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Epidemiology

C-Reactive Protein and Prediction of Coronary Heart Disease and Global Vascular Events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)

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Background—The role of C-reactive protein (CRP) in predicting vascular events and response to statin therapy remains uncertain. Additional large prospective studies are required.

Methods and Results—Baseline CRP was related to risk over 3.2 years for primary a combined end point (definite or suspected death from coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke; n=865 events) and secondary (coronary heart disease events or stroke alone) and tertiary (stroke plus transient ischemic attack) end points in the Prospective Study of Pravastatin in the Elderly at Risk (n=5804 men and women; age, 70 to 82 years). CRP levels were higher in subjects who had a subsequent primary end-point event compared with those who did not (geometric mean; 3.64 mg/L [SD, 3.08 mg/L] versus 3.01 mg/L [SD, 3.05 mg/L]; $P<0.0001$). CRP correlated positively with body mass index and smoking status and negatively with high-density lipoprotein cholesterol. The unadjusted hazard ratio for the primary end point was 1.48 (95% CI, 1.26 to 1.74) in a comparison of top and bottom thirds for CRP, falling to 1.36 (95% CI, 1.15 to 1.61) with adjustment for established predictors and body mass index. Similar results were obtained for other end points or when results were examined separately by history of vascular disease. However, baseline CRP added minimally to risk prediction beyond conventional predictors and did not relate to the magnitude of pravastatin benefit.

Conclusions—Elevated CRP minimally enhances cardiovascular disease prediction beyond established vascular risk factors and does not predict response to statin therapy in elderly subjects at risk. These data suggest that CRP has limited clinical value in cardiovascular disease risk stratification or predicting response to statin therapy in elderly people. (***Circulation***. 2007;115:981-989.)

Key Words: aged ■ cardiovascular diseases ■ forecasting ■ inflammation ■ risk factors ■ stroke

Interest in the inflammatory hypothesis for vascular disease is intense, with most attention focused on the association of plasma C-reactive protein (CRP) concentrations with coronary heart disease (CHD) events. CRP as a cause of vascular disease also is contested.[1,2] Early summaries of available prospective data suggested a 2-fold-higher risk of events in individuals with CRP levels in the top versus bottom third, broadly equivalent to CRP >3 versus <1 mg/L in the general middle-aged population.[3] However, recent large studies[4,5] suggest a lower adjusted hazard ratio for elevated CRP (hazard ratio, ≈1.5 for top versus bottom third), and as a result, some have questioned the added value of CRP for risk prediction.[5–7] Indeed, when tested directly in a continuous rather than dichotomized fashion, the additional discriminative ability of elevated CRP beyond traditional predictors has been minimal,[5,8,9] partly because CRP correlates with several known risk factors such as smoking, low levels of high-density lipoprotein (HDL) cholesterol, and obesity.[7,10] Nev-

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ertheless, the topic remains contentious, and interpretations of data can differ between investigators in respect to the association of CRP with cardiovascular disease (CVD).[4,5,11,12] Recent reviews have highlighted several unresolved concerns with the use of CRP for cardiovascular risk stratification.[13,14] Further large prospective studies would be useful.

In addition to the above debate, much of the existing prospective CRP data relate to middle-aged subjects, with fewer data in the elderly in whom CRP levels are higher. The existing data in the elderly also are somewhat conflicting. CRP was not independently predictive of either CHD (n=188) or stroke (n=60) events in the Health, Aging, and Body Composition study.[15] However, CRP was associated with CHD events (n=547) in the Cardiovascular Health Study (in patients >65 years of age),[4] and in that study, although the relative risk for events was only 1.45 (95% CI, 1.14 to 1.86) for CRP >3 versus <1 mg/L, CRP was suggested to enhance risk prediction in intermediate-Framingham-risk men and high-Framingham-risk women. The latter study did not use receiver-operating characteristic curves to test additional predictive ability, although it did adjust for known subclinical disease.[4]

Recently, we reported the results of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER, which was conducted in 5804 men (n=2804) and women (n=3000), demonstrated a 19% reduction in the risk for CHD death and nonfatal myocardial infarction with pravastatin compared with placebo.[16] A biobank of baseline samples for subsequent measurement of novel vascular risk parameters was collected, and CRP was measured in all subjects.

