Status of Coronary Calcium Scoring in the Lung Screening Setting

Matthew Cham, M.D.
Associate Professor of Radiology and Medicine
The Icahn School of Medicine at Mount Sinai

Lung Cancer Workshop X – Prevent Cancer Foundation
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Coronary artery calcification (CAC) is a very strong predictor of morbidity and mortality in asymptomatic individuals.

CAC is independently predictive of coronary events over and above traditional cardiac risk factors such as the Framingham Score.

Combined Lung and Cardiac Screening

Ungated Lung Screening CT

ECG-gated Calcium Score CT
CAC during lung screening CT

- Agatston CAC scores derived from low dose lung CT correlate well with ECG gated CAC CT (Kappa = 0.89)\(^1\)

- CAC is predictive of death from cardiovascular disease after adjusting for sex, age, pack years of smoking\(^2\)

CAC during lung screening CT

- CAC is a better predictor of cardiovascular events and all-cause mortality than FEV1 and emphysema extent\(^1\)

- CAC is an independent predictor of all-cause mortality and cardiovascular events\(^2\)

### TABLE 2: Annualized Event Rates for All-Cause Mortality, Fatal and Nonfatal Cardiovascular Disease (CVD) Events and Fatal and Nonfatal Coronary Heart Disease (CHD) Events According to Coronary Artery Calcium (CAC) Risk Categories

<table>
<thead>
<tr>
<th>CAC Risk Category&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All-Cause Mortality (&lt;i&gt;n&lt;/i&gt; = 56)</th>
<th>CVD Endpoint&lt;sup&gt;b&lt;/sup&gt; (&lt;i&gt;n&lt;/i&gt; = 127)</th>
<th>CHD Endpoint&lt;sup&gt;b&lt;/sup&gt; (&lt;i&gt;n&lt;/i&gt; = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.08 (2)</td>
<td>0.7 (10)</td>
<td>0.3 (4)</td>
</tr>
<tr>
<td>1–100</td>
<td>0.2 (8)</td>
<td>1.5 (27)</td>
<td>0.4 (8)</td>
</tr>
<tr>
<td>101–1000</td>
<td>0.6 (22)</td>
<td>1.7 (32)</td>
<td>1.0 (18)</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>1.1 (24)</td>
<td>6.1 (58)</td>
<td>3.2 (31)</td>
</tr>
</tbody>
</table>

Note—Data are percentage annualized event rate (no. of cases). Annualized event rates were calculated as follows: 100% × [no. of total events / (∑ person-days subcohort × 1/0.107)] × 365. The ∑ person-days of the subcohort was weighted by the inverse of the sampling fraction (~ 11%) for the subcohort (1/0.107).

<sup>a</sup>Median follow-up per case-group was 21.5 months for all-cause mortality, 9.5 months for CVD events, and 9.8 months for CHD events.

<sup>b</sup>CVD endpoint (<i>n</i> = 127) consists of 10 fatal events (myocardial infarction, <i>n</i> = 5; stroke, <i>n</i> = 3; aortic aneurysm, <i>n</i> = 1; and peripheral arterial occlusive disease, <i>n</i> = 1) and 117 nonfatal events (myocardial infarction, <i>n</i> = 13; angina pectoris, <i>n</i> = 43; aortic valve stenosis, <i>n</i> = 24; stroke, <i>n</i> = 14; aortic aneurysm, <i>n</i> = 12; and peripheral arterial occlusive disease, <i>n</i> = 11). Of these 127 events, all fatal and nonfatal myocardial infarctions (<i>n</i> = 18) and angina pectoris (<i>n</i> = 43) events were included in the CHD endpoint (<i>n</i> = 61).

ECG Gated CAC CT vs. Ungated Regular Dose Chest CT

\[ r = 0.97, \ p < 0.0001 \]

ECG-gated CAC score CT vs. Ungated lung screen CT

Analysis courtesy of Drs. Anthony Reeves, Alberto Biancardi, and Sergei Fotin
ECG-gated CAC score CT vs. Ungated lung screen CT

\[ R^2 = 0.99 \]

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# ECG-gated CAC score CT vs. Ungated lung screen CT

<table>
<thead>
<tr>
<th>Low-Dose CT</th>
<th>Very Low Risk (0)</th>
<th>Low Risk (&gt; 0–10)</th>
<th>Moderate Risk (&gt; 10–100)</th>
<th>Moderately High Risk (&gt; 100–400)</th>
<th>High Risk (&gt; 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk (0)</td>
<td>66</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (&gt; 0–10)</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Moderate risk (&gt; 10–100)</td>
<td>2</td>
<td>24</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Moderately high risk (&gt; 100–400)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>High risk (&gt; 400)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

