Highlighted Original Research: Vascular Medicine Year/Decade in Review Putting VOYAGER PAD in Context

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University of Colorado
Anschutz Medical Campus

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William R Hiatt Disclosures

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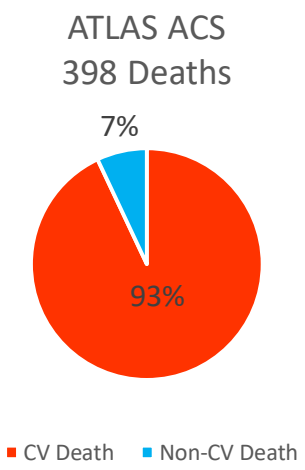
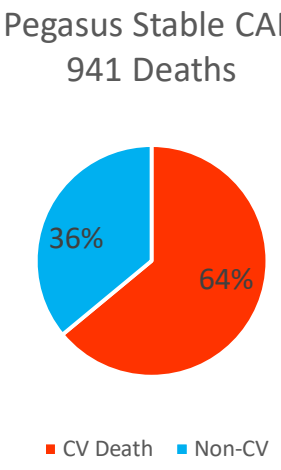
- **Bayer**
- **Janssen**
- **Amgen**

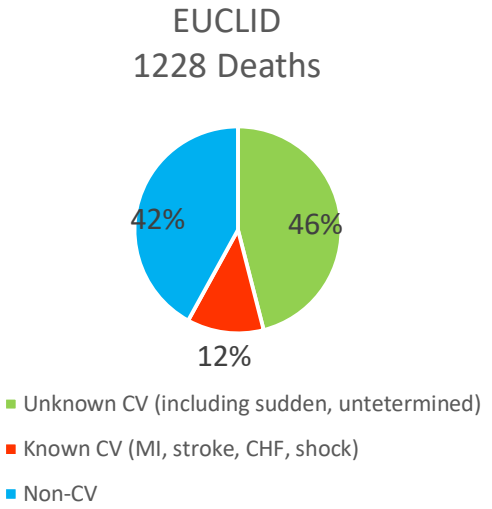
PAD is Clinically Distinct from CAD

Trial	Population	CAD	Prior MI
ATLAS ACS	Recent ACS	100%	27%
Pegasus	Prior MI	100%	100%
Compass PAD subgroup	CAD + PAD	66%	?
Euclid	Stable PAD	29%	18%
Voyager PAD	PAD revasc	31%	11%

Causes of Death

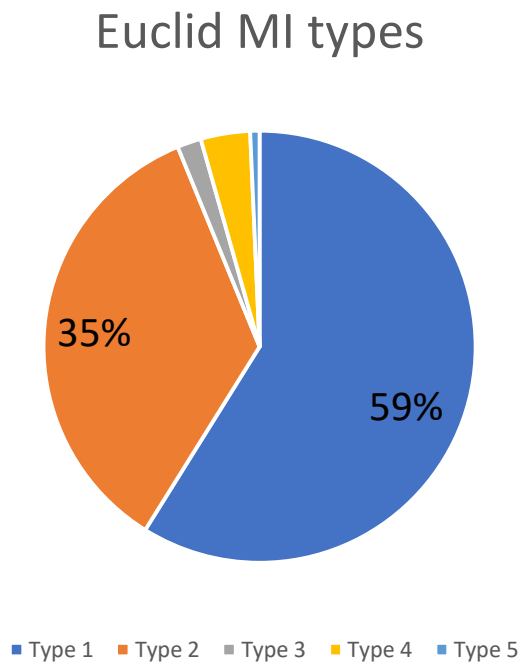






NEJM 2012;366:9-19, NEJM 2015;372:1791-1800, Lancet 2018;391:219-229, NEJM 2017;376:32-40, NEJM 2020;in press

Stable PAD Types of MI



Euclid stable PAD - MI rate 2.4/100 pt-years

- Type 1 modifiable by antithrombotic
- Type 2 not modifiable – supply-demand mismatch

JAMA Cardiol. 2019;4:7-15

PAD in Genetically Distinct from CAD

Thrombophilic Factor V Leiden variant *F5* p.R506Q

Disease	HR (95% CI)
CAD	1.01 (0.97-1.05)
Stroke	1.03 (0.89-1.20)
PAD (all)	1.20 1.14-1.27)
Claudication	1.20 (1.09-1.35)
Rest pain	1.42 (1.12-1.80)
Tissue loss	1.57 (1.34-1.83)

However, 19 loci (18 new) associated with LDL cholesterol had similar *associations with coronary, cerebral and peripheral vascular diseases*