Our present aim was to relate CRP to risk for the primary end points (combined vascular events, n=865), 2 secondary end points (CHD [n=638] or stroke alone [n=260] events), and 1 tertiary (stroke plus transient ischemic attack [TIA]; n=404) end point. As such, the present study would be one of the largest in terms of number of events to test the association of CRP with vascular events. The use of global CVD events was in accordance with recent recommendations from the various bodies.[17] We were also able to assess whether baseline CRP predicted response to statin therapy in the elderly, an important question because it is widely considered, at least in some studies of middle-aged subjects,[18,19] that statins may be more beneficial in subjects with higher baseline inflammatory levels, although relevant data in the elderly are lacking. Finally, we were able to examine whether CRP was associated with CVD events in the subgroups of elderly subjects with and without a history of vascular events at baseline and whether risk prediction was enhanced beyond traditional parameters using appropriate statistical tests.

Methods

The protocol of PROSPER has been published elsewhere.[20] The methodology and outcome of the main trial also have been published.[16]

Participants

Between December 15, 1997, and May 7, 1999, we screened and enrolled individuals from Scotland, Ireland, and the Netherlands.

Briefly, men and women 70 to 82 years of age were recruited if they had either preexisting vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes. Their plasma total cholesterol was required to be 4.0 to 9.0 mmol/L and their triglyceride concentrations to be <6.0 mmol/L. After screening, eligible individuals entered a 4-week single-blind placebo lead-in period. Those who used <75% or >120% of the placebo medication were excluded. The institutional ethics review boards of all centers approved the protocol, and all participants gave written informed consent. The protocol was consistent with the Declaration of Helsinki.

Protocol

Subjects were randomized to receive either pravastatin 40 mg daily or matching placebo.[16] We reviewed participants every 3 months, with a mean of 3.2 years of follow-up. Lipoprotein profiles were measured at the Centers for Disease Control–certified central lipoprotein laboratory in Glasgow. A 12-lead ECG was recorded annually and transmitted electronically to the ECG core laboratory at Glasgow Royal Infirmary, where all computer interpretations were reviewed and automated Minnesota coding was done. All data were processed and analyzed at the study data center in the Robertson Centre for Biostatistics (Glasgow, Scotland).

The primary outcome of the original trial was the combined end point of definite or suspected death from CHD, nonfatal myocardial infarction, and fatal or nonfatal stroke, assessed in the entire cohort. Secondary outcomes included examination of the coronary and cerebrovascular components separately. Additionally, we assessed the primary outcome separately for men and women and for those with and without preexisting disease. Tertiary end points included an assessment of transient ischemic attacks.

Laboratory Aspects

Baseline lipids, blood pressure, and body mass index (BMI) were measured as described in detail before.[16,20] CRP was measured on stored (at −80°C) and previously unthawed samples by automated particle-enhanced immunoturbidimetric assay (Roche UK, Welwyn Garden City, UK). The method has a lower limit of sensitivity of 0.1 mg/L and interassay and intra-assay coefficients of variation of <3%. Our laboratory participates in a national external quality control for high-sensitivity CRP. All samples were processed by technicians blinded to the identity of samples.

Statistical Analysis

The distribution of CRP was positively skewed; therefore, a logarithmic transformation was used. Baseline characteristics were compared between participants with and without the primary end point using the 2-sample t test for continuous variables and the χ^2 test for categorical variables. Relationships between log CRP and baseline characteristics were assessed through the use of the Pearson correlation coefficient for continuous variables and 2-sample t tests or ANOVA for categorical variables. Both unadjusted and adjusted (for age, sex, smoking status, BMI, and country) associations were calculated.

The influence of CRP on the end points of interest was investigated through the use of Kaplan-Meier curves and Cox proportional-hazards models, adjusting for randomized treatment and baseline covariates (age, sex, country, low-density lipoprotein cholesterol, HDL cholesterol, blood pressure, smoking status, BMI, history of diabetes, use of antihypertensive therapy, log triglycerides, history of CHD, history of peripheral artery disease, and history of stroke or TIA). CRP was categorized into tertiles. Results are reported as number and percentage of events and hazard ratios with 95% CIs for tertiles 2 and 3 compared with tertile 1. In addition, models for log CRP as a continuous measure were constructed to provide maximum power for detecting an association; these models are tested for miscalibration by including a term into each model representing deciles of predicted risk and testing for an improvement in model fit by means of likelihood ratio tests. Hazard ratios for tertiles are reported, along with probability values for a continuous association

