

# Relation of C-Reactive Protein and Fibrinogen to Coronary Artery Calcium in Subjects With Systemic Hypertension

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**C**-reactive protein (CRP) and fibrinogen, which are markers of inflammation, are associated with increased risk of cardiovascular events,<sup>1,2</sup> but their relation to coronary atherosclerotic burden in asymptomatic subjects remains poorly defined. Both CRP and fibrinogen have been described as “conditional” risk factors, implying that the risk conferred may depend on the background risk.<sup>3</sup> We hypothesized that in hypertensive subjects without a history of cardiovascular events, CRP and fibrinogen may be associated with coronary artery calcium (CAC), a surrogate of coronary atherosclerotic burden.

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Subjects included 354 non-Hispanic white hypertensive subjects from Rochester, Minnesota, who participated in the Genetic Network of Arteriopathy (GENOA) study, a community-based study of hypertensive siblings to identify genes influencing blood pressure.<sup>4</sup> By November 2001, 512 participants had completed measurement of CAC by electron beam computed tomography (EBCT). We excluded 106 normotensive subjects, 29 subjects with a history of myocardial infarction or stroke, and 23 subjects with missing data.

Diabetes was considered present if a subject was being treated with insulin or oral agents, or had a fasting glucose level  $\geq 126$  mg/dl. “Ever” smoking was defined as having smoked  $\geq 100$  cigarettes in the past. Hypertension diagnosis was based on blood pressure at the study visit ( $>140/90$  mm Hg), a report of prior diagnosis of hypertension, or current treatment with antihypertensive medications. Information about the use of statins, oral estrogen, and aspirin was provided by participants. The 10-year risk of a cardiovascular event was estimated based on the Framingham risk score.<sup>5</sup>

Blood was drawn after an overnight fast. Serum cholesterol, triglycerides, and high-density lipoprotein

cholesterol were measured by standard enzymatic methods. Plasma glucose was measured by the glucose oxidase method. Fibrinogen was measured by the von Clauss (clotting time-based) method<sup>6</sup> and CRP by a highly sensitive immunoturbidimetric assay.<sup>7</sup>

Presence and quantity of CAC were measured with an Imatron C-150 EBCT scanner (Imatron Inc., South San Francisco, California) as previously described.<sup>8</sup> CAC score was determined using Agatston et al’s method.<sup>9</sup> Age- and gender-specific CAC score percentiles were also estimated as previously described.<sup>10</sup>

Analyses were performed separately in men and women. Because the distribution of CAC scores was positively skewed and not all subjects had detectable CAC, the scores were log-transformed after adding 1. CRP values were log-transformed to reduce skewness. Log (CAC + 1) was determined in quintiles of CRP and fibrinogen, and Spearman’s correlations for log (CAC + 1) with log CRP and fibrinogen were computed. Univariate predictors of CAC were identified by simple linear regression. Multiple linear regression was used to investigate the association of log CRP and fibrinogen with quantity of CAC and with CAC score percentile after adjusting for conventional risk factors, body mass index, and use of statins, estrogen, and aspirin.

Because of the sibling relations in the sample (187 in all), population-averaged generalized estimating equations<sup>11</sup> were used to assess the possible impact of familial correlations on the relation between independent and dependent variables. Because inferences were the same, only the regression analyses are presented.

Subject characteristics are listed in Table 1. Mean CRP levels were significantly higher in women, but mean fibrinogen levels did not differ between genders. Most of the subjects had detectable CAC; the quantity of CAC was significantly higher in men. Approximately 1/3 of subjects reported statin use. Half of the women were on estrogen but were less likely than men to be receiving aspirin.

CRP and fibrinogen were significantly correlated both in women ( $r = 0.32$ ,  $p < 0.0001$ ) and in men ( $r = 0.49$ ,  $p < 0.0001$ ). CRP levels increased with age and body mass index and were higher in women (vs men, even after exclusion of women on estrogen), in women on estrogen (vs those not on estrogen), and in current smokers; fibrinogen levels also increased with age and body mass index and were higher in women and current smokers, and lower in women on estrogen (data not shown).

