Clinical Optimization of Lung Cancer Screening CT For CAC Theragnostics

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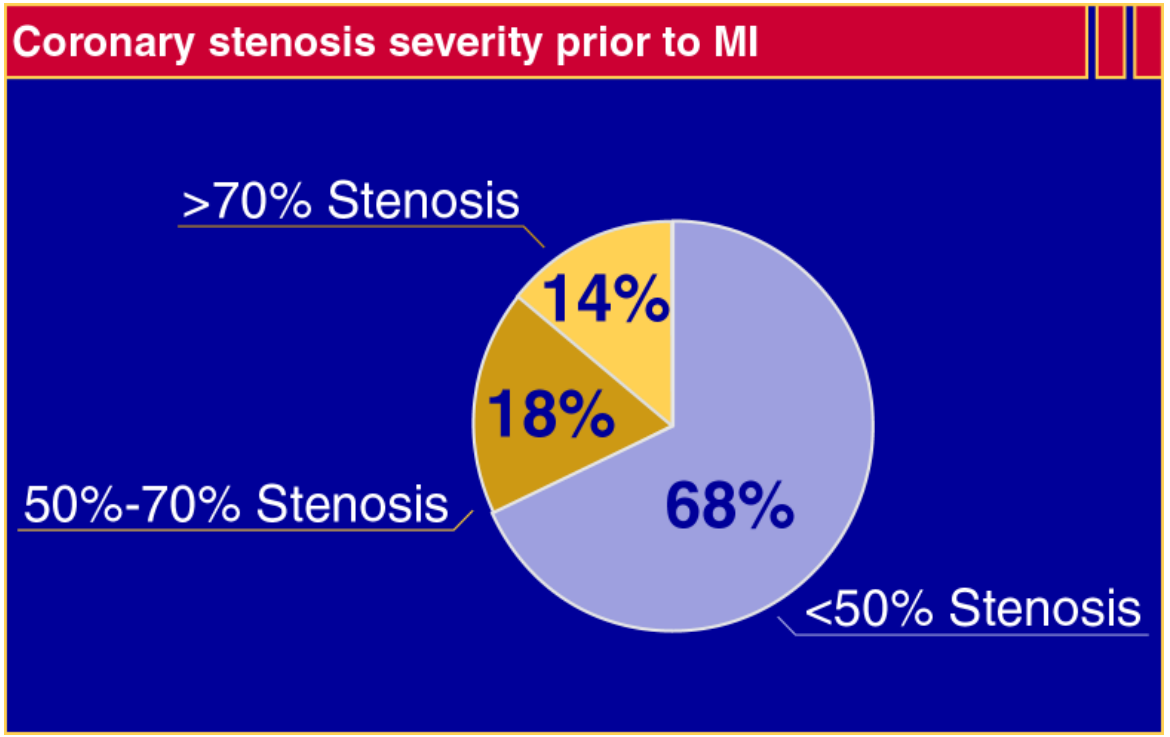
Disclosures

No disclosures

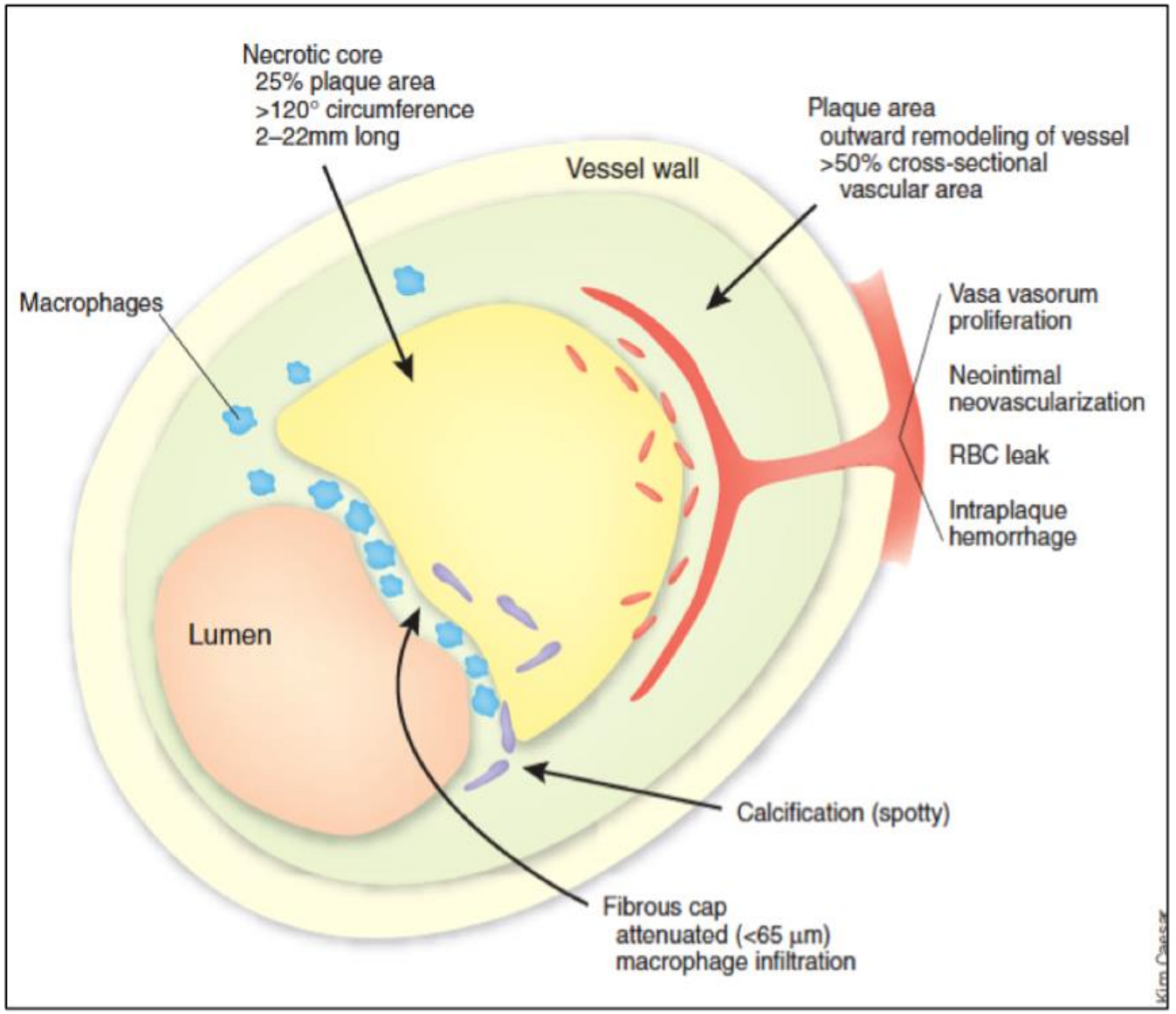
Prediction of CAD for preventive therapy

- Initial presentation for 50% is MI or death
- Conventional risk screening
  - Diabetes and FH
  - ASCVD risk score with risk factors
    - Low: <5% 10 year risk of MACE events
    - Borderline: 5-7.5%
    - Intermediate: 7.5-10%
    - High risk: >10%
- Risk stratification impacts preventive therapy
  - Balance benefits of risk reduction with adverse effects and costs
  - RCT data only for high- and low-risk patients
  - Intermediate-risk patients are unknown

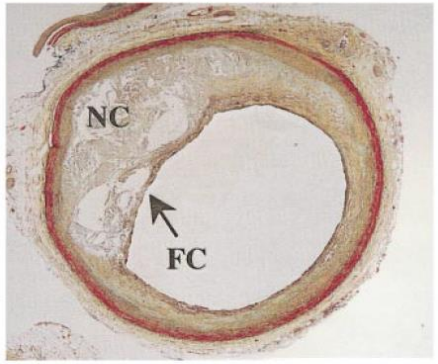


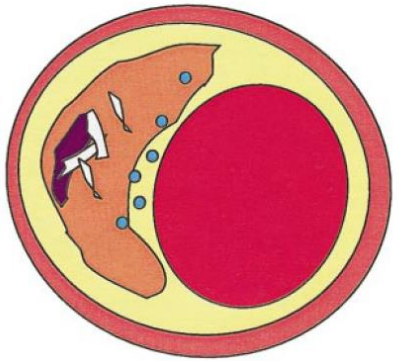
Source: Pooled data from 4 studies: Ambrose et al, 1988; Little et al, 1988; Nobuyoshi et al, 1991; and Giroud et al, 1992. (Adapted from Falk et al.)

