Biomarkers

Prognostic Value of Osteoprotegerin in Heart Failure After Acute Myocardial Infarction

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OBJECTIVES   We sought to determine the relationship between osteoprotegerin (OPG) and clinical outcomes in patients with heart failure (HF) after acute myocardial infarction (AMI).

BACKGROUND   Arterial calcification is a prominent feature of arterial atherosclerosis and is associated with the occurrence of AMI. Osteoprotegerin is a recently discovered member of the tumor necrosis superfamily that may link the skeletal with the vascular system.

METHODS   We assayed plasma OPG levels in 234 patients with AMI complicated with HF and their relation to adverse outcomes during follow-up in patients randomly assigned to angiotensin-converting enzyme inhibition or angiotensin II antagonism. Blood was sampled at baseline (median three days after AMI), one month, and at one and two years.

RESULTS   Elevated plasma levels of OPG at baseline were associated with adverse outcomes during a median of 27 months follow-up; OPG remained an independent prognostic indicator also after adjustment for other known predictors of mortality and cardiovascular events after AMI (e.g., creatinine clearance, N-terminal B-type natriuretic peptide, high-sensitivity C-reactive protein). In non-survivors, plasma OPG levels were persistently elevated during longitudinal testing, suggesting that OPG may be of value for monitoring patients at risk.

CONCLUSIONS   Osteoprotegerin is a novel marker for cardiovascular mortality and clinical events in patients with AMI complicated with HF. These findings are compatible with the hypothesis suggesting a possible association between mediators of bone homeostasis and cardiovascular disease. (J Am Coll Cardiol 2004;44:1970–6) © 2004 by the American College of Cardiology Foundation

Arterial calcification and mineral deposition are prominent features of atherosclerosis, and relationships between the extent of coronary artery calcification and the occurrence of acute myocardial infarction (AMI) (1) and death have been demonstrated (2). Furthermore, noncollagenous, bone

matrix-associated proteins such as osteocalcin, osteopontin, and osteonectin have been identified at sites of calcification (3–5), and endochondral bone formation in the coronary vasculature has been suggested as a possible mechanism of coronary calcification (6). Thus, there seem to be similarities between vascular and skeletal calcification suggesting a

regulatory role for osteogenic and calcitropic factors in the development of cardiovascular disease.

Osteoprotegerin (OPG) is a member of the tumor necrosis factor (TNF) receptor superfamily that can function as a soluble decoy receptor by binding receptor activator of nuclear factor-κB ligand (RANKL), thus competitively inhibiting interaction between RANKL and its receptor. These mediators have been identified as candidate factors for paracrine signaling in bone metabolism, but are also involved in immune responses by modulating T-cell function and antibody response (7). Furthermore, messenger ribonucleic acid and protein expression of OPG and RANKL have been detected in myocardial tissue and atherosclerotic plaques (3,5). Moreover, elevated OPG levels have been associated with the progression of vascular calcification in patients receiving long-term hemodialysis (8,9), with the presence and severity of coronary artery disease (10,11), with cardiovascular mortality in elderly women (12), and recently also as a risk factor of cardiovascular disease in the general population (13).

Patients with AMI frequently show evidence of heart failure (HF) with a high risk of morbidity and mortality. To further elucidate the potential role of OPG in cardiac disease, we prospectively investigated the prognostic value of circulating OPG levels in patients with AMI complicated with HF.

Abbreviations and Acronyms

AMI	=	acute myocardial infarction
HF	=	heart failure
hsCRP	=	high-sensitivity C-reactive protein
LVEF	=	left ventricular ejection fraction
N-BNP	=	N-terminal B-type natriuretic peptide
OPG	=	osteoprotegerin
OPTIMAAL	=	Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan
RANKL	=	receptor activator of nuclear factor-κB ligand
TNF	=	tumor necrosis factor

