**Clinical and Population Studies**

**Associations of Pentraxin 3 With Cardiovascular Disease and All-Cause Death**

The Cardiovascular Health Study

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**Objective**—We examined associations of pentraxin 3 (PTX3), a vascular inflammation marker, with incident cardiovascular disease (CVD) and all-cause death.

**Methods and Results**—1583 Cardiovascular Health Study participants free of prevalent CVD were included. Nonexclusive case groups were angina (n=476), myocardial infarction (MI; n=237), stroke (n=310), CVD death (n=282), and all-cause death (n=772). 535 participants had no events. PTX3 levels were higher in those with subclinical CVD (1.90±1.89 ng/mL) than those without (1.71±1.88 ng/mL; P=0.001). Using Cox regression adjusted for age, sex, and ethnicity, a standard deviation increase in PTX3 (1.89 ng/mL) was associated with CVD death (hazard ratio 1.11; 95% confidence interval 1.02 to 1.21) and all-cause death (1.08; 1.02 to 1.15). PTX3 was not associated with angina (1.09; 0.98 to 1.20), MI (0.96; 0.81 to 1.12), or stroke (1.06; 0.95 to 1.18). Adding C-reactive protein (CRP) or CVD risk factors to the models had no significant effects on associations.

**Conclusions**—In these older adults, PTX3 was associated with CVD and all-cause death independent of CRP and CVD risk factors. PTX3 likely reflects different aspects of inflammation than CRP and may provide insight into vascular health in aging and chronic diseases of aging that lead to death. *(Arterioscler Thromb Vasc Biol. 2009;29:594-599.)*

**Key Words:** cardiovascular diseases ■ epidemiology ■ inflammation ■ mortality ■ pentraxin 3

Many studies have examined associations between inflammation biomarkers and development and progression of cardiovascular disease (CVD). C-reactive protein (CRP), a pentraxin, is one of the best characterized biomarkers. Other pentraxins like pentraxin 3 (PTX3) and serum amyloid P (SAP) also hold promise as predictors of CVD and mortality.6,10 PTX3, hypothesized to be a marker of localized vascular inflammation and damage,6-5 is especially interesting. Unlike CRP and SAP, which are produced primarily by hepatocytes and are nonspecific markers of inflammation,6 PTX3 is synthesized by cells directly involved in atherosclerosis including vascular endothelial cells, smooth muscle cells, and macrophages.5,7 PTX3 also has key functions in innate immunity8 and has been identified in atherosclerotic lesions.9 Previously, PTX3 was associated with myocyte damage in myocardial infarction (MI),1 mortality after MI,1 and unstable angina.10 Because PTX3 release is likely a specific response to vascular damage, PTX3 levels may provide more explicit information on development and progression of atherosclerosis than nonspecific markers like CRP and interleukin-6 (IL-6). However, associations of PTX3 with CVD risk factors, subclinical CVD, and incident CVD events have not been clearly elucidated. We examined these associations in older adults from the Cardiovascular Health Study (CHS).

**Methods**

**Cardiovascular Health Study**

The CHS comprises 5888 men and women ≥65 years of age at baseline.11 The original cohort (n=5201) was enrolled in 1989 to 1990. An additional primarily black cohort (new cohort; n=687) was enrolled in 1992 to 1993. Baseline examinations included anthropometry, 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, MI, and stroke) was assessed. Self-reported clinical CVD not confirmed by examination or medication use was investigated by medical records review. All subjects gave informed consent for participation in the study and all procedures were conducted under institutionally approved protocols.

**Ascertainment of Events**

Potential events were identified by contacting participants or proxies. All events were investigated in detail using data from hospital or outpatient medical reports, participant interviews, and physicians
Table 1. Baseline Characteristics of Incident CVD Cases and Those Free of Events