TABLE 1.   Comparison of Baseline Characteristics by Primary End Point

	Event (N=865)	No Event (N=4815)	P
Continuous variables, mean (SD)			
Age, y	75.8 (3.5)	75.3 (3.3)	<0.0001
BMI, kg/m^2	26.9 (4.1)	26.8 (4.2)	0.54
Systolic blood pressure, mm Hg	155.2 (22.9)	154.5 (21.6)	0.34
Diastolic blood pressure, mm Hg	82.9 (11.8)	83.9 (11.3)	0.027
Total cholesterol, mmol/L	5.62 (0.87)	5.69 (0.91)	0.048
HDL cholesterol, mmol/L	1.24 (0.34)	1.29 (0.35)	<0.0001
LDL cholesterol, mmol/L	3.76 (0.76)	3.79 (0.80)	0.24
Triglycerides, mmol/L*	1.44 (1.53)	1.41 (1.51)	0.13
CRP, mg/L*	3.64 (3.08)	3.01 (3.05)	<0.0001
Categorical variables, n (%)			
Pravastatin	401 (46.4)	2426 (50.4)	0.029
Male	494 (57.1)	2250 (46.7)	<0.0001
Smoking	...	...	0.093
Never	269 (31.1)	1657 (34.4)	...
Current smoker	230 (26.6)	1292 (26.8)	...
Ex-smoker	366 (42.3)	1866 (38.8)	...
Country	...	...	<0.0001
Scotland	364 (42.1)	2123 (44.1)	...
Ireland	384 (44.4)	1759 (36.5)	...
The Netherlands	117 (13.5)	933 (19.2)	...
History of:			
Diabetes	129 (14.9)	479 (9.9)	<0.0001
Hypertension	520 (60.1)	2993 (62.2)	0.25
Coronary disease	380 (43.9)	1436 (29.8)	<0.0001
Peripheral artery disease	139 (16.1)	497 (10.3)	<0.0001
Stroke or TIA	126 (14.6)	512 (10.6)	0.0007
Any vascular disease	492 (56.9)	2023 (42.0)	<0.0001

LDL indicates low-density lipoprotein. Because of the design structure of the trial—recruiting more subjects with hypertension/smokers and diabetes (and women) into the low-risk primary prevention group—the significance or nonsignificance of univariate comparisons in this table could be potentially misleading. Probability values for continuous variables are from 2-sample t tests and for categorical variables from χ^2 tests.

*Values are geometric means (SD) calculated from the log-transformed distribution.

with log CRP and probability values for model miscalibration. The interaction between pravastatin therapy and each tertile of CRP also was calculated. C statistics (analogous to the area under the receiver-operating characteristic curve) were calculated for Cox proportional hazards survival models[21] with and without adjustment for log CRP as a continuous measure and are reported for selected models, along with probability values testing whether the inclusion of log CRP leads to predictions that are more concordant with observed events. Summary statistics are reported as mean and SD for continuous variables and number with percentage for categorical variables. Values of $P<0.05$ were considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

CRP levels were available in 5680 (97.9%) of the original 5804 patients. Of these 5680, 865 subjects (15.2%) had a primary vascular event.[16] Their baseline characteristics and those of subjects who did not have a primary end point are shown in Table 1. Subjects who had a primary vascular event during study follow-up were slightly older, more likely to be male, and more likely to have a history of diabetes, CHD, peripheral artery disease, stroke, or TIA but less likely to have been taking pravastatin. CRP was significantly higher, and HDL cholesterol was lower. Total cholesterol and diastolic blood pressure also were lower in those having a primary event compared with subjects remaining free from a primary end point. CRP concentrations were generally higher than levels seen in other middle-aged cohorts, in keeping with both the elderly age of our population and their high prevalence of existing disease and other risk factors.

Correlations of CRP With Other Risk Parameters

Unadjusted and adjusted (for age, sex, smoking status, BMI, and country) correlations of CRP with other parameters are

TABLE 2. Pearson Correlations Between Continuous Baseline Characteristics and Log CRP

Baseline Characteristics (N=5680)	Unadjusted		Adjusted*	
	Correlation	P	Correlation	P
Age	0.015	0.27	0.048	0.0003
Systolic blood pressure	0.038	0.0041	0.022	0.098
Diastolic blood pressure	0.018	0.18	−0.009	0.48
Total cholesterol	0.005	0.72	0.013	0.32
HDL cholesterol	−0.162	<0.0001	−0.118	<0.0001
LDL cholesterol	0.026	0.053	0.033	0.012
Log triglycerides	0.146	<0.0001	0.090	<0.0001
BMI	0.227	<0.0001	0.252	<0.0001

LDL indicates low-density lipoprotein.

