The Relationship Between Serum Markers of Collagen Turnover and Cardiovascular Outcome in the Elderly

The Cardiovascular Health Study

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Background—The deposition of collagen fibrils in the myocardial extracellular matrix increases with age and plays a key role in the pathophysiology of heart failure (HF). We sought to determine the predictive value of serum markers of collagen turnover for incident HF and cardiovascular (CV) morbidity, mortality, and all-cause mortality in elderly individuals.

Methods and Results—In 880 participants in the Cardiovascular Health Study (mean age, 77±6 years; 48% women), serum levels of carboxyl-terminal peptide of procollagen type I (PIP), carboxyl-terminal telopeptide of collagen type I (CITP), and amino-terminal peptide of procollagen type III (PIIINP) were measured in 4 groups: HF with reduced ejection fraction (HFREF; n=146, EF <55%); HF with preserved EF (HFPEF; n=175, EF ≥55%), control subjects with CV risk factors but not HF (CVD; n=280), and healthy control subjects free of CV disease (n=279). Relationships between these serum markers and outcome at follow-up of 12±4 years (range, 3–17 years) was determined in six models including those adjusted for conventional risk factors, renal function, NT-proBNP and agents which interfere with collagen synthesis. For the entire cohort, in unadjusted and adjusted models, both PIIINP and CITP were associated with myocardial infarction, incident HF, hospitalization for HF, cardiovascular and all-cause mortality. In healthy control subjects, CITP and PIIINP were associated with all-cause death. In control subjects with risk factors, CITP was associated with incident HF, and in participants with HFPEF, CITP was associated with hospitalization for HF. No collagen biomarker was associated with outcome in participants with HFREF, and PIP was not associated with outcome in the cohort or its subgroups.

Conclusions—In both healthy and elderly individuals with CV disease at risk of developing HF, CITP and PIIINP are significantly associated with multiple adverse cardiac outcomes including myocardial infarction, HF, and death.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00005133.

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Key Words: biomarkers ■ collagen ■ elderly ■ heart failure ■ outcomes

The prevalence and incidence of congestive heart failure (HF) continue to increase in the elderly population.1,2 Although a number of echocardiographic hemodynamic and biological markers have been found useful for risk stratification of patients with both acute and chronic HF,3-5 the ability to predict the occurrence of HF (ie, incident disease among healthy elderly or those with risk factors for developing HF), remains a challenge.

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Despite the fact that the etiologies of HF in the elderly with preserved ejection fraction (HFPEF) and HF with reduced ejection fraction (HFREF) can be different (eg, arterial hypertension and coronary artery disease or dilated cardiomyopathy, respectively), changes in the interstitial matrix are dynamic and might be a common finding in both conditions, with more interstitial than replacement fibrosis in HFPEF, which partially explain the increase in left ventricular (LV) diastolic stiffness and LV filling pressures despite preservation of systolic contraction.6

Excessive deposition of collagen in the myocardial extracellular matrix has a deleterious effect on both mechanical and electrophysiological properties of the heart muscle and may lead to an unfavorable outcome.7,8 Although nonspecific for the myocardium, serum markers of collagen turnover have been proposed to be used for identification of myocardial fibrosis.9-11 Types I and III collagens are the major myocardial fibrillar collagens, and both are synthesized as procolla-
gens with a small amino terminal and a larger carboxy terminal propeptide. Serum markers of collagen synthesis, carboxy-terminal propeptide of type I procollagen (PIP) and amino-terminal propeptide of type III procollagen (PIIINP), and degradation, carboxy-terminal telopeptide of collagen type I (CITP), result from the hydrolysis of collagen type I fibrils by matrix metalloproteinase (MMP)-1,9 and reflect intramyocardial collagen turnover6–11 which is also age related and involves the action of tissue inhibitors of MMPs (TIMPs), with greater serum levels of TIMP-1 in HFPEF than in HFREF and higher MMP-1/TIMP-1 ratio in HFREF than in HFPEF.12,13

In a prior study done in the same population, we found a strong association between the increased levels of fibrosis markers and prevalent HF.14 A number of other studies have evaluated the short-term15,16 and long-term7–17 prognostic value of serum biomarkers of collagen turnover in patients with HF of different etiologies or after acute myocardial infarction,18,19 but none enrolled exclusively free-living elderly populations.

