Discordant Association of C-Reactive Protein With Clinical Events and Coronary Luminal Narrowing in Postmenopausal Women: Data From the Women's Angiographic Vitamin and Estrogen (WAVE) Study

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ABSTRACT

Background: The incidence of cardiovascular events had been shown to be associated with C-reactive protein (CRP). However, it is unclear that the cardiovascular risk associated with CRP is due to progressive coronary narrowing or to other factors such as formation of unstable plaque. This study was designed to determine the effect of baseline CRP on cardiovascular events and on the progression of atherosclerotic narrowing among 423 postmenopausal women with angiographic stenosis between 15% and 75%.

Hypothesis: Baseline CRP levels may affect cardiovascular events and progression of atherosclerotic coronary artery narrowing among postmenopausal women.

Methods: Baseline and follow-up (2.8 years) angiographic data were analyzed among 320 women. Women were stratified into 4 quartiles according to baseline CRP levels. The changes in lumen diameter and clinical events in each quartile were compared.

Results: The annualized changes in minimal and average lumen diameter in diseased and nondiseased coronary segments were not significantly associated with baseline CRP levels. The composite end point of all-cause mortality and myocardial infarction (MI) increased from 3% (3/107) in the first CRP quartile to 14% (14/98) in fourth CRP quartile ($P < 0.001$). Similar results were found for cardiovascular death and MI (increased from 1% (2/107) in the first quartile to 11% (11/98) in fourth quartile). The difference remained significant even after adjustment for baseline differences and cardiovascular risk factors.

Conclusions: Higher baseline CRP was associated with increased risk of clinical events but was not associated with annualized change in luminal diameters. Thus, increased risk of adverse events among patients with higher baseline CRP events was independent of progression of atherosclerosis as measured by change in minimal or average luminal diameter.

Introduction

Inflammation plays an important role in the pathogenesis of atherosclerosis.^{1,2} Circulating markers of inflammations are found to be associated with poor cardiovascular outcomes and among these markers C-reactive protein (CRP) has emerged as the most important marker.^{3–5} CRP was also correlated with a higher degree of atherosclerosis

on coronary angiography.⁶ In a report of 124 patients with chronic stable angina who were awaiting elective percutaneous coronary intervention, elevated serum CRP level was an independent predictor of rapid progression based on visual examination of serial angiograms.⁷ Even though short-term studies have indicated an association between baseline CRP level and angiographic progression of atherosclerosis, overall data supporting this conclusion are weak. On the other hand, higher CRP levels are also found to be associated with a larger necrotic core, a thin fibrous cap, and more inflammatory cells in the fibrous cap. All 3 of these factors increase the risk of plaque rupture and acute coronary syndrome (ACS).^{8–10} Thus, evidence

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suggests that the inflammatory processes signaled by an increase in serum CRP may reflect increased risk of plaque rupture.

It remained unclear if worse clinical outcome associated with elevated CRP levels is due to increased luminal narrowing or due to formation and rupture of unstable plaque. In this study, we were able to make use of the database from the Women's Angiographic Vitamin and Estrogen (WAVE) trial¹¹ to assess the association between baseline CRP and the rate of coronary artery narrowing, and between CRP level and the incidence of clinical events over a nearly 3-year period.

Methods

The WAVE Trial

The National Heart, Lung, and Blood Institute sponsored the WAVE multicenter randomized trial, which was designed to test the effect of hormone replacement therapy (HRT) and antioxidant vitamins on the progression of atherosclerosis measured by quantitative coronary angiography (QCA) in postmenopausal women. After 3 years of careful follow-up, the study failed to show an effect of either intervention. Details of the study design and its main results have been reported.^{11,12} The institutional review boards of each clinical site approved the study.

Subjects: Women were recruited between July 1997 and August 1999 at 7 clinical sites in the United States and Canada. To be included, women had to: (1) be more than 55 years of age; or (2) have had bilateral oophorectomy; or (3) have a follicle-stimulating hormone level ≥ 40 mU/mL. For the study, women who underwent coronary angiogram for clinical indications within 4 months of study entry were screened for the eligibility. Postmenopausal women who had at least 1 coronary segment with stenosis 15% to 75% in a major coronary artery or a primary branch not subjected to intervention were considered eligible. If participants underwent coronary angiogram within 2 weeks of acute coronary syndrome, the qualifying lesion could not be a culprit lesion.