METHODS

Study population. The design and main results of the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) have previously been reported in detail (14). Briefly, 5,477 patients with AMI complicated with HF during the acute phase were randomly assigned and titrated to a target dose of losartan (50 mg every day) or captopril (50 mg three times a day) as tolerated. Median randomization time was three days, and patients were followed for a median 2.7 years for mortality and morbidity end points. Inclusion criteria confirmed AMI and left ventricular dysfunction (i.e., left ventricular ejection fraction [LVEF] <35% or a left ventricular end-diastolic dimension >65 mm) and/or HF during the acute phase as suggested by one or more of the following: treatment with diuretic or intravenous vasodilator therapy for HF, pulmonary rales, third heart sound, persistent sinus tachycardia (≥100 beats/min), or radiographic evidence of pulmonary congestion (14). The present study was a prospectively designed substudy of the main OPTIMAAL trial comprising 234 consecutively included patients performed at six centers designed to analyze plasma/serum levels of cytokines and other inflammatory mediators. There were no significant differences in baseline characteristics between the treatment groups. Except for a higher proportion of statin users and a lower incidence of re-infarctions, there were no differences in baseline characteristics between this substudy and the OPTIMAAL main trial. No hemodialysis patients were included in this study. For comparison, plasma OPG levels were also measured in 15 age- and gender-matched healthy controls.

Blood sampling. Blood samples were obtained at baseline and after one month, one year, and two years. Samples were drawn after an overnight fast into pyrogen-free vacuum blood collection tubes with EDTA (OPG and high-sensitivity C-reactive protein [hsCRP]) or EDTA and aprotinin (N-terminal B-type natriuretic peptide [N-BNP]). Tubes were immediately immersed in melting ice, centrifuged (1,000 *g* and 4°C for 15 min) within 15 min, and plasma was stored at −80°C in multiple aliquots until analyzed. Samples were thawed <3 times.
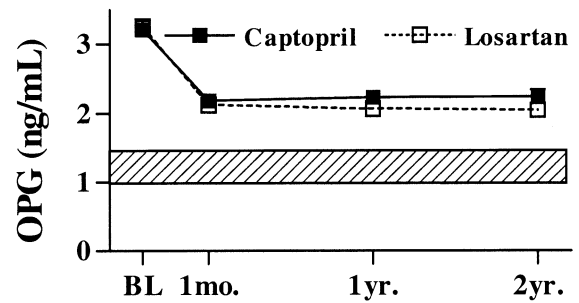

Figure 1. Plasma osteoprotegerin (OPG) levels during two years' follow-up in relation to randomization status. **Shaded area** represents 95% confidence interval for healthy age- and gender-matched controls. BL = baseline.

Biochemical analysis. Plasma OPG was quantified by an enzyme immunoassay using commercially available matched antibodies (R&D Systems, Minneapolis, Minnesota). The intra- and interassay coefficents of variation were 3.6% and 10.6%, respectively (15). The sensitivity, defined as the mean ± 3 SD of the zero standard, was calculated to be 15 pg/ml; N-BNP was analyzed as previously described (16). Plasma levels of hsCRP were measured by an immuno-nephelometric assay performed on the Behring nephelometer (BN II, Dade Behring, Liederbach, Germany).

Statistical methods. Kaplan-Meier survival curves were generated, and the log-rank test was used to compare survival rates in patients with high and low OPG levels. Differences in continuous variables were compared using Mann-Whitney U while the chi-square test was used for proportions. Associations between baseline risk factors, OPG concentrations (quartiles), and cardiovascular events were analyzed by univariate analysis a priori, and if $p < 0.2$, were subsequently included in a forced or forward conditional multivariate Cox regression. Cardiovascular events (end points) were: nonfatal myocardial infarction (n = 40), cardiovascular death (n = 26), total mortality death (n = 32), composite end point (all of the former plus stroke, n = 10) (n = 65). For investigating treatment effects, repeated-measures analysis of variance was performed a priori with time and treatment as fixed factors and subject as random; OPG was not normally distributed at baseline as evaluated by the Kolmogorov-Smirnov test, and, therefore, transformed before inclusion in the general linear model. Probability values are two-sided with $p < 0.05$ being considered statistically significant.

RESULTS

At baseline the study population had significantly raised plasma OPG levels compared with age- and gender-matched (not risk-factor-matched) healthy controls (Fig. 1), with a median of 3.0 ng/ml (interquartile range 2.1 to 4.1 ng/ml).

