C-Reactive Protein and Parental History Improve Global Cardiovascular Risk Prediction

The Reynolds Risk Score for Men

Paul M Ridker, MD; Nina P. Paynter, PhD; Nader Rifai, PhD; J. Michael Gaziano, MD; Nancy R. Cook, ScD

**Background**—High-sensitivity C-reactive protein and family history are independently associated with future cardiovascular events and have been incorporated into risk prediction models for women (the Reynolds Risk Score for women); however, no cardiovascular risk prediction algorithm incorporating these variables currently exists for men.

**Methods and Results**—Among 10,724 initially healthy American nondiabetic men who were followed up prospectively over a median period of 10.8 years, we compared the test characteristics of global model fit, discrimination, calibration, and reclassification in 2 prediction models for incident cardiovascular events, one based on age, blood pressure, smoking status, total cholesterol, and high-density lipoprotein cholesterol (traditional model) and the other based on these risk factors plus high-sensitivity C-reactive protein and parental history of myocardial infarction before age 60 years (Reynolds Risk Score for men). A total of 1294 cardiovascular events accrued during study follow-up. Compared with the traditional model, the Reynolds Risk Score had better global fit (likelihood ratio test \( P<0.001 \)), a superior (lower) Bayes information criterion, and a larger C-index \( (P<0.001) \). For the end point of all cardiovascular events, the Reynolds Risk Score for men reclassified 17.8% \( (1904/10,724) \) of the study population \((20.2\% [1392/6884])\) of those at 5% to 20% 10-year risk) into higher- or lower-risk categories, with markedly improved accuracy among those reclassified. For this model comparison, the net reclassification index was 5.3%, and the clinical net reclassification index was 14.2% \((\text{both } P<0.001)\). In models based on the Adult Treatment Panel III preferred end point of coronary heart disease and limited to men not taking lipid-lowering therapy, 16.7% of the study population \((20.1\% \text{ of those at 5% to 20% 10-year risk})\) were reclassified to higher- or lower-risk groups, again with significantly improved global fit, larger C-index \( (P<0.001) \), and markedly improved accuracy among those reclassified. For this model, the net reclassification index was 8.4% and the clinical net reclassification index was 15.8% \((\text{both } P<0.001)\).

**Conclusions**—As previously shown in women, a prediction model in men that incorporates high-sensitivity C-reactive protein and parental history significantly improves global cardiovascular risk prediction. *(Circulation. 2008;118: 000-000.)*

**Key Words:** epidemiology ▪ prevention ▪ inflammation ▪ genetics ▪ risk factors

Although inflammation and family history are independently associated with future vascular risk, commonly used global risk prediction algorithms do not incorporate information on these variables. In a large prospective cohort of American women, we recently developed and validated an improved algorithm for the assessment of global cardiovascular risk that added information on inflammation (high-sensitivity C-reactive protein [hsCRP]) and genetic risk (parental history of myocardial infarction before age 60 years) to that on age, blood pressure, smoking history, total cholesterol, and HDL cholesterol (HDL-C). Using that algorithm, known as the Reynolds Risk Score for women (www.reynoldsriskscore.org), we observed that \( \approx 30\% \) of initially healthy women estimated to be at “intermediate risk” could be reclassified into higher- or lower-risk categories with greatly improved accuracy. As such, outpatient use of the Reynolds Risk Score for women allows more accurate targeting of pre-
ventive therapies to those with the most appropriate levels of risk so as to decrease toxicity and increase benefit.

Clinical Perspective

To date, no comparable risk prediction algorithm incorporating hsCRP and parental history exists for men. To address this issue, we ascertained traditional risk factors, parental history of myocardial infarction before age 60 years, and blood levels of hsCRP, total cholesterol, and HDLC at baseline in a prospective cohort of 10,724 initially healthy nondiabetic American men who were followed up over a median period of 10.8 years for the development of first-ever myocardial infarction, stroke, coronary revascularization procedures, or cardiovascular death. Using these data, we compared global model fit, discrimination, calibration, and reclassification in 2 prediction models, 1 based on age, blood pressure, smoking status, total cholesterol, and HDLC (model A, traditional model) and the other based on these risk factors plus hsCRP and parental history of myocardial infarction before age 60 years (model B, Reynolds Risk Score model for men). In secondary analyses, we sought evidence as to whether or not hsCRP and parental history improved risk prediction for the Adult Treatment Panel III (ATP-III) preferred end point of coronary heart disease and whether or not treatment of hypertension or hyperlipidemia modified these effects.

