AT THE FOREFRONT
UChicago Medicine
Heart and Vascular Center

Pharmacologic risk reduction in peripheral arterial disease

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Disclosures

Affiliation/Financial Relationship	Company
• Consulting, Advisory Panel & Proctoring • Research, Data Monitoring & Steering Committee	Medtronic, Merit Medical, Terumo, Zoll CyndRX, Magenta Medical, Procyrion, Supira Medical, Zoll
• Major Stock Shareholder/Equity	None
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• Ownership / Founder	None
• Intellectual Property Rights	None
• Other Financial Benefit	None

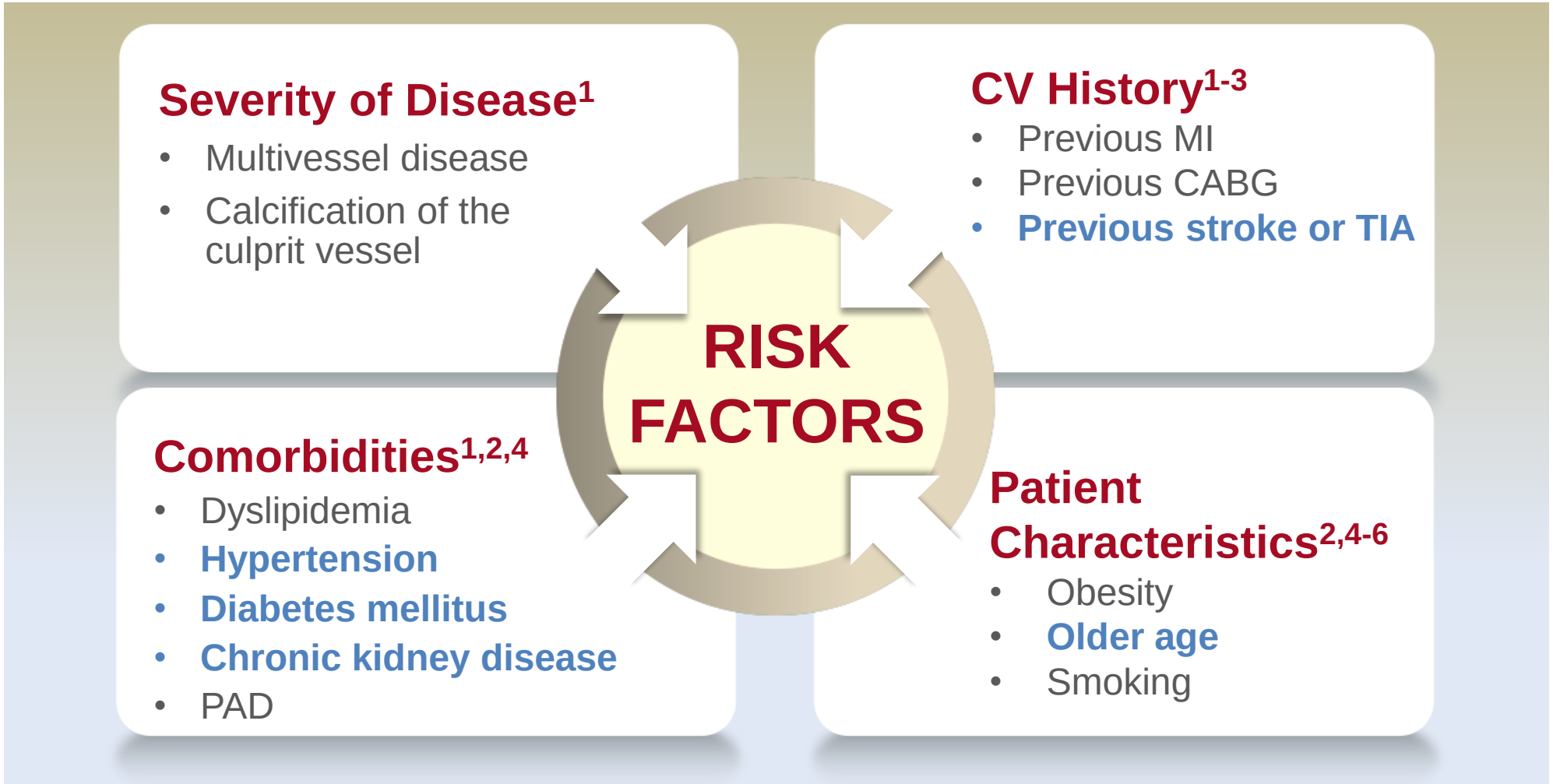
For all relevant COIs I will adhere to clinical recommendations which are evidence-based and free of promotional messaging or commercial bias. All investigational devices will be clearly labeled.

Global burden of CVD

- Cardiovascular diseases (CVDs) remain the leading cause of death globally.
- According to the World Health Organization (WHO) an estimated 17.9 million people died from CVDs in 2019
- CVD death represents 32% of all global deaths.
- Of these deaths, 85% were due to heart attack and stroke.

https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1

Factors associated with increased risk of recurrent CV events in CVD patients

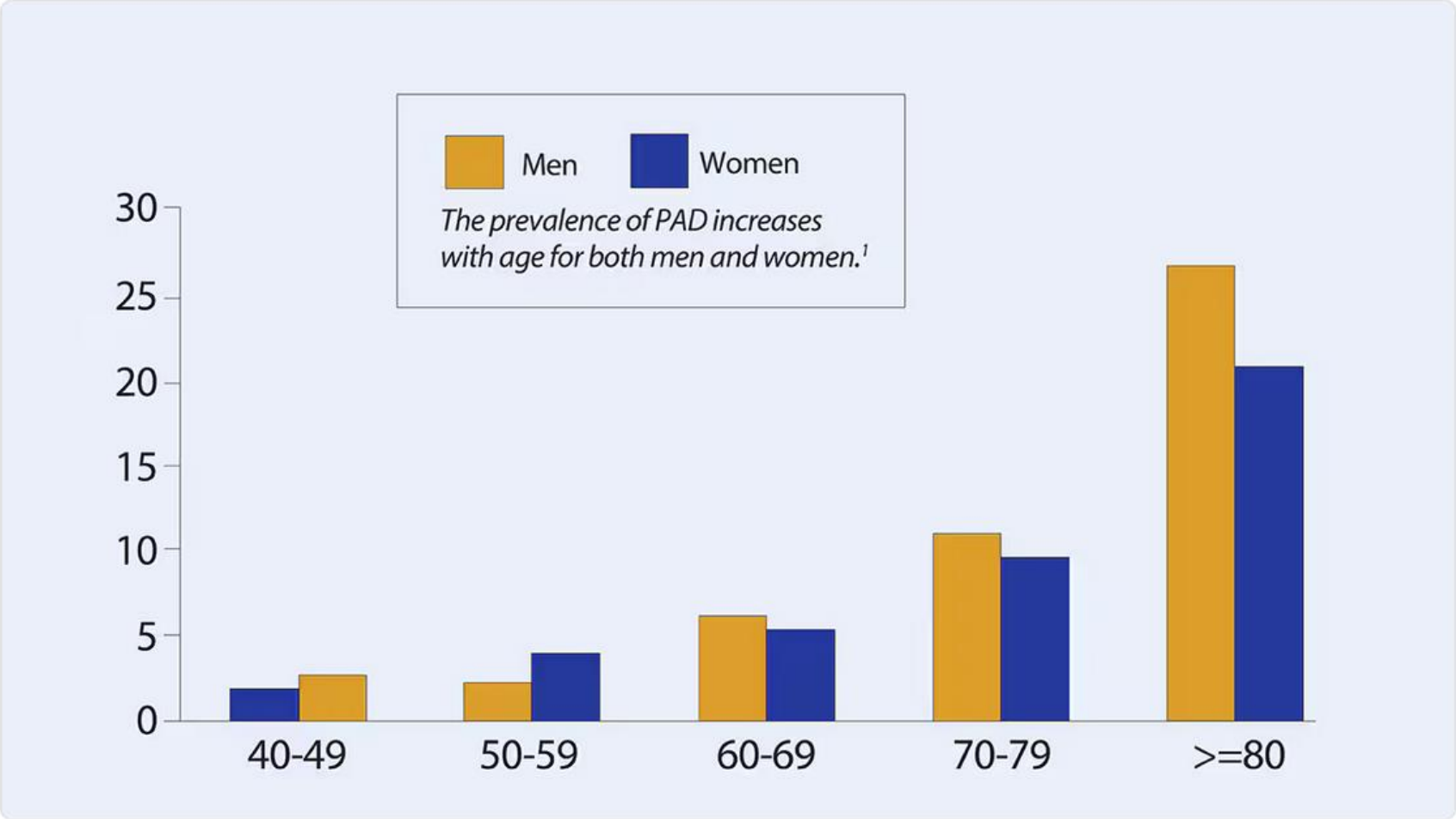


CABG=coronary artery bypass graft; PAD=peripheral artery disease; TIA=transient ischemic attack.

1. Kikkert WJ et al. *Am J Cardiol*. 2014;113:229-235. **2.** Nakatani D et al. *Circ J.* 2013;77:439-446. **3.** Ulvenstam A et al. *Stroke*. 2014;45:3263-3268. **4.** Thune JJ et al. *Eur J Heart Fail*. 2011;13:148-153. **5.** Leander K et al. *Cardiovasc Prev Rehabil*. 2007;14:532-537. **6.** Rea T et al. *Ann Intern Med.* 2002;137:494-500.

Epidemiology of atherosclerotic PAD

- **PAD affects 12-14% of the world's population.**
- **8+ million Americans** suffer from PAD.
- PAD affects **20% of patients over age 75.**
- **1/3 of diabetics over age 50** suffer from PAD.
- **Smoking increases the likelihood** of developing PAD by **400%.**
- PAD **prevalence is likely underestimated**

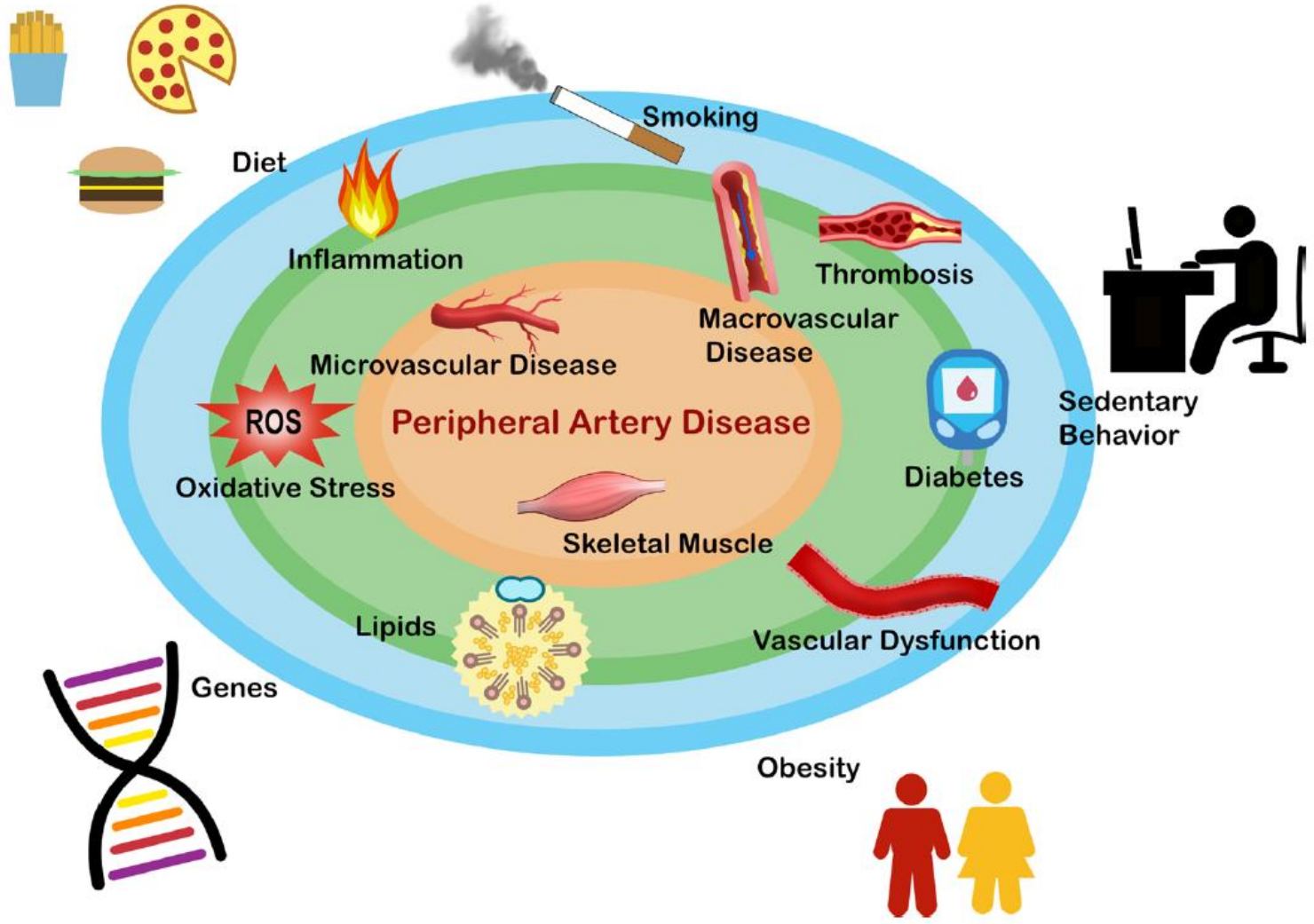


The prevalence of PAD increases with age for both men and women.

https://www.cdc.gov/heart-disease/about/peripheral-arterial-disease.html Accessed Sept 3, 2024.

Pathobiologic drivers and pathways in the development & progression of PAD

- PAD risk factors including **smoking, hypercholesterolemia, and diabetes, induce oxidative stress** that accelerates arterial damage and injury to skeletal muscle.
- **Inflammation with increased circulating biomarkers** relates to both incident disease and the rate of decline in walking distance in patients with PAD.
- **Chronic ischemia and inability to vasodilate to augment blood flow, together produces alterations in the leg skeletal muscle** that further limit walking ability.
- The **skeletal muscle myopathy of PAD is characterized by impaired oxygen metabolism, mitochondrial dysfunction, skeletal muscle fiber changes, and atrophy**



Bonaca MP, *et al.* *Circulation Research.* 2021;128:1868–1884. DOI: 10.1161/CIRCRESAHA.121.318258.

Association between major cardiovascular risk factors and various atherosclerotic diseases

Risk factor	
Smoking	PAD>CAD/stroke
Diabetes	PAD>CAD/stroke
Low-density lipoprotein cholesterol	PAD<CAD/stroke
Triglycerides	PAD>CAD/stroke
Hypertension	PAD=CAD/stroke*
Microvascular disease	PAD>CAD/stroke

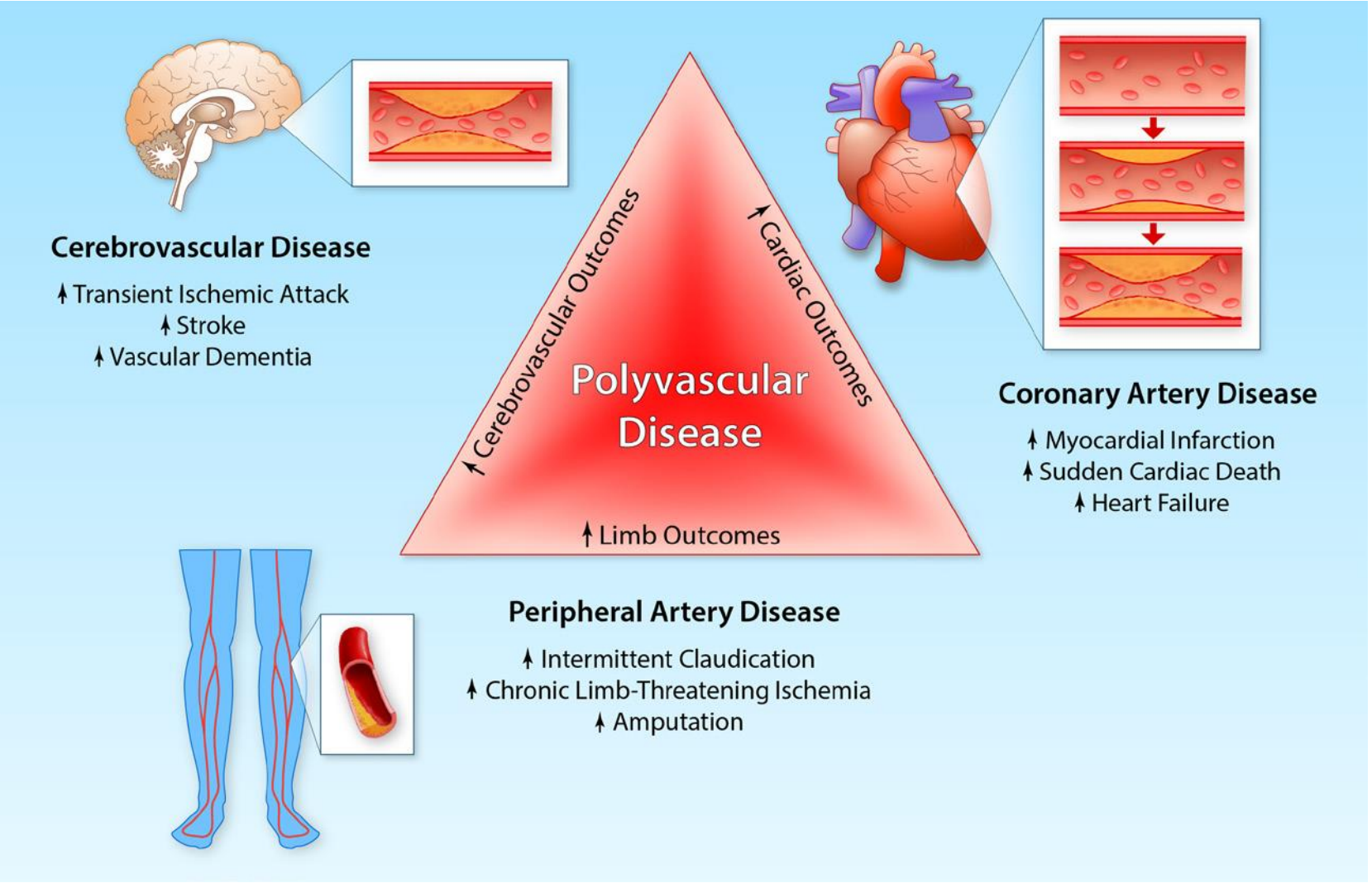
The table displays the magnitude of risk associated with each risk factor for the components of polyvascular disease. CAD indicates coronary artery disease; and PAD, peripheral artery disease.

