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Circulating Osteoprotegerin Levels and Long-Term Prognosis in Patients With Acute Coronary Syndromes

Torbjørn Omland, MD, PhD, MPH,*† Thor Ueland, PhD,‡ Anna M. Jansson, MD,§ Anita Persson, MSc,‖ Thomas Karlsson, MSc,¶ Camilla Smith, MD,‡ Johan Herlitz, MD, PhD,¶ Pål Aukrust, MD, PhD,‡ Marianne Hartford, MD, PhD,¶# Kenneth Caidahl, MD, PhD§‖

Lørenskog and Oslo, Norway; and Stockholm, Göteborg, and Mölndal, Sweden

Objectives This study was designed to assess the association between osteoprotegerin (OPG) levels on admission and long-term prognosis in patients with acute coronary syndromes (ACS).

Background Osteoprotegerin, a member of the tumor necrosis factor receptor superfamily, has pleiotropic effects on bone metabolism, endocrine function, and the immune system.

Methods Serum samples for OPG analysis were obtained within 24 h of admission in 897 ACS patients (median age 66 years, 71% men) and related to the incidence of death, heart failure (HF) hospitalizations, myocardial infarction (MI), and stroke.

Results A total of 261 patients died during a median follow-up of 89 months. The baseline OPG concentration was strongly associated with increased long-term mortality (hazard ratio [HR] for HR per 1 SD increase in logarithmically transformed OPG level 1.7 [range 1.5 to 1.9] $p < 0.0001$) and HF hospitalizations (HR 2.0 [range 1.6 to 2.5]; $p < 0.0001$) but weaker with recurrent MI (HR 1.3 [range 1.0 to 1.5]; $p = 0.02$) and not with stroke (HR 1.2 [range 0.9 to 1.6]; $p = 0.35$). After adjustment for conventional risk markers, including troponin I, C-reactive protein (CRP), B-type natriuretic peptide (BNP), and ejection fraction, the association remained significant for mortality (HR 1.4 [range 1.2 to 1.7]; $p < 0.0001$) and HF hospitalization (HR 1.6 [range 1.2 to 2.1]; $p = 0.0002$), but not recurrent MI. By comparison of the area under the receiver-operating characteristics curves, OPG performed similarly to BNP and ejection fraction and significantly better than CRP and troponin I as a predictor of death.

Conclusions Serum OPG is strongly predictive of long-term mortality and HF development in patients with ACS, independent of conventional risk markers. (J Am Coll Cardiol 2008;51:627–33) © 2008 by the American College of Cardiology Foundation

Acute coronary syndromes (ACS) encompass a range of clinical manifestations of the rupture or erosion of a coronary atherosclerotic plaque (1). Depending on whether the acute plaque rupture results in subtotal or transient or permanent total occlusion of the diseased vessel, as well as on the size and degree of collateral circulation to the jeopardized myocardium, the clinical presentation may vary from unstable angina pectoris to non–ST-segment elevation myocardial infarction (MI) or ST-segment elevation MI. The prognosis of patients with ACS varies widely, and a number of clinical, electrocardiographic, and biochemical markers have been shown to predict adverse short-term and long-term outcome. Although several classes of biomarkers, including markers of ischemia, inflammation, hemodynamic stress, accelerated atherosclerosis, and myocardial damage, have been associated with prognosis in acute coronary syndromes (2), cardiac-specific troponins are currently the only markers uniformly used for diagnosis and risk stratification (3).

An excessive inflammatory response to various forms of injurious stimuli to the arterial wall is characteristic for the process of atherosclerosis and plaque destabilization (4,5),

From the *Department of Medicine, Akershus University Hospital, Lørenskog, Norway; †Faculty of Medicine, University of Oslo, Oslo, Norway; ‡Research Institute for Internal Medicine, Rikshospitalet, Oslo, Norway; §Department of Molecular Medicine and Surgery, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; ‖Department of Clinical Physiology, Sahlgrenska University Hospital, Göteborg, Sweden; ¶Department of Cardiology, Sahlgrenska University Hospital, Göteborg, Sweden; and #AstraZeneca R&D, Mölndal, Sweden. This study was supported by the Swedish Research Council (14231), the Swedish Heart and Lung Foundation, the Västra Götaland Region, the Vardal Foundation, Göteborg University, and the Göteborg Medical Society. Drs. Aukrust and Ueland are listed as co-inventors on a pending patent application on the use of osteoprotegerin as a prognostic marker in cardiovascular disorders.

