Non-Invasive Imaging Section Roadmap

1 Risk Assessment in Asymptomatic Patients (1° Prevention)

2 The Symptomatic Patient

3 Case Vignette Discussion

CMHC
Cardiometabolic Health Congress

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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Module 1
Risk Assessment of the Asymptomatic Patient – Primary Prevention

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Baltimore, MD

Case Discussion – Asymptomatic Patient

- **52-year-old non-smoking, non-diabetic man with good diet and exercise habits**
  - Family history of premature CAD (father)
  - BP 139/85, HDL 60, LDL 135

12-lead EKG

- Cheap, rapid, non-invasive assessment of electrical signature of the heart
- Most useful in **symptomatic** patients for assessing acute coronary injury/ischemia and arrhythmia
- *Limited value in asymptomatic patients – not recommended for use in everyday cardiometabolic practice*
- *No clear role in routine risk assessment in primary prevention; only left ventricular hypertrophy has independent prognostic value*
- Pros: fast, cheap, can be diagnostic of myocardial injury, useful as a one-time baseline measure
- Cons: many findings non-specific, no role in routine primary prevention
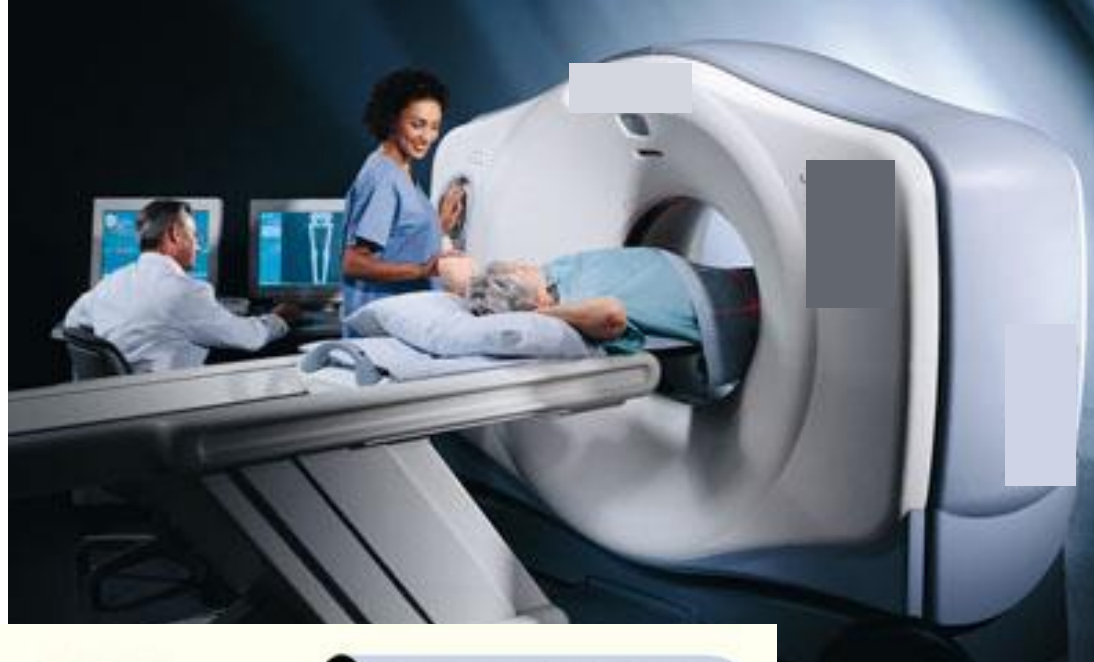
Resting 2D Echocardiography

- Non-invasive, ultrasound, relatively low cost
- Allows assessment of heart structure and function in real time
- Best tool to assess LVEF and for valvular heart disease
- Predominant use in **<u>symptomatic</u>** patients
- Screening – bicuspid aortic valve, conditions associated with cardiomyopathy, cardiotoxic drugs
- *No role in routine primary prevention – low yield and does not provide independent value for risk assessment*
- <u>Pros</u>: no radiation, functional assessment, relatively low cost
- <u>Cons</u>: operator dependent, limited by body habitus, no role in primary prevention
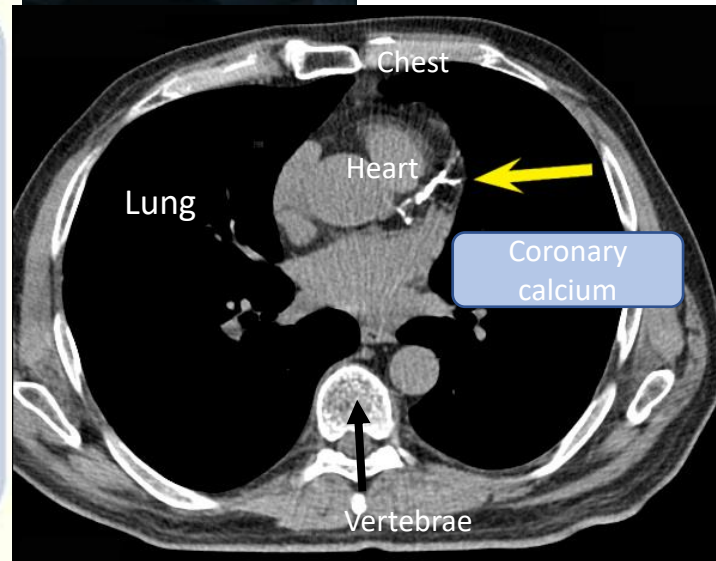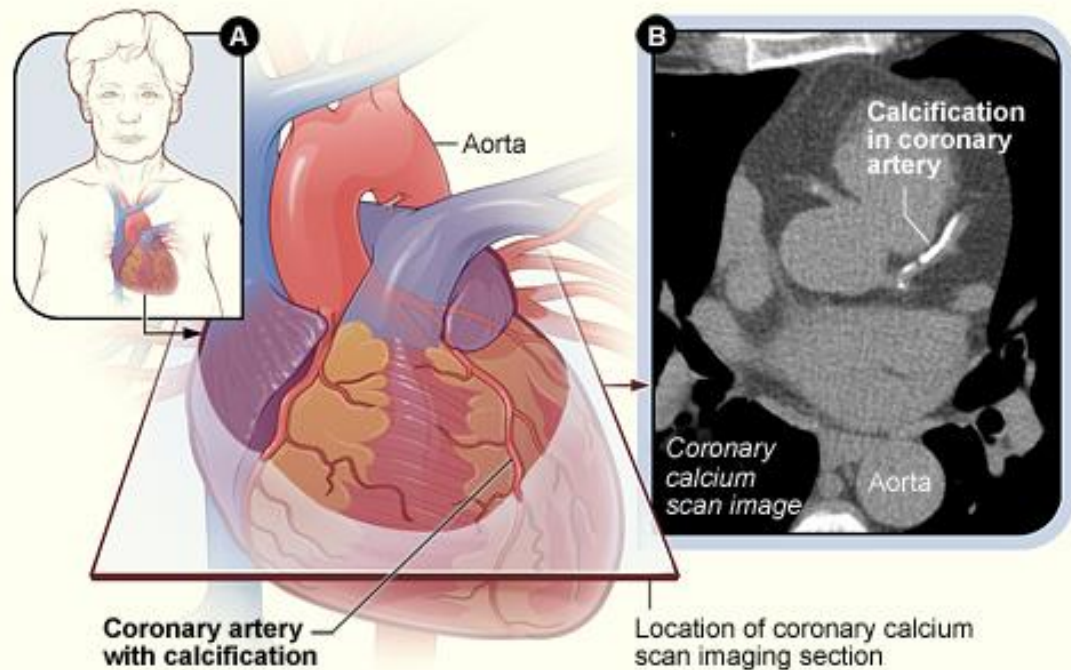
Coronary CT
(cardiac-gated, dedicated heart CT)

- Can be non-contrast or with IV contrast

- Non-contrast: **Coronary Calcium Score** (evaluate for atherosclerosis burden in coronaries, also aortic valve and aorta)

- Contrast: **Coronary CTA** (mimics invasive angiography, + can reveal early non-calcified plaque & specific plaque phenotypes)

- *Coronary calcium scoring has emerged as primary tool in routine primary prevention – best predictor of risk, guiding therapy decisions*

