Coronary Artery Calcium: An Opportunity for Precision Medicine and Public Health in Cardiovascular Disease Prevention

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Outline

1. Burden of cardiovascular disease (CVD)
2. Biological process of atherosclerosis – when to intervene?
3. Coronary artery calcium (CAC)
4. Current guidelines, future directions and opportunities

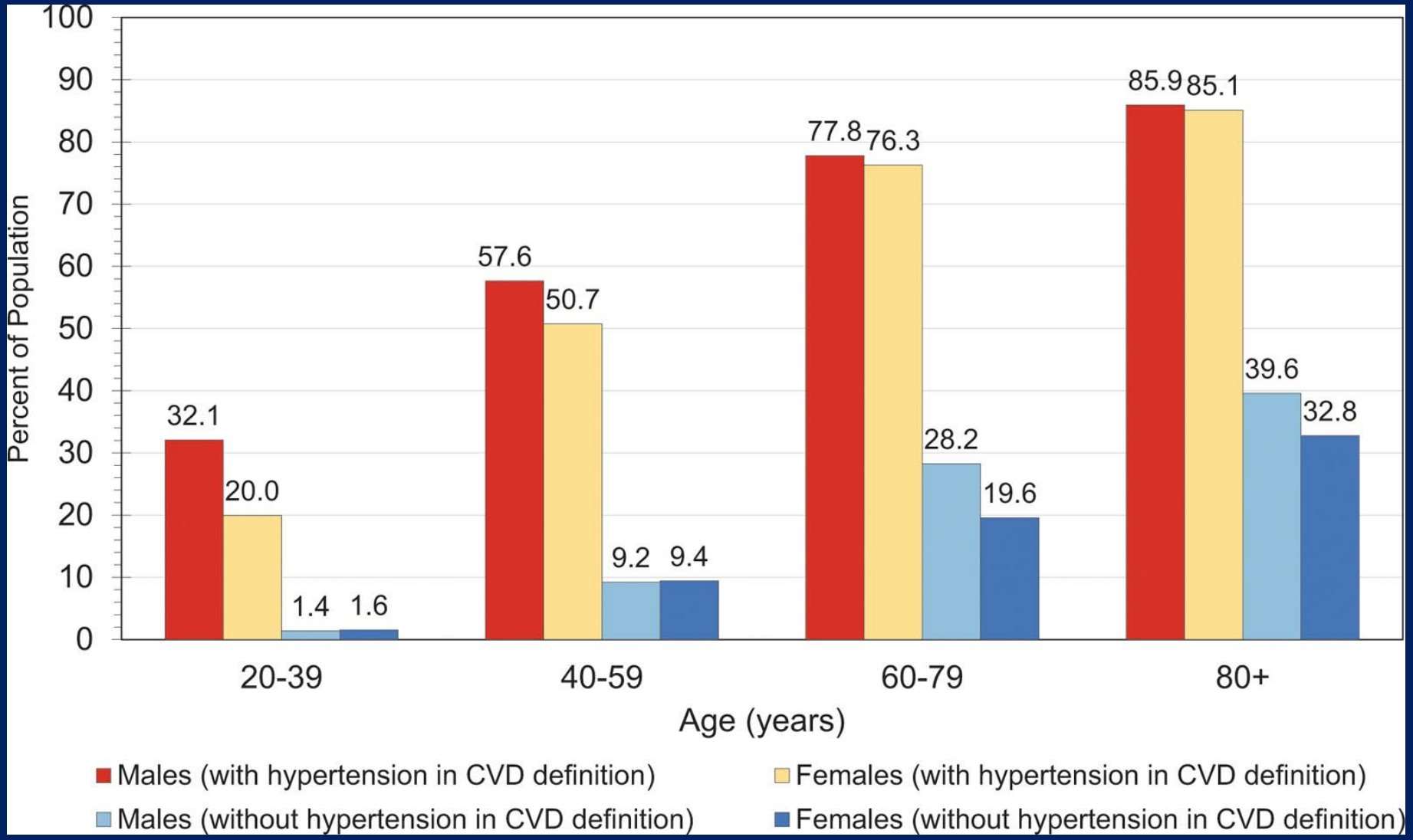
Cardiovascular Disease

- The prevalence of cardiovascular disease (CVD), including hypertension, coronary heart disease (CHD), stroke, and congestive heart failure, in United States (US) adults ≥20 years of age is 49% (~127.9 million)

- CVD remains the leading cause of morbidity and mortality in the US, and deaths attributable to CVD have increased in recent years

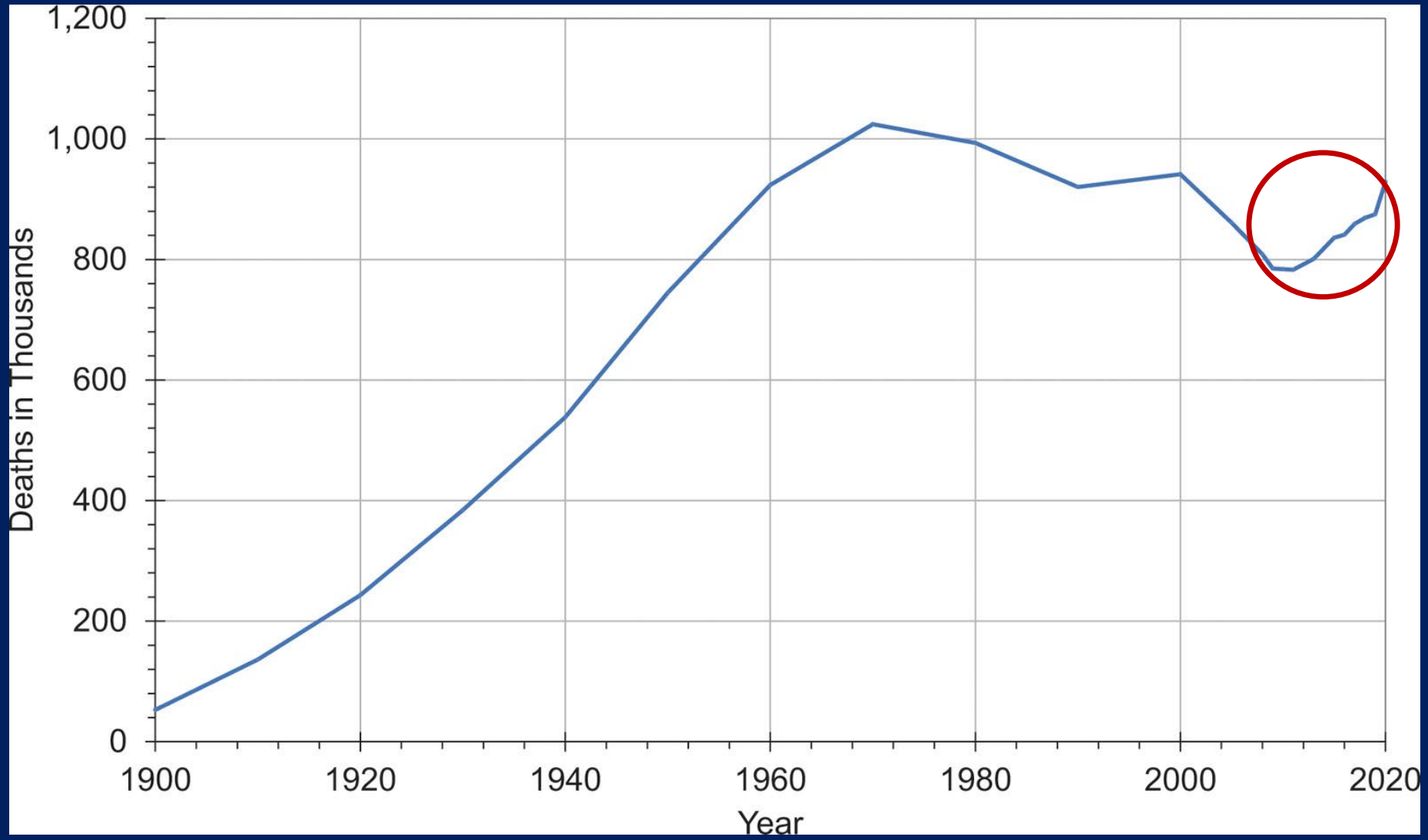
Virani SS et al. Heart disease and stroke statistics—2023 update: a report from the American Heart Association. Circulation. 2023.

Prevalence of CVD in US Adults ≥20 years old



Virani SS et al. Heart Disease and Stroke Statistics—2023 Update: A Report from the American Heart Association. Circulation. 2023.

Annual US Deaths Attributable to CVD



Virani SS et al. Heart Disease and Stroke Statistics—2023 Update: A Report from the American Heart Association. Circulation. 2023.

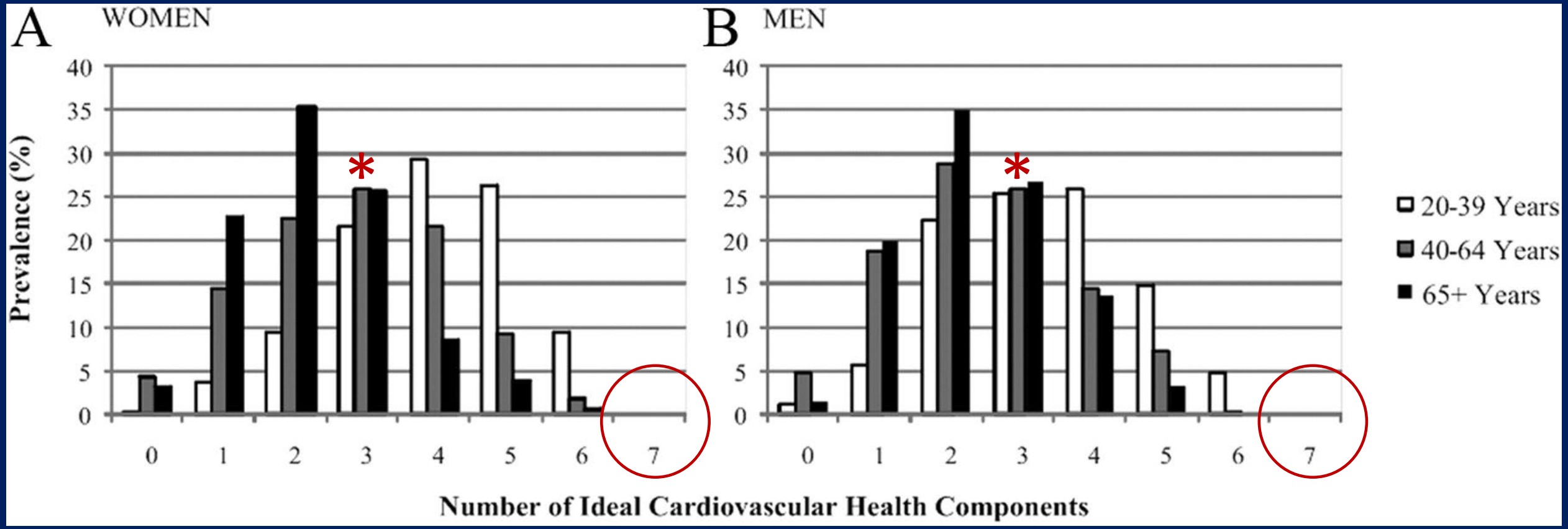
Risk Factors and Absence of Cardiovascular Health

- The high burden of CVD is directly attributable to poor control of upstream risk factors and underlying challenges associated with implementing precision prevention strategies

- Fewer than 1% of adults exhibit ideal cardiovascular health across all 7 common risk factor metrics
  - Smoking, diet, physical activity, body habitus
  - Blood pressure, cholesterol, fasting blood glucose

Shay CM et al. Status of Cardiovascular Health in US adults: Prevalence Estimates from the National Health and Nutrition Examination Surveys (NHANES) 2003–2008. Circulation. 2012.

