Atherosclerotic Cardiovascular Disease (ASCVD) Risk Prediction

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Disclosures

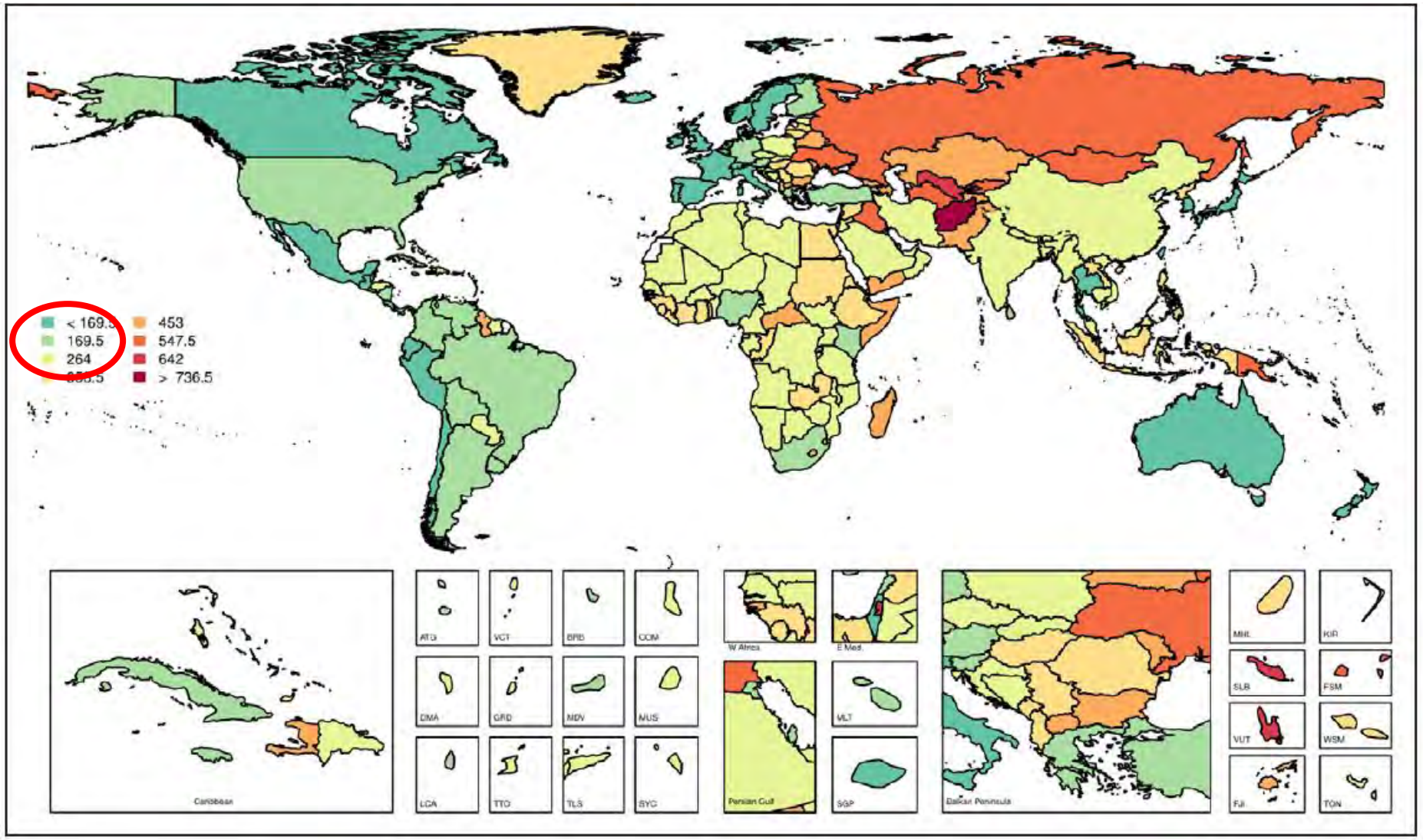
Jennifer G Robinson MD MPH:

- Received research grants to Institution from Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Esperion, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, Takeda
- Consultant for Amgen, Medicines Company, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, and Sanofi
- Vice Chair, 2013 ACC/AHA Cholesterol Guideline
- Member, 2013 ACC/AHA Risk Assessment Guideline

Burden of ASCVD

Global CVD mortality

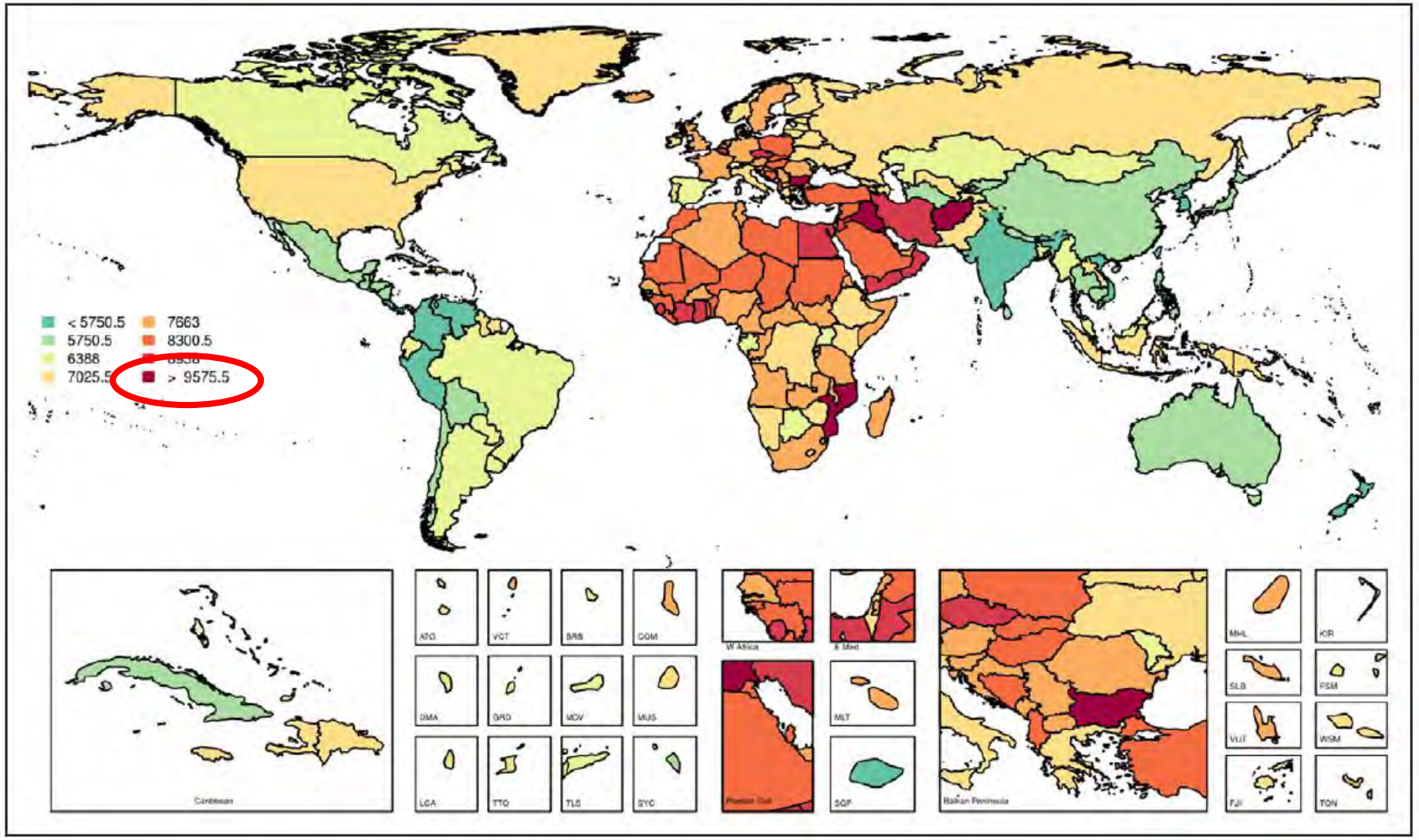
Age-standardized 2016



Benjamin E, et al. Circulation 2019; https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000659

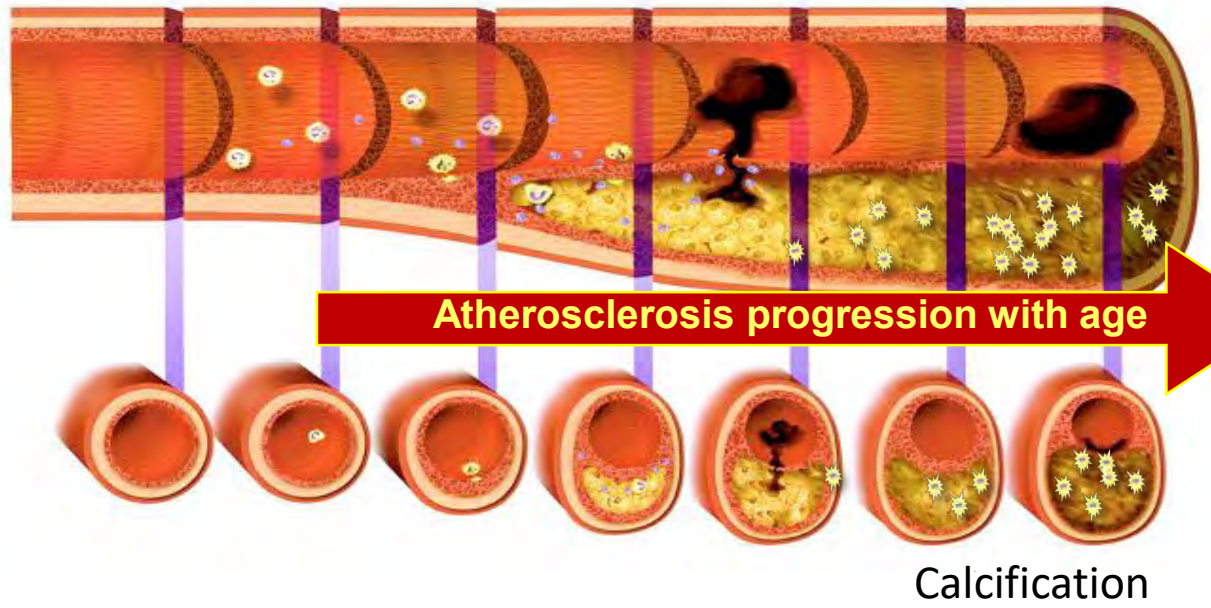
Global CVD prevalence

Age-standardized 2016



Benjamin E, et al. Circulation 2019; https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000659

