Evidence-Based Guidelines for Cardiovascular Disease Risk Assessment

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• Consultant, Re-Engineering Healthcare, AVIIR and Amarin

Outline
• Review the role and limitations of global risk assessment
• Review the evidence and recommendations for biomarkers in CVD risk assessment
• Review the evidence and recommendations for subclinical disease evaluation / imaging in CVD risk assessment
• Discuss features that will be considered in the new NHLBI risk assessment guidelines to be released in 2013

Concept of cardiovascular “risk factors”

Factors of Risk in the Development of Coronary Heart Disease Six-Year Follow-up Experience
The Framingham Study
William R. Favao, M.D., Norman R. Horvath, M.D., Ellis, Arnold Hersh, M.D., James Storniolo, M.D., and Joseph Henry, III, M.D.
Boston, Massachusetts

Age, sex, hypertension, hyperlipidemia, smoking, diabetes, (family history), (obesity)

Kannel et al., Ann Intern Med 1981
Estimated 10-Year CHD Risk in 55-Year-Old Adults According to Levels of Various Risk Factors

**Framingham Heart Study**

<table>
<thead>
<tr>
<th>Blood Pressure (mm Hg)</th>
<th>Total Cholesterol (mg/dL)</th>
<th>HDL Cholesterol (mg/dL)</th>
<th>Diabetes</th>
<th>Cigarettes</th>
<th>Framingham Total CVD (2008) 10-year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>120/80</td>
<td>200</td>
<td>50</td>
<td>No</td>
<td>No</td>
<td>3%</td>
</tr>
<tr>
<td>140/90</td>
<td>240</td>
<td>50</td>
<td>No</td>
<td>Yes</td>
<td>10%</td>
</tr>
<tr>
<td>140/90</td>
<td>240</td>
<td>40</td>
<td>No</td>
<td>No</td>
<td>10%</td>
</tr>
<tr>
<td>140/90</td>
<td>240</td>
<td>40</td>
<td>No</td>
<td>Yes</td>
<td>10%</td>
</tr>
</tbody>
</table>


**ATP III Assessment of CHD Risk**

For persons *without* known CHD, other forms of atherosclerotic disease, or diabetes:

- Count the number of risk factors:
  - Cigarette smoking
  - Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
  - Low HDL cholesterol (<40 mg/dL)
  - Family history of premature CHD
    - CHD in male first degree relative <55 years
    - CHD in female first degree relative <65 years
  - Age (men ≥45 years; women ≥55 years)
- Use Framingham scoring for persons with ≥2 risk factors* to determine the absolute 10-year CHD risk. (downloadable risk algorithms at www.nhlbi.nih.gov)

**CASE STUDY**

- 56 yo female without CVD,
- No medications
- Former smoker (quit 4 years ago)
- No family history of CHD
- Physically inactive
- BMI 31, waist 36 inches
- BP 138/76, FBS 109 mg/dl, TC 210 mg/dl, HDL 42 mg/dl, TG 201 mg/dl, LDL 128 mg/dl, hs-CRP 2.2 mg/L

Is this patient's risk LOW, INTERMEDIATE, or HIGH?

**Framingham Risk Score:**

- Age 56=8
- TC 210=4
- Smoker=0
- HDL=42
- SBP=138

Total 15: 3% 10-year CHD Risk

- Framingham Total CVD (2008) 10-year Risk=10%
- Reynolds 10-year Risk (incorporates CRP)=4%
- European SCORE (fatal CVD) = 1-2%
- Lifetime Risk for CVD = >=39%
Large Number of CV Events in Individuals not at High Risk

Proportion in each risk category NHANES 1999-2002

Estimated Number of CV Events

- 11% Low-risk
- 76% Inter-risk
- 13% High-risk

10-year CHD Events ( Millions)

Ajani UA et al. JACC 2006;48:1177

The Detection Gap in CHD

“Despite many available risk assessment approaches, a substantial gap remains in the detection of asymptomatic individuals who ultimately develop CHD”

“The Framingham and European risk scores… emphasize the classic CHD risk factors…. is only moderately accurate for the prediction of short- and long-term risk of manifesting a major coronary artery event…”

Pasternak and Abrams et al. 34th Bethesda conf. JACC 2003; 41: 1855-1917

Criteria required for a good screening test

• Provides an accurate determination of the likelihood that an asymptomatic person has the condition (accuracy)
• Reproducible results (reliability)
• Detect individuals where early intervention is likely to have a beneficial impact
• Should provide incremental value to risk predicted by office-based risk assessment