Never smoking, physical activity, healthy diet, BMI <25 kg/m^2, total cholesterol <200 mg/dL, blood pressure <120/<80 mmHg, fasting blood glucose <100 mg/dL



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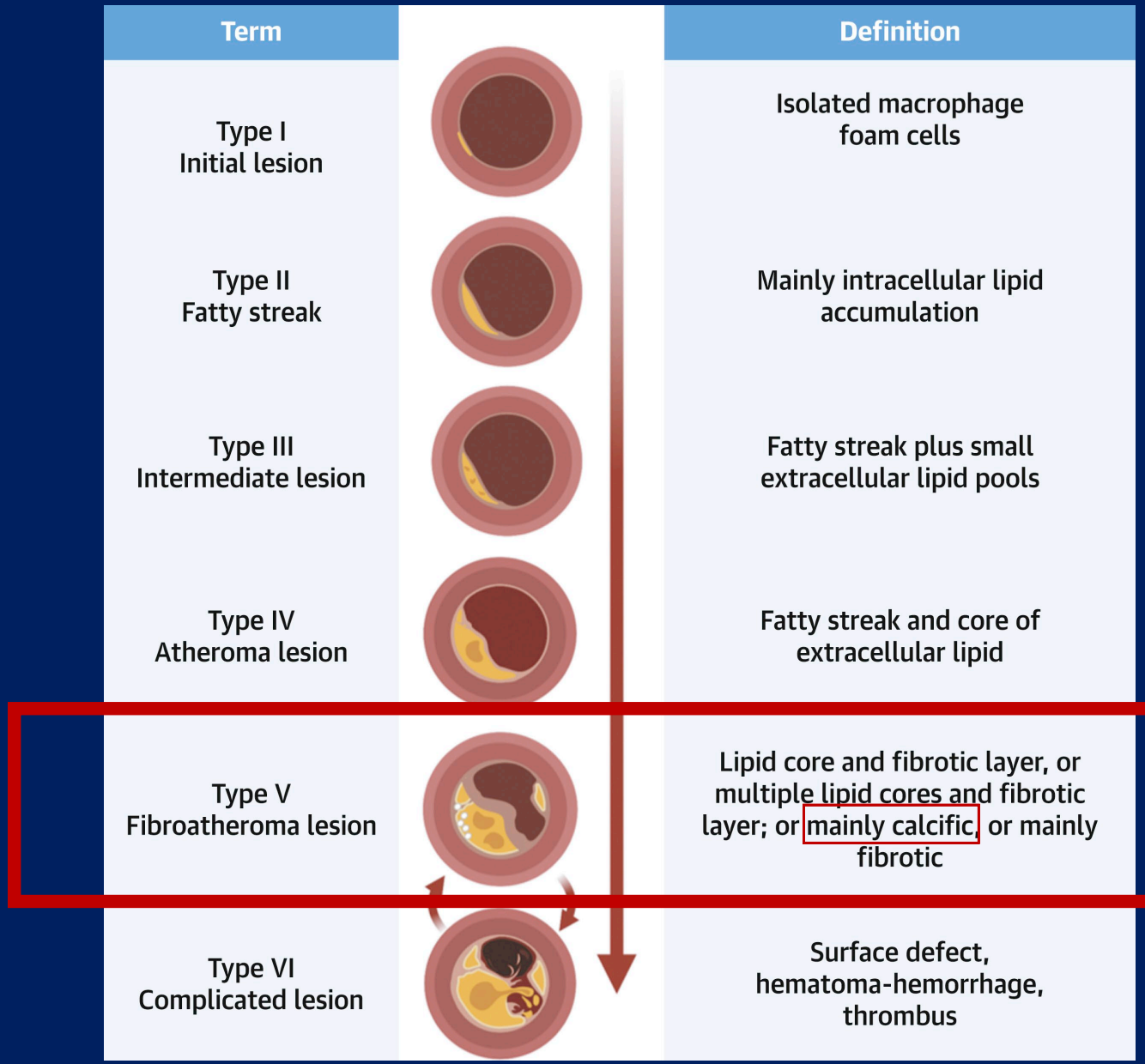
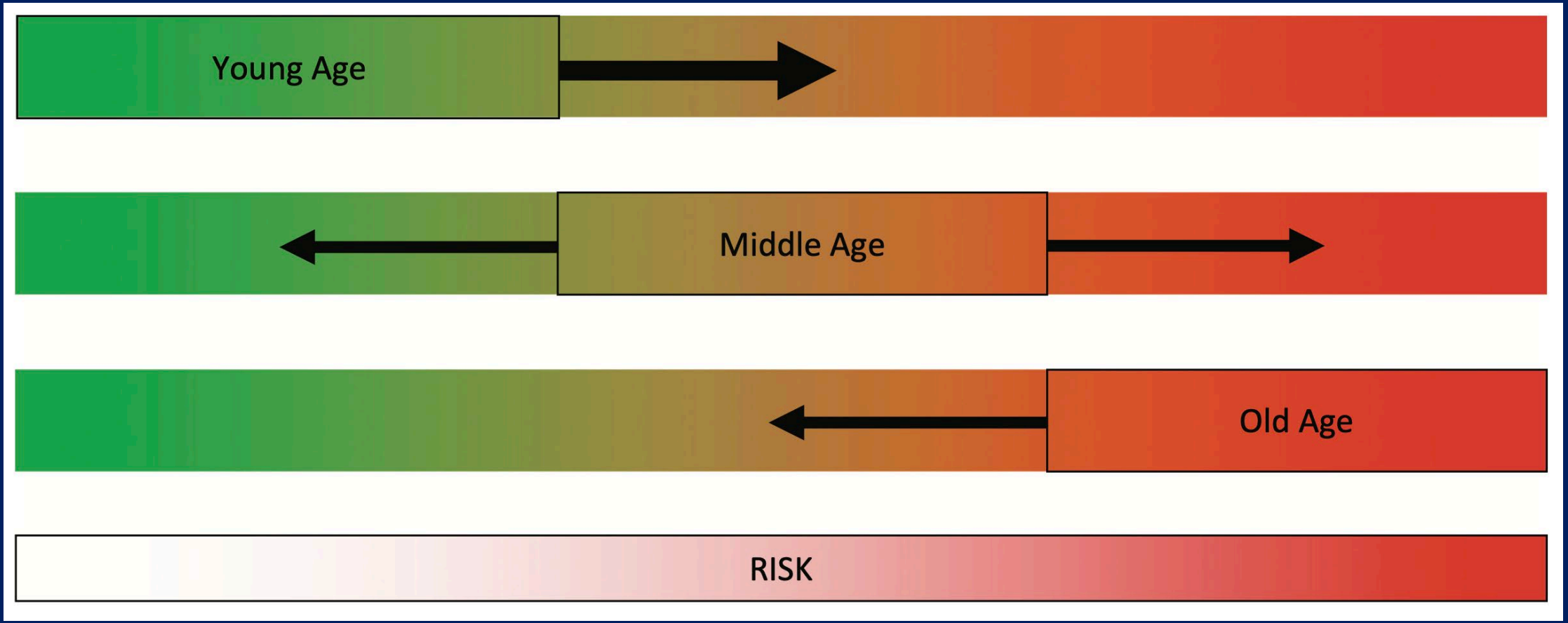


Dawson LP et al. Coronary Atherosclerotic Plaque Regression: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2022.

Characteristics of a Useful Clinical and Public Health-Based Test for Atherosclerosis



Razavi AC et al. Coronary Artery Calcium Testing in Young Adults. Current Opinion in Cardiology. 2023.

Outline

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3. Coronary artery calcium (CAC) scanning
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The CAC Scan

- The coronary artery calcium (CAC) scan is performed on non-contrast cardiac-gated computed tomography
- In 1990, Dr. Arthur Agatston and colleagues developed the CAC score
  - Agatston score = Σ (calcified plaque area x maximum calcium density)
- The exam is performed with the patient performing a 3-5 second breath hold; the scan itself lasts 20-30 seconds
- The average effect radiation dose for CAC scans is ≤1.0 mSV, comparable to mammography

1. Razavi AC, Agatston AS, Dzaye O et al. Evolving Role of Calcium Density in Coronary Artery Calcium Scoring and ASCVD Risk. JACC Cardiovasc Imaging. 2022.
2. Messenger B et al. Coronary Calcium Scans and Radiation Exposure in the Multi-Ethnic Study of Atherosclerosis. Int J Cardiovasc Imaging. 2016.

Patients undergoing CAC scan on non-contrast cardiac-gated computed tomography.

CAC scan without calcification (a), mild LAD calcification (b), moderate LAD calcification (c), severe LAD calcification (d).

