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Serum Amyloid A as a Predictor of Coronary Artery Disease and Cardiovascular Outcome in Women

The National Heart, Lung, and Blood Institute–Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Background—Serum amyloid-α (SAA) is a sensitive marker of an acute inflammatory state. Like high-sensitivity C-reactive protein (hs-CRP), SAA has been linked to atherosclerosis. However, prior studies have yielded inconsistent results, and the independent predictive value of SAA for coronary artery disease (CAD) severity and cardiovascular events remains unclear.

Methods and Results—A total of 705 women referred for coronary angiography for suspected myocardial ischemia underwent plasma assays for SAA and hs-CRP, quantitative angiographic assessment, and follow-up evaluation. Cardiovascular events were death, myocardial infarction, congestive heart failure, stroke, and other vascular events. The women's mean age was 58 years (range 21 to 86 years), and 18% were nonwhite. SAA and hs-CRP were associated with a broad range of CAD risk factors. After adjustment for these risk factors, SAA levels were independently but moderately associated with angiographic CAD ($P=0.004$ to 0.04) and highly predictive of 3-year cardiovascular events ($P<0.0001$). By comparison, hs-CRP was not associated with angiographic CAD ($P=0.08$ to 0.35) but, like SAA, was strongly and independently predictive of adverse cardiovascular outcome ($P<0.0001$).

Conclusions—Our results show a strong independent relationship between SAA and future cardiovascular events, similar to that found for hs-CRP. Although SAA was independently but moderately associated with angiographic CAD, this association was not found for hs-CRP. These results are consistent with the hypothesis that systemic inflammation, manifested by high SAA or hs-CRP levels, may promote atherosclerotic plaque destabilization, in addition to exerting a possible direct effect on atherogenesis. **(*Circulation*. 2004;109:726-732.)**

Key Words: inflammation ■ amyloid ■ proteins ■ coronary disease ■ women

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Serum amyloid A (SAA) is a family of proteins that form a major component of the acute-phase inflammatory response.[1] Like C-reactive protein (CRP), SAA is synthesized in the liver in response to infection, inflammation, injury, or stress.[2] Accordingly, SAA is a sensitive marker of an acute inflammatory state. During the acute-phase reaction, SAA is secreted as the predominant apolipoprotein on plasma HDL cholesterol particles, where it is thought to replace apolipoprotein A-I[3,4] and alter HDL-mediated cholesterol delivery to cells.[5,6] This observation may explain its increased concentration in patients with coronary artery disease (CAD).[7–9] Although other nonspecific inflammatory markers such as CRP also correlate with cardiovascular disease, the wider dynamic range and more rapid response of SAA has led some to suggest that it may be a better marker of disease activity[1,10–17] and may represent a different type of acute-phase response than CRP.[18]

Although the acute-phase response is a marker of chronic disease, it may also have direct pathological consequences.[19] For example, the lipoprotein changes that occur during the acute-phase response may be proatherogenic.[10–25] This is supported by recent findings that have consistently documented a strong independent relationship between CRP and future cardiovascular events[7–9,26–29]. Acute-phase reactants may also play a pathophysiological role in atherosclerotic plaque instability as manifested by elevated high-sensitivity CRP (hs-CRP) levels in the presence of ruptured coronary artery plaques.[30] However, some studies have failed to show

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an association between CRP levels and angiographic CAD severity.[31,32]

Although less studied than CRP, SAA has also been shown to be a predictor of cardiovascular events.[33–37] However, some studies suggest that this relationship may be dependent on other CAD risk factors.[9,38–41] Therefore, the independent predictive value of SAA for CAD and cardiovascular events remains unclear. Accordingly, the present study investigated the relationship between SAA and both CAD severity and the 3-year risk of cardiovascular events in women referred for coronary angiography for evaluation of suspected myocardial ischemia as part of the Women's Ischemia Syndrome Evaluation (WISE) study sponsored by the National Heart, Lung, and Blood Institute (NHLBI). To evaluate the strengths of these relationships, complementary findings for hs-CRP in this cohort of women are presented for comparison.