Vulnerable Plaque Characteristics



Thin fibrous cap atheroma

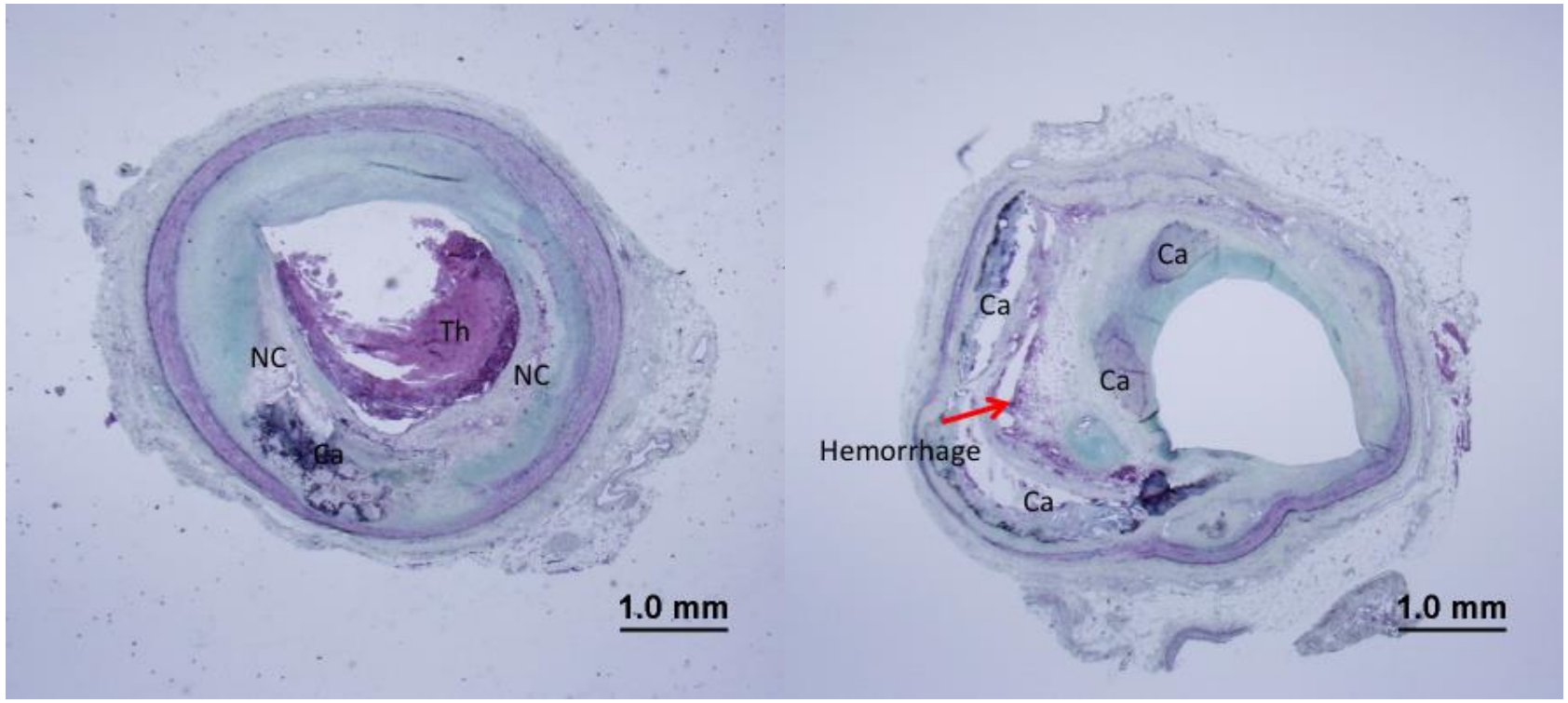




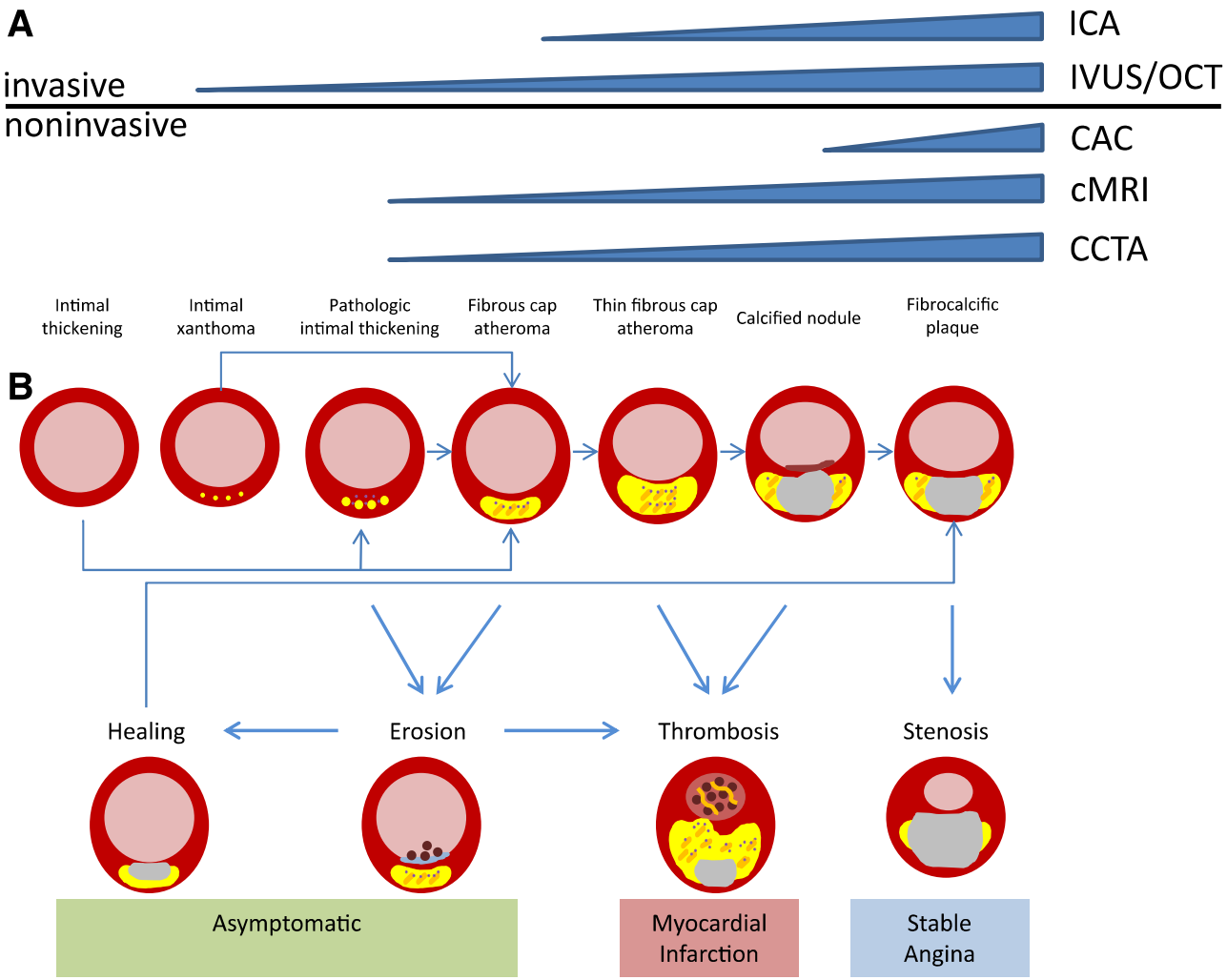
Virmani et al ATVB 2000

Calcium burden reflects total plaque burden

An integrated history of plaque progression



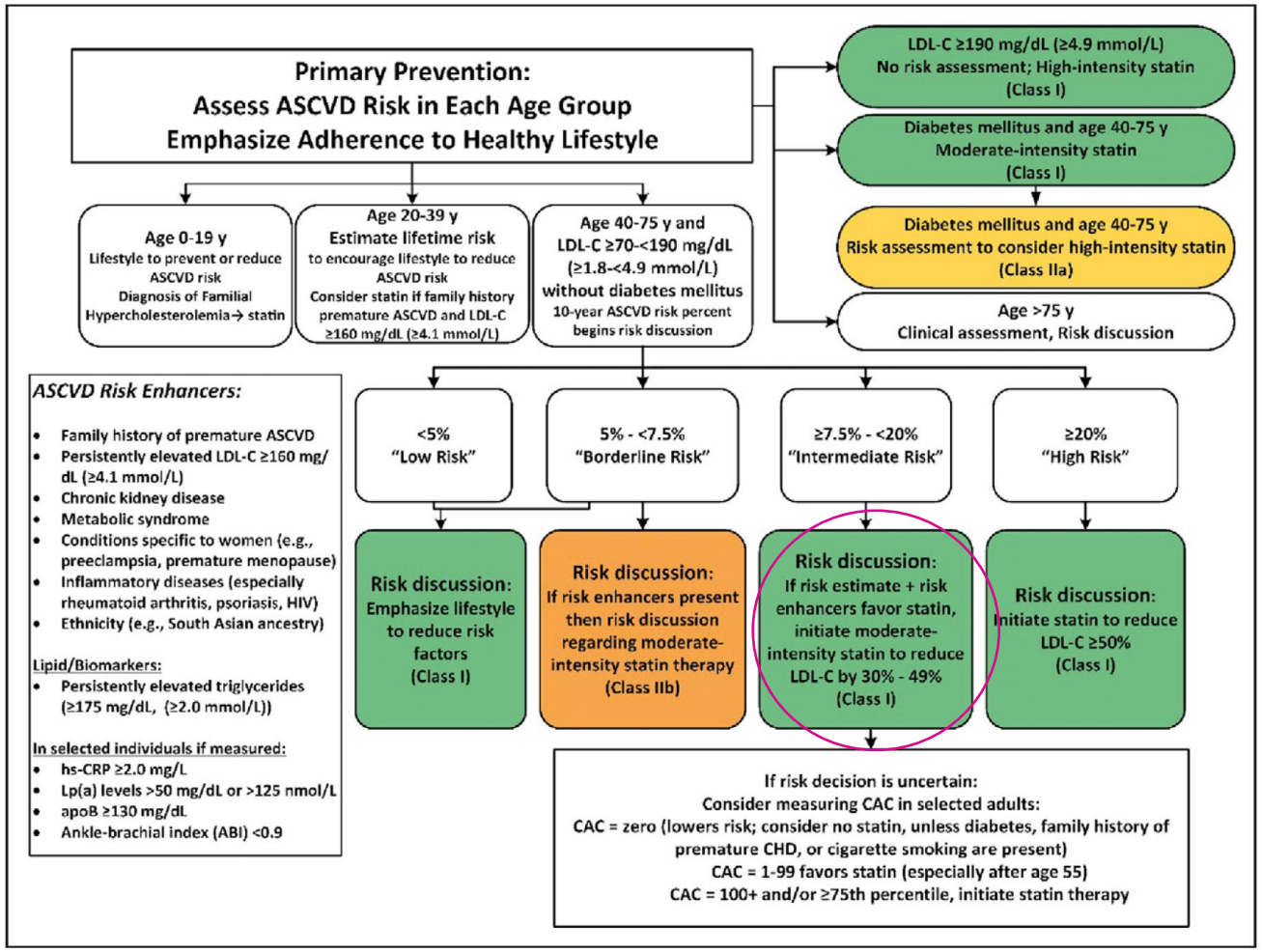
Plaque progression: the big picture



CAD primary prevention

Differences from lung cancer screening

- Indications for treatment even without CAC
- Competing risk factors besides CAC
- Treatment (statins) increase CAC