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Abbreviations and Acronyms

ACS = acute coronary syndromes
BNP = B-type natriuretic peptide
CI = confidence interval
CRP = C-reactive protein
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MI = myocardial infarction
OPG = osteoprotegerin
RANK = receptor activator of nuclear factor-κB
RANKL = receptor activator of nuclear factor-κB ligand

involving various inflammatory mediators including adhesion molecules, chemokines, and cytokines (5,6). Osteoprotegerin (OPG) is a soluble member of the tumor necrosis factor (TNF) receptor superfamily with pleiotropic effects on bone metabolism, endocrine function, and the immune system (7). Osteoprotegerin inhibits osteoclastogenesis by binding the receptor activator of nuclear factor-κB ligand (RANKL), acting as a decoy receptor to competitively inhibit RANKL interaction with its receptor, RANK (8). Recently, the OPG/RANKL/RANK axis has been implicated in various inflammatory responses and has also been linked to atherogenesis. Osteoprotegerin can be detected in atherosclerotic lesions (9,10), and in humans, elevated circulating OPG concentrations have been associated with aortic plaque (11), as well as with increased prevalence and severity of coronary artery disease (12–15), cerebrovascular disease (14), and peripheral vascular disease (16). Circulating OPG levels are increased both in patients with unstable angina (10) and ST-segment elevation MI (17). Limited prognostic data are currently available, but in a recent population-based study (14), elevated circulating OPG levels were predictive of future cardiovascular events. Moreover, in a small-scale study with no adjustment for objective measures of ventricular function, we have recently shown (18) that OPG levels are predictive of survival in patients with post-infarction heart failure (HF).

On the basis of this information, we hypothesized that OPG may be independently predictive of long-term prognosis across the spectrum of ACS. To test this hypothesis, we measured OPG in serum samples obtained from a large series of patients admitted to a Scandinavian teaching hospital with ACS. Because the presence of both systolic left ventricular dysfunction and clinical HF also are associated with activation of OPG (19,20), we were particularly interested in assessing the prognostic value of OPG after adjustment for left ventricular ejection fraction (LVEF) and after adjustment for the most widely used contemporary cardiovascular biomarkers: troponin I, C-reactive protein (CRP), and B-type natriuretic peptide (BNP).

Methods

Study design. Patients with ACS, defined as a diagnosis of unstable angina, non–ST-segment elevation MI, or ST-segment elevation MI, admitted to the coronary care unit of the Sahlgrenska University Hospital, Göteborg, Sweden, during the period November 30, 1996, to March 31, 2001, were eligible for inclusion in a prospective risk stratification program, PRACSIS (Prognosis and Risk in Acute Coronary Syndrome in Sweden) (21). During this period, a total of 1,753 patients were screened, out of whom 897 patients (51%) were included in the current study. The main exclusion criteria were age <18 or ≥80 years, non-CAD associated with an expected life expectancy <1 year, residence outside the city of Göteborg, unwillingness to participate or to provide blood samples, and prior admission resulting in inclusion in the study. The primary outcome measure was all-cause mortality from the time of inclusion in the study to December 31, 2006. Survival confirmation and date of death were obtained from the Swedish National Population Registry. Five patients, who emigrated from Sweden, were lost to follow-up and censored alive at the day of emigration. Secondary outcome measures were the incidence of acute MI (International Statistical Classification of Disease, Ninth Revision [ICD-9] code 410 or ICD-10 code I21 or I22), congestive HF (ICD-9 code 428 or ICD-10 code I50), and stroke (ICD-9 codes 431, 432, 433, or 436 or ICD-10 codes I61, I62, I63, or I64) from the time of inclusion in the study to January 2003, as obtained from the Swedish Hospital Discharge Registry. For quality control purposes, morbidity data from the Registry was checked against information in the patients' medical records by a cardiologist (M. H.) blinded to biomarker results. Because of a time lag in the publication of data from the Swedish Hospital Discharge Registry and the manual quality control, morbidity data are available only until January 2003. Patients were prospectively classified according to maximum Killip class on admission and during the index hospitalization. Electrocardiographic findings on admission were classified according to the presence or absence of ST-segment elevation and ST-segment depression. On the basis of hospital records and personal interviews, patients were classified as having or not having a history of MI, angina pectoris, chronic HF, diabetes mellitus, or arterial hypertension. The study protocol was approved by the Regional Ethics Committee before the initiation of the study. Informed consent was obtained from all participating patients.

