Colorado School of Public Health

ACC/AHA CVD Prevention Guidelines
Understanding Risk Assessment & Reduction

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Colorado School of Public Health
Co-Chair ACC/AHA CVD Risk Assessment Working Group

No Relationships with Industry
Guidelines in Context

- NHLBI convened panels in 2008
  - 3 GL panels and 3 WGs
  - Desire for fully evidence-based updates in IOM style
  - 5 layers of peer review; dozens of reviewers
  - GL completed 2012
- June, 2013 - NHLBI “out of GL business”
- August, 2013 - AHA/ACC move forward
Guidelines in Context

- November, 2013 – 4 executive summaries and full reports published online
  - Lifestyle Management
  - Management of Overweight and Obesity
  - Treatment of Blood Cholesterol to Reduce ASCVD Risk
  - Assessment of Cardiovascular Risk
  - (BP guidance published)
- (December, 2013 – HTN guidelines)
## ATP-III Update 2004

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Threshold to Initiate Lifestyle</th>
<th>Threshold to Consider Drug Therapy*</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL (Optional: &lt;100)</td>
<td>&lt;100 mg/dL (Optional &lt;70)</td>
</tr>
<tr>
<td>CHD, ASCVD, DM or 10-y risk &gt;20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod High Risk</td>
<td>≥130</td>
<td>≥130</td>
<td>&lt;130</td>
</tr>
<tr>
<td>2+ RFs and 10-y risk 10%-20%</td>
<td></td>
<td></td>
<td>(Optional: 100-129)</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>≥130</td>
<td>≥160</td>
<td>&lt;130</td>
</tr>
<tr>
<td>2+ RFs and 10-y risk &lt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Risk</td>
<td>≥160</td>
<td>≥190</td>
<td>&lt;160</td>
</tr>
<tr>
<td>0-1 RFs</td>
<td></td>
<td></td>
<td>(Optional: 160-189)</td>
</tr>
</tbody>
</table>
CTT 2005 Statin vs placebo

Everyone has similar RRR benefit!

<table>
<thead>
<tr>
<th>Groups</th>
<th>Events (%) Treatment (45,054)</th>
<th>Events (%) Control (45,002)</th>
<th>RR (O)</th>
<th>Heterogeneity/ trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous disease:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-MI</td>
<td>3515 (21.2%)</td>
<td>3860 (26.9%)</td>
<td>0.79 (0.75-0.83)</td>
<td>χ²=0.5; p=0.8</td>
</tr>
<tr>
<td>Other CHD</td>
<td>157 (19.3%)</td>
<td>1581 (24.2%)</td>
<td>0.80 (0.73-0.87)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2046 (8.5%)</td>
<td>2553 (10.6%)</td>
<td>0.78 (0.72-0.84)</td>
<td></td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>3454 (12.5%)</td>
<td>4448 (16.2%)</td>
<td>0.78 (0.73-0.82)</td>
<td>χ²=2.3; p=0.1</td>
</tr>
<tr>
<td>&gt;65</td>
<td>2900 (16.6%)</td>
<td>3546 (20.3%)</td>
<td>0.81 (0.77-0.86)</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5097 (14.9%)</td>
<td>6504 (19.0%)</td>
<td>0.78 (0.75-0.81)</td>
<td>χ²=3.1; p=0.08</td>
</tr>
<tr>
<td>Female</td>
<td>1257 (11.7%)</td>
<td>1490 (13.8%)</td>
<td>0.83 (0.76-0.91)</td>
<td></td>
</tr>
<tr>
<td>Treated Hypertension:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3525 (15.8%)</td>
<td>4783 (19.2%)</td>
<td>0.81 (0.77-0.85)</td>
<td>χ²=2.6; p=0.1</td>
</tr>
<tr>
<td>No</td>
<td>2479 (12.0%)</td>
<td>3711 (15.9%)</td>
<td>0.72 (0.65-0.80)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1485 (15.6%)</td>
<td>1282 (17.2%)</td>
<td>0.79 (0.72-0.86)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4889 (12.7%)</td>
<td>6212 (17.4%)</td>
<td>0.79 (0.76-0.82)</td>
<td></td>
</tr>
</tbody>
</table>

