Associations of pentraxin-3 with cardiovascular events, incident heart failure, and mortality among persons with coronary heart disease: Data from the Heart and Soul Study

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Background Pentraxin-3 (PTX3) is an inflammatory marker thought to be more specific to vascular inflammation than C-reactive protein (CRP). Whether PTX3 is independently associated with adverse events among persons with stable coronary heart disease (CHD), independently of CRP, and whether kidney dysfunction influences these associations are not known.

Methods We evaluated the associations of baseline PTX3 levels with all-cause mortality, cardiovascular (CV) events (myocardial infarction, stroke, or CHD death), and incident heart failure (HF) during 37 months among ambulatory persons with stable CHD participating in the Heart and Soul Study. Cox proportional hazards models were adjusted for age, sex, race, hypertension, diabetes, smoking, and CRP.

Results Among 986 persons with stable CHD, each 1 unit increase in log PTX3 at baseline was associated with an 80% increased risk of all-cause mortality (hazard ratio [HR] 1.8, 95% CI 1.5-2.1), a 50% increased risk of CV events (HR 1.5, 95% CI, 1.2-1.9), and an 80% greater risk of incident HF (HR 1.8, 95% CI, 1.3-2.5). Further adjustment for estimated glomerular filtration rate (eGFR) attenuated these associations to 1.6 (1.3-1.9) for mortality, 1.3 (1.0-1.6) for CV events and 1.5 (1.1-2.1) for incident HF. Stratification by eGFR >60 mL/min per 1.73m^2 or <60 mL/min per 1.73m^2 did not affect these associations (P interaction > .3 for all outcomes).

Conclusions Among persons with stable CHD, higher PTX3 concentrations were associated with increased risk for all-cause mortality, CV events, and incident HF independently of systemic inflammation. Adjustment for eGFR modestly attenuated these associations, suggesting that future studies of PTX3 should adjust for kidney function. (Am Heart J 2012;163:274-9.)

Pentraxin-3 (PTX3) has emerged as a novel marker thought to be more specific to vascular inflammation than other proteins in the pentraxin family such as C-reactive protein (CRP). Higher PTX3 levels are associated with worse cardiovascular (CV) outcomes after acute coronary syndromes, independently of CRP.[1,2] Pentraxin-3 is also associated with increased risk of CV death among elderly persons without established CV disease (CVD).[3] The biologic plausibility of its role in CVD risk is supported by its localization in atherosclerotic plaques[4] and the higher concentration of PTX3, but not CRP, in the coronary sinus of patients with heart failure (HF).[5] Whether PTX3 is a predictor of adverse outcomes among persons with stable coronary disease has not been well studied.

Kidney dysfunction may be an important factor in the association between PTX3 and adverse outcomes. Higher PTX3 concentrations are associated with lower estimated glomerular filtration rates (eGFRs) across all stages of established chronic kidney disease (CKD).[6,7] Chronic kidney disease is associated with endothelial dysfunction,[8,9] and in subjects with CKD, PTX3 is independently associated with endothelial dysfunction.[9] Chronic kidney disease is an independent risk factor for death, CV events, and incident HF, an association that is present at earlier stages of kidney dysfunction when eGFR is measured by cystatin C.[10-14] Thus, it is plausible that CKD may confound or modify the associations of PTX3 and adverse events. Understanding the influence of kidney dysfunction in these associations could elucidate pathways common to CKD and CVD and could provide guidance for future studies about whether responsible mechanisms may be driven by PTX3, inflammation or, through other mechanisms linked to kidney dysfunction.

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We evaluated the associations of PTX3 with all-cause mortality, CVD events, and incident HF in ambulatory persons with stable coronary heart disease (CHD) enrolled in the Heart and Soul Study. We also evaluated whether the potential associations between PTX3 and the outcomes of interest are influenced by kidney function (eGFR measured by cystatin C).