Factors associated with CAC included age, high-

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Variables	Women (n = 206)	Men (n = 148)	p Value
Age (yrs)	66 ± 7	66 ± 7	0.84
10-yr Framingham risk	10 ± 6%	17 ± 9%	<0.001
Systolic blood pressure (mm Hg)	142 ± 18	137 ± 15	0.006
Total cholesterol (mg/dl)	208 ± 34	191 ± 28	<0.001
HDL cholesterol (mg/dl)	56 ± 16	45 ± 12	<0.001
Diabetes mellitus	16%	17%	0.73
Ever smoker	35%	64%	<0.001
Body mass index (kg/m <sup>2</sup> )	30 ± 6	30 ± 5	0.84
CRP (mg/L)	5.9 ± 8.4	3.9 ± 9.5	<0.001
Log CRP	-1.03 ± 0.96	-1.58 ± 0.95	<0.001
Fibrinogen (mg/dl)	335 ± 82	326 ± 82	0.43
Detectable CAC	71%	89%	<0.001
CAC score	220 ± 508	558 ± 811	<0.001
Log (CAC score + 1)	3.23 ± 2.5	4.78 ± 2.4	<0.001
Statin use	30%	37%	0.14
Estrogen use	49%	—	—
Aspirin use	47%	60%	0.01

Continuous variables are presented as mean ± SD and categorical variables as percentages. p Values are for contrast of means or percentages between genders.  
HDL = high-density lipoprotein.

Risk Factor	Women		Men	
	β ± SE	p Value	β ± SE	p Value
Age	0.12 ± 0.02	<0.0001	0.09 ± 0.02	0.001
Total cholesterol	0.005 ± 0.005	0.32	-0.005 ± 0.007	0.45
HDL cholesterol	-0.033 ± 0.01	0.003	0.016 ± 0.016	0.37
Diabetes mellitus	1.14 ± 0.48	0.018	1.00 ± 0.51	0.05
Ever smoked	0.46 ± 0.36	0.20	0.21 ± 0.40	0.60
Statin use	0.72 ± 0.38	0.061	0.45 ± 0.40	0.26
Estrogen use	-1.31 ± 0.24	0.0002	—	—
Log CRP	<0.001	0.92	0.13 ± 0.20	0.52
Fibrinogen	0.009 ± 0.002	<0.0001	0.3 ± 0.2	0.26

β = regression coefficient; other abbreviation as in Table 1.

density lipoprotein cholesterol, diabetes, fibrinogen, and estrogen therapy in women, and age and diabetes in men (Table 2). CRP was not associated with CAC in either gender, whereas fibrinogen was significantly associated with CAC in women but not in men (Figure 1). After adjusting for conventional risk factors, body mass index, and statin and estrogen use, fibrinogen remained associated with CAC in women, although the strength of the association was attenuated (Table 3). In multivariable analyses, fibrinogen was weakly associated with age- and gender-specific CAC score percentiles in women ( $p = 0.052$ ) but not in men, whereas CRP was not associated with CAC score percentiles in either gender (data not shown).

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The main finding of our study is that 2 markers of inflammation, CRP and fibrinogen, are correlated but differ in their association with CAC in asymptomatic hypertensive subjects. CRP was not associated with CAC in either gender, whereas fibrinogen was associated with CAC in hypertensive women.

The association of CRP with CAC—an established measure of atherosclerotic burden—in asymptomatic patients remains unresolved. In prior studies of 172 post-

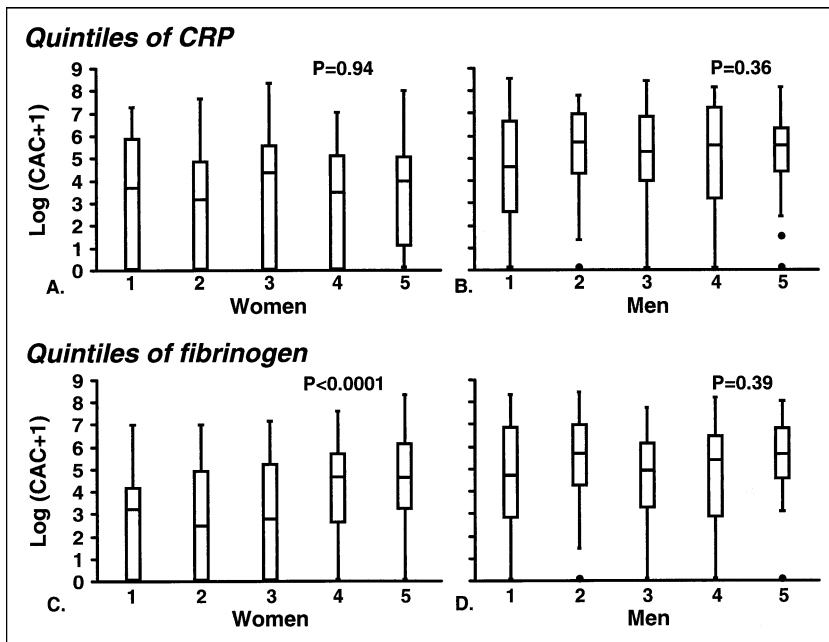
menopausal women (mean age 65 years)<sup>12</sup> and 188 asymptomatic healthy men (aged 40 to 45 years),<sup>13</sup> no association was found between CRP and CAC. In an elderly cohort of 614 patients (60% women, median CAC score 205 for women, 622 for men) CRP levels were related to CAC in women but not in men.<sup>14</sup> Wang and colleagues<sup>15</sup> recently reported that CRP levels were associated with increased CAC in both genders.

