Reduction in Venous Thromboembolism with Rivaroxaban versus Placebo in Peripheral Artery Disease after Lower Extremity Revascularization: Insights from VOYAGER PAD

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Disclosures

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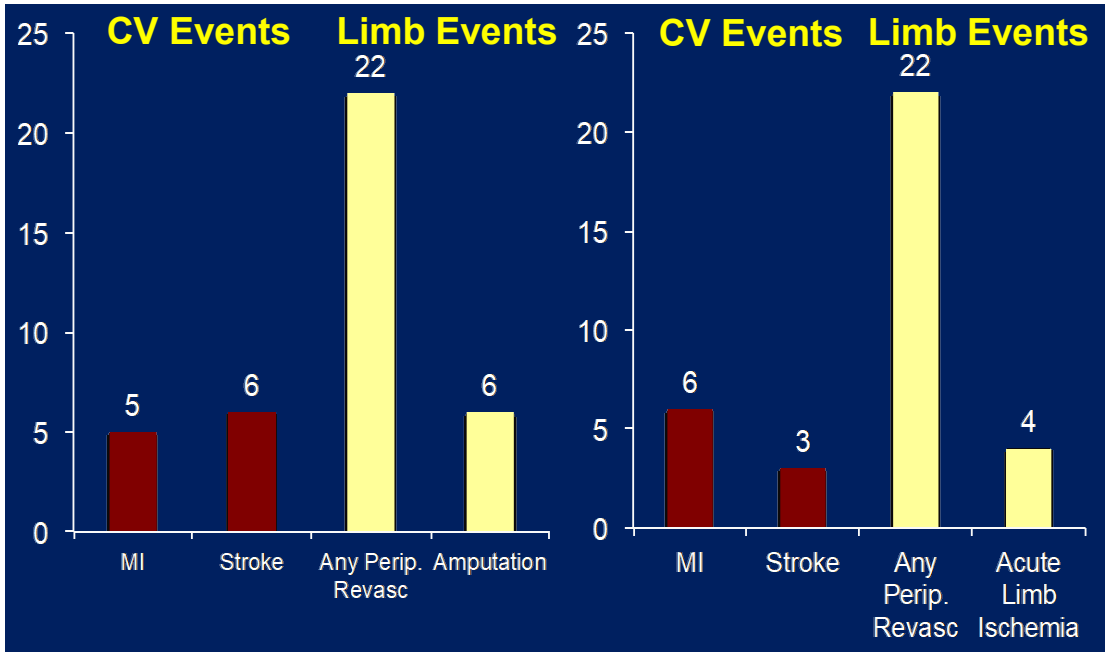
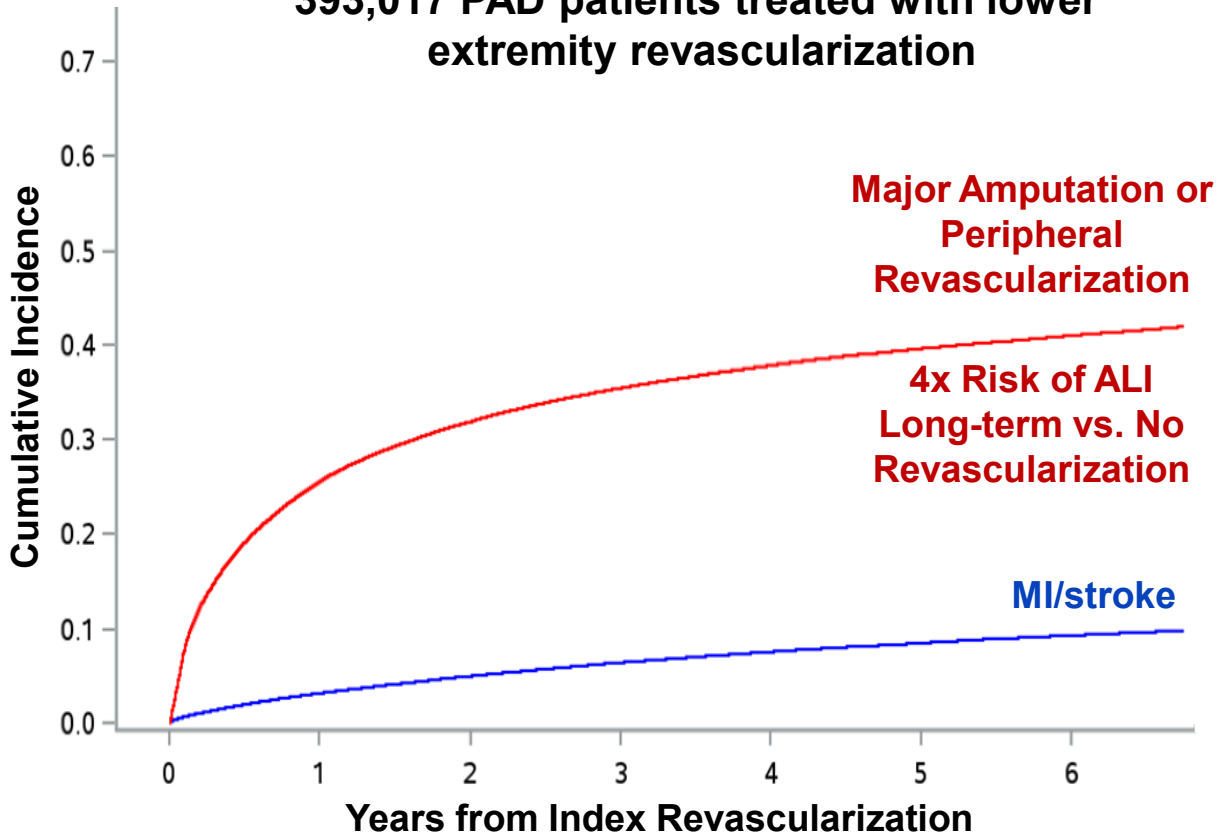
Peripheral Artery Disease (PAD) and Risk of Arterial Thrombosis

