# C-Reactive Protein and Reclassification of Cardiovascular Risk in the Framingham Heart Study

Peter W.F. Wilson, MD; Michael Pencina, PhD; Paul Jacques, DS; Jacob Selhub, PhD; Ralph D'Agostino, Sr, PhD; Christopher J. O'Donnell, MD, MPH

***Background***—The relationship of circulating levels of high-sensitivity C-reactive protein (CRP) with cardiovascular disease (CVD) risk, particularly with consideration of effects at intermediate levels of risk, has not been fully assessed.

***Methods and Results***—Among 3006 offspring participants in the Framingham Heart Study free of CVD (mean age, 46 years at baseline), there were 129 hard coronary heart disease (CHD) events and 286 total CVD events during 12 years of follow-up. Cox regression, discrimination with area under the receiver operating characteristic curve, and net reclassification improvement were used to assess the role of CRP on vascular risk. In an age-adjusted model that included both sexes, the hazard ratios for new hard CHD and total CVD were significantly associated with higher CRP levels. Similar analyses according to increasing homocysteine level showed significant protective associations for hard CHD but not for total CVD. In multivariable analyses that included age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, current smoking, hypertension treatment, and homocysteine, the log CRP level remained significantly related to development of hard CHD and total CVD and provided moderate improvement in the discrimination of events. The net reclassification improvement when CRP was added to traditional factors was 5.6% for total CVD ($P=0.014$) and 11.8% for hard CHD ($P=0.009$).

***Conclusions***—Circulating levels of CRP help to estimate risk for initial cardiovascular events and may be used most effectively in persons at intermediate risk for vascular events, offering moderate improvement in reclassification of risk.

**(*Circ Cardiovasc Qual Outcomes*. 2008;1:92-97.)**

**Key Words:** epidemiology ■ inflammation ■ risk factors ■ statistics

Traditional risk factors such as age, blood pressure, cholesterol, high-density lipoprotein cholesterol (HDL-C), and diabetes mellitus have been shown to be predictive of coronary heart disease (CHD) and cardiovascular disease (CVD) in a large number of prospective observational studies.[1] Novel biomarkers have also been suggested as indicators of increased risk and may contribute to vascular disease risk assessment over and above the use of traditional risk factors.[2–6] Descriptive statistics such as the relative risk of a new factor that is added to a multivariable prediction and the c statistic have been considered inadequate to convey how such new factors may mediate risk in a population setting, and there is great interest in the use of new methods to quantify such risks.[7,8]

**Clinical Perspective see p 97**

Information on circulating levels of C-reactive protein (CRP) may be used to refine estimates of cardiovascular risk stratification using newer methods of assessment.[9–11] This protein has generated interest as a potentially important biomarker of inflammation and cardiovascular risk, and recommendations for testing with this biomarker were made by the American Heart Association and the Centers for Disease Control in 2003.[12] We undertook analyses related to the development of both coronary disease and total CVD end points because there is growing interest in the prediction of total CVD as a vascular disease end point that is worthy of primary prevention; additionally, a recent Framingham publication has estimated risk of CVD as an initial vascular disease end point.[13]

With this background, we investigated the potential benefit of adding information on circulating levels of CRP and homocysteine to prediction equations that estimate vascular disease risk in a prospective study of middle-aged and older Framingham adults. We first analyzed the effects of these newer biomarkers using conventional assessment methods, and subsequently evaluated a newly described reclassification approach that used a multivariable model to predict an

Received October 23, 2008; accepted October 23, 2008.

From EPICORE (P.W.F.W.), Emory University School of Medicine, and the Atlanta VAMC Epidemiology and Genetics Section, Atlanta, Ga; National Heart, Lung, and Blood Institute (C.J.O.D.); National Heart, Lung and Blood Institute's Framingham Heart Study (M.P., R.D.A., C.J.O.D.), Framingham Mass; Department of Mathematics (M.P., R.D.A.), Boston University, Boston, Mass; Tufts USDA Nutrition Center (P.J., J.S.), Boston, Mass.