We hypothesized that in the elderly, serum markers of collagen turnover are predictors of incident HF and of major cardiovascular (CV) adverse events, including CV and all-cause mortality. To test this hypothesis, we analyzed 2 key markers of collagen I metabolism (PIP and CITP) and 1 of collagen III synthesis in association with a large number of clinical, echocardiographic, and biochemical variables in a selected cohort of participants in the Cardiovascular Health Study (CHS) who were followed for a mean period of 12±4 years (range, 3–17 years).

Methods

The CHS is a prospective, community-based, epidemiological, observational study designed to assess CV risk factors and outcomes in elderly persons in which 5888 were enrolled (age, 65–100 years at study entry), of whom 5201 were recruited in 1989–1990, and a supplemental cohort of 687 African-American participants were added in 1992–1993. The design, rationale, and examination details of the CHS Study have been published elsewhere.20

Fibrosis markers were assessed in a subcohort of the CHS (n=880), using a case-control design based on HF status. Clinical evaluations and blood draws were obtained during the same study visit. Participant characteristics are presented in Table 1. The presence of HF was determined by expert adjudication of clinical records as described previously.1 HF status was determined for all CHS participants alive at the 1993–1994 examination and updated to reflect clinical status in 1996–1997.

All patients who had an adjudicated HF diagnosis were selected from the full CHS cohort (n=5888) in year 1992–1993 and year 1996–1997 (n=310) and were compared with 2 control groups. The following participants were enrolled in this study: (1) 146 patients with HFREF (<55% EF), (2) 175 patients with HFPEF (EF ≥55%), (3) 280 control subjects with CV disease (CVD) risk factors but without HF, and (4) 279 healthy control subjects without HF, coronary heart disease, hypertension, diabetes mellitus, peripheral arterial disease, stroke, transient ischemic attack, or use of cardioactive and/or antiangiogenic agents.

Selection of participants in each of the 2 control groups was based on frequency matching for age and sex of the patients with HF. Matching was successful in approximating equivalent age and sex between groups (mean±SD age for HF=80.2±5.7 years; control subjects with CVD risk factors, 81.3±6.5 years; and healthy control subjects, 79.7±5.5 years; 48%, 49%, and 50% were female, respectively) even though statistical significant differences between groups exist.

Assays for fibrosis markers were done in blood samples obtained in 1992–1993 (n=633) or 1996–1997 (n=237), and samples were analyzed in 2005 at the University of Vermont. All clinical and biochemistry measures were obtained at the same evaluation visit for each patient when fibrosis markers were assessed (ie, 1992–1993 or 1996–1997, respectively) to ensure simultaneous assessments of fibrosis markers and covariates. There were no differences in clinical characteristics between participants with samples obtained between 1992–1993 and those with samples obtained in 1996–1997 (age-adjusted probability values ≥0.10).

Diseases relevant to fibrosis markers in the elderly were also recorded, including osteoporosis and arthritis, history of stroke, and obstructive peripheral artery disease. Prevalent disease status was updated on the basis of adjudicated incident events throughout the study.

Echocardiograms were used to determine cardiac structural and functional characteristics and were analyzed at a central core echocardiography laboratory (J.S.G.). Qualitative LVEF was estimated based on echocardiographic data obtained either at the baseline CHS examination and interpreted at the core echocardiog-
raphy reading laboratory or at the point of care as abstracted from clinical records.

**Covariates**
Prevalent CVD was defined as a history of myocardial infarction, stroke, or HF, at the time of the 1994–1995 examination cycle.

Demographic and subject characteristics were age, sex, race, weight, height, body mass index, history of hypertension, diabetes, hyperlipidemia, serum glucose, creatinine, C-reactive protein, cystatin C and NT-pro BNP, ACE, and aldosterone receptor inhibitors. Participants with a history of chronic liver disease or chronic pulmonary disease were excluded to minimize confounding effects of liver and pulmonary disease on fibrosis markers.

