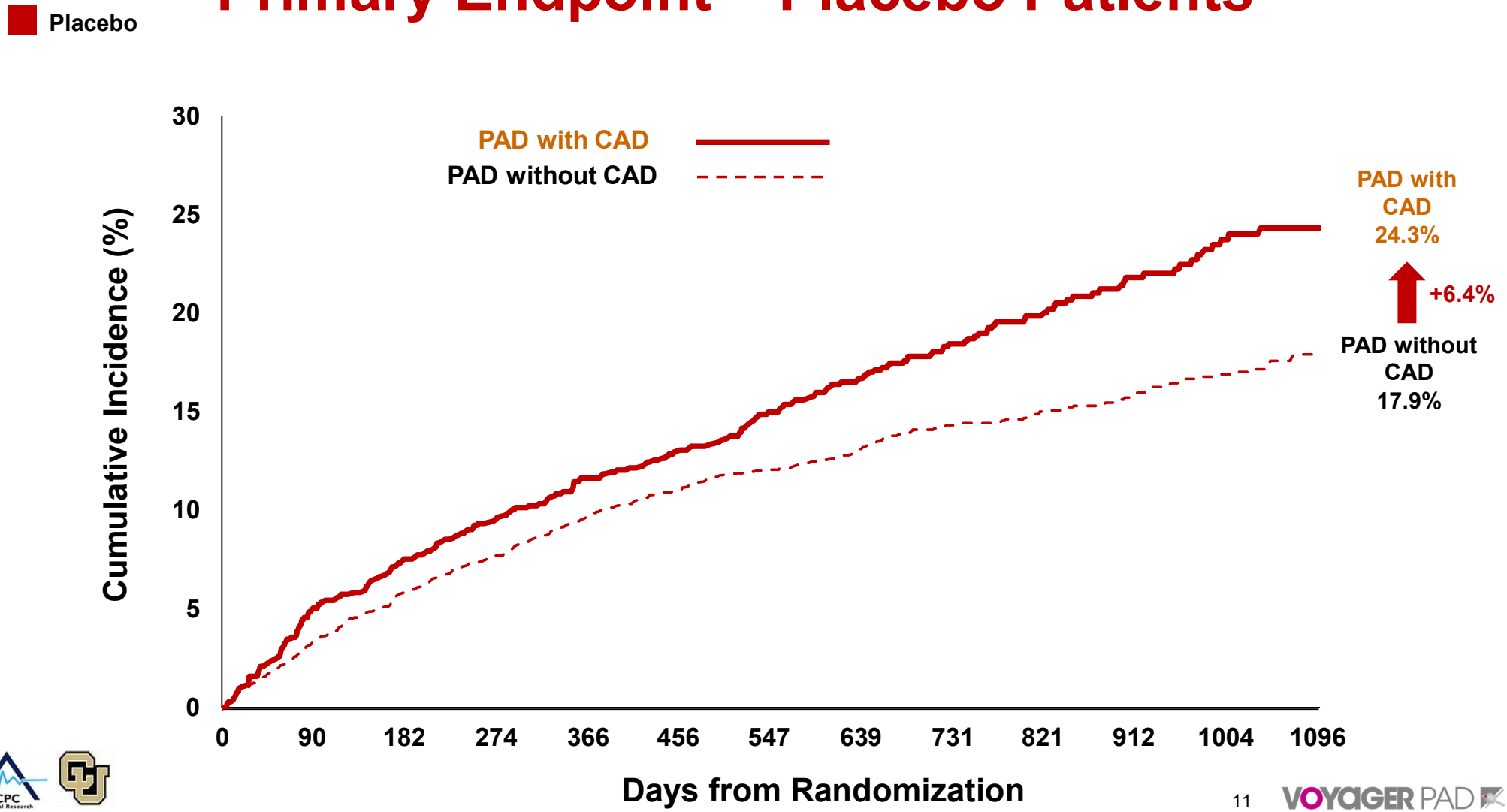
Baseline Characteristics

Baseline Characteristics	With CAD N=2067	Without CAD N=4496	P-value
Median age (IQR) – yr	68 (62 – 74)	66 (60 – 72)	<0.0001
Female no. (%)	22	28	< 0.0001
White Caucasian no. (%)	79	82	0.0168
Hypertension (%)	90	77	<0.0001
Diabetes Mellitus (type 2) (%)	51	35	<0.0001
Hyperlipidemia (%)	73	54	<0.0001
Current smoking (%)	27	38	<0.0001
eGFR < 60 ml/min.1.73m^2	26	18	<0.0001
Coronary artery disease (%)	100	0	<0.0001
Carotid stenosis ≥ 50% (%)	12	6	<0.0001
History of heart failure (%)	19	3	<0.0001

