Serum Amyloid P and Cardiovascular Disease in Older Men and Women
Results from the Cardiovascular Health Study

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Objective—Serum amyloid P (SAP), a pentraxin like C-reactive protein (CRP), functions in innate immunity. However, associations of SAP with cardiovascular disease (CVD) are unknown.

Methods and Results—We examined these associations in the Cardiovascular Health Study using a case–cohort design. Nonexclusive case groups were incident angina (n=523), myocardial infarction (MI; n=308), stroke (n=323), and CVD death (n=288). 786 participants had no events. SAP was correlated with CRP, CVD risk factors (obesity, blood pressure, lipids), common and internal carotid wall thickness, and ankle-brachial index (all P<0.02). In Cox regression models adjusted for age, sex, and ethnicity, a standard deviation increase in SAP (9.8 mg/L) was associated with angina (hazard ratio; 95% confidence interval 1.3; 1.2 to 1.5) and MI (1.3; 1.1 to 1.5), but not stroke (1.1; 0.9 to 1.3) or CVD death (1.1; 0.9 to 1.3). Adding CRP to the models had no significant effect on associations. Adjusting for CVD risk factors slightly attenuated SAP associations with CVD events; however, associations with angina and MI remained significant.

Conclusions—Although both are pentraxins, SAP and CRP may represent different facets of inflammation. The association of SAP with CVD in these older adults further supports the role of innate immunity in atherosclerosis. (Arterioscler Thromb Vasc Biol. 2007;27:352-358.)

Key Words: cardiovascular disease ■ serum amyloid P ■ C-reactive protein ■ elderly ■ atherosclerosis

Pentraxins like C-reactive protein (CRP) and serum amyloid P (SAP) are highly conserved in evolution and play key roles in innate immunity and inflammation. Expression of these homologous proteins is regulated by interleukin (IL)-1, tumor necrosis factor (TNF)-α, and IL-6.1 Both are produced mainly by hepatocytes,1 although CRP is produced as part of the acute phase response and SAP levels are only weakly influenced by acute inflammation.2 Like CRP, SAP activates the classical complement pathway3 and has opsonin activity.4 However, SAP also has functions distinct from those of CRP. SAP is a vital component of extracellular matrices, in particular glomerular basement membranes.5 SAP is perhaps best recognized as a component of amyloid deposits2 including cerebral amyloid in Alzheimer’s disease6 and amyloid in type 2 diabetes.7 Like CRP, SAP has been identified in atherosclerotic lesions.8 However, associations of SAP with cardiovascular disease (CVD) have not been studied. These associations are of particular interest because CRP and SAP may represent different aspects of inflammation and innate immunity in atherosclerosis.

We examined associations of circulating SAP with subclinical and clinical CVD in older adults from the Cardiovascular Health Study (CHS). Potential interactions between SAP and CRP were also assessed.

Methods

Cardiovascular Health Study
The comprises CHS 5888 men and women ≥65 years of age at baseline.9 The original cohort (n=5201) was enrolled from 1989 to 1990. An additional primarily African-American cohort (minority cohort; n=687) was added from 1992 to 1993. Baseline examinations included anthropomorphic measurements, medical and lifestyle histories, blood collection, resting 12-lead electrocardiography, carotid ultrasonography, and ankle-brachial blood pressure index (ABI). Prevalence and extent of clinical CVD (confirmed angina or use of nitroglycerin, myocardial infarction [MI], and stroke) was also assessed. Self-reports of clinical CVD not confirmed by examination or medication use were investigated by review of medical records. All subjects gave informed consent for participation in the study. All procedures were conducted under institutionally approved protocols for use of human subjects.
Ascertainment of Events

Potential events were identified through contact with participants or proxies. All events were investigated in detail based on initial identification through International Classification of Diseases diagnostic codes, hospital, or outpatient medical reports. Deaths were ascertained by review of local obituaries and contact with proxies for those who died. Medical documentation was obtained and reviewed by a committee using standardized published criteria to classify events and cause of death.10 CVD death was defined as death attributable to atherosclerotic coronary heart disease, cerebrovascular disease, atherosclerotic disease, or other CVD. There was 100% complete follow-up ascertainment of death status.

Clinical Definitions

Diabetes was classified by American Diabetic Association guidelines.11 Body mass index (BMI, kg/m²) was calculated. Smoking was defined as never, former (more than 30 days since last cigarette), or current. Hypertension was defined as seated systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or history of hypertension and use of antihypertensive medication. Dyslipidemia was defined as total/HDL cholesterol ratio >5 or taking lipid-lowering medication. Hormone replacement therapy (HRT) was defined as current use of unopposed estrogen or combined estrogen/progestin.