- *Little role for coronary CTA in asymptomatic patients*

- Pros: fast (test & interpretation), broadly available, low radiation

- Cons: not universally covered by insurance, incidental findings

~1 mSv

Aorta

A

B Calcification in coronary artery

Coronary calcium scan image

Aorta

Coronary artery with calcification

Location of coronary calcium scan imaging section

Chest

Heart

Lung

Coronary calcium

Vertebrae

Relationship of CAC to Coronary Atherosclerosis and Age

Square Root Sum of Plaque Areas

n = 38
r = 0.90
p < .001

Square Root Sum of Calcium Areas

Distribution of CAC Scores by Age

% in each CAC group

Age Groups	45-54	55-64	65-74	75-84
CAC > 100	6%	17%	34%	51%
CAC 1-100	19%	28%	30%	30%
CAC = 0	75%	55%	36%	19%
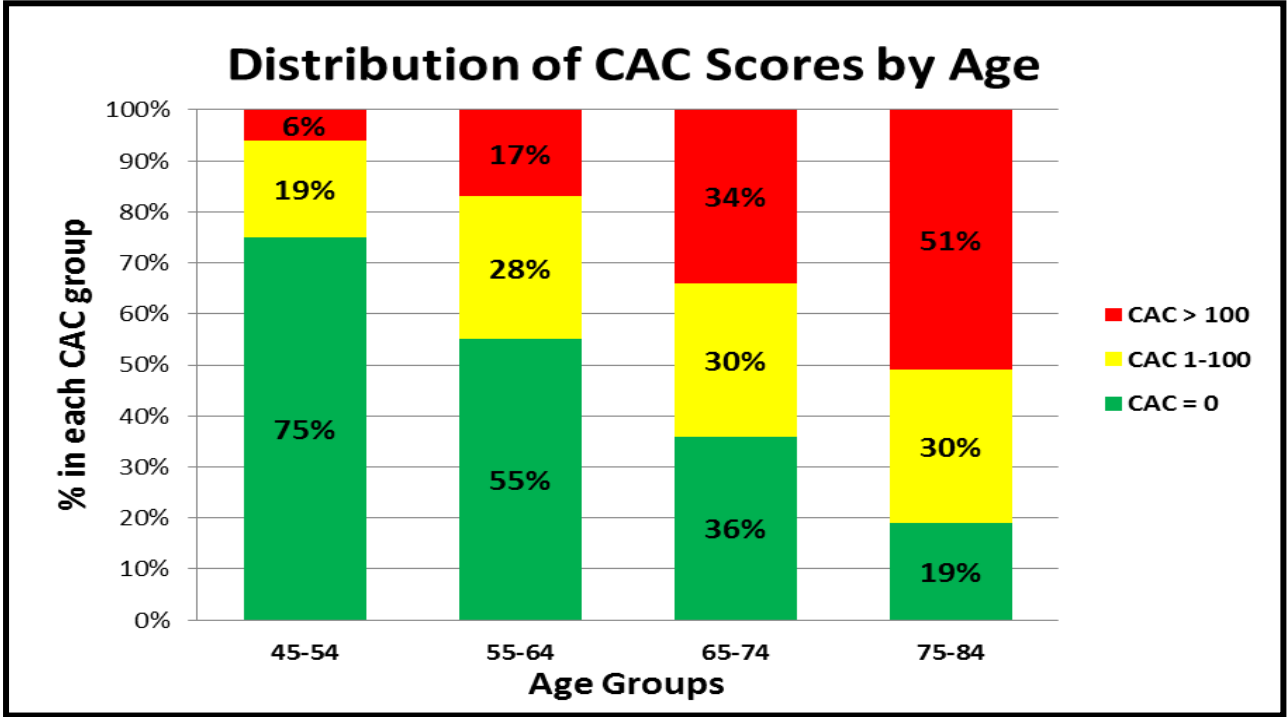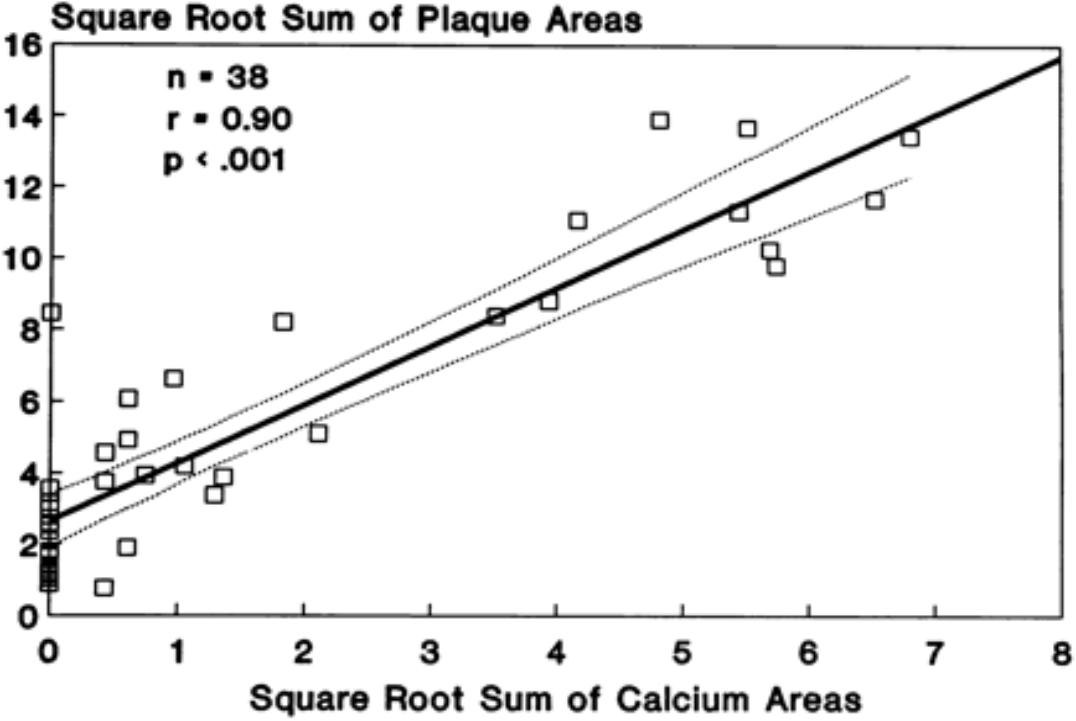
Rumberger et al. *Circulation*. 1995

Tota-Maharaj et al. *Mayo Clinic Proceedings*. 2014

Are You Really as Old as Your <u>Arteries?</u>
From MESA

Legend:
- CAC=0 (yellow)
- CAC 1-100 (blue)
- CAC>100 (red)

Age group	CAC=0	CAC 1-100	CAC>100
45-54 years	0.97	3.44	17.74
55-64 years	1.73	6.88	25.31
65-75 years	2.52	9.93	18.93
75-84 years	2.08	7.88	24.41

Tota Maharaj R, Blaha MJ, Nasir L, et al. *European Heart Journal*. 2012.
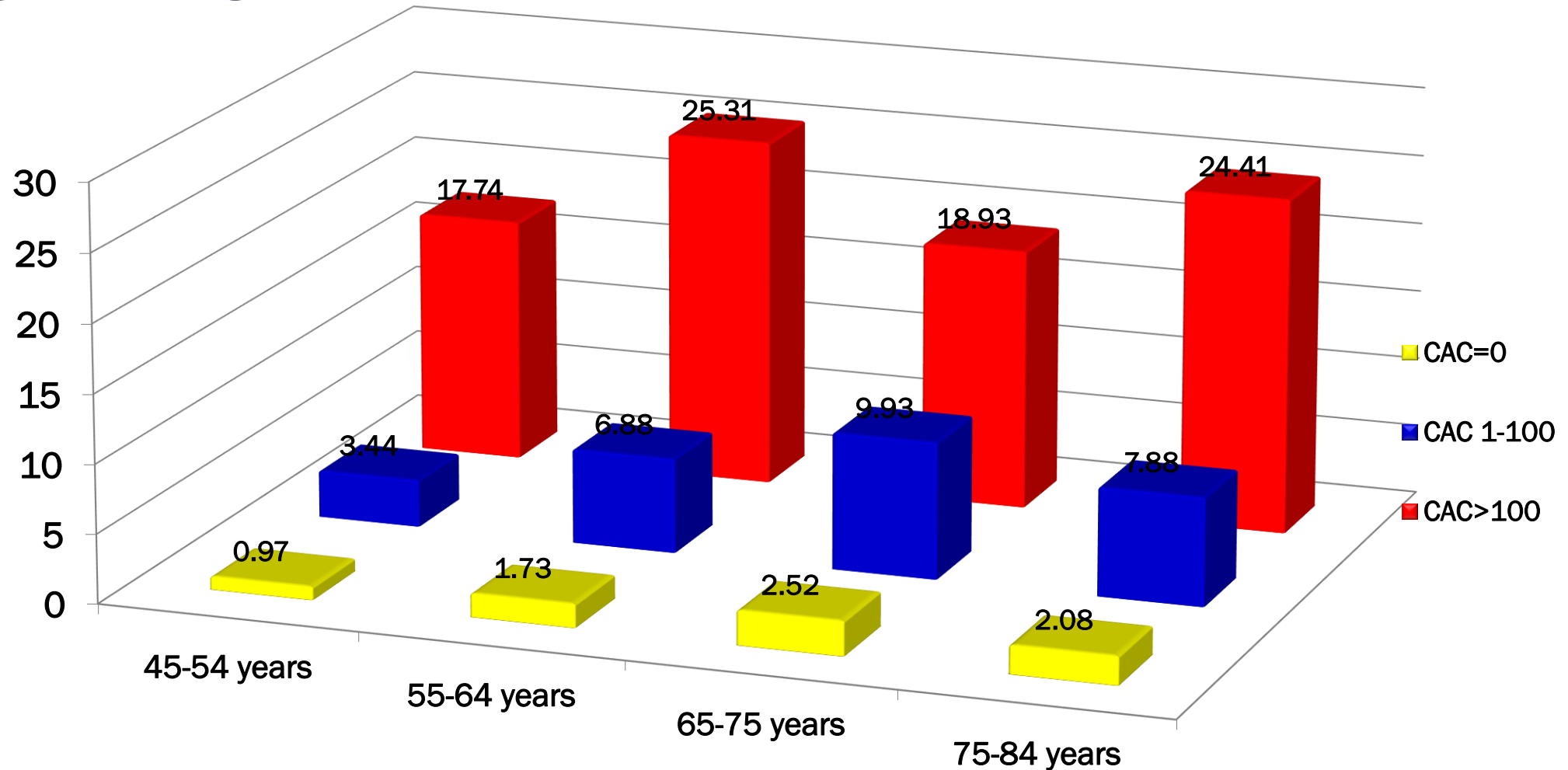
The Association of Coronary Artery Calcium With Noncardiovascular Disease