Average Effective Radiation Dose

Type of Scan	Average Effective Dose (mSV)
Anteroposterior and Lateral Chest X-Ray	0.1
Coronary Artery Calcium Scan	0.37 – 1.0
Low-Dose CT Chest for Lung Cancer Screening	0.65
Mammogram	0.7
Cardiac CT Angiography	2.7
Annual Passive Radiation Dose	3.1
Non-Cardiac CT Chest	8.0
Non-Cardiac CT Chest for Pulmonary Embolism	15.0

1. Messenger B et al. Coronary Calcium Scans and Radiation Exposure in the Multi-Ethnic Study of Atherosclerosis. Int J Cardiovasc Imaging. 2016.
2. Mettler FA et al. Effective Doses in Radiology and Diagnostic Nuclear Medicine: A Catalog. Radiology. 2008

CAC Epidemiology

- The prevalence of CAC is age-, gender-, and ethnicity-dependent

- Regardless of gender and ethnicity, the strongest determinant of CAC is age. Among adults ≥55 years old without CVD:
  - >50% have prevalent CAC

- Depending the sample studied, the prevalence of premature CAC in adults <45 years old has been reported to range between 7-34%

1. Bild DE et al. Ethnic Differences in Coronary Calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005.
2. Razavi AC et al. Coronary Artery Calcium Testing in Young Adults. Current Opinion in Cardiology. 2023.

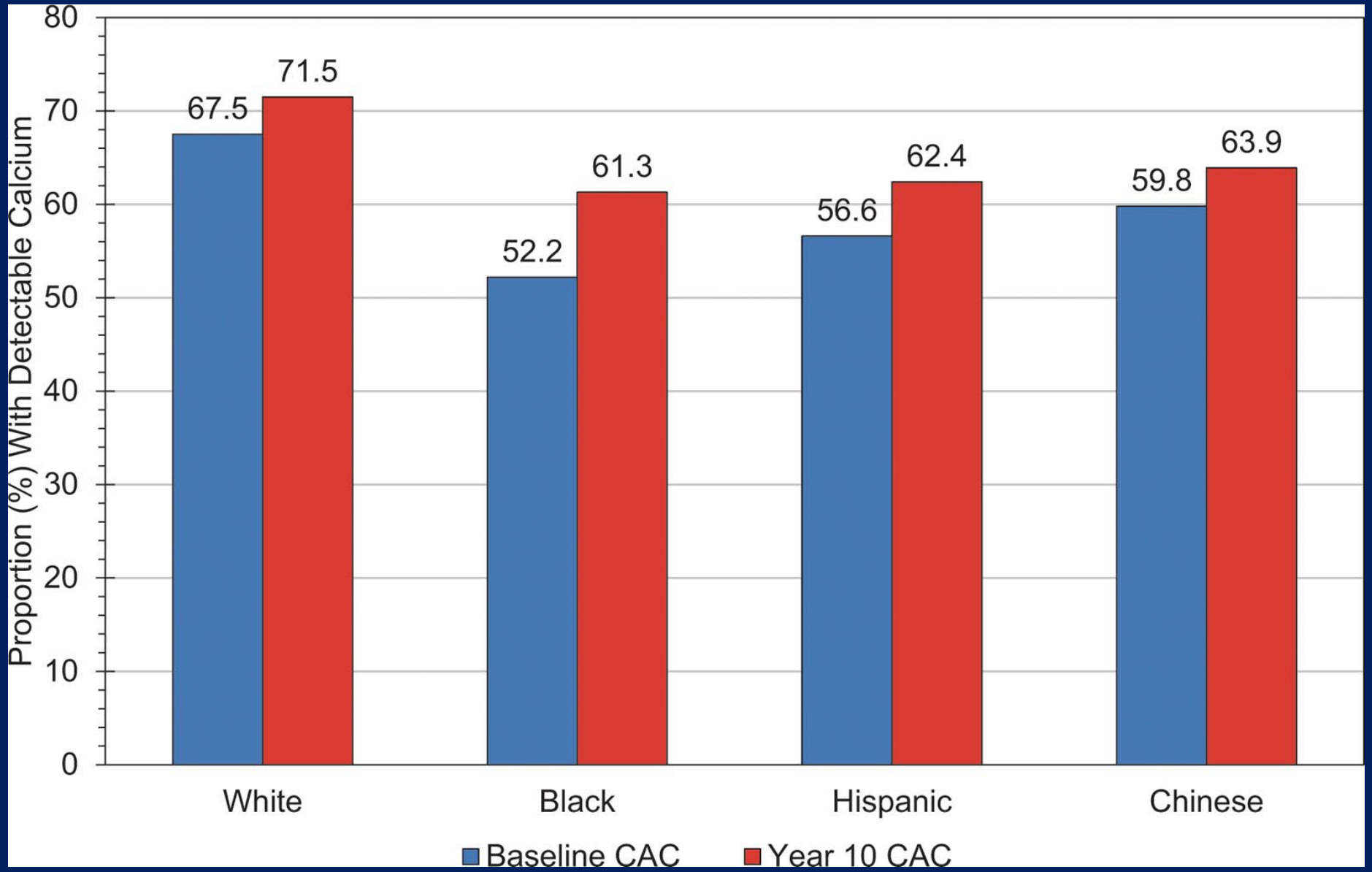


Bild DE et al. Ethnic Differences in Coronary Calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005.

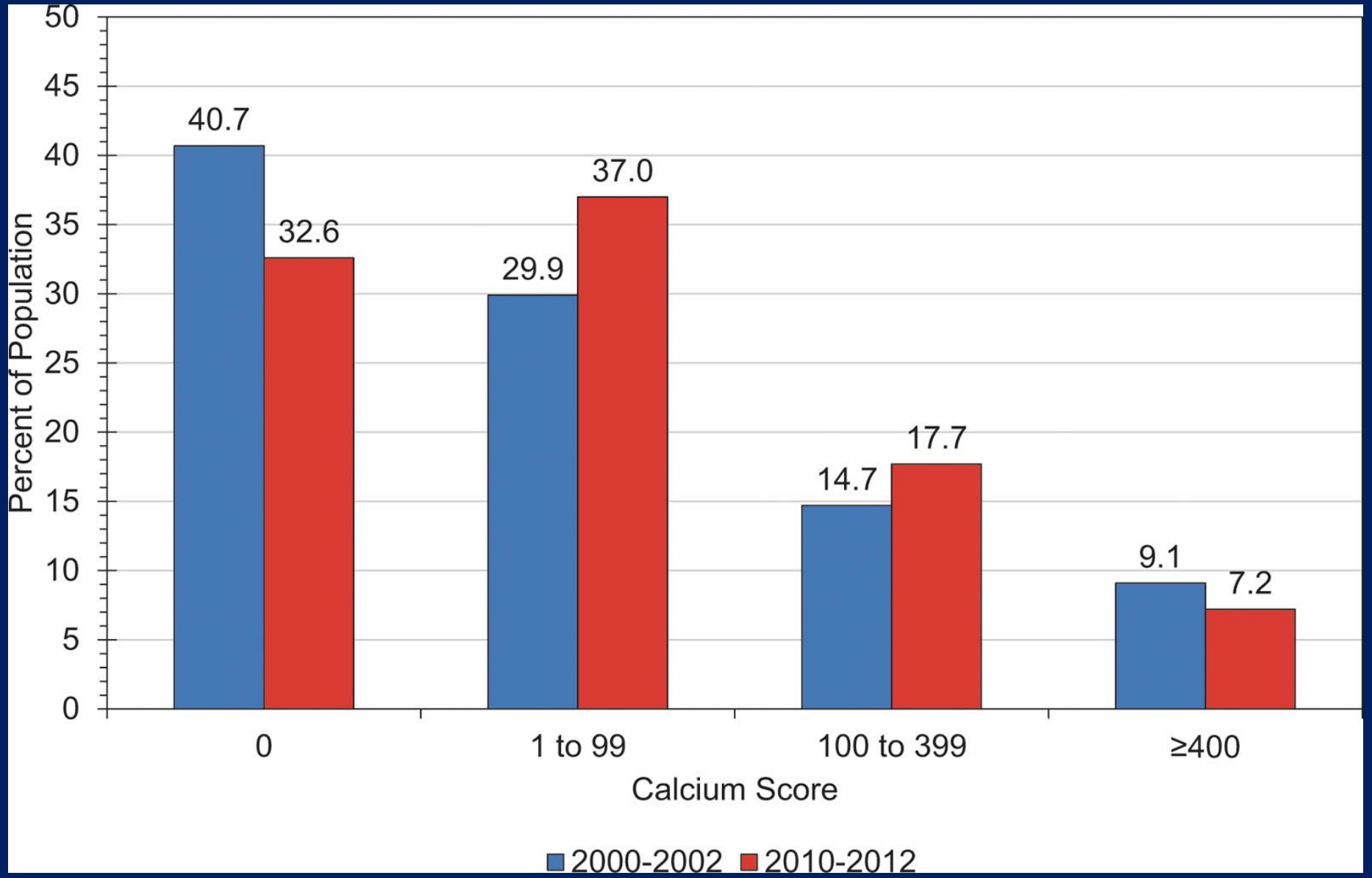


Bild DE et al. Ten-Year Trends in Coronary Calcification in Individuals without Clinical Cardiovascular Disease in the Multi-Ethnic Study of Atherosclerosis. PloS one. 2014.

Risk Factors for CAC

- The presence and duration of traditional risk factor exposure are strong risk factors for incident CAC (younger > older adults)

- There can be considerable heterogeneity between traditional risk factors and CAC, which may pose both challenges and opportunities for precision CVD risk assessment and prevention

1. Razavi AC et al. Risk Factors for Incident Coronary Artery Calcium in Younger Versus Intermediate Versus Older Persons. Am J Cardiol. 2022.
2. Razavi AC et al. Predicting Long-Term Absence of Coronary Artery Calcium in Metabolic Syndrome and Diabetes: The MESA study. J Am Coll Cardiol Img. 2021.