**Determination of Plasma PCPIIINP, PIP, and CITP**
Collagen biomarkers were measured from blood draws performed in 1992–1993 and 1996–1997, and the serum was stored and deep-frozen at −70°C.

Phlebotomy methods, blood processing, and handling of samples have been described previously.3 Aliquots were frozen at −70°C until analysis.

PIP was measured with the use of an enzyme immunoassay kit (Takara Mirus Bio Inc, Madison, WI). The assay range is 10–640 μg/L. Intra-assay and interassay variability range from 4.5–7.4% and 4.3–6.3%, respectively.

CITP was measured using the CITP radioimmunoassay from Orion Diagnostica on serum samples. Intra-and interassay coefficients of variation range from 4.5–7.4% and 4.3–6.3%, respectively.

PIIINP was determined by a coated-tube radioimmunoassay as described previously by Risteli et al,21 using commercial antisera specifically directed against the terminal amino terminal peptide (Orion Diagnostica, Espoo, Finland). The interassay and intra-assay variations for determining PIIINP are both about 5%. The sensitivity (lower detection limit) is 1.5 ng/mL.

**Statistical Analysis**
The distributions of PIP, PIIINP, and other clinical variables were described for the study groups: HFREF, HFPEF, control subjects (no HF), and CV-healthy participants. Because the distributions of biomarkers were skewed, results are presented as the median value (interquartile range); age is presented as mean±SD; categorical variables, such as sex, race, and so forth, are presented as percentages. Group comparisons were conducted using Kruskal-Wallis test, 1-way ANOVA, and χ² test, as appropriate; pairwise comparisons were performed with Bonferroni correction. Two-sided probability values are reported.

Six Cox proportional hazards regression models were performed: model 1 unadjusted; model 2 adjusted for age, sex, and race; model 3 adjusted for age, sex, race, hypertension, diabetes, hyperlipidemia; model 4 adjusted for demographics, risk factors, left atrium anteroposterior diameter, left atrium volume, transmitral E/A ratio, and LV mass; model 5 adjusted for demographics, risk factors, and serum glucose, creatinine, C-reactive protein, cystatin C, and NT-pro BNP; and model 6 adjusted for demographics, risk factors, and agents that interfere with collagen synthesis (ACE and aldosterone receptor inhibitors). The hazard ratios (95% confidence intervals) for the highest tertile versus the lowest tertile were reported. A value of P<0.05 by the 2-tailed test was considered statistically significant. All analyses were performed using version 9.1 of SAS (SAS Institute Inc, Cary, NC).

The study was approved by the institutional review committees of the participating medical centers.

**Results**

**Participant Characteristics**
The main demographic and medical history characteristics of the participants’ population are given in Table 1. Compared with the healthy control group, there were more white participants in the control and HF groups, in which there was a higher prevalence of risk factors for atherosclerosis and CV morbidity. Compared with the participants with HFPEF, the participants in the HFREF group had a higher prevalence of remote myocardial infarction (64% versus 38%, P<0.0001) with a similar prevalence of hypertension and diabetes. The median values and lower and upper quartiles of fibrosis biomarkers in the study groups are illustrated in Table 2. CITP and PIIINP serum levels were higher in the participants with HF compared with control groups (P<0.0001 for both biomarkers). When the serum fibrosis markers were compared by demographics and clinical characteristics (Table 3), PIP serum level was only related to sex (higher in women). In general, there was a weak correlation between fibrosis markers and age and only in the healthy control, control, and HFPEF groups for CITP (r=0.19, P=0.001; r=0.27, P=0.0001; and r=0.15, P=0.05, respectively), in HFPEF for

<table>
<thead>
<tr>
<th>Table 2. Median Values and Lower and Upper Quartiles of Fibrosis Biomarkers in the Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>PIP, μg/L</td>
</tr>
<tr>
<td>CITP, μg/L</td>
</tr>
<tr>
<td>PIIINP, ng/mL</td>
</tr>
</tbody>
</table>

HFPEF indicates heart failure (HF) with preserved ejection fraction (EF); HFREF, HF with reduced EF; PIP, carboxyl-terminal peptide of procollagen type I; CITP, carboxyl-terminal telopeptide of collagen type I; and PIIINP, amino-terminal peptide of procollagen type III. 