Methods

Participants

As described previously, the Heart and Soul Study is a prospective cohort study initially designed to evaluate the influence of psychosocial factors on CVD events in ambulatory persons with stable CHD.[15] Study participants were recruited from outpatient clinics in the San Francisco Bay Area using ≥1 of the following inclusion criteria: (1) history of myocardial infarction, (2) angiographic evidence of 50% stenosis in ≥1 coronary vessels, (3) evidence of exercise-induced ischemia by treadmill or nuclear testing, or (4) history of coronary revascularization. In addition, subjects who met the following criteria were excluded: myocardial infarction within the last 6 months, exercise tolerance <1 block, or likely to move out of the area within 3 years. The appropriate institutional review boards approved the protocol, and all participants gave written, informed consent.

Overall, 1,024 study participants were recruited between September 2000 and December 2002. For every participant, baseline evaluation was conducted at a 1-day appointment by trained research assistants and included questionnaires related to social and medical history and physical examination. Phlebotomy was performed after a 12-hour fast, and serum was frozen at 70°C. For all-cause mortality and composite CV event outcomes, we included 986 patients with PTX3 measures; for HF, we excluded 172 patients with baseline HF by self-report. We created a missing category for covariates with missing observations.

Measurements

Pentraxin-3. Pentraxin-3 was measured at University of Vermont Laboratory for Clinical Biochemistry Research, Department of Pathology, from frozen samples collected at the baseline study visit by Human Pentraxin 3/TSG-14 Immunoassay (R&D Systems, Minneapolis, MN). Coefficients of variation ranged from 4.1% to 8.1% (average analytic coefficient of variation 6.2%). The assay range is 0.31 to 20 ng/mL. Measurements were made in duplicate and averaged.

Kidney function. Glomerular filtration rate was estimated from serum cystatin C. Cystatin C is an alternative filtration marker with stronger and more linear associations with CV outcomes than creatinine.[11,13] Cystatin C–based estimates may be more accurate among persons with higher levels of kidney function.[16] Cystatin C was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Siemens, Deerfield, IL; formerly Dade Behring). Intra-assay coefficients of variation are <3.1%. Estimated glomerular filtration rate was calculated using the formula $76.7 \times \text{cysC}^{-1.19}$, which was developed from pooled data from cohorts with eGFR measured by iothalamate.[17]

Other measurements. At the baseline visit, all participants completed questionnaires related to social and medical history and underwent physical examinations. Blood pressure was measured by trained research assistants using calibrated blood pressure cuffs. Additional serologic measurements included total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations. The Friedewald equation was used to measure low-density lipoprotein (LDL) cholesterol.[18] High-sensitivity CRP was measured as previously described.[19]

Outcomes

We considered 3 outcomes: all-cause mortality, CV events (nonfatal myocardial infarction, stroke, or death due to CHD), and incident HF. Outcomes were initially ascertained by annual telephone interviews with study participants or family and were then confirmed by 2 blinded adjudicators after review of medical records. *Cardiovascular death* was defined as (1) death during the same hospitalization in which an acute myocardial infarction was documented or (2) death not explained by other causes and that occurred within 1 hour of the onset of terminal symptoms. Nonfatal myocardial infarction was defined by the American Heart Association diagnostic criteria.[20] *Stroke* was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other cause.[21] Persons were deemed to have incident HF if they did not have a known history of HF but were hospitalized with a clinical diagnosis of HF involving at least 2 of the following new or changed symptoms: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, and cardiomegaly or pulmonary edema on chest radiography.[22] Quantitative evidence of new-onset HF (echocardiograms or invasively measured hemodynamics) was obtained when possible. For the analysis of incident HF, 172 persons with prevalent HF were excluded. Death certificates and autopsy reports were used to determine all-cause mortality. For mortality, the median follow-up time was 49 months; for HF, 50 months; and for composite CV event, 49 months. Among 986 patients with PTX3 measures, 4 (<1%) were lost to follow-up.

