Are Lipids (or Risk Factors) the Optimal Marker for ASCVD Risk Assessment?

Time for Paradigm Shift?

Khurram Nasir, MD MPH

How Cardiovascular Disease Became Our Biggest Threat?

- **1900-1940**: Infectious diseases was the leading cause of death in the United States, and the average life expectancy was only 47 in 1930
- **Sanitation, TB & Pneumonia Control, Penicillin significantly improved outcomes**
- **1945**: 1 out of every 3 men in the United States developed CVD in their 50's with majority of dying in 60's
- **1946**: 44% of deaths in the US could be attributed to cardiovascular disease. That was an increase of about 20% since 1940

Yalta Conference: February 4–11, 1945

Franklin D. Roosevelt
32nd President of the United States
Born: January 30, 1882 Hyde Park, New York
FDR Blood Pressure Trends 1937-1945

Unfinished Portrait of FDR

Died: April 12, 1945 (aged 63) Warm Springs, Georgia
Cause of Death: Massive Cerebral Hemorrhage

1948: Major Headlines!

- Israel was born & Czech democracy was suppressed
- Gandhi assassinated and apartheid began
- Polaroid camera appeared on the market
- The World Health Organization was established
- Britain inaugurated its national health service
1948: Events That Did Not Make Headlines...

- Congress created the National Heart Institute
- The Framingham Heart Study enrolled its first patient.

Concept of cardiovascular “risk factors”

Statins: Journey from Discovery to “Established” Role in Primary Prevention

- 1960: Block & Lynen establish reduction of HMG-CoA is the major point of regulation on the pathway to cholesterol
- 1971: Akira Endo, a Japanese biochemist began the search for cholesterol lowering drug.
- 1984: Coronary Primary Prevention Trial demonstrated cholesterol lowering could significantly reduce the risk of heart attacks and angina
2001-2003

Framingham Based Risk Scores is Incorporated in National Guidelines to Use for Assessing Risk of Developing CVD & Management with statins in Asymptomatic Individuals

How do we classify Asymptomatic Individuals Based on FRS?

- <10%: Low Risk
  - Reassurance
  - Avoid further risk assessments for 5 years.
- >20% : High Risk
  - Candidates for aggressive management with LDL goals of <100 mg/dl and aspirin
- 10-20%: Intermediate Risk
  - Do not qualify for the most intensive risk factor interventions
  - Candidate for pharmacotherapy if LDL>160 mg/dl

2004: Case Study

- Name: WJC
- Age: 58 years old male
- Profession: Former chief executive
- Social: No Cigarette use
  - Blood pressure is 128/84 mm Hg after treatment with BP medicine
  - Total cholesterol level is 188 mg/dL
  - LDL Cholesterol 129 mg/dl
  - HDL cholesterol level is 42 mg/dL.
  - No family history of coronary artery disease.
- FRS: 9% ➔ No preventive treatment needed
2003: How Good are Traditional Strategies in Estimating CHD risk??

222 patients with 1st acute MI, no prior CAD
men <55 y/o (75%), women <65 (25%), no DM

High Risk
Intermediate Risk
Low Risk

18% 18% 18% 18%
10% 10% 10% 10%
72% 72% 72% 72%

Akosah Et al, JACC 2002;41:1473-9

Have We Been Focusing Too Much on “What’s Your Cholesterol?”

“Your cholesterol level is way too high.”
Significant overlap in risk factors in with and without CHD
Framingham Heart Study—26-Year Follow-up


Most People who Develop Heart Attacks have “Normal” LDL Values

GROUP 1: PEOPLE WITH CLINICAL ASCVD
GROUP 2: PEOPLE WITH LDL-C ≥ 190
GROUP 3: DIABETES, AGE 40–75, LDL-C 70–189, NO CLINICAL ASCVD
GROUP 4: AGE 40–75, LDL-C 70–189, NO ASCVD, BUT 10-YEAR RISK ≥ 7.5%
As compared with the ATP-III guidelines, the new guidelines would increase the number of U.S. adults receiving or eligible for statin therapy from 43.2 million (37.5%) to 56.0 million (48.6%).

Pencina MJ et al NEJM 2014

"If experts are having this debate over the new guideline, then what are practitioners and patients sitting on the sidelines going to think?"

Peter Libby, chief of the division of cardiovascular medicine at Brigham and Women's Hospital Boston

Risk for Mass Medicalization?