*Data suggest the risk association may be strongest for stroke.

Aday AW, *et al. Circulation Research.* 2021;128:1818–1832. DOI: 10.1161/CIRCRESAHA.121.318535.

Cardiovascular risks of polyvascular disease

- Atherosclerotic disease in a given vascular bed is **directly linked to adverse outcomes in that same organ**.
- Because polyvascular disease is indicative of systemic atherosclerosis, **individuals with polyvascular disease are at heightened risk for cardiovascular events in all vascular territories**



Aday AW, *et al.* *Circulation Research.* 2021;128:1818–1832. DOI: 10.1161/CIRCRESAHA.121.318535.

Long-term "cross risks" in CVD

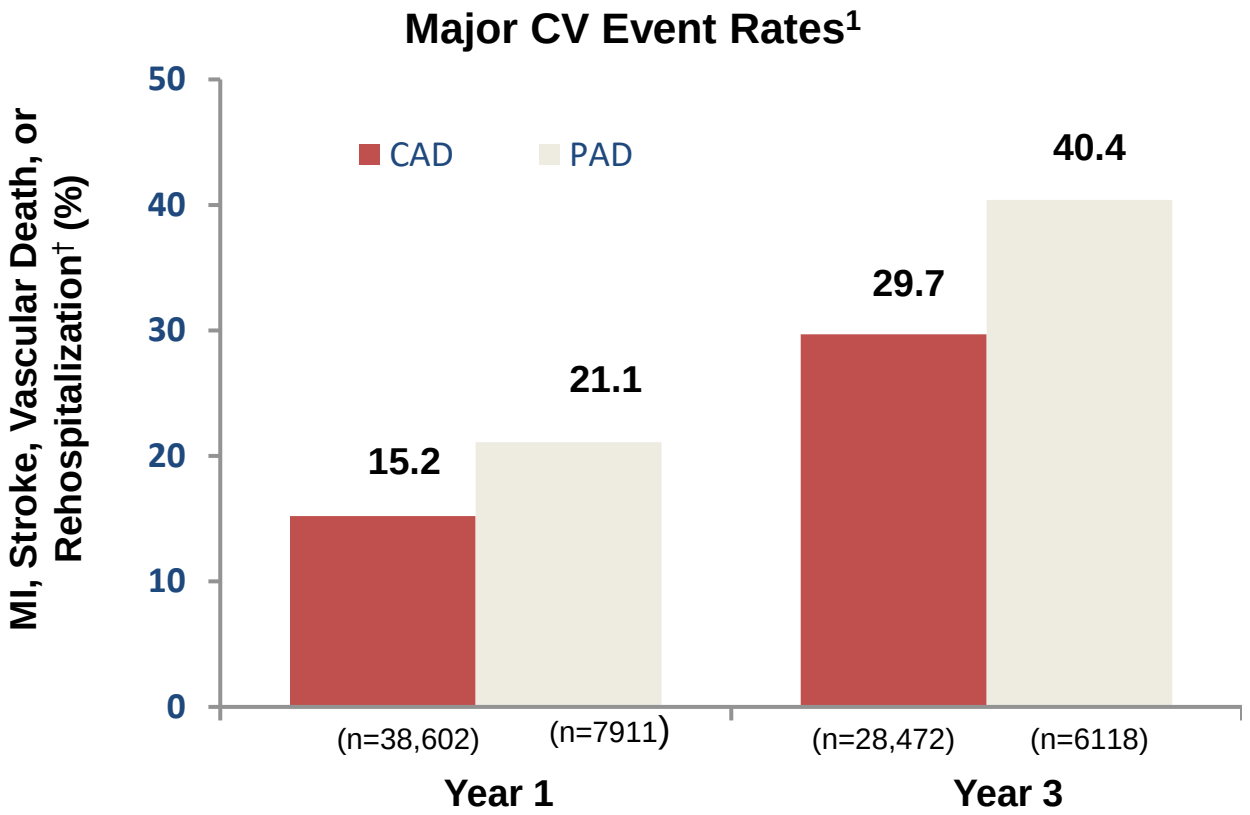
	Increased Risk of MI*	Increased Risk of Stroke*
Post-MI	**5-7 X greater risk**[1] (includes death)	**3-4 X greater risk**[2] (includes TIA)
PAD	**4 X greater risk**[4] (includes only fatal MI and other CHD death)	**2-3 X greater risk**[3] (includes TIA)

***Versus the general population.**

1. Adult Treatment Panel II. *Circulation*. 1994;89:1333-1435.
2. Kannel WB. *J Cardiovasc Risk.* 1994;1: 333-339.
3. Wilterdink JI, Easton JD. *Arch Neurol*. 1992;49:857-863.
4. Criqui MH et al. *N Engl J Med*. 1992; 326:381-386.

Long-term CV outcomes in patients with stable CAD or PAD

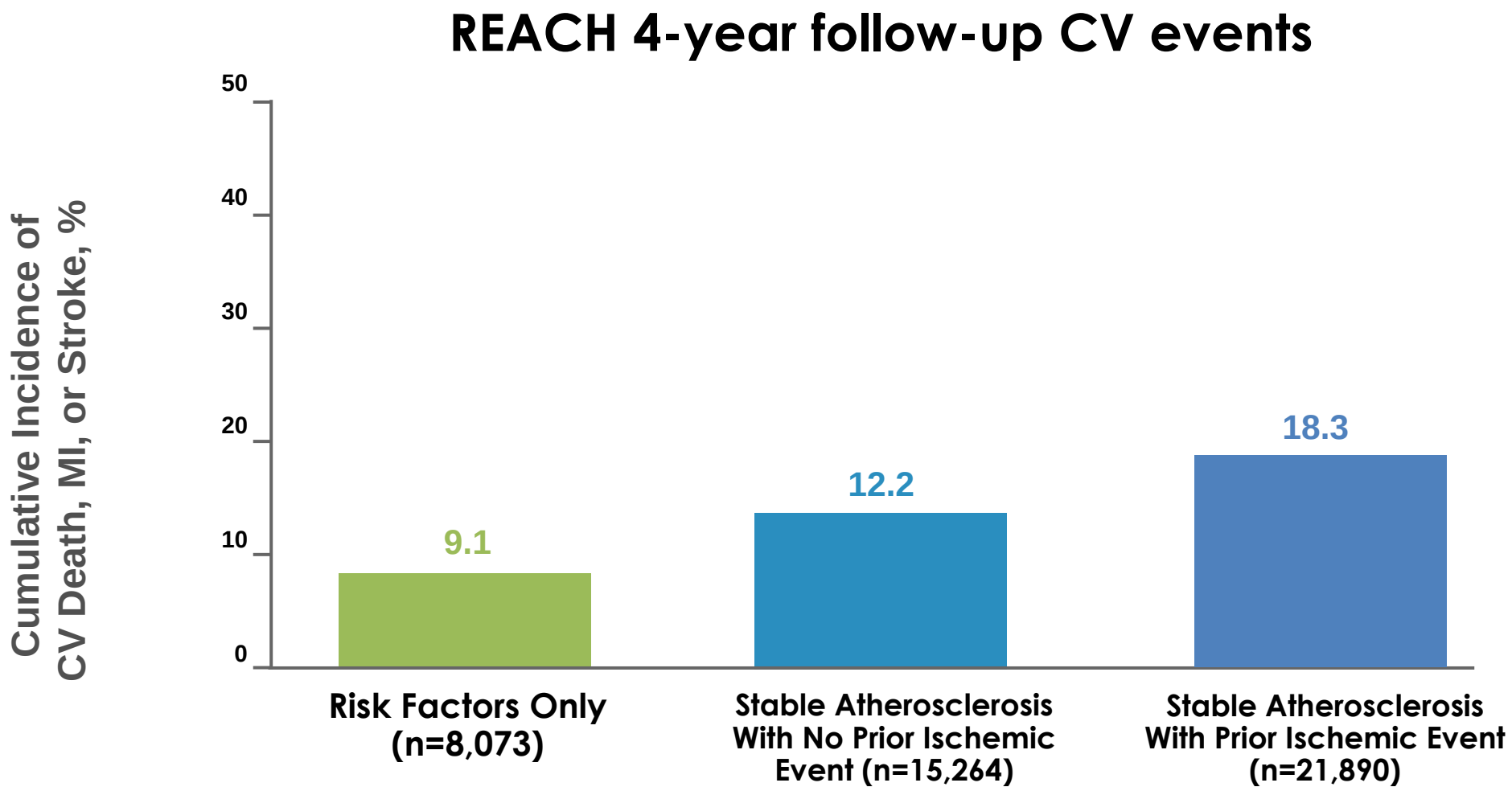
- **The REACH Registry:** Large, global observational registry of **~68,000 patients** (44 countries) who were **at high risk of atherothrombosis**
- Patients had **documented cerebrovascular disease, CAD or PAD, or ≥3 atherothrombotic risk factors**
- **Majority** of REACH Registry patients were on **guideline-directed medical therapies (GDMT)**



Major CV events (defined as MI, stroke, vascular death, or rehospitalization) in patients with symptomatic CAD/PAD eligible for 1-year (n=53,211) and 3-year (n=39,675) evaluations. †Rehospitalization for a vascular event other than MI, stroke, CV death (ie, congestive heart failure, unstable angina, vascular surgery, percutaneous coronary intervention).

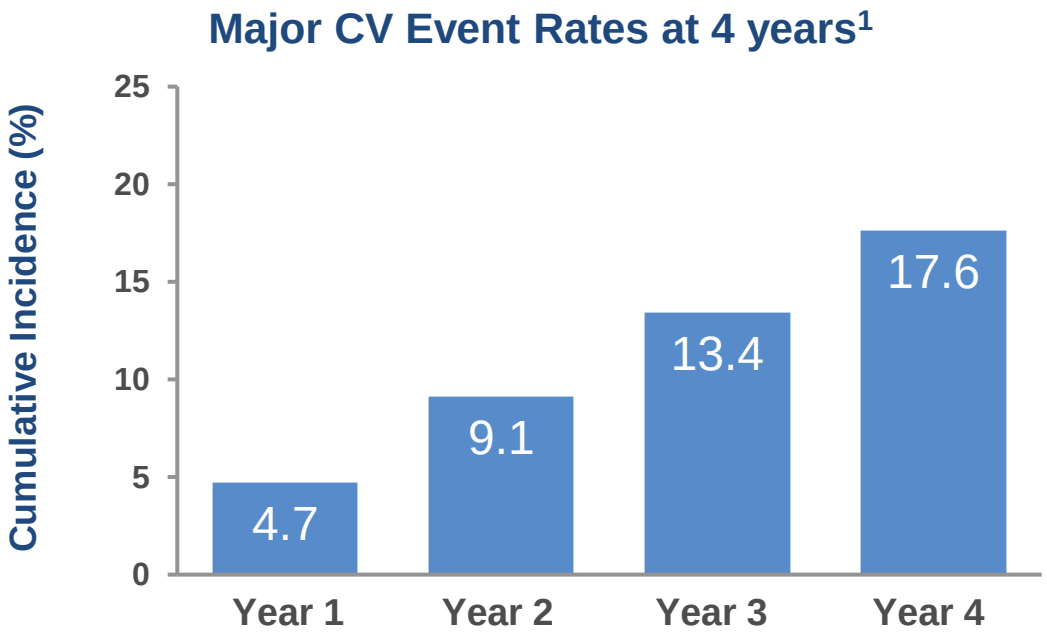
1. Alberts MJ, et al. *Eur Heart J.* 2009;30(19):2318-2326.
2. Gerhard-Herman MD, et al. *Circulation*. 2017;135(12):e726-e779.
3. Fihn SD, et al. *J Am Coll Cardiol*. 2012;60:e44-e164.

Long-term CV outcomes in patients with stable CAD



Bhatt DL et al. *JAMA*. 2010;304:1350-1357.

In patients with PAD*, major CV event† rates nearly quadrupled and limb events‡ persisted