Methods

Study Participants, Prospective Follow-Up, and Clinical End Points

Study participants were derived from the Physicians Health Study II (PHS-II), a nationwide cohort of US men 50 years and older who were free of cardiovascular disease, diabetes mellitus, and cancer, with blood collection initiated in December 1995. Men eligible for the present analysis were those younger than 80 years at baseline who had complete ascertainment of baseline exposure variables of interest, including age (years), blood pressure (mm Hg), smoking status (current, not current), and parental history of myocardial infarction before age 60 years (yes/no) and who provided an adequate baseline plasma sample for analysis of total cholesterol (mg/dL), HDLC (mg/dL), and hsCRP (mg/L). In total, 10,724 men had data available on all 7 covariates and were included in the

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Table 1. Hazard Ratios for Incident Cardiovascular Events According to Risk Factor Levels at Baseline

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariable Model</th>
<th>Multivariable Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>2.2 (1.9–2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥70</td>
<td>3.9 (3.3–4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>120–139</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥140</td>
<td>3.2 (2.7–3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>1.1 (0.95–1.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>≥220</td>
<td>1.3 (1.1–1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDLC, mg/dL</td>
<td>1.0 (Referent)</td>
<td></td>
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<tr>
<td>&lt;40</td>
<td>0.73 (0.64–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50</td>
<td>0.61 (0.53–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.7 (1.3–2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1.6 (1.4–1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥3</td>
<td>2.2 (1.9–2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental history of MI before age 60 y</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.6 (1.3–1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In the multivariable models, adjustment for other risk factors is done on a continuous basis (age, blood pressure, total cholesterol, HDLC, hsCRP) or on a binary basis (current smoker, parental history), as done in the formal Reynolds Risk Score for men. HR indicates hazard ratio.

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Circulation
November 25, 2008
primary analysis; 10,407 also had information available on treatment of hypertension or hyperlipidemia and were included in the secondary analyses.

All men were followed up through March 2008, for a median period of 10.8 years (interquartile range 7.8 to 11.2 years), for incident myocardial infarction, stroke, coronary revascularization, or cardiovascular death; these were adjudicated by an end-points committee after medical record review with standardized criteria. All participants provided written informed consent. The study protocol was approved by the institutional review board of Brigham and Women’s Hospital (Boston, Mass).

Analytic and Statistical Approach
The median and 75th and 25th percentiles (interquartile range [IQR]) are reported for all continuous variables. To normalize the distributions and improve the linearity of the associations with cardiovascular disease, the natural log transform was used for systolic blood pressure, lipids, and hsCRP. As done in the Reynolds Risk Score for women,1 our primary analysis in men was a comparison of the test characteristics of discrimination, global model fit, calibration, and reclassification in 2 prediction models for total incident cardiovascular events. 1 based on age, blood pressure, smoking status, total cholesterol, and HDLC (model A, traditional model) and the other based on these risk factors plus hsCRP and parental history of myocardial infarction before age 60 years (model B, Reynolds Risk Score for men).

The overall predictive values of models A and B were compared with several criteria. First, because model A was functionally nested within model B, the statistical significance of any differences between models for global fit was ascertained directly with the likelihood ratio test. Second, as also done in the Reynolds Risk Score for women, global fit was compared by use of the Bayes information criterion (BIC).1 The BIC is a likelihood-based measure in which lower values indicate better fit and in which a penalty is paid for increasing the number of variables; as the BIC adjusts the log likelihood for the number of variables, the magnitude of the BIC can be directly compared between model A and model B.

Third, discrimination, or the ability of the risk prediction models to distinguish those who go on to experience a cardiovascular event from those who do not, was evaluated with Harrell’s C-index, which is analogous to the area under the receiver operating characteristic curve (for which larger values indicate better discrimination) for survival data.4 C-indices for different models were compared with bootstrap sampling.

Fourth, to assess model calibration (or how closely the predicted probabilities reflect actual risk), the Hosmer-Lemeshow statistic was computed for all models. As suggested by D’Agostino and Nam,3 calibration χ² values >20 (P<0.01) suggest a lack of adequate calibration.

