

Clinical Optimization of Lung Cancer Screening CT For CAC Theragnostics

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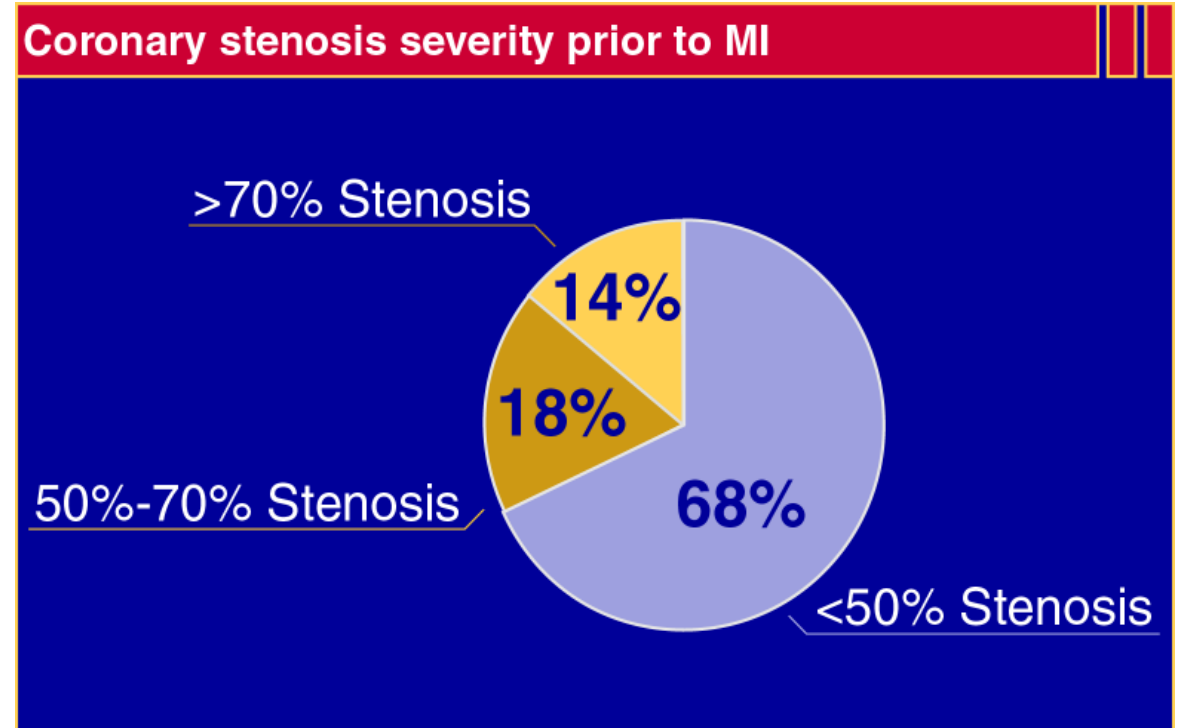
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Disclosures