Redberg and Vogel et al., 34th Bethesda Conf. JACC 2003; 41: 1855-1917

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


Redberg and Vogel et al., 34th Bethesda Conf. JACC 2003; 41: 1855-1917

JACC Nov. 15, 2010
C-Reactive Protein Recommendations

- **Class Ia**: men >=50 years or women >=60 years of age with LDL-C<130 mg/dl, not on lipid-lowering therapy, HRT, or immunosuppressant therapy, without CHD, DM, CKD, or other contraindications, can be useful in the selection of patients for statin rx (Level of Evidence B)

- **Class IIb**: asymptomatic intermediate risk men <=50 years or women <=60 years of age measurement may be reasonable for cardiovascular risk assessment

- **Class III**: asymptomatic high risk adults or lower risk men<50 or women<60 years of age, CRP not recommended

- May help guide intensity of therapy in those at intermediate risk or with CHD and to a lesser extent in those with a family history of premature CHD


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![ CFRP as a Risk Factor For Future CVD: Primary Prevention Cohorts](image1)

![ CFRP as a Risk Factor For Future CVD: Primary Prevention Cohorts](image2)

![ CFRP as a Risk Factor For Future CVD: Primary Prevention Cohorts](image3)
**Lp-PLA₂ and vascular disease: metaanalysis of 32 studies (n=79,036)**

<table>
<thead>
<tr>
<th>Coronary heart disease: 32 studies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary events</td>
<td>22,102</td>
</tr>
<tr>
<td>Stable disease</td>
<td>33,012</td>
</tr>
<tr>
<td>Overall</td>
<td>55,114</td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>0.86 (0.79-0.95)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1.03 (0.97-1.08)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.06 (1.00-1.12)</td>
</tr>
</tbody>
</table>

**LpPla2 Recommendations**

- Class IIb – Might be reasonable for cardiovascular risk assessment in intermediate risk asymptomatic adults (Level of Evidence B)
- Selected higher risk pts (CHD, family hx premature CHD)
- Not yet recommended for on-treatment management decisions since no randomized trials yet showing efficacy of intervention


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**B-Type Natriuretic Peptides and CVD Risk (Circulation 2009; 120: 2177-2187)**

- Meta-analysis of 40 long-term prospective studies involving 87,474 patients.
- Highest vs. lowest tertile, adjusted RR=2.82 (2.40-3.33).
- RRs similar for BNP (2.89) or NT-pro BNP (2.82) and in general populations (2.68), increased risk factors (3.35), and stable CVD (2.60).
- Modest improvements in risk discrimination (increase in C-statistic of 0.01 to 0.1).

**Natriuretic Peptides Recommendation**

- Class III: No benefit
  - Measurement of natriuretic peptides is not recommended for CHD risk assessment in asymptomatic adults (Level of Evidence B)

ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, Circulation 2010
A Multimarker Approach Should Focus on Multiple Mechanisms / Pathologies

Family History / Genomic Screening
- Evaluation of Family History (Class 1b)
  - Family family history of atherothrombotic CVD should be obtained in all asymptomatic adults (esp. premature hx occurring <55 male first deg. rel. or <65 female first degree rel.)
- Genomic Screening (Class IIIb)
  - Genomic screening not recommended due to lack of outcome studies showing benefit of genotype testing and limited added clinical utility

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

Other Measures / Circulating Markers
- HbA1c (Class IIb – may be reasonable for assessment of risk in those without a hx of DM)
- Urinary Albumin Excretion
  - Class Ila – may be reasonable for assessment of CV risk in those with HTN or DM
  - Class IIb – may be reasonable for assessment of CVD risk in those without HTN or DM

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

Additional Utility of Multiple Biomarkers for Prediction of Death: FHS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Adj HR Death per 1 SD</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>1.40</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>CRP</td>
<td>1.39</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Urine Alb/Cr</td>
<td>1.22</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>1.20</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Renin</td>
<td>1.17</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>SCORE</td>
<td>4.08*</td>
<td>0.80</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* HR for highest quintile v. lowest 2 quintiles

Wang TJ et al. NEJM 2006;355:2631

ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, Circulation 2010
Carotid B-Mode Ultrasonography