Laboratory Methods

Blood collection, laboratory procedures, and fibrinogen, lipid, and IL-6 measurements have been described.12,13 C-reactive protein (CRP) was measured with a high sensitivity assay developed in-house (analytical coefficient of variation [CV] = 8.9%).14 SAP was measured with an in-house ELISA using a monoclonal antibody to human SAP (Cymbus Biotechnology) as the capture antibody, a rabbit polyclonal antibody to human SAP (Dako Corporation) as the primary detection antibody, and a horseradish peroxidase-conjugated anti-rabbit antibody as the secondary detection antibody (Jackson Laboratories). Purified SAP for a standard was from EMD Biosciences (Calbiochem). SAP purity was certified by the manufacturer as ≥99% by immunochemical assay and ≥95% by sodium dodecyl sulfate polyacrylamide gel electrophoresis. In addition, at a concentration of 200 mg/L, SAP showed no reactivity in the CRP assay. The analytical CV of the SAP assay was 9%. All measurements for this study were made on baseline samples.

Study Design

We created a case–cohort based on a previous case–control design that included: (1) all participants who had incident MI, stroke, or angina before June 30, 1995; (2) a comparison group of participants with no apparent subclinical CVD; and (3) controls randomly selected from both the original and minority cohorts.13 In current analyses, we included all CVD events through June 30, 2002. Use of sample probability weights accounted for over-sampling of participants with early events and participants with no subclinical CVD.15,16 All CHS participants free of clinical CVD at baseline had a positive probability of being included in the case–control study sample. We used the inverse of that probability to compute sample weights to account for the case–control sampling scheme and produce results pertinent to all participants free of clinical CVD at baseline. We did not select participants based on risk factors, including sex and age, to study associations of risk factors with outcomes.

Statistical Analyses

Data were analyzed using STATA (version 8.0, Stata Corporation). Variables were In-transformed as necessary to achieve normal distributions. 1613 CHS participants free of clinical CVD at baseline had SAP measurements. In preliminary analyses, associations between medication use and SAP were determined. SAP levels have been reported to vary by HRT use.17 In this CHS sample, 14 women were using unopposed estrogen and 110 were using combined estrogen/progestin. Compared with women not using HRT, women using unopposed estrogen had significantly lower SAP; 23.1 versus 29.8 mg/L, respectively; P = 0.006. SAP did not differ significantly between women using combined estrogen/progestin (29.1 mg/L) and women not using HRT (P = 0.4). As the number of women using unopposed estrogen was small, these women were removed from subsequent analyses.

22 of the remaining 1599 participants reported use of 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (Csa) inhibitors (statins) at baseline. SAP did not differ significantly by statin use (32.8 mg/L for statin users and 31.6 mg/L for non-users; P = 0.4). SAP in those using nonsteroidal antiinflammatory agents (n = 196) was similar to remaining participants (31.1 versus 31.7 mg/L, respectively; P = 0.9) as was SAP in those using aspirin (n = 50) and remaining participants (33.3 versus 31.6 mg/L, respectively; P = 0.3).

In the 1599 selected participants, nonexclusive case groups were incident angina (n = 523), MI (n = 308), stroke (n = 323), and CVD-related death (n = 288). A combined angina, MI, and CVD death case group was also created (n = 685). 786 comparison subjects were free of any event of interest through June 30, 2002. All analyses were weighted based on sampling proportions.

To accommodate sample probability weighting, cross-sectional associations of SAP with continuous variables were determined by weighted linear regression adjusted for age, sex, and ethnicity. Associations of CRP with continuous variables were also determined in 1598 participants with CRP measurements. We used In-transformed CRP in these analyses to normalize CRP distribution, and these regression coefficients were exponentiated to represent coefficients for one standard deviation changes in variable levels. SAP or In-transformed CRP was the dependent variable. The continuous variable of interest was entered first, followed by age, sex, and ethnicity.

To facilitate comparisons between SAP and CRP, each marker was centered by its mean and divided by its standard deviation. Means±standard deviations were 31.5 ± 9.8 mg/L for SAP and 3.33 ± 5.13 mg/L for CRP. We used weighted Cox regression models to determine hazard ratios (HRs) and 95% confidence intervals (95% CIs) for SAP and CRP separately and in models containing both markers and their interaction term. Those with an event were compared with all remaining participants. Cox regression models were also used to examine associations of SAP quartiles with CVD events. Analyses were minimally adjusted for age, sex, and ethnicity and also adjusted for CVD risk factors (BMI, diabetes, smoking status, dyslipidemia, and hypertension).

