VOYAGER PAD
Efficacy and Safety of Rivaroxaban in Patients with Symptomatic PAD undergoing Revascularization with and without Clopidogrel

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**Drs. Hiatt and Bonaca Contributed Equally to this Presentation*

University of Colorado Anschutz Medical Campus

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

William R Hiatt Disclosures

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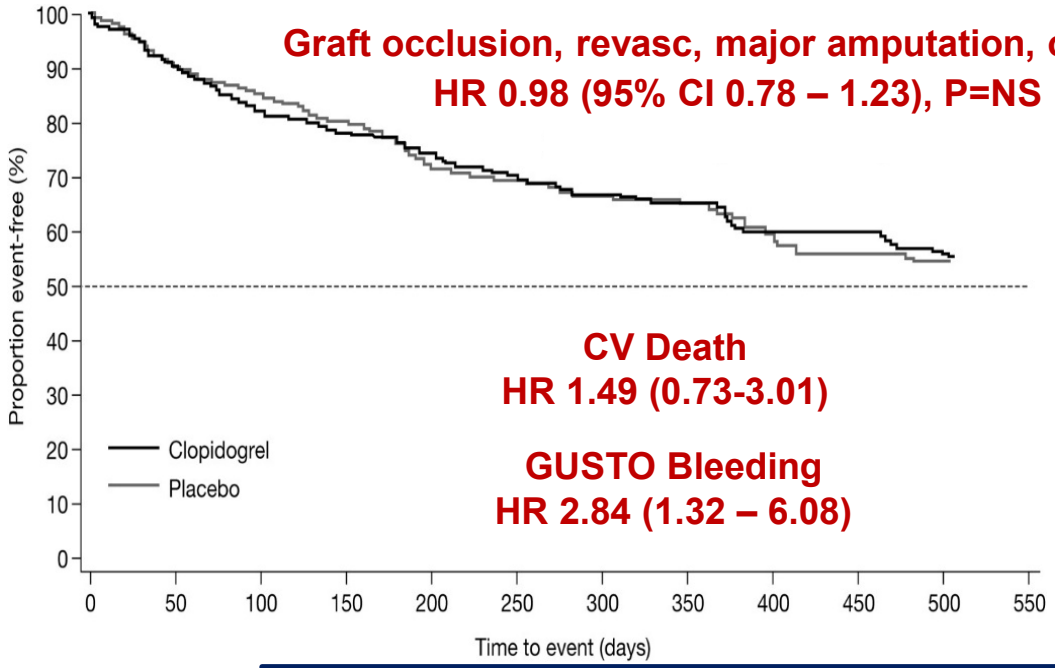
- **Bayer**
- **Janssen**
- **Amgen**

Background

CASPAR
N=851

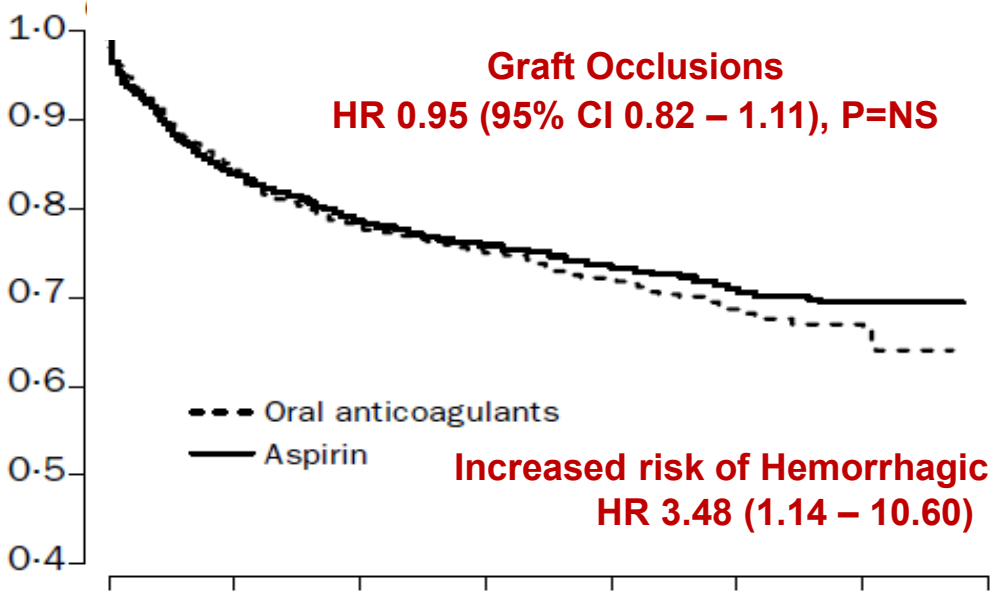


Graft occlusion, revasc, major amputation, or death
HR 0.98 (95% CI 0.78 – 1.23), P=NS

CV Death
HR 1.49 (0.73-3.01)

GUSTO Bleeding
HR 2.84 (1.32 – 6.08)

Dutch Bypass Oral Anticoagulants
N=2690



Graft Occlusions
HR 0.95 (95% CI 0.82 – 1.11), P=NS

Increased risk of Hemorrhagic Stroke
HR 3.48 (1.14 – 10.60)

DAPT Recommendations after PAD Intervention

ACC-AHA:	**IIb**	**C-LD**
ESC	**IIa**	**C**
Chest	**Grade Ia**	
Zilver PTX		
IN.PACT SFA		

DAPT may be reasonable to reduce the risk of limb-related events after LER

DAPT is recommended for 1 month after intervention

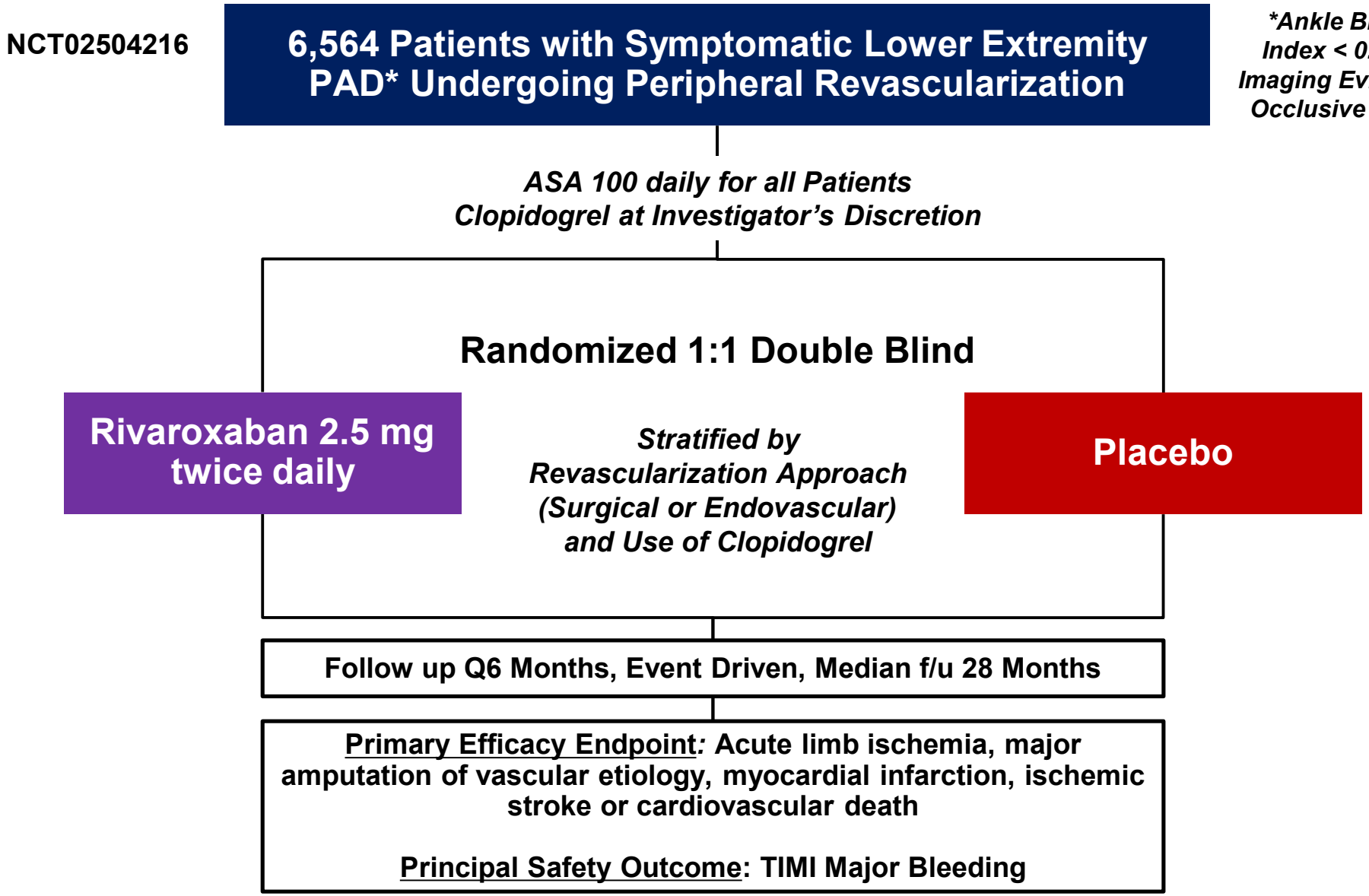
SAPT (single antiplatelet therapy). Recommend against DAPT