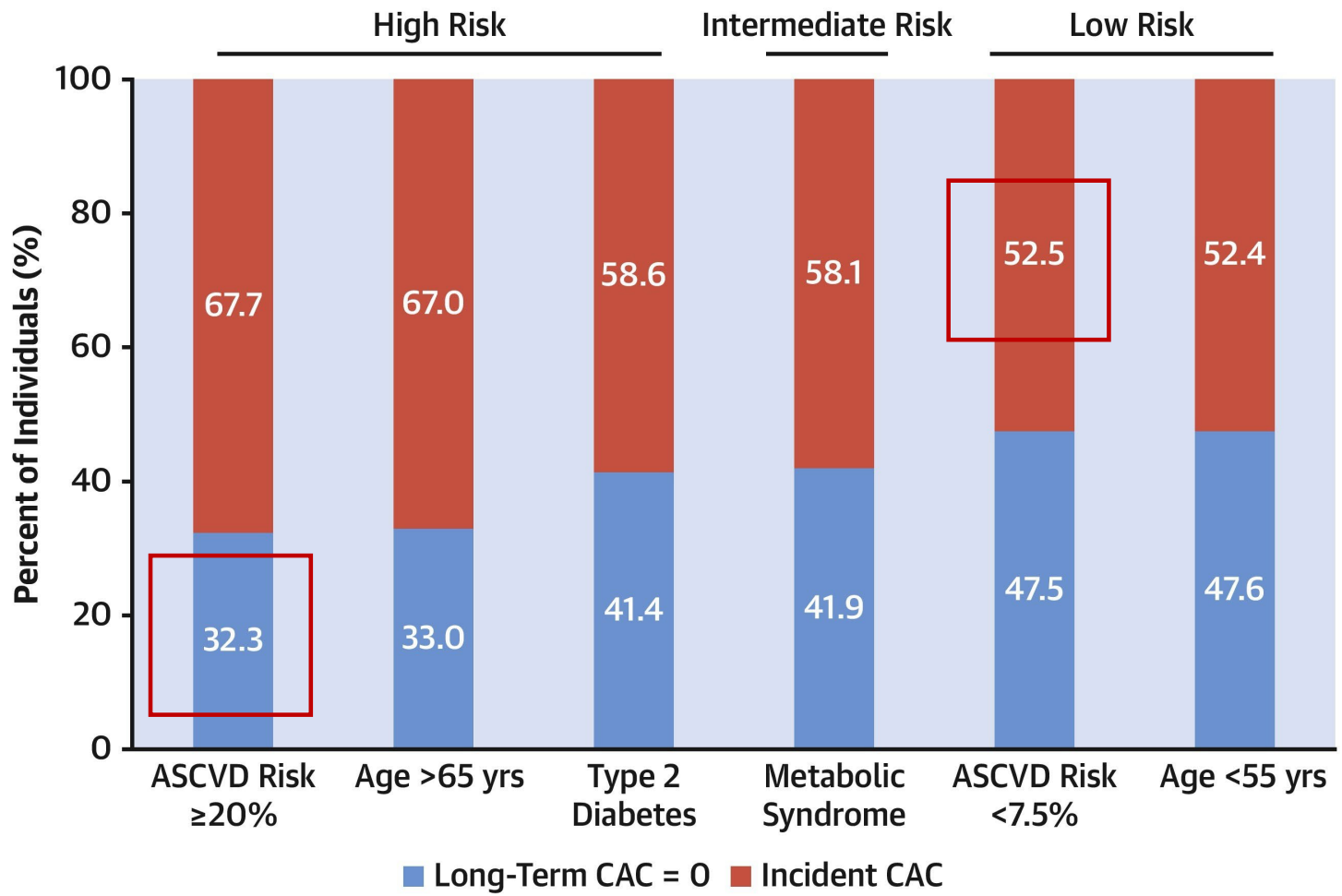
Association of Continuous Traditional CVD Risk Factors (per standard deviation change) with Incident CAC, Stratified by Age in the Multi-Ethnic Study of Atherosclerosis

	Age at the Time of Baseline CAC Scan (years)			
Risk Factor *†	32-45 (n=2,139) HR (95% CI)	46-64 (n=2,154) HR (95% CI)	65-84 (n=815) HR (95% CI)	Age*Risk Factor Interaction P-Value
Systolic Blood Pressure (13.9 mmHg, 18.5 mmHg, 21.8 mmHg)	1.27 (1.11-1.46)	1.12 (0.99, 1.26)	1.11 (0.96, 1.29)	p<0.01
Diastolic Blood Pressure (10.9 mmHg, 10.1 mmHg, 10.3 mmHg)	0.98 (0.85-1.13)	0.99 (0.88, 1.12)	0.98 (0.83-1.15)	p=0.08
Total Cholesterol (33.4 mg/dL, 35.6 mg/dL, 33.6 mg/dL)	1.17 (1.07-1.27)	1.14 (1.07, 1.22)	1.11 (0.99-1.24)	p=0.38
HDL-Cholesterol (14.4 mg/dL, 14.8 mg/dL, 15.2 mg/dL)	1.07 (0.96-1.19)	1.23 (1.12, 1.34)	1.10 (0.97, 1.25)	p=0.24
Total Cholesterol/HDL-Cholesterol ‡ (0.5, 1.2, 1.1)	1.17 (1.07-1.27)	1.17 (1.10, 1.26)	1.10 (0.99, 1.23)	p<0.01
Non-HDL-Cholesterol § (36.8 mg/dL, 36.0 mg/dL, 32.7 mg/dL)	1.20 (1.09-1.31)	1.14 (1.07-1.23)	1.11 (0.99, 1.23)	p=0.36
Fasting Blood Glucose (16.6 mg/dL, 27.4 mg/dL, 23.1 mg/dL)	1.12 (1.03-1.21)	1.05 (0.98-1.13)	1.06 (0.95, 1.19)	p=0.05
Body mass index (6.3 kg/m^2, 5.8 kg/m^2, 5.1 kg/m^2)	1.08 (0.97-1.20)	1.19 (1.09-1.30)	1.00 (0.87, 1.14)	p=0.33

Model includes: baseline age, sex, race/ethnicity, education, income, cigarette smoking, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, fasting blood glucose, body mass index, and blood pressure-lowering, lipid-lowering, and glucose-lowering medications
*Standard deviation in each age group is listed next to each risk factor.
† All associations are reported per SD-higher except for HDL-cholesterol, which is reported per SD-lower.
‡ In replace of total cholesterol and HDL-cholesterol in multivariable modeling.
§ In replace of total cholesterol in multivariable modeling

Razavi AC et al. Risk Factors for Incident Coronary Artery Calcium in Younger (Age 32 to 45 Years) Versus Intermediate (46 to 64 Years) Versus Older (65 to 84 Years) Persons. Am J Cardiol. 2022.

CENTRAL ILLUSTRATION: Proportion of Participants With Long-Term CAC=0 Versus Incident CAC Stratified by Baseline Risk



Razavi AC et al. Predicting Long-Term Absence of Coronary Artery Calcium in Metabolic Syndrome and Diabetes: The MESA study. J Am Coll Cardiol Img. 2021.

CAC and Incidence of CVD Events

- There is a stepwise higher risk of CHD events across increasing CAC burden
  - CAC 1-99: ~ 4 times greater risk
  - CAC ≥100: ~ 7-10 times greater risk
  - **similar pattern observed for sudden cardiac death
- There is a spectrum of commensurate secondary prevention level risk beginning at CAC ≥300
- Prevalent CAC confers an independent 3-fold higher risk of stroke

1. Detrano R et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. NEJM. 2008.
2. Razavi et al. Coronary Artery Calcium for Risk Stratification of Sudden Cardiac Death. J Am Coll Cardiol Img. 2022.
3. Hecht HS. Coronary Artery Calcium Scanning: Past, Present, and Future. J Am Coll Cardiol Img. 2015
4. Chaikriangkrai K et al. Coronary Artery Calcium Score as a Predictor for Incident Stroke: Systematic Review and Meta-Analysis. International Journal of Cardiology. 2017.

Table 3. Risk of Coronary Events Associated with Increasing Coronary-Artery Calcium Score after Adjustment for Standard Risk Factors.*

Coronary-Artery Calcium Score	Major Coronary Event†			Any Coronary Event		
	No./No. at Risk	Hazard Ratio (95% CI)	P Value	No./No. at Risk	Hazard Ratio (95% CI)	P Value
0	8/3409	1.00		15/3409	1.00	
1–100	25/1728	3.89 (1.72–8.79)	<0.001	39/1728	3.61 (1.96–6.65)	<0.001
101–300	24/752	7.08 (3.05–16.47)	<0.001	41/752	7.73 (4.13–14.47)	<0.001
>300	32/833	6.84 (2.93–15.99)	<0.001	67/833	9.67 (5.20–17.98)	<0.001
Log_2(CAC+1)‡		1.20 (1.12–1.29)	<0.001		1.26 (1.19–1.33)	<0.001

* CAC denotes coronary-artery calcium score, and CI confidence interval.
† Major coronary events were myocardial infarction and death from coronary heart disease.
‡ Each unit increase in log_2(CAC+1) represents a doubling of the coronary-artery calcium score.

Detrano R et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. New England Journal of Medicine. 2008.

66,636 asx primary prevention patients from the CAC Consortium

TABLE 2 Multivariable-Adjusted SHRs (95% CIs) for CAC Burden With SCD

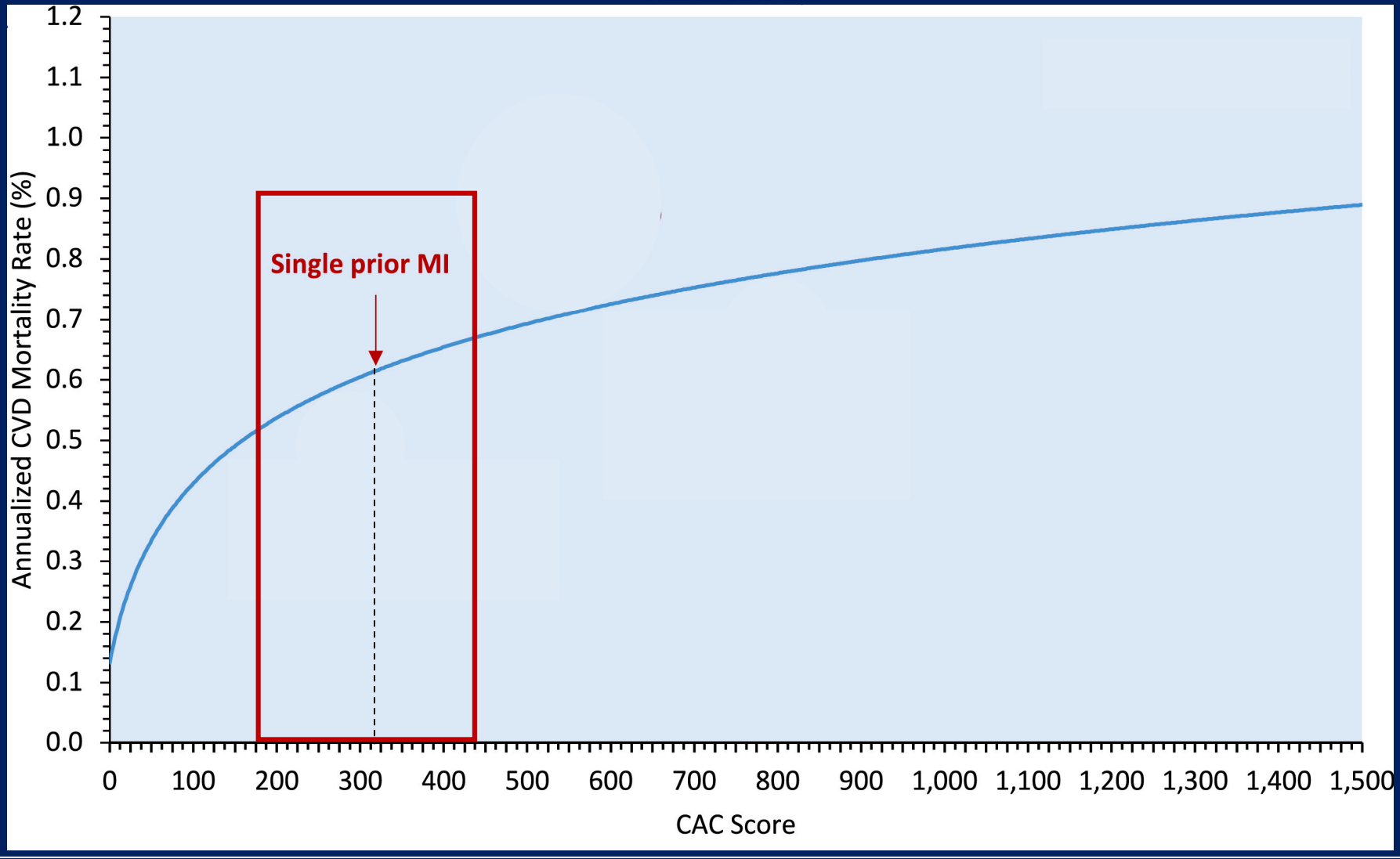
CAC Score Group	Events (n = 211)	Unadjusted		Model 1		Model 2	
		SHR (95% CI)	*P* Trend	SHR (95% CI)[a]	*P* Trend	SHR (95% CI)[b]	*P* Trend
CAC = 0	19	–	<0.001	–	<0.001	–	<0.001
CAC 1-99	33	2.5 (1.4-4.4)		1.4 (0.8-2.5)		1.3 (0.7-2.4)	
CAC 100-399	53	9.2 (5.5-15.6)		3.2 (1.8-5.6)		2.8 (1.6-5.0)	
CAC 400-999	49	17.8 (10.5-30.2)		4.7 (2.6-8.5)		4.0 (2.2-7.3)	
CAC >1,000	57	33.1 (19.7-55.7)		6.3 (3.4-11.8)		4.9 (2.6-9.2)	

