Epidemiology & Genetics of Coronary Calcium: What it Means to Clinical Medicine

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No disclosures
Lecture Outline

- CVD epidemiology & prevention 101
- CT measurement of calcified plaque
- Consensus Statements and Studies ‘04
- Clinical application
- Genomics, CTA and beyond
“We have been consistently unsuccessful in getting Americans to eat healthier and exercise regularly”
Primary Prevention of Cardiovascular Disease
Secondary Prevention of Cardiovascular Disease
Top Five Causes of Death U.S.

1. Cardiovascular diseases
2. Cancer
3. Chronic obstructive pulmonary disease
4. Accidents
5. Pneumonia & complications
CVD Mortality U.S. 945,836 / yr.
All CVD Mortality

- **CHD**: 54%
- **Stroke**: 18%
- **Other**: 28%

- CHD: 512,200 / yr
- Stroke: 167,661 / yr
Aging of the U.S. Population
% population > 65 years

2000: 12.6%
2010: 13.2%
2020: 16.5%

35 million
47 million
CHD Death Rates by age, sex, race

Love Your Cardiologist!
Measuring Coronary Calcium
Left Anterior Descending (LAD)
Calcified Coronary Plaque = Subclinical coronary atherosclerosis

- Ca+ in the arterial wall @ 2nd decade
- Ca+ is absent in normal vessel walls
- Ca+ is more common in complex and advanced lesions
- Coronary calcium is not an inevitable part of growing older!!!!!
Everyone

- Subclinical Atherosclerosis
- Clinical CVD Events
Coronary Calcified Plaque Negative by Cardiac CT

“...when no calcium is detected, does not absolutely rule out the presence of atherosclerotic plaque, including unstable plaque, ..........

but does imply a very low likelihood of significant luminal obstruction....and a low risk of cardiovascular events over the next 2-5 years.”

– American Heart Assoc. Coronary Artery Calcification Writing Group - Circulation 1996; 94:1175-1192
Coronary Calcified Plaque Positive by Cardiac CT

“...one in which some calcium is detected in at least one vessel, confirms the presence of atherosclerotic plaque....

....and may be consistent with a moderate to high risk of a cardiovascular event within the next 2 to 5 years.”

- American Heart Assoc. Coronary Artery Calcification Writing Group - Circulation 1996; 94:1175-1192
# Events & Calcified Plaque

**Single Center Studies - Pre 2000**

<table>
<thead>
<tr>
<th>Author</th>
<th>Relative Risk</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrano</td>
<td>2.3</td>
<td>1.2, 4.4</td>
</tr>
<tr>
<td>Agatston</td>
<td>16.9</td>
<td>1.0, 286.3</td>
</tr>
<tr>
<td>Arad</td>
<td>22.1</td>
<td>2.7, 179.0</td>
</tr>
<tr>
<td>Sullivan</td>
<td>1.0</td>
<td>0.3, 20.5</td>
</tr>
<tr>
<td>Raggi</td>
<td>7.2</td>
<td>2.5, 20.5</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>4.2</strong></td>
<td><strong>1.6, 11.3</strong></td>
</tr>
</tbody>
</table>

O'Malley, Am J Cardiol 2000; 85:945-948
Prevention V Conference & 2000 Consensus Statement

“The published literature does not completely answer the question of whether the EBCT calcium score is additive to the Framingham score for defining CHD risk in asymptomatic patients.”

“Selected use when a physician is faced with the patient with intermediate coronary disease risk may be appropriate.”
Risk Stratifications for Asymptomatic CHD

• **High Risk** (>$ 20% 10 yr)
  aggressive risk reduction (+/- Rx)

• **Intermediate Risk** (10-20%)
  further evaluation diagnostic testing

• **Low Risk** (< 10%)
  healthy life habits

AHA Prevention V - Circulation 2000;101:111-116
NCEP ATP III - 10 year CHD Risk strata
Traditional Risk Factors: Incomplete in CVD prediction

- 50% of acute MI victims have normal cholesterol profiles
- **Sudden death** is the first sign of CVD in 150,000-250,000 people/year
  - 680 deaths per day
  - 50% of all CHD

AHA Stat Book 2003 Update
Effective Prevention Strategies are Established for CVD

- Therapeutic Lifestyle Changes
- Statin’s
  - Reduce blood cholesterol ( ~ 60 mg/dl)
  - Reduce MI ~ 33%
  - 25-50 million in US could benefit
  - 4-5 million on statin therapy in U.S.
    (costs ~ $2,000/yr/Rx)
Calcified Coronary Plaque Predicts Events - ACC 2003

CORONARY CALCIFICATION, CORONARY DISEASE RISK FACTORS, AND Atherosclerotic Cardiovascular Disease Events: The St. Francis Heart Study

Yadon Arad, M.D., F.A.C.C., Marguerite Roth, R.N., David Newstein, M.S., Alan D. Guerci, M.D., F.A.C.C.
St. Francis Heart Study
Agatston Score ≥100 & Events

<table>
<thead>
<tr>
<th>Events</th>
<th>n</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ASCVD</td>
<td>122</td>
<td>9.5 (6.5-13.8)</td>
</tr>
<tr>
<td>All coronary</td>
<td>105</td>
<td>10.7 (7.1-16.3)</td>
</tr>
<tr>
<td>MI/coronary death</td>
<td>43</td>
<td>9.9 (5.2-18.9)</td>
</tr>
</tbody>
</table>
Calcified Coronary Plaque & Framingham Risk Index: Coronary Event Prediction

<table>
<thead>
<tr>
<th></th>
<th>Area under ROC Curve</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium score</td>
<td>$0.81 \pm 0.03$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Framingham</td>
<td>$0.71 \pm 0.03$</td>
<td></td>
</tr>
</tbody>
</table>

St. Francis Heart Study - ACC 2003
Clinical Application 2004
Risk Factor Assessment

Selected use in individual with:

Intermediate CHD risk

Reclassify Risk using Calcium Score
Positive Family History of Cardiac Death........