Methods

Study Population

The study population consisted of 705 women, 21 to 86 years of age, who were clinically referred for coronary angiography to evaluate suspected myocardial ischemia and enrolled in WISE[42] and who had baseline measurements of hs-CRP and SAA. Exclusion criteria included pregnancy, cardiomyopathy, New York Heart Association class IV congestive heart failure, recent myocardial infarction or revascularization, and any contraindications to provocative testing. All subjects provided informed consent and completed research forms approved by the institutional review board at their local WISE clinical site. Long-term clinical follow-up was available for 686 women.

Baseline Evaluation

On enrollment, baseline evaluation included the collection of demographic information, risk factors for CAD, medication use, medical and reproductive history, symptom and psychosocial evaluation, a physical examination with blood pressure and physical measurements, and sampling of blood in the fasting state for lipid, reproductive hormone, and inflammatory marker core laboratory evaluations. Lipoprotein determinations (total cholesterol, HDL cholesterol, and triglycerides) were performed at a lipid core laboratory enrolled in the Centers for Disease Control and Prevention lipid standardization program with experience in NHLBI-sponsored lipid-lowering intervention trials. LDL cholesterol was estimated by the Friedewald formula. Reproductive hormone determinations were performed at the WISE hormone core laboratory; specimens were assayed in batches of 150 to 350, and each determination was measured in duplicate. The complete research design and methodology of the WISE study have been described previously.[42]

Measurement of Inflammatory Markers

Plasma sampled at enrollment was frozen at −70°C for subsequent measurement of inflammatory markers. SAA and CRP levels were measured by a high-sensitivity method on a BNII analyzer (Dade Behring) by previously validated techniques.[31]

Quantitative Angiographic Assessment of CAD

All coronary angiograms obtained at enrollment were quantitatively analyzed offline by the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) by investigators blinded to all other WISE clinical data.[43] Luminal diameter was measured at all stenoses with electronic calipers or an electronic cine projector based on the cross-hair caliper technique (Vanguard Instrument Corp). The presence of significant CAD was defined as ≥50% stenosis in ≥1 major epicardial coronary artery. Additional angiographic variables that were considered were number of diseased vessels and number of obstructive lesions (≥50% stenosis). An angiographic CAD severity index was calculated based on stenosis severity weighted by proximal location.[43]

Follow-Up Procedures

Follow-up was conducted by telephone and/or mail contact at 6 weeks and then yearly thereafter. Follow-up consisted of a scripted interview by an experienced nurse or physician blinded to the inflammatory marker results. The median follow-up time among surviving patients was 36.5 months. When a major cardiovascular event was identified, the referring physician was contacted for confirmation, dates, and documentation of the occurrence. In the event of death, a death certificate was obtained. Event-free survival was defined as absence of death, myocardial infarction, congestive heart failure, stroke, or other vascular events.

Statistical Methods

Because of their highly skewed distributions, SAA and hs-CRP were either log transformed or analyzed as terciles, and all bivariate relationships were analyzed by nonparametric statistics such as Spearman correlations and Wilcoxon rank sum tests. *P* values for trend were obtained by the Mantel-Haenszel statistic for frequencies and the Jonckheere-Terpstra statistic for continuous variables.

Multivariate models used linear regression analysis for continuous outcomes such as the CAD severity score; logistic regression analysis for binary outcomes such as the presence/absence of CAD; and Cox proportional hazards regression analysis for estimating the likelihood of a cardiovascular event. All multivariate modeling was performed in 2 steps. The first involved stepwise modeling to develop the best predictive model of CAD variables or events and included known risk factors and other available baseline variables. Logarithmic transformations were attempted for variables that violated the normality assumption. Inflammatory markers were not included in this initial model but were then added to the final model as step 2.