The Multi-Ethnic Study of Atherosclerosis
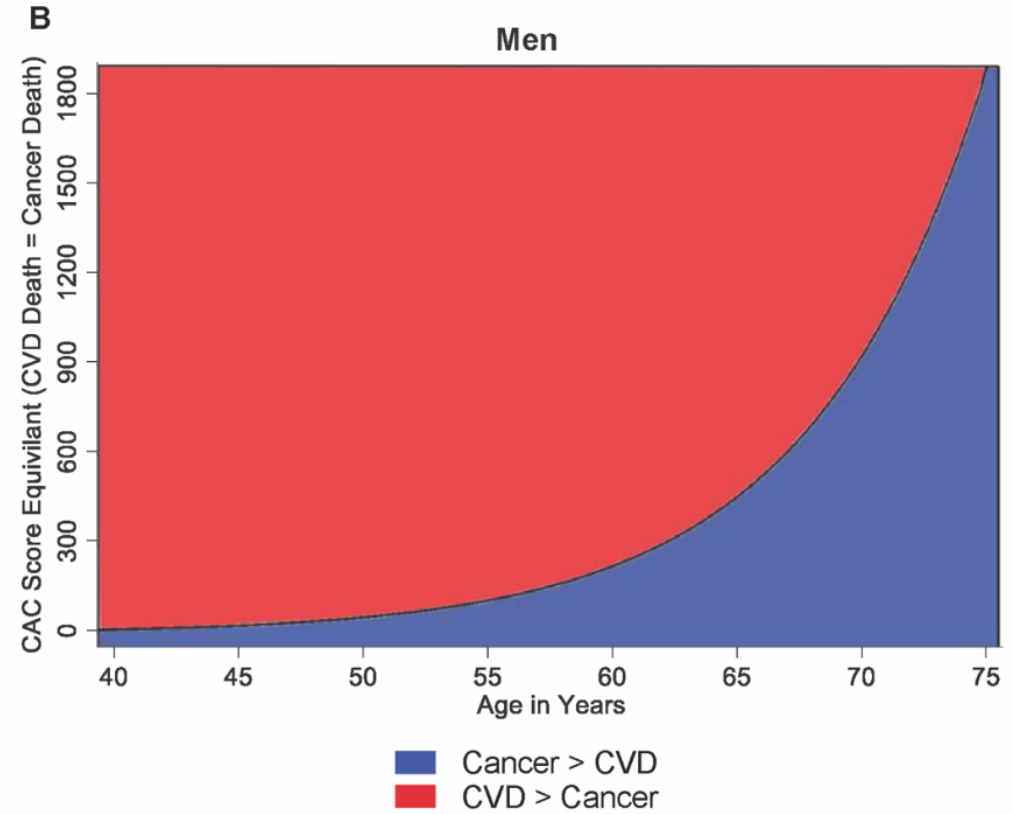
Catherine E. Handy, MD, MPH,[a] Chintan S. Desai, MD,[a] Zeina A. Dardari, MS,[a] Mouaz H. Al-Mallah, MD,[b] Michael D. Miedema, MD,[c] Pamela Ouyang, MD,[a] Matthew J. Budoff, MD,[d] Roger S. Blumenthal, MD,[a] Khurram Nasir, MD,[a,e,f,g] Michael J. Blaha, MD, MPH[a]

CAC and Competing Risk of CVD vs. Cancer

FIGURE 1 Proportion With Non-CVD by CAC Stratum
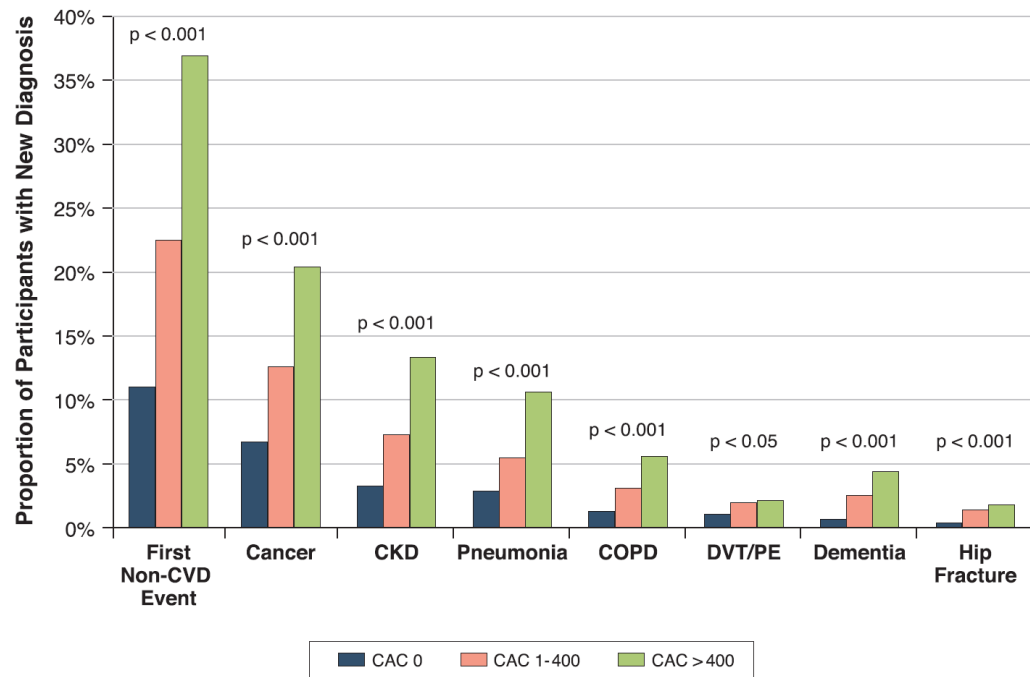
Comparing "Negative Risk Markers" in the Multi-Ethnic Study of Atherosclerosis

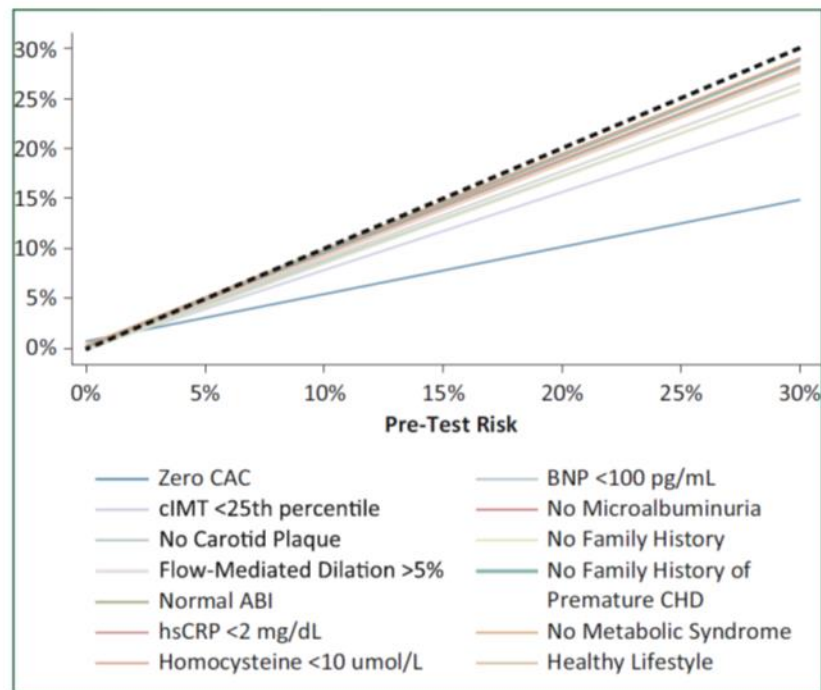FIGURE 4. **Relationship between pre-test and post-test cardiovascular disease risk after the knowledge of the negative result of each risk marker**. ABI, ankle brachial index; BNP, B-type natriuretic peptide; CAC, coronary artery calcium; CHD, coronary heart disease; cIMT, carotid intima-media thickness; hsCRP, high-sensitivity C-reactive protein. Reprinted with permission from Blaha et al. [46].