John A. Spertus, MD, handled this manuscript.

Correspondence to Peter W. F. Wilson, MD, Suite 1 North, Emory University School of Medicine, 1256 Briarcliff Rd, and the Atlanta VAMC Epidemiology and Genetics Section, Atlanta, GA 30306. E-mail peter.wf.wilson@emory.edu



*Circ Cardiovasc Qual Outcomes* **is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.108.831198**

individual's risk of developing or not developing a vascular outcome.[14]

## Methods

The second clinic visit of the Framingham Offspring Study from 1979 to 1983 served as the baseline for this study.[15] The examination included assessment of vascular disease prevalence and evaluation of vascular disease risk factors and was followed by surveillance for the development of new vascular events over the ensuing 12 years. New cases of "hard CHD" events during the follow-up interval included myocardial infarction and CHD-related death.[1] "Total CVD" was a composite measure of the CHD events listed above as well as angina pectoris, transient ischemic attack, stroke, and intermittent claudication. The diagnosis of angina pectoris was determined using information obtained at regular clinic visits and from personal medical records[1]; transient ischemic attack and stroke were determined from history, medical records, and adjudication by a panel of neurologists[16]; and intermittent claudication was evaluated on the basis of a structured questionnaire related to lower extremity symptoms that occurred when walking.[17]

During the clinic visit, information was obtained regarding cigarette smoking during the past year and medication use. Blood pressure after sitting for 5 minutes was measured using standardized methods.[18] Phlebotomy took place under fasting conditions. Lipid determinations were made at the time of the examination in the Framingham Heart Study laboratory. Plasma cholesterol was measured according to the Lipid Research Clinics Program Protocol, and HDL-C levels were determined after precipitation of non-HDL lipoproteins with heparin-manganese.[19] Aliquots were frozen at −20°C after the initial phlebotomy at the time of the baseline examination. In 2003, the previously unthawed specimens were thawed for measurement of high-sensitivity CRP and homocysteine. High-sensitivity CRP assays were performed in the Framingham laboratory using a previously described nephelometric method with Dade-Behring reagents.[20] Homocysteine values were determined in the laboratory of Dr Selhub using high-pressure liquid chromatography as previously described.[21]

Logarithmic transformations were used for homocysteine and CRP for analyses with continuous variables to decrease the effect of extreme observations. The hazard ratios (HRs) were estimated using a traditional Cox model that first evaluated age- and sex-adjusted effects, followed by a multivariable model that included the variables age, sex, cholesterol, HDL-C, systolic blood pressure, diabetes mellitus, blood pressure treatment, and cigarette smoking. The discriminatory capability of traditional variables and the novel risk factors CRP and homocysteine were evaluated using c statistics as described previously.[22,23] Similar analytic methods were used to test for the effects of 3 prespecified CRP categories (<1.00, 1 to 2.99, ≥3.00 mg/L) and tertiles of homocysteine on the risk of hard CHD and total CVD.

The effects of reclassification using CRP were assessed using recently published methods that estimated the net reclassification improvement (NRI),[14] which expands and improves on previously published reclassification methods.[23,24] The prediction model for each individual was reestimated with the information for the new factor included in the estimate. This method provides a more rigorous statistical approach to assess the improvement in reclassification by including new biomarker information into prediction models. The analyses used continuous variable information with evaluation of the effects on risk category reclassification for those cases and noncases during the follow-up interval. This approach separately analyzed the reclassification of persons who developed events and those who did not develop events. Reclassification to a higher risk group was considered upward movement/improvement in classification for those experiencing an event. On the other hand, reclassification downward was considered a failure for persons who developed an event. Conversely, among persons who did not experience an event, reclassification upward was considered disadvantageous, and reclassification downward was considered advantageous. Improvement in reclassification was estimated by taking the sum of differences in proportions of individuals reclassified upward minus the proportion reclassified downward for people who developed events and the proportion of individuals moving downward minus the proportion moving upward for those who did not develop events. Using this method, the overall reclassification sum is the NRI, and the statistical significance of the overall improvement is assessed with an asymptotic test, as described by Pencina et al.[14] The follow-up experience over 12 years was adjusted to 10-year categories of risk (0% to 6%, 6% to 20%, >20% risk) identified by the National Cholesterol Education Program and other experts for the reclassification analysis.[25,26] These estimates were made according to traditional variables (age, sex, systolic pressure, total cholesterol, HDL-C, diabetes mellitus, smoking status, and blood pressure therapy).

