Population Screening for CV Disease: Bringing New Science to the Problem

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Disclosures

• Grant Support from Roche Diagnostics, and Abbott Diagnostics
• Consulting from Roche Diagnostics
Large Number of CV Events in Individuals not at High Risk

Proportion in each risk category
NHANES 1999-2002

- Low-risk: 76%
- Intermediate-risk: 13%
- High-risk: 11%

Estimated Number of CV Events

- High Risk: 5 million
- Intermediate Risk: 3 million
- Low Risk: 5 million

10-year CHD Events (Millions)

Ajani UA et al, JACC 2006;48:1177
Identification of Susceptible Individuals for Targeted Intervention

Current Algorithms

Genetic Markers

Bio markers

Imaging

Current Algorithms
Candidates for Improving Cardiovascular Risk Prediction

Genetics

Biomarkers

Imaging
Genetics of Atherosclerotic CVD

Minority
Familial Hypercholesterolemia

- Single gene, Mendelian form
- Rare mutations
- Large effect

Majority

Polygenic, complex disorder
- Multiple mutations
- Small effect

Lusis AJ et al. *Annu Rev Hum Genet* 2004;5:189-218
Discovering New CAD Genes: Genome Wide Association Studies (GWAS)

- Study 1: 630 subjects
- Study 2: 630 subjects
- Study 3: 13,000 subjects

- Confirm 1: CCHS
- Confirm 2: DHS
- Confirm 3: OHS

- Risk: 30-40%

McPherson R et al. Science 2007;316:1488
Gene Score for Heart Disease Risk

Kathiresan S et al. *NEJM* 2008
Sequence Variations in \textit{PCSK9} Associated with Lower LDL Levels

- Dallas Heart Study
  - $n=3,557$
  - 50\% African-American

- Catalytic domain
  - N-terminal
  - Prodomain
  - C-terminal

- Dallas Heart Study
  - 3\% of Caucasians: \textit{R46L} allele $\rightarrow$ 21\% $\downarrow$ LDL-C
  - 2\% of AA: \textit{Y142X} or \textit{C679X} allele $\rightarrow$ 40\% $\downarrow$ LDL-C
Lifelong Reduction in LDL

~ 40% ↓ LDL

Coronary Heart Disease (%)

African American

Y142X or C679X

 Carrier - +

P = 0.008

Caucasian

R46L Carrier

 Carrier - +

P = 0.003

~ 20% ↓ LDL

• No role for genetic testing in 2016 for risk prediction or to identify candidates for lipid lowering therapy

• Important prevention lessens from PCSK9 story
  – Treating earlier will maximize benefit
  – Benefit proportional to intensity of LDL lowering
  – PCSK9 a very attractive drug target
Candidates for Improving Cardiovascular Risk Prediction

Genetics

Biomarkers

Imaging
CRP: Individual Subject Meta-Analysis

54 studies
160,309 Individuals
27,769 outcomes

No ↑ Discrimination
Small ↑ Reclassification

JUPITER Trial: A Test of CRP’s Utility?

Interaction between CRP and Statin Efficacy

Ridker Am J Cardiol. 2010;106:204-9
Can a cardiac specific biomarker do better?
Screening with Natriuretic Peptides

LVH or LVSD

Coronary Calcium

LVH or LVSD

P < 0.0001

log (NT-proBNP)

P < 0.0001

log (NT-proBNP)

n= 2116 303 154 79

<10 10-100 100-400 >400

<75th %ile 75th 90th 95th 97.5th 99th

LVH or LVSD

Coronary Calcium

de Lemos AHJ 2009

Abdullah et al. Am J Cardiol 2005
First major cardiovascular event according to baseline tertile of B-type natriuretic peptide: JUPITER

Everett BM et al. *Circulation*. 2015;131:1851
## NT-proBNP vs CRP for Risk Prediction in Men

<table>
<thead>
<tr>
<th>Endpoint/Metric</th>
<th>Base Model</th>
<th>+ CRP</th>
<th>+ NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-statistic</td>
<td>0.686</td>
<td>0.695</td>
<td>0.704*</td>
</tr>
<tr>
<td>NRI</td>
<td>3.8%</td>
<td>8.8%*</td>
<td></td>
</tr>
<tr>
<td>IDI</td>
<td>0.32</td>
<td>2.33*</td>
<td></td>
</tr>
<tr>
<td><strong>CVD death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-statistic</td>
<td>0.753</td>
<td>0.765</td>
<td>0.784*</td>
</tr>
</tbody>
</table>

