C-Reactive Protein and Risk of Cardiovascular Disease in Men and Women From the Framingham Heart Study

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Background: Determination of C-reactive protein (CRP) level has been suggested to improve cardiovascular disease (CVD) risk assessment. This study examines the utility of CRP levels to assess CVD risk in a community setting.

Methods: We performed a prospective observational cohort study on a community population sample. A total of 1949 men and 2497 women without CVD from the Framingham Heart Study underwent CVD risk factor assessment. Initial CVD events during 8 years of follow-up were recorded.

Results: There were 283 major CVD and 160 major coronary heart disease incident events. Age-, sex-, and multivariable-adjusted analyses generally used CRP level categories of less than 1, 1 to 3, and greater than 3 mg/L. In age- and sex-adjusted models, the traditional risk factors and elevated CRP levels indicated increased risk. The age- and sex-adjusted relative risk (RR) and 95% confidence interval (CI) of CRP level greater than 3 mg/L for major CVD was elevated (RR, 1.60; 95% CI, 1.19-2.14), with evidence of attenuation (RR, 1.22; 95% CI, 0.90-1.66) in multivariable models. The *C* statistic, a measure of the discriminatory capability of the prediction models, was 0.74 for prediction of major CVD with age and CRP level. In multivariable models that included traditional risk factors, the *C* statistic was 0.78, a value that was unchanged with the addition of CRP to the multivariable model. Similar relations were noted for major coronary heart disease events.

Conclusion: Elevated CRP level provided no further prognostic information beyond traditional office risk factor assessment to predict future major CVD and major coronary heart disease in this population sample.

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TRADITIONAL RISK FACTORS for coronary heart disease (CHD) and cardiovascular disease (CVD) have been shown to effectively predict vascular disease events.[1-3] Age, sex, blood pressure, total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, and cigarette smoking have been considered key factors to assess risk of vascular disease, using continuous or categorical variables. In addition, type 2 diabetes mellitus is highly related to CVD risk, and disease management guidelines in the United States now consider this diagnosis a coronary disease risk equivalent because it augments vascular disease risk so markedly.[4,5]

Considerable interest exists in moving beyond traditional risk factors to predict CHD events. Although traditional risk factors account for much of the risk for CHD events, and at least 1 risk factor precedes 87% to 100% of CHD deaths, not all CHD risk is explained by the combined effect of traditional risk factors.[6] The situation that stirs the greatest interest is screening of middle-aged and older individuals who have yet to experience clinical CVD. The factors and procedures that might improve CHD risk assessment in this

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situation are being scrutinized in observational studies that have follow-up for incident events.

Assessment of a novel risk factor requires an appreciation of several issues.[7] The first is whether the measurement is standardized, accurate, precise, and reproducible in a population setting. A second issue is whether the new factor pro-

vides added information over and above what is available with existing assessments. Finally, the existence of a sound biological basis for the measurement, consistent results in observational studies, the potential for interventions to alter the factor, and cost are concerns that need to be addressed before including a new factor in CHD risk assessment.[8,9]

The Framingham Heart Study provides an opportune cohort in which to test the usefulness of novel risk factors such as inflammatory markers to improve our prediction of initial CHD. Combining the experience of the original Framingham cohort and the second-generation Framingham offspring with 5 years of follow-up for new CVD events allowed this analytic approach to be tested in a community setting.

METHODS

Participants in the original Framingham cohort and the second-generation offspring were considered for this study. The original cohort examination took place in 1980 and served as the baseline for this investigation. The second-generation offspring baseline examination included participants who attended their fifth examination, which took place in 1991-1995. Only persons free of CVD at the baseline examination were considered for inclusion in this study, and all participants were followed up for 8 years for the development of new vascular disease events. A total of 1136 participants in the original cohort and 3310 from the offspring sample attended the baseline examination, had their C-reactive protein (CRP) level measured, and were free of prevalent CVD. The study was approved by the Boston University Medical Center Investigational Review Board, and all participants signed written informed consent.

