Age and Duration of Follow-up as Modulators of the Risk for Ischemic Heart Disease Associated With High Plasma C-Reactive Protein Levels in Men

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Background: Plasma C-reactive protein (CRP) levels recently have been identified as an emerging risk factor for ischemic heart disease (IHD). However, whether plasma CRP levels predict an increased risk for future IHD beyond traditional risk factors has yet to be evaluated in a large prospective, population-based study.

Methods: The association between elevated plasma CRP levels and the risk for future IHD was investigated in the prospective, population-based cohort of 2037 IHD-free middle-aged men from the Quebec Cardiovascular Study. During a 5-year follow-up, 105 first IHD events were recorded. Baseline plasma CRP levels were measured using a highly sensitive assay.

Results: High plasma CRP concentrations (equal to or above vs below the median level of 1.77 mg/L) were associated with a significant 1.8-fold increase in IHD risk (95% confidence interval [CI], 1.2-2.7). This association remained significant after adjustment for lipid risk factors but not when the simultaneous contribution of nonlipid traditional risk factors was taken into account. Multivariate analyses indicated that CRP level predicted short-term risk for IHD (events that occurred ≤2 years after the baseline evaluation), but not long-term risk (>2 years). Moreover, high plasma CRP levels predicted an increased risk for IHD, independent of any other confounder, in younger (≤55 years) but not in older (>55 years) individuals.

Conclusion: Plasma CRP levels may provide independent information on IHD risk only in younger middle-aged men and in the case of IHD events that may occur relatively soon after the baseline evaluation.

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Accumulating evidence suggests that inflammation may be etiologically important in the development of atherosclerosis.1 In this respect, plasma C-reactive protein (CRP), a marker of low to moderate systemic inflammation, has received much attention in recent years. Results from cross-sectional and prospective studies2 have indicated that raised plasma CRP levels were associated with an increased risk for future cardiovascular events among apparently healthy subjects3,4 as well as in individuals with stable and unstable angina5 or with previous myocardial infarction.6 Moreover, results from the Physicians’ Health Study disclosed that baseline plasma CRP concentration added to the predictive value of traditional lipid risk factors in determining risk for first myocardial infarction.7 Although these data suggest that adding plasma CRP levels to the list of cardiovascular risk factors commonly assessed in the clinical practice would improve our ability to predict future cardiovascular events, critical issues remain to be specifically addressed. First, our current interpretation of the relationship between plasma CRP level and the risk for ischemic heart disease (IHD) in middle-aged men is based almost exclusively on data derived from cross-sectional or prospective nested case-control studies,8 with only 1 population-based study9 conducted in a relatively small cohort of subjects. Second, the ability of plasma CRP levels to predict an increased risk for IHD has yet to be tested while considering a comprehensive number of lipid and nonlipid cardiovascular risk factors as confounders. Third, the CRP prognostic value of IHD risk showed a strong time-to-event dependency in the elderly,10 whereas it appeared to be stable during follow-ups of varying lengths in a nested case-control study in middle-aged men.11 Thus, the chronological relationship between plasma CRP levels and the risk for future IHD events remains to be fully elucidated using population-based, prospective data.

The purpose of the present study was to examine the association between plasma
SUBJECTS AND METHODS

STUDY POPULATION AND FOLLOW-UP

The Quebec Cardiovascular Study cohort has been described in detail previously.11,12 In 1973, a random sample of 4637 men (aged 35-64 years) was recruited using the provincial electoral lists from 7 cities of the Quebec metropolitan area for an evaluation of cardiovascular risk factors. Subsequent evaluations were performed at regular intervals, and data collected in 1985 were used as the baseline characteristics for the present prospective analyses. In 1985, 61.1% (n=2443) of the living cohort of men without IHD at the 1973 visit came to the lipid clinic in a fasting state for their evaluation. Among the 1357 other potential living participants, 10.0% could not be located, 18.8% showed up in a nonfasting state, and 71.4% refused to participate or underwent evaluation in a nonfasting state at their home by nurses of the project. Analyses of data collected in 1973 revealed that the age distribution of the 2443 participating men in 1985 was representative of the original cohort. During 1990 and 1991, all participants were contacted by mail and invited to answer a short standardized questionnaire on smoking habits, medication use, and history of cardiovascular diseases and diabetes mellitus. Telephone calls were made to participants who did not answer a second letter or, if unsuccessful, to a close family member. For those patients who reported cardiovascular diseases or diabetes and for those who died, hospital charts were reviewed. Mortality and morbidity data were obtained in 98.7% and 96.1%, respectively, of the participants of the 1973 initial screening.