- A CAC score of zero is the strongest "negative risk factor" for the development of ASCVD.

- **Imaging Hypothesis** – due to superior sensitivity, imaging tests for subclinical atherosclerosis are excellent at "ruling out" or "downgrading" risk estimates.

Blaha MJ, et al. *Circulation*. 2016

Conventional view of risk factors

Concept of negative risk factors

Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study

Michael J Blaha , Matthew J Budoff, Andrew P DeFilippis, Ron Blankstein, Juan J Rivera, Arthur Agatston, Daniel H O'Leary, Joao Lima, Roger S Blumenthal, Khurram Nasir

Interpretation CAC seems to further stratify risk in patients eligible for JUPITER, and could be used to target subgroups of patients who are expected to derive the most, and the least, absolute benefit from statin treatment. Focusing of treatment on the subset of individuals with measurable atherosclerosis could allow for more appropriate allocation of resources.

2018 Cholesterol Guidelines

Primary Prevention
Assess ASCVD Risk in Each Age Gr.

Emphasize Adherence to healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of FH then statin

Age 20-39y
Estimate Lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C >= 160mg/dl (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥ 70 ≤ 190 mg/dl) (≥1.8 -<4.9 mmol/L) w/o diabetes mellitus 10 yr ASCVD risk percent begins risk discussion

LDL-C ≥190 mg/dl (≥4.9 mmol/L)
No risk assessment; High intensity statin (Class I)

Diabetes mellitus and age 40-75 yr
Moderate - intensity statin (Class I)

Diabetes mellitus and age 40-75 yr
Risk assessment to consider high-intensity statin
(Class IIa)

Age > 75 yr
clinical assessment, Risk discussion

Grundy, Scott M., et al. Journal of the American College of Cardiology 73.24 (2019): e285-e350.

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and LDL-C ≥ 70 ≤ 190 mg/dl) (≥1.8 -<4.9 mmol/L)
w/o diabetes mellitus
10 yr ASCVD risk percent begins risk discussion

ASCVD RISK Enhancers
- Family history of premature ASCVD
Persistently elevated LDL-C ≥ 160mg/dl (≥ 4.1 nmol/L)
-CKD
-Metabolic Syndrome
Conditions specific to women (e.g. preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
-Ethnicity (e.g. South Asian ancestry)

LIPID/ BIOMARKERS:
-Persistently elevated TGLs (≥ 175 mg/dL, ≥2.0 mmol/L)
IN- SELECTED INDIVIDUALS IF MEASURED:
- hs-CRP ≥2.0 mg/L
-Lp(a) levels > 50 mg/dl or >125nmol/L
-apoB ≥130mg/dL
- Ankle-brachial index (ABI) <0.9

<5%
"Low Risk"

5%- <7.5 %
"Borderline Risk"

≥ 7.5 %- <20%
"Intermediate Risk"

≥20%
"High Risk"

Risk Discussion:
Emphasis lifestyle to reduce risk factors (CLASSI)

Risk Discussion:
If risk enhancers present then risk discussion regarding moderate-intensity stating therapy (Class IIb)

Risk discussion
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30%- 49% (Class I)

Risk Discussion:
initiate statin to reduce LDL-C ≥50%
(CLASS I)

If risk decision is uncertain:
Consider easuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigrette smoking are present)
CAC= 1.99 favors statin (especially after age 55)
CAC =100+ and/ or ≥75th percentile, initiate statin therapy

Grundy, Scott M., et al. Journal of the American College of Cardiology 73.24 (2019): e285-e350.

Current Guidelines – Coronary Artery Calcium

IIa	**B-NR**	**In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy.**

Grundy, Scott M., et al. Journal of the American College of Cardiology 73.24 (2019): e285-e350.

St. Francis Heart Randomized Controlled Trial

FIGURE 1 Relative and Absolute Treatment Benefit Across hsCRP and CAC Groups

Subgroup	Events	HR (95% CI)
by hsCRP		
hsCRP <1	17 / 249	0.58 (0.22 - 1.6)
hsCRP 1-2	20 / 219	0.50 (0.20 - 1.25)
hsCRP ≥2	42 / 492	0.86 (0.47 - 1.58)
by CAC		
CAC 1-100	0 / 104	1
CAC 100-400	26 / 434	0.89 (0.41 - 1.9)
CAC >400	55 / 465	0.58 (0.34 - 1.00)
Overall		

Atorvastatin Superior — Atorvastatin Inferior

Placebo Event Rate Per 100 person-years
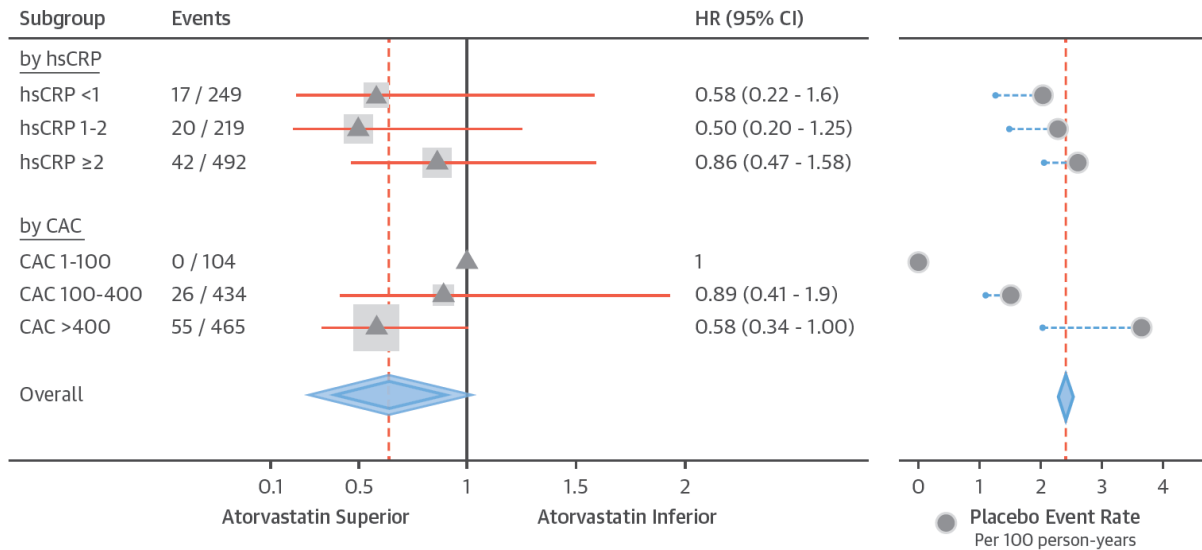
Biomarker*Statin Treatment Interaction Terms:
hsCRP (continuous) p = 0.76
CAC (continuous) p = *0.08*

5-year NNT:
hsCRP ≥2 mg/L = 61   CAC > 100 = 24
CAC > 400 = 13

(Left) Gray triangles = point estimates, **orange lines** = 95% confidence intervals (CIs). **(Right) Gray circles** = placebo event rates, and **dotted horizontal lines extending to the left** = absolute benefit (events reduced per 100 patient-years) with treatment. CAC = coronary artery calcium; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; NNT = number needed to treat.