Plasma OPG during follow-up. During follow-up, plasma OPG levels decreased markedly after one month, and remained at this level during the rest of the sampling

Table 1. Baseline Characteristics According to OPG Levels

	Quartiles				
	OPG <2.1	**OPG <3.0**	**OPG <4.1**	**OPG >4.1**	**p Value**
Demographics					
n	56	56	57	56	
Age (yrs)	63 ± 8	67 ± 10	69 ± 10	72 ± 11	<0.001
Male (%)	70	71	74	66	0.841
BMI (kg/m^2)	27 ± 3	26 ± 4	25 ± 3	26 ± 3	0.119
Smoking (%)	41	52	33	32	0.040
History					
Hypertension (%)	35	40	26	43	0.235
Previous myocardial infarction (%)	10	13	11	15	0.869
Diabetes (%)	4	16	9	18	0.065
Medication					
Diuretics (%)	63	73	83	80	0.037
Beta-blocker (%)	89	80	70	61	0.003
Statins (%)	71	66	72	48	0.028
ASA (%)	96	98	98	93	0.369
Warfarin (%)	20	18	12	21	0.610
Anterior, lateral infarct location (%)	66	70	53	52	0.117
Killip class (II–IV) (%)	71	82	86	84	0.205
Creatinine clearance ≤85 ml/min (%)	11	36	36	52	<0.001
hsCRP (mg/l)	44 ± 45	56 ± 39	81 ± 77	98 ± 77	<0.001
N-BNP (pmol/l)	873 ± 570	1,309 ± 654	1,406 ± 584	1,801 ± 749	<0.001

Data are mean ± SD.

ASA = acetylsalicylic acid; BMI = body mass index; hsCRP = high-sensitivity C-reactive protein; N-BNP = N-terminal probrain natriuretic peptide; OPG = osteoprotegerin; Statins = hydroxymethylglutaryl coenzyme A reductase inhibitors.

period (i.e., 24 months), with no differences between angiotensin-converting enzyme inhibition and selective angiotensin II antagonism (Fig. 1). Moreover, although there was a decline in OPG, plasma levels were markedly increased compared with controls throughout the study period.

Association between OPG levels and baseline clinical and biochemical variables. When baseline OPG levels in the study population were divided into quartiles, we found that patients with high OPG levels were significantly older, had higher N-BNP and hsCRP levels, and a higher rate of diuretic and beta-blocker use at discharge (Table 1). Although patients with high OPG levels had a lower creatinine clearance, those patients with normal creatinine clearance had significantly increased OPG compared with controls. There were no significant differences in other baseline variables between the quartiles (Table 1). All the women in this study were post-menopausal, and 11 (16%) received hormone replacement therapy, with no differences in OPG levels between those receiving and not receiving hormone replacement therapy.

OPG levels at baseline and cardiovascular events. During follow-up 32 patients (14%) died. Kaplan-Meier survival curves according to OPG quartiles at baseline are presented in Figure 2 and show a higher mortality rate in those with high OPG levels (i.e., ≥4.1 ng/ml). Moreover, OPG levels were significantly lower in long-term survivors than in patients dying from all-cause mortality (2.8 vs. 4.2 ng/ml, p < 0.001) or cause-specific cardiovascular events (2.8 vs. 4.2 ng/ml, p < 0.001); OPG levels at baseline in patients experiencing recurrent, nonfatal AMI during