EVALUATION OF RISK FACTORS

Data on demographic and lifestyle variables, medical history, and medication were obtained in 1985 through a standardized questionnaire administered to each participant by trained nurses and reviewed by a physician. Body weight and height were recorded. Resting blood pressure was measured after 5 minutes in a sitting position. The mean of 2 blood pressure measures obtained 3 minutes apart was used in the analyses. Information on personal and family history of IHD and diabetes, smoking habits, alcohol consumption, and medication use was also obtained. Diabetes was considered in men who self-reported the disease or who were treated with hypoglycemic agents. Only 1.1% of men were using hypolipidemic drugs in 1985, whereas 6.1% and 3.1% of men were using β-blockers and diuretics, respectively, on a regular basis at the 1985 screening. Family history of IHD was considered positive if at least 1 parent and/or 1 sibling had a history of IHD.

DEFINITION OF IHD EVENTS

The diagnosis of a first IHD event included typical angina of effort, coronary insufficiency, nonfatal myocardial infarction, and coronary death. All myocardial infarctions met the criteria previously described,11 ie, diagnostic electrocardiographic (ECG) changes alone or 2 of the following criteria: typical chest pain lasting at least 20 minutes, creatine kinase enzyme level at least twice the upper limit of the reference range, or characteristic ECG changes. Coronary insufficiency was considered if a typical retrosternal chest pain lasting at least 15 minutes was associated with transient ischemic ECG changes but without substantial elevation in levels of creatine kinase. Diagnoses of myocardial infarction and coronary insufficiency were all confirmed using hospital medical charts. All ECGs were read by the same cardiologist (G.R.D.), who was unaware of the participants' risk profile. The diagnosis of angina of effort, obtained by a cardiologist of the study (G.R.D.), was based on typical symptoms of retrosternal squeezing or pressure-type discomfort occurring on exertion and relieved by rest and/or nitroglycerine. Criteria for the diagnosis of coronary deaths included confirmation from death certificate or autopsy report describing the presence of coronary disease, without evidence of noncardiac disease that could explain death. Myocardial infarction was considered fatal if death occurred within 4 weeks of the initial event or if it

CRP levels and the risk for future IHD when controlling for a significant set of IHD risk factors in the prospective, population-based Quebec Cardiovascular Study. Baseline plasma CRP concentrations were measured in the entire cohort of 2037 middle-aged men initially free of clinical manifestations of IHD, among whom 105 developed IHD during the 5-year follow-up.

RESULTS

The baseline characteristics of the 2037 men who participated in the study are presented in Table 1. Men with incident IHD were older at baseline (P<.001) and had a higher systolic blood pressure (P<.001) and a higher prevalence of type 2 diabetes (P<.001), compared with men who remained free of clinical manifestations of IHD during the 5-year follow-up. Plasma concentrations of total cholesterol (P<.001), LDL cholesterol (P<.001), triglycerides (P<.001), and CRP (P=.01) were all significantly higher among those with incident IHD compared with IHD-free individuals. The 105 subjects who subsequently had a first IHD event during the 5-year follow-up also had reduced HDL cholesterol concentrations compared with those who did not (P<.001).