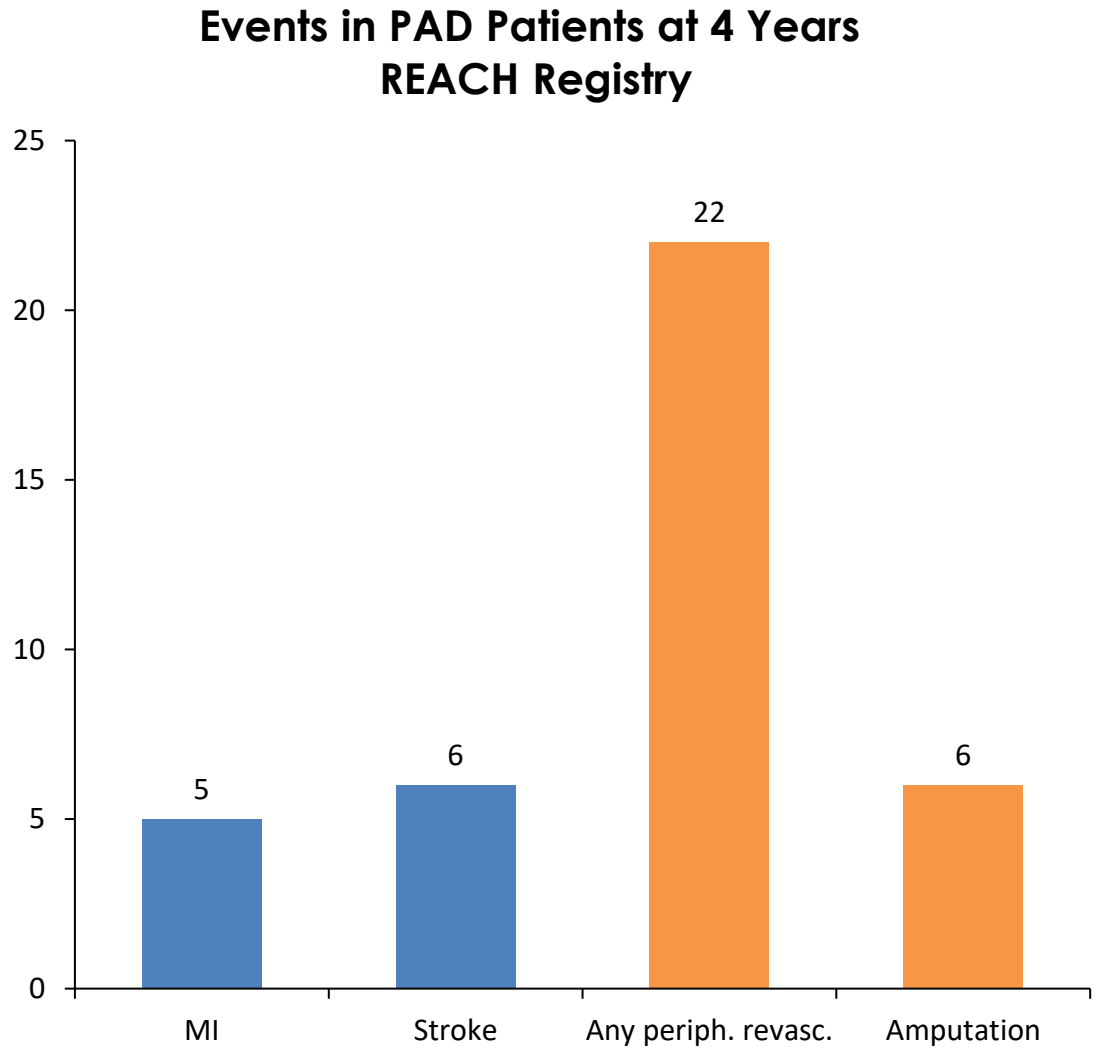


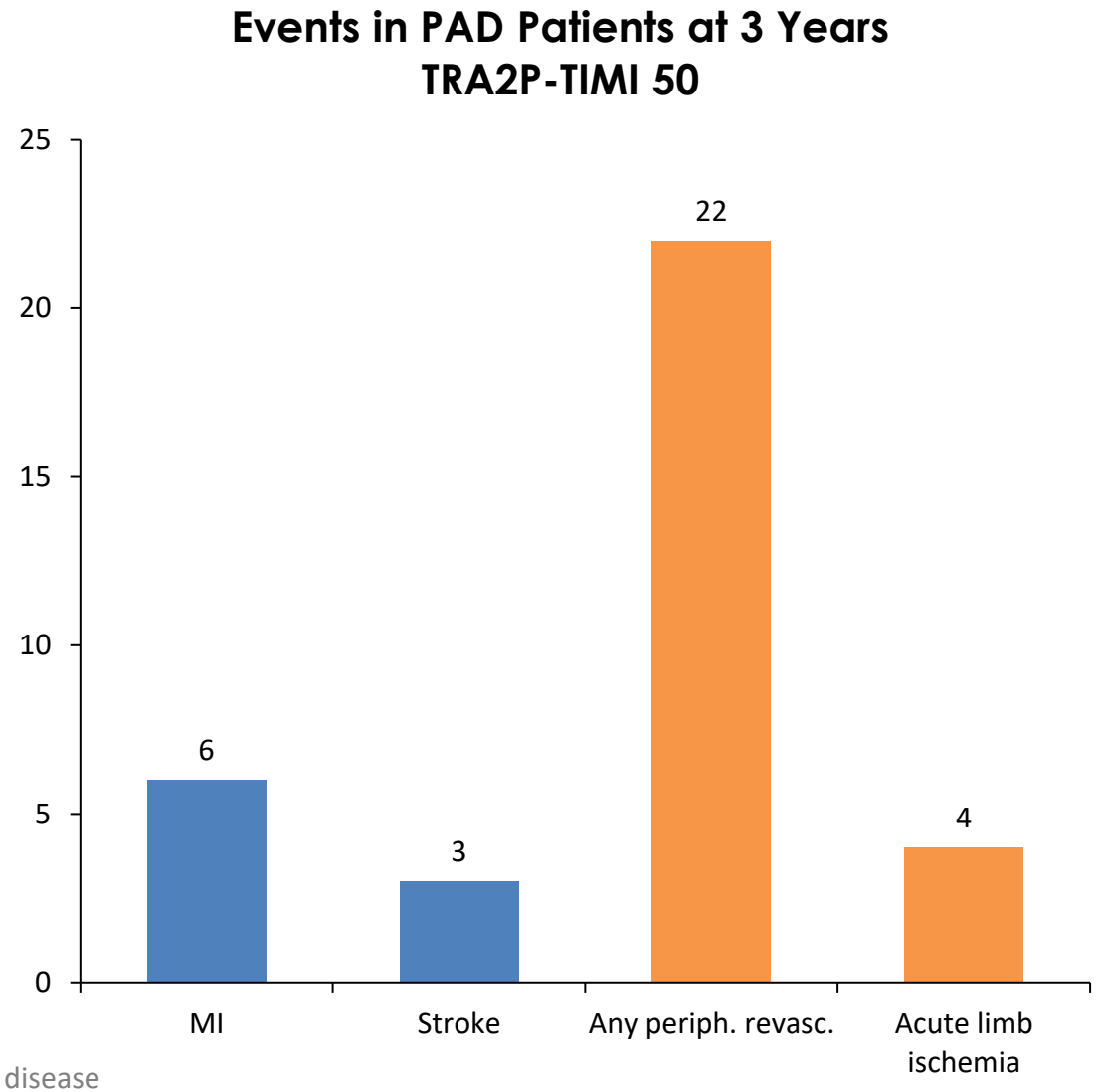
Majority of REACH Registry patients with symptomatic PAD, enrolled between 2003-2004, were on standard medications[1,2]

* Patients with symptomatic PAD, post-MI, and no history of stroke or TIA.
† Major CV events defined as CV death, MI, or stroke for post-MI patients.
‡ Limb events defined as the composite of lower limb amputation, peripheral bypass graft, and percutaneous intervention for PAD.

1. Abtan J, et al. *Clin Cardiol.* 2017;40:710-718. **2.** Gerhard-Herman MD, et al. *Circulation*. 2017;135(12):e726-e779.

Outcomes in patients with symptomatic PAD

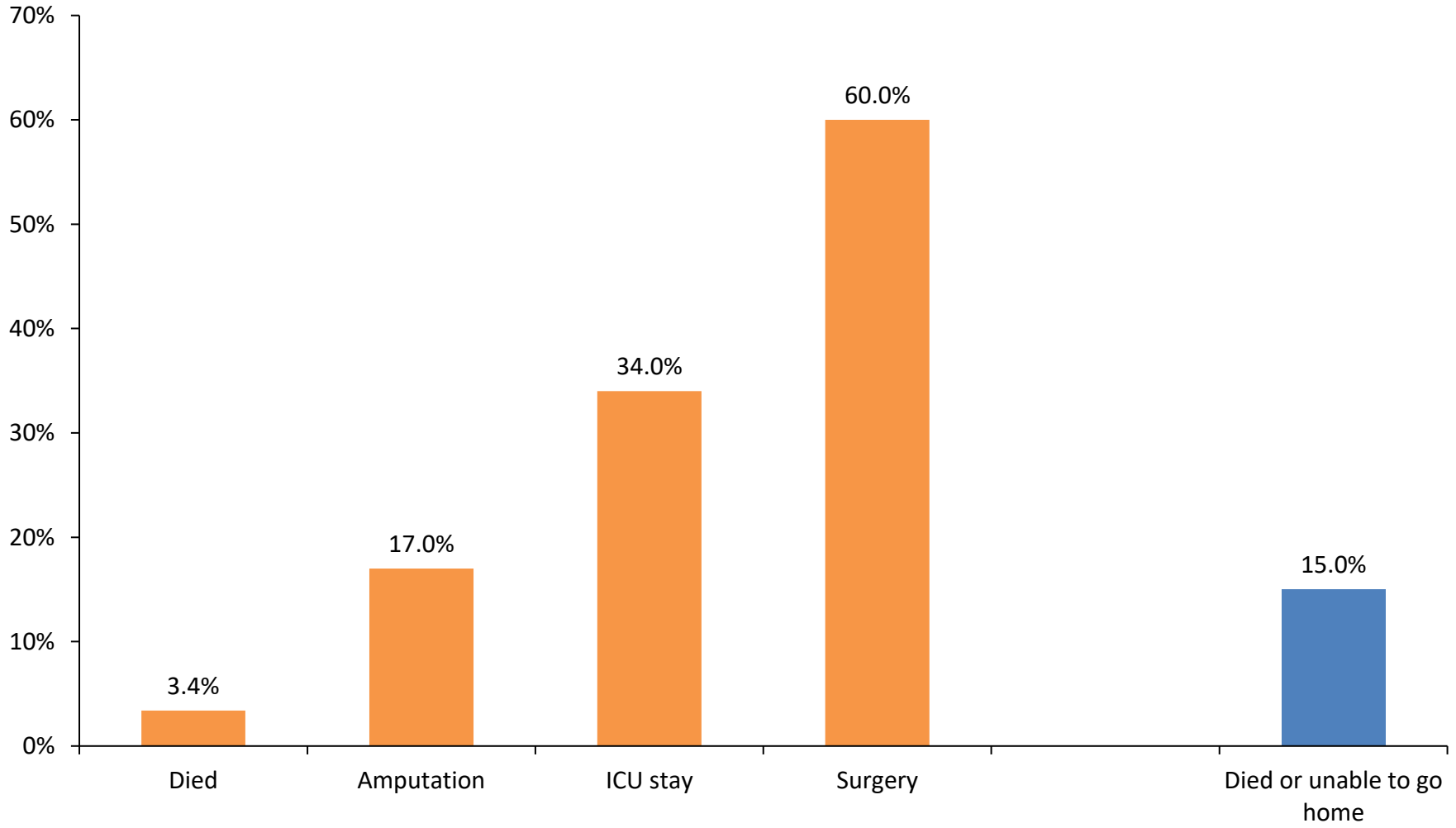




TIMI = thrombolysis in myocardial infarction; MI = myocardial infarction; PAD = peripheral artery disease

Adapted from Kumbhani DJ et al. *Eur Heart J.* 2014;35(41):2864-72.
Bonaca MP et al. *Circulation.* 2013;127(14):1522-9.

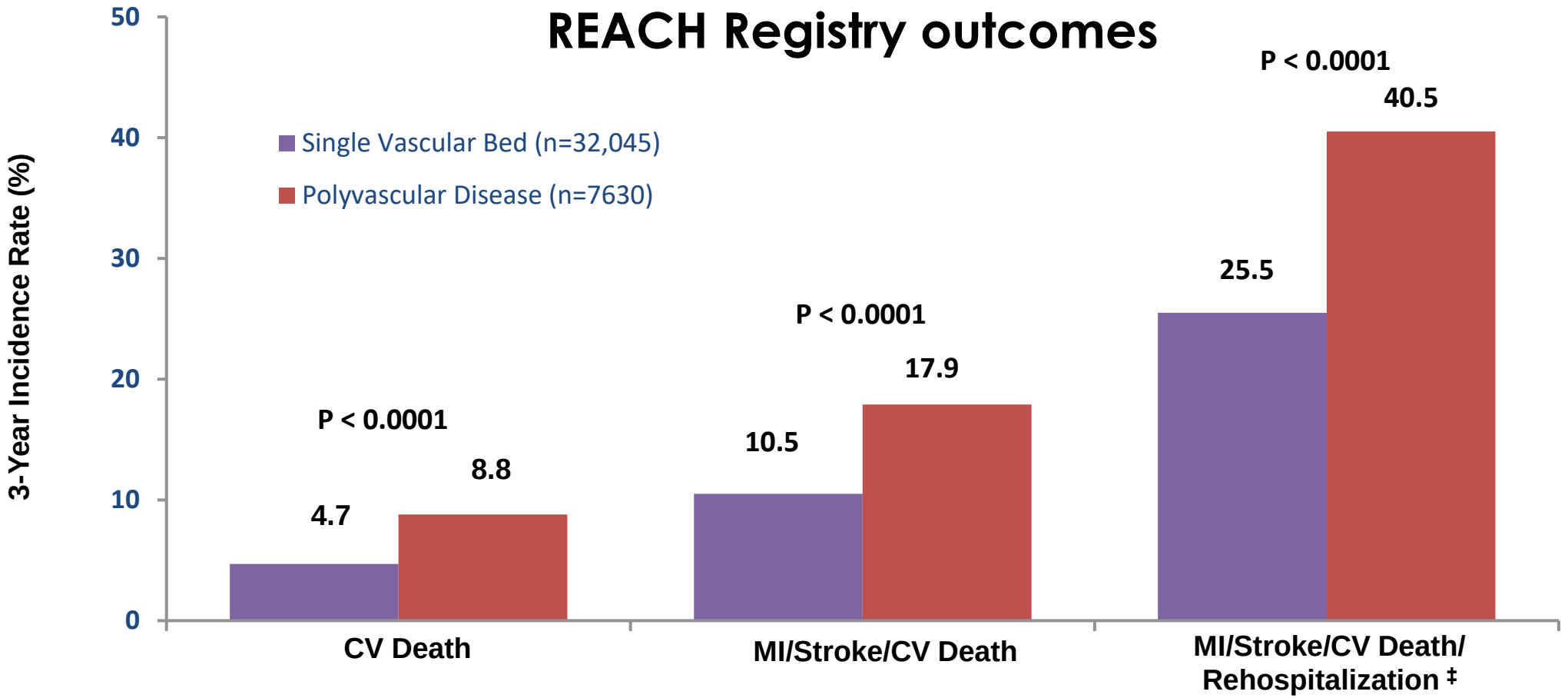
Outcomes in patients with acute limb ischemia (ALI)



ICU = intensive care unit

Adapted from Bonaca MP et al. *Circulation.* 2013;127(14):1522-9.

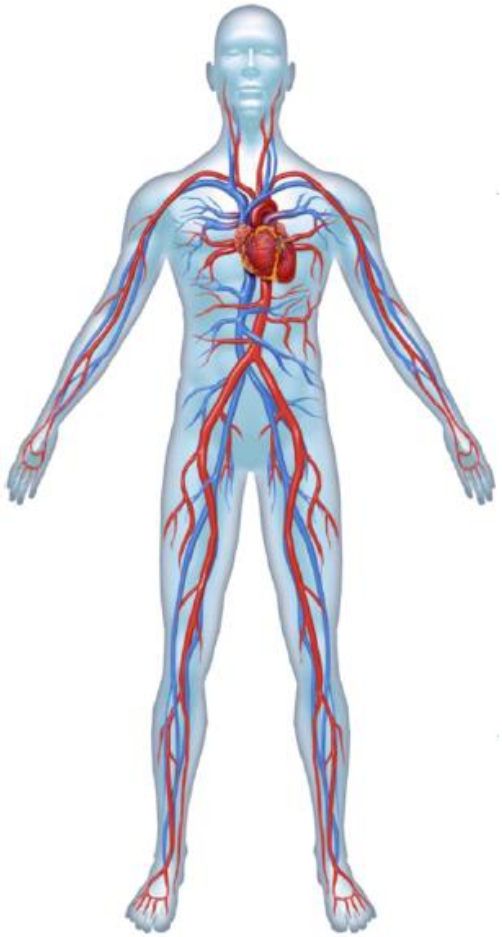
Long-term CV outcomes in patients with polyvascular atherosclerotic disease



*Baseline values from patients with atherosclerotic disease and eligible for 3-year follow-up (n=39,675).
†Polyvascular disease was defined as coexistent symptomatic (clinically recognized) arterial disease in 2 or 3 territories (coronary, cerebral, and/or peripheral) within each patient.[2]
‡Rehospitalization for a vascular event other than MI, stroke, CV death (ie, congestive heart failure, unstable angina, vascular surgery, percutaneous coronary intervention).

1. Alberts MJ, et al. *Eur Heart J.* 2009;30(19):2318-2326.
2. Bhatt DL, et al. *JAMA*. 2006;295:180-189.

Pharmacotherapies for reduction in the risk of MACE patients with PAD



Therapies for all Patients

- **Lifestyle Modification & Exercise**
- **Tobacco Cessation Therapies (behavioral and pharmacologic)**
- **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 (n.b. amputation benefit) , SGLT2 inhibitors**

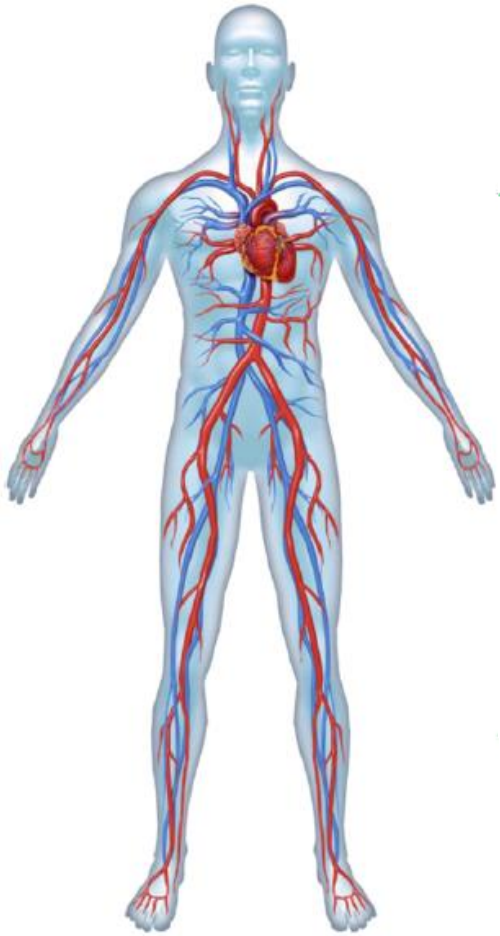
Prior MI or CAD (Polyvascular Disease) and low bleeding risk

- **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**

Major adverse cardiovascular events (MACEs) and major adverse limb events (MALE). ACEi indicates angiotensin-converting enzyme inhibitor; GLP-1, glucagon-like protein-1; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and SGLT2, sodium-glucose transporter 2 inhibitor.

Modified from Bonaca MP, *et al.* *Circulation Research.* 2021;128:1868–1884. DOI: 10.1161/CIRCRESAHA.121.318258.