Statistical analysis

We compared sociodemographic and anthropometric data and comorbidities by tertile of PTX3 using analysis of variance or χ^2. We evaluated the association between PTX3 and each outcome separately using Cox proportional hazards models. Pentraxin-3 was characterized as a linear variable, log transformed because of its skewed distribution, and also categorized into tertiles. We used staged models to evaluate the importance of potential confounders or mediators in observed associations. We first adjusted for age, gender, and race/ethnicity. We further adjusted for well-established risk factors associated with the outcomes of interest including diabetes, hypertension, and smoking (past or present). Because the pathways by which PTX3 may be associated with these outcomes are unknown, we further adjusted for covariates that were significantly associated with PTX3 in bivariate analyses and also associated with the outcome at $P < .1$. The variables evaluated included education, systolic blood pressure, fasting glucose, body mass index, LDL, HDL, triglycerides, and CRP. To understand the potential importance of eGFR in the associations of PTX3 and outcomes, we added eGFR to the fully adjusted

Table I. Demographic and clinical characteristics of Heart and Soul participants by PTX3 tertile

	Lower tertile, n = 330	Middle tertile, n = 329	Upper tertile, n = 327	*P*
PTX3 range (ng/mL)	0.250-0.470	0.471-0.803	0.809-9.770	
Age (y)	64.1 ± 10.5	67.3 ± 10.9	68.8 ± 11.1	<.001
Female	70 (21.2)	55 (16.7)	58 (17.7)	.298
Race				.070
White	170 (51.5)	201 (61.1)	223 (68.2)	
Black	61 (18.5)	50 (15.2)	50 (15.3)	
Education				.984
<High school	42 (12.7)	41 (12.5)	42 (12.8)	
High school graduate	56 (17.0)	62 (18.8)	60 (18.4)	
>High school	230 (69.7)	226 (68.7)	225 (68.8)	
Income				.732
<$20 000	163 (49.4)	151 (45.9)	161 (49.2)	
$20 000-$29 999	44 (13.3)	44 (13.4)	45 (13.8)	
$30 000-$39 999	29 (8.8)	31 (9.4)	33 (10.1)	
$40 000-$50 000	26 (7.9)	41 (12.5)	29 (8.9)	
>$50 000	65 (19.7)	61 (18.5)	57 (17.4)	
Diabetes*	95 (28.8)	78 (23.7)	87 (26.6)	.332
Hypertension†	231 (70.0)	228 (69.3)	235 (71.9)	.801
Current smoker	84 (25.5)	57 (17.3)	54 (16.5)	.006
History of CHF	47 (14.2)	55 (16.7)	70 (21.4)	.049
Ejection fraction by echo without CHF	63.3 ± 8.1	63.6 ± 8.8	61.5 ± 9.2	.008
Systolic blood pressure (mm Hg)	133.3 ± 21.5	133.3 ± 21.9	132.5 ± 19.7	.972
Fasting glucose (mg/dL)	118.2 ± 35.7	119.9 ± 43.0	121.9 ± 49.5	.974
Body mass index (kg/m^2)	28.4 ± 4.8	28.6 ± 5.3	28.2 ± 6.0	.344
LDL cholesterol (mg/dL)	106.7 ± 33.8	105.0 ± 34.9	101.4 ± 32.7	.261
HDL cholesterol (mg/dL)	45.7 ± 13.2	44.9 ± 13.0	46.4 ± 15.8	.602
Triglycerides (mg/dL)	154.0 ± 126.2	138.1 ± 135.8	130.6 ± 123.5	.001
eGFRcys‡ (mL/min per 1.73 m^2)	77.1 ± 21.4	71.2 ± 20.1	64.2 ± 25.0	<.001
Ln CRP (mg/L)	0.50 ± 1.32	0.70 ± 1.23	0.95 ± 1.35	<.001
Statins use	207 (62.7)	226 (68.7)	199 (60.9)	.092
ACE or ARB use	156 (47.3)	170 (51.7)	181 (55.4)	.116
β-Blocker use	188 (57.0)	190 (57.8)	189 (57.8)	.971
LV mass index	93.9 ± 25.8	99.5 ± 26.3	101.2 ± 26.5	<.001
Ejection fraction by echo (%)	62.4 ± 9.1	62.1 ± 10.3	60.5 ± 9.8	.007
Albumin-to-creatinine ratio >30 mg/g	44 (13.3)	38 (11.6)	64 (19.6)	.008

Note: All measures are presented as mean ± SD or n (%). *P* values obtained using Kruskal-Wallis test for continuous variables (nonnormality) except Ln (IL-6) and Ln (CRP), which were obtained using analysis of variance. *P* values are obtained using χ^2 test for categorical variables. *ACE,* Angiotensin-converting enzyme; *Echo,* echocardiogram; *ARB,* angiotensin receptor blocker.