The magnitude of the association between lipid or nonlipid risk factors and plasma CRP levels was estimated by correlation analyses in the entire cohort. Similar results were obtained among subjects with incident IHD and IHD-free subjects, taken separately (results not shown). Plasma CRP concentrations were weakly but significantly correlated with levels of triglycerides (r=0.21; P<.001), total cholesterol (r=0.06; P=.004), LDL cholesterol (r=0.06; P=.009), BMI (r=0.22; P<.001), and HDL cholesterol (r=−0.23; P<.001). Age and systolic blood pressure were also significant correlates of plasma CRP concentrations (r=0.17 and r=0.18, respectively; P<.001). Higher plasma CRP levels were documented among smokers and diabetic subjects (P<.001 for both).

Figure 1 depicts the Kaplan-Meier event-free survival curves according to plasma CRP levels equal to or
was diagnosed at autopsy. We confirmed IHD-related deaths from the Provincial Death Registry. Informed consent was obtained to review relevant hospital files. Autopsies were performed in about a third of deaths. The total IHD event frequency during the 5-year follow-up was similar in participants (5.4%) and nonparticipants (6.5%) in the study.

LABORATORY ANALYSES

Fasting lipoprotein-lipid and apolipoprotein levels were measured in fresh plasma samples in 1985 when participants came to the clinic for evaluation. Aliquots of fasting plasma frozen at time of collection were subsequently used for the assessment of baseline plasma CRP concentrations. Aliquots had been stored at −80°C since the 1985 baseline evaluation. Plasma cholesterol and triglyceride levels were determined on an autoanalyzer (Technicon RA-500; Bayer Corporation Inc, Tarrytown, NY) as previously described. Plasma high-density lipoprotein (HDL) cholesterol levels were measured in the supernatant fraction after precipitation of apolipoprotein B–containing lipoproteins using a combination of heparin and manganese chloride.

Low-density lipoprotein (LDL) cholesterol levels were estimated by means of the equation of Friedewald et al., as men with triglyceride levels of greater than 400 mg/dL (≥4.5 mmol/L) (n=52) were excluded from the analyses. Plasma apolipoprotein B levels were measured by means of the rocket immunoelectrophoresis method of Laurell, as described previously. The interassay coefficients of variation for cholesterol, HDL cholesterol, triglyceride, and apolipoprotein B levels were all less than 3%. Plasma CRP levels were measured using a commercially available, highly sensitive CRP assay (Behring Latex-Enhanced on the Behring Nephelometer BN-100; Behring Diagnostic, Westwood, Mass) and the calibrators provided by the manufacturer (N Rheumatology Standards SL; Behring Diagnostic). The sensitivity of the assay ranged from 0.175 to 11 mg/L. The mean interassay coefficient of variation for plasma CRP levels calculated using 2 separate measures of the same aliquot in 134 men was less than 1% at low and high plasma CRP concentrations (data not shown).

STATISTICAL ANALYSES

Baseline characteristics of men in whom IHD developed during the 5-year follow-up were compared with the characteristics of those who remained free of clinical manifestations of IHD by the t test or the χ2 statistic. Variables with a skewed distribution were logarithm-transformed, resulting in near-normal distributions. Geometric means were calculated and reported where indicated. Correlation analyses were performed using the Pearson and Spearman coefficients of correlation for parametric and nonparametric variables, respectively.

We investigated the relationship between plasma CRP levels and the risk for future IHD events by dichotomizing plasma CRP levels using the median (1.77 mg/L) of the entire cohort and quartiles of plasma CRP levels. Both approaches yielded similar results. Thus, only data derived from the dichotomized CRP levels are presented. The Kaplan-Meier event-free survival probability (estimated probability of not having IHD during 5-year follow-up) was compared among men with elevated or low plasma CRP levels (≥1.77 or <1.77 mg/L, respectively). The log-rank test was used to compare the survival distributions. Cox proportional hazard models were used to estimate the risk for IHD associated with low or high plasma CRP concentrations. Relative risks were adjusted for potential confounding effects of age, smoking habits (smokers vs non-smokers), diabetes mellitus (presence or absence), medication use at baseline (yes or no), systolic blood pressure, body mass index (BMI), and different plasma lipid variables. The potential confounding effects of age at baseline, smoking, and duration of follow-up in modulating the relationship between plasma CRP levels and the risk for future IHD events were investigated by introducing appropriate interaction terms into the multivariate Cox proportional hazard models. Statistical analyses were all performed using SAS software (SAS Institute, Cary, NC).
(<0.85 mg/L), was 2.1 (95% CI, 1.2-3.7). Adjustment for nonlipid traditional cardiovascular risk factors completely abolished the relationship between high plasma CRP levels (fourth quartile) and the risk for IHD (RR, 1.0; 95% CI, 0.5-1.8). Excluding smokers from the analyses yielded results that were comparable to those obtained in the entire population.