Pharmacotherapies for reduction in the risk of MALE patients with PAD



Therapies for MALE Reduction in all Patients

- LDL-C / Lp(a) 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 – *(only option shown efficacious in the immediate post-revascularization setting)*
- ASA + ticagrelor 60 mg BID (prior MI or other need for DAPT) – chronic PAD
- ASA and/or clopidogrel with vorapaxar – chronic PAD

Therapies for Claudication

Symptomatic Patients

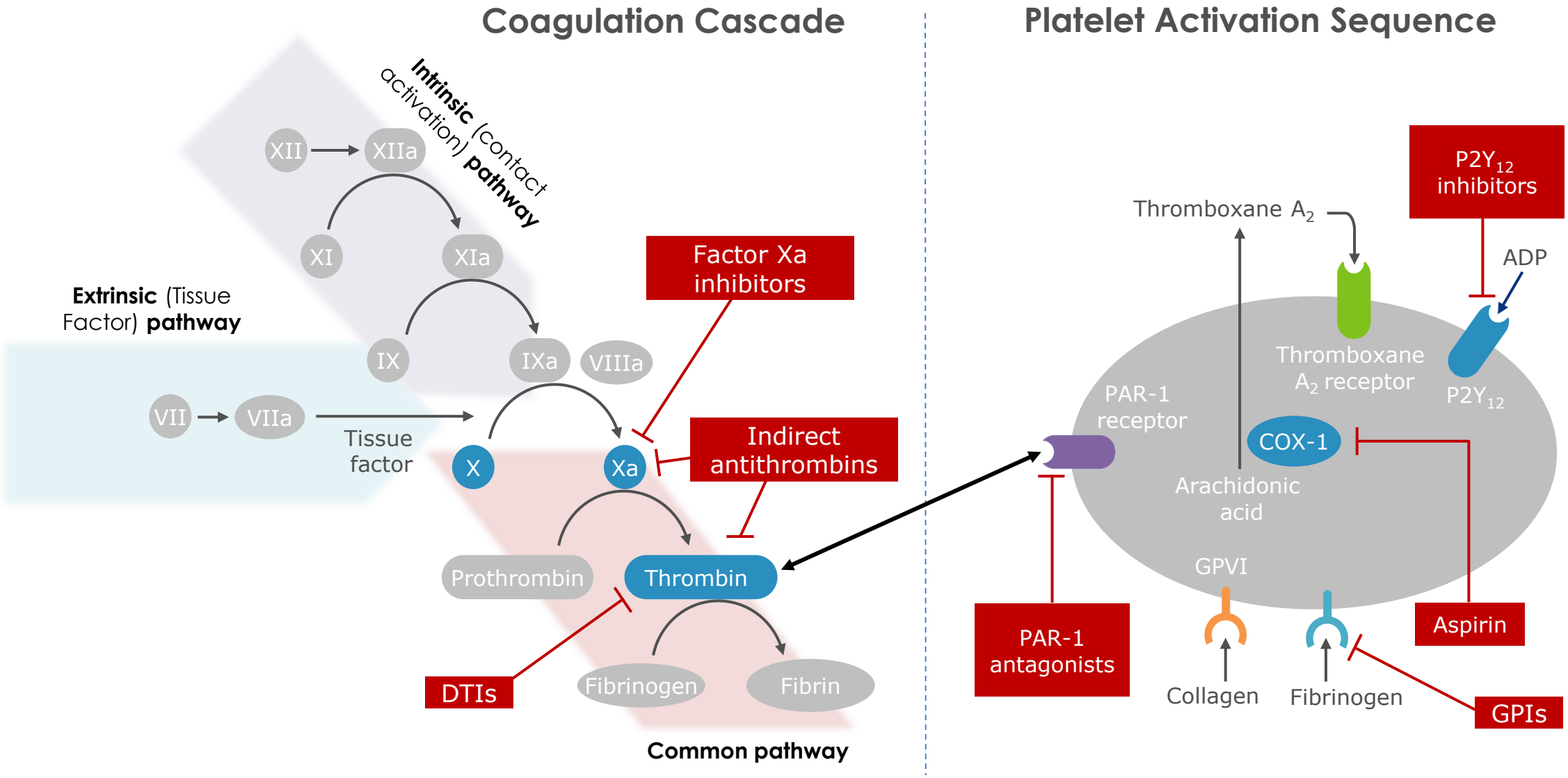
- Cilostazol 100 mg BID

Major adverse cardiovascular events (MACEs) and major adverse limb events (MALE). ACEi indicates angiotensin-converting enzyme inhibitor; GLP-1, glucagon-like protein-1; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and SGLT2, sodium-glucose transporter 2 inhibitor.

Modified from Bonaca MP, *et al.* *Circulation Research.* 2021;128:1868–1884. DOI: 10.1161/CIRCRESAHA.121.318258.

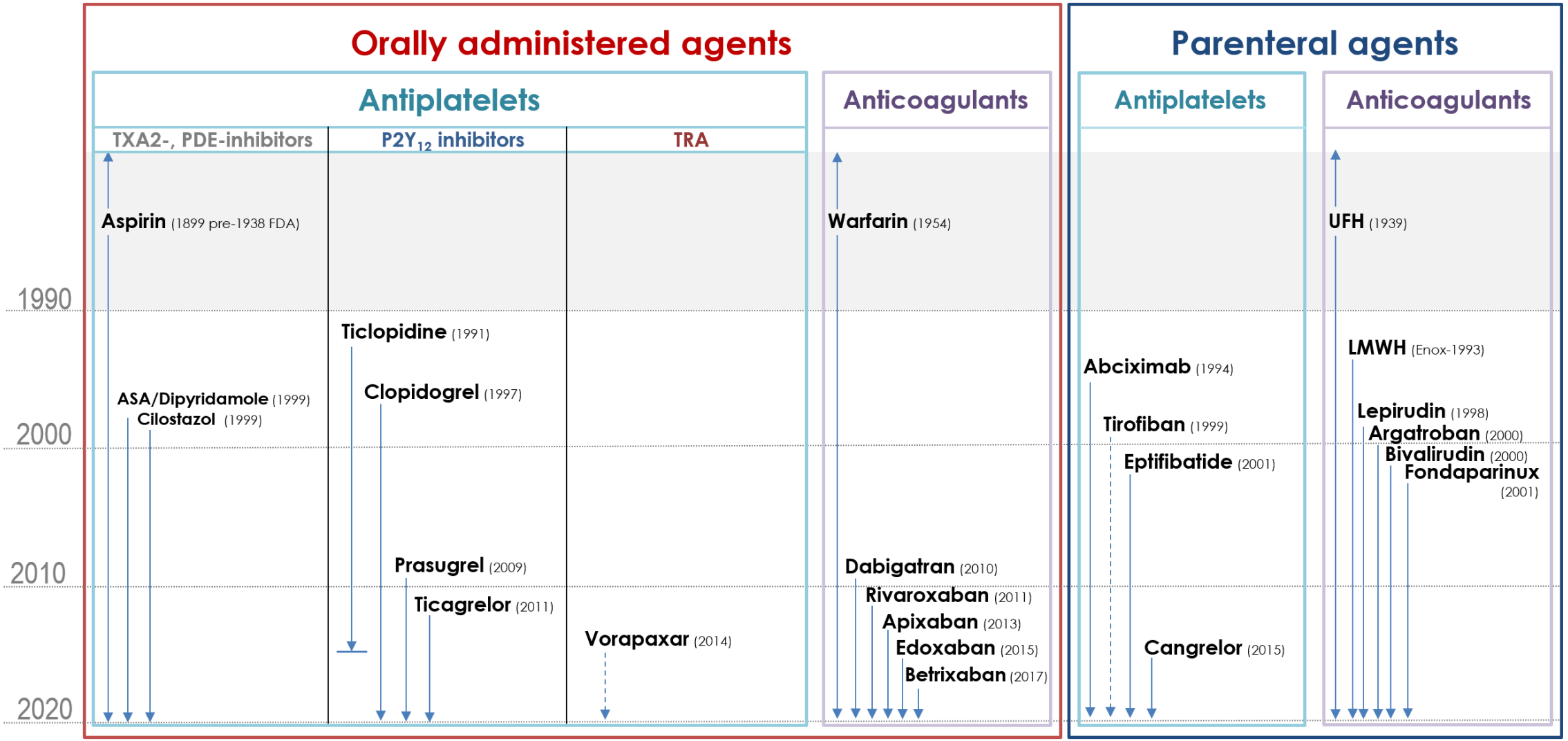
The coagulation and platelet cascades in CVD

Potential targets for antiplatelet & anticoagulant therapies

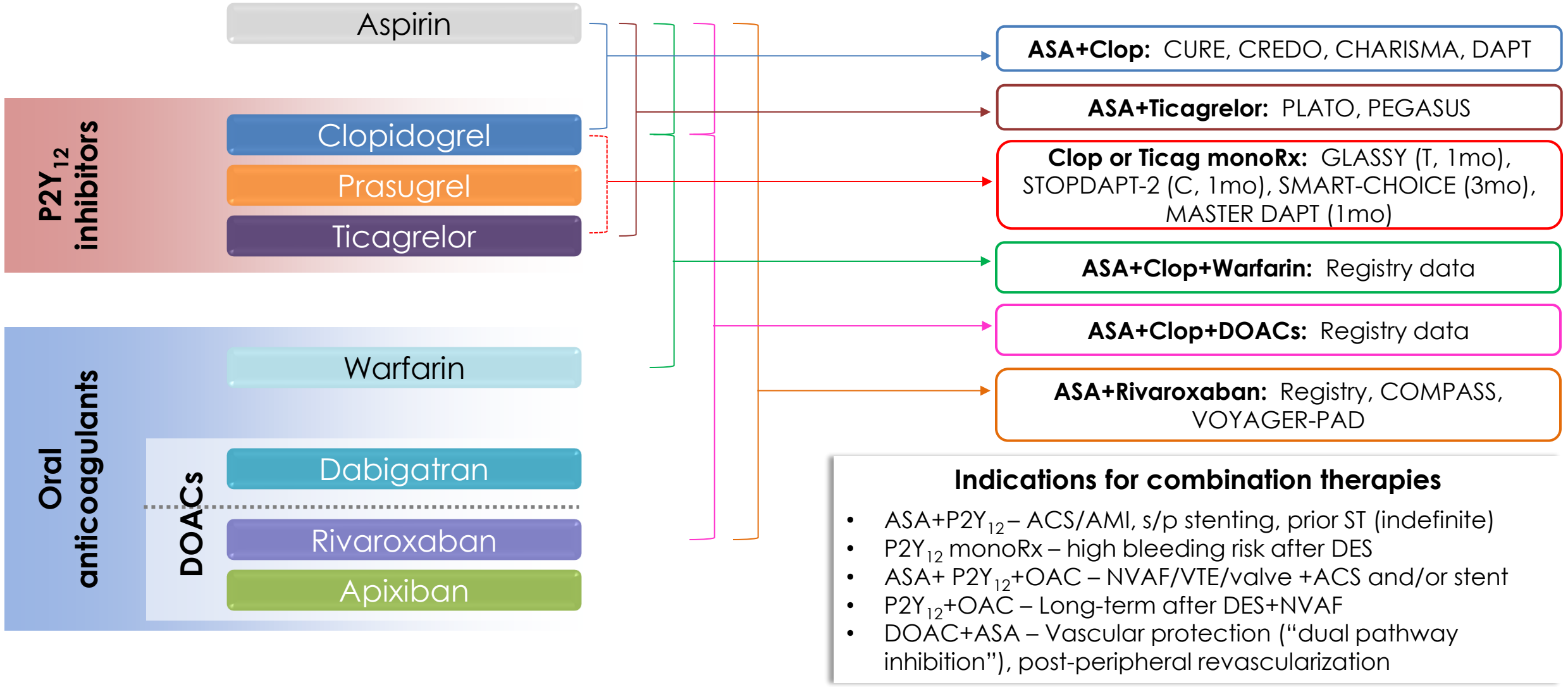


Modified from Angiolillo DJ, et al. *Circ Cardiovasc Interv*. 2016;9.e004395.

Landscape & historical timeline of FDA-approved antiplatelet and anticoagulant therapies



Common combinations of oral antiplatelet and anticoagulant therapies



Indications for combination therapies

- ASA+$P2Y_{12}$ – ACS/AMI, s/p stenting, prior ST (indefinite)
- $P2Y_{12}$ monoRx – high bleeding risk after DES
- ASA+ $P2Y_{12}$+OAC – NVAF/VTE/valve +ACS and/or stent
- $P2Y_{12}$+OAC – Long-term after DES+NVAF
- DOAC+ASA – Vascular protection ("dual pathway inhibition"), post-peripheral revascularization

Historical studies of oral antiplatelet and anticoagulant therapies in PAD

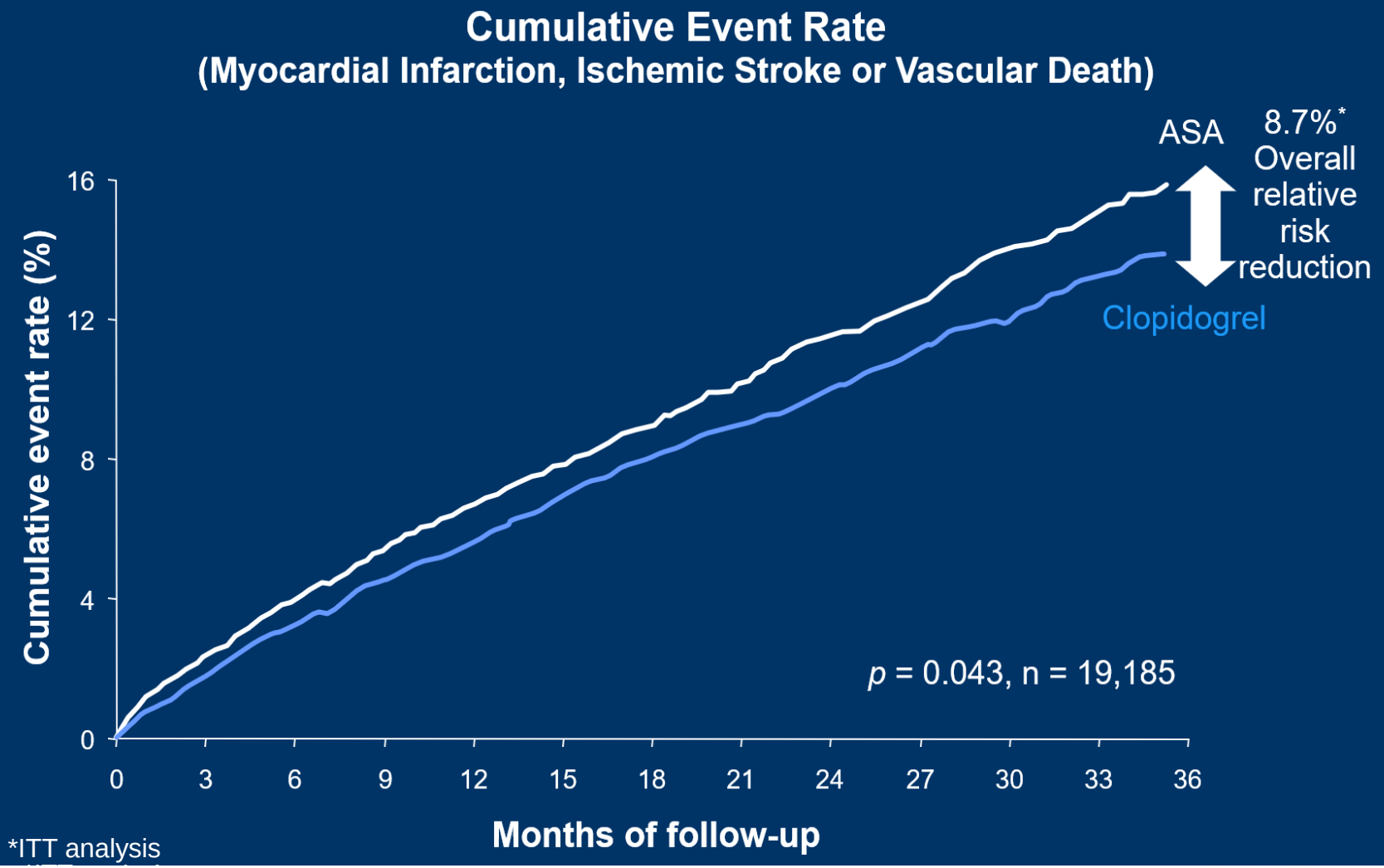
Regimen Comparison	Medications	Study	Population Size	Primary Efficacy Results	Primary Bleeding Results
Monotherapy vs Placebo	Aspirin vs Placebo	**Meta-analysis**[1]	87,654	Rate of nonfatal MI, nonfatal stroke, or vascular death OR (95% CI): 0.79 (0.76-0.83); *P*<0.0001	Major bleed rate OR (95% CI): 1.87 (1.51-2.32); *P*<0.0001
Monotherapy vs Monotherapy	Clopidogrel vs Aspirin	**CAPRIE**[2]	19,185	Rate of ischemic stroke, MI, or vascular death RRR (95% CI): 8.7% (0.3-16.5); *P*=0.043	Did not specifically evaluate bleeding events
	Ticagrelor vs Clopidogrel	**EUCLID**[3]	13,885	Rate of MI, ischemic stroke, or CV death HR (95% CI): 1.02 (0.92-1.13); *P*=0.65	TIMI major bleed rate HR (95% CI): 1.10 (0.84-1.43); *P*=0.49
Dual or Triple Antiplatelet Therapy vs Monotherapy	Clopidogrel + Aspirin vs Aspirin	**CHARISMA**[4]	15,603	Rate of MI, stroke, or CV death RR (95% CI): 0.93 (0.83-1.05); *P*=0.22	GUSTO severe bleed rate RR (95% CI): 1.25 (0.97-1.61); *P*=0.09
	Vorapaxar + Aspirin and/or Clopidogrel vs Aspirin and/or Clopidogrel*	**TRA 2P—TIMI 50**[5]	26,449	Rate of CV death, MI, or stroke HR (95% CI): 0.87 (0.80-0.94); *P*<0.001	GUSTO moderate or severe bleed rate HR (95% CI): 1.66 (1.43-1.93); *P*<0.001
Anticoagulant Therapy + Aspirin vs Aspirin	Warfarin + Aspirin vs Aspirin	**WAVE**[6]	2161	Rate of MI, stroke, or CV death RR (95% CI): 0.92 (0.73-1.16); *P*=0.48	Life-threatening bleed rate RR (95% CI): 3.41 (1.84-6.35); *P*<0.001 Moderate bleed rate RR (95% CI): 2.82 (1.43-5.58); *P*=0.002

*94% and 62% of patients received aspirin and thienopyridine, respectively.