Nature Medicine 2019;25:1274–1279

PAD not CAD at Risk for Chronic Limb-Threatening Ischemia

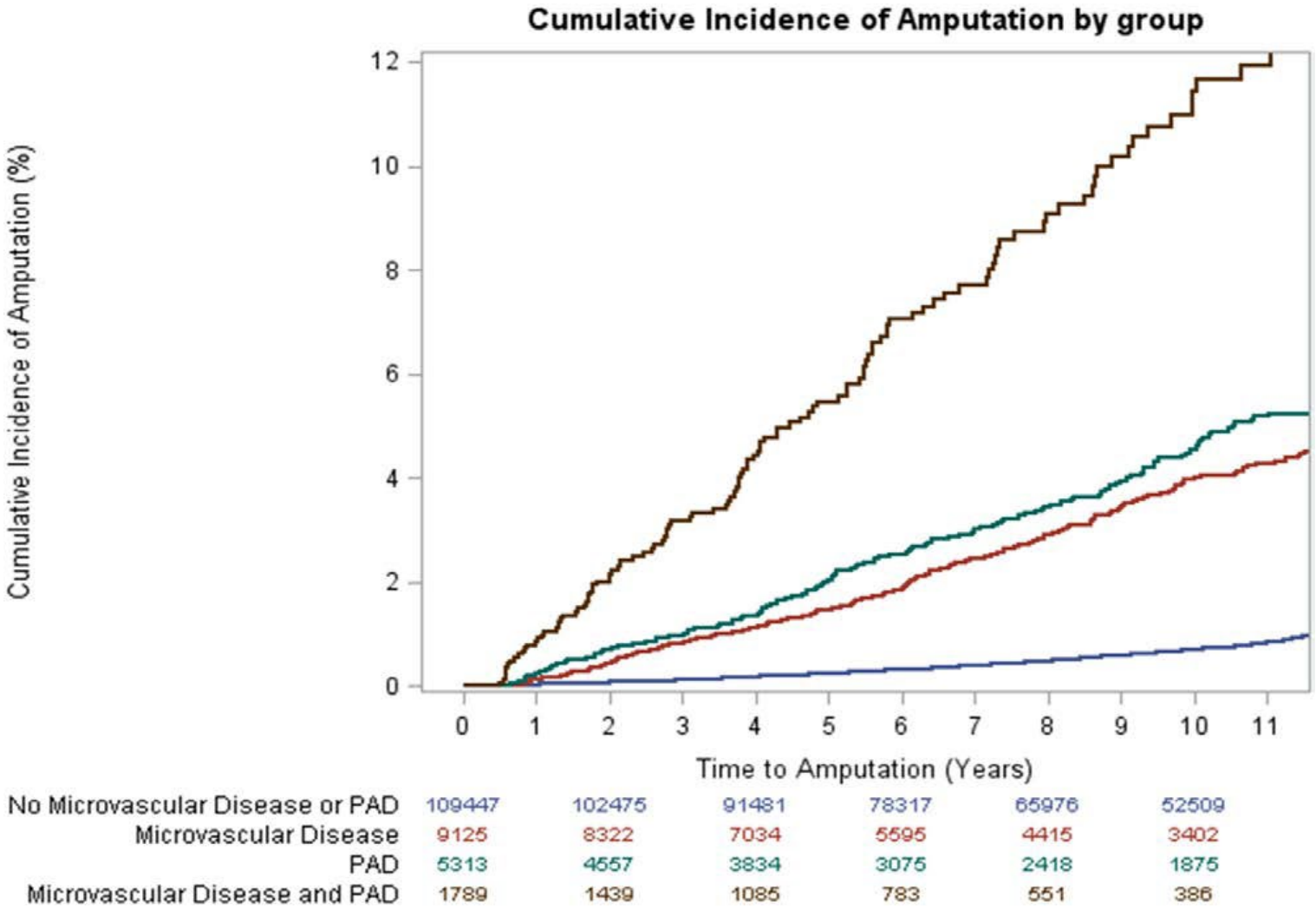
Wifi classification for CLTI

Wound		
Ulcer		Gangrene
Ischemia		
ABI	Ankle BP	$TcPO_2$
Foot infection		
Clinical manifestation	SVS grade	Infection severity

In addition to large vessel hemodynamics,
microvascular disease contributes to wounds, infection and limb loss