Further analyses were conducted to examine the relationship between plasma CRP levels and the risk for future IHD using "hard" endpoints only, ie, acute myocardial infarction and coronary death (n=61). Results were virtually identical to those obtained using the more generic IHD end point, which included cases of angina pectoris, coronary insufficiency, nonfatal myocardial infarction, and coronary death (results not shown). Indeed, elevated plasma CRP levels predicted an increased risk for IHD after adjustment for lipid risk factors but not after controlling simultaneously for several nonlipid risk factors.

To evaluate whether the duration of follow-up affected the ability of plasma CRP levels to predict future IHD events independent of lipid and nonlipid risk factors, participants were stratified according to number of years of follow-up. Figure 2A shows that plasma CRP levels of at least 1.77 mg/L predicted an increased risk for future IHD events within the first 2 years of follow-up, but not beyond 2 years of follow-up. The baseline plasma CRP concentrations in individuals stratified according to the number of years of follow-up essentially matched its ability to predict the risk for IHD during the same period (Figure 2B). Indeed, plasma CRP levels at baseline were higher among men whose follow-up was less than 2 years compared with men for whom follow-up exceeded 2 years. Evidently, most men followed up for less than 4 years belonged to the group of individuals who had a first IHD event during the follow-up. When we considered only incident IHD cases (n=105), baseline plasma CRP levels were significantly higher among men who had their first event within 2 years of the baseline evaluation compared with those in whom the event occurred more than 2 years into follow-up (geometric mean, 3.0 mg/L vs 1.9 mg/L; P=.03). Multivariate Cox proportional hazard analysis indicated that there was a significant interaction between duration of follow-up and plasma CRP levels in determining the risk for future IHD events, with plasma CRP levels of at least 1.77 mg/L predicting an increased risk for future IHD events only for a short follow-up (Table 3).

Analyses were conducted to further examine the potential confounding effects of age at baseline on the relationship between plasma CRP levels and the risk for IHD. Plasma CRP concentrations among younger subjects were lower than in older middle-aged men (geometric means, 1.5 and 2.1 mg/L, respectively; P<.001). Cox proportional hazard analysis showed that the multivariate term describing multiplicative interaction between age and plasma CRP levels was significant (P=.04). Thus, high plasma CRP levels predicted an increased risk for IHD, independent of the confounding effects of lipid and nonlipid cardiovascular risk factors, in younger but not in older individuals (Table 3).
A number of clinically relevant observations can be drawn from this prospective, population-based study. First, plasma CRP levels of at least 1.77 mg/L were associated with an approximately 2-fold increase in the risk for future IHD events. Second, this increased risk for IHD associated with elevated plasma CRP levels remained significant in multivariate analyses only when considering events that occurred no later than 2 years into follow-up, but not when considering those that occurred beyond 2 years of follow-up. Third, elevated plasma CRP levels at baseline predicted an increased risk for a first IHD event independent of lipid and nonlipid cardiovascular risk factors in men younger than 55 years, but not in older individuals.

**CRP LEVEL VS TRADITIONAL CARDIOVASCULAR RISK FACTORS**

Plasma CRP is a nonspecific marker of underlying systemic inflammation. Levels of CRP fluctuate into a wide range of concentrations, depending on several stimuli. Infections, physical trauma, and other inflammatory conditions clearly represent important sources of this variability. However, several other features, eg, age, diabetes, smoking status, obesity, exercise, anti-inflammatory drugs, and lipid-lowering agents, influence plasma CRP concentrations and IHD risk. Thus, any combination of these traditional risk factors could potentially confound the relationship between plasma CRP levels and IHD risk.