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.

**Table 1. Baseline Characteristics and Vascular Outcomes for Participants**

| Characteristic or Vascular Event | Men (n=1430) | Women (n=1576) |
|---|---|---|
| Age, years | 46 (9) | 45 (9) |
| Systolic blood pressure, mm Hg | 127 (15) | 119 (17) |
| Total cholesterol, mg/dL | 207 (36) | 203 (40) |
| HDL cholesterol, mg/dL | 43 (11) | 54 (14) |
| Diabetes mellitus, % | 4% | 1% |
| Current smoker, % | 35% | 37% |
| Blood pressure therapy, % | 11% | 9% |
| Body mass index, kg/m$^2$ | 26.8 (3.6) | 24.6 (4.7) |
| C-reactive protein, mg/L | 2.67 (5.17) | 2.28 (4.49) |
| Homocysteine, μmol/L | 7.69 (3.59) | 6.59 (3.99) |
| Vascular events, number | | |
| Hard CHD | 107 | 22 |
| Total CVD | 206 | 80 |

Data are presented as mean (SD), except where otherwise noted.

## Results

Table 1 shows the baseline characteristics of the participants and the number of vascular events. Their mean age was approximately 46 years, diabetes mellitus was uncommon and affected <5% of the men and women, and approximately 10% of the individuals were taking blood pressure medications. The mean CRP was 2.67 mg/L in men and 2.28 mg/L in women. The prevalence of CRP <1, 1 to 3, and >3 mg/L was 43%, 33%, and 24% in men and 52%, 28%, and 20% in women, respectively. The mean homocysteine levels were 7.69 μmol/L in men and 6.59 μmol/L in women. There were 129 hard CHD events and 286 total CVD events (intermittent claudication events, 26 in men and 16 in women; cerebrovascular disease events, 28 in men and 14 in women) during 12 years of follow-up.

Table 2 displays the age- and sex-adjusted HRs for new vascular disease events. The HRs show the effect on vascular disease risk per unit of log(homocysteine) and log(CRP). For example, the HR for the association of log(CRP) with hard CHD was 1.52 (95% CI, 1.32 to 1.76) after age and sex adjustment. The multivariable HR for the association of log(CRP) with hard CHD was 1.34 (95% CI, 1.14 to 1.58) in an analysis that included age, sex, systolic blood pressure,

**Table 2. CRP and Homocysteine Level HRs for Vascular Events**

| | Hard CHD | | Total CVD | |
|---|---|---|---|---|
| Factor | Age and Sex Adjusted* | Multivariable Adjusted† | Age and Sex Adjusted* | Multivariable Adjusted† |
| Log(CRP) | 1.52 (1.32–1.76) | 1.34 (1.14–1.58) | 1.42 (1.29–1.57) | 1.26 (1.12–1.40) |
| Log(homocysteine) | 0.53 (0.34–0.83) | 0.62 (0.40–0.95) | 0.85 (0.64–1.14) | 0.95 (0.72–1.27) |

*Adjusted for age and sex.

†Includes age, sex, systolic blood pressure, blood pressure therapy, cholesterol, HDL cholesterol, smoking, and diabetes mellitus.

blood pressure therapy, cholesterol, HDL-C, smoking, and diabetes mellitus. Statistically significant associations were also observed for associations of log(CRP) with total CVD in the age- and sex-adjusted analyses (HR, 1.42; 95% CI, 1.29 to 1.57), as well as for the multivariable analyses (HR, 1.26; 95% CI, 1.12 to 1.40). In age- and sex-adjusted models and in the multivariable models, lower homocysteine levels were associated with hard CHD with a HR in the 0.53 to 0.62 range, which was statistically significant. On the other hand, these effects were not observed for total CVD in the age- and sex-adjusted or multivariable-adjusted models.