Baseline risk factor information was available from the baseline examination cycle for age, cigarette smoking during the past year, presence of diabetes mellitus, systolic and diastolic blood pressure measurements obtained in the sitting position, use of blood pressure medications, and body mass index (calculated as weight in kilograms divided by the square of height in meters). Total cholesterol and HDL-C levels were measured at the time of the examinations,[10,11] and the laboratory participated in the quality control administered by the Lipid Research Clinics Program and the Centers for Disease Control and Prevention.[10] Persons with a fasting glucose level of 126 mg/dL or higher (≥6.99 mmol/L) or who were being treated with insulin or oral hypoglycemic agents were considered diabetic. Serum frozen at −20°C and thawed in 1999 was used to determine CRP level (Hemagen Diagnostics Inc, Columbia, Md).[12] Blood samples were collected from an antecubital vein between 8 and 9 AM, with participants in a supine position after an overnight fast. The coefficient of variation for the Hemagen CRP was 8% to 12% for a CRP level less than 1.0 mg/L and 5% to 8% for a CRP level of 1.0 mg/L or greater. On split specimens the correlation coefficient for the Hemagen CRP was 0.86, as previously reported.[13] The Pearson product moment correlation between the Hemagen and Dade Behring Inc (Deerfield, Ill) CRP methods for 80 specimens obtained at a later Framingham examination was 0.98, and assignment to CRP quartiles for those split specimens was identical for the Hemagen and Dade Behring techniques. The coefficient of variations for glucose determinations made for this article was 2.7%.

The participants were followed up for the development of initial major CHD (recognized myocardial infarction or CHD death), major CVD (major CHD, stroke, or stroke death), and total CVD (major CVD, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure) using previously described methods.[14] Surveillance for CVD events occurred during each examination cycle at the Framingham Heart Study clinic and included review of medical records from physician office visits and hospitalizations for heart and cerebrovascular disease. All outcomes were adjudicated by an end point committee that consisted of 3 trained physicians (P.W.F.W., E.J.B., and C.J.O.).[14]

Sex-pooled Cox proportional hazards regression was used to examine the risk factors that predicted 3 outcomes: major CHD, major CVD, and total CVD. The relative risks (RRs) were calculated for each risk factor in age- and sex-adjusted and multivariable-adjusted models. Variables included in the CVD prediction analyses were predetermined and based on the published experience for this cohort age. They included age, systolic blood pressure, total cholesterol/HDL-C ratio, diabetes mellitus, cigarette smoking, and blood pressure treatment. Obesity has been shown not to be statistically associated with CVD outcomes in this database, and body mass index and waist girth were not used in the analyses.

For age and systolic blood pressure, the RR and its 95% confidence interval (CI) are based on a 10-U increase. Discrimination, a model's ability to correctly distinguish events and nonevents or predict the order of events on the the basis of the baseline risk factor profile, was calculated using the overall *C* statistic.[15,16] It can be described as the probability that for any 2 people the model assigns a higher probability of event-free survival to the 1 who survives longer. Reported *C* statistic levels range from 0.50 (no discrimination) up to a maximum of 1.0 (perfect discrimination). Comparisons were made between the models with CRP and without CRP. Statistical methods included Cox proportional hazards regression and discrimination analyses that included *C* statistic comparisons with CIs around the estimates.[14,16] The Kaplan-Meier and log-rank procedures were used to test for effects of CRP tertiles on risk of vascular outcomes in persons with CHD estimated using a previously published equation that estimates risk of major CHD events with traditional variables. We used SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC) to perform all statistical analyses. All tests were 2 sided, and $P<.05$ was considered statistically significant.