- Measurement of intimal medial thickness
- Non-invasive, inexpensive, no radiation
- Well-established as an indicator of cardiovascular risk from epidemiologic studies
- Published clinical trials on utility of carotid IMT as measure of progression of atherosclerosis and effects of therapy
- Accuracy of assessments depends on experience of those interpreting scans
- ACCF/AHA 2010 Guideline: CIMT measurement may be reasonable for CV risk assessment in asymptomatic adults at intermediate risk (Class IIa-B)

Cardiovascular Health Study: Combined intimal-medial thickness predicts total MI and stroke

Cardiovascular Health Study (CHS) (aged 65+): MI or stroke rate 25% over 7 years in those at highest quintile of combined IMT (O’Leary et al. 1999)
CIMT w/w/o Plaque and CHD Incidence: ARIC Study (Nambi et al., JACC 2010)

Ankle-brachial blood pressure (ABI)
- Simple noninvasive test to confirm lower extremity peripheral arterial disease (PAD)
- Uses Doppler probe to measure SBP in brachial, posterior tibial, and dorsalis pedis arteries
- ABI < 0.9 in either leg is diagnostic of PAD
- ACCF/AHA 2010 Guideline: Measurement reasonable for CV risk assessment in asymptomatic adults at intermediate risk (IIa-B)
- Test most likely to be positive in those over 50 who have other risk factors
  - The higher of the SBP measures taken in each arm is the denominator for the ABI calculation for each leg.
  - The higher of the two pressures in each ankle (from posterior tibial and dorsalis pedis arteries) forms the numerator for the left and right ABI, respectively.

Ankle-Brachial Index as a Predictor of Cardiovascular Mortality in the CHS Study

Ankle-brachial blood pressure (ABI) – Simple noninvasive test to confirm lower extremity peripheral arterial disease (PAD) – Uses Doppler probe to measure SBP in brachial, posterior tibial, and dorsalis pedis arteries – ABI <0.9 in either leg is diagnostic of PAD – ACCF/AHA 2010 Guideline: Measurement reasonable for CV risk assessment in asymptomatic adults at intermediate risk (IIa-B) – Test most likely to be positive in those over 50 who have other risk factors

- The higher of the SBP measures taken in each arm is the denominator for the ABI calculation for each leg.
- The higher of the two pressures in each ankle (from posterior tibial and dorsalis pedis arteries) forms the numerator for the left and right ABI, respectively.

23% of 13,145 eligible subjects were reclassified by adding CIMT and plaque information over traditional risk factors

Table 3

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>% Reclassified</th>
<th>% Increase</th>
<th>% Decrease</th>
<th>% No Change</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>3.8</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Medium</td>
<td>5.2</td>
<td>2%</td>
<td>0%</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>High</td>
<td>12.9</td>
<td>10%</td>
<td>0%</td>
<td>87%</td>
<td>100%</td>
</tr>
<tr>
<td>All</td>
<td>5.4</td>
<td>3%</td>
<td>0%</td>
<td>95%</td>
<td>100%</td>
</tr>
</tbody>
</table>

23% of 13,145 eligible subjects were reclassified by adding CIMT and plaque information over traditional risk factors.
**ABI and Total Mortality**

(ABI Collaboration, JAMA 2008)

Figure 3. Hazard Ratios for Total Mortality in Men and Women by Ankle Brachial Index at Baseline for All Studies Combined in the ABI Collaboration.

- Hazard ratios are not adjusted for age or cardiovascular risk factors.

**Reclassification of Risk Category from ABI** (ABI Collaboration, JAMA 2008)

- 19% of men and 38% of women would be reclassified in their risk category from addition of ABI.

**Coronary Calcium and Atherosclerosis:**

**Pathology Evidence**

- Coronary calcium invariably indicates the presence of atherosclerosis, but atherosclerotic lesions do not always contain calcium (1-3).
- Calcium deposition may occur early in life, as early as the second decade, and in lesions that are not advanced (4-5).
- Correlates with plaque burden; highly sensitive for angiographic disease


**Cumulative Incidence of Any Coronary Event:** MESA Study

(Detrano et al., NEJM 2008)
Risk Factor-Adjusted Hazard Ratios by Coronary Calcium Score: MESA Study (Detrano et al., NEJM 2008)

<table>
<thead>
<tr>
<th>Coronary-Artery Calcium Score</th>
<th>Major Coronary Event</th>
<th>Any Coronary Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inc. (No.) at Risk</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>1/1400</td>
<td>1.00</td>
</tr>
<tr>
<td>1-250</td>
<td>22,712</td>
<td>3.80 (1.72-8.78)</td>
</tr>
<tr>
<td>251-499</td>
<td>25,712</td>
<td>7.88 (3.46-17.8)</td>
</tr>
<tr>
<td>≥500</td>
<td>32,803</td>
<td>6.84 (2.50-19.0)</td>
</tr>
<tr>
<td>log10(CAC+1)</td>
<td>1.20 (1.13-1.30)</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

* CAC denotes coronary calcium score, and CI confidence interval. 
† Risk reclassification due to CAC reflects a doubling of the coronary artery calcium score.