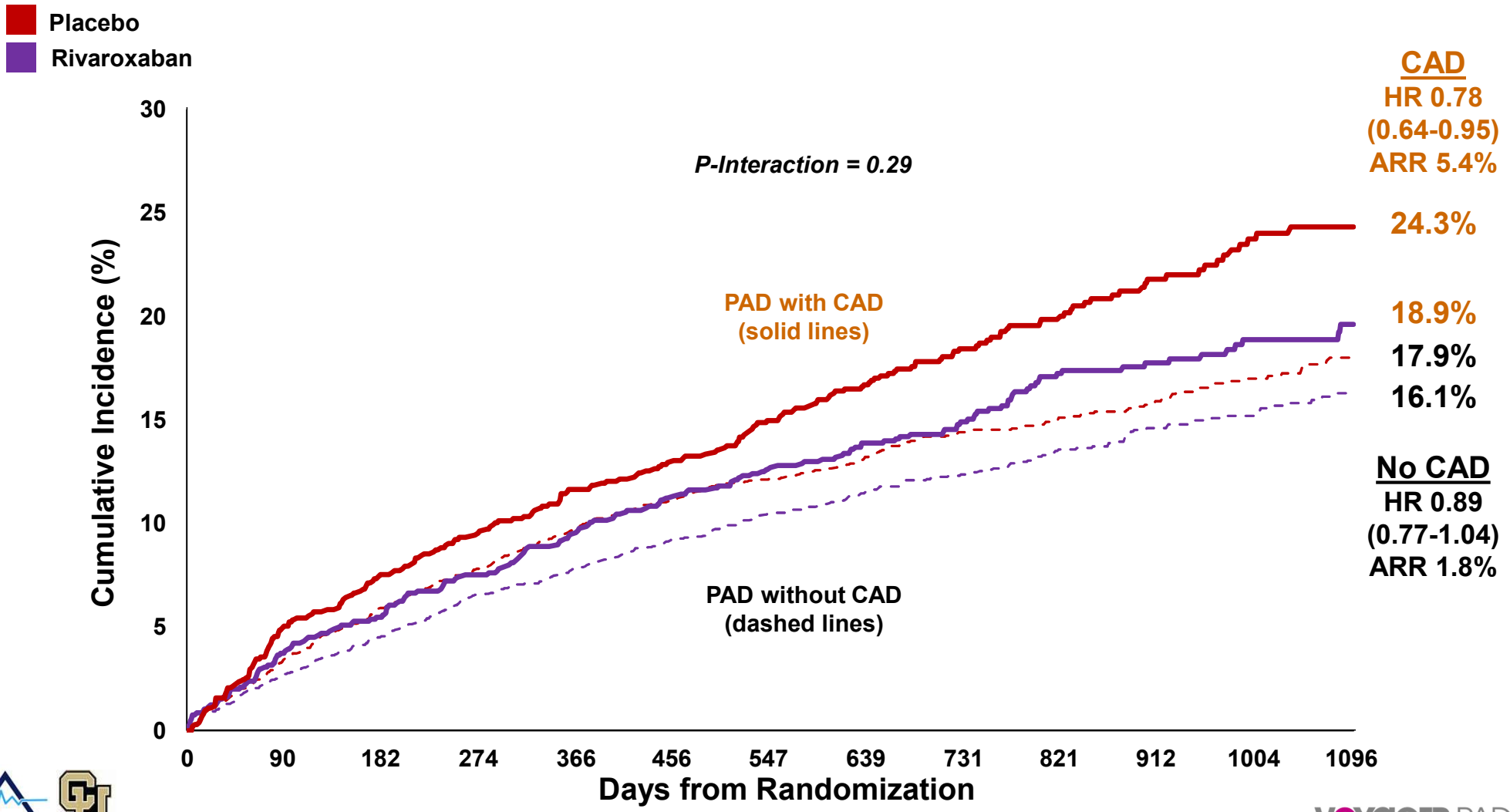
Baseline Characteristics

Baseline Characteristics	With CAD N=2067	Without CAD N=4496	P-value
Qualifying revascularization			**0.0192**
Surgical (%)	31	34	
Endovascular (%)	69	66	
Reason for revascularization			**0.0185**
Claudication (%)	96	95	
Critical limb ischemia (%)	22	24	
PAD Characteristics			
Prior limb revascularization (%)	43	32	<0.0001
ABI (median, IWR)	0.58 (0.44 – 0.69)	0.54 (0.41 – 0.66)	<0.0001
Prior Major Amputation (%)	0.9	1.0	0.5920
Medications			
Statins	90	76	<0.001
ACE/ARB	71	60	<0.0001
Clopidogrel at randomization	54	49	<0.0001

