Osteoprotegerin Predicts Long-Term Outcome in Patients with ST-Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention

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Key Words

Inflammation • Myocardial infarction • Osteoprotegerin • Percutaneous coronary intervention • ST-segment elevation • STEMI

Abstract

Background: Osteoprotegerin (OPG) is a glycoprotein with a regulatory role in immune, skeletal and vascular systems. Data suggest that high circulating OPG levels are associated with an increased risk of cardiovascular disease. We analyzed the association between OPG and long-term outcome in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI). **Methods:** We included 716 consecutive STEMI patients admitted to a single high-volume invasive heart center from September 2006 to December 2008. Endpoints were all-cause mortality, repeat myocardial infarction, admission due to heart failure and combinations thereof. Median follow-up lasted 27 months (interquartile range: 22–33). **Results:** OPG levels exhibited a non-Gaussian distribution and were therefore divided into quartiles. High levels of OPG

were significantly associated with a worse outcome. After adjustment for conventional risk factors (e.g. C-reactive protein, estimated glomerular filtration rate, symptom-to-balloon time and troponin I) using Cox regression, OPG remained a significantly independent predictor of death (HR per increase in OPG quartile: 1.28; CI: 1.03–1.59; $p = 0.03$), repeat myocardial infarction (HR: 1.30; CI: 1.00–1.68; $p = 0.05$) and admission with heart failure (HR: 1.50; CI: 1.18–1.90; $p = 0.001$). **Conclusion:** This study shows that OPG independently predicts long-term outcome in STEMI patients treated with pPCI. Eventually, this knowledge could improve risk stratification and overall outcome.

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Introduction

Coronary artery disease (CAD) is the leading cause of death and coronary heart failure in industrialized countries and causes decreases in quality of life as well as increases in health care burdens. Numerous efforts have been made to improve the prognosis in these patients. It

is now well established that the most effective treatment strategy of acute myocardial infarction (MI) is immediate reperfusion by primary percutaneous coronary intervention (pPCI) or thrombolytic agents [1, 2]. Nevertheless, patients surviving an acute MI have a 10% risk of mortality and a 25% risk of cardiac failure within 1 year [3]. Therefore, efforts to improve risk stratification, clarify the pathophysiological mechanisms and identify targets for therapeutic interventions should be done. One challenge is to elucidate why otherwise comparable MI patients (e.g. similar age, diabetes status and treatment delay) end up with very different outcomes. Apparently, conventional risk factors are inadequate in predicting adverse outcome and consequently increasing attention is directed towards improving risk stratification. A number of biomarkers have been associated with ischemia, inflammation, atherosclerosis and myocardial damage [4–7]. However, currently only cardiac-specific troponins [troponin T (TnT) and troponin I (TnI)] and creatine-kinase MB (CK-MB) are being used for diagnosis and – to some extent – risk stratification in patients with acute coronary syndromes.

Growing evidence suggests that inflammatory pathways influence the course of CAD, both with regard to the development of mild CAD, but also to outcome in patients with established severe CAD due to plaque destabilization and susceptibility to ischemia-driven myocardial damage [8–11].

Osteoprotegerin (OPG) is a glycoprotein which serves as a soluble receptor for two members of the tumor necrosis factor receptor superfamily – nuclear factor κ B ligand (RANKL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [12]. OPG is found in many different tissues, including bones, arteries and plasma. Current knowledge indicates that OPG plays not only an important role in the development of skeletal disorders but also in the course of cardiovascular diseases due to its proinflammatory effects [13]. In the general population, high plasma levels of OPG have been found to increase the risk of coronary artery calcium and coronary events, impaired left ventricular function and cardiovascular death [14–17]. In patients with established severe ischemic disease such as acute coronary syndromes, elevated plasma OPG has also been associated with an increased risk of impaired outcome [18–20]. The negative effect of OPG is likely caused by an increased migration of lymphocytes and neutrophils to the intimal layer of the vessel wall, which in turn increases the risk of atherosclerosis [21]. Furthermore, high plasma OPG reduces the thickness of the fibrous cap surrounding the athero-

sclerotic plaque by up-regulation of matrix metalloproteinase 9. This may eventually lead to plaque rupture, thrombus formation and MI [22–25] (fig. 1). In addition, as increased plasma OPG induces a higher degree of inflammation [26], this could lead to an increased risk of ischemia/reperfusion injury and, consequently, ST-segment elevation MI (STEMI) patients with high OPG levels undergoing rapid reperfusion during pPCI face a potential increased risk of ischemia/reperfusion injury and thus myocardial damage [27]. These OPG-induced mechanisms may eventually translate into an increased risk of heart failure, MI and death.

The role of OPG as a prognostic biomarker in STEMI patients treated with pPCI is unclear, and improved risk stratification in this subset of patients could eventually lead to an improved overall outcome. Consequently, we analyzed OPG in the plasma of STEMI patients treated with pPCI and evaluated its potential prognostic value.