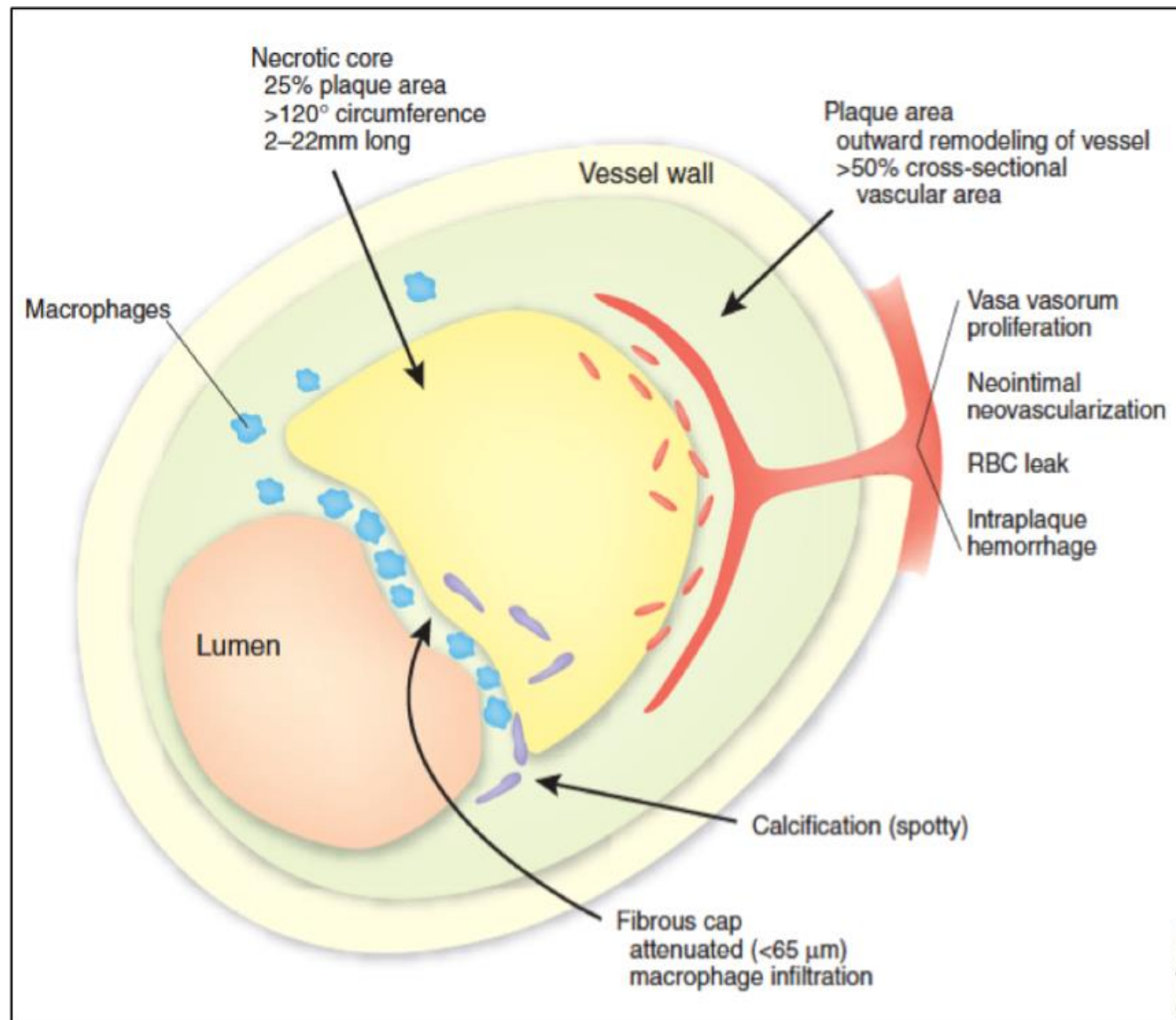
No disclosures

Prediction of CAD for preventive therapy

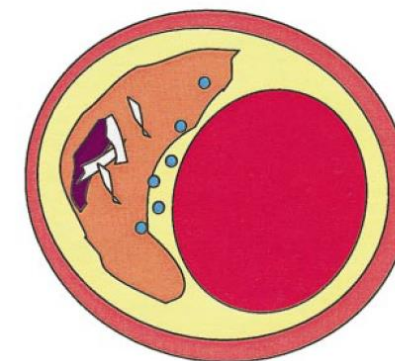
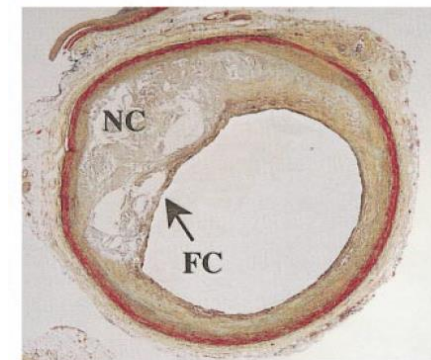
- Initial presentation for 50% is MI or death
- Conventional risk screening
 - Diabetes and FH
 - ASCVD risk score with risk factors
 - Low: <5% 10 year risk of MACE events
 - Borderline: 5-7.5%
 - Intermediate: 7.5-10%
 - High risk: >10%
- Risk stratification impacts preventive therapy
 - Balance benefits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