Fifth, the ability of hsCRP and parental history to reclassify study participants was assessed by dividing all participants into predicted 10-year risk groups of <5%, 5% to less than 10%, 10% to less than 20%, and ≥20%, as described by Cook et al.6 7 This was done with both model A (based on traditional covariates) and model B (the Reynolds Risk Score for men). We then calculated the proportion of participants in the cohort who were reclassified into either higher- or lower-risk categories using model B rather than model A and compared these predicted outcomes to actual observed data during the follow-up period to address the proportion reclassified correctly. Reclassification was considered to be correct if the observed rate based on Kaplan–Maier estimates was closer to the risk category predicted by model B than by model A. These observed and expected proportions were compared directly with tests of reclassification calibration with the J² statistic, which follows a χ² distribution with degrees of freedom equal to the number of categories minus 1.1 2 9 similar to the Hosmer-Lemeshow test, high values (P<0.01) indicate disagreement between observed and expected values. The net reclassification improvement (NRI)10 was calculated as a measure to estimate any overall improvement in reclassification with model B instead of model A, and the clinical net reclassification improvement (CNRI)11 was calculated to address parallel information among those considered to be at “intermediate” risk (ie, 5% to 20% 10-year risk by usual risk criteria). Both the NRI and the CNRI estimate the net proportion of cases that move to higher- or lower-risk strata.

Calibration and reclassification analyses were computed with risk at 7 years, because most individuals were followed up through this time. For the NRI and CNRI analyses, observations censored before 7 years were excluded. All risk calculations were extrapolated to 10 years for presentation purposes.

In contrast to the Reynolds Risk Score previously developed for women,1 the commonly used ATP-III global risk assessment tool incorporates treatment of hypertension as an additional covariate and uses a coronary heart disease end point rather than a total cardiovascular disease end point.12 Thus, in secondary analyses, we repeated the above procedures using a coronary heart disease end point and for direct comparison added a term for hypertension treatment into both models A and B; for completeness, we repeated all analyses after adding a term for lipid-lowering therapy into both models A and B. Finally, because the ATP-III coronary heart disease risk prediction score is often used by clinicians to make decisions about statin therapy, we performed a further coronary heart disease analysis comparing models A and B among the subgroup of study participants not taking lipid-lowering therapy at baseline. As part of a sensitivity analysis designed to address whether the choice of cut points had substantive impact on the present analysis, we repeated the above reclassification process using 3 predicted 10-year risk groups of <10%, 10% to less than 20%, and 20%. All analyses were conducted with R version 6.0 (R Foundation for Statistical Computing, Vienna, Austria).13 The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Results

Baseline Characteristics and Study Outcomes

For the 10 724 men in the primary analyses, median age at study entry was 63 years (IQR 57 to 70 years); median systolic blood pressure was 128 mm Hg (IQR 120 to 135 mm Hg), 3.2% were current smokers, and 10.8% had a parental history of myocardial infarction before age 60 years. Median values for total cholesterol, HDLC, and hsCRP at baseline were 203 mg/dL (IQR 180 to 227 mg/dL), 42.5 mg/dL (IQR 34.4 to 52.4 mg/dL), and 0.86 mg/L (IQR 0.43 to 1.71 mg/L), respectively. Antihypertensive therapy was reported by 24.2% and lipid-lowering therapy by 17.3%. During the prospective follow-up period, a total of 1294 incident cardiovascular disease events (nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or cardiovascular death) were adjudicated by the end-points committee, of which 1072 were classified as incident coronary heart disease events (coronary revascularization or fatal or nonfatal myocardial infarction).

Primary Study Results

As anticipated, all traditional covariates, as well as hsCRP and parental history, were statistically significant predictors of risk in both univariable and multivariable analyses, with a magnitude of risk comparable to that of prior studies (Table 1). In all models, fit and calibration were improved when a natural logarithm transformation was used for age, systolic blood pressure, total cholesterol, HDL cholesterol, and hsCRP; these were thus incorporated into the final forms of both model A and model B. The β-coefficients, SEs, and probability values associated with model A and model B are provided in the online-only Data Supplement, Appendix A.

Table 2 presents the primary comparisons of overall fit and discrimination for models A and B. For the end point of total cardiovascular events, model B (the Reynolds Risk Score for men that incorporated hsCRP and parental history of myocardial infarction before age 60 years) had a lower BIC, better overall model fit (likelihood ratio test *P*<0.001), and larger C-index (*P*<0.001) than did model A (limited to age, systolic blood pressure, smoking status, total cholesterol, and HDL cholesterol). In this primary analysis, models A and B demonstrated similar levels of calibration (Hosmer-Lemeshow χ² 11.3 and 12.9, respectively). Furthermore, as shown in Table 3, model B reclassified 17.8% of the study population (1904 of 10 724 people) into higher- or lower-risk categories and did so with 83.8% correct reclassification; for those at 5% to 10% or 10% to 20% estimated 10-year risk, 20.2% were reclassified (1392/6884), each into categories that more accurately reflected group outcomes when predicted and observed risks were compared. Reclassification calibration within Table 3 demonstrated significant lack of fit for model A (calibration χ² 40.1, *P*<0.001), whereas model B fit adequately (calibration χ² 15.6, *P*=0.08). In this primary analysis, the NRI associated with the addition of hsCRP and parental history was 5.3% (*P*=0.001), and the CNRI was 14.2% (*P*<0.001).

