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

Vulnerable Plaque Characteristics

Virmani et al. ATVB 2000
Calcium burden reflects total plaque burden

An integrated history of plaque progression
Plaque progression: the big picture

A

invasive
noninvasive

ICA
IVUS/OCT
CAC
cMRI
CCTA

B

Internal thickening
Intimal xanthoma
Pathologic intimal thickening
Fibrous cap atheroma
Thin fibrous cap atheroma
Calcified nodule
Fibrocalcific plaque

Healing
Erosion
Thrombosis
Stenosis

Asymptomatic
Myocardial Infarction
Stable Angina
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

<table>
<thead>
<tr>
<th>CAC-DRS category</th>
<th>Agatston</th>
<th>Visual score</th>
<th>Risk</th>
<th>Treatment recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Statin generally not recommended</td>
</tr>
<tr>
<td>1</td>
<td>1-99</td>
<td>1</td>
<td>Mild</td>
<td>Moderate intensity statin</td>
</tr>
<tr>
<td>2</td>
<td>100-299</td>
<td>2</td>
<td>Moderate</td>
<td>Moderate to high intensity statin + ASA 81 mg</td>
</tr>
<tr>
<td>3</td>
<td>&gt;300</td>
<td>3</td>
<td>Moderate to severe</td>
<td>High intensity statin + ASA 81 mg</td>
</tr>
</tbody>
</table>
International guidelines

**CENTRAL ILLUSTRATION:** Summary of Major Global CAC Guidelines

- **Major Worldwide Coronary Artery Calcium Guidelines**
  - CAC as a risk tool in high-risk individuals.
  - Local studies suggested.
  - CAC scoring to up-classify or down-classify their risk (T1DM <50 yrs old, T2DM 50-64 yrs old), with diabetes mellitus duration >10 years and without other risk factors.
  - CAC as an arbitrator for aspirin allocation.
  - CAC as a risk assessing tool, risk reclassification and therapy determinator.
  - Indicated in low risk with strong family history or other concern features.
  - High risk reluctant to accept treatment, CAC is indicated.

- **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.**

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
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

CVD event rate 0.5% over 5 years

### Prognostic Value of A CAC Score of Zero among Asymptomatic Individuals

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

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

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

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

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

**Study Population**
- 5,678 adults with incidental coronary artery calcium (CAC) quantified on routine, non-ECG-gated chest CTs performed between 2014-2019
- 51% Women
- 18% Asian
- 13% Hispanic/Latin

**Results**
- Multivariable-adjusted hazard ratios for cardiovascular events mortality of patients with DL-CAC ≥100 compared with DL-CAC=0
  - Outcome HR (95% CI)
  - All-Cause Mortality 1.51 (1.28-1.79)
  - Death/MI/Stroke 1.57 (1.33-1.84)
  - Death/MI/Stroke Revascularization 1.69 (1.45-1.98)

**Conclusions**
- Incidental CAC ≥100, quantified on routine non-ECG-gated chest CTs using a deep-learning algorithm (DL-CAC), was associated with worse CVD and mortality outcomes, beyond traditional risk factors.
- DL-CAC is a promising, equitable tool for population-wide opportunistic screening for incidental CAC, facilitating earlier intervention by identifying millions of patients at elevated risk for cardiovascular events and mortality.

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

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?