| Total cholesterol (mmol/L):  |                               |                            |            |                           |
|                               |                               |                            |            |                           |
| Previous disease:             |                               |                            |            |                           |
| Post-MI                       | 3051 (21.2%)                  | 3860 (26.9%)               | 0.79 (0.75-0.83) | χ²=0.5; p=0.8           |
| Other CHD                     | 1257 (19.3%)                  | 1581 (24.2%)               | 0.80 (0.73-0.87) |                           |
| None                          | 2046 (8.5%)                   | 2553 (10.6%)               | 0.78 (0.72-0.84) |                           |
| Age (years):                  |                               |                            |            |                           |
| ≤65                           | 3454 (12.5%)                  | 4448 (16.2%)               | 0.78 (0.73-0.82) | χ²=2.3; p=0.1           |
| >65                           | 2900 (16.6%)                  | 3546 (20.3%)               | 0.81 (0.77-0.86) |                           |
| Sex:                          |                               |                            |            |                           |
| Male                          | 5097 (14.9%)                  | 6504 (19.0%)               | 0.78 (0.75-0.81) | χ²=3.1; p=0.08          |
| Female                        | 1257 (11.7%)                  | 1490 (13.8%)               | 0.83 (0.76-0.91) |                           |
## CTT 2010 Statin/More vs Control/Less

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
</tr>
<tr>
<td>More vs less statin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>704 (4.6%)</td>
<td>795 (5.2%)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>1189 (4.2%)</td>
<td>1317 (4.8%)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>1065 (4.5%)</td>
<td>1203 (5.0%)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>517 (4.5%)</td>
<td>633 (5.8%)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>303 (5.7%)</td>
<td>398 (7.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>3837 (4.5%)</td>
<td>4416 (5.3%)</td>
</tr>
<tr>
<td>Statin vs control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>206 (2.9%)</td>
<td>217 (3.2%)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>339 (2.4%)</td>
<td>412 (2.9%)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>801 (2.5%)</td>
<td>1022 (3.2%)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>1490 (2.9%)</td>
<td>1821 (3.6%)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4205 (2.9%)</td>
<td>5338 (3.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>7136 (2.8%)</td>
<td>8934 (3.6%)</td>
</tr>
<tr>
<td>All trials combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>910 (4.1%)</td>
<td>1012 (4.6%)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>1528 (3.6%)</td>
<td>1729 (4.2%)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>1866 (3.3%)</td>
<td>2225 (4.0%)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>2007 (3.2%)</td>
<td>2454 (4.0%)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4508 (3.0%)</td>
<td>5736 (3.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>10973 (3.2%)</td>
<td>13350 (4.0%)</td>
</tr>
</tbody>
</table>
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease
Guideline Scope

• Focus on treatment of blood cholesterol to reduce ASCVD risk in adults
• Emphasize adherence to a heart healthy lifestyle
  ▪ See Lifestyle Management Guideline
• Identify individuals most likely to benefit from cholesterol-lowering therapy
  ▪ 4 statin benefit groups
• Use appropriate intensity to maximize benefit and minimize safety issues
4 Statin Benefit Groups

• Clinical ASCVD
• LDL–C ≥190 mg/dL without secondary cause
• Primary prevention/Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL
• Primary prevention/No Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL, ASCVD risk ≥7.5%*

* Requires risk discussion with clinician before statin prescription. Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator.
Major recommendations for initiating statin therapy - 2

1. Potential for ASCVD risk reduction
2. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L
3. Potential for adverse effects and drug-drug interactions
4. Healthy lifestyle
5. Management of other risk factors
6. Patient preferences

Clinician-Patient Discussion
Prior to initiating statin therapy, discuss:

Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence (See Fig 5)
Individuals Not in a Statin Benefit Group

- In those not clearly in a statin benefit group, additional factors may inform treatment decision-making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL–C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - Subclinical atherosclerosis
    - CAC score ≥300/75%ile or ABI<0.9

- Discussion of potential for ASCVD risk reduction benefit, potential for adverse effects, drug-drug interactions, and patient preferences
HPS2-THRIVE (N=25,000)

ER niacin/laropiprant-simvastatin vs. simvastatin: No ASCVD event reduction vs placebo-simvastatin