Tertiles of homocysteine and commonly used categories of CRP (<1, 1 to 3, >3 mg/L) were analyzed in age- and sex-adjusted proportional hazards analyses to test for associations with risk for new vascular events (Table 3). The referent group in each instance was the lowest category. Significantly lower risk for hard CHD events was observed at the higher categories of homocysteine in the age- and sex-adjusted models. On the other hand, no significant associations were observed for homocysteine categories on total CVD risk. Statistically significant increased multivariable HRs were observed in persons with CRP >3.0 mg/L for hard CHD (HR, 1.88; 95% CI, 1.18 to 3.00) and for total CVD (HR, 1.58; 95% CI, 1.16 to 2.15).

Table 4 shows the c statistics for hard CHD and total CVD outcomes according to different prediction models. The traditional variables were included in a core multivariable proportional hazards regression analyses and the effects of adding information on homocysteine and CRP were analyzed. The c statistic for the traditional multivariable approach was 0.863 for hard CHD and 0.795 for total CVD. Only a small increment in the c statistic was observed when CRP or homocysteine information was added to the prediction model.

A total of 110 persons developed hard CHD, and 2896 did not develop this event during 10 years of follow-up (Figure 1); the follow-up interval for this analysis was statistically adjusted from 12 years to 10 years, which resulted in a smaller number of events shown in the reclassification figure compared with Table 1. We initially undertook this analysis to test the net reclassification effect of adding CRP to a predetermined multivariable prediction model that included age, sex, systolic blood pressure, blood pressure therapy, cholesterol, HDL-C, smoking, and diabetes mellitus. Persons were classified in 3 different categories according to traditional multivariable risk models (initial probability) and models that included the traditional variables and log(CRP). The majority of persons remained at the same level of risk (along the diagonal from upper left to lower right) after the CRP information was included as an additional variable in the prediction model. Some persons were reclassified upward (above the diagonal) and some were reclassified downward (below the diagonal).

The estimates in Figure 1 allow calculation of the NRI using methods reported by Pencina et al.[14] A total of 18 (8+10) people who developed hard CHD were reclassified upward and 6 (5+1) people who developed an event were reclassified downward. The net estimate for the percentage classified upward was the difference between these 2 esti-

**Table 3. CRP and Homocysteine Categories and HRs for Vascular Events**

| | | CRP Level, mg/L | | |
|---|---|---|---|---|
| Vascular Event | Statistical Adjustment | <1.00 (615 Men, 820 Women) | 1.00–2.99 (472 Men, 441 Women) | ≥3.00 (343 Men, 315 Women) |
| Hard CHD | Age-Sex | Referent | 1.44 (0.90–2.31) | 3.05 (1.97–4.74) |
| | Multivariable | Referent | 1.02 (0.63–1.65) | 1.88 (1.18–3.00) |
| Total CVD | Age-Sex | Referent | 1.38 (1.03–1.87) | 2.44 (1.82–3.25) |
| | Multivariable | Referent | 1.05 (0.77–1.42) | 1.58 (1.16–2.15) |
| | | Homocysteine Tertile | | |
| Vascular Event | Statistical Adjustment | Low (477 Men, 525 Women) | Middle (477 Men, 525 Women) | High (477 Men, 525 Women) |
| Hard CHD | Age-Sex | Referent | 0.76 (0.49–1.16) | 0.54 (0.35–0.84) |
| | Multivariable | Referent | 0.86 (0.56–1.32) | 0.61 (0.39–0.96) |
| Total CVD | Age-Sex | Referent | 0.93 (0.69–1.25) | 0.81 (0.60–1.08) |
| | Multivariable | Referent | 1.04 (0.77–1.40) | 0.91 (0.67–1.24) |

HRs are adjusted for age and sex. Multivariable model includes age, sex, systolic blood pressure, blood pressure therapy, cholesterol, HDL cholesterol, smoking, and diabetes mellitus.