To our knowledge, the Monitoring Trends and Determinations in Cardiovascular Disease (MONICA) study is, to date, the only prospective, population-based study documenting the relationship between plasma CRP levels and the risk for future coronary events in a cohort of middle-aged men. It showed that the risk ratio of IHD events associated with a 1-SD increase in logarithm-CRP was 1.67 (95% CI, 1.29-2.17) and 1.50 (95% CI, 1.14-1.97), respectively, before and after adjustment for the combined confounding effect of age and smoking status. Similarly, we observed that individual adjustment for age and smoking habits did not materially affect the risk for IHD associated with high baseline plasma CRP concentrations (not shown). Further analyses indicated that the increased risk for IHD associated with elevated plasma

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**Table 3. Effects of Duration of Follow-up and Age at Baseline on Unadjusted and Adjusted Relative Risks for IHD**

<table>
<thead>
<tr>
<th>Subgroup Analysis</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of duration of follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>Short-term (≤2 y)</td>
<td>3.3 (1.6-6.8)</td>
</tr>
<tr>
<td>Long-term (&gt;2 y)</td>
<td>1.2 (0.7-2.0)</td>
</tr>
<tr>
<td><strong>Effect of age at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>≤55 y</td>
<td>3.9 (1.9-7.9)</td>
</tr>
<tr>
<td>&gt;55 y</td>
<td>1.0 (0.6-1.7)</td>
</tr>
</tbody>
</table>

*Indicates for men with CRP levels of at least 1.77 mg/L. Explanation of abbreviations is given in the first footnotes to Tables 1 and 2.
†Includes triglycerides and LDL cholesterol levels, and the ratio of total cholesterol to HDL cholesterol.
‡Includes age, smoking status, history of diabetes, systolic blood pressure, medication use at baseline, and body mass index.
§Indicates all lipid and nonlipid risk factors.

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CRP concentrations remained significant even after adjustment for these 2 risk factors simultaneously (RR, 1.5; 95% CI, 1.0-2.3; P=.04). On the other hand, the relationship between plasma CRP concentrations and the risk for future IHD events was substantially attenuated when other nonlipid risk factors (diabetes, hypertension, and BMI) were considered simultaneously (RR, 1.2; 95% CI, 0.8-1.9). Thus, results from the present study suggest that the relationship between plasma CRP levels and the risk for future IHD events is not independent of the sum of nonlipid risk factors.

These findings are in contrast with those of a previous prospective nested case-control study in middle-aged men, which suggested that the risk for IHD associated with elevated plasma CRP levels was not modified by other risk factors, including cardiovascular risk factors and possibly other nonlipid risk factors. However, it should be pointed out that the study by Koenig et al, Ridker as well as other studies, did not report the impact of a simultaneous adjustment for a comprehensive list of lipid and nonlipid cardiovascular risk factors. The impact that a number of relatively weak correlates of CRP (r<5%) such as age, systolic blood pressure, and smoking habits may exert on the relationship between plasma CRP levels and the risk for future IHD events. Results from our large, prospective, population-based study underline the simultaneous adjustment for these 2 risk factors simultaneously (RR, 1.5; 95% CI, 1.0-2.3; P=.04). On the other hand, the relationship between high plasma CRP concentrations and incident IHD was no longer apparent beyond 2 years of follow-up. It has been suggested that increased plasma CRP levels may reflect the presence of unstable plaques, which may be associated with a subsequent IHD event during a shorter time than stable plaques or atherosclerosis. This hypothesis is consistent with the fact that individuals who had IHD within the first 2 years of follow-up were characterized by higher baseline plasma CRP levels than patients in whom IHD occurred more than 2 years into the follow-up.