*P values for pairwise comparisons of CITP and PIIINP<0.0001 for all the groups with the exception of HF groups, in which comparisons were not significant (CITP=0.55 and PIIINP=0.24).
Table 3. Median Values and Lower and Upper Quartiles for Fibrosis Biomarkers in Relation to the Demographics and Prevalent Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PIP, μg/L</th>
<th>CITP, μg/L</th>
<th>PIIINP, μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n=426)</td>
<td>408 (343, 500)</td>
<td>4.7 (3.4, 6.4)</td>
<td>3.5 (2.6, 4.6)</td>
</tr>
<tr>
<td>Male (n=454)</td>
<td>386 (321, 462)</td>
<td>4.7 (3.4, 6.3)</td>
<td>4.0 (2.9, 5.4)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.003</td>
<td>NS</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (n=693)</td>
<td>397 (333, 478)</td>
<td>4.7 (3.3, 6.4)</td>
<td>3.6 (2.7, 5.0)</td>
</tr>
<tr>
<td>African American (n=181)</td>
<td>388 (324, 494)</td>
<td>4.8 (3.6, 6.2)</td>
<td>4.1 (3.0, 5.4)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>NS</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=412)</td>
<td>391 (325, 477)</td>
<td>5.0 (3.7, 6.9)</td>
<td>3.9 (2.9, 5.7)</td>
</tr>
<tr>
<td>No (n=467)</td>
<td>395 (333, 481)</td>
<td>4.3 (3.1, 5.9)</td>
<td>3.4 (2.2, 4.8)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=217)</td>
<td>381 (324, 476)</td>
<td>5.1 (3.7, 7.4)</td>
<td>4.0 (2.9, 5.8)</td>
</tr>
<tr>
<td>No (n=655)</td>
<td>399 (333, 479)</td>
<td>4.6 (3.2, 5.9)</td>
<td>3.6 (2.7, 5.0)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=114)</td>
<td>426 (332, 518)</td>
<td>5.9 (4.2, 7.3)</td>
<td>4.4 (3.2, 6.5)</td>
</tr>
<tr>
<td>No (n=713)</td>
<td>391 (328, 647)</td>
<td>4.5 (3.2, 6.1)</td>
<td>3.6 (2.7, 4.9)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=449)</td>
<td>391 (323, 471)</td>
<td>4.6 (3.3, 6.2)</td>
<td>3.6 (2.7, 4.8)</td>
</tr>
<tr>
<td>No (n=425)</td>
<td>396 (336, 487)</td>
<td>4.8 (3.4, 6.6)</td>
<td>3.8 (2.8, 5.3)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Stroke or TIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=154)</td>
<td>390 (324, 475)</td>
<td>4.7 (3.4, 6.2)</td>
<td>3.7 (2.7, 5.1)</td>
</tr>
<tr>
<td>No (n=686)</td>
<td>392 (332, 480)</td>
<td>4.6 (3.3, 6.3)</td>
<td>3.6 (2.7, 5.1)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=151)</td>
<td>407 (341, 477)</td>
<td>4.9 (3.5, 6.7)</td>
<td>4.0 (2.9, 6.5)</td>
</tr>
<tr>
<td>No (n=615)</td>
<td>391 (332, 481)</td>
<td>4.5 (3.3, 6.0)</td>
<td>3.5 (2.7, 4.8)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>0.03</td>
<td>0.003</td>
</tr>
</tbody>
</table>

PIP indicates carboxyl-terminal peptide of procollagen type I; CITP, carboxyl-terminal telopeptide of collagen type I; PIIINP, amino-terminal peptide of procollagen type III; and TIA, transient ischemic attack.

PIP (r=0.25, P=0.001), and in the control group for PIIINP (r=0.12, P=0.04). Overall, higher serum levels of CITP and PIIINP were found in those participants with CVD than in the healthy control group.