**Table 2. Effects of Niacin–Laropiprant on Selected Serious Adverse Events and Diabetes.***

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Niacin–Laropiprant (N=12,838)</th>
<th>Placebo (N=12,835)</th>
<th>Rate Ratio (95% CI)</th>
<th>Absolute Excess with Niacin–Laropiprant</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>percentage points</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>620 (4.8)</td>
<td>491 (3.8)</td>
<td>1.28 (1.13–1.44)</td>
<td>1.0±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Musculoskeletal event</td>
<td>481 (3.7)</td>
<td>385 (3.0)</td>
<td>1.26 (1.10–1.44)</td>
<td>0.7±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin-related event</td>
<td>86 (0.7)</td>
<td>51 (0.4)</td>
<td>1.67 (1.20–2.34)</td>
<td>0.3±0.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Infection event</td>
<td>1031 (8.0)</td>
<td>853 (6.6)</td>
<td>1.22 (1.12–1.34)</td>
<td>1.4±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding event</td>
<td>326 (2.5)</td>
<td>238 (1.9)</td>
<td>1.38 (1.17–1.62)</td>
<td>0.7±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>percentage points</td>
<td></td>
</tr>
<tr>
<td>New-onset diabetes in participants without diabetes at baseline</td>
<td>494/8704 (5.7)</td>
<td>376/8670 (4.3)</td>
<td>1.32 (1.16–1.51)</td>
<td>1.3±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disturbed diabetes control in participants with diabetes at baseline</td>
<td>460/4134 (11.1)</td>
<td>311/4165 (7.5)</td>
<td>1.55 (1.34–1.78)</td>
<td>3.7±0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
LDL-C and Lipid Changes

Simva 40 vs. Simva 40/Ezetimibe 10
7 years’ F/U (!)

Differences between groups

- LDL: -15 mg/dl
- Total Chol: -17 mg/dl
- Trig: -9 mg/dl
- HDL: +0.5 mg/dl
- hsCRP: -0.5 mg/dl
### Primary Endpoint

Cardiovascular Death, MI, Stroke, documented Unstable Angina requiring rehospitalization, or coronary revascularization (>30 days)

<table>
<thead>
<tr>
<th>Eze/Simva (N=9067)</th>
<th>Simva (N=9077)</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.7%</td>
<td>34.7%</td>
<td>0.94</td>
<td>(0.89, 0.99)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Kaplan-Meier event rates to 7 years  
Median follow-up 57 months  
Total patient years follow-up for primary endpoint = 80,286
Now That HPS2-THRIVE and IMPROVE-IT are Out, Don’t We Have to Change the Guidelines?

• “Clinicians treating high risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant, may consider the addition of non-statin cholesterol lowering therapy…. … In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects, drug-drug interactions and consider patient preferences.”

• Nothing informative on LDL goals
2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease
ASCVD Risk Calculator
Considerations

• RAWG endorsed the paradigm of 10-year risk estimation

• Existing risk scores vary with regard to:
  – Derivation populations
    • Age, sex, race, birth cohort, country/region of origin
  – Inputs
    • Traditional RFs ± family hx, BMI, SES, region, CRP
  – Outcomes
    • CVD death, Total CHD (incl revasc), Total CHD, Hard CHD, Total CVD (revasc), Hard CVD (incl HF)
ASCVD Risk Calculator
Development

• RAWG judged new risk tool was needed
  – Inclusive of African Americans and with expanded endpoint including stroke

• Sought cohorts representative of the US population as a whole
  – Community- or population-based
  – Whites and African Americans (at a minimum)
  – Recent follow up data of at least 10 years
    • Reflect more contemporary risk factor trends and event rates, ideally without significant downstream uptake of statins/revascularization
ASCVD Risk Calculator
Development

• Pooled Cohort Equations
  – Atherosclerosis Risk in Communities (ARIC)
  – Cardiovascular Heath Study (CHS)
  – Coronary Artery Risk Development in Young Adults (CARDIA)
  – Framingham Original and Offspring