We created a composite variable to examine potential synergistic effects between SAP and CRP. Those in SAP quartile 4 with CRP levels >3 mg/L (n = 192) were compared with those in SAP quartile 1 with CRP levels <1 mg/L (n = 195). Because of limited power for MI alone (83 events), we examined associations of the composite variable with angina (131 events) and combined CVD (167 events). Associations were modeled by Cox regressions adjusted as above.

Results

Baseline Characteristics

As reported previously in a small study of apparently healthy men and women18 and similar to the inflammatory marker fibrinogen, SAP was normally distributed in these older adults (Figure 1). Mean SAP was 31.5 ± 9.8 mg/L with a range of 5.7 to 73.8 mg/L. Similar to the previous study, we found SAP levels were higher in men than women (33.7 ± 9.8 vs 29.8 ± 9.4 mg/L, respectively; P < 0.001). SAP levels were also higher in African-Americans than Caucasians (34.5 ± 10.8 versus 30.7 ± 9.4 mg/L, P < 0.001).

Baseline characteristics of CVD event-free and incident CVD case groups are shown in Table 1. Compared with those who were event-free, cases were older and were more likely to be male, hypertensive, current/former smokers, and diabetic. Baseline levels of CRP and SAP also differed between
cases and those who were event-free. CRP levels were higher in cases of incident angina \((P < 0.001)\), MI \((P = 0.015)\), stroke \((P = 0.002)\), and CVD death \((P < 0.001)\) compared with the event-free group. Similarly, SAP levels were higher in cases of angina \((P < 0.001)\), MI \((P = 0.001)\), stroke \((P = 0.008)\), and CVD death \((P = 0.005)\) compared with the reference group. Dyslipidemia (total cholesterol/HDL cholesterol ratio >5 or use of lipid-lowering medication) and BMI did not differ significantly among groups.

**Associations of SAP and Risk Factors**

Associations of one standard deviation increases in each independent variable with SAP were determined (Table 2). SAP was positively associated with BMI, fasting glucose and insulin, systolic blood pressure, total and LDL cholesterol, and triglycerides and negatively associated with age and HDL cholesterol (Table 2). SAP was also associated with measures of subclinical CVD and inflammation: positively with common and internal carotid wall thickness, CRP, fibrinogen, and IL-6 and negatively with ABI. In addition, SAP levels were significantly higher in current \((33.5 \pm 10.4 \text{ mg/L}; n = 202)\) and former \((32.1 \pm 9.8 \text{ mg/L}; n = 645)\) compared with never smokers \((30.5 \pm 9.7 \text{ mg/L}; n = 758; P < 0.001 for both comparisons).

Associations of SAP with subclinical CVD were attenuated when CVD risk factors (BMI, hypertension, total cholesterol, diabetes, and smoking) were included in regression models. SAP remained significantly associated with ABI (regression coefficient = 1.14, \(P < 0.001\)) but was not associated with common \((0.18, P = 0.6)\) or internal \((0.26, P = 0.4)\) carotid wall thickness in fully adjusted models.

We also examined associations of CRP with CVD risk factors to compare SAP results to those for the other major plasma pentraxin. Most associations were similar; however, CRP was not associated with age or ABI and was associated with physical activity in these older adults (Table 2).

**Associations of SAP and Incident Events**

In minimally adjusted models, a one standard deviation increase in SAP \((9.8 \text{ mg/L})\) was significantly associated with risk of incident angina and MI (Model 1, Table 3). SAP was not associated with stroke or CVD death. We also examined the association of SAP with CVD death considering only atherosclerotic coronary heart disease, atherosclerotic disease, or other CVD deaths \((210 \text{ events})\). SAP was not associated with CVD death even when cerebrovascular disease was excluded \((HR: 95\% \text{ CI} = 1.17; 0.98 \text{ to } 1.40)\). SAP was associated with combined CVD events (angina, MI and CVD death; Model 1; Table 3).

The addition of CRP (divided by its standard deviation, \(5.13 \text{ mg/L}\)) to the Cox models had no significant effect on risk prediction by SAP level (Model 2, Table 3). There were no significant interactions between SAP and CRP for any outcome \((all \text{ interaction terms } P > 0.1)\).