1. Lièvre M, Cucherat M. *Fundam Clin Pharmacol*. 2010;24(3):385-391.
2. CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-1339.
3. Hiatt WR et al. *N Engl J Med*. 2017;376(1):32-40.
4. Cacoub PP et al. *Eur Heart J*. 2009;30(2):192-201.
5. Morrow DA et al. *N Engl J Med*. 2012;366(15):1404-1413.
6. Warfarin Antiplatelet Vascular Evaluation Trial Investigators. *N Engl J Med*. 2007;357(3):217-227.

Clopidogrel vs. ASA in CAD/CVA/PAD: The CAPRIE trial

- 19,185 patients, with atherosclerotic vascular disease manifested as either recent ischemic CVA, recent MI or symptomatic PAD were randomized to ASA 325 mg daily or clopidogrel 75 mg daily
- There were >6,300 in each clinical subgroups.
- Primary efficacy endpoint was MI, CVA, CV death and mean follow-up was1.91 years.
- No major differences in safety between A & C



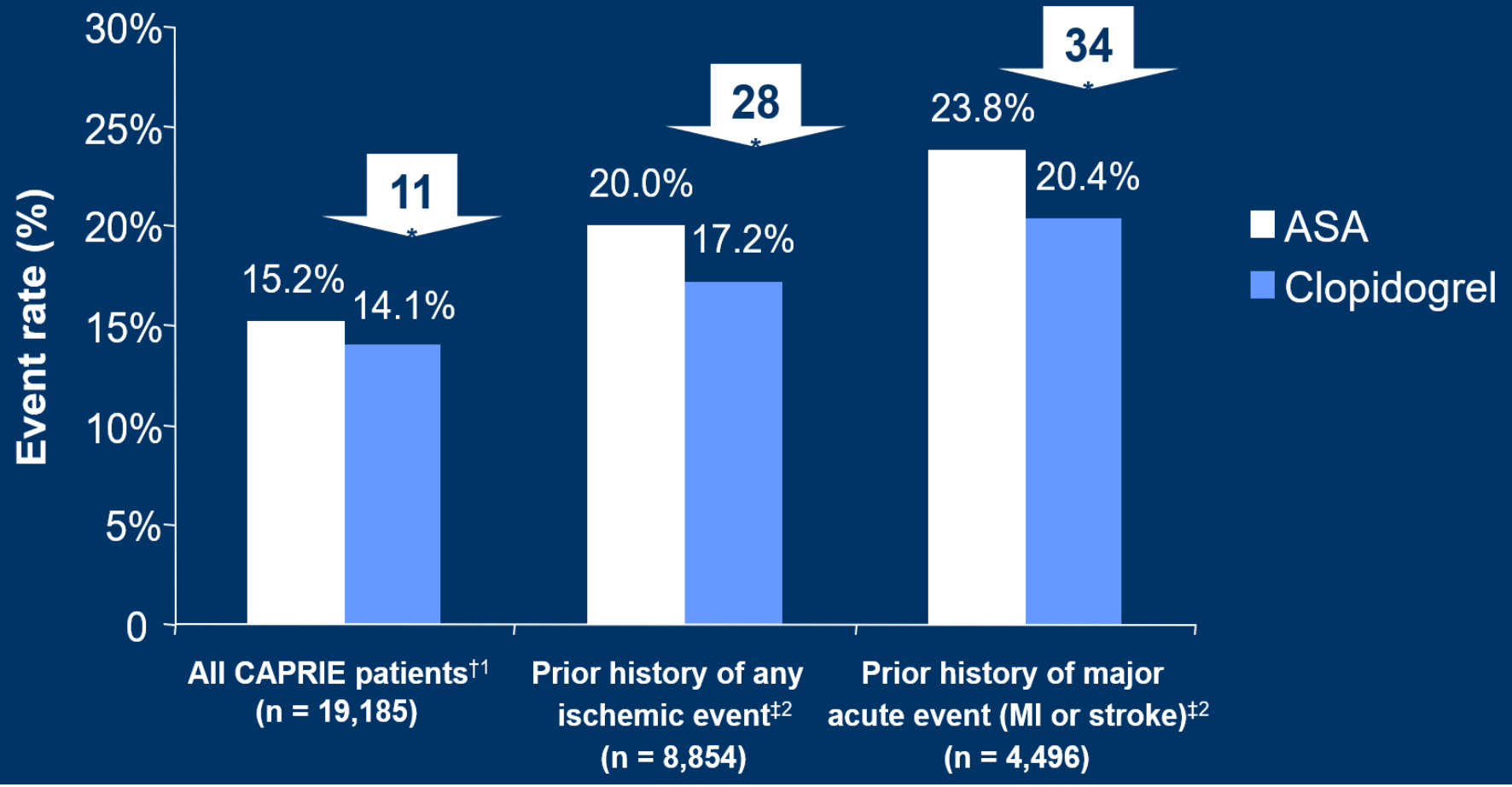
CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–39.

CAPRIE: Amplified benefit of clopidogrel in patients with higher vascular risk

* Number of events prevented/1,000 patients/year over ASA

† Cumulative proportion of patients experiencing event over 3 years (mean follow-up, 2 years)

‡ 3-year event rate

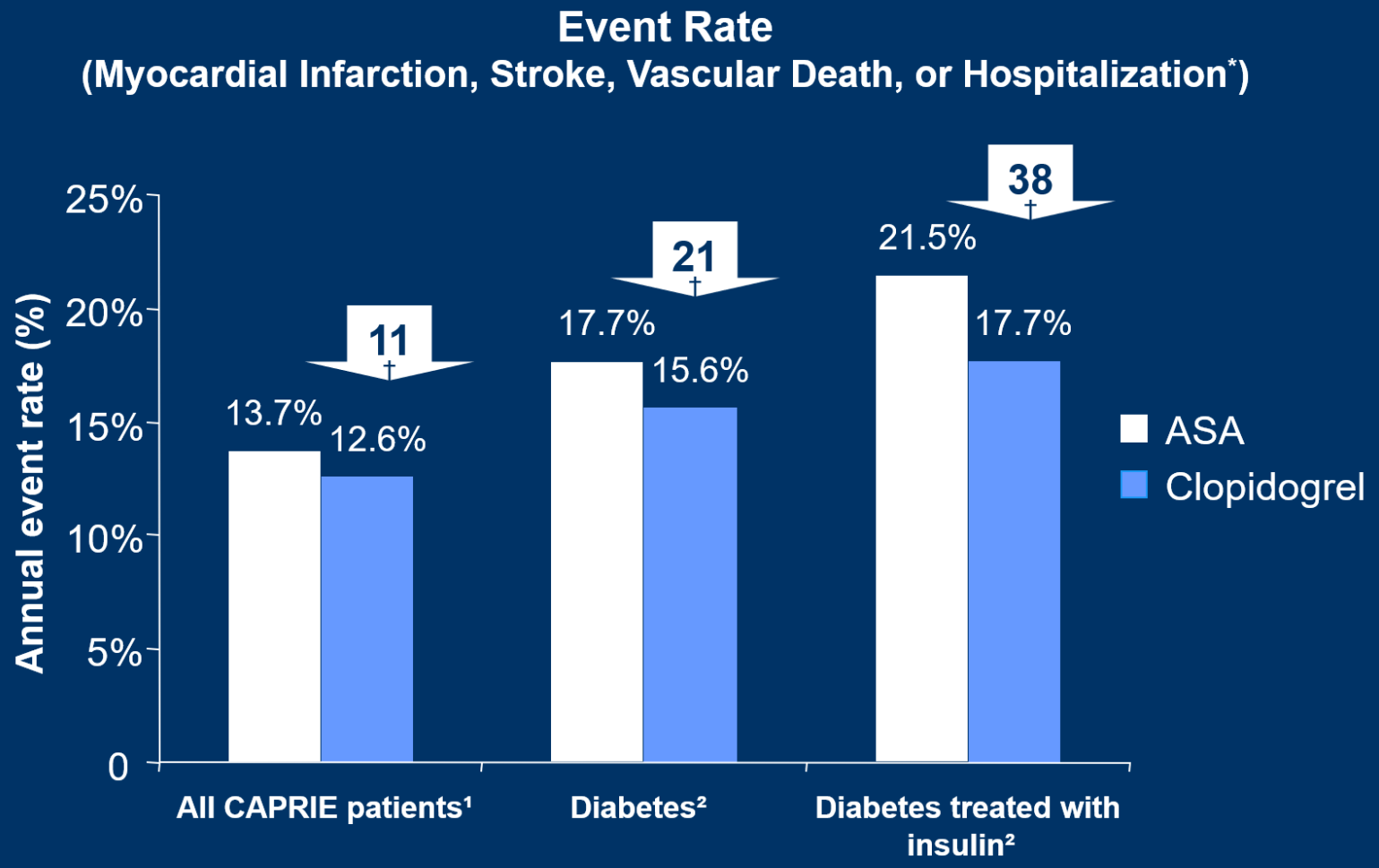


1. CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–39.
2. Jarvis B, Simpson K. *Drugs* 2000; 60: 347–77.

CAPRIE: Amplified benefit of clopidogrel in patients with diabetes mellitus

* For ischemic events or bleeding

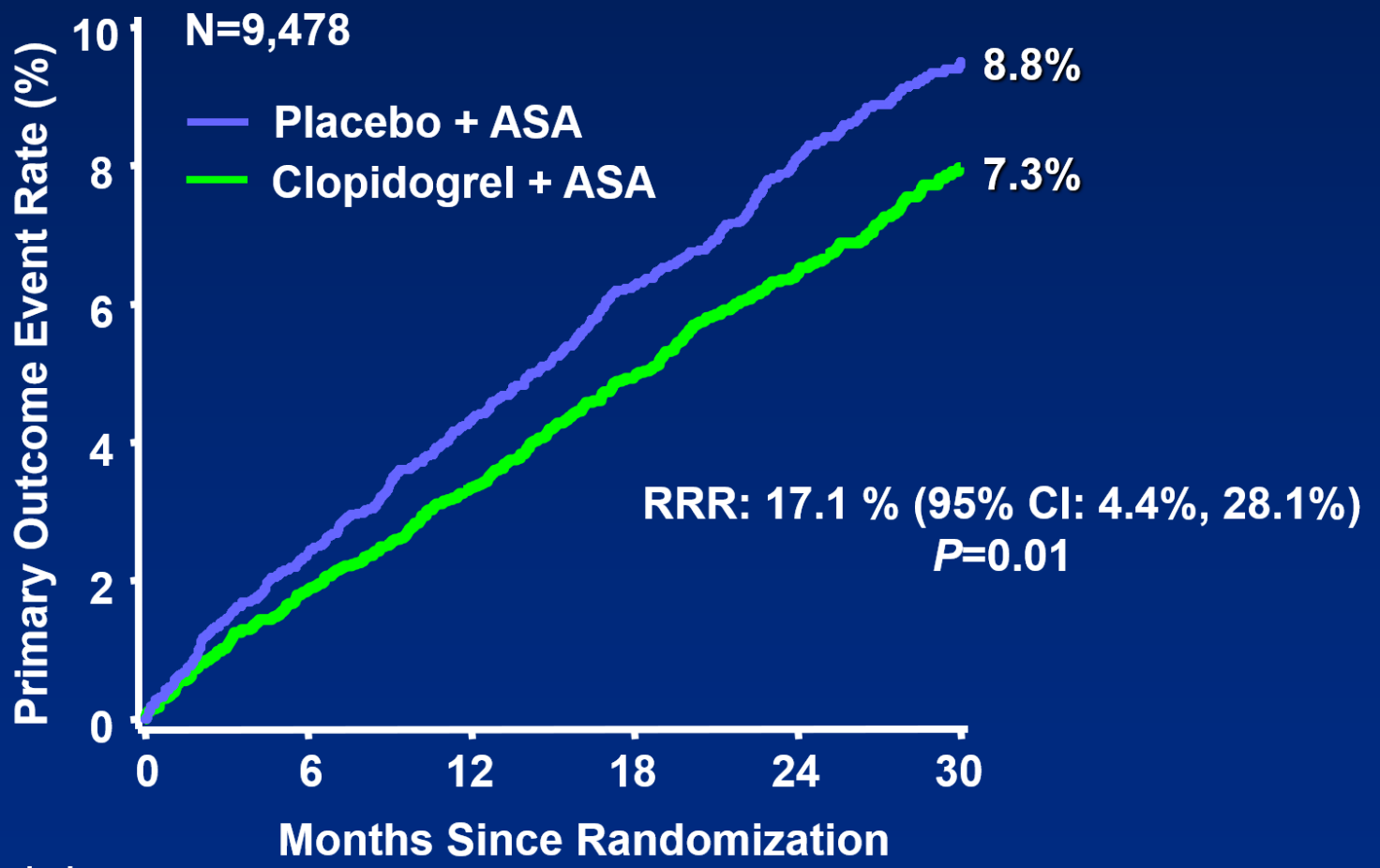
† Number of events prevented/1,000 patients/year over ASA



1. Bhatt DL *et al*. *Am Heart J* 2000; 140: 67–73.
2. Jarvis B, Simpson K. *Drugs* 2000; 60: 347–77.

CHARISMA: DAPT (C+A) vs ASA in a "CAPRIE-like cohort"

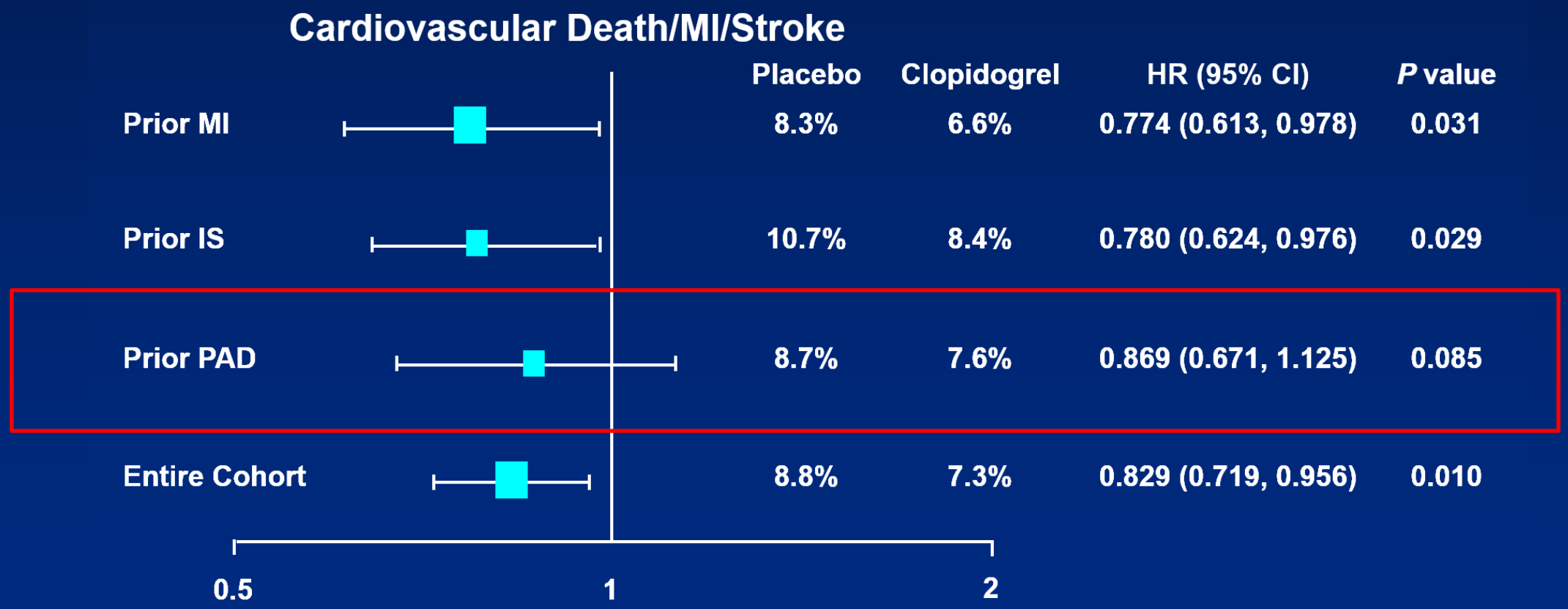
A post-hoc analysis of patients (n=9,478) with a previous MI, stroke, or PAD (similar to the entry criteria for the CAPRIE trial) showed a significant 17.1% RRR in favor of clopidogrel plus ASA over ASA alone



* Post hoc analysis.

Bhatt DL, Flather MD, Hacke W, et al. J Am Coll Cardiol. 2007;49:1982-1988.