<table>
<thead>
<tr>
<th>CVD Risk Factor</th>
<th>Event-Free (n=535)</th>
<th>Angina (n=476)</th>
<th>MI (n=237)</th>
<th>Stroke (n=310)</th>
<th>CVD Death (n=282)</th>
<th>All Death (n=772)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.1 (3.9)</td>
<td>72.4 (4.9)</td>
<td>72.7 (5.0)</td>
<td>74.1 (5.6)</td>
<td>74.6 (5.6)</td>
<td>74.2 (5.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>141 (26.4)</td>
<td>226 (47.5)</td>
<td>125 (52.7)</td>
<td>116 (37.4)</td>
<td>115 (40.8)</td>
<td>318 (41.2)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>411 (76.8)</td>
<td>413 (86.8)</td>
<td>206 (86.9)</td>
<td>260 (83.9)</td>
<td>239 (84.8)</td>
<td>644 (83.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 (4.7)</td>
<td>27.2 (4.9)</td>
<td>27.3 (6.0)</td>
<td>26.8 (4.6)</td>
<td>27.0 (4.9)</td>
<td>26.6 (4.8)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>176 (32.9)</td>
<td>222 (46.6)</td>
<td>118 (49.8)</td>
<td>173 (55.8)</td>
<td>151 (53.5)</td>
<td>371 (48.1)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>56 (10.5)</td>
<td>82 (17.2)</td>
<td>44 (18.6)</td>
<td>70 (22.6)</td>
<td>67 (23.8)</td>
<td>145 (18.8)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>52 (9.7)</td>
<td>56 (11.8)</td>
<td>26 (11.0)</td>
<td>35 (11.3)</td>
<td>38 (13.5)</td>
<td>107 (13.9)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>109 (20.4)</td>
<td>136 (28.6)</td>
<td>56 (23.6)</td>
<td>81 (26.1)</td>
<td>64 (22.7)</td>
<td>168 (21.8)</td>
</tr>
<tr>
<td>No alcohol use, n (%)</td>
<td>250 (46.7)</td>
<td>239 (50.2)</td>
<td>119 (50.2)</td>
<td>170 (54.8)</td>
<td>161 (57.1)</td>
<td>415 (53.8)</td>
</tr>
<tr>
<td>CRP, mg/l*</td>
<td>1.69 (2.68)</td>
<td>2.10 (2.72)</td>
<td>2.20 (2.77)</td>
<td>2.13 (2.78)</td>
<td>2.06 (3.09)</td>
<td>2.02 (2.87)</td>
</tr>
<tr>
<td>SAP, mg/l</td>
<td>30.1 (8.7)</td>
<td>33.5 (10.4)</td>
<td>32.9 (10.1)</td>
<td>31.8 (10.2)</td>
<td>31.6 (9.6)</td>
<td>31.8 (10.1)</td>
</tr>
<tr>
<td>PTX3, ng/ml*</td>
<td>1.64 (1.80)</td>
<td>1.88 (1.87)</td>
<td>1.87 (1.80)</td>
<td>2.00 (1.98)</td>
<td>2.06 (1.99)</td>
<td>2.01 (1.96)</td>
</tr>
</tbody>
</table>

Mean (standard deviation) unless otherwise noted. *From ln-transformed data.

Definitions
Diabetes was classified by American Diabetic Association guidelines. Body mass index (BMI, kg/m²) was calculated. Smoking was never, former (>30 days since last cigarette), or current. Hypertension was seated systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or history of hypertension and use of antihypertensive medication. Dyslipidemia was total/HDL cholesterol ratio >5 or taking lipid-lowering medication. Hormone replacement therapy (HRT) was current use of unopposed estrogen or combined estrogen/progestin. Alcohol use was none, low (1 to 7 drinks per week for women or 1 to 14 drinks for men), or high (>7 drinks per week for women or >14 drinks for men). Subclinical CVD was defined as: (1) ABI ≥0.9, (2) maximum common or internal carotid artery intima media thickness (IMT) ≥80th percentile, (3) carotid artery stenosis ≥25%, (4) presence of major ECG abnormalities, or (5) positive response for angina or intermittent claudication by Rose questionnaire.

Laboratory Methods
Blood collection and laboratory procedures have been described. CRP was measured by high sensitivity in-house ELISA; analytic coefficient of variation (CV) 8.9%. SAP was measured by in-house ELISA; CV 9.3. PTX3 was measured by PTX3 (human) Detection Set from Alexis Biochemicals (Axxora, LLC); CV 10.2%. Other biomarkers were fibrinogen, D-dimer, interleukin-6 (IL-6), and leukocyte count.