[a]Adjusted for age and sex. [b]Adjusted for age, sex, current cigarette smoking, diabetes, hypertension, hyperlipidemia, and a family history of coronary heart disease.

CAC = coronary artery calcification; SCD = sudden cardiac death; SHR = subdistribution hazard ratio.

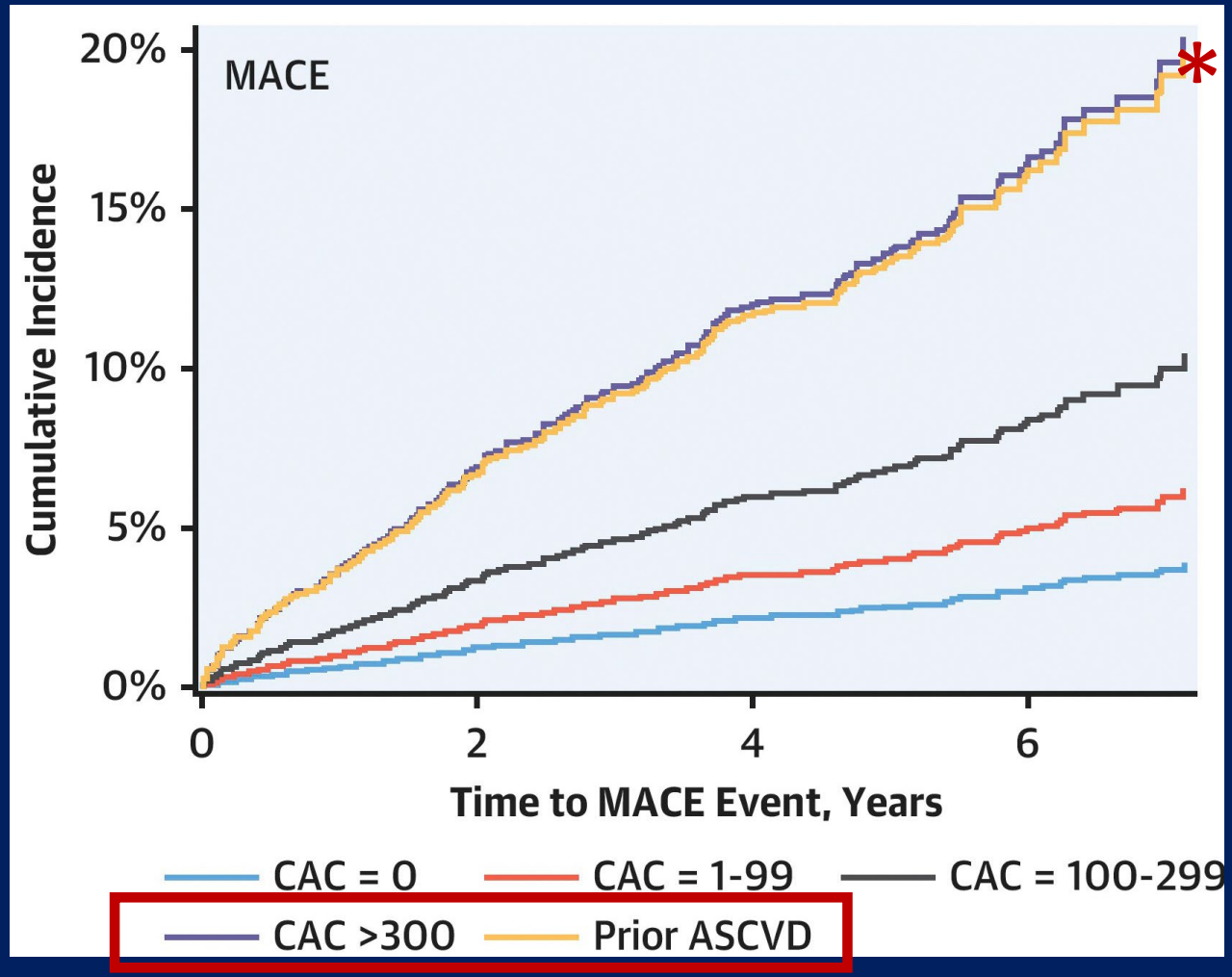
Razavi et al. Coronary Artery Calcium for Risk Stratification of Sudden Cardiac Death. J Am Coll Cardiol Img. 2022.

20,207 asx primary prevention patients from the CAC Consortium ≥50 years old with a 10-year risk ≥7.5%



Dzaye O, Razavi AC et al. Coronary artery calcium scores indicating secondary prevention level risk: findings from the CAC consortium and FOURIER trial. Atherosclerosis. 2022.

4,949 sx patients undergoing coronary CTA in CONFIRM Registry
(4,511 without prior ASCVD compared to 438 with prior ASCVD)



Budoff, Matthew J., et al. "When Does a Calcium Score Equates to Secondary Prevention?: Insights From the Multinational CONFIRM Registry." *JACC: Cardiovascular Imaging* (2023).

CAC and CVD Risk Prediction

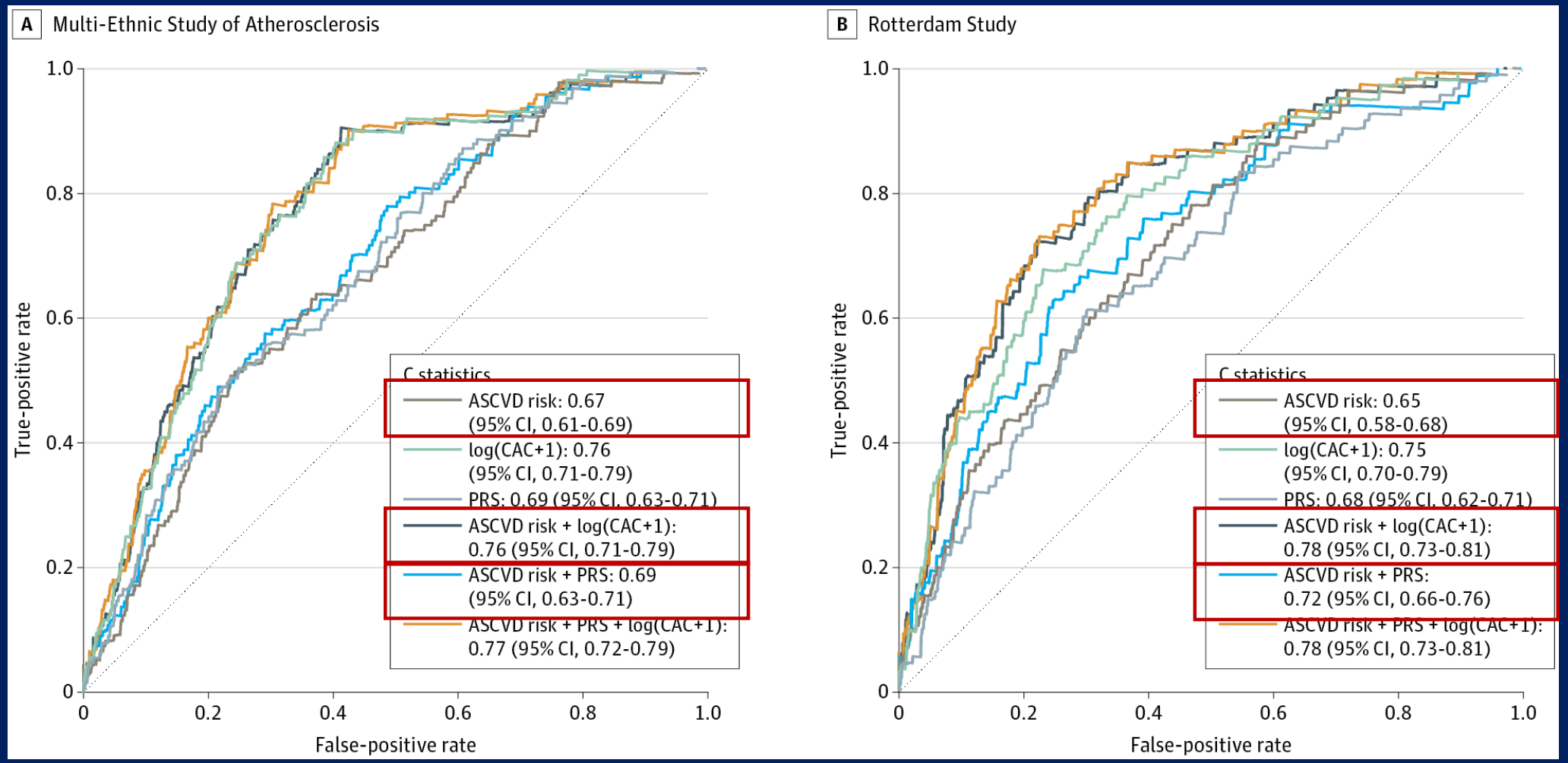
- When added to traditional risk factors, presence of CAC provides higher magnitude improvements in CHD risk prediction compared to:
  - Common measures of subclinical atherosclerosis, hs-CRP, family history, and polygenic risk scores

