CMHC
Cardiometabolic Health Congress

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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Peripheral Artery Disease: Epidemiology, Diagnosis, and Management

Marc P. Bonaca MD MPH
Professor of Medicine
Director of Vascular Research
University of Colorado School of Medicine

CPC Clinical Research

An Affiliate of:

University of Colorado Anschutz Medical Campus

Disclosures

- **Grant support from: Amgen, AstraZeneca, Bayer, Janssen, Medtronic, Merck, Novo Nordisk, Pfizer, Wraser**

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Peripheral Artery Disease: Burden, Clinical Presentation & Screening

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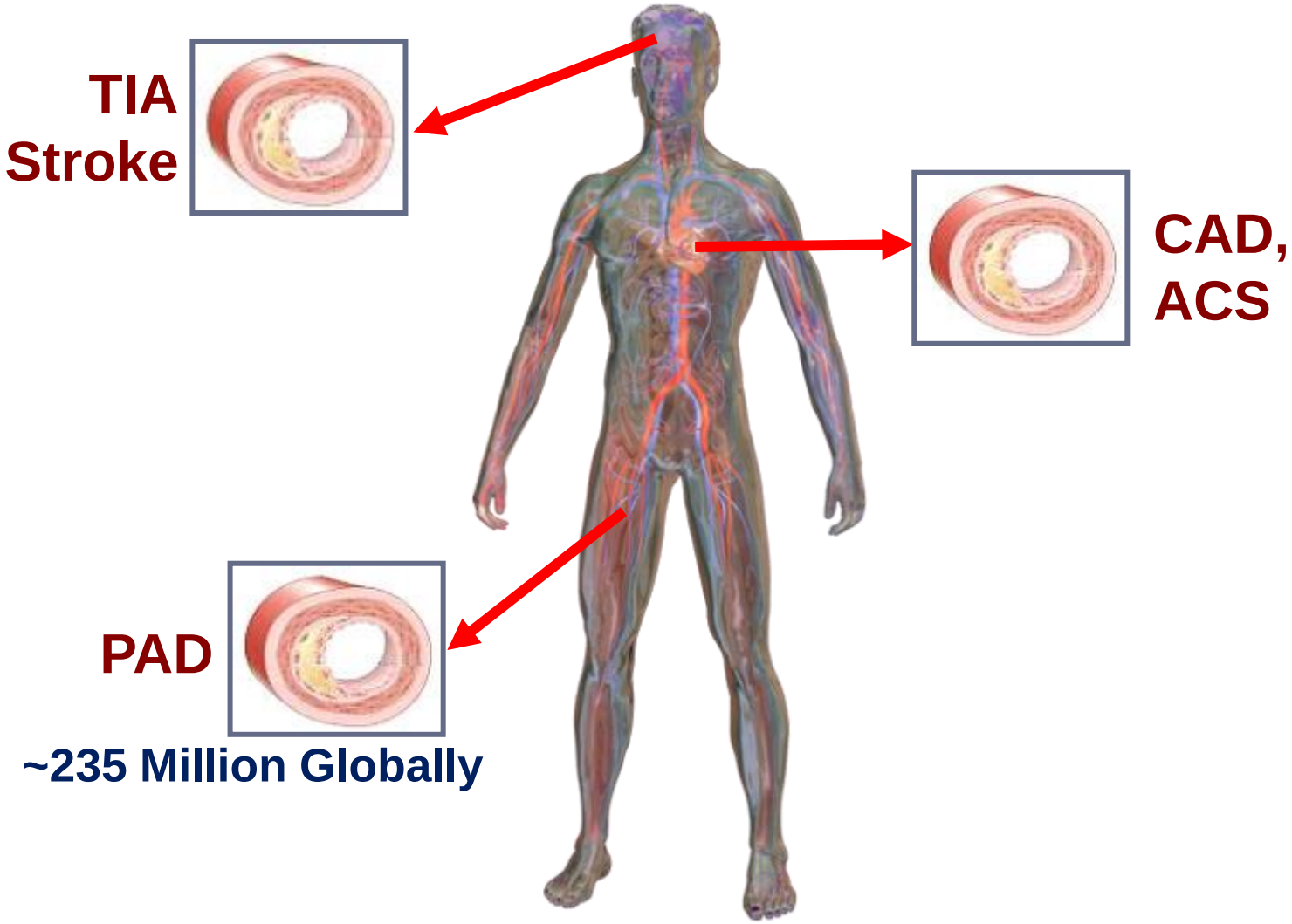
Definitions

- PAD – peripheral artery disease
- CAD – coronary artery disease
- Polyvascular disease – combination of CAD and PAD
- MACE – major adverse cardiovascular events
  - MI – myocardial infarction – “Heart Attack”
  - IS – ischemic stroke – “Stroke”
  - CVD – cardiovascular death – “Death”
- MALE – major adverse limb events
  - ALI – acute limb ischemia – “Heart Attack of the Leg”
  - Amputation – “Limb loss”
  - CLTI – critical limb threatening ischemia

Atherosclerosis is a Systemic Disease

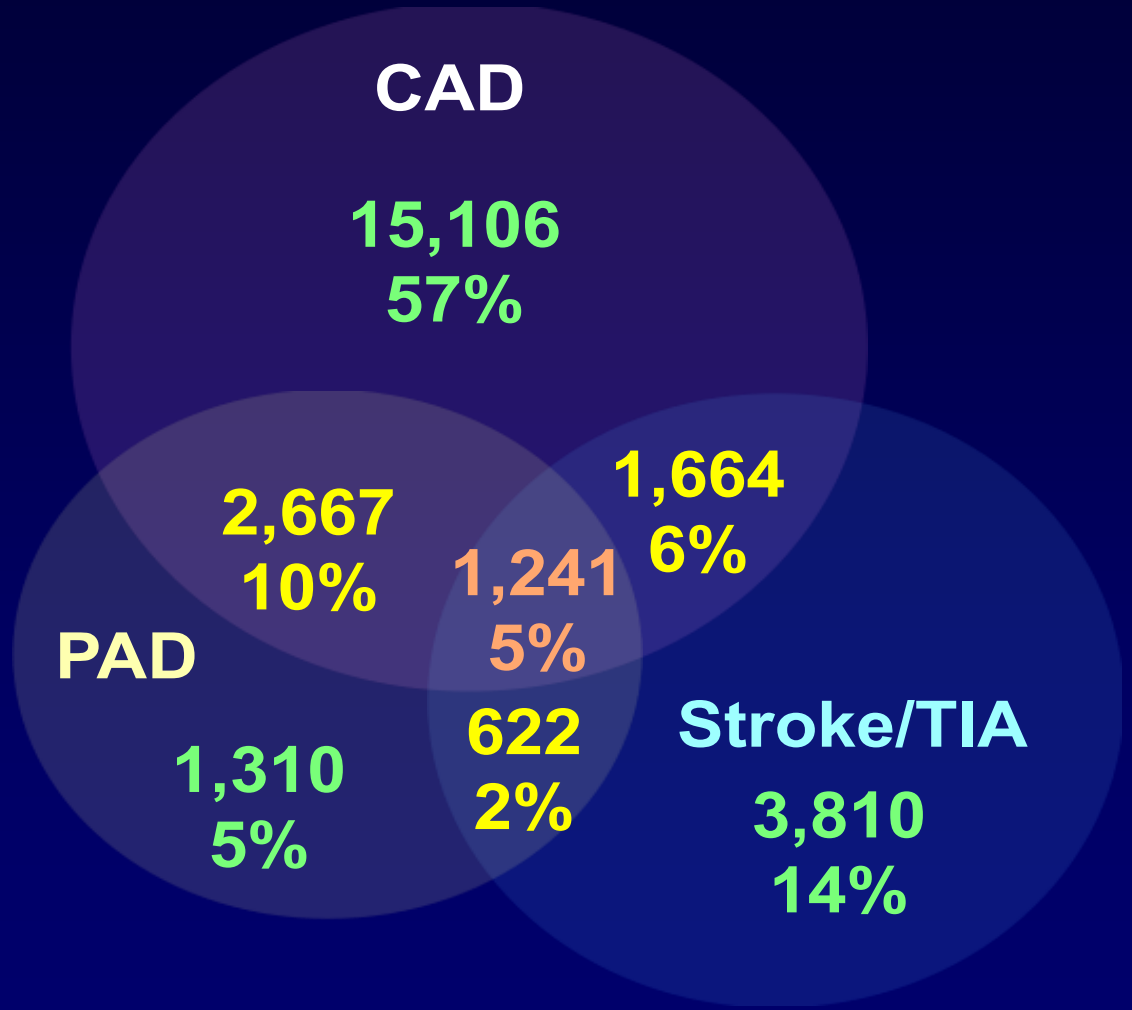


American Heart Association. *Heart Disease and Stroke Statistics – 2021 Update*.

Polyvascular Disease Common in Patients with Symptomatic PAD

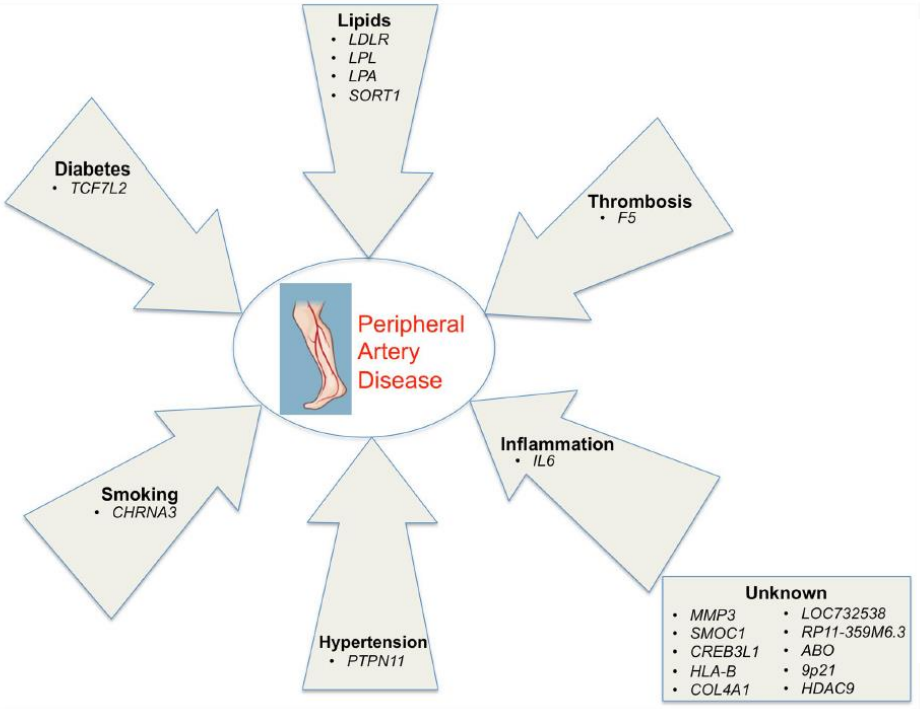
- 20,248 (76%) – one symptomatic vascular territory
- 4,954 (19%) – two symptomatic vascular territories
- 1,241 (5%) – three symptomatic vascular territories

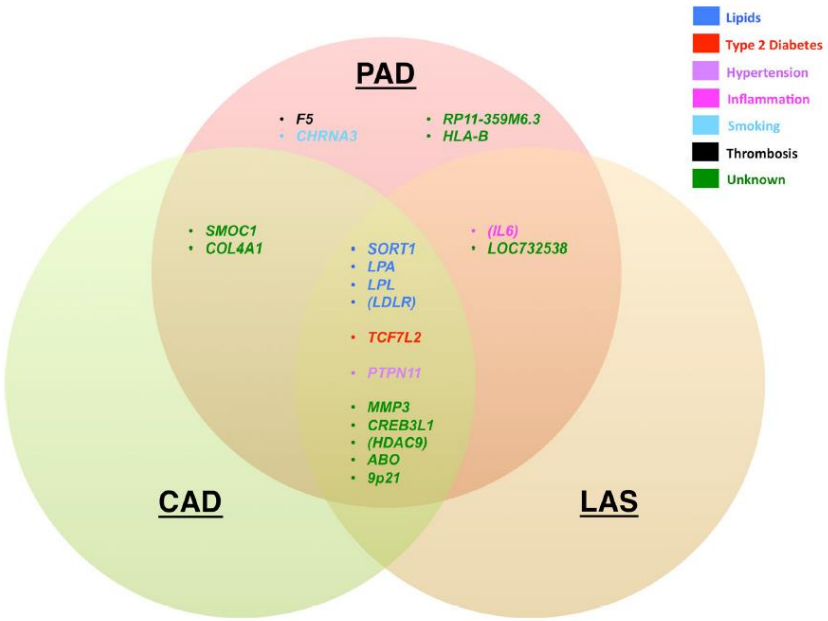
78% with Symptomatic LE PAD have concomitant CAD or prior Stroke

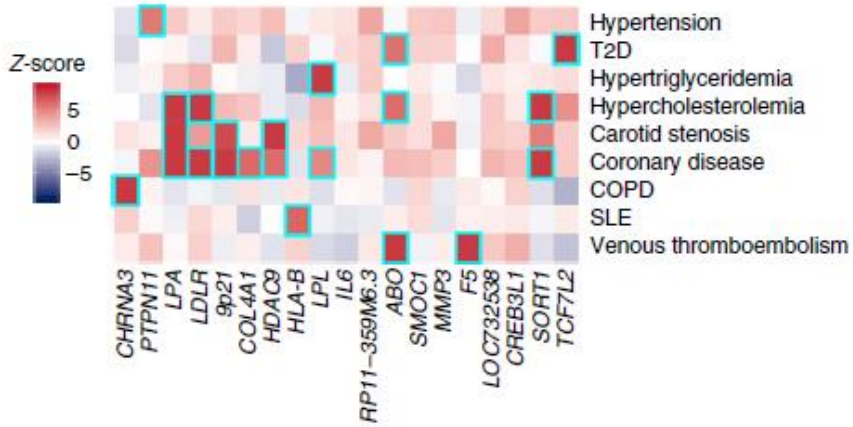


Bonaca et al. ACC 2013

GWAS in Peripheral Artery Disease



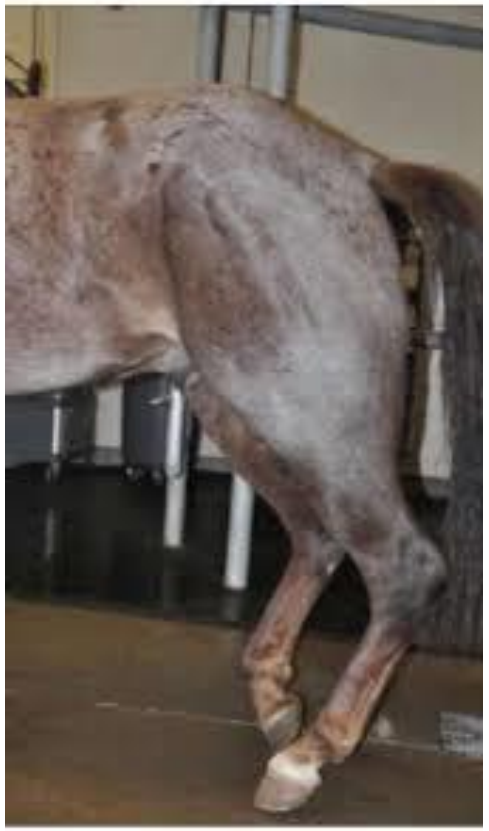




Klarin et al. Nature Medicine 2019

Peripheral Artery Disease

- **First described by a French veterinarian Bouley in a horse affected by progressive limping and lameness consequent to a fibrous clot that occluded the femoral arteries of the posterior limbs.**



Bouley JF. Claudication intermittente des membres posterieurs determinee par l' obliteration des arteres femorales. ***Rec Med Vet****. 1831; 8:517*

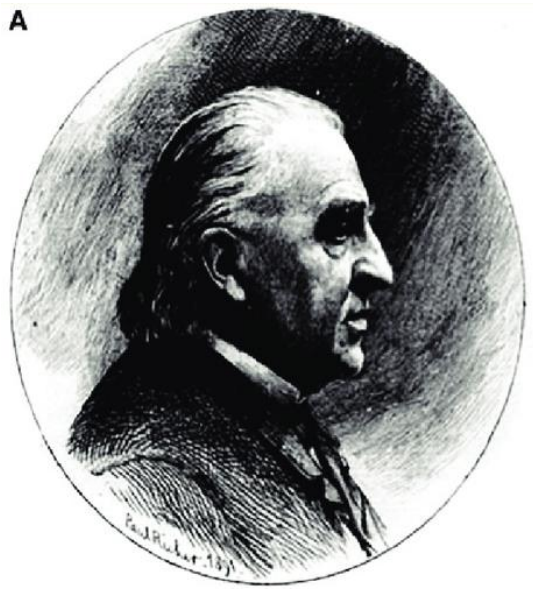
Peripheral Artery Disease

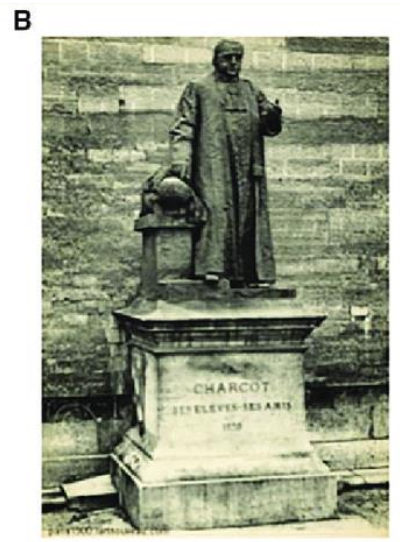
- **In humans, first noted by Brodie in 1846**

  Brodie BC. Lectures illustrative of various subjects in pathology and surgery. London, A Spottiswoode. 1846.

- **Charcot who in 1858 clearly defined and described the syndrome of “intermittent claudication”**

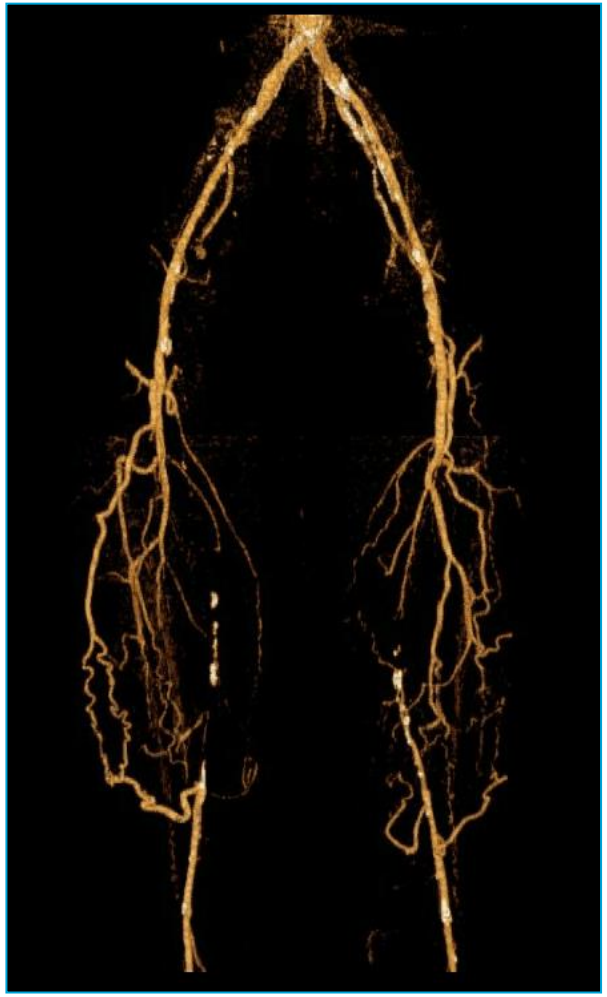
  Charcot JMC. Sur la claudication intermittente observe dans un cas d’obliteration complete de l’ une des arteres iliaques primitives. CR Soc Biol (Paris). 1858;5:225.





Peripheral Artery Disease (PAD)

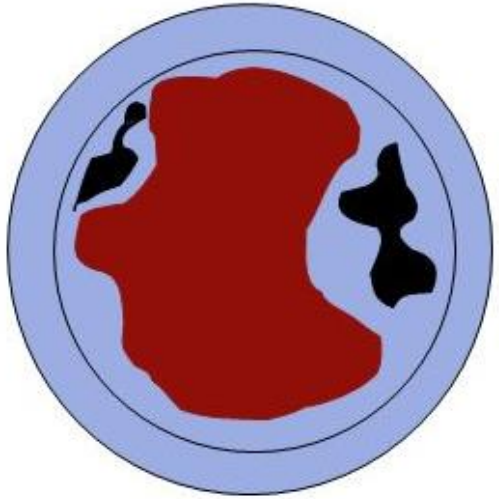
- The presence of a stenosis or occlusion in the aorta or arteries of the limbs
- Usually caused by atherosclerosis
- Associated with an increased risk of death, myocardial infarction, and stroke
- May impair walking or cause critical limb ischemia



Heterogeneity in Biology

Hyperlipidemia, Smoking, Hypertension, Inflammation, Stress, Diabetes

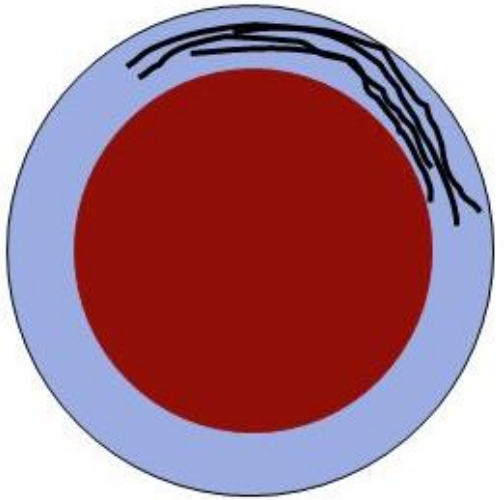
Intimal/subintimal Disease



Low ABI
≤ 0.9

Renal Dysfunction, Diabetes
(Calcium & Phosphate Regulation, Osteogenesis, Local Cellular Dysfunction)

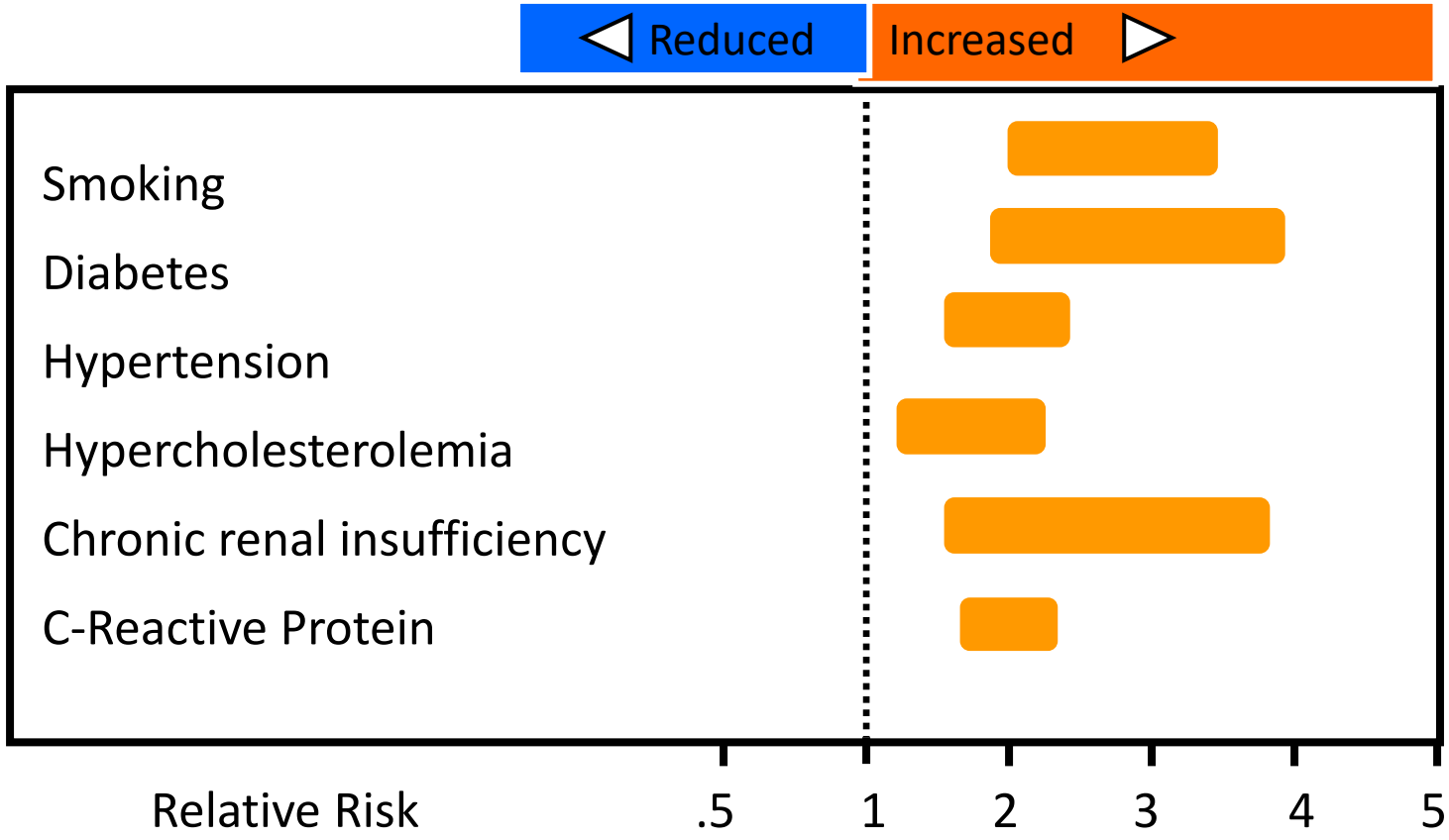
Medial Calcification



High ABI
≥ 1.3

Quehenberger O, Dennis EA. N Engl J Med 2011;365:1812-1823.

Risk Factors for PAD

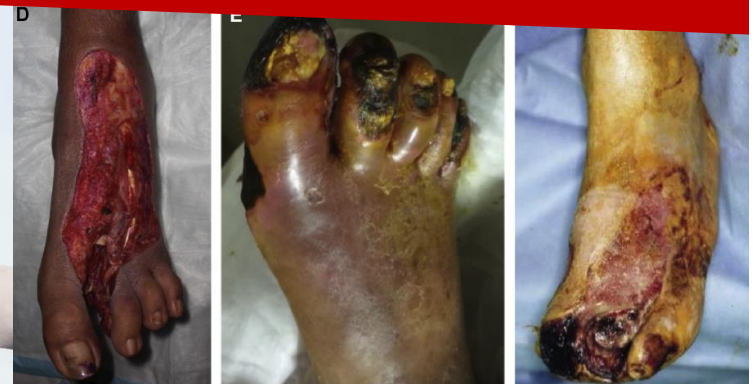


Disease Progression in PAD

Mild Functional Symptoms	Symptomatic PAD Patients	PAD Patients Requiring Revascularization	PAD Patients post Revascularization
	Without need for revascularization	**CLTI or Severe Claudication**	**Post-revascularization** (history of CLTI or ALI particularly high risk)

Quality of Life & Function

Major Adverse Limb Events



ALI=Acute Limb Ischemia; CLTI=Chronic Limb-Threatening Ischemia

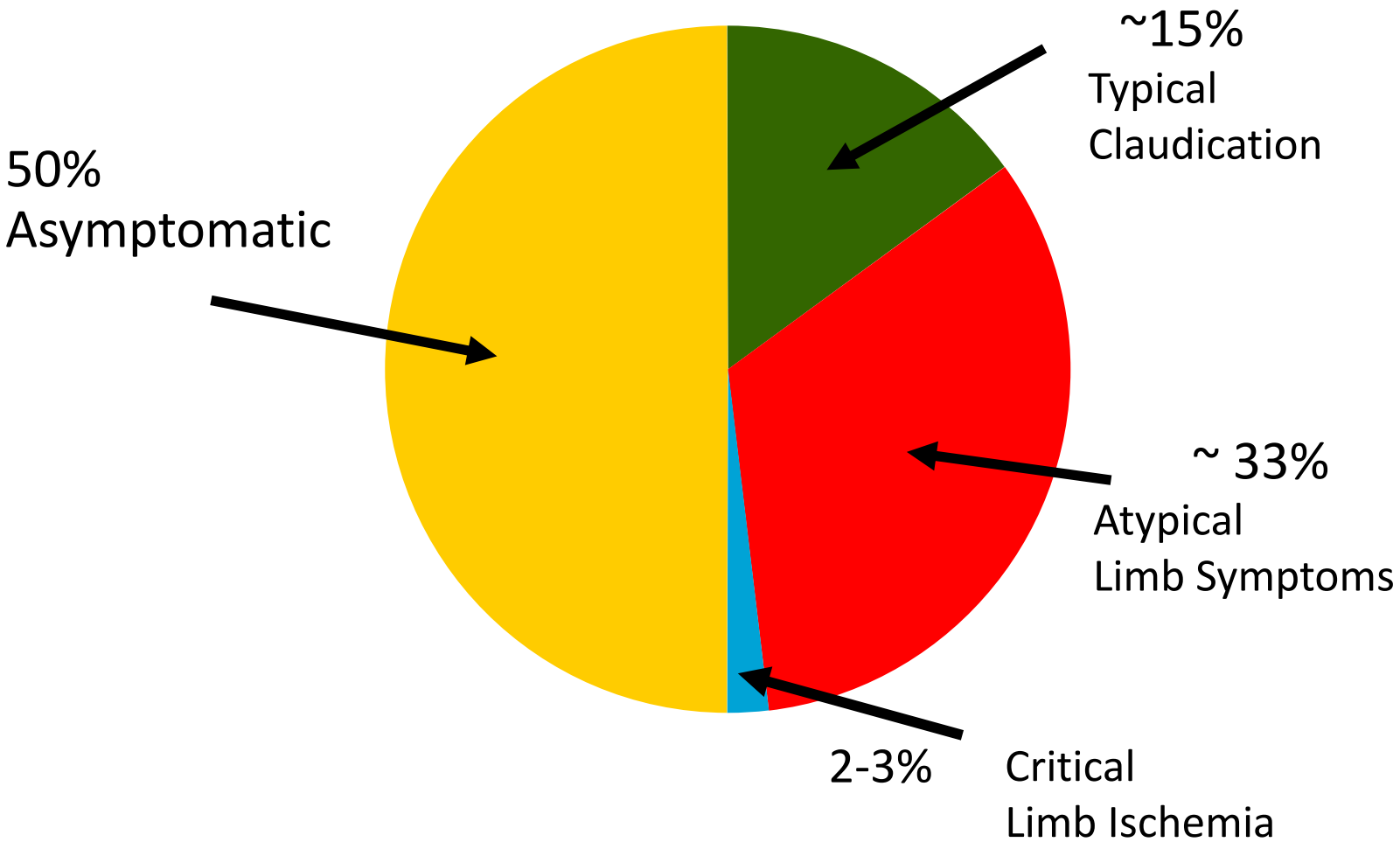
Claudication

- *Claudico* = to limp
- Reproducible discomfort of a defined group of muscles induced by exercise and relieved by rest
- Symptoms result from a supply-demand mismatch of blood flow

Clinical Classification

Fontaine		Rutherford		
Stage	**Clinical State**	**Grade**	**Category**	**Clinical State**
I	Asymptomatic	0	0	Asymptomatic
II a	Mild IC	I	1	Mild IC
II b	Moderate-severe IC	I	2	Moderate IC
		I	3	Severe IC
III	Ischemic rest pain	II	4	Ischemic rest pain
		III	5	Minor tissue loss
IV	Ulcers, gangrene	III	6	Major tissue loss

Clinical Presentation of PAD



Diagnosis Begins with Suspicion

- **Rest pain (night pain)**
- **Non-healing ulcers in the extremity**
- **Intermittent Claudication**
- **Risk factors for CVD (80% asx)**

- **Absent or diminished peripheral pulses**
  - **Absent posterior tibial pulse > 90% specific for diagnosis of PAD**
- **Bruits**
- **Hair loss**
- **Dystrophic nail changes**
- **Rapid elevation pallor or dependent rubor of the limb**
- **Evidence of tissue loss (ulceration, gangrene)**

Imaging Tests for PAD

- **Duplex ultrasonography**
- **Magnetic resonance angiography**
- **Computed tomographic angiography**
- **Conventional contrast angiography**

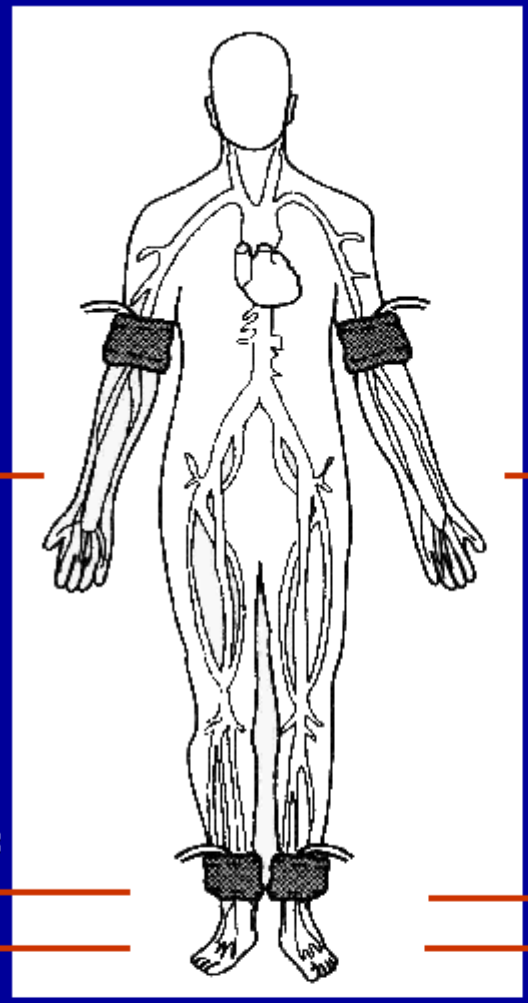
How to Perform and Calculate the ABI

PARTNERS Program ABI Interpretation

Above 0.90 — Normal
0.71-0.90 — Mild Obstruction
0.41-0.70 — Moderate Obstruction
0.00-0.40 — Severe Obstruction

Right Arm Pressure: _____

Left Arm Pressure: _____



Pressure:
PT _____
DP _____

Pressure:
PT _____
DP _____

Right ABI

$$\frac{\text{Higher Right Ankle Pressure}}{\text{Higher Arm Pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} = \text{——}$$

Left ABI

$$\frac{\text{Higher Left Ankle Pressure}}{\text{Higher Arm Pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} = \text{——}$$

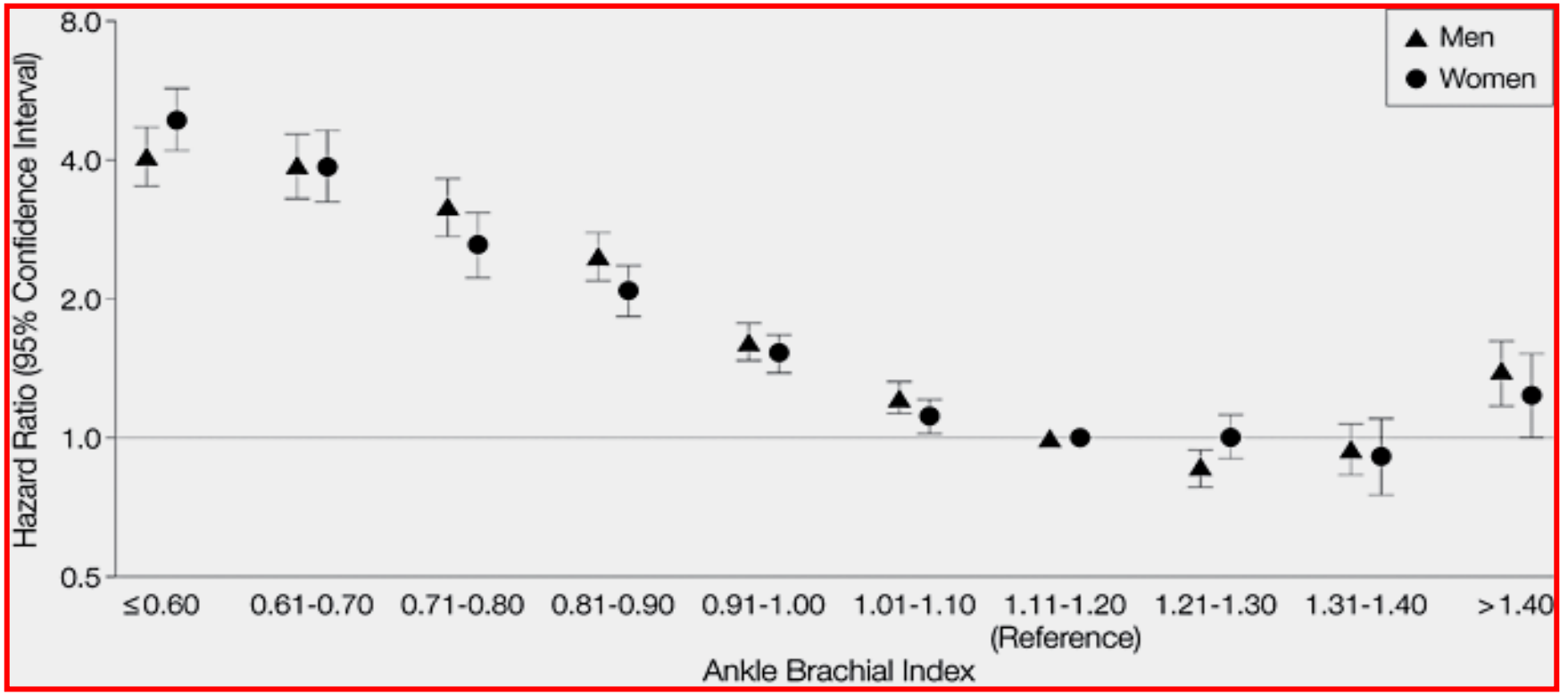
Example

$$\frac{\text{Higher Ankle Pressure}}{\text{Higher Brachial Pressure}} = \frac{92 \text{ mm Hg}}{164 \text{ mm Hg}} = 0.56$$

See ABI Chart

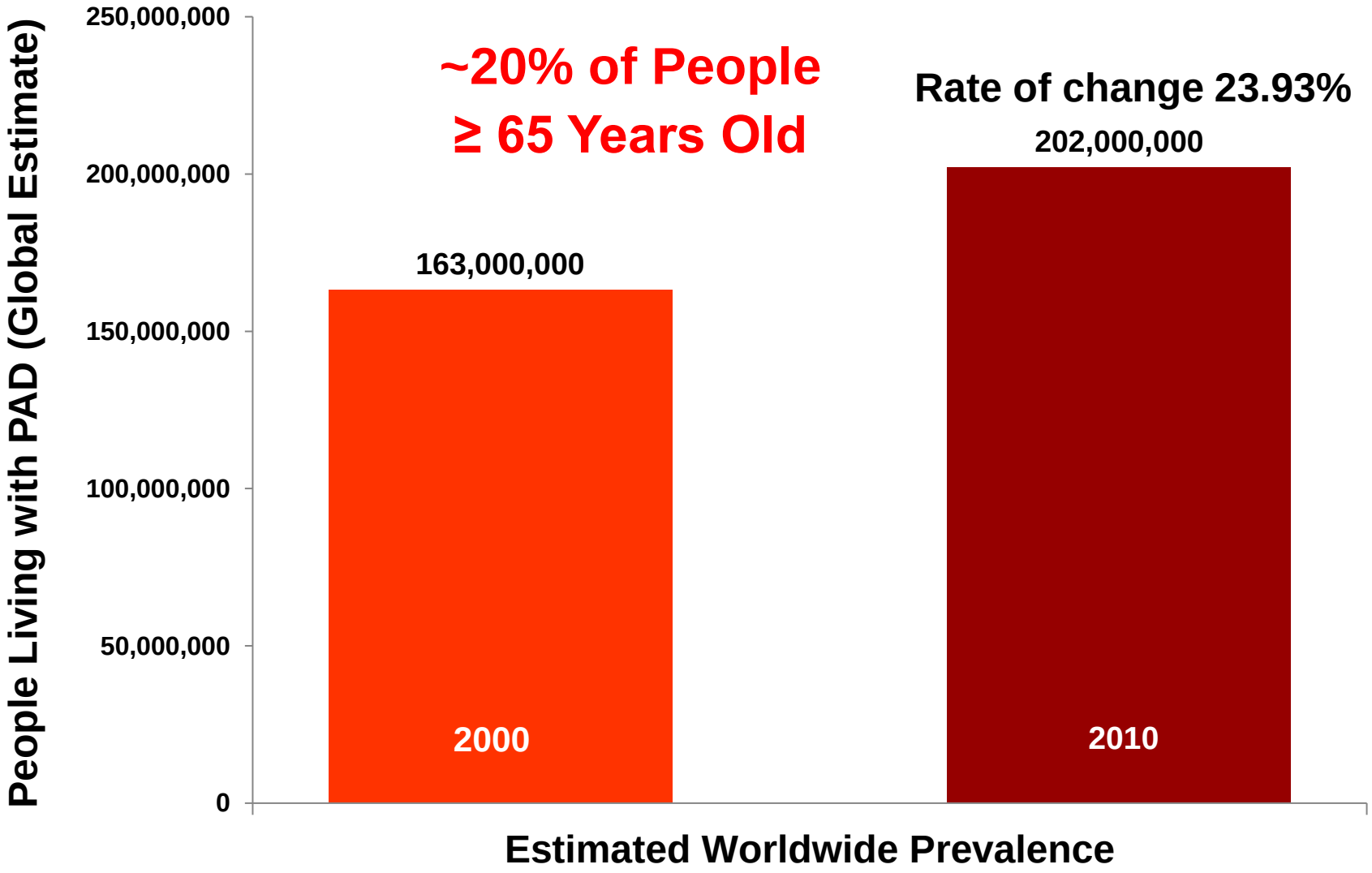
Low ABI and Mortality

Association of ABI with all-cause mortality in a meta-analysis of 16 cohort studies including 48,294 subjects and 480,325 person-years of follow-up.



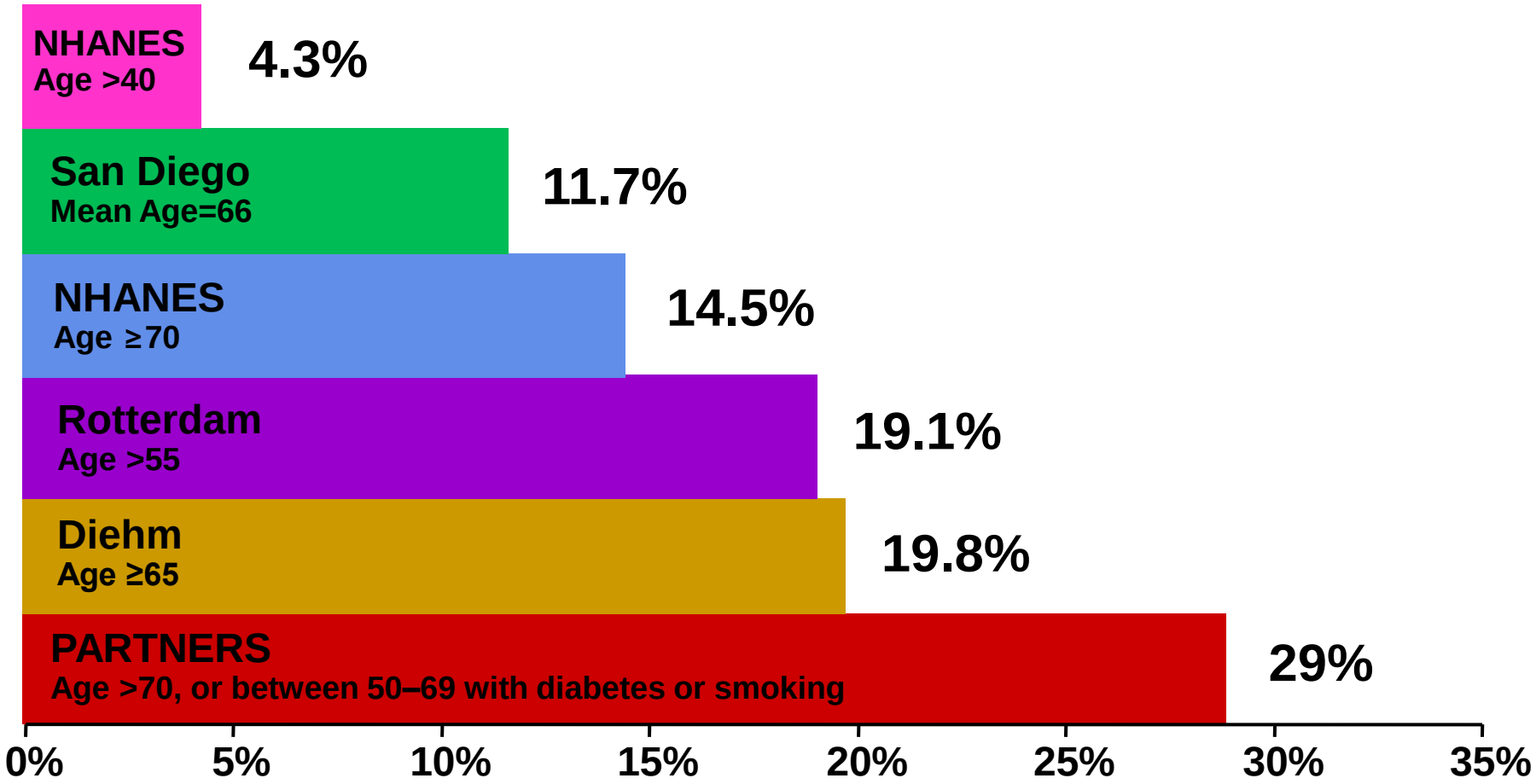
Ankle Brachial Index Collaboration. JAMA 2008.