**Table 4. Discrimination of Vascular Disease with Various Prediction Models**

| | c Statistic | |
|---|---|---|
| Model | Hard CHD | Total CVD |
| Multivariable | 0.863 | 0.795 |
| Multivariable + Log(CRP) | 0.865 | 0.799 |
| Multivariable + Log(Hcys) | 0.864 | 0.796 |
| Multivariable + Log(CRP) + Log(Hcys) | 0.867 | 0.799 |

Hcys indicates homocysteine. Multivariable model includes age, sex, systolic blood pressure, blood pressure therapy, cholesterol, HDL cholesterol, smoking, and diabetes mellitus.

mates divided by the total number of events [(18−6)/110=10.91%], which was statistically significant ($P$=0.014). Similar calculations for persons who did not develop an event revealed a total of 89 (74+15) people who were reclassified downward and 64 (51+13) people who were reclassified upward. The net estimate for those not developing a vascular event was the difference between these 2 estimates divided by the total number of people who did not develop an event [(89−64)/2896=0.86%], which was statistically significant ($P$=0.043). The NRI was then estimated by taking the sum of

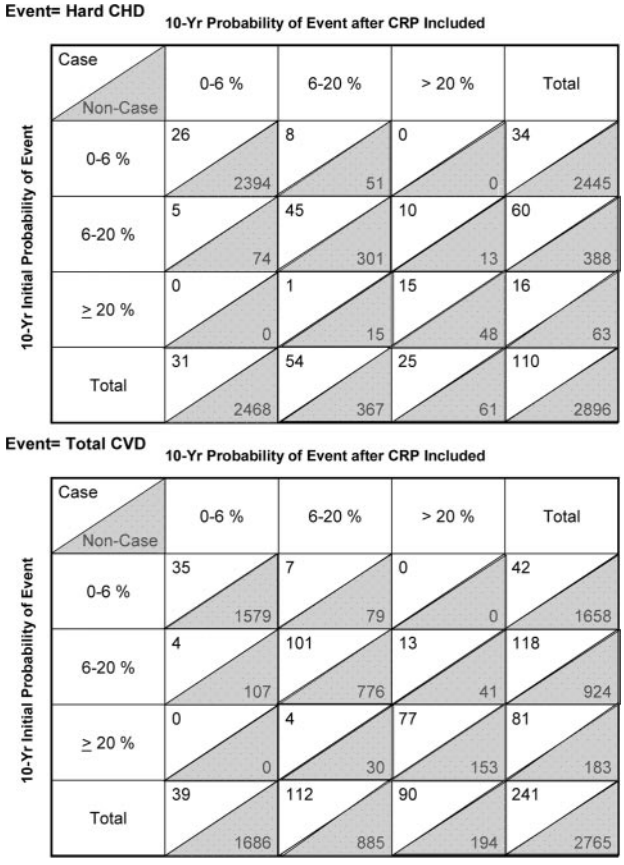


**Figure.** The number of participants in different categories of CHD risk with reclassification of risk category after inclusion of CRP information are displayed for hard CHD (top) and total CVD (bottom). Estimates of probabilities using traditional risk factors (vertical axis) and with traditional variables and inclusion of CRP information (horizontal axis) are shown. Each cell includes the number of cases (clear background) and noncases (shaded background).

the net estimates for those who developed an event and those who did not develop an event, which was 11.77% (10.91%+0.86%; $P$=0.009). Analogous calculations for total CVD from Figure 1 led to an estimated 4.98% ($P$=0.023) reclassified for those developing an event and 0.61% ($P$=0.289) for those not developing an event, which yielded an NRI of 5.59% ($P$=0.014).