AJR 2008;190:917-922.
Limitations in CAC scoring during lung screening CT

- **ECG-gated CAC score CT:**
  - 12-32% mean interscan variability\(^1\)

- **Ungated lung screening CT:**
  - 60-70% mean interscan variability (@ 3 mSv)\(^2\)
  - 25% had discordant risk categorization

- **Normal CAC progression = 14-27% per year**

Interscan variability

CAC scores measured using a calibrated stationary phantom during a no-change scenario at 120 kV, 100 mAs, 2.5 mm

<table>
<thead>
<tr>
<th></th>
<th>Lesion 1 (5 mm)</th>
<th>Lesion 2 (1 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan 1</td>
<td>211</td>
<td>3</td>
</tr>
<tr>
<td>Scan 2</td>
<td>250</td>
<td>1</td>
</tr>
<tr>
<td>Scan 3</td>
<td>224</td>
<td>3</td>
</tr>
<tr>
<td>Scan 4</td>
<td>276</td>
<td>1</td>
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# Lung versus Cardiac Screening

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<tr>
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<td>ECG gating</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Scan mode</td>
<td>Helical</td>
<td>Axial</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>0.6 mm</td>
<td>2.5 to 3.0 mm</td>
</tr>
<tr>
<td>Field of view</td>
<td>45 cm</td>
<td>20 cm</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>0.7 mSv (120kV, 15mAs)</td>
<td>0.7 mSv (120kV, 50mAs)</td>
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<td>Full chest</td>
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</table>
Slice thickness and CAC Scoring

- ECG-gated CACS using 1 mm slices (instead of 2.5 mm) overestimate calcium scores by:
  - +5% in stationary phantoms$^1$
  - +30% in patients$^1$
- CAC detection at lung screening CT:

<table>
<thead>
<tr>
<th>Protocol (Attenuation and Slice Thickness)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mm</td>
<td>98</td>
<td>53</td>
<td>60</td>
<td>98</td>
<td>72</td>
</tr>
<tr>
<td>2.5 mm</td>
<td>91</td>
<td>89</td>
<td>91</td>
<td>93</td>
<td>90</td>
</tr>
</tbody>
</table>

$^1$ Invest Radiol 2005;40:695-699

$^2$ AJR 2008;190:917-922.
Coronary calcium phantom

Device courtesy of Philips Healthcare and Harvey Hecht, M.D.
1.2 mm slice thickness
0.6 mm slice thickness
Slice thickness and CAC Scoring

- 2.5 mm thick CAC protocols may underestimate calcium scores relative to ground truth
- Chance of missing a 1mm calcified lesion of a given density

<table>
<thead>
<tr>
<th>Slice thickness</th>
<th>800 mg/cm³</th>
<th>400 mg/cm³</th>
<th>200 mg/cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mm</td>
<td>0%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.2 mm</td>
<td>0%</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>0.6 mm</td>
<td>0%</td>
<td>14%</td>
<td>95%</td>
</tr>
</tbody>
</table>
The traditional 2.5 and 3.0 mm thick CAC scoring protocols will miss smaller lesions and underestimate disease burden.

This limitation would affect primarily younger subjects with near zero or lower calcium scores and is encountered in clinical practice.
<table>
<thead>
<tr>
<th></th>
<th>Total Coronaries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>#ROI's</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>areaSq (sq.mm.)</strong></td>
<td>0</td>
</tr>
</tbody>
</table>
Risk of significant coronary stenosis with a zero CACS

- In asymptomatic subjects: 1%
  - 10 year cardiac event risk = 1%
- In asymptomatic diabetic patients: 5%
- In symptomatic patients: 5-19%

Treatment Guidelines for CAC

* National Cholesterol Education Program guidelines for asymptomatic individuals with moderate risk for CHD events

<table>
<thead>
<tr>
<th>CAC score/percentile</th>
<th>Framingham risk group equivalent</th>
<th>LDL goal (mg/dL)</th>
<th>Drug therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lower risk</td>
<td>&lt;160</td>
<td>≥190</td>
</tr>
<tr>
<td>1-10 and ≤75th percentile</td>
<td>Moderate risk (10-y risk &lt;10%)</td>
<td>&lt;130</td>
<td>160-189: drug optional</td>
</tr>
<tr>
<td>11-100 and ≤75th percentile</td>
<td>Moderately high risk; 2+ risk factors (10-y risk: 10-20%)</td>
<td>&lt;130</td>
<td>≥160</td>
</tr>
<tr>
<td>101-400 or &gt;75th percentile</td>
<td>High risk; CAD risk equivalent (10-y risk: &gt;20%)</td>
<td>&lt;100</td>
<td>100-129: consider drug</td>
</tr>
<tr>
<td>&gt;400 or &gt;90th percentile</td>
<td>Highest risk*</td>
<td>Optional goal &lt;70</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optional goal &lt;70</td>
<td>&lt;100: consider drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any LDL level</td>
</tr>
</tbody>
</table>