Table 2 also presents data for incident coronary heart disease rather than total cardiovascular disease; for this end point, model B again had a lower BIC, better overall model fit (likelihood ratio test *P*<0.001), and larger C-index (*P*<0.001) than did model A. As shown in Table 4 for
Global fit, C-index, and BIC values were again superior in at baseline and with the end point of coronary heart disease. The study cohort limited to men not taking lipid-lowering therapy BIC, C-index, NRI, and CNRI for models A and B, with the For comparability to ATP-III, Table 5 presents data on the 10% or 10% to in intermediate risk according to usual risk factors (ie, 5% to 20% estimated 10-year risk), 22% were reclassified. Reclassification calibration within Table 4 demonstrated significant lack of fit for model A (P<0.0001), whereas model B fit adequately (P=0.20). In this analysis, the NRI associated with the addition of hsCRP and parental history was 6.8% (P<0.001), and the CNRI was 13.6% (P<0.001).

Online-only Data Supplement Appendix B presents data on the BIC, C-index, NRI, and CNRI for analyses in which we incorporated baseline information on blood pressure treatment, lipid-lowering treatment, or both into models A and B. In all analyses, for both the cardiovascular disease and coronary heart disease end points, the BIC was minimized, the global model fit by likelihood ratio testing was significantly improved, the C-index was significantly larger, and reclassification calibration was superior for model B compared with model A.

Comparison to ATP-III Prediction Variables
For comparability to ATP-III, Table 5 presents data on the BIC, C-index, NRI, and CNRI for models A and B, with the study cohort limited to men not taking lipid-lowering therapy at baseline and with the end point of coronary heart disease. Global fit, C-index, and BIC values were again superior in models that included hsCRP and parental history of myocardial infarction (all P<0.001).

Table 6 presents reclassification for the ATP-III preferred end point of coronary heart disease using models built with all ATP-III covariates (ie, including a term for blood pressure treatment). The NRI for this analysis associated with the addition of hsCRP and parental history was 8.4% (P<0.001), and the Reynolds Risk Score for men reclassified 16.7% of the study participants (1432 people) to higher- or lower-risk groups. In this analysis, the CNRI was 15.8%. Reclassification calibration within Table 6 was again superior for model B compared with model A (calibration χ² 13.1 versus 50.5, respectively).

Sensitivity Analyses
As part of a sensitivity analysis designed to address the impact of choice of cut points on our findings, we repeated the above reclassification process using 5 predicted 10-year risk groups of <10%, 10% to less than 20%, and ≥20% (rather than 4 groups of <5%, 5% to less than 10%, 10% to less than 20%, and ≥20% 10-year risk) and again found similar significant benefits of model B over model A. Specifically, for the end point of total cardiovascular events, the latter analysis found that the Reynolds Risk Score for men reclassified 12.3% of the study population into higher- or lower-risk categories, with significantly improved accuracy among those reclassified (NRI 3.2%, P=0.006; CNRI 6.5%, P<0.001), and that for the end point of coronary heart disease, 12.7% were similarly reclassified (NRI 4.3%,...
To be 11.6%, whereas model B (including hsCRP and parental history of myocardial infarction. In this analysis, model A (based on hsCRP of 4.0 mg/L, and a positive parental history of total cholesterol of 205 mg/dL, HDL cholesterol of 45 mg/dL, smoking man with systolic blood pressure of 130 mm Hg, cardiovascular disease to a hypothetical 65-year-old non-

**Clinical Examples**

As a practical example, we applied models A and B for cardiovascular disease to a hypothetical 65-year-old non-smoking man with systolic blood pressure of 130 mm Hg, total cholesterol of 205 mg/dL, HDL cholesterol of 45 mg/dL, hsCRP of 4.0 mg/L, and a positive parental history of myocardial infarction. In this analysis, model A (based on traditional factors only) estimated 10-year cardiovascular risk to be 11.6%, whereas model B (including hsCRP and parental history) estimated 10-year cardiovascular risk to be 20.4%.

With regard to reclassification, in a hypothetical population of 100 000 nondiabetic men at intermediate risk by traditional risk factors (50 000 at 5% to <10% and 50 000 at 10% to <20% 10-year risk), 10 500 would cross the optimal treatment threshold of 10% 10-year risk, 4000 would cross the universally accepted treatment threshold of 20% 10-year risk, and 5700 would be reclassified at low risk (<5% 10-year risk).

