Osteoprotegerin Predicts Progression of Chronic Heart Failure: Results From CORONA

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**Background**—Osteoprotegerin (OPG) may be implicated in the pathogenesis of heart failure (HF), and circulating levels predict survival in patients with postinfarction HF. Our primary goal was to determine whether OPG provided independent prognostic information in patients with chronic HF, and to examine its potential interactions with statin therapy.

**Methods and Results**—OPG as a risk factor for the primary end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; n=318), all-cause mortality (n=329), and all-cause mortality/hospitalization for worsening of heart failure (WHF; n=475) was investigated in 1464 patients (≥60 years, New York Heart Association class II to IV, ischemic systolic HF, optimal pharmacological therapy) in the Controlled Rosuvastatin Multinational Trial in HF (CORONA) population, randomly assigned to 10 mg rosuvastatin or placebo. In multivariate analyses, OPG (continuous variable) added no significant predictive information for risk estimation of the primary end point (adjusting for left ventricular ejection fraction, New York Heart Association class, age, body mass index, diabetes, sex, intermittent claudication, heart rate, serum creatinine, apoA1, and N-terminal pro-B-type natriuretic peptide). However, OPG added independent predictive information for WHF hospitalization (hazard ratio [HR] 1.10 [1.04 to 1.16], P<0.001) and all-cause mortality/WHF hospitalization (HR 1.06 [1.01 to 1.11]). The HR indicated a reduced risk for all-cause mortality in the rosuvastatin group in those with lowest OPG values (tertile 1, HR=0.66 unadjusted [P=0.025]; HR=0.71 Cox adjusted [P=0.025]; interaction by treatment effect for the tertiles P=0.086).

**Conclusions**—OPG added no predictive information for the primary end point, but independently predicted WHF hospitalization in older patients with advanced chronic systolic HF of ischemic etiology.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00206310. (Circ Heart Fail. 2011;4:145-152.)

Key Words: heart failure ■ risk prediction ■ osteoprotegerin

Numerous reports confirm the involvement of tumor necrosis factor (TNF) α in the pathogenesis of heart failure (HF).1,2 Recently, a role for other ligands in the TNF superfamily in chronic HF have been suggested.1 Several pathways are activated by ligand/receptor interactions in the TNF superfamily, and of particular importance is the activation of the transcriptional factor nuclear factor (NF)-κB. This signaling pathway is activated in the failing human myocardium, leading to transcription of genes involved in apoptosis, cell survival, proliferation, inflammation, and hypertrophic responses within cardiomyocytes and myocardial fibroblasts.3

**Clinical Perspective on p 152**

We recently demonstrated that interactions between osteoprotegerin (OPG), a member of the TNF receptor superfamily, and the receptor activator of NFκB ligand (RANKL), and its cognate receptor RANK may be implicated in the pathogenesis of HF through different mechanisms such as promotion of matrix degradation and inflammation.4 A role for the OPG/RANK/RANKL axis has also been demonstrated in a range of other cardiovascular (CV) disorders, including diabetic macroangiography, aortic aneurysm, cardiac valvular disease, and different manifestations of atherosclerosis.5,6 Importantly, this spectrum of CV disorders displays increased circulating levels of OPG, commonly associated with disease severity as shown in both cross-sectional and longitudinal studies.

The significance of OPG for vascular biology also has gained epidemiological support, with a range of studies reporting associations between circulating OPG levels and incident CV disease.5 Moreover, several cohort studies in
selected patient groups at high vascular risk suggest that OPG can provide independent prognostic information on all-cause and CV mortality.5,7 Also, in a small-scale study with no adjustment for objective measures of left ventricular (LV) function, we showed that OPG levels are predictive of survival in patients with postmyocardial infarction (MI) HF.8 However, no studies have investigated the prognostic value of OPG in adverse events in patients with chronic HF.

The present study investigated the role of circulating OPG in predicting fatal and nonfatal outcomes in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) population, a contemporary cohort of older patients with chronic systolic HF receiving modern pharmacological therapy and randomly assigned to statin therapy (rosuvastatin) or placebo in a double-blind fashion.9,10 Our primary goal was to determine whether OPG provided independent prognostic information in population of patients with chronic HF. We also examined the interaction between statin therapy and OPG in these HF patients.