*Partial correlations adjusted for age, sex, smoking status, BMI, and country.

given in Tables 2 and 3. With respect to continuous variables, CRP correlated most strongly with BMI, followed by HDL cholesterol and triglycerides. CRP was weakly associated with age and low-density lipoprotein cholesterol. With respect to categorical variables, elevated baseline CRP was associated with smoking status; both current smokers and ex-smokers had higher CRP values than nonsmokers. CRP also was elevated in subjects with a history of CHD and most strikingly subjects with peripheral artery disease but was not elevated in subjects with diabetes or stroke/TIA.

## Associations of Elevated CRP With Primary, Secondary, and Tertiary End Points

In keeping with recent convention and to allow comparisons with data summarized in a recent meta-analysis, we compared

TABLE 3. Relationship Between Categorical Baseline Characteristics and Log CRP

Baseline Characteristics	n	Mean (SD)*	Unadjusted P	Adjusted P†
Diabetes				
Yes	605	3.17 (3.11)	0.58	0.84
No	5075	3.09 (3.06)	...	...
Nonsmoker	1926	2.83 (3.08)	Referent	Referent
Current smoker	1522	3.49 (3.15)	<0.0001	<0.0001
Ex-smoker	2232	3.08 (2.97)	0.0137	0.0004
History of:				
Coronary disease				
Yes	1816	3.17 (3.09)	0.29	0.0084
No	3864	3.06 (3.05)	...	...
Peripheral artery disease				
Yes	636	3.70 (3.14)	<0.0001	<0.0001
No	5044	3.02 (3.05)	...	...
Stroke/TIA				
Yes	638	3.13 (2.91)	0.76	0.35
No	5042	3.09 (3.08)	...	...

*Values are geometric means (SD) calculated from the log-transformed distribution for CRP.

†Probability values are adjusted for age, sex, smoking status, BMI, and country.
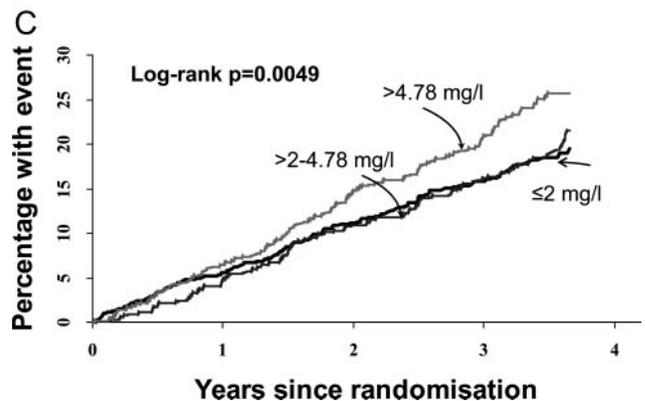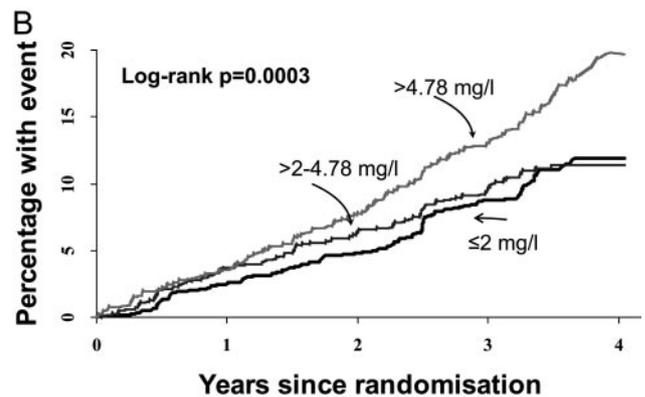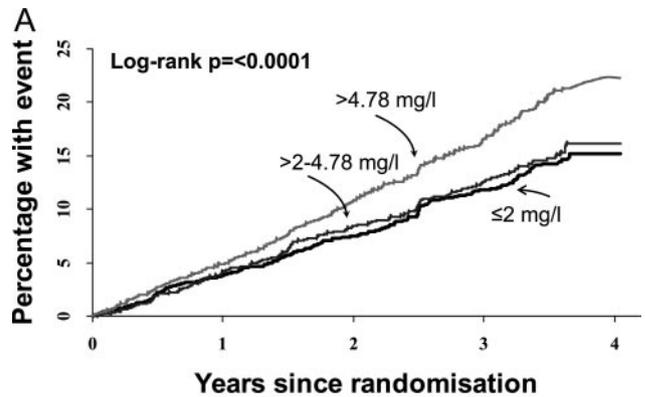
Kaplan-Meier curves of risk of primary end point (definite or suspect death from CHD, nonfatal myocardial infarction, and fatal or nonfatal stroke) by tertile of baseline CRP. A, In all subjects; B, in subjects without history of vascular disease (primary prevention); C, in subjects with history of vascular disease (secondary prevention). Note that the y axis has a different scale in each figure.