- Absence of CAC has the strongest negative predictive value for CVD compared to other negative risk markers
  - ”Power of Zero” → 10-year event rates almost consistently <5% across all ethnicities

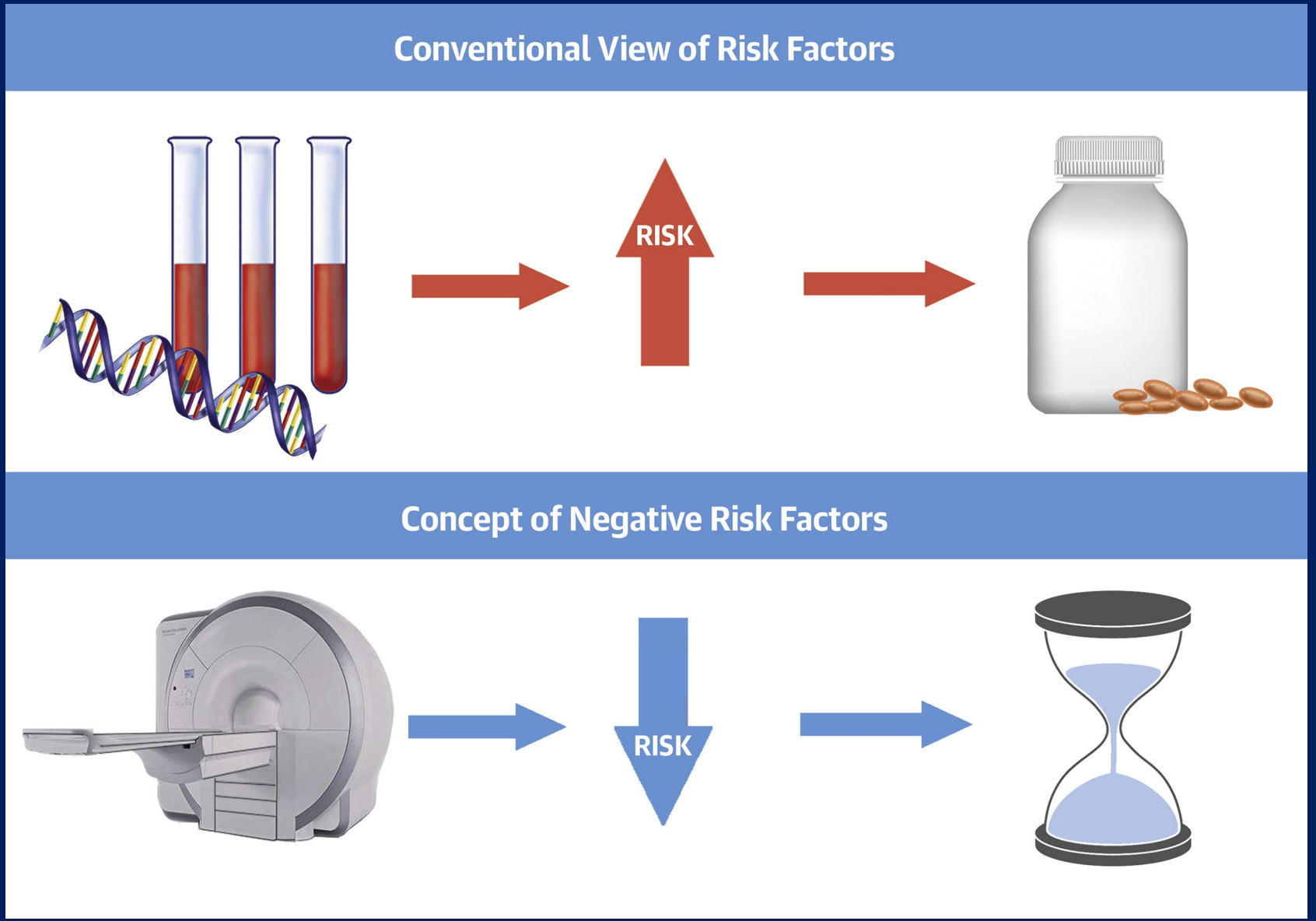
- CAC, or the absence thereof, has been identified in multiple studies for its potential to identify those most likely to benefit from pharmacotherapy for primary CVD risk reduction

1. Yeboah J et al. Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals. JAMA. 2012.
2. Khan SS et al. Coronary Artery Calcium Score and Polygenic Risk Score for the Prediction of Coronary Heart Disease Events. JAMA. 2023.
3. Razavi AC et al. Atherosclerotic Cardiovascular Disease Events Among Statin Eligible Individuals with and without Long-Term Healthy Arterial Aging. Atherosclerosis. 2021.
4. Cainzos-Achirica M et al. Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019. Circulation. 2020.

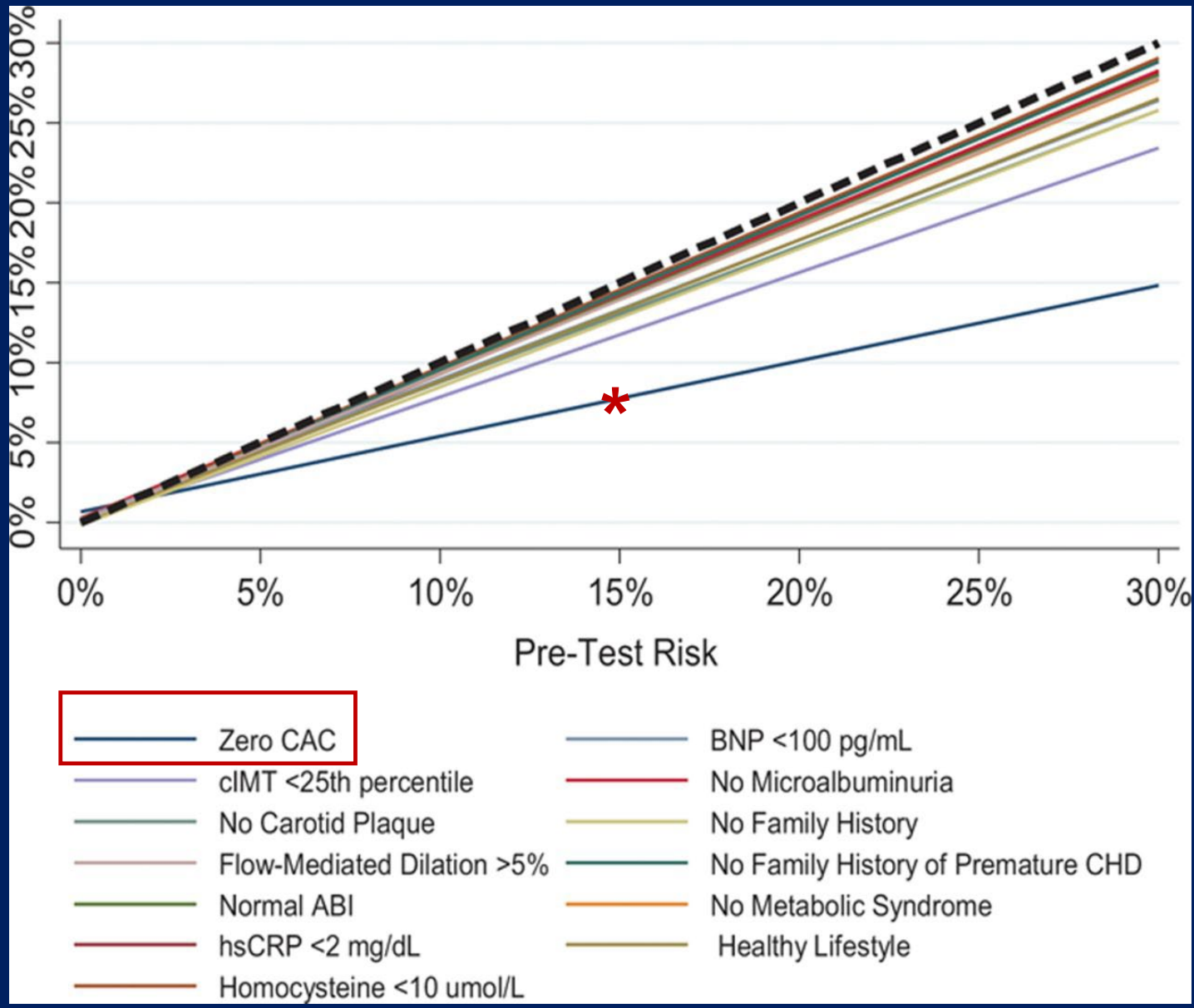
Receiver Operator Characteristic Curves and C Statistics for Prediction of Coronary Heart Disease in the MESA and the Rotterdam Studies



Khan SS et al. Coronary Artery Calcium Score and Polygenic Risk Score for the Prediction of Coronary Heart Disease Events. JAMA. 2023.



Blaha MJ et al. Coronary Artery Calcium Scores of Zero and Establishing the Concept of Negative Risk Factors. Journal of the American College of Cardiology. 2019.



Blaha et al. Role of Coronary Artery Calcium Score of Zero and Other Negative Risk Markers for Cardiovascular Disease. Circulation. 2016.