More Than a Billion People Taking Statins? Potential Implications of the New Cardiovascular Guidelines

What Does it Mean for Stakeholder?
Computed Tomography for Non-Invasive Imaging of Subclinical Coronary Atherosclerosis

Imaging of coronary artery calcification as a specific sign of atherosclerosis

Agatston AS, Janowitz WR et al. Quantification of coronary artery calcium using ultrafast computed tomography. JACC 1990

Coronary Artery Calcium Scanning Should be Used for Primary Prevention

Pros and Cons

Khosla S, N Monroe, MD, MPH, Leslie J. Row, PhD, Mark I. Rothberg, MD, Paci N. Rolleri, MD, MPH, James M. Peta, MD, MPH
New Haven, Connecticut, Baltimore, Maryland, Phoenix, California, Atlanta, Georgia, and Boston, Massachusetts

Table 1: Clinical Value of CT Testing

<table>
<thead>
<tr>
<th>Measure of Atherosclerosis</th>
<th>Initial Study (n = 4,550)</th>
<th>Future Study (n = 6,300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of coronary artery calcification</td>
<td>95.5% (95% CI: 94.6-96.4)</td>
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</tr>
<tr>
<td>Number of positive patients</td>
<td>87% (95% CI: 85.0-89.0)</td>
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</tr>
<tr>
<td>Measure of coronary artery calcification</td>
<td>Total population = 276,348, Total area under the curve = 0.70</td>
<td></td>
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When can I stop making wild guesses and start making educated guesses?
NRI Compared to Other Markers?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>% Not Cardiovascular</th>
<th>NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC=0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>MetawAnalysis*</td>
<td>71,595</td>
<td>29,312</td>
<td>(41%)</td>
<td>4.3</td>
<td>154 (0.47%) CVD events</td>
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<tr>
<td>Retrospective**</td>
<td>44,652</td>
<td>19,656</td>
<td>(45%)</td>
<td>5.6</td>
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<td>Prospective***</td>
<td>6,809</td>
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<td>4.1</td>
<td>17 (0.52%) CHD events</td>
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<thead>
<tr>
<th>Study Type</th>
<th>Population (n)</th>
<th>CAC=0 (%)</th>
<th>FU (Years)</th>
<th>Number of events (%)</th>
</tr>
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What is the value of CAC = 0?

Appropriate Resource Allocation

“Can we use CAC testing to identify those who may and may not benefit from preventive therapy?”
Two major comments

Low likelihood of absence & presence of CAC among those at extreme spectrum of risk profile

CAC testing will not have a meaningful impact in predicting “clinical events” these groups

Tale of Two Extremes

- 60 yr male
- Non smoker
- Treated HTN, SBP 135 mm Hg
- LDL 150 mg/dl
- HDL 38 mg/dl
- TG 160 mg/dl
- Prediabetic
- ASCVD risk score 16%
- Framingham risk score 18%

- 50 yr male
- Non smoker
- Normotensive, SBP 118 mm Hg
- LDL 126 mg/dl
- HDL 45 mg/dl
- TG 102/dl
- Normal glycemic control
- ASCVD risk score 3%
- Framingham risk score 4%
Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis

Michael G. Silverman 1,2, Michael J. Blaha 1, Harlan M. Krumholz 3, Matthew J. Budoff 4, Ron Blumstein 2, Christopher T. Sibley 5, Arthur Agatston 6, Roger S. Blumenthal 1, and Khurram Nasir 1,6,7,8*

Circulation. 2014;129:77-86; originally published online October 20, 2013; doi:10.1161/CIRCULATIONAHA.113.003625

Number needed to treat: CAC 0 549, CAC 1-100 94, CAC > 100 24

75% of all events occurred in 25% with CAC>100

 Associations between C reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study


Circulation. 2014;129:275-284; originally published online October 20, 2013; doi:10.1161/CIRCULATIONAHA.113.003662
Are all Diabetics Equivalent?

<table>
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<tr>
<th>Distribution of CAC Scores</th>
<th>% All Events by CAC Score Group</th>
</tr>
</thead>
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<tr>
<td></td>
<td>CAC Score Group</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CAC = 0</td>
</tr>
<tr>
<td></td>
<td>CAC = 1-600</td>
</tr>
<tr>
<td></td>
<td>CAC = &gt;600</td>
</tr>
</tbody>
</table>

Malik S, Budoff M, Katz R, Blementhal RJ, Alain Berton, Blumenthal RS, Nasir K, Szklo M, Barr G, Wong ND (Diabetes Care 2012)
Myths & Criticisms!!

...calcium scanning often leads to other unnecessary testing, including cardiac catheterization, which probably explains its popularity in our ‘fee for service’ health care environment.”

EISNER STUDY: Down Stream Test and Costs among those undergoing No CAC vs CAC Screening in 4 year Follow-up

<table>
<thead>
<tr>
<th></th>
<th>No-CAC Testing (n = 623)</th>
<th>CAC Testing (n = 1,311)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downstream Tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress Test</td>
<td>33.9%</td>
<td>34.0%</td>
<td>0.74</td>
</tr>
<tr>
<td>Cardiac CT</td>
<td>7.1%</td>
<td>7.7%</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiac Catheterization</td>
<td>2.9%</td>
<td>3.3%</td>
<td>0.71</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>1.8%</td>
<td>2.3%</td>
<td>0.46</td>
</tr>
<tr>
<td>Downstream Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Procedure costs*</td>
<td>$721</td>
<td>$904</td>
<td>0.56</td>
</tr>
<tr>
<td>Median Medication costs</td>
<td>$2,937</td>
<td>$3,149</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Include $150 for CAC testing.
Rozanski et al, J Am Coll Cardiol. 2011;57:1622-1632
“CAC assessment is unlikely to alter the treatment plan for these patients……..”