DAPT for 2 months

DAPT for 1 month (without stent) or 3 months (with stent)

Belch et al. J Vasc Surg 2010, Dutch Bypass Oral anticoagulants or Aspirin (BOA). Lancet 2000, Circulation. 2017;135:e726–e779, Eur Heart J. 2018;39:763-81, Chest 2012;141:e669s-e690s, Circulation 2016;133:1472-83, JACC 2015;66:2329, Circulation 2015;131:495-502

Trial Design



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

Inclusion & Exclusion

Inclusion

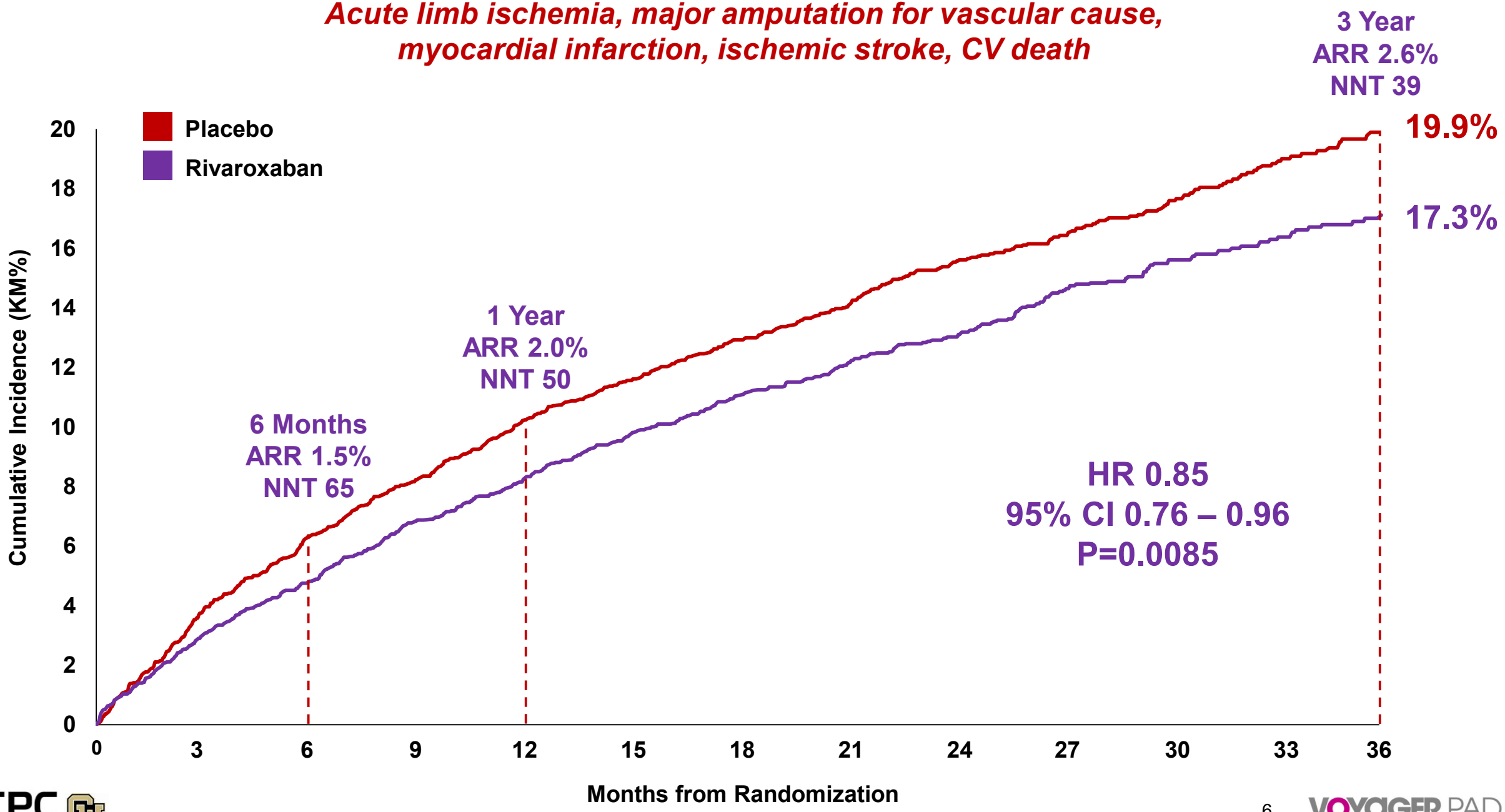
- Age ≥ 50
- Documented PAD including:
  - *Ischemic symptoms (functional limitation, rest pain or ischemic ulceration) AND*
  - *Imaging evidence of occlusion AND*
  - *Abnormal ABI*
- Successful lower extremity revascularization for ischemia

Exclusion

- Revascularization for asymptomatic disease
- Recent revascularization (within 10 days) or ALI (2 weeks) or ACS (30 days)
- Current major tissue loss
- Need for antiplatelet or anticoagulant other than aspirin and/or clopidogrel
- Need for long-term DAPT (intended > 6 months)
- High risk for bleeding (significant bleeding in last 6 months, prior stroke or other high-risk condition)

Primary Endpoint

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



Objectives

In symptomatic PAD patients undergoing lower extremity revascularization *randomized* to rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone, to evaluate whether:

- **Determine if efficacy and safety of rivaroxaban were consistent regardless of background clopidogrel use**

- **To explore temporal patterns of bleeding in relationship to exposure and duration of clopidogrel**

PAD & Procedural Characteristics

	Yes Clopidogrel N=3313 %	No Clopidogrel N=3234 %	P-value
PAD Indication and History			
Indication: Claudication	**80**	**73**	0.7826
Indication: Critical limb threatening ischemia	**20**	**27**	**<0.0001**
Prior limb revascularization	**40**	**31**	**<0.0001**
Prior major amputation	**1.2**	**0.8**	0.1287
ABI at Screening (Median – IQR)	**0.58 (0.46-0.70)**	**0.52 (0.40-0.64)**	**< 0.0001**
Type of Revascularization			**<0.0001**
Surgical	**9**	**58**	
Endovascular	**91**	**42**	

Baseline Characteristics

Characteristic at Randomization	Yes Clopidogrel N=3313 %	No Clopidogrel N=3234 %	P-value
Age, years (Median-IQR)	67 (61-73)	67 (61-73)	0.3519
Female n	28	24	<0.0001
White Caucasian	80	82	<0.0001
Hypertension	82	80	0.0265
Diabetes Mellitus (type 2)	43	34	<0.0001
Hyperlipidemia	65	55	<0.0001
Current smoking	34	35	0.1013
COPD	10	12	0.0477
eGFR < 60 ml/min/1.73m^2	22	19	0.0028
Coronary artery disease	34	29	<0.0001
Prior CABG	9	7	0.0399
Prior coronary intervention	16	10	<0.0001
Carotid stenosis ≥ 50%	9	7	0.0035

Clopidogrel Use

	Rivaroxaban 2.5 mg twice daily + aspirin N=3286 %	Placebo + aspirin N=3278 %	P-value
Clopidogrel use at randomization	50.5	50.5	0.7926
Median duration days (IQR)	29.0 (25.0-49.5)	29.0 (26.0-50.0)	0.0700
≤ 30 days	59.6	56.5	
31- 90 days	29.0	31.7	
91-180 days	6.3	6.3	
Median duration days (IQR) for drug-coated products*	31.0 (27.0-59.0)	32.0 (27.5-59.0)	0.9311