*Defined by self-reported diagnosis, diabetes medication, or fasting glucose ≥126 mg/dL.

†Defined by self-reported diagnosis, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.

‡eGFRcys equation: eGFR measured by cystatin was calculated as eGFRcys = $76.7 \times \text{cysC}^{-1.19}$.

model. Moreover, by adding a cross-term to models, we tested for interactions by the *presence of CKD*, defined as eGFR <60 mL/min per 1.73m^2, to understand whether CKD may modify the association of PTX3 with each outcome. In a secondary analysis, we also adjusted for left ventricular (LV) mass and ejection fraction to test whether these may mediate observed associations between PTX3 and CV outcomes.

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Results

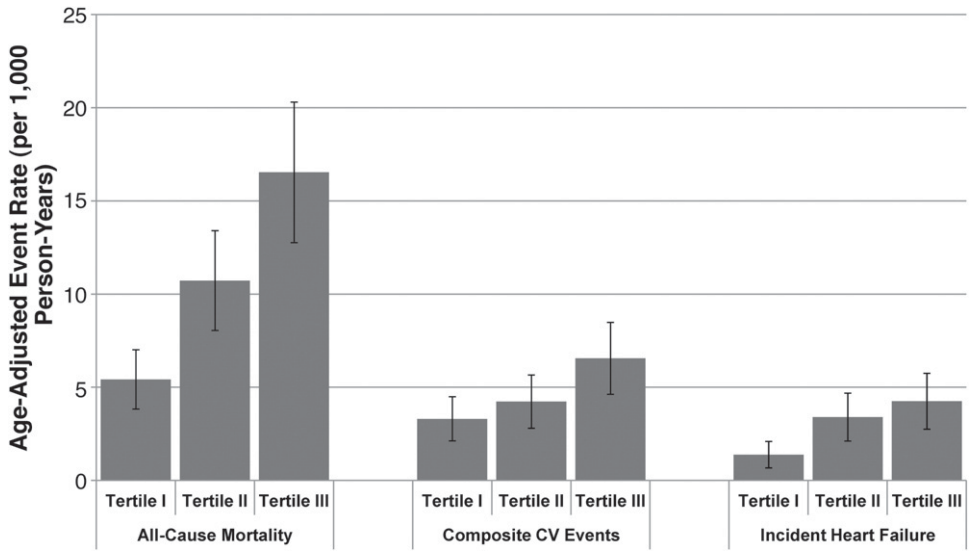
Among 986 participants, mean (SD) age was 67 years (11), median (25th, 75th percentiles) of PTX3 was 0.60 ng/mL (0.41, 0.96), and mean (SD) of eGFR was 70.8 (23.0). Persons with higher PTX3 were older, more likely to be of white race, more likely to have a history of chronic HF (CHF), and had lower eGFR, higher LV mass index, and lower ejection fraction by echocardiography. Persons in the highest tertile of PTX3 were less likely to smoke, had lower triglycerides, and had lower levels of CRP and urine albumin to creatinine ratio (Table I).

Table II. Association of PTX3 with all-cause mortality, incident HF, and composite CV events