CV Morbidity, Incident HF, and Hospitalization for HF

During a mean follow-up of 12±4 years (range, 3–17 years), of the 880 participants, 151 had myocardial infarction, 128 new (incident) HF, 132 had strokes, and 31 had transient ischemic attacks. Of all the participants with HF, 259 had hospitalization for HF exacerbation (131 in HFPEF versus 128 in HFREF group, P=0.43). The highest events rate was in HFREF, followed by HFPEF, control subjects with risk factors, and healthy control subjects. Hazard ratios between the lowest and highest tertiles of the fibrosis markers for outcome events in the combined cohort are presented in Table 4. In models further adjusted for serum glucose, creatinine, cystatin C, C-reactive protein, and NT-proBNP, in addition to demographics and risk factors, CITP and PIIINP remained modestly associated with myocardial infarction (area under the curve [AUC]=0.58 for both) and PIIINP with hospitalization for HF (AUC=0.58). Finally, in models adjusted for demographics, risk factors, and agents that interfere with collagen synthesis (eg, ACE and aldosterone receptor inhibitors), CITP remained associated with myocardial infarction and HF (AUC=0.63 and 0.59, respectively) and PIIINP with myocardial infarction, HF, and hospitalization for HF (AUC=0.62, 0.58, and 0.78, respectively).

In the healthy control group, no associations were found between fibrosis markers and incident HF or myocardial infarction. In the control group, CITP was associated with incident HF in unadjusted, adjusted for demographics, and adjusted for demographics and risk factors models (hazard ratio [HR], 2.9; 95% confidence interval [CI], 1.7–4.8; HR, 2.3; 95% CI, 1.2–4.0; and HR, 2.3; 95% CI, 1.2–3.6) and PIIINP was associated in unadjusted models with incident HF (HR, 2.3; 95% CI, 1.2–3.6). In the participants with HFPEF, CITP was associated with hospitalization for HF in both demographic and demographic and risk factors adjusted models (HR, 2.0; 95% CI, 1.2–3.2, and HR, 2.3; 95% CI, 1.2–4.0, respectively). In the HFREF group, no significant associations were found in any model.

All-Cause and CV Death

At the end of the follow-up period, all-cause death was recorded in 564 and CV mortality in 242 participants. The highest mortality rate was recorded in the HFREF group (92.4% for all-cause and 59.2% for CV death) and the lowest in the healthy control group (all-cause and CV mortality, 53.4% and 14.5%, respectively).

Hazard ratios of the fibrosis markers for all-cause and CV death in the combined cohort are given in Table 4. In models adjusted for demographics, risk factors, ACE, and aldosterone receptor inhibitors, CITP was modestly associated with all cause-death and CV death (AUC=0.59 and 0.52, respectively), whereas PIIINP was associated only with all-cause death (AUC=0.59). Adjustments for the biochemical variables described above eliminated the association of CITP and PIIINP with death.

In per-group analyses, in the healthy control group, CITP and PIIINP were associated with all-cause death: CITP in unadjusted models (HR, 1.7; 95% CI, 1.2–2.6) and PIIINP in models 1–3 (unadjusted: HR, 2.0; 95% CI, 1.2–2.9; adjusted for demographics: HR, 1.7; 95% CI, 1.2–2.9, and adjusted for demographics and risk factors, the same HR). In the control group, CITP and PIIINP were associated only in unadjusted models with all-cause death (HR, 2.3; 95% CI, 1.2–4.0; and HR, 1.7; 95% CI, 1.2–2.6, respectively). In both HF groups, the fibrosis markers were not associated with death. Finally, the addition of parameters of LV diastolic function (left atrial size and transmural E/A ratio) and a potential substrate for its alteration (LV mass) to the demographic and risk factors.
variables denied the association of collagen turnover markers with both CV morbidity and mortality in every group.

**Discussion**

The principal finding of this study is that in community-dwelling elderly individuals, CITP and PIIINP were significantly associated with multiple adverse cardiac outcomes including myocardial infarction, HF, and death. Notably these findings included subgroups of participants who are CV healthy (ie, without prevalent CVD, hypertension, subclinical disease, or risk factors), as well as those without HF, but with subclinical disease and/or risk factors. Moreover, in participants with HFPEF, CITP is associated with increased hospitalization for HF. These results provide further support for the hypothesis that fibrosis is an important contributor to CVD and outcomes among the elderly and serum markers of collagen turnover are predictors of incident HF and of major CV adverse events, including CV and all-cause mortality.