Vulnerable Plaque Characteristics



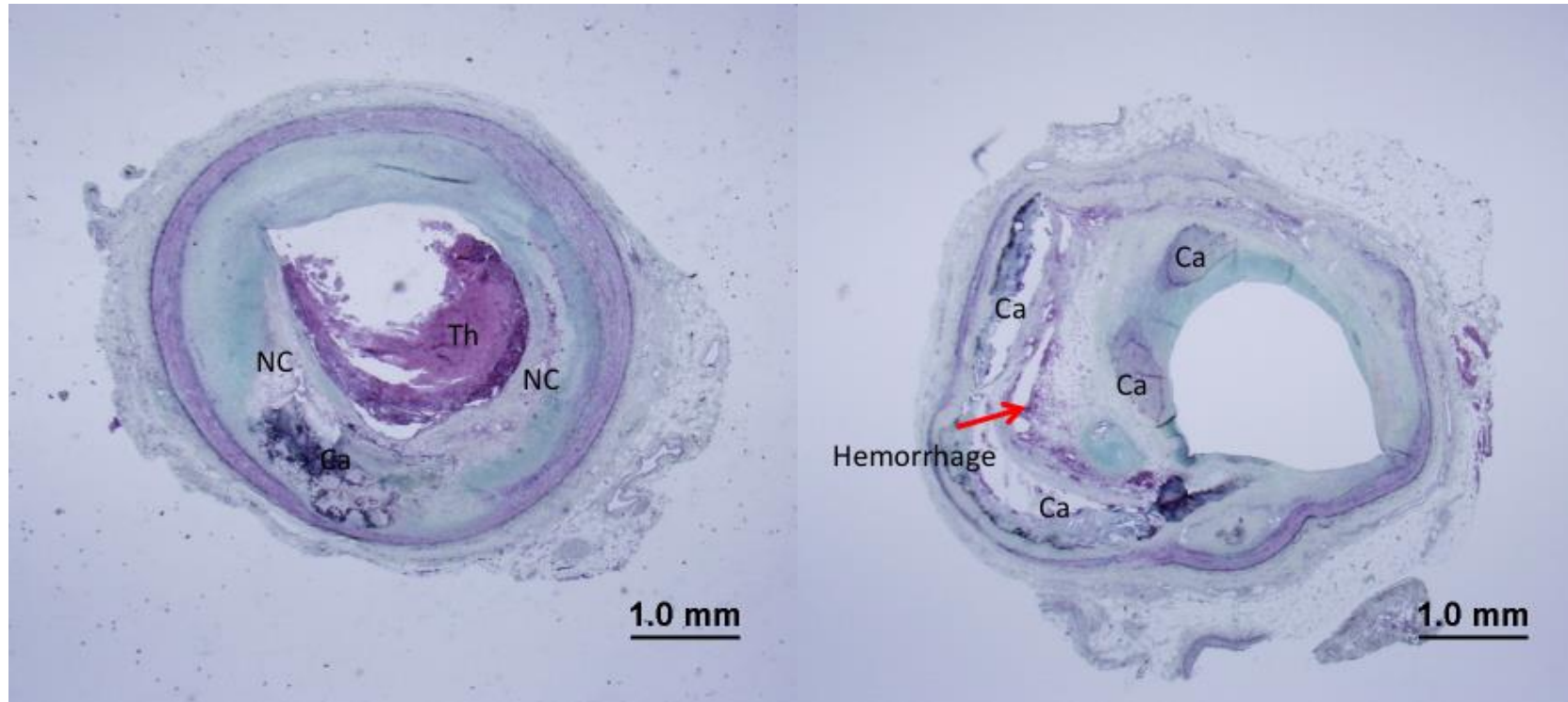
Thin fibrous cap atheroma



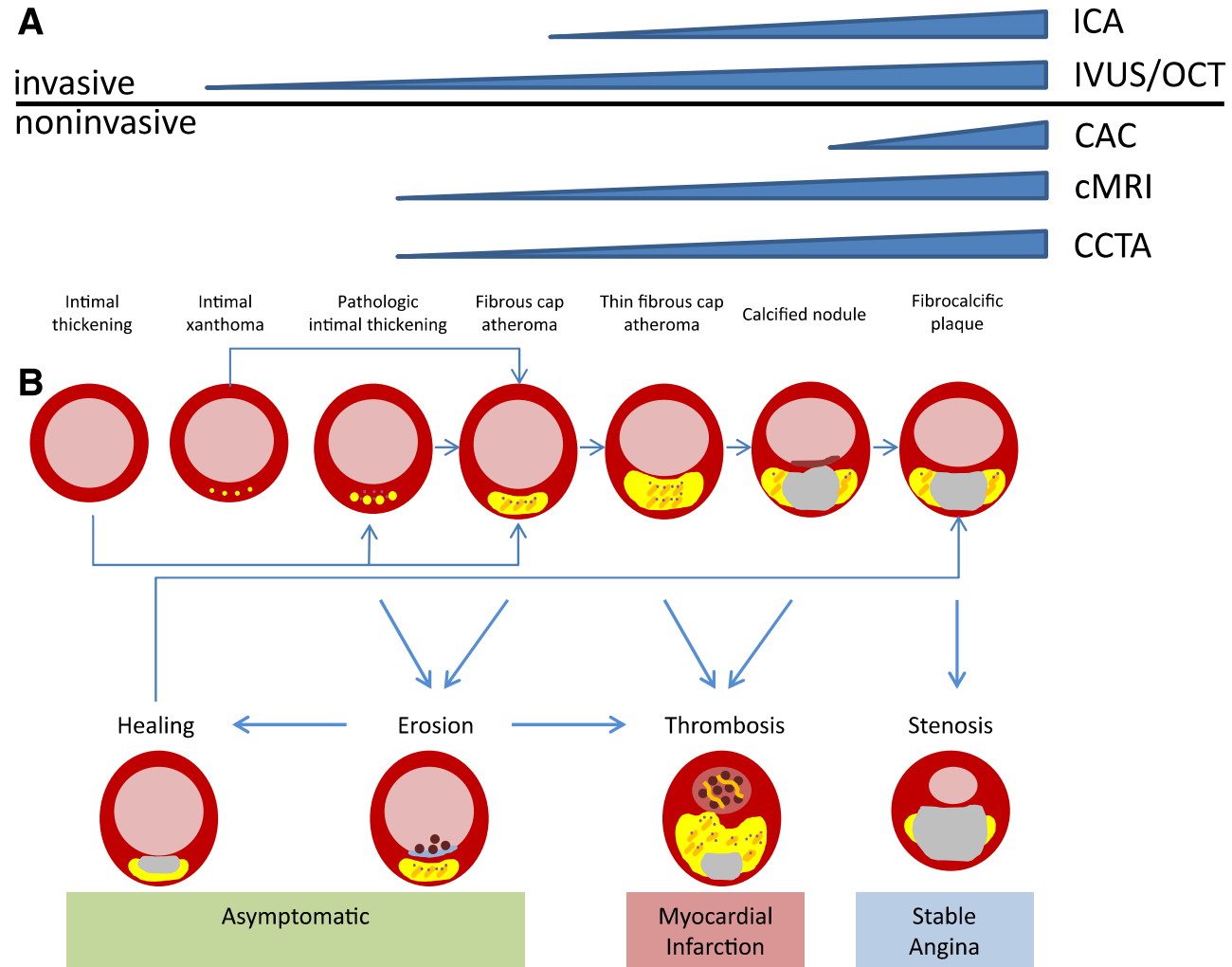
Virmani et al ATVB 2000

Calcium burden reflects total plaque burden

An integrated history of plaque progression



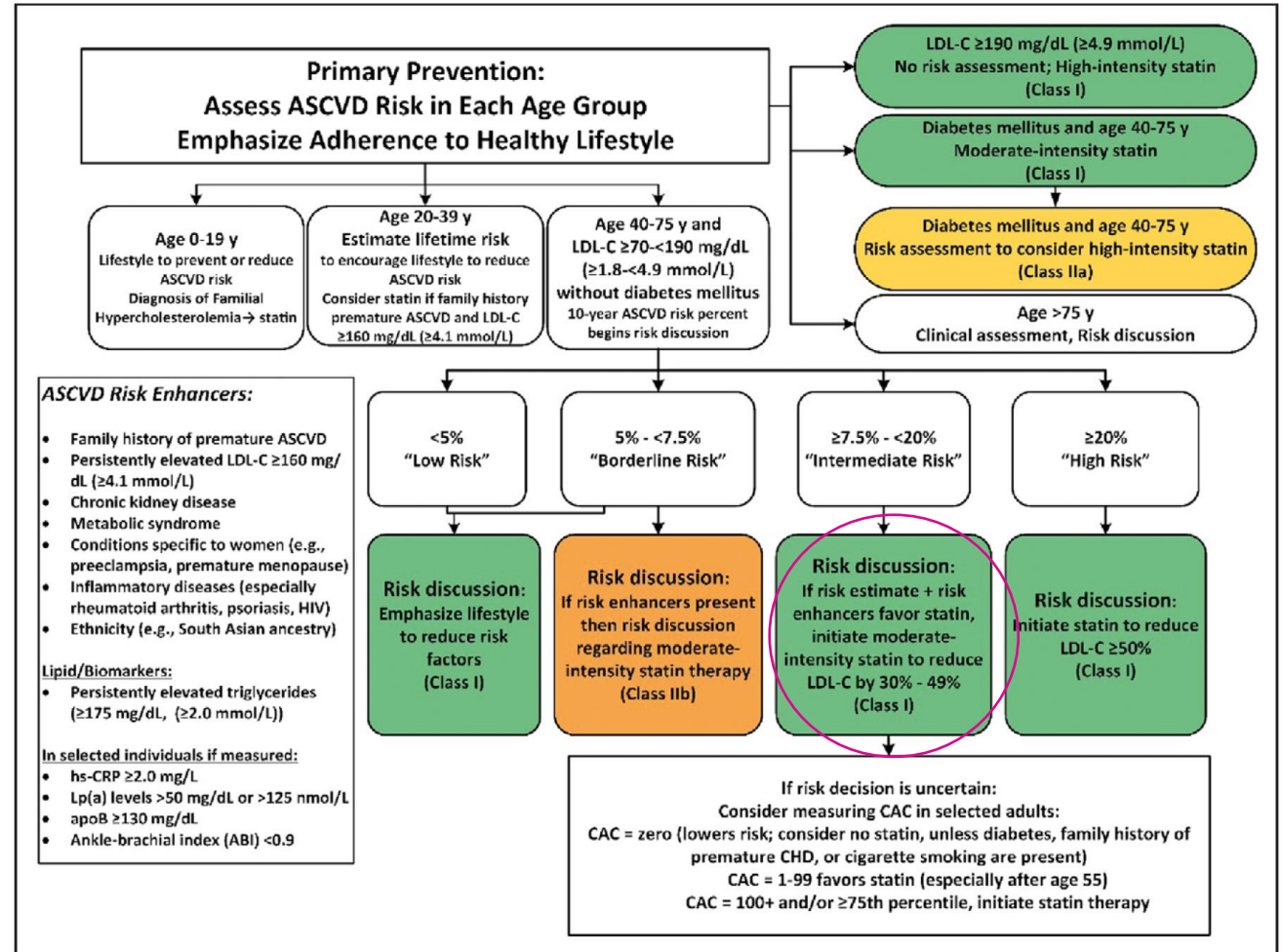
Plaque progression: the big picture



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



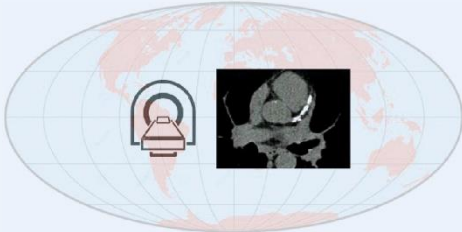
CAC-DRS


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


CENTRAL ILLUSTRATION: Summary of Major Global CAC Guidelines

Major Worldwide Coronary Artery Calcium Guidelines







- CAC as an arbitrator of statin use on intermediate risk.