Study Design
As we had limited samples available for PTX3 measurement, we created a subcohort using a previous case–control design that included all participants who had (1) incident MI, stroke, or angina before June 30, 1995; (2) a comparison group with no apparent subclinical CVD; and (3) controls randomly selected from both the original and new cohorts. In current analyses, we included all CVD events through June 30, 2004 and weighted participants using sample probability weights to represent a random sample of the original cohort (accounting for oversampling of those with early events and no subclinical CVD) and allow inclusion of further events. All CHS participants free of clinical CVD at baseline had a positive probability of being included in the case–control study sample. Using the inverse of that probability to compute sample weights, we accounted for the case–control sampling and produced results pertinent to all participants free of clinical CVD at baseline. In the 1583 participants in the current study, nonexclusive case groups were incident angina (n=476), MI (n=237), stroke (n=310), CVD-related death (n=282), and all-cause death (n=772). 535 comparison subjects (comprised of participants with and without subclinical CVD from groups 2 and 3 above, weighted to represent the original cohort) were free of any event of interest through June 30, 2004.

Statistical Analyses
Data were analyzed using STATA (version 8.0, Stata Corporation). PTX3 and CRP were ln-transformed to achieve normal distributions. Because levels of CRP and SAP have been reported to vary with medication use, we examined associations between PTX3 and HRT, 3-hydroxy-3-methylglutaryl coenzyme A inhibitor (statin), nonsteroidal antiinflammatory, and aspirin use. To accommodate sample probability weighting, cross-sectional associations of PTX3 with continuous variables were determined by adjusted weighted linear regression. PTX3 (ln-transformed) was the dependent variable. The continuous variable of interest was entered first, followed by age, sex, and ethnicity. 99.6% of the subcohort (n=1576) had CRP measurements, and 86.7% (n=1373) had SAP measurements. We used weighted Cox regression to determine hazard ratios (HRs) and 95% confidence intervals (95% CIs) for PTX3 alone and in models containing PTX3 and CRP or SAP and their respective interaction terms. Those with an event were compared to all remaining participants. Participants were followed until the event of interest, death, or the end of follow-up, at which time they were censored.

Results
Baseline Characteristics of the CHS Subcohort
Table 1 shows baseline characteristics by case status. Compared to those free of events, cases were more likely to be older, white, hypertensive, diabetic, and have higher CRP and SAP (P<0.010 for all comparisons). With the exception of strokes, cases were more likely to be male (P<0.001 for all comparisons) and have higher levels of current smoking (P<0.042 for all comparisons) compared with event-free participants. Compared to referents, alcohol use was similar in angina (P=0.17) and MI (P=0.29) and lower in stroke (P=0.046), CVD death (P=0.013), and all-cause death (P=0.037) cases. Compared to the event-free group, PTX3...
was higher in cases (P<0.001 for angina, P=0.005 for MI, P≤0.001 for stroke, CVD death and all-cause death).

**Associations of PTX3 With CVD Risk Factors**

PTX3 distribution was skewed; geometric mean±standard deviation (from ln-transformed PTX3) 1.82±1.89, range 0.25 to 23.10 ng/mL. PTX3 was higher in men than women (1.97±1.91 versus 1.73±1.88 ng/mL, respectively; P<0.001) and higher in whites than blacks (1.91±1.84 versus 1.46±2.03 ng/mL; P<0.001). CRP distribution was also skewed (mean±standard deviation 1.90±2.76 mg/L for ln-CRP). SAP was normally distributed (mean±standard deviation 31.4±9.8 mg/L).

Adjusting for age, sex, and ethnicity, we determined associations between medication use and PTX3. PTX3 did not differ significantly by HRT use (1.76±1.75 ng/mL unopposed estrogen, n=15 women, 1.74±1.90 ng/mL combined estrogen/progestin, n=116 women and 1.74±1.87 ng/mL no HRT; P=0.9; analyses adjusted for age and ethnicity). PTX3 did not differ by statin use (1.83±1.89 ng/mL for 24 participants using statins versus 1.54±1.93 ng/mL nonusers; P=0.6). PTX3 in those using nonsteroidal antiinflammatory agents (n=204) was similar to remaining participants (1.90±1.98 versus 1.81±1.88 ng/mL, respectively; P=0.2) as was PTX3 in those using aspirin/aspirin-containing medications (n=664) and remaining participants (1.84±1.91 versus 1.81±1.87 ng/mL; P=0.9).