**Discussion**

In this prospective cohort of 10 724 initially healthy nondiabetic American men, the addition of information on inflammation (hsCRP) and genetics (parental history of myocardial infarction before age 60 years) significantly improved global risk prediction algorithms based on the traditional risk factors of age, systolic blood pressure, smoking status, and total and HDL cholesterol. Overall, compared with model A (based on traditional risk factors), model B (the Reynolds Risk Score for men) reclassified ≈20% of men into higher- or lower-risk categories, and it did so with highly improved accuracy and superior calibration. Thus, not only do these data prospectively validate the use of hsCRP and a family history of premature atherosclerosis as additive independent biomarkers of risk, as initially reported with the Reynolds Risk Score for women, but they provide a comparable database from which an analogous Reynolds Risk Score for men can be computed (see Appendix C).

In these data, the NRI associated with hsCRP and parental history was 5.3%, and the CNRI was 14.2%, similar to values previously described in women and similar to the NRI and CNRI values for total and HDL cholesterol in the present cohort. Beyond providing an opportunity for improved risk stratification in men similar to that currently available for women, we believe these data have potential importance for the targeting of preventive therapies. Current treatment guidelines in the United States, Canada, and Europe take into account the risks, benefits, and costs of preventive therapies.

In these guidelines, lipid lowering is usually considered cost-effective for those with 10-year risk estimates of 20% or higher and is considered a therapeutic option for those with 10-year risks of 10% or more. Thus, application of the Reynolds Risk Score for men could allow more accurate targeting of lipid-lowering therapy to those with the most appropriate levels of risk, thereby increasing its net benefit and decreasing toxicity.

Although the present data derive from a large, well-characterized cohort of initially healthy men, limitations merit consideration. Participants in the PHS-II are all US male physicians ≥50 years of age with relatively high socioeconomic status and excellent access to health care and information on preventive therapies. We do not believe these characteristics affect the validity of our data; rather, we believe these data demonstrate the importance that inflammation and parental history can have in risk prediction, even in the setting of optimized access to preventive care. However, because minority representation in the study cohort was low, comparable studies among black, Hispanic, and Asian groups are needed. Because the present data do not include men <50

<table>
<thead>
<tr>
<th>Covariates/Measure</th>
<th>Model A: Without hsCRP or Parental History</th>
<th>Model B: With hsCRP and Parental History</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td>13 886</td>
<td>13 864</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.704</td>
<td>0.714</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>J²</td>
<td>38.4‡</td>
<td>14.1</td>
<td>...</td>
</tr>
<tr>
<td>NRI</td>
<td>...</td>
<td>5.3%</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>CNRI</td>
<td>...</td>
<td>14.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Traditional plus BP treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td>13 891</td>
<td>13 870</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.704</td>
<td>0.714</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>J²</td>
<td>47.1‡</td>
<td>12.3</td>
<td>...</td>
</tr>
<tr>
<td>NRI</td>
<td>...</td>
<td>8.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNRI</td>
<td>...</td>
<td>15.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

*Traditional factors include age, blood pressure, smoking status, total cholesterol, and HDL-C. The J-squared and c-statistics are based on survival estimates at 7 years, and the NRI and CNRI are based on case-control status as of 7 years, ignoring censored observations.

† Likelihood ratio test for comparison of models, bootstrap for comparison of C-indices.

P=0.003; CNRI 7.8%, P<0.001). We also applied the 3-category reclassification scheme in analyses limited to study participants not undergoing lipid-lowering therapy. The traditional factors include age, blood pressure, smoking status, total cholesterol, and HDL cholesterol. The J-squared and c-statistics are based on survival estimates at 7 years, and the NRI and CNRI are based on case-control status as of 7 years, ignoring censored observations.

In these guidelines, lipid lowering is usually considered cost-effective for those with 10-year risk estimates of 20% or higher and is considered a therapeutic option for those with 10-year risks of 10% or more. Thus, application of the Reynolds Risk Score for men could allow more accurate targeting of lipid-lowering therapy to those with the most appropriate levels of risk, thereby increasing its net benefit and decreasing toxicity.
brain natriuretic peptide were not available in the present risk prediction. \(^{19}\) Although data on troponin, cystatin, and premature atherosclerosis may also prove useful for global approaches that go beyond inflammation and parental history of predictors of risk, which suggests that multimarker approaches are self-reported; however, this potential limitation is extremely unlikely to represent any source of bias, because direct ascertainment was performed.

