Coronary Calcium Scoring for Risk Stratification and Guidelines

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Disclosure

I have no relevant financial relationships with commercial interests.
Total Coronary Artery Plaque and EBCT Coronary Calcium

- 20% Calcified
- 80% Lipid Rich
- 20% Fibrotic
- 80% Plaque Detectable by IVUS, Pathology
Prediction of Cardiac Events in
The St. Francis Heart Study, JACC 2005

Baseline EBT

Annual Event Rate (%)

Calcium Score >100 vs <100

Relative Risk

0 > 0 > 100 > 200 > 600

Any Event
Cor. Event
MI/SCD

0.12
0.7
2
2.4
3.3
0
0.5
1
1.5
2
2.5
3
3.5

9.5
10.7
9.9

Any Event
Cor. Event
MI/SCD
All Cause Mortality and CAC Scores:
Long Term Prognosis in 25,253 patients

Budoff, et al. JACC 2007; 49: 1860-70
MESA Study – 6,814 Patients: 3.5 year follow-up

Nonfatal MI & CHD Death

Hazard Ratio

None 1-100 100-300 >300

Ref 4.47 (2.45,8.13) 10.26 (5.62,18.71) 14.13 (7.91,25.22)

Fully adjusted – Detrano et al – NEJM - 2008
NEW GUIDELINES

2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance

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Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk).

Measurement of CAC may be reasonable for cardiovascular risk assessment persons at low to intermediate risk (6% to 10% 10-year risk).

In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment.
Computed tomography for coronary calcium should be considered for cardiovascular risk assessment in asymptomatic adults at moderate risk. IIa
• If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.

• The contribution to risk assessment for a first ASCVD event using ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present.

• CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.
“assessing CAC is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment.”
Prevention Guidelines AND Blood Cholesterol Guidelines 2013

High Risk: CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity*

Low Risk: <300 Agatston units and <75 percentile for age, sex, and ethnicity*
Warranty of a CAC Score

Kaplan-Meier survival estimates

6,944 (42%) CAC=0

48 deaths

99.3%

99.6%

Followup (years)

FH CHD (-)  FH CHD (+)

Ketlogetswe AHA
2010
**FIGURE 1** The 15-Year Cumulative Mortality Rate for the Study Period

- **Overall** (N = 9,715)
- FRS < 10% (N = 3,954)
- NCEP ATP III < 10% (N = 5,185)
- No CV risk factors (N = 545)
- CAC = 0 (N = 4,864)
Figure. Receiver Operator Characteristic Curves Showing Area Under the Curve for Incident Coronary Heart Disease and Incident Cardiovascular Disease in Intermediate-Risk MESA Participants
**Figure. Multivariable-adjusted HR for incident coronary heart disease.**

<table>
<thead>
<tr>
<th>Marker</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td>2.5 (1.7–3.6)</td>
</tr>
<tr>
<td>vWF antigen</td>
<td>1.2 (0.9–1.6)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.4 (1.1–2.0)</td>
</tr>
<tr>
<td>CKD</td>
<td>1.4 (1.1–1.8)</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>1.8 (1.3–2.5)</td>
</tr>
<tr>
<td>CRP</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.9 (0.7–1.3)</td>
</tr>
<tr>
<td>CAC score</td>
<td>6.2 (3.4–11.5)</td>
</tr>
<tr>
<td>cIMT</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td>PAD</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>PWV</td>
<td>1.2 (0.8–1.8)</td>
</tr>
</tbody>
</table>

CAC = coronary artery calcium; cIMT = carotid intima–media thickness; CKD = chronic kidney disease; CRP = C-reactive protein; HR = hazard ratio; NT-proBNP = N-terminal fragment of prohormone B-type natriuretic peptide; PAD = peripheral arterial disease; PWV = pulse wave velocity; vWF = von Willebrand factor.
Net Reclassification Improvement (NRI)