Blaha MJ *JACC* 2018

Walter Reed Clinical Experience

CENTRAL ILLUSTRATION: Cumulative Incidence of MACE Stratified by Statin Treatment and CAC Severity

CAC 0 — Statin vs. No Statin aSHR 1.00, 95% CI 0.79-1.27 p = 0.99

CAC 1-100 — Statin vs. No Statin aSHR 0.83, 95% CI 0.60-1.16 p = 0.29

CAC 101-400 — Statin vs. No Statin aSHR 0.32, 95% CI 0.21-0.48 p < 0.0001

CAC 401+ — Statin vs. No Statin aSHR 0.56, 95% CI 0.34-0.90 p = 0.017
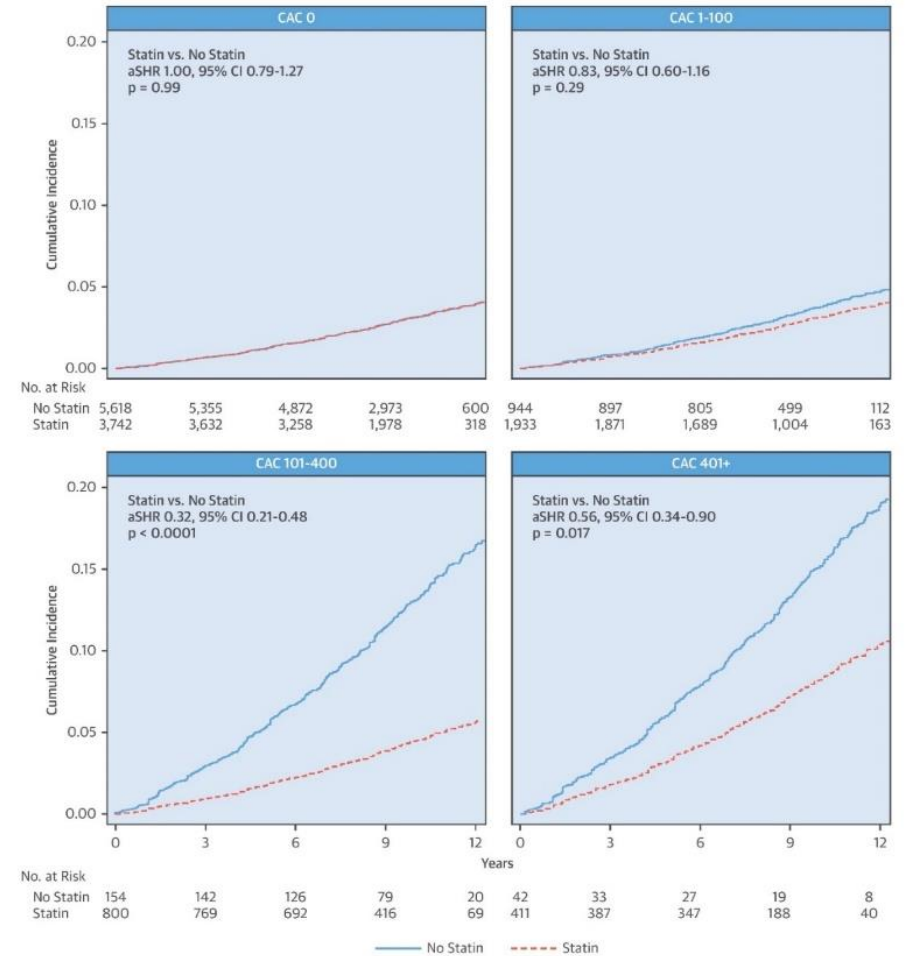
Mitchell, J.D. et al. J Am Coll Cardiol. 2018;72(25):3233-42.

Continuum of ASCVD Risk
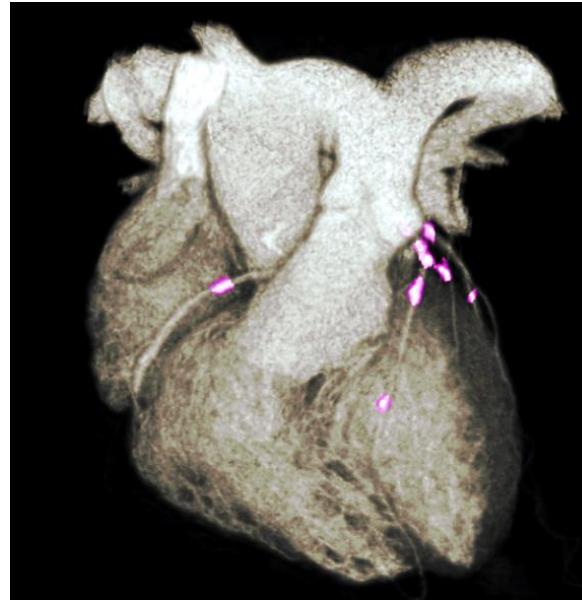
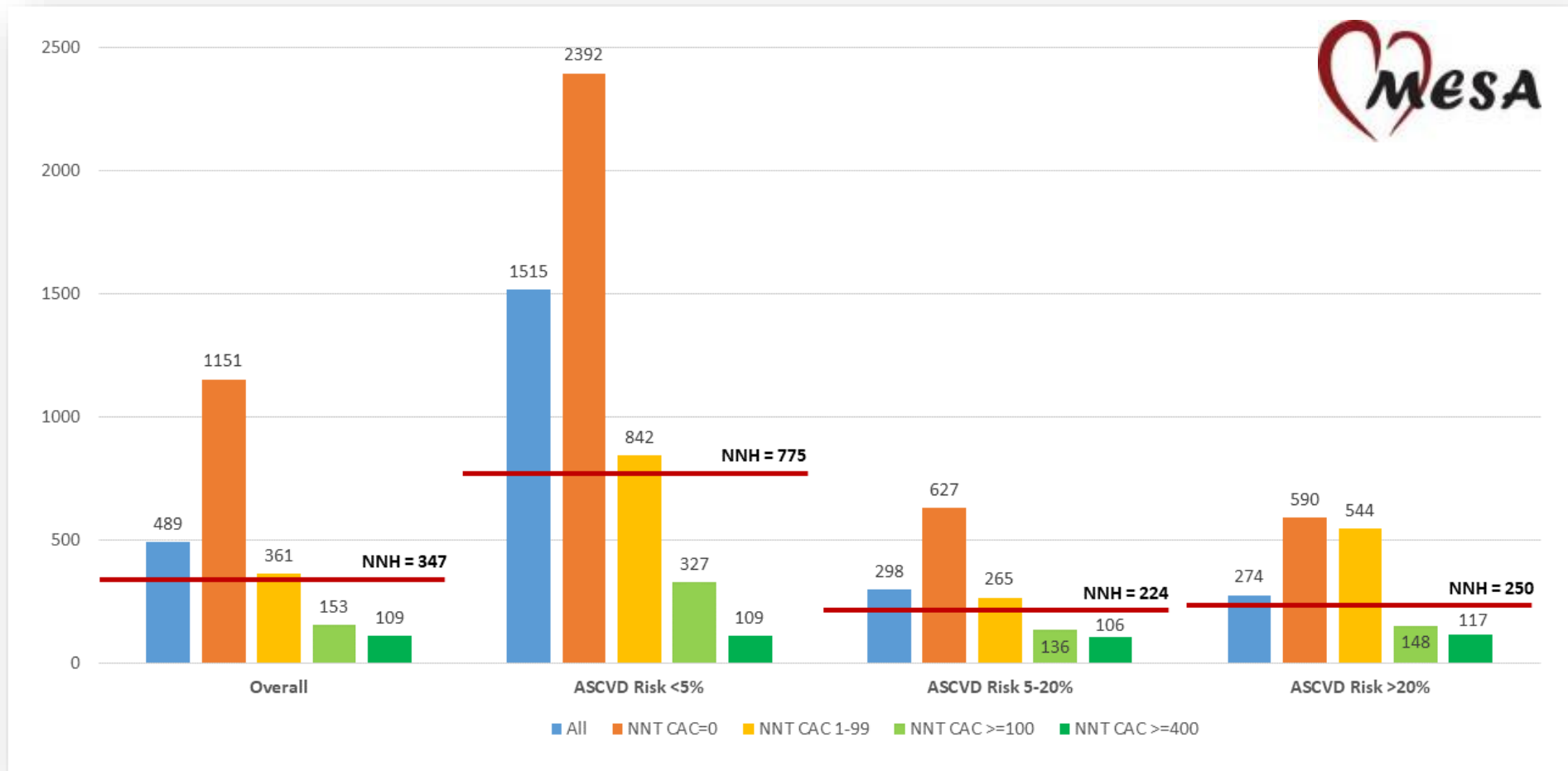**Primary Prevention** → **Advanced Subclinical Atherosclerosis?** → **Secondary Prevention**
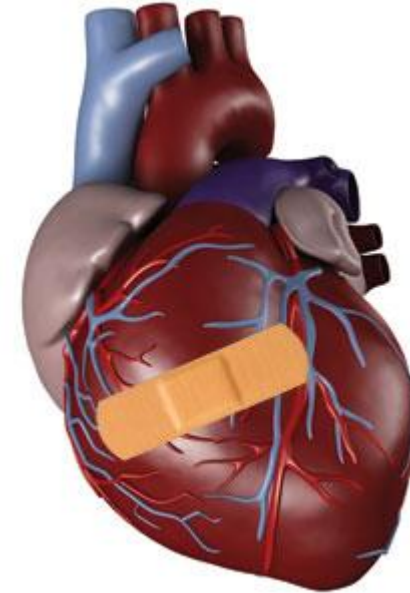
Aspirin Net Benefit According to CAC Scores – Updated 2020 Analysis

Cainzos-Achirica, et al.– *Circulation* 2020

ORIGINAL RESEARCH ARTICLE

Coronary Artery Calcium to Guide a Personalized Risk-Based Approach to Initiation and Intensification of Antihypertensive Therapy

John W. McEvoy, Seth S. Martin, Zeina A. Dardari, Michael D. Miedema, Veit Sandfort, Joseph Yeboah, Matthew J. Budoff, David C. Goff, Bruce M. Psaty, Wendy S. Post, Khurram Nasir, Roger S. Blumenthal and Michael J. Blaha

Conclusions—Combined CAC-imaging and assessment of global ASCVD risk has potential to guide personalized SBP goals (e.g., choosing a traditional goal of 140 or a more intensive goal of 120 mmHg), particularly among adults with estimated ASCVD risk 5-15% and pre-hypertension or mild hypertension.