Beyond traditional risk factors, we limited the addition of novel biomarkers to hsCRP and parental history of myocardial infarction are self-reported; however, this potential limitation is extremely unlikely to represent any source of bias, because self-reported risk factors in the present cohort of physicians have consistently been shown to accurately reflect actual measured values, \(^{17,18}\) and the magnitude of risk associated with each of these variables in the present data (Table 1) is entirely consistent with that from multiple other studies in which direct ascertainment was performed.

For comparability to ATP-III, data are shown for the end point of incident coronary heart disease and are limited to men not taking lipid-lowering therapy at study entry, and both models include information on treatment of hypertension. The observed rate was based on Kaplan–Maier estimates; reclassification was considered correct when the observed rate was closer to the risk category predicted by model B than by model A. Observed and expected rates and risk strata were based on survival estimates at 7 years and extrapolated to 10 years for display.

Table 6. Risk Reclassification for Men Comparing Model A (Based on Traditional Risk Factors Alone) to Model B (Traditional Risk Factors Plus hsCRP and Parental History, the Reynolds Risk Score for Men)

<table>
<thead>
<tr>
<th>Model A Traditional Covariates and Antihypertensive Therapy: Categories of Predicted 10-Year Risk</th>
<th>Model B Reynolds Covariates and Antihypertensive Therapy: Categories of Predicted 10-Year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>N</td>
<td>2209</td>
</tr>
<tr>
<td>% Reclassified</td>
<td>...</td>
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<tr>
<td>Observed rate, %</td>
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<tr>
<td>5% to &lt;10%</td>
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<tr>
<td>% Reclassified</td>
<td>11.3</td>
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<tr>
<td>Observed rate, %</td>
<td>2.2</td>
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<tr>
<td>10% to &lt;20%</td>
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<tr>
<td>% Reclassified</td>
<td>...</td>
</tr>
<tr>
<td>Observed rate, %</td>
<td>...</td>
</tr>
<tr>
<td>≥20%</td>
<td>N</td>
</tr>
<tr>
<td>% Reclassified</td>
<td>...</td>
</tr>
<tr>
<td>Observed rate, %</td>
<td>...</td>
</tr>
</tbody>
</table>

For comparability to ATP-III, data are shown for the end point of incident coronary heart disease and are limited to men not taking lipid-lowering therapy at study entry, and both models include information on treatment of hypertension. The observed rate was based on Kaplan–Maier estimates; reclassification was considered correct when the observed rate was closer to the risk category predicted by model B than by model A. Observed and expected rates and risk strata were based on survival estimates at 7 years and extrapolated to 10 years for display.

years of age, extrapolation of these data to young individuals should be done with caution.

Second, data in the present study for blood pressure, smoking history, and parental history of myocardial infarction are self-reported; however, this potential limitation is extremely unlikely to represent any source of bias, because self-reported risk factors in the present cohort of physicians have consistently been shown to accurately reflect actual measured values, \(^{17,18}\) and the magnitude of risk associated with each of these variables in the present data (Table 1) is entirely consistent with that from multiple other studies in which direct ascertainment was performed.

Beyond traditional risk factors, we limited the addition of novel biomarkers to hsCRP and parental history of myocardial infarction before age 60 years, because each of these consistently has been found to independently predict vascular risk in multiple other cohorts, and because these are the 2 factors proven to add predictive value in the Reynolds Risk Score for women. \(^{1}\) Nonetheless, in a recent study of elderly patients with and without coronary disease that focused on mortality, it was found that hsCRP, troponin I, cystatin C, and brain natriuretic peptide were all statistically significant predictors of risk, which suggests that multimarker approaches that go beyond inflammation and parental history of premature atherosclerosis may also prove useful for global risk prediction. \(^{19}\) Although data on troponin, cystatin, and brain natriuretic peptide were not available in the present cohort, other potential biomarkers of risk, including glomerular filtration rate, did not improve risk prediction in the present data, nor are they included in Framingham-based guidelines.

Our inclusion of parental history of premature atherosclerosis in the current Reynolds Risk Score for men is not only consistent with the Reynolds Risk Score for women but is also consistent with 2 cardiovascular risk scores that have been developed in the United Kingdom, QRISK \(^{20}\) (a risk score that uses the QRESEARCH database) and ASSIGN \(^{21}\) (ASsessing cardiovascular risk using SIGN guidelines to assign potential patients to preventive treatment). Because some cohorts have defined premature atherosclerosis as having a male first-degree relative with infarction before age 55 years, a female first-degree relative with infarction before age 65 years, or a sibling with vascular disease, it is possible that a more inclusive definition of family history could have an impact on the present results. The QRISK and ASSIGN risk scores additionally include social deprivation, a variable difficult to evaluate in the present cohort but also worth considering in future guidelines. Finally, our primary focus on total cardiovascular events in the Reynolds Risk Scores for men and women is consistent not only with QRISK and ASSIGN but also with recent work from the Framingham Heart Study investigators. \(^{22}\)

