Understanding High-Risk Coronary and Peripheral Artery Disease (CAD/PAD) Patient Populations

July 15, 2020

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This material is being presented by a healthcare professional in collaboration with the American Medical Group Association and is intended for providers involved in the care of patients with CAD and/or PAD. Speaker is a paid consultant of Janssen Pharmaceuticals, Inc.

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Agenda

- What is CAD/PAD?
- What are the current guideline recommendations for CAD/PAD?
- Why the standard of care may not be enough
- What can we do better?
  - Risk assessment tools
  - Identification of high-risk patient populations

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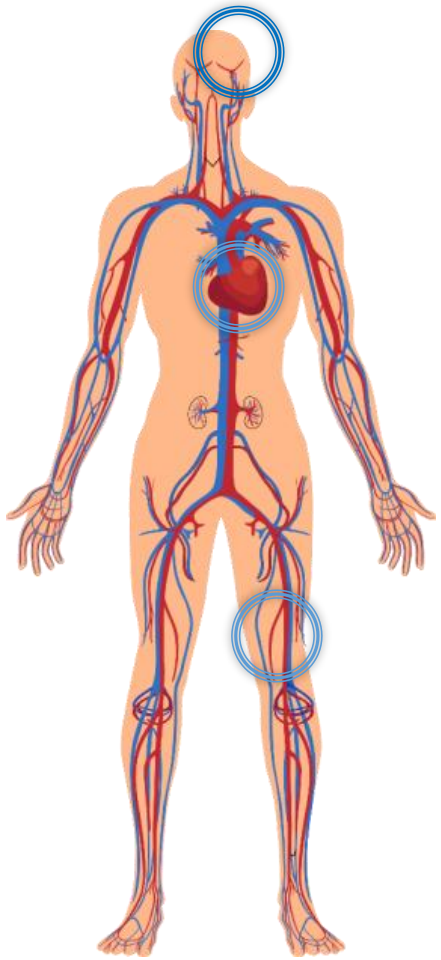
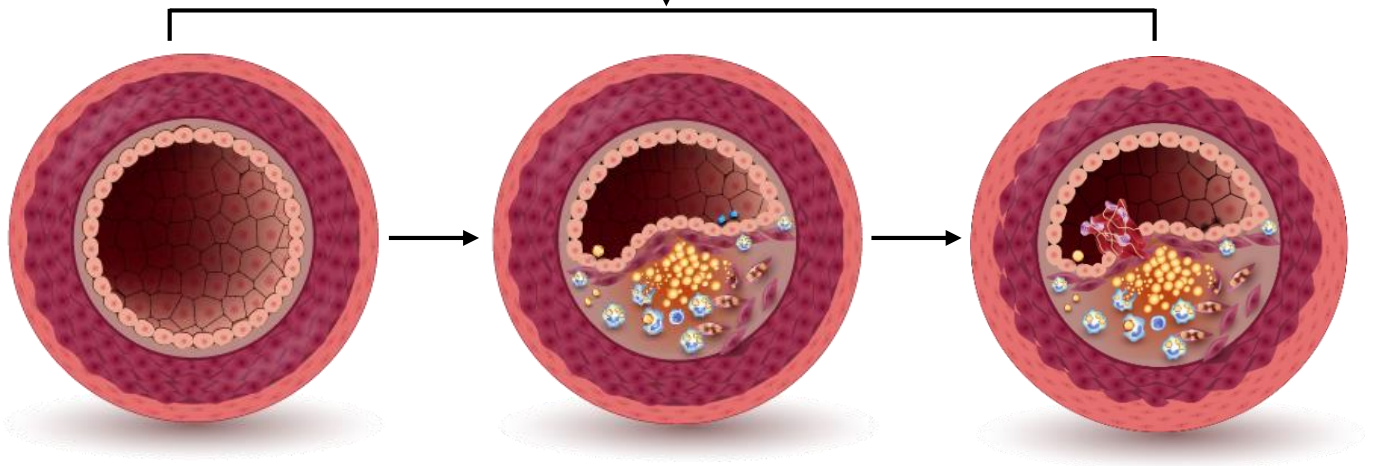
Overview of CAD/PAD

Atherosclerosis is a CHRONIC and PROGRESSIVE DISEASE[1,2]



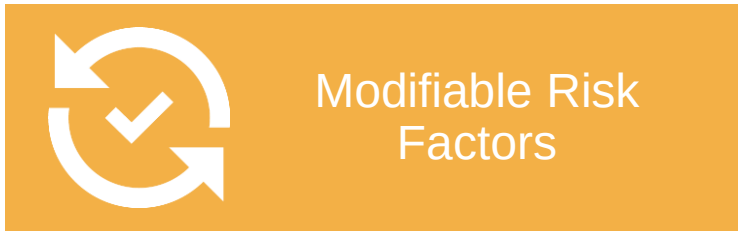
Inflammation + Hyperlipidemia + Diabetes + Hypertension + Stress + Smoking[3,4]



1. Turpie AG, Esmon C. *Thromb Haemost*. 2011;105:586-596. 2. Piazza G, Goldhaber SZ. *Circulation*. 2010;121:2146-2150.
3. Libby P et al. *Nature*. 2011;473(7347):317-325. 4. Hansson GK et al. *J Intern Med*. 2015;278(5):483-493.

Common Risk Factors of ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD)[1-6]

- Age
- Family history
- Kidney function
- Sex
- Years since disease manifestation

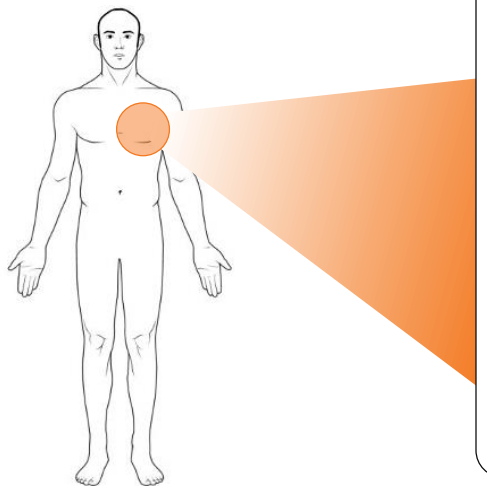


- Blood pressure
- Cholesterol
- Type 2 diabetes
- Diet and exercise
- Weight/obesity
- Smoking status

1. Bhatt DL et al; REACH Registry Investigators. *JAMA*. 2010;304(12):1350-1357. 2. Hirsch AT et al. *Circulation*. 2006;113:e463-e654. 3. National Heart, Lung and Blood Institute. Who is at risk for atherosclerosis? 2016. https://www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis/atrisk. Accessed February 3, 2020. 4. American Stroke Association. Let's talk about risk factors for stroke. http://www.strokeassociation.org/idc/groups/stroke-lcantpublic/@wcm/@hcm/documents/downloadable/ucm_309713.pdf. Accessed February 3, 2020. 5. Gerhard-Herman MD et al. *Circulation*. 2017;135(12):e686-e725. 6. Fihn SD et al. *J Am Coll Cardiol*. 2012;60:e44-e164.