Net Reclassification of CHD Risk by Coronary Calcium: MESA Study (Polonsky et al., JAMA 2010)

The addition of CAC to models with age, gender, ethnicity and risk factors alone resulted in net reclassification of 0.25 (p<0.001); 23% of those with events were reclassified as high risk and 13% without events were reclassified as low risk.

Area Under Curve for Risk Factors Alone and Risk Factors Plus CAC by Ethnic Group: MESA Study (Detrano et al., NEJM 2008)

<table>
<thead>
<tr>
<th>Racial or Ethnic Group</th>
<th>Major Coronary Event</th>
<th>Any Coronary Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC for Risk Factors Alone</td>
<td>AUC for Risk Factors Plus CAC</td>
</tr>
<tr>
<td>White</td>
<td>0.76</td>
<td>0.79</td>
</tr>
<tr>
<td>Chinese</td>
<td>0.83</td>
<td>0.86</td>
</tr>
<tr>
<td>Black</td>
<td>0.79</td>
<td>0.87</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.84</td>
<td>0.86</td>
</tr>
<tr>
<td>Total</td>
<td>0.78</td>
<td>0.83</td>
</tr>
</tbody>
</table>

* Separate models are fit for each racial or ethnic group. AUC denotes area under the receiver operating characteristic curve. P values are for the comparison between AUC without and AUC with the coronary artery calcium score.
† Major coronary events were myocardial infarction and death from coronary heart disease.

Annual CHD Event Rates (in %) by Calcium Score Events by CAC Categories in Subjects with DM, MetS, or Neither Disease (Malik and Wong et al., Diabetes Care 2011)

ACC/AHA 2010 Guideline: CAC Scoring for CV risk assessment in asymptomatic adults aged 40 and over with diabetes (Class IIA-B)
Progression of Coronary Calcium and CHD Events: Multiethnic Study of Atherosclerosis (Budoff and Wong et al., JACC 2013, in press)

In 703 men and women aged 28-84 who received scanning for coronary calcium by EBCT, calcium score remained independently associated with:

- new aspirin usage
- new cholesterol medication
- consulting with a physician
- losing weight
- decreasing dietary fat

…but also increased worry

…potentially important risk-reducing behaviors may be reinforced by the knowledge of a positive coronary artery scan, independent of preexisting coronary risk factor status.

Impact of Coronary Artery Calcium Scanning on Coronary Risk Factors and Downstream Testing (Rozanski A et al. JACC 2011)

- We compared the clinical impact of conventional risk factor modification to that associated with the addition of coronary artery calcium (CAC) scanning.
- 2,137 volunteers underwent CAC scanning or did not undergo CAC scanning before risk factor counseling.
- Primary end point was 4-year change in coronary artery disease risk factors and Framingham Risk Score; also examined medical resource utilization
Eisner Study Results

- Compared with the no-scan group, the scan group showed improvement in systolic blood pressure ($p = 0.02$) and LDL-C ($p = 0.04$), and waist circum in those with increased abdominal girth ($p = 0.01$).
- Increase in Framingham Risk Score (FRS) in the no-scan group, but no change in the scan group ($0.7 \pm 5.1$ vs. $0.002 \pm 4.9$, $p = 0.003$).
- Within the scan group, increasing baseline CAC score was associated with an improvement in risk factors and FRS ($p<0.01$).
- Downstream medical testing and costs in the scan group were similar to the no-scan group.