*38% of endovascular procedures with clopidogrel were for drug coated products

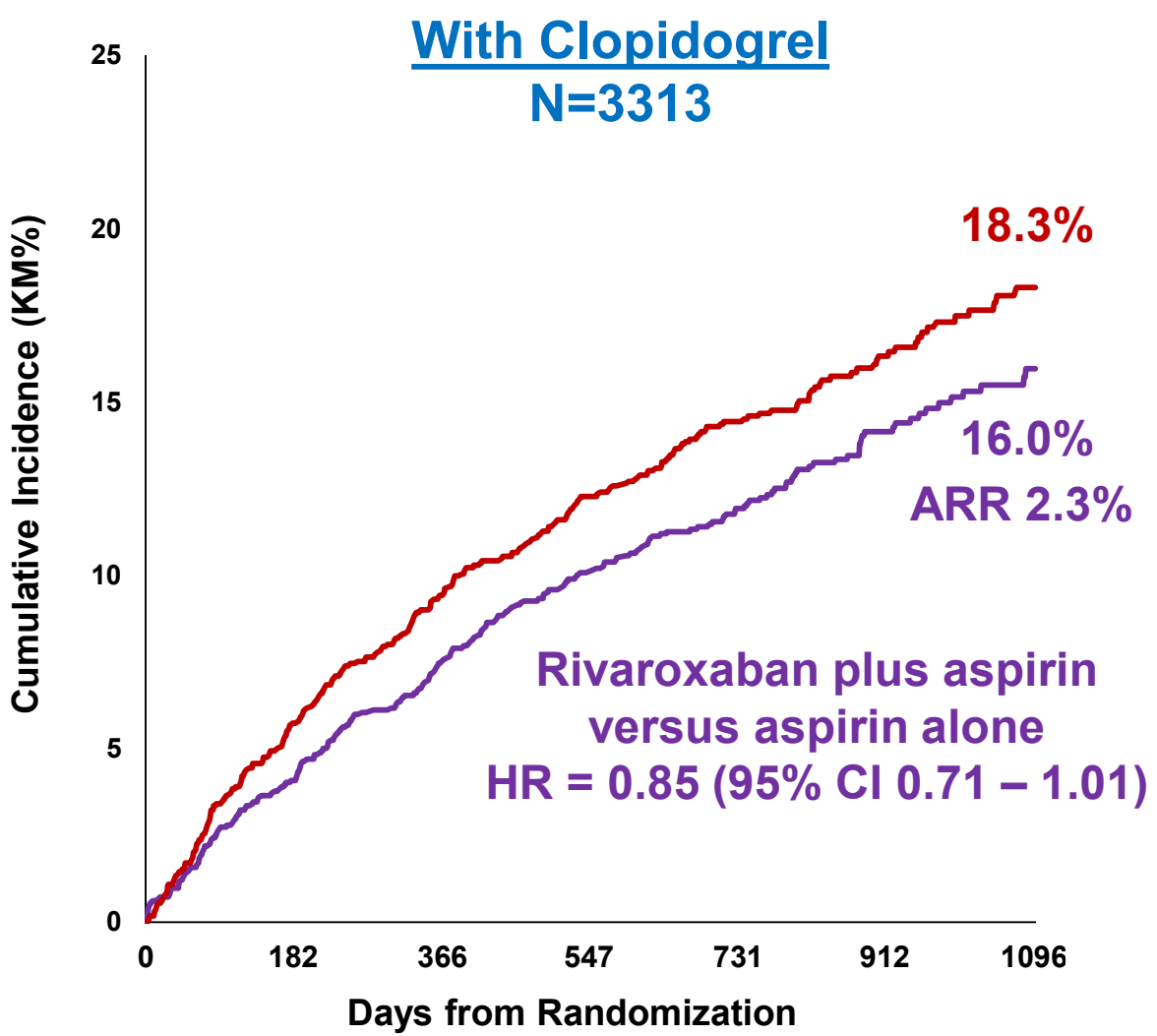
Primary Endpoint

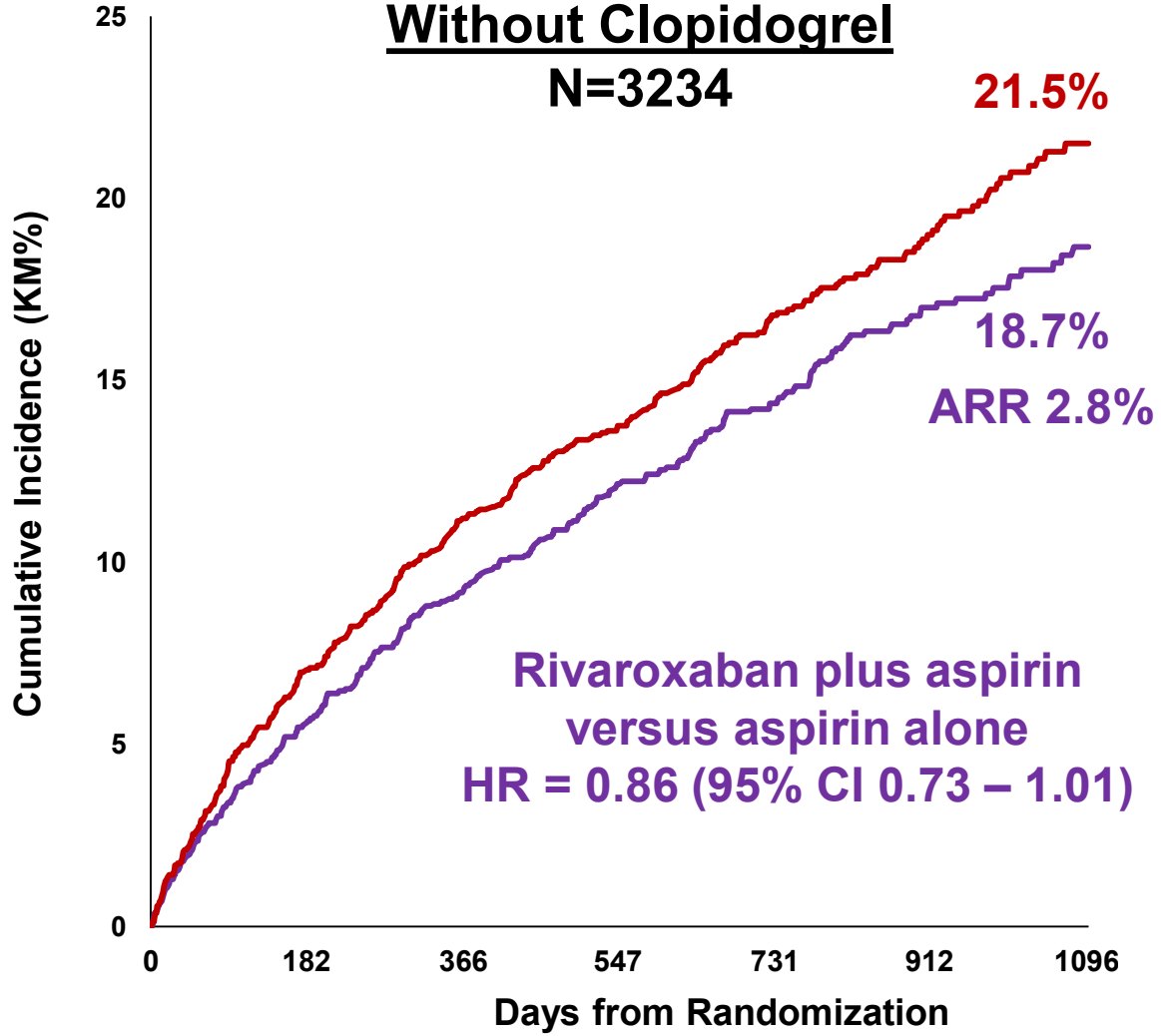
Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death