follow-up were not statistically different from those spared this end point (3.6 vs. 3.2 ng/ml, p = 0.128). Finally, we constructed a composite end point consisting of all-cause mortality, stroke, and nonfatal myocardial infarction and found that these patients also had significantly higher OPG levels than the rest of the study group (3.7 vs. 3.1 ng/ml, p = 0.003). The association between OPG levels at baseline and clinical events during follow-up is illustrated in Figure 3, showing the unadjusted risk estimates based on baseline OPG quartiles.
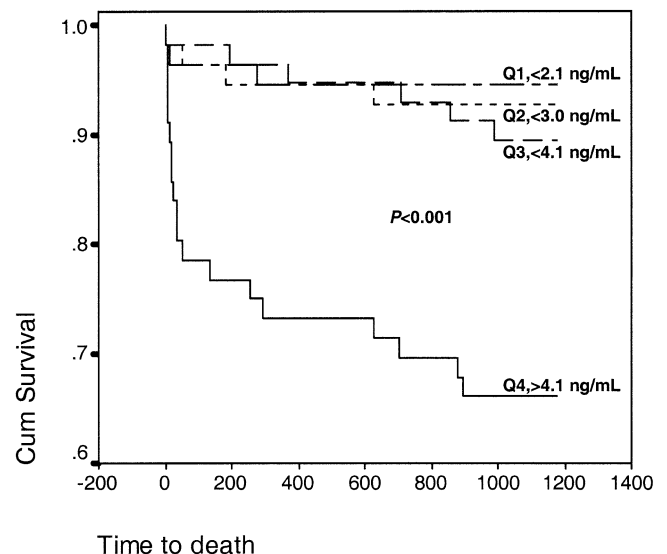

Figure 2. Kaplan-Meier curves showing the cumulative incidence of death during the entire study (median follow-up 27 months), according to the quartiles (Q) of plasma osteoprotegerin at enrollment.
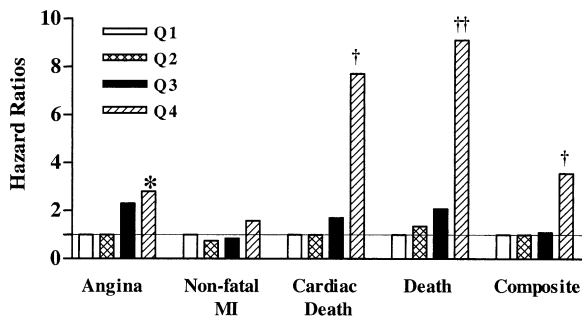
Figure 3. Unadjusted risk ratios for quartiles (Q) of osteoprotegerin at baseline in relation to incidence of angina, nonfatal myocardial infarction (MI), cardiac death, total mortality, or the composite end point (all-cause mortality, stroke, and nonfatal MI). *p < 0.05; †p < 0.01; ††p < 0.001 vs. Q1.

Other baseline predictors of cardiovascular events. The associations between potential confounder variables and all-cause mortality and cardiovascular events are summarized in Table 2. Several variables were univariate predictors of all-cause mortality and cardiovascular death, including age, diabetes, previous myocardial infarction, hypercholesterolemia, creatinine clearance, and N-BNP. In general, these variables were significant predictors of the composite end point as well. Still, for all these end points we included variables with associations p < 0.2 in a multivariate analysis. **Multivariate analysis.** In a multivariate model, adjusting for potential confounders (see the preceding text), plasma OPG levels were still associated with long-term, all-cause mortality, cardiovascular death, and the composite end point (Table 3). Similar results were obtained with both stepwise (Table 3) and forced addition of independent predictors as well as by entering all potential confounders, regardless of association with adverse events (all variables in Table 2). Thus, high plasma OPG levels measured during the acute phase after AMI remain an independent and strong determinant of all-cause mortality and cardiovascular death in this study population.

Plasma OPG and other parameters of HF. Because this is an HF population, we also compared the prognostic value of OPG with other prognostic markers in this patient population; LVEF was not routinely recorded in this substudy, but LVEF data (baseline) were available from 69 patients showing no relationships with cardiovascular or composite end points (data not shown) or plasma OPG (r = −0.169, p = 0.168). Although these findings suggest that OPG remains a significant predictor even if LVEF has been corrected for, caution is needed when interpreting these data because of a low number of LVEF observations. As for N-BNP, an important prognostic marker in HF patients, we found a significant correlation with OPG levels both at baseline (r = 0.51, p < 0.001) and at all time points during the study. However, OPG remained a significant predictor of death also when correcting for N-BNP (Table 3). Thus, it seems that plasma OPG may not only reflect the degree of HF, but may independently predict mortality in these subjects. Moreover, we found only a weak correlation between OPG levels and the degree of myocardial damage during AMI as assessed by creatinine kinase-MB (CK-MB) (n = 159, r = 0.141, p = 0.042), but not troponin T (n = 126, r = 0.044). Thus, although these markers of myocardial damage were not available in all patients; our data suggest that increased CK-MB/troponin T after AMI is not a major confounder in the present study.