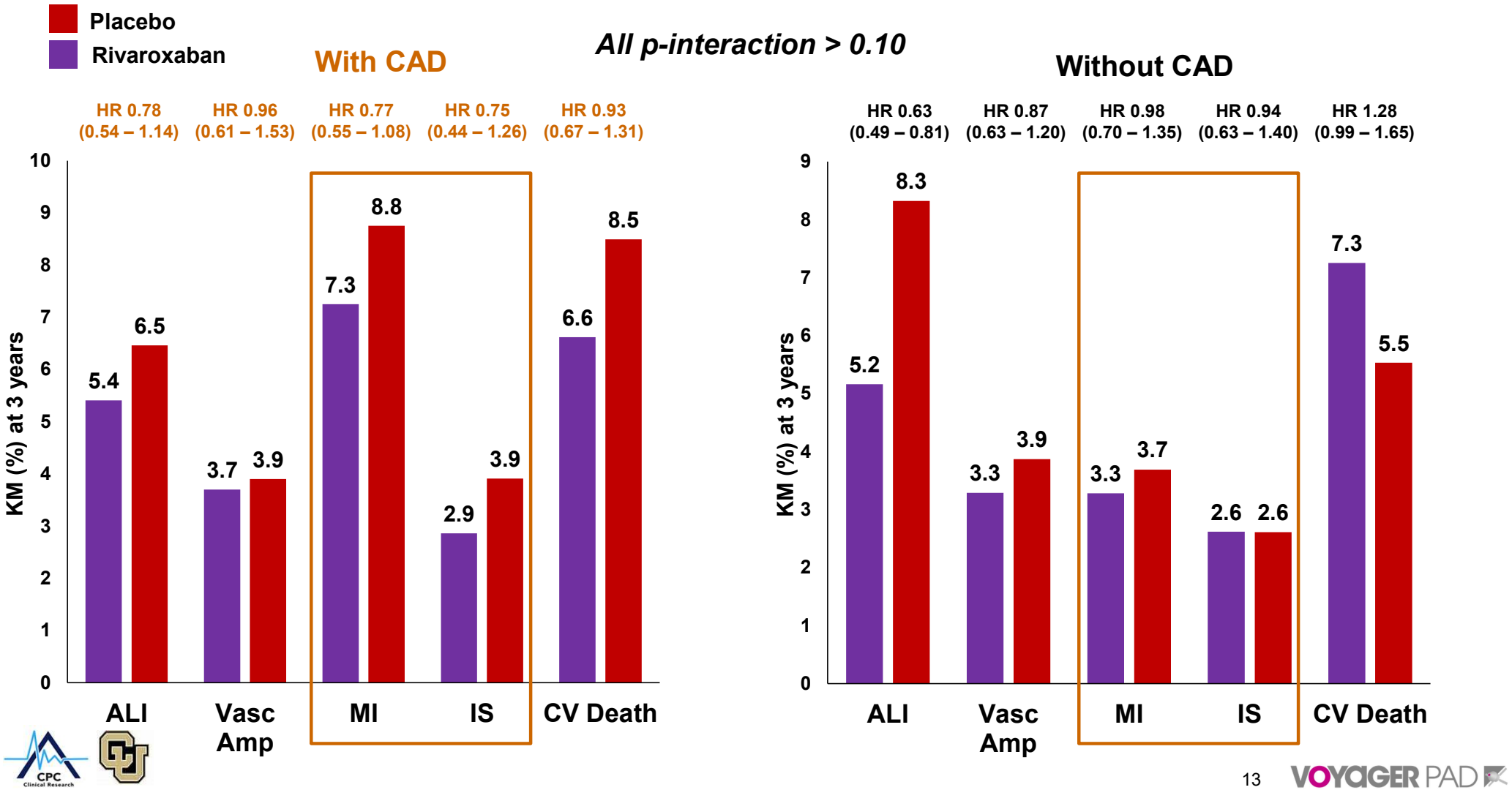
Primary Endpoint – Placebo Patients