RESULTS

There were 1136 participants from the original cohort, including 433 men and 703 women. Correspondingly, there were 3310 offspring participants, including 1516 men and 1794 women. A total of 283 new major CVD events, 160 new major CHD events, and 466 new total CVD events occurred during follow-up (**Table 1**). Mean levels and frequencies of traditional risk factors are given in **Table 2** for men and women. The average age was 57 years in men and 59 years in women. The total cholesterol level was in the 205 to 215 mg/dL (5.31-5.57 mmol/L) range for most participants, current or previous cigarette smoking was reported in approximately 20%, blood pressure treatment was reported in 20% of the sample, and approximately 7% had type 2 diabetes mellitus.

Table 3 gives the RRs for development of new major CHD, major CVD, and total CVD events after adjustment for age and sex and each of the single traditional risk factor variables. Initial multivariable analyses using the traditional variables did not show different effects for the variables in men or women, and there was no evidence of differential effects in the first- and second-generation

Table 1. Number of CVD Events During 8 Years and Participants at Risk*

Events	Original Cohort		Offspring Cohort		Total	
	Men	Women	Men	Women	Men	Women
Major CHD†	67	31	43	19	110	50
Major CVD‡	97	75	69	42	166	117
Total CVD§	137	124	137	68	274	192
Participants at risk	433	703	1516	1794	1949	2497

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.
*Data are presented as number of participants.
†Major CHD includes recognized myocardial infarction and CHD death.
‡Major CVD includes major CHD, stroke, and stroke death.
§Total CVD includes major CVD, angina pectoris, coronary insufficiency, intermittent claudication, and congestive heart failure.

samples (data not shown), so we have presented the analyses using combined data for both sexes and including the offspring and first-generation cohort experience. Increasing age, systolic blood pressure, total cholesterol/HDL-C ratio, diabetes mellitus, cigarette smoking, and blood pressure drug treatment were each significantly and independently related to the development of new CVD events in both sexes, with a few exceptions.

The age- and sex-adjusted RRs for the development of new major CHD, major CVD, and total CVD using the lowest category of CRP as the referent group are given in **Table 4**. The age- and sex-adjusted RRs for major CHD and major CVD in the participants with a CRP level greater than 3.0 mg/L were 1.68 (95% CI, 1.14-2.49) and 1.60 (95% CI, 1.19-2.14), respectively. There was evidence of a sex interaction with CRP level only for the outcome total CVD ($P=.05$). Statistically significant effects of CRP were observed only when the level exceeded 3.0 mg/L; effect sizes for the intermediate category of CRP level of 1.00 to 3.00 mg/L were more modest and not statistically significant.

The multivariable RRs for new CVD according to traditional variables and the 3 clinically relevant CRP categories are given in **Table 5**. Statistical significance for the traditional variables in Table 5 generally paralleled the individual risk factor analyses presented in Table 3, but the RRs for CRP were attenuated in the multivariable analyses compared with the age-adjusted CRP results (Table 4). Furthermore, after multivariable adjustment, none of the RR estimates for the CRP categories of 1.00 to 3.00 mg/L or greater than 3.00 mg/L were statistically significant compared with the referent level of CRP less than 1.00 mg/L.

The ability to discriminate CVD cases was evaluated by calculation of the *C* statistic for men and women (**Table 6**). For age- plus sex-adjusted CRP levels alone, the *C* statistics (measures of discrimination of cases vs noncases) of major CHD and major CVD were 0.75 and 0.74, respectively. This result implies that given any 2 individuals we have a 75% chance of correctly predicting the individual who will develop the event vs the individual who will not develop the event. For the age- plus sex-adjusted total cholesterol/HDL-C ratio, the comparable *C* statistics were 0.77 and 0.76, respectively. A model that incorporated all the traditional CVD risk factors was superior to either the model incorporating age- plus sex-adjusted CRP levels or age- and sex-adjusted total cholesterol/HDL-C ratio in its ability to discriminate major CHD ($C=0.80$) and major CVD ($C=0.78$) cases vs noncases during follow-up. A full predictive model, including traditional risk factors and the CRP categories, provided no added discriminatory capability over and above the traditional model in both sexes ($C=0.80$ for major CHD, $C=0.78$ for major CVD).