Role of Coronary Artery Calcium for Stratifying Risk in Adults with Hypertension
The Coronary Artery Calcium Consortium
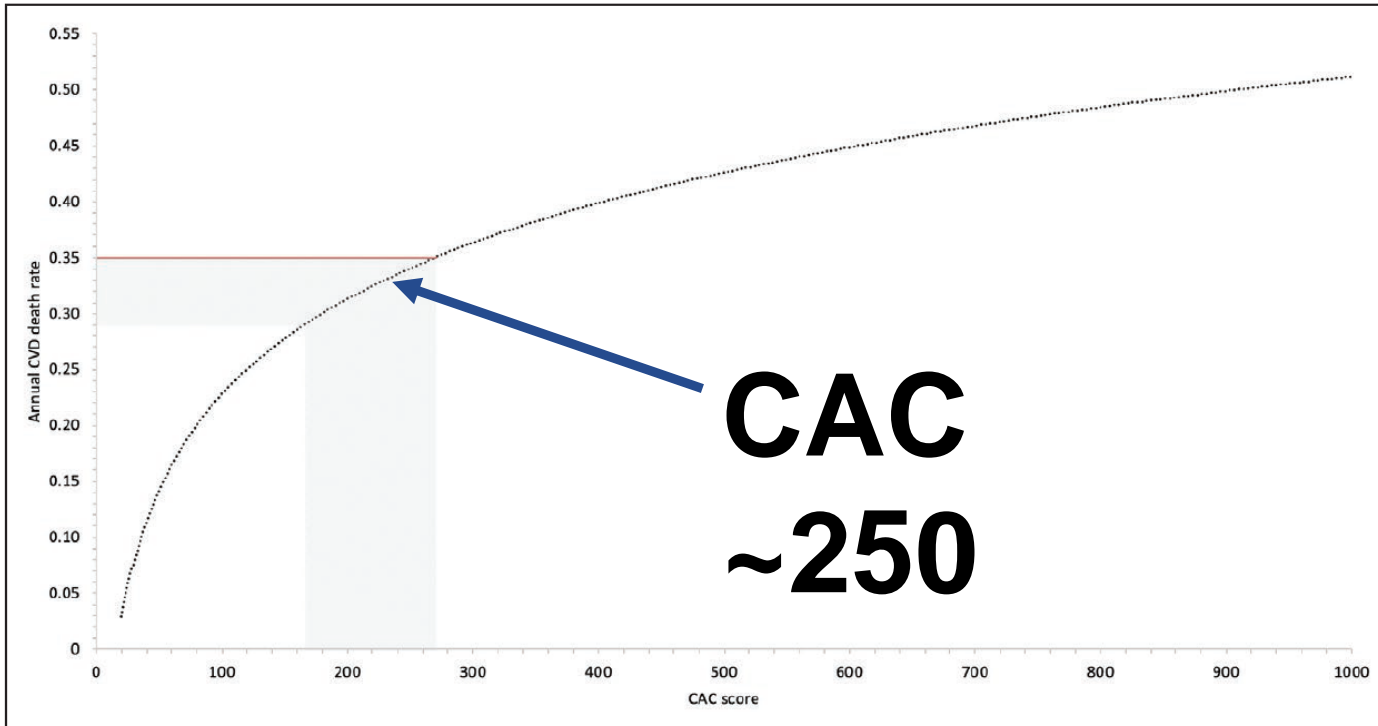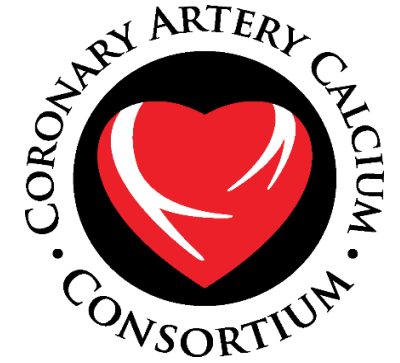
Figure 2. Coronary artery calcium (CAC) score equivalent of SPRINT (Systolic Blood Pressure Intervention Trial)-level risk among participants age >50 y. Graph shows the annual cardiovascular disease (CVD) mortality rate as a function CAC scores among hypertensive patients age >50 y. Horizontal red line represents the age-adjusted CVD death rate observed in the SPRINT trial (0.35%/y). These lines intersect at CAC=270, with lower limit of confidence (accounting for possible 15% underestimation of risk in the CAC Consortium) at CAC=165.

SPRINT TRIAL

9,361 patients (age ≥50 years) with ≥1 of the following: prior MI, PCI, CABG, CEA, or carotid stenting, ACS, CAD but no DM or stroke.

Intensive, target SBP <120 mm Hg (n=4,678)
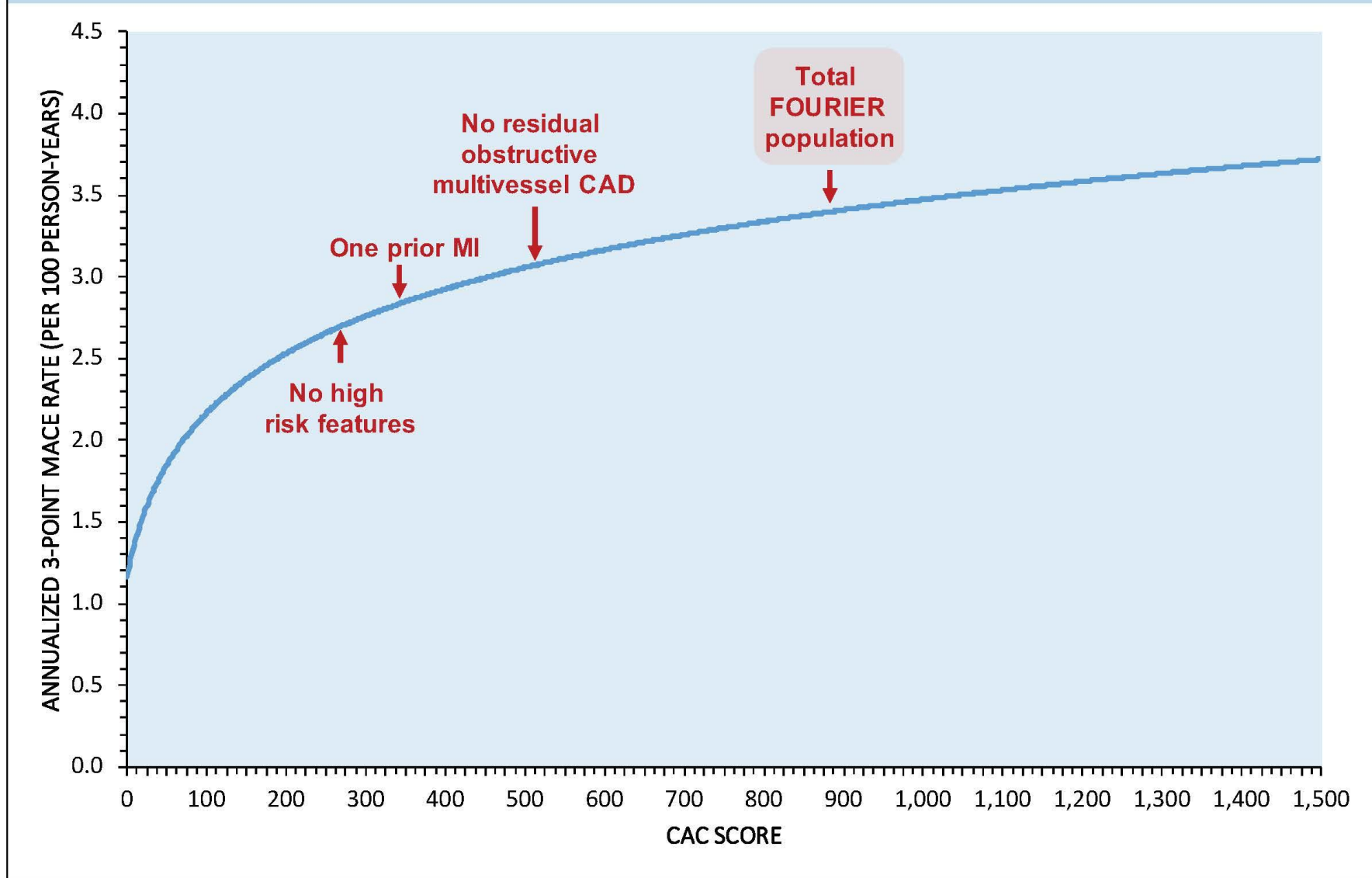
vs