J Vasc Surg 2019;69:3S-125S

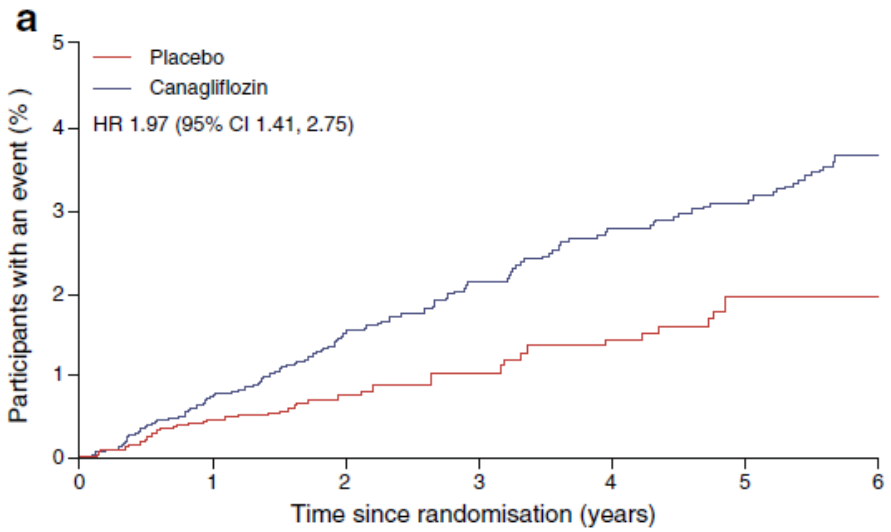
Microvascular Disease and Amputations



Circulation 2019;140:449-58

Heterogenous Effects for SGLT2 Inhibition for MACE and Amputation

All Amputations with Canagliflozin



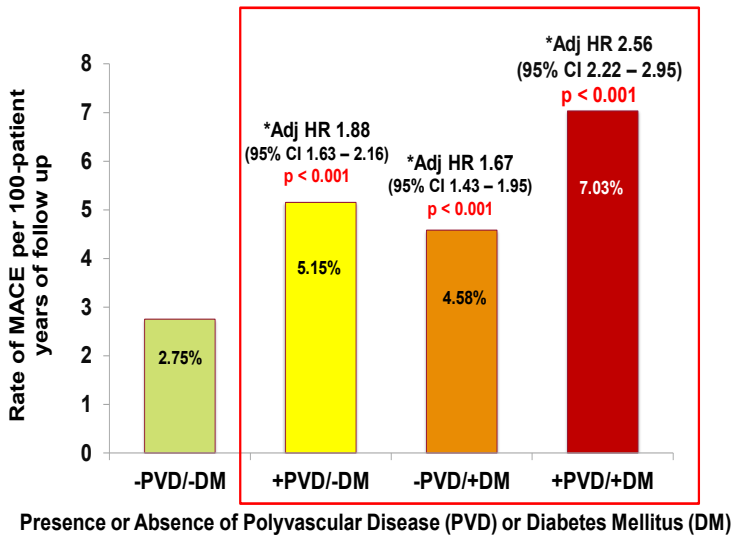
	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)
History of amputation			
Yes	96.30	59.16	2.15 (1.11–4.19)
No	4.68	2.48	1.88 (1.27–2.78)
History of peripheral vascular disease			
Yes	12.09	8.16	1.39 (0.80–2.40)
No	5.20	2.41	2.34 (1.53–3.58)

MACE HR 0.86 (0.75 – 0.97)
Amputation HR 1.97 (1.41-2.75)

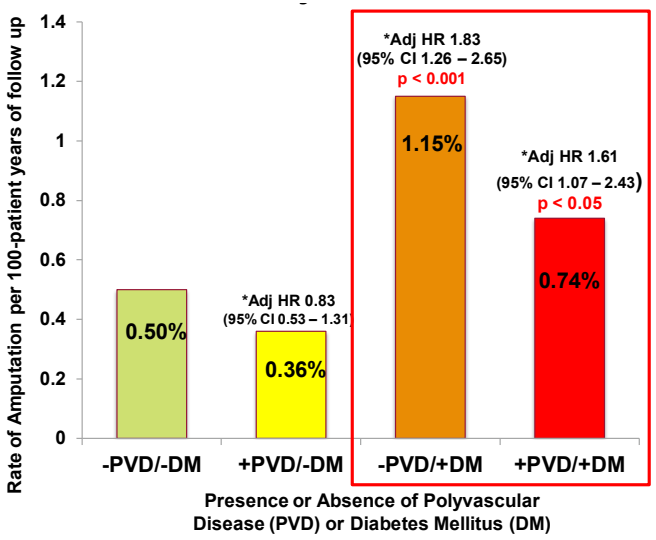
Neal et al. NEJM 2017,
Matthews, .Hiatt, .Nehler Diabetologia 2019;62:926-38

EUCLID – Polyvascular Disease and Diabetes Risks

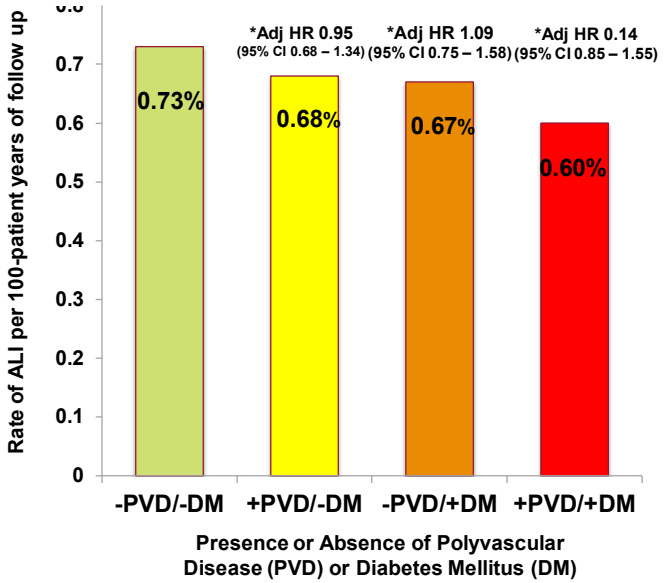
Both polyvascular disease and diabetes independently associated with MACE