4 Year Events in REACH Registry

3 Year Events in TRA2P-TIMI 50



393,017 PAD patients treated with lower extremity revascularization



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CPC Clinical Research

Kumbhani et al. EHJ 2014
Bonaca MP et al. Circulation 2013

Hess CN et al. JACC 2020
Bonaca MP et al. Circulation 2016

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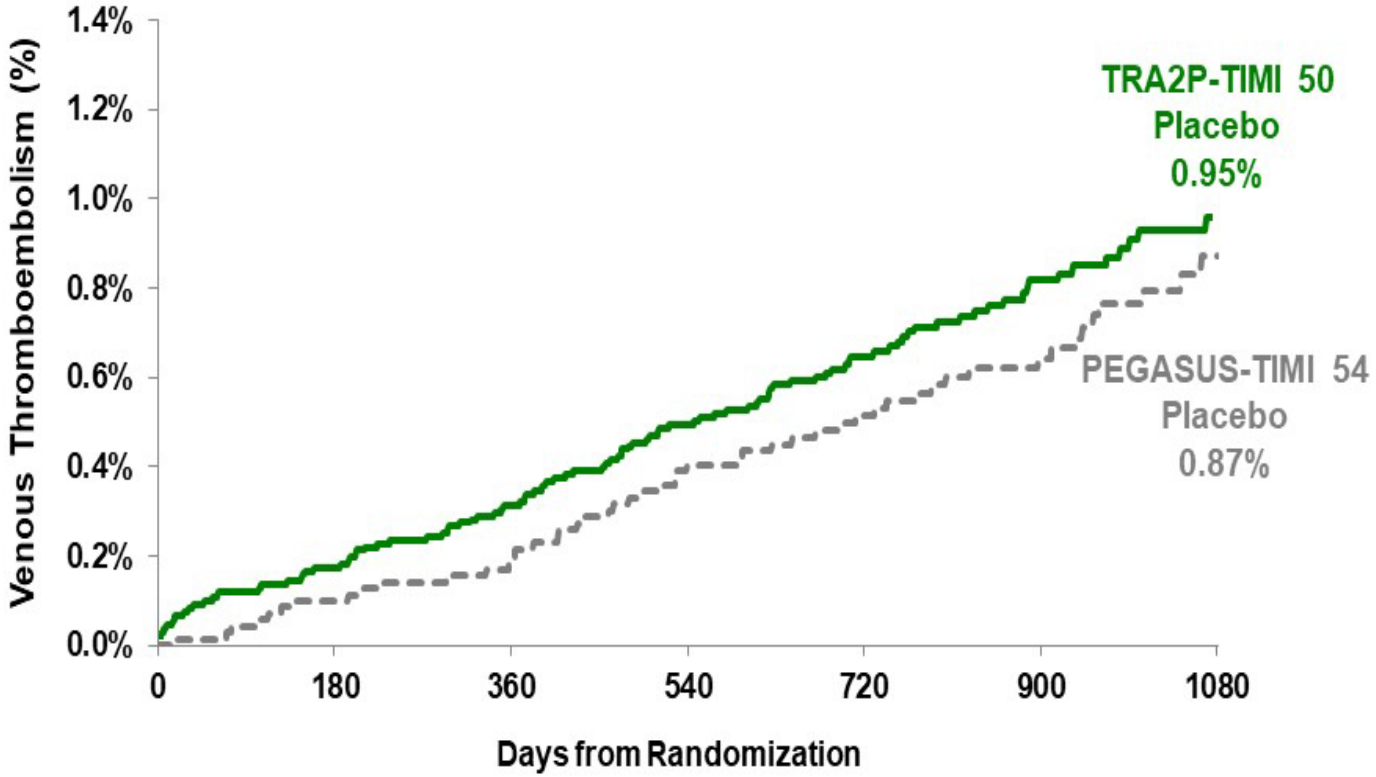
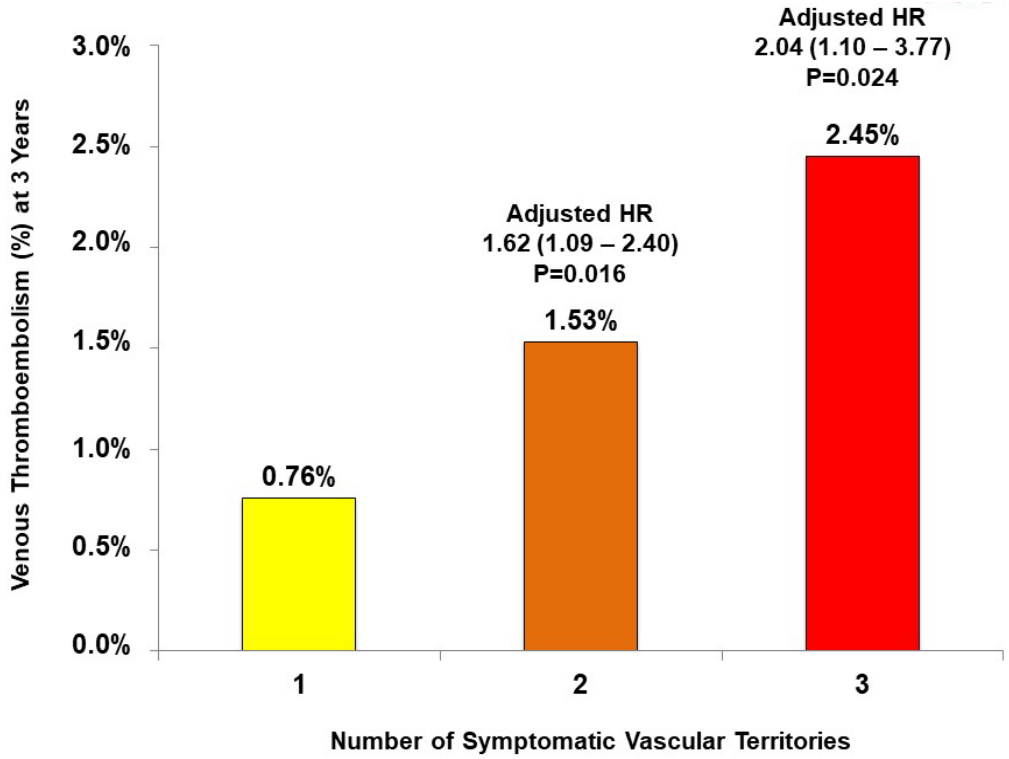
Risk for Venous Thromboembolism (VTE) in Atherosclerosis and Polyvascular Disease

