C-Reactive Protein and the 10-Year Incidence of Coronary Heart Disease in Older Men and Women

The Cardiovascular Health Study

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Background—High C-reactive protein (CRP) is associated with increased coronary heart disease risk. Few long-term data in the elderly are available.

Methods and Results—Baseline CRP was measured in 3971 men and women ≥65 years of age without prior vascular diseases; 26% had elevated concentrations (>3 mg/L). With 10 years of follow-up, 547 participants developed coronary heart disease (CHD; defined as myocardial infarction or coronary death). With elevated CRP, the 10-year cumulative CHD incidences were 33% in men and 17% in women. The age-, ethnicity-, and sex-adjusted relative risk of CHD for CRP >3 mg/L compared with <1 mg/L was 1.82 (95% CI, 1.46 to 2.28). Adjusting for conventional risk factors reduced the relative risk to 1.45 (95% CI, 1.14 to 1.86). The population-attributable risk of CHD for elevated CRP was 11%. Risk relationships did not differ in subgroups defined by baseline risk factors. We assessed whether CRP improved prediction by the Framingham Risk Score. Among men with a 10-year Framingham-predicted risk of 10% to 20%, the observed CHD incidence was 32% for elevated CRP. Among women, CRP discriminated best among those with a 10-year predicted risk >20%; the incidences were 31% and 10% for elevated and normal CRP levels, respectively.

Conclusions—In older men and women, elevated CRP was associated with increased 10-year risk of CHD, regardless of the presence or absence of cardiac risk factors. A single CRP measurement provided information beyond conventional risk assessment, especially in intermediate-Framingham-risk men and high-Framingham-risk women. (Circulation. 2005;112:25-31.)

Key Words: coronary disease • epidemiology • inflammation • myocardial infarction • risk factors

Older adults are the demographic group at highest risk of myocardial infarction (MI). Although cardiovascular risk factor levels in middle-aged individuals are important in MI prediction, utility of some risk factors such as lipid measures has been questioned among older individuals.1,2 The inflammation marker C-reactive protein (CRP) has been reported as a risk factor for MI in several studies of initially healthy subjects.3 In 4 studies including middle-aged subjects, CRP measurement added to the predictive value of the Framingham Risk Score or lipid determination.4–8 A consensus panel reported possible roles of CRP measurement in primary prevention, suggesting that concentrations of 1 to 3 mg/L indicate intermediate risk, levels >3 mg/L indicate increased risk, and levels >10 mg/L might indicate other inflammatory diseases.3 However, a recent large study reported only a modest association of CRP with future coronary heart disease (CHD), and the investigators questioned these recommendations.9

Long-term prospective studies assessing CRP and MI in elderly men and women are not available. In prospective studies of elderly subjects without baseline coronary disease, CRP was associated with short-term risk of MI or angina in the population assessed here10 and with vascular mortality in 2 other studies11,12 but not with MI in older adults in the Rotterdam Study13 or with acute coronary syndrome in the Health, Aging and Body Composition cohort.14

In several studies, associations of CRP with MI were substantially reduced by adjustment for conventional cardiovascular risk factors.9,15–20 Measures of subclinical atherosclerosis such as carotid intima-media thickness and ankle-brachial index predict future MI, possibly because they reflect the lifetime burden of cardiac risk factors or host response to
risk factors. Adjustment for subclinical disease might provide more complete adjustment for potential confounding, yielding new information on the independence of the association of CRP with MI.

In this report, we analyzed baseline CRP and 10-year incidence of first MI or CHD death in the Cardiovascular Health Study (CHS), a cohort of men and women ≥65 years of age. We assessed the recommended clinical cut points for elevated CRP: independence of CRP associations with CHD from risk factors, including subclinical disease; and associations of CRP with CHD in subgroups defined by baseline risk factors, including subclinical disease and the Framingham Risk Score.

Methods
The CHS is an observational study of risk factors for cardiovascular disease in 5888 men and women ≥65 years of age who were enrolled as 2 cohorts at 4 centers in either 1989 to 1990 or 1992 to 1993. The first cohort consisted of 5201 primarily white participants; the second consisted of 687 blacks. Invited participants were a random sample of Health Care Financing Administration eligibility lists and their household members. Exclusion criteria included institutionalization, active cancer treatment, or expectation of moving from the area within 2 years. Participants provided informed consent, and institutional review committees approved the study methods.