Table 2. Characteristics of the Study Participants*

Factor	Men (n = 1949)	Women (n = 2497)
Age, y	57 (11)	59 (11)
Systolic blood pressure, mm Hg	131 (18)	128 (21)
Total cholesterol, mg/dL	204 (36)	215 (41)
HDL-C, mg/dL	44 (12)	56 (15)
Diabetes mellitus, %	9	6
Current smoking, %	19	20
Blood pressure treatment, %	20	21
BMI	27.9 (4.1)	26.7 (5.3)
CRP level in <1.0-mg/L group, mg/L	0.3 (0.3)	0.3 (0.3)
Participants with CRP level <1.0 mg/L, %	38	35
CRP level in 1- to 3-mg/L group, mg/L	1.8 (0.6)	1.9 (0.6)
Participants with CRP level of 1-3 mg/L, %	27	24
CRP level in >3.0-mg/L group, mg/L	9.7 (8.5)	11.1 (15.4)
Participants with CRP level >3.0 mg/L, %	35	41

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol.
SI conversion factor: To convert total cholesterol and HDL-C to millimoles per liter, multiply by 0.0259.
*Data are presented as mean (SD) unless otherwise indicated.

Table 7 gives the estimated 10-year major CVD rates according to CRP levels after prior stratification of persons according to their 10-year CHD risk estimate using a major CHD risk score model developed by D'Agostino et al[2] that takes into consideration sex, age, blood pressure, total cholesterol level, HDL-C level, smoking, and diabetes mellitus. The 8-year follow-up information was used to generate the table, and the results were extrapolated to 10 years to aid the comparisons between estimates and actual experience. Tertiles of CRP were used in these analyses to ensure an adequate representation of CRP levels for all strata under investigation. The CRP tertiles generally had no effect at low (<10.00%), intermediate (10.00%-19.99%), or high (≥20.00%) 10-year risk level. The CRP tertiles showed an effect at low (<10.00%), but not at intermediate (10.00%-19.99%) or high (<20.00%) 10-year risk level.

Table 3. Relative Risks for New Major CHD and Major and Total CVD Associated With Traditional Risk Factors*

Risk Factor	Unit Effect	RR (95% CI)		
		Major CHD	Major CVD	Total CVD
Model adjusted for age and sex				
Age	10 y	1.95 (1.68-2.28)	2.09 (1.86-2.34)	2.04 (1.87-2.23)
Model adjusted for age, sex, and the following risk factor†				
Systolic blood pressure	10 mm Hg	1.13 (1.04-1.23)	1.14 (1.07-1.21)	1.15 (1.09-1.20)
Total cholesterol/HDL-C ratio	1 Unit	1.20 (1.11-1.31)	1.15 (1.08-1.23)	1.18 (1.12-1.24)
Diabetes	Yes/no	2.16 (1.45-3.22)	2.02 (1.48-2.76)	2.01 (1.57-2.57)
Current smoking	Yes/no	1.63 (1.11-2.40)	1.52 (1.13-2.03)	1.43 (1.13-1.80)
Blood pressure treatment	Yes/no	1.22 (0.87-1.73)	1.23 (0.95-1.60)	1.34 (1.09-1.64)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; RR, relative risk.
*Analyses include persons with diabetes mellitus.
†Age- and sex-adjusted model entries are for the individual models predicting the specified outcomes after adjustment for age, sex, and the variable in the column.

Table 4. Age- and Sex-Adjusted CRP Level and Relative Risk for Major CHD and Major and Total CVD Incidence

CRP Level, mg/L	RR (95% CI)		
	Major CHD	Major CVD	Total CVD
<1.00	Referent	Referent	Referent
1.00-3.00	1.44 (0.93-2.23)	1.35 (0.97-1.88)	1.19 (0.92-1.55)
>3.00	1.68 (1.14-2.49)	1.60 (1.19-2.14)	1.54 (1.23-1.93)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; RR, relative risk.