**MESA: Intermediate Risk (n=1,330)**

<table>
<thead>
<tr>
<th>Addition to FRS</th>
<th>NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS + Brachial FMD</td>
<td>0.024</td>
</tr>
<tr>
<td>FRS + ABI</td>
<td>0.036</td>
</tr>
<tr>
<td>FRS + Hs-CRP</td>
<td>0.079</td>
</tr>
<tr>
<td>FRS + Family History</td>
<td>0.160</td>
</tr>
<tr>
<td>FRS + C-IMT</td>
<td>0.102</td>
</tr>
<tr>
<td><strong>FRS + CAC</strong></td>
<td><strong>0.659</strong></td>
</tr>
</tbody>
</table>

**NRI: Improved Detection of Low & High Risk Individuals**

\[ \text{NRI} = \frac{\text{Prob} (\text{being correctly reclassified to higher-risk category/event}) - \text{Prob} (\text{being incorrectly reclassified to lower-risk category/event}) + \text{Prob} (\text{being correctly reclassified to lower-risk category/nonevent}) - \text{Prob} (\text{being incorrectly classified to higher-risk category/nonevent})}{\text{Prob}(\text{event}) - \text{Prob}(\text{nonevent})} \]

**NRI: FRS Model vs. FRS + Screening Test**

Models estimating 7-y MI, CHD death, resuscitated cardiac arrest, or angina followed by PCI/CABS

Shemesh - Ungated Studies
8782 patients, 6 year f/u

- 1.2% CV death - 0
- 1.8% for a score of 1–3
- 5.0% for a score of 4–6,
- 5.3% for score of 7–12
- A CAC ordinal score of at least 4 was a significant predictor of CV death (odds ratio 4.7; \( P < .0001 \))
Reclassification of ATP III Risk Categories Using CAC

CAC Score
- high
- Intermediate
- Zero

<10%  10-20  >20  % 10-year risk

14% To High Risk
63% To Low Risk

ATPIII Score Risk Assessment
Scheme according to Wilson PWF et al
JACC 41:1889 – 1906, 2003 with HNR data
Table 3: Cardiovascular Risk Reclassification Comparing the Framingham Refitted Model With the Model Additionally Including CAC

Addition of CRP did not improve C Statistic or Reclassification

<table>
<thead>
<tr>
<th>10-Year Risk Categories</th>
<th>&lt;10%</th>
<th>10%-20%</th>
<th>&gt;20%</th>
<th>n (%) Reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 1,438</td>
<td>1,278 (88%)</td>
<td>156 (11%)</td>
<td>4 (1%)</td>
<td>160 (12%)</td>
</tr>
<tr>
<td>Observed risk (95% CI)</td>
<td>0.03 (0.02–0.05)</td>
<td>0.13 (0.08–0.20)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>10%-20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 451</td>
<td>134 (30%)</td>
<td>216 (48%)</td>
<td>101 (22%)</td>
<td>235 (52%)</td>
</tr>
<tr>
<td>Observed risk (95% CI)</td>
<td>0.09 (0.05–0.16)</td>
<td>0.14 (0.10–0.20)</td>
<td>0.29 (0.20–0.41)</td>
<td></td>
</tr>
<tr>
<td>&gt;20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 144</td>
<td>7 (5%)</td>
<td>42 (29%)</td>
<td>95 (66%)</td>
<td>49 (34%)</td>
</tr>
<tr>
<td>Observed risk (95% CI)</td>
<td>0.49 (0.15–0.94)</td>
<td>0.13 (0.05–0.31)</td>
<td>0.31 (0.21–0.44)</td>
<td></td>
</tr>
</tbody>
</table>

CAC = coronary artery calcium; CI = confidence interval; NA = not applicable.
EISNER Randomized Controlled Trial

2137 middle-aged + risk factors without CVD
45-79y without CAD/CVD followed 4 years

No Scan
• Clinical evaluation
• Questionnaire
• Risk factor consultation

Scan
• Clinical evaluation
• Questionnaire
• Risk factor consultation
• CAC scan
• Scan consultation
Does CAC scanning improve outcomes?