In models adjusted for age, sex, ethnicity, and CVD risk factors, SAP remained associated with risk of angina, MI, and combined CVD events (Model 3, Table 3). Total cholesterol, diabetes, and hypertension were the primary confounders in

**TABLE 1. Baseline Characteristics of CVD Case Groups and Those Free of CVD Events**

<table>
<thead>
<tr>
<th>CVD Risk Factor</th>
<th>Event-Free (n=786)</th>
<th>Angina (n=523)</th>
<th>MI (n=308)</th>
<th>Stroke (n=323)</th>
<th>CVD Death (n=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71.1 (4.7)</td>
<td>72.8 (5.0)</td>
<td>73.1 (5.0)</td>
<td>74.2 (5.3)</td>
<td>75.0 (5.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>259 (33)</td>
<td>268 (51)</td>
<td>172 (56)</td>
<td>125 (39)</td>
<td>141 (49)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>608 (77)</td>
<td>460 (88)</td>
<td>272 (88)</td>
<td>275 (85)</td>
<td>248 (86)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8 (4.8)</td>
<td>27.0 (4.9)</td>
<td>26.9 (4.8)</td>
<td>26.8 (4.5)</td>
<td>27.0 (4.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>418 (47)</td>
<td>364 (70)</td>
<td>214 (70)</td>
<td>256 (79)</td>
<td>218 (76)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>109 (14)</td>
<td>96 (18)</td>
<td>64 (21)</td>
<td>68 (21)</td>
<td>75 (26)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>98 (13)</td>
<td>68 (13)</td>
<td>42 (14)</td>
<td>37 (12)</td>
<td>42 (15)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>162 (21)</td>
<td>166 (32)</td>
<td>92 (30)</td>
<td>91 (28)</td>
<td>85 (30)</td>
</tr>
<tr>
<td>CRP, mg/l*</td>
<td>2.29 (2.72)</td>
<td>2.77 (2.72)</td>
<td>2.72 (2.77)</td>
<td>2.69 (2.65)</td>
<td>2.89 (2.92)</td>
</tr>
<tr>
<td>SAP, mg/l</td>
<td>30.8 (9.5)</td>
<td>33.4 (10.3)</td>
<td>33.0 (10.0)</td>
<td>31.9 (10.0)</td>
<td>32.1 (9.5)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) unless otherwise noted. *Values derived from in-transformed data.
these models. Adding CRP to these models had no significant
effect on risk prediction by SAP level (data not shown).

For comparison, associations of CRP with events were
explored. In models adjusted for age, sex, and ethnicity, a
standard deviation increase in CRP (5.13 mg/L) was signifi-
cantly associated with angina (1.10; 1.01 to 1.19), MI (1.11;
1.01 to 1.22), CVD death (1.17 (1.07 to 1.29), and combined
CVD (1.13; 1.04 to 1.23), but not stroke (1.01; 0.90 to 1.14).
In models including adjustments for CVD risk factors, CRP
remained significantly associated with CVD death (1.14; 1.03
to 1.25) and combined CVD (1.11; 1.01 to 1.21). Associations
of CRP with angina (1.07; 0.98 to 1.17) and MI (1.09;
0.99 to 1.20) in fully adjusted models were similar to
minimally adjusted models. The association of CRP with MI
in this study parallels the association of CRP with combined
MI and coronary heart disease death recently reported for
the CHS cohort.19

We also examined associations of SAP quartiles with
incident CVD events. Comparing upper quartiles to quartile
1, only the highest quartile was associated with angina, MI,
and combined CVD events in minimally adjusted models
(Model 1, Table 4). Adjustments for CVD risk factors
attenuated associations, although quartile 4 remained signif-
ically associated with angina and combined CVD (Model 2,