Placebo

Rivaroxaban

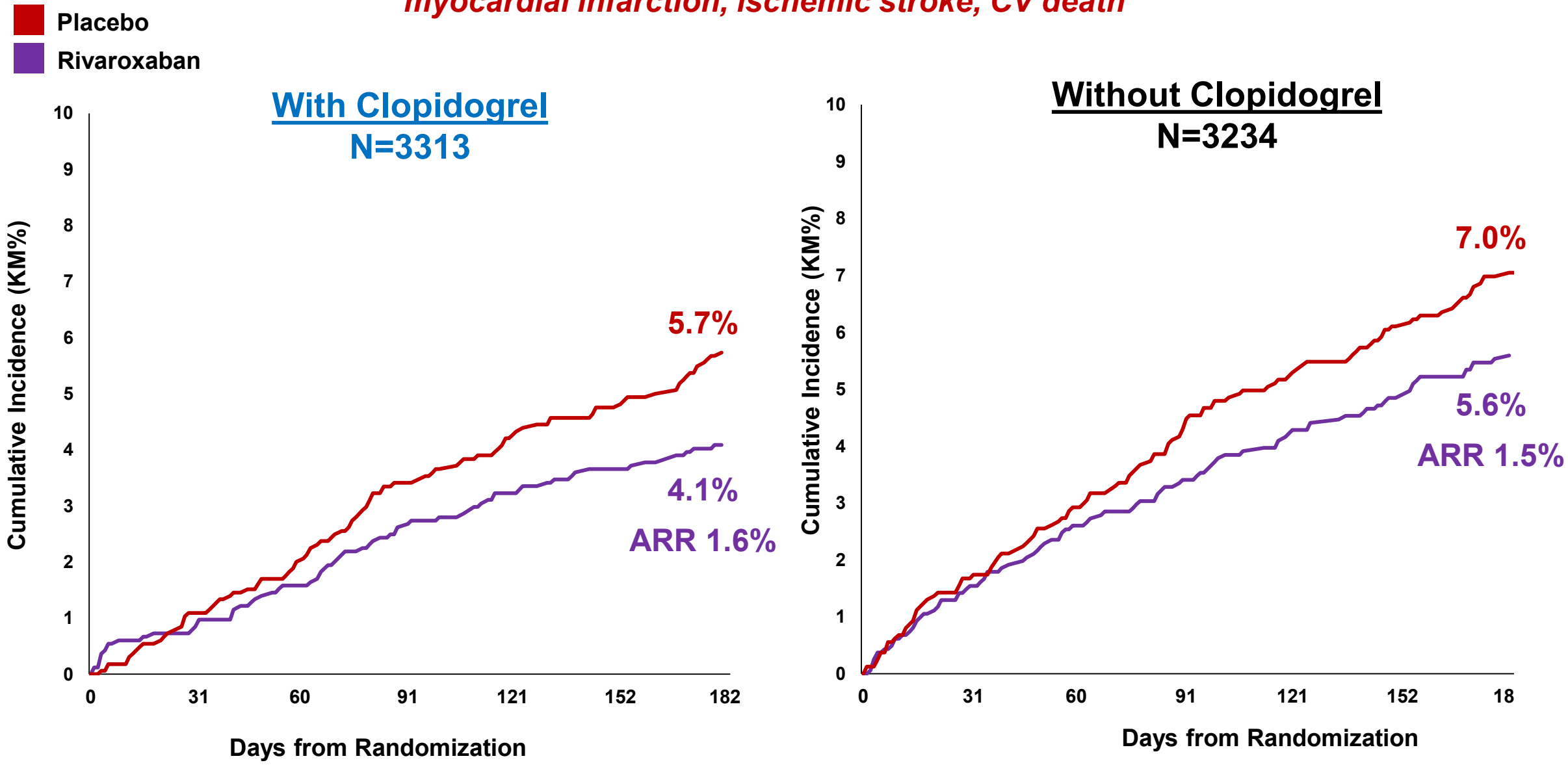
P-interaction 0.9163



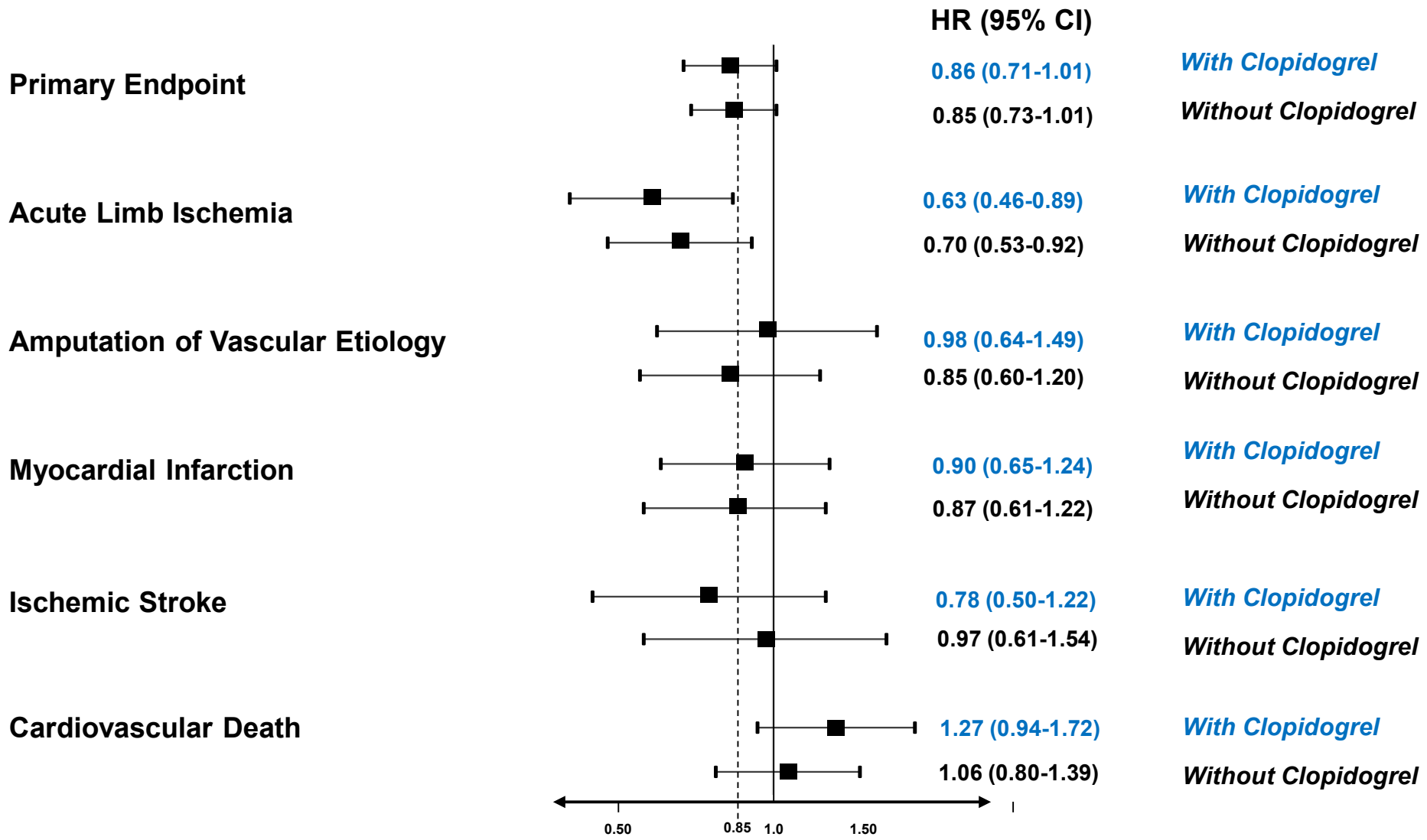


Primary Endpoint at 180 Days

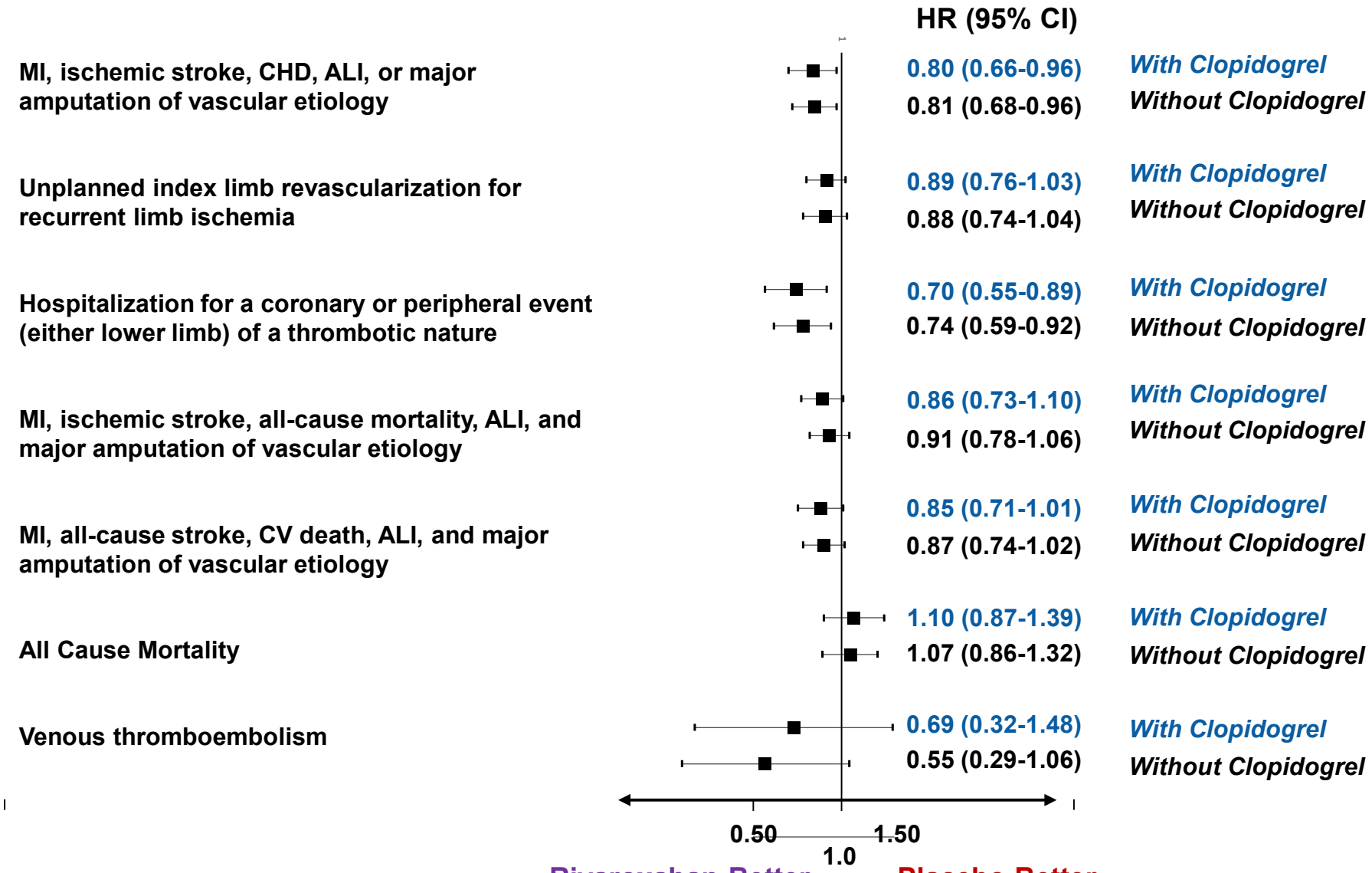
Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death