- With age and 1-2 risk factors, most older adults have an indication for statins
  - CAC = 0 to reduce polypharmacy not to intensify treatment

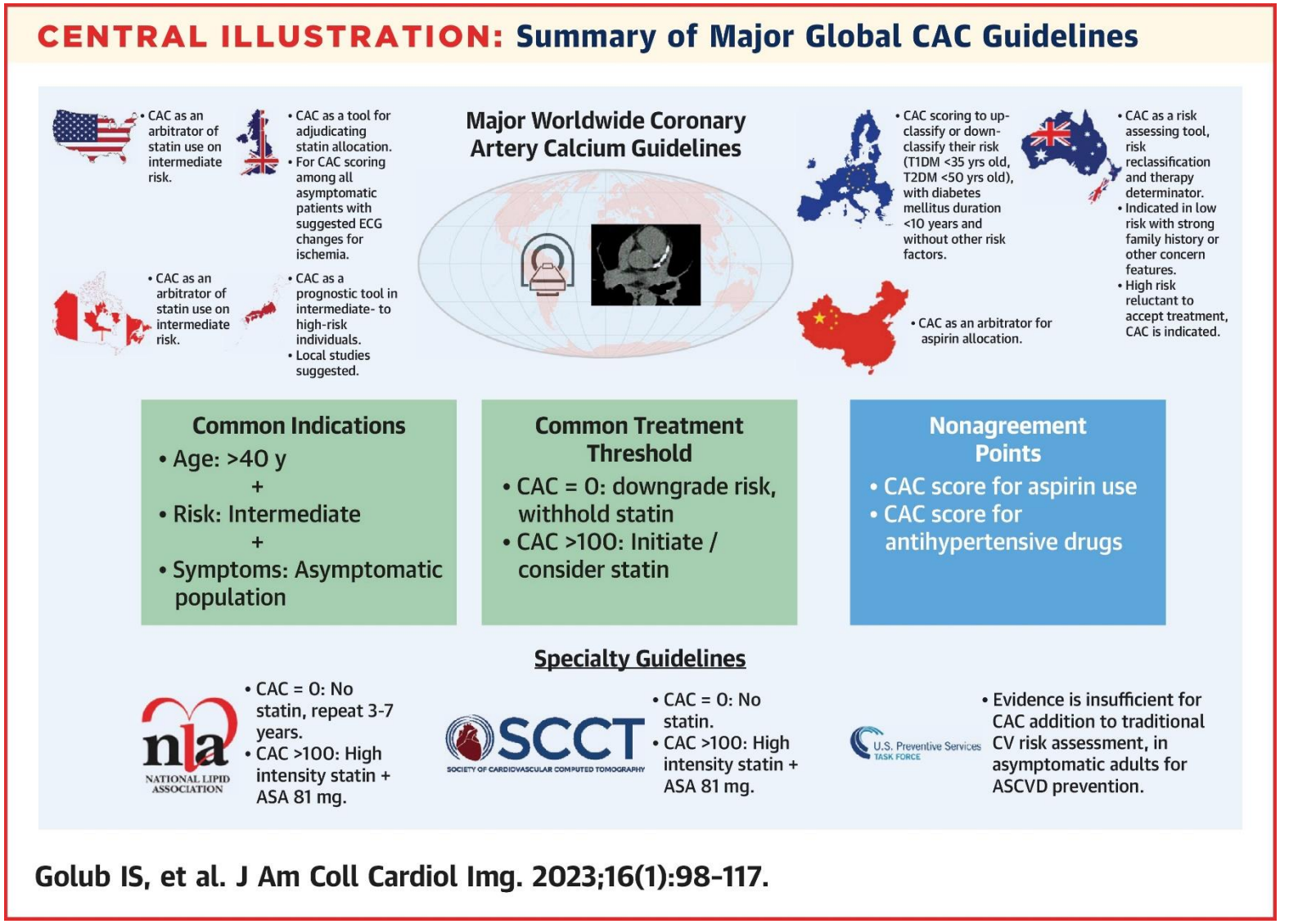


Arnett DK and the ACC/AHA Task Force Members Circulation 209:140

CAC-DRS

CAC-DRS category	Agatston	Visual score	Risk	Treatment recommendations
0	0	0	Very low	Statin generally not recommended
1	1-99	1	Mild	Moderate intensity statin
2	100-299	2	Moderate	Moderate to high intensity statin + ASA 81 mg
3	>300	3	Moderate to severe	High intensity statin + ASA 81 mg