Increasing Prevalence of Peripheral Artery Disease



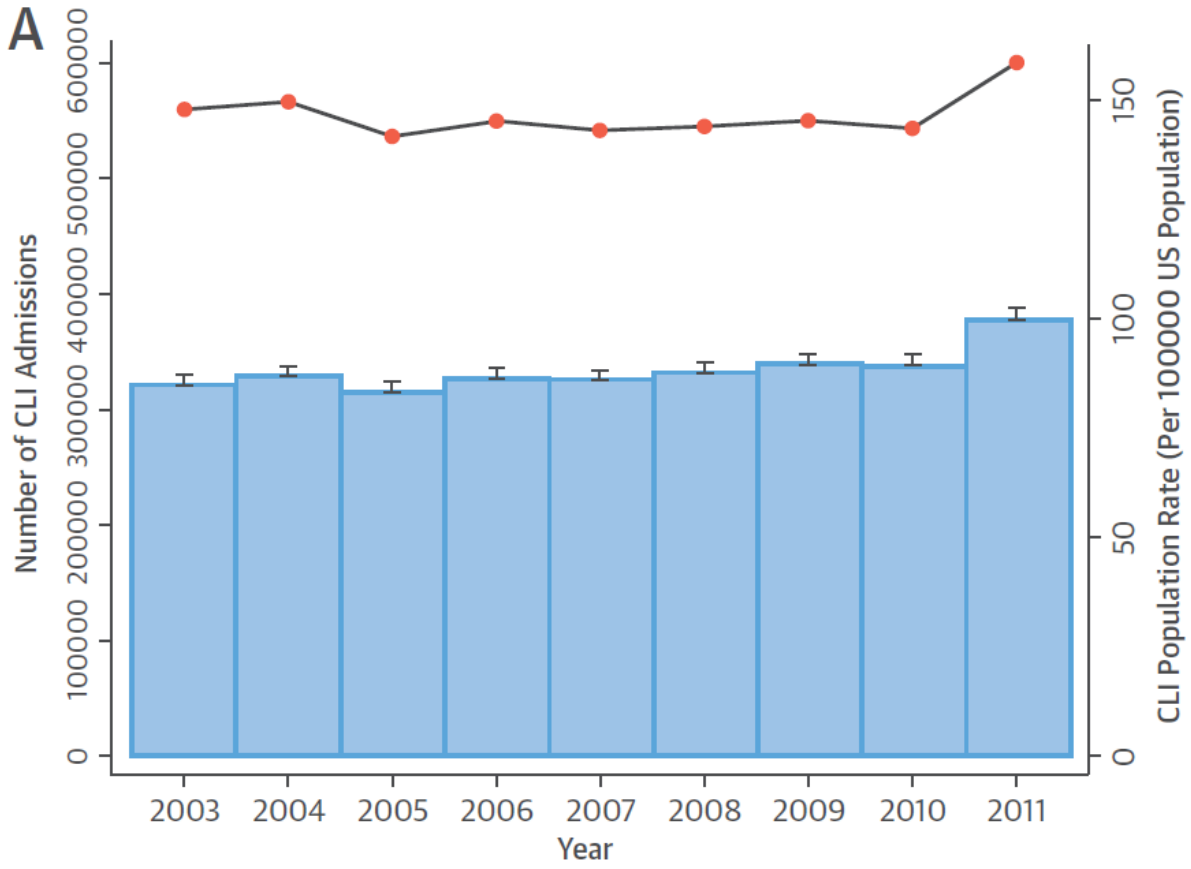
Fowkes et al. Lancet 2017;14:156-170

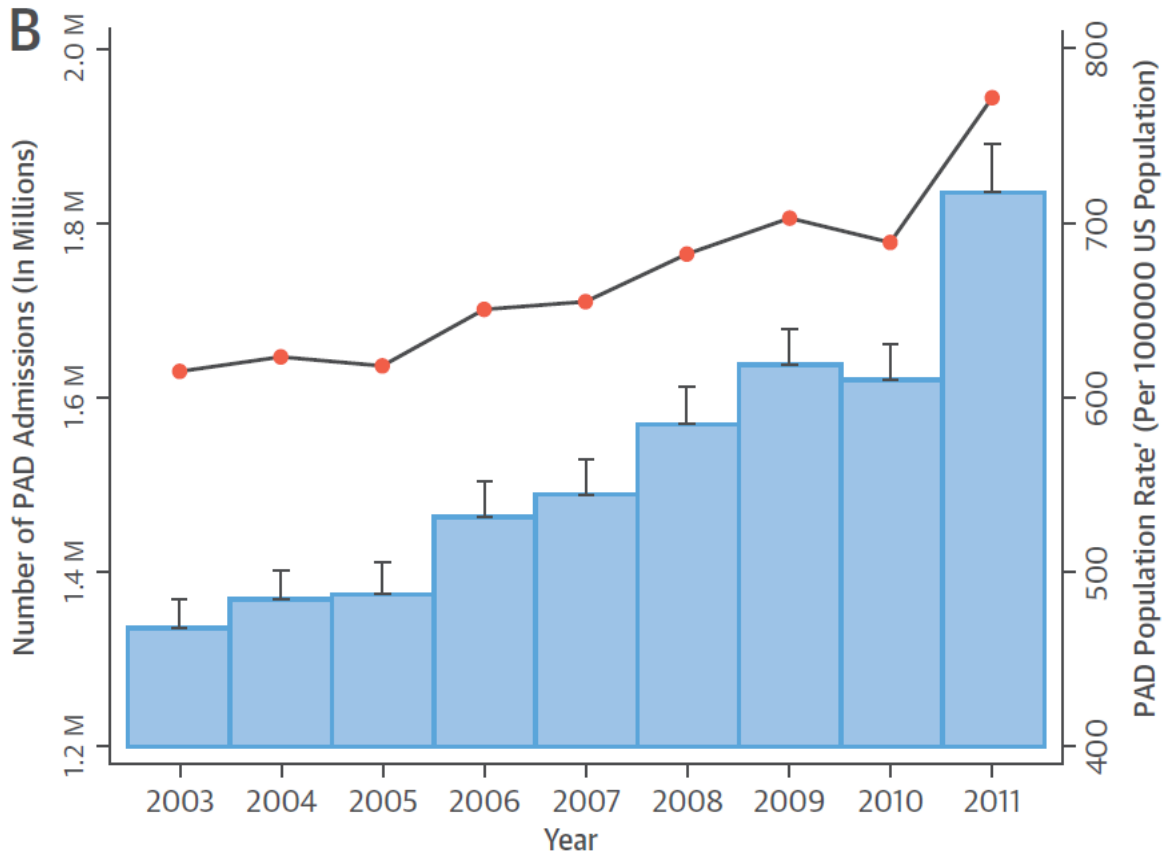
Documented Prevalence of PAD



Circulation. 2004;110:738-743. Circulation. 1985;71:510-515.
Arterio Thromb Vasc Biol. 1998;18:185-192. Atherosclerosis. 2004;172:95-105.
JAMA. 2001;286:1317-1324.

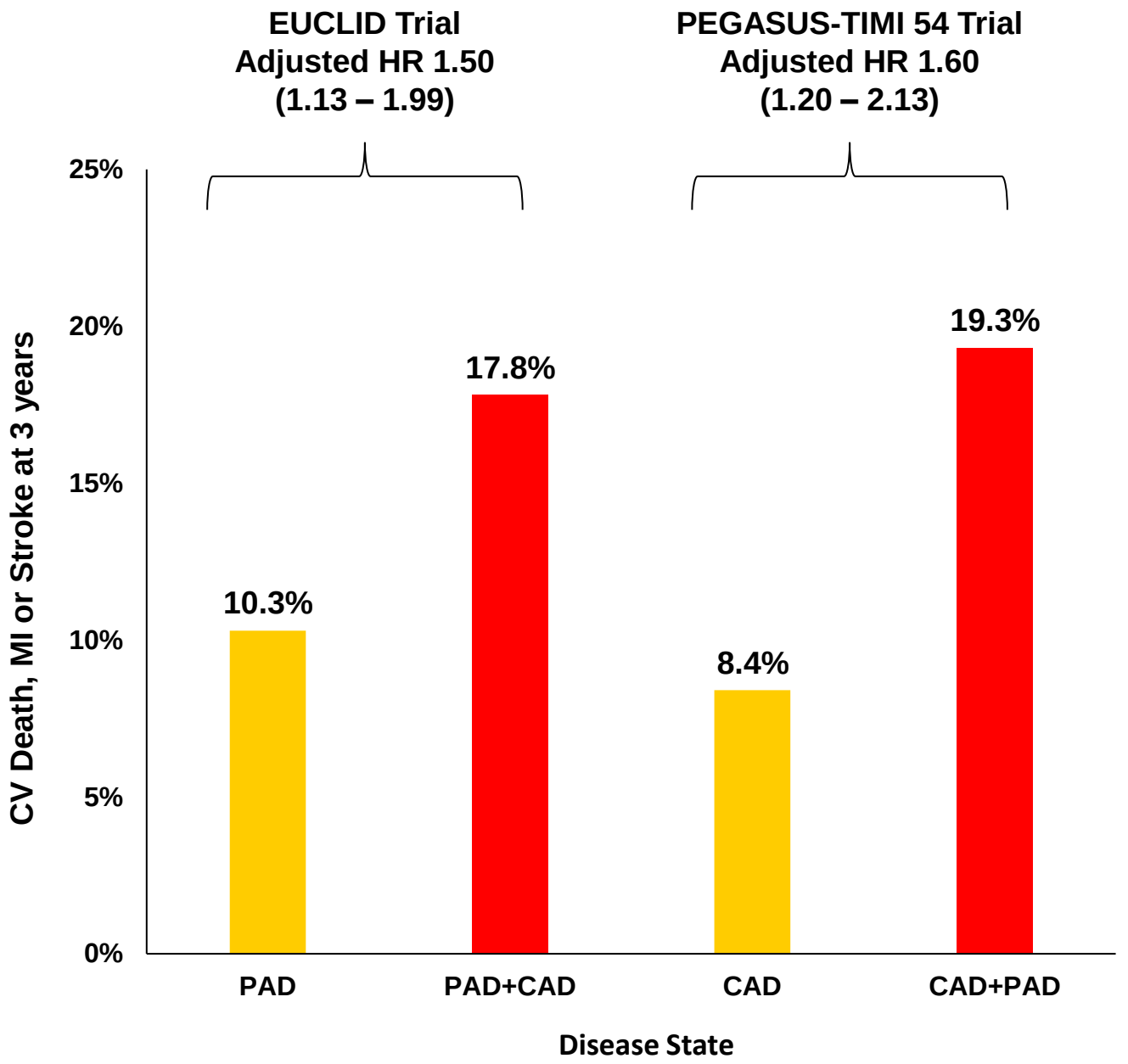
Increasing Rates of Critical Limb Ischemia and Hospitalizations





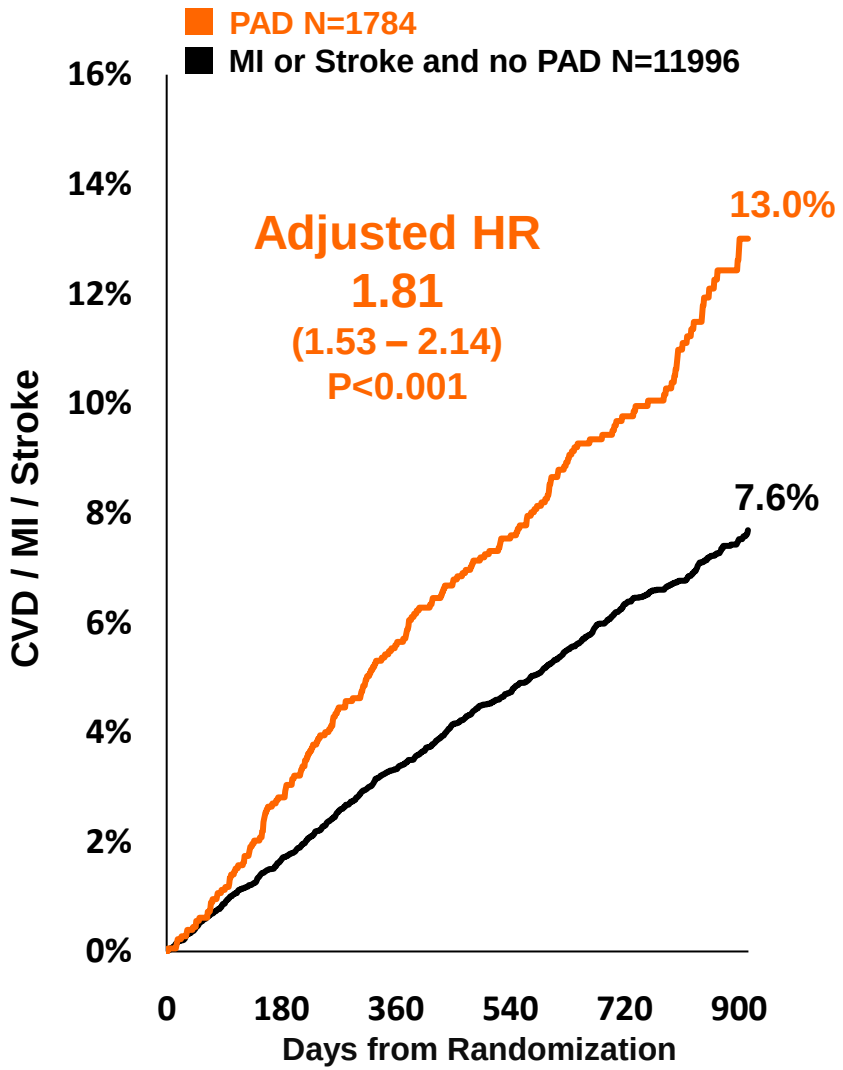
Agarwal S *et al. JACC* 2016;67:1914–1916

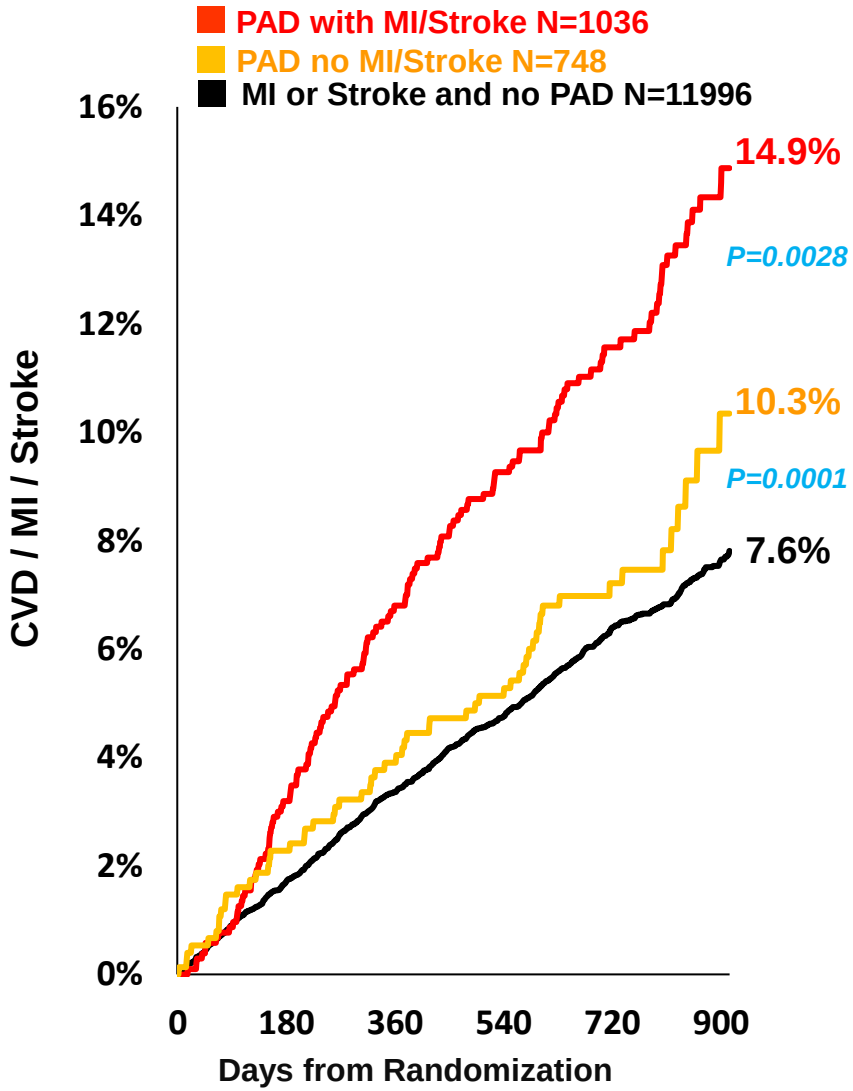
Polyvascular Disease in PAD is Associated with Increased MACE Risk



Bonaca Vasc Med 2018

PAD and Risk of Major Adverse Cardiovascular Events

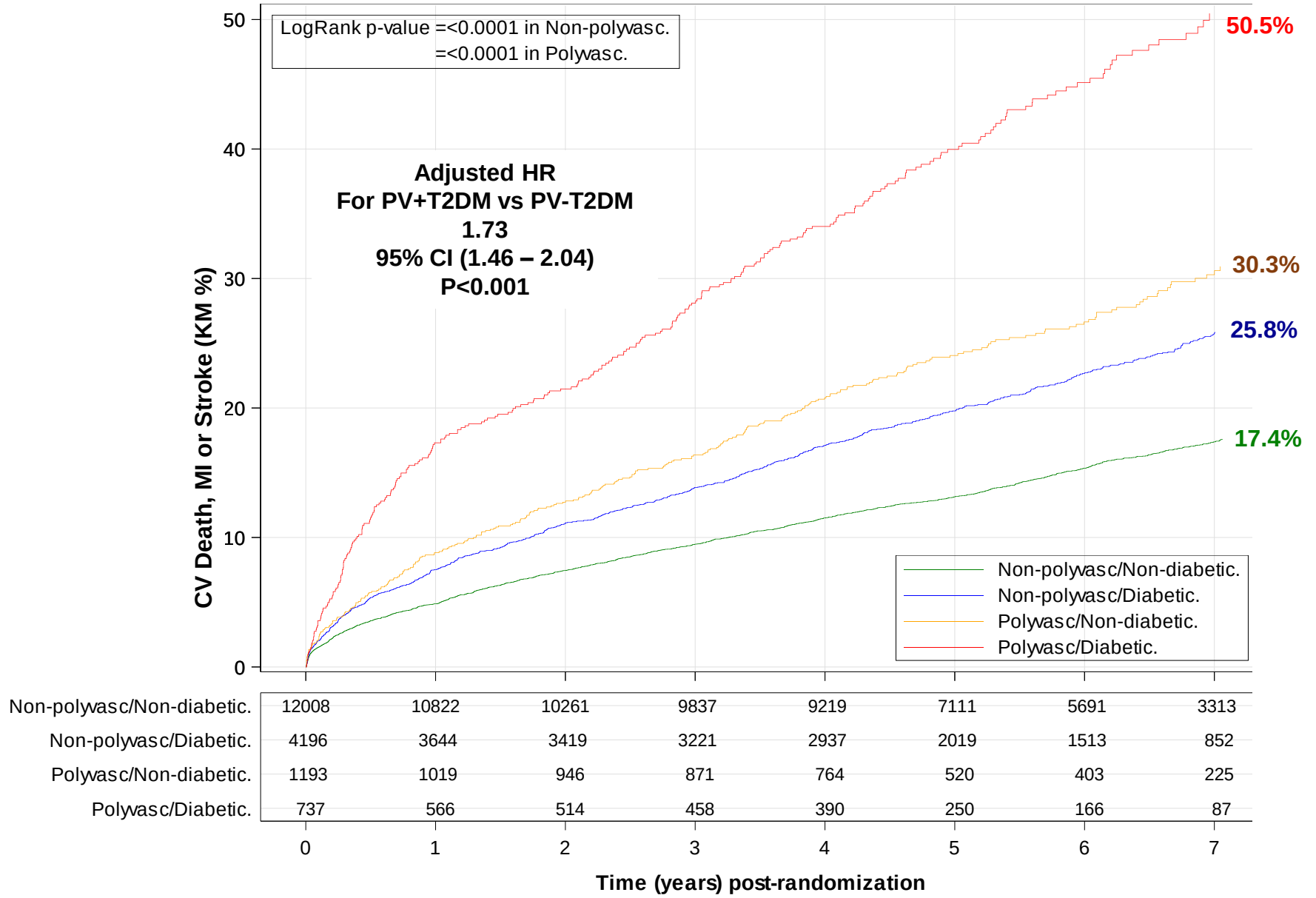




Bonaca et al. Circulation 2018

adjusted age, sex, race, BMI, diabetes, hypertension, smoking, eGFR, CHF, prior MI, CABG/PCI, and history of stroke or TIA.

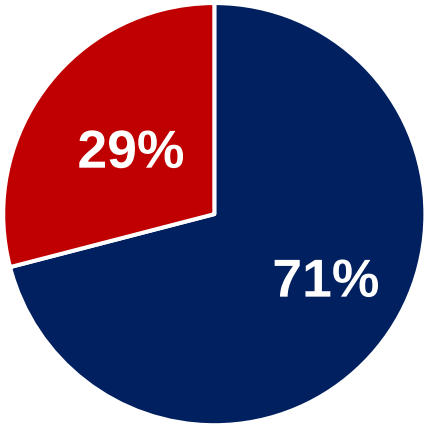
Risk after ACS with PAD and Diabetes



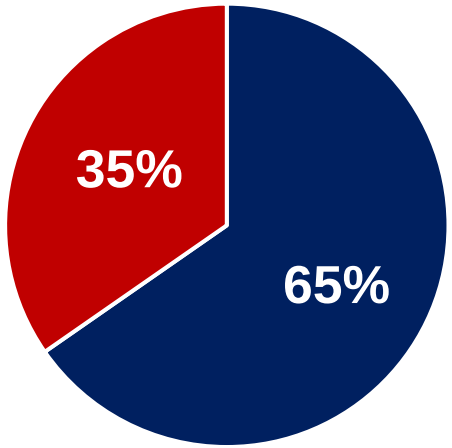
Bonaca et al. Lancet Diabetes & Endocrinology

Many PAD Patients Do Not Have Known CAD and Mortality Is Largely Unrelated to Atherothrombosis

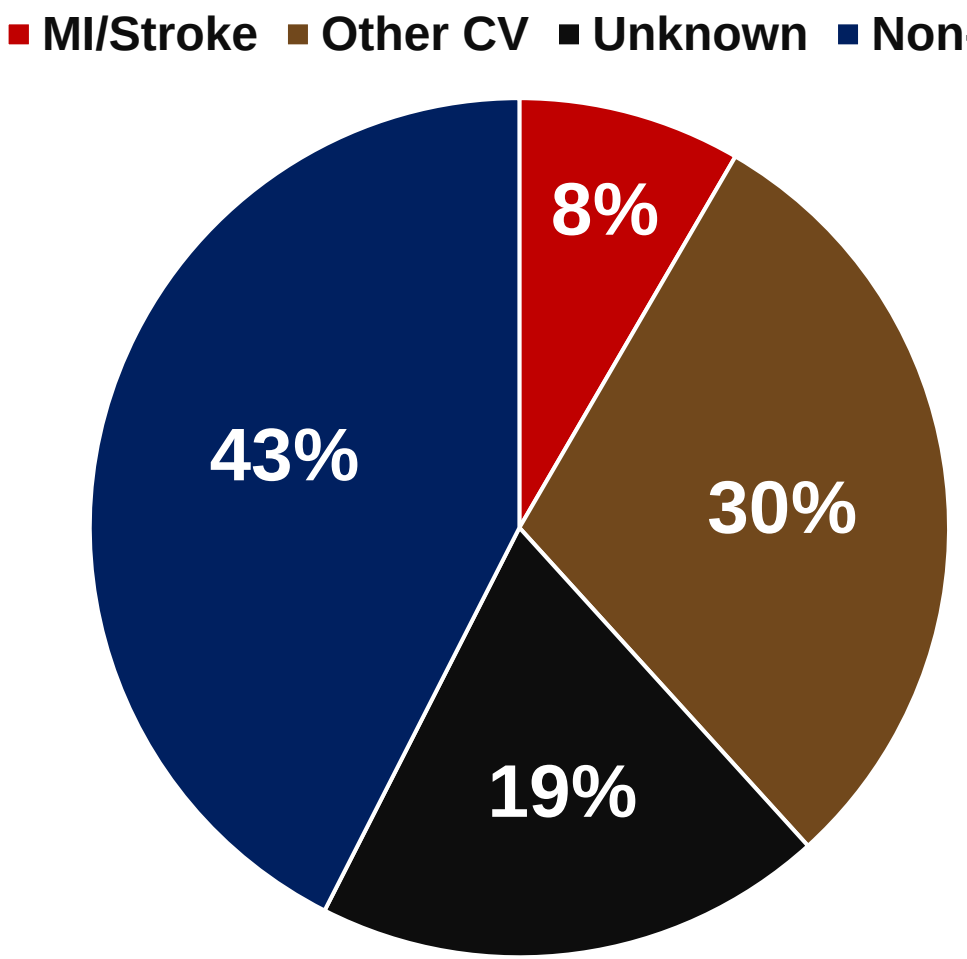
EUCLID Trial (N=13,885)[1]



CASPAR Trial (N=851)[2]



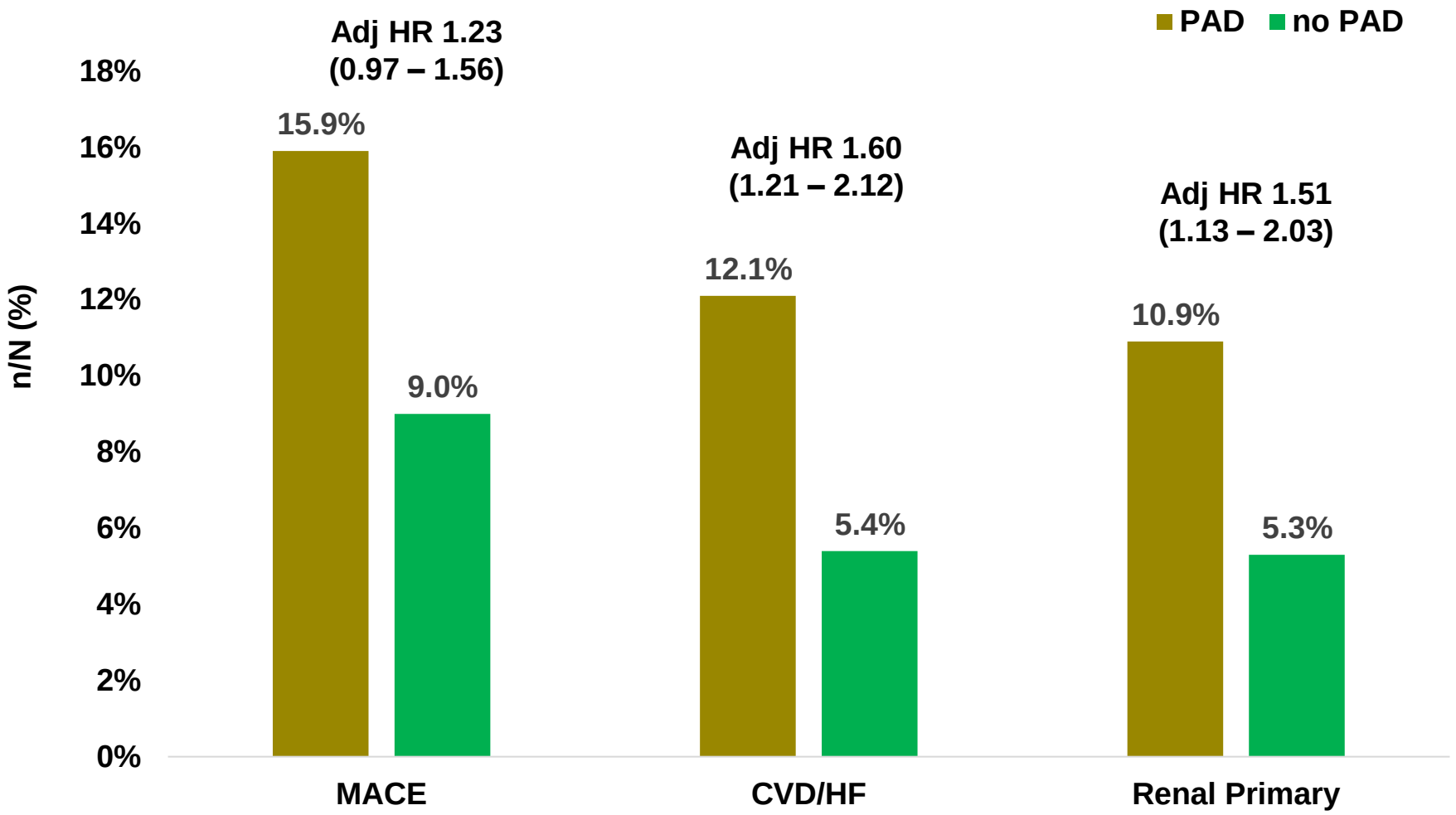
1,228 Deaths in EUCLID



1. Hiatt W, et al. *NEJM* 2017; 2. Belch et al. JVS 2010

Kochar et al. Under Review

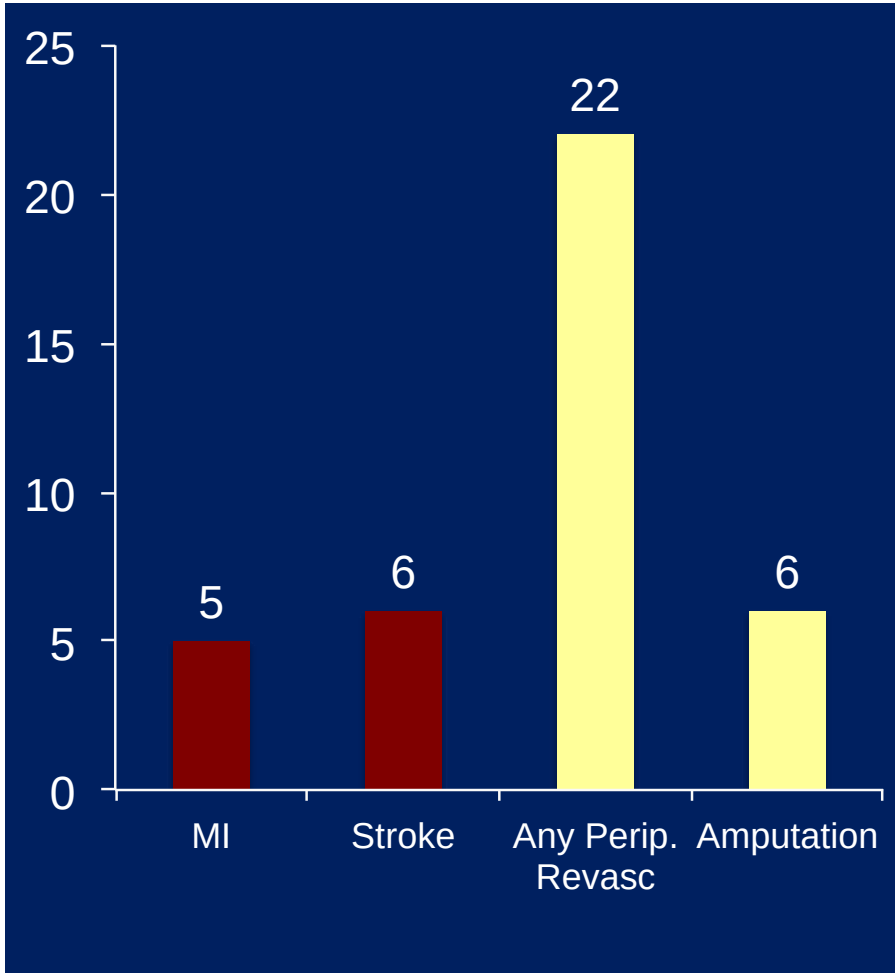
Cardiovascular & Renal Risk by PAD in Placebo Patients



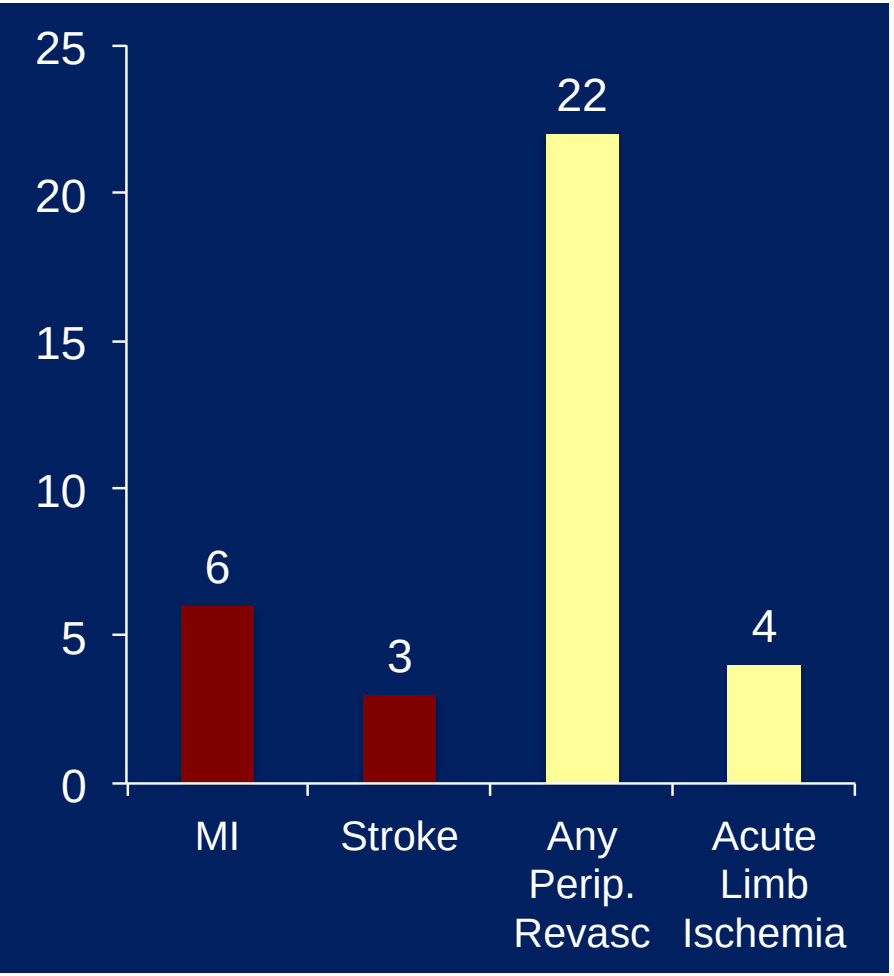
Adjusted for age, sex, race, BMI, hypertension, dyslipidemia, smoking, duration of DM, A1c, eGFR, hx CAD, and hx cerebrovascular disease

Burden of Risk in PAD is Driven by Limb Events

Events in PAD Patients at 4 Years
REACH Registry



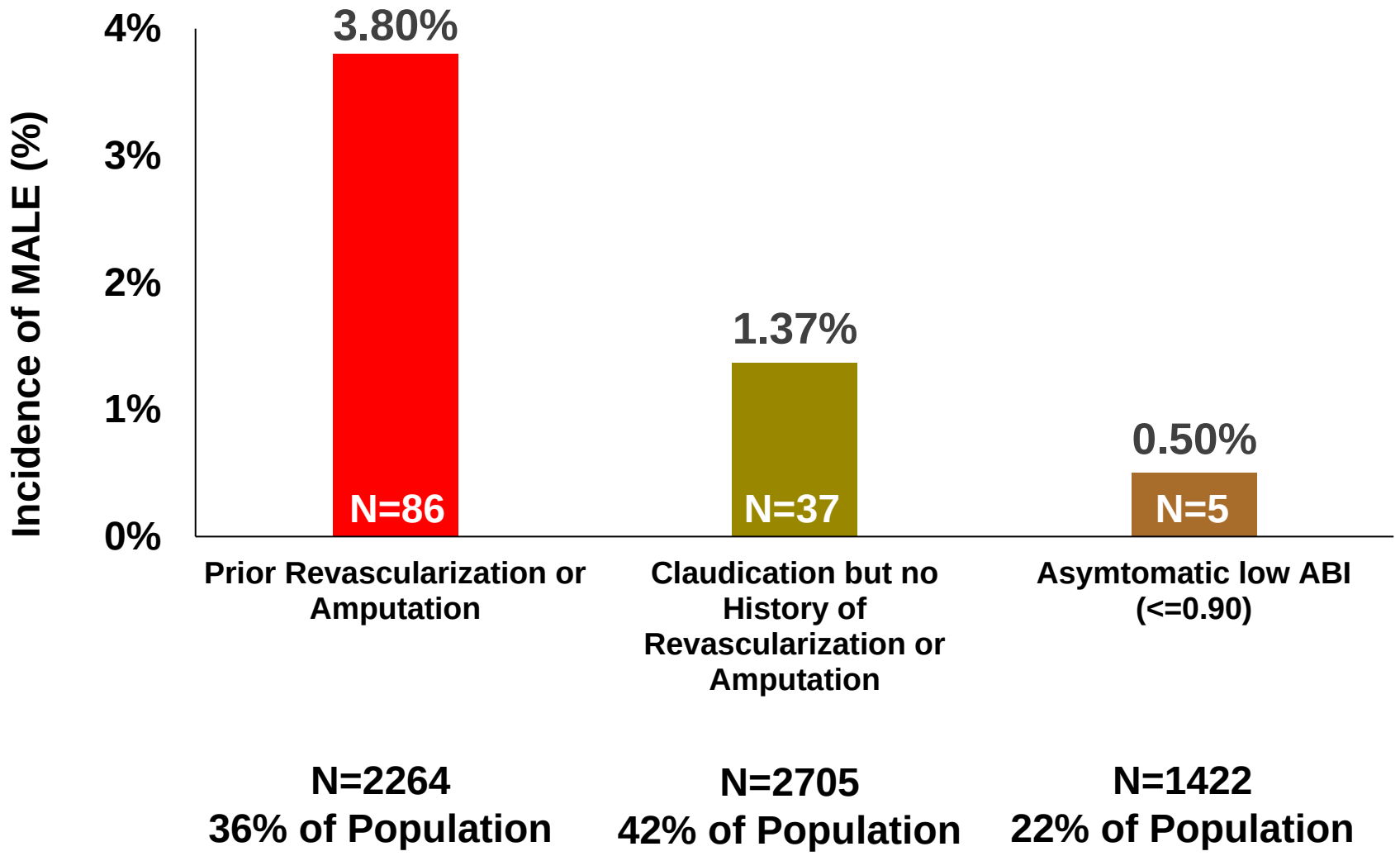
Events in PAD Patients at 3 Years
TRA2P-TIMI 50



- **>200 million with PAD globally**
- **Incidence is increasing with key risk factors of age, obesity and diabetes**
- **Key morbidity is limb symptoms (claudication → critical limb ischemia)**
- **Most common outcome is the need for a limb revascularization procedure**
- **Limb tissue loss events (e.g. amputation and ALI) are as common as MI and stroke**

Kumbhani et al. EHJ 2014
Bonaca et al. Circulation 2013
Fowkes *et al. Lancet* 2017;14:156-170

Prior Limb Revascularization Associated with Greater Limb Risk – COMPASS Trial



Spectrum of Limb Outcomes in PAD

Limb Ischemic Events Occur in a Spectrum Similar to Cardiac Ischemic Events

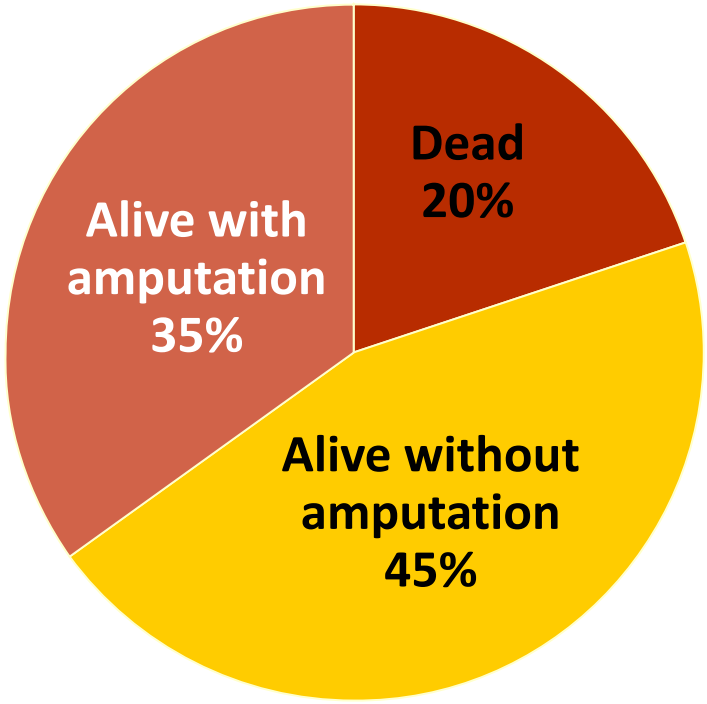
CARDIAC	Stable Angina	Elective Coronary Revasc.	Severe Stable Angina	Unstable Angina (UA)	UA Leading to urgent Coronary Revasc.	Myocardial Infarction
LIMB	Claudication	Elective Peripheral Revasc.	Chronic Critical Limb Ischemia	Urgent Peripheral Revasc.		Acute Limb Ischemia

DEFINITION	**Subjective**	**Objective**
REASON FOR INTERVENTION	**Symptom Relief**	**Prevent Irreversible Tissue Loss**
ETIOLOGY	**Multifactorial/Atherosclerotic**	**Thrombosis** (artery, stent, graft)

Critical Limb Ischemia (CLI)

Fate of Patients With CLI After Initial Treatment

Summary of 6-month outcomes from 19 studies



Critical limb ischemia is defined as ischemic rest pain, non-healing wounds, or gangrene.

Dormandy JA, Rutherford RB. J Vasc Surg. 2000;31:S1-S296.