Methods

Patients

The design and principal findings of CORONA have been reported in detail.9,10 Patients ≥60 years with chronic HF of ischemic cause, in New York Heart Association (NYHA) class II to IV and with an LV ejection fraction (LV-EF) ≤40% (≤35% if NYHA II), were eligible, provided the investigator thought they did not need treatment with a cholesterol-lowering drug. Criteria for exclusion included recent CV events; current or planned procedures or operations; acute or chronic liver disease or alanine aminotransferase >2.5 times the upper limit of normal; serum creatinine ≥2.5 mg/dL; thyroid-stimulating hormone ≥2 upper limit of normal; any condition substantially reducing life expectancy.

Study Procedures

The trial was approved by the Ethics Committees of the participating hospitals and patients provided written informed consent. Patients were allocated, equally, to 10 mg of rosuvastatin or matching placebo, once daily. The first patient was randomly assigned on September 15, 2003. The present study was a substudy of the main CORONA trial comprising 1464 consecutively included patients designed to analyze plasma/serum levels of cytokines and other inflammatory mediators/markers. There were no significant differences in baseline characteristics between those included in this substudy and all randomly assigned in CORONA.

Study Outcomes and Definitions

The primary predefined outcome was the composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke, analyzed as time to the first event. The secondary predefined outcome was all-cause mortality, any coronary event (defined as sudden death, fatal or nonfatal MI, percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG], ventricular defibrillation by an implantable cardioverter-defibrillator [ICD], resuscitation from cardiac arrest, or hospitalization for unstable angina), cardiovascular mortality (cause-specific cardiovascular death was also analyzed), and number of hospitalizations (for cardiovascular causes, unstable angina, and worsening heart failure [WHF]). Before analyzing OPG levels, we also included 1 additional post hoc composite outcome: death resulting from any cause or hospitalization for WHF, which is commonly reported in HF trials. The definition and adjudication of all outcomes have been described in detail previously as have data on C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP).9–12

Blood Sampling and Biochemical Analyses

With the exception of OPG, all blood samples were nonfasting and analyzed on fresh samples at a central laboratory (Medical Research Laboratories [MRL], Zaventem, Belgium). NT-proBNP was analyzed using commercially available assay (Roche Diagnostics, Basel, Switzerland). An immunonephelometric method was used to measure C-reactive protein (Dade Behring, Atterbury, UK; sensitivity, 0.04 mg/L). Plasma OPG was measured by enzyme immunoassay (R&D Systems, Stillwater, MN) as described.13

Statistical Analysis

We present baseline variables in all patients with OPG measured at baseline, and in these also for subgroups based on tertiles of baseline OPG values (Table 1). For continuous variables, differences in baseline variables between the patients in each OPG tertile were tested with the Student t test (for NT-proBNP with the Wilcoxon test), for categorical variables with the Fisher exact test. Numbers of hospital admissions (episodes) were analyzed using a permutation test.

In multivariate analyses, besides OPG as a continuous variable, demographic and clinical variables LV-EF, NYHA class, body mass index (BMI), diabetes mellitus (DM), sex, intermittent claudication, and heart rate, being the 7 most important variables; for details, see reference,10 and 2 biochemical measures (creatinine and apoA1) were included in step 1. We did not include age because it was strongly interrelated with OPG. Importantly, when comparing the impact of age versus OPG, OPG added more information for the end point all-cause mortality and hospitalization for WHF (higher Wald and significant, which age was not). In step 2, NT-proBNP was included. The importance of OPG as a risk factor for the primary end point, for all-cause mortality, coronary end point, hospitalization for WHF, and for the composite end point of all-cause mortality or hospitalization for WHF (time to first event) was investigated. The discrimination ability of the survival models was validated by calculating the c-index, and the impact of OPG on the models was determined by comparing the models with and without OPG using the −2 log likelihood test.14,15 In this study, all analyses were performed in all patients randomly assigned, as well as in the 2 randomization groups separately to investigate whether the outcome would be different in the rosuvastatin group compared with the placebo group. The adjusted Cox regression model investigating the treatment effect of rosuvastatin versus placebo within each tertile used the same 10 variables as in the multivariate analyses, with the exception that OPG was replaced by age and that a treatment group exception was added. A 2-sided probability value of <0.05 was considered to be significant, except for interaction terms, for which probability values <0.10 were accepted.

Results

Clinical characteristics according to OPG levels at baseline are shown in Table 1. Higher OPG levels were associated with older age, increasing NYHA class, lower LV-EF, lower BMI, lower diastolic blood pressure, higher heart rate, history of angina pectoris, previous CABG or PCI, DM, implanted pacemaker, ICD, lower total and low-density lipoprotein cholesterol, lower triglycerides, lower apolipoprotein A:apolipoprotein B-1 ratio, higher serum creatinine, lower estimated glomerulus filtration rate, higher NT-proBNP and C-reactive protein levels, current use of loop diuretics, β blockers, digitalis, antiarrhythmic therapy, and antiplatelet and/or anticoagulant therapy.