• Hard ASCVD
  – CHD death, non-fatal MI, fatal/non-fatal stroke

• Models tested using traditional RFs + newer markers when possible

• Internal and external validation
## ASCVD Risk Calculator

### Model Characteristics

<table>
<thead>
<tr>
<th></th>
<th>White Women</th>
<th>AA Women</th>
<th>White Men</th>
<th>AA Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>11,240</td>
<td>2641</td>
<td>9098</td>
<td>1647</td>
</tr>
<tr>
<td><strong>Age Range</strong></td>
<td>40-79</td>
<td>40-79</td>
<td>40-79</td>
<td>40-79</td>
</tr>
<tr>
<td><strong>C statistic</strong></td>
<td>0.81</td>
<td>0.82</td>
<td>0.75</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Calibration X²</strong></td>
<td>6.43</td>
<td>7.25</td>
<td>4.86</td>
<td>6.71</td>
</tr>
</tbody>
</table>

**Helping Cardiovascular Professionals Learn. Advance. Heal.**
http://thespudd.com/i-just-know-replaces-systematic-reviews-at-top-of-evidence-pyramid/

"I just know"

Figure 1. Levels of evidence
ASCVD Risk Estimator

Search “ASCVD risk estimator”

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>HDL - Cholesterol (mg/dL)</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment for Hypertension</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>African American</td>
</tr>
<tr>
<td>Smoker</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
ASCVD Risk Calculator
55 yo AA and White Women

- African American Women: 7.7%
- White Women: 3.6%
The race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a first hard ASCVD event should be used in non-Hispanic African Americans and non-Hispanic Whites, 40 to 79 years of age.

Use of the sex-specific Pooled Cohort Equations for non-Hispanic Whites may be considered when estimating risk in patients from populations other than African Americans and non-Hispanic Whites.
External Validation: REGARDS*

*5-year follow up

Muntner et al, JAMA 2014
External Validation: REGARDS*

Medicare-linked sample

$X^2 = 5.4, \ p = 0.71$

$C = 0.67$

5-year follow up
Muntner et al, JAMA 2014
Rotterdam

A. ACC/AHA guideline (hard ASCVD)

Men

<table>
<thead>
<tr>
<th>10-y Predicted Risk Category, %</th>
<th>&lt;5</th>
<th>5 to &lt;7.5</th>
<th>7.5 to &lt;10</th>
<th>≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>6</td>
<td>63</td>
<td>109</td>
<td>1335</td>
</tr>
<tr>
<td>No. with hard ASCVD</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>10-y Predicted Risk Category, %</th>
<th>&lt;5</th>
<th>5 to &lt;7.5</th>
<th>7.5 to &lt;10</th>
<th>≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>466</td>
<td>342</td>
<td>269</td>
<td>843</td>
</tr>
<tr>
<td>No. with hard ASCVD</td>
<td>13</td>
<td>12</td>
<td>22</td>
<td>104</td>
</tr>
</tbody>
</table>
Rotterdam

ESC guideline (CVD mortality)

Men

Women

No. of participants

No. with CVD mortality

10-y Predicted Risk Category, %

CVD Mortality, %

Observed risk

Predicted risk

<1

1 to <5

5 to <10

≥10

174

0

1214

17

333

12

95

8

602

5

531

21

233

24

Kavousi, JAMA 2014
EPIC-Norfolk

ACC-AHA risk categories

- Predicted 10-year total CVD by ACC-AHA
- Predicted 10-year fatal CVD by SCORE
- Observed 10-year total CVD
- Observed 10-year fatal CVD

Colorado School of Public Health

Ray, EHJ 2014
Dallas Heart Study

ACC/AHA 2013 Strategy Compared with:

- Prevented ASCVD events
- Excess diabetes cases

Events per 10,000 individuals screened:
- Moderate dose statin
  - Original NCEP/ATPIII LDL-C goals: 3.6
  - Optional NCEP/ATPIII LDL-C goals: 0.5
- High dose statin
  - Original NCEP/ATPIII LDL-C goals: 4.9
  - Optional NCEP/ATPIII LDL-C goals: 1.5
- Moderate dose statin
  - Original NCEP/ATPIII LDL-C goals: 1.6
  - Optional NCEP/ATPIII LDL-C goals: -0.3
- High dose statin
  - Original NCEP/ATPIII LDL-C goals: 2.2
  - Optional NCEP/ATPIII LDL-C goals: -0.8