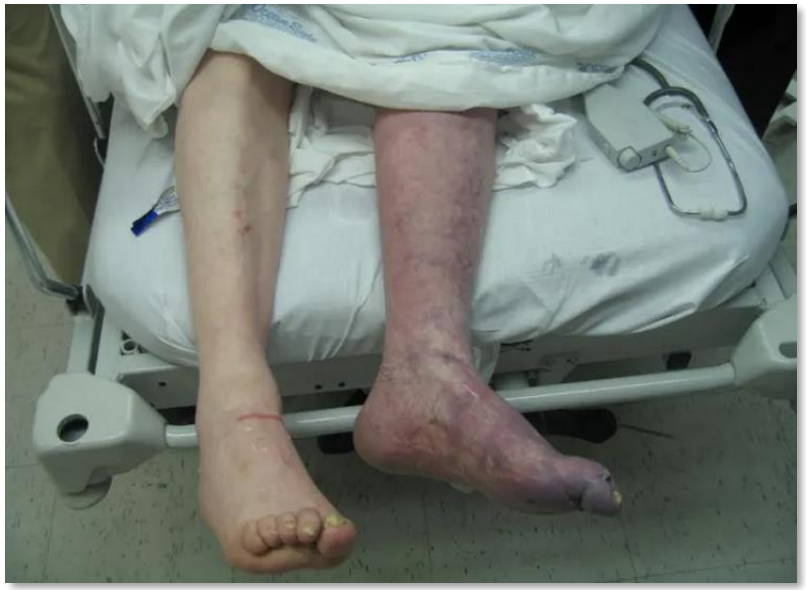
The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Acute Limb Ischemia

Mark A. Creager, M.D., John A. Kaufman, M.D., and Michael S. Conte, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*



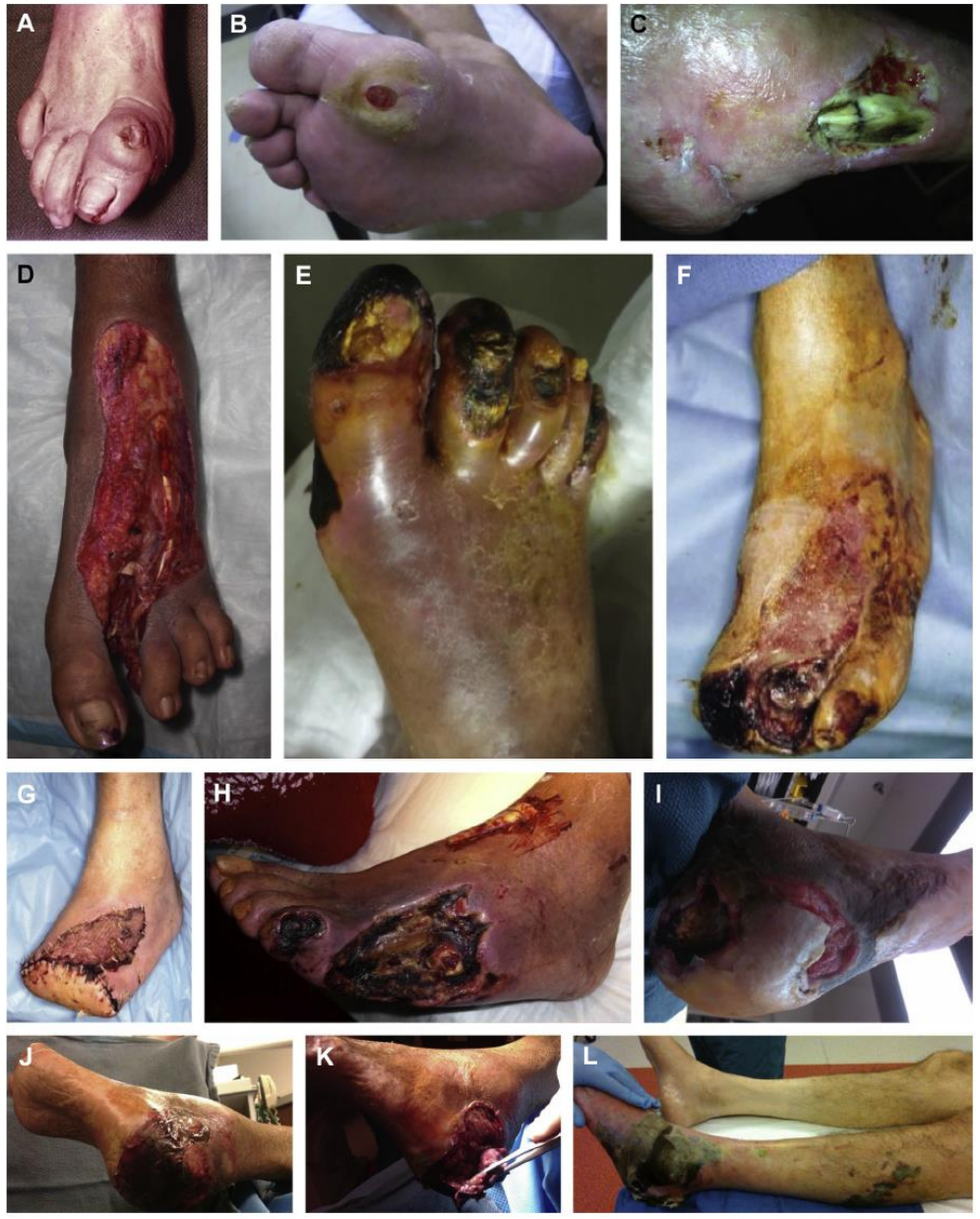
"This is a potentially catastrophic condition that can progress rapidly to limb loss and disability…"

"…Rates of death and complications among patients who present with acute limb ischemia are high…"

10-15% require amputation with majority above the knee

15-20% die within 1 year of presentation

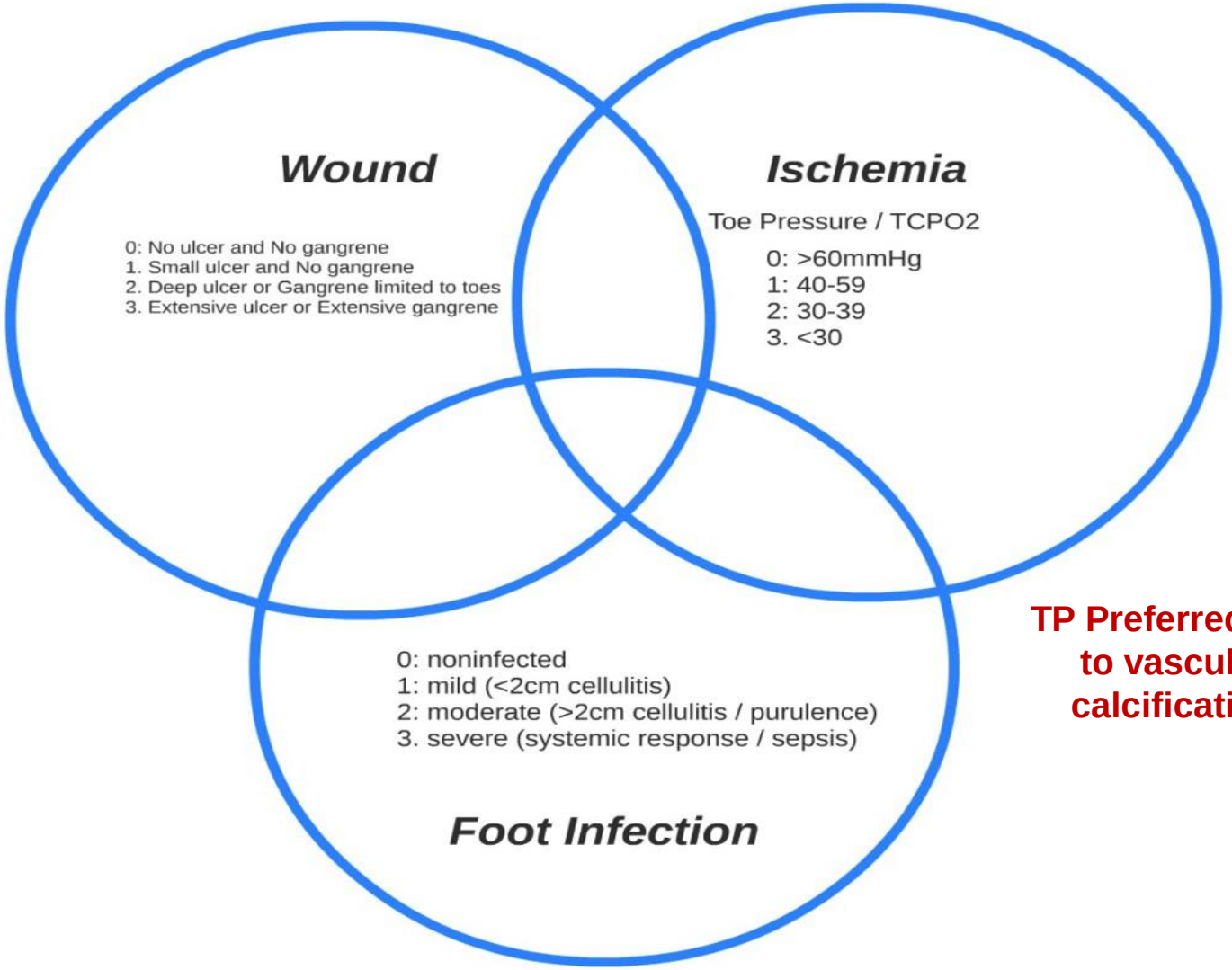
Creager MA, et al. *NEJM* 2012.
Image from: http://blog.clinicalmonster.com/2017/02/07/black-blue-red/.



Chronic Critical Limb Ischemia

- **Tissue loss in the lower extremities**
- **Traditionally focused on ischemia as mediator**
- **Strongly associated with Diabetes**
- **Pathobiology poorly understood increasingly recognized as multifactorial**

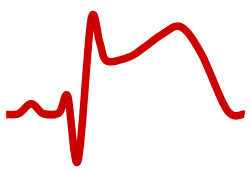
WiFi Concept for Diabetic Wound Assessment

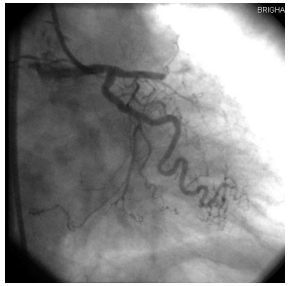


TP Preferred due to vascular calcification

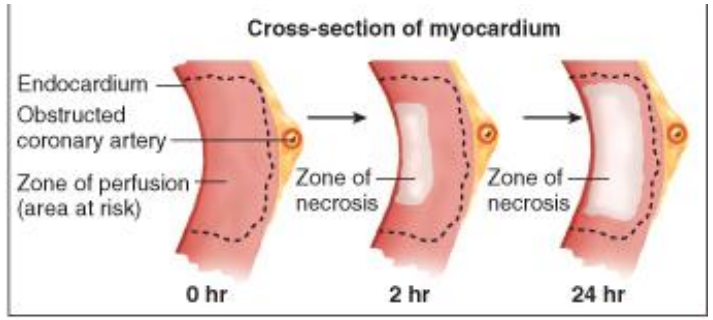
Slide Courtesy of Patrice Nault JVS 2014

STEMI





- Acute thrombotic occlusion of an artery threatening tissue loss
- “Time Is Muscle”
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication



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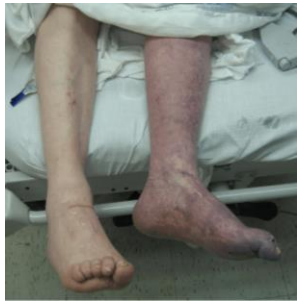
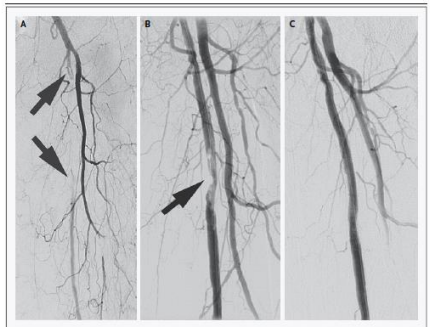
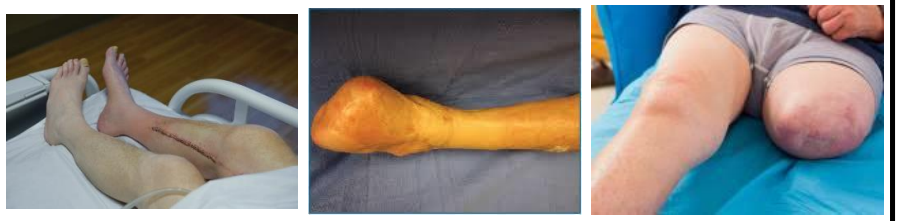
- Mortality at 1 year 8.1%[1]
- Recurrent MACE at 1 year 3.4%[1]
- HF at 1 year 7.4%[1]

ALI





- Acute thrombotic occlusion of an artery threatening tissue loss
- “Time Is Muscle”
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication



0 Hour → 24 Hour

- Mortality at 1 year 12.1%[2]
- MACE 11.7%, Recurrent ALI 24% (1 yr) [2]
- Amputation at 1-year 27%[2]

1. Zeymer et al. EORP EU STEMI Registry 2019

2. Bonaca et al. Circulation 2016

CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Medical Therapy for PAD: The Basics

Marc P. Bonaca MD MPH
Professor of Medicine
Director of Vascular Research
University of Colorado School of Medicine

CPC Clinical Research

An Affiliate of:

University of Colorado Anschutz Medical Campus

Medical Therapy for PAD 1990-2010

1990 2000 2010

Therapies for MACE (PAD subgroups)

ATT
ASA vs Placebo
↓ MACE 23%
↑ Major Bleed 60%

CAPRIE
Clopidogrel vs ASA
↓ MACE 24%
Bleeding similar
FDA Approved for PAD

HOPE
ACEi vs Placebo
↓ MACE 22%
FDA Approved for PAD

WAVE
VKA+ASA vs ASA
Neutral MACE
↑ Life threatening Bleeding >3X

HPS
Statin vs Placebo
↓ MACE 22%
FDA Approved for PAD

CHARISMA
DAPT vs ASA
Neutral MACE
↑ Mod Bleed 60%

Therapies for MALE (Acute Limb Ischemia, Amputation)

No limb benefit described

No difference in Amputations

No limb benefit described

No difference in Limb ischemia

↓ Peripheral Revasc 20%

? Lower Hosp Risk

Dutch BOA
Warfarin
after Bypass
No benefit
↑ Hemorrhagic Stroke > 3X

CASPAR
DAPT vs ASA
after Bypass
No benefit

CAMPAR
DAPT vs ASA
after ENDO
Not completed

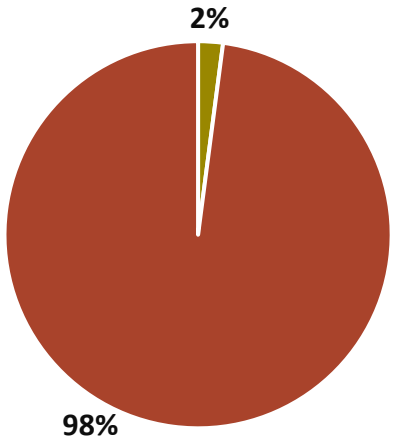
Therapies for Symptoms (Claudication)

Pentoxifylline
Approved 1984
Unclear if it works

Cilostazol Improves Symptoms
Approved in 1999
FDA Approved for PAD

Evolution Since 2010

TRA2P-TIMI 50



CLI No CLI

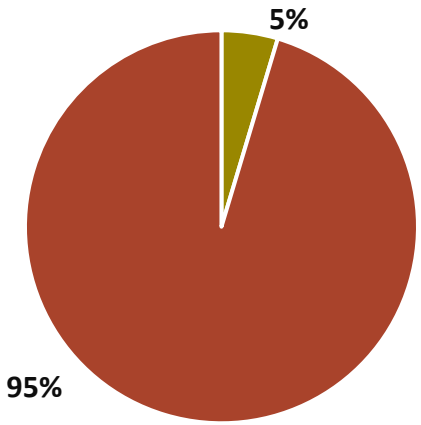
N=7,971

PAD Subgroup

Vorapaxar vs. Placebo
MACE Benefit Overall
Consistent in PAD
Reduction in ALI
Increased Bleeding

Bonaca MP, et al. *AHA* 2018

EUCLID



CLI No CLI

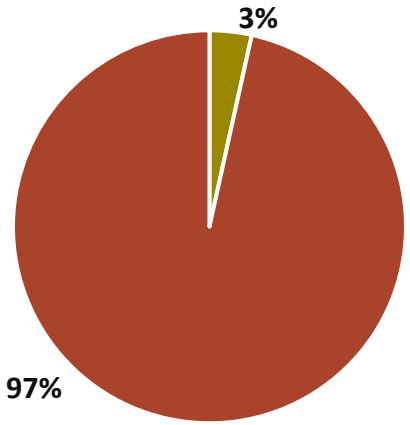
N=13,885

Dedicated PAD Trial

Ticagrelor vs. Clopidogrel
No benefit for MACE or MALE
(ALI or Amputation)

Norgren L, et al. *EJVS* 2017

FOURIER



CLI No CLI

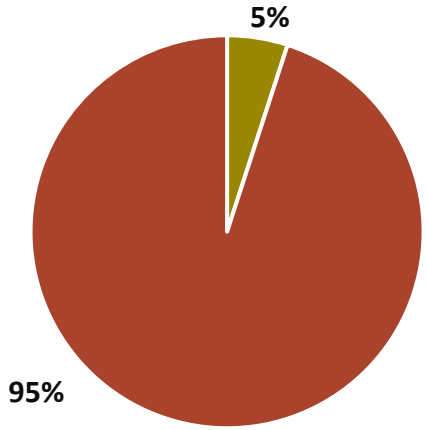
N=3,642

PAD Subgroup

Evolocumab vs. Placebo
MACE Benefit Overall
Consistent in PAD subgroup
Reduction in MALE

Bonaca MP, et al. *Circ* 2018

COMPASS PAD



CLI No CLI

N=4,129

PAD Subgroup

Rivaroxaban vs. Placebo
MACE Benefit Overall
Consistent in PAD
Reduction in ALI & Amputation
Increased Bleeding

Anand SS, et al. *Lancet* 2017

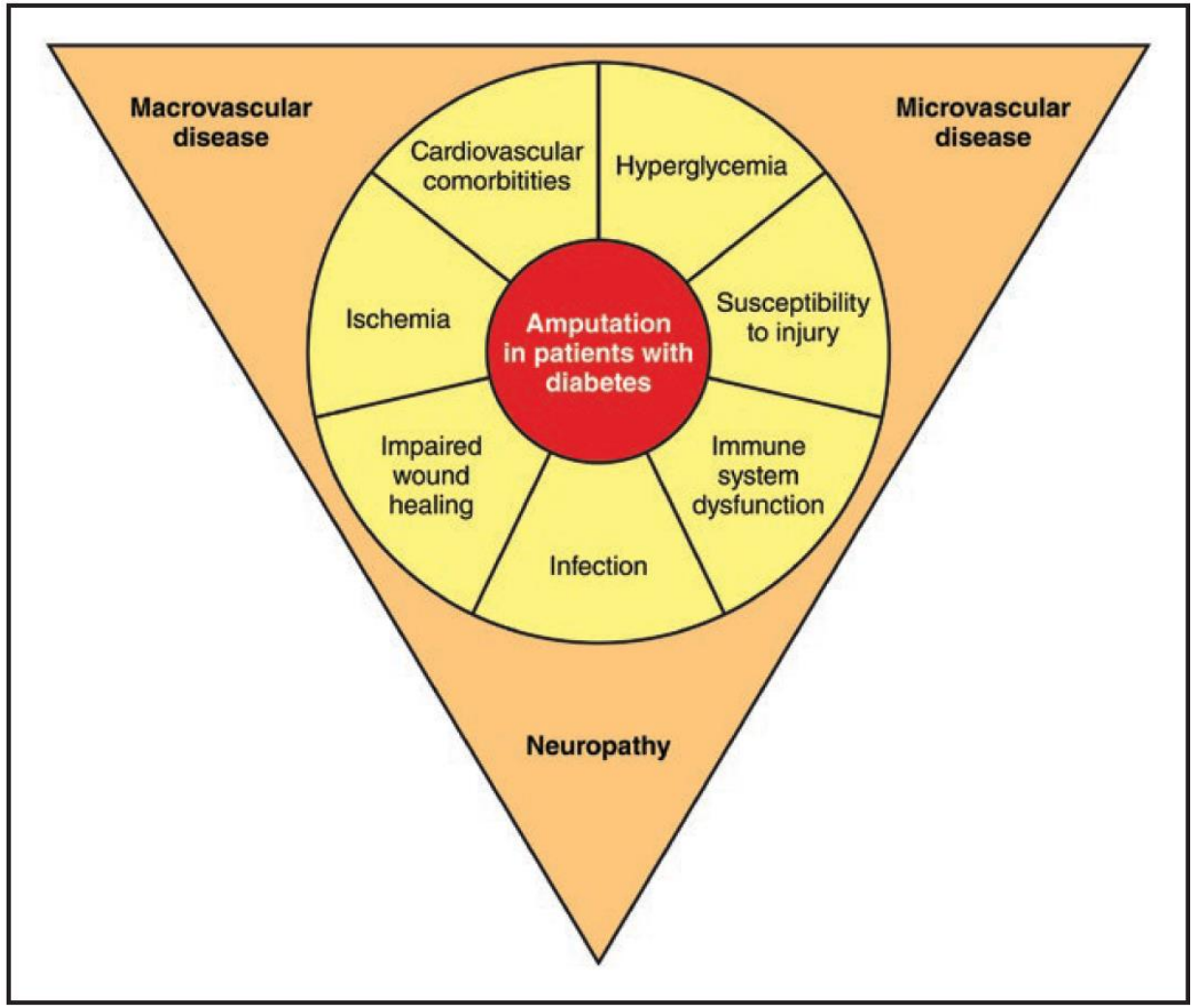
Total CLI=1,140

Only dedicated PAD trial was neutral

Positive studies

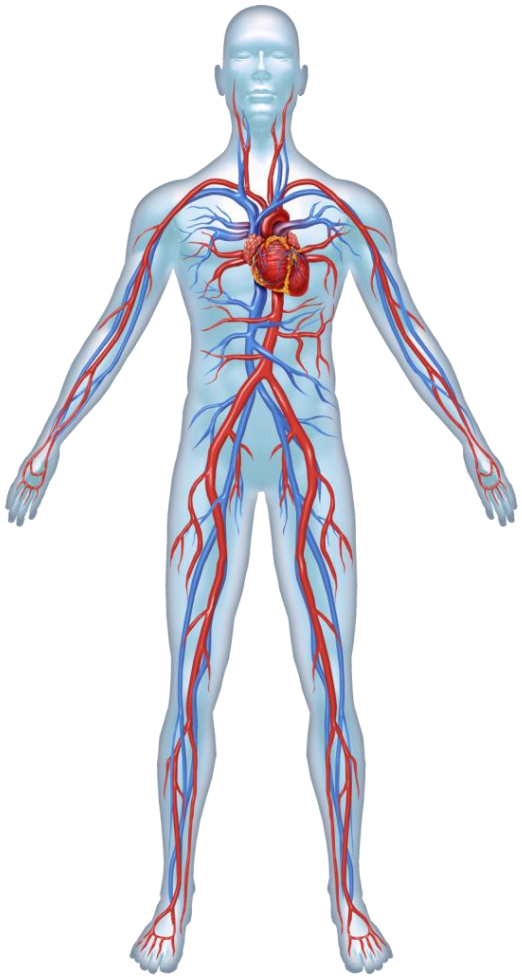
- Subgroups of chronic ASCVD populations
- MACE Primary outcomes
- Excluded "acute" patients
- Minimal exposure in CLI (<5%)

CLI in Diabetes



Bonaca MP, Beckman JA. Circulation. In Press

Predictors of Amputation in Diabetes



22 year prospective observation study of 1,461 patient with diabetes and w/o foot ulcer

136 amputations (65% above ankle) – 5.3/1000 pt-years

79% were preceded by foot ulcer

Patient Factors

Renal dysfunction (1-SD decr in GFR) HR 1.18 (1.00 – 1.38)

Poor vision HR 1.70 (1.05 – 2.73)

Lower body weight

Younger age

Limb Factors

Macrovascular Atherosclerosis

• ABI ≤ 0.5 (obstructive arterial disease)
HR 3.98 (2.31 – 6.85)

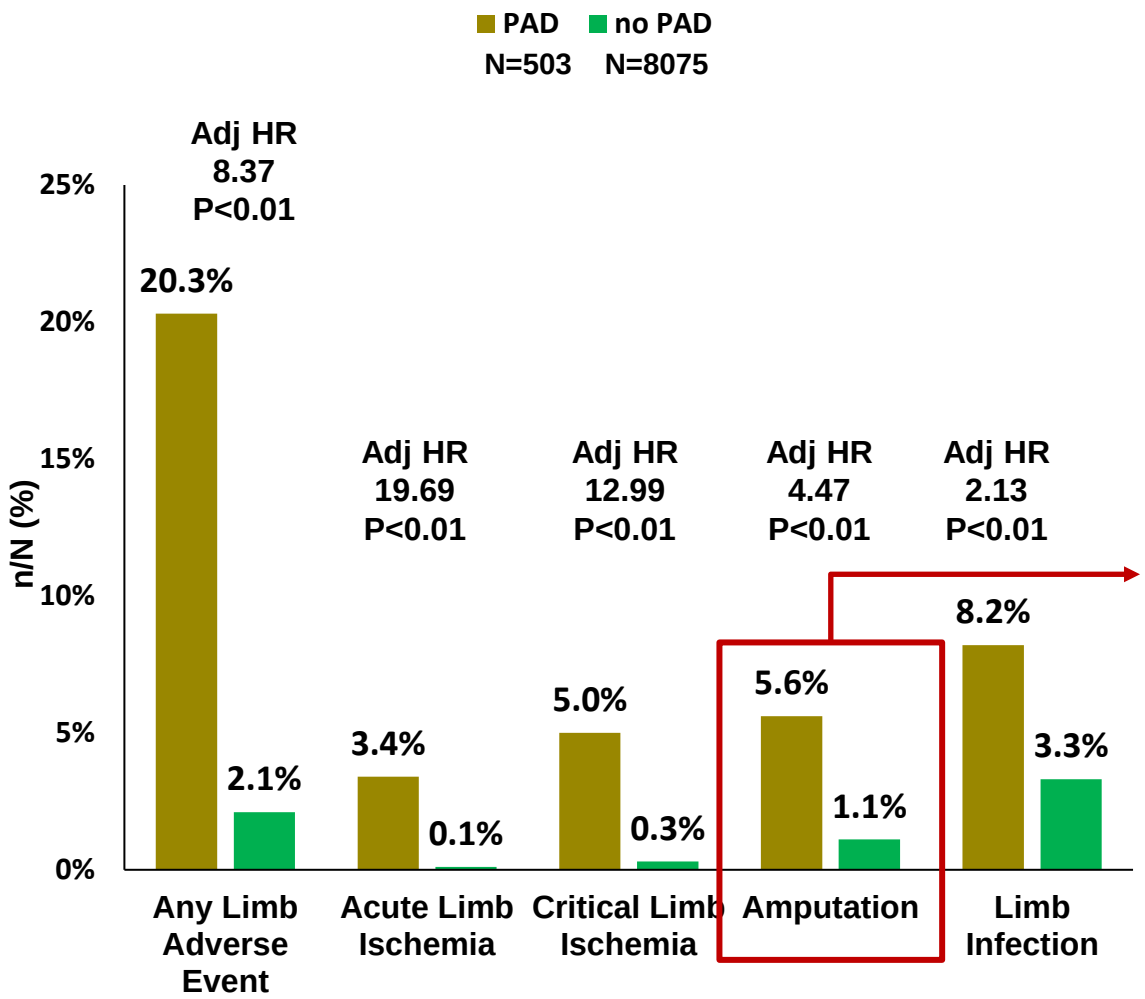
• ABI ≥ 1.3 (medial arterial disease) +
$TcPO_2$ < 26 mmHg
HR 2.20 (1.18 – 4.09)

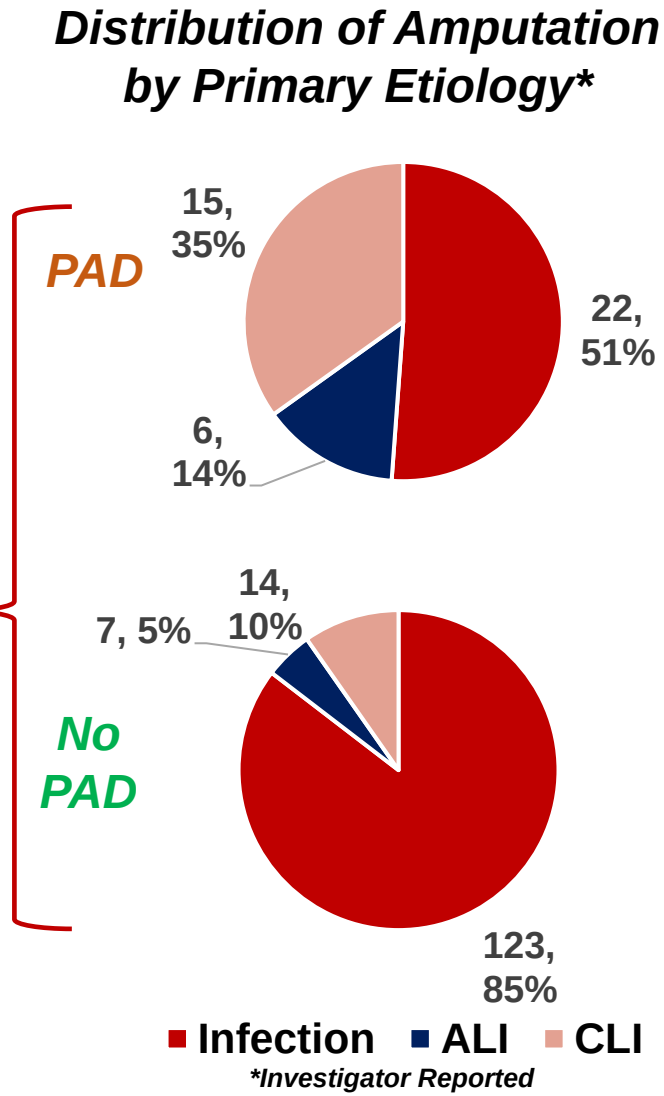
Microvascular Disease – Neuropathy

• 10-g monofilament testing
HR 3.09 (2.02 – 4.74)

Boyko et al. Diabetes Care 2017

Limb Outcomes by PAD Status in Placebo Patients



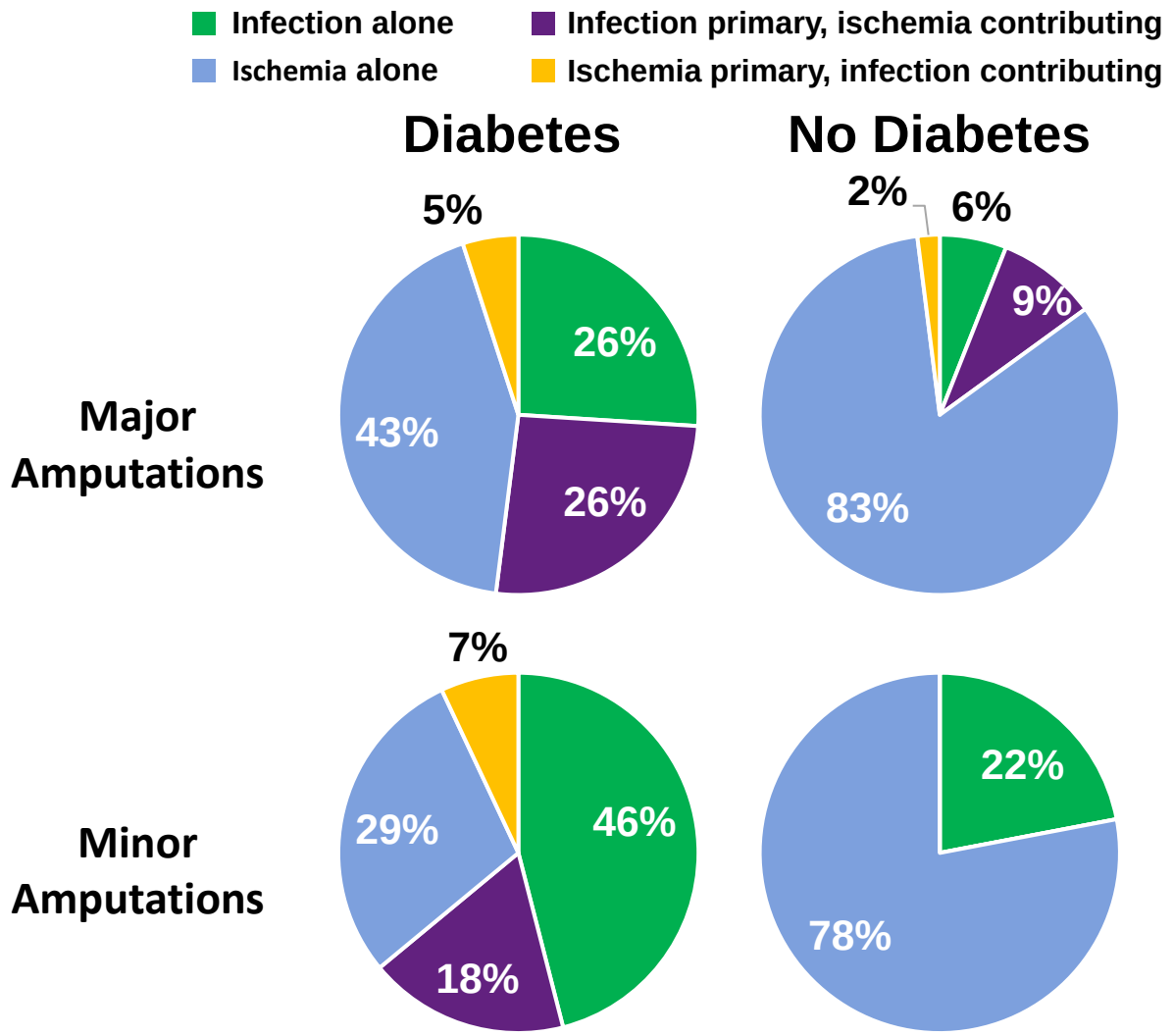


Adjusted for age, sex, race, BMI, hypertension, dyslipidemia, smoking, duration of DM, A1c, eGFR, hx CAD, and hx cerebrovascular disease

Amputation May Be Necessary to Control Infection in CLI
EUCLID Trial

Complex Outcome in PAD

- **Not a biological event but a response which maybe indicated**
  - Local practice pattern
  - Viability of limb at presentation (e.g. delays in care)
  - Patient viability (amputation safer than revascularization
- **Multifactorial in etiology with an important role of infection in patients with PAD, particularly those with concomitant diabetes**

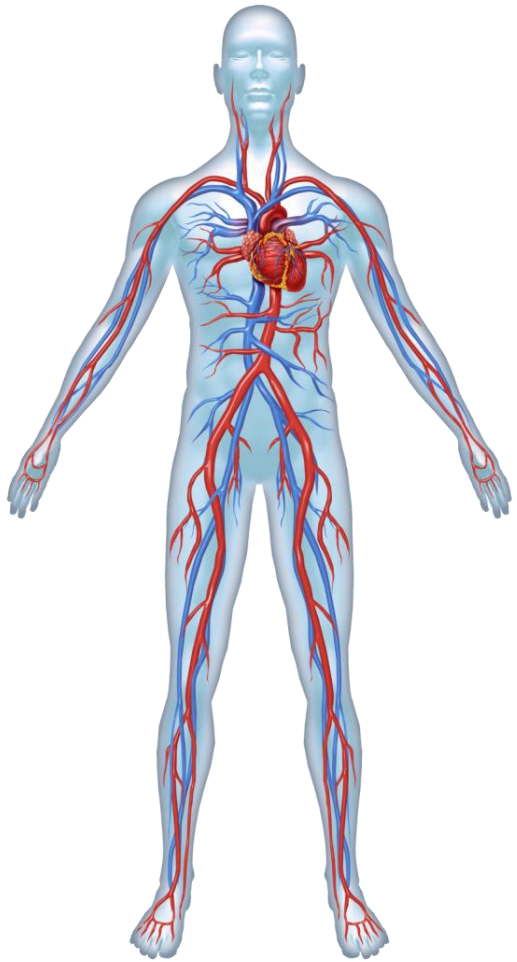


CLI=Critical Limb Ischemia

Govsyeyev N, et al. *AHA* 2020

Goals of Medical Therapy in PAD

Reduce Risk of Systemic Atherothrombosis (e.g. MI, Stroke)

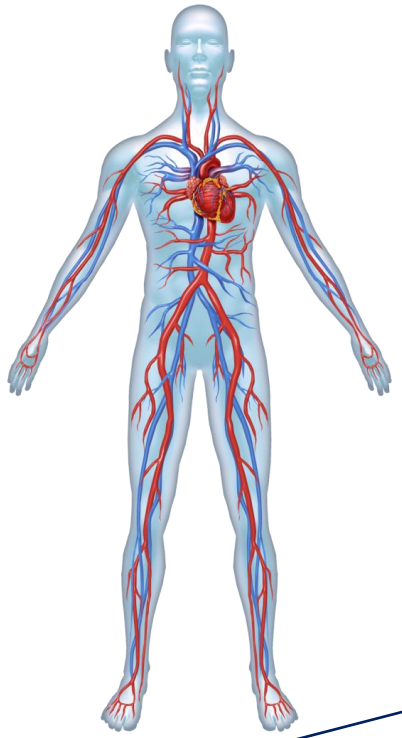


Improve Function

Reduce Risk of Major Adverse Limb Events (e.g. CLTI, ALI, Amputation)

Goals of Medical Therapy in PAD

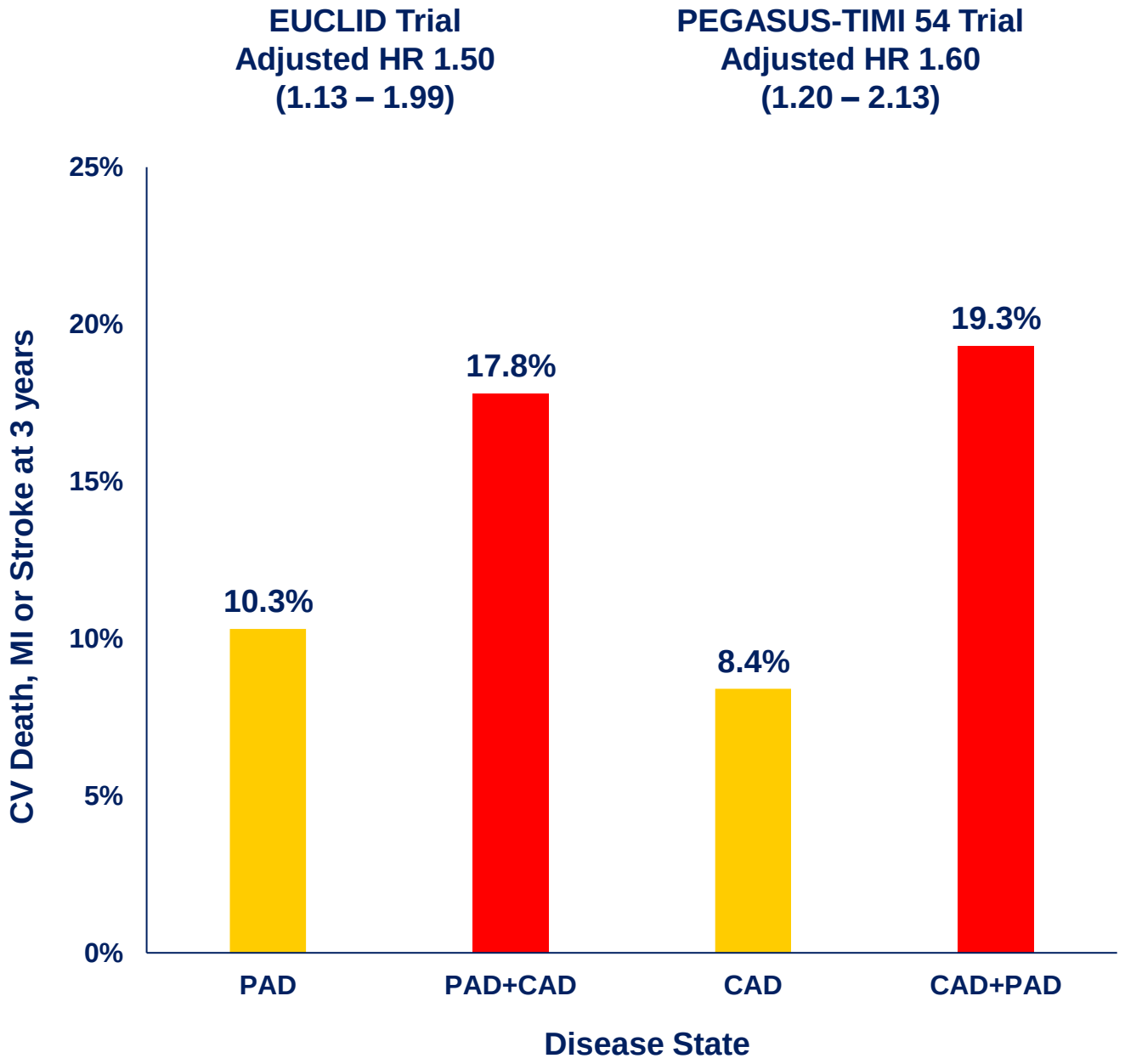
Reduce Risk of Systemic Atherothrombosis (e.g. MI, Stroke)



Risk Stratification may help personalization of therapy…especially for therapies with risk/benefit considerations

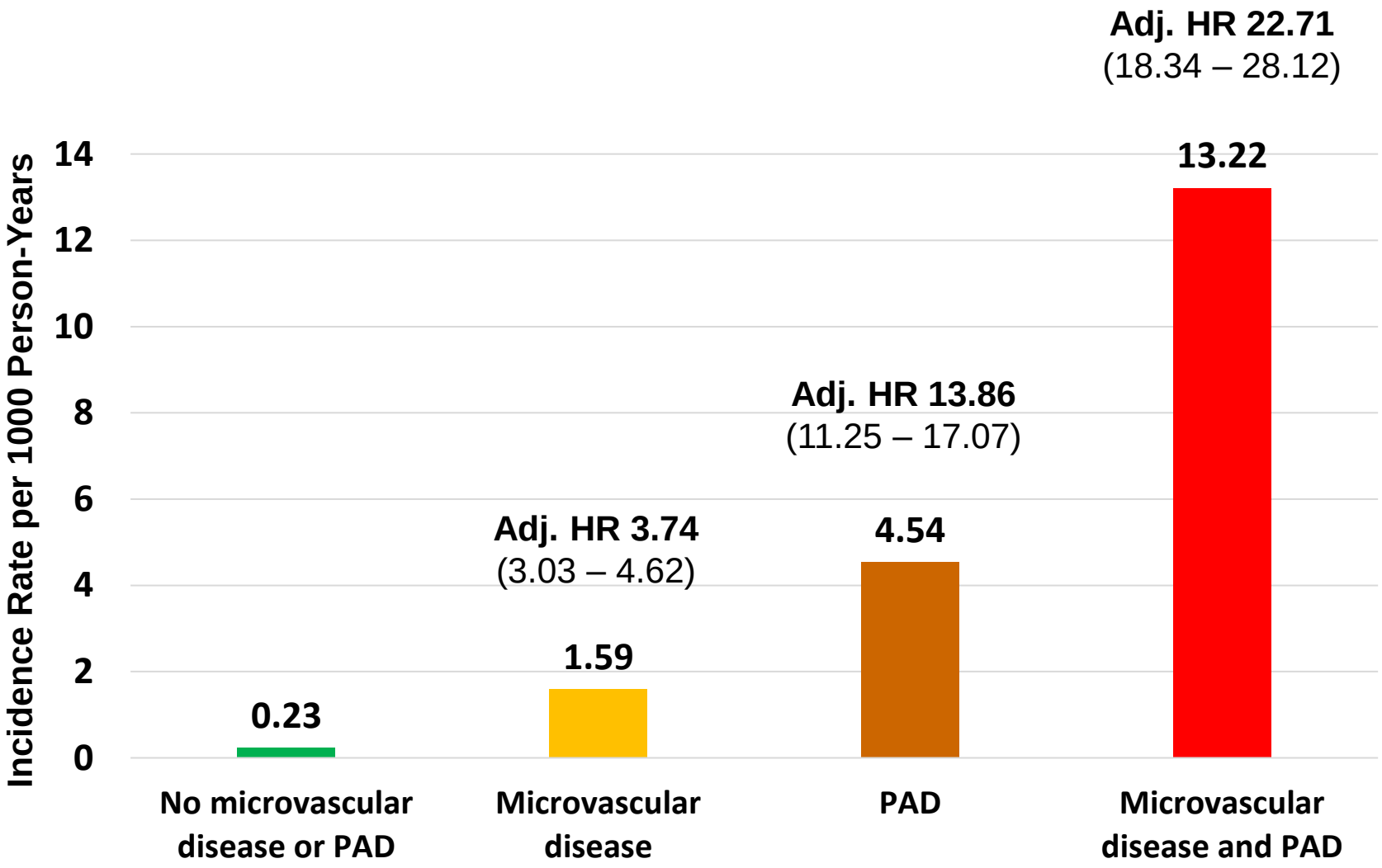
Reduce Risk of Major Adverse Limb Events (e.g. CLTI, ALI, Amputation)