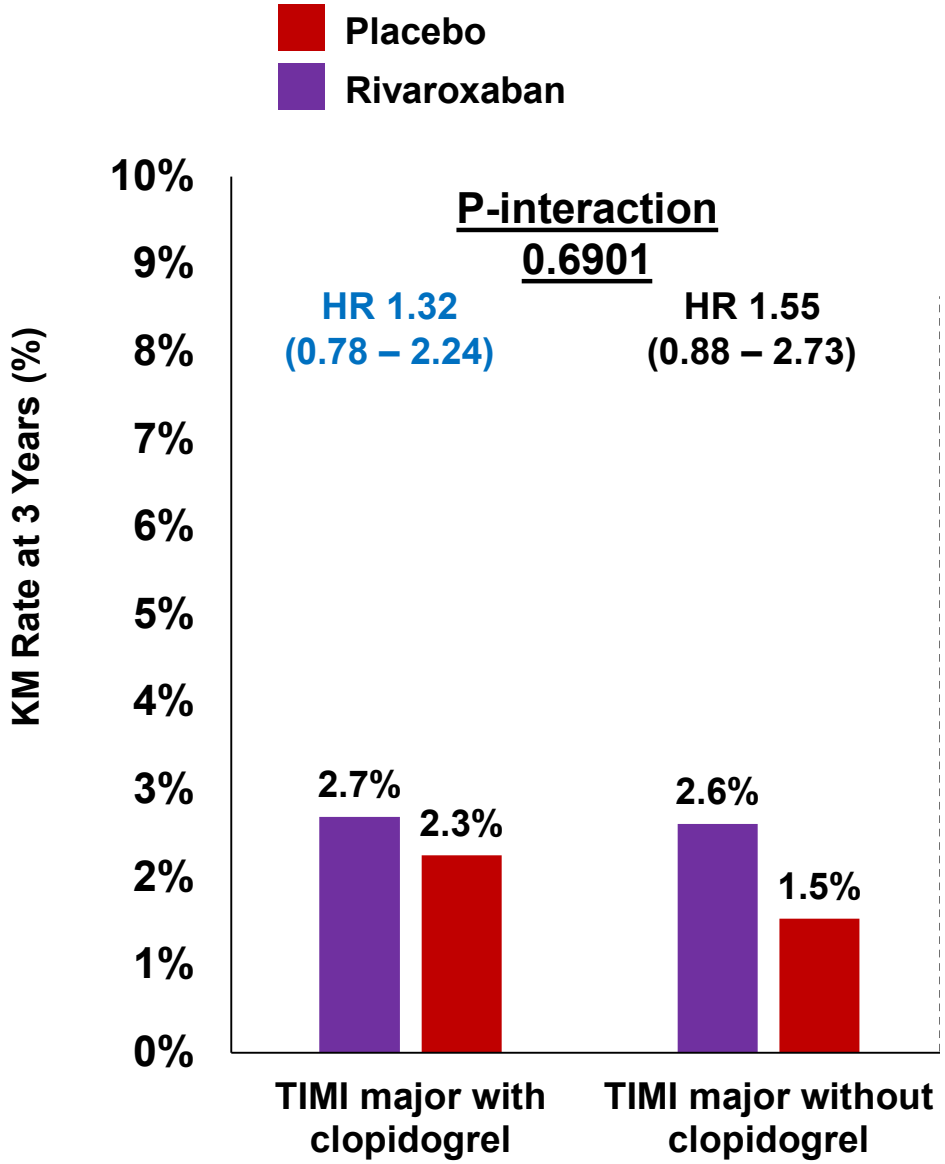
Benefit of Rivaroxaban for the Primary Outcome and Components with and without Background Clopidogrel



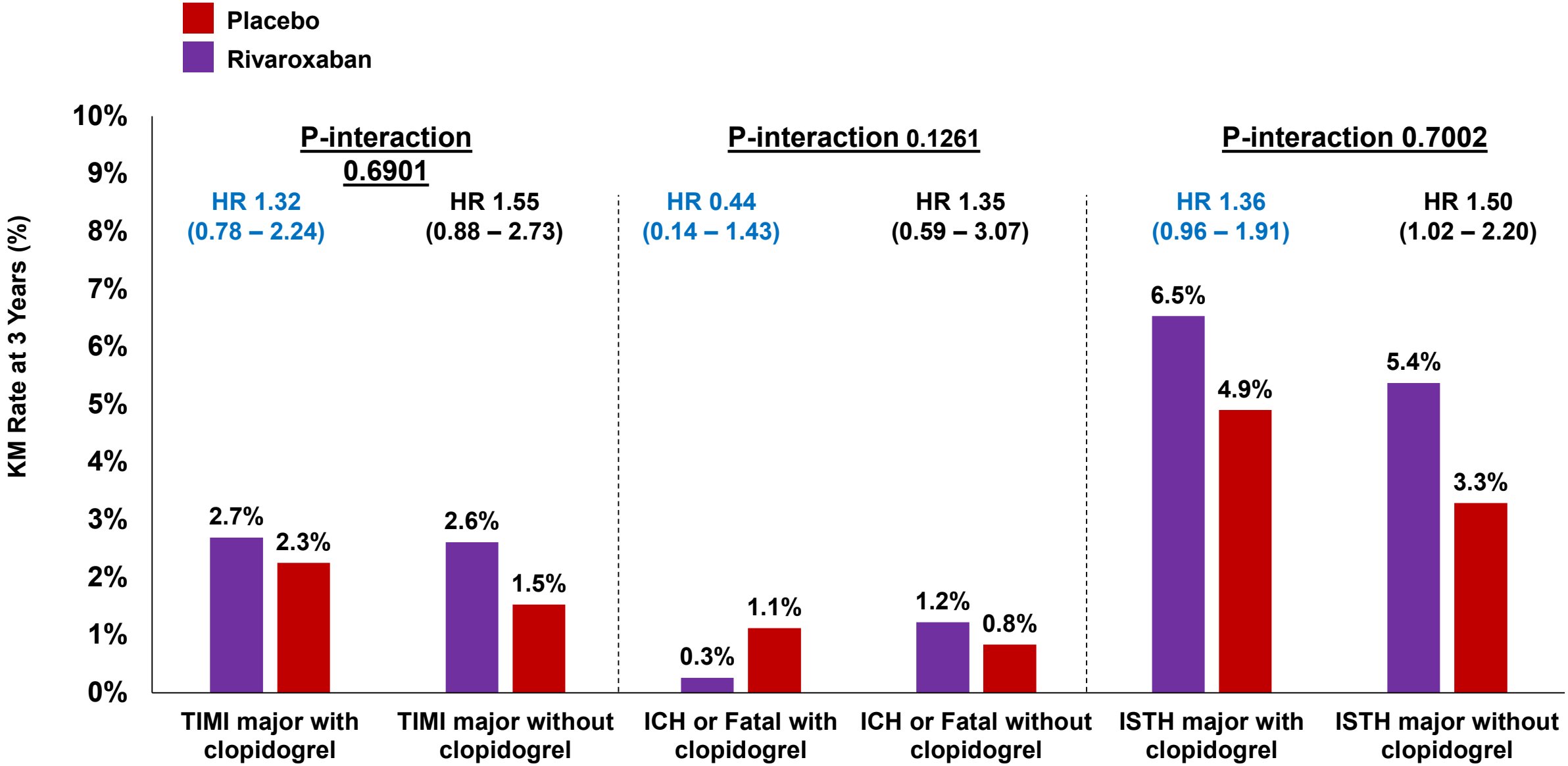
Benefit of Rivaroxaban for Secondary Outcome with and without Background Clopidogrel