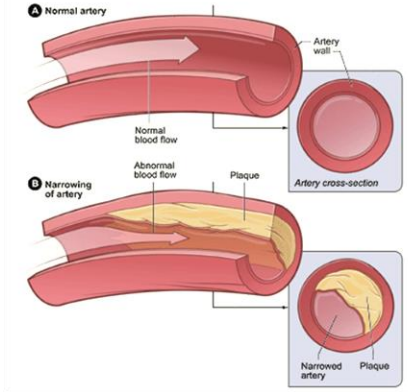
CV Disease Is a Potentially Deadly Condition Caused by Atherosclerosis, Often Manifesting as CAD or PAD[1,2]

Coronary Artery Disease (CAD)

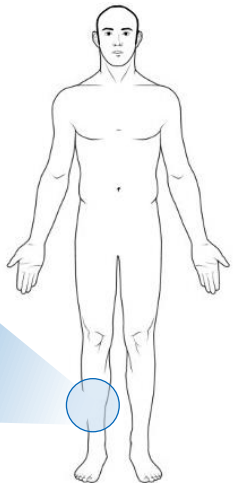


Cardiovascular (CV) Disease
Atherosclerosis[2]

Thickening and hardening of arteries from plaque restricts blood flow



Peripheral Artery Disease (PAD)



CAD and PAD are associated with morbidity and mortality[3-5]

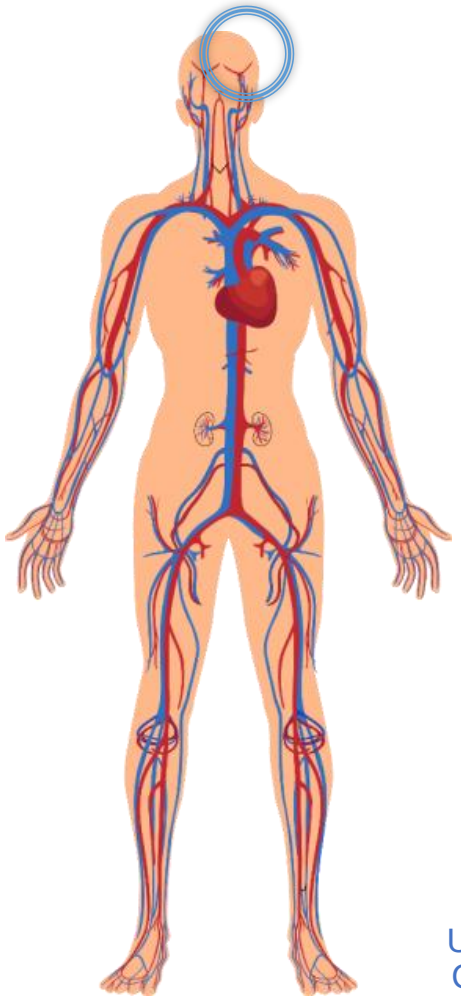
CAD
- Heart attack
- Stroke/TIA
- CV death

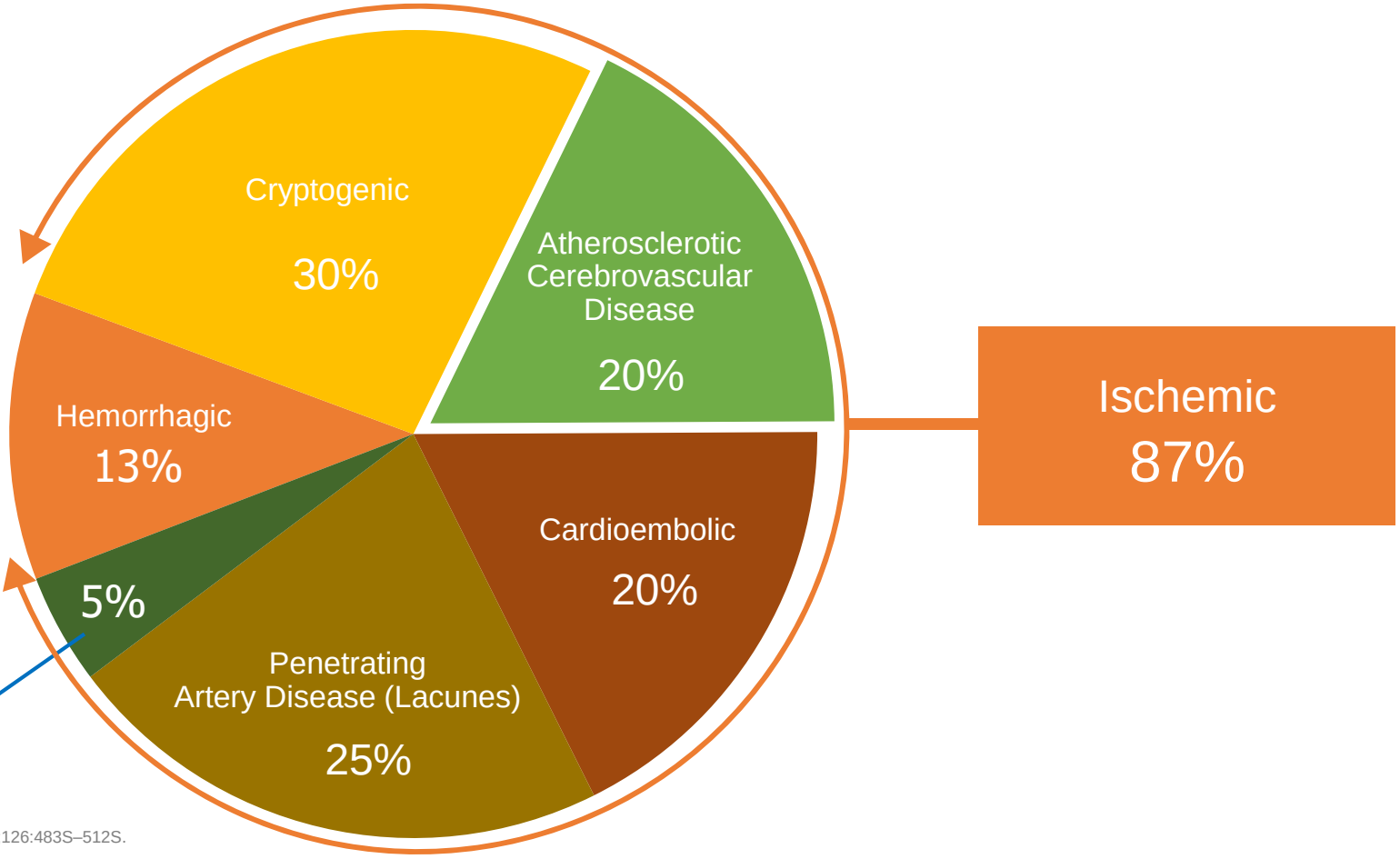
PAD
- Acute limb ischemia
- Leg amputation
- Revascularization

TIA, transient ischemic attack.

References: 1. Benjamin EJ et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2017;135(10):e146-e603. 2. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/atherosclerosis. Accessed February 26, 2020. 3. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/stroke. Accessed February 26, 2020. 4. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/peripheral-artery-disease. February 26, 2020. 5. Gerhard-Herman MD et al. *J Am Coll Cardiol.* 2017;69(11):1465-1508.