Diabetes but not polyvascular disease independently associated with Amputation



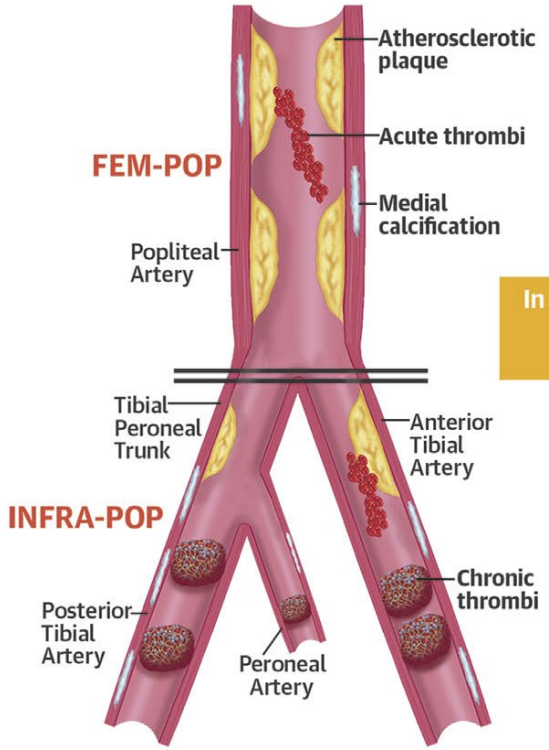
Neither polyvascular disease or diabetes independently associated with Acute limb ischemia

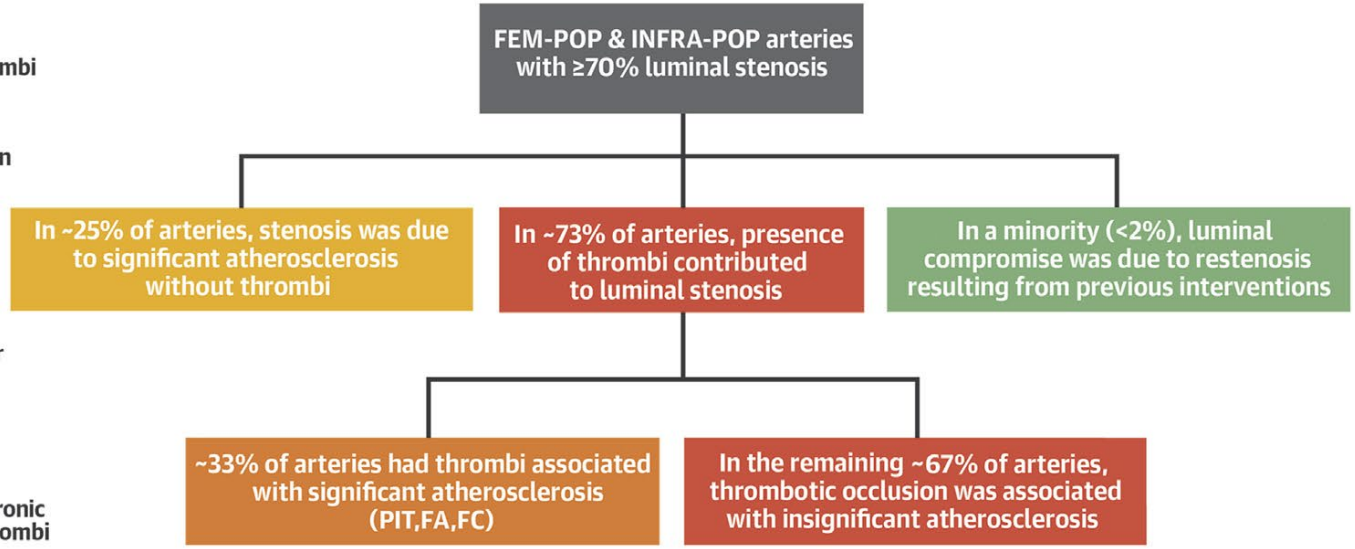


The predictors of MACE and limb outcomes may differ and the predictors of limb outcomes may depend on the type and underlying biology

Sean Behan, MD ACC abstract 2020

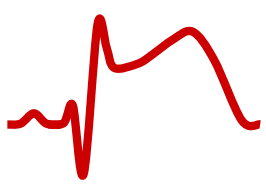
Thrombosis in CLTI Amputations

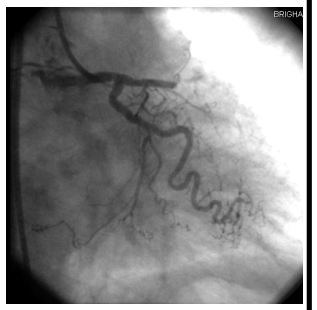




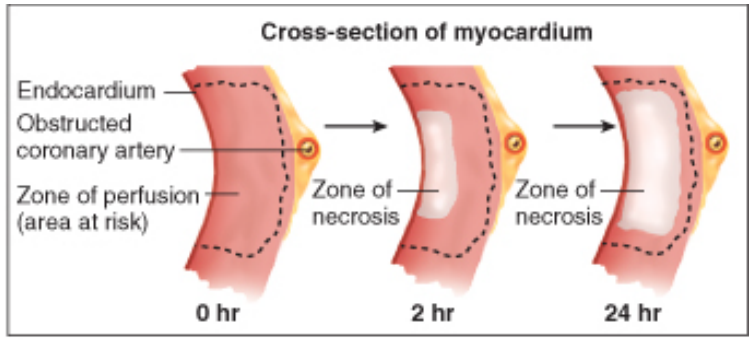
J AM Coll Cardiol 2018;72:2152-

STEMI





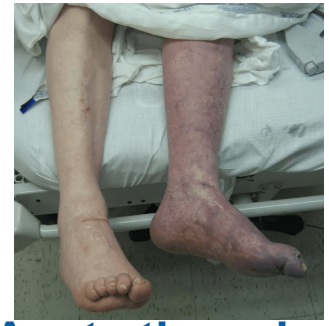
- Acute thrombotic occlusion of an artery threatening tissue loss
- "Time Is Muscle"
- Outcomes determined by time to acute reperfusion