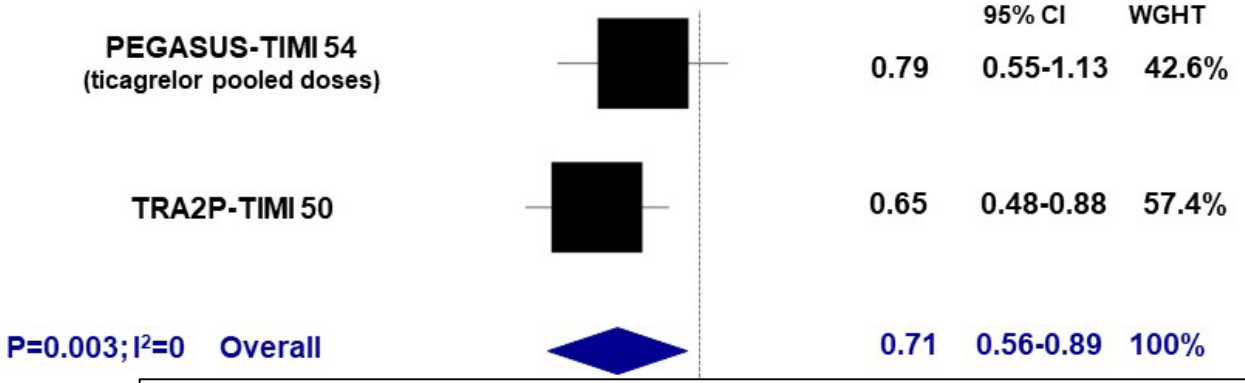
47,611 patients followed for 3 years



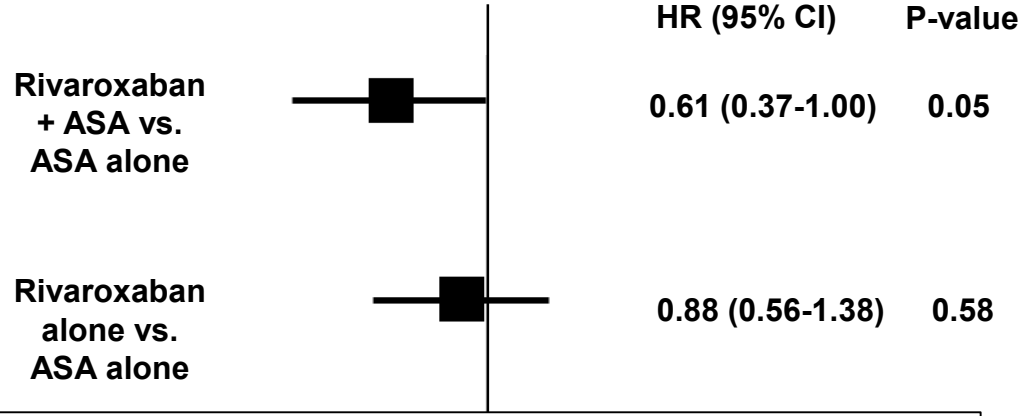


More Intense Antithrombotic Therapy Reduces VTE Risk in Stable Vascular Disease

More intensive antiplatelet therapy



Rivaroxaban 2.5 mg twice daily plus aspirin (COMPASS)



- Risk of VTE and effect of vascular dose rivaroxaban in symptomatic PAD undergoing revascularization has not been described
- Whether effect of vascular dose rivaroxaban on VTE is modified by background dual antiplatelet therapy is unknown

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Cavallari I et al. Circulation 2018
Eikelboom JW et al. NEJM 2018

VOYAGER PAD

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Trial Design

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

Placebo

Stratified by Revascularization Approach (Surgical or Endovascular) and Use of Clopidogrel