Is CAC related to inducible myocardial ischemia?
Frequency of Abnormal SPECT According to CCS

<table>
<thead>
<tr>
<th>SS ≥ 4</th>
<th>SS ≥ 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.5%</td>
<td>20%</td>
</tr>
<tr>
<td>25%</td>
<td>20%</td>
</tr>
</tbody>
</table>


Prevalence of Multi-Site Atherosclerosis by Gender and Age: MESA Study (CAC, AAC, ABI, and/or CIMT)

Wong ND et al. Atherosclerosis 2011

Prevalence of Inducible Ischemia Associated with Presence of Metabolic Abnormality and Coronary Calcium Score
(Wong et al., Diabetes Care 2005; 28: 1445-50)

P=0.0001 for trend across CCS groups for both metabolic abnormality present and absent; similar relation for those with metabolic syndrome excluding diabetes

ACCF/AHA 2010 Guideline: Stress MPI may be considered for advanced CV risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of 400 or greater (Class IIb – Level of Evidence C)
Intermediate Risk MESA Subjects (n=1330)

C-statistics:
- FRS alone 0.623
- FRS+CAC 0.784 (p<0.001)
- FRS+CIMT 0.652 (p=0.01)
- FRS+FMD 0.639 (p=0.06)
- FRS+CRP 0.640 (p=0.03)
- FRS+FamHx 0.675 (p=0.001)
- FRS+ABI 0.650 (p=0.01)

Yeboah J et al, JAMA 2012

ACCF / AHA Nov 2010 Guidelines for Risk Assessment in Asymptomatic Persons
- Resting ECG in those with HTN/DM (IIa – C)
- Transthoracic Echo in those with HTN (IIb – B)
- Stress Echocardiography (III – C)
- Myocardial Perfusion Imaging (IIb-C for those with DM or strong family hx, or CAC>=400)
- Carotid IMT for intermediate risk (IIa – B)
- Brachial/Peripheral FMD (III – B)
- Arterial Stiffness (III – C)
- Ankle Brachial Index for intermediate risk (IIa – B)
- Coronary Calcium Screening (IIa – B for 10-20% 10-year risk or DM, IIb – B for 6-10% 10-year risk, III – B for <6% risk)
- Coronary CT Angiography, MRI Plaque Imaging (III – C)

Risk Assessment Work Group (RAWG) Charge
- To examine the scientific evidence regarding risk assessment for CVD and to develop an approach for risk assessment that can serve as a platform for use by the integrated CVD guidelines panel and for use or adaptation by the risk factor update panels (cholesterol, blood pressure, obesity) in their guidelines and algorithms.

Critical Question 1
- Are long-term (or lifetime) risk models effective in assessing variation in risk among adults at low and/or intermediate short term risk?
Rationale for question 1

- Goal for the RAWG is to identify best prediction model(s) to assess risk
- Risk assessment may be helpful for informing decisions about initiating or intensifying lifestyle counseling and drug therapy
- Previous guidelines (ATP III) used Framingham 10-yr CHD risk score
- Critical question looked at CVD risk rather than CHD risk
- Many young men and women have high lifetime risk but low 10-year risk and may get false reassurance from 10-year risk

Critical question 2

What is the evidence regarding reclassification or contribution to risk assessment when
- family history,
- hs-CRP,
- apo B,
- microalbuminuria,
- chronic kidney disease (or glomerular filtration rate [GFR]),
- cardiorespiratory fitness,
- coronary artery calcium (CAC),
- carotid intima-media thickness (CIMT), or
- ankle-brachial index (ABI)
are considered in addition to the variables that are in the traditional risk scores?

Rationale for question 2

- Current risk models have sub-optimal discrimination with low sensitivity and specificity.
- New risk factors might improve discrimination, but impose cost and complexity, and, in some instances, potential harm.
- Two approaches taken
  - Modeling: data combined from multiple databases to enhance generalizability, assess discrimination, calibration, and reclassification.
    - Framingham Heart Study and Offspring
    - Atherosclerosis Risk in Communities (ARIC)
    - Cardiovascular Health Study (CHS)
    - Coronary Artery Risk Development in Young Adults (CARDIA)
  - Review of published systematic reviews on variables of interest

Next steps

- Draft evidence statements and recommendations based on evidence from systematic reviews and risk prediction modeling
- Voting process incorporates method for dealing with relationships with industry or other interests
- Compile evidence report and recommendations for public review
Summary

- Screening tests for subclinical atherosclerosis should provide incremental risk prediction for CHD events over global risk assessment.
- Guidelines suggest intermediate risk subjects may be suitable for such screening that may help identify those needing more aggressive risk factor intervention.
- However, it is not known whether screening for subclinical atherosclerosis will ultimately lead to long-term clinical benefit and save lives.
- New guidelines due in 2013 will give us further guidance regarding evidence-based risk assessment.

Thank you!

www.heart.uci.edu

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