Atherosclerotic cardiovascular disease (ASCVD) progression through the lifespan

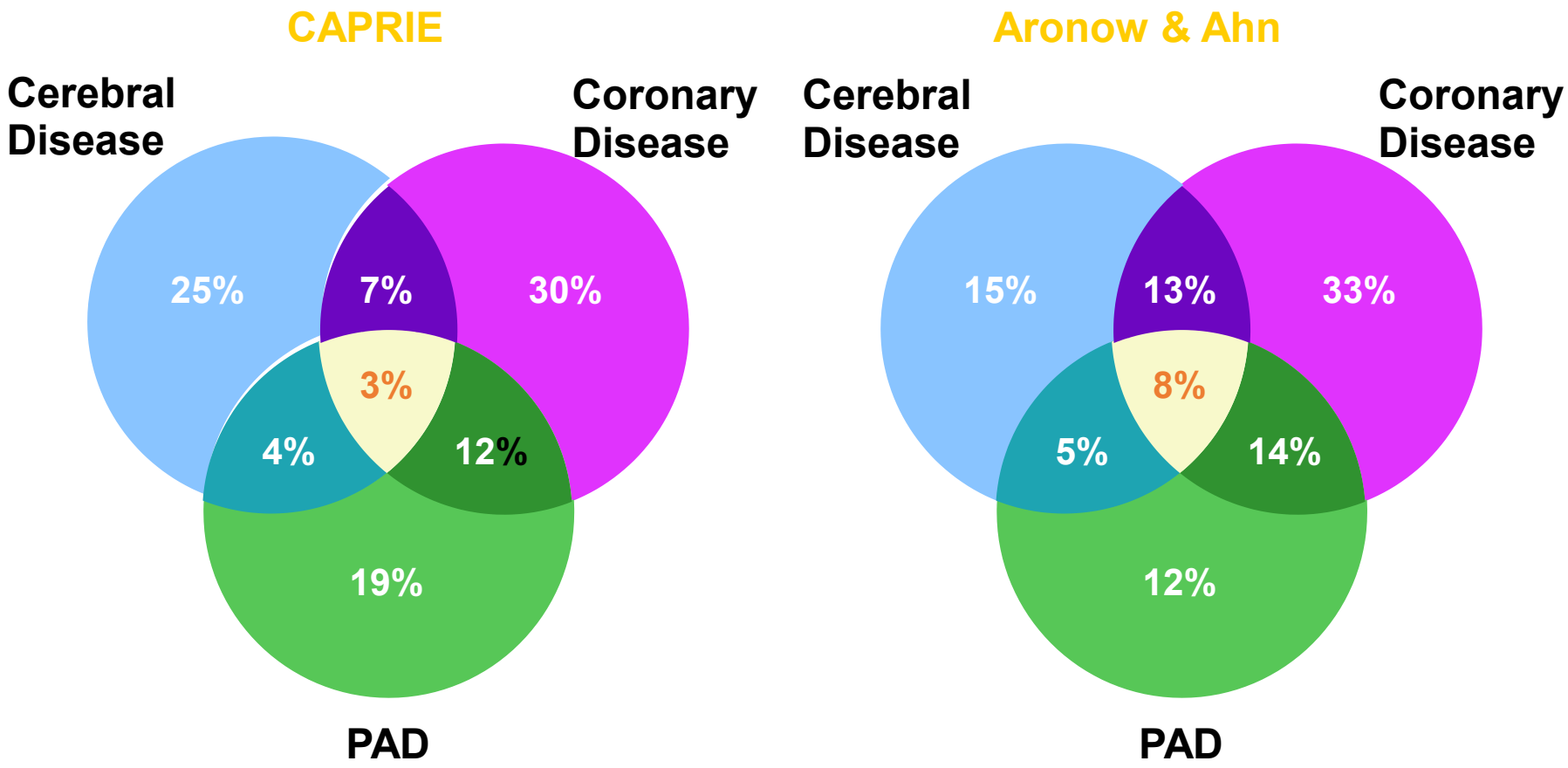


ASCVD EVENTS

- Acute coronary syndromes - MI/Unstable angina
- Ischemic stroke/TIA
- Critical leg ischemia
- Intermittent claudication
- CV death

Illustration Adapted from Libby P. Circulation 2001;104:365–372

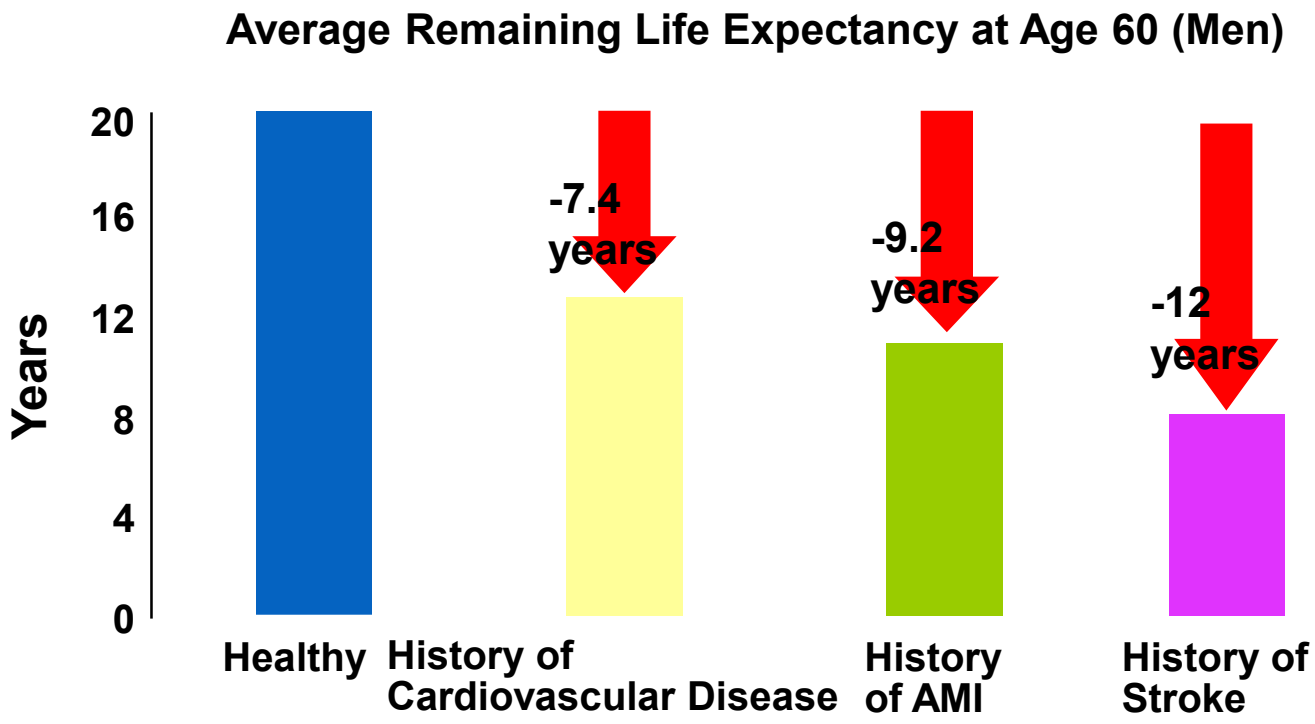
Overlap of clinical manifestations of ASCVD



PAD, peripheral artery disease.
Adapted from TransAtlantic Inter-Society Consensus Group. *J Vasc Surg*. 2000;31:S16.

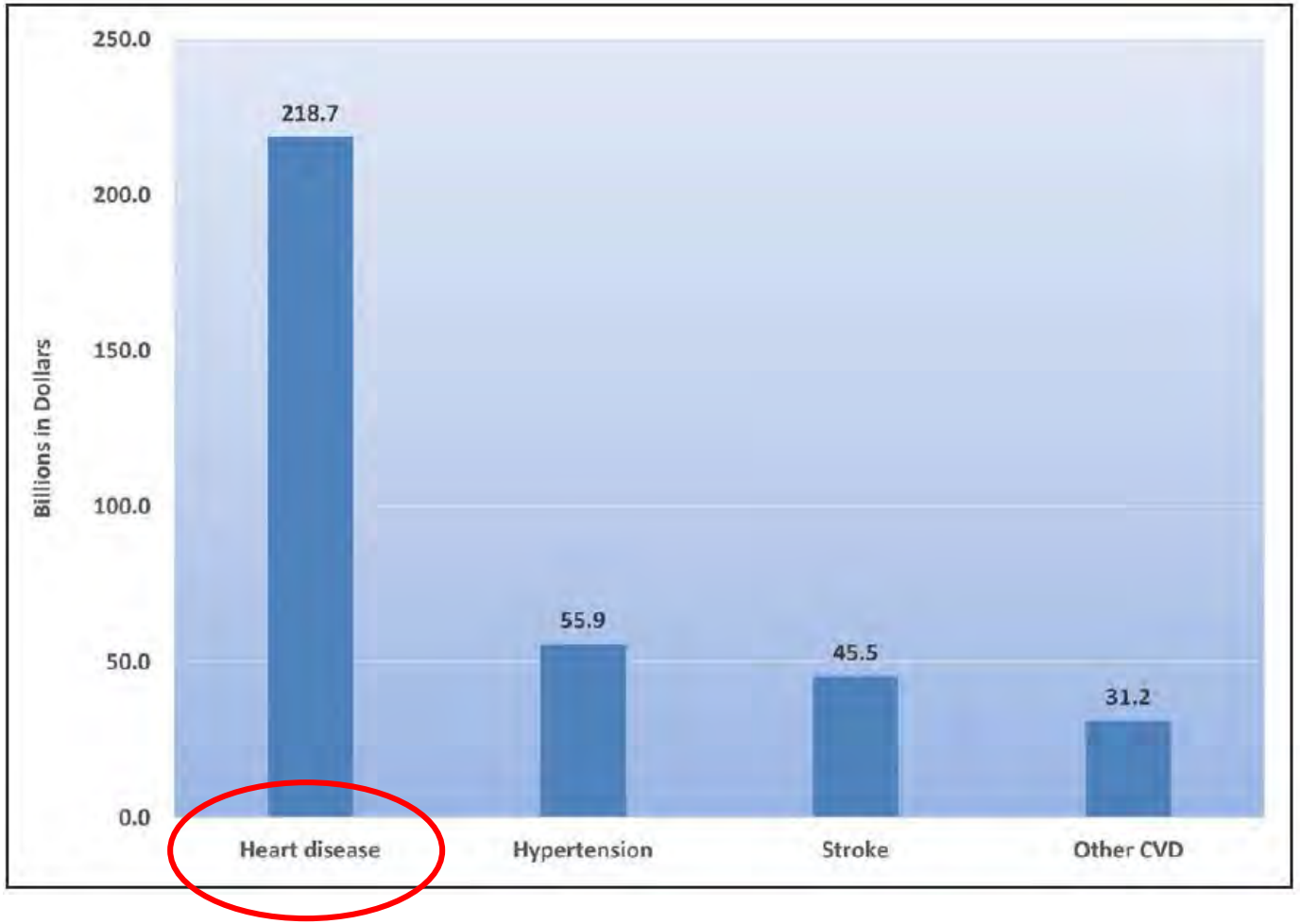
ASCVD Shortens Life Expectancy

ASCVD reduces life expectancy by around 8-12 years in patients aged over 60 years[1]



Analysis of data from the Framingham Heart Study.
Peeters A, et al. *Eur Heart J.* 2002;23:458-466.