561 Statin Eligible Candidates from MESA who had CAC=0 at Baseline and Underwent a Follow-Up CAC Scan 10 Years Later

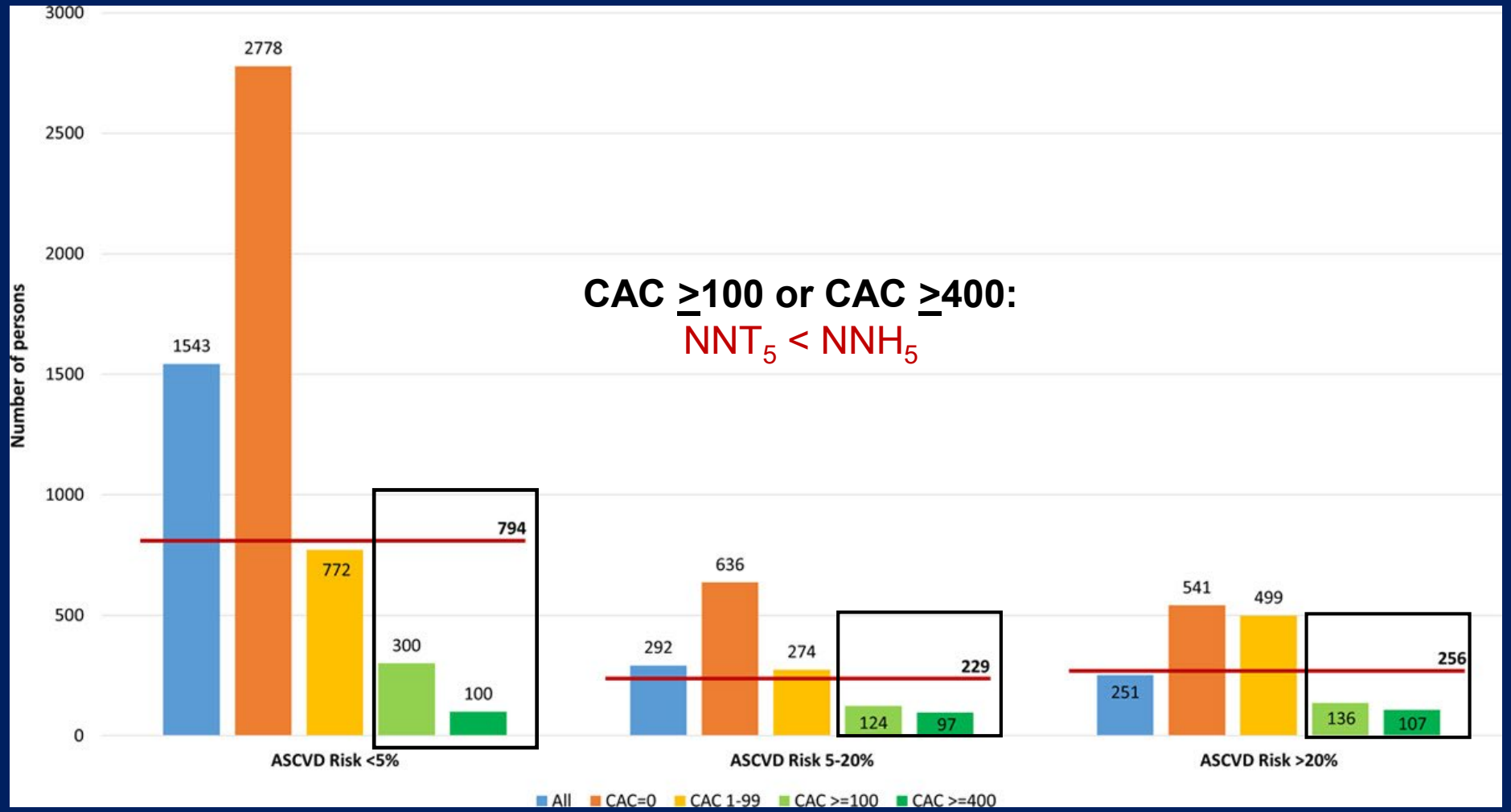
Table 2
Absolute event rates and estimated 10-year number needed to treat for ASCVD and CHD according to CAC status.

Outcome		Persistent CAC = 0 (N = 244)	Incident CAC (N = 317)
All ASCVD	N (%)	16 (6.6)	41 (12.9)
	Event rate (95% CI)[a]	4.3 (2.2, 6.4)	8.6 (6.0, 11.2)
	10-year NNT	117	54
Coronary heart disease	N (%)	4 (1.6)	24 (2.5)
	Event rate (95% CI)[a]	1.1 (0.0, 2.1)	5.0 (3.0, 6.9)
	10-year NNT	398	106

NNT calculations assume a 30% relative risk reduction of events on statin therapy.
ASCVD = atherosclerotic cardiovascular disease. CAC = coronary artery calcification. NNT = number needed to treat.
[a] Events per 1,000 person-years.

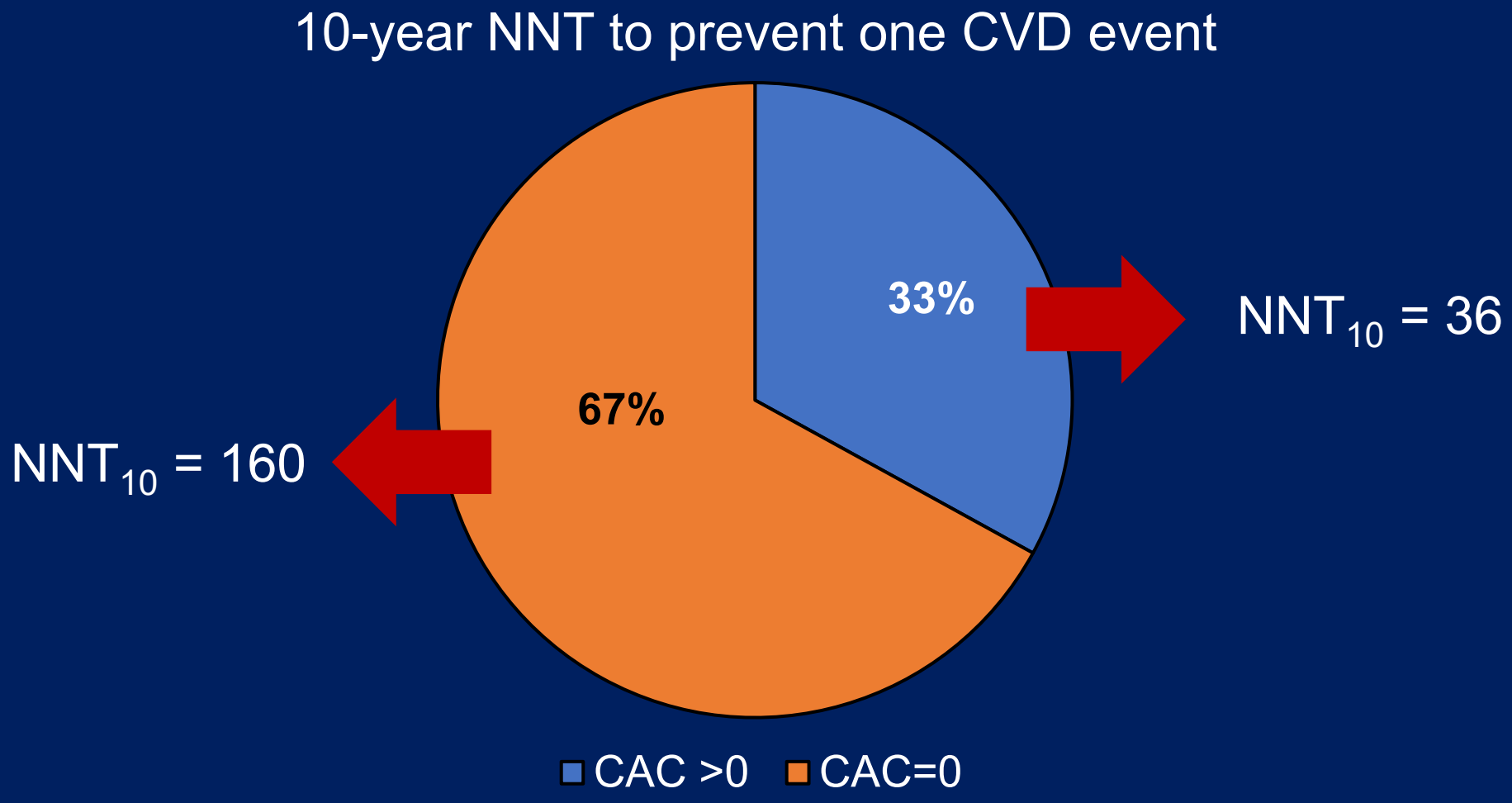
Razavi AC et al. Atherosclerotic Cardiovascular Disease Events Among Statin Eligible Individuals with and without Long-Term Healthy Arterial Aging. Atherosclerosis. 2021.

3,540 MESA participants, aspirin naïve, <70 years old, not at high-risk for bleeding



Cainzos-Achirica M et al. Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019. Circulation. 2020.

1,537 participants with elevated blood pressure (120-129/<80 mmHg) from three observational cohort studies (MESA, CARDIA, JHS)



Parcha V et al. Coronary Artery Calcium Score for Personalization of Antihypertensive Therapy: A Pooled Cohort Analysis. Hypertension. 2021.

CAC Scan Initiation and Rescan Intervals

- The modeled optimal age to initiate a CAC is directly related to the burden of CVD risk factors, including family history
- The ”warranty period” of CAC=0 is between 3 to 7 years
- Identifying the right age to scan, and potentially rescan can help personalize our approach to prevention for patients and populations across the spectrum of CVD risk

1. Dzaye O, Razavi AC et al. Modeling the Recommended Age for Initiating Coronary Artery Calcium Testing Among At-Risk Young Adults. JACC. 2021.
2. Dzaye O, et al. Warranty Period of a Calcium Score of Zero. JACC. 2021.

Predicted Age of CAC >0 Conversion According to ASCVD Risk Factor Status

Risk Factor	Women Age to CAC >0 Conversion (Years)*	Men Age to CAC >0 Conversion (Years)*	All Average Years Earlier to CAC >0*
None	58 (56-60)	42 (41-44)	Reference
Family History of CHD	53 (52-55)	39 (38-41)	-3.5
Current Cigarette Smoking	53 (51-55)	40 (39-42)	-3.5
Dyslipidemia	52 (51-54)	39 (38-41)	-4.5
Hypertension	53 (52-55)	39 (38-41)	-4
Diabetes	50 (49-52)	37 (36-38)	-6.5
Family History of CHD + Dyslipidemia	48 (46-50)	36 (35-38)	-8
Family History of CHD + Hypertension	49 (47-51)	36 (35-38)	-7.5

*Using a 25% testing yield for CAC >0

Dzaye O, Razavi AC et al. Modeling the Recommended Age for Initiating Coronary Artery Calcium Testing Among At-Risk Young Adults. JACC. 2021.

TABLE 3 Summary Look-Up Table for Individualized Risk Estimation and Appropriate Timing of CAC Rescans

Risk Group	Recommended Rescan Interval
Low-risk (<5% 10-yr risk)	6-7 yrs
Borderline to Intermediate risk (5-20% 10-yr risk)	3-5 yrs
High risk (>20% 10-yr risk)	3 yrs
Diabetes	3 yrs

Look-up table for individualized risk estimation and appropriate timing of CAC rescans. CAC = coronary artery calcium.