Major exclusion criteria were: HRT use within 3 months; evidence of breast, uterine, or cervical cancer; myocardial infarction (MI) within 4 weeks; prior or planned coronary bypass surgery; uncontrolled diabetes or hypertension; fasting triglyceride >500 mg/dL; creatinine level >2.0 mg/dL; New York Heart Association class 4 heart failure or left ventricular ejection fraction $<25\%$; symptomatic gallstones; history of bleeding diathesis, pulmonary embolism, hemorrhagic stroke, deep vein thrombosis, or untreated osteoporosis.

Data Collection and Follow-up Procedures: Of the screened individuals, 423 were enrolled. Data regarding the prevalence of clinical comorbidities had been collected for the study. Physical examination and laboratory tests were performed at baseline, during follow-up visits, and at the end of study participation. At each follow-up visit, patients were queried about the occurrence of any clinical events. Primary source documents regarding all reported events were obtained. Primary source documents describing all intercurrent events were used by a clinical events committee made up of 4 investigators to determine the nature of the event. At the end of the study period, a routine exit coronary

angiogram was performed to determine the progression of angiographic atherosclerosis.

Angiographic Analysis and Clinical Outcome: QCA was performed by an independent core laboratory (Stanford University, Edwin L. Alderman, MD, Director). Details of the conduct of the QCA and the quality assurance methods used are described elsewhere.^{11,12} Measurements were carried out on up to 10 proximal epicardial artery segments. Care was taken to obtain as nearly identical views of the segments evaluated at entry as possible. At the baseline angiogram, segments containing no stenosis of as much as 15% were considered "normal." When minimal lumen diameter (MLD) was measured by the same technician, the mean change in MLD was -0.004 ± 0.22 mm, and when it was measured by a different technician the mean change in MLD was 0.005 ± 0.081 mm.¹²

The primary end point for progression of coronary narrowing was the annualized change in the QCA-measured MLD and average lumen diameter (ALD). The primary clinical end point was the composite of all-cause mortality or nonfatal MI. Cardiovascular death or nonfatal MI, as well as a composite outcome labeled "total number of cardiovascular events," are reported as secondary end points. The total cardiovascular events consisted of incidence of MI, cerebrovascular accident (CVA), or congestive heart failure (CHF).

Statistical Analysis

For the purpose of the present study, subjects were divided into quartiles based on baseline CRP level. Clinical characteristics as well as clinical and angiographic outcomes were compared between quartiles. Continuous variables are expressed as mean ± 1 standard deviation, whereas dichotomous variables are expressed as proportions and percentage.

To compare differences between CRP quartiles, analysis of variance was used for continuous and contingency tables for dichotomous variables. Tests were 2-sided, and a $P < 0.05$ set as the level of significance. Statistical analysis software (SAS version 8; SAS Institute Inc., Cary, NC) was used for all analyses.

The relationships between CRP quartiles and clinical outcomes are expressed as odds ratio and 95% confidence intervals and are presented to reflect the magnitude of effect. Multiple logistic regression analysis was performed to adjust for baseline differences and traditional cardiovascular risk factors such as age, diabetes, total and high-density lipoprotein (HDL) cholesterol, smoking, systolic blood pressure, assignment to hormone replacement therapy, and antioxidant vitamins.

Results

Baseline clinical findings and laboratory values together with medications used at study entry are shown in Table 1. Postmenopausal women with CRP level in the upper quartile were more likely to be younger, to be Caucasian, and to be obese. With regard to traditional cardiac risk factors, they more often had diabetes mellitus, and on average, lower levels of HDL cholesterol and higher levels of triglycerides. Notably, renal function as measured by cystatin C was unrelated to CRP quartile.