International guidelines



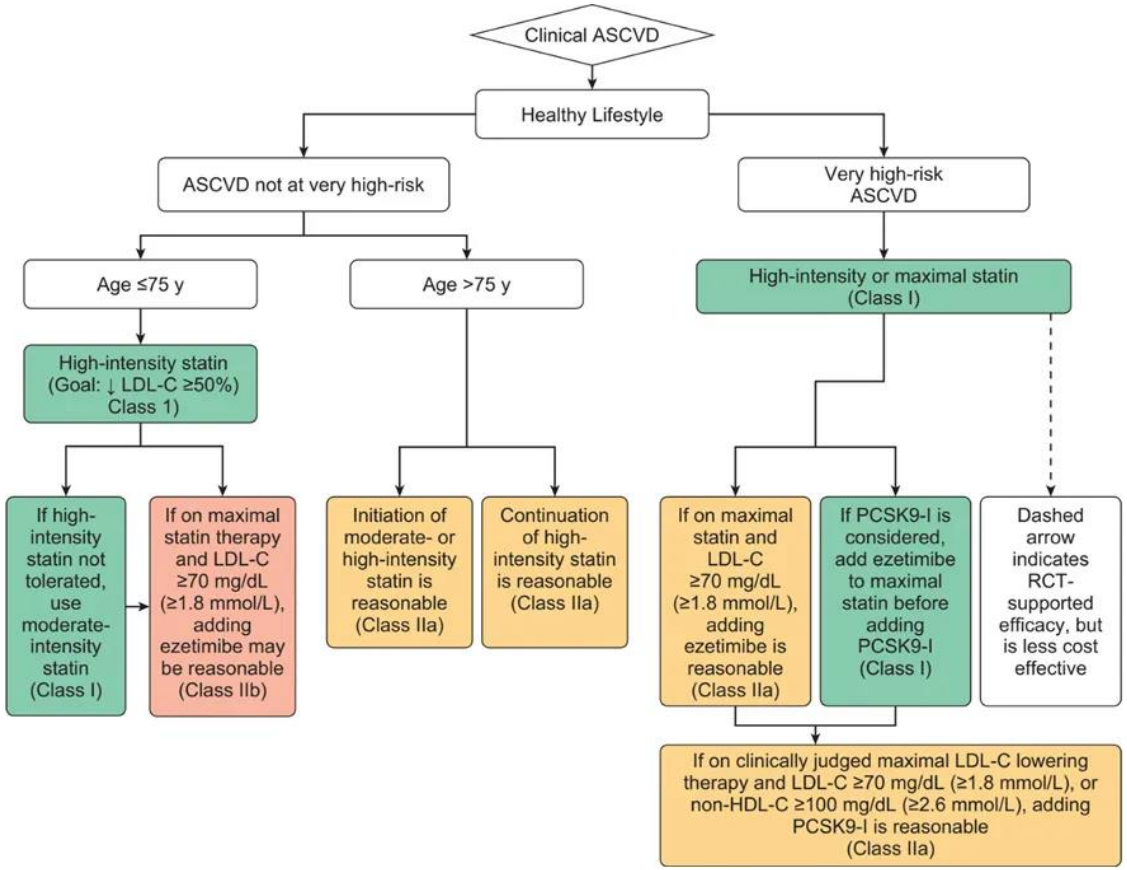
Golub IS, et al. J Am Coll Cardiol Img. 2023;16(1):98-117.

The challenge for theragnostics

Treatment strategy that combines therapeutics with diagnostics

- Recommendations are not supported by trials
- No consistent recommendations for thresholds of treatment
- No consistent recommendations for treatment
  - ASA 81 can cause harm in elderly
- Appropriate primary prevention population?
  - Diabetes and familial hyperlipidemia: statins regardless of CAC
  - Symptomatic or secondary prevention population: statin intensity based on clinical risk

Secondary treatment guidelines



Grundy SM et al JACC 2019 73:3168

CAC thresholds for action

- Zero
- Population nomograms
- CAC 100 for >10% 10 year risk
- Integrated into clinical risk score for >10% 10 year risk

CAC=0 has high negative predictive value for events

Prognostic Value of A CAC Score of Zero among Asymptomatic Individuals

Study and Study Type*	Total Population	No. of Subjects with Zero CAC†	Follow-up (y)	No. of Events†
Sarwar et al (32), meta-analysis	71,595	29,312 (41)	4.3	154 CVD events (0.47)
Blaha et al (33), retrospective	44,052	19,898 (45)	5.6	104 deaths (0.52)
Budoff et al (34), prospective study	6809	3414 (50)	4.1	17 CHD events (0.52)

* Reference numbers are in parentheses.

† Data are in parentheses are percentages. CHD = coronary heart disease, CVD = cardiovascular disease.