Association Between Baseline OPG Levels and Outcomes

The unadjusted associations between different outcomes and tertiles of OPG are shown in Table 1. Decreased all-cause, CV, and non-CV mortality was observed with increasing OPG levels. Also, the combined primary end point and
composite of all-cause mortality or HF hospitalization showed a similar trend. Kaplan-Meier estimates showing associations with the primary end point, all-cause mortality, HF hospitalization, and the combined end point of all-cause mortality and HF hospitalization are shown in the Figure. We have previously identified history of DM, LV-EF, body mass index, NYHA class, apoA1 concentration, history of intermittent claudication, sex, age, and heart rate as independent
predictors of mortality in this population. When entered as a continuous variable and adjusting for these factors in a multivariate model, OPG was an independent predictor of all-cause mortality. Breakdown of all-cause mortality showed that OPG was not associated with CV death (Table 2), although a modest effect was observed for death because of WHF (n=81, step 1 [see Table 2 for definition] HR 1.16 [1.06 to 1.28] P=0.002). No association between OPG and nonmyocardial CV death (ie, stroke) and sudden death was observed (data not shown). In contrast, OPG was a significant predictor for non-CV death (Table 2). Also, a strong association was found with HF hospitalization and the combined end point of this and all-cause mortality (Table 2). We have recently shown that NT-proBNP is by far the strongest predictor of the specified outcomes in these patients, with few variables adding to model fits. A marked increase across the tertiles of OPG was seen for NT-proBNP (Table 1). When adjusting for NT-proBNP in the existing multivariate model (step 2, Table 2), the predictive value for OPG was weakened, including its association with death because of WHF (data not shown), but remained significant for HF hospitalization, the combined end point of all-cause mortality or HF hospitalization and, in particular, for non-CV mortality (Table 2). The discrimination properties of the survival models above was validated by the c-index (Table 3). Comparing the models with and without OPG mirrored the results of the multivariate analyses showing a significant impact of OPG on HF hospitalization, the combined end point of all-cause mortality or HF hospitalization and non-CV mortality (Table 3).

**OPG Levels at Baseline and Changes in OPG and Lipids during Follow-Up**

Serum OPG levels were similar at baseline in the 2 treatment groups. During the course of the study, no modifying effect of placebo or rosuvastatin therapy was observed on OPG levels in all randomly assigned patients or in any of the OPG tertiles.
(Table 4). Notably, serum levels of OPG were markedly higher in nonsurvivors compared with survivors, not only at baseline, but also after 3 months, with the same pattern in the placebo and the rosuvastatin group (Table 4). When combining both treatment arms, a significant difference ($P=0.033$) in the change in OPG levels between survivors (mean change and 95% CI: $-0.02 [-0.10$ to $0.05]$ ng/mL) and nonsurvivors (0.13 [0.00 to 0.26]) was seen. In line with this, linear regression confirmed that mortality was associated with OPG at 3 months when adjusting for baseline OPG levels ($P=0.001$). For each tertile of OPG, rosuvastatin exerted a similar net percentage mean decrease versus placebo in low-density lipoprotein cholesterol from baseline to the 3-month follow-up visit (42%, 44%, and 44%, in low, middle, and upper tertiles, respectively). A similar percentage increase during follow-up, with no difference in change between OPG tertiles, was observed for high-density lipoprotein cholesterol (6.8%, 4.7%, and 4.6% with increasing tertiles).

**Association Between Rosuvastatin Treatment and Clinical Outcomes According to Baseline OPG**

When looking at event rates within the OPG tertiles, we observed that the primary end point and total mortality were significantly reduced by rosuvastatin in tertile 1 (Cox unadjusted HR 0.66 [0.44 to 0.98], $P=0.037$ and 0.64 [0.42 to 0.96], $P=0.025$, respectively), but not in tertile 2 or 3 (Table 5). However, the Cox-adjusted values were not significant for these associations. Nonetheless, when looking at the interaction by treatment comparing the 3 OPG tertiles, a significant association was observed for all-cause mortality ($P=0.086$). No significant effect compared with placebo was observed in any of the OPG tertiles with regard to total number of patients hospitalized or total number of hospitalizations (Table 6).