Blood sampling procedures and echocardiography. Peripheral venous blood was obtained within 24 h of admission by direct venipuncture of an antecubital vein after the patients had been supine for >30 min. Blood samples for OPG determination were drawn into sterile serum tubes and centrifuged within 1 h. Blood samples for determination of troponin I, CRP, and BNP were drawn into pyrogen-free tubes with ethylenediaminetetra-acetic acid (EDTA) as anticoagulant, immediately immersed in ice water and centrifuged at 2,000 g for 10 min within 1 h. All plasma and serum samples were stored at −70 °C and thawed only once before analyses. Echocardiographic investigation was performed by an experienced investigator within 5 days of hospital admission as described previously (22).

Biochemical analysis. Serum OPG was quantified in duplicate by an enzyme immunoassay using commercially available matched antibodies (R&D Systems, Minneapolis, Minnesota). The intra- and interassay coefficients of variation were 3.6% and 10.6%, respectively. The coefficient of variation percentage was evaluated at the median concentration observed in normal subjects. The sensitivity, defined as the mean ± 3 SD of the 0 standard, was calculated to be 15 pg/ml (18). Creatine kinase (CK)-MB fraction in serum was measured on a modular platform (Roche Diagnostics, Mannheim, Germany). The BNP, CRP, and troponin I were measured using immunofluorescent assays calibrated with spiked plasma (Biosite Inc., San Diego, California). Each sample was tested in duplicate. Samples for CRP analyses were diluted (factor 1600) to get the concentration into the measurable range. The minimal detectable concentration upper range was 5 to 1,300 pg/ml for BNP, 0.05 to 30 μg/l for troponin I, and 0.3 to 100 mg/l for CRP. Creatinine and total cholesterol concentrations in serum were determined by routine laboratory methods. Glomerular filtration rate in ml/min was estimated using the Cockcroft-Gault formula (140 − age) × weight (kg)/serum creatinine [μmol/l]) multiplied by a constant of 1.23 in men and 1.04 in women.

Statistical analysis. Categorical variables are reported as proportions and continuous variables as median values with interquartile ranges (25th to 75th percentile) or mean ± SD. The association between OPG and baseline demographic variables and cardiovascular risk factors was tested by the Mann-Whitney U test (comparing subjects with and without a specific characteristic) and Spearman rank correlation statistics (for testing of the association between continuous variables and OPG). Accordingly, individual OPG values (not the median of each OPG quartile) were used for calculation of p values in Table 1.

To visualize the relationship between OPG quartiles and long-term prognosis, Kaplan-Meier plots were generated, and the log-rank test was used for the comparison of the resulting curves.

Cox proportional hazards regression analyses were used to calculate the crude and adjusted risk estimates associated with a 1-SD increase in logarithmically transformed OPG levels for the end points mortality from all causes and the first hospitalization due to MI, stroke, or HF, respectively. In the multivariable analyses, we adjusted for potential confounders deemed to be clinically relevant. Because of a skewed distribution of data, the following continuous variables were logarithmically transformed: OPG, CRP, troponin I, BNP, CK-MB, estimated glomerular filtration rate, and heart rate. With the exception of CK-MB and estimated glomerular filtration rate, logarithmic transformation resulted in reduced skewness of these variables. To assess any nonlinear association with outcome, we also examined the association between OPG quartiles and the specific end points. The multivariable models included the following covariates: age, gender, index diagnosis, smoking status, prior MI, diabetes, hypertension, congestive HF, Killip class (dichotomous, i.e., Killip class 1 vs. Killip class 2, 3, and 4), estimated glomerular filtration rate, heart rate, peak CK-MB, troponin I, CRP, BNP, and LVEF. Hazard ratios (HR) are given with 95% confidence intervals.