As an exploratory analysis concerning effects of reclassification, we undertook a stepwise strategy that sequentially estimated the effects for several risk factors with the outcome of total CVD. We included age and sex as core factors and estimated the percent net reclassified and the c statistic for each variable added. For the addition of systolic blood pressure and treatment to the model, the percent net reclassification and the c statistic were 10.8% and 0.740, respectively; for the addition of lipids, 7.0% and 0.767, respectively; for the addition of smoking, 7.7% and 0.787, respectively; for the addition of diabetes, −0.5% and 0.795, respectively; and for the addition of log(CRP), 5.6% and 0.799, respectively. The order of adding the variables can affect the statistical significance of the contribution for each factor, and it is interesting that most factors add several percentage points to the reclassification index at the same time that modest increments in the c statistic are observed. The net reclassification effect for total CVD is identical to what we reported for the Figure 1 calculation of the net reclassification related to the multivariable model from Table 4.

## Discussion

This prospective study tested whether circulating levels of homocysteine and high-sensitivity CRP affected risk of first CHD events in middle-aged adults. The results showed a statistically significant association of high-sensitivity CRP with the incidence of hard CHD and total CVD in continuous variable analyses (Table 2) and in categorical analyses for CRP levels >3.0 mg/L (Table 3). The overall effect on discrimination with homocysteine, CRP, or both biomarkers was relatively insignificant for both hard CHD and for total CVD (Table 4). These results suggested that including each of these factors in an initial screening for vascular disease risk assessment did not measurably improve the ability to discriminate future cases and noncases. We report a significant association of lower homocysteine levels with greater risk for hard CHD in age-, sex-, and multivariable-adjusted regression models, but there was no significant association in models of homocysteine with total CVD (Tables 2 and 3). Reclassification methods that assessed CRP and vascular disease risk showed significant multivariable-adjusted effects of CRP on total CVD, although adding CRP to the list of traditional CHD risk factors had a minimal effect on discrimination of future events using the c statistic (Table 3), as shown in previous publications.[23,27] In our reclassification analysis that tested for CRP effects at different strata of CHD risk according to traditional risk factors, the analyses showed highly significant CRP effects (Table 4) and a NRI in the 7% to 9% range for hard CHD or total CVD when compared with models without CRP information being used in the initial estimation. Similar results have been reported by Cook[28] for CRP in a recently published letter, and she reported a 5.7% reclassification index value for CRP in the Women's Health

Study and a range of 4.7% to 8.4% for net reclassification in the various models used to develop the Reynolds risk score. Our results and those recently reported by Cook are relatively concordant and provide more conservative estimates of reclassification than what was reported previously by Cook et al[4] or in the original Reynolds risk score by Ridker et al[24] when both CRP and parental history were used in the reclassification model. Unfortunately, parental history of heart disease was not available for all Framingham participants at the 1979 examination, and the analyses did not allow incorporation of that element into the effects on reclassification without substantial reduction in sample size.

Reclassification can be considered from a variety of vantage points, and the exact utility of the method is not clear at the present time. Differences in reclassification with CRP or other new variables can stem from a variety of sources. The choice and number of categories used and absolute event rates for the study participants are key sources of variation that can help to explain the differences, as well as the use of NRI, described by Pencina et al,[14] as the performance measures. The NRI considers effects of upward, neutral, and downward reclassification of cases and noncases during follow-up, leading to a net reclassification that provides a more accurate estimate than that obtained with other approaches.

There is considerable interest in the development of effective strategies to identify persons at risk for CHD. Traditional risk factors such as age, sex, blood pressure, cholesterol, HDL-C, cigarette use, and diabetes mellitus have been used to screen persons at risk for CHD in the United States,[29] Europe,[30,31] and around the world.[32] Other biomarkers have been tested in prospective cohort studies for effects in prediction models that have included traditional vascular disease risk models. As with our results, newer biomarkers such as CRP may be statistically related to the development of CHD but using the test for screening or clinical practice is less certain. The addition of newer biomarkers in a previous Framingham publication and results of other studies of CRP in risk prediction have generally shown modest effects in terms of their discriminatory ability to help identify new cases of CHD during follow-up, and there was minimal change in the area under the receiver operating characteristic curve with the new biomarker added.[23,33]