Strokes Subtypes[1,2]

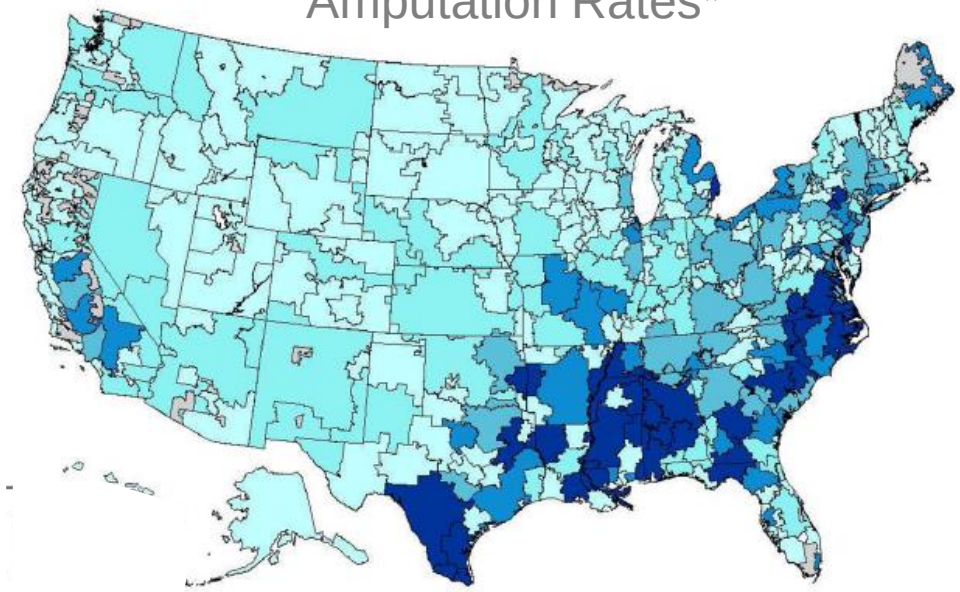




1. Benjamin EJ et al. *Circulation*. 2017;135:e146-e603. 2. Albers GW et al. *Chest*. 2004;126:483S–512S.

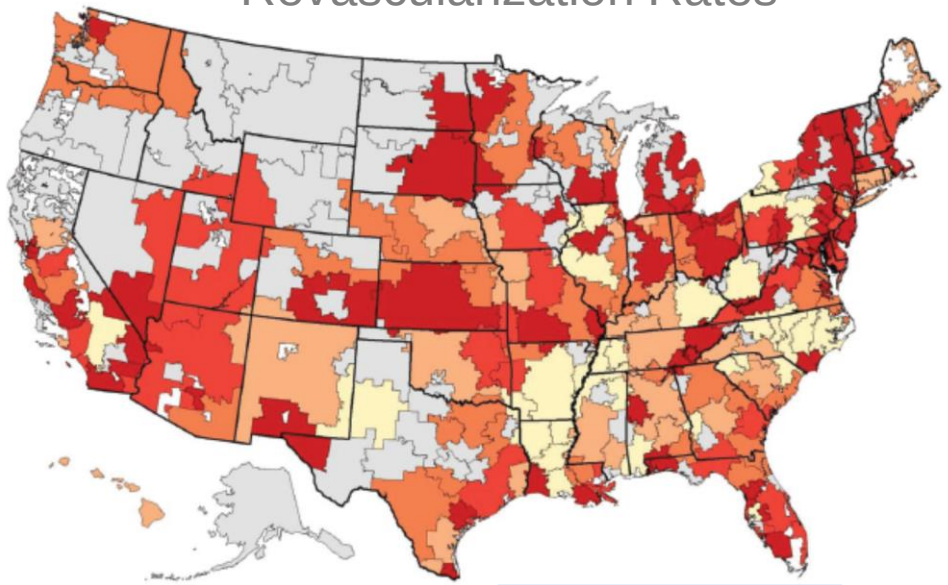
Revascularization and Amputation Rates in PAD Patients VARY BY GEOGRAPHY

Amputation Rates*



- 22+ Amputations/Year
- 18-21 Amputations/Year
- 14-17 Amputations/Year
- 9-13 Amputations/Year
- 0-8 Amputations/Year
- Not Populated

Revascularization Rates†



Rate of Revascularization in the Year Prior to Amputation for PAD by Hospital Referral Region (2003-06)

- 0.4120 or greater (68)
- 0.3801-<0.4120 (34)
- 0.3430-<0.3801 (40)
- 0.2901-<0.3430 (35)
- <0.2901 (32)
- Insufficient data (97)
- Not populated

*Based on in-patient Medicare data from 2007-2009 (per 10,000 Medicare patients).
†Based on Medicare data from 2003-2006 in year prior to amputation for PAD.
Reprinted from *Journal of Vascular Surgery*, 2013;57(6):1471-1480, with permission from Elsevier.

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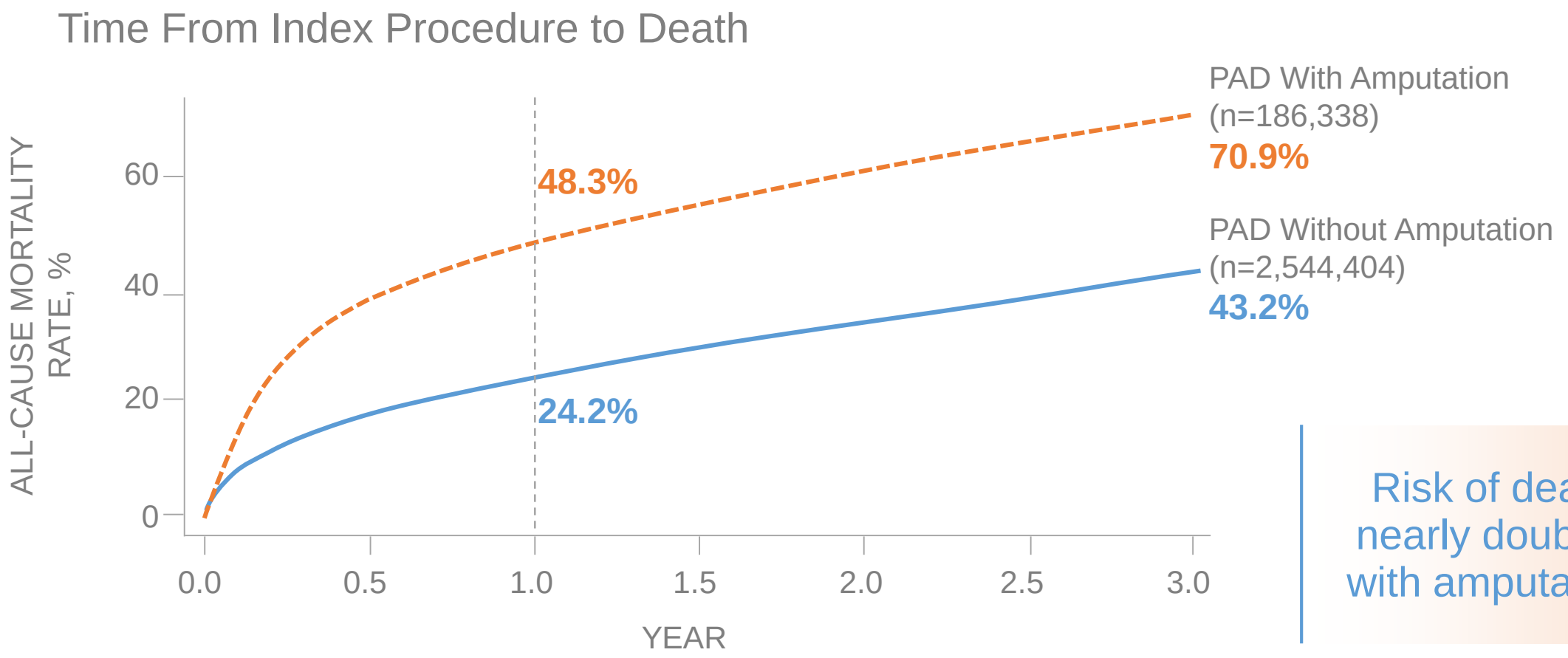
High Mortality Rates Associated With Amputation