The relative prognostic value of troponin I, CRP, BNP, or LVEF versus OPG was assessed by comparing areas under receiver-operating characteristics curves using the minimal common follow-up time of 69 months. All probability values are 2-tailed and were considered significant when <0.05. All statistical analyses were performed by using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Characteristics at baseline. The characteristics of patients at baseline according to OPG quartile are presented in Table 1. In total, 897 patients (median age 66 years, interquartile range 58 to 73, 71% men) had OPG values obtained within 24 h of admission. Examination of strata based on time from symptom onset to blood collection did not reveal any time-dependent differences in OPG concentrations (<12 h vs. 12 to 24 h vs. >24 h: 3,336 vs. 3,061 vs. 3,209 pg/ml; p = 0.79). Patients with higher OPG levels were more likely to be older; to have lower body mass index; to be non-smokers; and to have a medical history of congestive HF, diabetes mellitus, or hypertension. An index diagnosis of ST-segment elevation MI was associated with higher OPG levels, and, consequently, an index diagnosis of unstable angina was associated with lower OPG levels. Accordingly, higher OPG levels were associated with increased likelihood of ST-segment elevation and pathological Q waves on the electrocardiogram; increased concentrations of the biochemical markers of myocardial necrosis, such as troponin I and creatine kinase-MB fraction; and increased use of primary percutaneous coronary intervention and thrombolytic agents. Furthermore, patients with higher OPG levels were more likely to present with arterial hypotension or clinical signs of HF, to be users of diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and to have impaired left ventricular systolic function as assessed by echocardiography. Moreover, higher OPG levels were associated with increased levels of BNP and CRP and with decreased renal function, as expressed by estimated glomerular filtration rate. The correlations between OPG and other circulating biomarkers were modest, but highly significant (BNP: r = 0.34; CRP: r = 0.29; troponin I: r = 0.20).

Osteoprotegerin and long-term mortality. During a median follow-up of 89 months (interquartile range 75 to 105) months, 261 patients died. The concentration of OPG at baseline was closely associated with long-term all-cause mortality (Fig. 1). By univariable analysis, the HR associated with a 1-SD increase in logarithmically transformed OPG levels at baseline was 1.7 (95% confidence interval [CI] 1.5 to 1.9); $p < 0.0001$). When comparing the fourth

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Table 1 Characteristics at Baseline

	OPG ≤2,316 (n = 225)	OPG 2,317–3,171 (n = 224)	OPG 3,172–4,540 (n = 224)	OPG >4,540 (n = 224)	p Value*
Age (yrs)	59 ± 10	65 ± 9	67 ± 9	69 ± 8	<0.0001
Women (%)	25	29	30	33	0.05
Previous myocardial infarction (%)	23	22	20	21	0.71
Previous angina (%)	41	42	39	48	0.30
Previous chronic heart failure (%)	4	8	10	9	0.009
Previous diabetes (%)	13	12	21	22	0.003
Previous hypertension (%)	32	39	44	48	0.0006
Previous hypercholesterolemia (%)	32	33	27	23	0.01
Current smoker (%) (17 missing)	39	35	26	30	0.02
ST-segment elevation MI (%)	33	40	45	55	<0.0001
Non–ST-segment elevation MI (%)	36	35	37	31	0.34
Unstable angina (%)	31	25	18	14	<0.0001
ST-segment elevation on admission (%)	29	36	43	50	<0.0001
ST-segment depression on admission (%)	12	11	13	12	0.61
Q-wave on admission (%)	8	8	17	17	<0.0001
Systolic blood pressure <100 mm Hg (%)	2	2	2	6	0.03
Heart rate (beats/min)	74 (60, 86)	72 (60, 86)	70 (60, 85)	78 (62, 90)	0.12
Creatine kinase-MB max (μg/l)	43 (6, 129)	42 (7, 153)	77 (16, 226)	97 (22, 264)	<0.0001
Troponin I (μg/l)	2.39 (0.07, 9.90)	3.58 (0.22, 13.88)	5.96 (0.59, 22.16)	7.93 (0.91, 20.84)	<0.0001
B-type natriuretic peptide (pg/ml)	101 (52, 211)	196 (101, 332)	208 (104, 410)	278 (150, 552)	<0.0001
C-reactive protein (mg/l)	9.2 (4.3, 21.0)	12.2 (4.0, 27.0)	16.6 (6.8, 56.6)	26.0 (10.8, 69.9)	<0.0001
Glomerular filtration rate (μmol/l) (14 missing)	81 (64, 95)	64 (55, 80)	63 (51, 77)	57 (45, 68)	<0.0001
Body mass index (kg/m^2) (26 missing)	27 (24, 29)	26 (24, 28)	26 (23, 29)	25 (23, 28)	0.0002
Killip class II to IV on admission (%)	2	5	7	8	0.002
Max Killip class II to IV (%)	6	10	21	32	<0.0001
Thrombolysis/primary PCI (%)	27	33	33	44	0.0001
Other PCI or CABG during hosp. (%)	34	27	29	21	0.002
LVEF (%) (173 missing)	59 (51, 63)	55 (45, 62)	52 (44, 60)	50 (42, 59)	<0.0001
Beta-blocker (%)	28	37	35	32	0.40
ACEI/ARB (%)	11	16	14	19	0.02
Lipid-lowering drugs (%)	16	17	12	12	0.08
Aspirin (%)	29	33	30	30	0.99
Calcium channel blocker (%)	13	14	15	15	0.42
Diuretics (%)	8	11	14	15	0.005