The Kaplan-Meier method was used to compare the 3-year event-free survival rate among women in the low, medium, and high terciles of SAA or hs-CRP. For all event-rate analyses, women not experiencing an adverse event were censored at either 3 years or the last date of follow-up before 3 years.

Results

Baseline Characteristics

The baseline characteristics of the study population are presented in Table 1. The women's mean age was 58 years (range 21 to 86 years); 18% were nonwhite racial/ethnic minorities (primarily black); and 76% were postmenopausal. Half of the women had used hormone therapy (HT), and 40% were currently taking various formulations of HT. Of note in this population is the high rate of risk factors, including diabetes (24%), dyslipidemia (54%), hypertension (58%), history of smoking (52%), and obesity (mean body mass index of 29.6, range 14.0 to 57.2). Despite this high prevalence of risk factors, only approximately one third of the women had significant angiographic CAD, defined as ≥50% stenosis in ≥1 coronary artery. There was also a high prevalence of comorbidity, with 43% having a chronic disease other than CAD (eg, diabetes, chronic obstructive pulmonary disease, renal dysfunction, and autoimmune disease). SAA levels ranged from 0.8 to 731 mg/L with a mean±SD of 17.9±69.7 mg/L (median 5.5 mg/L). Plasma hs-CRP levels ranged from 0.2 to 170 mg/L, with a mean±SD of 8.5±15.5 mg/L (median 3.9 mg/L). The distributions of SAA and hs-CRP were highly skewed. The Spearman correlation between SAA and hs-CRP was 0.58 ($P<0.0001$). Approximately 25% of the women had SAA

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TABLE 1. Demographic Characteristics, Risk Factors, and Angiography (n=705)

Characteristic	Mean or Prevalence
Age, y, mean±SD (range)	58±12 (21–86)
Nonwhite, %	18
Postmenopausal, %	76
HT use, %	
Current	40
Ever	52
CAD risk factors, %	
Diabetes	24
History of dyslipidemia	54
History of hypertension	58
Family history of CAD	66
Current smoking	20
Ever smoked	52
BMI, kg/m^2, mean±SD (range)	29.6±6.7 (14.0–57.2)
Waist/hip ratio, mean±SD (range)	0.85±0.11 (0.67–1.62)
Systolic BP, mean±SD (range)	137±21 (82–247)
Diastolic BP, mean±SD (range)	76±11 (40–112)
Comorbidity	
No. of comorbid conditions, mean±SD (range)	2.0±1.4 (0–7)
Chronic disease other than CAD, %	43
Quantitative coronary angiography	
≥50% stenosis (%)	36
No. of diseased vessels, mean±SD (range)	0.64±0.99 (0–3)
No. of lesions ≥50%, mean±SD (range)	0.84±1.46 (0–7)
Maximum % stenosis, mean±SD (range)	37±36 (0–100)
Severity score, mean±SD (range)	14.2±13.8 (5–78.2)
SAA, mg/L, mean±SD (range)	17.9±69.7 (0.8–731)
>10 mg/L, %	25
hs-CRP, mean±SD (range)	8.5±15.5 (0.2–170)
>3 mg/L, %	58

BMI indicates body mass index; BP, blood pressure; and HT, hormone therapy.

values >10.0 mg/L, and 58% had hs-CRP values >3 mg/L, values that are considered abnormally high.[44,45]

Relationship Between SAA and hs-CRP and Baseline Characteristics

Tables 2 and 3 report the associations between inflammatory marker levels and baseline characteristics, with Table 2 providing the Spearman correlations with continuous variables and Table 3 giving the SAA and hs-CRP values across binary variables. These tables list only those variables that were significantly related to SAA and/or hs-CRP. These data demonstrate that SAA levels were significantly higher in women with hypertension and obesity, but not among those with other traditional CAD risk factors. In contrast, hs-CRP levels were significantly higher across a broad range of risk factors, including hypertension, obesity, history of smoking, higher triglyceride levels, bilateral oophorectomy, and current HT use. In addition, hs-CRP correlated significantly with nonwhite race and assayed female reproductive hormones. Age, diabetes, aspirin usage, or statin usage were not related to SAA or hs-CRP levels.