COMMENT

We found no additional predictive value of CRP measurements in estimating risk of new cardiovascular events in this study. The blood biomarker CRP is thought to be the best indicator of vascular inflammation that can be reliably measured,[7] and knowing CRP levels in our study showed little benefit in discriminating future major CHD and major CVD cases from noncases. From the Framingham experience, inclusion of CRP testing at the time of screening for CVD and CHD risk does not appear to provide a great benefit for CVD risk assessment, especially because the *C* statistic results did not increase with the addition of CRP levels over and above traditional risk factors.

In our study, CRP level alone was an effective discriminator of future major CHD and major CVD cases, a finding that is consistent with most clinical and subclinical vascular disease studies in which CRP levels have been highly related to CVD.[17,18] Meta-analyses have also generally shown an increased risk for CHD in persons with higher CRP levels,[19,20] and it has been reported that CRP levels may improve estimation of risk for CHD events in both sexes.[20-22] In addition, CRP and interleukin 6 may be increased in persons before the development of type 2 diabetes mellitus.[17,19,23,24]

A variety of environmental factors may be associated with higher CRP levels, including exogenous estrogen use and adiposity.[25,26] On the other hand, lower levels of CRP may occur with statins, physical activity, and alcohol intake.[27-29] There has been some concern about the accuracy and precision of CRP testing,[7] but the newer assays appear to categorize individuals consistently and the Centers for Disease Control and Prevention is enacting a quality control program.[30]

A critical issue for CRP testing is whether the assay improves prediction of clinical CVD events. A number of observational studies[21,31-37] have suggested that CHD prediction is improved for men and women, using cross-sectional and prospective designs. Some prospective studies[20] have not confirmed a clinically important independent predictive ability of CRP over and above traditional risk factors. Reports[7,37-40] have also suggested that selective testing should be considered, and measuring CRP levels, or other novel markers, may provide benefit for individuals at an intermediate level of CVD or CHD risk.

Our findings suggest that the incremental benefit of CRP testing would be negligible. Some differences have occurred in some of the published reports that might help to explain the more modest incremental predictive value of CRP in our cohort. First, in the Framingham Heart Study all risk factors were determined in an identical manner as a typical office evaluation. Blood pressure was measured directly by a physician as a standardized procedure, and diabetes status and lipid levels were determined by blood testing. Other studies obtain some of the risk factor information by report in a questionnaire rather than direct measurement. Self-reported risk factors may lead to misclassification of risk factor status and a poorer performance of risk factors in risk algorithms. Second, different results might be obtained for prediction of more specific CVD outcomes. It is possible that CRP is more highly related to the occurrence of specific atherothrombotic CVD events, such as myocardial infarction or CHD death, especially in the setting of acute coronary syndromes.[41] Our study had insufficient numbers of individual myocardial infarction or CHD death events to test this hypothesis. Finally, it is possible that high-sensitivity assays may differ in their ability to discriminate future CVD cases. In our study, CRP alone performs well in risk discrimination, in concordance with many other positive studies of CRP. The coefficient of

Table 5. CRP Level and Multivariable Adjusted Relative Risks for New Major CHD and Major and Total CVD*

Factor	Unit Effect	RR (95% CI)		
		Major CHD	Major CVD	Total CVD
CRP level <1.00 mg/L	. . .	Referent	Referent	Referent
CRP level 1.00-3.00 mg/L	Yes/no	1.38 (0.88-2.15)	1.32 (0.95-1.85)	1.16 (0.89-1.50)
CRP level >3.00 mg/L	Yes/no	1.22 (0.81-1.84)	1.22 (0.90-1.66)	1.16 (0.92-1.47)
Age	10 y	1.83 (1.54-2.17)	1.90 (1.66-2.16)	1.81 (1.64-2.00)
Systolic blood pressure	10 mm Hg	1.13 (1.04-1.23)	1.14 (1.07-1.21)	1.15 (1.09-1.20)
Total cholesterol/HDL-C ratio	1 Unit	1.20 (1.10-1.30)	1.15 (1.07-1.23)	1.17 (1.11-1.24)
Diabetes mellitus	Yes/no	2.16 (1.44-3.23)	2.02 (1.47-2.76)	2.00 (1.56-2.55)
Current smoking	Yes/no	1.59 (1.08-2.35)	1.48 (1.10-2.00)	1.40 (1.11-1.77)
Blood pressure treatment	Yes/no	1.21 (0.86-1.73)	1.22 (0.94-1.59)	1.32 (1.08-1.62)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; RR, relative risk.
*Statistical model includes all of the traditional factors in the left column and indicator variables for CRP level of 1.00 to 2.99 mg/L and CRP level of 3.00 mg/L or higher.