Direct and indirect costs of cardiovascular disease (CVD) and stroke (in billions of dollars), United States, 2015.



Benjamin E, et al. Circulation 2019; https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000659

ASCVD Risk Factors

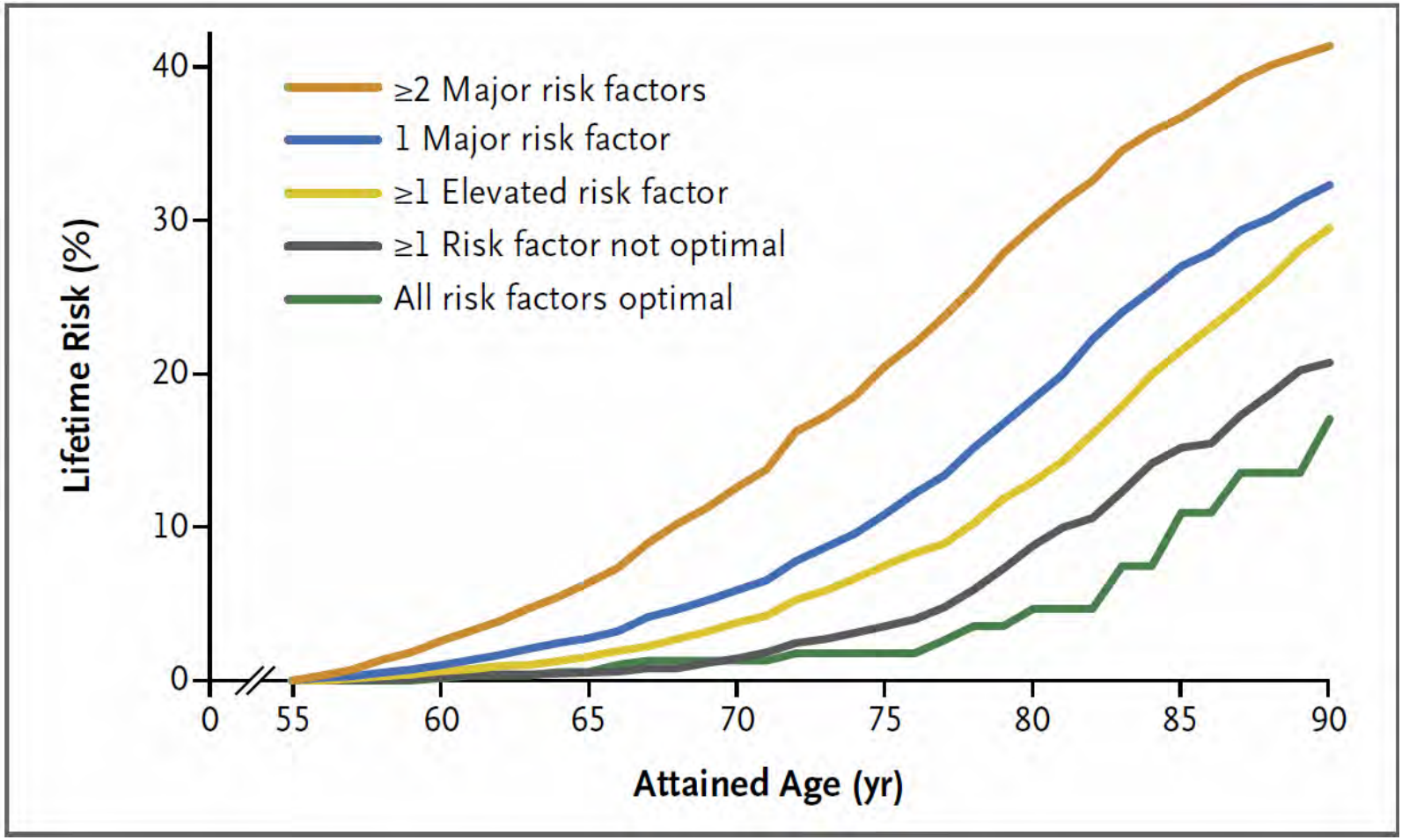
“Traditional” CVD risk factors

- Age
- Sex
- Smoking
- High blood pressure
- High total /LDL-cholesterol
- Low HDL-cholesterol
- Family history premature CVD
- Diabetes mellitus

Risk factors are important

- Traditional risk factors cause >85% of lifetime CVD risk
- Effective risk factor treatment can lower lifetime CVD risk by >80%
- Effective risk factor treatment can prolong life by at least 11 years (if started by age 55)
- Risk factors are additive

Number of “traditional” risk factors predict lifetime risk of ASCVD

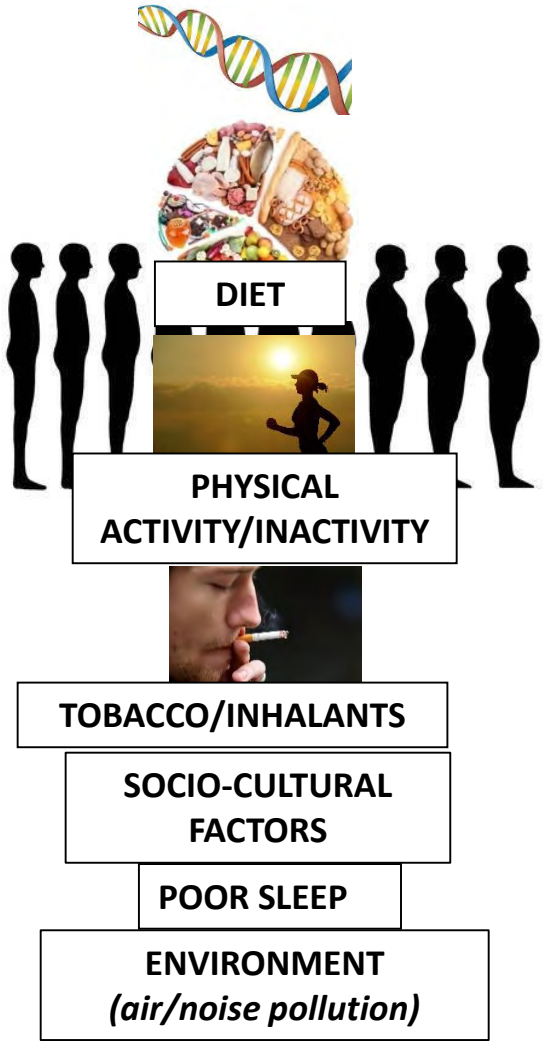


Berry, J.D., et al. N Engl J Med, 2012. **366**(4): p. 321-329.

Lifestyle risk factors

- Obesity
- Lack of physical activity
- Poor diet
  - High fat/saturated fat
  - Low fruits/vegetables
  - Low fiber/whole grains
- Poor sleep
- Increased levels of other risk factors
- Also have independent effects

ASCVD risk



GENES

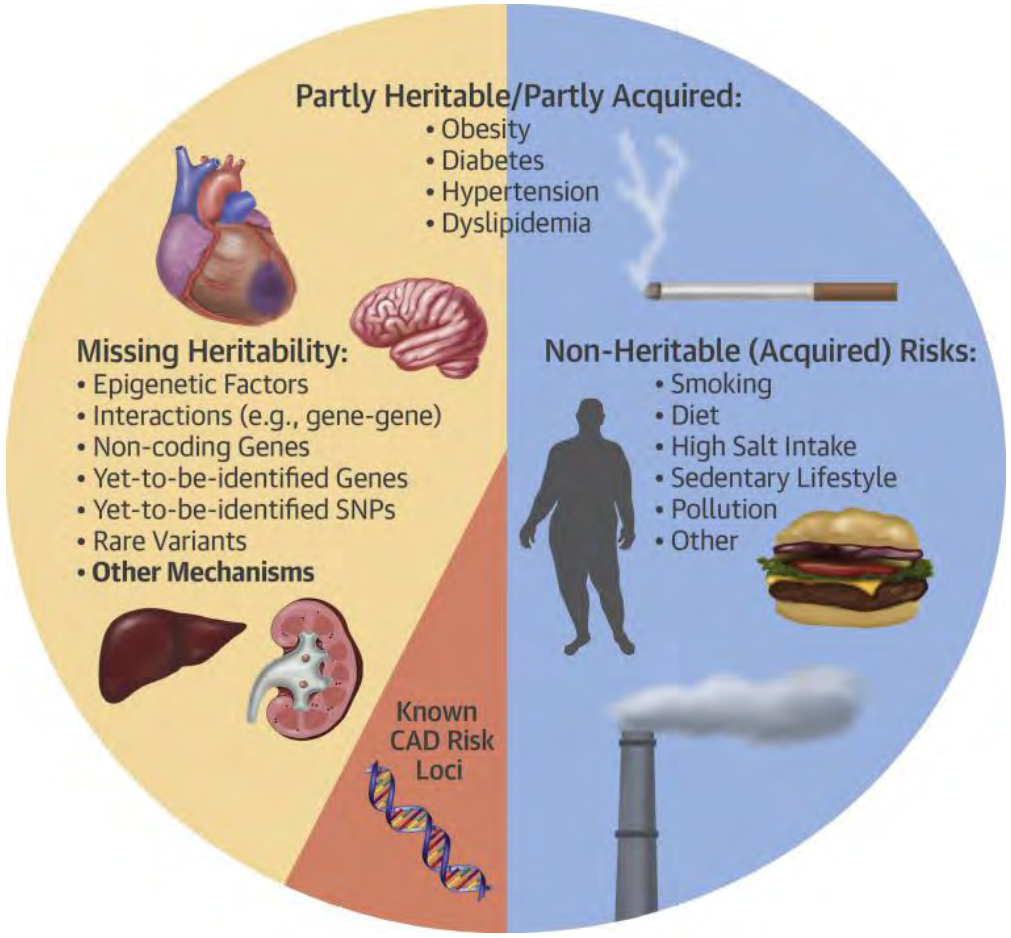
X

LIFESTYLE & EXPOSURES

Measured as & effect mediated by "Traditional Risk Factors"