**Discussion**

The main finding of our study is that circulating OPG is predictive of hospitalization for HF in patients with advanced chronic systolic HF and ischemic heart disease independently of conventional risk markers. The predictive power was reduced, but remained significant, when NT-proBNP was included in the analysis. No significant beneficial effect of rosuvastatin was observed according to tertiles of OPG, although a trend toward a favorable outcome of statin treatment on all-cause mortality was noted for patients with OPG levels in the lower tertile.

Previously, elevated OPG levels have been found to predict all-cause and, in particular, CV mortality in patients with HF following acute MI, to predict HF hospitalization following...
acute coronary syndromes, and to correlate with higher LV end-systolic volume and lower LV-EF in the general population. Our findings in the CORONA cohort extend these previous findings by showing that circulating OPG is independently related to the incidence of HF hospitalizations in patients with chronic HF secondary to ischemic heart disease. After adjustment for clinical and demographic covariates, OPG was also a significant predictor of all-cause mortality (CV and non-CV death). However, in contrast to the effect of OPG on hospitalization because of WHF, that was significant (CV and non-CV death). Also, whereas the association with CV death was weak, OPG was the strongest predictor for non-CV death, even after adjustment for NT-proBNP. However, the event rate for non-CV death was modest, and it seems that the impact of OPG on the combined end point (total mortality and hospitalization because of WHF) is largely carried by WHF. Taken together, these data may suggest that OPG, at least in this population of older individuals, is associated with worsening of myocardial function, but not with progression of vascular disease.

The association between OPG levels and HF severity could have several nonmutually exclusive explanations. Recent

### Table 4. Baseline, 3-Month Follow-Up (Median and Interquartile Range in Brackets) and Median Change Values for OPG (ng/mL) During Follow-Up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>Rosuvastatin</th>
<th>Difference in Change (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>3.31 (2.87, 3.66)</td>
<td>3.37 (2.88, 3.84)</td>
<td>0.20</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>4.56 (4.28, 5.01)</td>
<td>4.50 (3.97, 5.20)</td>
<td>0.20</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>6.95 (6.06, 8.28)</td>
<td>6.69 (5.66, 8.07)</td>
<td>0.20</td>
</tr>
<tr>
<td>All patients</td>
<td>4.67 (3.65, 6.05)</td>
<td>3.54 (4.47, 6.00)</td>
<td>0.20</td>
</tr>
<tr>
<td>Survivors</td>
<td>4.45 (3.53, 5.76)</td>
<td>4.29 (3.46, 5.63)</td>
<td>0.20</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>5.10 (3.94, 6.78)</td>
<td>5.02 (3.85, 6.82)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### Table 5. Association Between Rosuvastatin Treatment and Clinical Outcomes According to Baseline OPG

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (Rate)*</th>
<th>Rosuvastatin (Rate)*</th>
<th>Hazard Ratio†</th>
<th>95% CI†</th>
<th>Subgroup P Value‡</th>
<th>Interaction P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>60 (10.3)</td>
<td>41 (6.7)</td>
<td>0.66 (0.71)</td>
<td>0.44–0.98 (0.48–1.07)</td>
<td>0.037 (0.099)</td>
<td>0.153</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>76 (10.3)</td>
<td>68 (11.8)</td>
<td>0.88 (0.89)</td>
<td>0.64–1.22 (0.64–1.24)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>79 (15.3)</td>
<td>87 (16.2)</td>
<td>1.07 (1.03)</td>
<td>0.79–1.45 (0.76–1.41)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>All randomly assigned</td>
<td>215 (12.9)</td>
<td>196 (11.4)</td>
<td>0.92 (0.92)</td>
<td>0.83–1.02 (0.83–1.02)</td>
<td>0.12 (0.10)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.086</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>58 (9.6)</td>
<td>38 (6.1)</td>
<td>0.64 (0.71)</td>
<td>0.42–0.96 (0.47–1.08)</td>
<td>0.025 (0.11)</td>
<td></td>
</tr>
<tr>
<td>Tertile 2</td>
<td>74 (12.6)</td>
<td>64 (10.7)</td>
<td>0.85 (0.85)</td>
<td>0.60–1.19 (0.60–1.19)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>90 (16.6)</td>
<td>100 (18.2)</td>
<td>1.10 (1.07)</td>
<td>0.83–1.47 (0.81–1.43)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>All randomly assigned</td>
<td>222 (12.8)</td>
<td>202 (11.4)</td>
<td>0.89 (0.90)</td>
<td>0.74–1.08 (0.74–1.09)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Coronary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.237</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>56 (9.8)</td>
<td>45 (7.5)</td>
<td>0.77 (0.80)</td>
<td>0.52–1.19 (0.54–1.19)</td>
<td>0.20 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Tertile 2</td>
<td>53 (9.6)</td>
<td>54 (9.6)</td>
<td>0.99 (1.02)</td>
<td>0.68–1.46 (0.69–1.50)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>53 (10.1)</td>
<td>65 (12.2)</td>
<td>1.23 (1.24)</td>
<td>0.86–1.77 (0.85–1.79)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>All randomly assigned</td>
<td>162 (9.8)</td>
<td>164 (9.7)</td>
<td>0.98 (1.01)</td>
<td>0.79–1.23 (0.811.25)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality or HF hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.507</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>84 (15.3)</td>
<td>66 (11.5)</td>
<td>0.76 (0.78)</td>
<td>0.55–1.05 (0.57–1.08)</td>
<td>0.096 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Tertile 2</td>
<td>103 (19.9)</td>
<td>96 (18.5)</td>
<td>0.93 (1.01)</td>
<td>0.71–1.23 (0.76–1.34)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td>124 (26.6)</td>
<td>123 (25.4)</td>
<td>0.96 (0.96)</td>
<td>0.75–1.23 (0.70–1.17)</td>
<td>&gt;0.2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>All randomly assigned</td>
<td>311 (20.3)</td>
<td>285 (18.1)</td>
<td>0.89 (0.89)</td>
<td>0.76–1.05 (0.76–1.05)</td>
<td>0.17 (0.17)</td>
<td></td>
</tr>
</tbody>
</table>