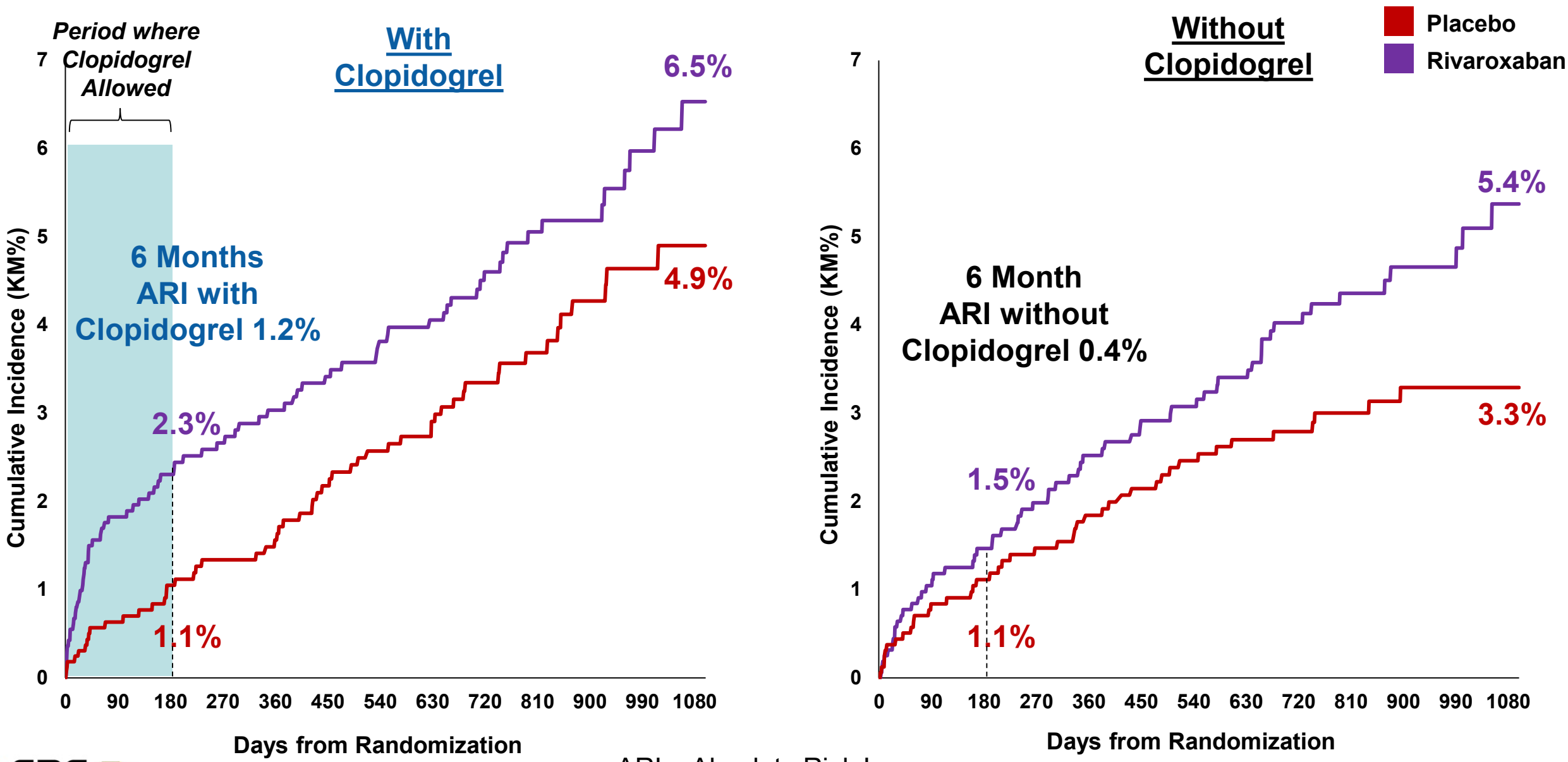
Safety of Rivaroxaban With and Without Clopidogrel