- CAC as a tool for adjudicating statin allocation.
- For CAC scoring among all asymptomatic patients with suggested ECG changes for ischemia.




- CAC scoring to up-classify or down-classify their risk (T1DM <35 yrs old, T2DM <50 yrs old), with diabetes mellitus duration <10 years and without other risk factors.




- CAC as a risk assessing tool, risk reclassification and therapy determinant.
- Indicated in low risk with strong family history or other concern features.
- High risk reluctant to accept treatment, CAC is indicated.



- CAC as an arbitrator of statin use on intermediate risk.



- CAC as a prognostic tool in intermediate- to high-risk individuals.
- Local studies suggested.



- CAC as an arbitrator for aspirin allocation.

Common Indications

- Age: >40 y
+
- Risk: Intermediate
+
- Symptoms: Asymptomatic population


Common Treatment Threshold

- CAC = 0: downgrade risk, withhold statin
- CAC >100: Initiate / consider statin


Nonagreement Points

- CAC score for aspirin use
- CAC score for antihypertensive drugs


Specialty Guidelines



- CAC = 0: No statin, repeat 3-7 years.
- CAC >100: High intensity statin + ASA 81 mg.



- CAC = 0: No statin.
- CAC >100: High intensity statin + ASA 81 mg.



- Evidence is insufficient for CAC addition to traditional CV risk assessment, in asymptomatic adults for ASCVD prevention.

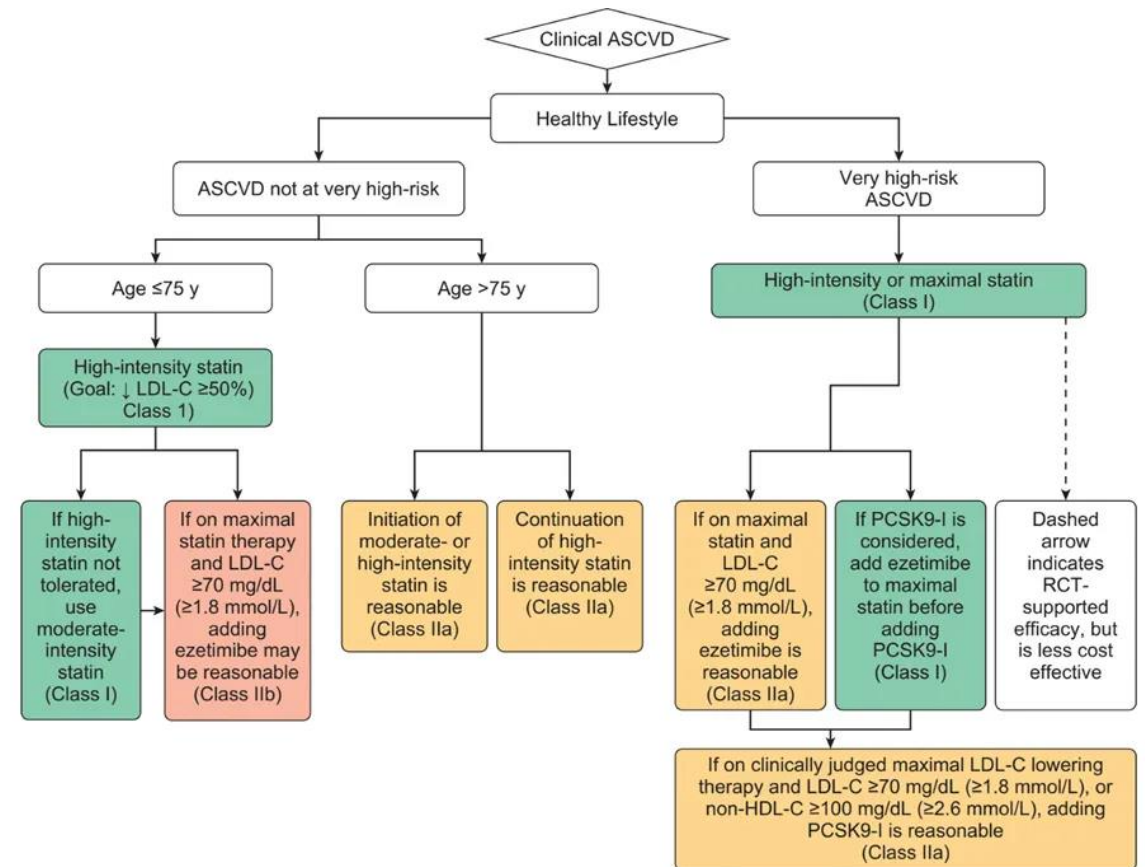
Golub IS, et al. J Am Coll Cardiol Img. 2023;16(1):98-117.

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



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)
Blaaha 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.