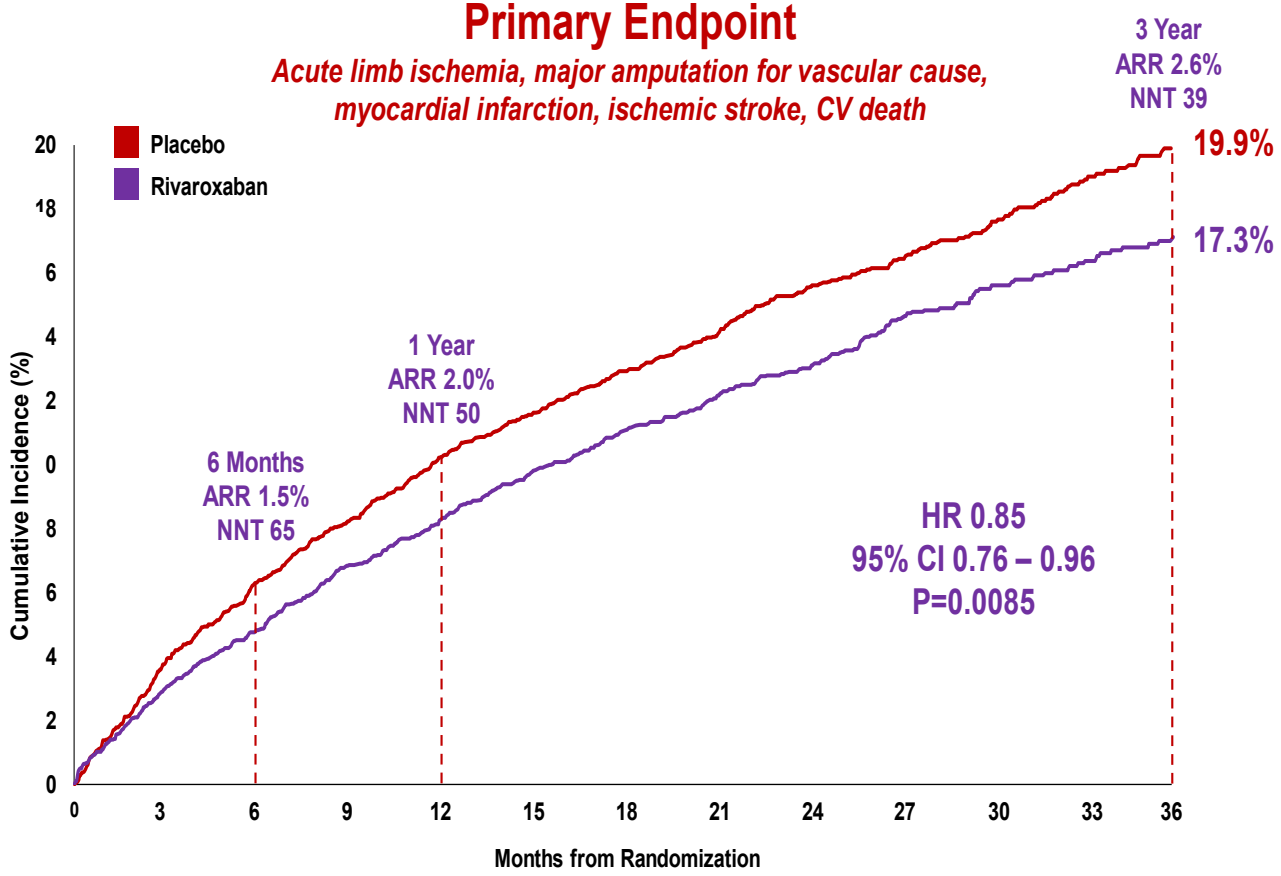
Follow up Q6 Months, Event Driven, Median f/u 28 Months

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

Principal Safety Endpoint: TIMI Major Bleeding

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

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Bonaca MP, et al. NEJM 2020

VOYAGER PAD

Objectives

In symptomatic PAD patients undergoing lower extremity revascularization (LER):

- **To characterize the pattern of risk for VTE**

- **To evaluate the effect of rivaroxaban 2.5 mg twice daily plus low dose aspirin versus low dose aspirin alone on VTE as well as the spectrum of acute arterial and venous thrombotic events**

Methods

- Prespecified secondary analysis of VOYAGER PAD
- Primary outcome symptomatic VTE
- VTE prospectively ascertained and a prespecified secondary endpoint
- Exploratory outcome composite of acute venous or arterial thrombotic events (VTE, acute limb ischemia, major amputation of vascular etiology, myocardial infarction, or ischemic stroke)
- Effect of rivaroxaban estimated with Cox proportional hazards model

Baseline Characteristics

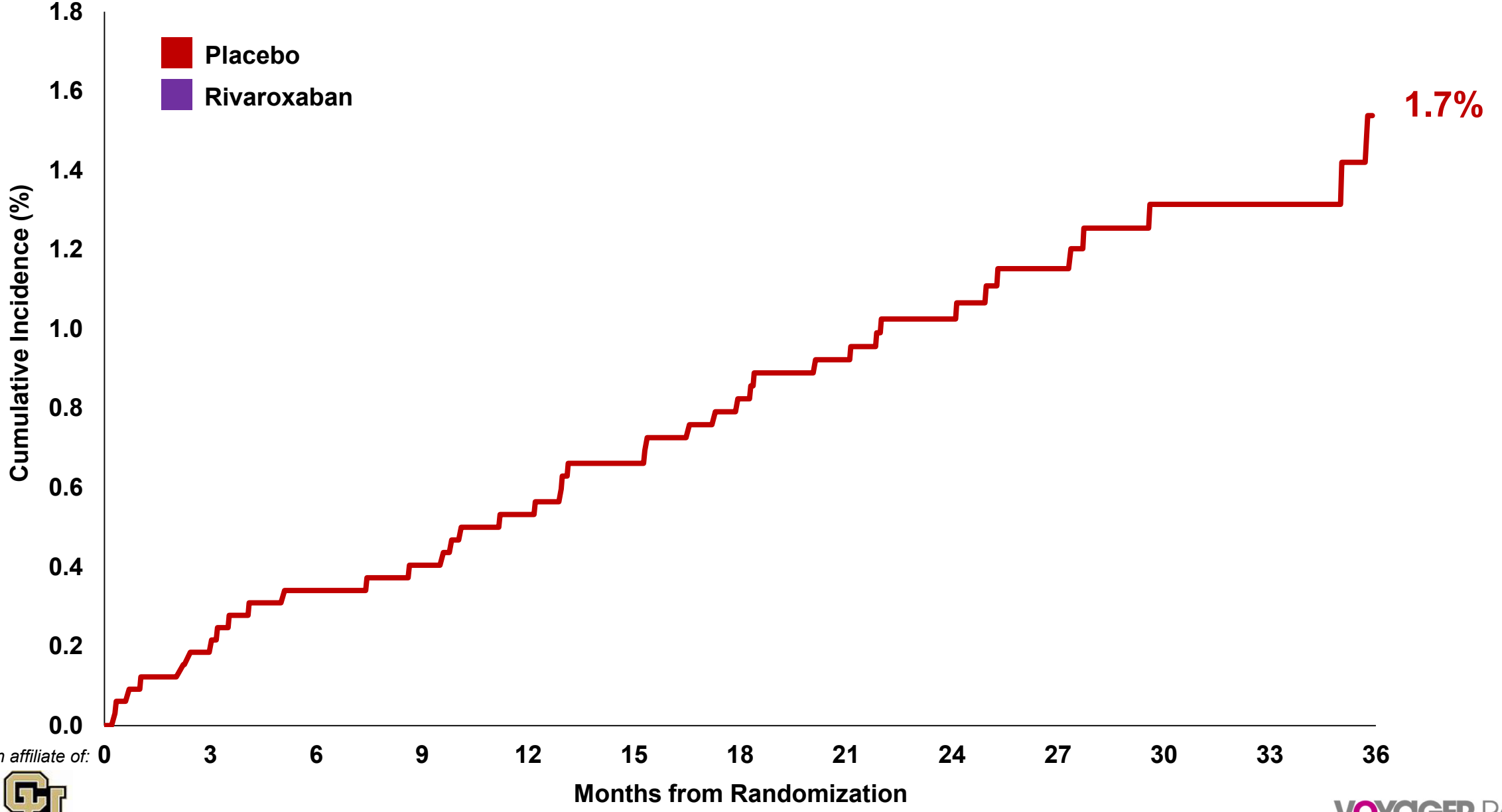
66 patients with VTE by efficacy cut-off date
Incidence of 0.42 per 100 patient-years