CHARISMA: DAPT (C+A) vs ASA in a "CAPRIE-like cohort"

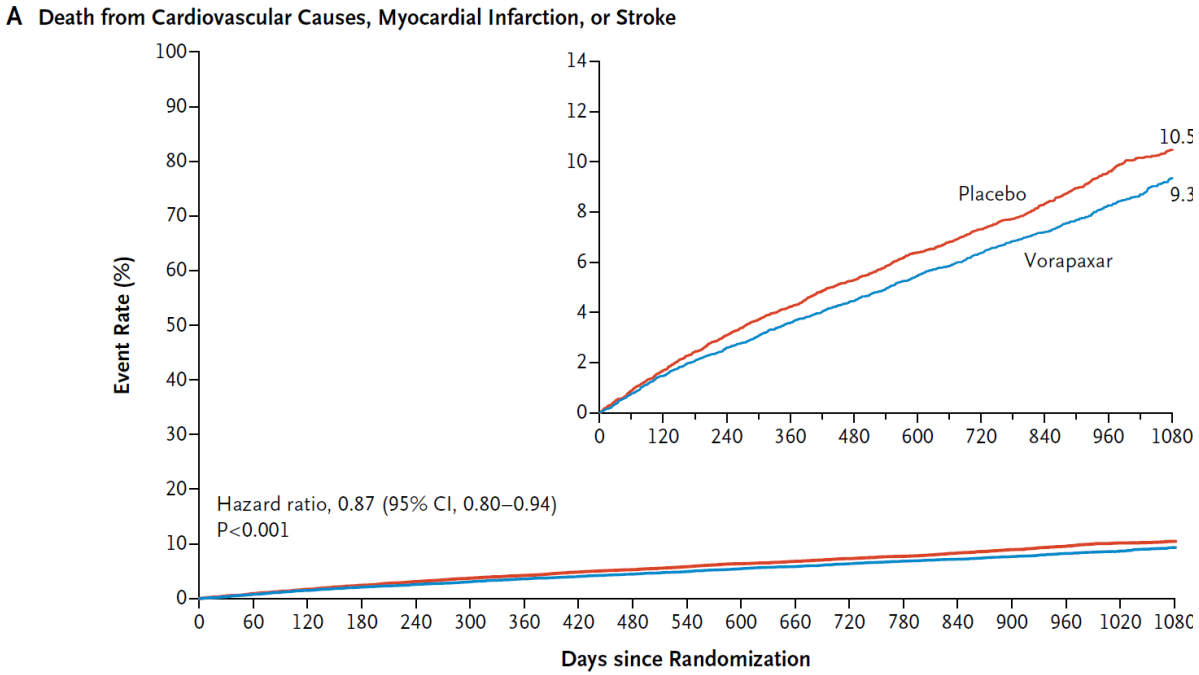


*Post hoc analysis.

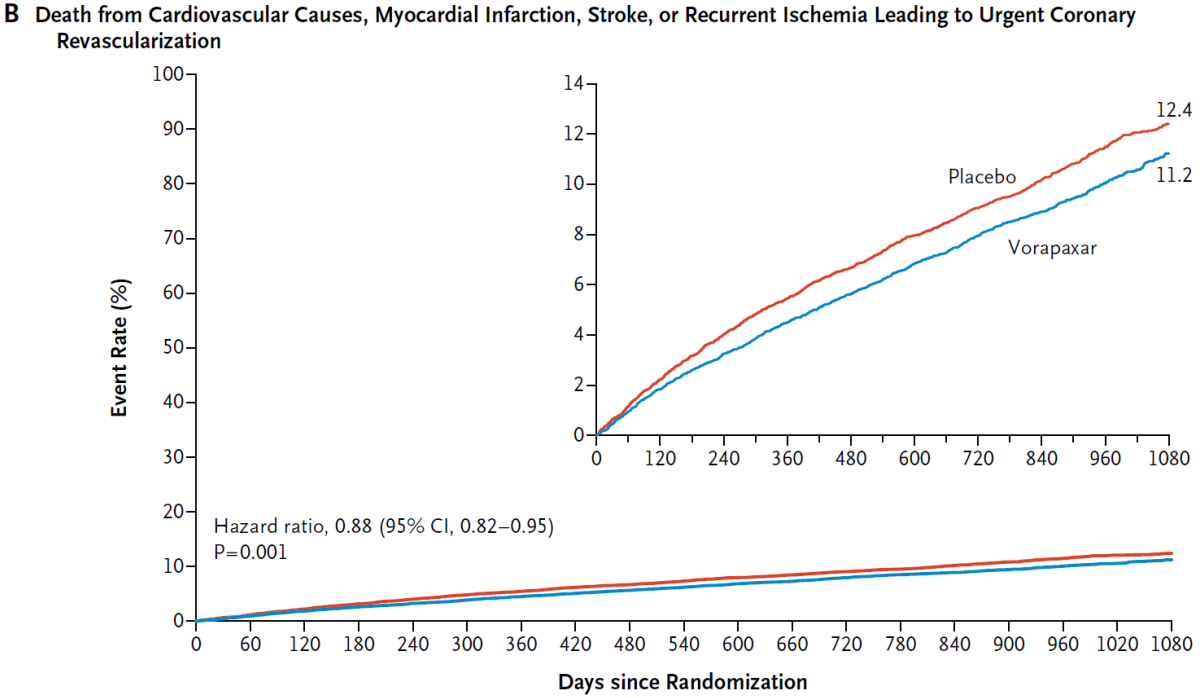
Bhatt DL, Flather MD, Hacke W, et al. J Am Coll Cardiol. 2007;49:1982-1988.

Vorapaxar vs. placebo (+ ASA ± clopidogrel)

Cardiovascular endpoints in TRA 2P-TIMI 50 study



No. at Risk						
Placebo	13,224	12,727	12,365	12,013	9,366	6,239
Vorapaxar	13,225	12,784	12,479	12,162	9,463	6,287



No. at Risk						
Placebo	13,224	12,631	12,207	11,824	9,180	6,104
Vorapaxar	13,225	12,720	12,364	12,003	9,295	6,147

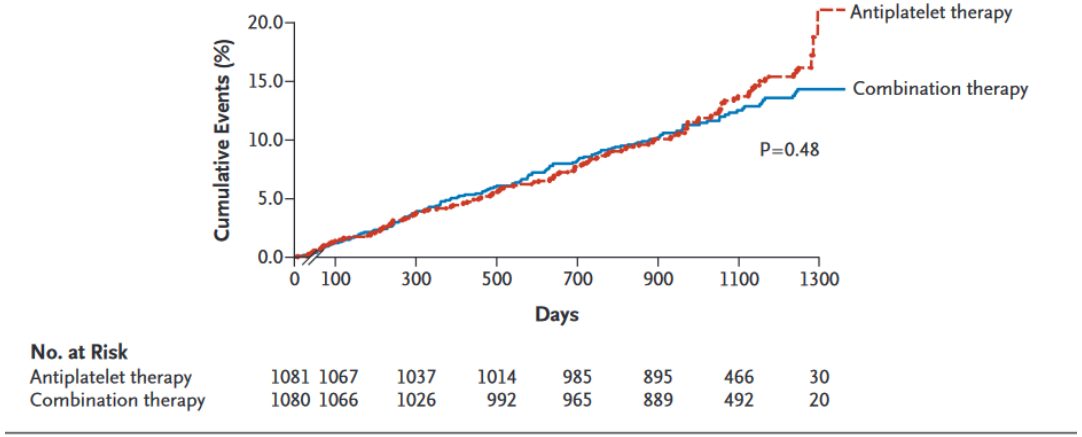
Inhibition of PAR-1 with vorapaxar reduced the risk of cardiovascular death or ischemic events in patients with stable atherosclerosis who were receiving standard therapy (90% of patients on aspirin, majority of patients also on a thienopyridine, <1% on prasugrel).

Morrow DA, et al. *N Engl J Med* 2012;366:1404-13.

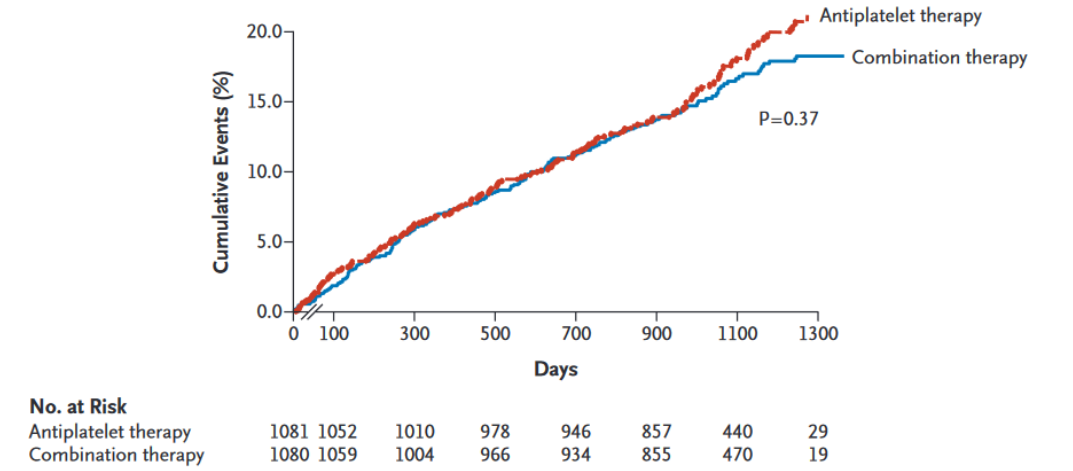
Oral anticoagulation (VKA) combined with antiplatelet therapy in PAD: The WAVE trial

2,161 patients PAD were randomly assigned to combination therapy with an antiplatelet agent and an oral anticoagulant agent (target international normalized ratio [INR], 2.0 to 3.0) or to antiplatelet therapy alone

Panel A shows the cumulative incidence of the first coprimary end point (myocardial infarction, stroke, or death from cardiovascular causes). **There was no significant difference in outcome between the group receiving combination therapy with an oral anticoagulant and an antiplatelet agent and the group receiving an antiplatelet agent alone** (relative risk, 0.92; 95% CI, 0.73 to 1.16; P = 0.48).

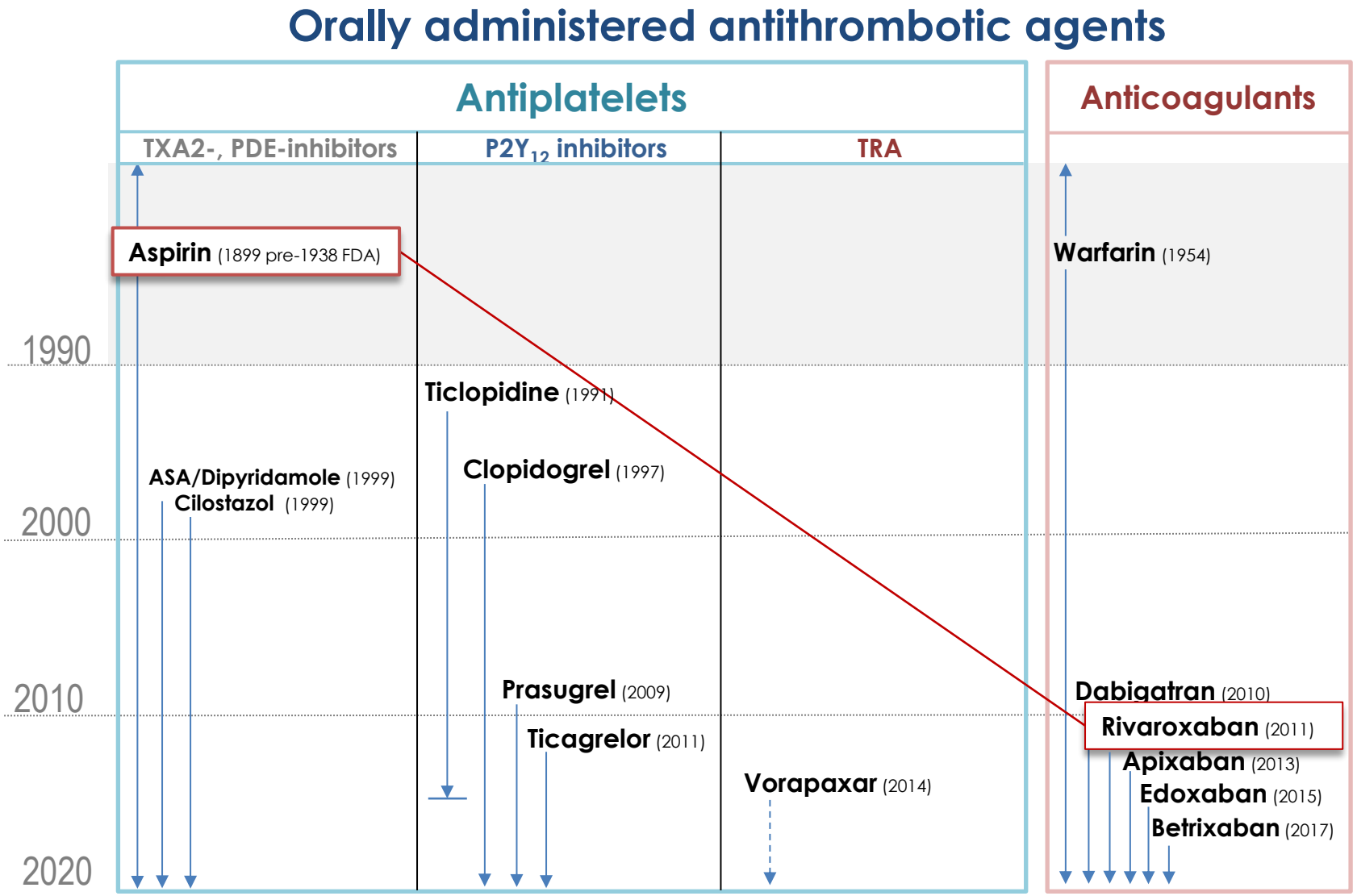


Panel B shows the cumulative incidence of the second coprimary end point (myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent in-tervention, or death from cardiovascular causes). **There was no significant difference in outcome between the two groups** (relative risk, 0.91; 95% CI, 0.74 to 1.12; P = 0.3



WAVE Trial Investigators. *N Engl J Med* 2007;357:217-27.

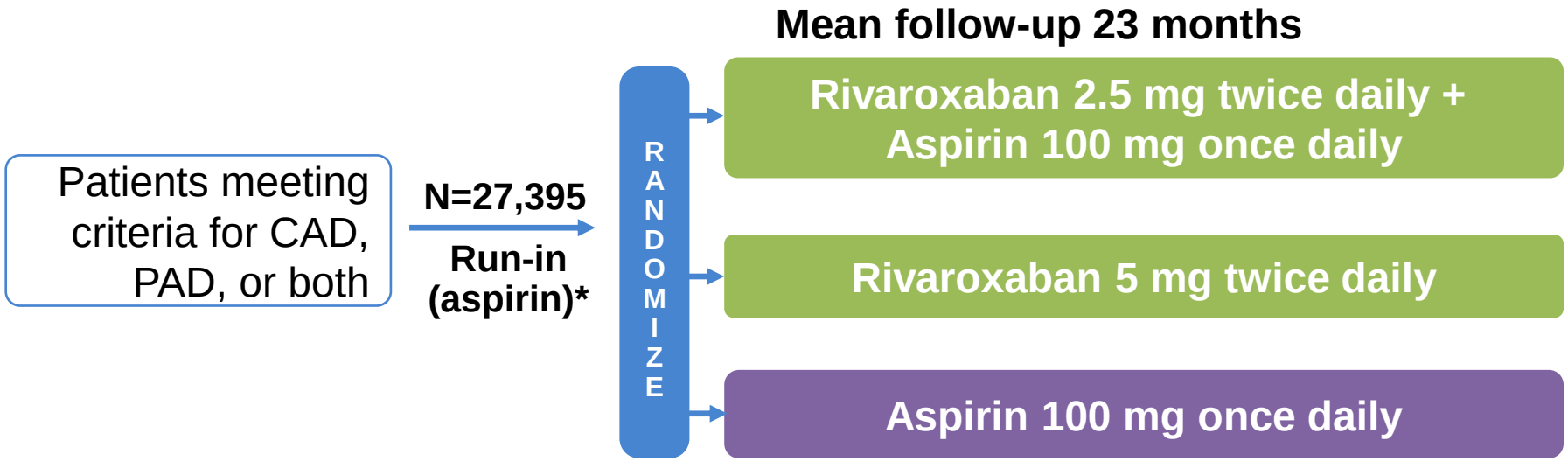
Oral antiplatelet and anticoagulant therapies commonly used in combination



- **Combining oral SAPT/DAPT with DOAC anticoagulation** is often clinically necessary
- The **combination of low-dose ASA with low-dose rivaroxaban** has been evaluated in several trials, including:
  - **ATLAS ACS-TIMI 46** (Phase II, dose-ranging, Lancet 2009, n=3,491)
  - **ATLAS ACS 2-TIMI 51** (NEJM 2012, n=15,526)
  - **COMPASS** (NEJM 2017, n=27,395)
  - **VOYAGER PAD** (NEJM 202, n=6,564)

COMPASS: Cardiovascular OutcoMes for People using Anticoagulation StrategieS

- COMPASS was a randomized, double-blind, double-dummy, trial comparing the efficacy and safety of rivaroxaban 5 mg BID vs. rivaroxaban 2.5 mg BID + ASA 100 mg QD vs. ASA 100 mg QD alone in patients with stable CAD, PAD or both
- COMPASS was terminated early due to a consistent benefit in the primary efficacy outcome for rivaroxaban 2.5 mg BID + aspirin 100 mg QD compared with aspirin alone
- Because the 5 mg dose alone was not superior to aspirin alone, only the data concerning the 2.5 mg BID dose plus aspirin were considered by the FDA



Primary efficacy outcome: Composite of CV death, stroke, or myocardial infarction
Principal safety outcome: Major bleeding (modified ISTH)

Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

COMPASS eligibility criteria

CAD cohort

- ≥1 of the following:
  - MI within 20 years, or
  - multivessel CAD(stenosis ≥50% in ≥2 coronary arteries or in 1 coronary territory if ≥1 other territory has been revascularized) with symptoms or history of stable or unstable angina, or
  - multivessel PCI, or
  - multivessel CABG
- Patients with CAD must also have ≥1 of the following:
  - age ≥65, or
  - age <65 and documented atherosclerosis or revascularization involving ≥2 vascular beds (ie, an additional vascular bed to coronary), or ≥2 additional risk factors (current smoking, DM, CKD with eGFR <60 mL/min, CHF, non-lacunar ischemic stroke ≥1 month earlier

PAD cohort

- ≥1 of the following:
  - Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infrainguinal arteries, or
  - Previous limb or foot amputation for arterial vascular disease, or
  - History of intermittent claudication with ≥1 of the following:
    - Ankle/arm blood pressure (ABI) ratio <0.90, or
    - Significant peripheral artery stenosis (≥50%) documented by angiography, or by duplex ultrasound, or
  - Previous carotid revascularization or asymptomatic carotid artery stenosis ≥50% as diagnosed by duplex ultrasound or angiography

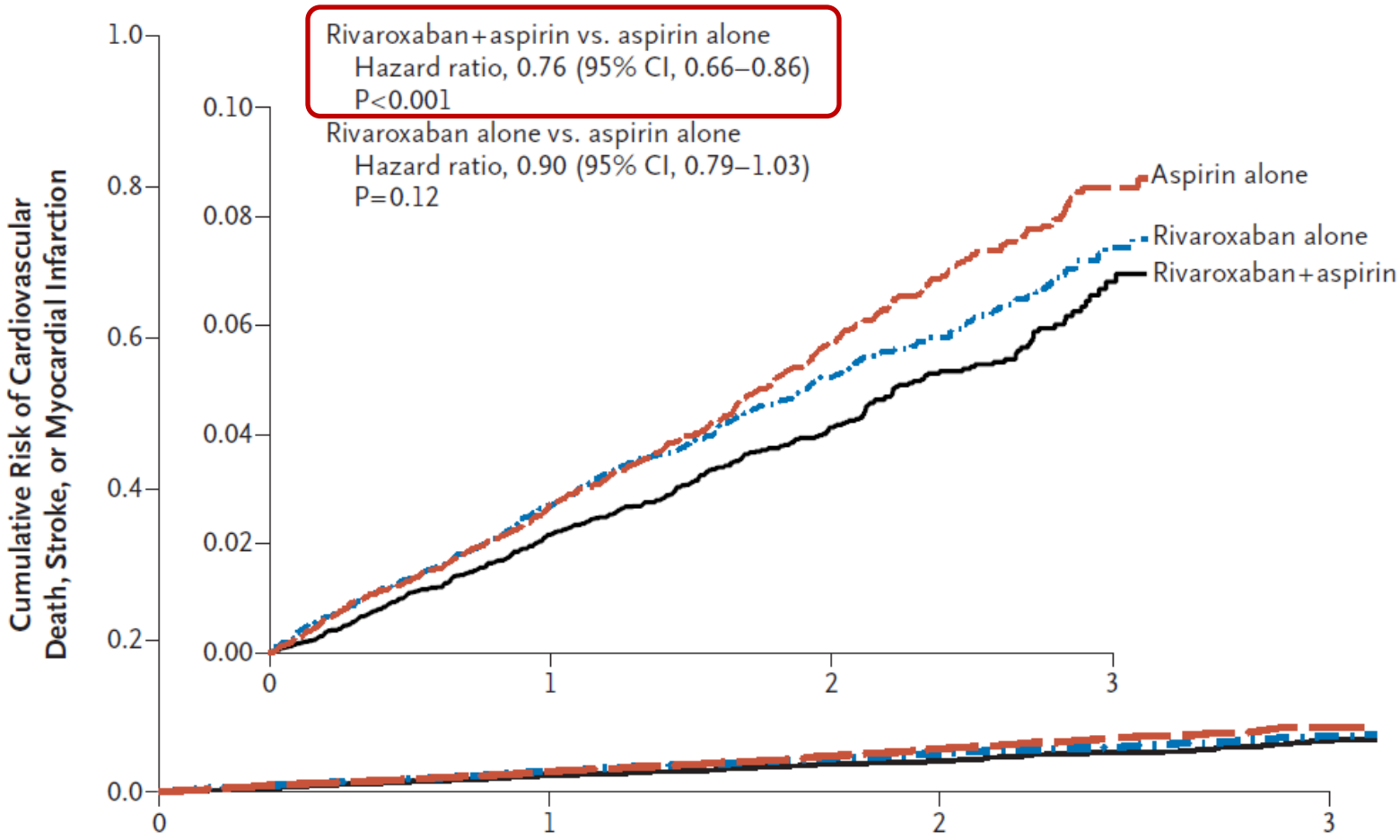
Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

COMPASS exclusion criteria

- **High bleeding risk**
- Recent stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known ejection fraction <30% or NYHA class III or IV symptoms
- eGFR <15 mL/min
- Use of DAPT, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy
- Noncardiovascular disease that is associated with a poor prognosis
- Treatment with strong inhibitors of CYP3A4 as well as p-glycoprotein inhibitors, or strong inducers of CYP3A4

Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

COMPASS primary efficacy outcome

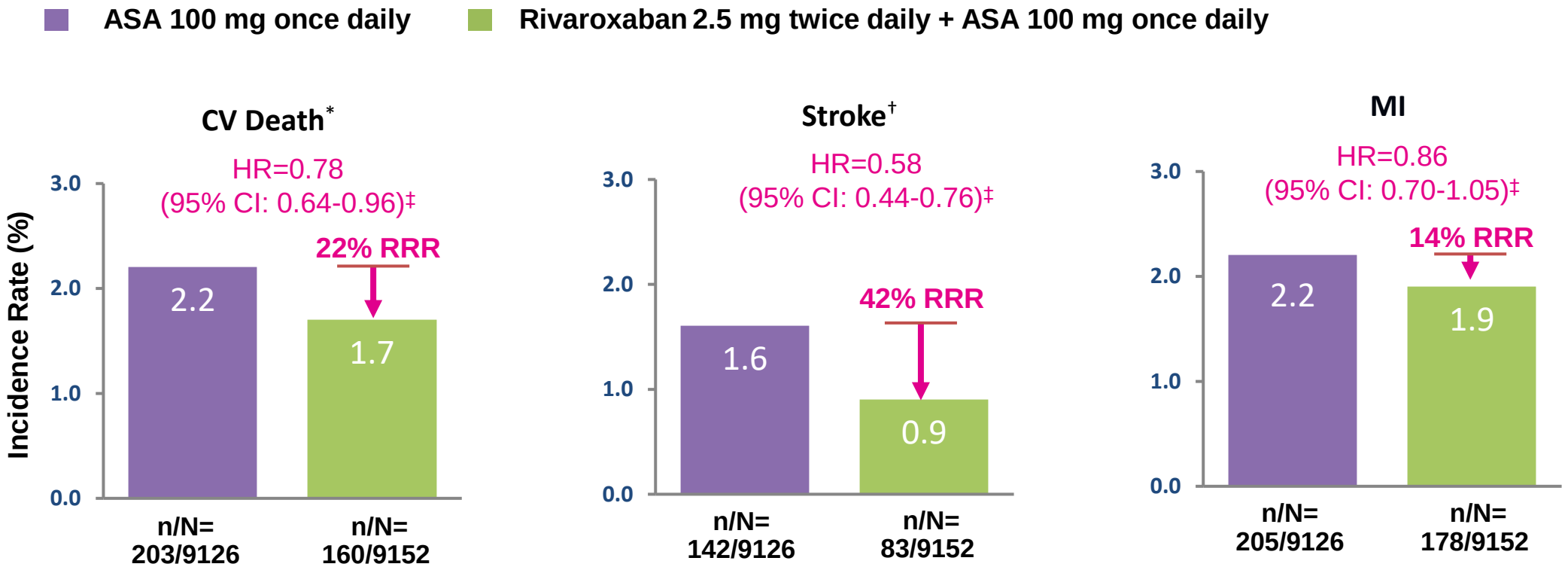


No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

- Primary efficacy endpoint = composite of CV death, stroke, or MI
- RRR in primary efficacy outcome of **24% HR=0.76, (95% CI: 0.66-0.86) P<0.001** in R+A vs. A groups
- The comparison of R alone to A alone failed to meet statistical significance

Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

COMPASS individual components of the primary efficacy outcome

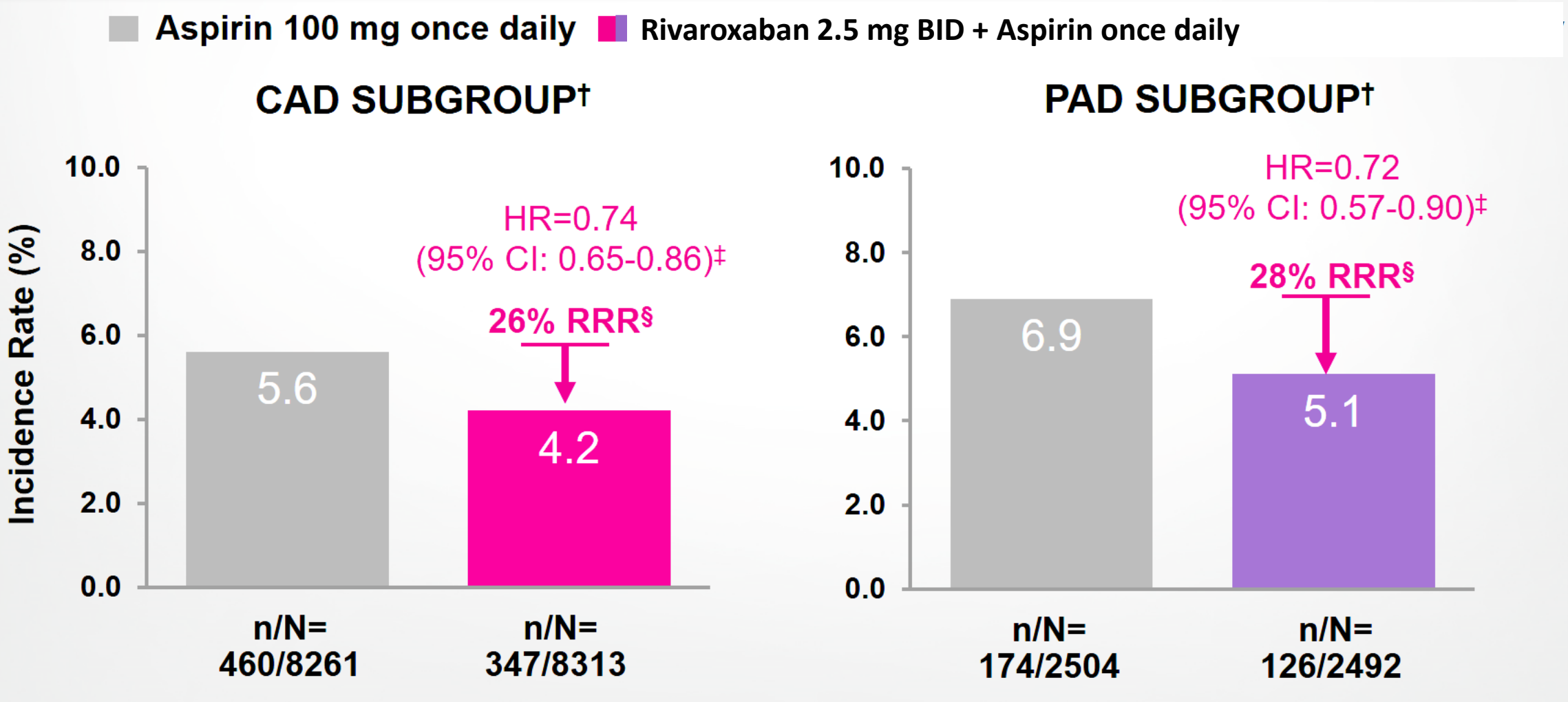


- Consistent results for each of the components of the primary endpoint
- These endpoints were not adjusted for multiplicity

*CV death was defined as death for which a definite non-CV cause has not been identified. Uncertain causes of death are presumed to be CV unless proven otherwise.
†A total of 7 participants in the rivaroxaban-plus-aspirin group and 11 participants in the aspirin-alone group who were reported to have atrial fibrillation had a stroke.[1]
‡Not adjusted for multiplicity.

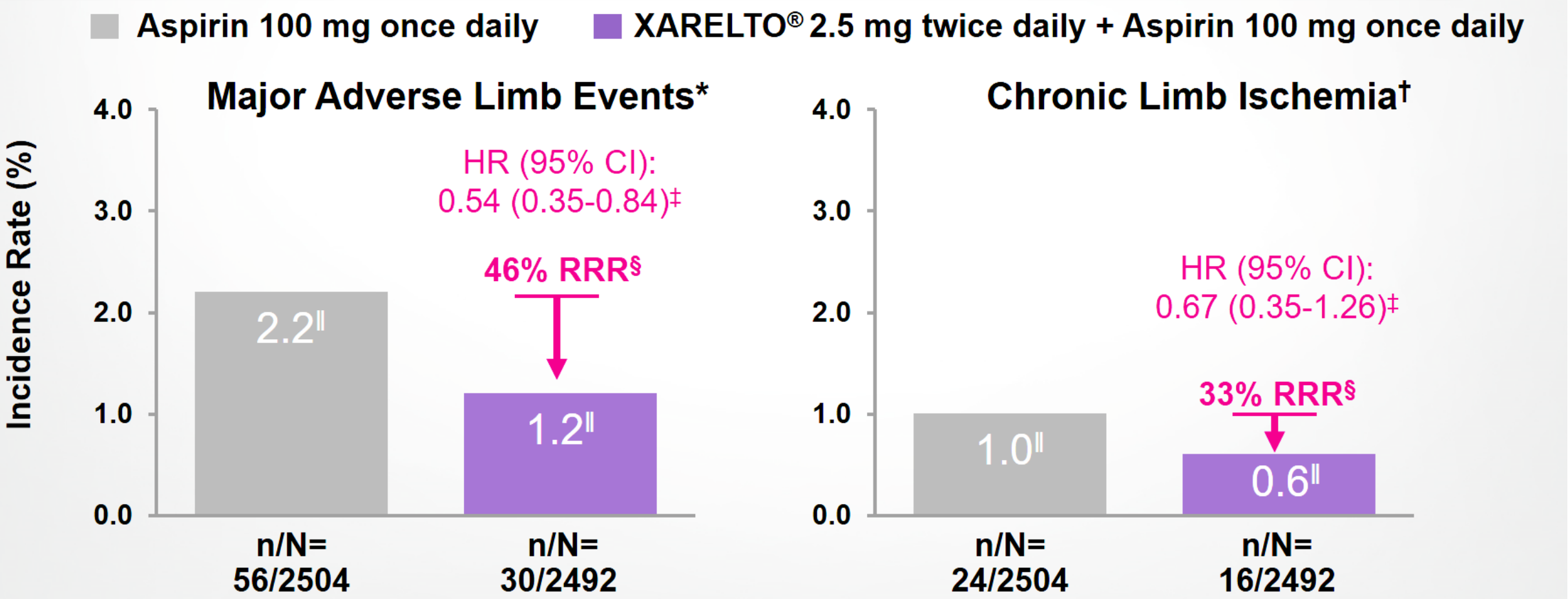
Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

COMPASS primary efficacy outcome in patients with CAD and PAD



Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

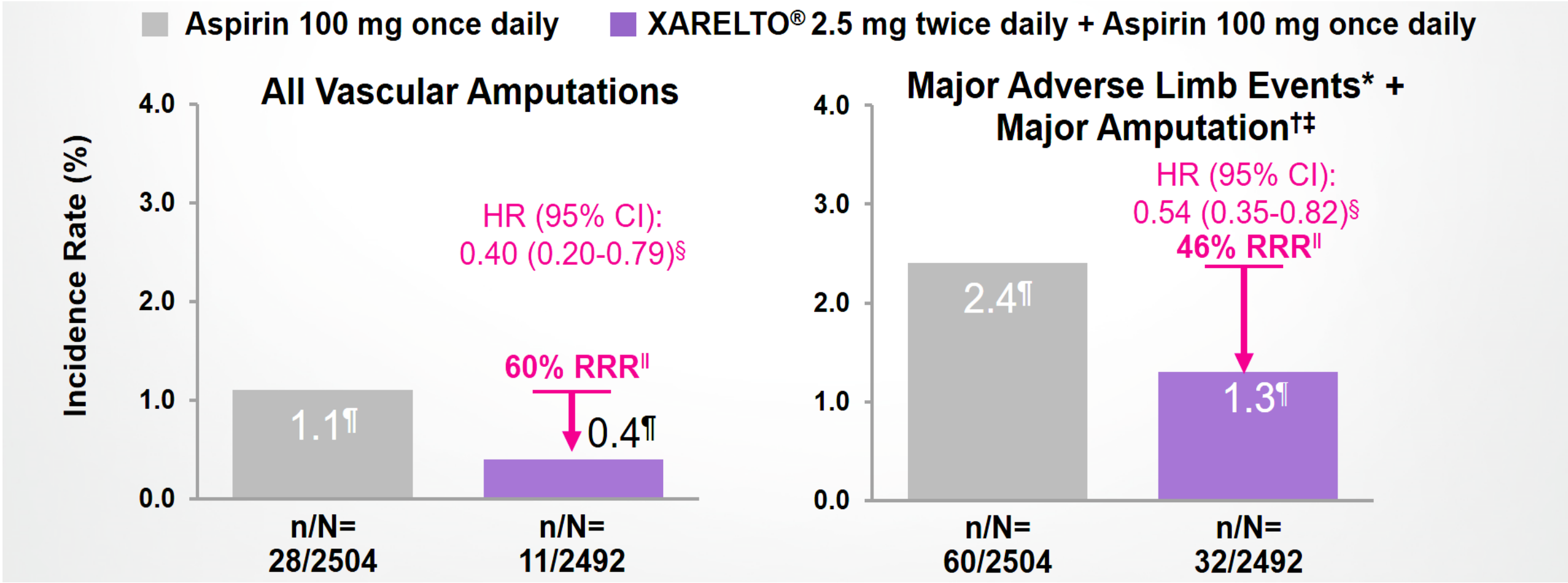
Prespecified limb outcomes in COMPASS in patients with PAD



Major adverse limb events were defined as development of acute or chronic limb ischemia (defined as severe limb ischemia leading to a vascular intervention) over the course of the trial follow up, including any major amputation due to a vascular event that was not included in acute or chronic limb ischemia. P-values not adjusted for multiplicity.