Safety of Rivaroxaban With and Without Clopidogrel

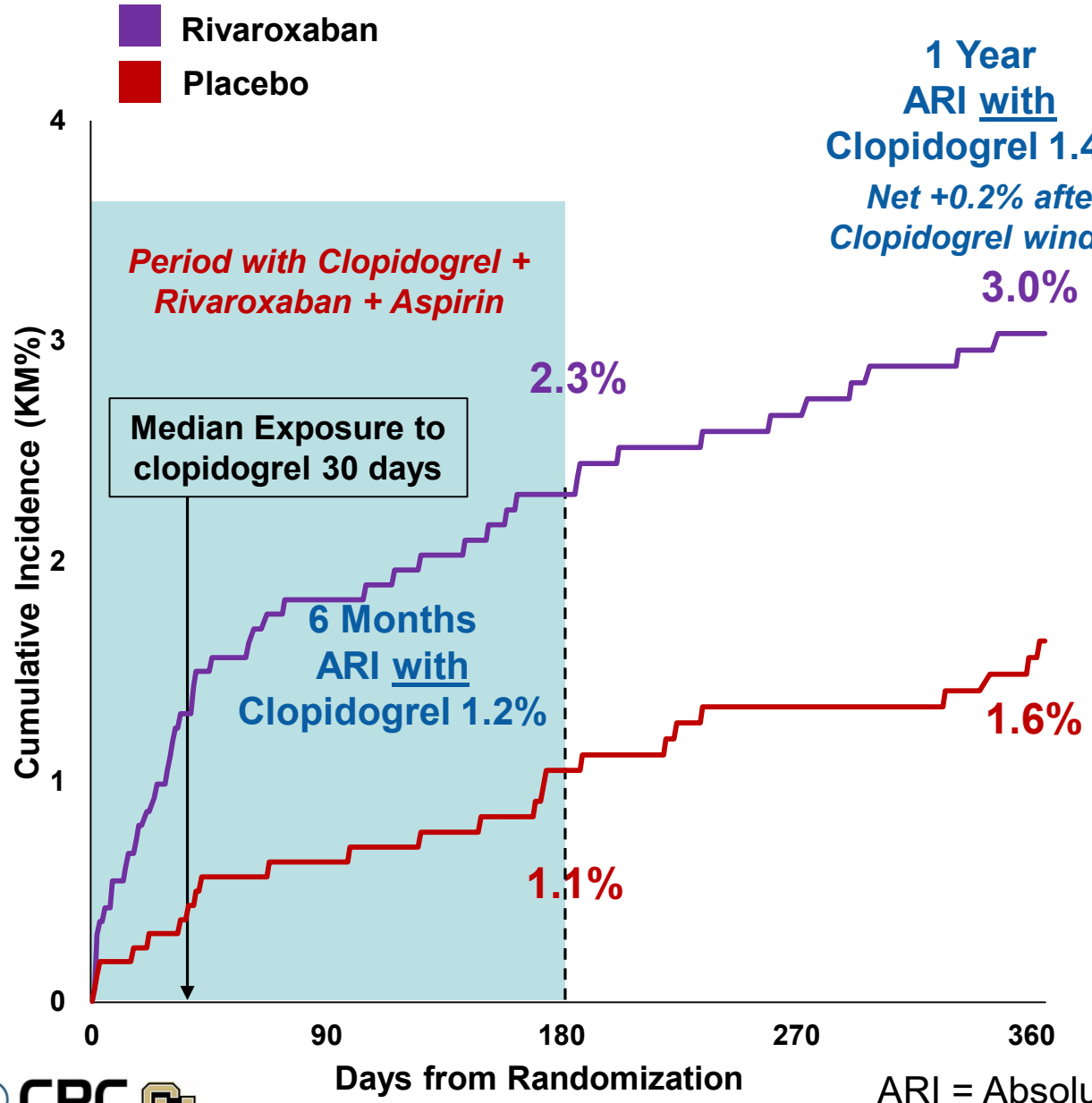


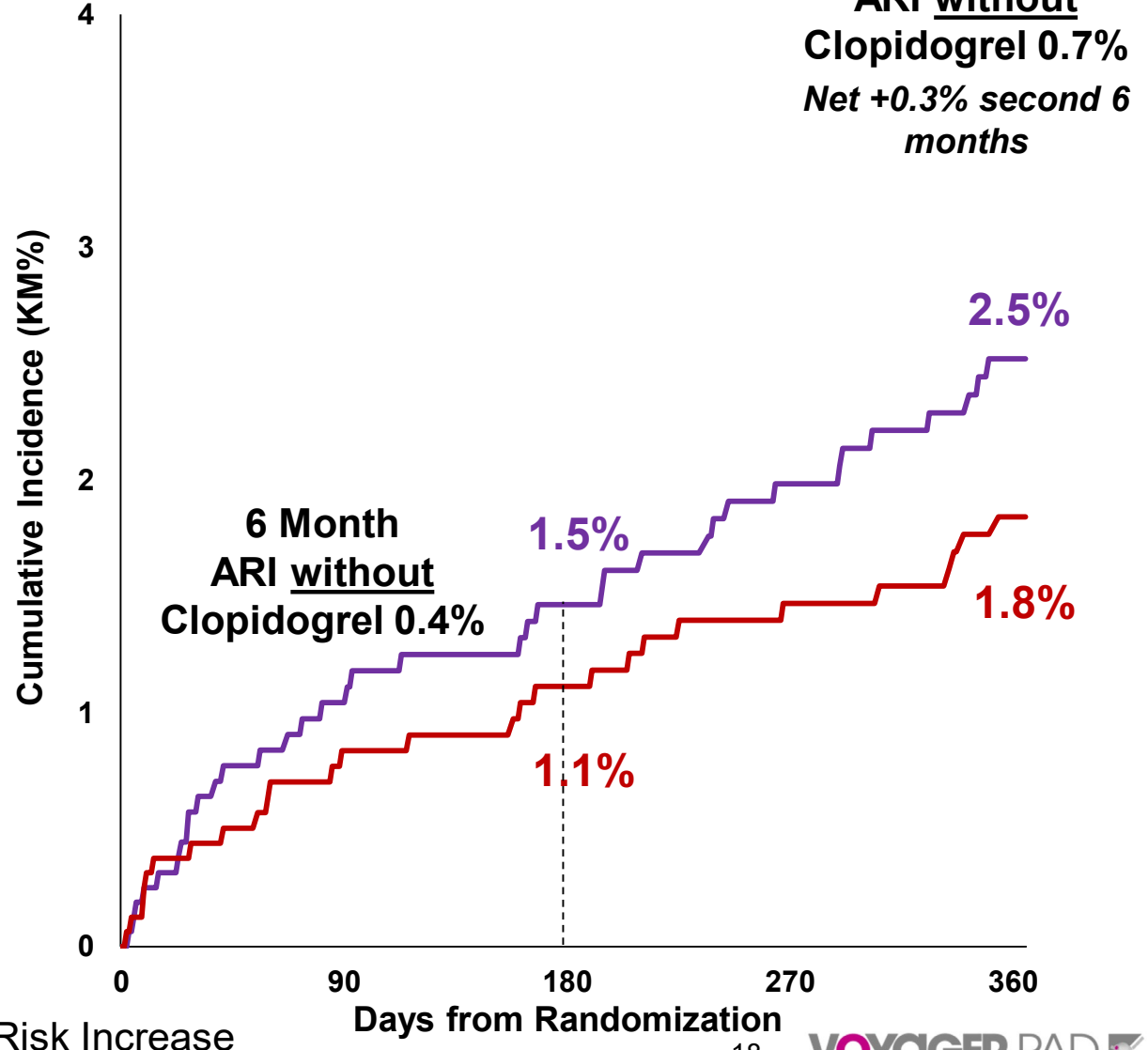
ISTH Major Bleeding With and Without Clopidogrel



ARI = Absolute Risk Increase

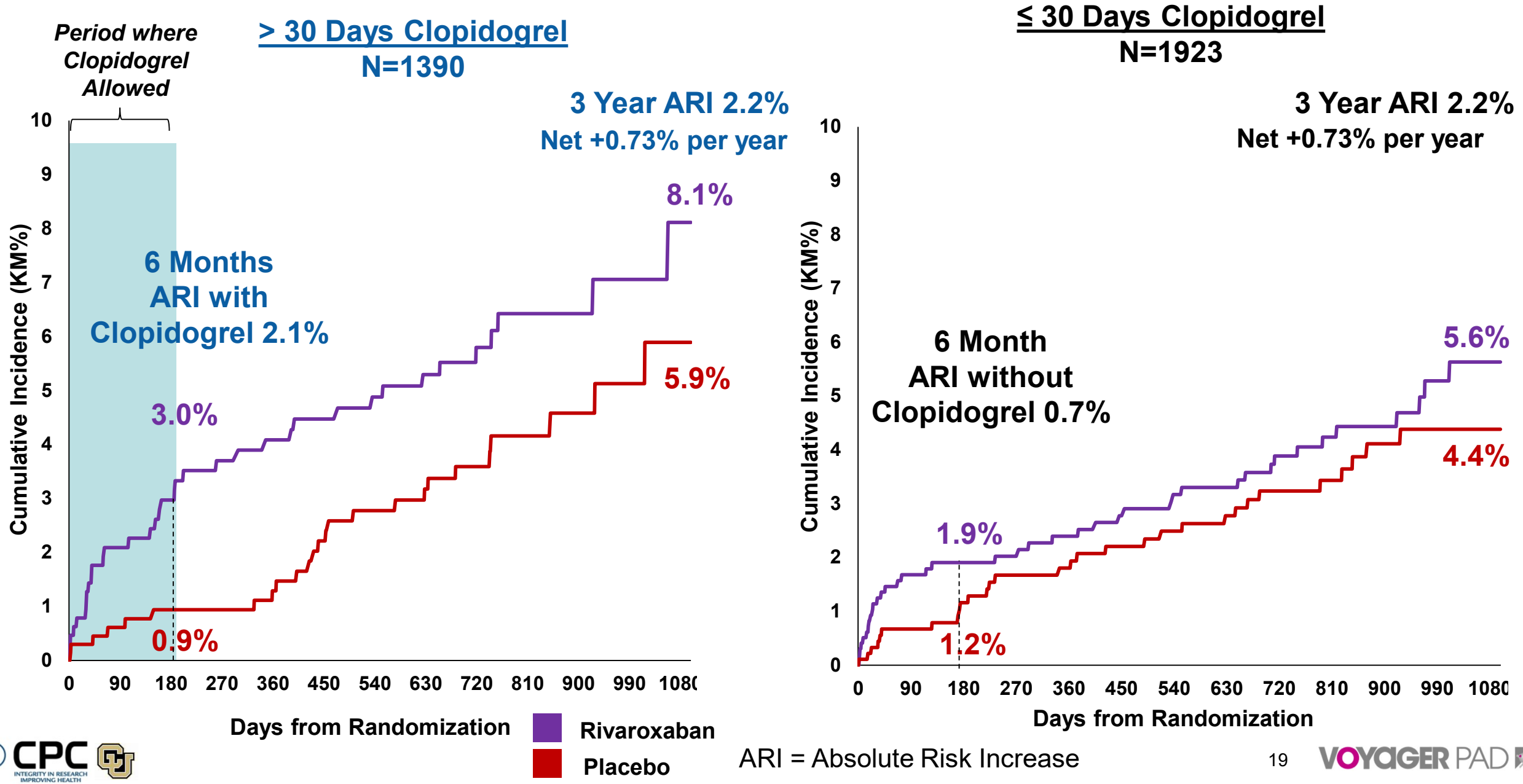
ISTH Major Bleeding With and Without Clopidogrel in Year 1