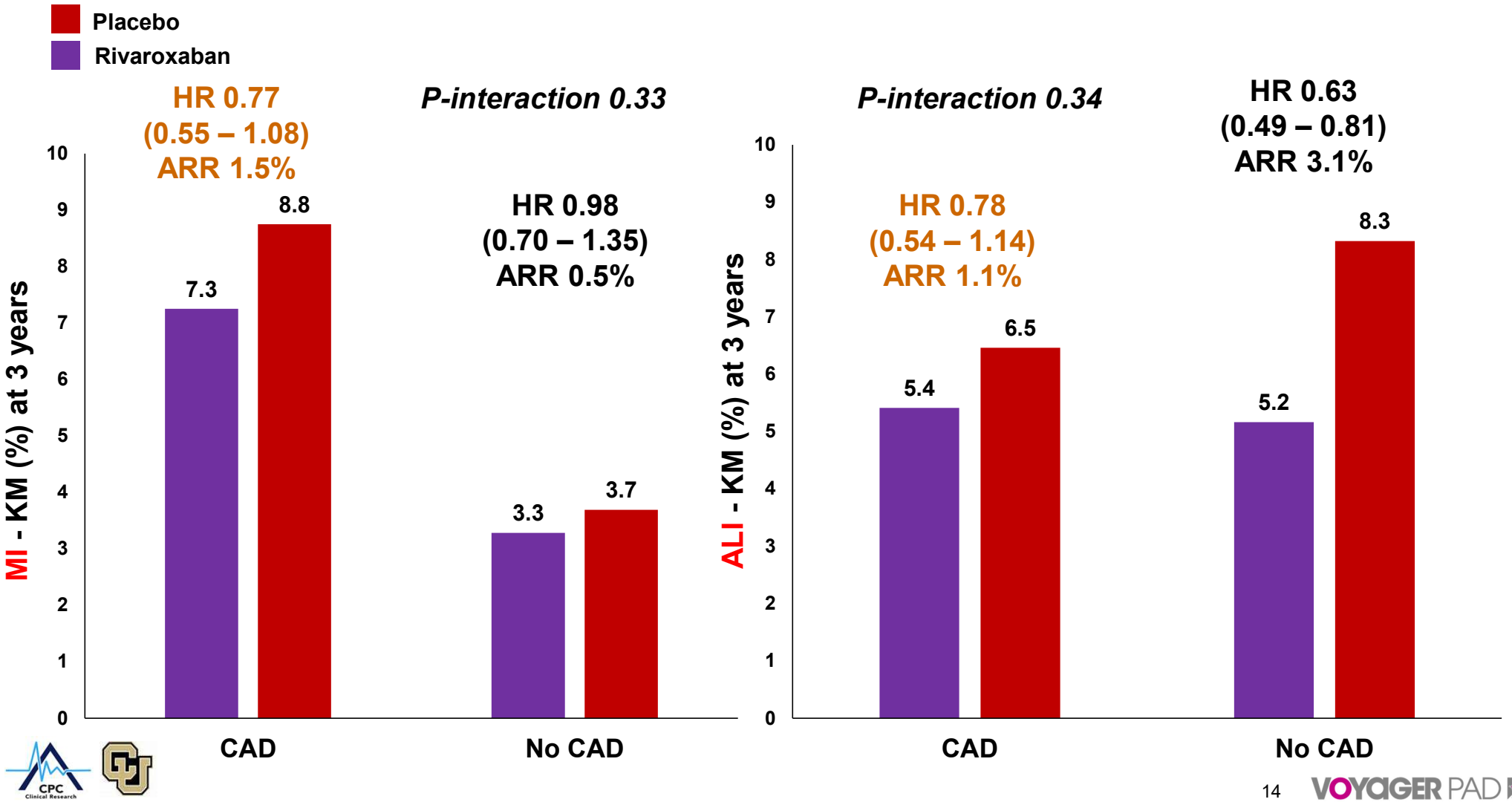
Primary Endpoint with Rivaroxaban with and without CAD