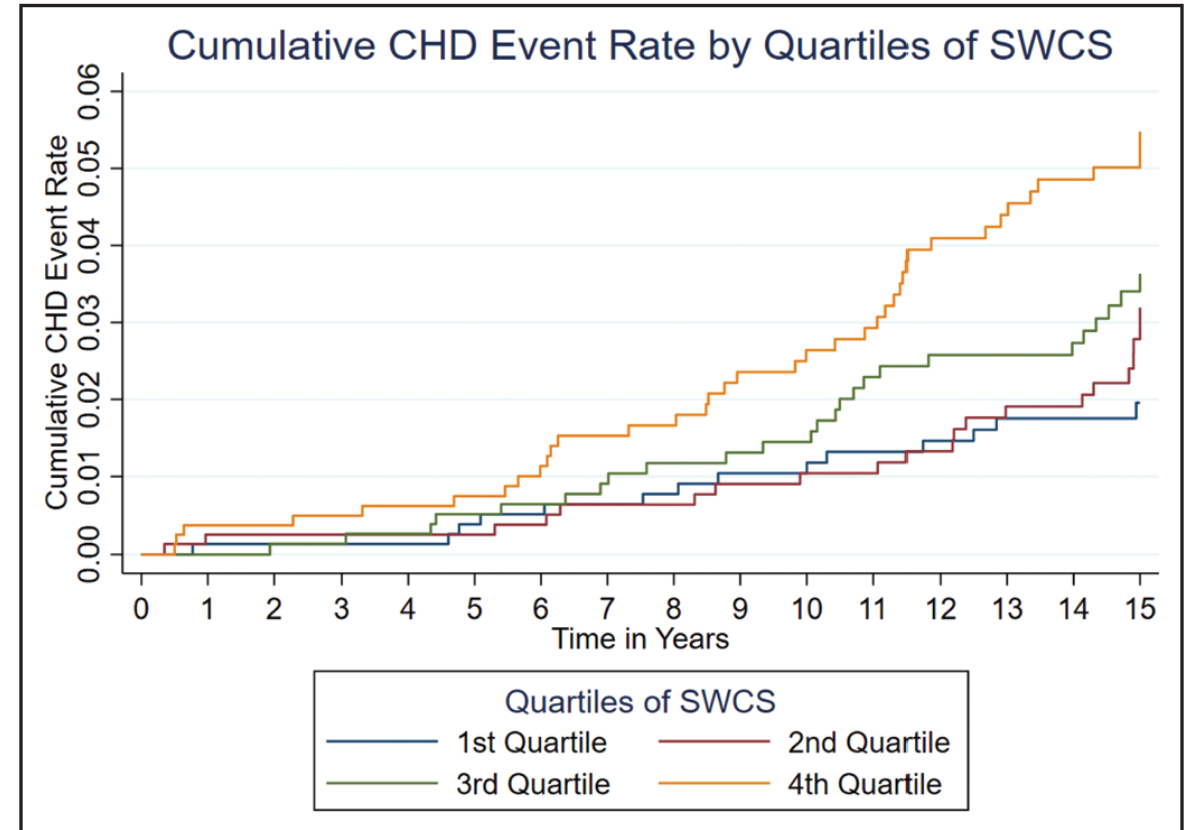
CVD event rate 0.5% over 5 years

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

MESA study: Agatston score

Population based normal values ages 45-75

The screenshot shows a web browser window with the URL `www.mesa-nhlbi.org/Calcium/input.aspx`. The page features the MESA logo and the text "The Multi-Ethnic Study of Atherosclerosis". Below the logo is a link "Back to MESA CAC". The main content area contains instructions: "Input your age, select your gender and race/ethnicity, input (optionally) your observed calcium score and click 'Calculate'." The form includes the following fields:

- Age (45-84):
- Gender:
- Race/Ethnicity:
- Observed Agatston Calcium Score (optional):

A "Calculate" button is located below the optional score field. The browser's address bar and bookmark bar are visible at the top of the window.

Integrated risk score

The screenshot shows a web browser window with the URL `mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx`. The page features the MESA logo and the title "MESA 10-Year CHD Risk with Coronary Artery Calcification". Below the title is a "Back to CAC Tools" link. The main content area is a light blue form with 12 numbered input fields:

- 1. Gender:** Radio buttons for Male and Female.
- 2. Age (45-85 years):** A text input field followed by "Years".
- 3. Coronary Artery Calcification:** A text input field with "Agatston" as a placeholder.
- 4. Race/Ethnicity:** A "Choose One" section with radio buttons for Caucasian, Chinese, African, American, and Hispanic.
- 5. Diabetes:** Radio buttons for Yes and No.
- 6. Currently Smoke:** Radio buttons for Yes and No.
- 7. Family History of Heart Attack:** Radio buttons for Yes and No, with a subtext "(History in parents, siblings, or children)".
- 8. Total Cholesterol:** Two text input fields, one for "mg/dL or" and one for "mmol/L".
- 9. HDL Cholesterol:** Two text input fields, one for "mg/dL or" and one for "mmol/L".
- 10. Systolic Blood Pressure:** A text input field followed by "mmHg" and "or", and another text input field followed by "kPa".
- 11. Lipid Lowering Medication:** Radio buttons for Yes and No.
- 12. Hypertension Medication:** Radio buttons for Yes and No.

At the bottom of the form is a button labeled "Calculate 10-year CHD ri". A footer at the very bottom of the page reads "©2023 Collaborative Health Studies Coordinating Center | Risk Score API Help".