Paixao, Circ CQO 2014
Table 2. Predicted and Observed Events for Each Risk Score

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Predicted Events, n (%)</th>
<th>Observed Events, n (%)</th>
<th>Signed Absolute Difference</th>
<th>Discordance, %*</th>
<th>C-Statistic</th>
<th>Discrimination Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 4227)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS-CHD†</td>
<td>397.6 (9.41)</td>
<td>263 (6.22)</td>
<td>3.18</td>
<td>51</td>
<td>0.68</td>
<td>0.05</td>
</tr>
<tr>
<td>FRS-CVD‡</td>
<td>561.3 (13.28)</td>
<td>448 (10.60)</td>
<td>2.68</td>
<td>25</td>
<td>0.71</td>
<td>0.09</td>
</tr>
<tr>
<td>ATPIII-FRS-CHD§</td>
<td>288.7 (6.83)</td>
<td>134 (3.17)</td>
<td>3.66</td>
<td>115</td>
<td>0.71</td>
<td>0.06</td>
</tr>
<tr>
<td>RRS‖</td>
<td>314.0 (7.43)</td>
<td>323 (7.64)</td>
<td>-0.21</td>
<td>-3</td>
<td>0.72</td>
<td>0.07</td>
</tr>
<tr>
<td>AHA-ACC-ASCVD¶</td>
<td>387.2 (9.16)</td>
<td>218 (5.16)</td>
<td>4.00</td>
<td>78</td>
<td>0.71</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 5. Predicted and Observed Risk for Each Risk Score Among Never-Treated Participants*

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Predicted Events, n (%)</th>
<th>Observed Events, n (%)</th>
<th>Signed Absolute Difference</th>
<th>Discordance, %†</th>
<th>C-Statistic</th>
<th>Discrimination Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 790)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS-CHD</td>
<td>57.5 (7.28)</td>
<td>12 (1.52)</td>
<td>5.76</td>
<td>379</td>
<td>0.75</td>
<td>0.07</td>
</tr>
<tr>
<td>FRS-CVD</td>
<td>68.1 (8.62)</td>
<td>18 (2.28)</td>
<td>6.34</td>
<td>278</td>
<td>0.77</td>
<td>0.08</td>
</tr>
<tr>
<td>ATPIII-FRS-CHD</td>
<td>36.6 (4.63)</td>
<td>10 (1.27)</td>
<td>3.37</td>
<td>266</td>
<td>0.80</td>
<td>0.07</td>
</tr>
<tr>
<td>AHA-ACC-ASCVD</td>
<td>44.3 (5.60)</td>
<td>14 (1.77)</td>
<td>3.83</td>
<td>216</td>
<td>0.79</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Analysis included Chinese Americans and Hispanics, known to be lower risk & not included in Pooled Cohort Equations (COR IIb LOE C). MESA participants underwent CAC screening, known to influence treatments. Over 80% of MESA participants treated with aspirin, statin, blood pressure lowering medication, or revascularization. Only 6% (n=14) of ASCVD events occurred among non-treated. Perhaps a better cohort for studying residual risk than untreated risk.
Take Home Message

• The Pooled Cohort Equations were designed to help physicians judge whether an untreated patient is at high enough risk to warrant consideration of treatment with a statin, not to predict risk in highly treated groups of study participants.
1. Encourage adherence to healthy lifestyle
2. Statin treatment based on ASCVD risk and net clinical benefit:
   • Clinical ASCVD
   • LDL-C ≥190 mg/dl
   • Diabetes, age 40-75 y
   • Primary prevention ≥7.5% 10-year ASCVD risk age 40-75 y
3. Statins are first-line therapy for ASCVD risk reduction
   • Use recommended or maximally tolerated statin intensity
   • May consider nonstatins in selected individuals; nonstatins proven to reduce ASCVD events safely in RCTs preferred
4. In primary prevention, clinician-patient discussion to guide decision to initiate statin therapy for ASCVD prevention
   • Encourage healthy lifestyle
   • Control other risk factors
5. Continue to obtain a lipid panel to monitor adherence
Are We Over Treating Based on Over Estimating Risk?