Characteristic at Randomization	With VTE N=66 %	Without VTE N=6498 %	P-value
Age, years median (IQR)	68 (64-75)	67 (61-73)	0.14
Age ≥75 years	29	20	0.09
Female	24	26	0.89
Caucasian	89	81	0.14
Weight ≤60 kg	8	17	0.05
Hypertension	91	81	0.05
Diabetes mellitus	39	40	>0.99
Hyperlipidemia	55	60	0.37
Current smoking	29	35	0.41
eGFR < 60 ml/min/1.73m^2	26	20	0.28
Coronary artery disease	32	31	>0.99
Baseline clopidogrel use	52	60	0.24
Baseline statin use	77	80	0.54

PAD & Procedural Characteristics

	With VTE N=66 %	Without VTE N=6498 %	P-value
Peripheral Artery Disease History			
Prior endovascular revascularization	38	29	0.13
Prior surgical revascularization	15	10	0.21
Prior amputation	11	6	0.11
ABI at screening, median (IQR)	0.5 (0.4-0.7)	0.6 (0.4-0.7)	0.69
Indication for Revascularization			
Critical limb ischemia	26	23	0.66
Claudication	74	77	
Qualifying Revascularization			
Surgical	38	33	0.43
Endovascular or hybrid	62	67	

Effect of Rivaroxaban 2.5 mg on VTE



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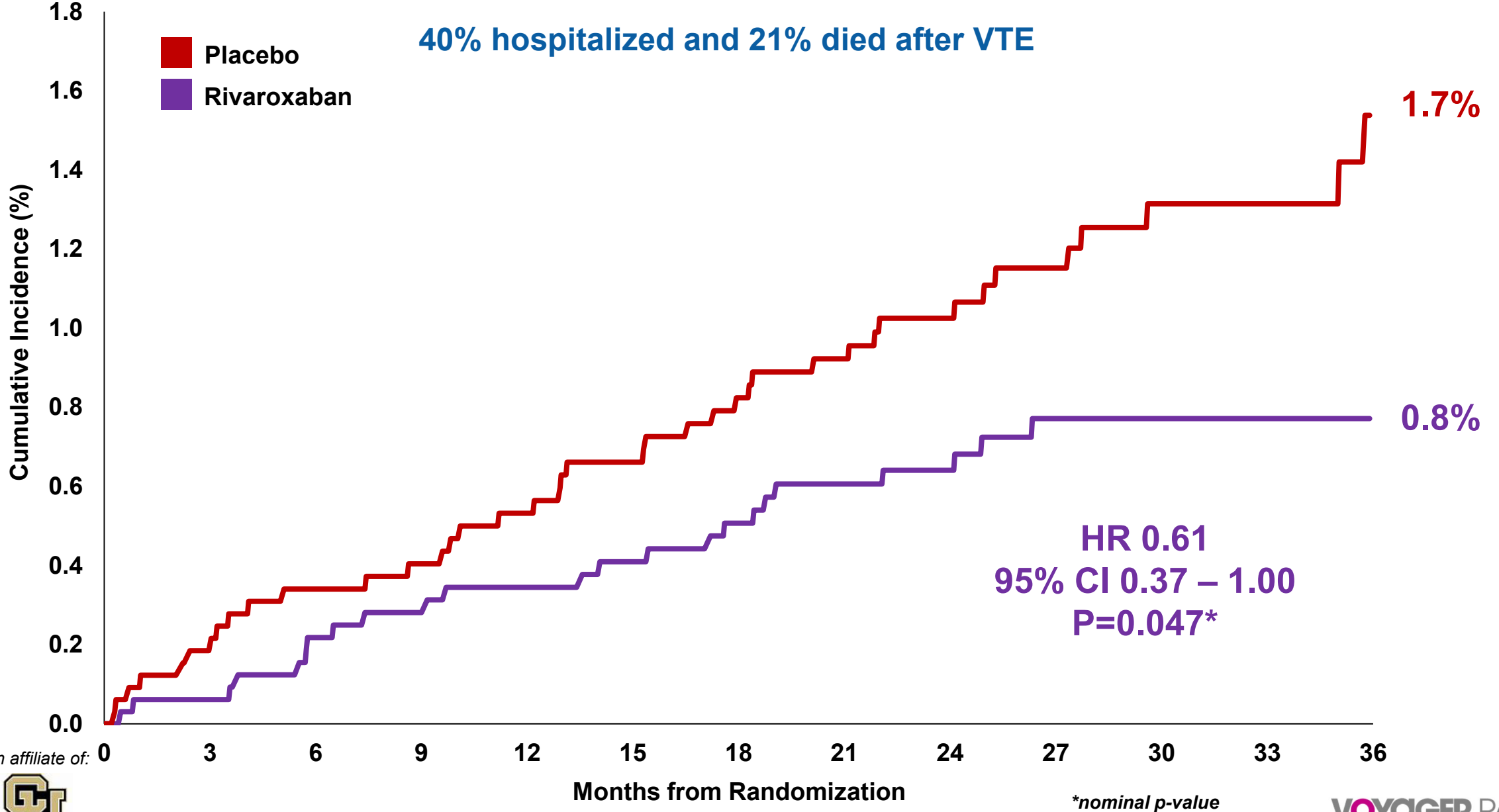
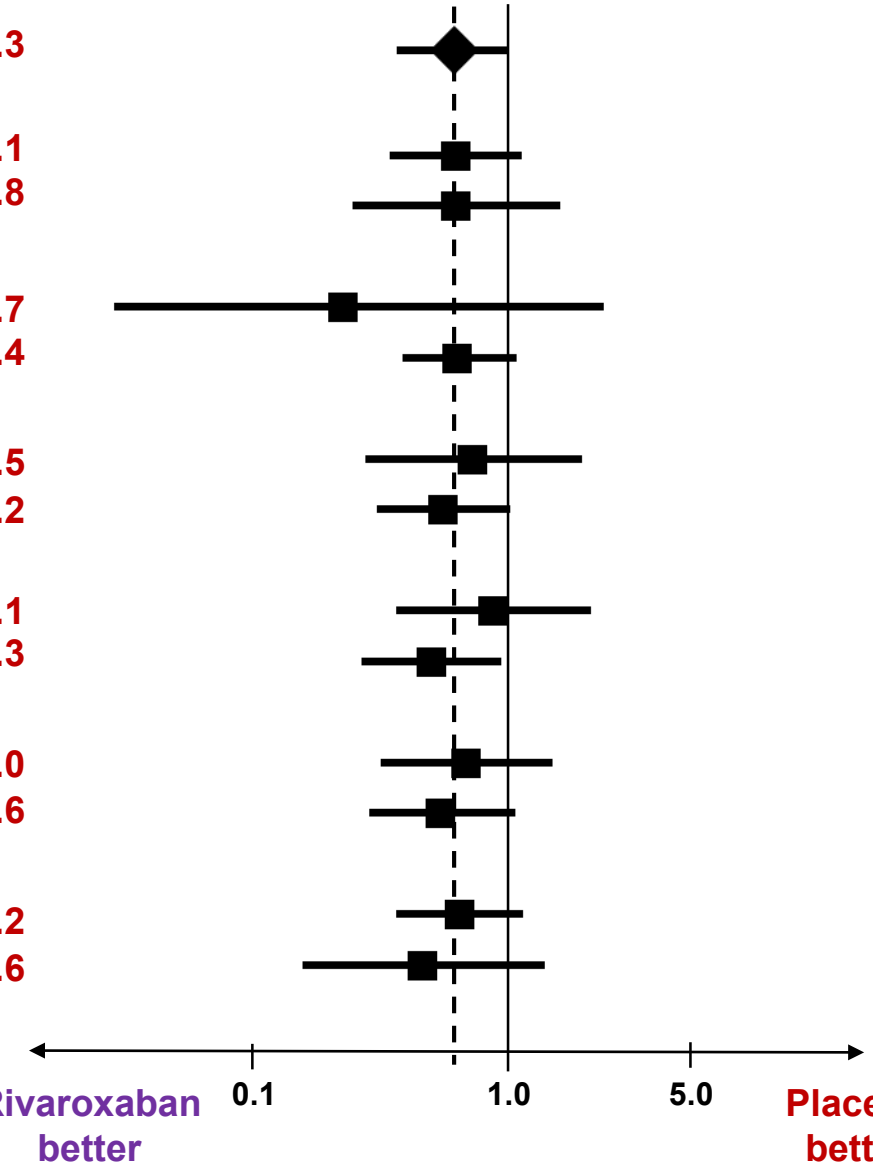
Effect of Rivaroxaban 2.5 mg on VTE



*nominal p-value

Effect of Rivaroxaban 2.5 mg on VTE in Selected Subgroups

	Characteristic	Rivaroxaban n/N (%)	Placebo n/N (%)	HR (95% CI)	P-interaction
All subjects		0.8	1.3	0.61 (0.37, 1.00)	
Age	<75 years	0.7	1.1	0.63 (0.35, 1.13)	0.89
	≥75 years	1.0	1.8	0.63 (0.25, 1.59)	
Weight	≤60 kg	0.2	0.7	0.26 (0.03, 2.33)	0.42
	>60 kg	0.9	1.4	0.64 (0.39, 1.08)	
eGFR	<60 ml/min/1.73m^2	1.1	1.5	0.73 (0.28, 1.92)	0.65
	≥60 ml/min/1.73m^2	0.7	1.2	0.56 (0.31, 1.02)	
CAD	Yes	1.0	1.1	0.88 (0.37, 2.08)	0.31
	No	0.7	1.3	0.51 (0.27, 0.94)	
Baseline clopidogrel	Yes	0.7	1.0	0.69 (0.32, 1.48)	0.67
	No	0.9	1.6	0.55 (0.29, 1.07)	
Baseline statin	Yes	0.8	1.2	0.65 (0.37, 1.14)	0.62
	No	0.7	1.6	0.47 (0.16, 1.38)	