Despite the evidence provided here for men and its consistency with our prior Reynolds Risk Score data for
women, whether or not physicians should employ statin therapy among individuals with elevated levels of hsCRP will depend in part on forthcoming data from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a randomized, double-blind, placebo-controlled evaluation of rosuvastatin in the prevention of first cardiovascular events among apparently healthy middle-aged men and women with LDL cholesterol levels <130 mg/dL who are at increased risk owing to hsCRP levels >2 mg/L. The JUPITER data are also likely be informative with regard to whether thresholds for statin therapy stay the same or are lowered in future guidelines.

Appendix C in the online-only Data Supplement contains the computational formula for 10-year risk of total incident cardiovascular events using the Reynolds Risk Score for men. A user-friendly calculator for the Reynolds Risk Score for men, along with our prior Reynolds Risk Score for women, can be freely accessed at http://www.reynoldsriskscore.org. Beyond computation of 10-year risk, this Web site also includes patient-centered data on lifetime risk and provides estimates of risk reductions that can be anticipated with the implementation of lifestyle change, smoking cessation, blood pressure control, and lipid reduction.

Sources of Funding

These analyses were funded by grants from the National Heart, Lung, and Blood Institute (Bethesda, Md) and the Donald W. Reynolds Foundation (Las Vegas, Nev). The Physicians Health Study is supported by grants from the National Heart, Lung, and Blood Institute. The funding agencies had no involvement in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the drafting of the manuscript.

Disclosures

Dr Ridker reports that he currently or in the past 5 years has received research funding support from multiple not-for-profit entities including the National Heart, Lung, and Blood Institute; the National Cancer Institute; the American Heart Association; the Doris Duke Charitable Foundation; the Leducq Foundation; the Donald W. Reynolds Foundation; and the James and Polly Annenberg La Vea Charitable Trusts. Dr Ridker also reports that currently or in the past 5 years he has received investigator-initiated research support from multiple for-profit entities including Astra-Zeneca, Dade-Behring, Novartis, Pharmacia, Sanofi-Aventis, Abbott and that he has served as a consultant to Schering-Plough, Sanofi-Aventis, Astra-Zeneca, Novartis, Isis Pharmaceuticals, Dade-Behring, Vascular Biogenics, and Merck. Dr Ridker is listed as a coinventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. Dr Rifai reports receiving research grant support from Merck Research Laboratories and serving as a consultant to Merck Research Laboratories and Sanofi-Aventis. Dr Gazzano reports having received research funding from Bayer Inc. Dr Cook reports having received funding from the National Heart, Lung, and Blood Institute; the National Cancer Institute; and Roche Diagnostics. Dr Cook has also served as a consultant to Bayer Health Care. Dr Paynter reports no conflicts.

References


High-sensitivity C-reactive protein and family history are independently associated with cardiovascular events and have been incorporated into risk prediction models for women (the Reynolds Risk Score for women); however, no cardiovascular risk prediction algorithm incorporating these variables exists for men. We assessed the incremental benefit of adding high-sensitivity C-reactive protein and parental history of premature atherosclerosis to the traditional factors of age, blood pressure, smoking, and total and high-density lipoprotein cholesterol in a prospective cohort of 10,724 initially healthy nondiabetic men. Compared with the traditional model, the Reynolds Risk Score had better global fit, a superior (lower) Bayes information criterion, and a larger C-index. More importantly, use of the Reynolds Risk Score for men reclassified 18% of the study population (and 20% of those at intermediate risk) into higher- or lower-risk categories, with markedly improved accuracy among those reclassified. Thus, as previously shown in women, a prediction model in men that incorporates high-sensitivity C-reactive protein and parental history significantly improves global cardiovascular risk prediction. User-friendly calculators for the Reynolds Risk Scores for men and women can be freely accessed at http://www.reynoldsriskscore.org. Beyond computation of 10-year risk, this World Wide Web site also includes patient-centered data on lifetime risk and provides estimates of risk reductions that can be anticipated with the implementation of lifestyle change, smoking cessation, blood pressure control, and lipid reduction. Use of the Reynolds Risk Scores could allow more accurate targeting of lipid-lowering therapy to those with the most appropriate levels of risk, thus increasing its net benefit and decreasing toxicity.
C-Reactive Protein and Parental History Improve Global Cardiovascular Risk Prediction. 
The Reynolds Risk Score for Men
Paul M Ridker, Nina P. Paynter, Nader Rifai, J. Michael Gaziano and Nancy R. Cook

Circulation. published online November 9, 2008;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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**Appendix A.** Beta-coefficients (standard errors) and P-values for incident cardiovascular events for covariates in Model A (based on traditional risk factors) and for covariates in Model B (the Reynolds Risk Score for men, based additionally on hsCRP and parental history).