Standard, target SBP 135-139 mm Hg (n=4,683)

Primary Outcome
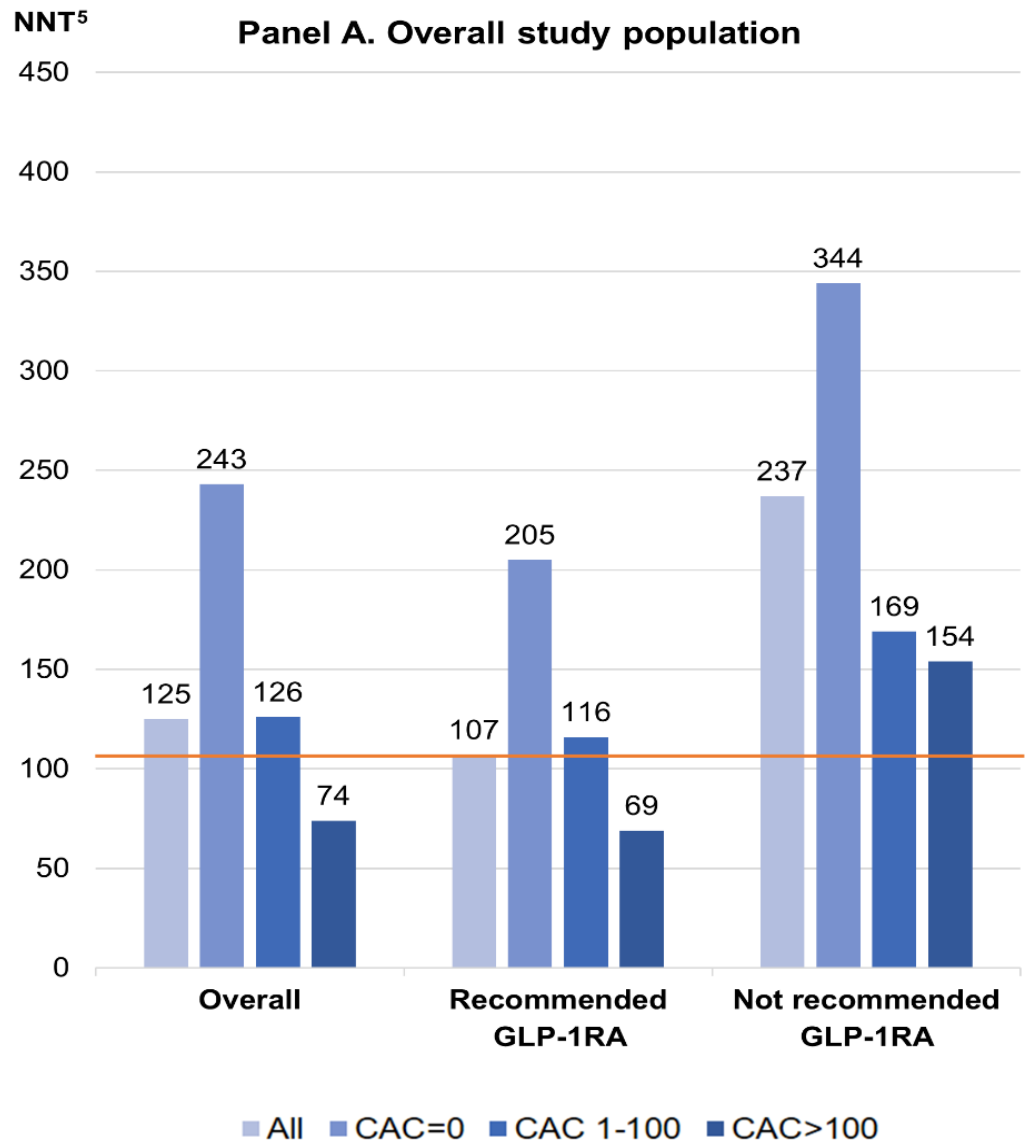First ACS, stroke, HF, or CV death
HR 0.75; 95% CI 0.64-0.89; P<0.001; NNT 63
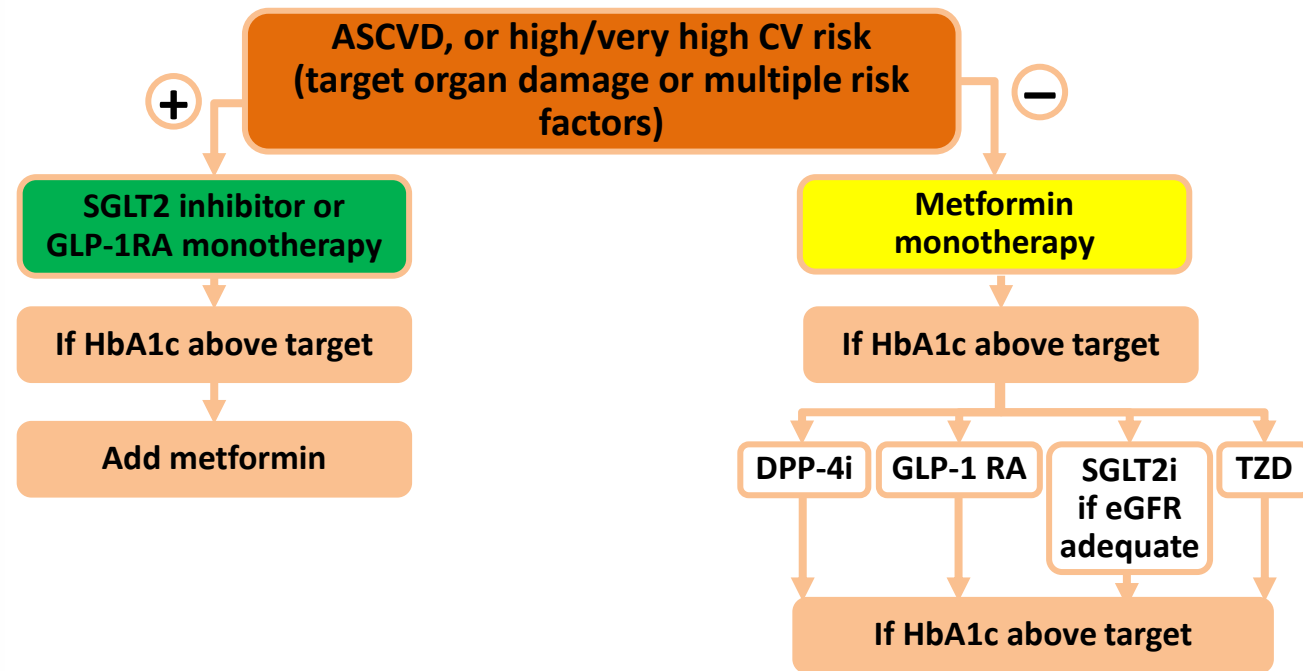
5.2%   6.8%

Uddin et al. *Hypertension*. 2019

FIGURE Analysis of Secondary Prevention Equivalent Risk by CAC Score in MESA

From: Peng AW, Dardari ZA, Blumenthal RS et al. Very high coronary artery calcium (CAC ≥ 1000) and association with CVD events, non-CVD outcomes, and mortality: Results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation in press.