Table 1. Baseline Characteristics, Laboratory Variables, and Medication Usage in Each Quartile Stratified by Baseline CRP Levels

	All Participants	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
CRP levels (mg/dL)		≤0.24	0.25–0.42	0.43–0.76	≥0.77	
Number	423	107	95	100	98	
Age, y	65.2 ± 8.6	66.6 ± 8.7	65.5 ± 8.7	63.2 ± 8.1	64.6 ± 8.8	0.035
Race/Caucasian	66% (280/423)	76% (81/107)	61% (58/95)	70% (70/100)	57% (56/98)	0.021
Diabetes	37% (267/421)	22% (24/107)	37% (35/94)	40% (40/100)	45% (44/97)	0.005
Hypertension	76% (319/421)	70 % (75/107)	80% (75/94)	75% (75/100)	80% (78/97)	0.274
Heart failure	15% (15/421)	15% (16/107)	12% (11/94)	12% (12/100)	21% (20/97)	0.268
Myocardial infarction	43% (181/421)	41% (44/107)	47% (44/94)	48% (48/100)	38% (37/97)	0.453
Family history of CHD	43% (181/421)	49% (51/104)	40% (37/93)	46% (45/98)	50% (48/95)	0.460
History of CVA	11% (45/421)	10% (10/107)	12% (11/94)	6% (6/100)	12% (12/97)	0.428
Presence of claudication	15% (65/421)	10% (11/107)	15% (14/94)	16% (16/100)	14% (14/97)	0.648
Current smoker	27% (78/286)	28% (17/60)	27% (17/62)	26% (20/77)	25% (19/75)	0.979
Body mass index (kg/m ²)	30.69 ± 6.08	28.71 ± 5.52	30 ± 5.31	31.44 ± 6.08	33.06 ± 6.66	<0.001
SBP, mm Hg	138.8 ± 19.8	139.13 ± 20.65	138.86 ± 19.12	139.19 ± 20.17	138.45 ± 19.36	0.993
DBP, mm Hg	75.8 ± 10.2	74.81 ± 9.49	75.58 ± 10.51	77.04 ± 11.29	75.84 ± 10.06	0.489
CRP levels, mg/dL	0.60 ± 0.58	0.13 ± 0.06	0.33 ± 0.05	0.59 ± 0.10	1.39 ± 0.67	<0.0001
Total cholesterol, mg/dL	200.4 ± 42.3	201.4 ± 40.6	195.7 ± 41.8	201.5 ± 41.5	201.7 ± 43.1	0.703
LDL cholesterol, mg/dL	112.9 ± 35.9	119.6 ± 38.1	115.9 ± 38.3	118.6 ± 36.6	120.6 ± 38.0	0.847
HDL cholesterol, mg/dL	50.2 ± 12.6	53.2 ± 14.1	51.4 ± 12.2	48.1 ± 12.3	47.5 ± 10.4	0.002
Triglyceride level, mg/dL	159.5 ± 86.2	147.9 ± 82.5	142.9 ± 74.9	178.4 ± 94.2	170.6 ± 91.8	0.009
Hemoglobin A1c	6.61 ± 1.7	6.22 ± 1.73	6.67 ± 1.61	6.66 ± 1.70	6.99 ± 1.93	0.055
Cystatin C, mg/dL	1.21 ± 0.57	1.21 ± 0.57	1.17 ± 0.51	1.18 ± 0.60	1.29 ± 0.62	0.471
Medication usage at study entry						
Anticlotting agent	89% (376/422)	90% (96/107)	90% (85/95)	90% (90/100)	86% (83/97)	0.731
Dihydropyridine	16% (66/422)	15% (16/107)	15% (14/95)	13% (13/100)	19% (18/97)	0.744
ACE inhibitor	40% (168/421)	39% (42/107)	38% (36/95)	39% (39/100)	45% (43/96)	0.765
β-Blocker	63% (265/422)	63% (67/107)	72% (68/95)	58% (58/100)	56% (54/97)	0.110
CCB	28% (117/422)	27% (29/107)	28% (27/95)	34% (34/100)	25% (24/97)	0.521
Insulin use	16% (67/422)	10% (11/107)	19% (18/95)	16% (16/100)	17% (16/97)	0.361
Antidiabetic agent	20% (86/422)	15% (16/107)	19% (18/95)	21% (21/100)	26% (25/97)	0.279
Lipid-lowering agent	59% (174/422)	64% (68/107)	62% (59/95)	56% (56/100)	50% (48/97)	0.168
Antioxidants	50% (211/422)	51.89% (55/106)	52% (49/95)	49% (49/100)	45 % (44/98)	0.743
HRT	50% (210/423)	40.19% (43/107)	52% (49/95)	58% (58/100)	51% (50/98)	0.078
Abbreviations: ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; CHD, coronary heart disease; CRP, C-reactive protein; CVA, cerebrovascular accident; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein; SBP, systolic blood pressure.						