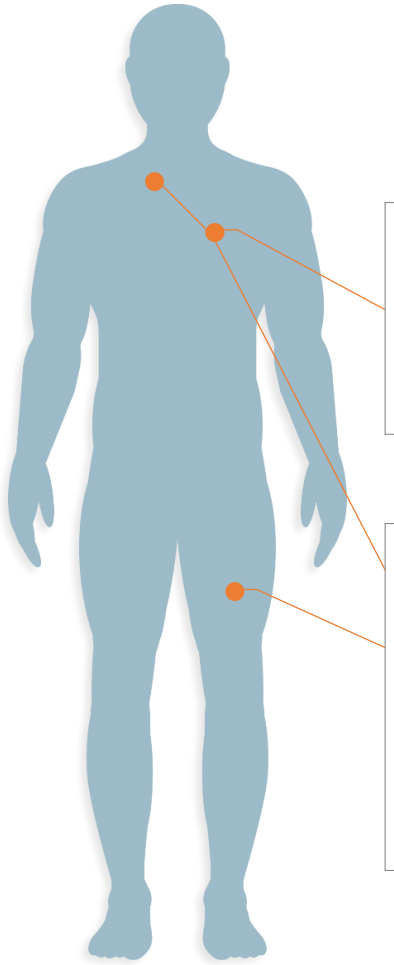
Risk of death nearly doubled with amputation

Reprinted from *American Heart Journal*. 2013;165(5):809-815, with permission from Elsevier.

Incidence/Prevalence of CAD and PAD

CV diseases are the leading cause of death in the United States and accounted for

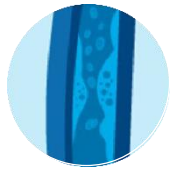
More than 850,000 deaths in 2017.[1]



CAD

occurs in the vessels that feed the heart.[2,3]

18.2 million Americans ≥20 years of age had CAD in 2016.[1]



PAD

occurs in other blood vessels in the body—most often in the legs but also in the brain, arms, and abdomen.[4,5]

8.5 million Americans ≥40 years of age had PAD in 2000.[1]

CAD, coronary artery disease; CV, cardiovascular; PAD, peripheral artery disease.

1. Virani SS et al; *Circulation*. doi: 10.1161/CIR.0000000000000757. 2. Cardiovascular diseases. World Health Organization website. Accessed January 22, 2020. 3. Coronary artery disease (CAD). Centers for Disease Control and Prevention website. Accessed January 22, 2020. 4. Gerhard-Herman MD et al. *J Am Coll Cardiol*. 2017;69(11):e71-e126. 5. Facts about peripheral arterial disease (P.A.D.). National Institutes of Health National Heart, Lung, and Blood Institute website. Accessed January 22, 2020.

Escalating Cost of Atherosclerotic Disease in the United States

Medical Cost of Atherosclerotic Disease in 2015 was **$318 Billion**
= 10% of Health Expenditures (2014)[1]

CAD[1]

In 2015, cost of coronary heart disease was **$188 billion**

By 2035, costs are projected to **nearly double**

CVD[1]

In 2015, cost of stroke was **$66 billion**

By 2035, costs are projected to **more than double**

PAD[2,3]

Annual US total costs exceed **$21 billion**

Estimated **$10.6 billion** for amputations

1. Projections of cardiovascular disease prevalence and costs: 2015-2035. https://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491513.pdf. Accessed March 3, 2020. 2. CardioVascular Coalition. Peripheral artery disease (PAD). http://cardiovascularcoalition.com/cardiovascular-care/peripheral-artery-disease-pad/ Accessed March 3, 2020. 3. Yost ML. *Endovasc Today*. 2014:29-36.

Polling Question

Who holds the primary responsibility for the management of these patients?

- ☐ Cardiologist
- ☐ Vascular Surgeon/Physician
- ☐ PCP
- ☐ More than 1 of the above

Current Standards of Care

ACC/AHA Guidelines

Level 1A Recommendations on Antithrombotic Therapy for Patients With CAD or PAD

CAD	**Acute treatment:** DAPT up to 12 months[1,2*]
	Chronic treatment (>12 months): aspirin monotherapy[1-3]
Symptomatic PAD	**Aspirin monotherapy or clopidogrel**[1,4]

Additional recommendations on secondary prevention and risk reduction therapy in these patients include smoking cessation, BP control, lipid management, physical activity, weight management, T2D management, RAAS blockers, beta-blockers, influenza vaccination, treatment of depression, and cardiac rehabilitation.[1]

ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; T2D, type 2 diabetes.

*A $P2Y_{12}$ receptor antagonist in combination with aspirin after acute coronary syndrome or PCI with stent placement.[1]

1. Smith SC Jr et al. *J Am Coll Cardiol.* 2011;58(23):2432-4246. 2. Levine GN et al. *Circulation.* 2016;134(10):e123-e155. 3. Fihn SD et al. *J Am Coll Cardiol.* 2012;60(24):e44-e164. 4. Gerhard-Herman MD et al. *Circulation.* 2017;135(12):e686-e725.

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2019 Guidelines Recommend Individualized Antithrombotic Therapy According to Individual Risk of Ischemia

2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes

Recommendations Antithrombotic therapy in patients with CCS and in sinus rhythm	Class	Evidence level
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention should be considered in patients with a **high risk of ischemic events** and without high bleeding risk*	IIa	A
Adding a **secondary antithrombotic drug** to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk of ischemic events** and without high bleeding risk*	IIb	A

See the full 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes for all recommendations.

High ischemic risk defined as diffuse multivessel CAD with **at least 1** of the following:

- Diabetes mellitus requiring medication
- Recurrent MI
- PAD
- CKD with eGFR 15 to 59 mL/min/1.73m^2

Moderate ischemic risk defined as at least 1 of the following:

- Diabetes mellitus requiring medication
- Recurrent MI
- PAD
- Multivessel/diffuse CAD
- HF
- CKD with eGFR 15 to 59 mL/min/1.73m^2

CAD, coronary artery disease; CCS, chronic coronary syndromes; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease. *High bleeding risk is defined as prior history of intracerebral hemorrhage or ischemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73m^2.

Knuuti J, et al. *Eur Heart* J. 2019. pii: ehz425.