TABLE 2. Significant Spearman Correlations Between SAA and hs-CRP With WISE Baseline Variables

Baseline Variable	Spearman *r* With SAA	Spearman *r* With hs-CRP
Age	0.07	0.03
Triglycerides	0.09*	0.26†
HDL cholesterol	0.07*	−0.06
Estrone (E_1)	0.08*	0.24†
Estradiol (E_2)	0.04	0.14‡
Bioavailable E_2	0.03	0.09*
Follicle-stimulating hormone	−0.06	−0.14†
Luteinizing hormone	−0.03	−0.10§
No. of miscarriages	0.07*	0.04
Body mass index	0.20†	0.29†
Waist circumference	0.24†	0.31†
Waist-hip ratio	0.13‡	0.22†
Systolic blood pressure	0.14‡	0.12‡
Diastolic blood pressure	0.08*	0.02
No. of comorbid conditions	0.03	0.11§
ATP-III risk score	0.06	0.10§
No. of CAD risk factors	0.06	0.12§

ATP-III indicates Adult Treatment Panel III of the National Cholesterol Education Program.

*P≤0.05; †P≤0.0001; ‡P≤0.001; §P≤0.01. Nonsignificant correlations: total cholesterol, LDL cholesterol, progesterone, creatinine, fasting blood glucose, number of pregnancies, and number of live births.

Relationship Between SAA and hs-CRP and Angiographic CAD

The Figure presents the distribution of various quantitative angiography measures across SAA and hs-CRP terciles. These data demonstrate significant increases in both CAD prevalence and severity across the low, medium, and upper terciles of SAA. For example, the prevalence of CAD (≥50% stenosis) was 29%, 36%, and 44%, respectively, with increasing terciles of SAA (P=0.0006). Mean CAD severity scores were 12.8, 14.2, and 15.6 among increasing SAA terciles (P=0.006). In contrast, similar analysis across terciles of hs-CRP demonstrated no significant differences in CAD prevalence and severity among hs-CRP terciles. For example, the prevalence of CAD was 33%, 38%, and 38% among increasing hs-CRP terciles (P=NS); mean CAD severity scores were 13.3±13.3, 13.5±12.4, and 15.7±15.5 among hs-CRP terciles (P=NS).

Multivariate analyses were adjusted for variables that significantly predicted CAD prevalence and severity, including age, lipids, reproductive hormone levels, CAD risk factors, smoking, body mass index, HT use, and blood pressure. After a basic predictive model was established, log SAA or log hs-CRP was added as a predictor to each model. As seen in Table 4, log SAA was independently associated with the binary definition of significant angiographic CAD (OR 1.29, 95% CI 1.08 to 1.54, P=0.004), whereas log

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TABLE 3. Median SAA and hs-CRP Levels for Women With and Without Various Risk Factors, Comorbidities, and Medication Use