Associations between one standard deviation increases in CVD risk factors and PTX3 are shown in Table 2. PTX3 was significantly associated with age, fasting glucose, and insulin and ABI. PTX3 was strongly associated with CRP but was not associated with SAP. PTX3 was associated with other inflammatory markers, but not the fibrinolysis marker D-dimer (Table 2). Results did not significantly differ in men alone, women alone, or whites alone (minorities alone, n=293, were not examined because of lack of power).

We also stratified on mean age (70.1 years) and the presence of subclinical CVD. Although associations were generally similar to the whole group, there were some notable differences. In participants younger than 70.1 years, PTX3 was associated with common carotid IMT (regression coefficient 0.341, P=0.048). In participants with no detectable subclinical CVD (n=662), PTX3 was not associated with CRP (0.020, P=0.54). PTX3 association with CRP (0.089, P<0.001) was limited to those with subclinical CVD.

In age, sex, and ethnicity adjusted models, PTX3 levels did not differ significantly by smoking status. Geometric means±standard deviations were 1.81±1.93 ng/mL in never smokers (n=777), 1.83±1.85 in former smokers (n=620), and 1.83±1.87 in current smokers (n=186; P=0.96). PTX3 decreased with increasing alcohol consumption; 1.87±1.94 in nondrinkers, 1.81±1.87 in low consumers, and 1.66±1.89 ng/mL in the highest consumers (P<0.001). PTX3 was weakly associated with carotid stenosis; 1.73±1.91 ng/mL in those with no evidence of stenosis, 1.80±1.95 for 1% to 25%, and 1.91±1.83 for stenosis ≥25% (P=0.046). PTX3 was also higher in those who had evidence of subclinical CVD by a composite measure14 (n=921, 1.90±1.89 ng/mL) than those with no subclinical CVD (n=662, 1.71±1.88 ng/mL; P=0.001). PTX3 increased as the number of elements within the composite measure increased; PTX3 was 1.85±1.85 for 1 element, 1.88±1.85 for 2, 1.98±1.97 for 3, and 2.20±2.04 ng/mL for 4 elements (P=0.002).

**Associations of PTX3 With Incident Events and Mortality**

In minimally adjusted models, a 1-SD increase in PTX3 (1.89 ng/mL) was significantly associated with risk of CVD death and all-cause death (Model 1, Table 3). PTX3 was not associated with incident angina, MI, or stroke, nor was PTX3 associated with combined CVD events (combined angina, MI, stroke, and CVD death). For combined events, the HR for a 1-SD increase in PTX3 was 1.05 (95% CI 0.98 to 1.13). The addition of CRP (divided by its standard deviation, 2.76 mg/L) had no significant effect on risk prediction by PTX3 (Model 2, Table 3). There were no significant interactions between PTX3 and CRP for any outcome (all interaction terms P>0.1). Likewise, the addition of SAP (divided by its standard deviation, 9.8 mg/L) had no significant effect on risk prediction by PTX3 (data not shown) nor were any interaction terms statistically significant.