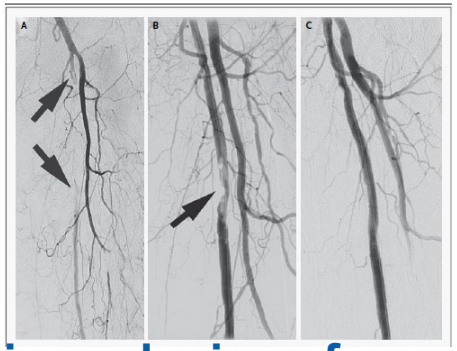


- Mortality at 1 year 8.1%
- Recurrent MACE at 1 year 3.4%
- HF at 1 year 7.4%

Zeymer et al. EORP EU STEMI Registry 2019

ALI





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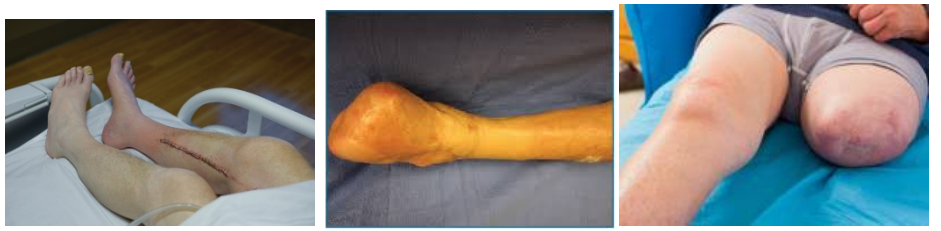


0 Hour → 24 Hour

- Mortality at 1 year 12.1%
- MACE 11.7%, Recurrent ALI 24% (1 yr)
- Amputation at 1 year 27%

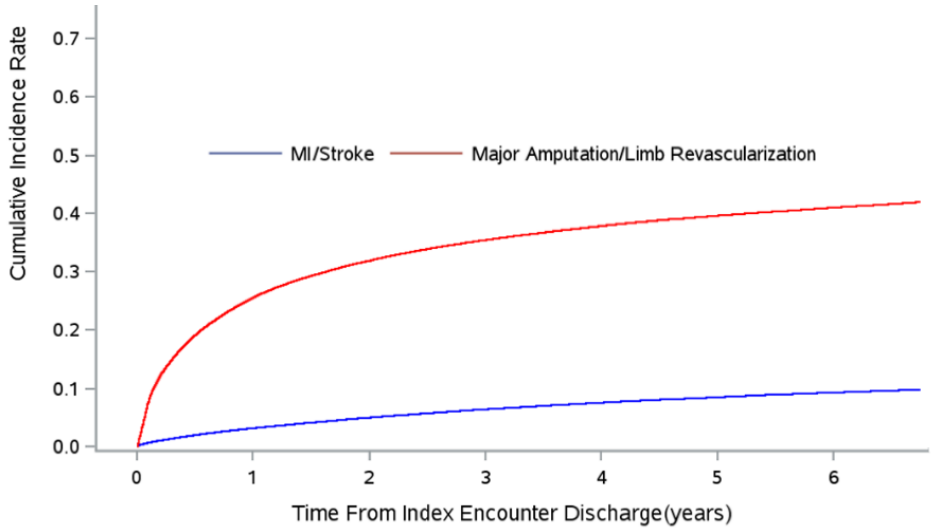
Bonaca et al. Circulation 2016

Courtesy of Marc Bonaca

PAD High Risk for ALI After Intervention

PEGASUS-TIMI 54 PAD
Prior revascularization
aHR for ALI 3.76 (2.26 – 6.25)

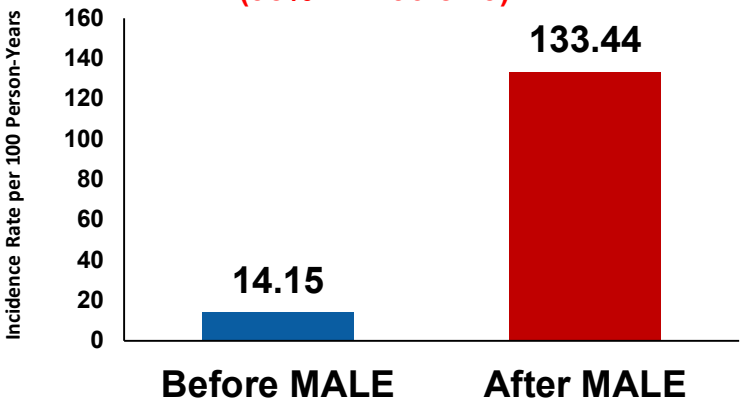
EUCLID
Prior revascularization
aHR for ALI 4.23 (2.86 – 6.25)