The Framingham offspring experience reported in this study reflects that of a suburban, community-based population sample that is largely white, and follow-up took place from the middle of the 1990s onward. At baseline, the participants often had relatively normal blood pressure levels, and during follow-up, blood pressure medication was common. The overall effects of baseline blood pressure on CHD risk has been previously reported as smaller in the Framingham offspring than in the first-generation Framingham cohort during the first 12 years of follow-up, and effects were largely related to diastolic blood pressure levels.[34] Similarly, drug treatment for lipoprotein cholesterol abnormalities was uncommon at the 1990 index examination for the offspring included in this investigation. Additionally, the participants had a mean age of 46 years at baseline, their risk factor burden was relatively light concerning hypertension and diabetes mellitus, and the incidence of cardiovascular events during follow-up was relatively modest in comparison with older population groups. Different results may be obtained in other settings, especially in more recent times, when treatment of risk factors has become much more prevalent, and both excess adiposity and diabetes mellitus are more common.

The significant reclassification effects of CRP highlight the need to use risk factor assessment strategies that focus testing on those most likely to benefit. One possible approach would be a 2-step strategy that first would identify persons at intermediate risk for the vascular outcome via traditional risk factors and then further stratify risk based on follow-up testing.[26,35] Additional research is needed regarding the effectiveness of 2-step approaches that use reclassification of risk after consideration of additional risk factor information, and cost-effectiveness strategies should provide even more information concerning the absolute degree of risk and costs to detect persons at higher risk.

Identifying persons at risk for CVD is a dynamic field, and newer tests and analytic strategies are constantly being evaluated to improve our ability to assess risk more accurately so that the most appropriate follow-up and care can be provided. Our findings in a cohort with a moderate proportion of persons at intermediate risk for CVD showed no improvement in the c statistic, but with a reclassification approach, we saw a net reclassification that was in the 5% to 10% range. There are many unanswered questions concerning estimation of cardiovascular risk that are related to discrimination and reclassification. The order in which variables are included in risk prediction equations can affect some of the results and interpretation of the findings. Intermediate risk is an arbitrary condition that will change as risk factors are more effectively controlled. Such changes alone will pose new challenges to researchers. Our analytic approach included traditional cardiovascular risk factors first and then evaluated the role of CRP as a new biomarker, but other analytic strategies are possible. We have a better understanding of how risk prediction works at the present time compared with the past, but much is left to be accomplished to improve the identification of persons who will later develop cardiovascular events.

## Acknowledgments

The authors acknowledge the computer programming assistance of Peter Shrader.

## Sources of Funding

This study was supported by grant R01 HL073272 (to P.W.F.W.) from the Framingham Heart Study of the National Heart, Lung, and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (contract N01 HC-25195).

## Disclosures

None.

## References

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
2. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836–843.
3. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. *Circ Res*. 2001;89:763–771.

4. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med*. 2006;145:21–29.
5. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation*. 1999;100:230–235.
6. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA*. 2001;285:2481–2485.
7. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007;115:928–935.
8. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol*. 2004;159:882–890.
9. Bostom AG, Silbershatz H, Rosenberg IH, Selhub J, D'Agostino RB, Wolf PA, Jacques PF, Wilson PW. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular disease mortality in elderly Framingham men and women. *Arch Intern Med*. 1999;159:1077–1080.
10. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PWF, Belanger AJ, O'Leary DH, Wolf PA, Schaefer EJ, Rosenberg IH. Association between plasma homocysteine and extracranial carotid stenosis. *N Engl J Med*. 1995;332:286–291.
11. Vasan RS, Beiser A, D'Agostino RB, Levy D, Selhub J, Jacques PF, Rosenberg IH, Wilson PW. Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction. *JAMA*. 2003; 289:1251–1257.
12. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
13. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
14. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172.
15. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med*. 1975;4:518–525.
16. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;3:312–318.
17. Murabito JM, D'Agostino RB, Silbershatz H, Wilson PWF. Intermittent claudication: a risk profile from the Framingham Heart Study. *Circulation*. 1997;96:44–49.
18. Wilson PW, Garrison RJ, Castelli WP, Feinleib M, McNamara PM, Kannel WB. Prevalence of coronary heart disease in the Framingham Offspring Study: role of lipoprotein cholesterols. *Am J Cardiol*. 1980;46:649–654.
19. Manual of Laboratory Operations: Lipid Research Clinics Program, Lipid and Lipoprotein Analysis. 2ed. Washington, DC: National Institutes of Health, US Dept of Health and Human Services; 1982.
20. Wang TJ, Larson MG, Levy D, Benjamin EJ, Kupka MJ, Manning WJ, Clouse ME, D'Agostino RB, Wilson PW, O'Donnell CJ. C-reactive protein is associated with subclinical epicardial coronary calcification in men and women: the Framingham Heart Study. *Circulation*. 2002;106:1189–1191.
21. Selhub J, Jacques PF, Wilson PWF, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in the elderly. *JAMA*. 1993;270:2693–2698.
22. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med*. 2004;23:2109–2123.
23. Wilson PW, Nam BH, Pencina M, D'Agostino RB Sr, Benjamin EJ, O'Donnell CJ. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham heart study. *Arch Intern Med*. 2005;165:2473–2478.
24. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297:611–619.
25. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
26. Greenland P, Smith JS Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation*. 2001;104:1863–1867.
27. Folsom AR, Aleksic N, Catellier D, Juneja HS, Wu KK. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2002;144:233–238.
28. Cook NR. Comments on "Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond." *Stat Med*. 2008;27:191–195.
29. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
30. Assmann G, Schulte H, Oberwittler W. New aspects in the prediction of coronary artery disease: the Prospective Cardiovascular Munster Study. In: Fidge NH, Nestel PJ, eds. *Atherosclerosis VII*. Amsterdam: Elsevier; 1986: 19–24.
31. Ferrario M, Chiodini P, Chambless LE, Cesana G, Vanuzzo D, Panico S, Sega R, Pilotto L, Palmieri L, Giampaoli S. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol*. 2005;34:413–421.
32. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA*. 2004;291:2591–2599.
33. Albert MA, Glynn RJ, Ridker PM. Plasma concentration of C-reactive protein and the calculated Framingham Coronary Heart Disease Risk Score. *Circulation*. 2003;108:161–165.
34. Wilson PWF, Anderson KM, Castelli WP, Kannel WB. Twelve-year incidence of coronary heart disease in middle-aged adults during the era of hypertensive therapy: the Framingham Offspring Study. *Am J Med*. 1991; 90:11–16.
35. Wilson PW, Smith SC Jr, Blumenthal RS, Burke GL, Wong ND. 34th Bethesda Conference: Task Force #4: How do we select patients for atherosclerosis imaging? *J Am Coll Cardiol*. 2003;41:1898–1906.


## CLINICAL PERSPECTIVE

This study investigated the relationship of circulating levels of high-sensitivity C-reactive protein (CRP) with cardiovascular disease (CVD) risk and evaluated the role of risk reclassification. The study was based on the experience of 3006 Framingham Offspring participants in the Framingham Heart Study who were free of CVD at baseline. The relative risk for new hard CHD and total CVD were significantly associated with higher CRP levels, and in multivariable analyses that included age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, current smoking, hypertension treatment, and homocysteine, the log(CRP) level remained significantly related to development of hard CHD and total CVD and provided moderate improvement in the discrimination of events. The net reclassification improvement when CRP was added to traditional factors was 5.6% for total CVD ($P=0.014$) and 11.8% for hard CHD ($P=0.009$). We concluded that circulating levels of CRP help to estimate risk for initial cardiovascular events and may be used most effectively in persons at intermediate risk for vascular events, offering moderate improvement in reclassification of risk.

# C-Reactive Protein and Reclassification of Cardiovascular Risk in the Framingham Heart Study

Peter W.F. Wilson, Michael Pencina, Paul Jacques, Jacob Selhub, Ralph D'Agostino, Sr and Christopher J. O'Donnell

*Circ Cardiovasc Qual Outcomes.* 2008;1:92-97; originally published online November 9, 2008;
doi: 10.1161/CIRCOUTCOMES.108.831198
*Circulation: Cardiovascular Quality and Outcomes* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713