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No SCAN</th>
<th>CACS&gt;400</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LDL-C</td>
<td>-11 mg/dL</td>
<td>-29 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in SBP</td>
<td>-5 mm Hg</td>
<td>-9 mm Hg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise</td>
<td>36%</td>
<td>47%</td>
<td>0.03</td>
</tr>
<tr>
<td>New Lipid Rx</td>
<td>19%</td>
<td>65%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New BP Rx</td>
<td>18%</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New ASA Rx</td>
<td>7%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid Adherence</td>
<td>80%</td>
<td>88%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

EISNER Study – Costs Compared to No Scan Group

P<0.005 for both measures

Rozanski JACC 2011
ST FRANCIS RANDOMIZED TRIAL
Randomized Double Blind Placebo Controlled Trial of
Atorvastatin in the Prevention of Cardiovascular Events
Among Individuals With Elevated CAC Score

- Mean duration of treatment was 4.3 years.
- Treatment with atorvastatin reduced clinical endpoints by 30% (6.9% vs. 9.9%), and MI/Death by 44% (NNT 30)
- Event rates were more significantly reduced in participants with baseline calcium score >400 (8.7% vs. 15.0%, p=0.046 [42% reduction]). (NNT 16)

Chest pain of recent onset

Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin
1.3.4.7 For people with chest pain in whom stable angina cannot be diagnosed or excluded by clinical assessment alone and who have an estimated likelihood of CAD of 10–29% (see recommendation 1.3.3.16) offer CT calcium scoring. If the calcium score is:

- zero, consider other causes of chest pain
- 1–400, offer 64-slice (or above) CT coronary angiography
- greater than 400, offer invasive coronary angiography. If this is not clinically appropriate or acceptable to the person and

NICE clinical guideline 95 – Chest pain of recent onset
NICE ALGORITHM

Stable chest pain pathway

1. Diagnostic testing for people in whom stable angina cannot be diagnosed or excluded by clinical assessment alone

- Estimated likelihood of CAD 10 to 29%
  - Score is zero
    - Investigate other causes of chest pain**
  - Score is 1-400
    - 64-slice (or above) CT coronary angiography
    - Follow pathway for 61-90% CAD

- Estimated likelihood of CAD 30-60%
  - Appropriate functional imaging test (see box 5 overleaf). If reversible myocardial ischaemia found, treat as stable angina. If not, investigate other causes of chest pain**
  - Investigate other causes of chest pain**

- Estimated likelihood of CAD 61-90%
  - Invasive coronary angiography if appropriate*
  - Significant CAD
    - See box 4
  - Uncertain
    - Appropriate functional imaging test (see box 5 overleaf)

- Reversible myocardial ischaemia
  - Treat as stable angina
  - Reversible myocardial ischaemia
    - Treat as stable angina
    - Invasive coronary angiography

Box 4 Definition of significant coronary artery disease

Significant coronary artery disease (CAD) found during invasive coronary angiography is a 70% diameter stenosis of at least one major epicardial artery segment or ≤50% diameter stenosis in the left main coronary artery.

* Factors intensifying ischaemia. Such factors allow less severe lesions (for example ≤50%) to produce angina.
Global cardiovascular risk (Framingham risk score) + Consideration of family history of cardiovascular disease and lifestyle factors (eg, strenuous exercise)

Risk classification:
- Low
- Low-intermediate
- Intermediate
- High

Coronary artery calcium score
- Low (CAC=0)
- Intermediate (CAC=1–100)
- High (CAC>100)

Risk reclassification:
- Low (CAC=0)
- Intermediate (CAC=1–100)
- High (CAC>100)
  - Consider statin therapy
Testing and Costs Go Down after implementation of NICE – BMD 2015

Figure 1  Mean costs of investigations per patient pre-CG95 (Clinical Guideline 95) and post-CG95.

Figure 2  Mean number of investigations per patient preimplementation and postimplementation of CG95 (Clinical Guideline 95).