OPG during longitudinal follow-up in relation to cardiovascular events. As described previously, plasma OPG levels decreased early (i.e., after one month) and remained at this level during the rest of the study period (Fig. 1). In fact, the intraindividual variation from one month to two years was 11 ± 8% (mean ± SD). When comparing OPG levels in survivors and non-survivors (all-cause mortality), we found that the latter group had persistently higher OPG levels at all time points during follow-up (Fig. 4). Furthermore, the prognostic value of plasma OPG measurements in relation to all-cause mortality and cardiovascular events

Table 2. Univariate Associations Between Baseline Variables and All-Cause Mortality, Cardiovascular Death, or the Composite End Point (All-Cause Mortality, Stroke, or Nonfatal MI)

	All-Cause Mortality		Cardiovascular Death		Composite End Point	
	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Age >67 yrs*	11.4 (3.3–33.5)	<0.001	8.2 (2.4–27.9)	<0.001	3.1 (1.7–5.8)	<0.001
Male gender	0.9 (0.4–2.1)	0.837	1.1 (0.4–2.6)	1.000	1.1 (0.6–2.2)	0.405
Hypertension	2.0 (0.9–4.3)	0.074	2.8 (1.2–6.3)	0.018	1.1 (0.6–2.0)	0.744
Previous myocardial infarction	3.7 (1.5–9.3)	0.007	3.6 (1.4–9.5)	0.011	3.3 (1.5–7.4)	0.003
Smoke	0.5 (0.2–1.1)	0.095	0.4 (0.2–1.0)	0.054	0.7 (0.4–1.3)	0.281
Diabetes mellitus	2.6 (1.0–6.7)	0.069	3.1 (1.2–8.3)	0.027	2.0 (0.9–4.5)	0.103
Anterior, lateral infarct location	0.7 (0.3–1.5)	0.438	0.7 (0.3–1.6)	0.537	1.0 (0.5–1.7)	0.869
Killip class (II–IV), %	1.3 (0.5–3.7)	0.808	1.1 (0.4–3.1)	1.000	1.2 (0.6–2.6)	0.605
Treatment (losartan or captopril)	1.1 (0.5–2.4)	0.849	1.0 (0.4–2.1)	1.000	0.8 (0.5–1.5)	0.498
Creatinine clearance ≤85 ml/min*	7.1 (3.0–17.0)	<0.001	6.7 (2.7–16.8)	<0.001	3.4 (1.9–6.2)	<0.001
N-BNP ≥1,246 pM*	2.1 (1.0–4.4)	0.060	2.2 (1.0–5.0)	0.048	1.4 (0.8–2.6)	0.226
hsCRP ≥50 mg/l*	0.7 (0.3–1.6)	0.432	0.7 (0.3–1.5)	0.305	1.3 (0.7–2.3)	0.450

*Dichotomized at median.
   CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; MI = myocardial infarction; N-BNP = N-terminal probrain natriuretic peptide; RR = risk ratio.

Table 3. Multivariate Models for All-Cause Mortality, Cardiac Death, and Composite End Point (All-Cause Mortality, Stroke, or Nonfatal MI) During Follow-Up (Average 27 Months)

End Point	Q1: OPG <2.1	Q2: OPG <3.0	Q3: OPG <4.1	Q4: OPG >4.1	p Value
		Hazard Ratio (95% CI) for Quartiles			
All-cause mortality					
Crude	1	1.4 (0.3–6.4)	2.1 (0.5–8.7)	9.1 (2.5–32.8)	<0.001
Age-adjusted	1	0.9 (0.2–4.3)	1.3 (0.3–5.2)	4.3 (1.2–14.7)	0.003
Multivariate	1	2.9 (0.3–24.9)	3.9 (0.5–32.5)	12.5 (1.7–94.6)	0.001
Cardiac death					
Crude	1	1.0 (0.2–5.2)	1.7 (0.4–7.5)	7.7 (2.1–28.1)	<0.001
Age-adjusted	1	0.7 (0.1–3.6)	1.1 (0.3–4.6)	3.8 (1.1–13.4)	0.005
Multivariate	1	2.1 (0.2–20.4)	3.3 (0.4–28.3)	11.2 (1.5–85.4)	0.002
Composite end point					
Crude	1	1.1 (0.4–2.5)	1.1 (0.4–2.7)	3.5 (1.5–8.2)	0.002
Age-adjusted	1	0.9 (0.4–2.2)	1.0 (0.4–2.2)	2.3 (1.1–4.8)	0.011
Multivariate	1	1.1 (0.5–2.8)	1.2 (0.5–3.0)	2.9 (1.3–6.2)	0.007