Primary Endpoint Components with and without CAD

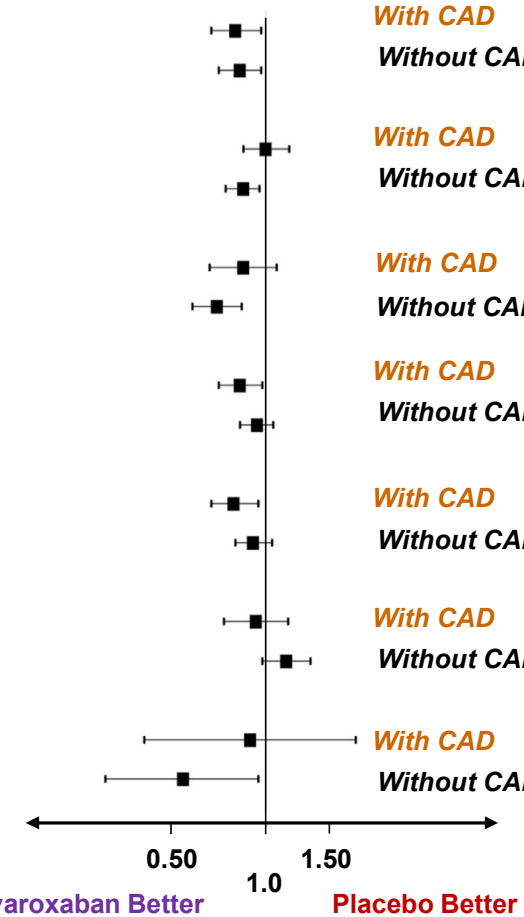


MI and ALI with and without CAD



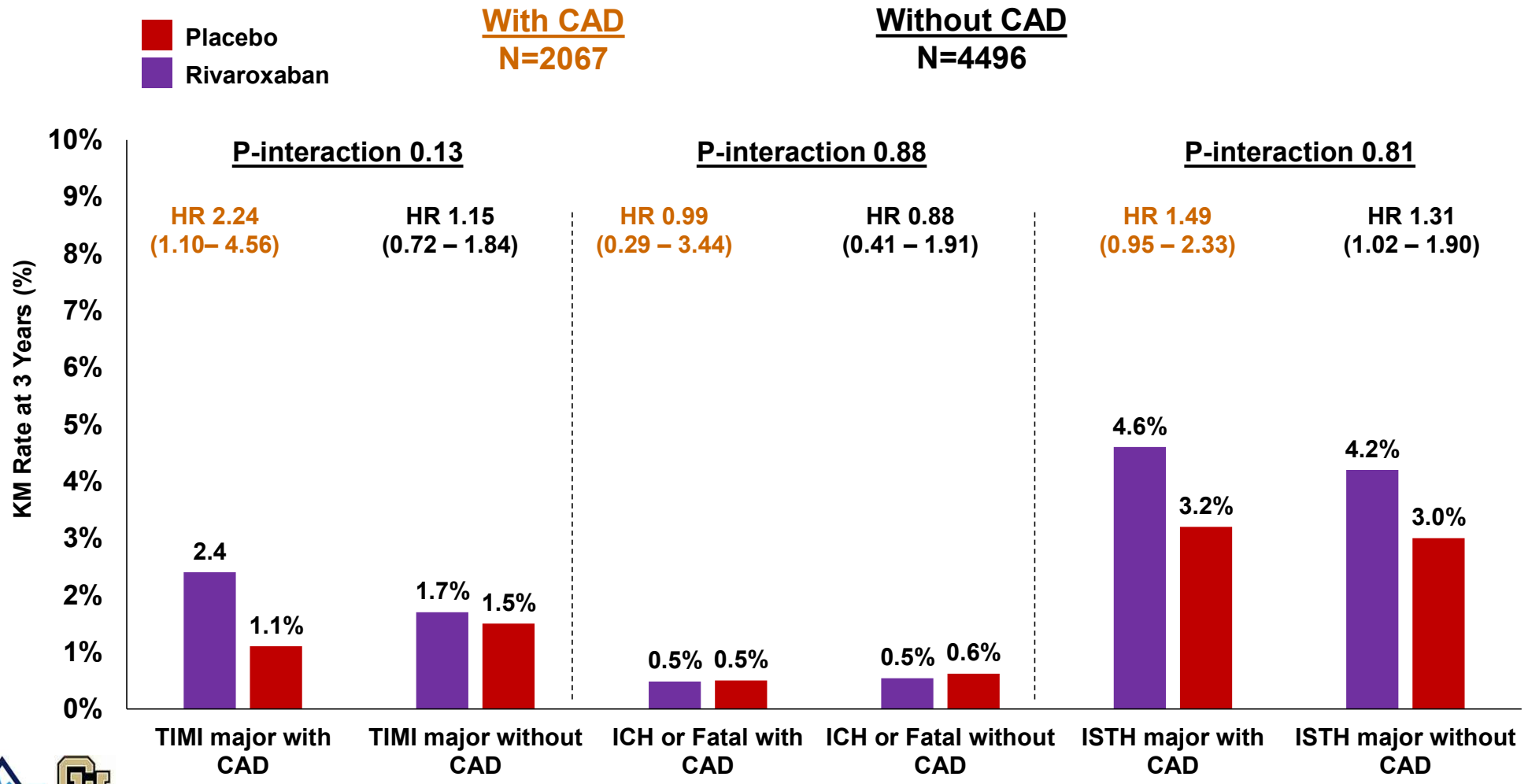
Secondary Endpoints With and Without CAD