Values given as percentage, mean ± SD, or median (25th, 75th percentile). *Actual osteoprotegerin value used in p value calculations.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OPG = osteoprotegerin (pg/ml); PCI = percutaneous coronary intervention.

versus first quartile of OPG concentrations, the HR was 4.2 (range 2.8 to 6.3), $p < 0.0001$. After adjustment for age, gender, index diagnosis, smoking status, prior MI, diabetes, hypertension, HF, Killip class, estimated glomerular filtration rate, heart rate, peak CK-MB, troponin I, CRP, and BNP, the HR was 1.4 (range 1.2 to 1.6); $p = 0.0003$ (Table 2). The relationship remained significant in patients in Killip class I (HR 1.3 [range 1.1 to 1.5]; $p = 0.002$) and regardless of index diagnosis (ST-elevation MI [n = 388]: HR 1.3 [range 1.0 to 1.6]; $p = 0.02$; non–ST-segment elevation ACS [n = 509]: HR 1.4 [range 1.1 to 1.7]; $p = 0.003$; unstable angina [n = 198]: HR 1.7 [range 1.2 to 2.4]; $p = 0.005$). Osteoprotegerin was a strong and independent prognostic indicator in the subgroup of patients in whom echocardiographically determined LVEF were available and adjusted for together with a number of clinical variables (n = 724; HR 1.4 [range 1.2 to 1.6], $p < 0.0001$).

Comparison of the overall prognostic merit of OPG versus troponin I, CRP, BNP, and LVEF as assessed by the area under the receiver-operating characteristics curve showed that OPG (area: 0.68 [95% CI 0.64 to 0.73]) provided significantly better prognostic information than troponin I (area 0.55 [95% CI 0.50 to 0.60] $p < 0.001$) and CRP (area 0.59 [95% CI 0.54 to 0.63], $p = 0.002$) and similar information as BNP (area 0.70 [95% CI 0.66 to 0.74]; $p = 0.28$) and LVEF (area 0.71 [95% CI 0.66 to 0.76]; $p = 0.09$). However, the addition of OPG only marginally, and not significantly, improved the overall predictive ability of a multivariable model consisting of the following variables: age, gender, index diagnosis, smoking

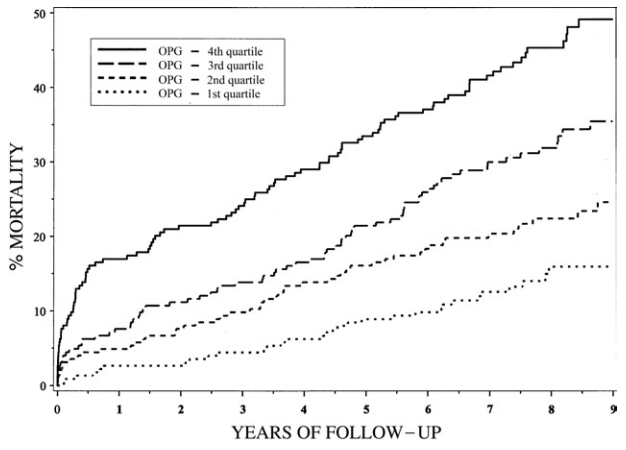

Figure 1 **Osteoprotegerin and Long-Term Mortality**

Association between osteoprotegerin levels by quartiles and long-term mortality.

status, prior MI, diabetes, hypertension, congestive HF, heart rate, Killip class (>I) on admission, estimated glomerular filtration rate, peak CK-MB, and troponin I (area without OPG 0.797 [95% CI 0.760 to 0.830] vs. area with OPG: 0.805 [95% CI 0.768 to 0.838]; p = 0.38).