risk by tertiles of baseline CRP. We initially examined whether association of baseline CRP with a subsequent primary end point differed in the placebo and statin groups. There was no significant interaction (P>0.10); as a result, data from placebo and statin groups were combined. The Figure demonstrates Kaplan-Meier curves of association of the 3 CRP tertiles with risk for the primary end point in the entire cohort and separated by history of vascular disease. It is clear that risk was higher only in tertile 3; hence, subsequent results focus mainly on comparisons of tertiles 3 and 1. Table 4 reports hazard ratios adjusted for randomized treat-

TABLE 4.   Numbers of Events and Hazard Ratios (95% CIs) for Tertiles of CRP for Primary End Point in Entire Cohort and Separated by History of Vascular Disease (Primary/Secondary Prevention) and for Secondary and Tertiary End Points in Entire Cohort

End Points	Tertile 1, ≤2 mg/L	Tertile 2, >2–4.78 mg/L	Tertile 3, >4.78 mg/L	P*	Calibration P† Including CRP	Calibration P† Excluding CRP
Primary‡						
Entire cohort (N=5680)						
Events, %	251 (13.2)	263 (14.0)	351 (18.6)	...	...	...
Model A	1	1.07 (0.90–1.27)	1.48 (1.26–1.74)	<0.0001	0.74	...
Model B§	1	1.02 (0.86–1.21)	1.35 (1.15–1.60)	0.0002	0.68	0.34
Model C§	1	1.02 (0.86–1.22)	1.36 (1.15–1.61)	0.0002	0.36	0.80
Primary prevention (n=3165)						
Events, %	109 (9.9)	109 (10.6)	155 (14.9)	...	...	...
Model A	1	1.08 (0.83–1.41)	1.58 (1.23–2.01)	0.0002	0.47	...
Model B	1	1.04 (0.79–1.35)	1.47 (1.15–1.89)	0.0021	0.69	0.58
Model C	1	1.05 (0.80–1.38)	1.51 (1.17–1.95)	0.0015	0.84	0.62
Secondary prevention (n=2515)						
Events, %	142 (17.6)	154 (18.0)	196 (23.0)	...	...	...
Model A	1	1.02 (0.81–1.28)	1.37 (1.10–1.70)	0.0015	0.19	...
Model B	1	1.00 (0.80–1.26)	1.32 (1.06–1.65)	0.0067	0.054	0.73
Model C	1	1.00 (0.79–1.26)	1.30 (1.04–1.64)	0.011	0.28	0.62
Secondary/tertiary						
Coronary events						
Events, %	184 (9.7)	197 (10.5)	257 (13.6)	...	...	...
Model A	1	1.10 (0.90–1.34)	1.47 (1.22–1.78)	<0.0001	0.19	...
Model B§	1	1.04 (0.85–1.27)	1.35 (1.11–1.64)	0.0006	0.35	0.34
Model C§	1	1.03 (0.84–1.27)	1.33 (1.09–1.62)	0.0013	0.72	0.26
Stroke events						
Events, %	78 (4.1)	79 (4.2)	103 (5.4)	...	...	...
Model A	1	1.03 (0.76–1.41)	1.38 (1.03–1.85)	0.043	0.59	...
Model B§	1	1.00 (0.73–1.38)	1.29 (0.95–1.74)	0.17	0.22	0.62
Model C§	1	1.04 (0.76–1.43)	1.37 (1.00–1.86)	0.092	0.55	0.55
Stroke or TIA events						
Events, %	120 (6.3)	127 (6.7)	157 (8.3)	...	...	...
Model A	1	1.08 (0.84–1.38)	1.37 (1.08–1.74)	0.014	0.98	...
Model B§	1	1.05 (0.82–1.35)	1.28 (1.01–1.64)	0.085	0.70	0.19
Model C§	1	1.06 (0.82–1.37)	1.32 (1.03–1.69)	0.061	0.62	0.54

First tertile is referent. Model A was adjusted for randomized treatment; model B, adjusted for randomized treatment, age, sex, low-density lipoprotein cholesterol, HDL cholesterol, systolic blood pressure, current smoker, diabetes, use of antihypertensive therapy, and country; model C, model B also adjusted for log triglycerides, BMI, diastolic blood pressure, and ex-smoker. Other relevant comparisons for primary end point in entire cohort in fully adjusted model (model C): hazard ratio, 1.14 (95% CI, 1.07 to 1.23) for 1-SD log CRP; hazard ratio, 1.53 (95% CI, 1.23 to 1.91) for CRP in quintile 5 vs 1; hazard ratio, 1.35 (95% CI, 1.07 to 1.71) for CRP >3 mg/L (51.9% of population) vs <1 mg/L (13.9% of population).