Interview, lipid determination, and testing for subclinical atherosclerosis were completed at enrollment. Subclinical disease was measured by carotid ultrasound, ECG, and ankle-brachial blood pressure index as previously described. Previous vascular diagnoses were confirmed by medical record review. In 1997, CRP was measured in stored baseline plasma by immunoassay with a coefficient of variation of 6.2%. Baseline Definitions
Primary analysis of CHD events categorized CRP as low (<1 mg/L), intermediate (1 to 3 mg/L), or elevated (>3 mg/L) to address the utility of recent guidelines. CRP >10 mg/L was assessed in secondary analyses. Diabetes was defined using the American Diabetes Association criteria. Hypertension was defined as blood pressure ≥140/90 mm Hg or self-reported hypertension with the use of antihypertensive drugs. Hyperlipidemia was defined as cholesterol ≥6.22 mmol/L (240 mg/dL), LDL cholesterol ≥4.14 mmol/L (160 mg/dL), or use of medications for hyperlipidemia. Cigarette use was categorized as never, former, or current and by number of pack-years. Presence of subclinical vascular disease was defined as any 1 of the following: ankle-brachial index <0.9, internal or common carotid artery wall thickness >80th percentile, carotid stenosis >25%, major ECG abnormalities, or positive response to the Rose questionnaires for angina and claudication. Regular aspirin use was defined as use during at least 7 of the previous 14 days or by prescription. Framingham Risk Score was calculated and reported as low (<10%), intermediate (10% to 20%), or high (>20%) 10-year predicted risk of CHD.

Subjects Included in Analysis
We excluded 1536 participants with confirmed prebaseline cardiovascular disease (MI, angina, congestive heart failure, stroke, transient ischemic attack, claudication, coronary artery bypass surgery, angioplasty, carotid endarterectomy; 715 women, 821 men). Of the remaining women, 326 using oral postmenopausal hormones were excluded because users have higher CRP concentrations with uncertain clinical consequence. Fifty-five subjects did not have CRP levels available. Exclusions yielded 3971 participants.

Events Ascertainment
Subjects were followed up every 6 months by alternating field center visits and telephone calls between enrollment and June 30, 2000. Vascular outcomes were ascertained by self-report and review of discharge codes for all hospitalizations. For suspected coronary events, medical records were abstracted and then reviewed and classified by a committee using standardized criteria. CHD death was defined as the absence of nonatherosclerotic cause of death and 1 or both of the following: chest pain within 72 hours of death or history of chronic ischemic heart disease in the absence of valvular heart disease or nonischemic cardiomyopathy.

Statistical Analysis
The SPSS package was used for analysis with a CHS database updated November 18, 2002. Associations of CRP with risk factors were assessed by tests for trend across categories of CRP through the use of χ² statistics or ANOVA. When indicated, CRP was log transformed and described by its geometric mean. Incidence rates of CHD by CRP category were calculated separately for men and women and within categories of the Framingham Risk Score. Cox proportional-hazards models were used to compute hazard ratios as estimates of relative risk of CHD with increasing category of CRP with adjustment for age, sex, and race in all participants and in subgroups defined by known risk factors. Censoring occurred at death, last follow-up, or June 30, 2000, whichever occurred first. Differences in findings by sex, race, and presence or absence of vascular risk factors were evaluated formally by adding interaction terms of each for these factors with CRP to the model (P = 0.05 indicated significance). To determine whether CRP remained predictive after adjustment for known risk factors, 2 additional levels of adjustment were considered. First, models were additionally adjusted for field center and the risk factors related to CRP or MI: hypertension, diabetes, smoking status, pack-years of smoking, body mass index, waist circumference, total and HDL cholesterol, and regular aspirin use. Second, subclinical atherosclerosis measures were added to the models.

Results
Among 3971 participants, 29% had CRP <1.0 mg/L, 45% had levels of 1 to 3 mg/L, and 26% had elevated values (>3 mg/L). The median CRP was 1.76 mg/L (interquartile range, 0.88 to 3.10 mg/L). Associations of CRP with risk factors and subclinical and clinical cardiovascular disease are shown in Table 1. CRP was higher among women and blacks and with obesity, aspirin use, lower HDL cholesterol, hypertension, diabetes, smoking, and pack-years. CRP was higher with than without subclinical disease, with geometric mean values of 1.64 mg/L without subclinical disease and 1.98 mg/L with subclinical disease (P <0.001).