CVD event rate 0.5% over 5 years

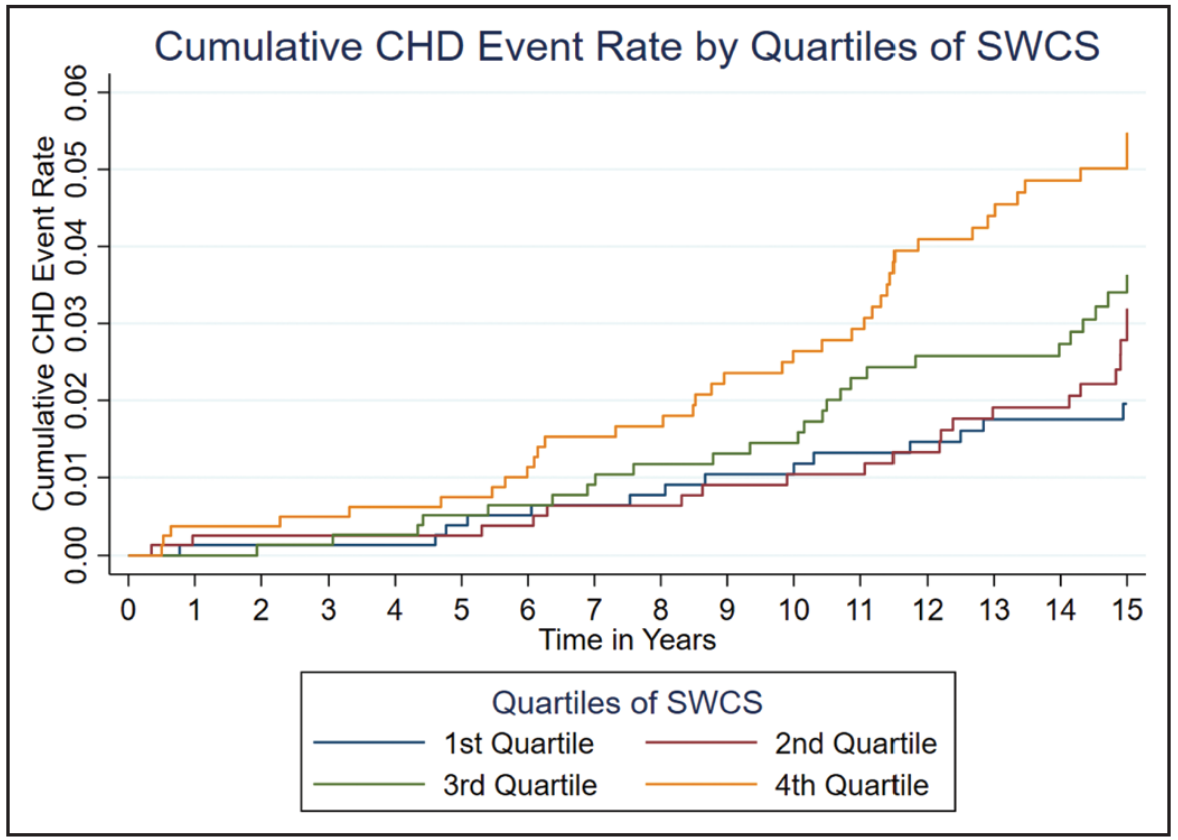
Nasir K Radiology 2012 264:3

Report extremely low density calcium in CAC=0

MESA cohort with CAC=0

- N = 3286

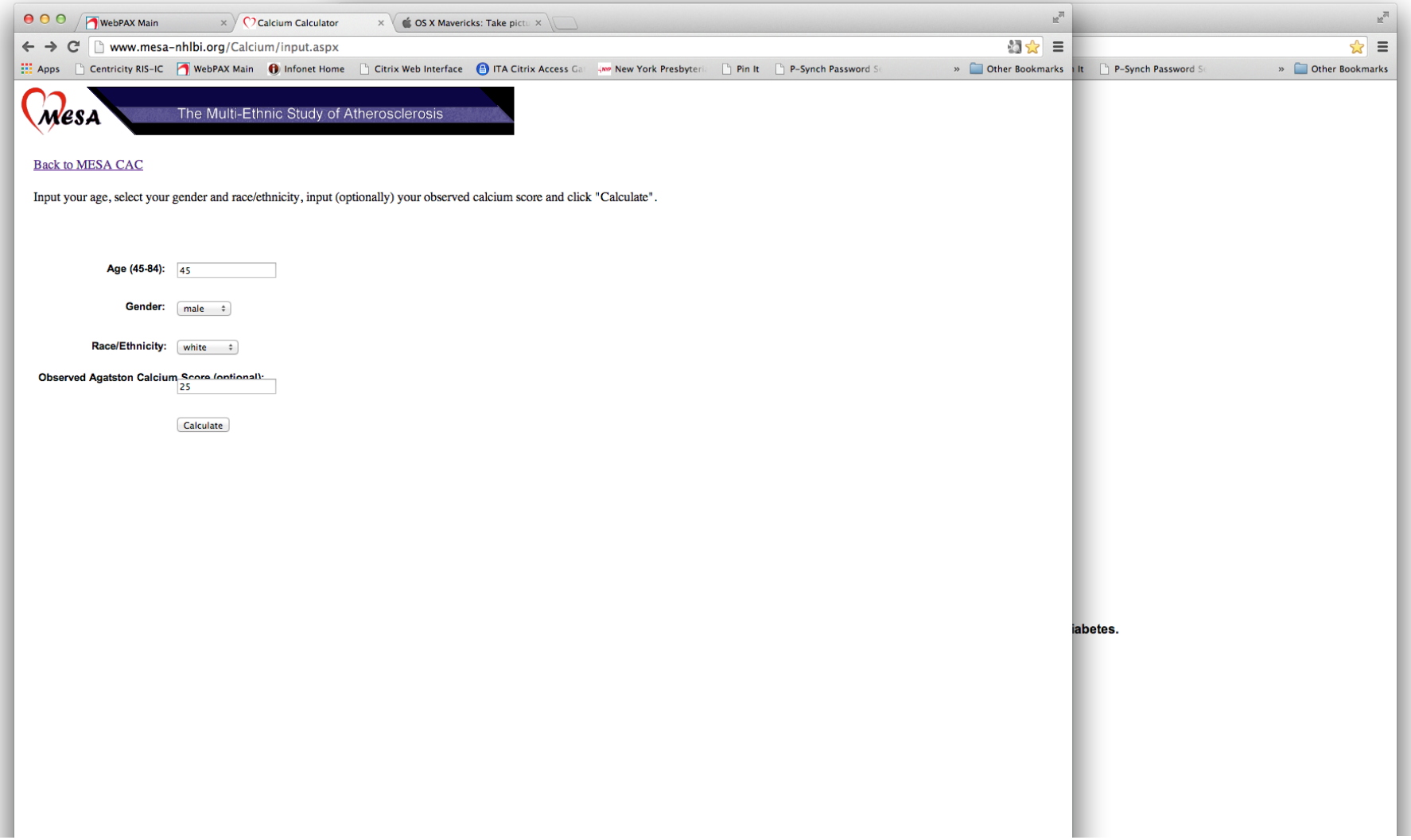
Predicts CHD and incident CAC adjusted for MESA risk score



SWCS = Calcium compared to phantom instead of HU130

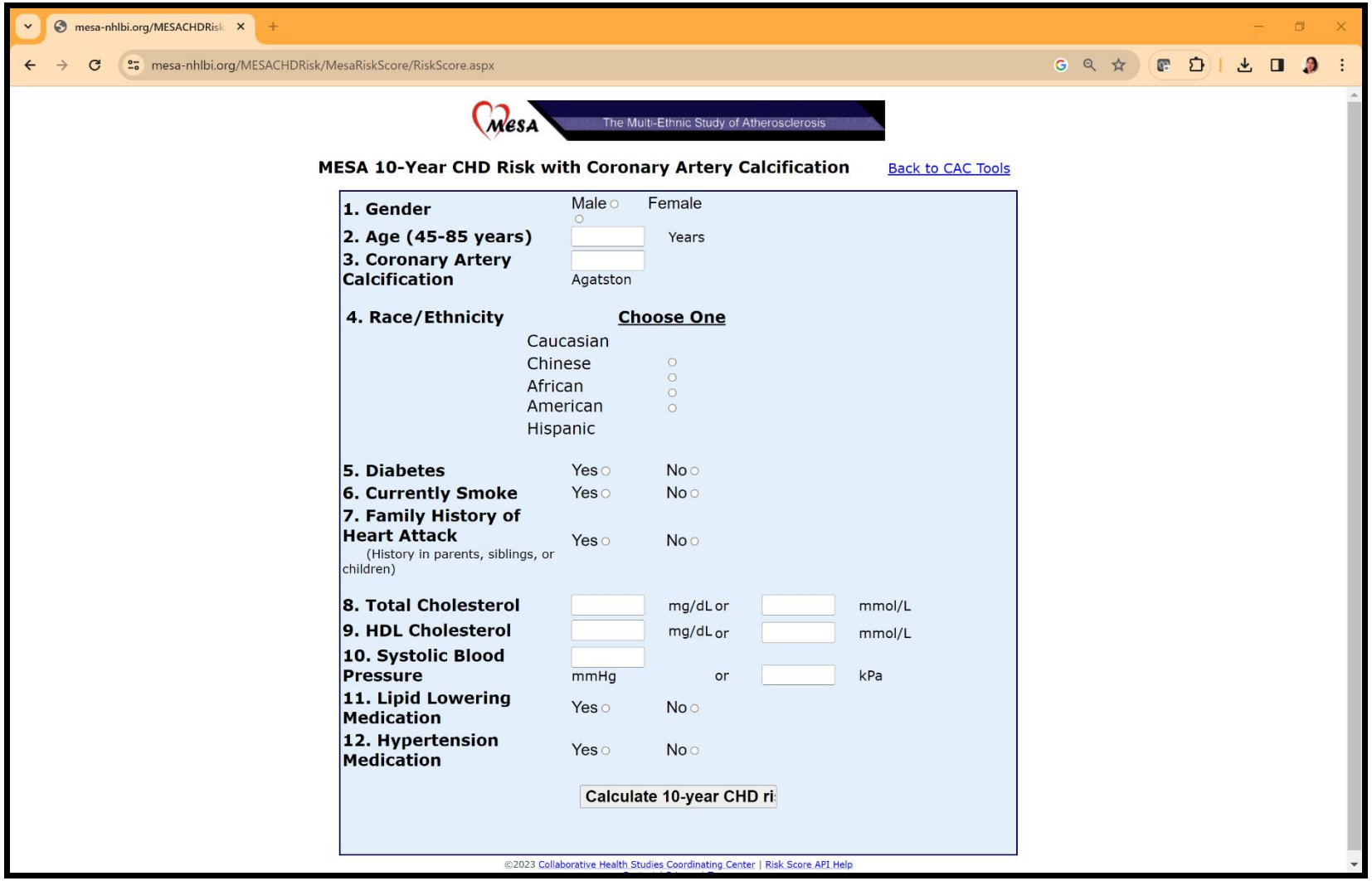
Circ Cardiovasc Imaging 2021 14:e011981

MESA study: Agatston score
Population based normal values ages 45-75



McClelland RL 2006 113:30

Integrated risk score



Standardized Agatston CAC score

Patient population

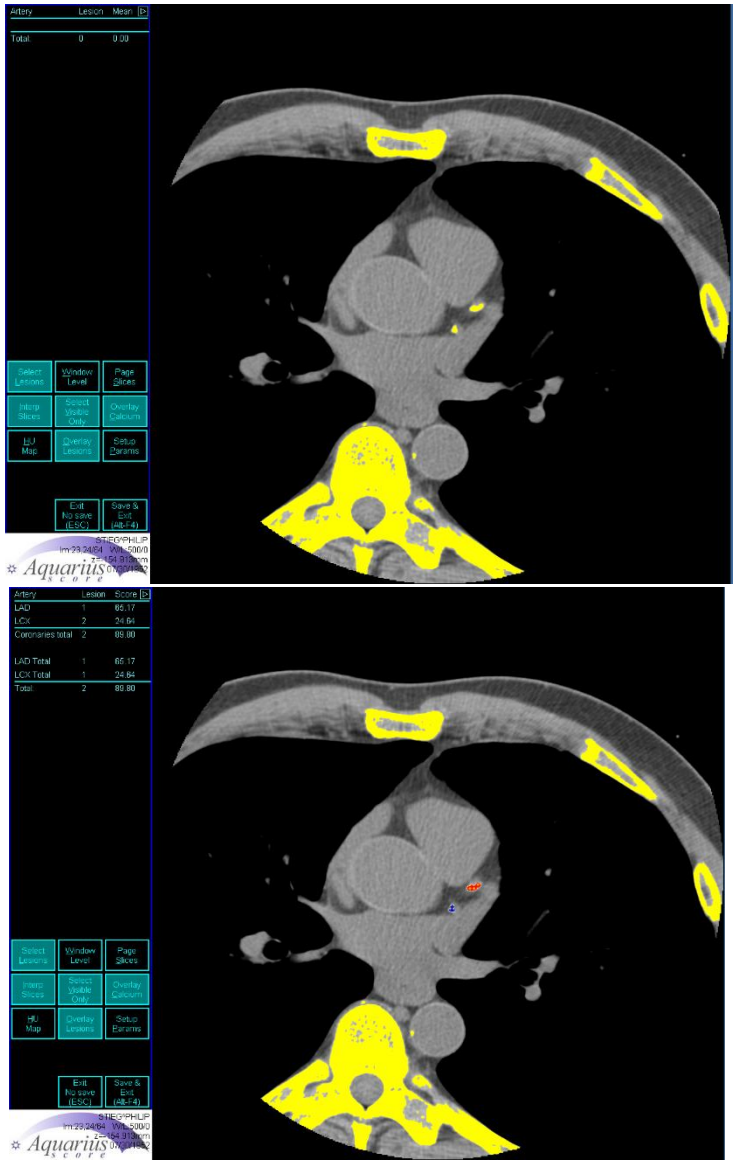
- Asymptomatic, primary prevention

Acquisition

- EBCT or MDCT
- 120 keV
- 2.5-3mm slice
- ECG gated for mid-diastole or end-systole