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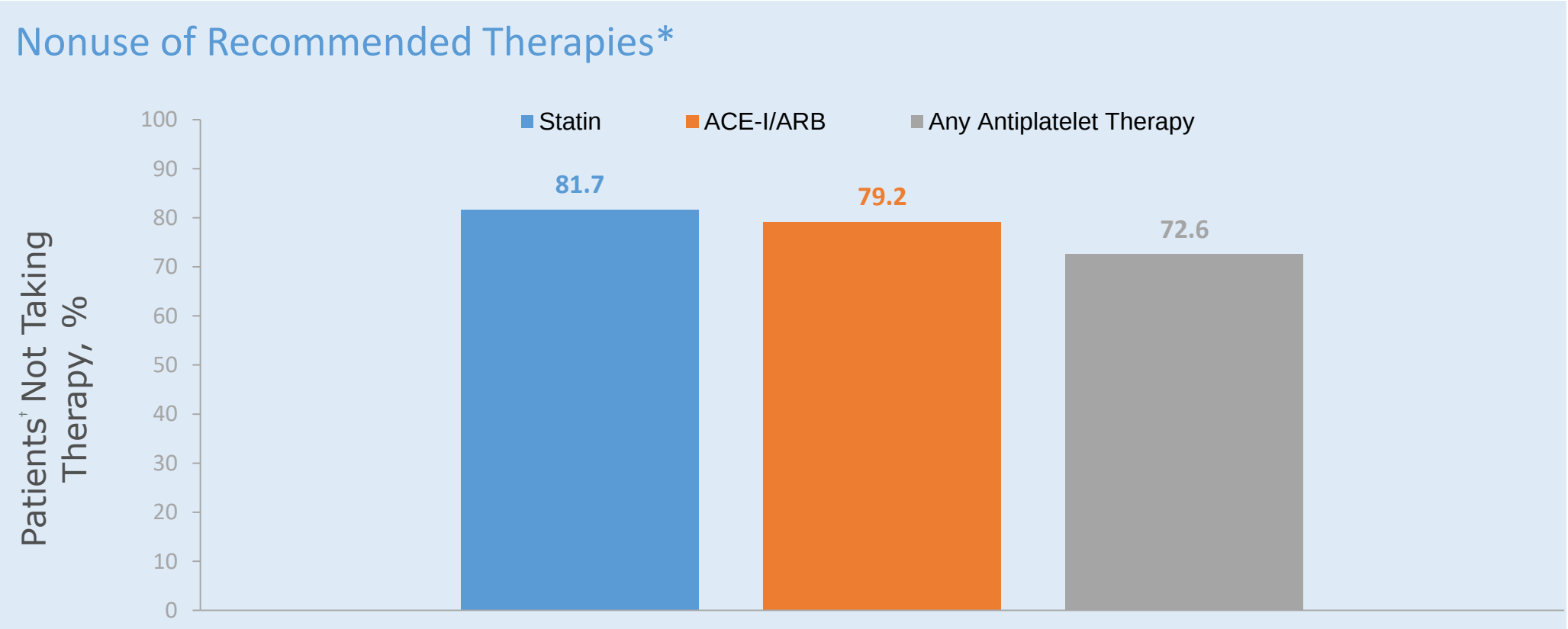
Polling Question

Were you aware there are updated therapy guidelines that recommend evaluating high-risk patients for individualized therapy?

- ☐ Yes
- ☐ No

Opportunities for Improvement in Standards of Care

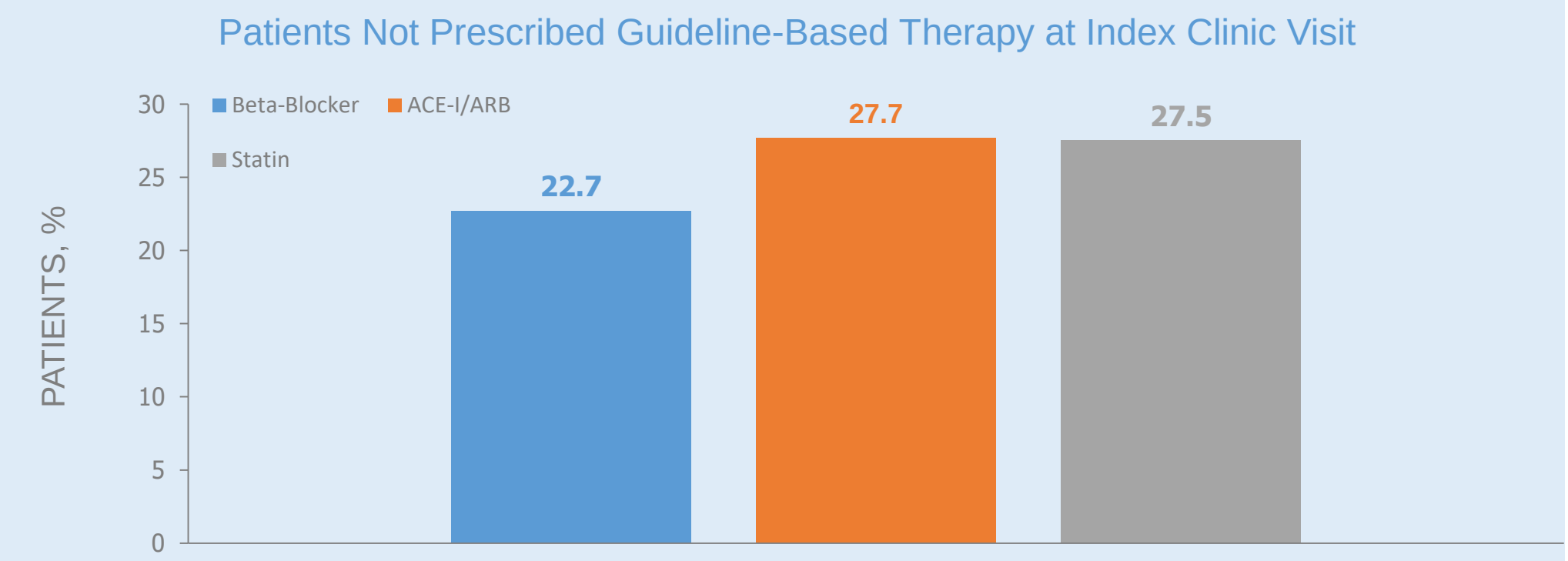
Undertreatment in PAD Is Common



*Data are from 1999-2004.
†PAD patients without CV disease (defined as MI, angina, coronary heart disease, or stroke).
Pande RL et al. *Circulation*. 2011;124(1):17-23.

Undertreatment of CAD Patients Is Common

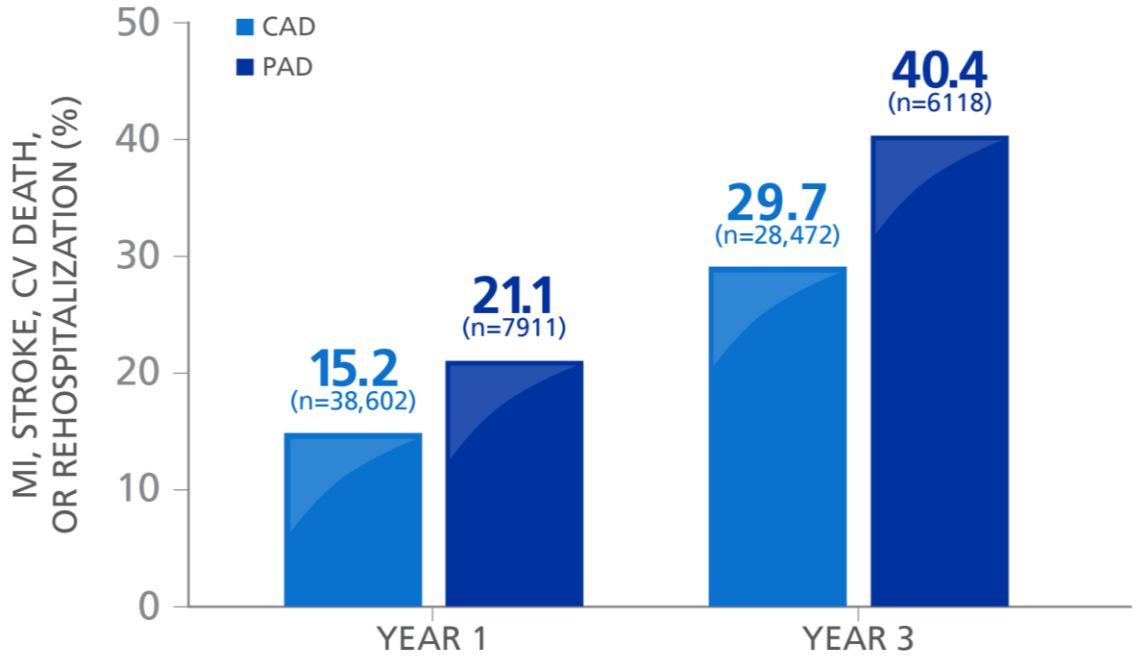
1 in 3 (33.5%) of Eligible CAD Patients Were NOT Prescribed Guideline-Based Therapy With Antiplatelet, Beta-Blocker, ACE-I/ARB, and Statin*