*Consider β blockers and angiotensin-converting enzyme inhibitors for CAC score >1000.
# Treatment Guidelines for CAC

- National Cholesterol Education Program guidelines for asymptomatic individuals with moderate risk for CHD events

## Table II. Guidelines for treatment in asymptomatic patients classified as moderately high-risk patients by NCEP (Framingham 10-20% 10-year risk)

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*Consider β blockers and angiotensin-converting enzyme inhibitors for CAC score >1000.

Am Heart J 2006; 151: 1139-46.
The 1st SHAPE Guideline
Toward the National Screening for Heart Attack Prevention and Education (SHAPE) Program

Apparently Healthy Population Men >45 yr, Women >55 yr*

Step 1

Very Low Risk

Exit

All >75 yr receive unconditional treatment†

CACS

or

CIMT & Carotid Plaque§

Atherosclerosis Test

Step 2

Negative Test

CACS = 0

CIMT <50th percentile

No Risk Factors‖

Risk Factors

Step 3

Lower Risk

Moderate Risk

Moderately High Risk

High Risk

Very High Risk

LDL Target

<160 mg/dL

<130 mg/dL

<130 mg/dL

<100 mg/dL

<70 mg/dL

Retest Interval

5–10 years

5–10 years

Individualized

Individualized

Individualized

Follow Existing Guidelines

Myocardial Ischemia Test

Angiography

Am J Cardiol 2006;98(2A):2H-15H.
Why 2.5 mm slices?

- **1984: Electron beam CT**
  - Temporal resolution = 100ms
  - Spatial resolution = 2-3mm

- **1995: ECG-gated MDCT**
  - Temporal resolution = 160ms
  - Spatial resolution = 1.25mm

- **2005: Dual Source CT**
  - Temporal resolution = 75-83ms
  - Spatial resolution = 0.3mm
IF YOU DON'T JUMP INTO THE VOLCANO, THE LIVES OF PREVIOUS VOLCANO JUMPERS WILL HAVE BEEN WASTED!
Slice thickness and CAC Scoring

- Detection of small CAC requires thinner slices
- However image noise increases with thinner slices given a constant radiation dose
Slice thickness and CAC Scoring

1mm slices

3mm slices

A

B

1 Invest Radiol 2005;40:695-699
Lung versus CAC Screening

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- The dose of CAC CT would have to be reduced by about 60% in order to match the very low dose of lung screening CT (0.7 mSv for entire chest).
FBP Reconstruction – Bone Kernel
FBP Reconstruction – Soft Tissue Kernel
2009 - Iterative Reconstruction (100%)
Effect of iterative reconstruction on CAC scores

- The maximum variability using iterative reconstruction is 2% in a stationary phantom

- This is much lower than our observed maximum interscan variability of 24% in a phantom
Effect of iterative reconstruction on CAC scores

- Iterative reconstruction underestimates CAC scores by 6-22% compared to traditional filtered back projection.

1 Gebhard C, et al. Int J Cardiol 2012; Sept 5. [epub]
The 0.2 mSv CACS CT

- 100 kV and 80 mAs, ECG-gated
- Employed a threshold of 147 HU (vs. 130 HU)
- High correlation w/ 120 kV 80 mAs scan (r=0.99)
- 3% of cases were unreadable due to noise
- Overestimation of CAC scores by about 11
- 7% had a misclassified risk categorization

Future directions

- How much interscan variability is acceptable?
- Should the gold standard always be 2.5 mm?
- Can the 130 HU threshold be optimized?

How is CACS affected by:

- Field of view
- Helical versus axial CT
- Increased noise (Slice thickness, Dose, Patient Size)
- Newer noise reduction strategies
- Other calcium scoring techniques (volume, mass)
Conclusion

- Combined lung and cardiac CT screening will require the latest technologies to optimize radiation dose and diagnostic accuracy
- Existing limitations in CAC measurements should be recognized and addressed
- CT protocols may need to be individually tailored to improve risk stratification
Thank You!