	Median SAA, mg/L (Interquartile Range)			Median CRP, mg/L (Interquartile Range)		
Condition (% With Condition)	Condition Absent	Condition Present	*P**	Condition Absent	Condition Present	*P**
Risk factors						
History of HTN (58)	5.1 (3.0–9.7)	5.9 (3.5–10.3)	≤0.05	3.1 (1.3–7.4)	4.7 (2.2–9.2)	≤0.001
History of smoking (52)	5.5 (3.4–9.4)	5.6 (3.0–10.9)		3.6 (1.6–8.2)	4.2 (1.9–9.9)	≤0.05
Current HT (40)	5.4 (3.1–9.4)	5.8 (3.4–11.2)		3.4 (1.4–7.3)	5.3 (2.2–10.6)	≤0.0001
Ever used HT (52)	5.5 (3.0–9.7)	5.6 (3.4–10.6)		3.0 (1.3–7.1)	5.0 (2.2–10.3)	≤0.0001
Nonwhite (18)	5.5 (3.2–9.8)	6.2 (3.3–11.3)		3.7 (1.6–8.7)	5.3 (2.3–9.1)	≤0.05
BSO (26)	5.4 (3.1–9.6)	5.9 (3.5–10.4)		3.5 (1.4–7.9)	5.4 (2.5–10.1)	≤0.001
HTN risk† (67)	4.6 (2.8–8.9)	5.9 (3.5–10.8)	≤0.01	2.8 (1.3–7.0)	4.7 (2.0–9.3)	≤0.0001
CAD/comorbidity						
CAD (36)	5.4 (3.0–9.0)	6.2 (3.7–11.6)	≤0.01	3.7 (1.6–8.3)	4.5 (2.0–10.3)	≤0.05
Prior CHD (8)	5.5 (3.2–9.6)	7.9 (3.8–14.8)	≤0.05	3.7 (1.6–8.2)	7.6 (3.6–14.7)	≤0.0001
History of PVD (8)	5.4 (3.1–9.5)	8.3 (4.6–15.1)	≤0.01	3.7 (1.6–8.2)	6.4 (2.7–13.3)	≤0.01
COPD (5)	5.5 (3.1–9.8)	8.3 (4.0–18.1)	≤0.05	3.9 (1.7–8.4)	8.0 (2.7–20.0)	≤0.01
Chronic renal dysfunction (3)	5.5 (3.2–9.7)	10.6 (4.3–19.4)	≤0.01	3.9 (1.6–8.7)	3.9 (2.1–8.8)	
Depression (24)	5.4 (3.2–9.8)	5.9 (3.4–10.6)		3.6 (1.5–7.9)	4.8 (2.3–10.5)	≤0.01
Chronic disease‡ (59)	5.0 (3.0–8.4)	5.9 (3.4–11.2)	≤0.01	2.9 (1.3–6.5)	5.0 (2.0–10.3)	≤0.0001
Medications prior week						
ACE inhibitor (25)	5.5 (3.2–10.0)	5.5 (3.5–10.4)		3.6 (1.5–8.3)	5.1 (2.3–10.3)	≤0.01
Diuretics (28)	5.4 (3.0–9.0)	6.2 (3.8–13.3)	≤0.001	3.5 (1.5–7.8)	5.5 (2.2–11.3)	≤0.0001
Vasodilators (8)	5.5 (3.2–10.2)	5.4 (3.6–8.5)		3.7 (1.6–8.4)	5.3 (2.7–10.5)	≤0.05
Diabetic medications (20)	5.6 (3.1–9.6)	5.2 (3.5–12.5)		3.8 (1.6–8.3)	4.7 (2.2–10.4)	≤0.05

HTN indicates hypertension; BSO, bilateral salpingo-oophorectomy; CHD, congestive heart disease; PVD, peripheral vascular disease; HT, hormone therapy; and COPD, chronic obstructive pulmonary disease.

*Nonsignificant relationships were found for diabetes; history of dyslipidemia; family history of CAD; postmenopausal status; self-described daily stress level; typical angina (vs other symptoms); prior myocardial infarction, CABG, or PTCA; history of cerebrovascular disease, malignancy, or use of aspirin, β-blockers, calcium antagonists, statins, or other lipid-lowering drugs.

†HTN risk defined as systolic blood pressure >140 mm¦Hg or diastolic blood pressure >90 mm¦Hg.

‡Chronic disease includes diabetes, COPD, renal disease, autoimmune disease, alcoholism, Wilson's disease, myasthenia gravis, Parkinson's disease, HIV infection, Sheehan's syndrome, multiple sclerosis, and Hashimoto's disease.

hs-CRP levels were only nominally suggestive of an association with significant angiographic CAD (OR 1.16, 95% CI 0.98 to 1.37, $P=0.08$). Similar results were observed when the presence of CAD was evaluated with discrete and continuous variable measurements. Thus, SAA remained a significant independent predictor of angiographic CAD after adjustment for covariates. In contrast, log hs-CRP was not an independent predictor for angiographic CAD.