- ~1/3rd of Americans die from heart disease & stroke, many from their first event.
- ~60% have a major vascular event during life.
- 1/3rd of US adults 40-79 (~32M) will have ASCVD risk > 7.5% → merit risk discussion & statin consideration for primary prevention.
- Other tests may be considered when risk-based treatment uncertain.
- Until we get serious about lifestyle prevention of dyslipidemia and hypertension, tens of millions of Americans, and many more worldwide, will need medications!
  - In MESA, it was ~80% on some treatment!
Questions
Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction
Take-Home

• Make decisions on drug treatment in primary prevention based on the patient not just the LDL
  – Risk discussion with patient is required
  – Do not focus on LDL cholesterol levels as drug initiation or therapy goals – focus on net clinical benefit
  – Assessment of absolute benefits and harms

• Use proven medications (statins and/or proven drug if statin intolerant or resistant) to reduce ASCVD risk
  – Individualize after that
  – Lower LDL is better, but it matters how you get there
NHLBI Charge to the Expert Panel

Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk

- Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
  - Cholesterol Panel: 3 CQs
  - Risk Assessment Work Group: 2 CQs
  - Lifestyle Management Work Group: 3 CQs

- RCTs and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality

- Develop recommendations based on RCT evidence
A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
Vignettes: Putting a face on patients in whom ASCVD risk reduction works

- 63 yo woman with STEMI, discharged on a high-intensity statin
- 26 yo woman with elevated LDL–C of 220 mg/dL, noted in teens + family history CHD
- 44 yo woman with diabetes, well-controlled hypertension and micro-albuminuria
- 56 yo African-American woman with multiple ASCVD risk factors
Major recommendations for initiating statin therapy - 1

Heart healthy lifestyle habits are the foundation of ASCVD prevention (See 2013 AHA/ACC Lifestyle Management Guideline)

Adults age >21 y and a candidate for statin therapy

Clinical ASCVD

Yes

Age ≤75 y
High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

No

Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin

LDL–C ≥190 mg/dL

Yes

High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

No

Diabetes
Type 1 or 2
Age 40-75 y

Yes

Estimated 10-y ASCVD risk ≥7.5%
High-Intensity statin

No

Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy (See Table 5)

High
Daily dose lowers LDL–C by approx. ≥50%

Moderate
Daily dose lowers LDL–C by approx. 30% to <50%
# Intensity of Statin Therapy

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.*

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

<table>
<thead>
<tr>
<th></th>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C, on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C, on average, by &lt;30%</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
<td></td>
</tr>
</tbody>
</table>

---

Colorado School of Public Health
New Perspective on LDL–C & Non-HDL–C Goals

• Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
• Unknown net benefit from treat-to-target strategy
  • Nonstatin drugs added to statin to reach goal
    • Unknown magnitude of additional benefit
    • Somewhat known rates of additional adverse effects
• May result in suboptimal statin therapy
  • 2° prevention LDL 95 on pravastatin 10 mg
  • Safety concerns: Reduce dose of atorvastatin from 80 to 20 mg to add niacin 2 g or fenofibrate
Nonstatin Therapy

1. Use the maximum tolerated intensity of statin
2. Consider addition of a nonstatin cholesterol-lowering drug(s)
   • Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
     ▪ Clinical ASCVD <75 years of age
     ▪ Baseline LDL–C ≥190 mg/dL
     ▪ Diabetes mellitus 40 to 75 years of age
3. Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred
Regularly Monitor Adherence to Lifestyle & Drug Therapy

1. Assess adherence, response to therapy, and adverse effects within 4-12 weeks following statin initiation or change in therapy.

2. Every 3-12 months once adherence has been established.

3. Laboratory monitoring
   - Measure a fasting lipid panel*
   - Do not routinely monitor ALT or CK unless symptomatic
   - Screen and treat type 2 diabetes according to current practice guidelines.
     - Heart-healthy lifestyle habits should be encouraged to prevent progression to diabetes.