Polyvascular Disease in PAD is Associated with Increased MACE Risk



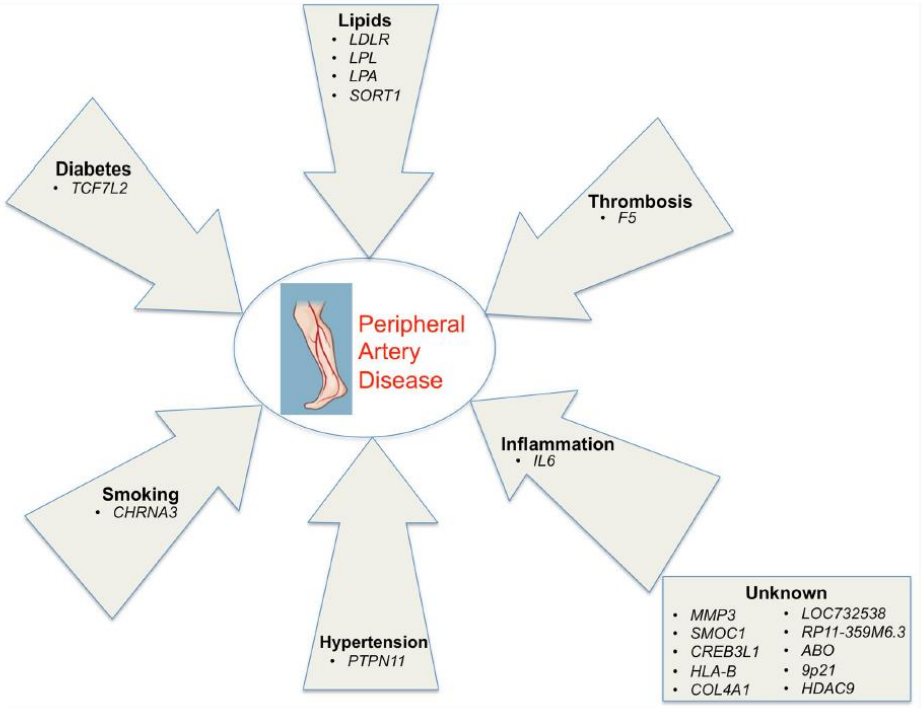
Bonaca Vasc Med 2018

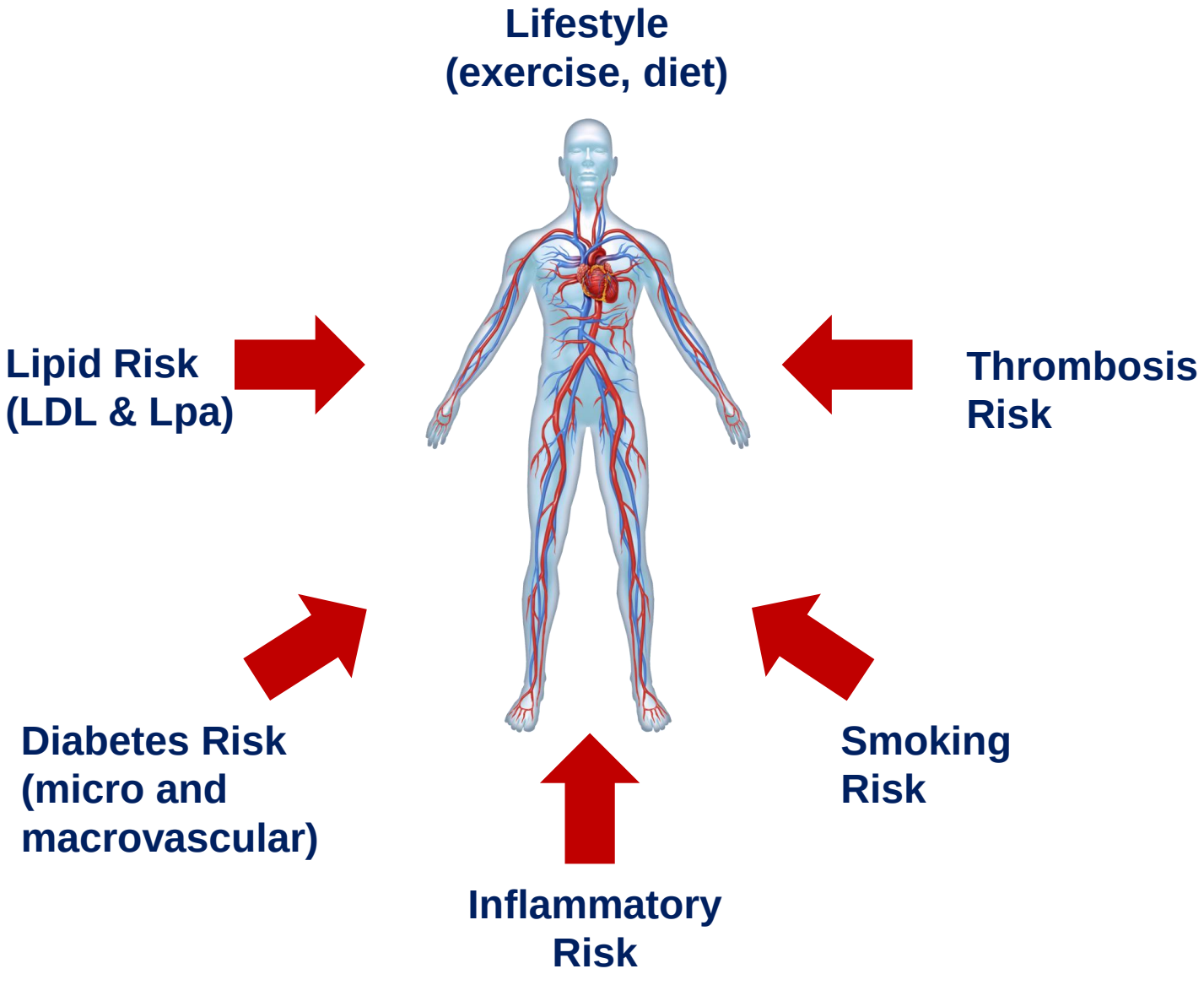
Amputation Risk in Peripheral Artery Disease



Beckman et al. Circulation 2019

Pathways of Risk in PAD



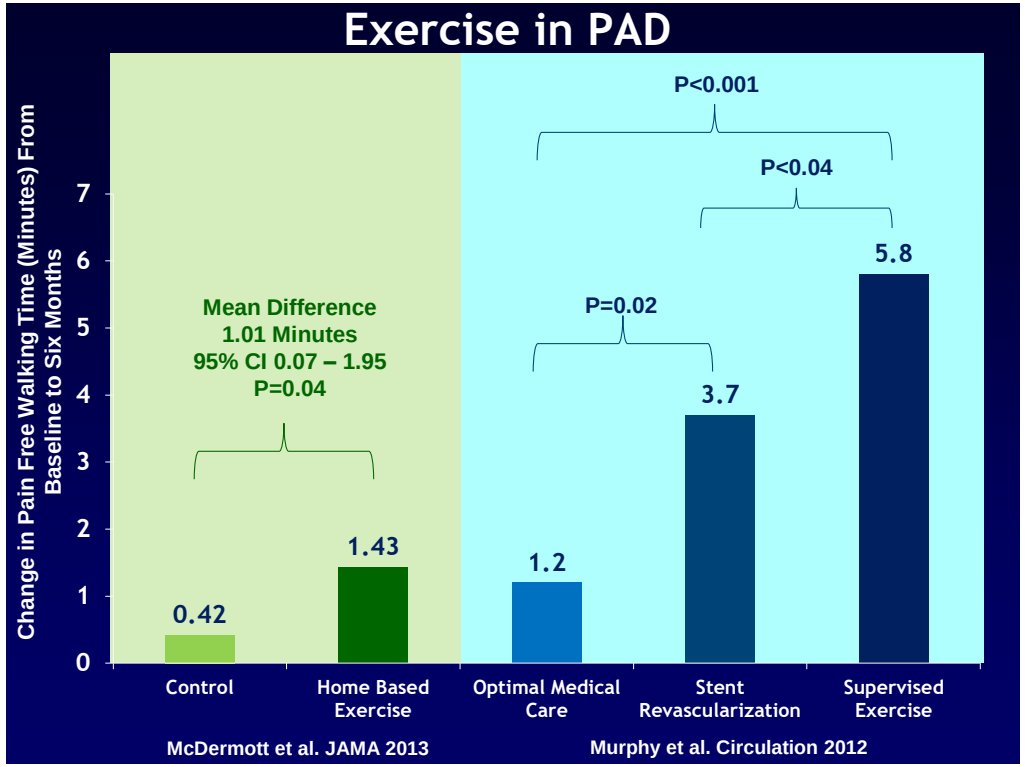


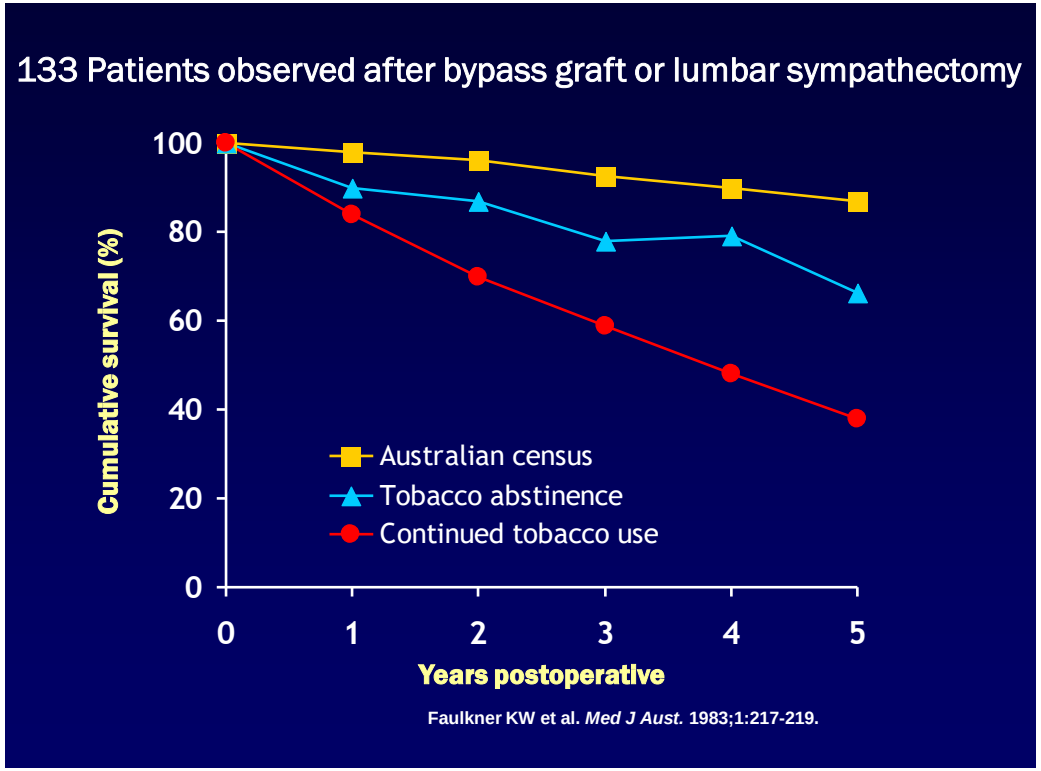
Klarin et al. Nature Medicine 2019

Therapies for All Patients

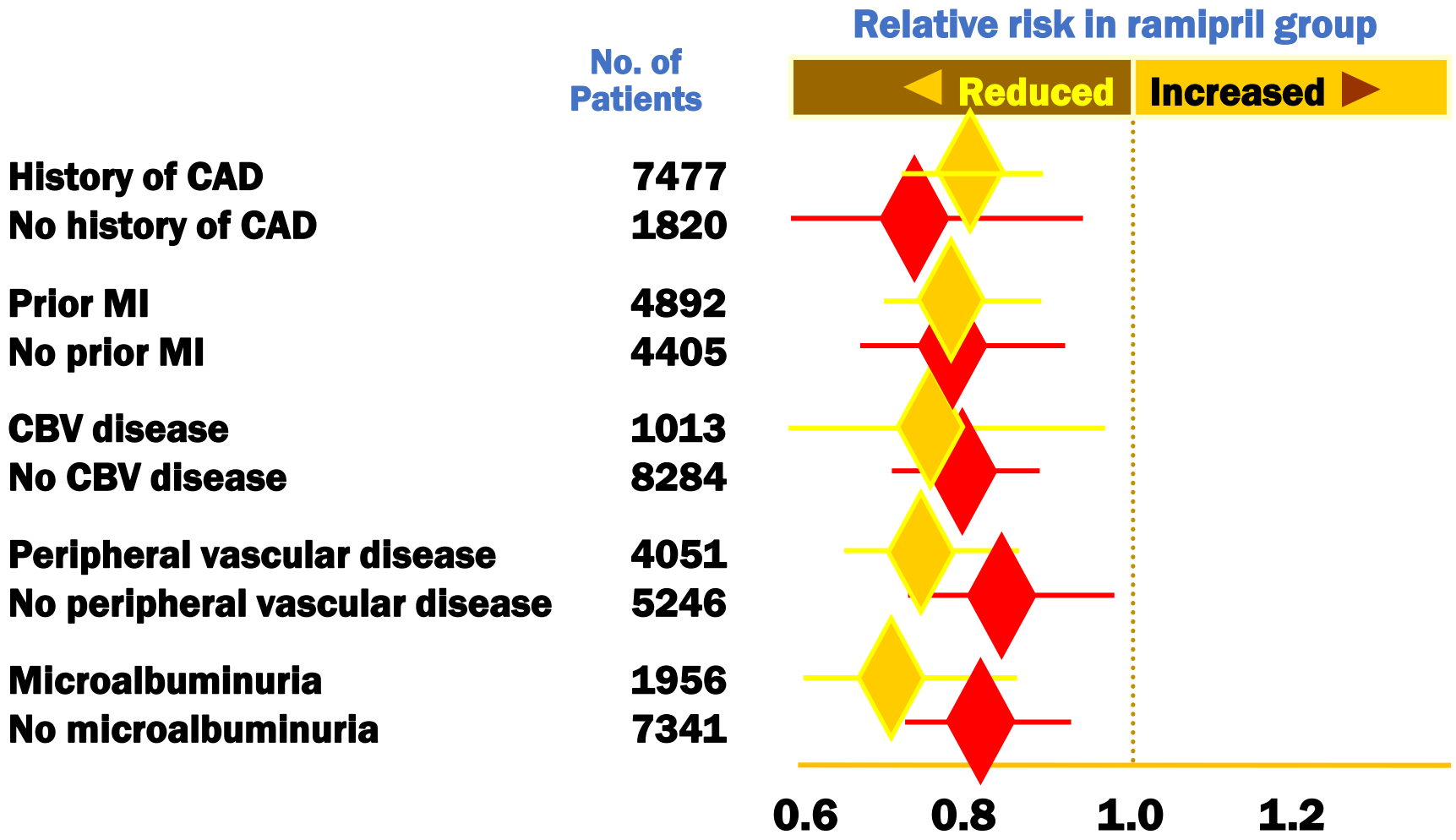
Lifestyle Interventions – they work!

- **Healthy diet**
- **Exercise (supervised exercise preferred)**
- **Smoking Cessation**



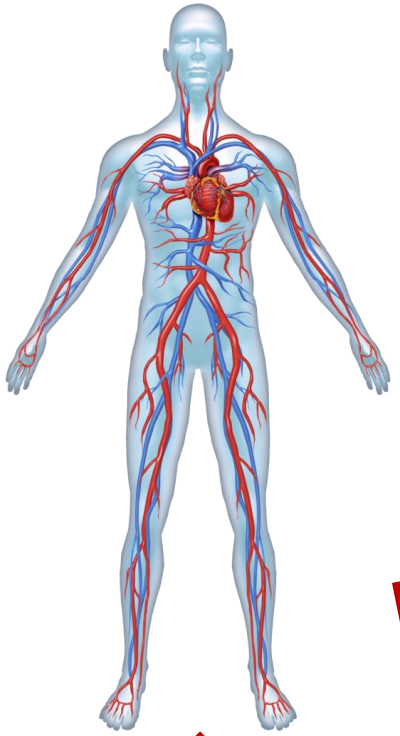


HOPE: Benefits of Ramipril in CV Risk Subgroups



Axes of Risk and Treatment Targets in PAD

<u>Lifestyle & Function</u> (exercise, diet, BP control, cilostazol where not contraindicated)



Lipid Risk (LDL & Lpa)

Thrombosis Risk

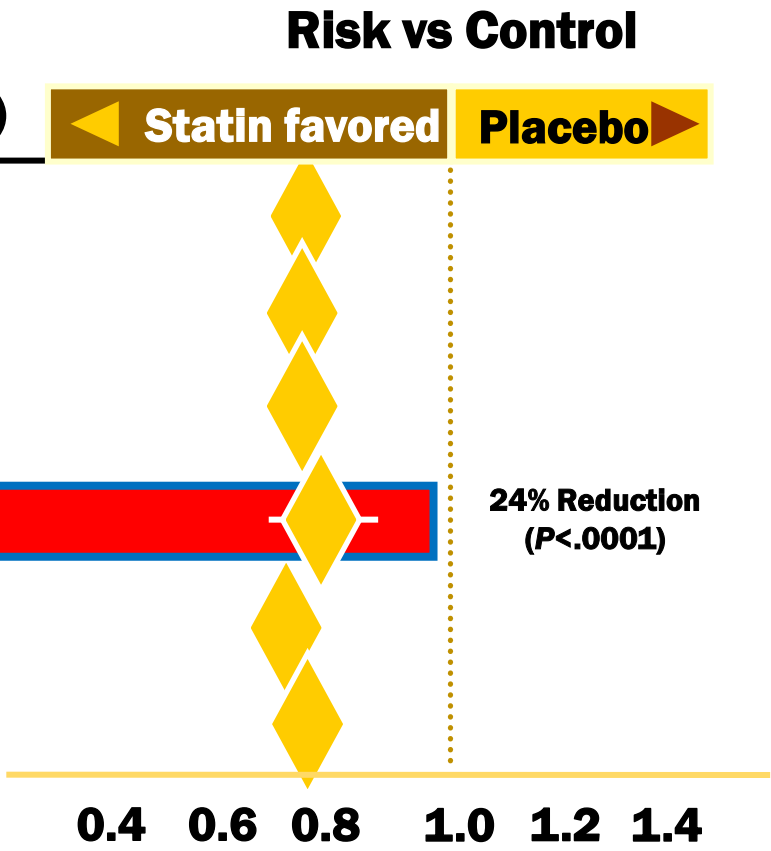
Diabetes Risk (micro and macrovascular)

<u>Smoking Risk</u>

Inflammatory Risk

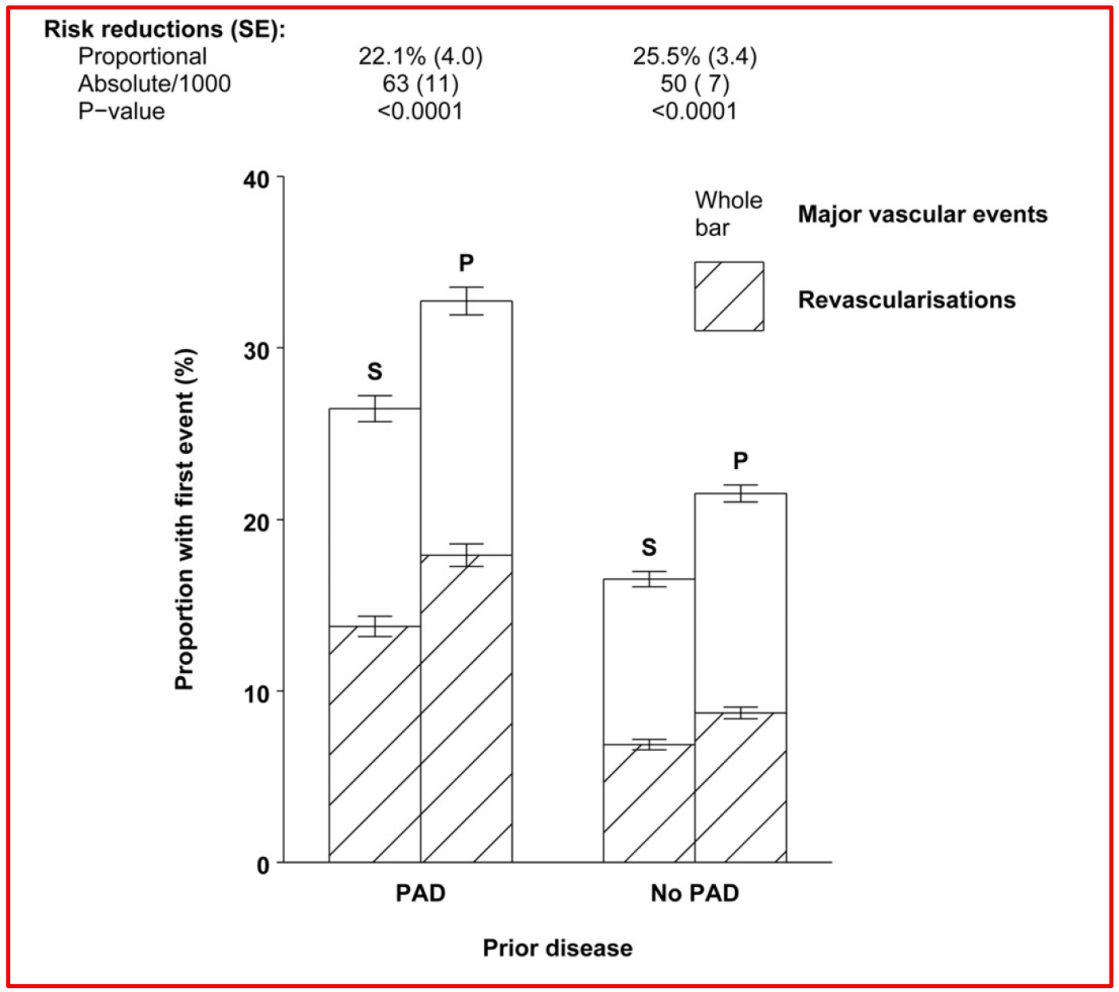
Heart Protection Study: Vascular Event by Prior Disease

Existing disease	Incidence of events: Statin (n=10,269)	Incidence of events: Control (n=10,267)
Previous MI	23.5	29.4
Other CHD	18.9	24.2
No prior CHD or CBV disease	18.7	23.6
PAD	24.7	30.5
Diabetes	13.8	18.6
All patients	19.8	25.2



Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22.

Statin Therapy and Vascular Events



HPS
Simvastatin vs. Placebo

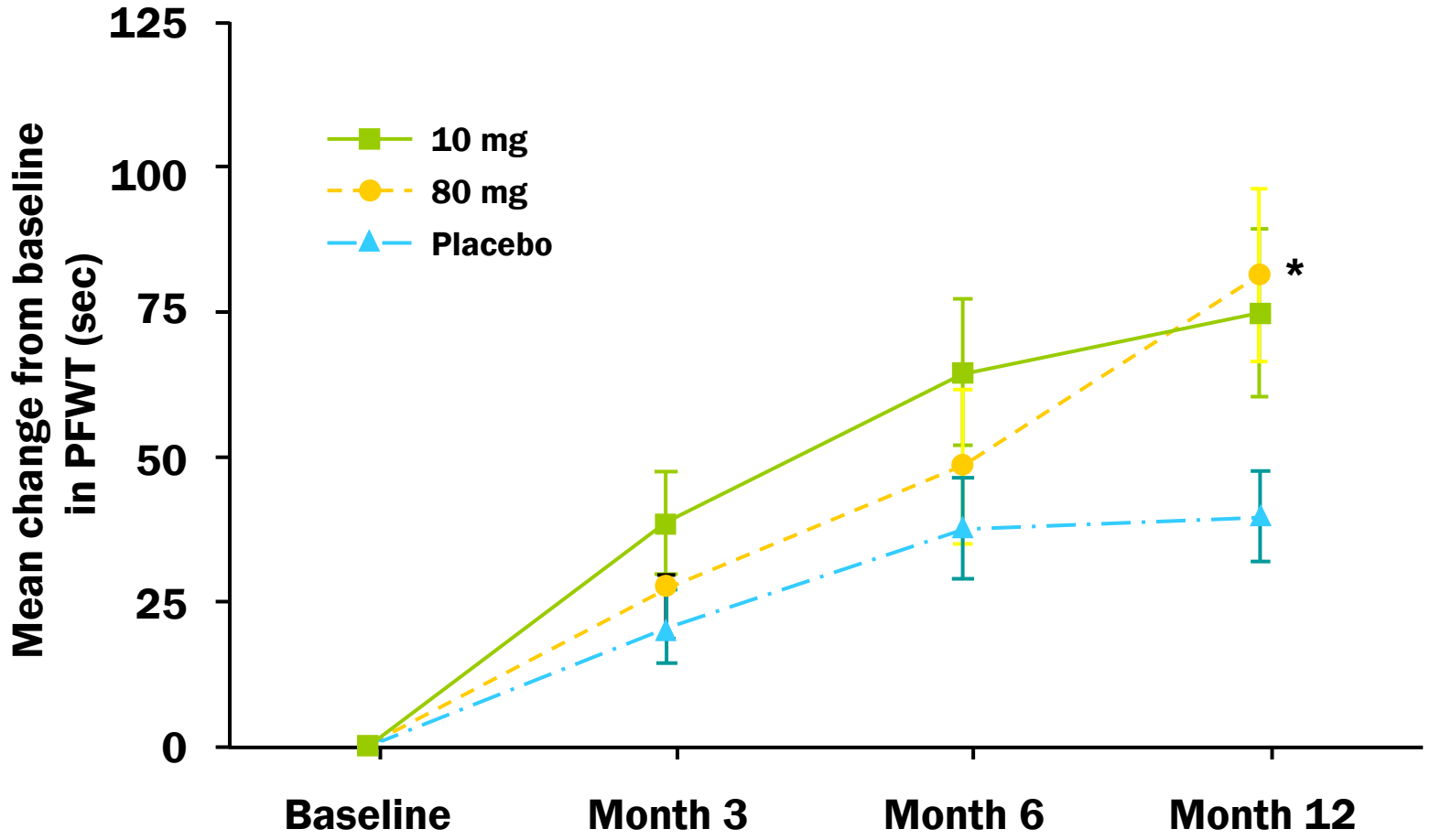
16% reduction in peripheral vascular events

20% reduction in non-coronary revascularization

Unclear effect on amputation

Heart Protection Study. JVS 2007

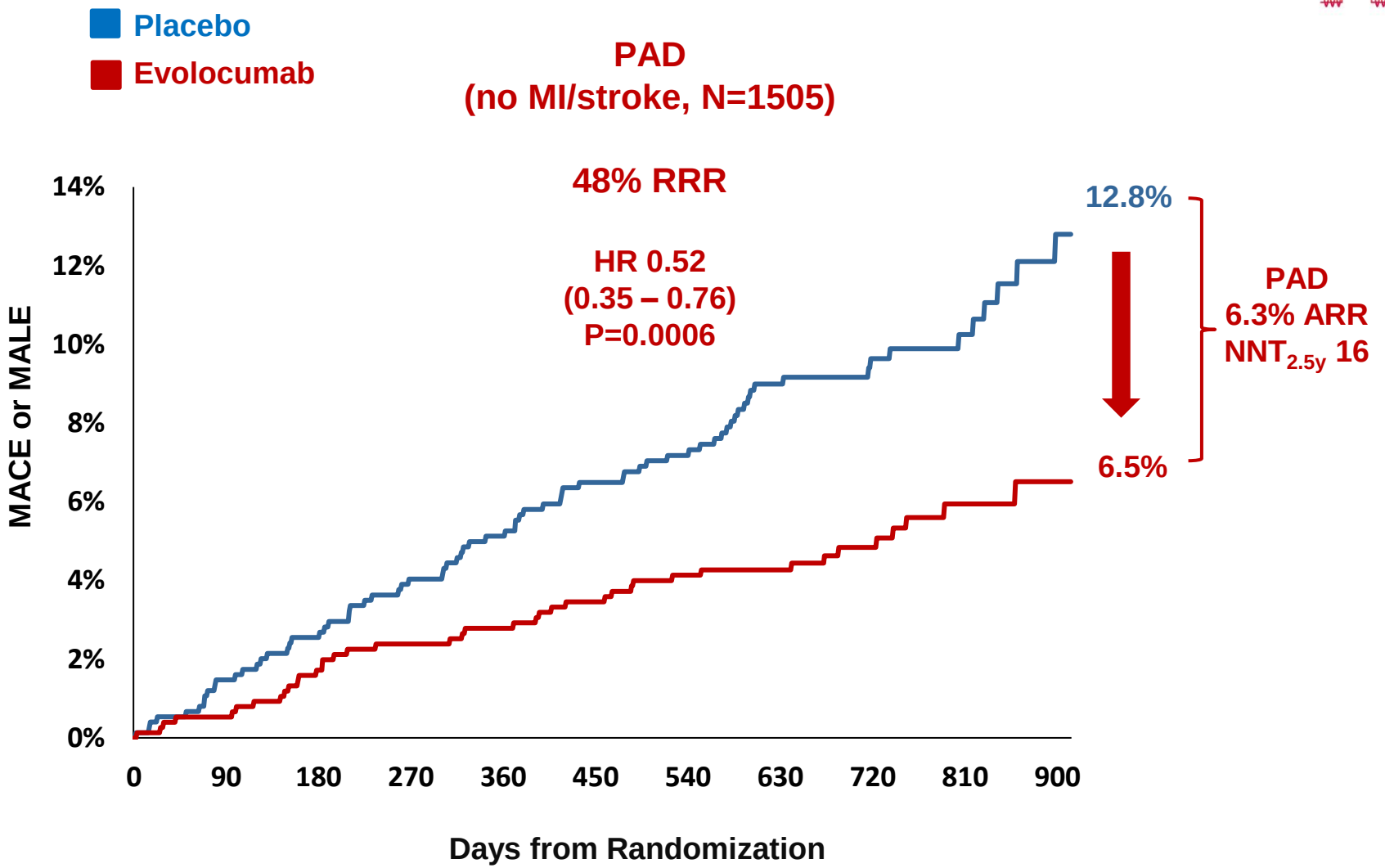
Atorvastatin in Patients With Claudication and PAD



PFWT=pain-free walking time.
*P=.03. No change in ABI over 12 months.

Mohler ER et al. *Circulation.* 2003;108:1481-1486.

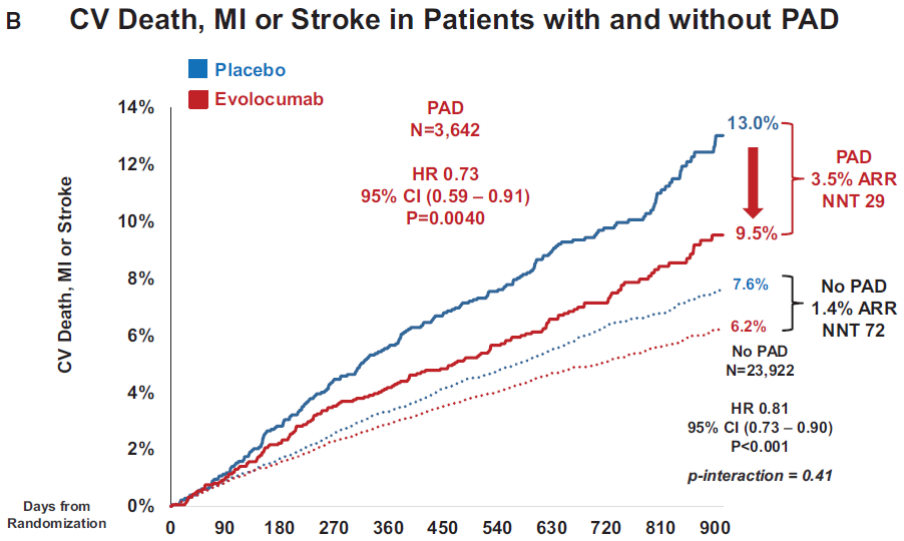
MACE or MALE
In Patients with PAD and no MI or Stroke

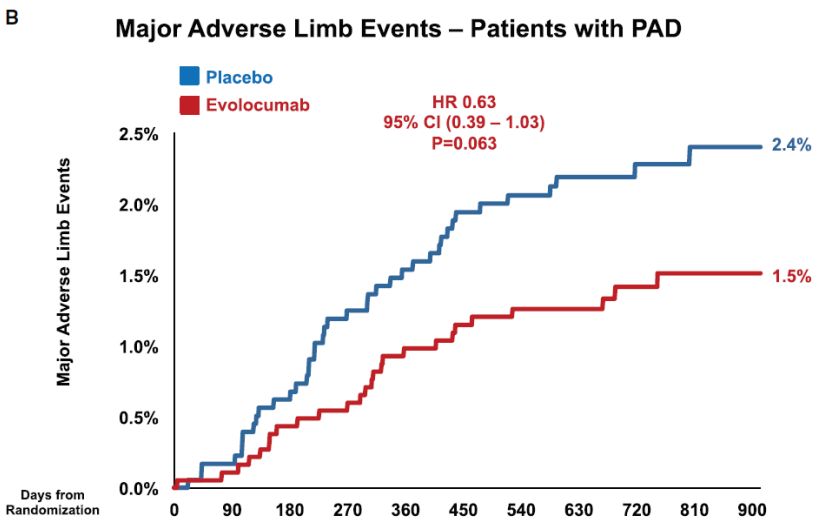


Bonaca et al. Circulation 2018

PCSK9i Reduce both MACE and Major Adverse Limb Events (MALE)

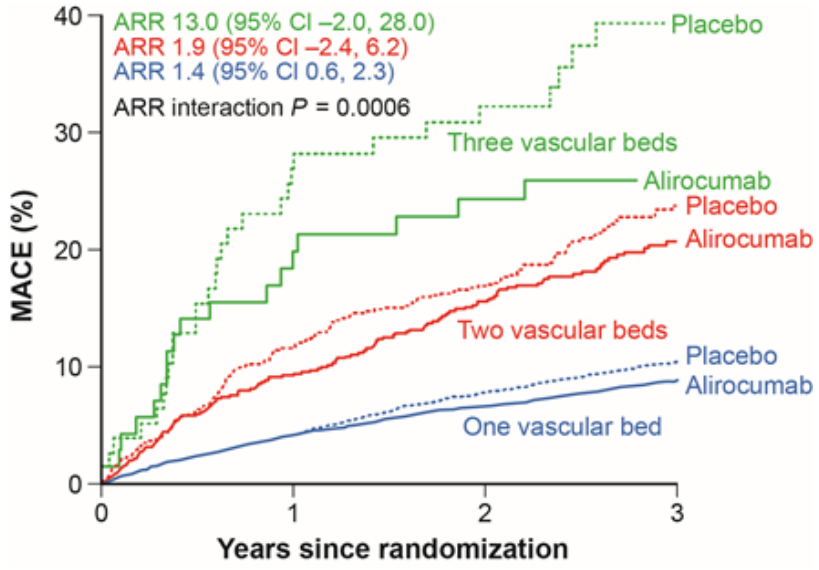
FOURIER, Bonaca et al. Circ 2018



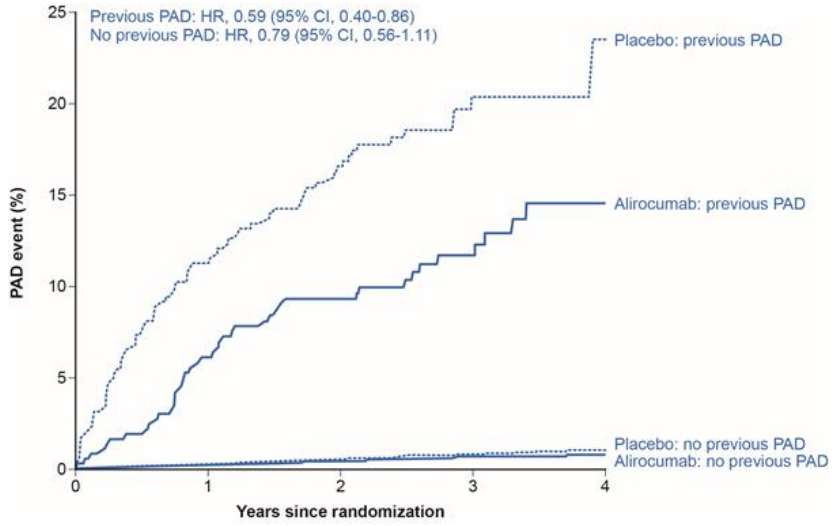


ODYSSEY, Jukema et al. Circ 2019; Schwartz et al. Circ 2020

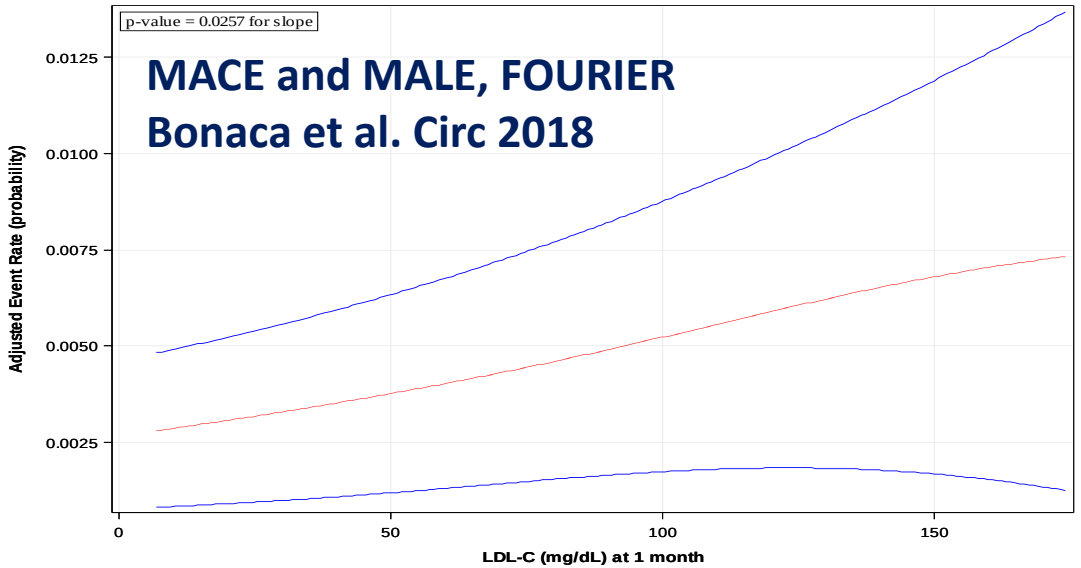
MACE



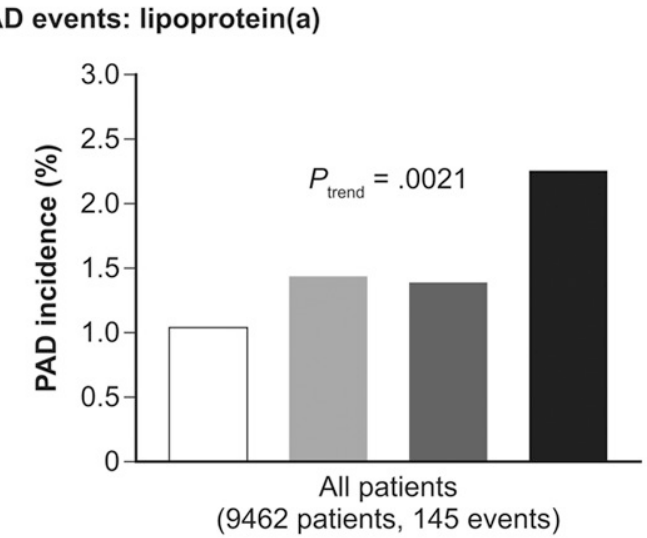
MALE



Reduction of MACE and MALE with PCSK9i is associated with levels of LDL-C and Lp(a)

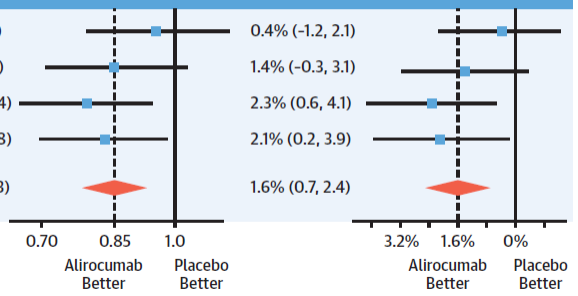


Incidence of MALE in PBO group of ODYSSEY OUTCOMES by quartile baseline Lp(a)



MACE

Subgroup	MACE Incidence Alirocumab n/N (%)	Placebo n/N (%)	HR (95% CI) ($p_{interaction}$ = 0.55)	Absolute Risk Reduction (95% CI) ($p_{interaction}$ = 0.0011)
Quartile 1	211/2,327 (9.1)	228/2,403 (9.5)	0.95 (0.79, 1.15)	0.4% (-1.2, 2.1)
Quartile 2	219/2,438 (9.0)	239/2,293 (10.4)	0.85 (0.71, 1.03)	1.4% (-0.3, 3.1)
Quartile 3	212/2,356 (9.0)	269/2,373 (11.3)	0.79 (0.66, 0.94)	2.3% (0.6, 4.1)
Quartile 4	261/2,341 (11.2)	316/2,393 (13.2)	0.83 (0.70, 0.98)	2.1% (0.2, 3.9)
Overall	903/9,462 (9.5)	1,052/9,462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7, 2.4)



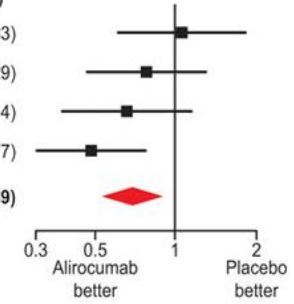
Treatment HR for according to quartile baseline Lp(a) in ODYSSEY OUTCOMES

MALE

PAD events: lipoprotein(a)

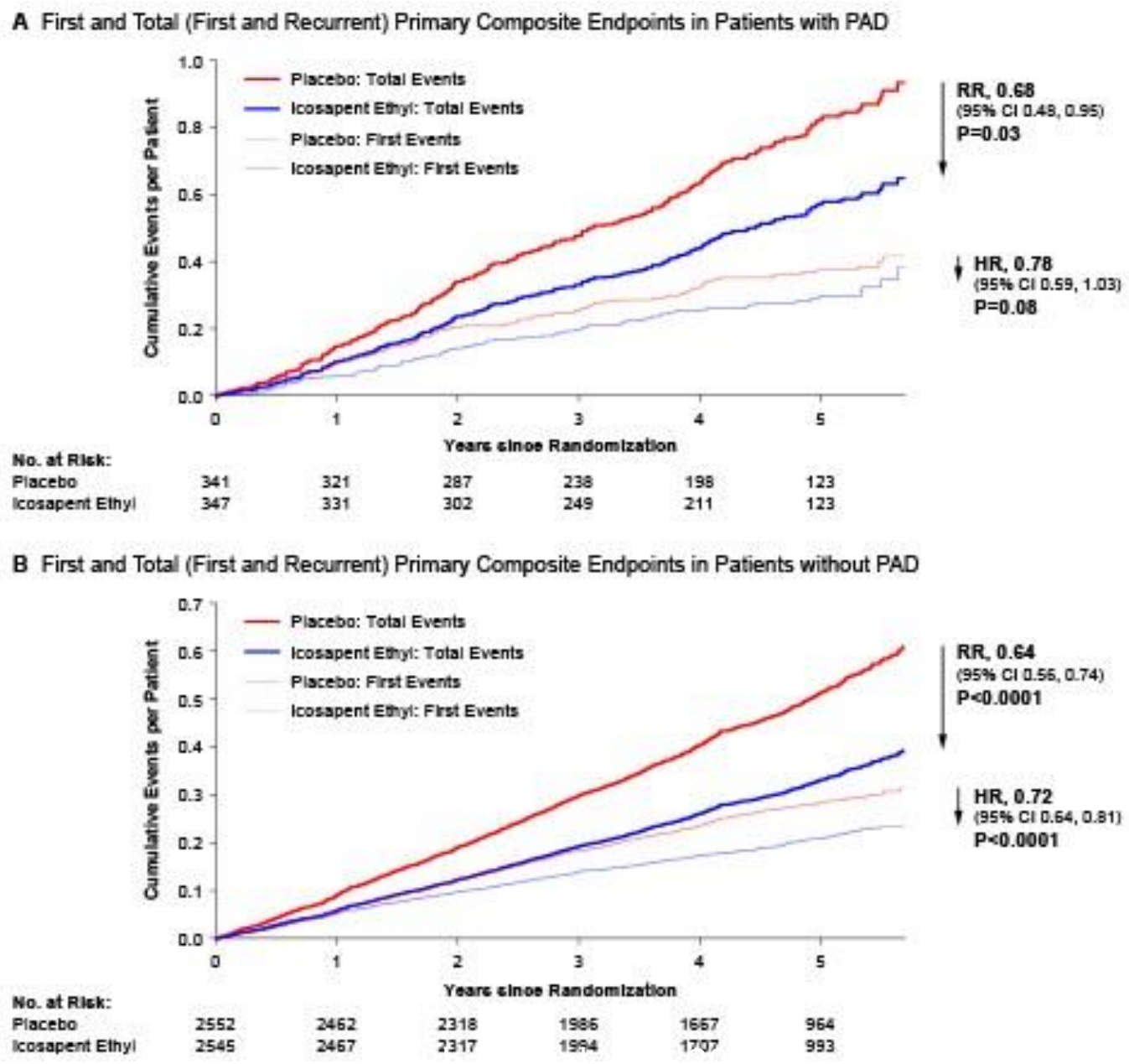
Subgroup	PAD incidence Alirocumab n/N (%)	Placebo n/N (%)	Relative risk reduction HR (95% CI)
Quartile 1	26/2327 (1.1)	25/2403 (1.0)	1.05 (0.61-1.83)
Quartile 2	28/2438 (1.1)	33/2293 (1.4)	0.78 (0.47-1.29)
Quartile 3	21/2356 (0.9)	33/2373 (1.4)	0.66 (0.38-1.14)
Quartile 4	26/2341 (1.1)	54/2393 (2.3)	0.48 (0.30-0.77)
Overall	**101/9462 (1.1)**	**145/9462 (1.5)**	**0.69 (0.54-0.89)**