*Data are from 2008-2010.
ACE-I angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker
Maddox TM et al. *J Am Coll Cardiol*. 2014;63:539-546.

In the REACH Registry following patients with CAD/PAD, MAJOR CARDIOVASCULAR EVENT RATES DOUBLED even with high use of standard medications and treatments[1]

Major cardiovascular event rates at 1 and 3 years*



* In patients with symptomatic disease, major cardiovascular events (defined as MI; stroke; cardiovascular death; rehospitalization for a vascular event other than cardiovascular death, MI, or stroke) in patients eligible for 1-year (n-53,211) and 3-year (n=39,675) evaluations. Patient enrollment began in December 2003 and ended in December 2004.

1. Alberts MJ, Bhatt DL, Mas JL, et al; REduction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J*. 2009;30(19):2318-2326.

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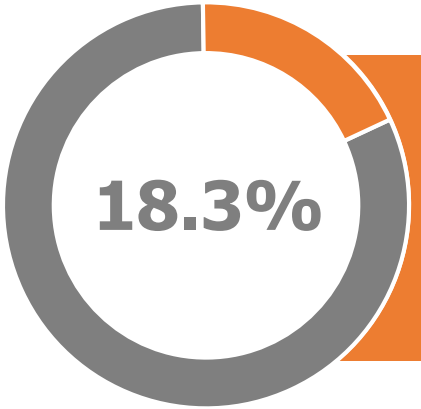
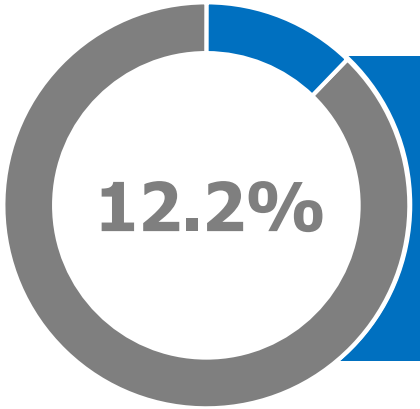
Patients With Chronic CAD/PAD in REACH Remained at Residual Risk of CV Events

Risk of CV death, MI, or stroke at 4 years

Most clinical events result from unstable plaques; however, patients with stable disease are also at risk.



Patients with atherosclerosis with a prior ischemic event*



Patients with stable disease without prior ischemic events

CV Risk Factors

- **Hypertension**
- **Hypercholesterolemia**
- **Diabetes**
- **Obesity (BMI ≥30)**
- **Smoker**
- **Heart failure**
- **Atrial fibrillation**

CV, cardiovascular; BMI, body mass index; MI, myocardial infarction; REACH indicates REduction of Atherothrombosis for Continued Health.
*Prior ischemic event is defined as MI or stroke.
Bhatt DL et al; REACH Registry Investigators. *JAMA*. 2010;304(12):1350-1357.

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Strategies for Improved Patient Care

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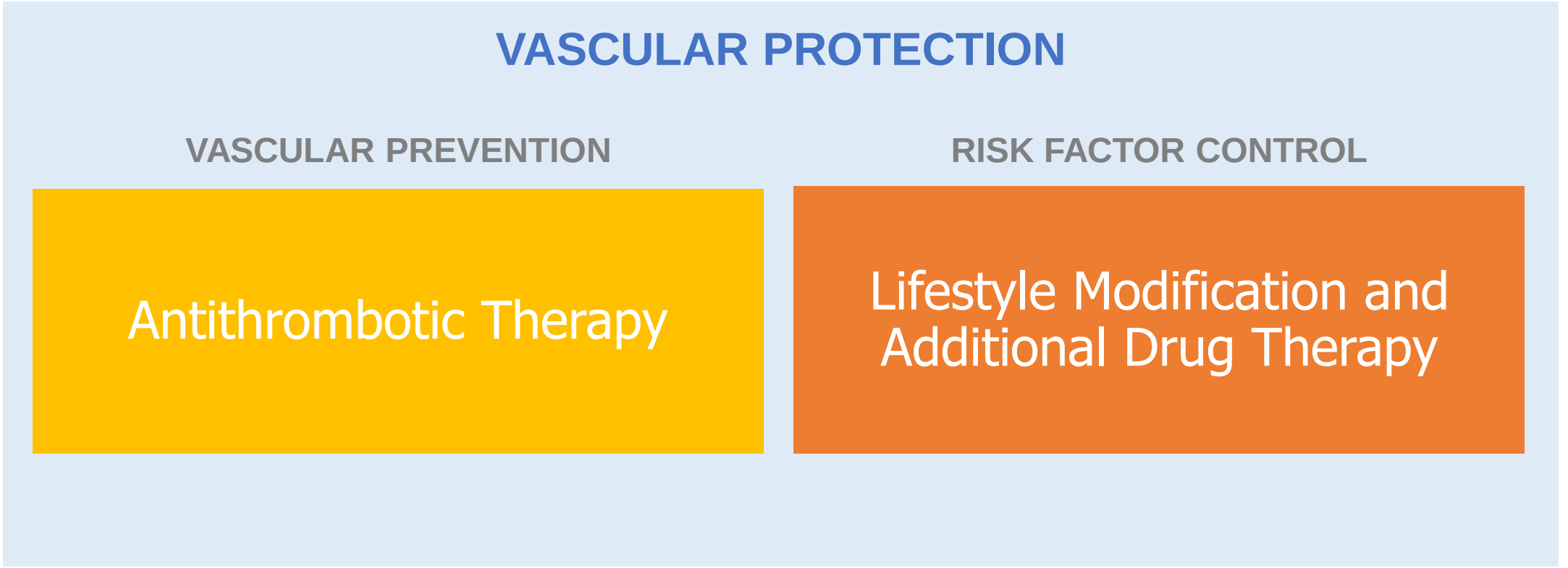
Vascular Protection Requires a Combination of Antithrombotic and Risk Factor Management[1,2]



1. Cortes-Beringola A et al. *Eur J Prevent Cardiol.* 2017;24:22-28. 2. Knuuti J et al. *Eur Heart J.* 2019; doi:10.1093/eutheart/ehz425.