### TABLE 2. Regression Coefficients for CVD Risk Factors in Separate Linear Models of SAP and CRP

<table>
<thead>
<tr>
<th>Variable (SD)</th>
<th>SAP</th>
<th>P Value</th>
<th>CRP§</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (5.2 years)</td>
<td>-0.91</td>
<td>0.001</td>
<td>1.00</td>
<td>0.93</td>
</tr>
<tr>
<td>BMI (4.7 kg/m²)</td>
<td>2.35</td>
<td>&lt;0.001</td>
<td>1.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (38 mg/dl)</td>
<td>1.72</td>
<td>&lt;0.001</td>
<td>1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (26 μIU/ml)</td>
<td>1.16</td>
<td>0.006</td>
<td>1.13</td>
<td>0.016</td>
</tr>
<tr>
<td>Systolic blood pressure (22 mm Hg)</td>
<td>0.89</td>
<td>0.005</td>
<td>1.05</td>
<td>0.17</td>
</tr>
<tr>
<td>Diastolic blood pressure (11 mm Hg)</td>
<td>0.17</td>
<td>0.58</td>
<td>1.07</td>
<td>0.037</td>
</tr>
<tr>
<td>Physical activity (1999 kcal)</td>
<td>-0.42</td>
<td>0.14</td>
<td>-1.10</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (40 mg/dl)</td>
<td>2.34</td>
<td>&lt;0.001</td>
<td>1.03</td>
<td>0.40</td>
</tr>
<tr>
<td>HDL cholesterol (16 mg/dl)</td>
<td>-1.84</td>
<td>&lt;0.001</td>
<td>-1.12</td>
<td>0.007</td>
</tr>
<tr>
<td>LDL cholesterol (36 mg/dl)</td>
<td>2.04</td>
<td>&lt;0.001</td>
<td>1.03</td>
<td>0.34</td>
</tr>
<tr>
<td>Triglycerides (68 mg/dl)</td>
<td>3.20</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Subclinical CVD Measures</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Common carotid IMT* (0.21 mm)</td>
<td>0.97</td>
<td>0.005</td>
<td>1.09</td>
<td>0.011</td>
</tr>
<tr>
<td>Internal carotid IMT* (0.56 mm)</td>
<td>0.80</td>
<td>0.019</td>
<td>1.10</td>
<td>0.003</td>
</tr>
<tr>
<td>ABI (0.16)</td>
<td>-1.01</td>
<td>&lt;0.001</td>
<td>-1.06</td>
<td>0.10</td>
</tr>
<tr>
<td>Left ventricular mass (35 g)</td>
<td>1.94</td>
<td>&lt;0.001</td>
<td>1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Inflammatory Markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (1.01)</td>
<td>3.93</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SAP (9.8 mg/l)</td>
<td>—</td>
<td>—</td>
<td>1.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (64 mg/dl)</td>
<td>3.61</td>
<td>&lt;0.001</td>
<td>1.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 (0.62)</td>
<td>2.67</td>
<td>&lt;0.001</td>
<td>1.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Not adjusted for age. **IMT=intima media thickness. § ln-transformed CRP was used in analyses. Regression coefficients were exponentiated. Bolded values are significant at P<0.05.

### TABLE 3. Risk of CVD Events for a Standard Deviation Increase in SAP Level

<table>
<thead>
<tr>
<th>Event</th>
<th>Model 1# HR (95% CI)*</th>
<th>Model 2# HR (95% CI)*</th>
<th>Model 3# HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>1.32 (1.17–1.49)</td>
<td>1.33 (1.15–1.54)</td>
<td>1.25 (1.09–1.43)</td>
</tr>
<tr>
<td>MI</td>
<td>1.27 (1.09–1.48)</td>
<td>1.27 (1.07–1.51)</td>
<td>1.22 (1.03–1.45)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.10 (0.94–1.29)</td>
<td>1.09 (0.90–1.33)</td>
<td>1.06 (0.90–1.25)</td>
</tr>
<tr>
<td>CVD Death</td>
<td>1.12 (0.96–1.32)</td>
<td>1.17 (0.96–1.42)</td>
<td>1.04 (0.88–1.23)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.23 (1.10–1.37)</td>
<td>1.27 (1.10–1.46)</td>
<td>1.16 (1.03–1.30)</td>
</tr>
</tbody>
</table>

* Model 1 adjustments: age, sex and ethnicity. Model 2 adjustments: age, sex, ethnicity and CRP divided by its standard deviation (5.13 mg/dl). Model 3 adjustments: age, sex, ethnicity, BMI, smoking, diabetes, dyslipidemia and hypertension. *Hazard ratios (HRs) and 95% confidence intervals (95% CIs) computed for a standard deviation increase (9.8 mg/l) in SAP. Bolded values are significant at P<0.05.
Table 4). Associations of SAP with CVD events appeared to be linear in the quartile models.

**Combined Associations of SAP and CRP**
Having both high SAP and CRP (SAP quartile 4 and CRP > 3 mg/L), compared with low (SAP quartile 1 and CRP < 1 mg/L), was associated with angina and combined CVD in models adjusted for age, sex, ethnicity, and CVD risk factors (Figure 2). HRs were slightly higher for the composite variable compared with each marker alone (Figure 2).