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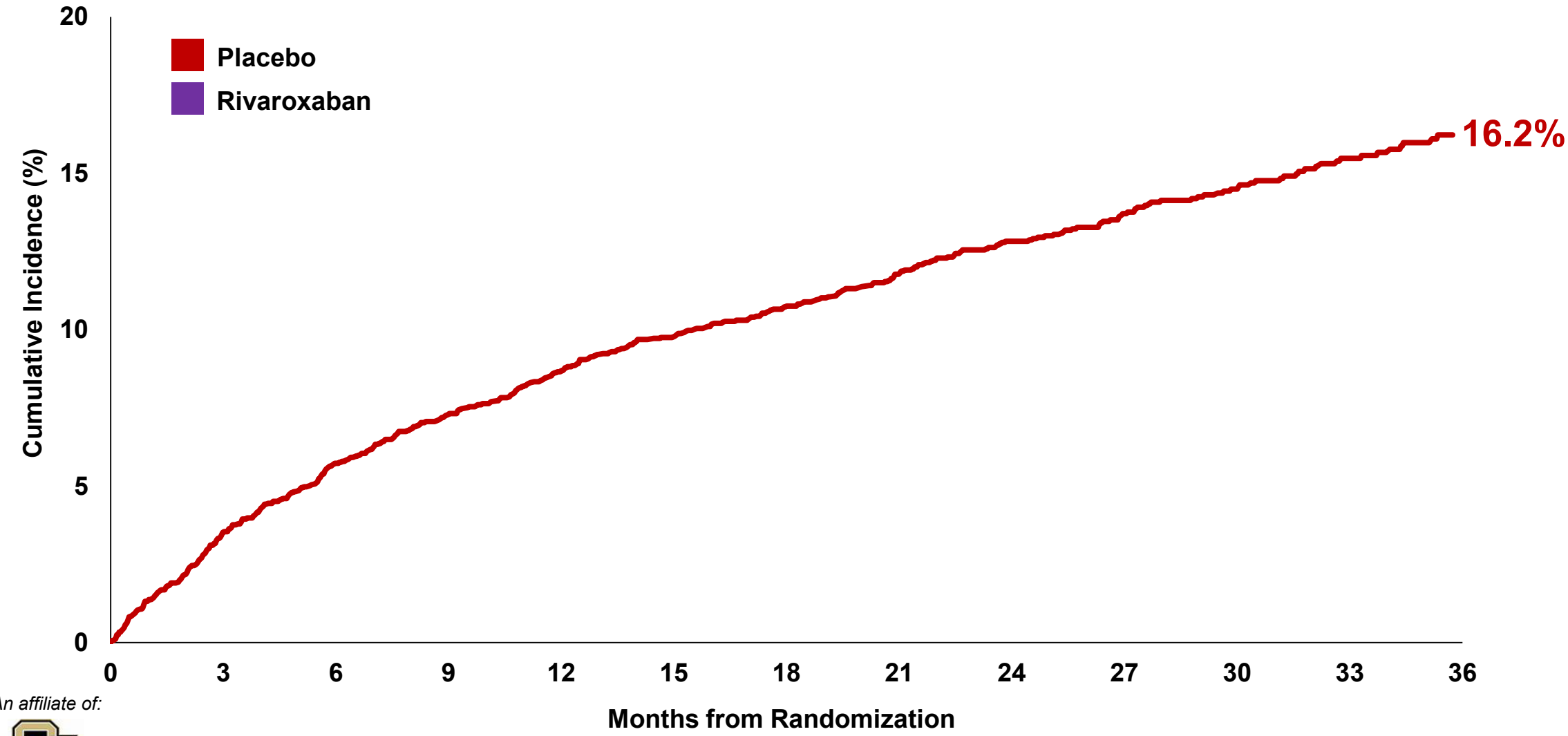
Effect of Rivaroxaban 2.5 mg on Acute Venous and Arterial Thrombotic Events

VTE, acute limb ischemia, major amputation of vascular etiology, myocardial infarction, or ischemic stroke



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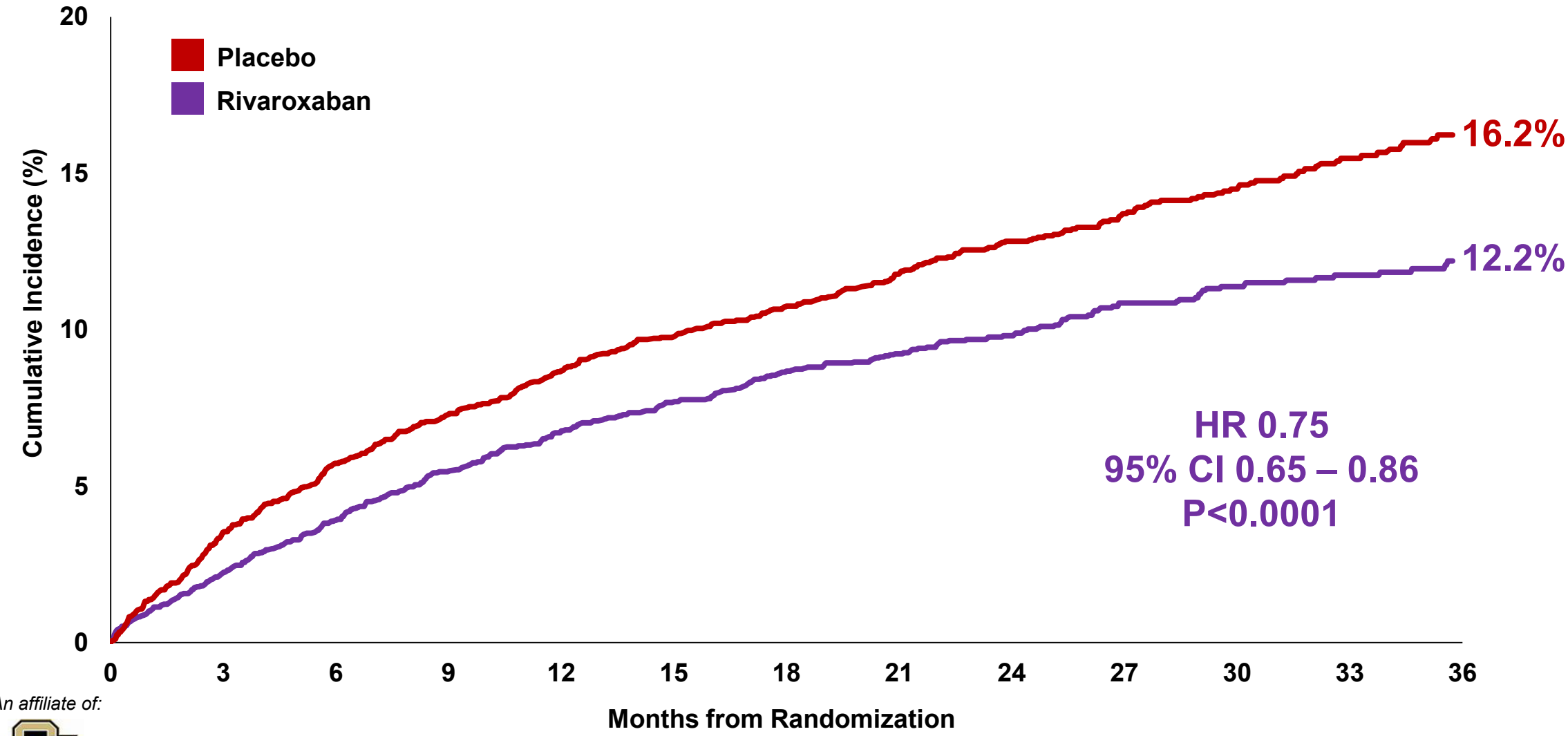

