Emerging CVD Risk Factors: Where Do They Fit in with the New Guidelines?

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Case 1:

50 y/o man presents for routine care. He has not seen a physician in a number of years. Besides being a little overweight and fairly sedentary he is otherwise healthy. He does not take any medications. He does have a family history of premature coronary heart disease. He does not exercise. He has not smoked for many years. He drinks alcohol only occasionally. His review of systems is essentially negative.

Exam: BP 128/80  Wt-188  BMI 27  WC 39”
otherwise normal exam
Labs: Tchol 239  TG 238  HDL 39  LDL 152
   Glu-105  AST-12  ALT-16

Case 1: Assessment

• CVD Risk?
  – Traditional CRFs:
    + Age/gender
    + Family history of premature CAD
    + Low HDL-C
  – Other CRFs
    • Overweight (central?)
    • Elevated triglycerides?
    • Impaired fasting glucose
    • Sedentary
    • Others?
2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

Four Major Statin Benefit Groups:
1. Individuals with known clinical ASCVD
2. Individuals with LDL ≥ 190 mg/dl
3. Individuals with Diabetes (40-75 yrs, LDL >70 mg/dl)
4. Individuals who are 40-75 yrs and LDL >70 mg/dl and have an estimated 10-year ASCVD risk ≥ 7.5%

Risk Calculator:
Pooled Cohort Equations for ASCVD

- Risk factors used to assess risk:
  - Sex
  - Age
  - Race (White, African American, other)
  - Total Cholesterol (untreated)
  - HDL
  - Systolic BP (current)
  - Treatment for HTN (Y/N)
  - Diabetes (Y/N)
  - Smoker (Y/N)
Case 1: Assessment

- CVD Risk
  - Intermediate risk?
  - No known ASCVD or Diabetes and LDL <190 mg/dl
  - Current guidelines recommend to estimate the patient's 10-year risk of ASCVD
    - His 10-yr risk of MI and/or Stroke is 5.8%
  - But this doesn’t take other risk factors in consideration such as his metabolic syndrome, central adiposity, hypertriglyceridemia, IFG, and family history

Is this enough?
Aren't there other risk factors that independently predict CVD risk?

Reduction of CVD: Need for Improvement?

| % with CAD event |  |
|------------------|--|---|
| Placebo          | 30-40% |
| Statins          | 60-70% |
“Other” CVD Risk Factors:
Life-Habit Risk Factors

- Obesity
  - central/abdominal
- Insulin Resistance
- Sedentary Lifestyle
- Atherogenic Diet
- Psychosocial Factors

“Other” Cardiac Risk Factors:
Emerging Risk Factors

- Hypertriglyceridemia
- Impaired glucose metabolism (IFG, IGT, prediabetes)
- Apolipoprotein B
- LDL particle number
- LDL particle size/density
- Lipoprotein (a)
- Homocysteine
- Markers of Inflammation (hsCRP)
- Pro-Thrombotic Factors
- Subclinical Atherosclerosis
- Others?

Emerging Risk Factors
ATPIII - 2001

- Apolipoprotein B
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Lipid Metabolism

Exogenous
- Dietary Fat
- Chylomicron
- LDL
- HDL

Endogenous
- LPL
- Remnant Receptor
- LDL Receptor
- Liver
- Intestine

APO: B = 70  LDL = 130 mg/dl  APO: B = 150  LDL = 130 mg/dl
Apolipoprotein B

- One apolipoprotein B-100 per particle
- Assesses particle number of potentially atherogenic particles (VLDL, IDL, LDL)
- Does not need to be measured in fasted state
- Highly correlated with non-HDL cholesterol
  - 0.95 when TG < 300 mg/dl
  - 0.8 when TG > 300 mg/dl
- May help to distinguish CVD risk in patients with hypertriglyceridemia

Lipids and Apolipoproteins Were Equal in Predicting CHD Risk


Correlations Between Apo B, Cholesterol, LDL Cholesterol and Non-HDL Cholesterol

**Odds Ratios for the Development of CHD: Lipid and Lipoprotein Phenotypes**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>OR</th>
<th>Adjusted for age, smoking, alcohol, blood pressure, gender, and medications</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1.0</td>
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<tr>
<td>Nl</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>TG↑</td>
<td>3.1</td>
<td></td>
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<tr>
<td>TG↓</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lamarche B et al, Am J Card 75:1189, 1995