Scoring

- Coronary arterial silhouette (no hardware, aortic, or mitral calc)
- ≥3 contiguous pixels with peak attenuation >130
- Weighted sum by HU
  - 130-200: 1
  - >400: 4



Major considerations for AI CAC

Patient population

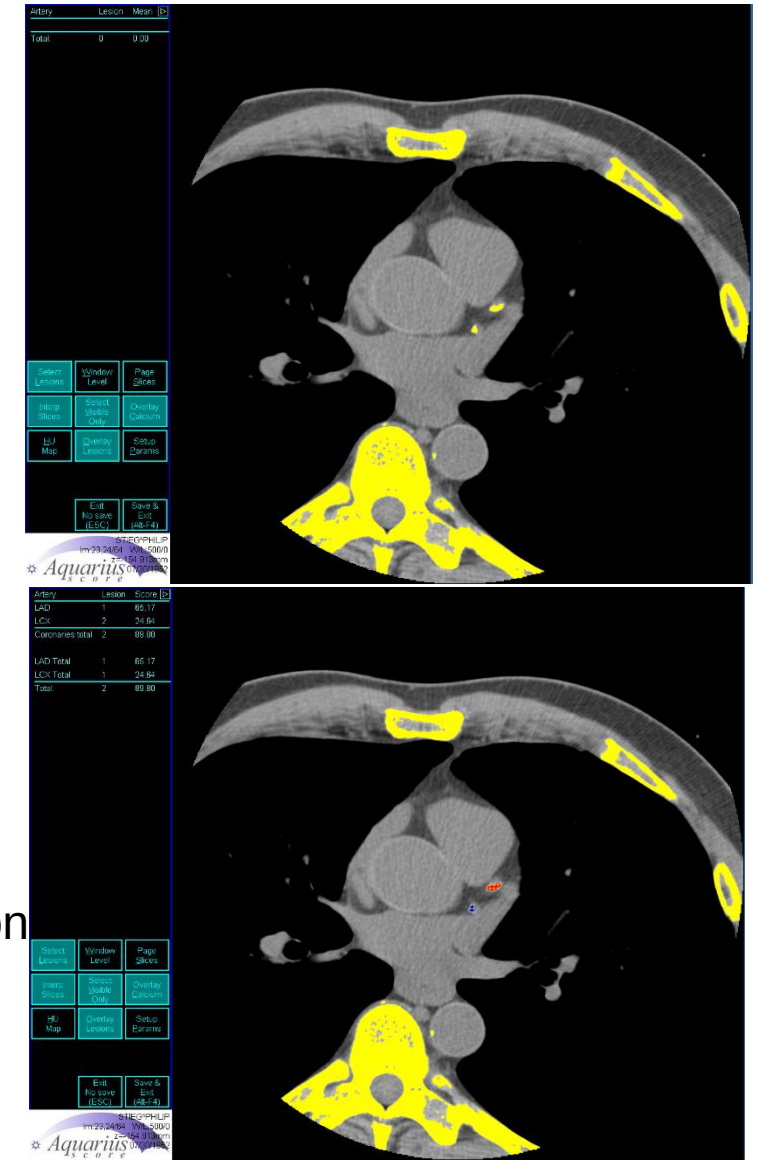
- Primary prevention
- ASCVD risk
- Integration with EHR and LLMs

Acquisition

- Model generalizability across keV, scanners, protocols
- Motion
  - Misclassification of CAC=0

Scoring

- Model generalizability with hardware and noncoronary calcification
- Integration with RF into risk score
- Progression and statins
- Explainability to referrings and patients



Qualitative CAC evaluation in ungated CT

	Agreement			Diagnostic Performance*		
Studies	Scoring in Nontriggered CT	Reference Scoring in Triggered CT	Agreement Between Nontriggered and Triggered CT	False-Negative Calcium Score, %	Underestimated High Calcium Score, %	Overestimated High Calcium Score, %
Budoff 2011	CS	CS	r=0.96	0	0	8.6
Einstein 2010	6 categories of CS‡	6 categories of CS‡	κ=0.89, concordance=63%	14.0	23.4	4.9
Kim 2008	CS	CS	r=0.89	9.3	0	0
Kirsch 2011	Visual grading score*	CS	r=0.83	n/c	n/c	n/c
Wu 2008	CS	CS	r=0.95	2.3	15.2	0.9

Xie Circulation:Cardiovascular Imaging 6:514 2013

Statins favor progression of high-density and 1K plaque

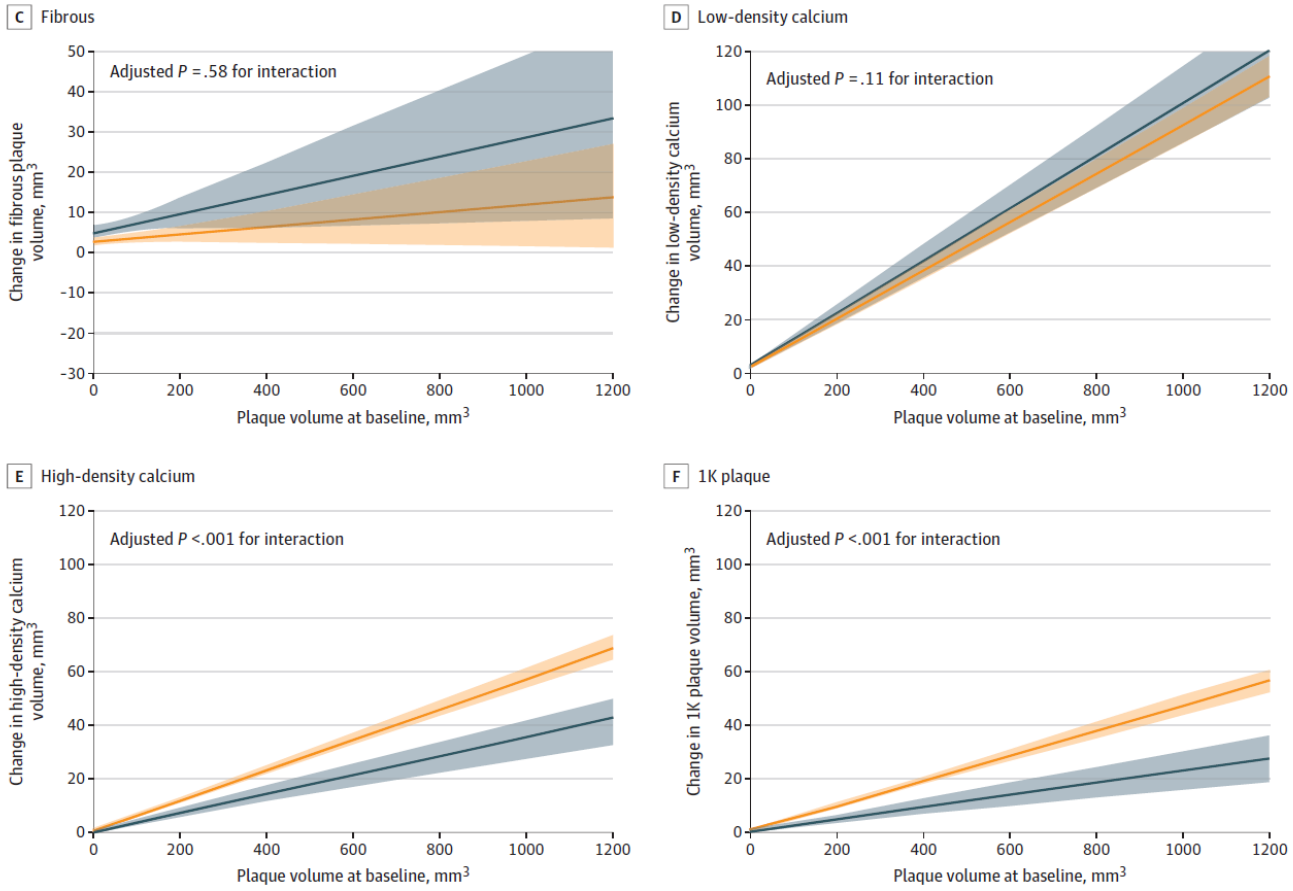
PARADIGM substudy

857 subjects with serial CCTA >2y, known statin history and presence of coronary plaque