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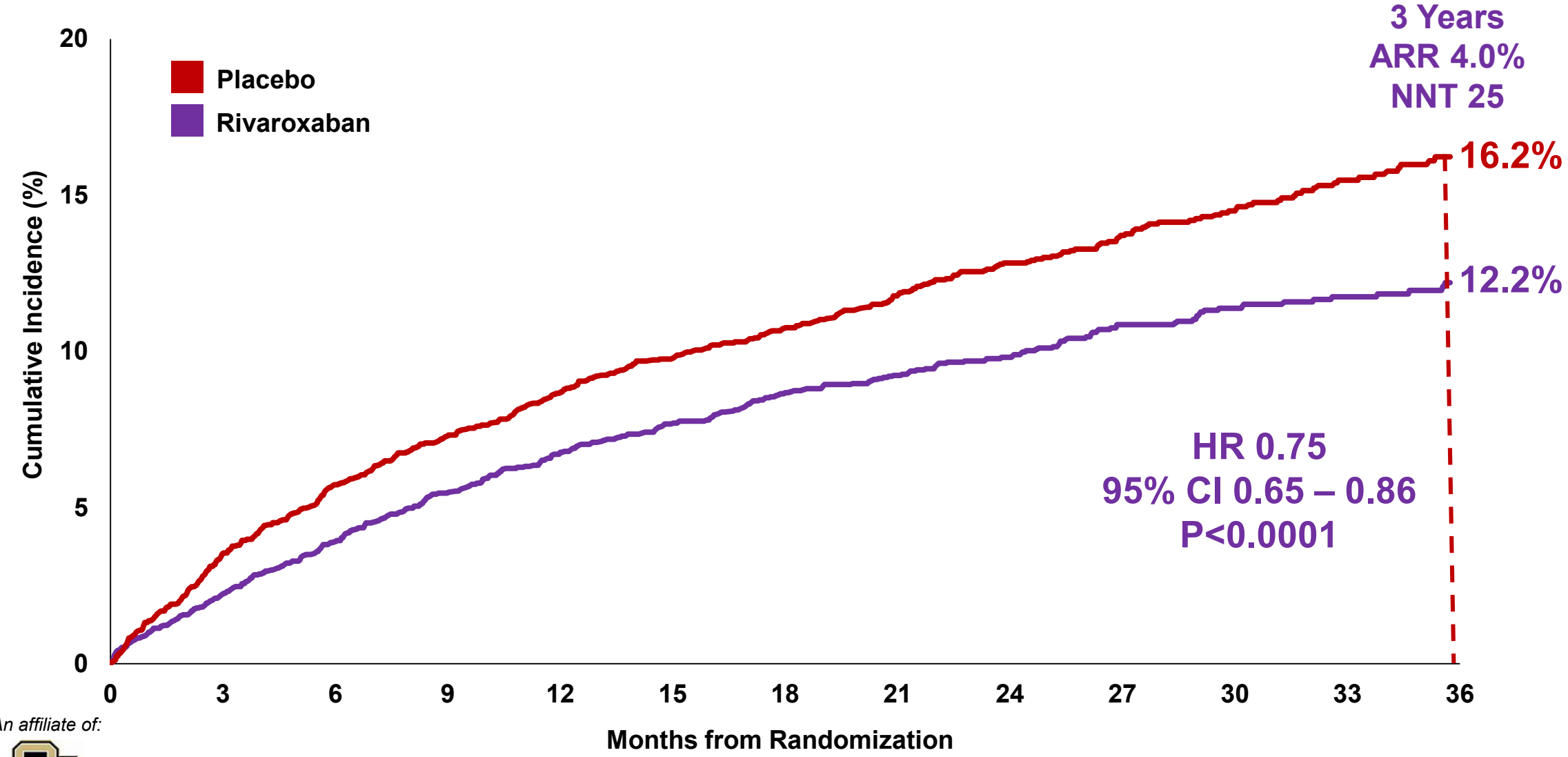

Summary

- VTE risk is linear after revascularization for PAD and occurs at a rate ~2x that observed in stable vascular disease populations
- Risk of VTE is lower with Rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone
- This benefit appears early, persists over time, and is consistent in major subgroups, including:
  - *Age, body weight, renal dysfunction, polyvascular disease, statin use*
  - *Background clopidogrel/DAPT use*
- Rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone reduces risk of acute venous and arterial thrombotic events

Conclusions

- **Atherosclerosis severity is a risk factor for VTE, and patients with symptomatic PAD undergoing revascularization are at high risk**
- **Outcomes after VTE are poor**
- **Rivaroxaban plus aspirin provides protection against the full spectrum of acute venous and arterial thrombotic events after LER regardless of background therapy and should be considered early to reduce this risk**

Thank You