*Probability values are from associations with log CRP as a continuous measure.

†Probability values for likelihood ratio test for inclusion of term representing deciles of predicted risk into the model (based on models either including or excluding log CRP as a continuous measure).

‡CHD death, nonfatal myocardial infarction, or fatal or nonfatal stroke.

§Additionally adjusted for history of CHD, peripheral artery disease, stroke, or TIA.

ment only and baseline covariates for tertiles 3 and 2 versus tertile 1 for the primary end point in the entire population and separated by history of vascular disease at baseline. In the entire cohort, subjects in top tertile for CRP had an ≈50% higher risk of events, falling to 35% higher risk after accounting for traditional risk factors, with no further atten-

uation in risk with inclusion of triglyceride, BMI, diastolic blood pressure, and ex-smoker categorization in the model.

CRP appeared somewhat more strongly associated with risk in subjects without a history of vascular disease (51% higher risk in the fully adjusted model) compared with those with a history of vascular disease (30% higher risk), but this

TABLE 5.   Pravastatin Treatment Effect by Tertile of Baseline CRP

End Point	HR Reduction in Point by Thirds of CRP Distribution, %			P for Interaction
	Lower Third	Middle Third	Top Third	
End Point				
All subjects	−13	−2	−22	0.36
History of CVD	−15	−19	−28	0.71
No CVD history	−15	29	−17	0.19
Secondary (coronary events)				
All subjects	−14	−15	−22	0.81
History of CVD	−20	−35	−22	0.86
No CVD history	−11	27	−24	0.22

HR indicates hazard ratio. Negative numbers represent a lower event rate in pravastatin- vs placebo-treated subjects. Data are presented for all subjects and are subdivided into those with and without a history of vascular disease. The HR was adjusted for treatment allocation, age, sex, country, low-density lipoprotein cholesterol, HDL cholesterol, systolic blood pressure, smoking status, history of diabetes, and history of hypertension. Probability values are the significance of interaction term for tertile-by-treatment effect.

*CHD death, nonfatal myocardial infarction, or fatal or nonfatal stroke.

difference was not significant; risks for other end points, namely CHD, stroke alone, or stroke plus TIA, were similar (32% to 37% higher risks) in the fully adjusted models (Table 4), and once again, tertile 2 was not associated with increased risk in either univariate or multivariate models. The hazard ratio comparing the proposed cutoff for elevated CRP (>3 mg/L), present in ≈52% of the population at baseline, with subjects with CRP <1 mg/L, the proposed low-risk group (≈14% of all subjects), was 1.35 (95% CI, 1.07 to 1.71) for the primary end point in a fully adjusted model. We also noted no significant interaction of age with the association of CRP with any of the end points. Finally, there appeared to be no significant miscalibration in the models either before or after the addition of CRP.

Baseline CRP and Prediction of Response to Pravastatin Treatment

There was no significant interaction between baseline CRP and statin effect for any of the end points examined in the present study (Table 5). In other words, baseline CRP did not relate significantly to the magnitude of cardiovascular risk benefit seen with pravastatin.

CRP Versus Traditional Risk Factors in the Prediction of Risk

The C statistic was calculated with and without adjustment for log CRP as a continuous measure. In this case, CRP-adjusted predictions tended to be more concordant with observed events but resulted in C statistics that were increased only minimally beyond those obtained by Framingham risk factors (63.0% to 63.7% for CVD; 65.5% to 66.3% for CHD; Table 6).