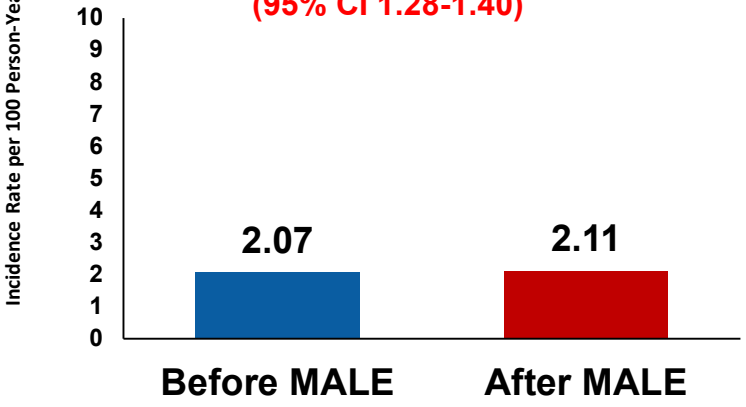
Number of Patients at Risk

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
MI or Stroke	393017	304589	232371	167787	111471	64488	27580
Major amputation or limb revascularization	393017	235121	167604	116188	74888	42218	17328

Major Amputation or Limb Revascularization
Adjusted HR 8.13
(95% CI 7.96-8.29)



MI or Stroke
Adjusted HR 1.34
(95% CI 1.28-1.40)



Hess et al JACC 2020, Bonaca et al. Circulation 2016, Jones et al. Circulation 2014

Courtesy of Marc Bonaca

Antithrombotic Trials in PAD

- Most PAD evidence derived from subgroups of larger cardiovascular (CAD) outcome trials
- Primary focus has been MACE
  - New evidence supports Major Adverse Limb Events (MALE) including Acute Limb Ischemia (ALI), major amputation and complex (surgical) revascularization
- Challenge to sort out effect modification of CAD (PAD often a component of polyvascular disease)

Antithrombotic Trials in PAD/PAD Subgrops

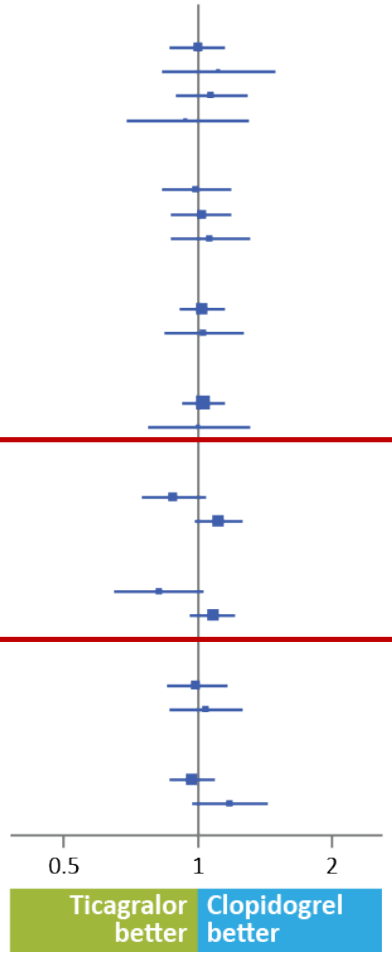
Trial	Study Population	Background Rx	Study Drug	MACE in PAD/ PAD subgroup	MALE
Pegasus	100% CAD (5.4% CAD + PAD)	Aspirin	Ticagrelor	HR 0.75 (0.55-1.01)	ALI/revasc - HR 0.65 (0.44-0.95)
TRA 2°P	100% CAD (4.3% PAD + CAD)	Aspirin/P2Y12	Vorapaxar	HR 0.80 (0.73-0.89)	ALI - HR 0.58 (0.39-0.86) Revasc - HR 0.82 (0.72-0.93)
Compass	90% CAD 27% PAD + CAD	Aspirin	Rivaroxaban	HR 0.72 (0.57-0.90)	MALE - HR 0.54 (0.35-0.82)
Euclid	100% PAD 29% PAD + CAD	Clopidogrel comparator	Ticagrelor	HR 1.02 (0.92-1.13)	ALI - HR 1.03 (0.79–1.33)
Voyager	100% PAD 29% PAD + CAD	Aspirin	Rivaroxaban	MI and stroke HR 0.88 (0.73-1.07)	MALE HR 0.74 (0.62-0.88)

NEJM 2017;376:32-40, J Am Coll Cardiol 2016;67:2719-28, Circulation. 2016;133:997-1005, Lancet 2018;391:219-229