Follow-up coronary angiograms were obtained in 320 (76%), with a mean follow-up period of 2.86 years. During the study period, 30 women had intercurrent events (22 women died and 8 had nonfatal MI), 74 had scheduled a visit but did not have an exit angiogram, and 13 were lost to follow-up. Out of 30 women with clinical events during the study period, 14 had intercurrent coronary angiograms, which are included in the final analysis.

Table 2 shows QCA measurements of MLD and ALD at baseline and at mean follow-up period of 2.8 ± 0.9 years. There was essentially no significant difference in annualized change in these measurements (Table 2, Supporting Figure 1). Results remained similar even after analysis was adjusted for multiple segments measured in each participant. Moreover, we also performed segment level analysis. A total of 1741 coronary segments were analyzed among participants who had baseline CRP levels measured. There was no significant relationship between baseline CRP levels and annual change in MLD (P for trend = 0.25) or ALD (P for trend = 0.15) (Supporting Figure 2). Consistent with the observation that CRP level is not associated with progression of coronary narrowing, the level was unassociated with a need for revascularization (Figure).

In contrast to the lack of influence of CRP on the rate of coronary narrowing, the composite outcome of all-cause death/MI (3%, 1%, 8%, and 14% with increase in CRP quartile, $P < 0.001$) as well as cardiovascular death/MI (1%, 1%, 6%, and 11% with increase in CRP quartile, $P = 0.004$) increased significantly with increase in CRP quartile (Table 2, Figure). Total cardiovascular events (composite outcome of MI, CVA, and CHF) also increased with increase in CRP quartile but did not reach a statistically significant level (Table 2).

Unadjusted and adjusted odds ratio for the primary (all-cause death/MI) and secondary end point (cardiovascular death/MI) is shown in the Table 3. CRP level was independently associated with the primary end point (all cause death/MI) after being adjusted for traditional cardiovascular risk factors and baseline differences. Similar results were found for cardiovascular death and nonfatal MI (Table 3).

Further analysis showed that participants who experienced primary clinical events showed significant decrease in minimal luminal diameter (-0.10 ± 0.2 vs -0.03 ± 0.15 , $P = 0.09$) and average luminal diameter (-0.12 ± 0.16 vs -0.01 ± 0.13 , $P = 0.006$) at diseased segment in comparison with women who did not experienced clinical events. The relationship between baseline CRP, luminal narrowing

Table 2. Angiographic Variables and Clinical Events in Each Quartile Stratified by Baseline CRP Level