Relationship Between SAA and hs-CRP and Risk of Cardiovascular Events

Among the 686 women with available follow-up, 117 (17%) had a cardiovascular event. These events included 41 deaths (6%), 18 nonfatal myocardial infarctions (3%), 22 strokes (3%), 28 admissions for congestive heart failure (4%), and 32 other vascular events, including blood clots, transient ischemic attacks, and peripheral and cerebrovascular revascularization (5%). Among women who remained alive, the mean follow-up time was 3.2 years (range 2 weeks to 6 years). Of those without a cardiovascular event, 94 (21%) had less than 2 years of follow-up, 76 (17%) had between 2 and 3 years, and 281 (62%) had 3 or more years. Modeling of the 3-year risk of a cardiovascular event incorporated CAD risk factors, demographic characteristics, prior history of CAD, the CAD severity score, and either SAA or hs-CRP levels. Independent predictors of event-free survival are presented in Table 5. In the model that included SAA levels, SAA and diabetes mellitus were the strongest independent predictors of future cardiovascular events ($P<0.0001$). For SAA, the adjusted hazard ratio of 1.032 indicates that there was a 3.2% increase in the 3-year risk for major cardiovascular events for each increase of 1 mg/dL in SAA concentration. The results were similar when log SAA was used in place of the nontransformed values of SAA. There was no interaction demonstrated between CAD and SAA, which suggests that SAA levels are associated with the same relative cardiovascular event risk independent of the presence of preexisting CAD.

The relationship between hs-CRP and cardiovascular events was very similar to that found for SAA. Statistical modeling demonstrated that hs-CRP and diabetes mellitus were the strongest independent predictors of future cardiovascular events ($P<0.0001$). Again, there was no evidence of interaction between CAD and hs-CRP. For comparison of the predictive values of both inflammatory markers for cardio-

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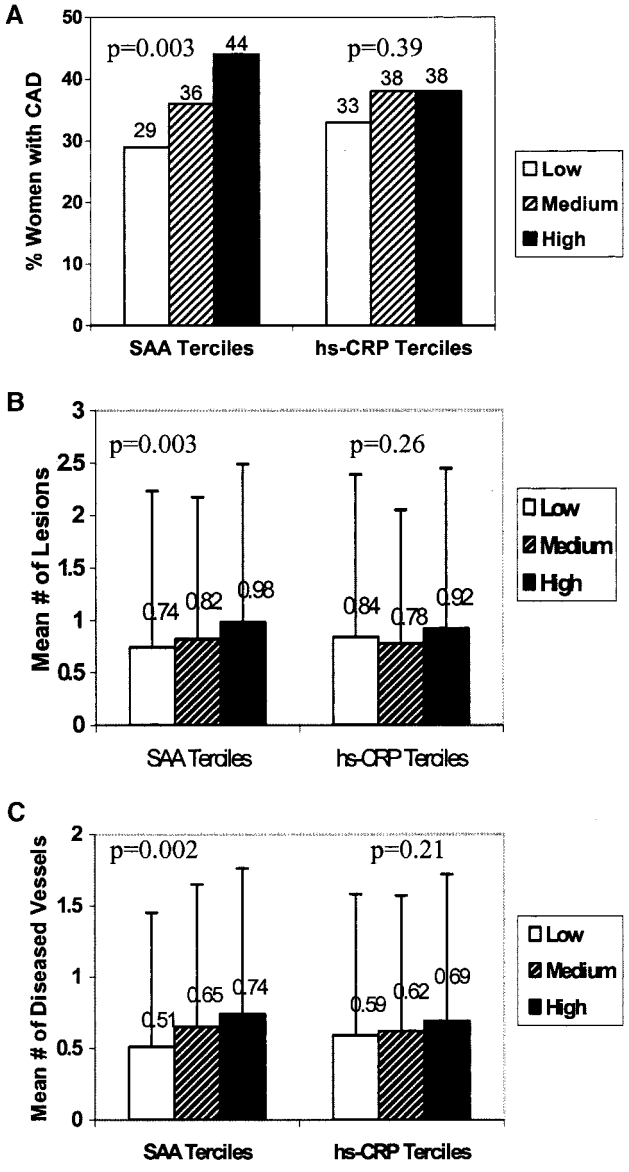