Our results do not support an association of CRP with CAC in hypertensive subjects at intermediate risk, on average, for cardiovascular events and differ from those of Wang and colleagues.<sup>15</sup> Several methodologic differences may be relevant. The subjects in our study were older, had a higher prevalence of hypertension, and greater quantity of CAC. In addition, CRP levels were obtained 4 to 8 years before the measurement of CAC in their study, and different statistical models were used to control for risk factors in assessing the relation between CRP and CAC. In the present study, female gender, body mass index, current smoking, and estrogen use were associated with higher CRP levels, thereby providing an “internal validation” of our CRP assay.

In men in this study, only age and diabetes were significant independent predictors of CAC. The relation of risk factors to atherosclerotic disease may be attenuated with age, as has been previously noted.<sup>14</sup> We cannot exclude the possibility of an association of CRP with CAC in younger subjects or with rate of progression of atherosclerosis. Because we excluded subjects with a history of cardiovascular events, there is also a possibility of survivor bias.

Fibrinogen was associated with CAC in women, although the strength of the association was attenuated after adjusting for conventional risk factors. This finding reflects the correlation of fibrinogen with several of conventional risk factors. Bielak and colleagues<sup>16</sup> also detected a gender-specific association of fibrinogen with CAC in a community-based sample. In their study, plasma fibrinogen was positively associated with high levels of CAC in women aged 50 to 59 years. Fibrinogen, like CRP, has been associated with increased risk of cardiovascular events in both genders.<sup>2</sup> Our results suggest that fibrinogen is also associated with the extent of subclinical coronary atherosclerosis in hypertensive women.

The differential association of CRP and fibrinogen with CAC is intriguing. The correlation of CRP and fibrinogen suggests that fibrinogen levels in part reflect inflammation. Fibrinogen is a known acute phase



**FIGURE 1.** Log (CAC + 1) by quintiles of CRP (A and B) and fibrinogen (C and D) in men and women. Medians and interquartile ranges are displayed for log (CAC + 1). The p values shown are for Spearman's correlation for log (CAC + 1) with CRP and fibrinogen.

Risk Factor	Women (n = 206)		Men (n = 148)	
	$\beta \pm SE$	p Value	$\beta \pm SE$	p Value
Age	0.133 $\pm$ 0.024	<0.0001	0.096 $\pm$ 0.03	<0.0007
Total cholesterol	0.014 $\pm$ 0.005	0.006	-0.002 $\pm$ 0.007	0.742
HDL cholesterol	-0.024 $\pm$ 0.01	0.028	0.024 $\pm$ 0.016	0.155
Diabetes mellitus	0.78 $\pm$ 0.44	0.082	1.07 $\pm$ 0.52	0.042
Ever smoked	1.03 $\pm$ 0.34	0.003	0.254 $\pm$ 0.40	0.530
Body mass index	0.050 $\pm$ 0.27	0.090	0.03 $\pm$ 0.04	0.446
Statin use	0.77 $\pm$ 0.37	0.038	0.35 $\pm$ 0.41	0.398
Estrogen use	-0.44 $\pm$ 0.33	0.18	—	—
Model R <sup>2</sup>	0.27		0.13	
+ Log CRP	-0.070 $\pm$ 0.180	0.703	0.087 $\pm$ 0.21	0.678
Model R <sup>2</sup>	0.27		0.13	
+ Fibrinogen	0.004 $\pm$ 0.002	0.080	0.002 $\pm$ 0.002	0.329
Model R <sup>2</sup>	0.28		0.13	

Abbreviations as in Tables 1 and 2.

reactant.<sup>17</sup> In addition, fibrinogen has several potential proatherogenic effects, such as increasing plasma viscosity, promoting platelet aggregability, and stimulating smooth muscle proliferation.<sup>18</sup> These proatherogenic properties may explain the association of fibrinogen with CAC in women in this study, possibly through inflammation-independent pathways.

**In conclusion, this study does not provide evidence to support an association between CRP and atherosclerotic burden in hypertensive patients who are, on average, at intermediate risk for cardiovascular events. Because elevated levels of CRP as well as increased CAC have been associated in previous studies with increased risk of cardiovascular events, a combined assessment of CRP and CAC may have greater predictive value for events than**

**either measure alone.<sup>19</sup> This hypothesis is amenable to testing in a prospective study. In women, fibrinogen was associated with CAC, and therefore, may have atherogenic effects that are mediated independently of its role as a marker of inflammation.**

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