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
CRP levels (mg/dL)	≤ 0.24	0.25–0.42	0.43–0.76	≥ 0.77	
Number	75	76	80	69	
Nondisease segment atherosclerosis progression					
MLD at baseline	2.69 ± 0.55	2.50 ± 0.64	2.66 ± 0.65	2.70 ± 0.57	0.174
MLD at follow-up	2.65 ± 0.55	2.51 ± 0.52	2.63 ± 0.64	2.65 ± 0.56	0.415
Annual change in MLD	-0.00 ± 0.15	0.01 ± 0.15	-0.03 ± 0.15	-0.01 ± 0.10	0.404
ALD at baseline	2.89 ± 0.57	2.69 ± 0.64	2.86 ± 0.67	2.90 ± 0.60	0.193
ALD at follow-up	2.85 ± 0.58	2.69 ± 0.54	2.84 ± 0.66	2.86 ± 0.58	0.326
Annual change in ALD	0.00 ± 0.15	0.01 ± 0.15	-0.03 ± 0.16	-0.01 ± 0.12	0.528
Disease segment atherosclerosis progression					
MLD at baseline	2.06 ± 0.54	1.93 ± 0.45	1.95 ± 0.53	2.04 ± 0.42	0.254
MLD at follow-up	1.98 ± 0.58	1.91 ± 0.48	1.88 ± 0.49	1.96 ± 0.48	0.605
Annual change in MLD	-0.05 ± 0.17	-0.00 ± 0.12	-0.04 ± 0.13	-0.05 ± 0.16	0.160
ALD at baseline	2.57 ± 0.57	2.47 ± 0.47	2.43 ± 0.57	2.56 ± 0.51	0.287
ALD at follow-up	2.53 ± 0.58	2.47 ± 0.48	2.41 ± 0.52	2.51 ± 0.53	0.532
Annual change in ALD	-0.03 ± 0.13	0.02 ± 0.15	-0.03 ± 0.14	-0.03 ± 0.12	0.090
Clinical events					
All-cause death + MI	3% (3/107)	1% (1/95)	8% (8/100)	14% (14/98)	<0.001
Cardiovascular death + MI	1% (2/107)	1.1% (1/95)	6.0% (6/100)	11% (11/98)	0.004
Cardiovascular events	7% (8/107)	9% (9/95)	11% (11/100)	16% (16/98)	0.219
CABG or PTCA	20 % (21/107)	16% (15/95)	17% (17/100)	18% (18/98)	0.903

Abbreviations: ALD, average luminal diameter, CABG, coronary artery bypass graft, CRP, C-reactive protein; MI, myocardial infarction, MLD, minimal lumen diameter, PTCA, percutaneous transluminal coronary angioplasty.

Figure 1. Clinical outcome based on CRP quartile. Composite outcome of death + MI and cardiovascular death + MI and cardiovascular events (MI + CVA + HF) increased significantly with increase in CRP quartiles. Need for revascularization remained similar. Abbreviations: CABG, coronary artery bypass grafting; CRP, C-reactive protein; CVA, cardiovascular accidents; HF, heart failure; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

at diseased segment, and clinical events is shown in Table 4. In univariate analysis, lumen narrowing was associated with increased risk of clinical events. In multivariate regression analysis, baseline CRP level remained an independent predictor of clinical events.

Discussion

These data demonstrate that a higher CRP level at baseline is associated with an increased incidence of mortality and nonfatal MI as well as cardiovascular death and nonfatal MI in postmenopausal women during a 3-year follow-up. The increase in adverse events was independent of progression of coronary artery narrowing. Thus, it seems likely that the risk associated with a higher CRP level over a 3-year follow-up period may be mediated through pathogenetic mechanisms other than luminal narrowing. Rather, it may reflect the presence of an inflammatory process that may, in turn, be associated with the development of plaque instability, resulting in increased adverse cardiovascular outcomes.

Inflammation is believed to play a pivotal role during all phases of the development of atherosclerosis, beginning with the formation of fatty streaks, proceeding through the recruitment and deposition of macrophage and oxidized low-density lipoprotein (LDL) cholesterol, to the rupture of the thin fibrous cap of vulnerable plaques.^{1,2} CRP, a serum marker of an inflammatory process, has been associated with subclinical atherosclerosis as well as cardiovascular events such as atherothrombosis, ischemic stroke, and myocardial infarction.^{3–5} However, it remains uncertain whether CRP has a pathogenic role in the initiation and development of atheroma or is merely a reflection of ongoing inflammation in the coronary or systemic vasculature.¹³

Preclinical studies have demonstrated numerous potential mechanisms by which CRP may induce or accelerate atherosclerosis progression: (1) downregulation of nitric oxide (NO) expression,¹⁴ (2) activation of the complement system,¹⁵ (3) increasing expression of adhesion molecules and chemoattractant proteins,^{16–18} and (4) increasing the uptake of oxidized LDL particles by macrophages resulting in greater foam cell deposition.¹⁹ On the other hand, there are data that do not confirm CRP as being causally linked with initiation and progression of atherosclerosis. A Mendelian analysis failed to show an association between an increased risk of coronary heart disease and those variants of the CRP locus that result in a lifelong increase in CRP levels.²⁰ Similarly, the LURIC (Ludwigshafen Risk and Cardiovascular Health) study reported finding no association between a CRP genotype associated with higher levels of circulatory CRP and angiographic atherosclerosis.²¹