Standardized Agatston CAC score

Patient population

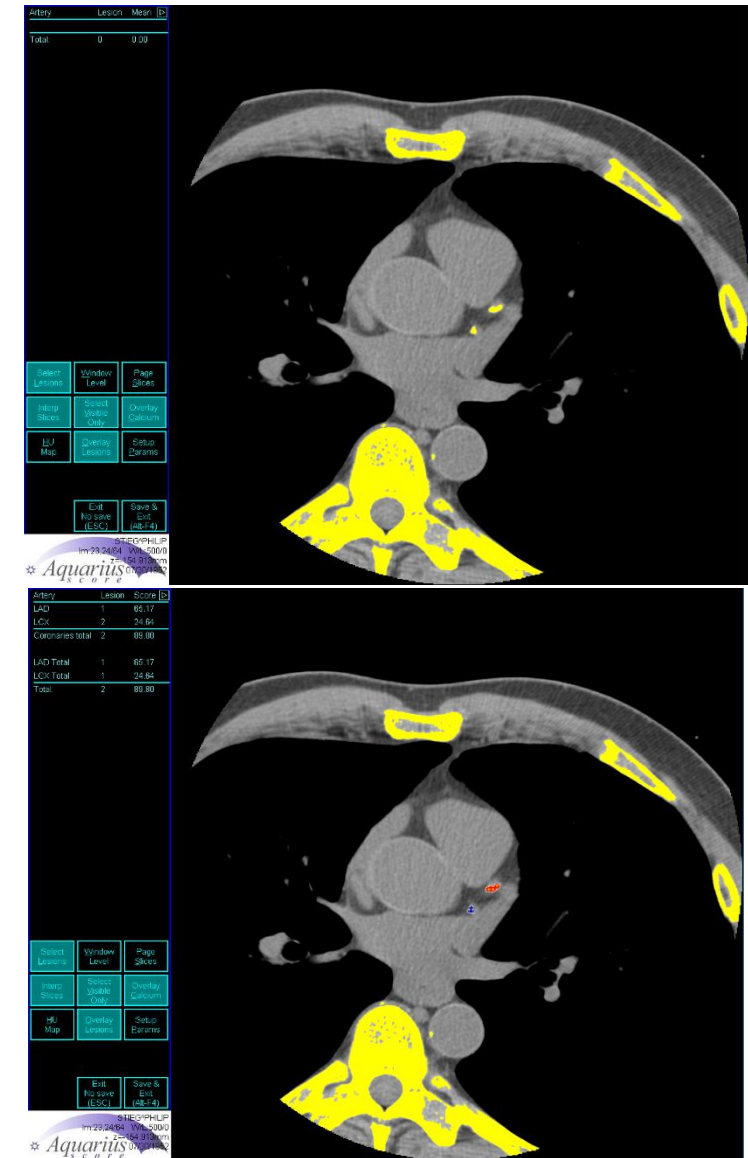
- Asymptomatic, primary prevention

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

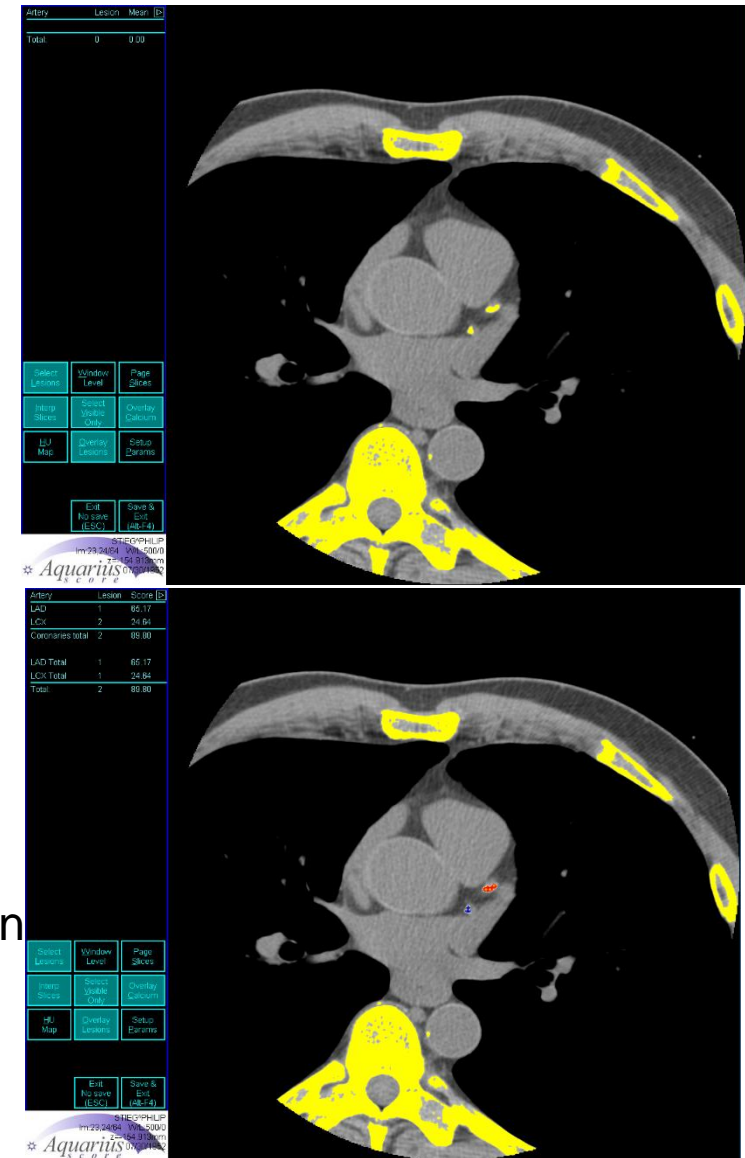
- Primary prevention
- ASCVD risk
- Integration with EHR and LLMs

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 referrals and patients



Qualitative CAC evaluation in ungated CT

Studies	Agreement			Diagnostic Performance*		
	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

Statins favor progression of high-density and 1K plaque

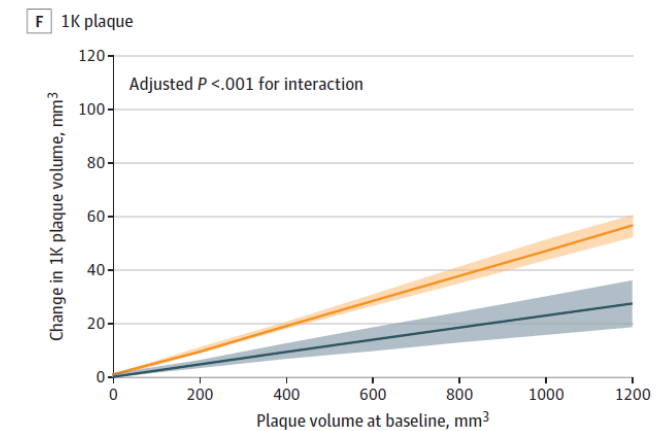
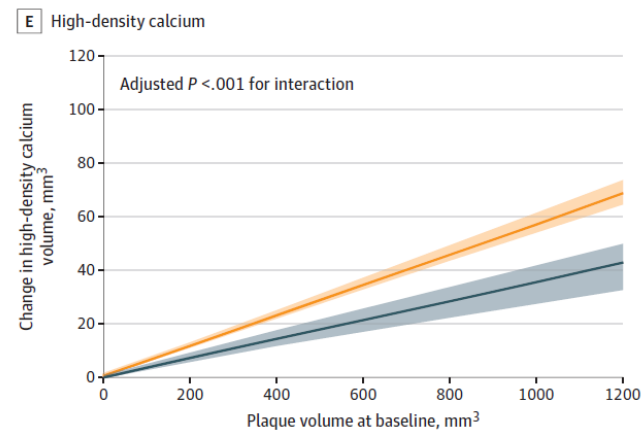
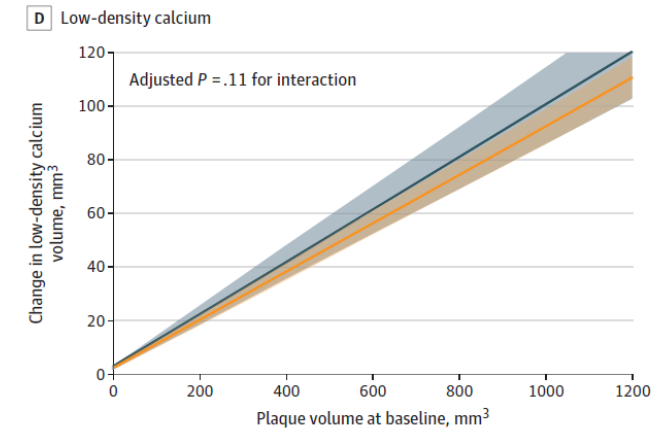
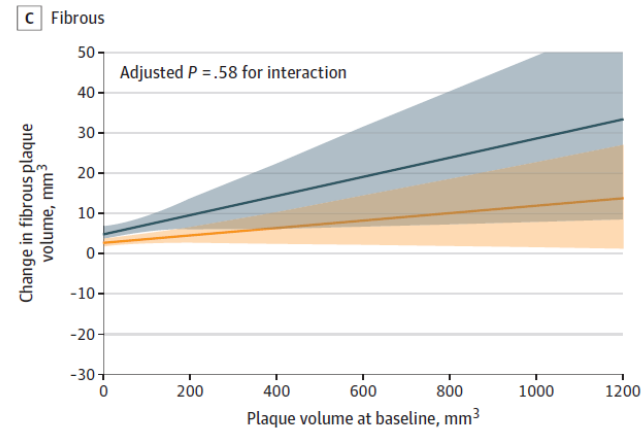
PARADIGM substudy