Anand SS, et al. *Lancet* 2017.

Prespecified limb outcomes in COMPASS in patients with PAD



Major adverse limb events were defined as development of acute or chronic limb ischemia (defined as severe limb ischemia leading to a vascular intervention) over the course of the trial follow up, including any major amputation due to a vascular event that was not included in acute or chronic limb ischemia. P-values not adjusted for multiplicity. Amputations of the forefoot and digits were considered minor amputations; above the forefoot were considered major amputations.

Anand SS, et al. *Lancet* 2017.

COMPASS primary safety outcome

	%/Year (n/N)		
	Rivaroxaban 2.5 mg twice daily + Aspirin 100 mg once daily	Aspirin 100 mg once daily	HR (95% CI)
Modified ISTH* major bleeding†	**1.6** (263/9134)	**0.9** (144/9107)	1.84 (1.50-2.26)
Fatal bleeding	**<0.1** (12/9134)	**<0.1** (8/9107)	1.51 (0.62-3.69)
Symptomatic bleeding in critical organ (nonfatal)	**0.3** (58/9134)	**0.3** (43/9107)	1.36 (0.91-2.01)
Bleeding into surgical site requiring reoperation (nonfatal, not in critical organ)	**<0.1** (7/9134)	**<0.1** (6/9107)	1.17 (0.39-3.48)
Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)	**1.1** (188/9134)	**0.5** (91/9107)	2.08 (1.62-2.67)

†Modified ISTH defined as i) fatal bleeding, or ii) symptomatic bleeding in a critical area or organ, such as intra-articular, intramuscular with compartment syndrome, intraspinal, intracranial, intraocular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or iii) bleeding into the surgical site requiring reoperation, or iv) bleeding leading to hospitalization.

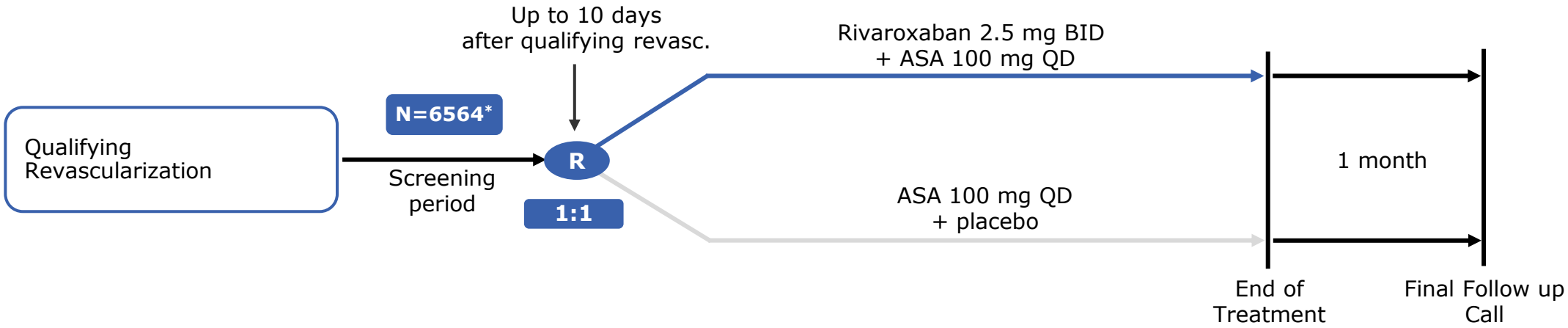
*Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

VOYAGER PAD: Objective and Study Design

Objective

Rivaroxaban added to ASA is superior to ASA alone in symptomatic PAD patients undergoing lower extremity revascularization



Primary Efficacy Outcome

- ALI
- Major amputation for vascular causes
- MI
- Ischemic stroke
- Death from CV causes

Principal Safety Outcome

- Major bleeding according to the TIMI classification

Key Inclusion Criteria

- Age ≥ 50
- Documented lower extremity PAD including:
- Ischemic symptoms (functional limitation, rest pain, or ischemic ulceration)
- Imaging evidence of occlusion
- Abnormal ABI
- Successful lower extremity revascularization within 10 days prior to randomization

Key Exclusion Criteria

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

* 6564 patients underwent randomization. 1080 (33.2%) in the rivaroxaban group and 1011 (31.1%) in the placebo group discontinued treatment prematurely.

ABI = ankle-brachial index; ALI = acute limb ischemia; ACS = acute coronary syndrome; ASA = aspirin; CV = cardiovascular; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PAD = peripheral artery disease; TIMI = Thrombolysis In Myocardial Infarction; TBI = toe-brachial index.

1. Bonaca MP et al. *N Engl J Med.* 2020. doi:10.1056/NEJMoa2000052.
2. Supplement to: Bonaca MP et al. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2000052.

VOYAGER PAD: Secondary Endpoints

Secondary Efficacy Outcomes

- ALI, major amputation of a vascular etiology, MI, ischemic stroke, or CHD death
- Unplanned index limb revascularizations for recurrent limb ischemia
- Vascular hospitalizations for a peripheral or coronary event of a thrombotic nature
- ALI, major amputation of a vascular etiology, MI, ischemic stroke or all-cause mortality
- ALI, major amputation of a vascular etiology, MI, stroke from any cause, or death from any cause
- Death from any cause
- VTE

Secondary Safety Outcomes

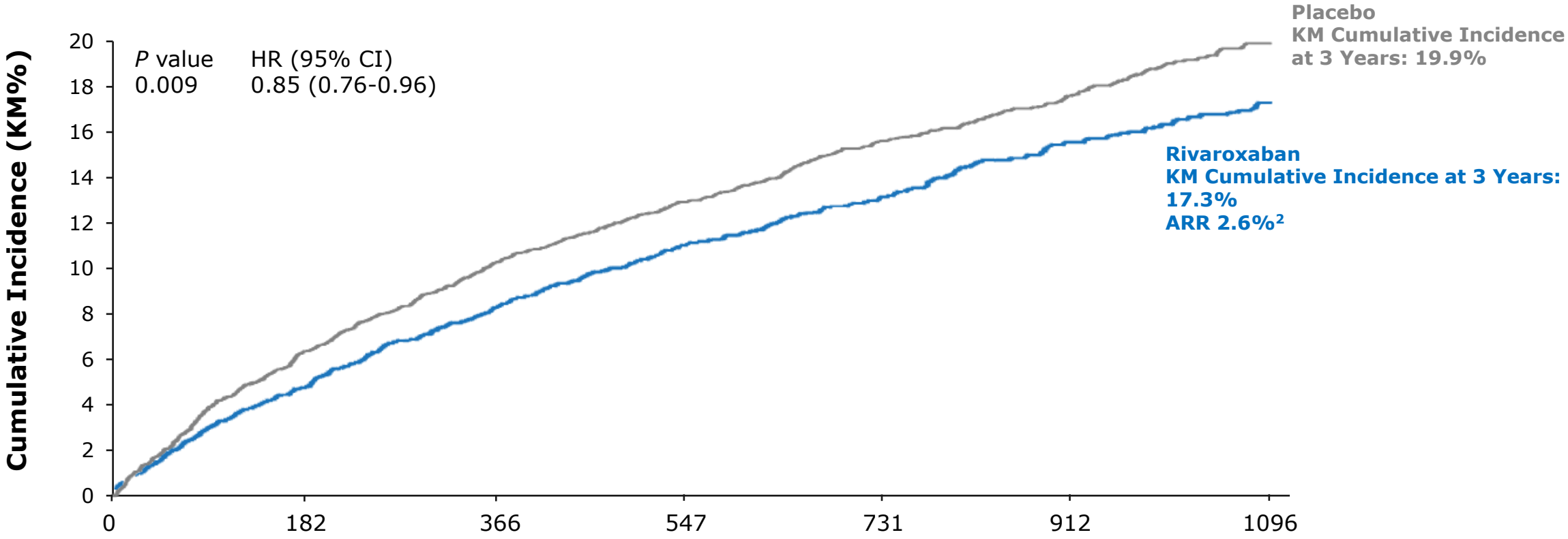
- BARC major bleeding (grade ≥3b)
- ISTH major bleeding

ALI = acute limb ischemia; BARC = Bleeding Academic Research Consortium; CHD = coronary heart disease; CV = cardiovascular; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; PAD = peripheral artery disease; VTE = venous thromboembolism.

Supplement to: Bonaca MP et al. *N Engl J Med.* 2020. doi:10.1056/NEJMoa2000052.

VOYAGER PAD: Primary Composite Efficacy Outcome

ALI, major amputation for vascular cause, MI, ischemic stroke, CV death



No. at Risk							
Rivaroxaban	3286	3082	2938	2834	2219	1415	684
Placebo	3278	3030	2881	2773	2151	1351	642

ALI = acute limb ischemia; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction.

1. Bonaca MP et al. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2000052. 2. Bonaca MP et al. Symposium presented at: ACC 2020; March 28, 2020; Chicago, IL.

VOYAGER PAD: Primary Efficacy Outcome and Components*

	Rivaroxaban (N=3286)		Placebo (N=3278)		HR (95% CI)	*P*-value
	Patients with Event *no. (%)*	KM Estimate at 3 Yr *%*	Patients with Event *no. (%)*	KM Estimate at 3 Yr *%*		
ALI, major amputation for vascular causes, MI, ischemic stroke, or death from CV causes	508 (15.5)	17.3	584 (17.8)	19.9	**0.85 (0.76–0.96)**	**0.009**
ALI	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation of vascular etiology	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
MI	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
Death from CV causes	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	

* All efficacy outcomes were analyzed on an intention-to-treat basis.
ALI = acute limb ischemia; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction.

Bonaca MP et al. *N Engl J Med.* 2020. doi:10.1056/NEJMoa2000052.

VOYAGER PAD: Primary Efficacy Outcomes On-Treatment

	Rivaroxaban (N=3286)		Placebo (N=3278)		HR (95% CI)	*P*-value
	Patients with Event *no. (%)*	KM Estimate at 3 Yr *%*	Patients with Event *no. (%)*	KM Estimate at 3 Yr *%*		
Cardiovascular death, MI, ischemic stroke, ALI, major amputation of vascular etiology	335 (10.3)	13.5	448 (13.8)	17.3	**0.75 (0.65 – 0.86)**	**0.0001**
ALI	124 (3.8)	4.8	195 (6.0)	7.3	0.64 (0.51 – 0.80)	
Major amputation of vascular etiology	52 (1.6)	2.1	66 (2.0)	2.6	0.80 (0.56 – 1.15)	
MI	82 (2.5)	3.4	111 (3.4)	4.5	0.75 (0.56 – 1.00)	
Ischemic stroke	49 (1.5)	2.2	62 (1.9)	2.5	0.80 (0.55 – 1.17)	
Cardiovascular death	79 (2.4)	3.7	87 (2.7)	4.0	0.92 (0.68 – 1.25)	

ALI = acute limb ischemia; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction.

Bonaca MP et al. *N Engl J Med.* 2020. doi:10.1056/NEJMoa2000052.

Summary

- In patients with **PAD who had undergone lower-extremity revascularization**, **rivaroxaban at a dose of 2.5 mg BID plus aspirin was associated with a significantly lower incidence of the composite outcome of ALI, major amputation for vascular causes, MI, ischemic stroke, or death from CV causes than aspirin alone**
- The incidence of **TIMI major bleeding did not differ significantly** between the groups
- The incidence of **ISTH major bleeding was significantly higher with rivaroxaban** than with placebo

ALI = acute limb ischemia; CV = cardiovascular; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; PAD = peripheral artery disease; TIMI = Thrombolysis in Myocardial Infarction.

Bonaca MP et al. *N Engl J Med.* 2020. doi:10.1056/NEJMoa2000052.

Antithrombotic management strategies in chronic polyvascular disease (CAD+PAD)

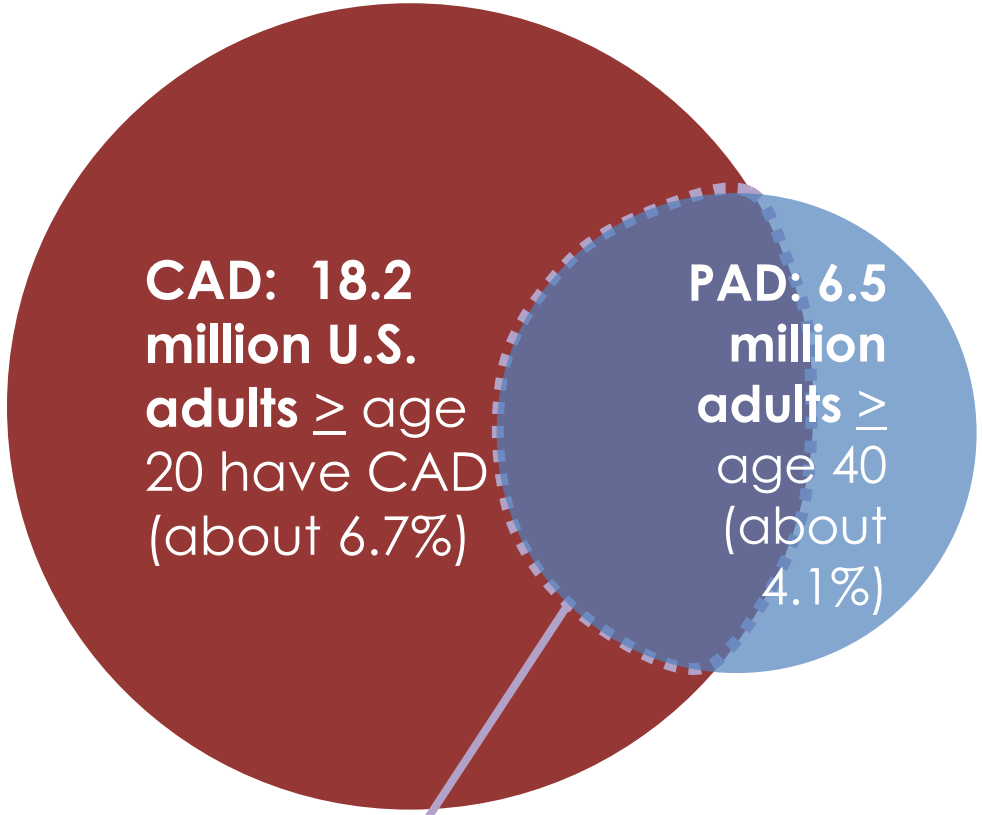
Comprehensive CV risk reduction, lifestyle/dietary modification for ALL patients

Coronary Artery Disease

Long-term 2° prevention & post-CABG
- ASA

Post ACS/AMI
- DAPT: A+C/T x 12 mo if med mgt or A+C/T/P x 12 mo if PCI
- A+T 1-3 yrs after MI (60 mg BID)

Post-PCI
- DAPT for 1-12 mo (>12mo?)



R (2.5 mg BID) + A (100 mg QD)

Long-term 2° prevention & post-surgical bypass
- ASA alone
- C alone

Post PTA/stenting
- DAPT: A+C x 1-6 mo (>6 mo?)

Peripheral Arterial Disease

- DAPT=dual antiplatelet therapy, A=aspirin, T=ticagrelor, P=prasugrel, R=rivaroxaban

https://www.cdc.gov/heartdisease/facts.htm. Accessed 11/19/2020.
https://www.cdc.gov/heartdisease/PAD.htm. Accessed 11/19/2020.
Virani SS, et al. *Circulation*. 2020;141(9):e139–e596.

Summary & key takeaways

- Patients with **PAD manifest a very high lifetime risk of CV events**
- Patients with **polyvascular disease represent the highest risk cohort** for CV morbidity and mortality
- **Modifiable risk factors for reducing CV risk** in patients with PAD include **cigarette smoking, dyslipidemia, diabetes, diet, obesity** and **physical inactivity**
- **Medical therapies have been demonstrated to reduce both MACE and MALE events in PAD patients**, but remain vastly **underutilized**
- **Guideline-recommended therapies, including smoking cessation, lipid lowering drugs, optimal glucose control** and **antithrombotic medications with a focus of low dose antiplatelet+low dose DOAC**

Thank you!

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