Statins reduce noncalcified plaque

No impact on low-density calcium

Increases calcified plaque >700 HU



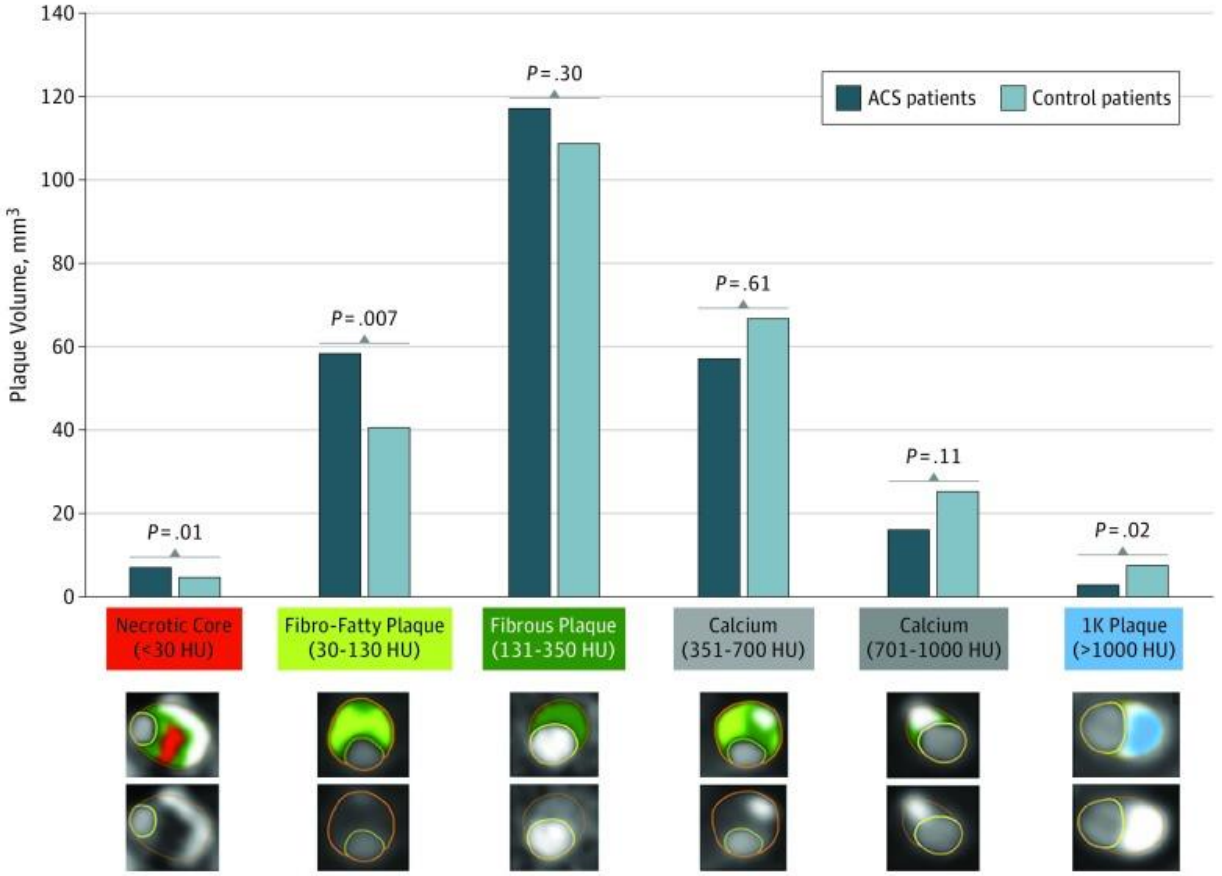
Van Rosendael et al JAMA Cardiol 2020 5: 282

Higher density calcium is protective against ACS

ICONIC study

189 pairs of ACS after baseline CCTA compared to propensity matched controls

1K plaque volume is higher in controls

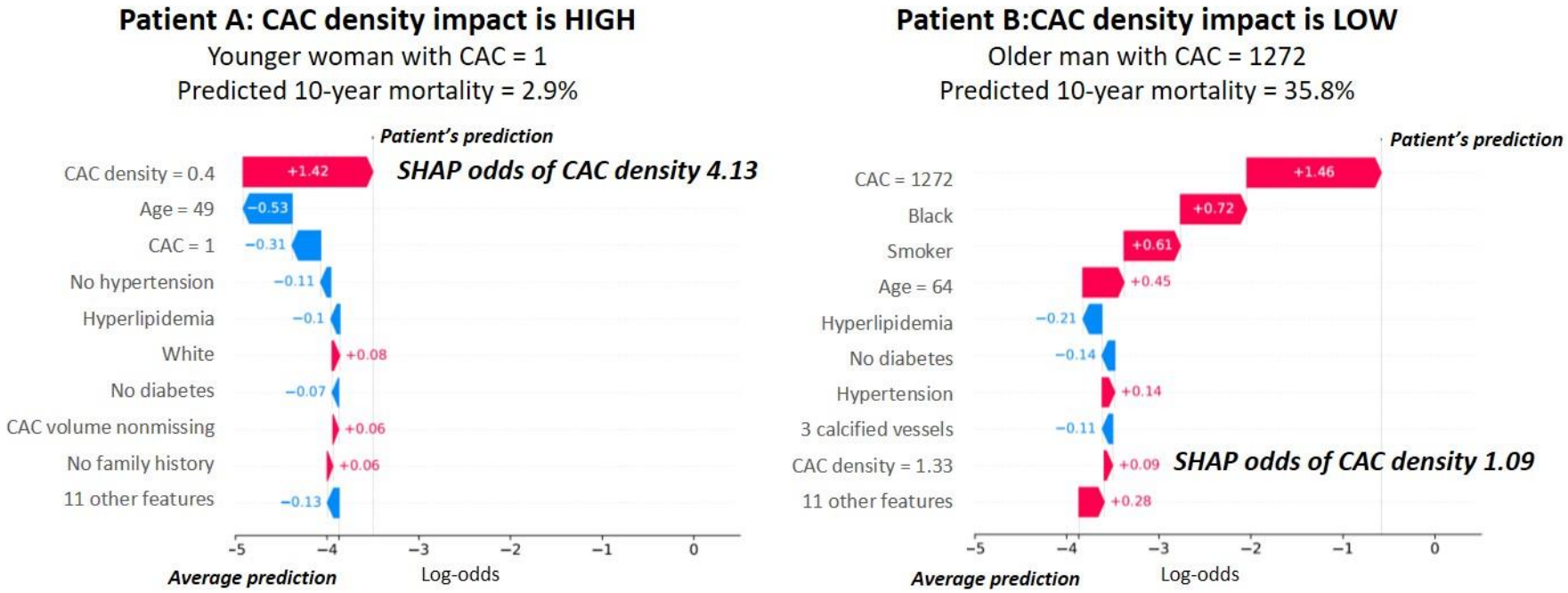


Van Rosendael et al JAMA Cardiol 2020 5: 282

Explainable ML to tailor care

CAC Consortium cohort, asymptomatic (n=63 215)