There is inconsistent information regarding the association of CRP level and progression of coronary atherosclerosis. In small studies, higher baseline CRP levels were associated with rapid progression of angiographic atherosclerosis among patients with stable angina as well as patients with an ACS over a period of 6 to 12 months.^{7,22–24} However, the effect of CRP on the angiographic progression of atherosclerotic disease over a long-term follow-up has not been studied. Moreover, CRP level was not a predictor of plaque burden as noted by intravascular ultrasound (IVUS).²⁵ Also, similar to the present study, the IVUS study demonstrated similar baseline CRP levels among those who had progressive vs regressive disease among the patients

Table 3. Multivariate Logistic Regression Analysis for Clinical Outcomes and Baseline C-Reactive Protein Level

	Death and MI	Cardiovascular Death and MI
Unadjusted OR	2.14 (1.39–3.29) ($P = 0.0001$)	2.19 (1.34–3.59) ($P = 0.0005$)
OR adjusted for baseline differences ^a	2.18 (1.36–3.50) ($P = 0.0013$)	2.38 (1.34–4.24) ($P = 0.0031$)
OR adjusted for baseline differences and traditional cardiovascular risk factors ^b	1.82 (1.04–3.20) ($P = 0.036$)	2.07 (0.99–4.33) ($P = 0.054$)
OR adjusted for baseline differences, traditional cardiovascular risk factors, medication usage, assignments to HRT and antioxidant group ^c	1.82 (1.02–3.23) ($P = 0.043$)	2.23 (1.03–4.81) ($P = 0.042$)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HRT, hormone replacement therapy; MI, myocardial infarction; OR, odds ratio.

^aOR adjusted for age, race, diabetes, BMI, triglyceride levels, and HDL cholesterol. ^bOR adjusted for age, race, diabetes, BMI, triglyceride levels, total and HDL cholesterol, systolic blood pressure, and smoking. ^cOR adjusted for age, race, diabetes, BMI, triglyceride levels, total and HDL cholesterol, systolic blood pressure, smoking, and the use of antioxidant vitamins, HRT, and medication usage.

Table 4. Univariate and Multivariate Analysis for CRP Levels and Change in Minimal Lumen Diameter at Diseased Segment

	All-Cause Death and MI	Cardiovascular Death and MI
Univariate analysis		
Baseline CRP level	2.14 (1.39–3.29) ($P = 0.0001$)	2.19 (1.34–3.59) ($P = 0.0005$)
Angiographic progression of MLD at disease segment	0.09 (0.006–1.50) ($P = 0.09$)	0.06 (0.004–1.08) ($P = 0.05$)
Angiographic progression of ALD at disease segment	0.01 (0.00–0.28) ($P = 0.006$)	0.01 (0.001–0.358) ($P = 0.01$)
Multivariate analysis for CRP and MLD		
Baseline CRP level	3.27 (1.42–7.54) ($P = 0.005$)	3.63 (1.43–9.25) ($P = 0.0067$)
Angiographic progression of MLD at disease segment	0.14 (0.006–3.57) ($P = 0.278$)	0.09 (0.004–2.46) ($P = 0.158$)
Multivariate analysis for CRP and ALD		
Baseline CRP level	3.31 (1.41–7.76) ($P = 0.006$)	3.70 (1.43–9.58) ($P = 0.007$)
Angiographic progression of ALD at disease segment	0.04 (0.001–1.26) ($P = 0.067$)	0.05 (0.001–1.99) ($P = 0.108$)
Abbreviations: ALD, average luminal diameter; CRP, C-reactive protein; MI, myocardial infarction; MLD, minimal lumen diameter.		

with low LDL.²⁶ Furthermore, inconsistent data have been published regarding an association between CRP level and progression of carotid intima-media thickness.^{27,28}