Effect of concomitant CAD

Euclid Trial

Characteristic	Total Patients	KM % at Month 36 Ticagralor	KM % at Month 36 Clopidogrel	HR (95% CI)	P-val (int)
Geographic region					0.82
Europe	7498	11.1	11.4	1.00 (0.86, 1.15)	
Asia	1602	14.1	12.1	1.11 (0.83, 1.49)	
North America	3045	16.2	15.8	1.07 (0.89, 1.29)	
Central/South America	1740	9.8	11.0	0.94 (0.69, 1.30)	
Age group					0.87
<65 years	5885	9.5	9.7	0.99 (0.83, 1.19)	
65-75 years	5775	12.8	13.1	1.02 (0.87, 1.19)	
>75 years	2225	19.9	18.8	1.06 (0.87, 1.31)	
Sex					0.91
Male	9997	12.9	13.1	1.02 (0.91, 1.15)	
Female	3888	11.5	11.1	1.03 (0.84, 1.27)	
Prior antiplatelet therapy					0.88
Yes	11695	12.7	12.8	1.03 (0.92, 1.15)	
No	2188	11.0	10.6	1.00 (0.77, 1.31)	
History of coronary or carotid revascularization					0.03
Yes	3815	15.5	18.3	0.88 (0.75, 1.04)	
No	10068	11.3	10.2	1.11 (0.98, 1.26)	
History of coronary stent implantation					0.03
Yes	1968	15.4	20.3	0.82 (0.65, 1.03)	
No	11915	12.0	11.2	1.08 (0.96, 1.21)	
Metabolizer status for CYP2C19					0.69
Normal function	5681	12.1	12.4	0.99 (0.85, 1.16)	
At least 1-LOF-allele	4129	12.3	11.8	1.04 (0.86, 1.26)	
Statin at baseline and ongoing during treatment					0.09
Yes	10181	11.8	12.6	0.97 (0.86, 1.09)	
No	3704	14.5	12.1	1.18 (0.97, 1.43)	