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

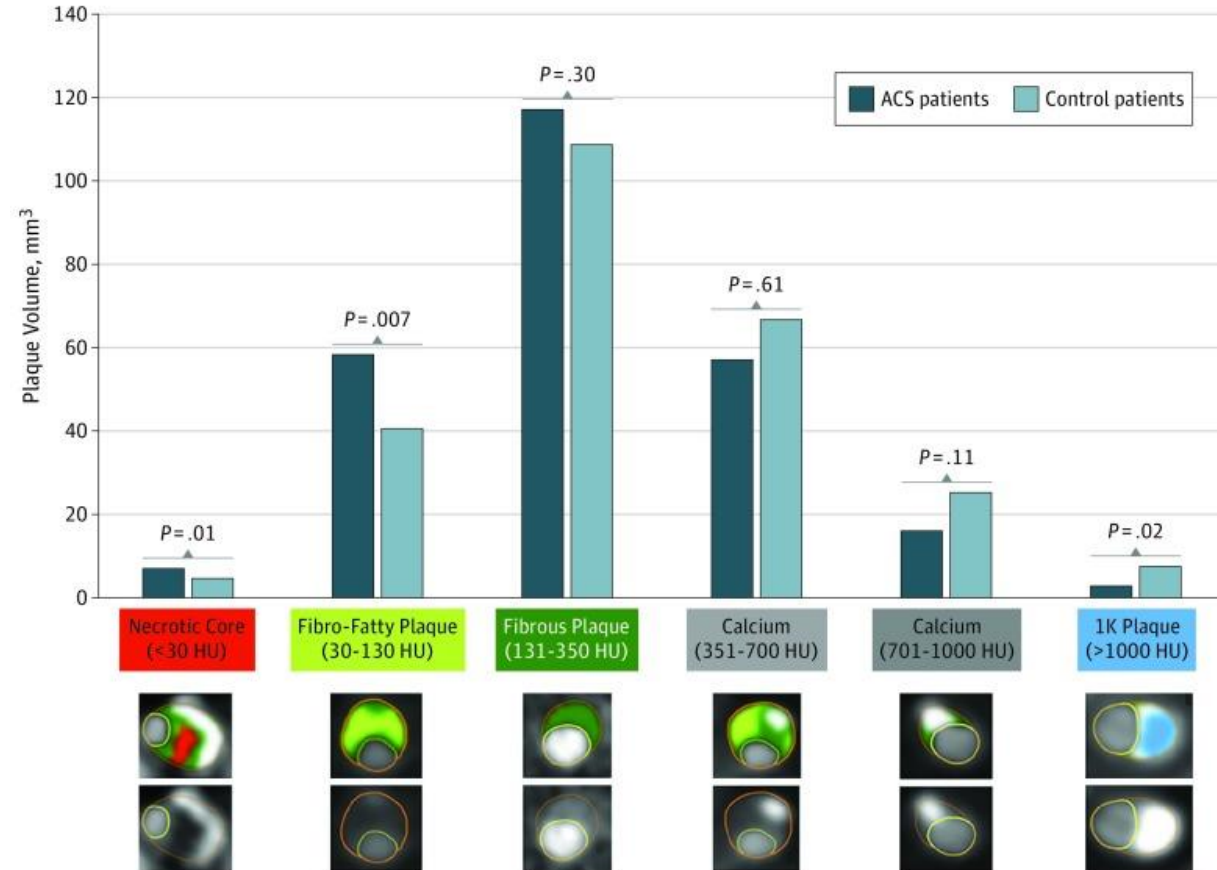


Higher density calcium is protective against ACS

ICONIC study

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

1K plaque volume is higher in controls



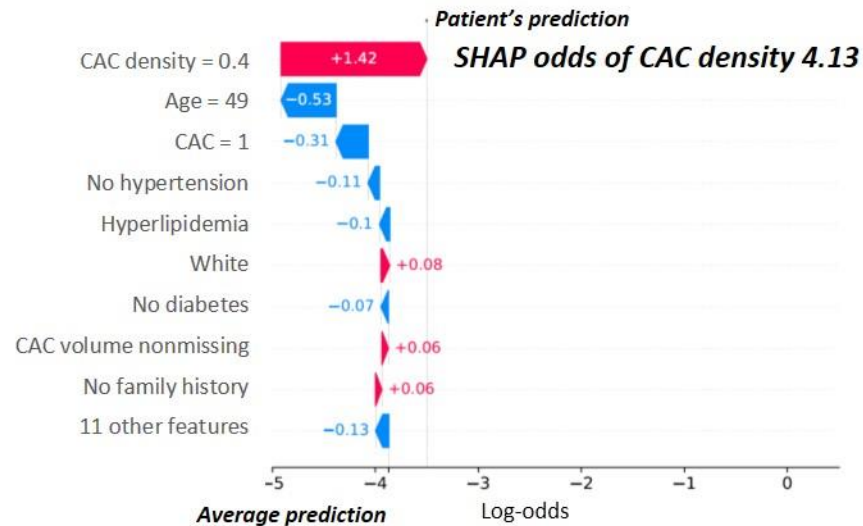
Explainable ML to tailor care

CAC Consortium cohort, asymptomatic (n=63 215)