**Discussion**
This is the first study to examine associations of circulating SAP with CVD risk factors and events in a prospective epidemiological setting. In older adults from the CHS, SAP was associated with inflammatory biomarkers, some CVD risk factors, measures of subclinical CVD and incident angina, and MI. There was no association of SAP with stroke or CVD death.

While the association of higher SAP with MI was attenuated by adjustment for CVD risk factors, the association of SAP with angina remained significant. This likely reflects the larger number of angina events compared with MI events (523 versus 308, respectively). SAP may serve as a marker of atherosclerotic development and/or progression underlying angina and MI. In support of this, SAP was strongly associated with ABI, a marker of peripheral arterial disease.

Neither pentraxin was associated with stroke in this study. In a previous study, CRP was associated with incident stroke in 5471 CHS participants (469 strokes) in models adjusted for age, sex, ethnicity, and the same CVD risk factors we included in analyses. The different findings are likely attributable to participant selection. We excluded participants with angina, MI, and stroke at baseline whereas the previous study excluded those with stroke or chronic atrial fibrillation. Irrespective, we will need to confirm our findings regarding SAP in other studies.

In addition, SAP was not associated with CVD death even when cerebrovascular events were excluded. CRP, however, was significantly associated with CVD death in these older adults and has been associated with acute coronary events in many studies. Although both proteins function in innate immunity, these pentraxins are quite different. CRP is a major acute phase protein whereas SAP is only mildly affected by acute inflammation. Both proteins differ in lipid-binding functions as well. SAP binds HDL and very low density lipoprotein but not unmodified LDL cholesterol. CRP binds unmodified and oxidized LDL likely mediating metabolism, clearance, and deposition of LDL. In vitro, CRP promotes uptake of oxidized LDL by macrophages. CRP may thus initiate foam cell formation and early atherosclerosis. However, SAP binding to amyloid-like structures in oxidized LDL blocks macrophage uptake of modified LDL serving to...
prevent atherosclerosis. CRP and SAP may therefore represent distinct aspects of inflammation.

Although SAP and CRP were independent predictors of CVD events in this study and exhibited some differences in associations with CVD risk factors, there were no apparent synergistic effects on CVD event prediction when the two biomarkers were combined. The effect appeared to be additive. However, if SAP and CRP are truly markers of different stages or processes of atherosclerosis, SAP will have unique clinical potential in monitoring atherosclerotic progression before acute events associated with elevated CRP. To understand the potential for SAP in the clinical setting, it will be necessary to further explore these relationships in other cohorts, particularly in younger men and women with less advanced atherosclerosis.

SAP may simply be a biomarker of ongoing atherosclerosis; however, there is evidence to suggest that SAP, like CRP, may play a role in the causal pathway. Similar to CRP, SAP functions in activation of the complement pathway and is localized in atherosclerotic lesions, potentially promoting lesion progression through the innate immune response. SAP associations with lipoprotein moieties likely impacts atherosclerosis as well. Another distinguishing feature of SAP is its ubiquitous presence in amyloid deposits, particularly those associated with Alzheimer disease. There is considerable evidence linking Alzheimer disease to CVD. The importance of pentraxins in the development and progression of atherosclerosis is further supported associations of another pentraxin, pentraxin 3, with atherosclerosis. Pentraxin 3 is reported to be localized to atherosclerotic plaques and may serve as an early indicator of acute MI.

Strengths of this study include the availability of different measures of clinical and subclinical CVD and CVD risk factors in a large population-based sample of older adults from a prospective epidemiologic study. Limitations of this study should also be noted. Selected participants were part of a case–control group within the CHS. Although sample probability weights were used to compensate for this design, selection bias may still exist. Levels of CRP and SAP were only measured once, and intrapatient variation cannot be accounted for. However, assay variability would be expected to bias findings toward the null so the observed associations are potentially underestimations. In addition, participants were older adults and predominantly Caucasian. The results of this study may not generalize to other ethnic groups or younger individuals with less advanced atherosclerosis.

In summary, we report that in older men and women, circulating SAP was associated with CVD risk factors, subclinical CVD and incident angina, and MI. SAP and CRP potentially reflect different aspects of inflammation and innate immunity in atherosclerosis. Our results further strengthen the importance of these processes in later, as well as early, CVD. Additional studies will continue to shed light on the multiple roles of the pentraxin family of proteins.

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Disclosures

None.

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