Of the 3 biomarkers analyzed, PIP had the weakest association with the CV morbidity and mortality. Whereas in smaller series enrolling younger patients were reported associations of PIP with HF, other studies found a lack of association between PIP with prevalent HF, possibly because of predominance of type I collagen destruction over its synthesis, a shift from type I to type III collagen synthesis, or plateau of collagen type I synthesis in the elderly individuals. These findings strengthen our previous observation, which, in using similar Cox regression models, we found an association between CITP and PIIINP but not PIP, with prevalent HF.

The predictive value of serum fibrosis biomarkers for adverse events was previously reported in patients with acute myocardial infarction, arterial hypertension, and hypertrophic cardiomyopathy. A limited number of studies enrolling smaller and younger number of patients than in the present study have evaluated the prognostic value of these markers in patients with HF. Cicoira et al reported on 106 patients (age, 64 ± 6 years) with dilated cardiomyopathy that a higher serum level of PIIINP was associated with a restrictive mitral inflow pattern and 2-fold higher mortality than those with a nonrestrictive pattern. In RALES, which enrolled 261 elderly patients with EF < 35% in New York Heart Association classes III and IV, those with baseline PIIINP > 3.85 μg/L had a higher relative risk of death and/or HF hospitalization.

Recently, investigators from the Framingham study described the association of PIIINP and TIMP-1 with mortality and incident CVD in community-based participants. Another recent study reported the value of a large number of biomarkers panel for identification of LV hypertrophy and HFPEF including NT pro-BNP, PIIINP, and CITP, concluding that multibiomarker panels performed better than any single biomarker for this purpose.

The present study confirms the association of PIIINP with incident disease and mortality and extends those findings by additionally evaluating CITP and PIP. Moreover, our population differs in evaluating older subjects, not selected by echocardiographic criteria and who were stratified on the basis of CV health status, including subgroups that were CV healthy, had prevalent CVD without HF, as well as prevalent HFREF, and prevalent HFPEF. In addition, rather than using a single CVD end point, we evaluated separate CVD end points including CV mortality, myocardial infarction, incident HF, and hospitalization for HF.

Our findings support the hypothesis that myocardial fibrosis plays an important role in the development of CVD and its presence is associated with adverse outcomes. Significant efforts toward finding antifibrotic treatments are under way. Three large completed clinical studies using aldosterone antagonists also support the role of fibrosis in HF and the impact of these agents on decreasing collagen formation.

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**Table 4. Association of Fibrosis Biomarkers With Cardiovascular Morbidity, All-Cause Mortality, and Cardiovascular Mortality for the Entire Cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Myocardial infarction</th>
<th>HF§</th>
<th>Hospitalization for HF†</th>
<th>All-cause death</th>
<th>Cardiovascular death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)†</td>
<td>HR (95% CI)‡</td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)*</td>
</tr>
<tr>
<td>PIP</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–2.0)</td>
<td>2.0 (1.2–2.9)</td>
<td>2.0 (1.2–2.9)</td>
</tr>
<tr>
<td>PIP</td>
<td>1.0 (0.6–1.7)</td>
<td>1.2 (1.0–1.7)</td>
<td>1.0 (0.6–1.4)</td>
<td>2.6 (1.4–4.0)</td>
<td>4.4 (3.2–5.8)</td>
</tr>
<tr>
<td>PIP</td>
<td>1.2 (1.0–1.7)</td>
<td>1.2 (0.8–1.4)</td>
<td>1.2 (1.0–1.7)</td>
<td>2.9 (2.3–3.6)</td>
<td>2.6 (2.0–3.6)</td>
</tr>
<tr>
<td>PIP</td>
<td>1.2 (1.0–1.4)</td>
<td>1.0 (0.8–1.4)</td>
<td>1.0 (0.8–1.4)</td>
<td>2.0 (1.7–2.6)</td>
<td>2.0 (1.4–2.3)</td>
</tr>
<tr>
<td>PIP</td>
<td>1.2 (1.0–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.8–1.7)</td>
<td>2.0 (1.4–2.9)</td>
<td>2.0 (1.4–2.6)</td>
</tr>
</tbody>
</table>

*Unadjusted.
†Adjusted by age, sex, and race.
‡Adjusted by age, sex, race, hypertension, diabetes, and hyperlipidemia.
§Control and healthy control groups.
†Pertains only to the HF groups.