P_{trend} = .03



Bittner et al. JACC 2020; Schwartz et al. Circ 2020

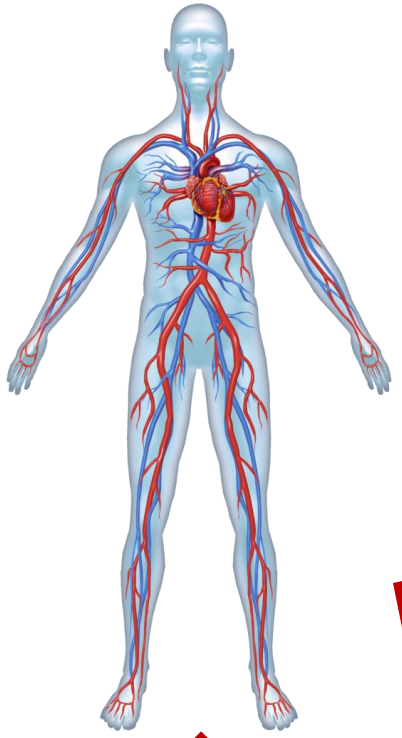
Icosapent Ethyl in PAD



Bhatt et al. Circulation 2021

Axes of Risk and Treatment Targets in PAD

<u>Lifestyle & Function</u> (exercise, diet, cilostazol where not contraindicated)



<u>Lipid Risk</u>
(LDL & Lpa)
High intensity statin +/- ezetimibe and PCSK9i, icosapent ethyl

Thrombosis Risk

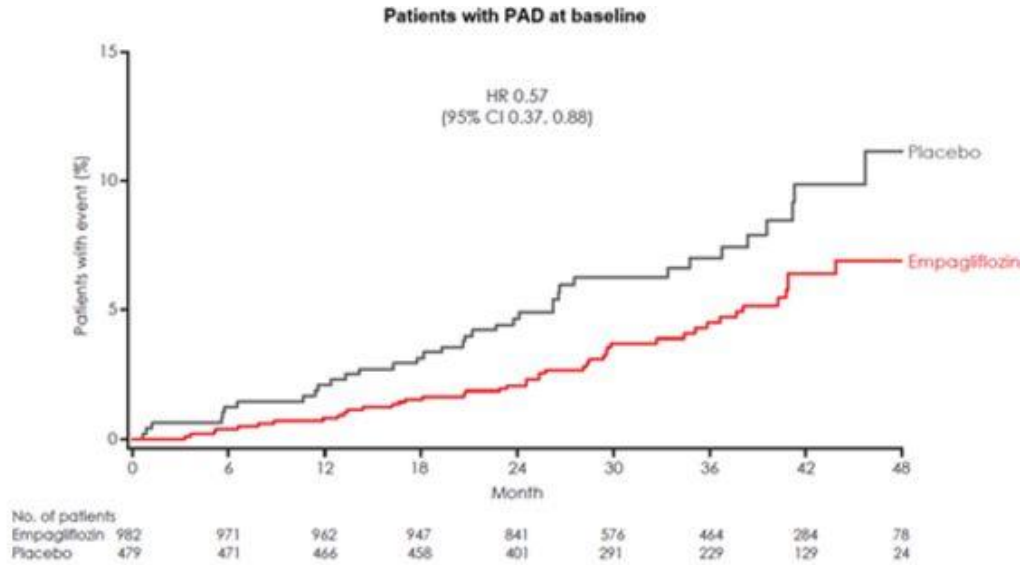
Diabetes Risk (micro and macrovascular)

<u>Smoking Risk</u>

Inflammatory Risk

Specific Glucose Lowering Targets in PAD

SGLT2 Inhibition



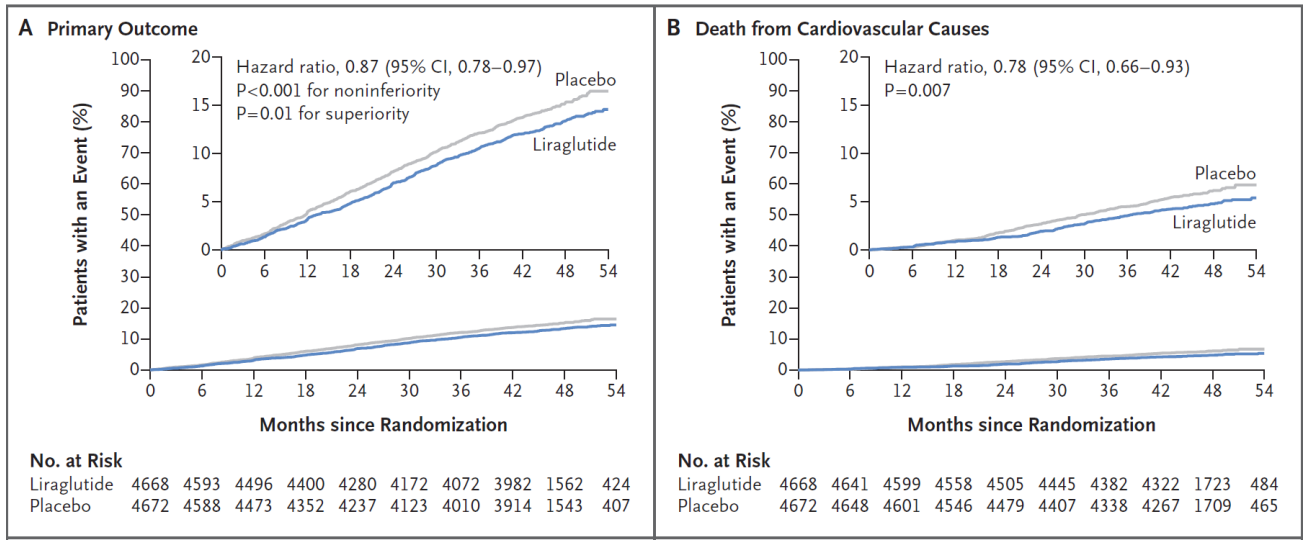
MACE
HR 0.84 (0.62 – 1.14)

CV Death or HF
HR 0.65 (0.45 – 0.93)

CV Death
HR 0.57 (0.37 – 0.88)

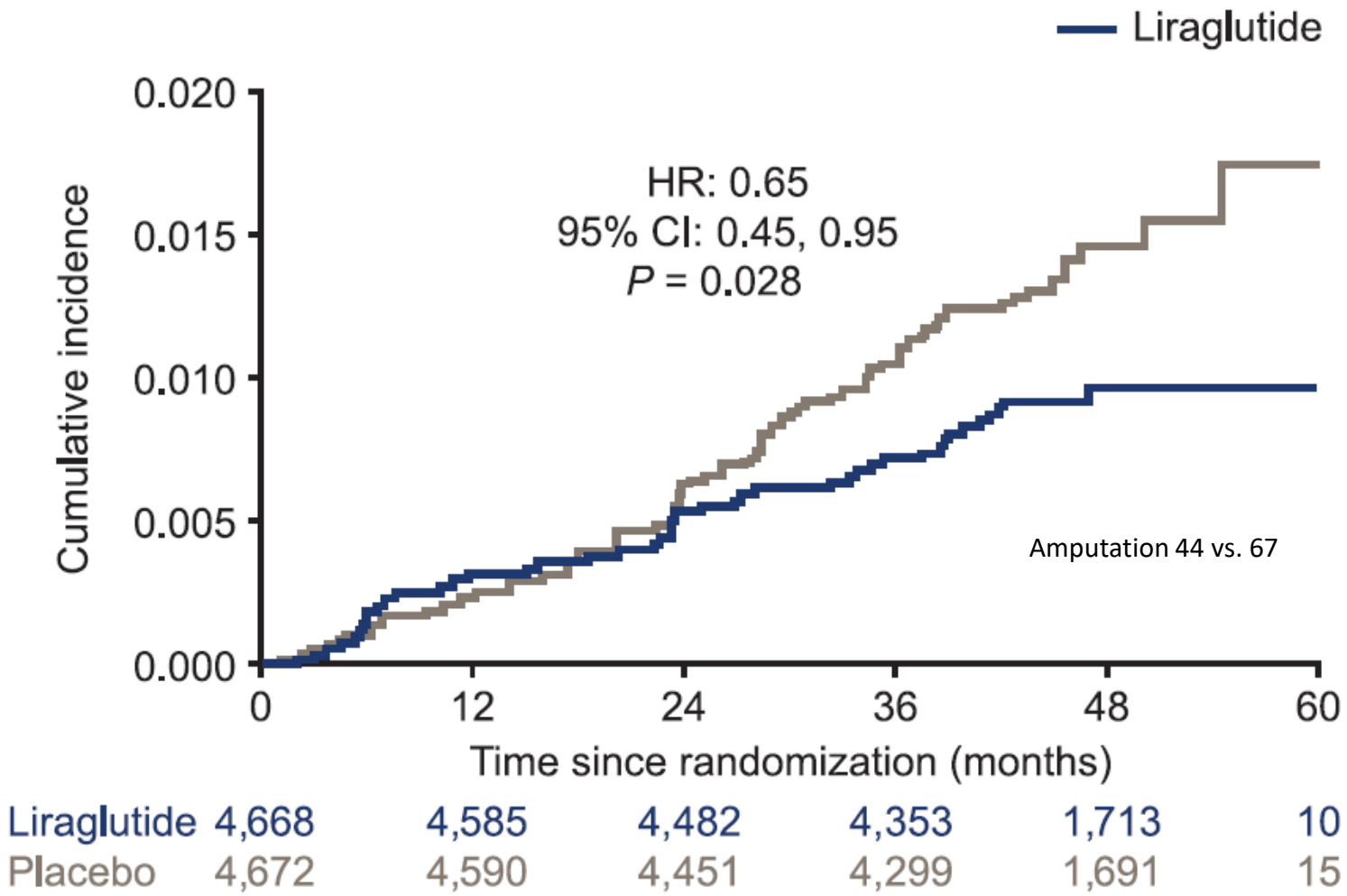
Verma et al. Circulation 2017

GLP1 Agonism



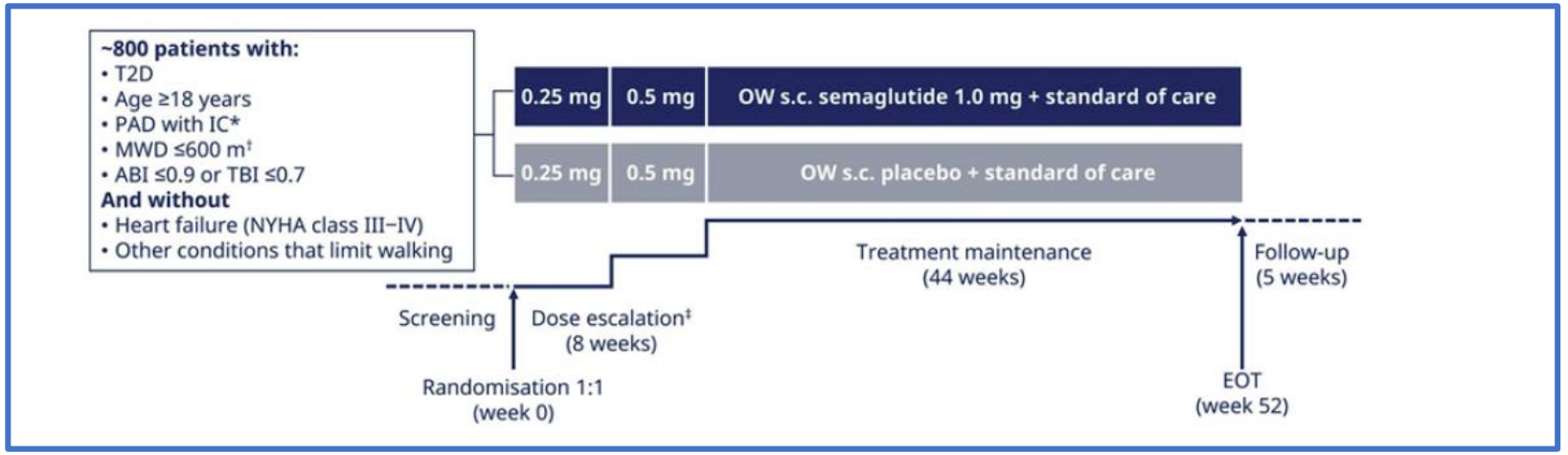
Dhatariya et al. *Diabetes Care* 2018

Liraglutide and Limb Events



Dhatariya et al. Diabetes Care 2018

STRIDE Trial: Functional Outcomes Trial in PAD



Primary objective:
To compare the effect of semaglutide s.c. 1.0mg OW vs. placebo on a functional capacity in terms of maximum walking distance in patients with T2D and PAD

Secondary objective:
To compare the effect of semaglutide s.c. 1.0 mg OW vs. placebo on clinical, biochemical, and patient reported outcomes in patients with T2D and PAD

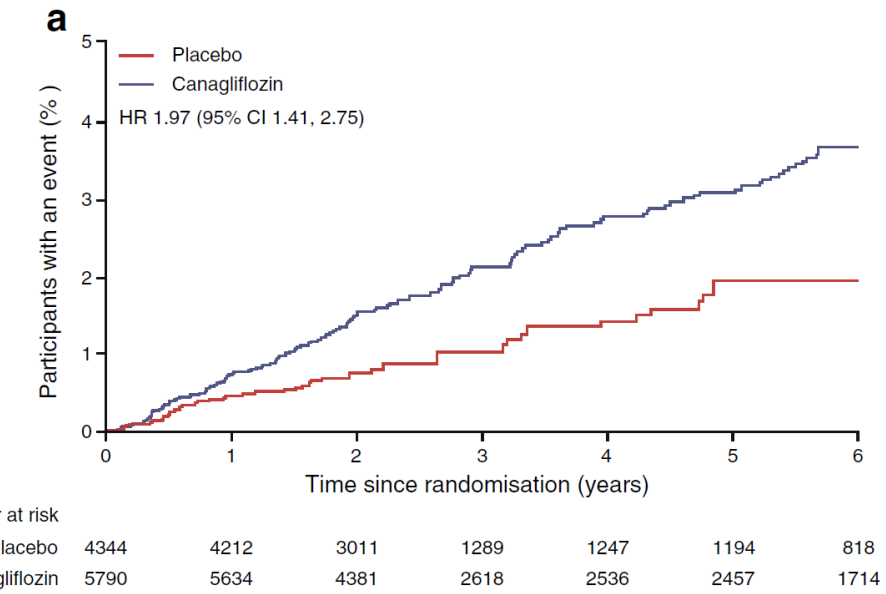
Primary endpoint:
Ration to baseline at week 52 in MWD on a graded treadmill test at constant speed and incline (3.2 km/h, 12%)

Secondary confirmatory endpoints
- Ratio to baseline at week 52 in PFWD on a graded treadmill test at constant speed an incline (3.2 km/h, 12%)
- Change from baseline in global score of WIQ

Supportive secondary endpoints
Change from baseline in:
- Body weight
- HbA1c
- Systolic and diastolic blood pressure
- ABI and TBI
- Individual WIQ scores (distance, speed, stair climbing)

Neal et al. European Heart Journal 42.Supplement_1 (2021): ehab724-2027

Canagliflozin and Amputation in CANVAS



	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)

Significant Benefit for MACE

CVD/MI/Stroke

0.86 (0.75 – 0.97)

Amputation
1.97 (1.41 – 2.75)

ARI 3.93% in PAD

Neal et al. NEJM 2017

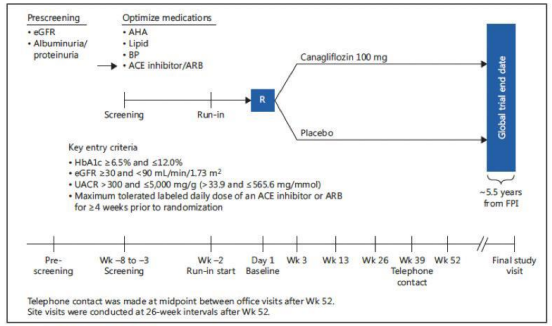
Canagliflozin and Amputation in CANVAS

CREDENCE: Patients With T2DM and CKD

Objective: Designed to formally test whether canagliflozin reduces the risk of kidney failure and cardiovascular events in patients with T2DM and markers of established kidney disease compared to placebo when used in addition to standard of care

Design:

- Randomized, double-blind, multicenter, event-driven Phase III study
- 4,401 patients randomized 1:1 100 mg canagliflozin vs placebo



Jardine et al. Am J Nephrol 2017;46:462–472

Exclusion

History of atraumatic amputation within past 12 months of screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening.

Care During Trial

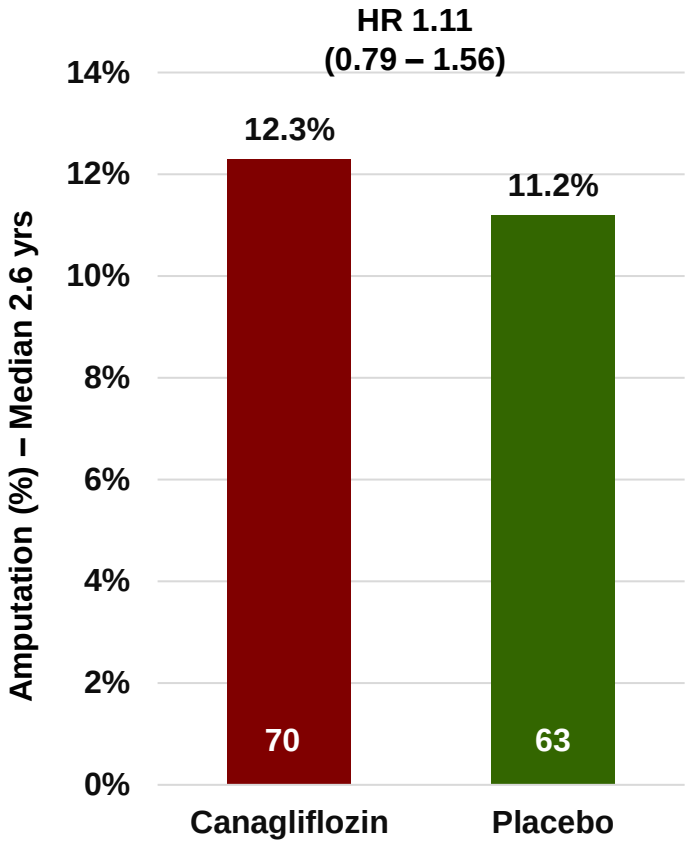
Provide or ensure that all subjects have had general foot self-care education.

Perform a comprehensive foot evaluation at each visit to identify risk factors for ulcers and amputations. The examination should include inspection of the skin, assessment of foot deformities, neurological assessment including pinprick or vibration testing or assessment of ankle reflexes, and vascular assessment including pulses in the legs and feet.

Subjects who have history of prior lower extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease should be referred to foot care specialists for ongoing preventive care.

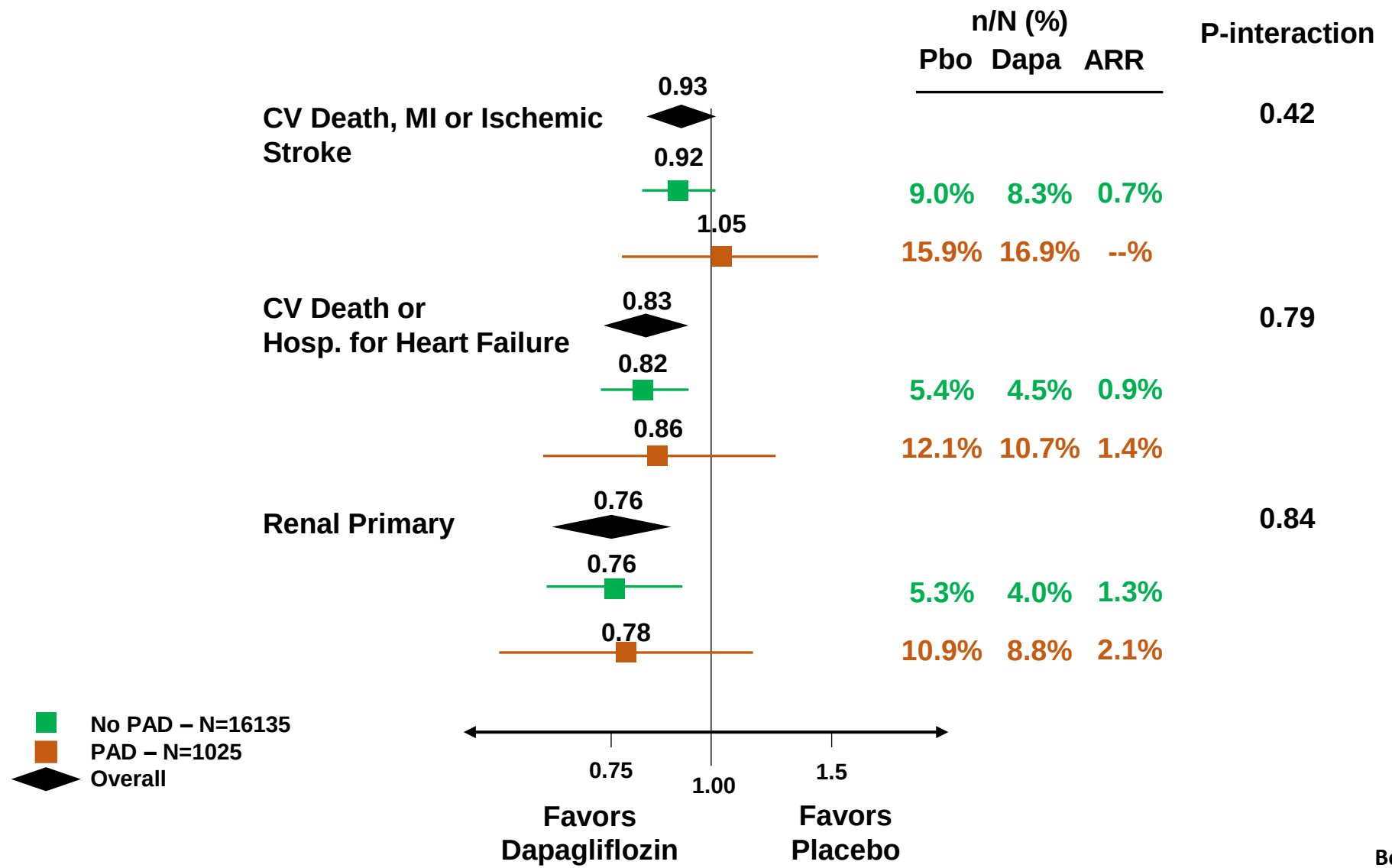
Management of Study Drug

Added statement that study drug should be interrupted for subjects who develop conditions that are associated with amputation.



Perkovic et al. NEJM 2019

DECLARE-TIMI 58: Consistent Benefit of Dapagliflozin in Patients with and without PAD



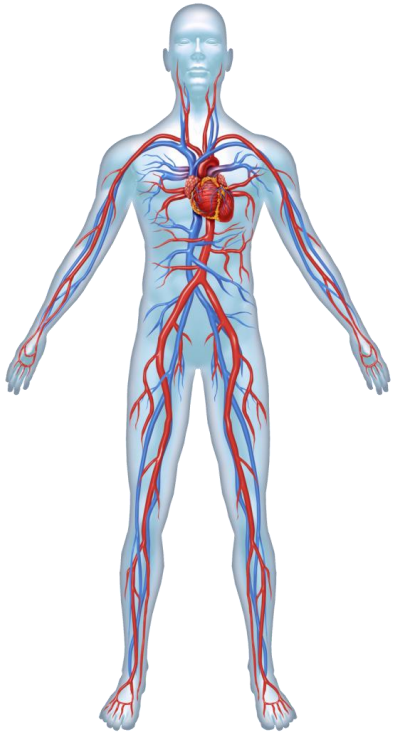
Bonaca et al. Circulation 2020

SGLT2 Inhibitors in Peripheral Artery Disease

↓ MACE risk in patient with CVD

↓↓ Heart failure in primary and secondary prevention

↓↓ Kidney complications in primary and secondary prevention



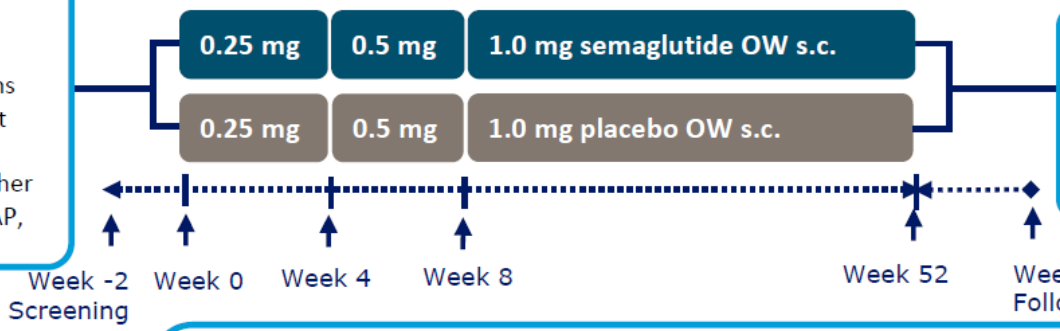
↑ Amputation signal with a single agent in 1 study

Absence of risk in second study could be due to no true risk or attenuation of risk with protocol changes (e.g. good foot care, stopping if high risk condition, patient selection)

Important benefits for PAD patients, especially those with CAD, HF, and kidney disease. Risk (if true) may be reasonably managed by foot hygiene, patient selection, agent selection, and drug management during high risk periods.

Functional Outcome Trial in Peripheral Artery Disease (PAD)

Population:
N ~ 628
- T2D, age >18 years old
- PAD with IC stage Fontaine IIa ≥ 3 months
- MWD ≤ 600 m on a graded treadmill test
- ABI ≤ 0.90 *OR* TBI ≤ 0.70
- Key exclusion criteria:, HF NYHA II-IV, other conditions limiting walking ability (e.g. AP, COPD, PD)



Trial Information:
- Randomisation 1:1
- Double-blind
- Standard of care
- Follow-up period of 5 weeks
- Assumed effect size: 20%

Primary objective:
To compare the effect of semaglutide s.c. 1.0 mg OW versus placebo on functional capacity in terms of maximum walking distance in patients with T2D and PAD

Secondary objective:
To compare the effect of semaglutide s.c. 1.0 mg OW versus placebo on clinical, biochemical, and patient reported outcomes in patients with T2D and PAD

Primary endpoint:
Ratio to baseline at week 52 in MWD on a graded treadmill test at constant speed and incline (3.2 km/h, 12%)

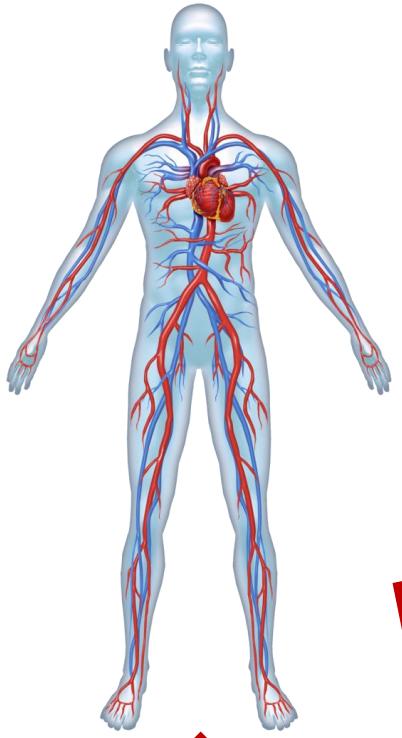
Secondary confirmatory endpoints:
- Ratio to baseline at week 52 in PFWD on a graded treadmill test at constant speed and incline (3.2 km/h, 12%)
- Change from baseline in global score of WIQ

Supportive secondary endpoints:
Change from baseline in:
- Body weight
- HbA_{1c}
- Systolic and diastolic blood pressure
- ABI and TBI
- Individual WIQ scores (distance, speed, stair climbing)

ABI, ankle-brachial index; TBI, toe-brachial index; MWD, maximal walking distance; OW, once weekly; PFWD, pain-free walking distance; WIQ, walking impairment questionnaire; AP, angina pectoris; HF, heart failure; COPD, chronic obstructive pulmonary disease; CCS, Canadian Cardiovascular Scale; NYHA, New York Heart Association; MRC, Medical Research Council Scale; PD, Parkinson's disease

Axes of Risk and Treatment Targets in PAD

Lifestyle & Function (exercise, diet, cilostazol where not contraindicated)



Lipid Risk
(LDL & Lpa)
High intensity statin +/- ezetimibe and PCSK9i
icosapent ethyl

Thrombosis Risk

Diabetes Risk (micro and macrovascular)
A1C to reduce microvascular risk and target specific therapies (e.g. GLP1a, SGLT2i)

Smoking Risk

Inflammatory Risk

CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Antiplatelet Therapy for PAD

Marc P. Bonaca MD MPH
Professor of Medicine
Director of Vascular Research
University of Colorado School of Medicine

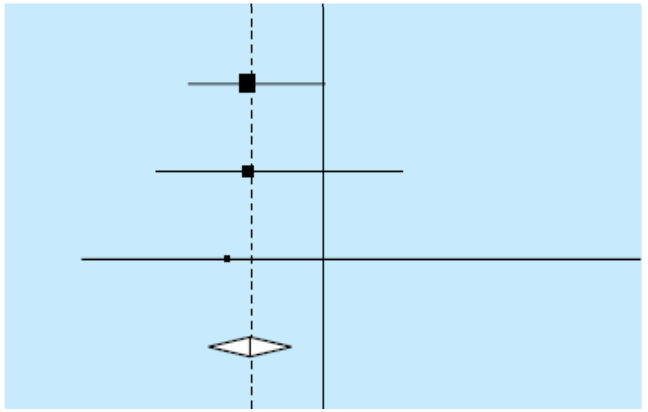
CPC Clinical Research

An Affiliate of:

University of Colorado Anschutz Medical Campus

Antiplatelet Therapy for PAD

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Peripheral arterial disease:						
Intermittent claudication	26	201/3123 (6.4)	249/3140 (7.9)	-22.3	86.6	23 (9)
Peripheral grafting	12	67/1249 (5.4)	81/1248 (6.5)	-7.3	29.1	22 (16)
Peripheral angioplasty	4	12/472 (2.5)	17/474 (3.6)	-2.0	5.8	29 (35)
Subtotal	42	280/4844 (5.8)	347/4862 (7.1)	-31.6	121.5	23 (8)



22% Reduction of CVD/MI/Stroke in high risk patients

23% Reduction of CVD/MI/Stroke in PAD patients

OR for major extracranial bleeding 1.6 (1.4 – 1.8)

No difference between the high risk groups

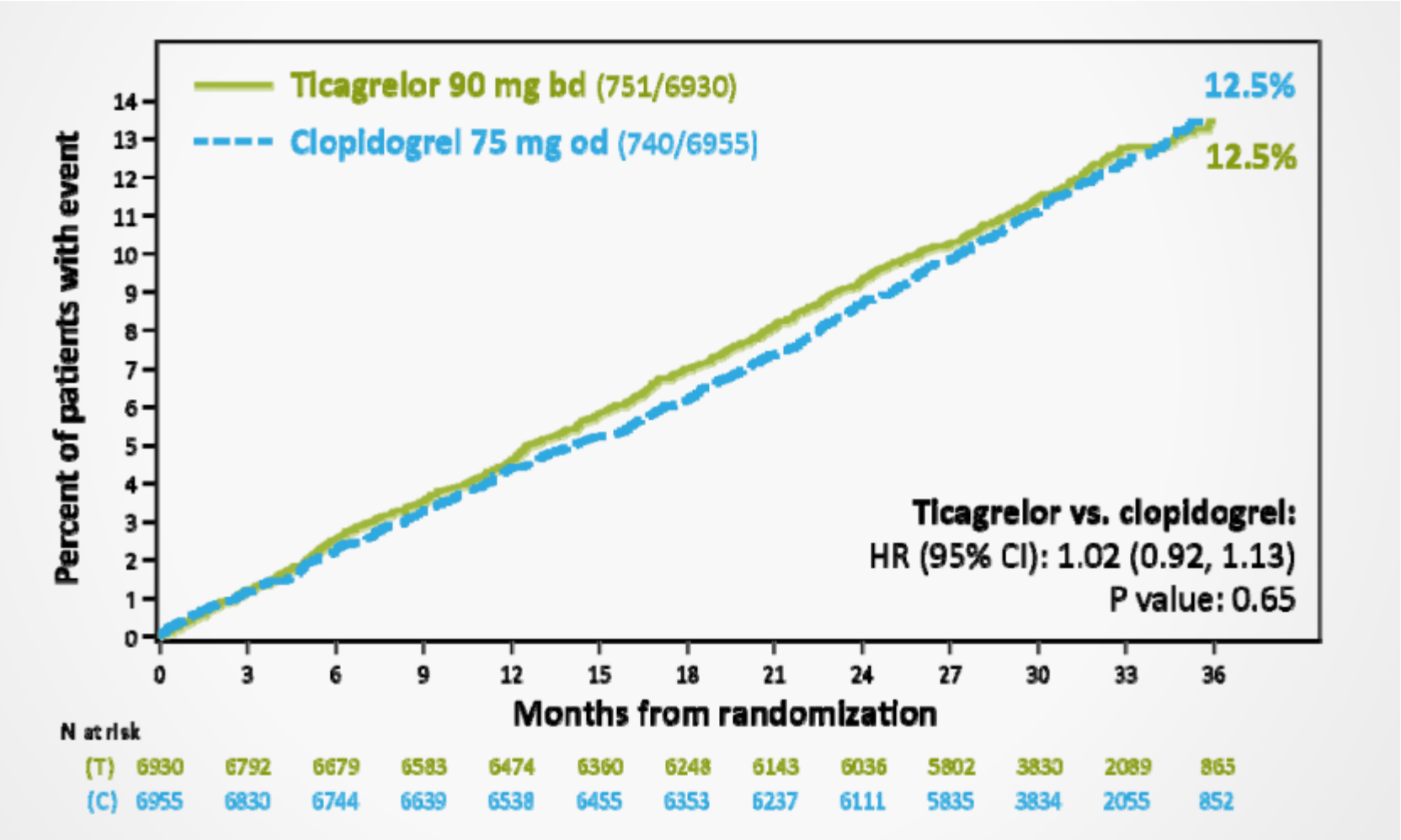
Antithrombotic Trialists' Collaboration. BMJ 324, 71-86 (2002)

Baigent et al. Lancet 2009

Ticagrelor vs. Clopidogrel for "Symptomatic PAD"

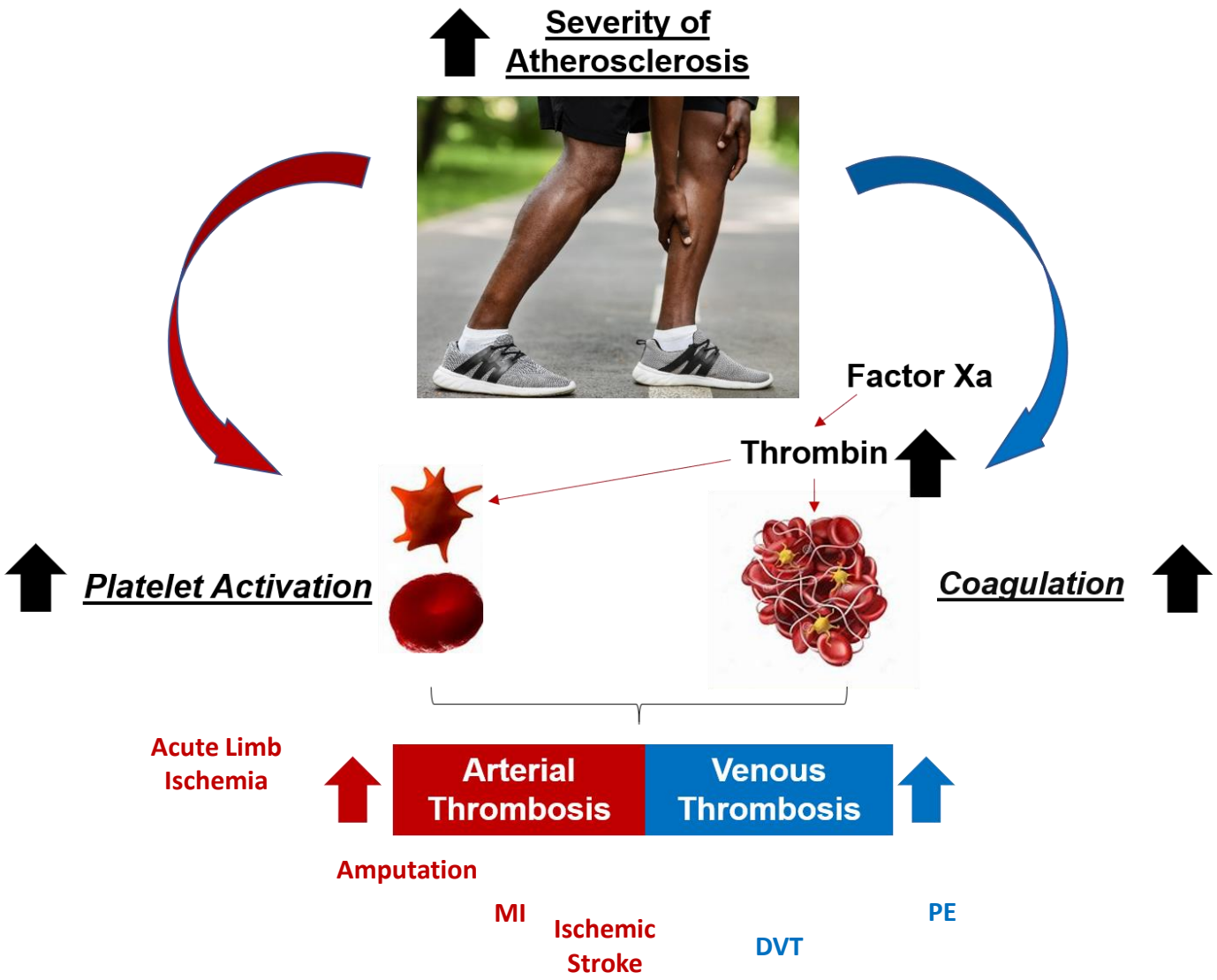
Only ~30% with CAD

Statistical Interaction with benefit** w/CAD & **PCI (HR 0.82, p-interaction 0.03)



Hiatt et al NEJM 2016

Atherosclerosis (PAD) Associated with Arterial & Venous Thrombosis



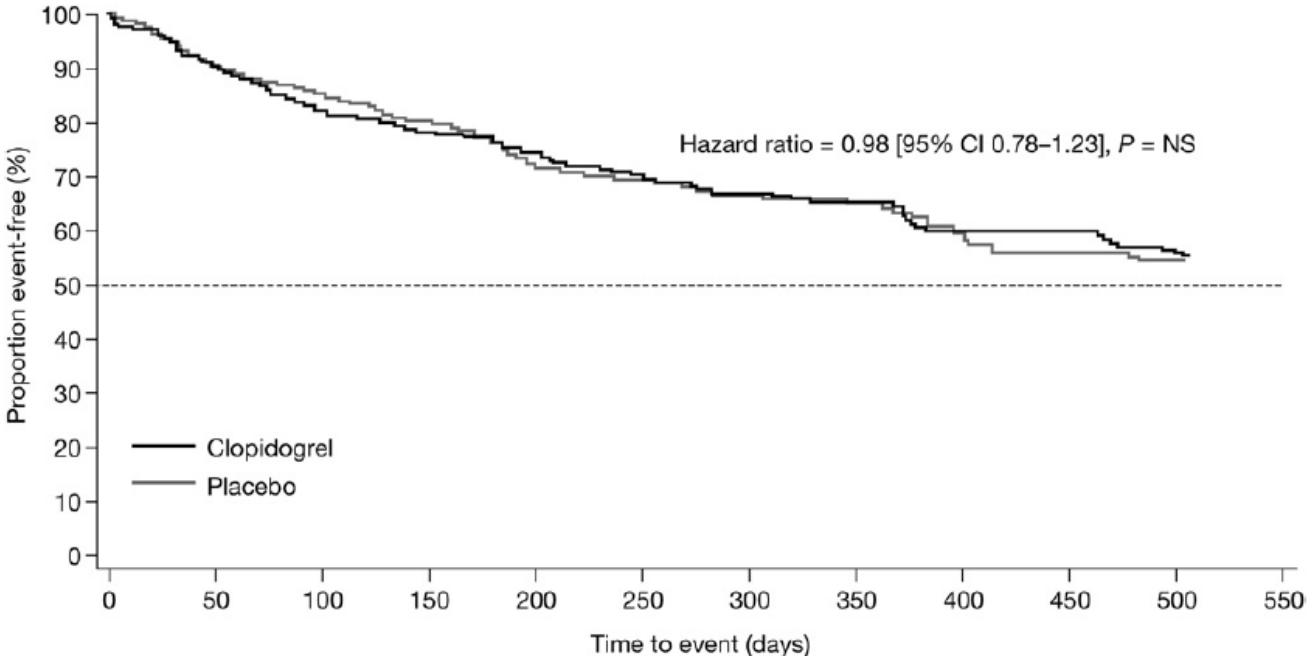
- Clinically manifested atherosclerosis: heightened risk of venous thromboembolism (VTE)[1,2]
- Patients with VTE: increased risk of atherothrombosis[3-6]
- Shared pathobiologies: endothelial dysfunction, inflammation, and thrombin and platelet activation[7]
- Strategies targeting >1 pathway may provide broad benefit across vascular territories in atherosclerosis[8]

From Berkowitz S et al. ISTH 2021 Late Breaking Science

Refs: [1]Prandoni P et al. NEJM 2003; [2]Cavallari I et al. Circulation 2018. [3]Prandoni P et al. J Thromb Haemost 2006; [4]Sorensen HT et al. Lancet 2007; [5]Spencer FA et al. J Thromb Haemost 2008; [6]Klok FA et al. Blood 2009. [7]Prandoni P. Internal and Emergency Medicine. 2020; [8]Weitz JI et al. Thromb Haemost 2020.

Dual Antiplatelet Therapy after Bypass

- **851 patients undergoing unilateral below-knee bypass grafting for atherosclerotic PAD**
- **ASA (75 mg – 100 mg) + clopidogrel vs. ASA alone**



Benefit in subgroup with prosthetic grafts?