**Lipid Goals: American College of Cardiology and American Diabetes Association**

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or DM ≥ 1 RF</td>
<td>&lt; 70 mg/dl</td>
<td>&lt; 100 mg/dl</td>
<td>&lt; 80 mg/dl</td>
</tr>
<tr>
<td>≥ 2 RFs or DM</td>
<td>&lt; 100 mg/dl</td>
<td>&lt; 130 mg/dl</td>
<td>&lt; 90 mg/dl</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 51:1512, 2008
Diabetes Care 31, 2013

**Apolipoprotein B: If and How to Use**

- Consider use as a marker of risk especially in those with hypertriglyceridemia
- May be helpful in those at intermediate risk or in those without other significant risk factors yet who have known disease
- If apoB >80-90 mg/dL consider more aggressive LDL lowering
- Not recommended by new guidelines
Emerging Risk Factors
ATPIII - 2001

- Apolipoprotein B
- Lipoprotein (a)
- Homocysteine
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Lipoprotein (a)

- Lipoprotein (a) is an apo B lipoprotein (LDL) that includes Lp(a) covalently bound to apo B
- Concentration is strongly influenced by genetics
- Lp(a) can vary between 0 to >200 mg/dL
- 2-3 fold higher levels in populations of African descent.
- Plasma levels >30 mg/dL are associated with an increased atherosclerotic risk

Lipoprotein (a)

- The atherogenicity relates to multiple features of the particle including:
  - the inability of the particle to be cleared by the LDL receptor
  - anti-fibrinolytic properties due to the structural homology to plasminogen and competition with plasminogen for its binding site
  - the particle carrying more atherogenic pro-inflammatory oxidized phospholipids
- Potential link between atherosclerosis and thrombosis?

Probability of CVD Events According to Increasing Quintiles of Lp(a)

Lp(a) and CHD: The Reykjavik Study
**Lp(a) and CVD: The AIM-HIGH Trial**

Time to first CVD Event for Statin + Placebo Arm by Baseline Lp(a)

![Graph](image1)

Albers et al., J Am Coll Cardiol 62:1575, 2013

**Lp(a) and CVD Risk in Healthy Women**

Probability of Cardiovascular Events According to Increasing Quintile of Lp(a) in Women Not Taking HRT

![Graph](image2)

Suk et al., JAMA 296:1363, 2006

**Lp(a) and CVD Risk in Healthy Women**

<table>
<thead>
<tr>
<th>quintile</th>
<th>Lp(a), mg/dL</th>
<th>no. of women</th>
<th>cardiovascular events, no. (%)</th>
<th>age-adjusted HR (95% CI)</th>
<th>P value</th>
<th>fully adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>quintile 5</td>
<td>64 (42-22)</td>
<td>68 (49)</td>
<td>10/3 (15.9%)</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>quintile 4</td>
<td>22 (14-42)</td>
<td>68 (49)</td>
<td>11/5 (16.2%)</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>quintile 3</td>
<td>10 (7-14)</td>
<td>68 (49)</td>
<td>10/3 (15.9%)</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>quintile 2</td>
<td>5 (3-7)</td>
<td>68 (49)</td>
<td>8/5 (12.1%)</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>quintile 1</td>
<td>2 (0-3)</td>
<td>68 (49)</td>
<td>5/3 (7.3%)</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
<td>1.00 (1.00-1.00)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Table 3. Future Cardiovascular Events among Healthy Women According to Prespecified Thresholds of Lp(a)*

Suk et al., JAMA 296:1363, 2006
Lipoprotein (a)

• Presently, however, no data exist to confirm that lowering Lp(a) reduces CVD risk.
• Lp(a) can be potentially be reduced by:
  – Niacin
  – Mipomersen
  – LDL apheresis
  – Estrogens
    • estrogens may confer benefit on CVD events in post-menopausal women with the highest quintile of Lp (a).
  – Colesteryl ester transfer protein (CETP) inhibitors
  – PCSK9 inhibitors

Lipoprotein (a): If and How to Use

• Consider use as a marker of risk
• May be helpful in those at intermediate risk or in those without other significant risk factors yet who have known disease
• If Lp (a) >30 mg/dL consider more aggressive LDL lowering
• If >150-200 consider other therapies like LDL apheresis
• Not recommended by new guidelines