CAD prevalence/severity by SAA or hs-CRP terciles (*P* values for trend). Error bars represent SDs. SAA terciles: low, <3.9 mg/L; medium, 3.9 to <8.2 mg/L; high, ≥8.3 mg/L. Hs-CRP terciles: low, <2.26 mg/L; medium, 2.26 to <6.58 mg/L; high, ≥6.58 mg/L. A, Women with CAD. B, Mean number of lesions of ≥50% stenosis. C, Mean number of vessels with ≥50% stenosis.

vascular events, SAA and hs-CRP levels were converted to unit-independent z-scores. The hazard ratios for zSAA and zCRP in separate but identical models were 1.24 and 1.32, respectively.

Discussion

The present study demonstrates that in women undergoing coronary angiography for diagnosis of suspected ischemia, SAA levels were independently but moderately associated with angiographic CAD. Nevertheless, SAA levels were strong predictors of 3-year cardiovascular events, independent of the presence of angiographic CAD, atherosclerosis risk factors, and comorbid conditions. By comparison, hs-CRP levels were not significantly associated with angiographic CAD in women with chest pain but, like SAA, were strongly and independently predictive of adverse cardiovascular outcome.

TABLE 4. Relationship Between Log SAA or Log CRP and CAD Prevalence/Severity After Adjustment for Significant Covariates*

Dependent Variables	Log SAA	Log CRP
Binary CAD variables		
≥50% stenosis		
OR	1.29	1.16
95% CI	1.08–1.54	0.98–1.37
P	0.004	0.08
Continuous CAD variables		
No. of lesions (log)		
β	0.10	0.04
SE	0.05	0.04
P	0.04	0.35
No. of diseased vessels (log)		
β	0.10	0.04
SE	0.05	0.04
P	0.02	0.35
Severity score (log)		
β	0.05	0.04
SE	0.02	0.02
P	0.04	0.08

*Significant covariates included (in different models): age, log triglycerides, log HDL, serum estrone, serum progesterone, history of diabetes, history of dyslipidemia, history of smoking, current smoking, log body mass index, history of HT use, log pulse pressure.

The exact mechanism for the association between inflammation and future cardiovascular risk is not known. Laboratory studies have demonstrated that inflammation plays a pathophysiological role in atherogenesis and may promote the development of atherosclerotic plaques in coronary arteries. For instance, proinflammatory cytokines have been isolated in atherosclerotic lesions and have proatherogenic properties.[46–48] Alternatively, inflammation may be associated with or be a marker for instability and rupture of preexisting atherosclerotic plaques. Recent studies have demonstrated that high hs-CRP levels are associated with atherosclerotic plaque rupture,[30] which may be related to ongoing inflammation within the fibrous cap of the plaque.[30,49,50] These pathophysiological findings may explain epidemiological observations that have consistently reported that levels of circulating inflammatory markers and myeloperoxidase predict the risk for future cardiovascular events.[8,9,51,52] Furthermore, clinical trials demonstrate that anti-inflammatory drugs such as aspirin and statins decrease both inflammatory markers and cardiovascular risk.[37,53]

The hypothesis that inflammation plays a role in destabilization of vulnerable atherosclerotic plaques is supported by studies that demonstrate that hs-CRP levels predict cardiovascular outcome in patients with low cardiovascular risk manifested by low levels of LDL cholesterol.[7] The present