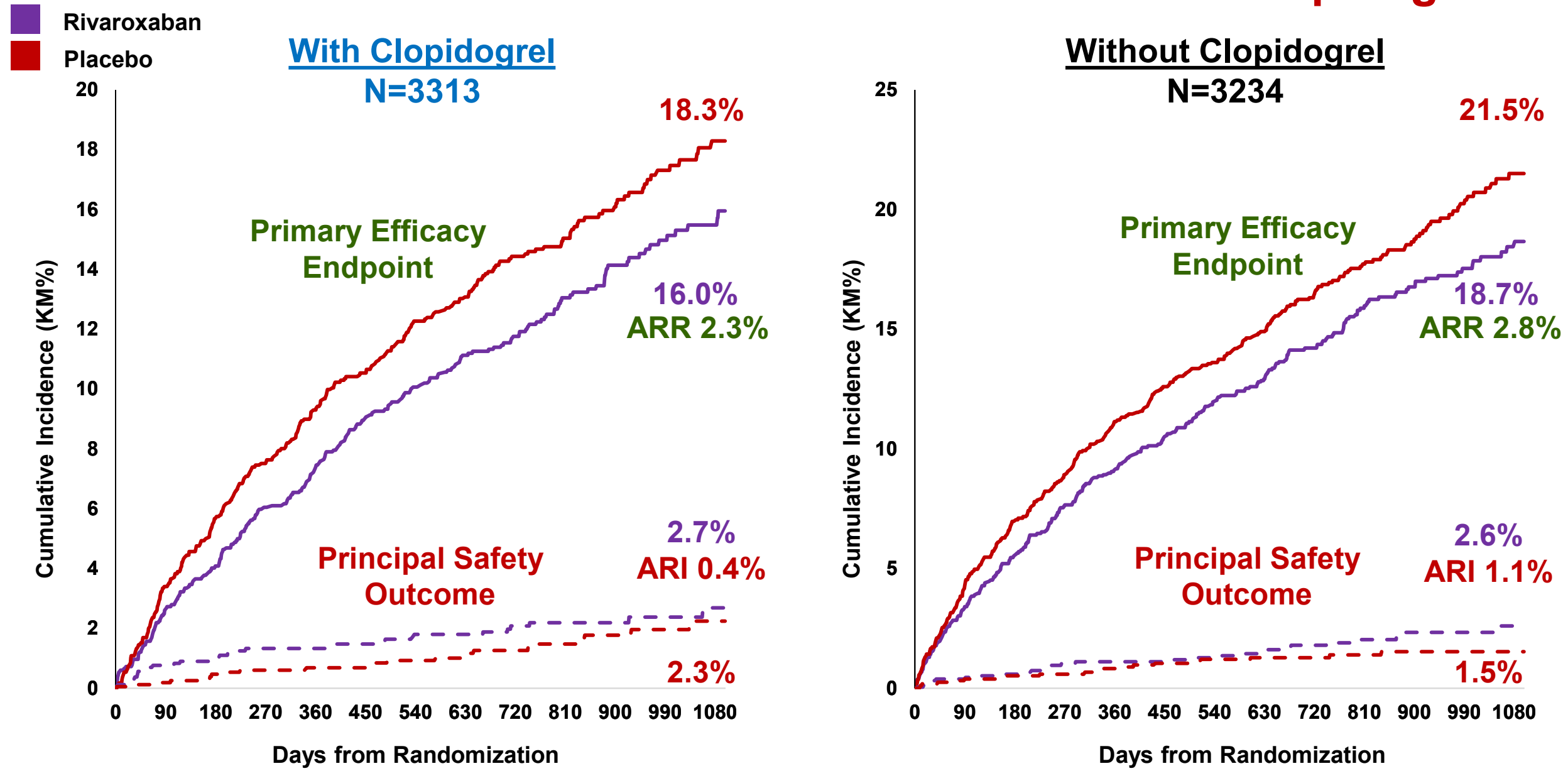
ARI = Absolute Risk Increase

ISTH Major Bleeding by Clopidogrel Duration



ARI = Absolute Risk Increase

Risk and Benefit of Rivaroxaban with and without Clopidogrel



Summary

- **In patients with symptomatic PAD undergoing revascularization:**
  - **The benefit of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of background clopidogrel**
    - ***Primary efficacy endpoint HR ~0.85 with rivaroxaban regardless of clopidogrel with NNT < 50 with or without clopidogrel***
  - **The safety of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of background clopidogrel**
    - ***Principal safety outcome TIMI major bleeding HR ~1.3-1.5 regardless of clopidogrel with NNH > 90 with or without clopidogrel***
  - **However, clopidogrel exposure was associated with higher rates of bleeding overall, particularly with longer durations (e.g. > 30 days)**

Conclusions & Perspective

In patients with symptomatic PAD undergoing revascularization:

- The benefit of DAPT is uncertain, with the only RCT in surgical bypass showing no benefit and significantly increased bleeding
- Rivaroxaban added to aspirin significantly reduces limb and cardiovascular risk with consistent benefits regardless of clopidogrel
- The safety and risk/benefit of rivaroxaban plus aspirin are consistent regardless of background clopidogrel
- In patients receiving rivaroxaban, the addition of clopidogrel as a third agent, is associated with higher rates of bleeding during exposure
- ***More bleeding with background clopidogrel, even if not severe by adjudication, may be associated with broad consequences, including discontinuation of therapies. In the absence of clear benefit, clopidogrel exposure along with aspirin and rivaroxaban should be minimized or avoided to reduce this risk***

Extra Slides

CASPAR (DAPT in PAD Surgical Bypass)

851 patients with PAD undergoing surgical bypass randomized aspirin + placebo or clopidogrel + aspirin. DAPT had no benefit on the composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death, HR 0.98 (95% CI 0.78-1.23, p=NS

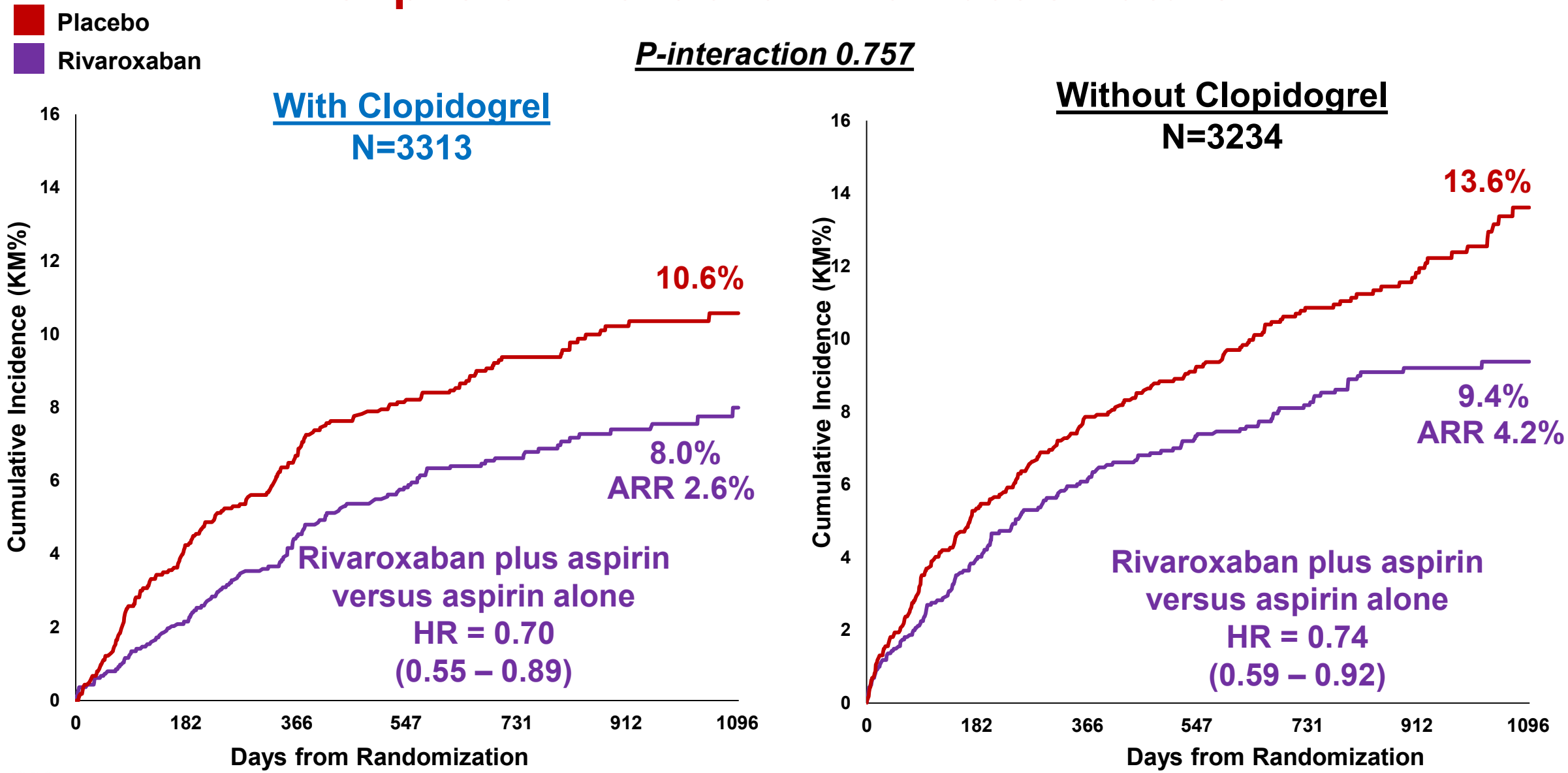
GUSTO bleeding was increased on aspirin + clopidogrel - HR 2.84 (95% CI 1.32-6.08)

Study drug discontinuation (median follow up 1 year) was 21% on placebo and 25% on clopidogrel

All-cause mortality HR 1.44 (95% CI, 0.77-2.68), CV death HR 1.49 (95% CI, 0.73-3.01)

J Vasc Surg 2010;52:825-3

Hospitalization for Coronary or Peripheral Event of a Thrombotic Nature



Unplanned Index Limb Revascularization