Mean Number of Investigations per Patient

Number of Investigations

Pre-CG95  Post-CG95

Mean Costs of Investigations per Patient

Cost (£)

Pre-CG95  Post-CG95
• Risk factors are almost free to obtain (family history, DM, smoking history, age, gender, blood pressure and cholesterol)

• They can be used to predict events so we know who to treat

• So, WHAT IS THE PROBLEM?
Overall Non-diabetic 40-75 Years Old, n = 307,591

Cumulative 5-year Risk (%)

5-Year Predicted Risk Group

- <2.5%: 0.20%
- 2.5% to <3.75%: 0.65%
- 3.75% to <5.0%: 0.90%
- ≥5.0%: 8.72%
CONCLUSIONS:

- In a large, contemporary “real-world” population, the ACC/AHA Pooled Cohort Risk Equation substantially overestimated actual 5-year risk in adults without diabetes, overall and across sociodemographic subgroups.
Using the Coronary Artery Calcium Score to Guide Statin Therapy: A Cost-Effectiveness Analysis

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>FRS (%)</th>
<th>TC</th>
<th>HDL</th>
<th>QALY Difference</th>
<th>Cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 yo woman</td>
<td>7.5%</td>
<td>221</td>
<td>40</td>
<td>+229</td>
<td>$18,000</td>
</tr>
<tr>
<td>55 yo man</td>
<td>7.5%</td>
<td>159</td>
<td>40</td>
<td>+248</td>
<td>$19,000</td>
</tr>
</tbody>
</table>

Treat if CAC>0

Women

- QALY Difference: +229
- Cost per QALY: $18,000

Men

- QALY Difference: +248
- Cost per QALY: $19,000

Treat All

Women

- QALY Difference: +172
- Cost per QALY: $78,000

Men

- QALY Difference: +144
- Cost per QALY: $80,000

Can Coronary Artery Calcium Scanning Solve the problem of **gross overtreatment**, which also leads to problems with compliance?
### Very High NNT in Almost 50% of Individuals Meeting JUPITER Criteria in MESA

<table>
<thead>
<tr>
<th>JUPITER population</th>
<th>Percent of Patients in MESA</th>
<th>CHD event rate at 5.8 years</th>
<th>Hazard Ratio (95% CI)</th>
<th>5-year NNT for CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC=0</td>
<td>47%</td>
<td>0.48%</td>
<td>1 (ref)</td>
<td>549</td>
</tr>
<tr>
<td>CAC 1-100</td>
<td>28%</td>
<td>2.79%</td>
<td>4.91</td>
<td>94</td>
</tr>
<tr>
<td>CAC &gt;100</td>
<td>25%</td>
<td>10.76%</td>
<td>27.8</td>
<td>24</td>
</tr>
</tbody>
</table>
### JAMA: Coronary Artery Calcium Guided Statin Use

<table>
<thead>
<tr>
<th>% of population</th>
<th>CHD event rate (per 100 patient-years)</th>
<th>5-year NNT with 35% event reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC=0</td>
<td>50%</td>
<td>0.18</td>
</tr>
<tr>
<td>CAC 1-100</td>
<td>37%</td>
<td>0.72</td>
</tr>
<tr>
<td>CAC &gt;100</td>
<td>13%</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Coronary Artery Scanning

- SEVERE CALCIFICATION
Figure 1. Percentage of subjects with ASA initiation, dietary changes, and increased exercise, according to CAC scores.
Figure 1: Incidence of Statin Use During 6-Year Actuarial Follow-Up in the PACC Project Cohort

Men only; n = 1,640. Ever-use of a statin was noted in 23% of participants, including 48.5% of those with coronary artery calcium and 15.5% of those without coronary artery calcium (p < 0.001), which remained significant after controlling for National Cholesterol Education Program risk variables (odds ratio 3.53; 95% confidence interval 2.66 to 4.69).

Figure 2: Incidence of Aspirin Use During 6-Year Actuarial Follow-Up in the PACC Project Cohort

Men only; n = 1,640. Ever-use of aspirin was noted in 31.2% of participants, including 51.5% of those with coronary artery calcium versus 25.3% of those without coronary artery calcium (p < 0.001), which remained significant after controlling for National Cholesterol Education Program risk variables (odds ratio 3.05; 95% confidence interval 2.30 to 4.05).
CAC IMPROVES STATIN DELIVERY

- Better Risk Stratification
  - matching risk with intensity of therapy
- 50% (or MORE) will have zero scores
  - Statins and additional testing can be avoided and significant $$ saved
  - Current guidelines overtreat 50% of patients.