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TABLE 5. Independent Predictors of 3-Year Risk of Major Cardiovascular Event*

	Model 1 (Basic Model)		Model 2 (With SAA)		Model 3 (With hs-CRP)	
Independent Risk Factor	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
SAA	...	...	1.032 (1.02–1.05)	<0.0001	...	...
hs-CRP	...	...	...	...	1.20 (1.11–1.29)	<0.0001
Diabetes mellitus	2.22 (1.48–3.33)	0.0001	2.32 (1.54–3.50)	<0.0001	2.30 (1.52–3.47)	<0.0001
Pulse pressure	1.02 (1.01–1.03)	0.0008	1.02 (1.01–1.03)	0.001	1.01 (1.004–1.02)	0.006
History of CAD†	1.95 (1.30–2.92)	0.001	2.03 (1.35–3.03)	0.0006	2.03 (1.36–3.05)	0.0006
History of smoking	1.78 (1.20–2.64)	0.004	1.77 (1.19–2.63)	0.005	1.77 (1.19–2.64)	0.005
CAD severity score	1.02 (1.004–1.03)	0.01	1.02 (1.002–1.03)	0.02	1.02 (1.003–1.03)	0.02
Total cholesterol	1.005 (1.001–1.008)	0.02	1.005 (1.001–1.008)	0.02	1.005 (1.001–1.009)	0.02

HR indicates hazard ratio.

*Includes any death, myocardial infarction, congestive heart failure, stroke, and other vascular events (eg, blood clot, carotid endarterectomy, transient ischemic attack).

†Defined as prior myocardial infarction, CABG, or PTCA.

findings confirm this observation of the predictive value of hs-CRP in a cohort of relatively low-risk women with suspected myocardial ischemia, of whom only approximately one third had significant obstructive angiographic CAD. In addition, the present results indicate that hs-CRP levels are at most only nominally associated with the presence of preexisting angiographic CAD in these women. When viewed in the context of our reported strong independent relationship between SAA and cardiovascular outcome and only a moderate association between SAA and angiographic CAD, these results further support the role of inflammation in the pathophysiology of destabilization of vulnerable coronary artery atherosclerotic plaques, as was recently reported in other clinical studies.[30] However, the present study was not designed to evaluate the exact mechanism of the association among inflammatory markers, angiographic CAD, and cardiovascular outcome. Alternative explanations for our findings include the possibility that inflammation may serve as a mediator between atherosclerosis risk factors and cardiovascular events.[54] This is supported by the reported observation that inflammatory markers such as SAA may promote stress-induced modification of cholesterol transport[6] and increased affinity of macrophages for HDL.[55]

Generalization of our results is limited by our focus on women who were referred for clinically indicated coronary angiography to evaluate suspected myocardial ischemia. However, although the cohort excluded men, it included women who exhibited a broad range of angiographically documented CAD. This study design provided a unique opportunity to evaluate associations among inflammation, atherosclerosis risk factors, reproductive hormone levels, angiographic CAD, and cardiovascular risk in women.

In conclusion, our results demonstrate a strong independent relationship between SAA and future cardiovascular events and an independent but moderate association between SAA and angiographic CAD in women. In addition, while confirming the previously reported association between hs-CRP and cardiovascular risk, the present data suggest at most a nominal independent association between hs-CRP and angiographic CAD. These results are consistent with the hypothesis that systemic inflammation, manifested by high SAA or hs-CRP levels, may possibly be associated with increased cardiovascular risk by promoting atherosclerotic plaque destabilization, in addition to exerting a possible direct effect on atherogenesis. Future studies evaluating potential mechanisms for the epidemiological association between inflammation and cardiovascular risk should focus on the relationship between inflammation, atherosclerotic plaque instability, and modulation of the effects of atherosclerosis risk factors.

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