With 10 years of follow-up, there were 547 first MI or CHD deaths (354 nonfatal MI, 41 fatal MI, and 152 CHD deaths). Incidence rates were 22.2 and 12.0 per 1000 person-years in men and women, respectively. Figure 1 shows the cumulative incidence of CHD by gender and baseline CRP. There was little difference between participants with low and intermediate CRP levels, but for those with elevated CRP, the incidence was higher, with a 10-year cumulative incidence of 33% in men and 17% in women. Figure 2 shows the incidence of CHD over the full range of CRP values, demonstrating an increase in risk throughout the range. Incidence rates and relative risks of CHD by baseline CRP categories are shown in Table 2. Incidence increased with each higher CRP category. Age, sex, and race-adjusted relative risks of CHD were slightly increased for intermediate CRP and were nearly doubled for CRP >3 mg/L. Adjustment for other risk factors attenuated these relative risks, leaving little association with CHD for CRP 1 to 3 mg/L and a 45%
increased risk for CRP >3 mg/L. There was no effect of additional adjustment for baseline statin use. Further adjustment for subclinical disease yielded little attenuation; a 37% increased risk of CHD for elevated CRP remained. When CRP was considered a continuous variable, with adjustment for risk factors, the relative risk associated with a 1-ln-unit-higher baseline CRP was 1.27 (95% CI, 1.12 to 1.44). There were no significant differences in associations by sex or race. The population-attributable risk percentage for elevated CRP was 11%.

Table 3 shows the relative risks of incident CHD for CRP >3 mg/L compared with CRP <1 mg/L in subgroups based on the presence or absence of cardiovascular risk factors. Baseline CRP was associated with CHD in all of these groups, including those without subclinical disease and those at low risk by the Framingham Risk Score (P for interaction >0.05 for all). Although the relative risk did not differ by subclinical disease status, among men and women, the presence of elevated CRP together with subclinical disease was associated with a higher incidence of CHD compared with those with lower CRP and no subclinical disease (Figure 3).

Figure 4 shows the 10-year sex-specific incidence of CHD according to CRP concentration in categories of the Framingham Risk Score. In intermediate- and low-risk women, CRP >3 mg/L added little to risk prediction, whereas in high-risk women, CRP provided additional risk information. Among women with a 10-year predicted risk >20%, for intermediate or elevated CRP, the observed incidences were 28%, and 31%, respectively, compared with only 16% for those with low CRP. In men, CRP provided additional risk information in intermediate- and high-Framingham-risk groups. Among men with a 10-year predicted risk 10% to 20%, those with CRP >3 mg/L had an observed risk of 32%. Among high-Framingham-risk men, this observed risk was 41%.

We investigated the utility of CRP >10 mg/L for determining risk of CHD and the impact of hormone replacement therapy among women. Of participants with elevated CRP, 22% were >10 mg/L. Of these 233 participants, 49 (21%) developed CHD during follow-up compared with 498 of 3738 (13.3%) with lower CRP. The age-, sex-, and race-adjusted relative risk of CHD was 2.16 (95% CI, 1.55 to 3.00) for CRP >10 compared with <1 mg/L and 1.78 (95% CI, 1.26 to 2.51) after adjustment for traditional risk factors. Among 326
women excluded from analysis for hormone replacement therapy use, the age-adjusted relative risk of CHD for CRP >3 mg/L was 1.35 (95% CI, 0.42 to 4.32).

Discussion

In this 10-year prospective study in men and women ≥65 years of age, CHD risk increased with increasing CRP. When recent clinical guidelines were applied, intermediate CRP concentrations (1 to 3 mg/L) were weakly related to future CHD, and elevated CRP (>3.0 mg/L) was associated with a 1.45-fold increased risk of CHD, with adjustment for other vascular risk factors. There was less further confounding with adjustment for the presence of noninvasively assessed subclinical atherosclerosis. Elevated CRP was associated with CHD in all subgroups defined by conventional cardiac risk factors or subclinical disease. Among men with intermediate and high Framingham Risk Scores, CRP identified those with higher-than-predicted risk. Among women, CRP discriminated risk best among those at high Framingham-predicted risk.

The relative risk of CHD for elevated CRP observed here was smaller than in most studies of middle-aged subjects and might seem modest at 1.45. However, event rates were high in this age group, so the attributable risk percent for elevated CRP was high at 11%, even given a modest relative risk.30 Thus, a much higher percentage of subjects with elevated CRP subsequently had events in this study compared with studies of younger subjects.7,8 In a recent report by Danesh et al.

TABLE 2. Association of Baseline CRP With Incident MI or CHD Death Over 10 Years+

<table>
<thead>
<tr>
<th>CRP Categories</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0 mg/L</td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td>1.0–3.0 mg/L</td>
<td>1.08 (0.86–1.35)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>&gt;3.0 mg/L</td>
<td>1.37 (1.06–1.78)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

N is number at risk in given group; n, number of cases in given group; and ref, reference.

*Model 1 is adjusted for age, race, and sex. Model 2 is adjusted for age, sex, race, field center, hypertension, diabetes, smoking status, log pack-years, body mass index, waist circumference, total cholesterol, HDL cholesterol, and regular aspirin use. Model 3 is adjusted for model 2 variables plus ankle-arm index <0.9, internal or common carotid intima-media thickness >80th percentile, positive responses to the Rose angina or claudication questionnaires, major ECG abnormalities, and maximum stenosis of the carotid artery >25%.
a similar adjusted relative risk was observed in a large population, but in that case-control study, attributable risk was not estimated. If elevated CRP represents a causal risk factor as suggested by several experimental studies, our estimate of attributable risk indicates a hypothesis that correction of elevated CRP could eliminate up to 11% of incident CHD in this age group.