- IMPROVE COMPLIANCE
  - We all recognize the new guidelines (treat most) will lead to low compliance in asymptomatics
**CAC Expert Panel Algorithm**

**For Individuals Age 40-75, LDL 70-189, and Without Clinical ASCVD**

**Step 1**
Calculate 10 yr Risk Using ACC/AHA ASCVD Risk Calculator

- **10 yr Risk <5%**
  - Follow ACC/AHA guidelines for low risk

- **10 yr Risk 5% to <7.5%**
  - >50% of CAD events occur in the <7.5% Risk Group
  - Consider pharmacologic lipid Rx

- **10 yr Risk ≥7.5%**
  - Follow ACC/AHA guidelines for ASCVD Statin Benefit Groups

**Step 2**
Family history of ASCVD

**Coronary Artery Calcium (CAC) Score**

- **CAC = 0**
  - Lifestyle Management Reassess risk at 4-6 years

- **CAC = 1-299 & <75th %**
  - Lifestyle Management Consider pharmacologic lipid Rx

- **CAC ≥300 or ≥75th %**
  - Lifestyle Management Add pharmacologic lipid Rx

**Step 3**
Updated Risk Classification

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1 ASCVD = atherosclerotic cardiovascular disease


3 ACC/AHA 2013 Cholesterol Guidelines state “for those with a 5% to <7.5% estimated 10-year ASCVD risk, the potential for adverse effects may outweigh the potential for ASCVD risk reduction benefit when high-intensity statin therapy is used in this risk group. However, for moderate-intensity statin therapy the ASCVD risk reduction clearly exceeds the potential for adverse effects.”

4 ACC/AHA 2013 Cholesterol Guidelines state “Before initiating statin therapy, the clinician and patient discussion should include consideration of the potential for ASCVD risk reduction benefits, adverse effects, and drug-drug interactions. Additional factors may also be considered to inform treatment decision making in selected individuals. Factors that may contribute to assessment of ASCVD risk include...coronary artery calcium score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity.” For additional information, see [http://www.mesa-nhlbi.org/CACReference.aspx](http://www.mesa-nhlbi.org/CACReference.aspx).
11. Quantitative evaluation of coronary calcium to be used as a triage tool for lipid-lowering therapy in patients with an intermediate to high Framingham risk score.

12. Quantitative evaluation of coronary calcium in patients with an equivocal stress imaging test or in cases in which discordance exists between stress imaging testing and clinical findings.
UTILITY OF CORONARY ARTERY CALCIUM MEASUREMENT
IN CARDIOVASCULAR DISEASE

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of coronary
understand it, the CTAF panel voted to accept the following recommendation:

That the use of EBCT to measure Coronary Artery Calcium:

(1) As a screening test for asymptomatic patients who are at intermediate risk for coronary heart disease, EBCT calcium scoring meets CTAF Technology Assessment Criteria 1 through 5.

(2) As a diagnostic test in patients with symptoms suggestive of CAD (patients with chest pain), EBCT calcium scoring is a useful technology to predict those patients who will have underlying coronary heart disease, and meets CTAF Technology Assessment Criteria 1 through 5.

(3) To assess response to therapy for coronary heart disease does not meet CTAF Technology Assessment Criteria.
“Imaging has at least 3 virtues”

It individualizes risk assessment beyond use of age, which is a less reliable surrogate for atherosclerosis burden.

It provides an integrated assessment of the lifetime exposure to risk factors.

It identifies individuals who are susceptible to developing atherosclerosis beyond established risk factors.
Once subclinical atherosclerosis is detected, intensity of drug therapy could be adjusted for plaque burden

Superior doctors prevent the disease.
Mediocre doctors treat the disease before evident.  
Coronary Calcium
Inferior doctors treat the full-blown disease.
--Huang Dee: Nai-Ching
(2600 BC First Chinese Medical Text)
Widowmakerthemovie.com

WATCH THIS FILM – IT COULD SAVE YOUR LIFE

The Widowmaker - watch the trailer
Questions?

● Contact Me:
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  ■ (310) 222-4107