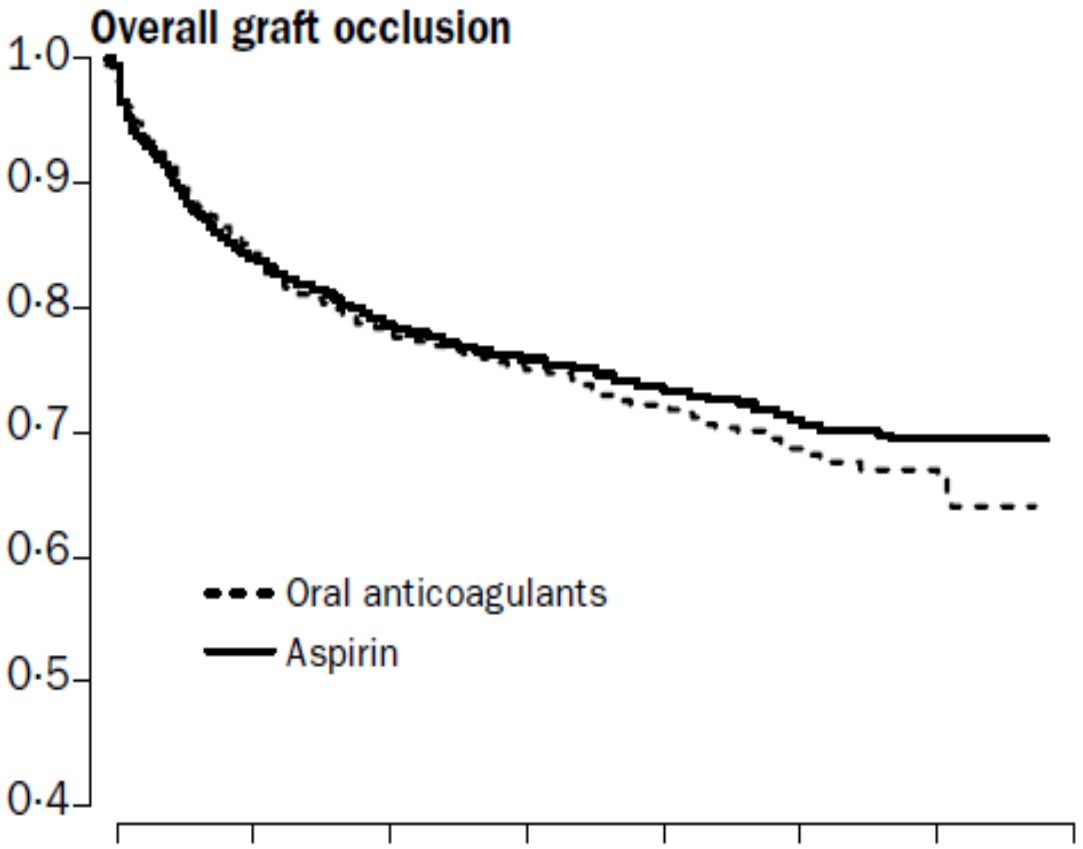
DAPT with Aspirin and Clopidogrel
GUSTO Moderate or Severe Bleeding
HR 2.84 (1.32 – 6.08)

Outcome	Clopidogrel N=425	Placebo N=426	HR (95% CI)	P-value
Primary Composite*	149	151	0.98 (0.78 – 1.23)	P=NS
Graft Occlusions	93	97	0.94 (0.71 – 1.25)	P=NS
Amputation	31	45	0.68 (0.43 – 1.08)	P=NS
Index Revascularization			0.89 (0.65 – 1.23)	P=NS
Myocardial Infarction			0.81 (0.32 – 2.06)	P=0.66
Stroke			1.02 (0.41 – 2.57)	P=0.96
CV Death			1.49 (0.73 – 3.01)	P=0.27
CV Death, MI, Stroke			1.09 (0.65 – 1.82)	P=0.75
All Cause Mortality	24	17	1.44 (0.77 – 2.68)	
GUSTO Moderate or Severe Bleeding	**19**	**5**	**2.84 (1.32 – 6.08)**	**0.007**

Belch et al. Journal of Vascular Sugery. 2010

Warfarin after Bypass

2,690 patients with infrainguinal bypass grafting
Randomized to warfarin (INR 3-4.5) vs warfarin



	Oral anticoagulants (n=1326)	Aspirin (n=1324)	Hazard ratio (95% CI)
Patient-years of observation*	2287	2273	. .
First outcome event			
Occlusion	308	322	0·95 (0·82–1·11)
Vascular death, non-fatal myocardial infarction, non-fatal stroke, or amputation	248	275	0·89 (0·75–1·06)
Death from all causes	211	205	1·02 (0·85–1·24)
Death from vascular causes	137	146	0·94 (0·74–1·18)
Myocardial infarction	29	42	0·69 (0·42–1·10)
All stroke	35	47	0·74 (0·48–1·14)
Ischaemic stroke	17	34	0·50 (0·28–0·89)
Haemorrhagic stroke	14	4	3·48 (1·14–10·6)
Undefined stroke (no CT scan available)	4	11	0·36 (0·12–1·14)
All amputation	100	110	0·90 (0·69–1·19)
Ipsilateral amputation	89	91	0·98 (0·73–1·31)
Vascular intervention	429	446	0·95 (0·84–1·09)
Haemorrhage (including intracranial)	108	56	1·96 (1·42–2·71)

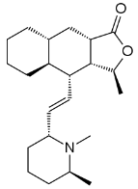
CT=computed tomography. *Patient-years are given for secondary-outcome event. Number of patient-years for other outcome events differ slightly.

? Benefit for vein grafts HR 0.69 (0.54 – 0.88)
vs. non-vein grafts HR 1.26 (1.03 – 1.55)

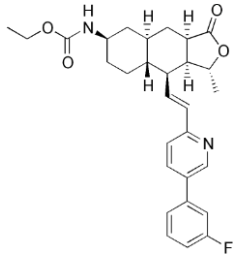
Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet. 2000

Vorapaxar – First in Class PAR-1 Antagonist

Himbacine

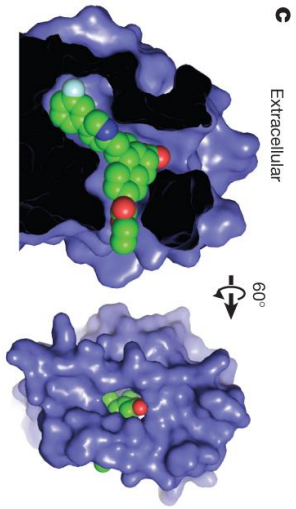


Vorapaxar



Bark of the Australian Magnolia (*Galbulimima baccata*)

Found in the tropical zones of eastern Malaysia, New Guinea, northern Australia and the Solomon Islands.

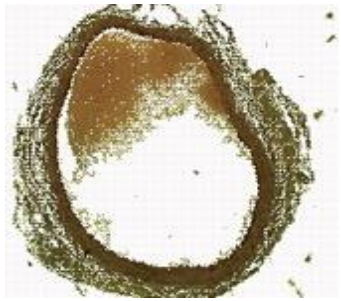


Zhang C et al. *Nature* 2012;492:387-92

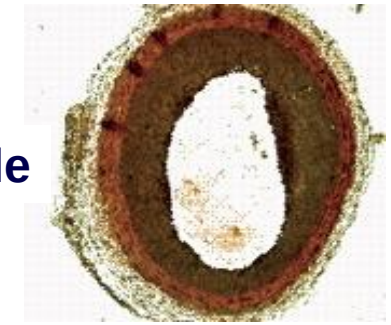
Varopaxar Label

Restenosis after vascular injury in rats

Sham



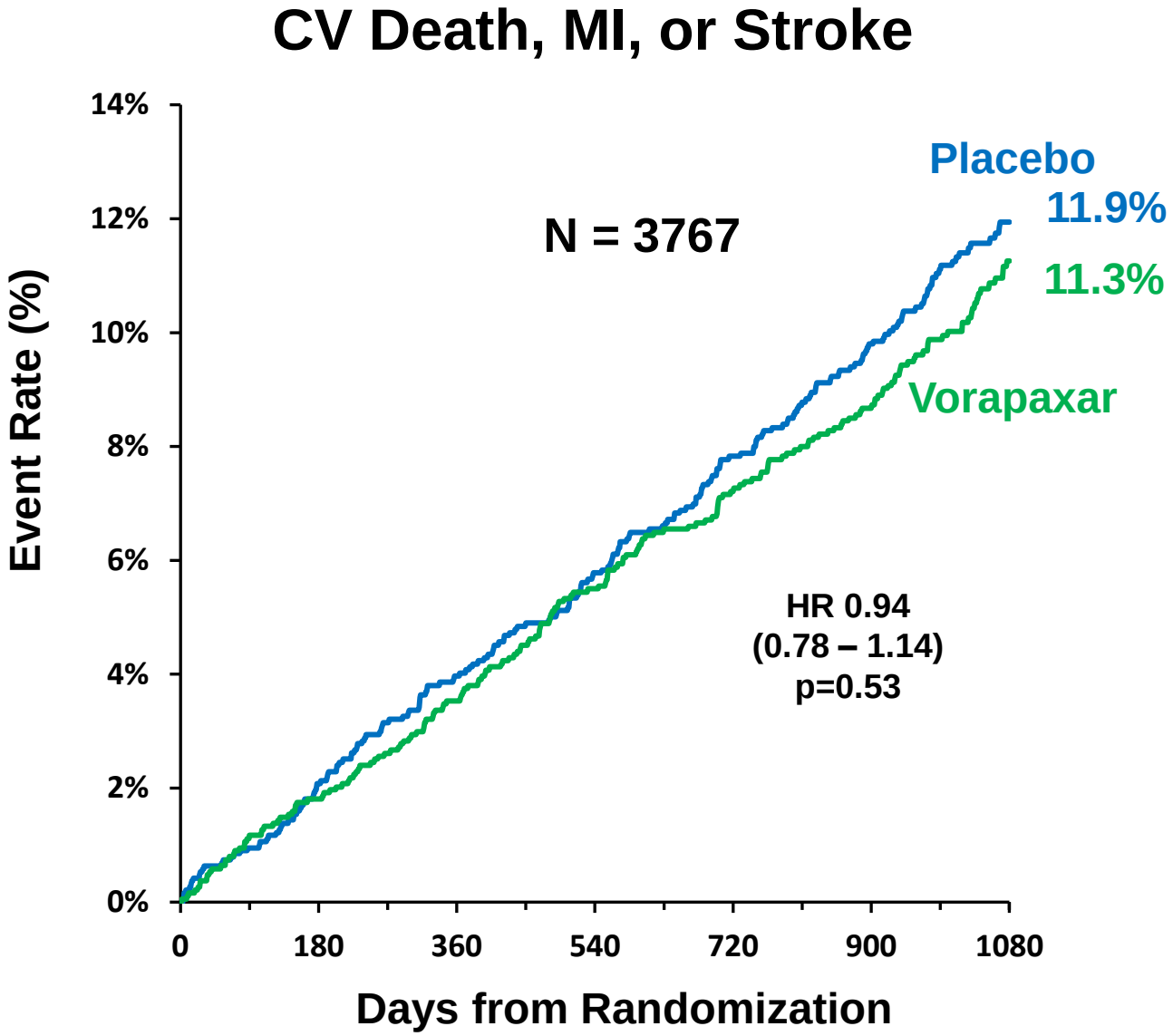
Vehicle

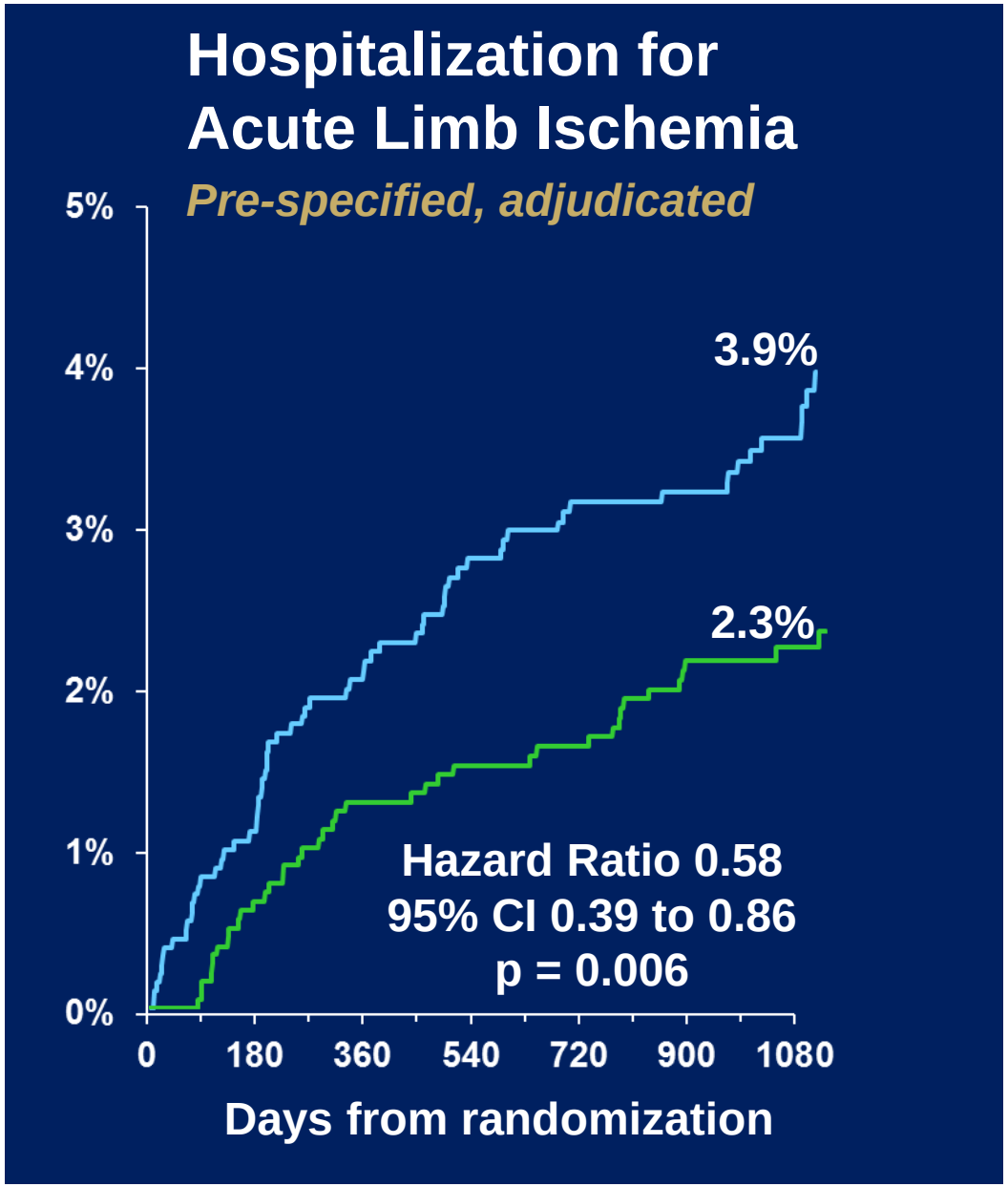


PAR-1 Antagonist

Modified from Chieng-Yan et al. J Pharm. and Exp Therapeutics 2010;336:643

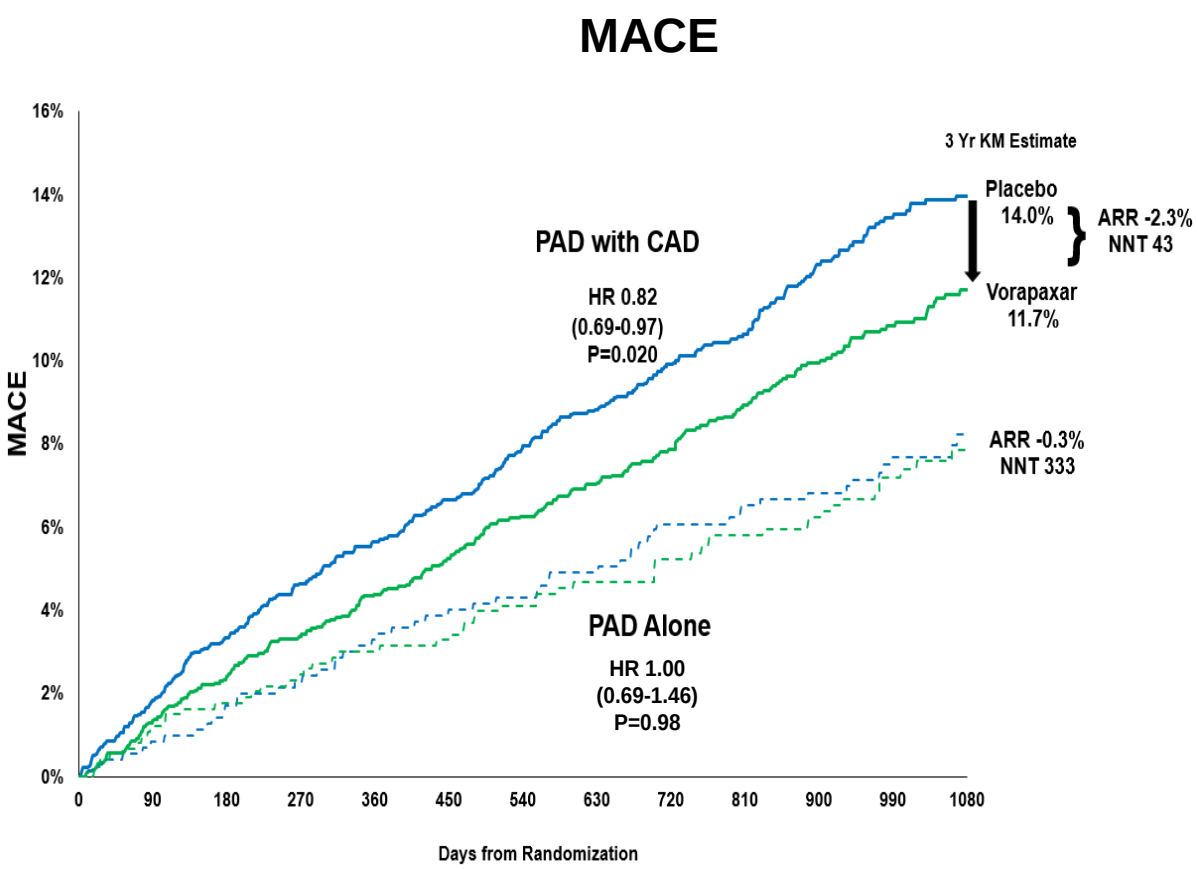
Vorapaxar in Lower Extremity PAD

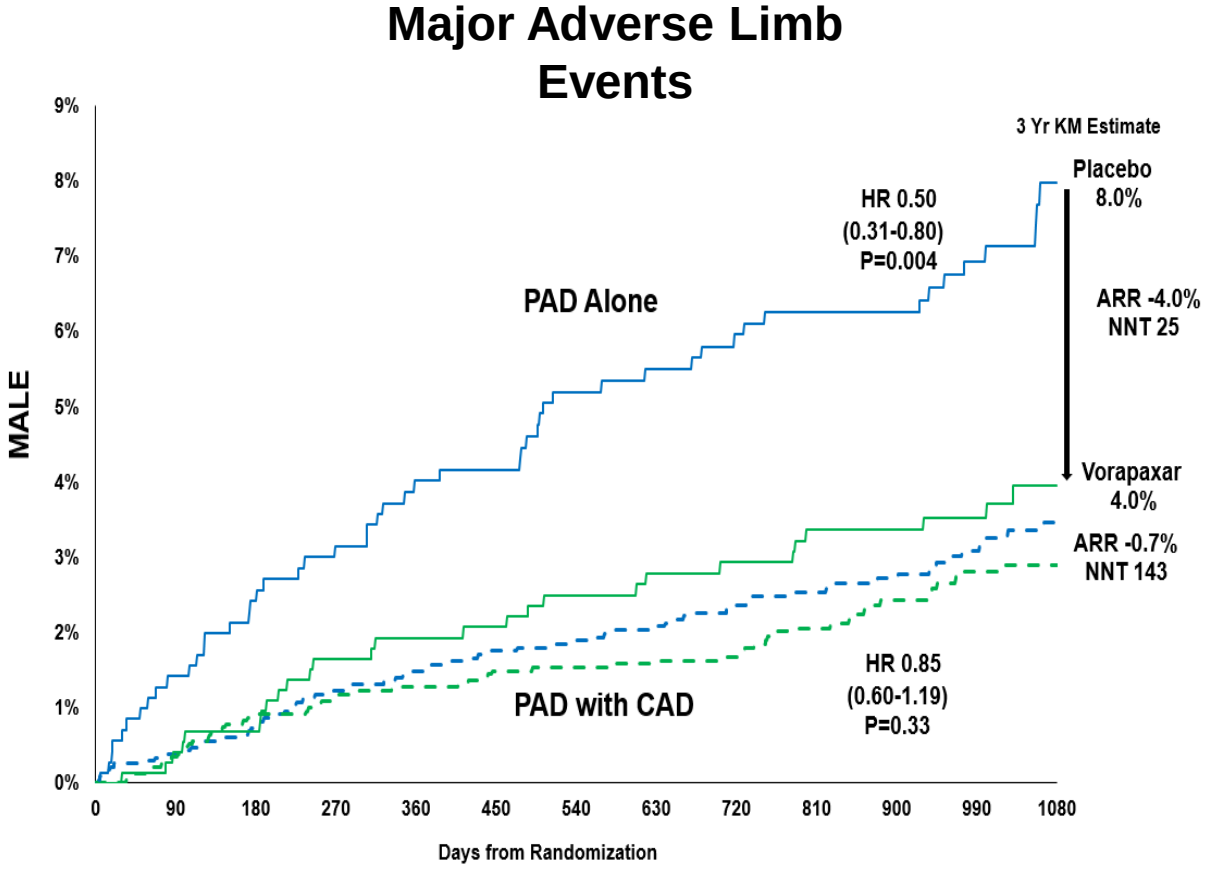




Bonaca et al. Circulation 2013

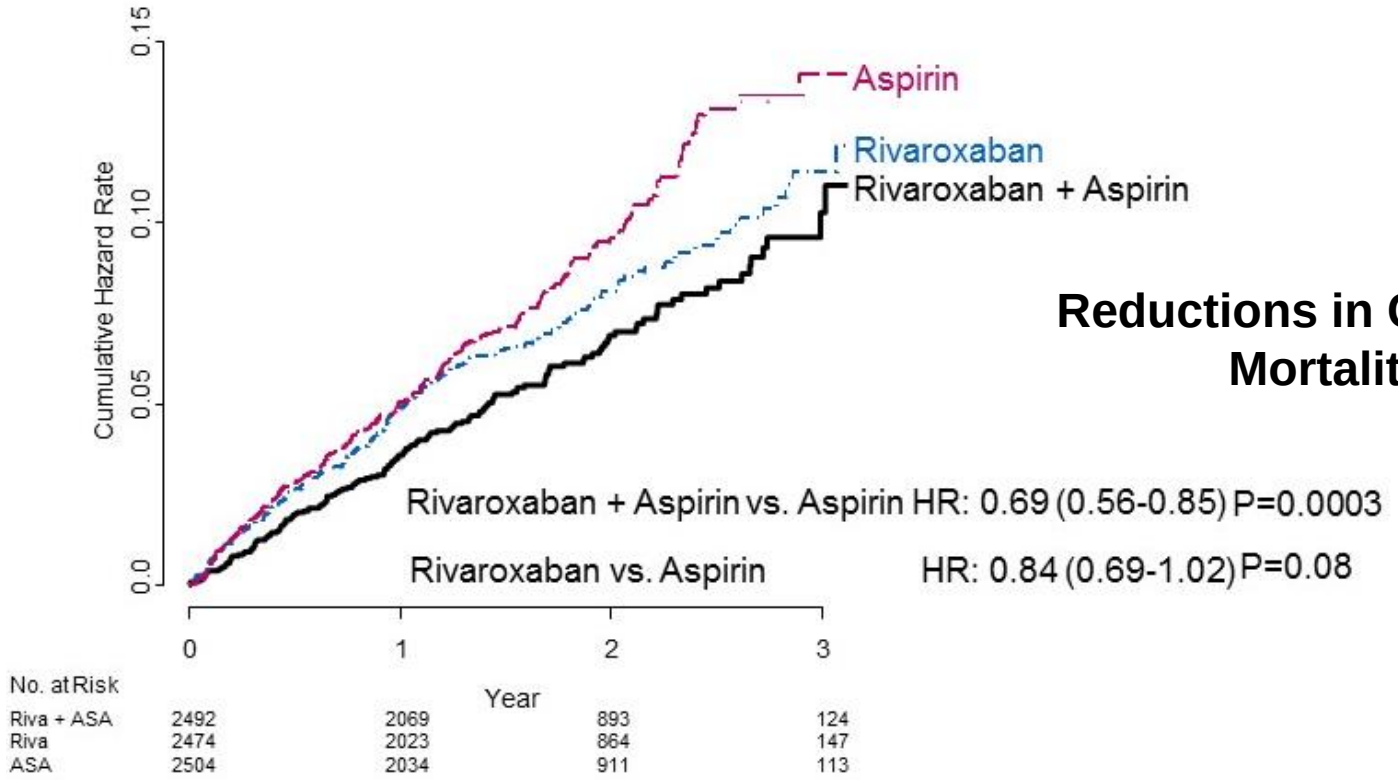
Effect of Vorapaxar in Patients in PAD for MACE and Major Adverse Limb Events by CAD Status





Qamar A…Bonaca MP. Vascular Medicine 2019

COMPASS Trial



Reductions in CV Death Mortality

HR for Major Bleeding 1.70 (1.40 – 2.05), p<0.001

>90% with CAD, large subgroup with Concomitant PAD, consistent benefits for both

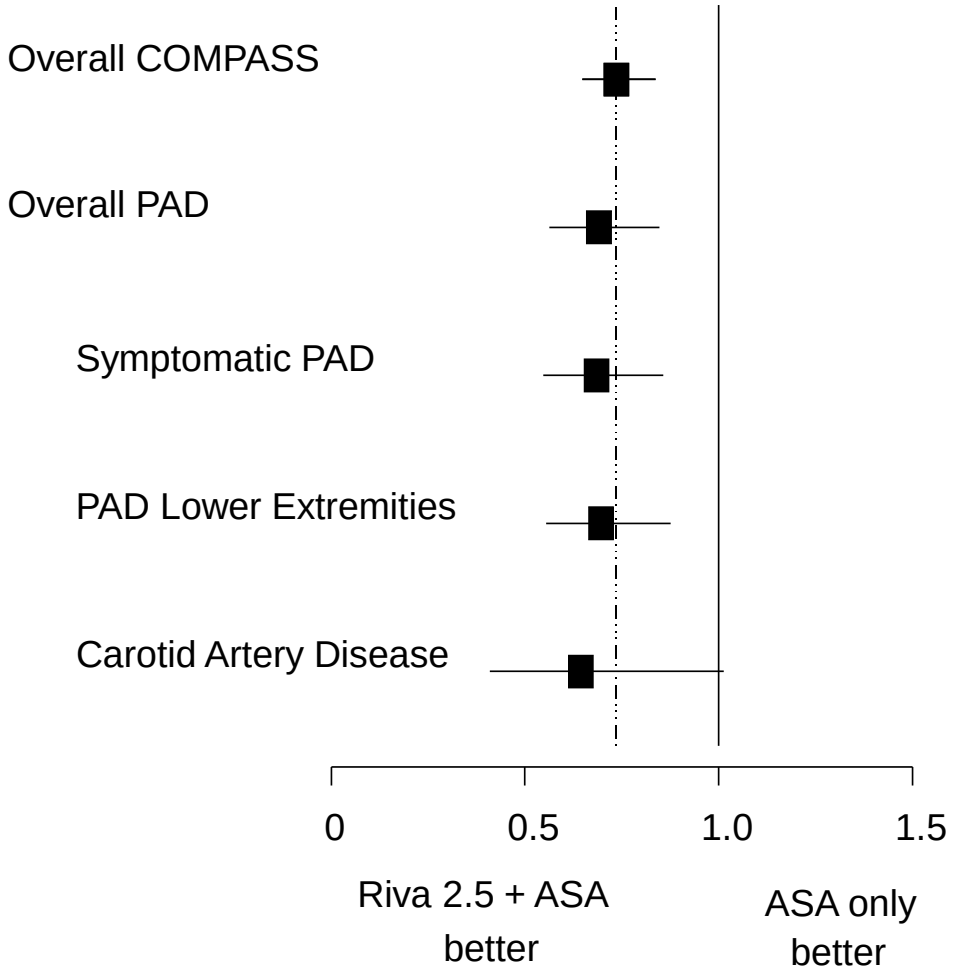
Adapted from: N Engl J Med 2007;357:217-27.

Efficacy Outcomes in PAD

Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. Aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57-0.90)	0.005	0.86 (0.69-1.08)	0.19
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53-1.09)	-	0.84 (0.59-1.20)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33-0.87)	-	0.93 (0.61-1.40)	-
CV Death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59-1.14)	-	0.86 (0.62-1.19)	-
MALE	30 (1.2)	35 (1.4)	56 (2.2)	0.54 (0.35-0.84)	0.005	0.63 (0.41-0.96)	0.03
Major amputation	5 (0.2)	8 (0.3)	17 (0.7)	0.30 (0.11-0.80)	0.01	0.46 (0.20-1.08)	0.07

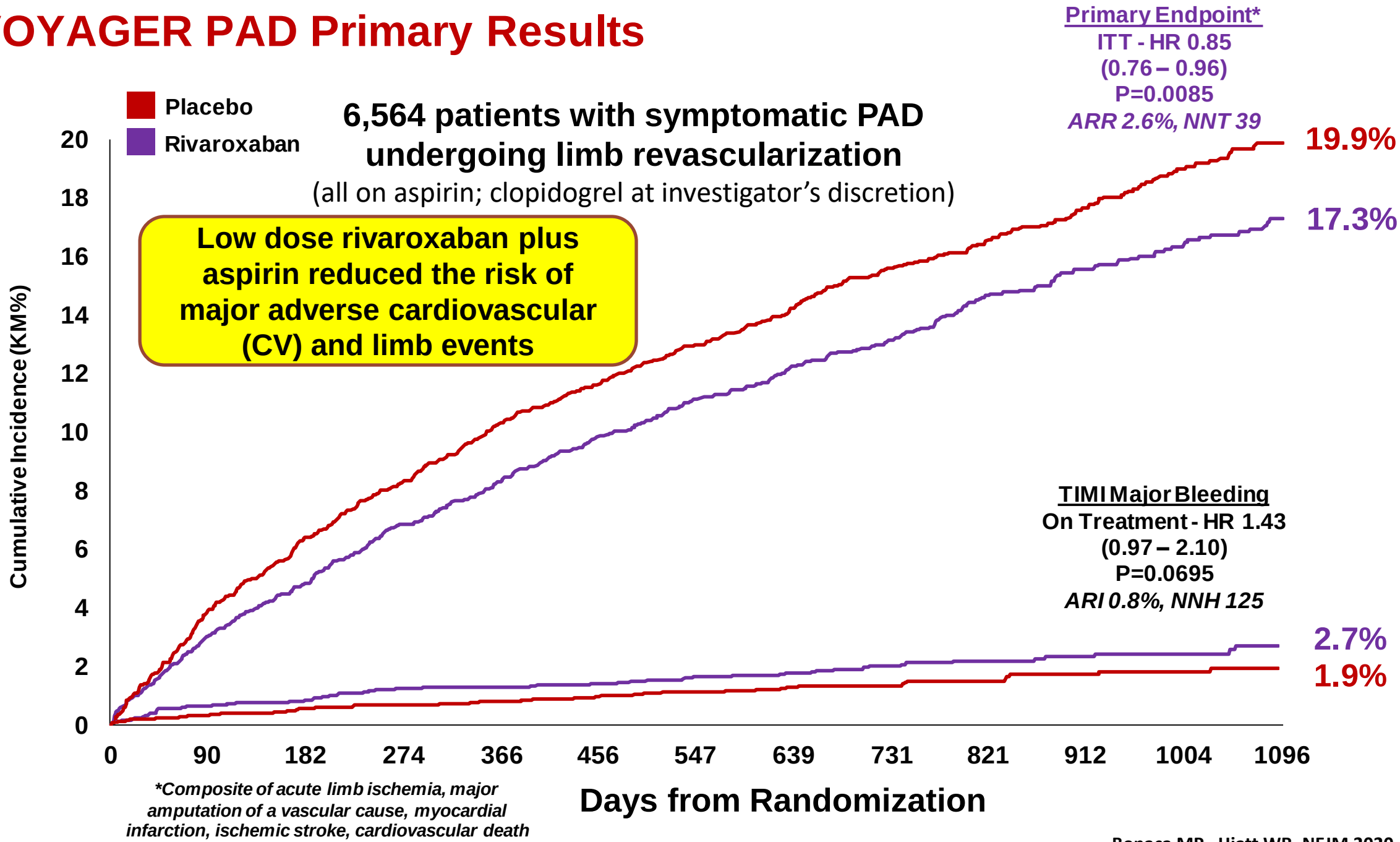
Anand S et al. The Lancet. 2017

MACE, MALE, or Major Amputation



Anand et Lancet 2019

VOYAGER PAD Primary Results



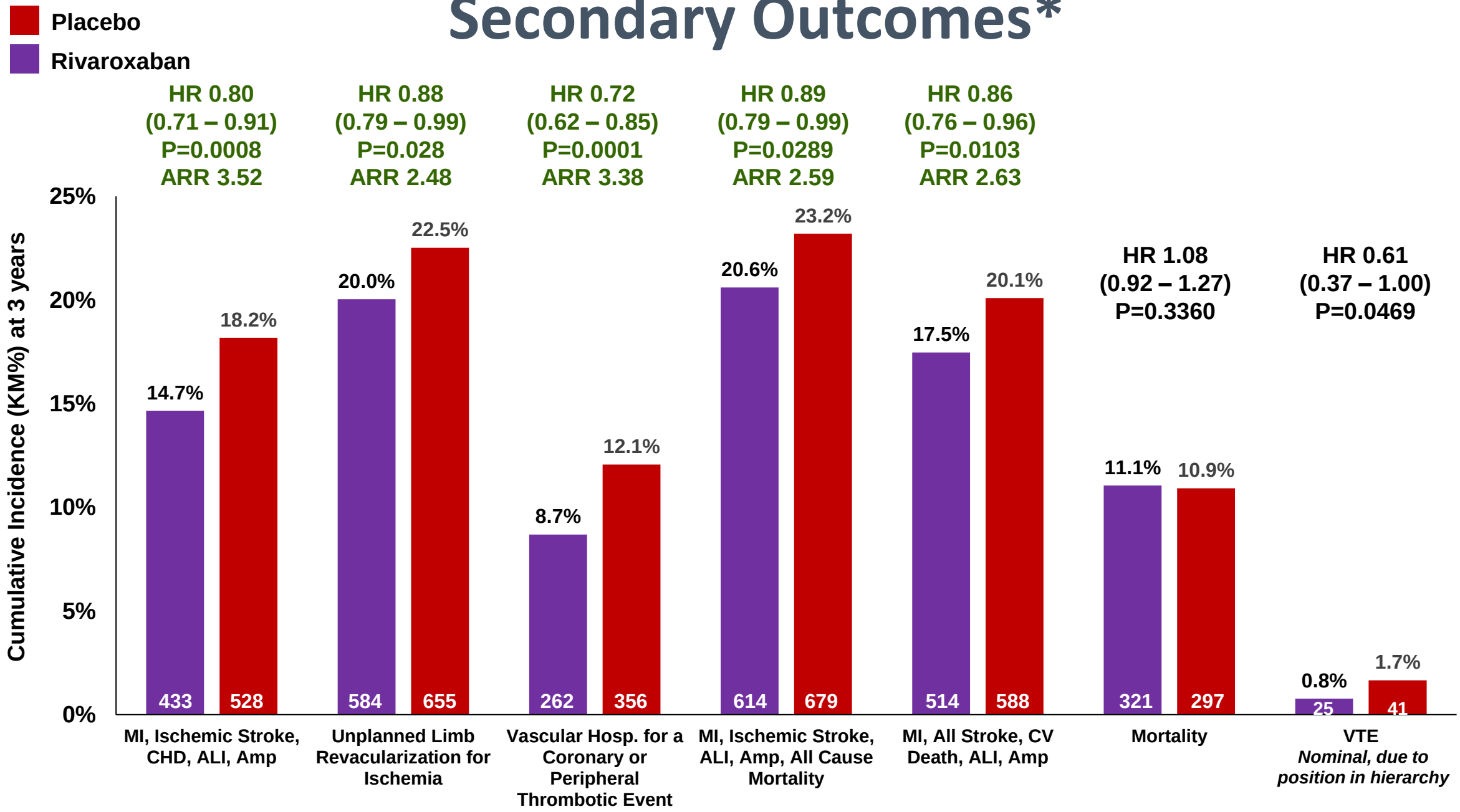
Bonaca MP…Hiatt WR. NEJM 2020

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	5.2	7.8	0.67 (0.55–0.82)
Major vascular amputation	3.4	3.9	0.89 (0.68–1.16)
Ischemic stroke	2.7	3.0	0.87 (0.63–1.19)
Myocardial infarction	4.6	5.2	0.88 (0.70–1.12)
CV death	7.1	6.4	1.14 (0.93–1.40)

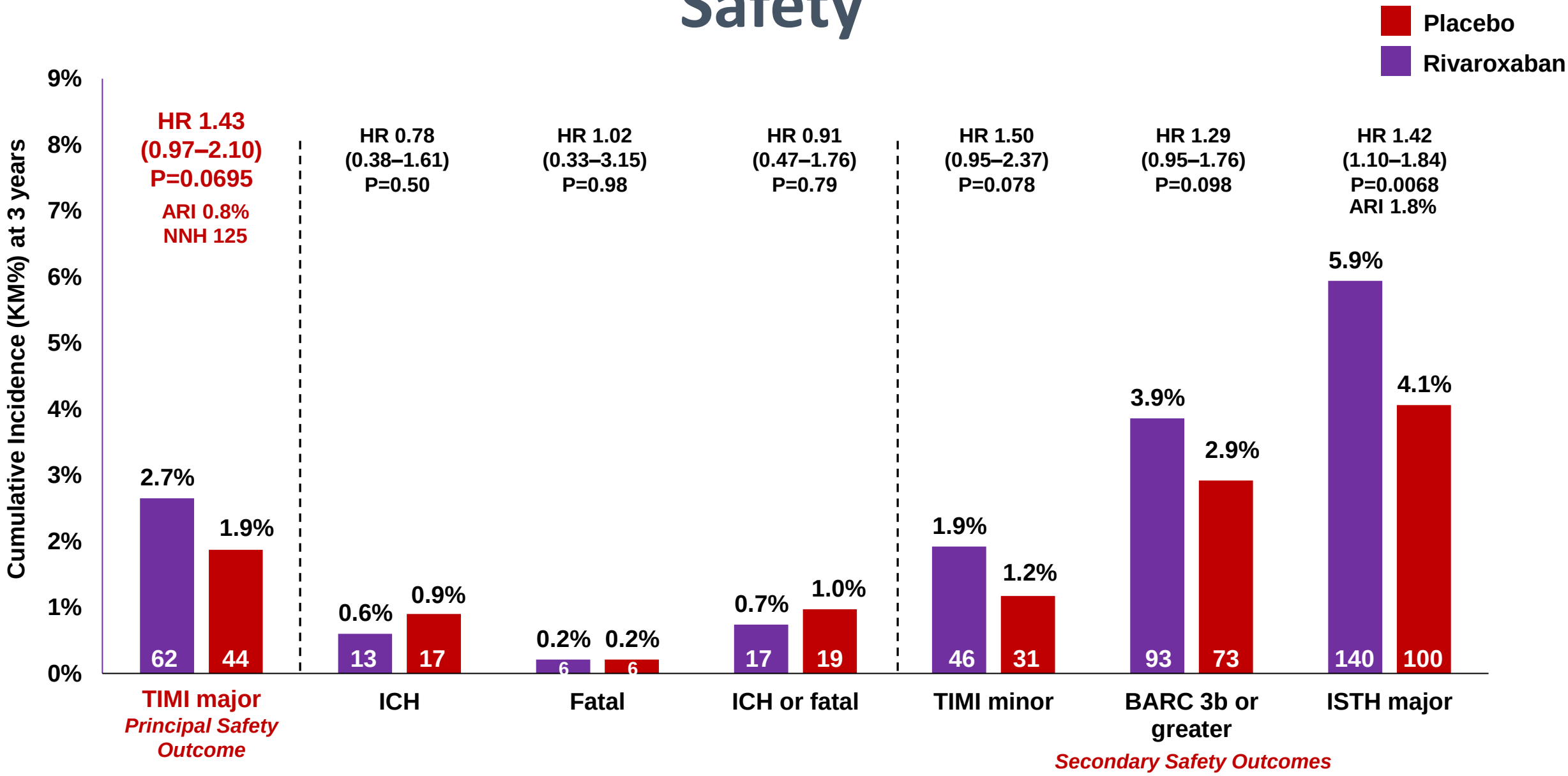
Bonaca MP…Hiatt WR *et al*. *N Engl J Med* 2020;382:1994–2004

Secondary Outcomes*



Presented in order of hierarchy from left to right

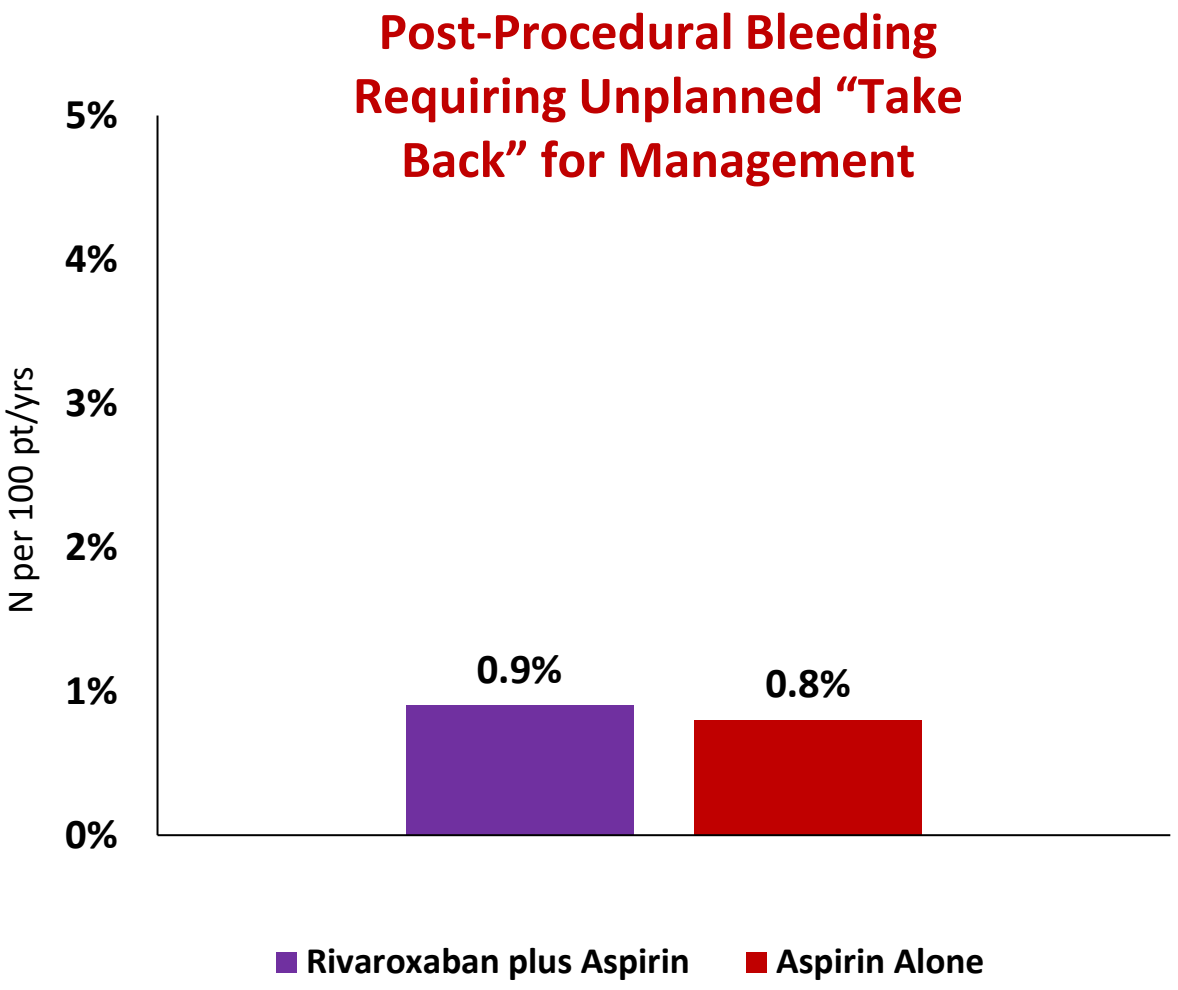
Safety

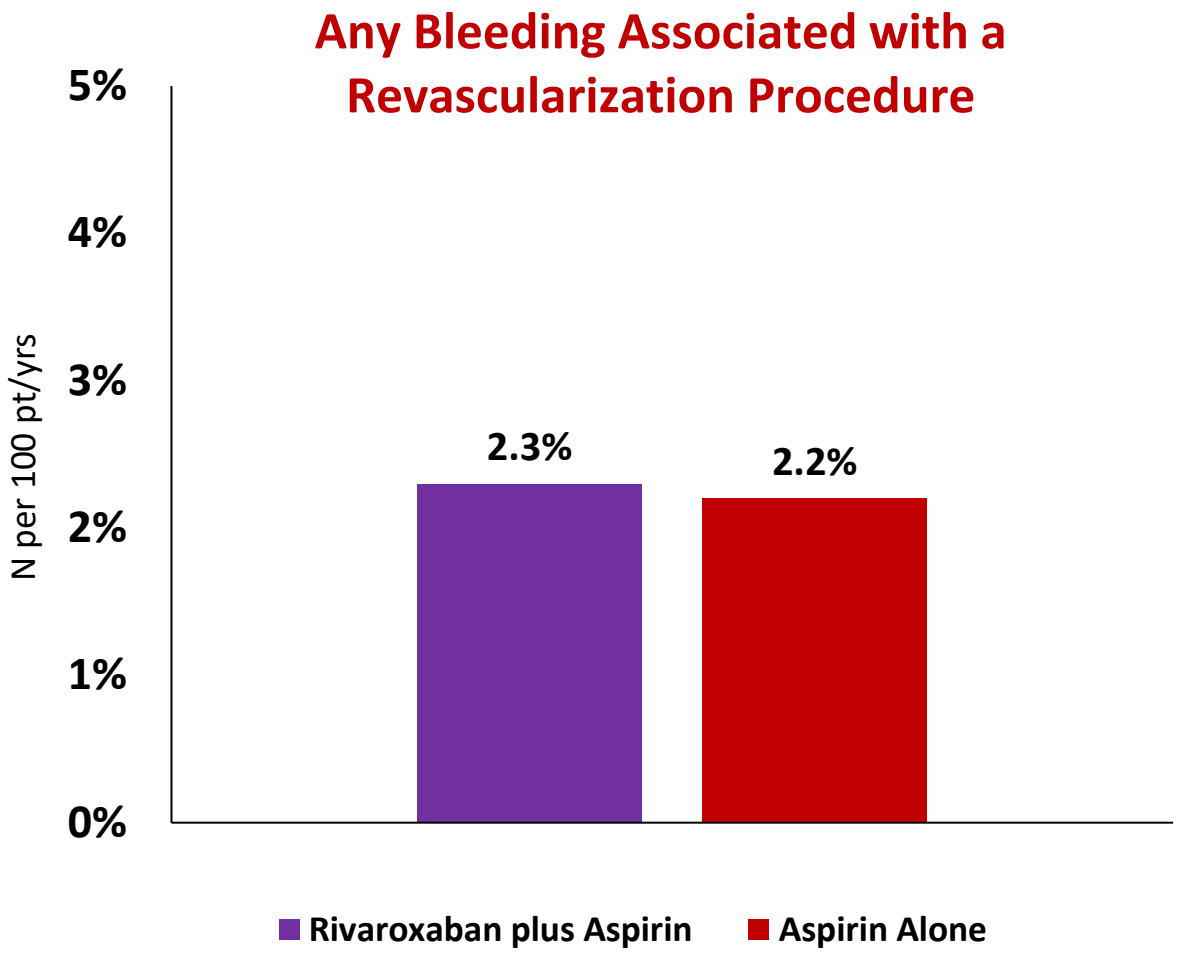


ARI, absolute risk increase;
NNH, number needed to harm

Bonaca MP…Hiatt WR *et al*. *N Engl J Med* 2020;382:1994–2004
Bonaca MP *et al*. Presented at ACC 2020. Slides available at
www.clinicaltrialresults.org/Slides/ACC%202020/Bonaca_VOYAGER-PAD.pptx