p value, test of trend.
  CI = confidence interval; MI = myocardial infarction; OPG = osteoprotegerin.

during follow-up increased at one month and one year after inclusion compared with baseline (Table 4).

DISCUSSION

The present study demonstrates that elevated plasma levels of the soluble decoy receptor OPG are associated with adverse prognosis in patients who develop HF in the acute phase after AMI. Furthermore, the predictive value of OPG at baseline provided risk prediction independent of creatinine clearance, N-BNP, hsCRP, and other known predictors of mortality and cardiovascular events after AMI. Of importance, OPG remained a significant predictor of cardiovascular death also when correcting for N-BNP, an important prognostic marker in HF patients. Finally, in non-survivors plasma OPG levels were not only increased in the acute phase of AMI, but also during follow-up, suggesting that OPG may be valuable for monitoring HF patients both immediately after AMI as well as during follow-up.

An increasing number of osteogenic factors have been detected in atherosclerotic plaques and received attention in relation to vascular biology (3–5). The OPG/receptor activator of NF-kappaB system plays an important role in bone

Figure 4. Plasma osteoprotegerin (OPG) levels during two-year follow-up in survivors and non-survivors. *p < 0.01; **p < 0.001 non-survivors versus survivors. Four non-survivors died after the last sampling (two year). **Shaded area** represents 95% confidence interval for healthy age- and gender-matched controls. BL = baseline.

metabolism, and, in the present study, we report a strong association between high plasma levels of OPG and increased mortality and occurrence of cardiovascular events in patients who develop HF after AMI, further supporting a role for mediators in bone metabolism in cardiovascular disease. These findings support a recent study showing that high-serum OPG was found to be an independent risk factor of progressive atherosclerosis and incident cardiovascular disease in the general community (13). We found significant associations between baseline levels of OPG and other risk factors for cardiovascular events such as age, creatinine clearance, and circulating levels of N-BNP and hsCRP. However, when adjusting for these variables in a multivariate analysis, OPG levels remained a significant predictor of fatal and nonfatal cardiovascular events. In fact, OPG at admission appeared to be a stronger predictor of adverse events than N-BNP and hsCRP, two markers of cardiovascular events that have received much attention recently (16).

Cross-sectional associations between circulating OPG and mortality have recently been shown in other populations (12,17). A major finding in the present study was that, in addition to being an excellent risk marker at baseline, OPG levels were persistently high in non-survivors. In fact, the association with subsequent cardiovascular events was even stronger during follow-up than at baseline, suggesting that OPG measurements may be used to monitor patients at risk and help identifying subgroups that may benefit from aggressive intervention.

We can only speculate as to the source and mechanism for the enhanced systemic OPG levels found in this study because OPG is produced in many tissues including the cardiovascular system, lung, kidney, intestine, bone, and circulating immune cells (7,18). Moreover, the present study was not designed to compare OPG levels after AMI in those with and without post-infarction HF, and we cannot make any firm conclusion concerning the relative contribution of ischemia and HF in itself to the raised OPG
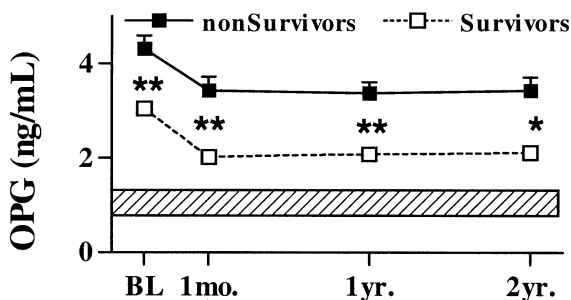
Table 4. Unadjusted Risk Ratios for All-Cause Mortality and Cardiovascular Events After Various Time Points in Relation to High (>4.1 ng/ml [4th Quartile]) and Low (≤4.1 ng/ml [Quartiles 1 to 3]) Osteoprotegerin Levels During Follow-Up