- Age
- Sex
- Race
- Hypertension (high blood pressure)
- Smoking
- High "bad" cholesterol (LDL-cholesterol)
- Low "good" cholesterol (HDL-cholesterol)
- Diabetes

Heritability of CHD



Suspected and Known Factors Responsible for CAD
The basis of "missing heritability" remains a topic of intense ongoing speculation. The factors depicted here illustrate specific aspects that appear to be of potential relevance, rather than being in any way a definitive or exhaustive list of all factors that cause coronary artery disease (CAD). SNP = single nucleotide polymorphism.

Kovacic JC. JACC 2017; 69: 837-840

Biomarkers or "Non-traditional risk factors"
Add little or no new information to traditional risk factors

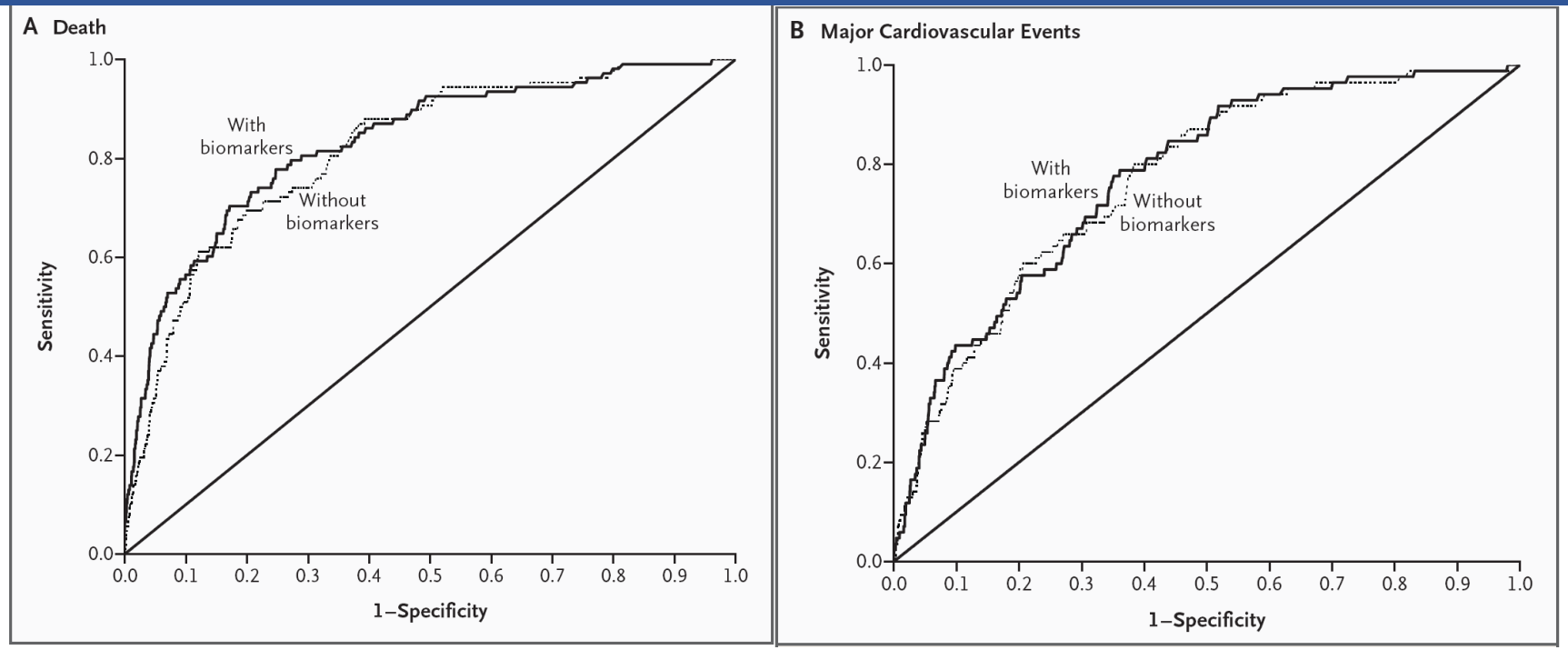


Figure 2. Receiver-Operating-Characteristic Curves for Death (Panel A) and for Major Cardiovascular Events (Panel B) during 5-Year Follow-up.

For each end point, curves are based on models of the prediction of risk with the use of conventional risk factors with or without biomarkers (multimarker score). Biomarkers for death were B-type natriuretic peptide, C-reactive protein, the urinary albumin-to-creatinine ratio, homocysteine, and renin. Biomarkers for major cardiovascular events were B-type natriuretic peptide and the urinary albumin-to-creatinine ratio.

Wang TJ, Gona P, Larson MG, et al. N Engl J Med 2006;355(25):2631-9

Explanations for Dramatic Decline CHD Mortality in US over 30 years

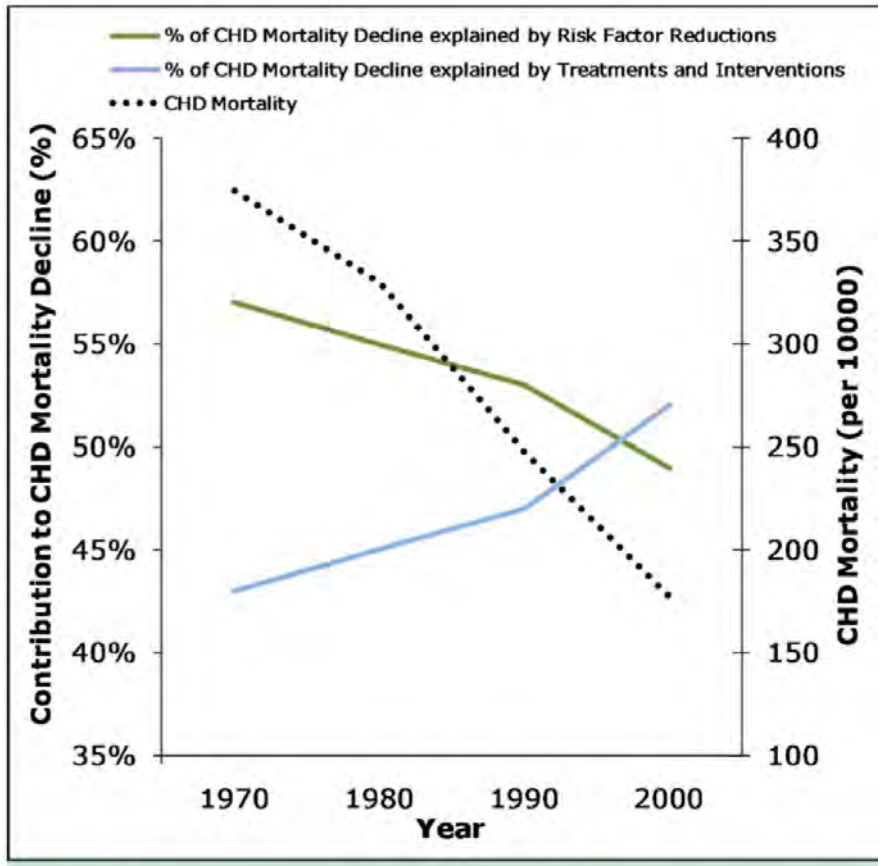


Figure 2 Contribution to the decline of coronary heart disease mortality of risk factor control, medical treatments, and interventions in the US from 1968 to 2000. Data drawn from the National Vital Statistics System of the US and Goldman and Cook,[20] Hunink et al,[21] and Ford et al.[22]