All p-interaction > 0.10



		HR (95% CI)	P-Interaction
MI, ischemic stroke, CHD, ALI, or major amputation of vascular etiology	*With CAD*	0.78 (0.64-0.96)	0.75
	Without CAD	0.81 (0.69-0.96)	
Unplanned index limb revascularization for recurrent limb ischemia	*With CAD*	1.00 (0.83-1.21)	0.11
	Without CAD	0.83 (0.72-0.95)	
Hospitalization for a coronary or peripheral event (either lower limb) of a thrombotic nature	*With CAD*	0.83 (0.63-1.09)	0.21
	Without CAD	0.67 (0.55-0.82)	
MI, ischemic stroke, all-cause mortality, ALI, and major amputation of vascular etiology	*With CAD*	0.81 (0.68-0.97)	0.24
	Without CAD	0.93 (0.81-1.06)	
MI, all-cause stroke, CV death, ALI, and major amputation of vascular etiology	*With CAD*	0.77 (0.64-0.94)	0.21
	Without CAD	0.90 (0.78-1.05)	
All Cause Mortality	*With CAD*	0.92 (0.71-1.20)	0.13
	Without CAD	1.18 (0.94-1.44)	
Venous thromboembolism	*With CAD*	0.88 (0.37-2.08)	0.31
	Without CAD	0.51 (0.27-0.94)	

Safety of Rivaroxaban With and Without CAD



Summary

- **In patients with lower extremity PAD undergoing revascularization for ischemia:**
  - **Patients with PAD and CAD appear to have higher rates of MI and IS relative to those with PAD and no CAD**
  - **Patients with PAD and no CAD have higher rates of major adverse limb events relative to MI and IS**
  - **The efficacy and safety of rivaroxaban in PAD are consistent regardless of CAD with no significant interactions, however, the absolute benefits of rivaroxaban appear greater in those with CAD particularly for MI and IS**

Conclusion

- **A strategy of rivaroxaban 2.5 mg twice daily plus low dose aspirin versus low dose aspirin alone reduces ischemic events of the limb, brain and heart and increases bleeding with an overall net benefit in patients with lower extremity symptomatic PAD after revascularization**
  - **The benefits of this strategy for MI and IS are robust particularly in patients with PAD and CAD and consistent with data from COMPASS (Lancet 2018)**
  - **In those without known CAD, benefits appear to be driven by reductions in severe limb events**
- **These findings suggest heterogeneity of prognostic risk for ischemic events in lower extremity PAD patients and may support shared decision making with patients**