An acute coronary event commonly results from the rupture of atherosclerotic plaque and formation of thrombus in a coronary artery.²⁹ The sequence of events that leads to plaque rupture is not completely understood.²⁹ An association between acute phase reactants such as CRP and an acute coronary event has been suggested. It can further be postulated that chronic inflammation of vasculature might have an important role in the susceptibility of a plaque to rupture.¹⁰ Examinations of plaque morphology have been consistent with this postulate. “Virtual histology” processing of IVUS examinations has shown a correlation between higher high-sensitivity (hs)-CRP and a larger necrotic core in both culprit and nonculprit lesions. This technique also demonstrates a higher incidence of plaque rupture among patients with high CRP.⁹ Moreover, an autopsy study demonstrated an association between higher hs-CRP with an increased number of thin-cap fibroatheromas and greater macrophage infiltration in the fibrous cap.⁸ CRP accompanied by factors that lead to acute coronary syndrome, such as increased metalloproteinase expression or collagenase activity in macrophages, exaggerated vascular remodeling, increased apoptosis in the endothelial cells, and augmented the prothrombotic state.^{13,14,18,30,31} Thus, the association of more frequent cardiovascular events with higher CRP levels may well be due to the conversion of stable coronary plaques to an unstable state and not to an influence on gradual atherosclerotic progression.

It is important to note that “silent” plaque rupture has an important role in intermittent episodic progression of angiographic luminal narrowing.^{7,32} Smooth muscle cell proliferation in arterial wall and secretion of glycosaminoglycans, however, may also lead to a gradual increase in plaque size and continuous slow progression of angiographic narrowing.^{33,34} Findings of our study do not refute the possibility of silent plaque rupture and rapid progression of angiographic stenosis, which may perhaps lead to clinical

events among patients with elevated CRP levels. However, among participants who did not develop clinical events, the study showed elevated CRP levels were not associated with gradual luminal narrowing over 3 years of follow-up.

A recently published genome-wide association study provides a pathogenetic mechanism that could explain the apparent discordance between the lack of association between CRP levels and rate of progression in coronary narrowing, on 1 hand, and the relationship of this inflammatory marker with an increased risk of adverse clinical events on the other. This genome-wide association study described more than 1 relevant genetic polymorphism. Some appear to promote development of stable atherosclerosis, and some are associated with the occurrence of ACS in the presence of coronary atherosclerosis.³⁵ Thus, genetic polymorphisms as well as cardiovascular risk markers and risk factors may be different among those who have stable coronary artery disease (CAD) and among those who have a propensity to develop ACS in the presence of underlying coronary atherosclerosis. Our findings demonstrated that elevated CRP may suggest a higher degree of inflammation and predisposition to develop the enhanced cytokine response to any stress or inflammatory stimuli, which may lead to development and rupture of vulnerable plaque rather than progression of stable coronary arterial narrowing.

Limitations

Our study has several limitations. The data were not specifically collected to answer the research question addressed in this analysis. Even though number of clinical events were small, the association between CRP and clinical events was similar to that reported in previous studies.^{3–5} Moreover, out of 30 patients who developed clinical events, only 14 patients had an intercurrent angiogram. Further, only postmenopausal women were studied, and findings may not be generalized. IVUS studies may provide more accurate information about progression of atherosclerosis. Slower rate of atherosclerosis progression among women³⁶ may have resulted in this study being underpowered to detect the effect of CRP on angiographic progression. Moreover,

data do not provide information regarding inflammatory conditions among study participants, which may lead to an increase in CRP levels. However, within these limitations the study is unique in focusing on postmenopausal women with angiographically documented CAD who are at greater risk of developing cardiovascular events, and the study has the ability to correlate clinical events as well as progression of angiographic atherosclerosis.

Conclusion

A high CRP level in postmenopausal women with angiographic diagnosis of CAD does not reliably predict accelerated progression of atherosclerosis or need for revascularization procedures but clearly predicts an increased likelihood of “hard” adverse cardiac events. Moreover, increased risk of cardiovascular events associated with higher CRP levels was independent of angiographic atherosclerosis progression.

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