- 50% due to ↓risk factors
- 50% due to acute treatment/interventions

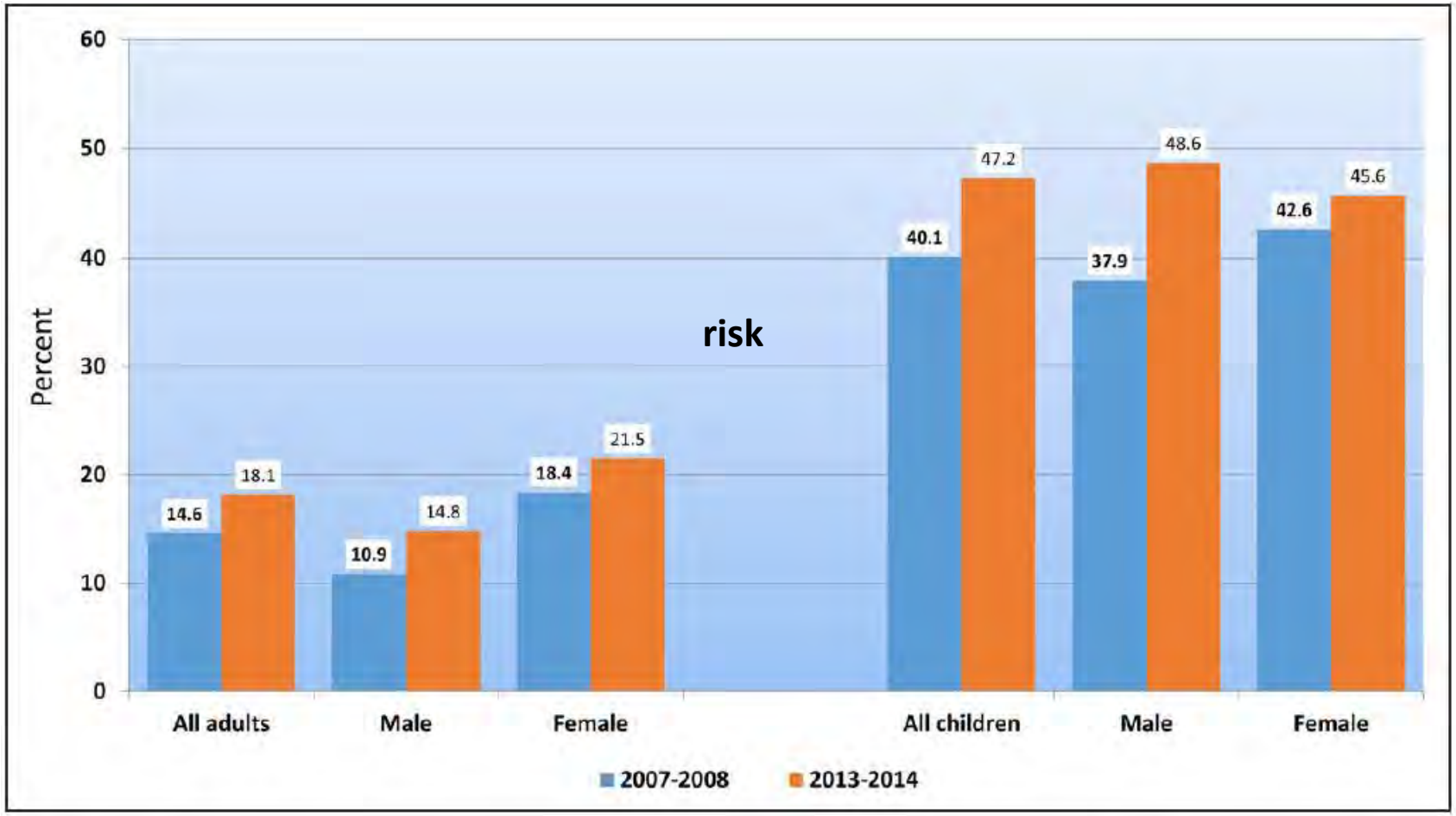
Franco, et al. Am J Med 2011; 124: 95-102

AHA's 7 Metrics of Ideal CV Health
Low lifetime ASCVD risk

- **Never/Nonsmoker >12 months**
- **BMI <25 mg/kg^2**
- **150+ min/week moderate or 75+ vigorous**
- **4-5 Healthy diet components**
- **Total cholesterol <200 mg/dl**
  - **LDL-C <100 mg/dl (2.6 mmol/L)**
  - **Non-HDL-C <130 mg/dl (3.4 mmol/L)**
- **BP <120/<80 mm Hg**
- **Fasting glucose <100 mg/dl**

Benjamin E, et al. Circulation 2019; https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000659

Prevalence of meeting ≥5 of 7 Ideal CV Health metrics, US



Benjamin E, et al. Circulation 2019; https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000659

ASCVD Risk Prediction

ASCVD Risk Prediction

- **Why:**
  - Prioritize patients for intervention
  - Guide intensity of intervention
- **Who:**
  - Primary prevention LDL-C <190 mg/dl (4.9 mmol/L) risk estimation to guide treatment
    - Age 20-75 years
    - No history of clinical ASCVD event
    - Not on statin therapy
  - Secondary prevention – Considered high/very high risk all guidelines
    - No validated equations yet to predict ASCVD risk in patients with subclinical or clinical ASCVD
- **When:**
  - Lifetime risk: Age 20-55 years, every 4-6 years thereafter
  - 10-year ASCVD risk: age 40-75 years, every 4-6 years thereafter
- **How:**
  - US PCEs adapted to your country

Types of events predicted

- **ASCVD - US**
  - **Myocardial infarction, stroke, CVD death**
- **Cardiovascular death - Europe**
- MACE (Major adverse cardiovascular events) – clinical trial endpoint
  - ASCVD + arterial revascularizations (coronary ± carotid ± peripheral) + hospitalized(unstable) angina
- Heart failure
  - Ischemic & noniscehmic causes
  - HfPEF & HfREF
- All-cause death

Risk prediction equations - US

- **U.S. Pooled Cohort Equations (PCE) – 10-year & Lifetime ASCVD Risk**
  - Variables: Age, sex, race, smoking, total cholesterol, HDL-C, systolic BP/antihypertensive treatment, diabetes
  - Derived from 5 US epidemiologic cohorts of Caucasian & African American women & men
    - Validated in general US population of Caucasian & African Americans
      - Overestimates ASCVD risk in lower risk populations
        - East Asian ancestry (China, Japan, Korea), insured, volunteers)
      - Underestimates risk in higher risk populations
        - South Asians (India, Pakistan, Bangledesh), Pacific Islanders, Native Americans
      - Has not been evaluated in Middle-Eastern ancestry US population

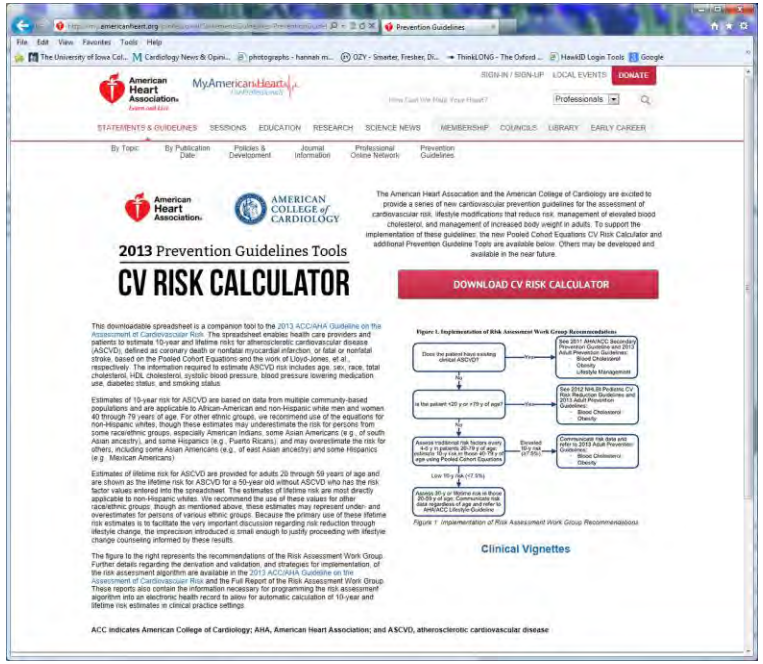
US PCE Risk Calculator/Apps

- http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

- iTunes (iPhones, iPads) -> https://itunes.apple.com/us/app/ascvd-risk-estimator/id808875968?mt=8&ign-mpt=uo%3D2

- Google Play (Android phones/tablets) -> https://play.google.com/store/apps/details?id=org.acc.cvrisk&hl=en