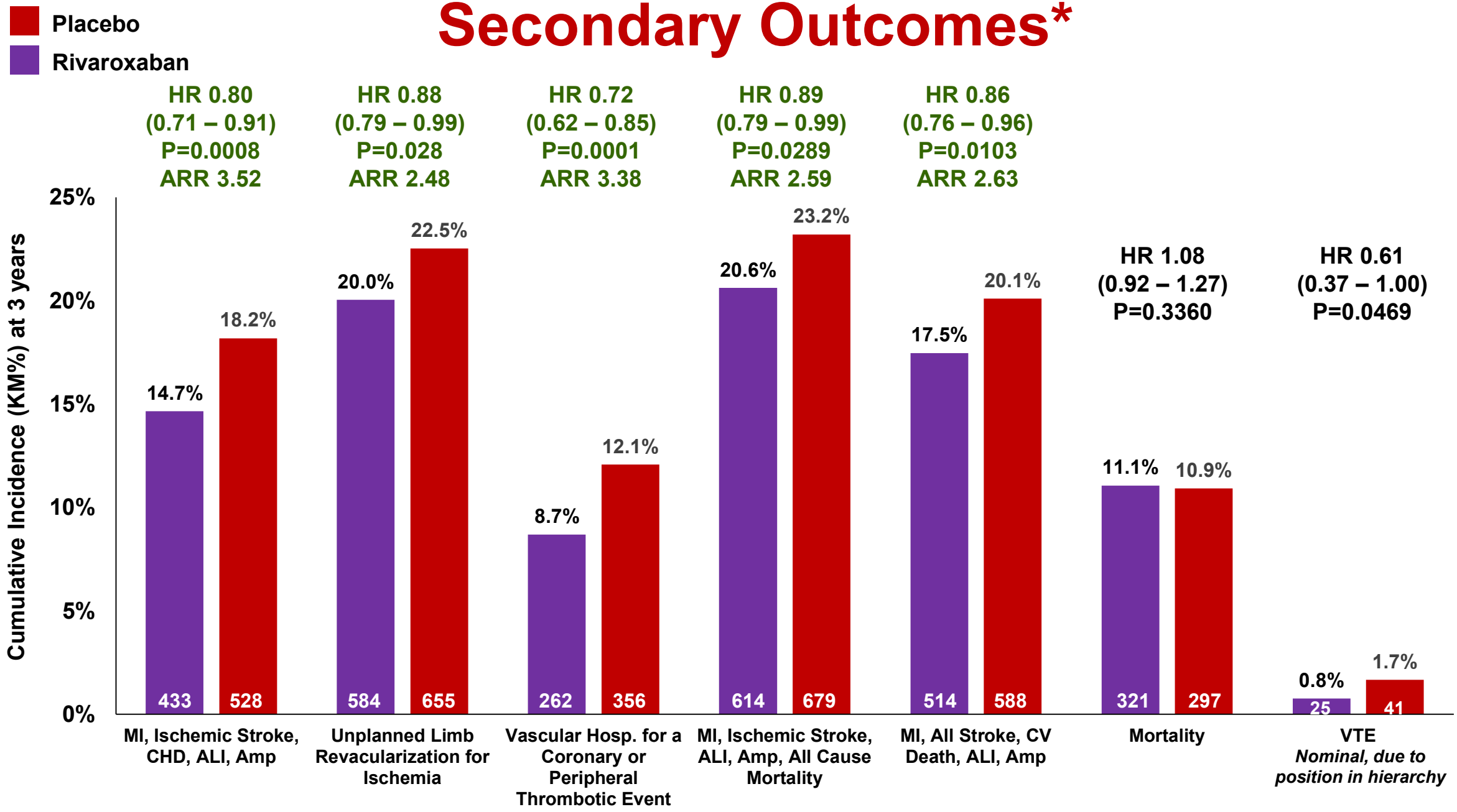


NEJM 2017;376:32-40

Voyager Primary Endpoint & Components

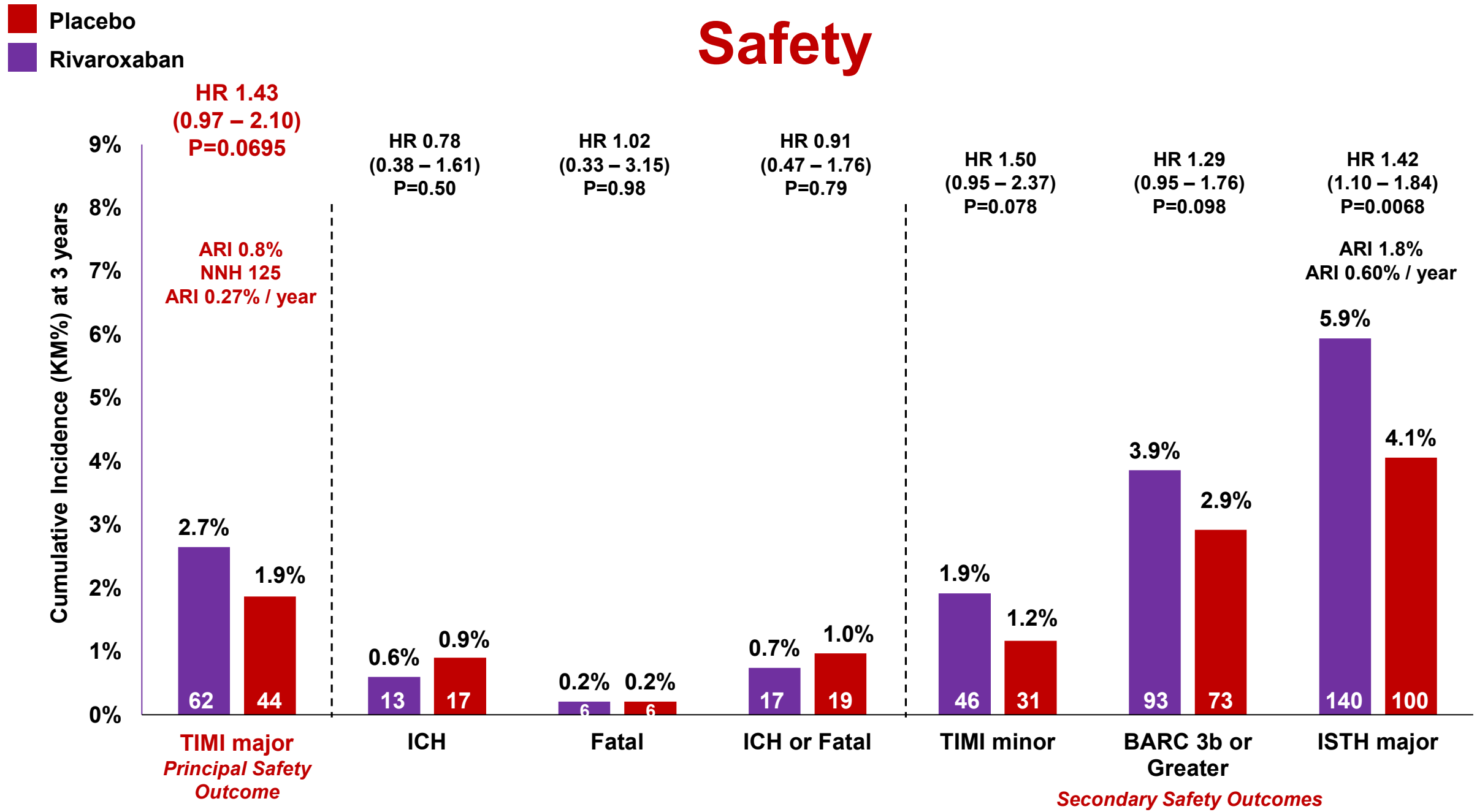
	KM% 3 Years (n) Rivaroxaban N=3286	KM% 3 Years (n) Placebo N=3278	HR (95% CI)
Primary Efficacy Outcome	17.3	19.9	0.85 (0.76 – 0.96)
Acute Limb Ischemia	5.24	7.74	0.67 (0.55 – 0.82)
Major Vascular Amputation	3.42	3.87	0.89 (0.68 – 1.16)
Ischemic Stroke	2.70	3.01	0.87 (0.63 – 1.19)
Myocardial Infarction	4.55	5.22	0.88 (0.70 – 1.12)
CV Death	7.05	6.43	1.14 (0.93 – 1.40)

Secondary Outcomes*



*Presented in order of hierarchy from left to right

Safety



ARI – absolute risk increase, NNH number needed to harm

PAD is Distinct from CAD

- PAD presentation and pathophysiology:
  - Clinical coronary artery disease and prior MI are infrequent
  - Mostly non-thrombotic cases of death
  - Polyvascular disease/CAD, prior MI with PAD are important determinants to response to antithrombotic therapies
  - Lower extremity ischemia with ALI and Amputation major (MALE) are irreversible harm events, have long-term morbidity yet minimal treatments
  - Peripheral thrombosis, microvascular disease and infections drive CLTI
- PAD evidence-based treatments
  - In symptomatic PAD in the setting of lower extremity revascularization, rivaroxaban plus aspirin provides immediate and long-term benefit in reducing the risk of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke and CV death