Osteprotegerin and cardiovascular events. During follow-up, 107 patients were hospitalized with a main diagnosis of MI, 85 patients were hospitalized with a main diagnosis of HF, and 43 patients were hospitalized with a main diagnosis of stroke. By univariable analyses, the baseline OPG concentration was strongly associated with the incidence of HF hospitalizations (HR per 1-SD increase in logarithmically transformed OPG level 2.0 [range 1.6 to 2.5]; p < 0.0001) but weaker with the incidence of recurrent MI (HR 1.3 [range 1.0 to 1.5]; p = 0.02) and not with stroke (HR 1.2 [range 0.9 to 1.6]; p = 0.35).

The association between OPG quartiles and the incidence of HF hospitalizations is depicted in Figure 2. Using the first quartile as the reference, an OPG level in the fourth quartile was associated with a more than 7-fold increase in the risk of HF hospitalizations (HR 7.4 [95% CI 3.1 to 17.5]; p < 0.0001). After adjustment for conventional risk factors, OPG remained independently associated with the incidence of HF hospitalizations (HR per 1-SD increase in logarithmically transformed OPG level 1.6 [range 1.2 to 2.1]; p = 0.0002) but not to the incidence of recurrent MI (HR 1.0 [range 0.8 to 1.3]; p = 0.70) (Table 2). After further adjustment for LVEF, the association between OPG and the incidence of HF hospitalizations remained significant (HR 1.6 [range 1.2 to 2.1]; p = 0.001) (Table 2). Despite a low number of end points (HF: n = 19, recurrent MI: n = 20), the same pattern was evident in the subgroup of patients with unstable angina (HF: HR 2.4 [range 1.2 to 4.8]; p = 0.02; recurrent MI: HR 1.0 [range 0.5 to 1.7]; p = 0.92).

Discussion

The salient new information obtained from the current study is that serum levels of OPG are strongly related to long-term mortality and the incidence of HF hospitalizations across the spectrum of ACS. These associations were attenuated but still highly significant after adjustment for conventional risk factors as well as LVEF and multiple contemporary cardiovascular biomarkers (i.e., troponin I, CRP, and BNP) in multivariable analyses. In contrast to the strong association with the incident HF, secondary analyses showed that the association between OPG levels and MI, although significant by univariable analysis, was no longer significant after adjustment for potential confounders. These findings add important information to our knowledge of the prognostic value of OPG in patients with cardiac disease and are compatible with the theory that OPG levels

Table 2 **Associations Between Osteoprotegerin Concentrations and Events During Follow-Up in Acute Coronary Syndromes**

	Unadjusted		Adjusted*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Complete cohort (n = 897)				
Mortality	1.7 (1.5–1.9)	<0.0001	1.3 (1.1–1.5)	0.0003
Heart failure	2.0 (1.6–2.5)	<0.0001	1.6 (1.2–2.1)	0.0002
Recurrent MI	1.3 (1.0–1.5)	0.02	1.0 (0.8–1.3)	0.70
Stroke	1.2 (0.9–1.6)	0.35	0.9 (0.6–1.3)	0.61
Cohort with echocardiographically determined ejection fraction (n = 724)				
Mortality	1.7 (1.5–2.0)	<0.0001	1.4 (1.2–1.7)	<0.0001
Heart failure	1.9 (1.5–2.3)	<0.0001	1.6 (1.2–2.1)	<0.001
Recurrent MI	1.2 (1.0–1.5)	0.06	1.1 (0.8–1.4)	0.61
Stroke	1.1 (0.8–1.5)	0.55	0.8 (0.6–1.2)	0.36

*Adjusted for age, gender, index diagnosis, smoking status, prior myocardial infarction, diabetes, hypertension, congestive heart failure, heart rate, Killip class (>I) on admission, estimated glomerular filtration rate, peak creatine kinase-MB, troponin I, B-type natriuretic peptide, C-reactive protein, and ejection fraction.

HR = hazard ratio per 1-SD pg/ml increase in the natural logarithm of osteoprotegerin; MI = myocardial infarction.