It has been suggested that novel risk factors or atherosclerosis imaging may identify those at intermediate CHD risk who might benefit from aggressive risk factor interventions. Along with findings in middle-aged populations, our data provide evidence that CRP assessment can identify older patients at higher or lower than their predicted risk of coronary events. Our findings with regard to women at low and intermediate risk differ from findings in middle-aged women in which CRP predicted cardiovascular events across the entire range of Framingham Risk Scores. Further work is needed to validate our findings in this age group and to determine appropriate values defining elevated CRP in various age and sex groups.

Other studies reported weak or no associations of CRP with subclinical disease measures. Here, in the absence of clinical disease, CRP was higher among those with any single type of subclinical disease. Moreover, CHD incidence was higher among those with elevated CRP and subclinical disease compared with groups with only 1 or neither of these risk factors. In this cohort, the 10-year stroke risk associated with elevated CRP was larger among those with higher compared with lower carotid intima-media thickness. Taken together, findings from these few studies suggest possible roles for the assessment of both inflammation and subclinical disease. It is also possible that CRP is a marker of subclinical disease, and if better measures of subclinical disease were available, adjustment for subclinical disease would further lessen the association of CRP with CHD.

The CDC/AHA guideline for CRP testing suggest that values >10 mg/L indicate acute inflammation and have uncertain implications for vascular risk prediction. In this older population, 6% of subjects had CRP >10 mg/L; when traditional risk factors were accounted for, these subjects had a 1.8-fold increased risk of CHD, a higher risk estimate than

### Table 3. Relative Risk of CHD for CRP >3 mg/L Compared With <1 mg/L by Categories of Baseline Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor Present</th>
<th>Risk Factor Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (former + current)</td>
<td>307/2076</td>
</tr>
<tr>
<td>Pack-years (&gt;median; ever smokers only)</td>
<td>171/967</td>
</tr>
<tr>
<td>Hypertension</td>
<td>365/2219</td>
</tr>
<tr>
<td>Diabetes or impaired fasting glucose</td>
<td>213/1130</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>139/966</td>
</tr>
<tr>
<td>Regular aspirin use</td>
<td>123/788</td>
</tr>
<tr>
<td>Estimated 10-year Framingham Risk Score &gt;20%</td>
<td>181/772</td>
</tr>
<tr>
<td>Subclinical disease</td>
<td>417/2477</td>
</tr>
<tr>
<td>Carotid wall thickness &gt;80th percentile</td>
<td>250/1167</td>
</tr>
<tr>
<td>Ankle-arm index &lt;0.9</td>
<td>95/381</td>
</tr>
<tr>
<td>Carotid stenosis ≥25%</td>
<td>315/1726</td>
</tr>
<tr>
<td>Major ECG abnormality</td>
<td>177/886</td>
</tr>
</tbody>
</table>

n/N indicates number of events/number at risk in all 3 levels of CRP in specified category of each risk factor.

*Adjusted for age, race, and sex.
for CRP >3.0 mg/L. Our finding agrees with recently reported results in middle-aged women.33 Thus, CRP values >10 mg/L appear to be important in CHD risk prediction. Limitations of this study merit consideration. The cohort, free-living elderly who were willing to enroll in the study, may not represent the general older population. The observational study design, even with extensive multivariate analysis, cannot prove causal relationships. Competing risks may have diluted associations of CRP with CHD because CRP may be associated with other disease outcomes. In some cases, analysis of subgroups was limited by small sample sizes. Finally, CRP was measured only once at baseline, and it has been suggested that repeated testing for confirmation be considered in those with high values.3

Strengths of this study include its large size, extensive baseline data collection, and long-term event follow-up. Several new findings were observed on the basis of unique aspects of the study. First, we confirmed an association of elevated CRP with CHD incidence in an older age group; most previous studies included younger subjects or clinical trial participants. Second, independence of associations from noninvasively measured subclinical atherosclerosis was documented. Third, more complete adjustment for smoking status was made by assessing pack-years, a major determinant of CRP concentration in smokers.34 Fourth, because CRP was measured in the whole cohort, incidence rates of CHD by baseline CRP were calculated, and subgroup analyses could be done.

In conclusion, we extend previous reports on the association of CRP with CHD to men and women ≥65 years of age. CRP appears to be useful for risk assessment in this age group. Because event rates are high overall in older age, further study is required to determine optimal clinical roles of CRP measurement, especially as related to interventions for elevated CRP.

Acknowledgments

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