Procedural Bleeding

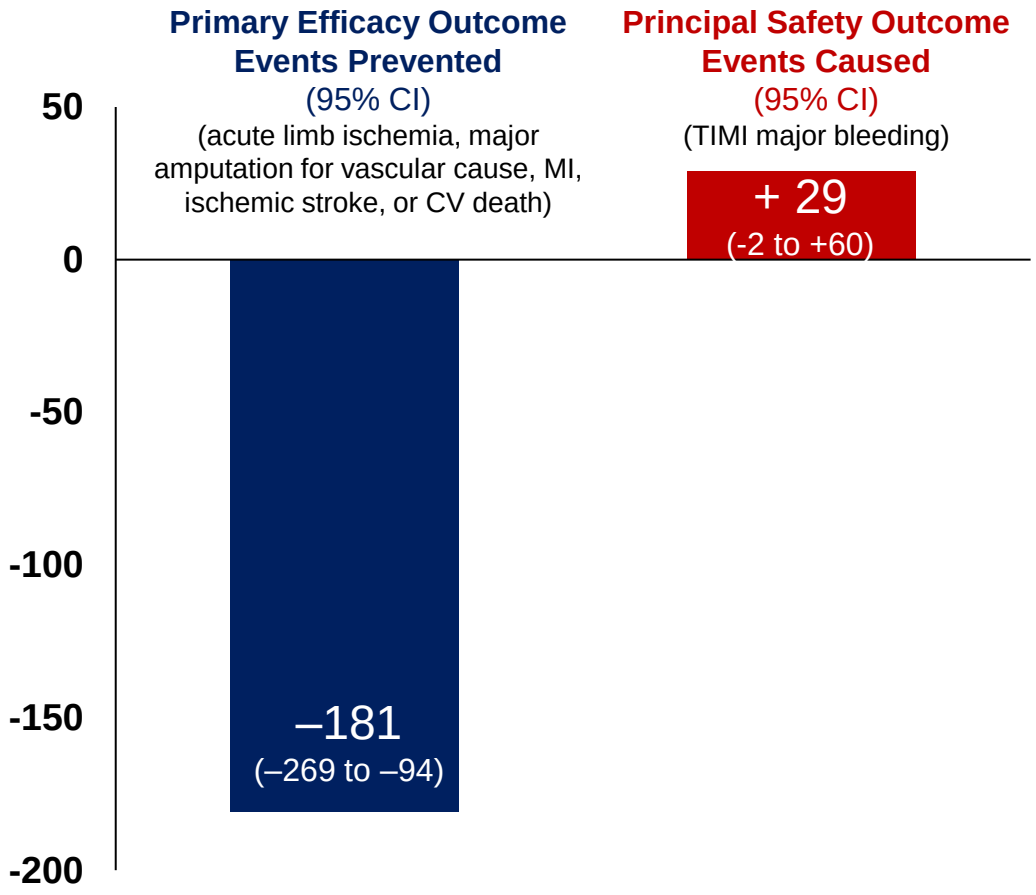




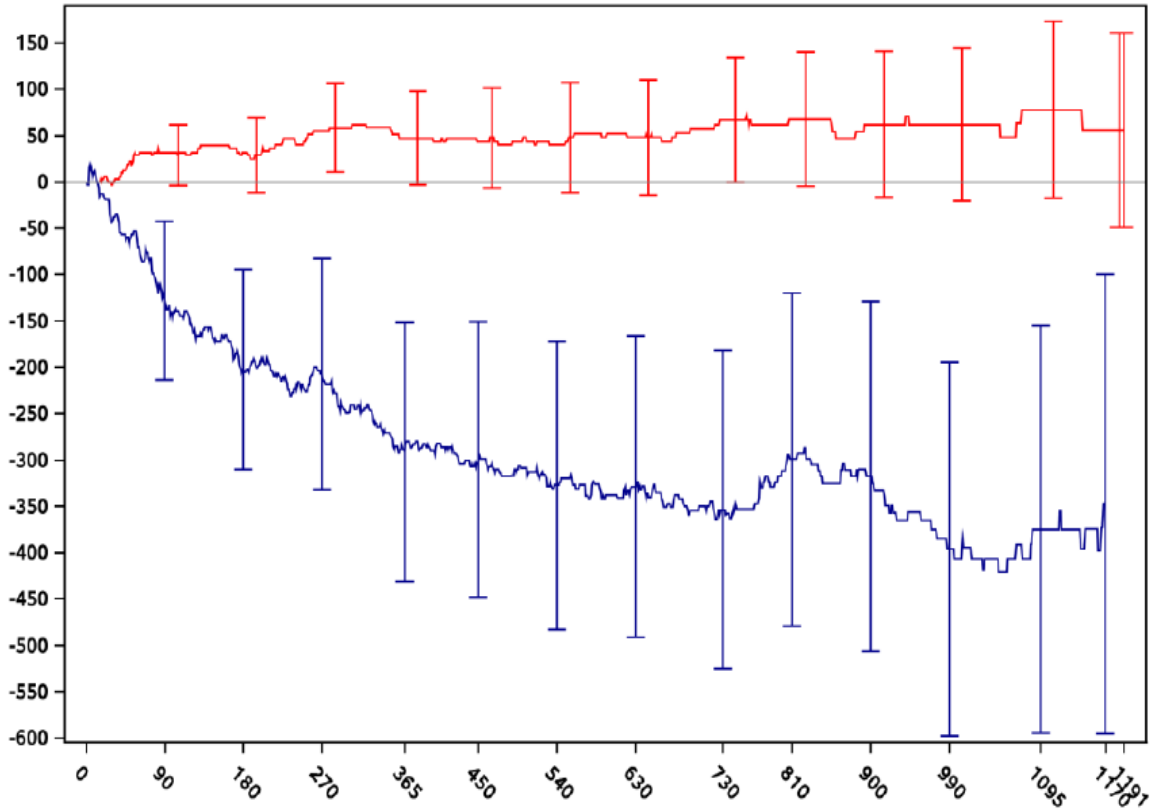
Bonaca MP…Hiatt WR *et al*. *N Engl J Med* 2020;382:1994–2004
Bonaca MP *et al*. Presented at ACC 2020. Slides available at
www.clinicaltrialresults.org/Slides/ACC%202020/Bonaca_VOYAGER-PAD.pptx

Risk–Benefit

First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year



First Events Prevented / Caused from Time from Randomization

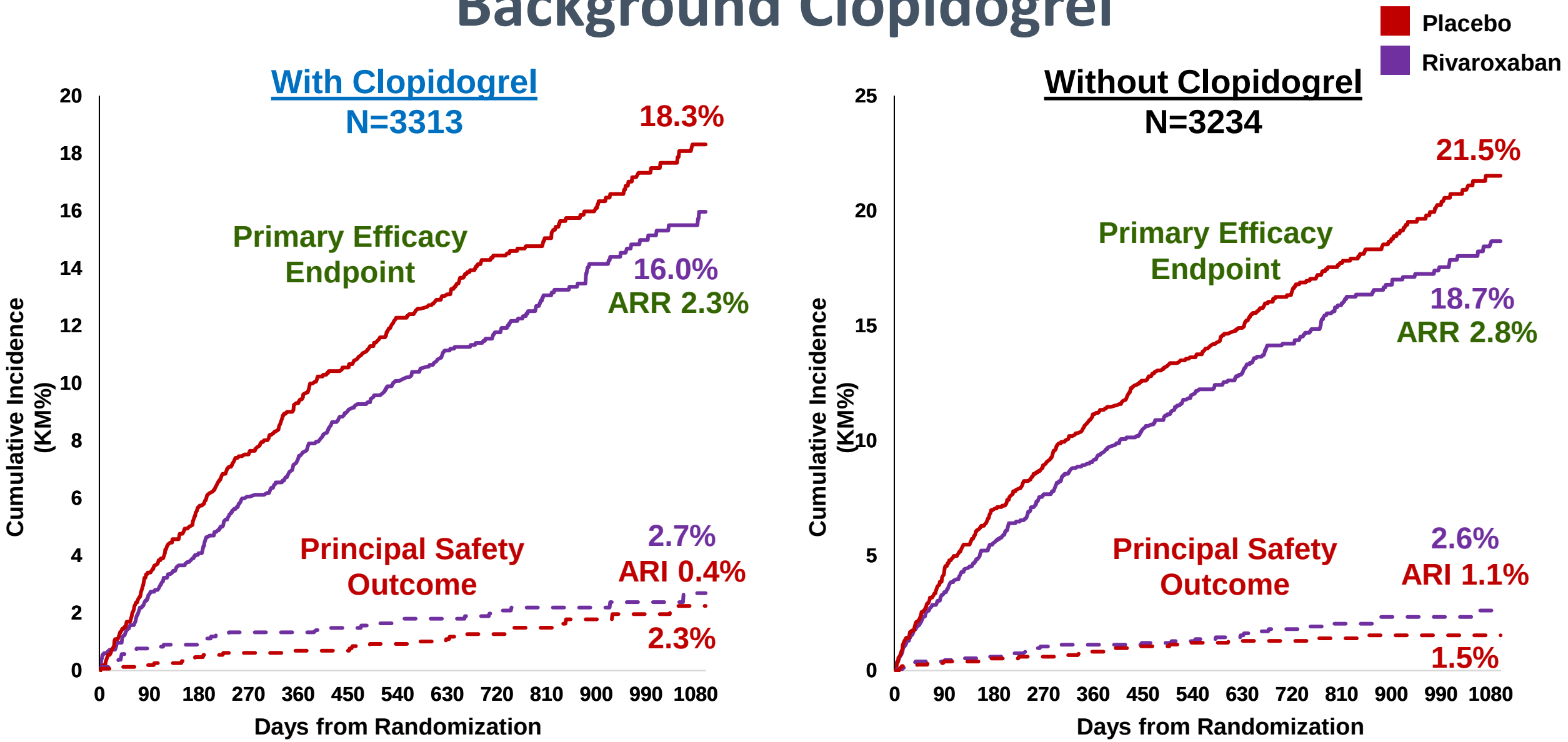


Efficacy and safety on treatment

Bonaca MP…Hiatt WR *et al*. *N Engl J Med* 2020;382:1994–2004
Bonaca MP *et al*. Presented at ACC 2020. Slides available at
https://cpcclinicalresearch.org/wp-content/uploads/2020/03/CPC-VOYAGER-PAD-Primary-Results-Slide-Presentation-by-Marc-P.-Bonaca.pdf

VOYAGER PAD

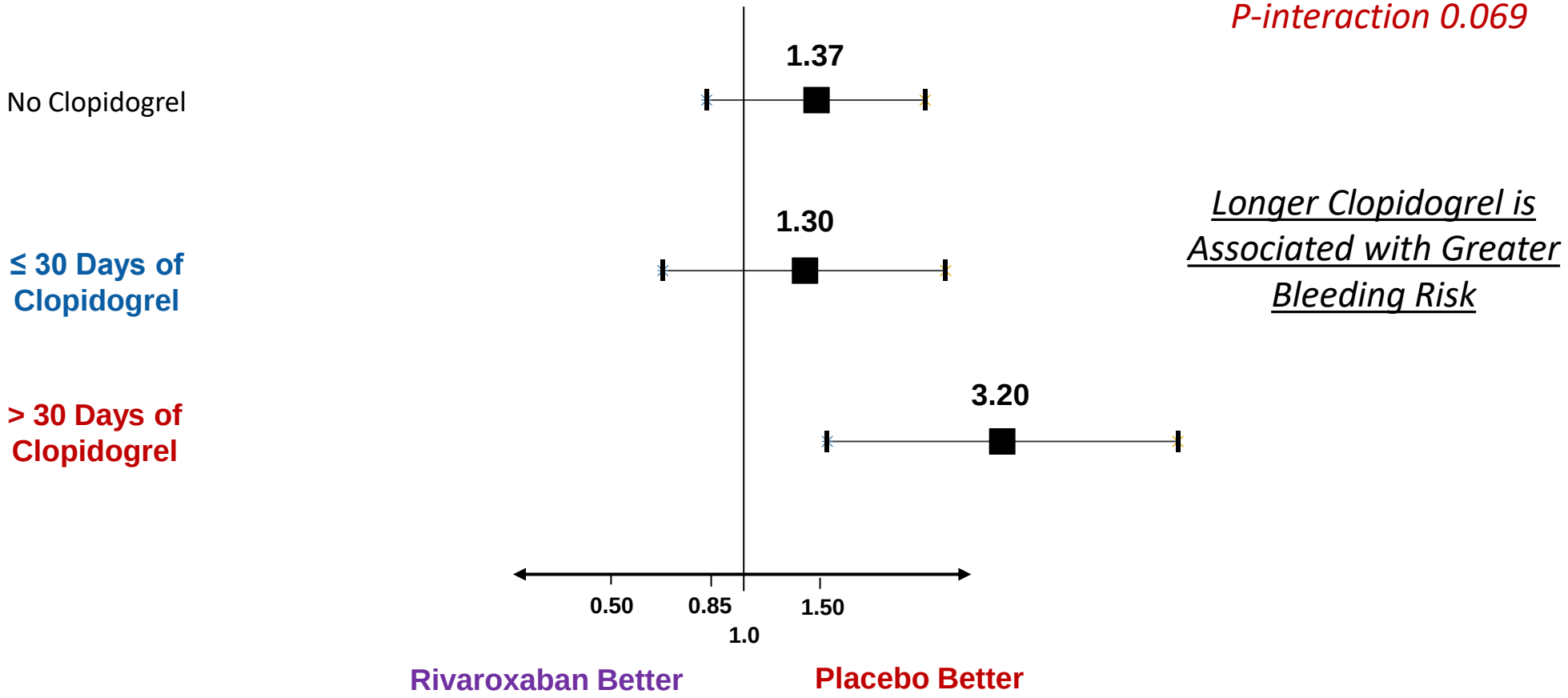
Background Clopidogrel



Hiatt WR et al. Circulation 2020

VOYAGER PAD

Risk of ISTH Bleeding with Rivaroxaban by Use and Duration of Concomitant Clopidogrel



Hiatt WR et al. Circulation 2020

Pathology of Peripheral Artery Disease in Patients With Critical Limb Ischemia

Navneet Narula, MD,[a,b] Andrew J. Dannenberg, MD,[a] Jeffrey W. Olin, DO,[c] Deepak L. Bhatt, MD, MPH,[d] Kipp W. Johnson, BS,[c] Girish Nadkarni, MD,[c] James Min, MD,[a] Sho Torii, MD,[e] Priti Poojary, MD, MPH,[c] Sonia S. Anand, MD,[f] Jeroen J. Bax, MD, PhD,[g] Salim Yusuf, MD,[f] Renu Virmani, MD,[e] Jagat Narula, MD, PhD[c]

FIGURE 1 Continued

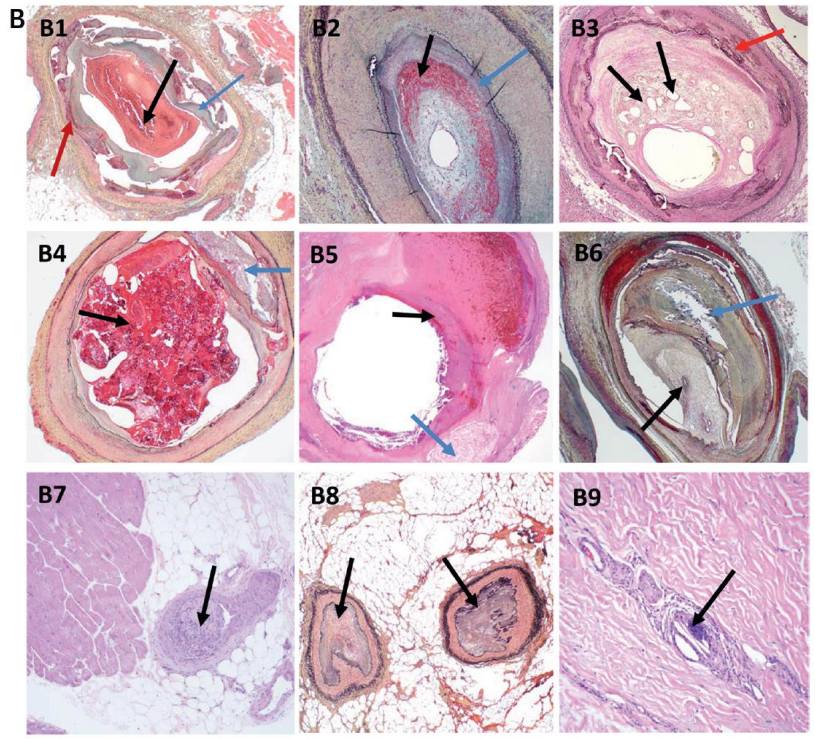
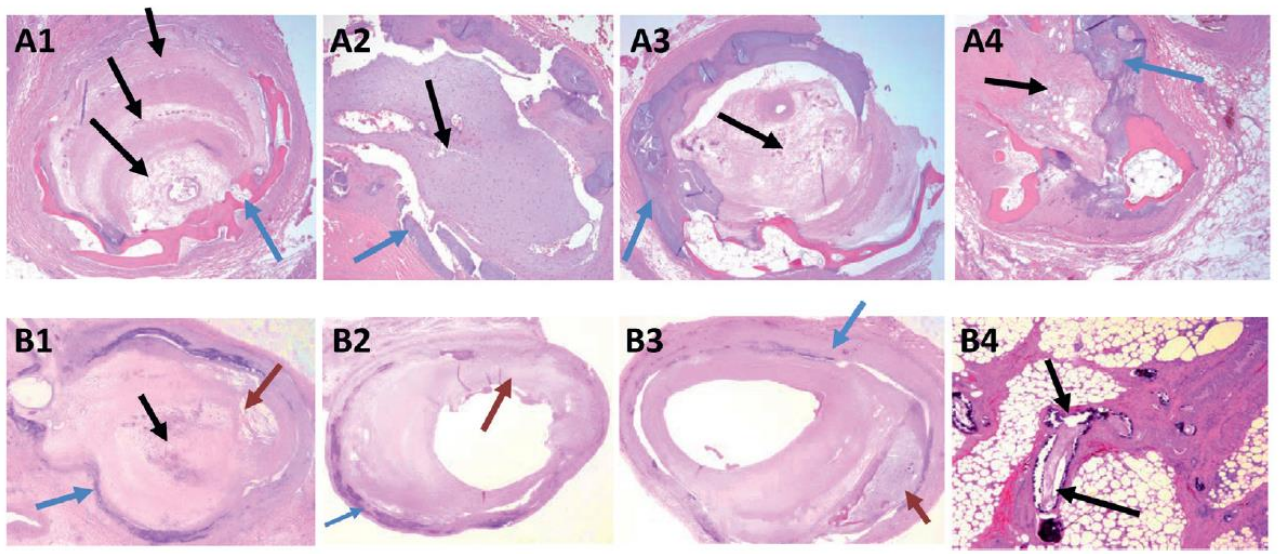
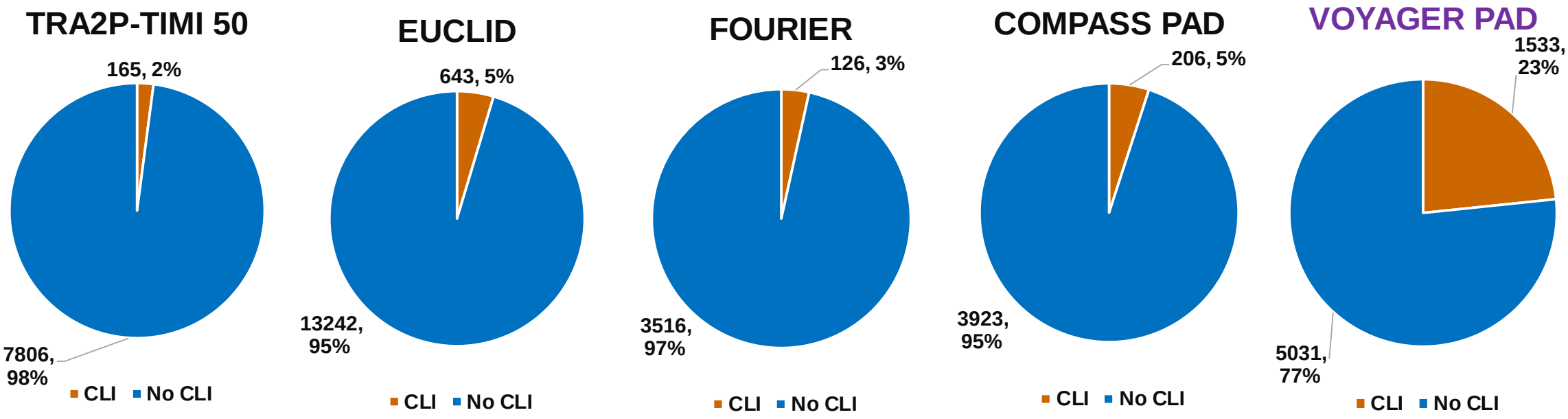


FIGURE 2 Clinical Examples of CLI With Minimal Atherosclerotic Disease in BKA Arteries, and Plaque Rupture in AKA Specimen



Trials with PAD Subgroups

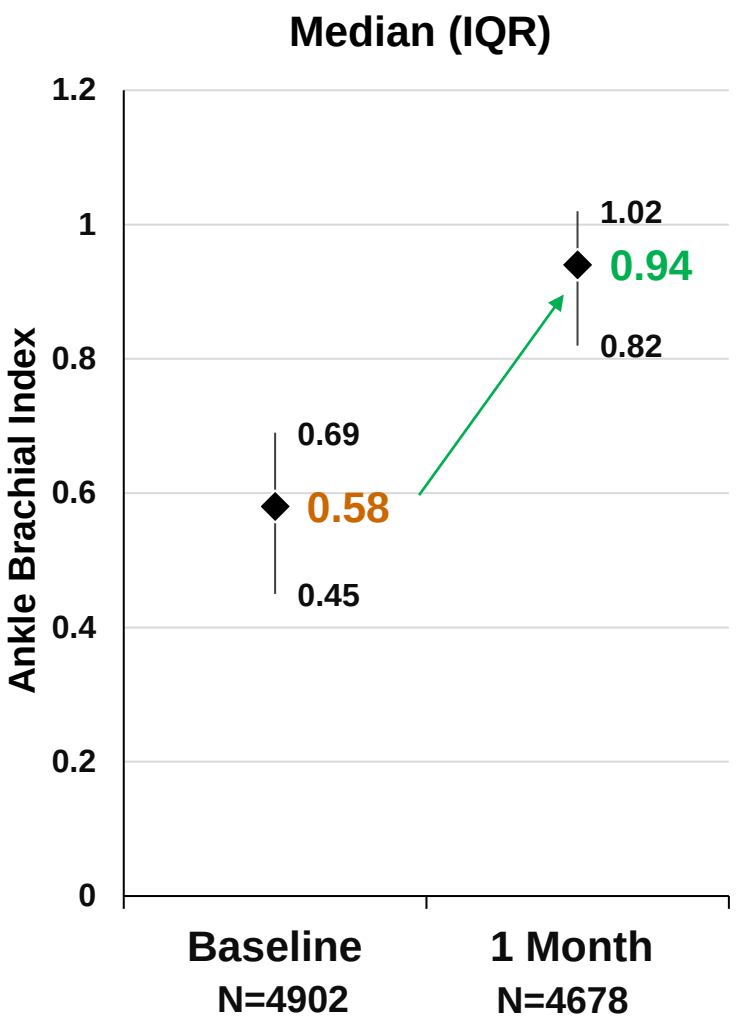


Total = 1,140

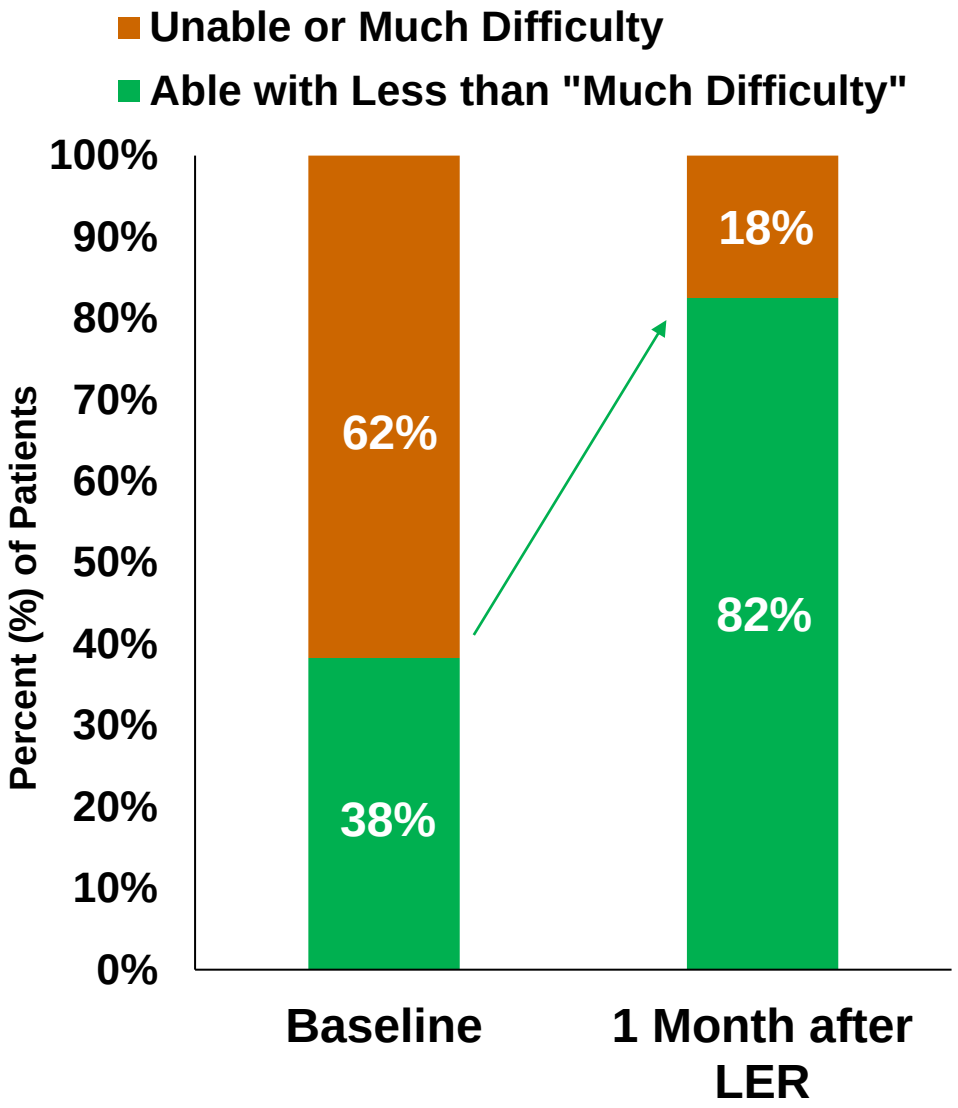
VOYAGER PAD Patients with CLI at Baseline = 1,533

Changes at From Baseline to 1 Month after LER

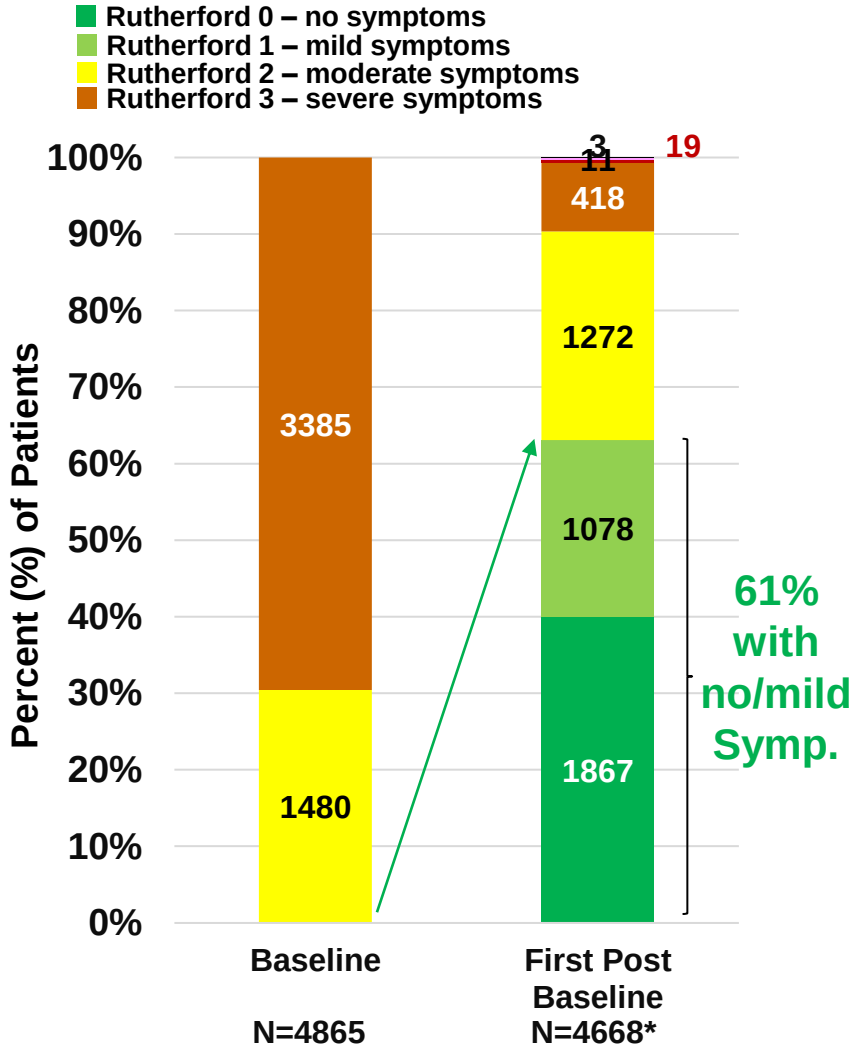
Index Limb ABI at Baseline and 1 Month



WIQ – Walking 2 Blocks



Rutherford at Baseline and First Post LER Assessment



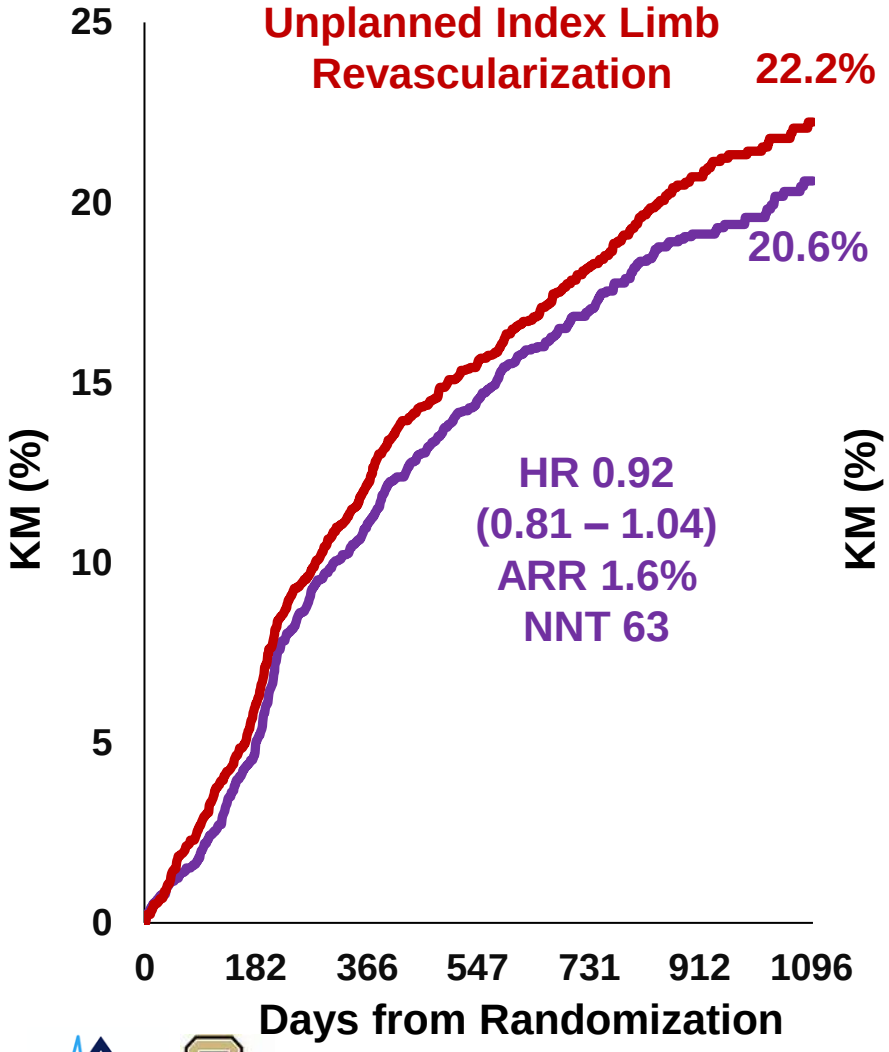
*197 died/missing

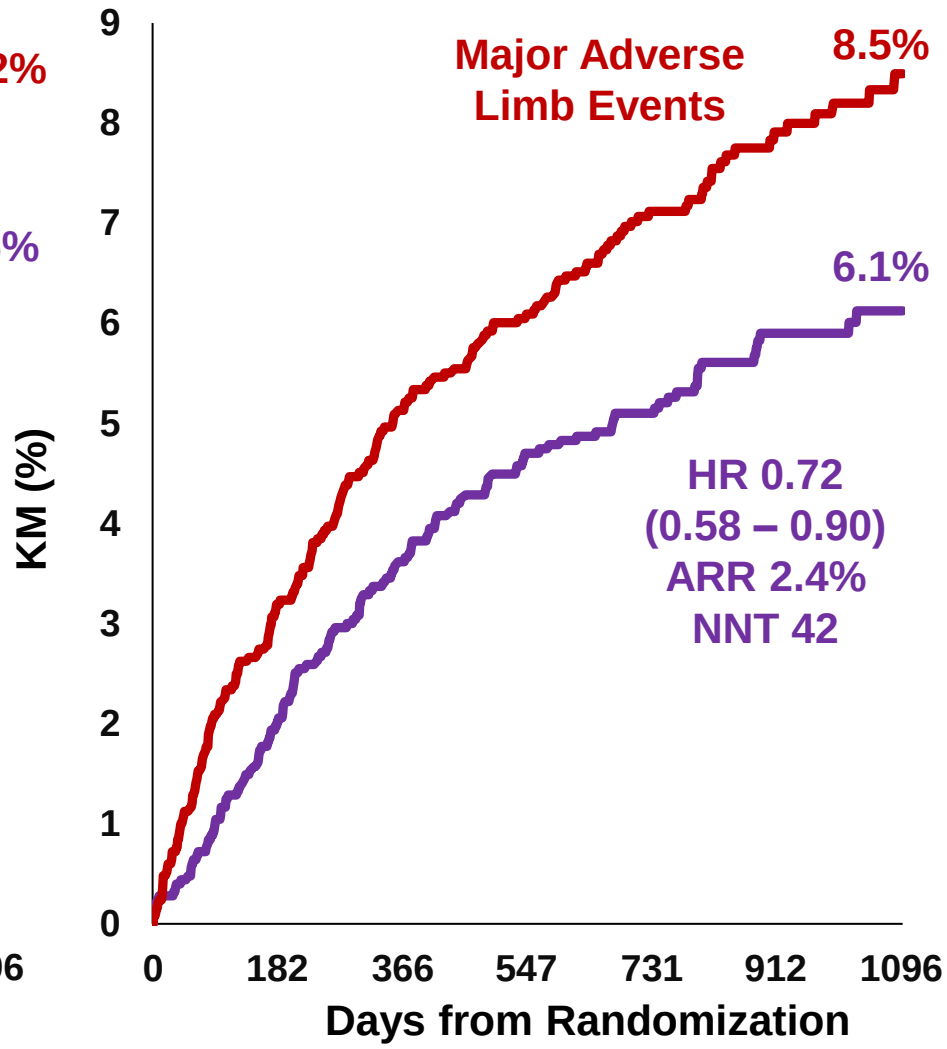
5031 Patients with Claudication at Baseline

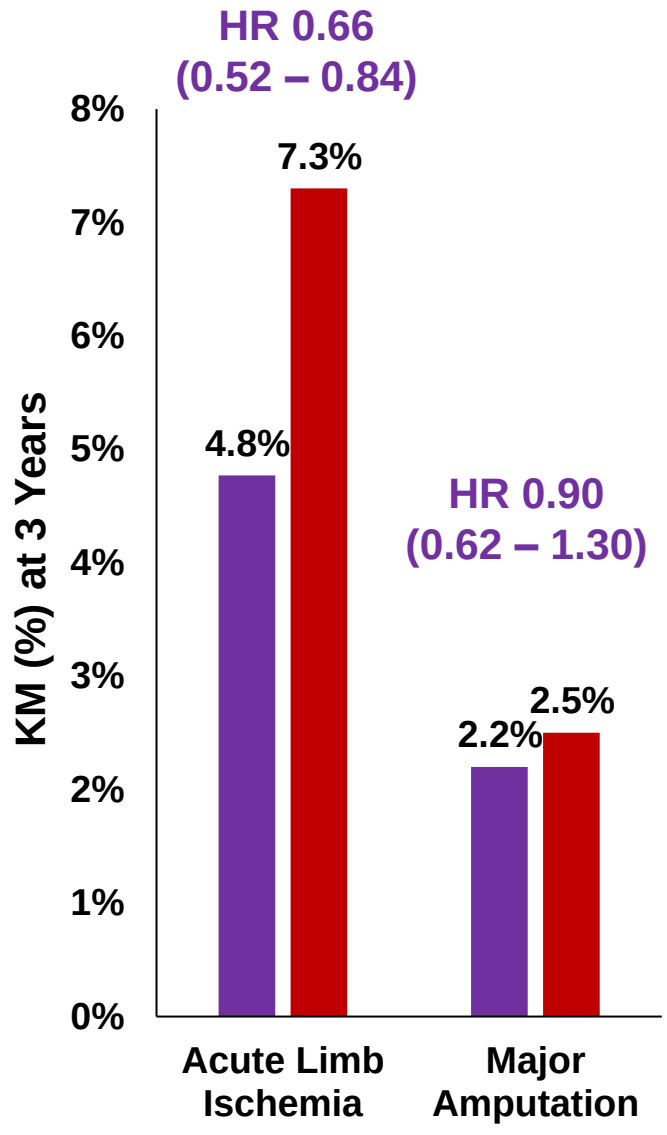
Limb Outcomes after LER for Claudication