Emerging Risk Factors
ATPIII - 2001

• Apolipoprotein B
• Lipoprotein (a)
• Homocysteine
• Pro-Thrombotic Factors
• Pro-Inflammatory Factors
• Impaired Fasting Glucose
• Sub-Clinical Atherosclerosis

Homocysteine

- Hyperhomocysteinemia was first associated to CVD risk as it relates to the rare autosomal recessive disorder, homocystinuria.
- Homocystinuria is associated with markedly elevated homocysteine levels and high risk of CVD if untreated.
- Hyperhomocysteinemia can also be as a result of deficiencies of vitamin B6, folic acid or vitamin B12.
- Homocysteinemia appears to be associated with endothelial dysfunction and increased thrombosis.
- Observational studies have shown that even moderate elevations in Homocysteine even within the normal range are also associated with a higher risk of CVD.

Effects of Lowering Homocysteine Levels with B Vitamins on CVD:
Meta-Analysis of 8 Randomized Trials

Despite a 25% Decrease in Homocysteine, B Vitamins Do Not Appear to Reduce CVD, Cancer or Mortality
Emerging Risk Factors
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Pro-Thrombotic Factors

- Platelet aggregation and acute thrombosis are critical processes in the pathophysiology associated with acute CVD events such as acute coronary syndromes.
- Platelet activation has also been shown to play an important role in driving atherosclerosis progression as a mediator of endothelial function and inflammation.
- There is strong evidence supporting the benefits of antiplatelet agents such as aspirin in the primary and secondary therapy of CVD.

Effect of Aspirin on Serious CVD Events in High Risk Primary Prevention Trials
Aspirin and CVD Prevention

- Secondary Prevention - ↓ CVD
- Men - ↓ CHD
- Women - ↓ ischemic CVA
- Diabetes – borderline benefit

Fibrinogen Level and the Risk of CVD

Biomarkers of Thrombosis

- Fibrinogen
  - major coagulation protein that plays a key role in blood viscosity and platelet aggregation
  - a meta-analysis of prospective observational studies a moderately strong association has been found between fibrinogen levels and the risk of CVD.
  - because of analytical/assay concerns and uncertainty in treatment strategies, the measurement of fibrinogen in clinical practice is not currently recommended.

- Other Markers of Thrombosis:
  - Tissue plasminogen activator (t-PA) antigen, Total plasminogen inhibitor-1 (tPAI-1), D-dimer, von Willebrand factor
  - Associated with increased CVD risk, but more studies are needed to assess their clinical applicability.
  - There are no known related therapeutic interventions that are available or proven successful.
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hsCRP and Risk of Future CVD in Apparently Healthy Men: Physicians Heart Study

LDL-C and hsCRP in the Prediction of First Ever CVD Events Among Women

Ridker PM et al. NEJM. 347:1557, 2002

Meta-Analysis of 54 Prospective Cohort Studies: hsCRP and Risk of CVD Events


Secondary Prevention: LDL-C and hsCRP after Treatment with Statin (PROVE-IT)

Ridker PM et al. NEJM. 352:20, 2005
Clinical Relevance of Achieved LDL-C and hsCRP after Treatment with Statin (PROVE-IT)

Based on PROVE-IT, in Primary Prevention: Whom Should We Treat?

JUPITER: Primary Endpoint (MI, CVA, UA/Revascularization, CV Death)
Pro-Inflammatory Factors

- Inflammation is a key process in the development of atherosclerosis and acute thrombosis.
- There is evidence that individuals with elevated levels of inflammatory biomarkers such as hsCRP are at higher CVD risk even when other risk factors are acceptable.
- There is evidence that individuals identified at increased CVD risk due to inflammation (elevated hsCRP) benefit from a therapy they otherwise would not have received.
- There is little to no evidence, however, that lowering hsCRP or other markers of inflammation prevents CVD events.

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Impact of Impaired Fasting Glucose on CVD – Meta-Analysis

Ford et al, J Am Coll Cardiol 51:1310, 2010
Impaired Glucose Metabolism

• IFG, IGT and elevated A1c are independently associated with higher CVD risk
• Is this, though, just on a continuum with Type 2 Diabetes?
• Consider using prediabetes as a reason to be more aggressive in an intermediate risk individual
• Prediabetes should be also treated to prevent progression to Type 2 Diabetes with lifestyle modification and weight loss being the primary modality of treatment
• There is no evidence, however, that treating prediabetes, per se, prevents CVD events.