Dzaye O, et al. Warranty Period of a Calcium Score of Zero.
Journal of the American College of Cardiology. 2021

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Society	Class	Level	Recommendation
ACC / AHA	IIb	B	In adults at **intermediate risk (7.5-10%)** or selected adults at **borderline risk (5-7.5%)**, if risk-based decisions for preventive interventions (eg. statin therapy) remain uncertain, it is reasonable to measure a CAC score to guide clinician-patient risk discussion
ESC / EAS	IIb	B	CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at **low** or **moderate** risk

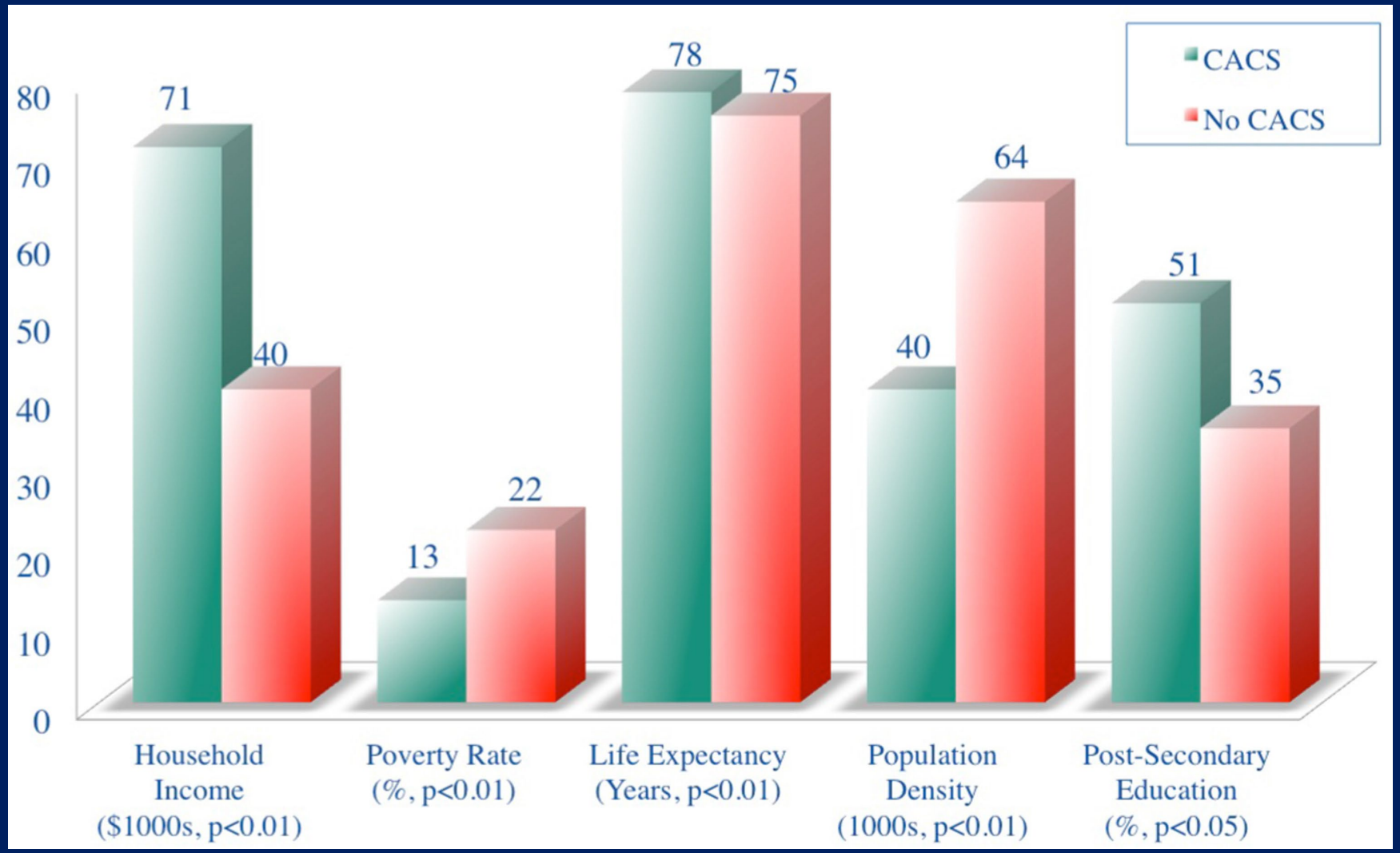
ACC = American College of Cardiology; AHA = American Heart Association; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology

Barriers

- Cost: CAC is not covered by insurance and is charged to patients out-of-pocket
  - $100-200 per scan
- Availability: CAC accessibility is associated with socioeconomic status and ethnicity
- Cohesion: Lack of a national/international standard to guide CAC testing

Neighborhoods with and without Access to CAC

Comparison of socioeconomic characteristics of hospital areas in Chicago.
Values listed on the bars represent the mean of each category.



Ikram et al. Socioeconomics of CAC: Is it Scored or is it Ignored?. Journal of Cardiovascular Computed Tomography. 2022.

Future Directions / Opportunities

- Insurance coverage for guideline-indicated utilization of CAC scanning
- Using CAC as an enrollment criteria in future randomized controlled trials in primary CVD prevention
- Randomized controlled trials of CAC testing in young adults (<45 yo) and older adults (≥75 yo) to guide the precise use preventive therapies

Future Directions / Opportunities

- CAC testing to guide intensity of LDL-C and SBP lowering
- CAC and atherosclerosis staging, who is eligible for non-statin therapy in primary prevention ?
- What areas in the U.S. do not have access to CT technology ?
  - RURAL Study
- Opportunistic CAC detection from non-gated chest CT scans using artificial intelligence

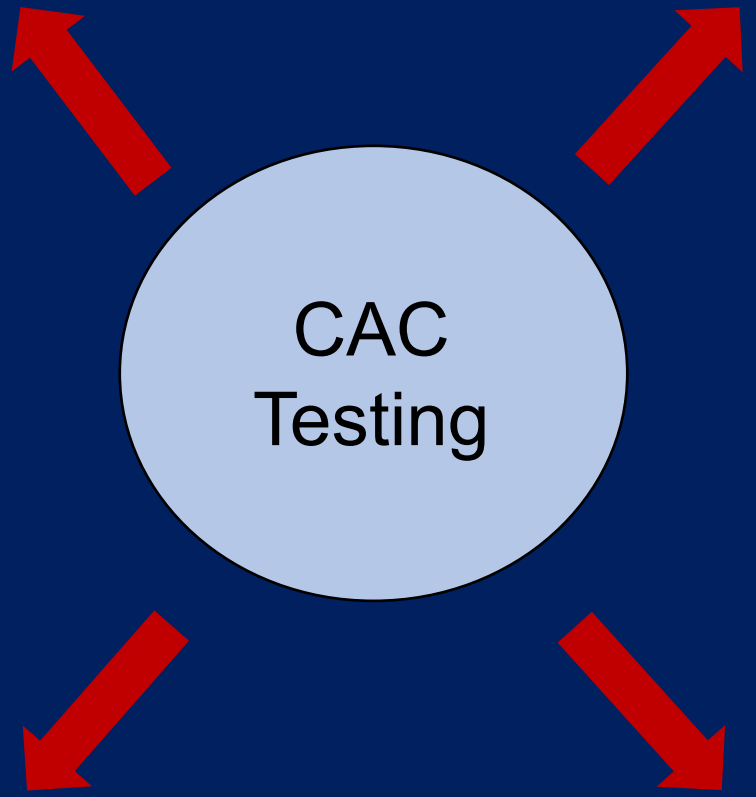
RURAL (Risk Underlying Rural Areas Longitudinal Study)

- RURAL is a NHLBI-funded study that examines cardiovascular health in rural communities across the Southeastern United States across four states (Alabama, Kentucky, Louisiana, and Mississippi) in the Appalachia and Mississippi Delta region.
- Measurement / study of CAC using mobile CT

https://theruralstudy.org

Precision Medicine

- Safely recommending lifestyle interventions for asymptomatic individuals with CAC=0
- Initiation of statin, aspirin, anti-HTN therapy, and residual risk-lowering therapies
- Intensive treatment of elevated blood pressure in CAC >0
- Treatment intensity and precise LDL-C goals according to CAC burden



Precision Public Health

- Identification of the group of individuals (ex: family hx of premature CHD) who could benefit from earlier initiation of primary prevention therapies (targeted scanning)
- Detection of subclinical atherosclerosis and expanding uptake of prevention interventions in vulnerable populations
- Linkage to care prior to incident event: identifying “missed” atherosclerosis cases and/or high-risk individuals

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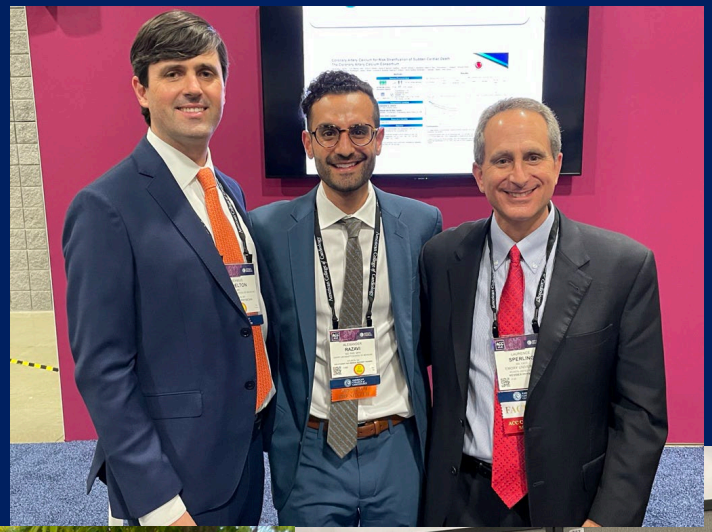
- Family



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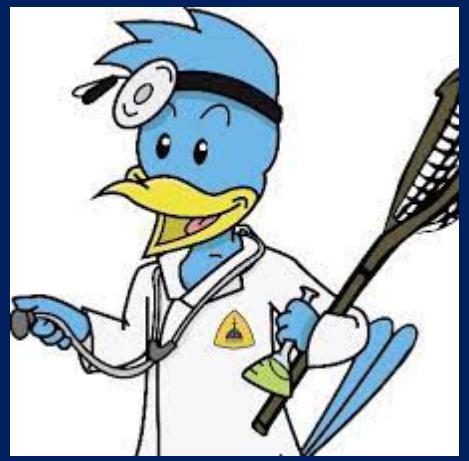

Right Care
Initiative

Questions?