Placebo
Rivaroxaban

5031 Patients with Claudication at Baseline, all to be on aspirin, 80% on statin, 54% on DAPT with clopidogrel



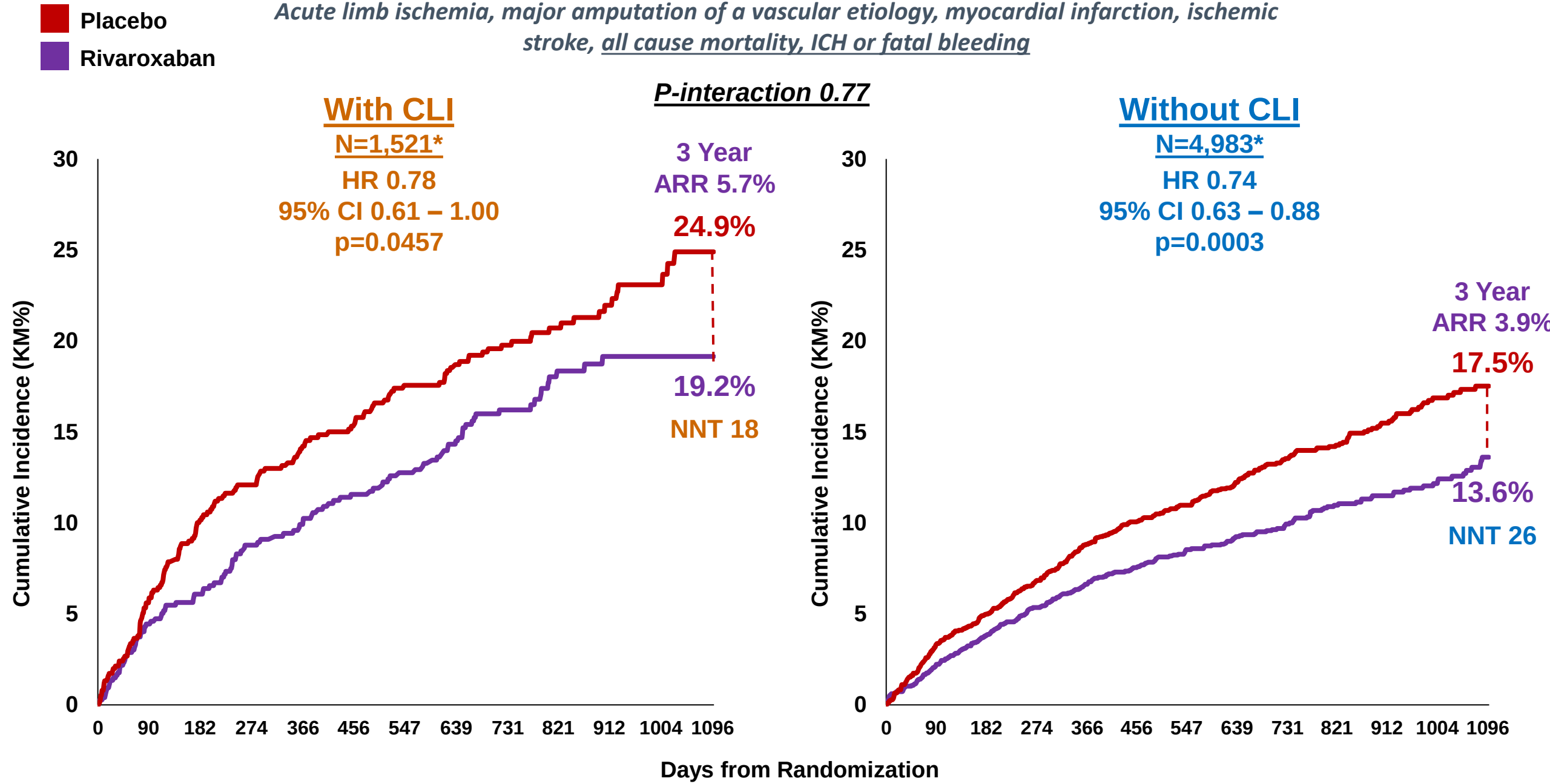




All p-interaction for claudication vs. CLI > 0.05

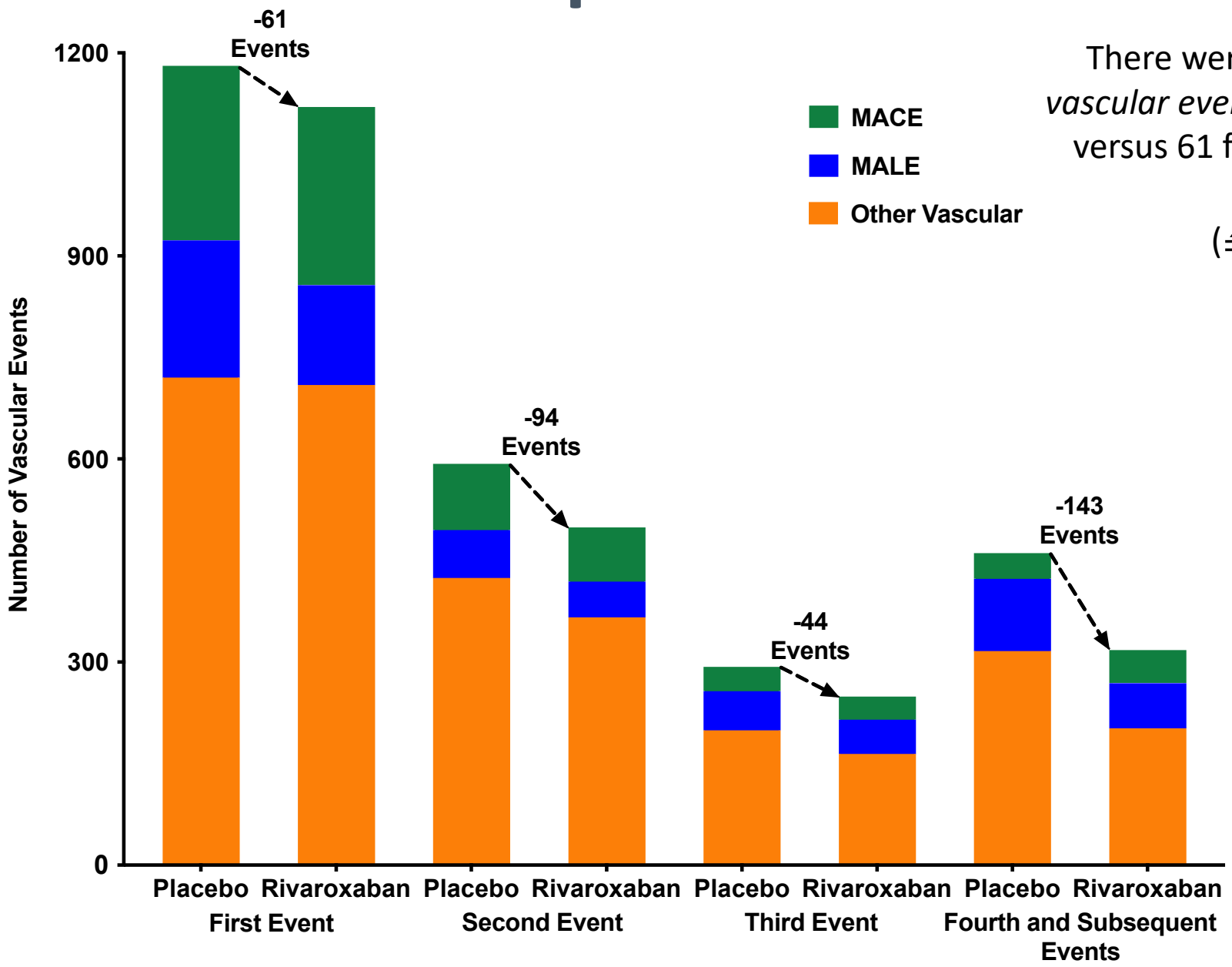
Net Clinical Benefit

Acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, all cause mortality, ICH or fatal bleeding



**Safety Population, On-Treatment Scope*

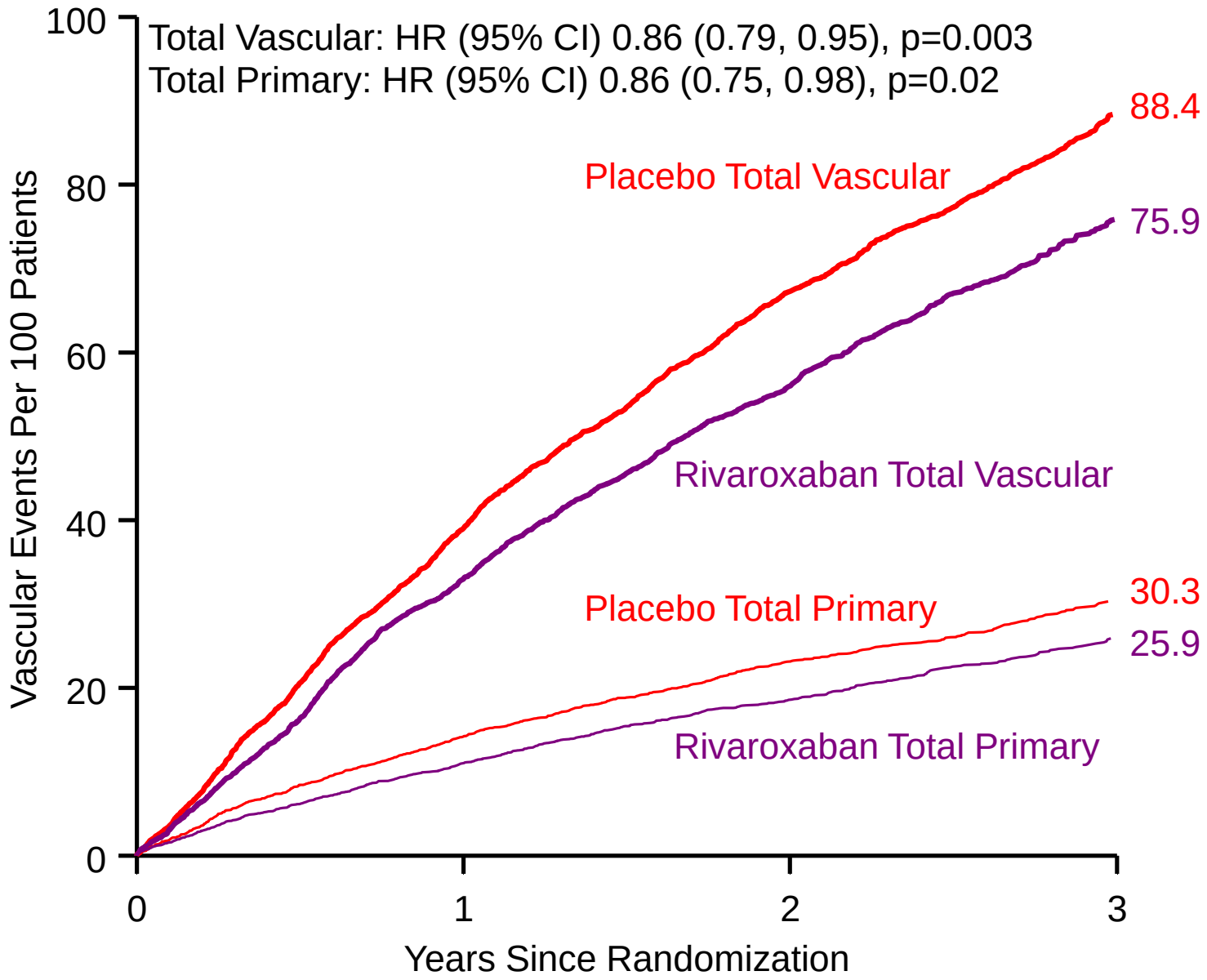
First and Subsequent Vascular Events



There were *342 fewer <u>total</u> vascular events* with rivaroxaban versus 61 fewer <u>first</u> vascular events (≙ 18 %).

MACE = major adverse cardiovascular event; MALE = major adverse limb event.

Accrual of Events per 100 Patients



CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

PAD: Other Therapeutic Approaches and Individualization of Treatment

Marc P. Bonaca MD MPH
Professor of Medicine
Director of Vascular Research
University of Colorado School of Medicine

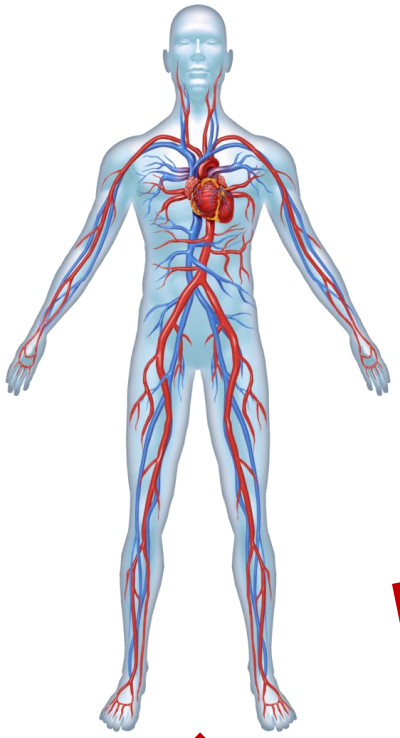
CPC Clinical Research

An Affiliate of:

University of Colorado Anschutz Medical Campus

Axes of Risk and Treatment Targets in PAD

<u>Lifestyle & Function</u> (exercise, diet, cilostazol where not contraindicated)



<u>Lipid Risk</u>
(LDL & Lpa)
High intensity statin +/- ezetimibe and PCSK9i
icosapent ethyl

<u>Thrombosis Risk</u>
(AP monotherapy if high bleeding risk, ASA+rivaroxaban if acceptable bleeding risk)

<u>Diabetes Risk (micro and macrovascular)</u>
A1C to reduce microvascular risk and target specific therapies (e.g. GLP1a, SGLT2i)

<u>Smoking Risk</u>

Inflammatory Risk
? IL-6 inhibition

Pharmacotherapy for Claudication
FDA Approved Drugs

Pentoxifylline

- Methylxanthine
- Approved August 1984
- Decreases plasma viscosity, improves RBC deformability, some vasodilation

Cilostazol

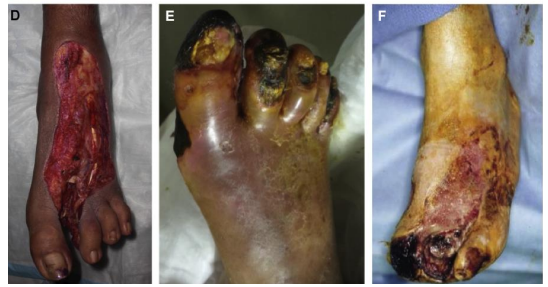
- Phosphodiesterase III inhibitor derivative
- Approved January 1999
- Platelet inhibitor, vasodilation, ↑HDL-cholesterol, ↓triglycerides
- Contraindicated if history of CHF of any severity

The Role of Vascular Intervention in PAD

Chronic PAD

Revascularization is reasonable if limiting in spite of inadequate response to guideline directed therapy (Class IIa)

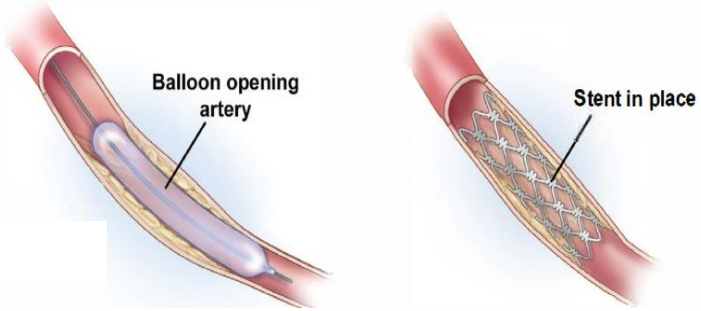
ALI / CLI



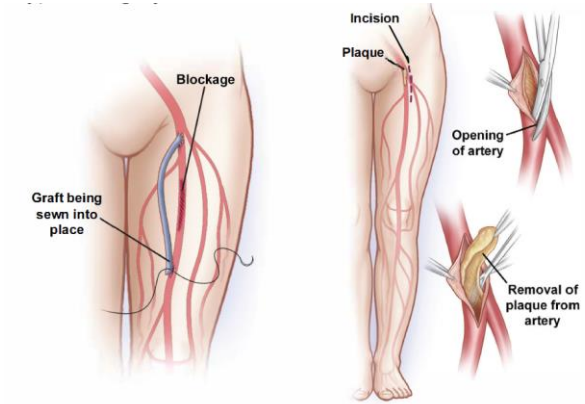
CLI / CLTI

Revascularization Recommended (Class I)

Revascularization Options



Endovascular | ***Surgical***



- Less invasive & faster recovery
- No incision
- Minimal anesthesia
- Can be done inpatient and outpatient
- Patency (durability) variable

Decision of which depends on:

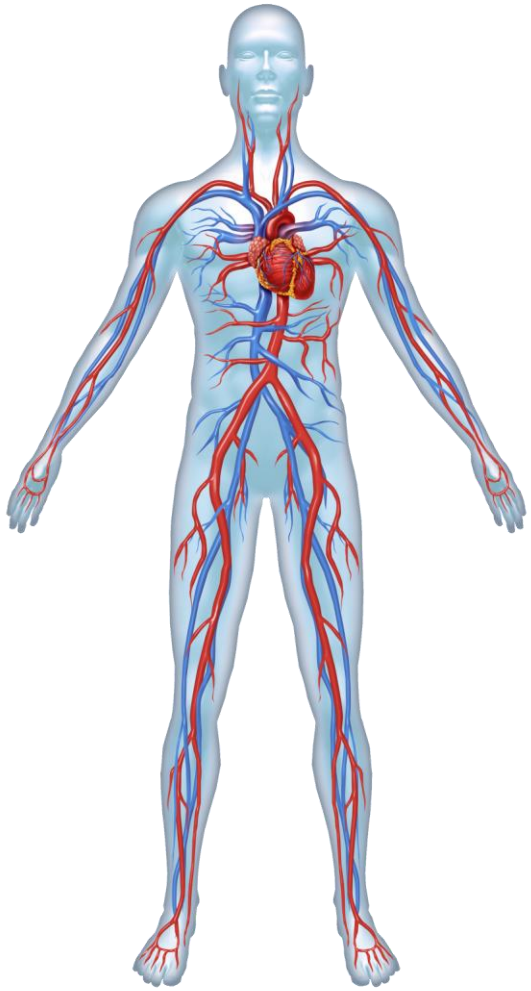
- Anatomy (lesion length)
- Patient comorbidity / surgical risk
- Patient choice
- Geography / practice pattern
- Local options and skill sets
- Clinical setting (inpatient vs. outpatient)
- Costs in some regions

What is the best initial approach in CLI?
Equipoise exists → BEST-CLI Trial

- Requires surgery & OR (hospitalization)
- Longer recovery
- Requires anesthesia
- Options for patients with anatomy not amenable for endovascular

Society of Vascular Surgery – Accessed 11/20/2020

PAD Risk-reduction Therapies



Therapies for all Patients

- **Lifestyle Modification & Exercise**
- **Tobacco Cessation Therapies**
- **Targeting blood pressure goals with preference for ACEi**
- **LDL-C lowering with statin ± ezetimibe and/or PCSK9i**
- **Antiplatelet monotherapy (symptomatic), preference for $P2Y_{12}$ inhibition**

Therapies for MACE Reduction in Selected Patients

Diabetes

- **Glucose lowering to reduce microvascular risk**
- **GLP-1 , SGLT2 inhibitors**

Prior MI or CAD (Polyvascular Disease) and low bleeding risk

- **ASA + rivaroxaban 2.5 BID (broad polyvascular definition)**
- **ASA + ticagrelor 60 mg BID (prior MI or other need for DAPT)**
- **ASA and/or clopidogrel with vorapaxar**

Therapies for MALE Reduction in all Patients

- **LDL-C lowering with statin ± ezetimibe and/or PCSK9i**

Therapies for MALE Reduction in Selected Patients

Prior peripheral revascularization & low bleeding risk

- **ASA + rivaroxaban 2.5 BID**
- **ASA + ticagrelor 60 mg BID (prior MI or other need for DAPT)**
- **ASA and/or clopidogrel with vorapaxar**

Therapies for Claudication

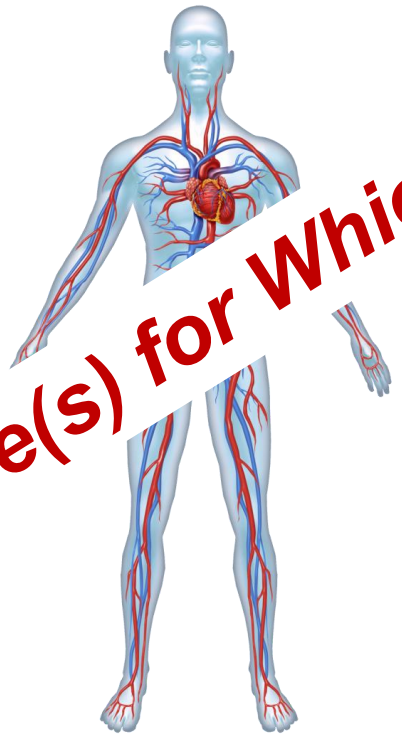
Symptomatic Patients

- **Cilostazol 100 mg BID (only if no history of heart failure)**

Novel Therapeutic Approaches in PAD

Antithrombotic Therapy

Targeted ... Glucose Lowering Therapies



Which One(s) for Which Patient?

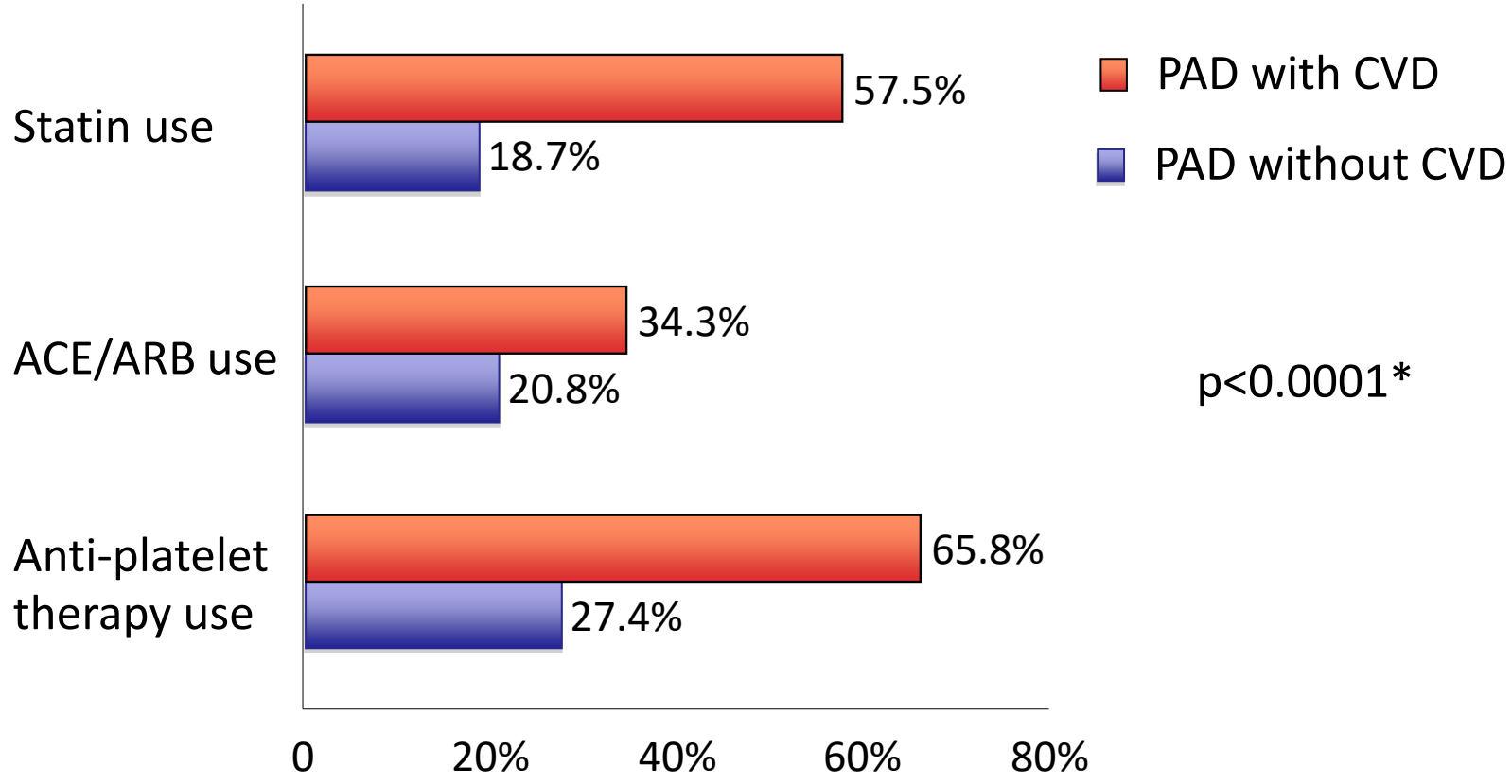
Lipid Modifying Therapy

Anti-Inflammatory Therapies

An Approach to Risk Factor Modification in PAD

Axis of Therapy	Symptomatic PAD No prior Revasc No CAD No CVD	Symptomatic PAD with Prior Revasc Or Polyvascular Disease
Lifestyle	**Smoking Cessation, Diet, Exercise**	**Smoking Cessation, Diet, Exercise**
Antithrombotic	**Antiplatelet Monotherapy**	**Aspirin and either Rivaroxaban or Vorapaxar (both approved in PAD)** ***If low bleeding risk***
Lipid Lowering	**High Intensity Statin + eze and/or PCSK9i** **(target LDL-C < 55 mg/dL)** **Icosapent ethyl?**	**High Intensity Statin + eze and/or PCSK99** **(target LDL-C < 55 mg/dL)** **Icosapent ethyl?**
Angiotensin Inhibition	**If HTN then ACEi**	**If HTN then ACEi**
Glucose Lowering	**If DM then GLP1 agonist and/or SGLT2i**	**If DM then GLP1 agonist and/or SGLT2i**
For Symptoms	**Cilostazol**	**Cilostazol**

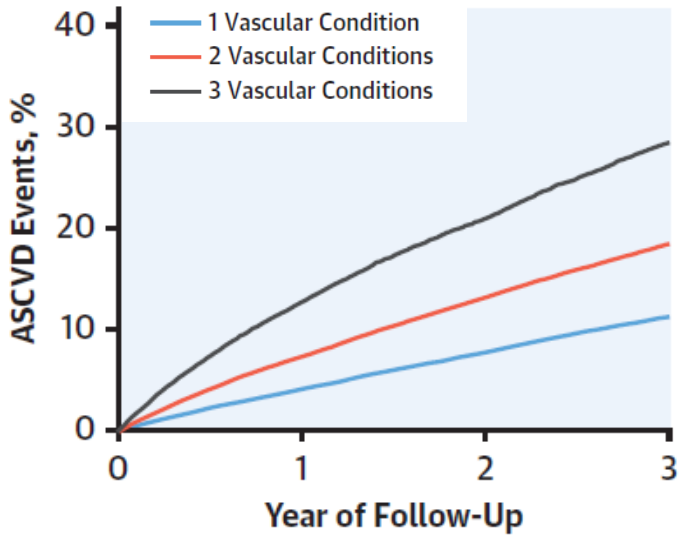
Use of Secondary Prevention Medications in NHANES – How were we doing in the early 2000s?

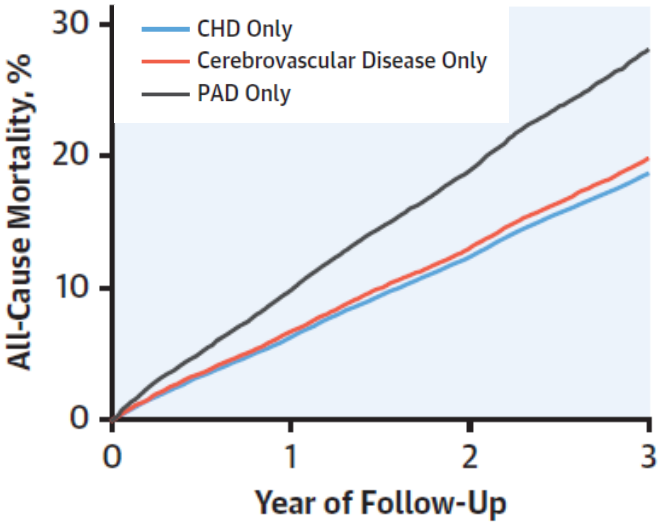


* Statistical comparison by Chi-square test

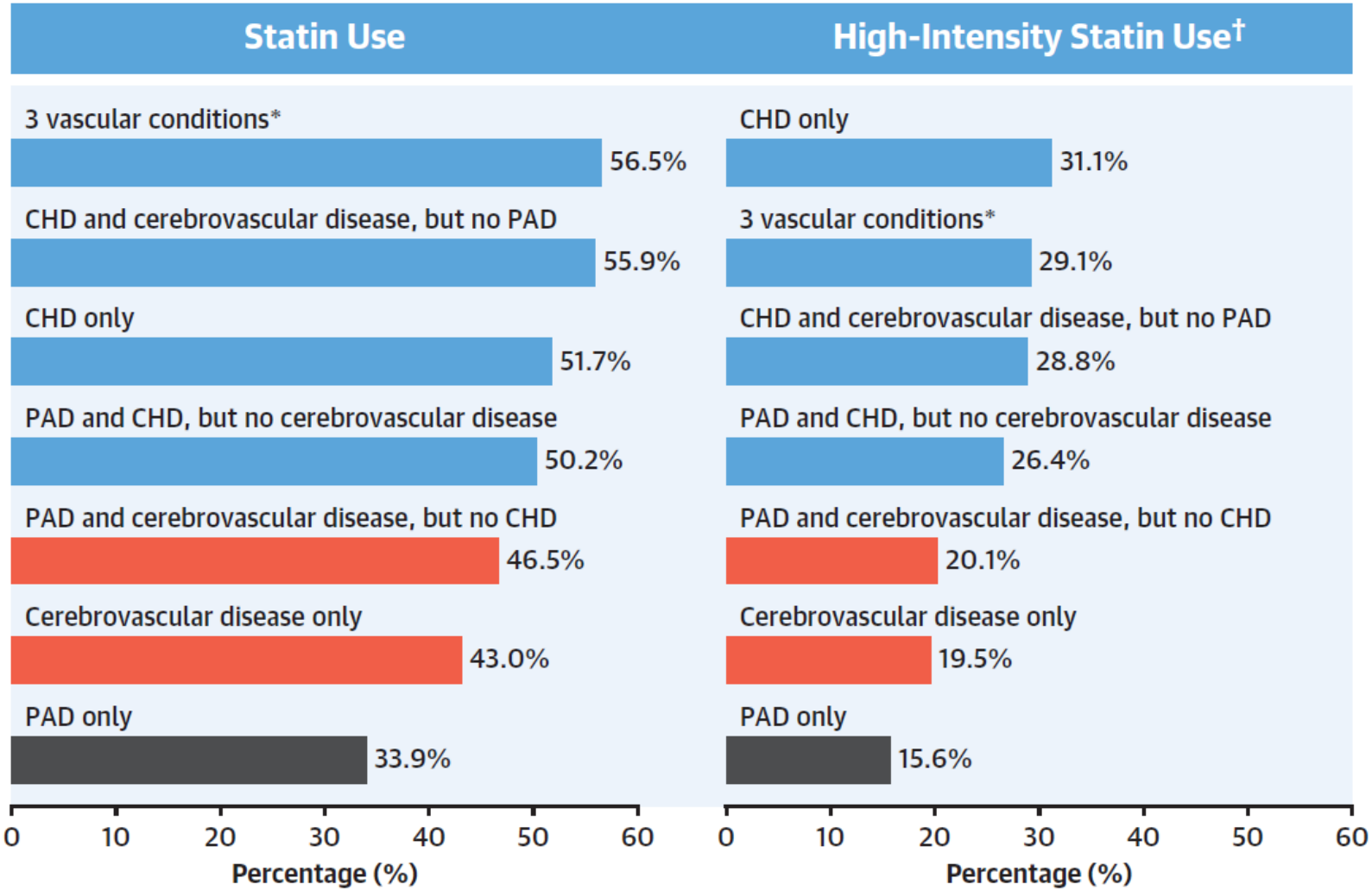
Pande et al., Circulation, 2011

Statin Use in ASCVD and PAD – How are we doing now?





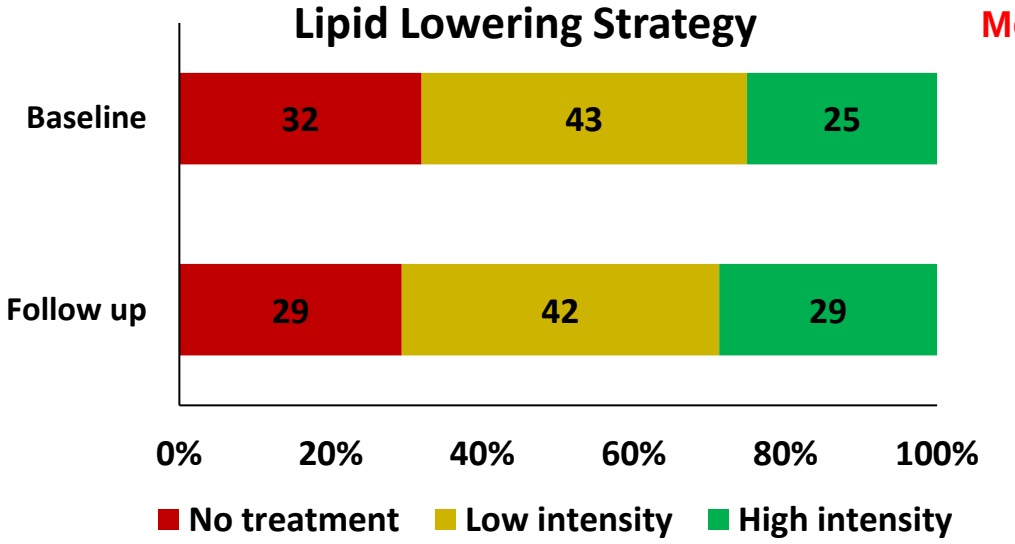
943,232 Medicare patients – December 2014 through December 2017

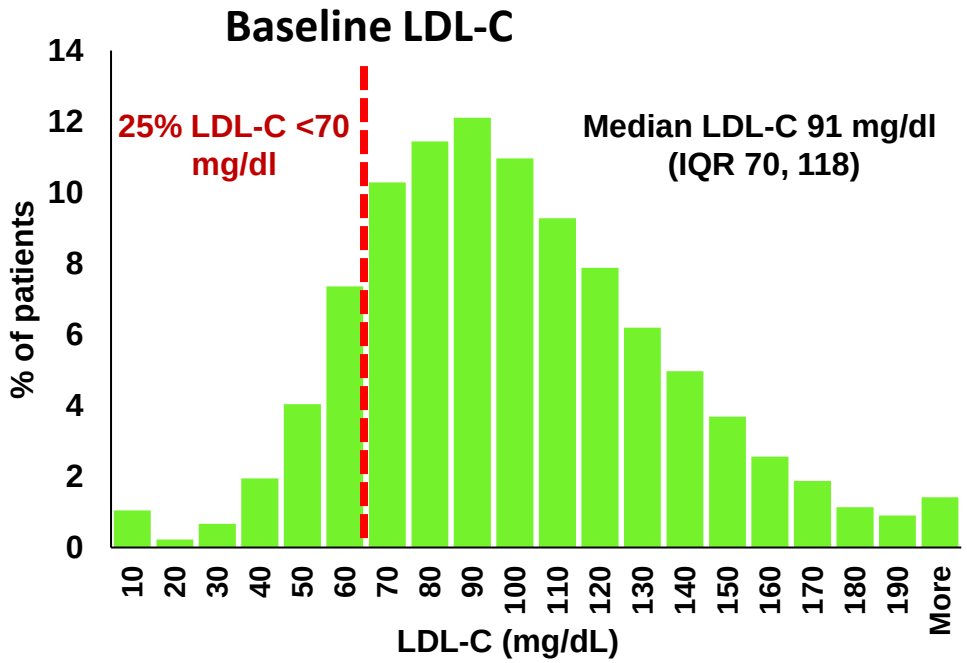


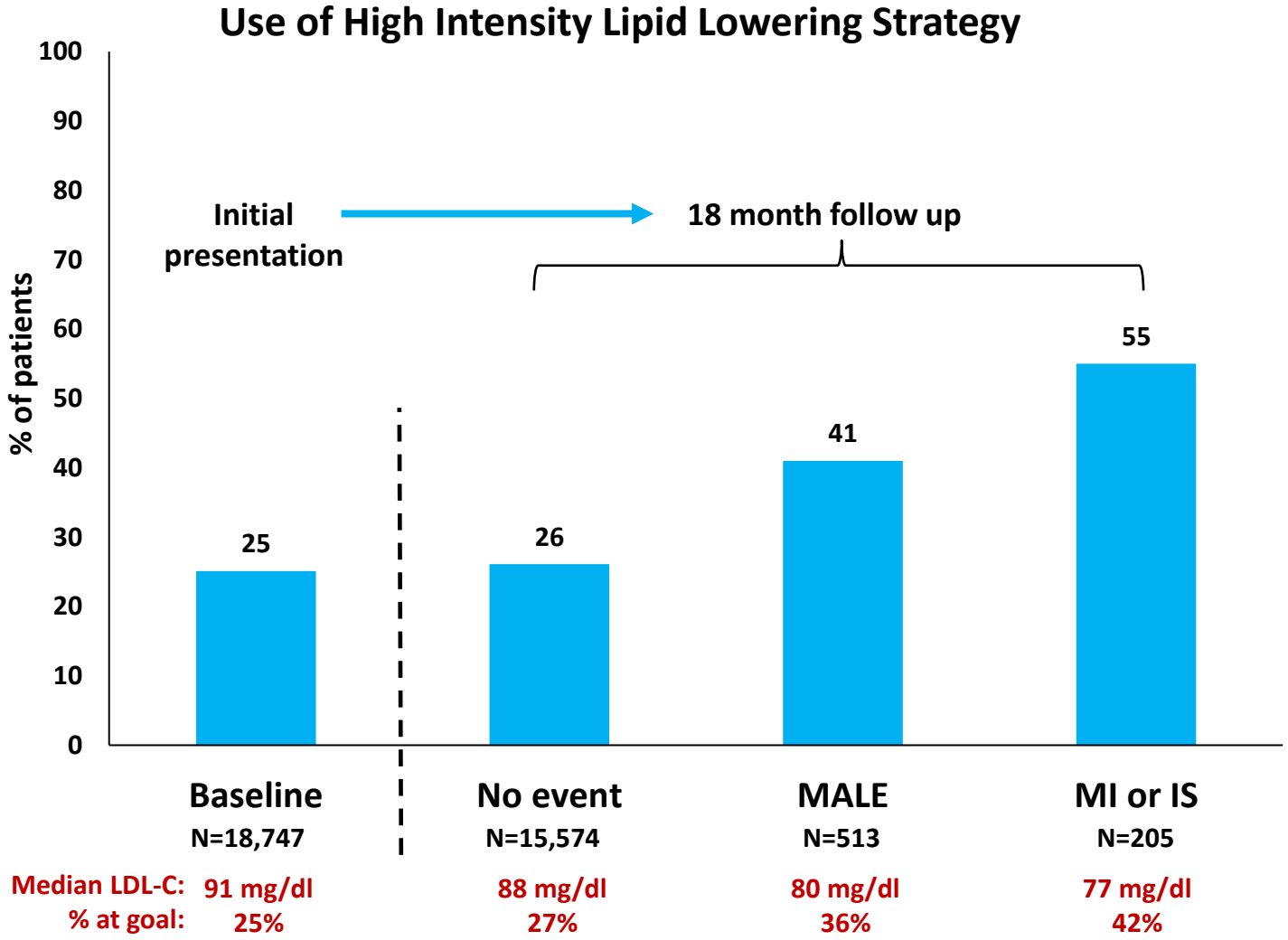
Colantonio et al. JACC 2020

Current Lipid Lowering Therapy in PAD After Intervention

18,747 patients with PAD
Median follow up 18 months







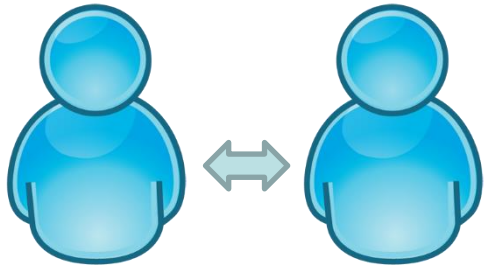
IS = ischemic stroke; MALE = major adverse limb event; MI = myocardial infarction

Hess…Bonaca et al. JACC 2021

How do we Translate to Practice?

Current Model

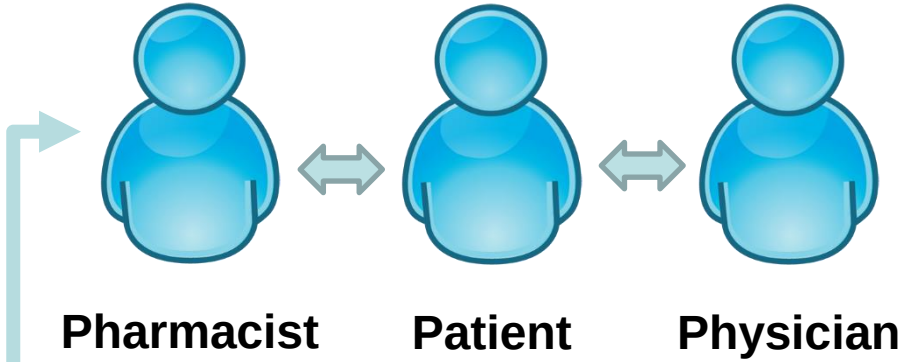
15-minute visit every 6 months



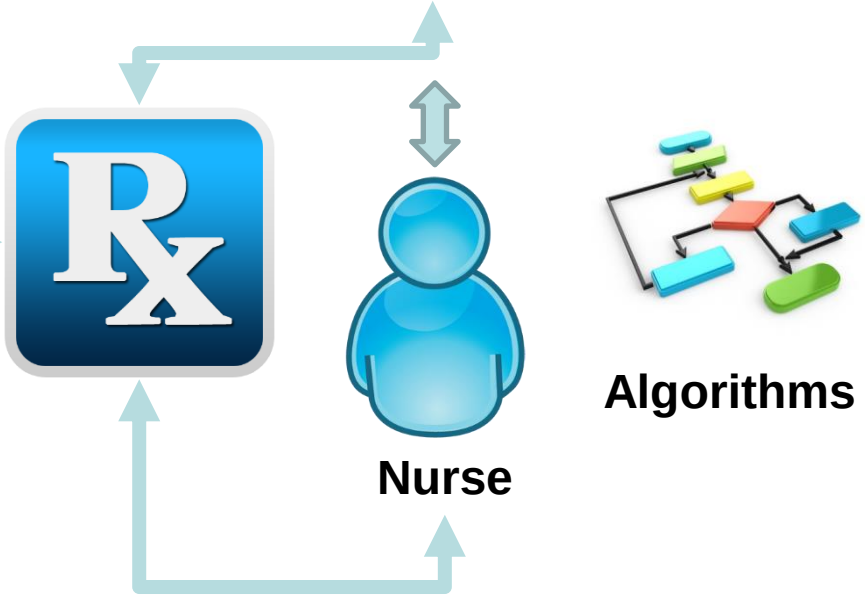
Patient **Physician**

Intervention Model

Comprehensive Initial Visit to Assess Risk and Determine Goals followed by Frequent Contact (phone and visits) as well as Pharmacy Support



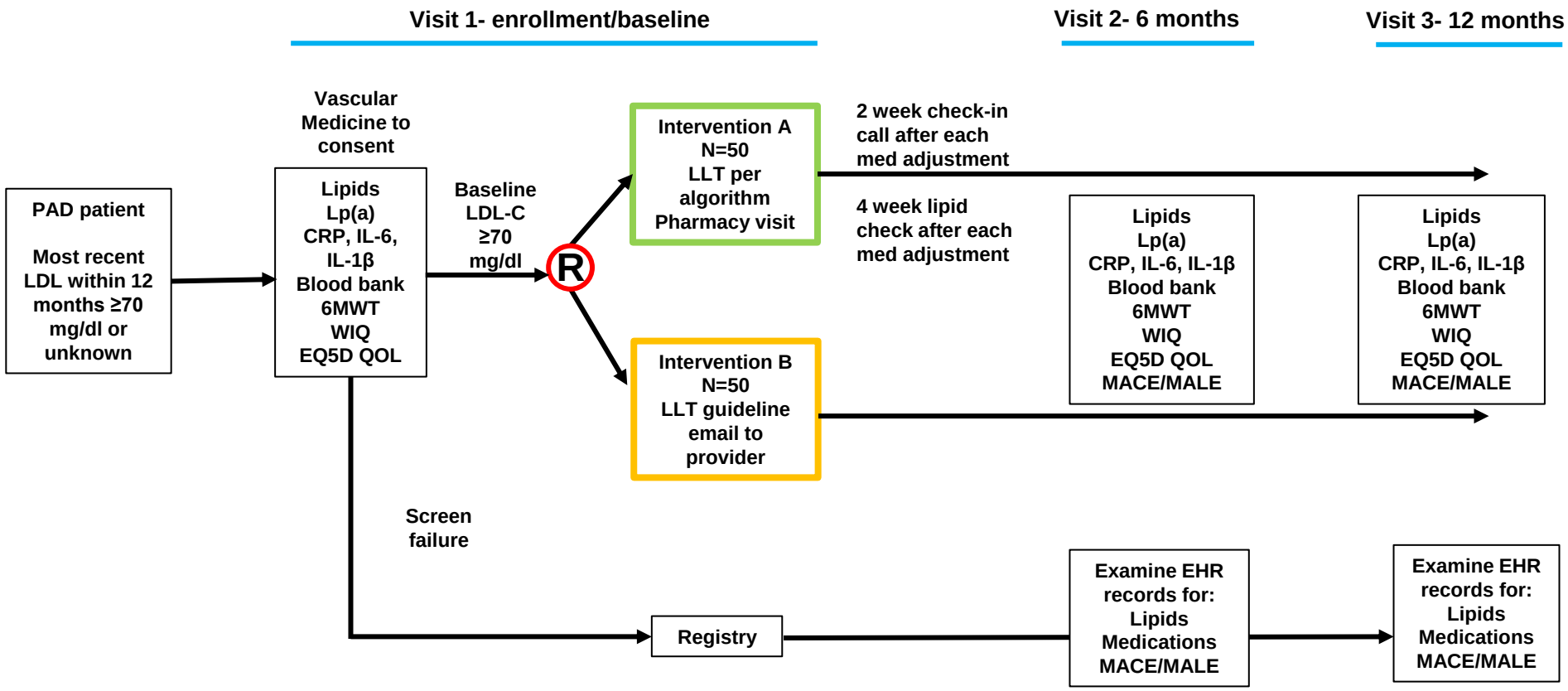
Pharmacist **Patient** **Physician**



Nurse

Algorithms

OPTIMIZE PAD-1: Study Design



PEP: % change in LDL-C from BL to 12 months (secondary at 6 months)
Others: QoL, Adherence, biomarkers, MACE & Limb Outcomes

ClinicalTrials.gov, NCT04400409

Summary & Conclusion

- **Peripheral artery disease is an increasingly prevalent and severe form of atherosclerosis affecting more than 200 million globally**
- **Patients suffer from both cardiovascular (heart attack, stroke) and limb (acute limb ischemia, amputation) outcomes**
- **Subgroups of this population are at particularly high risk (prior revascularization, concomitant coronary disease) and the combination of PAD and DM represents a group at particularly high risk MACE and amputation**
- **Few therapies studies in dedicated PAD trials and with focus on limb outcomes with large unmet needs**
- **Gaps in applying existing therapies must be addressed including implementation science and addressing disparities in care**