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Imaging of Coronary Subclinical Atherosclerosis

<table>
<thead>
<tr>
<th>Non invasive Methods</th>
<th>Invasive Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG</td>
<td>CORONARY ANGIOGRAPHY</td>
</tr>
<tr>
<td>ECHOCARDIOGRAPHY</td>
<td>OCT</td>
</tr>
<tr>
<td>PET</td>
<td>CT</td>
</tr>
</tbody>
</table>

Modified according to Erbel et al /HERZ 32:351, 2007
Carotid Intima-Media Thickness (CIMT)

- Less expensive than CT and no radiation
- Poor standardization with significant variability and measurement issues
- CIMT is associated with CHD but does not add much to traditional risk factors
- CIMT associated with a only a 0.8 to 3.6% “improvement” in classification of risk

Ruitjter et al. JAMA 308:796, 2012

Electron Beam CT
Severe Coronary Calcification

Cumulative Survival

All Cause Mortality and Coronary Artery Calcium Scores (CCS)

Predictive Value of Coronary Calcifications for Future Cardiac Events in Asymptomatic Individuals

Coronary Artery Calcium Score and Incident CHD Events

Risk Prediction Value of CAC Combined with Framingham Score in Asymptomatic Individuals
Coronary Artery Calcium Score and Incident CHD Events

Church, et al.
Atherosclerosis 190:224, 2006

Coronary Artery Calcium and Calcium Density and Risk of CHD

Criqui, et al.
JAMA 311:271, 2014

Subclinical Atherosclerosis: If and How to Use

- CIMT or other measures not currently recommended
- Coronary Artery Calcium Score appears to have added value to risk assessment
- Consider use as a marker of risk in those at intermediate risk for which decisions regarding statin therapy may be altered
- Current guidelines recommend to consider a Coronary Calcium Score ≥ 300 Agatston units or ≥ 75th percentile for age, sex, ethnicity as a marker of increased risk.
Emerging Risk Factors
2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk

• Final list of risk markers evaluated:
  – hs-CRP
  – Apolipoprotein B
  – Creatinine or eGFR
  – Microalbuminuria
  – Subclinical CVD
    • CAC
    • CIMT
  – Family history of premature CVD
  – Cardiorespiratory fitness

Goff et al. Circulation Nov 12, 2013

2013 ACC/AHA Guidelines on the Treatment of Cholesterol to Reduce ASCVD Risk

• In those whose 10-year risk is <7.5% (5-7.5%) or when the decision is unclear, other factors may be used to enhance the treatment decision making:
  – Family History of Premature ASCVD
  – LDL-C > 160 mg/dl
  – hsCRP ≥ 2 mg/dl
  – Coronary Calcium Score ≥ 300 Agatston units or ≥ 75th percentile for age, sex, ethnicity
  – Ankle-Brachial Index < 0.9
  – Elevated “lifetime risk” of ASCVD

Stone et al. Circulation 2013

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Stone et al. Circulation 2013
Is a Basic Fasting Lipid Panel Enough?

- Apo B: marker of particle number; most useful in those with ↑TG
- Lp(a): independent marker of risk. Useful in those with unexplained risk?
- Homocysteine: no added value
- Pro-Thrombotic Factors: no clear marker recommended; use aspirin as indicated
- Pro-Inflammatory Factors: hsCRP helps further stratify risk in intermediate risk individuals
- Impaired Glucose Metabolism: unclear if added value beyond screening for diabetes
- Sub-Clinical Atherosclerosis: Coronary Calcium Score helps further stratify risk in intermediate risk individuals

If it potentially changes your management then consider further risk assessments? Most useful in “moderate risk” patients

<table>
<thead>
<tr>
<th>Emerging Risk Factor</th>
<th>European</th>
<th>Canadian</th>
<th>ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo B</td>
<td>Screening not recommended</td>
<td>Screening not recommended</td>
<td>Screening not recommended</td>
</tr>
<tr>
<td>Lipoprotein (a)</td>
<td>Screening not recommended</td>
<td>Screening not recommended</td>
<td>Screening not recommended</td>
</tr>
<tr>
<td>Homocysteine</td>
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</table>

- Consider screening with LDL for intermediate risk patients and consider statin therapy for patients with LDL ≥3.5 mg/dL and a family history of CVD.