Discussion

There has been considerable ongoing debate regarding the usefulness or otherwise of CRP as a potential risk predictor of CVD events[4–7,9,12–14,18] and its potential causal role or otherwise in the atherogenic process.[1,2] Our study is one of the largest in terms of number of events to examine the associ-

ation of CRP with vascular events and the largest such study in the elderly. Our findings are therefore an important addition to the literature. As expected, elderly subjects at elevated vascular risk display considerably greater burden of inflammation (more than half had CRP >3 mg/L at baseline and <14% had CRP <1 mg/L) compared with middle-aged adults; circulating CRP, like many other inflammatory parameters, increases in concentration with age.[7] CRP was independently associated with total CVD events in the entire cohort, and when the cohort was subdivided into those with and without a history of vascular disease at baseline, with the adjusted odds ratios comparing the top third with the bottom (≈1.30 to 1.50), our present findings were nearly identical to those of a recent large meta-analysis of data mostly from middle-aged populations.[5] Findings also were nearly identical to the previous largest study in the elderly[4] when we stratified the population based on American Heart Association–suggested cutoffs for CRP of >3 versus <1 mg/L.[22] Despite such independence, however, prediction (or discriminative ability) for either total global CVD events or CHD events alone in subjects without a history of vascular disease at baseline was not substantially improved with the addition of CRP to conventional Framingham-based risk factors as measured by the calculated C statistic. Of equal importance, CRP was not

TABLE 6.   C Statistic for Multivariate Models Including Only Subjects With No History of Vascular Disease in the Placebo Group

Model*	C Statistic, %	P for Increased Concordance
Primary end point	. . .	0.020
Adjusted model	63.0	. . .
Adjusted model plus log CRP	63.7	. . .
Secondary end point, CHD	. . .	0.028
Adjusted model	65.5	. . .
Adjusted model plus log CRP	66.3	. . .

*All models include age, sex, country, low-density lipoprotein cholesterol, HDL cholesterol, systolic blood pressure, smoking, history of diabetes, and history of hypertension.

significantly associated with response to statin therapy in terms of risk reduction for CVD and CHD in the entire cohort or when subjects were subgrouped by the absence of presence of vascular disease at baseline. The totalities of our observations suggest that the measurement of CRP, while offering statistically significant improvements in risk prediction, is unlikely to be of clinical benefit for CVD risk screening or targeting its prevention in the elderly.

Plentiful evidence indicates a generally weaker association with events of some conventional risk factors such as low-density lipoprotein cholesterol in the elderly compared with middle-aged populations.[16,23] One potential school of thought is that inflammation may be a key confounding factor in the elderly because inflammation may alter lipid levels.[24,25] In keeping with this notion, low-density lipoprotein cholesterol and, more so, HDL cholesterol levels were (inversely) correlated with elevated CRP in the present study, although the extent of the correlations was modest. Elevated BMI and smoking were more strongly related to CRP in the elderly. In full multivariate models, CRP remained significantly associated with CVD events. However, despite this observation, the addition of CRP only minimally increased the C statistic to beyond that obtained by Framingham risk factors (63.0% to 63.7% for CVD; 65.5% to 66.3% for CHD). This latter finding concurs with data from the Reykjavik cohort,[5] the largest prospective study in this area. Although Cushman and colleagues[4] reported that CRP may add to Framingham risk score in intermediate-risk men and high-risk women in the Cardiovascular Health Study, a potential limitation in their analyses is the use of a dichotomized rather than continuous risk score. Even so, their relative risk of 1.45 (95% CI, 1.14 to 1.86) for CRP >3 versus <1 mg/L was in keeping with ours (1.35; 95% CI, 1.07 to 1.71), and as argued cogently by Greenland and O'Malley,[6] even individual tests with relative risks of between 2.0 and 3.0 are simply not capable of increasing the area under the receiver-operating characteristic curve to any significant clinical degree. Thus, our results suggest caution in recommending use of CRP for CVD risk stratification in the elderly at risk.

Of relevance, a recent study[26] in middle-aged and older women suggested that risk stratification by the addition of CRP was improved among those with a 10-year Framingham risk of 5% to 20%. However, some women were reclassified downward with unclear clinical ramifications, and the actual number of all women "meaningfully" reclassified was actually very small because the vast majority of the population has an initial risk score in the 0% to <5% category.[26] In addition, short-term variability for CRP remains unclear, so repeated CRP measurements would be needed even after an initial risk score was derived, which makes clinical use complex. Such factors and other concerns raised in an accompanying editorial[27] reiterate the need for caution and for further studies before robust recommendations on use or otherwise of CRP for risk stratification are made. Of interest, a recent report from the Atherosclerosis Risk in Communities study suggested negligible improvement in CHD risk prediction from addition of CRP to routine risk factors.[9]

Of course, beyond association with subsequent vascular events, measurement of CRP could still be clinically useful

should it help to guide response to statin therapy. Some previous studies,[18,19] including some using pravastatin, have suggested that statins may give greater relative risk reduction in those with higher CRP levels because of their potential antiinflammatory action. However, in the present study, baseline CRP was not significantly associated with response to therapy for total CVD or CHD events. Of interest, baseline CRP and white cell count (unpublished observation) were not associated with CHD event reduction in the West of Scotland Coronary Prevention study.[28] In contrast, we have already determined that lipid levels, particularly a low baseline HDL cholesterol, may help to predict better response to statin therapy in the elderly.[29] Thus, once again, CRP seems to yield limited additional value compared with conventional CVD risk markers.