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL-C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.
Monitoring & Safety

• Measure LDL-C on therapy to assess adherence, need for further lifestyle modification, potential need for additional therapy in high-risk patients

• Safety
  – RCTs & meta-analyses of RCTs used to identify important safety considerations
  – Allow estimation of net benefit from statin therapy
    ○ ASCVD risk reduction versus adverse effects
• Expert guidance on management of statin-associated adverse effects, including muscle symptoms
What About Diabetes with Statins?

• HR for CVD for ~0.8; HR for DM ~1.20
• MUST know absolute risk for context
• At a 10-year predicted risk of ~10% for hard ASCVD (f/nf MI or stroke)
  – Treat with high-dose statin
    • *NNT to prevent 1 MI/stroke in 10 years is ~20*
    • *NNH to “cause” 1 excess case of diabetes is 33*
  – Treat with moderate-dose statin
    • *NNT to prevent 1 MI/stroke in 10 years is ~30*
    • *NNH to “cause” 1 excess case of diabetes is 100*
What About Diabetes with Statins?

**Moderate intensity statin assumptions**
CVD 35% RRR & New onset diabetes NNH=100

- NNT to prevent 1 CVD event over 10 years
  - 120
  - 110
  - 100
  - 90
  - 80
  - 70
  - 60
  - 50
  - 40
  - 30
  - 20
  - 10
  - 0

- 10-year CVD risk
  - 0.0%
  - 5.0%
  - 10.0%
  - 15.0%
  - 20.0%
  - 25.0%

- 2.5%
- 5.0%
- 7.5%
- 10.0%
- 15.0%
- 20.0%
- 25.0%

**High intensity statin assumptions**
CVD 45% RRR & New onset diabetes NNH=33

- NNT to prevent 1 CVD event over 10 years
  - 120
  - 110
  - 100
  - 90
  - 80
  - 70
  - 60
  - 50
  - 40
  - 30
  - 20
  - 10
  - 0

- 10-year CVD risk
  - 0.0%
  - 5.0%
  - 10.0%
  - 15.0%
  - 20.0%
  - 25.0%

- 2.5%
- 5.0%
- 7.5%
- 10.0%
- 15.0%
- 20.0%
- 25.0%

NNH=33
ACC/AHA Risk Assessment Guideline

Work Group

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Acknowledgements

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Denise Simons-Morton, MD, PhD

American College of Cardiology
Helping Cardiovascular Professionals

American Heart Association
NHLBI Charge to the Work Group

• Examine the scientific evidence on risk assessment for initial ASCVD events, and develop an approach for risk assessment that could be used in practice and used or adapted by the risk factor panels in their guidelines.

• Specifically, the Work Group was charged with 2 tasks:

  1. To develop or recommend an approach to quantitative risk assessment that could be used to guide care; and

  2. To pose and address a small number of questions judged to be critical to refining and adopting risk assessment in clinical practice, using systematic review methodology.
Dallas Heart Study

Compared with Original ATP-III Recommendations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Additional Statin Eligibility*</th>
<th>Event Rate Among Newly Statin Eligible</th>
<th>NNT Among Newly Statin Eligible†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>4.8%</td>
<td>15.8%</td>
<td>14–21</td>
</tr>
<tr>
<td>CHD</td>
<td>4.8%</td>
<td>11.7%</td>
<td>19–29</td>
</tr>
<tr>
<td>ATP III statin eligibility determined by optional cholesterol goals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>-2.8%</td>
<td>15.7%</td>
<td>14–21</td>
</tr>
<tr>
<td>CHD</td>
<td>-2.8%</td>
<td>12.4%</td>
<td>18–27</td>
</tr>
<tr>
<td>Restricting to individuals aged ≥40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>9.0%</td>
<td>15.8%</td>
<td>14–21</td>
</tr>
<tr>
<td>CHD</td>
<td>9.0%</td>
<td>11.6%</td>
<td>19–29</td>
</tr>
</tbody>
</table>

ASCVD indicates atherosclerotic cardiovascular disease; ATP III, Third Adult Treatment panel; CHD, coronary heart disease; and NNT, number needed to treat.

*Additional statin eligibility is the net product of those newly statin eligible and those no longer statin eligible under the new guidelines.