	No. of events	HR (95% CI), by tertile			HR (95% CI), by PTX3	*P*
		Tertile 1	Tertile 2	Tertile 3		
All-cause mortality	344					
Demographic-adjusted model*		1.0	1.4 (1.0-2.0)	1.9 (1.3-2.6)	1.8 (1.5-2.1)	<.001
Multivariate-adjusted model†		1.0	1.5 (1.0-2.1)	1.9 (1.4-2.7)	1.8 (1.5-2.1)	<.001
eGFRcysC-adjusted model‡		1.0	1.5 (1.0-2.1)	1.7 (1.2-2.4)	1.6 (1.3-1.9)	<.001
Incident CHF	102					
Demographic-adjusted model*		1.0	1.9 (1.1-3.4)	2.2 (1.2-3.9)	2.0 (1.5-2.8)	<.001
Multivariate-adjusted model†		1.0	1.9 (1.1-3.5)	1.9 (1.1-3.4)	1.8 (1.3-2.5)	.001
eGFRcysC-adjusted model‡		1.0	1.9 (1.0-3.4)	1.5 (0.8-2.7)	1.5 (1.1-2.1)	.021
Composite CV events	205					
Demographic-adjusted model*		1.0	1.1 (0.7-1.7)	1.5 (1.0-2.3)	1.5 (1.2-1.9)	<.001
Multivariate-adjusted model†		1.0	1.2 (0.7-1.8)	1.5 (1.0-2.3)	1.5 (1.2-1.9)	.001
eGFRcysC-adjusted model‡		1.0	1.1 (0.7-1.8)	1.4 (0.9-2.1)	1.3 (1.0-1.6)	.024

Note: Results are HR (95% CI). eGFRcysC, cystatin C–based eGFR.
*Demographic-adjusted model is adjusted for age, sex, and race.
†Multivariate-adjusted model is adjusted for age, sex, race, diabetes, hypertension, tobacco, and CRP.
‡eGFRcysC-adjusted model is adjusted for age, sex, race, diabetes, hypertension, tobacco, CRP, and eGFRcysC.

Figure 1



Age-adjusted event rate per 1,000 person-years (95% CI).

Higher PTX3 levels were associated with overall mortality independently of demographics, comorbidities, and CRP concentrations. For every unit increase in log PTX3, there was an 80% increased hazard for death after multivariate adjustment. Further adjustment for eGFR resulted in attenuation of the β coefficient by 12%, and it remained statistically significant (Table II). When we categorized PTX3 into tertiles, the age-adjusted death rate was >3-fold higher for persons in the highest tertile of PTX3 compared with the lowest (Figure 1). Compared with the lowest tertile, participants in the second and third tertiles had a stepwise increase in the hazard for all-cause death after multivariate adjustment. The addition of eGFR to the models mildly attenuated the associations in the highest tertile and in the linear analysis (Table II).

Higher PTX3 concentrations were also associated with a 50% increased hazard of CV events and an 80% increased hazard of incident HF in linear models after multivariate adjustment. The addition of eGFR to the model resulted in attenuation of the β coefficient by 33% for CV events and by 24% for HF, but they remained statistically significant (Table II). Comparing study participants in tertiles 3 to 1

by age-adjusted event rate per 1,000 person-years, increased levels of PTX3 were associated with increased CV events (P = .018), incident HF (.002), and overall mortality (<.001) (Figure 1). Participants in the highest tertile of PTX3 had a 50% increased risk of CV event (P = .05) and 90% increased risk of incident HF (P = .03) compared with the lowest tertile. Additional adjustment for eGFR attenuated these associations to 40% for CV events and 50% for incident HF (Table II).

In an exploratory analysis, we found that further adjustment for LV mass index and ejection fraction had no meaningful effect on associations of PTX3 with CV outcomes. Hazard ratio (HR) for CV events was 1.3 (P = .04) adjusted for LV mass index and 1.3 (P = .05) when adjusted for ejection fraction; HR for incident HF was 1.5 (P = .04) adjusted for LV mass index and 1.4 (P = .08) adjusted for ejection fraction. We also tested whether eGFR is an effect modifier in multivariate models using the product of eGFR and continuous log PTX3. Results were similar among persons with or without CKD; P value for interaction was .4 for CV events, .3 for incident HF, and .9 for overall mortality. Point estimates for overall mortality in the multivariate model (not adjusted for eGFR), using log PTX3 as predictor, were identical for subjects with eGFR >60 mL/min per 1.73m^2 and <60 mL/min per 1.73m^2, 1.7 (1.3-2.2) (P < .001).