### Table 2. Regression Coefficients for CVD Risk Factors in Separate Linear Models of ln-Transformed PTX3

<table>
<thead>
<tr>
<th>Variable (SD)</th>
<th>Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (5.2 years)</td>
<td>0.076</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (4.8 kg/m²)</td>
<td>-0.021</td>
<td>0.33</td>
</tr>
<tr>
<td>Fasting glucose (37 mg/dl)</td>
<td>0.039</td>
<td>0.018</td>
</tr>
<tr>
<td>Fasting insulin (28 μIU/ml)</td>
<td>0.041</td>
<td>0.032</td>
</tr>
<tr>
<td>Systolic blood pressure (22 mm Hg)</td>
<td>-0.003</td>
<td>0.88</td>
</tr>
<tr>
<td>Diastolic blood pressure (11 mm Hg)</td>
<td>-0.008</td>
<td>0.71</td>
</tr>
<tr>
<td>Physical activity (2060 kcal)</td>
<td>-0.006</td>
<td>0.72</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (39 mg/dl)</td>
<td>-0.001</td>
<td>0.95</td>
</tr>
<tr>
<td>HDL cholesterol (16 mg/dl)</td>
<td>-0.018</td>
<td>0.38</td>
</tr>
<tr>
<td>LDL cholesterol (36 mg/dl)</td>
<td>-0.004</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglycerides (67 mg/dl)</td>
<td>0.028</td>
<td>0.12</td>
</tr>
<tr>
<td>Subclinical CVD measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common carotid IMT# (0.20 mm)</td>
<td>0.006</td>
<td>0.87</td>
</tr>
<tr>
<td>Internal carotid IMT# (0.55 mm)</td>
<td>0.016</td>
<td>0.42</td>
</tr>
<tr>
<td>ABI (0.16)</td>
<td>-0.058</td>
<td>0.006</td>
</tr>
<tr>
<td>Left ventricular mass (35 g)</td>
<td>0.010</td>
<td>0.71</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (2.76 mg/l)</td>
<td>0.049</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAP (9.8 mg/l)</td>
<td>0.016</td>
<td>0.48</td>
</tr>
<tr>
<td>IL-6 (1.87 pg/ml)</td>
<td>0.070</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (65 mg/dl)</td>
<td>0.089</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D-dimer* (2.24 μg/ml)</td>
<td>0.0001</td>
<td>0.14</td>
</tr>
<tr>
<td>Leukocytes (1.31 × 1000/ml)</td>
<td>0.085</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values were divided by their standard deviations (SD) shown in parentheses. Analyses were weighted and adjusted for age, sex, and ethnicity. #IMT indicates intima media thickness. *SD from ln-transformed data. Bold values are significant at P<0.05.
In models adjusted for age, sex, ethnicity, and CVD risk factors, PTX3 remained associated with risk of CVD and all-cause death (Model 3, Table 3). Adding CRP, SAP, other inflammatory markers, D-dimer, or the composite measure of subclinical CVD individually to these models had no significant effect on risk prediction by PTX3 (data not shown). However, adding alcohol use to the models adjusted for age, sex, ethnicity, and CVD risk factors significantly attenuated the association of PTX3 with CVD death (Model 4, Table 3) but not all-cause death. Results were similar in men alone, women alone, and in whites.

Stratifying on mean age (70.1 years), a standard deviation increase in PTX3 was associated with incident angina (HR 1.19; 95% CI 1.01 to 1.40), CVD death (1.25; 1.04 to 1.51), and all-cause death (1.15; 1.01 to 1.31) in younger participants in models adjusted for age, sex, and ethnicity. In models including CVD risk factors, HRs (95% CIs) were 1.15 (0.96 to 1.38) for angina, 1.32 (1.07 to 1.64) for CVD death, and 1.14 (0.98 to 1.31) for all-cause death. In older participants, higher PTX3 was associated with CVD death (1.11; 1.00 to 1.24) and all-cause death (1.08; 1.02 to 1.15) in models adjusted for age, sex, ethnicity, and CVD risk factors. In participants with no detectable subclinical CVD, PTX3 was associated only with all-cause death but not CVD death. HRs (95% CIs) were 1.11 (1.04 to 1.19) and 1.06 (0.85 to 1.32), respectively, in models adjusted as above. In those with subclinical CVD, increased PTX3 was associated with CVD death (1.16; 1.04 to 1.30) and all-cause death (1.09; 1.02 to 1.18) in models adjusted for age, sex, ethnicity, and CVD risk factors.

We also examined associations of PTX3 quartiles with events, comparing upper quartiles to quartile 1. Quartiles 3 and 4 were associated with CVD death (1.61; 1.00 to 2.58 and 1.62; 1.01 to 2.61, respectively) and quartile 4 with all-cause death (1.41; 1.07 to 1.86) in minimally adjusted models. Adjustment for CVD risk factors attenuated associations although quartile 4 remained associated with all-cause death (1.37; 1.03 to 1.81). Higher levels of PTX3 were not associated with risk of incident angina, MI, or stroke even in minimally adjusted models.

**Discussion**

This is the first study examining associations of circulating PTX3 with CVD risk factors, subclinical CVD, and incident CVD events in a prospective epidemiological setting. In apparently healthy older adults free of clinical CVD at baseline, PTX3 was associated with CRP, other inflammatory markers, some CVD risk factors (age, fasting glucose, and insulin), and the presence of subclinical CVD. PTX3 was associated with CVD death and all-cause death, but not angina, MI, and stroke; events comprised fatal and nonfatal cases. The strengths of associations of PTX3 with CVD and all-cause death were similar to CRP in these participants.