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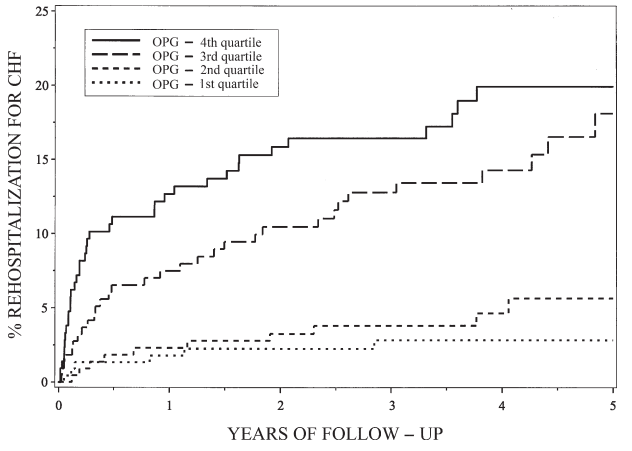

Figure 2 **Osteoprotegerin and Heart Failure Hospitalization**

Association between osteoprotegerin levels by quartiles and the incidence of heart failure hospitalizations.

do not exclusively reflect myocardial injury and subsequent left ventricular dysfunction in patients with ACS, but may be an independent pathophysiological factor of potential importance for the progression of HF.

As both atherosclerosis and myocardial failure are associated with increased OPG levels (10,18), both these factors may contribute to an association of OPG with outcome in patients with ACS. Demonstration of an independent association between OPG levels at baseline and the incidence of hospitalizations for HF strongly suggests that OPG's ability to predict mortality can be explained, at least partially, by its prediction of HF development. Recent studies suggest that the cardiovascular system may be an important contributor to circulating OPG levels. We have recently shown (20) strong OPG immunostaining within the failing myocardium, and it is possible that the ability of OPG levels to predict development of HF may reflect the contribution of the myocardium itself to the circulating OPG levels.

The OPG/RANKL/RANK axis is known to play a role in modulating immune function, including both innate and adaptive immune responses. Accordingly, these factors have been shown to enhance activation of T-cells and dendritic cells and to promote B-cell maturation and antibody responses (23) and have recently been found (10) to induce matrix degradation and inflammation in ACS. Moreover, we have previously shown that both experimental and clinical HF is associated with increased expression of the OPG/RANKL/RANK axis (20), and activation of this system seems not only to be a marker of development of HF, but also a mediator in this process, at least partly by promoting matrix degrading, inflammation, and ventricular remodeling (20). Because OPG circulates at much higher levels than RANKL, it may be a more stable overall measure of RANKL/RANK activity. The ability of OPG to reflect RANKL/RANK activity, a potential important mediator in left ventricular remodeling and a more general marker of inflammation, could contribute to its prognostic impact.

In our study, OPG performed better than the prototypical inflammatory biomarker CRP as a predictor of death. This observation, in combination with the strong association between OPG and HF, suggests that OPG should not be regarded exclusively as an unspecific marker of inflammation. On the basis of our previous findings of strong immunostaining for OPG in the failing heart (20), it is tempting to speculate that OPG reflects the degree of myocardial damage more directly than CRP.

Atherosclerosis is characterized by persistent inflammation in the vascular wall (24). Mineral deposition and arterial calcification are other common features of the atherosclerotic process, and endochondral bone formation has been suggested (25) as potential pathophysiological mechanisms of coronary calcification. Accordingly, several bone matrix-associated regulatory proteins, including OPG and RANKL, have been shown to be localized within human atherosclerotic plaques and at sites of arterial calcification (9,10). However, the lack of an independent association with acute atherosclerotic events (i.e., MI and stroke) does not favor the hypothesis that OPG plays an important role in the pathogenesis of plaque destabilization.

The potential therapeutic consequences of our findings are unclear. However, as OPG appears to predict HF development and not ischemic events, it is tempting to speculate that OPG can be used to target ACS patients who may receive particular benefit from interventions known to delay or prevent HF development, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Strengths and limitations. The prospective design, large sample size, long duration of follow-up, high number of most of the end points, and echocardiographic information concerning left ventricular systolic function in a considerable proportion of patients are all important strengths of the current single-center study. Limitations include the relatively high proportion of screened patients that were not included in the study and the modest number of stroke events. All-cause mortality was used as a main outcome measure in the current study. Data on cardiovascular mortality would have been preferable, as this would have ruled out the possibility that the relation between OPG and mortality could be partially ascribed to an unspecific association between inflammation and non-cardiovascular disease. Accordingly, future studies should address the association between OPG and cardiovascular mortality. The analytical performance and sensitivity of the troponin assay used in the current study are not optimal. Moreover, the use of single rather than serial measurements of troponin does not mirror clinical practice, and both these factors may tend to overstate the independent prognostic value of a new marker. In addition, the study does not provide an answer to the question whether OPG plays a pathophysiological role

or is merely a marker of severity of atherosclerosis and/or degree of ventricular dysfunction.