Lifestyle Modifications for SECONDARY CV EVENT PREVENTION

2011 AHA/ACC and 2019 ESC guidelines recommend lifestyle modifications for the secondary prevention and reduction in the risk of CV events in patients with CAD and PAD and other atherosclerotic vascular disease.[1,2]

Smoking cessation

Healthy diet

Physical activity

Weight management

Medication adherence

Please consult the full 2019 ESC and 2011 AHA/ACC Guidelines for all recommendations.

ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease; CV, cardiovascular; ESC, European Society of Cardiology; PAD, peripheral artery disease.

1. Smith SC Jr, et al. *Circulation*. 2011;124(22):2458-2473. 2. Knuuti J, et al. *Eur Heart J*. 2019. pii: ehz425.

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Pharmacologic Treatment Is Recommended for Patients With CAD and PAD

Current AHA/ACC guidelines recommend pharmacologic treatments for the secondary prevention and reduction in the risk of CV events in patients with CAD and PAD.

	Goal	Interventions
Blood Pressure Control	**BP <140/90 mm Hg**	Initial treatment with β-blockers and/or ACE inhibitors, with addition of other drugs as needed
Lipid Management	**LDL <100 mg/dL** **Non-HDL <130 mg/dL** VERY HIGH-RISK PATIENTS: **LDL <70 mg/dL** **Non-HDL <100 mg/dL** If triglycerides are ≥200 mg/dL, **Non-HDL <130 mg/dL**	Statin therapy in the absence of contraindications or documented adverse effects If triglycerides are ≥200 mg/dL, statin therapy to lower non-HDL to <130 mg/dL If triglycerides are >500 mg/dL, fibrate therapy in addition to statin therapy
Antithrombotic Therapy	N/A	Aspirin 75-325 mg daily or clopidogrel 75 mg daily
Type 2 Diabetes Management	**HbA1c ≤7%** may be considered*	Initiate pharmacotherapy to achieve target HbA1c Metformin as first-line pharmacotherapy, if not contraindicated

Please consult the full AHA/ACC Guidelines for all recommendations

ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AHA, American Heart Association; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; HbA1c, glycated hemoglobin, HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable; PAD, peripheral artery disease.

*A less stringent HbA1c goal may be considered in certain patients (eg, those with a history of severe hypoglycemia, limited life expectancy, advanced vascular complications, or extensive comorbidities, or those who are unable to attain goal HbA1c despite intensive therapy). Smith SC Jr et al; World Heart Federation and the Preventive Cardiovascular Nurses Association. *Circulation*. 2011;124(22):2458-2473.

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The Use of Risk Assessment Tools for Targeted Treatment

Risk assessment tools have been generally based on the Framingham Risk Score and the pooled cohort equations.

Both have been shown to overestimate and underestimate risk in some individuals.
Additional tests (for nontraditional risk factors) that could improve risk prediction need to be identified.

Accurate identification of patients at high risk enables more intensive risk factor management to reduce the chance of a CV event.

Risk estimation in patients with CVD can help support decision-making for targeted secondary prevention of CV events.

CV, cardiovascular; CVD, cardiovascular disease.
Curry SJ et al; US Preventive Services Task Force. *JAMA*. 2018;320(3):272-280.

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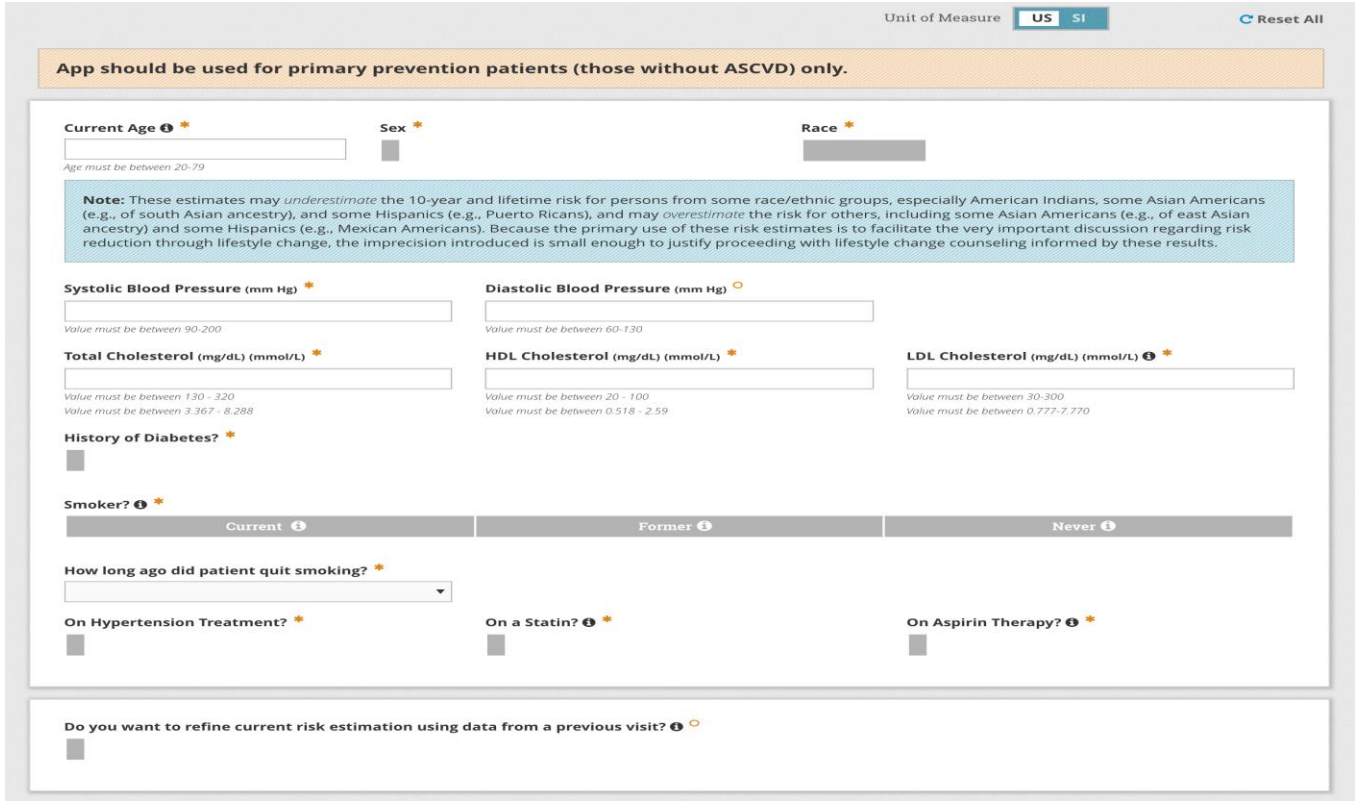
ACC ASCVD Primary Prevention Risk Evaluator Plus Tool



Low Risk	Borderline Risk	Intermediate Risk	High Risk
<5.0%	5.0%-7.4%	7.5%-19.9%	≥20.0%

- Estimates individual 10-year ASCVD risk at initial visit*
- Assumes no previous cardiovascular disease
- Forecasts potential impact of interventions on patient risk
- Aids clinician-patient discussions on risk and risk-lowering interventions

ACC, American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease. *App is intended for primary prevention for patients without ASCVD.
American College of Cardiology. ASCVD risk estimator plus. American College of Cardiology website. Accessed January 22, 2020.

