Overestimation of Risk  
with the 2014 ACC/AHA Risk Prediction Calculator:  
Should Clinicians Worry or Not?

Paul M Ridker, MD  
Eugene Braunwald Professor of Medicine  
Harvard Medical School  
Director, Center for Cardiovascular Disease Prevention  
Brigham and Women’s Hospital, Boston MA

Dr Ridker has received investigator-initiated research support from the NHLBI, NCI, American Heart Association, Donald W Reynolds Foundation, Leduc Foundation, Doris Duke Charitable Foundation, AstraZeneca, Novartis, and Pfizer.  
Dr Ridker has served as a consultant to Vascular Biogenics, Merck, ISIS, and Genzyme.  
Dr Ridker is listed as a co-inventor on patents held by the Brigham and Women’s Hospital (BWH) that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Siemens and AstraZeneca. Dr. Ridker and the BWH receive royalties on sales of the hsCRP test. However, neither Dr. Ridker nor the BWH receives any royalties attributable to sales of the hsCRP test used in connection with the CIRT or CANTOS trials.

Evidence Based Prevention of CV Disease

- Evidence based guidelines are intended to be based on rigorous and expert analysis of available data, documenting relative benefits and risks of procedures, prediction models, and therapies
- Evidence based guidelines are intended to help improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies
- Evidence based guidelines are very hard to write and gain consensus.
- Evidence based guidelines are not static; failures in the past can be fixed as long as we have the will to do so.
Definitions

Primordial Prevention: Prevention of CHD risk factors

Primary Prevention: Modification of risk factors in order to prevent or delay the onset of CHD

Secondary Prevention: Initiation of therapy to reduce recurrent CHD events and decrease cardiac mortality in patients with established CHD

CHD = Coronary heart disease

Ridker PM, Wilson PWF. JAMA 2013;310:1123-4 (September 18, 2013)

Middle Aged Men and Women Free of Cardiovascular Disease

Diabetes

Yes

No

LDL > 160

Yes

No

hsCRP > 2

Yes

Statin

No

Yes

LDL > 130

HDL < 45

Yes

No

No

Encourage Healthy Lifestyle

Supporting Clinical Trials

CARDS

WOSCOPS

MEGA

AFCAPS

TexCAPS

JUPITER

Figure 1
Model Accuracy - Discrimination

- Discrimination
  - Ability to separate cases and controls
  - Based on sensitivity and specificity
  - Most popular measure is the ROC curve
  - Function of ranks only
- C-statistic = area under the ROC curve
  - Range = 0.5 (no discrimination)
  - to 1.0 (perfect discrimination)

Model Accuracy - Calibration

- How closely the predicted probabilities agree with the actual outcomes
  - Function of predicted risk
- Calibration-in-the-large
  - Mean predicted risk should = overall observed risk in data
- Calibration in groups
  - Quantiles (e.g., deciles)
  - Pre-specified groups (e.g., fixed intervals of risk)

Model Efficiency - Reclassification

- Addresses how well a new score places individuals into clinically relevant risk categories compared to an older score.
- Reclassification involves a direct comparison between two risk scores for the same target endpoint and is only appropriate for calibrated models
- NRI – net reclassification index
C-Reactive Protein and Reclassification of Cardiovascular Risk in the Framingham Heart Study


The net reclassification improvement when CRP was added to traditional risk factors was 11.8% for hard CHD (P=0.009), a value greater than that of LDL, HDL, or blood pressure in the Framingham Data.

www.reynoldsriskscore.org


www.reynoldsriskscore.org
**Reynolds Risk Score – Example**

**Clinical Example:**
72 year old non-diabetic woman, smoker, systolic BP 145 mm Hg, TC 216 mg/dL, HDLC 82 mg/dL, hsCRP 7.7 mg/L, and a positive family history for MI.

**Predicted 10-year risk**
- **Framingham Covariates:** 6.9 percent
- **Reynolds Covariates:** 23.2 percent

---

**Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women’s Health Initiative**

Nancy R. Cook, Jo-Ann E. Pfeffer, MD, Charles B. Easton, MD, Jordan E. Manson, MD, DrPH, Lisa W. Martin, MD, Jennifer G. Robinson, MD, MPH, Jacques E. Rossouw, MD, Sylvia Wassertheil-Smoller, PhD, Paul M. Ridker, MD

**Background:** Framingham-based and Reynolds Risk scores for cardiovascular disease (CVD) prediction have not yet been directly compared in an independent validation cohort.

**Methods and Results:** We selected a case-cohort sample of the multiethnic Women’s Health Initiative Observational Cohort comprising 1722 women of age ≥70 years, with a mean follow-up of 11.2 years.

The Reynolds Risk Score was better calibrated than the Framingham model in this large external validation cohort. The Reynolds score also showed improved discrimination overall in black and white women. Large differences in risk estimates exist between models, with clinical implications for statin therapy.

**What Was the ACC/AHA Prediction Algorithm Based Upon? (Discrimination C-Statistics)**

---

Cook NR et al, Circulation 2012;125:1748-1756
What Was the ACC/AHA Prediction Algorithm Based Upon? (Calibration)

Calibration plot: AHA/ACC Model in WHS

Major CVD
In all three of the primary prevention cohorts, the new AHA/AHA risk prediction algorithm systematically overestimated observed risks by 75 to 150 percent, roughly doubling the actual observed risk.