SHAP analysis applied to XGBoost model for all-cause mortality



Lin et al J Cardiovasc Comput Tomogr. 2023 Jan-Feb;17(1):28-33

Major considerations for AI CAC

Patient population restricted to primary prevention

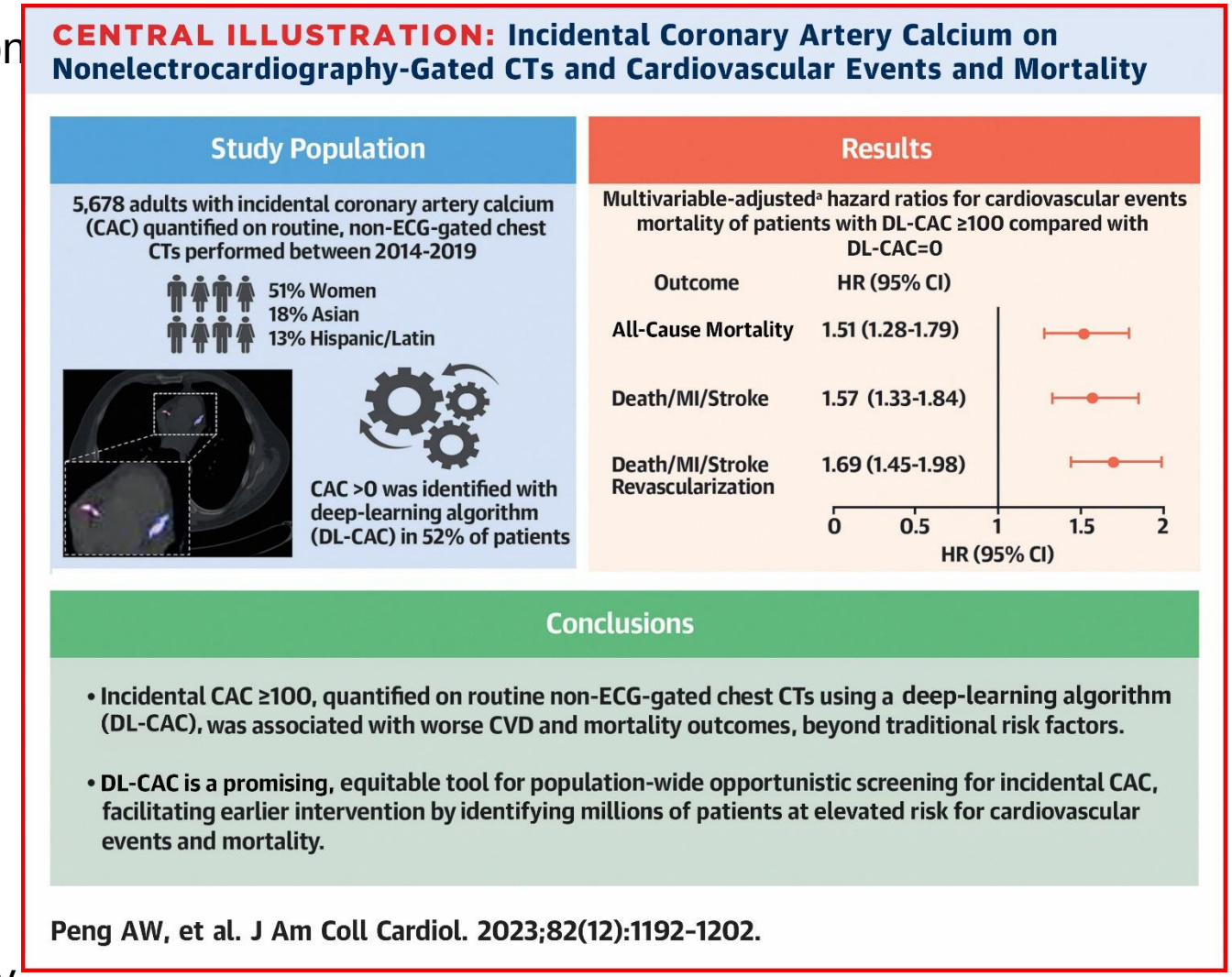
- Excluded outside referrals without pre-CT encounter
- Excluded existing ASCVD and metastatic cancer
- Calculated ASCVD risk

Acquisition and generalizability

- Tested on Stanford Health Care
- Previously tested on 6 external cohorts
- PPV 93.5%, sensitivity 95%, false negative 5%

Scoring and integration into treatment

- Unknown performance in valvular calcium
- Retrospective, no communication or therapy



EISNER study

- 2137 RCT of risk factor counseling with and without CAC
- Risk factor counseling in specialty clinic included showing the patient their coronary calcium
- Primary endpoint: Improvement in risk factors
  - Improved SBP
  - Improved LDL
  - Improved weight control
- FRS endpoint:
  - Less increase in FRS

Costs and downstream care

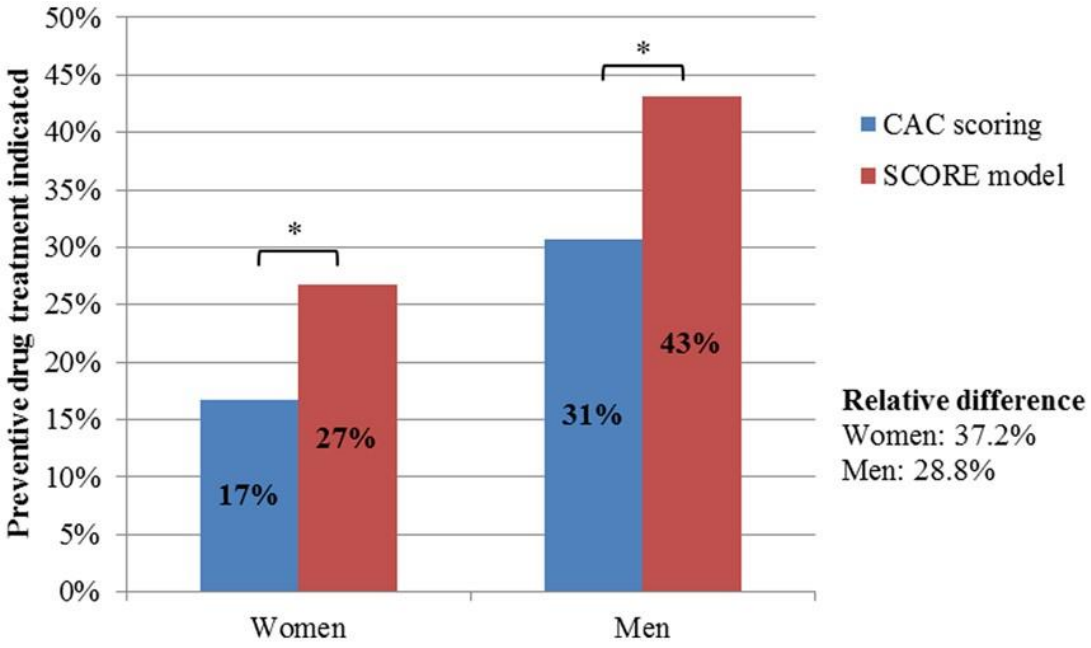
- No change in overall costs
- Low CAC/Normal: Reduced medication and procedure costs
- High CAC: Increased costs with downstream medical testing
  - Stress testing in 2/3 with CAC>400
  - Reduced ICA and revascularization

Rozanski JACC 2011 57:1622

Population based screening trial

ROBINSCA baseline study

- CAC scoring for preventive treatment
- 28928 population based RCT
  - CAC ↓ risk estimate compared to clinical
- Outcomes pending



DANCAVAS trial

- RCT of population based screening with CAC, ABI, lipids/DM screen coupled w treatment in specialty clinic
- 46,611 male age 65-74, 63% completed screen
- Screening ↑ antiplatelet/statin, ≅adherence
- 5.6 y no difference in CV outcomes. 10y pending
- Subgroup analysis: younger patients

Subgroup	Screened Invited Participants	Unscreened Invited Participants	Hazard Ratio (95% CI)
	no. of events per 1000 person-yr		
Age			
<70 yr	18.73	20.90	0.89 (0.83–0.96)
≥70 yr	30.71	30.33	1.01 (0.94–1.09)
Cardiovascular disease			
No	20.32	21.40	0.95 (0.89–1.01)
Yes	47.50	47.93	0.99 (0.89–1.10)

Van der Aalst et al, EHJ CVI 2020 21:1216; Lindholt JS NEJM 2022 387:1385

AI for risk scoring: considerations

- Agatston Score
- Calcium density
- Calcium distribution
- Chamber quantification
- LV Mass
- Thoracic and aortic valve calcium
- Epicardial fat

- Which patient population?
  - Does risk score generalize to this group?
- What is pretest probability?
- Is there targeted treatment?
- Is treatment indicated regardless of imaging?
- Does treatment reduce risk?
- Is risk reduction with treatment reflected in imaging?
- How to couple with treatment?
  - What threshold?
  - What is post-test probability?
  - How to communicate with referring?
  - How to communicate with patient?