Panel A. Overall study population

NNT[5]

Bar chart showing NNT values for Overall, Recommended GLP-1RA, and Not recommended GLP-1RA groups across All, CAC=0, CAC 1-100, CAC>100 categories:

- Overall: All = 125, CAC=0 = 243, CAC 1-100 = 126, CAC>100 = 74
- Recommended GLP-1RA: All = 107, CAC=0 = 205, CAC 1-100 = 116, CAC>100 = 69
- Not recommended GLP-1RA: All = 237, CAC=0 = 344, CAC 1-100 = 169, CAC>100 = 154

Legend: ■ All ■ CAC=0 ■ CAC 1-100 ■ CAC>100

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk—drug naïve

ASCVD, or high/very high CV risk (target organ damage or multiple risk factors)

+

SGLT2 inhibitor or GLP-1RA monotherapy

If HbA1c above target

Add metformin

−

Metformin monotherapy

If HbA1c above target

DPP-4i | GLP-1 RA | SGLT2i if eGFR adequate | TZD

If HbA1c above target

Recommendations	Class	Level
CAC score with CT may be considered a risk modifier in CV risk assessment of moderate-risk asymptomatic patients with DM	IIb	B

Cosentino et al. *European Heart Journal*. 2020

Case Discussion – Asymptomatic Patient

- **52-year-old non-smoking, non-diabetic man with good diet and exercise habits**
  - Family history of premature CAD (father)
  - BP 139/85, HDL 60, LDL 135
- **Pooled Cohort Equations**
  - 4.7% 10-year risk of ASCVD
- **CAC = 325 (95th percentile)**

How Would <u>You</u> Treat This Patient in a Cardiometabolic Clinic?

How would **<u>you</u>** treat this patient?
1. Lifestyle therapy only
2. Moderate intensity statin
3. High Intensity statin and aspirin
4. Intensive lifestyle, High intensity statin, aspirin, consider anti-hypertensive and non-statin add-on to achieve LDL<70 & non-HDL<100

Future CAC-Based Treatment Recommendations?

CAC Score	Lifestyle	Statin and Statin Intensity	Non-Statin Add-on*	Aspirin	Blood Pressure Goals	Secondary Prevention Meds**
0	✓					
1-99 < 75th % ≥ 75th %	✓ ✓	*Consider Mod* Moderate			Routine Routine	
100-299	✓	Moderate to High		✓	Routine	
≥ 90th %	✓✓	High	Consider	✓	Aggressive	Consider
> 300	✓	High	Consider	✓	Aggressive	Consider
>1000	*SECONDARY PREVENTION!!*					

* To achieve an optional LDL-C target of <70 mg/dL.
** Icosapent Ethyl, Low dose Rivaroxaban, GLP1-RA, SGLT2i

Coronary Artery Calcium vs. Coronary CT Angiography in Primary Prevention

Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study

Iksung Cho[1,2,3], Subhi J. Al'Aref[1], Adam Berger[4], Bríain Ó Hartaigh[1], Heidi Gransar[5], Valentina Valenti[1], Fay Y. Lin[1], Stephan Achenbach[5], Daniel S. Berman[6], Matthew J. Budoff[7], Tracy Q. Callister[8], Mouaz H. Al-Mallah[9], Filippo Cademartiri[10], Kavitha Chinnaiyan[11], Benjamin J.W. Chow[12], Augustin DeLago[13], Todd C. Villines[14], Martin Hadamitzky[15], Joerg Hausleiter[16], Jonathon Leipsic[17], Leslee J. Shaw[4], Philipp A. Kaufmann[18], Gudrun Feuchtner[19], Yong-Jin Kim[20], Erica Maffei[10], Gilbert Raff[11], Gianluca Pontone[21], Daniele Andreini[21], Hugo Marques[22], Ronen Rubinshtein[23], Hyuk-Jae Chang[2], and James K. Min[1]*

| Models		Compared with CACS + traditional RF	P-value
Baseline models			
Traditional RF		NA	NA
Traditional RF + CACS		NA	NA
Adding degree of stenosis Information by CCTA			
No. of segments with any stenosis		5.65	0.059
No. of segments with stenosis ≥50%		5.03	0.080
No. of vessels with stenosis ≥50%		9.69	0.046
Adding plaque characterization Information by CCTA			
No. of segments with calcified plaques		0.30	0.860
No. of segments with NCP or mixed plaque		2.86	0.240
Adding plaque location information by CCTA			
No. of proximal segment with any stenosis		5.12	0.080
No. of proximal segment with stenosis ≥50%		5.10	0.080

Conclusions

Coronary computed tomographic angiography improved prognostication of 6-year all-cause mortality beyond a set of conventional RF alone, although, no further incremental value was offered by CCTA when CCTA findings were added to a model incorporating RF and CACS.
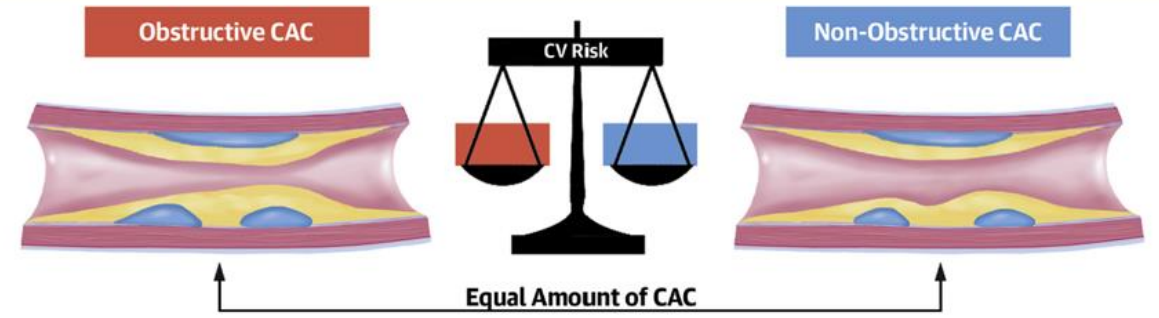
Plaque Burden (Coronary Artery Calcium) vs. Coronary Stenosis (Coronary CT Angiography)

CENTRAL ILLUSTRATION Atherosclerosis Plaque Burden, Not Stenoses Per Se, Is the Main Predictor of Risk for Cardiovascular Disease Events in Patients With Stable Coronary Artery Disease
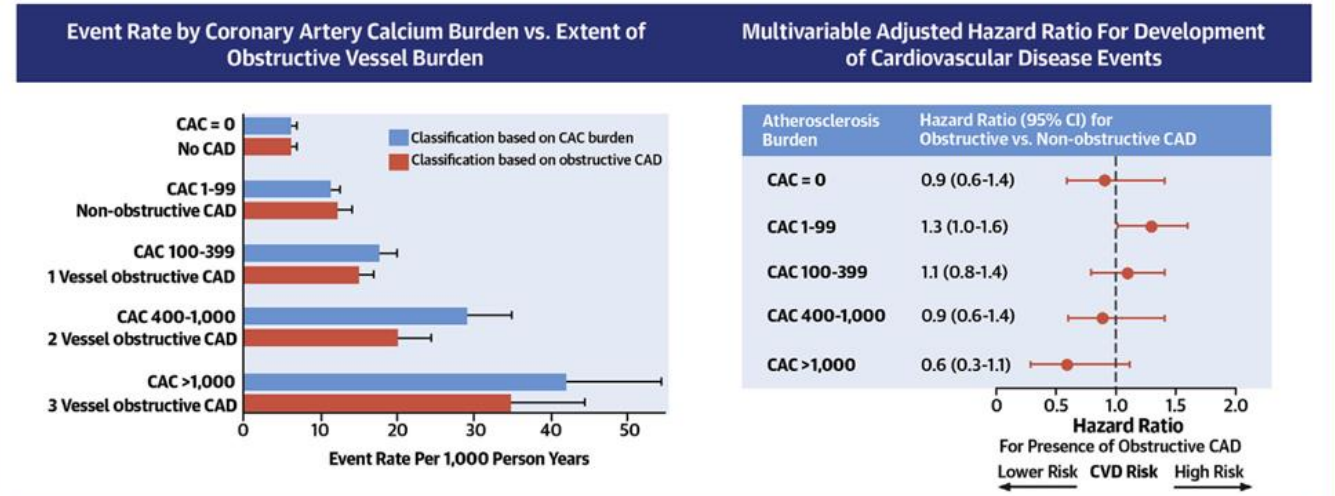
Mortensen, M.B. et al. J Am Coll Cardiol. 2020;76(24):2803–13.

(Top left) Risk for major cardiovascular disease (CVD) events increases stepwise with both atherosclerotic plaque burden as assessed by coronary artery calcium (CAC) and with number of vessels with obstructive coronary artery disease (CAD). **(Top right)** However, when stratified by groups of CAC burden, patients with obstructive versus nonobstructive CAD had similar CVD event rates. **(Bottom)** For the same atherosclerotic plaque burden, patients with nonobstructive CAD have a similar risk for CVD as patients with obstructive CAD.

Conclusion

- Non-invasive imaging has a role for risk assessment in primary prevention after consideration of traditional risk factors and risk enhancing factors (like metabolic syndrome)

- There is currently little role for routine EKGs and/or Echocardiograms for this purpose

- CAC is single best routinely used predictor of cardiovascular risk

- Coronary CTA can see non-calcified plaque, but does not add much to CAC in primary prevention

- CAC can guide intensity of lifestyle therapy, and choices about aspirin, blood pressure, cholesterol lowering therapy, and cardiometabolic drugs