- Web Version (Desktops) -> http://tools.cardiosource.org/ASCVD-Risk-Estimator/

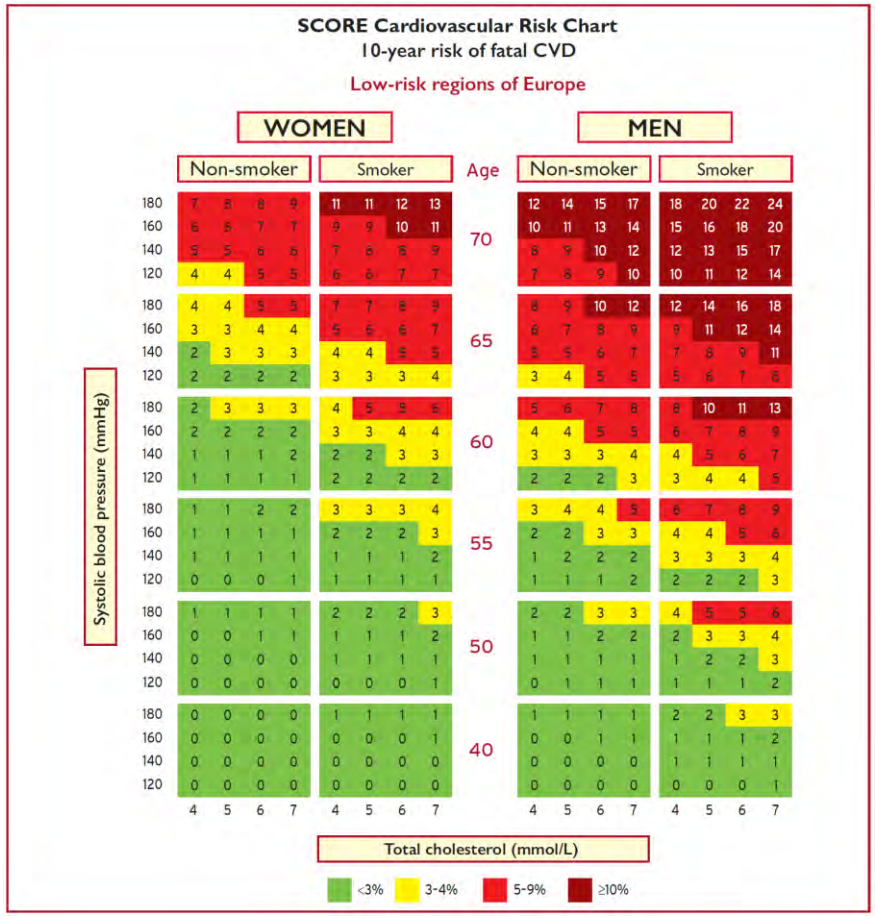


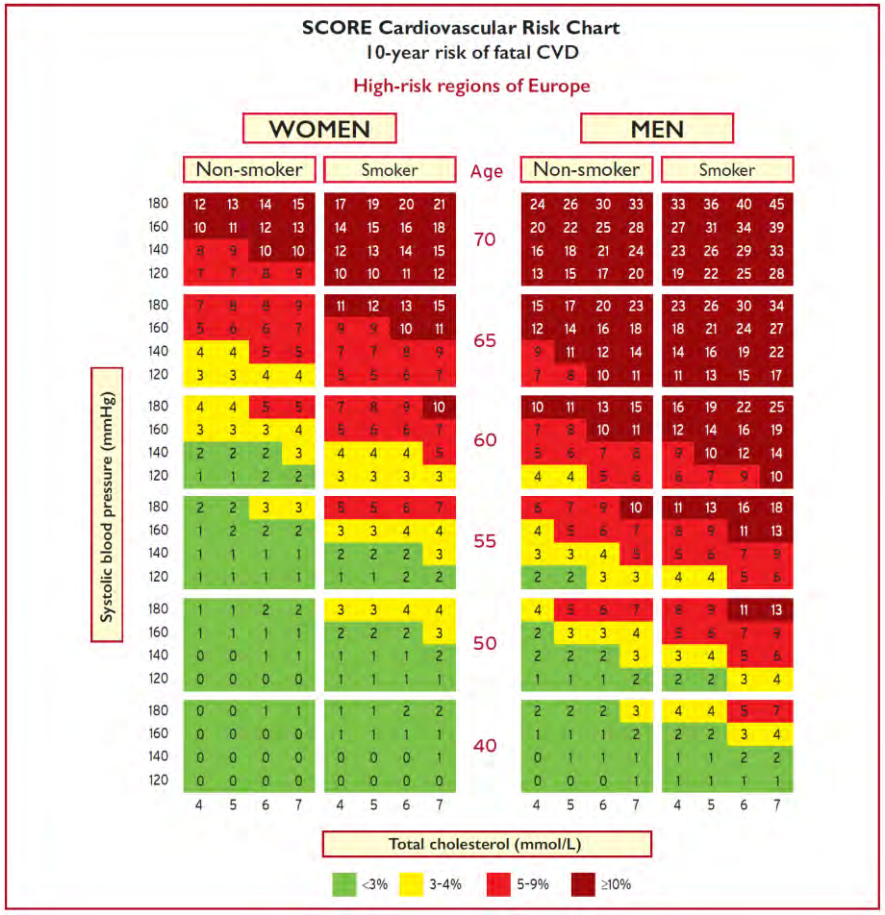
Risk stratification – ESC/EAS guideline

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

Mach F, et al. Eur Heart J 2020; 41: 111-188

SCORE – 2019 ESC/EAS Dyslipidemia Guideline





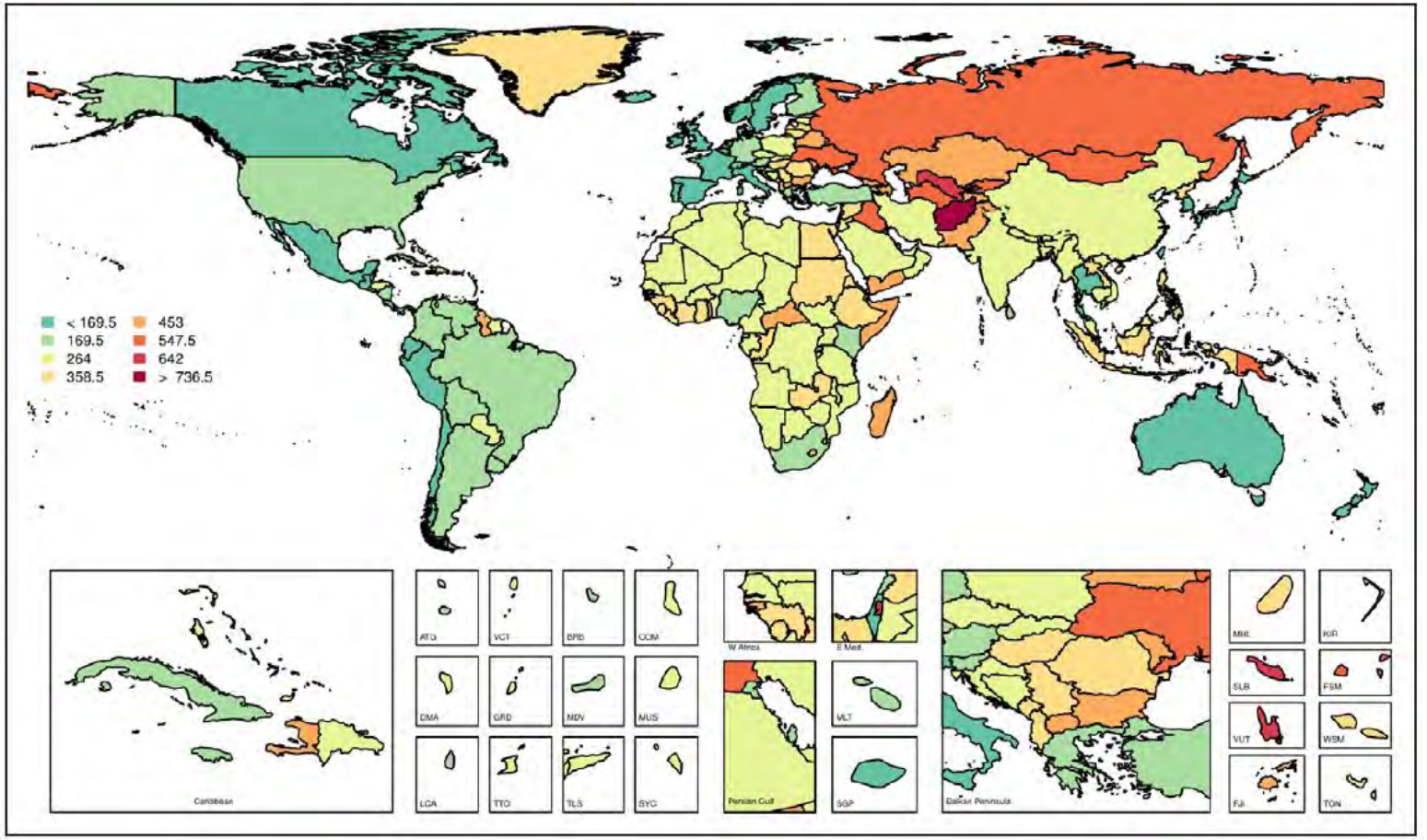
Mach F, et al. Eur Heart J 2020; 41: 111-188

Risk prediction equations – Europe

- SCORE – 5-year CV death
  - CVD deaths 25% of ASCVD events
  - Low risk and high risk European countries
  - **PCE perform better in all populations** for predicting population burden of ASCVD and benefit from statin therapy
- QRISK3 – 10-year risk CHD, stroke, TIA
  - Highly specific to UK
  - 18 variables including socioeconomic risk factors & comorbidities

Mach F, et al. Eur Heart J 2019; 41: 111-188; Mortenson MB, et al. JAMA Cardiol 2019; 4: 1131-1138; Hippisley-Cox J, et al BMJ 2017; 357: j2099 doi: 10.1136/bmj.j2099

Global CVD mortality, Age-standardized 2016



Oman 264/US 169.6 =
1.56 X higher risk in Oman

Oman 264/Low Europe 150 =
1.76 X higher risk in Oman

Average Omani risk estimate could be 50-75% higher than US PCE or ESC/EAS SCORE!!

Benjamin E, et al. Circulation 2019; https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000659

Application of Risk Prediction Equations

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary

Arnett D, et al . Journal of the American College of Cardiology 2019; 74: 1376-1414 and *Circulation* 2019;
https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000677

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Assessment of Cardiovascular Risk

Recommendations for Assessment of Cardiovascular Risk		
COR	**LOE**	**Recommendations**
I	B-NR	1. For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using the pooled cohort equations (PCE).
IIa	B-NR	2. For adults 20 to 39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4 to 6 years.
IIa	B-NR	3. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors* to guide decisions about preventive interventions (e.g., statin therapy).

*Our recent analyses found risk enhancing factors do not increase risk.

Base treatment decisions on the estimated 10-year ASCVD risk

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Assessment of Cardiovascular Risk (cont'd)

Recommendations for Assessment of Cardiovascular Risk		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**4. In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions (e.g., statin therapy) remain uncertain, it is reasonable to measure a coronary artery calcium score to guide clinician–patient risk discussion.**
IIb	**B-NR**	**5. For adults 20 to 39 years of age and for those 40 to 59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered.**

Table 3. Risk-Enhancing Factors for Clinician-Patient Risk Discussion

Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions,** such as psoriasis, RA, lupus, or HIV/AIDS

Our recent analyses found risk enhancing factors do not increase risk.
Base treatment decisions on the estimated 10-year ASCVD risk

ABI indicates ankle-brachial index; AIDS, acquired immunodeficiency syndrome; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and RA, rheumatoid arthritis.

Table 3. Risk-Enhancing Factors for Clinician-Patient Risk Discussion (cont'd)

Risk-Enhancing Factors
• **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia** • **High-risk race/ethnicity** (e.g., South Asian ancestry) • **Lipids/biomarkers**: associated with increased ASCVD risk • Persistently elevated,* primary hypertriglyceridemia (≥175 mg/dL, nonfasting); • If measured: ▪ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L) ▪ **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a). ▪ **Elevated apoB** (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor ▪ **ABI** (<0.9)

*Optimally, 3 determinations.

LDL-C Lowering Therapy

Primary prevention statin therapy		
COR	**LOE**	**Recommendations**
I	**A**	**1. In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended.**
I	**A**	**2. In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more.**

LDL-C Lowering Therapy

Primary prevention statin therapy		
COR	**LOE**	**Recommendations**
I	**A**	**3. In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.**
I	**B-R**	**4. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.**

LDL-C Lowering Therapy

Primary prevention statin therapy- Diabetes		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**5. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.**
IIa	**B-R**	**6. In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy*.**

* recent analyses show risk enhancing factors do not increase risk
Base treatment decisions on risk cut-point

LDL-C Lowering Therapy

Primary prevention – Optional CAC scoring		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**7. In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND** • **If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking, LDL-C <130 mg/dl);** • **If coronary artery calcium score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age;** • **If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.**

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Adults with High Blood Cholesterol (cont'd)

Recommendations for Adults with High Blood Cholesterol		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**8. In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.**

Fig. 3.