SMART Assessment Tools

SMART Risk Score[2]

Estimates individual 10-year risk for MI, stroke, or vascular death in patients with previous CVD (including CAD and PAD) if standard care is provided.[1] Developed through an analysis of a secondary prevention population of patients with vascular disease (N = 6904) from the SMART study.[3]

The results of this analysis indicated that[3]:

- A total of 18% of patients had a <10% risk of recurrent CV event at 10 years; 22% had a >30% risk at 10 years
- If all modifiable risk factors were at guideline-recommended targets, 10-year risk of recurrent vascular events could be reduced to <10% for about half of the patients with vascular disease; 20% remained at >20% risk. and 9% remained at >30% risk of recurrent event

SMART–REACH Model[4]

Estimates 10-year CV event risk and improvement in life expectancy without recurrent CV events in individuals with CAD and/or PAD, if preventive treatment is provided.[4]

CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral artery disease; SMART, Secondary Manifestations of ARTerial disease.

1. Dorresteijn JA, et al; SMART Study Group. *Heart*. 2013;99(12):866-872. 2. The SMART Risk Score. European Society of Cardiology website. escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score. Published June 20, 2017. Accessed January 31, 2020. 3. Kaasenbrood L, et al. *Circulation*. 2016;134(19):1419-1429. 4. Kaasenbrood L, et al. *J Am Heart Assoc*. 2018;7(16):e009217.

ACC/AHA Very High-Risk Criteria

REACH Cohort

MACE: **2773 events**

Average incidence of recurrent MACE: **5.1/100 PY**

Median follow-up: **1.8 years**

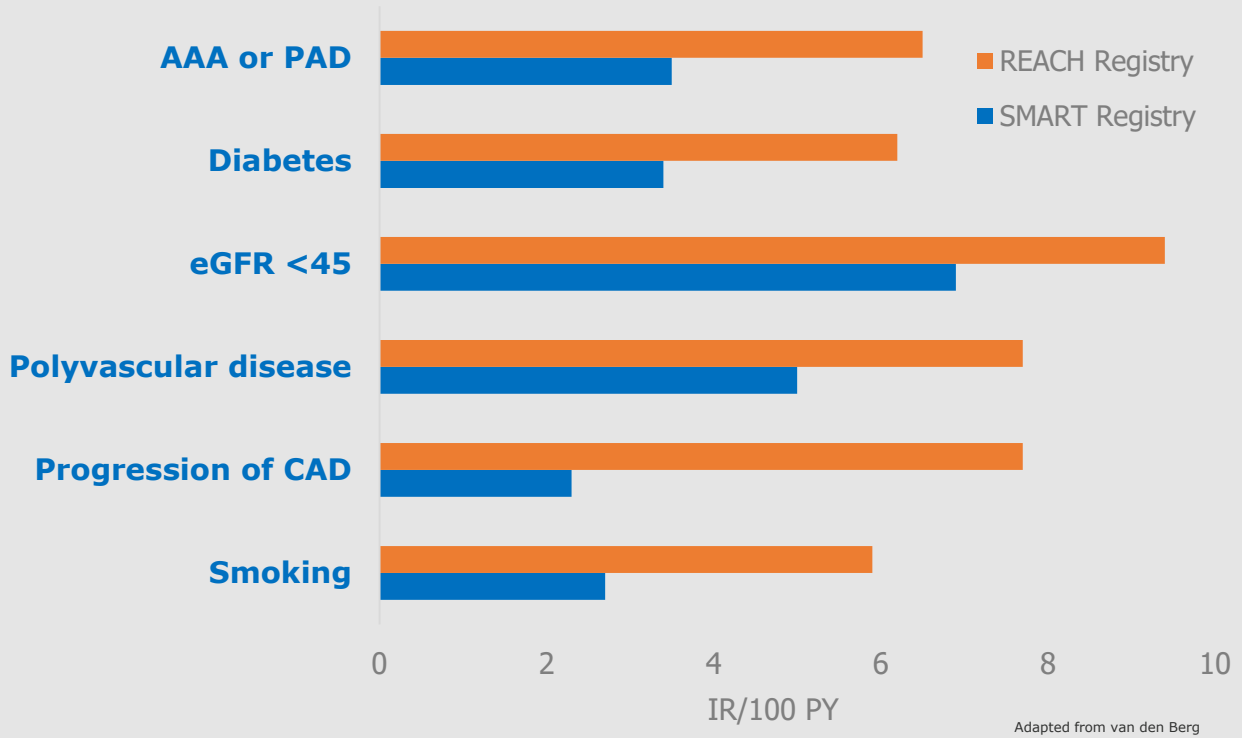
SMART Cohort

MACE: **1185 events**

Average incidence of recurrent MACE: **2.4/100 PY**

Median follow-up: **6.5 years**

Incidence for Recurrent MACE With Select High-Risk Factors



Adapted from van den Berg

AAA, abdominal aortic aneurysm; ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; IR, incidence rate; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; PY, person years; REACH, REduction of Atherothrombosis for Continued Health; SMART, Second MAnifestations of ARTerial disease.

Van den Berg MJ et al. *Eur Heart J.* 2017;38(43):3211-3218.

janssen

Which Patients Are at HIGHEST RISK For Ischemic Events?

Diffuse Multivessel CAD (Polyvascular)*

PAD

Heart Failure

Renal Insufficiency†

Recurrent MI

Diabetes‡

*>2 vascular beds
†eGFR 15-59 mL/min.
‡Requires medication.

Knuuti J, et al. *Eur Heart J*. 2019;00:1-71.

Polling Question

What will you do differently after this presentation?

- ☐ Create care pathway for CAD/PAD patients
- ☐ Apply patient identification at point of EHR
- ☐ Educate health system on CAD/PAD
- ☐ Nothing different
- ☐ Other

CAD, coronary artery disease; PAD, peripheral artery disease.

Webinar Summary

Overview of CAD and PAD

- Chronic CAD/PAD cost the US healthcare system billions of dollars a year and these patients are at risk of secondary thrombotic events associated with ASCVD[1-6]

Current Standards of Care

- Updated therapy guidelines recommend evaluating high-risk patients for individualized therapy[7]

Opportunities for Improvement in Standards of Care

- Risk of CV events exists even for patients with stable disease[8]

Strategies for Improved Patient Care

- Targeted risk assessment tools can help to accurately identify high-risk CAD/PAD patients who can benefit from more intensive risk factor management and follow up strategies[9]

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; PAD, peripheral artery disease.

1. Projections of cardiovascular disease prevalence and costs: 2015-2035. https://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491513.pdf. Accessed March 3, 2020. 2. CardioVascular Coalition. Peripheral artery disease (PAD). http://cardiovascularcoalition.com/cardiovascular-care/peripheral-artery-disease-pad/ Accessed March 3, 2020 3. Yost ML. *Endovasc Today*. 2014:29-36. 4. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/stroke. Accessed March 3, 2020. 5. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/peripheral-artery-disease. Accessed March 3, 2020. 6. Gerhard-Herman MD et al. *J Am Coll Cardiol*. 2017;69(11):1465-1508. 7. Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2019. 8. Bhatt DL, Eagle KA, Ohman ME, et al; REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304(12):1350-1357. 9. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Risk assessment for cardiovascular disease with nontraditional risk factors: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(3):272-280