Our findings agree with previous reports and extend these observations to a large sample from a well-characterized population-based cohort. We found PTX3 was associated with fatal events, similar to Latini at al who reported that PTX3 was associated with outcomes in acute MI patients and Suzuki et al who reported that PTX3 was associated with adverse clinical outcomes in heart failure patients. In addition, in patients with chronic kidney disease, PTX3 is reported to predict all-cause mortality. PTX3 was associated with a limited number of CVD risk factors in our apparently healthy population, consistent with Inoue et al who did not identify any associations of PTX3 with similar risk factors in a small sample (n = 162) of patients with hypertension, hyperlipidemia, diabetes, or CVD. We saw no association of PTX3 with incident angina comprised of both stable and unstable disease. In the previous report, PTX3 levels did not differ between stable angina cases and controls.

PTX3 was associated with CRP, but not SAP, another pentraxin that functions in innate immunity. SAP was associated with risk of incident angina and MI, but not CVD death, in a similar study of CHS participants. SAP was also strongly correlated with a number of CVD risk factors including obesity, blood pressure, and lipids as well as carotid IMT, while PTX3 was not associated with these factors.

Potential role of PTX3 as a specific marker of localized vascular inflammation rather than a marker of chronic sub-
clinical inflammation. In a small study of men under conditions of caloric restriction and bed rest, Bosutti et al.\textsuperscript{24} reported inverse associations of PTX3 with fat mass and hypothesized that nutrition may play a role in regulation of PTX3 levels. This may account for associations of PTX3 with fasting glucose and insulin in our study. Unfortunately, we did not have detailed dietary information to examine this further.

Given the differences between PTX3 and CRP, it is not surprising that both independently predicted CVD and all-cause death. We found no synergistic effects when the two biomarkers were combined. PTX3 and CRP may represent different inflammatory processes and reflect different aspects of inflammation in atherosclerosis and perhaps other diseases. Furthermore, unlike CRP and SAP, PTX3 was associated only with fatal events in these older adults. PTX3 expression is reported to increase as atherosclerotic lesions progress from fatty streaks to advanced lesions.\textsuperscript{9} In older adults with more advanced atherosclerosis, PTX3 may have unique potential in monitoring acute changes in vascular health related to aging and chronic diseases of aging that lead to death. However, to elucidate a role for PTX3 in risk prediction, further exploration of PTX3 in other cohorts is needed. In particular, cohorts comprising younger men and women with less advanced atherosclerosis as PTX3 may be more strongly associated with subclinical CVD progression and CVD events in this setting. Even in our older cohort, PTX3 was more strongly associated with subclinical CVD measures and was also weakly associated with nonfatal events (angina) in the younger age stratum. The presence of subclinical CVD itself may also modify associations. In our study, PTX3 was more strongly associated with inflammatory markers and CVD death in those with detectable subclinical CVD than those without.

In conjunction with its potential role as a specific marker of vascular inflammation/damage, PTX3 may also play a causal role in atherosclerosis. PTX3 functions in innate immunity as a soluble pattern recognition receptor and is localized in atherosclerotic lesions,\textsuperscript{9} potentially promoting lesion progression through the innate immune response. PTX3 has been reported to induce tissue factor expression in monocytes and endothelial cells\textsuperscript{25,26} and may contribute to thrombosis through this mechanism.

This study has a number of strengths: availability of measures of subclinical CVD, CVD risk factors, and multiple incident CVD events in a large population-based sample of older adults from a prospective epidemiological study. Limitations of this study are also important. Participants were a subcohort within the parent study and power was limited for some analyses within this group. PTX3 was only measured once, and we cannot account for intrindividual variation. However, assay variability would be expected to bias findings toward the null so the observed associations are potentially underestimations. Additionally, study participants were older, primarily white adults. These results may not generalize well to other ethnicities or younger individuals.

In summary, we report that in a population-based study of older men and women, PTX3 was associated with subclinical CVD and mortality, both CVD-related and all-cause. PTX3 likely reflects different aspects of the inflammatory process in atherosclerosis than other members of the pentraxin family like CRP. Additional studies will continue to shed light on potential clinical roles for this interesting biomarker.

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\textbf{References}


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