*Events per 100 patient years of follow-up.
†Cox unadjusted with Cox adjusted within brackets.
‡For unadjusted Cox, P value from log rank test, for adjusted from Cox within brackets.
§By treatment comparing the 3 OPG subgroups.
¶Cardiovascular death or nonfatal myocardial infarction or nonfatal stroke (time to first event).
studies suggest the CV system may be an important contributor to circulating OPG levels, and we have recently shown strong OPG immunostaining within the failing myocardium. Thus, the ability of OPG levels to predict development of HF may reflect the contribution of the myocardium itself to the circulating OPG pool. We have previously shown that activation of the OPG/RANKL/RANKL axis may promote matrix degradation, inflammation, and ventricular remodeling. Thus, circulating OPG as a stable and reliable indicator of the overall activity of this axis, as well as a more general marker of inflammation, could contribute to its prognostic impact. Whereas raised levels of NT-proBNP is the result of, rather than the cause of, worsening myocardial function, the activation of the OPG/RANKL axis may promote matrix degradation, inflammation, and ventricular remodeling. Thus, circulating OPG as a stable and reliable indicator of the overall activity of this axis, as well as a more general marker of inflammation, could contribute to its prognostic impact. Whereas raised levels of NT-proBNP is the result of, rather than the cause of, worsening myocardial function, the activation of the OPG/RANKL axis may promote matrix degradation, inflammation, and ventricular remodeling.

In conclusion, circulating OPG levels added no predictive information for the primary end point, was poorly associated with fatal and nonfatal CV events, but independently predicts WHF hospitalization in patients with advanced chronic systolic HF of ischemic etiology. Although the predictive value was reduced after adjustment for conventional risk markers and NT-proBNP, in particular, it remained significant, further supporting a role for the OPG/RANKL/RANKL axis in the pathogenesis of chronic myocardial failure.

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References


CLINICAL PERSPECTIVE

Raised levels of inflammatory cytokines are associated with disease progression and adverse outcomes in patients with chronic heart failure (HF). Thus, circulating inflammatory biomarkers may play a critical role in the diagnosis and management of these patients. We have recently implicated osteoprotegerin (OPG), a member of the tumor necrosis factor receptor superfamily, in the pathogenesis of HF through different mechanisms such as promotion of matrix degradation and inflammation. To determine the role of circulating OPG in predicting fatal and nonfatal outcomes in HF, we investigated plasma OPG in a large contemporary cohort of older patients with systolic HF, receiving modern pharmacological therapy, randomly assigned to statin therapy or placebo in a double-blind fashion. OPG added no clear significant predictive information for risk estimation of the primary end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, all-cause mortality), was poorly associated with fatal and nonfatal vascular outcomes, but independently predicted hospitalization because of worsening HF. Although the predictive value was reduced after adjustment for conventional risk markers and N-terminal pro-B-type natriuretic peptide, it still remained significant. Our data suggest that OPG could be a useful marker to predict the worsening of HF, and further support a role for the OPG and related molecules in the pathogenesis of chronic HF.
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