PIIP indicates carboxyl-terminal peptide of procollagen type I; CITP, carboxyl-terminal telopeptide of collagen type I; PIIINP, amino-terminal peptide of procollagen type III; HR, hazard ratio; CI, confidence interval; and HF, heart failure.

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which was translated in a better outcome,16,30,31 while an ongoing NHLBI sponsored trial addresses the RAAS inhibition on the outcome of patients with HFPEF: TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist).

Strength and Limitations

The main strengths of this study are the large cohort of well-characterized, community-dwelling population based on elderly age range subjects; the large number of prospectively assessed covariates available for entry in the statistical models; the formal adjudication and detailed information on events; the unusually long follow-up period with a low rate of loss; and the presence of a healthy comparison cohort. Despite the fact that the fibrosis markers investigated are not myocardial-specific, they have been used before as serum surrogates for the excessive collagen presence in the myocardial extracellular matrix.10,11 Moreover, participants with conditions known to elevate serum collagen markers (eg, liver disease, severe pulmonary disease, metabolic bone disease) were not enrolled in the study, and we previously showed failure of bone mineral density to affect the relationship of fibrosis markers to prevalent HF.14 Although this investigation was limited to evaluation of only 3 biomarkers of collagen metabolism, research is ongoing of many biomarkers that reflect multiple facets of the pathophysiology of HF, including inflammation, cell death and injury, interstitial repair, and diastolic load. It is likely that use of multiple biomarkers will prove particularly valuable for the prediction of incident HF and of the outcome of prevalent HF.29,32

Conclusions

Serum markers of collagen synthesis turnover (PIIINP, CITP) are associated with CV morbidity, mortality, and all-cause mortality. Among the 3 biomarkers evaluated, only CITP and PIIINP are predictors of both incident CVD, hospitalization for HF exacerbation in those participants with HFPEF, and death. In the elderly, healthy or with CVD, increased serum level of biomarkers of collagen turnover suggest that fibrosis may be a key mechanism of new CVD and adverse outcomes. These results have specific therapeutic implications, some of which are being tested currently in clinical trials.

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Disclosures

None.

References

Myocardial fibrosis is associated with significant alteration of left ventricular function, which may lead to heart failure (HF). Serum markers of collagen turnover may reflect the presence myocardial fibrosis and have been associated with prevalent HF. Their predictive value for incident HF and cardiovascular morbidity and mortality in the elderly is less known. We measured serum levels of carboxyl-terminal peptide of procollagen type I (PIP), carboxyl-terminal telopeptide of collagen type I (CITP), and amino-terminal peptide of procollagen type III (PIIINP) in 4 groups of participants in the Cardiovascular Health Study: HF with reduced ejection fraction (n = 146), ejection fraction < 55%; HF with preserved EF (n = 175, ejection fraction ≥ 55%), control subjects with cardiovascular risk factors but not HF (cardiovascular disease; n = 280); and healthy control subjects free of cardiovascular disease (n = 279). For the entire cohort, only CITP and PIIINP were associated with incident HF, hospitalization for HF, cardiovascular morbidity, and death in unadjusted and fully adjusted models for potential confounding variables that included medications that interfere with collagen metabolism. The individual group analysis revealed different association strengths between fibrosis markers and outcome variables. Importantly, in healthy individuals, CITP and PIIINP were associated with all-cause death, and no collagen biomarker was associated with outcomes in participants with HF with reduced ejection fraction. In the elderly healthy or in elderly patients with cardiovascular disease, the association of biomarkers of collagen turnover with adverse outcomes suggest that fibrosis may be a key mediator of incident cardiovascular disease and disease progression. CITP and PIIINP may be useful for risk stratification of elderly individuals.
The Relationship Between Serum Markers of Collagen Turnover and Cardiovascular Outcome in the Elderly: The Cardiovascular Health Study
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