British Regional Heart Study; n=3649 men 60-79 years old  
CVD events=CVD death, MI, stroke  
* * p<0.01  

Wannamertthee et al. JACC 2011;58:58-64.
What about a biomarker of cardiac injury?
Proportion of Adults with Detectable hs-cTnT

<table>
<thead>
<tr>
<th>Age</th>
<th>DHS N</th>
<th>CHS N</th>
<th>ARIC N</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-65</td>
<td>3546</td>
<td>≥65</td>
<td>54-74</td>
</tr>
<tr>
<td>3546</td>
<td>4221</td>
<td>9698</td>
<td>4221</td>
</tr>
</tbody>
</table>

- **DHS**: 75% have detectable hs-cTnT (25% do not)
- **CHS**: 33.8% have detectable hs-cTnT (66.2% do not)
- **ARIC**: 33.5% have detectable hs-cTnT (66.5% do not)
Independent determinants of cTnT

Male sex
Age
Diabetes
eGFR
LV mass
  LV EDV
  LV Wall Thickness
Black Race
Hypertension
History of Heart Failure

**Prior MI, Angina, and CAC not independently associated

de Lemos JA et al. JAMA 2010;304:2503-12.
Association with All-Cause Mortality

de Lemos JA et al. JAMA 2010;304:2503-12.
Differential Association with CVD endpoints

Saunders, Circulation 2011
Change in cTnT level from baseline to follow-up
Association with CVD Death

Independent of Standard Risk Variables
Same association with Heart Failure

Rate of CV death (per 100 person-yrs)

Baseline cTnT (pg/mL)

<3  3.00-5.44  5.45-8.16  8.17-12.94  >12.94

P<.001  P<.001  P=.001  P=.001  P=.004

>50% Decrease  Change <=50%  >50% Increase

deFilippi C et al. JAMA 2010; 304:2494-2502.
Influence of Physical Activity on Troponin Changes

defilippi C, et al. JACC 2012; 60:2539-47
Blood Sugar Control and Cardiac Injury

Biomarkers—Take home

• CRP is not very useful as a risk predictor or tool to select candidates for prevention
  – Consistent, but small associations with risk
  – Not in causal pathway
  – Nonspecific marker with no biological link with statins

• NT-proBNP and hs-cTn more promising
  – Predict HF/fatal CVD > ASCVD
  – Likely would be gatekeeper tests
Candidates for Improving Cardiovascular Risk Prediction

- Genetics
- Biomarkers
- Imaging
Atherosclerosis Imaging: Clinically Used Modalities

- Carotid Intimal Medial Thickness
- Coronary Artery Calcium Scanning
- CT Angiography
CAC and Coronary Events: The Multiethnic Study of Atherosclerosis

Coronary artery calcium score

<table>
<thead>
<tr>
<th>Coronary artery calcium score</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>0.79</td>
</tr>
<tr>
<td>RF + CAC</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Detrano R et al. NEJM 2008;358:1336
Reclassification with CAC Scanning

**MESA Study**

\[ n=6813; \text{mean age 62} \]

<table>
<thead>
<tr>
<th>Group</th>
<th>NRI (events)</th>
<th>NRI (no events)</th>
<th>Total NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort</td>
<td>23%</td>
<td>2%</td>
<td>25%</td>
</tr>
<tr>
<td>Intermed risk</td>
<td>29%</td>
<td>26%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Polonsky JAMA 2010;303:1610-16
Multimodality Risk Prediction
CAC, ECG-LVH, hs-cTnT, NT-proBNP

Cumulative Incidence of Composite CV Event (%)

- 0 (n=1027)
- 1 (n=783)
- 2 (n=314)
- ≥3 (n=91)

log-rank p<0.0001

Adj. HR
7.7 [4.0, 14.7]
3.9 [2.2, 6.9]
2.8 [1.6, 4.7]
Referent
Final summary

- Standard risk factors alone or in combination do not predict risk well enough
  - Missed opportunities for prevention
- The bar should be very high before adopting new tests into clinical practice
- Genetic testing not ready for clinical use
- Markers of existing disease (including imaging tools) much more useful than inflammatory markers
  - CAC scanning clearly leading the pack
  - NT-proBNP and high sensitivity troponins promising
  - Different tests predict different adverse outcomes
- Multi-modality risk assessment is likely the way of the future