	One Month		One Year		Two Years	
	RR (95% CI)	p Value	RR (95% CI)	p value	RR (95% CI)	p Value
Angina	2.5 (0.6–10.9)	0.207	5.6 (1.2–26.2)	0.015	2.3 (0.4–13.0)	0.343
Nonfatal MI	17.9 (3.4–93.0)	<0.001	8.9 (1.9–42.5)	0.001	7.1 (1.3–37.4)	0.009
Cardiac death	22.4 (4.8–103.5)	<0.001	13.8 (2.1–88.7)	<0.001	1.0 (0.9–1.0)	0.736
Death	22.4 (4.8–103.5)	<0.001	9.7 (1.6–59.0)	0.014	1.0 (0.9–1.0)	0.696
Composite	11.8 (2.3–60.5)	<0.001	5.8 (1.2–27.2)	0.0139	4.7 (1.0–24.8)	0.044

CI = confidence interval; MI = myocardial infarction; RR = risk ratio.

levels in the present study population. However, although previous studies have reported high levels of OPG in patients with angina (10,11), we have recently found raised OPG levels in chronic HF with no differences between ischemic and idiopathic cardiomyopathy (T. Ueland, P. Aukrust, submitted for publication, 2004), suggesting that HF in itself is a potent stimuli for OPG release. Importantly, OPG expression has been demonstrated in different vascular cell types, and both coronary smooth muscle cells and endothelial cells have been implicated as cellular sources and targets of vascular OPG production (19,20).

Thus, the contribution by many recognized risk factors (e.g., diabetes) for mortality after uncomplicated AMI may be cushioned in the present study by the impact of HF on OPG; OPG has been shown to play a role in the regulation of the immune response and is regulated by the ligation of several cytokines involved in the inflammatory response after AMI. Thus, both CD40L, TNF-alpha, and interleukin-1-beta have been shown to enhance OPG expression in various cells (21,22), and these cytokines are persistently activated in the chronic phase during infarction healing (23–26). Moreover, in post-menopausal osteoporosis, human immunodeficiency virus infection, and Cushing's syndrome, high-serum OPG is suggested to reflect enhanced RANKL activity (15,27). Thus, although OPG may protect against harmful effects of RANKL and TRAIL, another ligand for OPG (28), the strong association between high OPG and cardiovascular mortality could indicate that plasma OPG level is a parameter of the overall activity in the OPG/RANK system as well as a stable marker of inflammation.

In the present study we found a rapid decline (i.e., within one month) in OPG levels, and the reason for this is at present unclear. However, several non-mutually exclusive mechanisms may exist. First, as mentioned above, OPG is a potentially stable and reliable marker of inflammation, and the early decrease in OPG may reflect attenuated inflammation during the one month after AMI. Second, we have recently detected high OPG expression in myocardial tissue from both human and experimental HF (see the preceding text), and, although we found only a weak correlation between OPG levels and the degree of myocardial damage during AMI, we cannot exclude that the high OPG levels at baseline, at least partly, reflect release from damaged myocardial tissue secondary to AMI. Finally, although the present study was not placebo controlled, we cannot rule out the effects of angiotensin II blockade on regulating serum OPG because angiotensin II has been shown to upregulate OPG expression in vascular smooth muscle cells (29).

In summary, plasma OPG levels provide impressive independent prognostic information in patients who develop HF after AMI, both in the acute phase as well as during follow-up, representing a noninvasive tool for monitoring morbidity of mortality in these patients. Future studies must determine if these results apply solely to post-infarction HF or if OPG can provide prognostic information for a wider group of AMI patients. Nonetheless, the identification of OPG as a novel cardiovascular risk marker suggests an association between mediators of bone homeostasis and cardiovascular disease and supports a link between bone and vascular calcification.

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