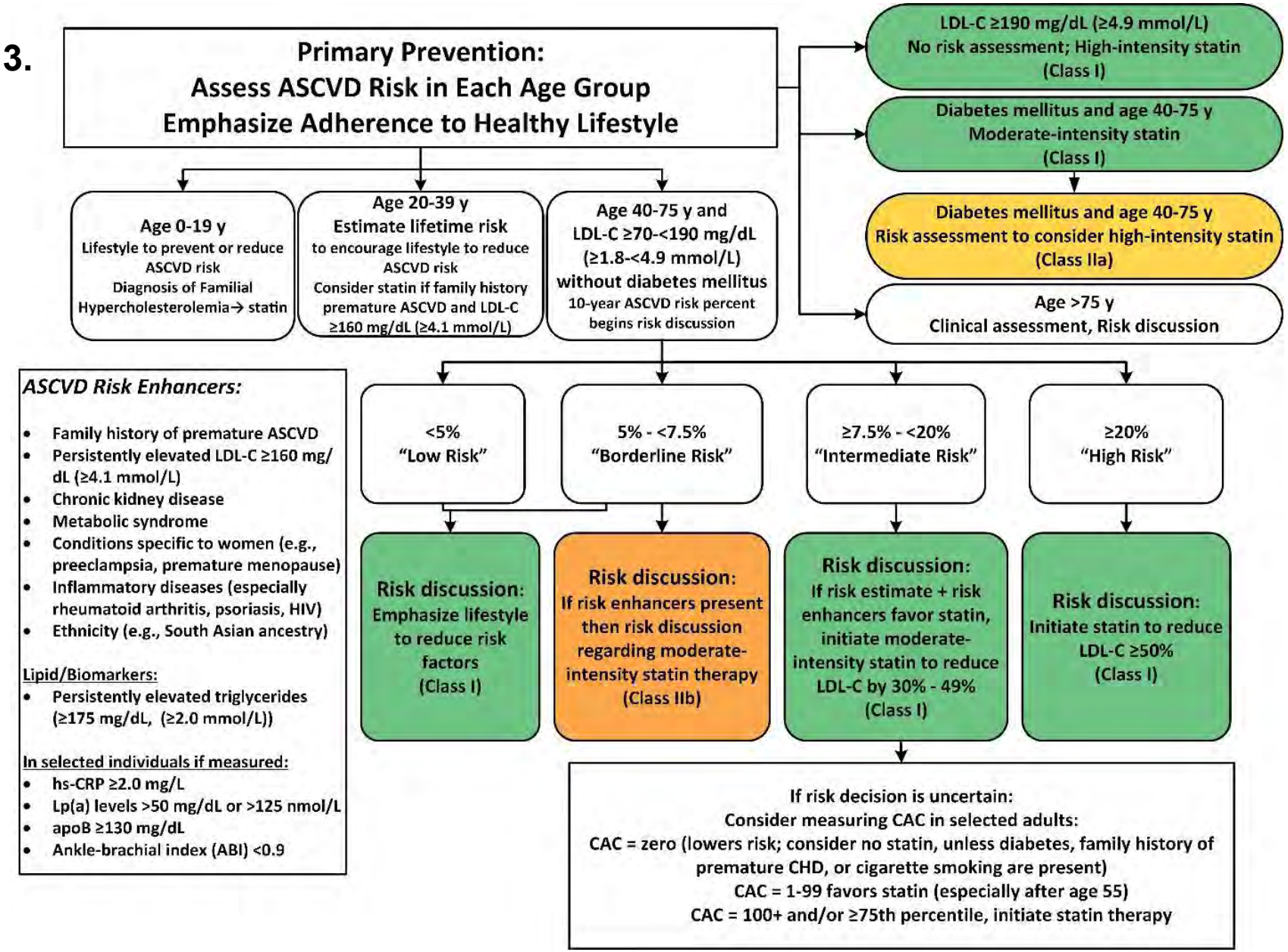


Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers in Diabetic Patients
• Long duration (≥10 years for T2DM (S4.3-36) or ≥20 years for type 1 diabetes mellitus (S4.3-16)) • Albuminuria ≥30 mcg albumin/mg creatinine (S4.3-37) • eGFR <60 mL/min/1.73 m^2 (S4.3-37) • Retinopathy (S4.3-38) • Neuropathy (S4.3-39) • ABI <0.9 (S4.3-40, S4.3-41)

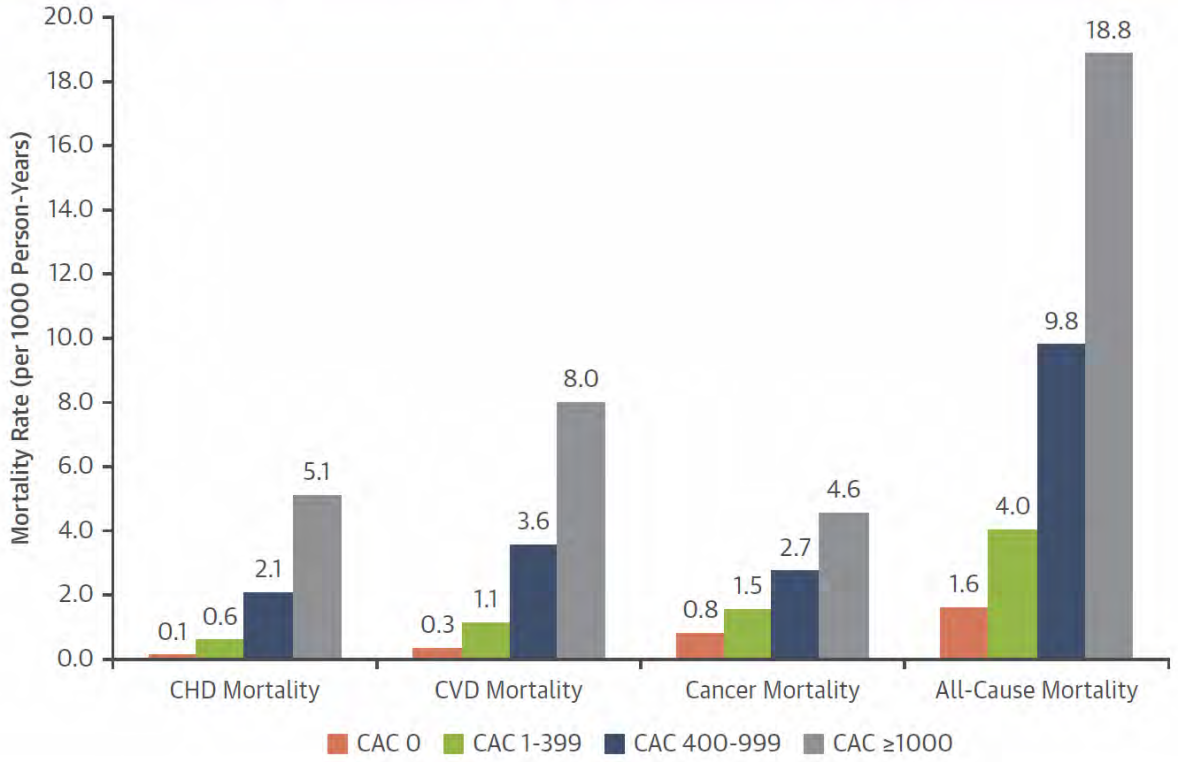
ABI indicates ankle-brachial index; eGFR, estimated glomerular filtration rate; and T2DM, type 2 diabetes mellitus.

Table 6. Selected Examples of Candidates for CAC Measurement Who Might Benefit from Knowing Their CAC Score is Zero

CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero
• Patients reluctant to initiate statin who wish to understand their risk and potential for benefit more precisely • Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms • Older patients (men 55–80 y of age; women 60–80 y of age) with low burden of risk factors (S4.4-42) who question whether they would benefit from statin therapy • Keep CAC zero! I disagree with this one: Adults (40–55 y of age) with PCE-calculated 10-year risk for ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group.

Presence of CAC predicts all-cause death

FIGURE 1 Mortality Rate Per 1,000 Person-Years for CVD, CHD, Cancer, and All-Cause Mortality by CAC Score Group



Incidence rates increased for all-cause and cause-specific mortality with increasing CAC scores. Particularly those with CAC score ≥1,000 had a 5.1, 8.0, 4.6, and 18.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively. In contrast, those with CAC scores from 400 to 99 had a 2.1, 3.6, 2.7, and 9.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively. *A version of this figure including error bars for 95% confidence interval can be found in Supplemental Figure 1. CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease.

Blaha M, et al JACC Imaging 2020; 13: 83-83

Adults with High Blood Pressure or Hypertension

Recommendations for Adults with High Blood Pressure or Hypertension		
COR	**LOE**	**Recommendations**
I	**SBP: B-R[SR]**	**5. In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg.**
	DBP: C-EO	
I	**C-LD**	**6. In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended.**

Secondary Prevention
ASCVD Risk Prediction

Journal of Clinical Lipidology (2019) 13, 525–537

Journal of Clinical Lipidology

Scientific Statement

Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. A consensus statement from the National Lipid Association

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KEYWORDS:
PCSK9 inhibitors;
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Cost-effectiveness

Abstract: Acquisition costs and cost-effectiveness have limited access and recommendations to use proprotein convertase subtilisin/kexin type 9 (PCSK9)–inhibiting monoclonal antibodies (mAbs). Recently, prices were reduced by 60% for alirocumab and evolocumab. This statement systematically reviewed subgroup analyses from statin and PCSK9 mAb trials to identify higher risk groups for which PCSK9 mAbs at the new price could be considered a reasonable (<US$100,000 per quality adjusted life year [QALY]) or high (<US$50,000 per QALY) value. In patients at extremely high risk, with a high burden of atherosclerotic cardiovascular disease (ASCVD) or ASCVD with multiple poorly controlled or adverse risk factors, PCSK9 mAbs can provide reasonable value when low-density lipoprotein cholesterol (LDL-C) is ≥70 mg/dL. In patients at very high risk (ASCVD without peripheral arterial disease and lower levels of poorly controlled risk factors), PCSK9 mAbs provide a reasonable

Extremely high risk ≥40% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
EXTREMELY HIGH ATHEROSCLEROTIC BURDEN	**EXTREMELY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	
• Polyvascular clinical ASCVD (coronary heart disease†, ischemic stroke, and symptomatic peripheral arterial disease) • Symptomatic peripheral arterial disease** in addition to a coronary heart disease† or ischemic stroke • A clinical ASCVD event (coronary heart disease†, stroke, or symptomatic peripheral arterial disease**) with multi-vessel coronary artery disease defined as ≥40% stenosis in ≥2 large vessels • Recurrent myocardial infarction within 2 years	• Heterozygous familial hypercholesterolemia with clinical ASCVD (or coronary artery calcium >100) • History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** with at least one of: o Diabetes o LDL-C >100 mg/dl o Less than high intensity statin therapy o High sensitivity C-reactive protein >3 mg/L • Poorly controlled hypertension and clinical ASCVD