†Number needed to treat with moderate to high potency statin to prevent one atherosclerotic cardiovascular event assuming a 30% to 45% relative risk reduction.
Dallas Heart Study

Supplemental Table 3: Net Reclassification of Statin Eligibility among Individuals with and without ASCVD Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Additional statin eligibility among events</th>
<th>Additional statin eligibility among non-events</th>
<th>NRI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>37.1%</td>
<td>3.9%</td>
<td>0.332</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CHD</td>
<td>40.4%</td>
<td>4.1%</td>
<td>0.363</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ATPIII statin eligibility determined by optional cholesterol goals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>16.5%</td>
<td>-3.4%</td>
<td>0.199</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CHD</td>
<td>19.1%</td>
<td>-3.2%</td>
<td>0.223</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Restricting to individuals ≥40 years of age</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD</td>
<td>37.8%</td>
<td>7.6%</td>
<td>0.302</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CHD</td>
<td>41.3%</td>
<td>8.0%</td>
<td>0.334</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Compared with Original ATP-III Recommendations
• 3076 patients referred for CTA
• “Under the NCEP guideline, 59% of patients with ≥50% stenosis of the left main coronary artery and 40% of patients with ≥50% stenosis of other branches would not have been treated. The comparable results for the GACR were 19% and 10%. The use of low-density lipoprotein targets seriously degraded the accuracy of the NCEP guideline for statin assignment. The proportion of patients assigned to statin therapy was 15% higher under the GACR.”
Accuracy of Statin Assignment Using the 2013 AHA/ACC Cholesterol Guideline Versus the 2001 NCEP ATP III Guideline

Correlation With Atherosclerotic Plaque Imaging

**TABLE 5** Proportions of Patients Assigned to Statin Therapy Given Various Plaque and Prognostic Features

<table>
<thead>
<tr>
<th>Disease Feature</th>
<th>All Patients</th>
<th>Patients Not on Statins at Time of Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>NCEP</td>
</tr>
<tr>
<td>Any or none</td>
<td>3,076</td>
<td>0.531</td>
</tr>
<tr>
<td>SPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>954</td>
<td>0.411</td>
</tr>
<tr>
<td>Mild</td>
<td>991</td>
<td>0.600</td>
</tr>
<tr>
<td>Moderate</td>
<td>584</td>
<td>0.608</td>
</tr>
<tr>
<td>Heavy</td>
<td>547</td>
<td>0.532</td>
</tr>
<tr>
<td>SSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>1,424</td>
<td>0.458</td>
</tr>
<tr>
<td>Mild</td>
<td>682</td>
<td>0.622</td>
</tr>
<tr>
<td>Moderate</td>
<td>497</td>
<td>0.576</td>
</tr>
<tr>
<td>Heavy</td>
<td>473</td>
<td>0.573</td>
</tr>
</tbody>
</table>
NHLBI Charge to the Work Group

• Examine the scientific evidence on risk assessment for initial ASCVD events, and develop an approach for risk assessment that could be used in practice and used or adapted by the risk factor panels in their guidelines.

• Specifically, the Work Group was charged with 2 tasks:
  1. To develop or recommend an approach to quantitative risk assessment that could be used to guide care; and
  2. To pose and address a small number of questions judged to be critical to refining and adopting risk assessment in clinical practice, using systematic review methodology.
Systematic Review Process

• CQs relevant to clinical practice
• A priori inclusion/exclusion (I/E) criteria
• Independent contractor conducted literature search
• Literature search through April, 2011
• Updated search for CQ#1 through September, 2013
Critical Question #1

• CQ1: “What is the evidence regarding reclassification or contribution to risk assessment when the following are considered in addition to the variables that are in the traditional risk scores?”
  • High-sensitivity C-reactive protein (hs-CRP)
  • Apolipoprotein B (ApoB)*
  • Glomerular filtration rate (eGFR)*
  • Microalbuminuria*
  • Family history
  • Cardiorespiratory fitness*
  • Ankle-brachial index (ABI)
  • Carotid intima-media thickness (CIMT)
  • Coronary artery calcium (CAC) score

* No recommendation
Recommendations for Additional Testing if Uncertainty Remains After 10-Year Risk Assessment

If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following — family history, hs-CRP, CAC score, or ABI — may be considered to inform treatment decision making.

CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.