Conclusions

The current study documents that serum OPG levels are strongly predictive of long-term mortality and HF hospitalizations in patients with ACS independently of conventional risk markers. Notably, the prognostic information obtained from OPG in ACS appears to be of the same order of magnitude as obtained from determination of LVEF and BNP, currently considered to be 2 of the most powerful prognostic indicators in patients with ACS. To further elucidate the role that OPG plays in atherosclerosis, plaque destabilization and myocardial failure should be the objectives of future investigations.

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Reprint requests and correspondence: Dr. Kenneth Caidahl, Department of Clinical Physiology N2:01 & Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, SE-171 76 Stockholm, Sweden. E-mail: kenneth.caidahl@ki.se.

REFERENCES

1. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365–72.
2. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation 2006;113:2335–62.
3. Maisel AS, Bhalla V, Braunwald E. Cardiac biomarkers: a contemporary status report. Nat Clin Pract Cardiovasc Med. 2006;3:24–34.
4. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
5. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481–8.
6. Hartford M, Wiklund O, Mattsson Hulten L, et al. CRP, interleukin-6, secretory phospholipase A2 group IIA, and intercellular adhesion molecule-1 during the early phase of acute coronary syndromes and long-term follow-up. Int J Cardiol 2006;108:55–62.
7. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89:309–19.
8. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423:337–42.
9. Dhore CR, Cleutjens JP, Lutgens E, et al. Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 2001;21:1998–2003.
10. Sandberg WJ, Yndestad A, Oie E, et al. Enhanced T-cell expression of RANK ligand in acute coronary syndrome: possible role in plaque destabilization. Arterioscler Thromb Vasc Biol 2006;26:857–63.
11. Abedin M, Omland T, Ueland T, et al. Relation of osteoprotegerin to coronary calcium and aortic plaque (from the Dallas Heart Study). Am J Cardiol 2007;99:513–8.
12. Anand DV, Lahiri A, Lim E, Hopkins D, Corder R. The relationship between plasma osteoprotegerin levels and coronary artery calcification in uncomplicated type 2 diabetic subjects. J Am Coll Cardiol 2006; 47:1850–7.
13. Jono S, Ikari Y, Shioi A, et al. Serum osteoprotegerin levels are associated with the presence and severity of coronary artery disease. Circulation 2002;106:1192–4.
14. Kiechl S, Schett G, Wenning G, et al. Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. Circulation 2004;109:2175–80.
15. Schoppet M, Sattler AM, Schaefer JR, Herzum M, Maisch B, Hofbauer LC. Increased osteoprotegerin serum levels in men with coronary artery disease. J Clin Endocrinol Metab 2003;88:1024–8.
16. Ziegler S, Kudlacek S, Luger A, Minar E. Osteoprotegerin plasma concentrations correlate with severity of peripheral artery disease. Atherosclerosis 2005;182:175–80.
17. Crisafulli A, Micari A, Altavilla D, et al. Serum levels of osteoprotegerin and RANKL in patients with ST elevation acute myocardial infarction. Clin Sci (Lond) 2005;109:389–95.
18. Ueland T, Jemtland R, Godang K, et al. Prognostic value of osteoprotegerin in heart failure after acute myocardial infarction. J Am Coll Cardiol 2004;44:1970–6.
19. Omland T, Drazner MH, Ueland T, et al. Plasma osteoprotegerin levels in the general population: relation to indices of left ventricular structure and function. Hypertension 2007;49:1392–8.
20. Ueland T, Yndestad A, Oie E, et al. Dysregulated osteoprotegerin/RANK ligand/RANK axis in clinical and experimental heart failure. Circulation 2005;111:2461–8.
21. Perers E, Caidahl K, Herlitz J, et al. Spectrum of acute coronary syndromes: history and clinical presentation in relation to sex and age. Cardiology 2004;102:67–76.
22. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 2002;106:2913–8.
23. Anderson DM, Maraskovsky E, Billingsley WL, et al. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. Nature 1997;390:175–9.
24. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–95.
25. Fitzpatrick LA, Turner RT, Ritman ER. Endochondral bone formation in the heart: a possible mechanism of coronary calcification. Endocrinology 2003;144:2214–9.