SHAP analysis applied to XGBoost model for all-cause mortality

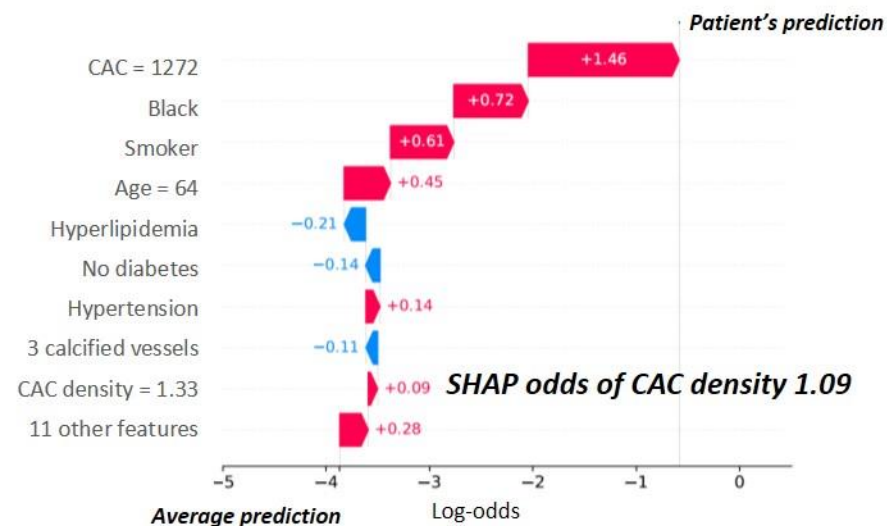
Patient A: CAC density impact is HIGH

Younger woman with CAC = 1
Predicted 10-year mortality = 2.9%



Patient B: CAC density impact is LOW

Older man with CAC = 1272
Predicted 10-year mortality = 35.8%



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

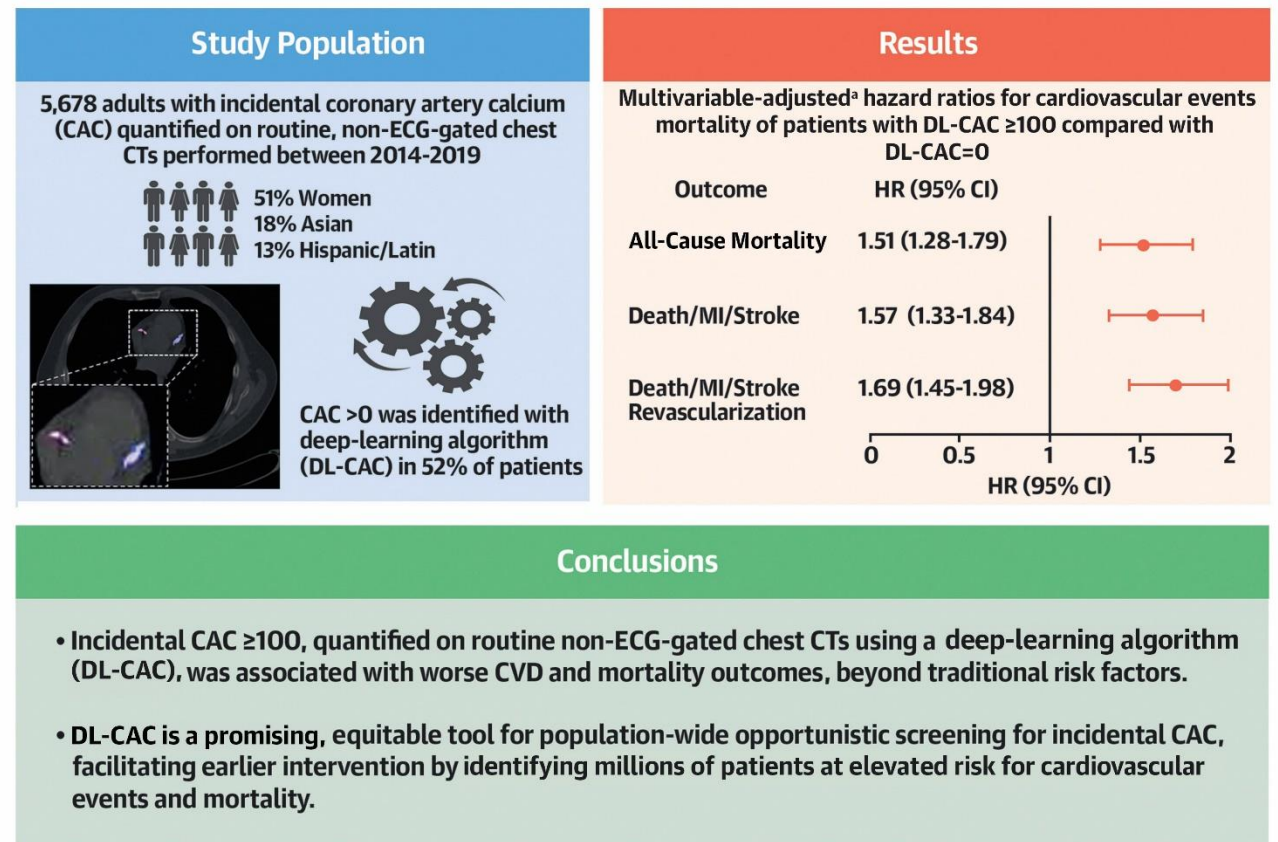
Acquisition and generalizability

- 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

CENTRAL ILLUSTRATION: Incidental Coronary Artery Calcium on Nonelectrocardiography-Gated CTs and Cardiovascular Events and Mortality



Peng AW, et al. J Am Coll Cardiol. 2023;82(12):1192-1202.

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

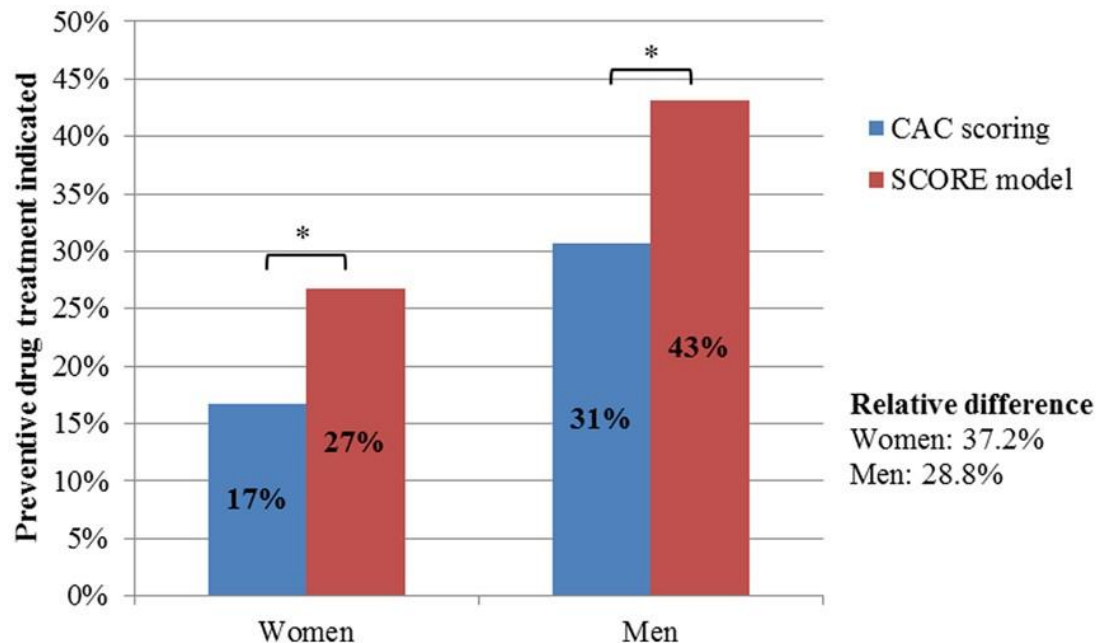
Costs and downstream care

- 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

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 <i>no. of events per 1000 person-yr</i>	Unscreened Invited Participants <i>no. of events per 1000 person-yr</i>	Hazard Ratio (95% CI)
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)

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?