**Behavioral & Medication Changes According to CAC Scores**

<table>
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<th>Result</th>
<th>Medication Adherence**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher CAC independently strongly associated with dietary changes and increased exercise</td>
<td></td>
</tr>
<tr>
<td>Increased LLM adherence with increasing CAC scores (0=44%, 1-99=62%, 100-399=75%, &gt;400%=92%)</td>
<td></td>
</tr>
<tr>
<td>34-83% increased chance of initiation of ASA, BPLM and LLM with higher CACS in the Multi-ethnic Study of Atherosclerosis</td>
<td></td>
</tr>
</tbody>
</table>

**Kalia NK, Miller LS, Nasir K, Budoff MJ. Atherosclerosis. 2006

“It is imprudent to use a technology we know is associated with radiation exposure, expense, without knowing that it actually identifies individuals who preferentially benefit from any specific therapy.”
Radiation dose

- "dose [EBT dose 0.7 mSv, MDCT dose 1.5 mSv]"
- AHA Scientific Statement Circulation 2005
- CAC Dose = 1 mSv (Gerber AHA Scient Statement on Ionizing Radiation 2009)
  - Similar to Mammogram
  - Similar to long distance air flight
  - 1/3 annual background radiation

CAC in 2014: The question to ask is "Why Not" rather than "Why"?

- Most precise measure for risk of clinical CVD event
- Widely available
- Inexpensive (75-100 $)
- Easy to perform (takes 2-3 minutes) and interpret
- Radiation equivalent to mammogram

Advantages to stakeholders

- **Health System**: Appropriately allocating healthcare resources to groups likely to receive net benefit from proven Interventions.
- **Clinician**: personalized assessment of risk on case by case situation
- **Patient**: Shared decision making
Acknowledgements

- Arthur Agatston MD
- Warren Janowitz MD PhD
- Jonathan Fialkow MD
- Theodere Feldman MD
- Ricardo Cury MD
What Difference Does This Information Makes?

<table>
<thead>
<tr>
<th>Candidates for Lifelong statin + -</th>
<th>Outcome of CAC testing</th>
<th>Number needed to scan (Cost)</th>
<th>Reclassified 10 Y CVD Risk</th>
<th>Number needed to treat</th>
<th>Lifestyle interventions</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia and/or high Global CVD Risk Score</td>
<td>At least 1/3rd will have CAC=0</td>
<td>At least 1/3rd will have CAC&gt;0</td>
<td>3 (300)</td>
<td>&lt;5%</td>
<td>Eligible for lifestyle improvements</td>
<td>Flexible goals</td>
</tr>
<tr>
<td>Normal Lipids and/or Low Global CVD Risk Score</td>
<td>At least 1/3rd will have CAC=0</td>
<td>At least 1/3rd will have CAC&gt;0</td>
<td>3 (300)</td>
<td>&gt;7.5%</td>
<td>Likely harmful</td>
<td>Likely Beneficial</td>
</tr>
</tbody>
</table>

CVD distribution and Statin Eligibility criteria

Multi-Ethnic Study of Atherosclerosis, Population at Baseline:

n = 6814

Missing Cardiovascular or Coronary Heart Disease Outcome n = 9

Evaluated due to missing lipid values or risk factor information in IL

Evaluated due to current use of lipid lowering medication n=100

Meeting lipid lowering therapy criteria n=1008

Not meeting lipid lowering therapy criteria n=572 (8.3%)

Hard CVD Events n=299 (9.6%)

Hard CVD Events n=55 (2.2%)

10.2 Median FU

Hard CVD Events=354 (6.3%)

Meeting CAC distribution and Statin Eligibility criteria

<table>
<thead>
<tr>
<th>CAC</th>
<th>Eligible</th>
<th>Not Eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>1</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>&gt;1</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>&gt;100</td>
<td>5%</td>
<td>95%</td>
</tr>
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Flexibility Likely Beneficial Likely Harmful Flexible goals Strongly Consider

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Absolute CVD Incident (%) Across CAC Burden Among Candidates for LLM (>7.5% 10 Year CVD Risk) & Not Candidates for LLM (<7.5% 10 Year CVD Risk)

CAC distribution Across Spectrum of 10 Year Risk Score Among those >7.5% Risk Score (LLM Eligible)

Absolute Hard CVD Incident (%) Across Spectrum of CVD Risk Score & CAC Burden Among Candidates Eligible for Statins (>7.5% 10 Year CVD Risk) in Median FU of 10.2 (IQR 9.6-10.7)