Paul M Ridker
Nancy R Cook
Lancet November 19, 2013
“Similar overestimation of risk was observed in two external validation cohorts used by the guideline developers themselves, an issue readily acknowledged in the report.”

“Thus, on the basis of data from these two external validation cohorts, it is possible that as many as 40 to 50 percent of the 33 million middle-aged Americans targeted by the new ACC/AHA guidelines for statin therapy do not actually have risk thresholds that exceed the 7.5 percent risk threshold suggested for treatment.”

“Miscalibration to this extent should be reconciled and addressed in additional external validation cohorts before these new prediction models are widely implemented.”

Paul M Ridker
Nancy R Cook
Lancet November 29, 2013

Observed Event Rate
Predicted Event Rate

CONCLUSIONS AND RELEVANCE: In this cohort of US adults for whom statin initiation is considered based on the ACC/AHA Pooled Cohort risk equations, observed and predicted 5-year atherosclerotic CVD risks were similar, indicating that these risk equations were well calibrated in the population for which they were designed to be used, and demonstrated moderate to good discrimination.

“Calibration for the overall population was poor (Hosmer-Lemeshow Chi-sq = 84.2, P<0.001). The Pooled Cohort risk equations overestimated risk for men and women and whites and blacks.”

“Calibration was better in [those being considered for statin initiation] with less overestimation of risk (Hosmer-Lemeshow Chi-sq = 19.9, P = 0.01)”.


Comparison of Application of the ACC/AHA Guidelines, Adult Treatment Panel III Guidelines, and European Society of Cardiology Guidelines for Cardiovascular Disease Prevention in a European Cohort

Unadjusted Accounting for statin use and confounding by indication

Accounting for statin use, confounding by indication, and incident revascularizations

Discordance (%)

Under-estimation       Over-estimation

FRS

CHD

FRS

CVD

ATT

RRS

AHA

ACC

ASCVD

+ 45 %

+ 25 %

+ 115 %

+ 78 %

- 3 %

- 15 %

- 20 %

- 25 %

- 30 %

- 35 %

Adapted from Blaha / DeFilipis et al, AHA 2014
Secular Trends in Cardiovascular Event Rates Over Time

Nabel E, Braunwald E. NEJM 2012;366:54-63.

Figure 2

Figure 3
<table>
<thead>
<tr>
<th></th>
<th>Modified ACC/AHA Risk Calculator</th>
<th>Modified ACC/AHA Risk Calculator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>170</td>
<td>220</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>BP-treated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Smoker</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Estimated 10-year risk</td>
<td>13 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Risk-Based Recommendation</td>
<td>Moderate to high-intensity statin therapy</td>
<td>Risk-Based Recommendation</td>
</tr>
<tr>
<td>Trial-Based Recommendation</td>
<td>Would this patient have qualified for one of the pivotal statin trials that have proven efficacy?</td>
<td>Would this patient have qualified for one of the pivotal statin trials that have proven efficacy?</td>
</tr>
</tbody>
</table>

Figure 2

ACC/AHA 10-year Risk > 7.5 %

Figure 3

ACC/AHA 10-year Risk > 5 %

Figure 4

Trial Entry Criteria
+ Age > 50
+ Age > 55
+ Age > 60

Figure 5

Figure 6

Figure 7
Problems with the Lifetime Risk Calculator:
Example 1: 10-year risk estimate exceeds lifetime risk estimate

59 year old white male
Total cholesterol 169 mg/dL
HDL-C 51 mg/dL
SBP 119 mm Hg
No diabetes
Non-smoker

10-year risk = 5.9 percent
Lifetime risk = 5.0 percent

Problems with the Lifetime Risk Calculator:
Example 2: Large change in lifetime risk estimate with trivial change in risk factor profile

46 year old white female
Total cholesterol 170 mg/dL
HDL-C 50 mg/dL
SBP 118 mm Hg
No diabetes
Non-smoker

10-year risk = 1.5 percent
Lifetime risk = 5.0 percent

46 year old white female
Total cholesterol 170 mg/dL
HDL-C 50 mg/dL
SBP 120 mm Hg
No diabetes
Non-smoker

10-year risk = 1.6 percent
Lifetime risk = 36.0 percent

Predicted 10-Year Risks for Recurrent Vascular Events Among Patients with Known Arterial Disease: the SMART Risk Score

Prediction based on age, gender, diabetes status, smoking status, SBP, TC, HDL-C, hsCRP, eGFR, years since first event, primary vascular bed involved (coronary, cerebral, or peripheral).

How might the physician community respond to consistent evidence regarding over-estimation of risk when using the 2014 AHA/ACC risk prediction tool to determine statin use?

• One approach would be to re-calibrate the algorithm so that it tracks more closely with contemporary evidence.
• Another would be to simultaneously calculate multiple risk algorithms as currently done in some Mayo Clinic prevention programs.
• Another would be to incorporate trial data into a hybrid guideline so that data is made explicit.
• Alternative I: Physicians can elect to ignore the problem altogether and accept that more individuals will be treated with a class of drugs proven to reduce vascular event rates.
• Alternative II: Abandon risk prediction scores entirely and base practice on actual trial data.
• Alternative III: Start over and accept data based on contemporary epidemiology and contemporary science.