<table>
<thead>
<tr>
<th>Risk Score results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
</tr>
<tr>
<td>Gender:</td>
</tr>
<tr>
<td>Total Cholesterol:</td>
</tr>
<tr>
<td>HDL Cholesterol:</td>
</tr>
<tr>
<td>Smoker:</td>
</tr>
<tr>
<td>Systolic Blood Pressure:</td>
</tr>
<tr>
<td>On medication for HBP:</td>
</tr>
<tr>
<td>Risk Score*</td>
</tr>
</tbody>
</table>

The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see ATP III Executive Summary and ATP III At-a-Glance.
Outcome # 1
Total Calcium Score = 0
Framingham/NCEP CHD risk (7% over 10 years - low risk)

Coronary Calcium Score = Negative / Low
↓
Low near term CHD risk (supports Framingham Risk Index)
↓
Healthy lifestyle habits
Conservative management
Outcome #2
Total Calcium Score = 287
Framingham/NCEP CHD risk
(7% over 10 years - low risk)

Coronary Calcium Score = Intermediate

↓

Intermediate-High CHD risk

↓

Treatment based on Global Risk Assessment
(+/- Rx)
Outcome #3
Total Calcium Score = 4,632

3D MIP - Frontal Projection

3D MIP - Projection from below
Framingham/NCEP CHD risk (7% over 10 years - low risk)

Coronary Calcium Score = High

↓

High Burden Atherosclerosis

*** High CHD risk ***

↓

Aggressive risk factor modification and further evaluation for inducible ischemia and/or flow limiting lesion in coronary circulation
Coronary Calcium Scores: a Practical Synthesis

<table>
<thead>
<tr>
<th>Calcium Score</th>
<th>Risk Strata</th>
<th>Recommendations to reduce CHD risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>Low &lt;10%</td>
<td>• Healthy lifestyle choices</td>
</tr>
<tr>
<td>11-399</td>
<td>Intermediate 10-20%</td>
<td>• Mgmt. based on combined risk factor levels (+/- Rx)</td>
</tr>
</tbody>
</table>
| > 400         | High > 20%  | • Aggressive risk factor reduction (+ Rx)  
|               |             | • Evaluation for ischemia          |

Calcium Score thresholds based on correlation with coronary angiography work of Rumberger et. al. Mayo Clinical Proceedings - Risk Strata based on Prevention V Criteria
Absolute vs. Percentile Score
“why you didn’t like being graded on the curve”

66% of Americans are overweight or obese ....

...... do you feel good having a weight at the 50th percentile?

...... likewise during an epidemic of CVD is having the 50th percentile of coronary plaque burden “O.K.”?
Cardiac CT Technologies

EBCT vs. MSCT

Images courtesy - J. Breen – Mayo Clinic
EBCT vs. MSCT

Images courtesy - J. Breen – Mayo Clinic
“Effect of scanner type and calcium measure on the re-scan variability of calcium quantity by CT”

Rescan variability similar between EBCT and MDCT

Detrano et. al. Paper @ AHA 2002.
<table>
<thead>
<tr>
<th></th>
<th>MDCT</th>
<th>EBCT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agatston Score</td>
<td>24.7</td>
<td>22.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Calcium Volume</td>
<td>15.8</td>
<td>13.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Volume Score</td>
<td>11.9</td>
<td>11.0</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Median Re-Scan Variability |\(|scan2 – scan1|, N = 3190\) (Adjusted for mean score, and BMI)
Genetics Research with Cardiac CT

LAD

RCA
Heritability of CAC 40-50% in Type 2 Diabetes

- Coronary Calcium has significant genetic component
- Heritability estimate ($h^2$) = 0.40-0.50
Heritability of CAC 42-44% in Asymptomatic Adults

• 42% variability (44% unadjusted) observed in CAC explained by genetic factors
• Asymptomatic adults in Rochester, NY
Diabetes Heart Study @ WFU
Heritability Estimate = 0.5

DHS 1001
Coronary Calcium = 1,549

DHS 1002
Coronary Calcium = 1,055

DHS 1003
Coronary Calcium = 23

CT as a tool for Genomics

- Family Study Design (n ~ 3,400)
- Genome wide scans & CT exams in all Sites: UAB, UMN, Framingham, Utah, WFU
- Calcified plaque
  - Coronary arteries
  - Abdominal aorta

http://www.biostat.wustl.edu/
Conclusions

- CVD will cause increasing morbidity & mortality
- Coronary calcified plaque can be measured accurately with Cardiac gated CT (MDCT & EBCT) and can be used to identify those at risk
- Preliminary studies indicate CAC adds to Traditional CVD risk estimators
- Mounting evidence suggests that CAC will have a significant role in CVD prevention