Table 6. *C* Statistics for Discrimination of CHD and CVD Outcomes With Various Predictive Models

Model	*C* Statistic (95% CI)		
	Major CHD	Major CVD	Total CVD
CRP levels*	0.75 (0.72-0.79)	0.74 (0.71-0.77)	0.74 (0.72-0.76)
Total cholesterol/ HDL-C ratio*	0.77 (0.78-0.80)	0.76 (0.73-0.78)	0.76 (0.74-0.78)
Traditional†	0.80 (0.77-0.83)	0.78 (0.76-0.80)	0.78 (0.76-0.80)
Traditional and CRP levels	0.80 (0.77-0.83)	0.78 (0.75-0.80)	0.78 (0.76-0.80)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol.
*All models are adjusted for age and sex.
†Traditional risk factor variables include age, sex, systolic blood pressure, total cholesterol/HDL-C ratio, diabetes mellitus, and cigarette smoking.

Table 7. CRP Tertile and Calculated 10-Year Risk of Vascular Events According to CHD Risk Level Determined With Traditional Risk Factors*

Variable	CHD Risk Level, %		
	<10.00	10.00-19.99	≥20.00
Persons at risk, No.	2548	1222	676
Incident cases, No.	60	124	99
CRP level of 0-0.81 mg/L, %	2.64	14.99	15.39
CRP level of 0.82-3.78 mg/L, %	3.45	16.65	23.36
CRP level of 3.79-333 mg/L, %	6.10	14.01	24.18
P value	.03	.77	.42

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease.
*The traditional risk factor variables age, sex, systolic blood pressure, total cholesterol/HDL-C ratio, diabetes mellitus, and cigarette smoking were used in the analyses. The follow-up interval for CVD events was 8 years, and the results in this table were extrapolated to 10 years by multiplying the 8-year rates by 1.25.

variation for our CRP assay is acceptable at higher levels (CRP ≥1.00 mg/L), above which consensus groups have suggested that a CRP value is a potential risk marker, although the coefficient of variation for our assay is somewhat higher at low levels (CRP <1.00 mg/L).

Investigators from the Atherosclerosis Risk in Communities (ARIC) study[42,43] have reported that a battery of novel risk factors added to the prediction of major CHD events in persons with and without type 2 diabetes mellitus, but single novel factors were generally unimpressive in their ability to improve the prediction of CHD events. The ARIC study results and those reported in the current investigation suggest that development of new CHD and CVD risk estimating equations should proceed with caution, bearing in mind that single factors may add little to the prediction of CVD in the community. It has been suggested that the same situation might not hold for prediction of CHD risk within specific subgroups. For example, coronary artery calcification scoring improved assessment of CHD risk for persons believed to be at intermediate risk using traditional risk factor assessment.[44,45] In addition, the ARIC investigators have recently shown that the highest tertile of CRP, in the setting of low-density lipoprotein cholesterol levels less than 130 mg/dL (3.37 mmol/L) and elevated phospholipase A_2 assay, identified persons at elevated risk for CHD events.[37] Further research may be needed to identify the patient subgroups in which testing for CRP, other new biomarkers, and other imaging tests might offer clinically important incremental value in terms of both risk prediction and preventive treatment benefit.

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