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Model A Without hsCRP or Parental History</th>
<th>Model B With hsCRP and Parental History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (SE)   P</td>
<td>Beta (SE)   P</td>
</tr>
<tr>
<td>Age (ln years)</td>
<td>4.376 (0.260) &lt;0.001</td>
<td>4.385 (0.264) &lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (ln mm Hg)</td>
<td>2.779 (0.291) &lt;0.001</td>
<td>2.607 (0.292) &lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (ln mg/dL)</td>
<td>0.981 (0.162) &lt;0.001</td>
<td>0.963 (0.162) &lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (ln mg/dL)</td>
<td>-0.824 (0.080) &lt;0.001</td>
<td>-0.772 (0.082) &lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.485 (0.127) &lt;0.001</td>
<td>0.405 (0.127) &lt;0.001</td>
</tr>
<tr>
<td>hsCRP (ln mg/L)</td>
<td>---- ---- ----</td>
<td>0.102 (0.027) &lt;0.001</td>
</tr>
<tr>
<td>Parental History</td>
<td>---- ---- ----</td>
<td>0.541 (0.078) &lt;0.001</td>
</tr>
</tbody>
</table>
Appendix B. Model fit, discrimination, and reclassification indices in a global risk prediction algorithm based on traditional* factors (Model A) and on traditional factors plus hsCRP and parental history of myocardial infarction before age 60 years (Model B). Models also include terms for blood pressure (BP) treatment, lipid treatment, or both.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Endpoint</th>
<th>Measure</th>
<th>Model A Without CRP or Parental History</th>
<th>Model B With CRP and Parental History</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional + BP treatment</td>
<td>CVD</td>
<td>BIC</td>
<td>22625</td>
<td>22592</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-index</td>
<td>0.699</td>
<td>0.708</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J²</td>
<td>46.3***</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRI</td>
<td>---</td>
<td>5.2 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNRI</td>
<td>---</td>
<td>10.7 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traditional + lipid treatment</td>
<td>CHD</td>
<td>BIC</td>
<td>18838</td>
<td>18805</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-index</td>
<td>0.689</td>
<td>0.700</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J²</td>
<td>45.8***</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRI</td>
<td>---</td>
<td>2.9 %</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNRI</td>
<td>---</td>
<td>10.1 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traditional + BP treatment + lipid treatment</td>
<td>CVD</td>
<td>BIC</td>
<td>22610</td>
<td>22577</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-index</td>
<td>0.703</td>
<td>0.711</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J²</td>
<td>26.7***</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRI</td>
<td>---</td>
<td>3.8 %</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNRI</td>
<td>---</td>
<td>11.9 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traditional + BP treatment + lipid treatment</td>
<td>CHD</td>
<td>BIC</td>
<td>18817</td>
<td>18784</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-index</td>
<td>0.695</td>
<td>0.706</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J²</td>
<td>40.2***</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NRI</td>
<td>---</td>
<td>4.8 %</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNRI</td>
<td>---</td>
<td>13.8 %</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Traditional factors include age, blood pressure, smoking status, total and HDL cholesterol. BIC = Bayes Information Criterion; C-index = Harrell’s C-index, analogous to the area under the receiver operating characteristic curve; NRI = net reclassification improvement; CNRI = clinical net reclassification improvement. The J-squared and c-statistics are based on survival estimates at 7 years, and the NRI and CNRI are based on case-control status as of 7 years, ignoring censored observations.
** Likelihood ratio test for comparison of models, bootstrap for comparison of C-indices
*** P<0.01, indicating significant deviation of observed and predicted risk in reclassified strata
Appendix C: Computational formula for the Reynolds Risk Score for men

10-year cardiovascular disease risk (%) = \[1 - 0.8990 \cdot \exp(\text{B-33.097})\] \times 100\% where

\[
B = 4.385 \times \text{natural logarithm(age)} + 2.607 \times \text{natural logarithm(systolic blood pressure)} + 0.963 \times \text{natural logarithm(total cholesterol)} - 0.772 \times \text{natural logarithm(high-density lipoprotein cholesterol)} + 0.405 \text{ (if current smoker)} + 0.102 \times \text{natural logarithm(high-sensitivity C-reactive protein)} + 0.541 \text{ (if parental history of premature myocardial infarction)}
\]