Discussion

In this cohort of persons with stable CHD, we found that PTX3 is significantly associated with all-cause mortality, CV events, and incident HF independently of demographics, traditional CVD risk factors, and systemic inflammation (CRP). Adjustment for eGFR modestly attenuated these associations. Our findings suggest that this novel marker of vascular inflammation may be an important mechanism involved in vascular injury and repair among persons with stable CHD.

To our knowledge, we are the first to report an independent association of PTX3 with overall mortality among persons with established and stable CVD, independent of systemic inflammation. Pentraxin-3 is produced by multiple cell types (peripheral leukocytes, vascular endothelial cells, and smooth muscle cells, to name a few) and is produced in response to both inflammatory stimuli (interleukin [IL] 1, tumor necrosis factor-α, agonists of toll like receptor, lipopolysaccharide) and anti-inflammatory stimuli (IL-10 and HDL).[23] The finding that PTX3 is strongly associated with overall mortality in our cohort invites at least 2 interpretations. Vascular pathology may contribute to the overall risk of death in a cohort of subjects with CVD. Conversely, it is possible that this strong association with overall mortality relates to a nonvascular function of PTX3. The mechanism by which PTX3 is associated with overall mortality requires further study.

Our findings that PTX3 is associated with CV events and incident HF, independent of systemic inflammation, are noteworthy. These findings are in accordance with prior reports suggesting that PTX3 may be more strongly associated with adverse outcomes after acute coronary ischemia than CRP and troponin[1,2] and that it may be associated with CV death in an elderly cohort free of CVD.[3] The association with incident HF is supported by previous findings that PTX3 is elevated in patients with HF with normal ejection fraction.[5] The mechanisms by which PTX3 is associated with CV outcomes remain unclear. Current investigations suggest that PTX3 may be part of a protective mechanism in vascular repair. Pentraxin-3 binds and inactivates fibroblast growth factor (FGF)-2, an angiogenic growth factor responsible for smooth muscle proliferation involved in atherosclerosis.[24,25] Knockout models in mice have been used to demonstrate that atherosclerotic lesions develop faster in PTX3-deficient mice.[26] Cardiac ischemia-reperfusion injury was exacerbated in PTX3 knockout mice.[27] Taken together, these findings suggest that PTX3 may be elevated in vascular injury as a protective mechanism, much like white blood cells are elevated during infection. Very high levels of PTX3 may indicate a more severe vascular disease state, explaining its ability to detect increased risk of adverse outcomes. Elucidating PTX3 pathways in vascular pathology may lead to a better understanding of risk for secondary events among persons with stable CHD.

Interestingly, the addition of eGFR as an adjustment variable resulted in some attenuation of associations of PTX3 with CV events and incident HF, albeit PTX3 remained statistically significantly associated with these outcomes even after adjustment for eGFR. Several possibilities may explain these findings. One is that vascular injury is a parallel process present in persons with kidney dysfunction and CHD. Another is that kidney dysfunction is a confounder due to filtration of PTX3 by the kidney. It is less likely that PTX3 is filtered in the glomerulus, given its molecular weight (42 kd) and our group's findings that the association of PTX3 and eGFR differs by race/ethnicity.[6] In the exploratory analysis, the addition of LV mass index and ejection fraction had little effect on CV outcomes. This would suggest that if PTX3 is related to vascular injury, these echocardiographic measures inadequately measure the effect of this injury in the heart. Future studies are needed to elucidate the mechanisms of these associations.

Strengths of the current study include the large sample size, the extended follow-up time, the comprehensive assessment of risk factors, and the availability of adjudicated outcome classifications. There are also several important limitations. Because the Heart and Soul cohort is recruited primarily from a Veteran population and is comprised mainly of white men, our results may not generalize to more heterogeneous

populations. Some misclassification may have occurred because CV outcomes were assessed by review of medical records, and incident HF was defined by hospitalization. All participants had prevalent CHD, and results may differ in other settings.

In summary, we found that PTX3 is associated with overall mortality, CV events, and incident HF among persons with stable coronary disease. These findings were independent of systemic inflammation, kidney dysfunction, and traditional CV risk factors. The addition of eGFR to predictive models provided substantial attenuation, suggesting that future studies of PTX3 should take kidney function into account.

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Potential conflicts of interest
None declared.

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