Very high risk 30-39% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

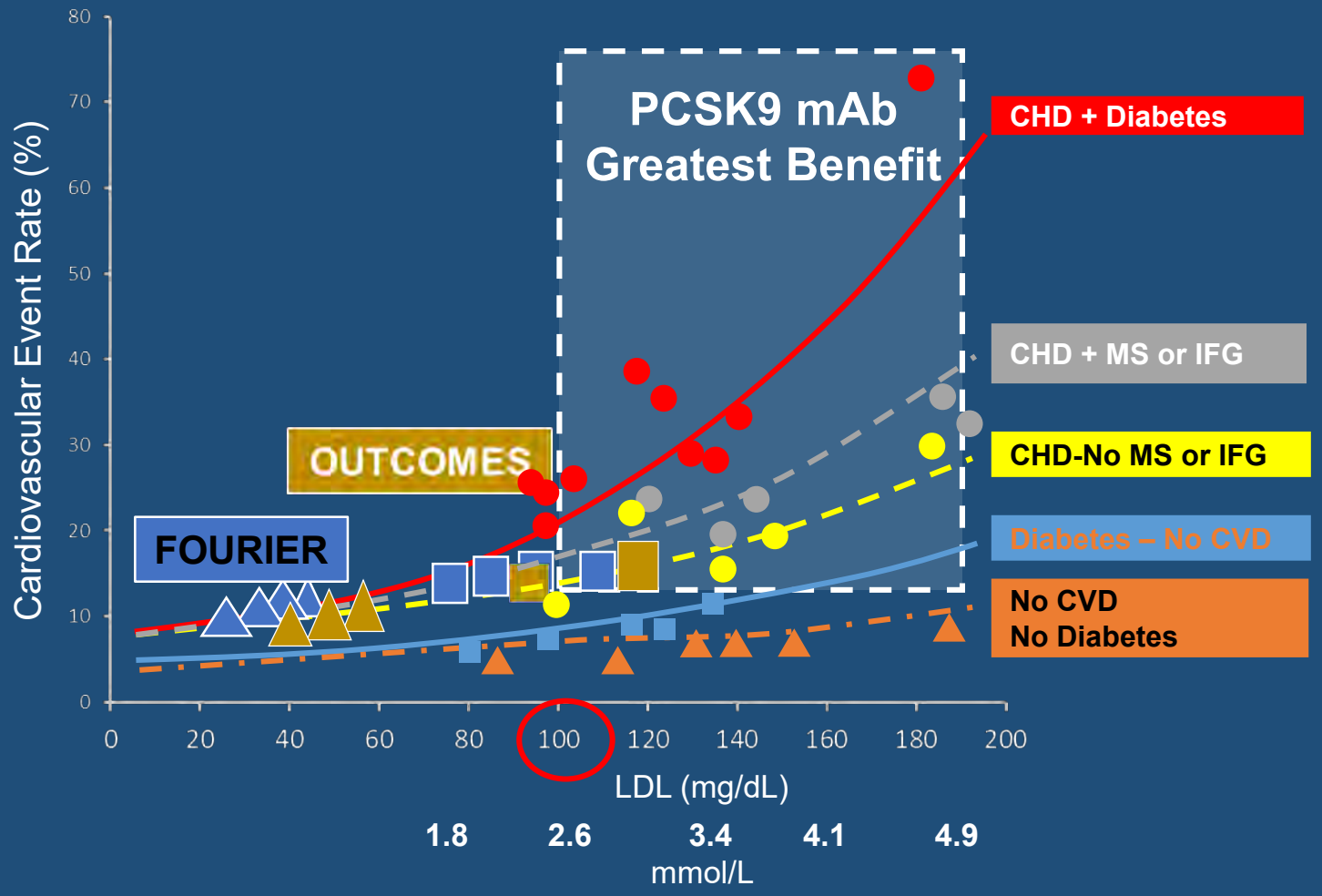
ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
VERY HIGH ATHEROSCLEROTIC BURDEN	**VERY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	
• Recent acute coronary syndrome (only if no subsequent event within 2 years) • Coronary heart disease† and ischemic stroke without symptomatic peripheral arterial disease** • Coronary artery bypass grafting	Clinical ASCVD and one or more of: • Age ≥65 years • Chronic kidney disease • Lipoprotein(a) ≥37 nmol/L • High sensitivity C-reactive protein 1-3 mg/L • Metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** • Smoking

High risk 20-29% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	
HIGH ATHEROSCLEROTIC BURDEN	**WELL-CONTROLLED RISK FACTORS**
<u>High burden (20-29% 10-year ASCVD risk)</u> • Coronary heart disease† only • Ischemic stroke only • Symptomatic peripheral arterial disease only** • Acute coronary syndrome with no subsequent ASCVD event after 2 years	

Log Linear Association LDL-C & CV Event Reduction



Diminishing returns at lower LDL-C levels

CVD, cardiovascular disease; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; MS, metabolic syndrome; PCSK9, proprotein convertase subtilisin/kinexin type 9.

Adapted from Risk curve concept: Robinson JG, Stone NJ. *Am J Cardiol*. 2006:98;1405-1408.; FOURIER median of baseline LDL-C quartiles from Sabatine M, et al. Presented ACC Scientific Sessions; March 2017; Washington DC; Schwartz G, et al *N Engl J Med 2019;* 379: 2097-2017

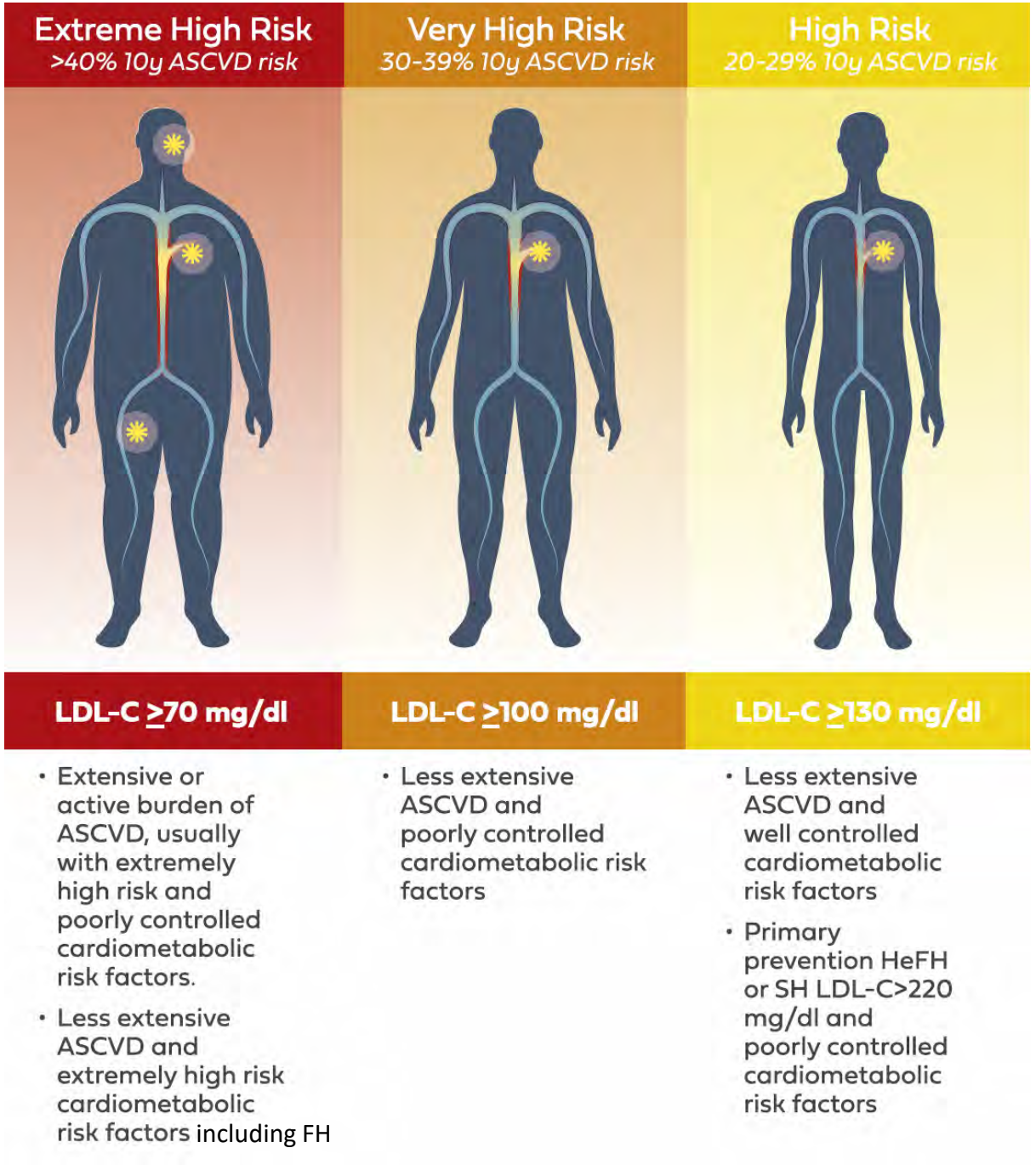
5-year NNTs, Acquisition Costs, and Quality Adjusted Life-years (QALY)

5-year NNT 10-14	**No discount ($14,000/year) /≈ $150,000 QALY (Poor value)**
5-year NNT 21-28	Discount ≈ 50% (≈ $7700/year) /$150,000 QALY (Low value) **Discount ≈ 60% (≈ $5400/year) /$100,000 QALY (Reasonable value)** Discount ≈ 77% (≈ $3200/year) /$50,000 QALY (High value) Discount ≈ 85% (≈ $2200/year) to avoid exceeding growth targets US healthcare costs

US dollars; Based on ICER JAMA Int Med 2016; 176: 107-108 in Robinson JG, et al. J Am Coll Cardiol 2016; 68: 2412-2421

NLA Statement

PATIENT GROUPS WITH REASONABLE TO HIGH VALUE FROM ADDING PCSK9 mAb



Robinson JG, et al. J Clin Lipidol 2019; 13: 525-537