These results provide further insight into our understanding of the chronological relationship between CRP and the risk for future coronary events, which essentially remained unresolved to date. Indeed, Ridker et al. found that the risk for arterial thrombosis associated with increasing plasma CRP levels was stable during long periods of follow-up. On the other hand, results from the Helsinki Ageing Study in elderly subjects suggested that increased plasma CRP levels predicted cardiovascular events less than 1 year after blood collection better than events that occurred after 1 year of follow-up. The nested case-control design of the study by Ridker et al and the limited number of subjects in the Helsinki Ageing Study limited our ability to draw firm conclusions as to the confounding effect of follow-up duration on the relationship between plasma CRP levels and the risk for IHD. The population-based design of our study, the size of the study cohort, and the analytical strategy used (time-censoring design vs case-control approach, which does not take into account the time of the event in the matching procedure) provided a more valid model for the analysis of the IHD risk associated with elevated plasma CRP levels in relation to the duration of follow-up compared with previous nested case-control and smaller prospective studies. As in previous studies, however, we measured plasma CRP levels only once. Whether having a more stable CRP concentration by measuring it more than once would have modified this time-dependent relationship between elevated plasma CRP levels and IHD onset remains to be clarified.

CRP LEVEL VS DURATION OF FOLLOW-UP

Results from the present population-based study also indicated that the relationship between plasma CRP levels and the risk for future IHD onset was strong during a short-term follow-up, but virtually absent during a longer follow-up. Specifically, increased plasma CRP levels were associated with a 2-fold increase in the risk for IHD during the first 2 years of follow-up, even after adjustment for a series of lipid and nonlipid cardiovascular risk factors. On the other hand, the relationship between high baseline plasma CRP concentrations and incident IHD was no longer apparent beyond 2 years of follow-up. It has been suggested that increased plasma CRP levels may reflect the presence of unstable plaques, which may be associated with a subsequent IHD event during a shorter time than stable plaques or atherosclerosis. This hypothesis is consistent with the fact that individuals who had IHD within the first 2 years of follow-up were characterized by higher baseline plasma CRP levels than patients in whom IHD occurred more than 2 years into the follow-up.

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CRP LEVEL VS AGE AT BASELINE

Among the correlates of plasma CRP concentrations, age was of particular interest. Indeed, results from our study indicated that elevated plasma CRP levels predicted an increased IHD risk independent of all other confounding risk factors in younger but not in older individuals. This observation was rather unexpected, because older individuals tended to have higher plasma CRP levels at baseline than did younger subjects in the present study and in other reports. It could be speculated that a greater number of possible covariates of plasma CRP levels, including cardiovascular risk factors and possibly other conditions associated with an increasing inflammatory response with aging, could dilute to a greater extent the impact of high plasma CRP levels on IHD risk in older compared with younger subjects. Thus, although younger men had lower plasma CRP concentrations than did older men, the increased risk for IHD associated with increasing plasma CRP levels was independent of the simultaneous confounding effects of lipid and nonlipid cardiovascular risk factors only in the younger men. These results in middle-aged men concur with recent observations by Strandberg and Tilvis, who have suggested that the ability of plasma CRP levels to predict the risk for IHD in the elderly was diluted in older individuals.

CONCLUSIONS

To the best of our knowledge, the Quebec Cardiovascular Study is the first large-scale, population-based prospective study of the relationship between plasma CRP levels, a marker of systemic inflammation, and the risk for future IHD events in men. Our results have indicated that (1) high plasma CRP levels were associated with an increased risk for future IHD events, independent of concomitant variations in plasma lipid levels and of a series of nonlipid risk factors in short-term (≤2 years)
but not long-term (>2 years) follow-up; and (2) elevated plasma CRP levels were an independent predictor of future IHD events in younger but not in older men. These results suggest that measuring plasma CRP levels in an integrated strategy for primary prevention of IHD could be useful, but only in specific situations. Particularly, younger middle-aged men may benefit the most from having their plasma CRP levels measured for short- to long-term assessment of IHD risk. Future studies will be needed to validate and confirm these hypotheses.

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