Study Limitations and Strengths

We recognize that our work examines prediction of CRP for vascular events in the context of a statin trial. However, lack of interaction between CRP and treatment group in terms of association with incident CVD prediction suggests validity in combining all data for the present analyses. Moreover, CRP levels in this study were all made before statin or placebo allocation. Even so, we were also careful to include the treatment group as a potential explanatory variable. We also recognize that the work examines CRP in elderly subjects at risk and thus may not necessarily apply to the general middle-aged population without risk factors. Of note, however, the adjusted hazard ratio for CVD events comparing the top and bottom thirds for CRP (1.36; 95% CI, 1.15 to 1.61) was very similar to that seen in a recent meta-analysis of 22 prospective studies (many in the general population) and even more so in relation to the 4 largest studies, each with >500 events (1.49; 95% CI, 1.37 to 1.62).[5] We accept that we did not adjust for physical activity or other lifestyle/dietary factors that also relate to CRP. We also accept that more potent statins lower CRP to a greater extent than pravastatin and that the lack of association of baseline CRP with pravastatin-induced reduction in vascular events may not necessarily apply to all statins. However, prior work in the Cholesterol and Recurrent Events study, a secondary prevention study that also used pravastatin, reported an association between baseline CRP levels and response to therapy.[19] We appreciate that the C statistic and other available measures of discrimination could be considered blunt instruments to test clinical utility and that there is a need to determine more acceptable methods. Such statistical issues have been nicely detailed in recent relevant reviews.[13,30] Nevertheless, the C statistic is a widely accepted method of discrimination and gives more meaningful information than hazard ratios in isolation. Finally, we accept that our work cannot be used to argue against causality of CRP for vascular events, which is a separate question and an area of considerable ongoing debate.[1,2] Of interest, a recent development of a specific CRP blocker[31] may help to dissect causality better.

Regarding strengths, ours is one of the largest studies of CRP in relation to vascular events in any population. Moreover, this study also is the largest to examine whether baseline CRP predicts response to therapy and includes not

only CHD events but also stroke and TIA. Because we measured all baseline CRPs, we had added power to examine associations in subgroups with and without vascular disease at baseline; we showed that the relationship of CRP to incident vascular events is essentially similar in both groups. Finally, we also analyzed CRP using previously proposed cutoffs[22] and tertile analyses, and findings with each method were consistent.

Conclusions

The results of the present large prospective study suggest that CRP is only modestly associated with either global CVD events or CHD and does not meaningfully enhance such prediction beyond established risk factors in the elderly at risk. Moreover, contrary to some reported previous observations in middle-aged populations, CRP does not appear to predict response to statin therapy in elderly subjects. These data suggest that CRP may have limited value in predicting CVD risk or response to statin therapy in the elderly.

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CLINICAL PERSPECTIVE

The role of C-reactive protein (CRP) in predicting vascular events and response to statin therapy remains uncertain generally, more so in the elderly; thus, additional large prospective studies are required. We examined the association of CRP with risk over 3.2 years for vascular end points (definite or suspected death from coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke; n=865 events) in the Prospective Study of Pravastatin in the Elderly at Risk (n=5804 men and women; age, 70 to 82 years). CRP levels demonstrated the expected associations with other variables and were higher in subjects who had a subsequent primary end-point event compared with those who did not (geometric mean, 3.64 mg/L [SD, 3.08 mg/L] versus 3.01 mg/L [SD, 3.05 mg/L]; $P<0.0001$). After appropriate adjustments for established predictors and body mass index, subjects in the top versus bottom third for CRP had a 36% (95% CI, 15 to 61) higher risk for an incident vascular event. Although independently associated with incident events, baseline CRP added minimally to risk prediction (determined with model discrimination and calibration) beyond conventional predictors and did not relate to the magnitude of pravastatin benefit in the elderly. In other words, the results of our present study indicate that CRP has limited clinical value in CVD risk stratification or predicting response to statin therapy in elderly people.