Methods

Study Population

Routine treatment with pPCI for STEMI was introduced and implemented in Denmark in 2002 following the presentation of the DANAMI-2 trial at the American College of Cardiology Meeting in 2002 [1]. The Gentofte University Hospital has a pPCI catchment population of 1.2 million citizens, i.e. >20% of the total Danish population, and is the invasive hub for 10 noninvasive centers, serving a predominantly urban population. On-site cardiac surgery is present and >1,500 PCI procedures are performed annually (approx. 500 as pPCI), with each individual PCI operator performing approximately 300 PCI and 100 pPCI per year (mean: 89 pPCI per year; median: 99 pPCI per year, range: 11–138 pPCI).

From September 2006 to December 2008, a total of 716 STEMI patients were admitted and treated with pPCI and plasma samples were analyzed for OPG. In the instance of >1 pPCI procedure within this period, the first procedure was defined as the index procedure. Inclusion criteria and definition of STEMI was: presence of chest pain for >30 min and <12 h and cumulative persistent ST-segment elevation ≥ 4 mm in at least 2 contiguous precordial ECG leads or ≥ 2 mm in at least 2 contiguous limb ECG leads [a limited number ($n = 10$) of patients were triaged to pPCI due to newly developed left bundle branch block]. Furthermore, a significant increase in TnI (>0.40 $\mu\text{g/l}$) was required for inclusion in the present study [TnI kit: the commercially available Siemens Healthcare, Diagnostics Immulite 2500, STAT-Troponin I (ref <0.40 $\mu\text{g/l}$)].

Baseline and Procedural Data

The baseline data were prospectively collected from all patients and entered in a dedicated registry. Hypertension was defined as use of blood pressure-lowering drugs on admission. Diabetes was defined as use of glucose-lowering drugs on admission, fasting plasma glucose concentration ≥ 7 mmol/l or non-fasting

Fig. 1. Increasing OPG levels leading to atherosclerosis. Increased expression of inflammatory cytokines close to the endothelial cells leads to up-regulation of OPG expression and endothelial cell adhesion molecules. The adhesion molecules facilitate entering of monocytes and leukocytes to the intimal layer of the vessel wall. The monocytes and leukocytes enhance the expression of

RANKL and the formation of vascular smooth muscle cells. RANKL and OPG promote the activity of matrix metalloproteinase, which results in the degradation of the extracellular matrix. This degradation leaves the fibrous cap thinner and more fragile, which can lead to thrombus formation and MI. MMP = Matrix metalloproteinase.

plasma glucose concentration ≥ 11.1 mmol/l. Multivessel disease was defined as 2- or 3-vessel disease and complex lesions such as type C lesions.

TnI levels were determined on admission, and 6 and 12 h after admission. Peak TnI was used in the statistical analyses divided into quartiles. C-reactive protein (CRP) and estimated glomerular filtration rate (eGFR) were also assessed on admission.

STEMI patients treated with pPCI at our institution are admitted from several primary hospitals, and post-PCI treatment is performed at these hospitals in ~50% of all cases. At our institution, echocardiography is performed during the initial 5-day period of admission, while other institutions have other protocols. In order to present a homogeneous estimate of left ventricular ejection fraction (LVEF), only patients with echocardiography performed within 5 days after STEMI were included in the echosubstudy. Echocardiography was performed using GE Vivid 7 and 9, 1–5 days after MI [median: 2, interquartile range (IQR): 1–3]. LVEF was ‘eyeballed by experts’ guided by wall motion index.

pPCI Procedure

Outside normal office hours, the catheterization laboratory staff was activated from their homes (<30 min away) by the cardiologist at the invasive center who had performed the triage for pPCI. During office hours, the crew was present at the catheterization laboratory. pPCI was performed according to contemporary interventional guidelines and 10,000 IU of unfractionated heparin, 300 mg acetyl salicylic acid and 600 mg clopidogrel were given preoperatively. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. The transfemoral approach was

used with 6- or 8-french sheaths, conventional devices and Iomeron contrast fluid (Bracco, Milan, Italy). Subsequent medical treatment included anti-ischemic, lipid-lowering and anti-thrombotic drugs according to current treatment guidelines. Importantly, at our institution, all STEMI patients treated with pPCI after January 2004 were discharged with a prescription of a 75-mg daily dose of clopidogrel for 12 months – regardless of the stent type implanted.

Measurement of Plasma OPG

Peripheral arterial blood was drawn from the femoral sheath at the beginning of the procedure, thus avoiding contamination with contrast fluid. Blood was allocated to different containers including 4-ml EDTA containers and was centrifuged at 10,000 rpm for 10 min within 0.5 h. Plasma was stored in NuncCryo tubes (Nunc, Roskilde, Denmark) at -80°C .

Plasma levels of OPG were quantified using commercially available monoclonal antibodies (DY085E; R&D Systems, Abingdon, UK) by a time-resolved immunofluorometric assay as previously described [1]. Briefly, wells were coated with 0.1 μg anti-OPG antibody. Recombinant OPG in the range from 4,000 to 31.25 ng/l was used as standard and EDTA plasma samples were diluted 4-fold in PBS with 1% BSA and incubated overnight at 4°C . Bound OPG was determined by incubation with 20 ng biotinylated anti-OPG detection antibody followed by addition of 10 ng Eu^{3+} -labelled streptavidin (Perkin Elmer, Life Sciences, Turku, Finland). Bound europium was detected by the addition of 200 μl of enhancement solution and reading the time-resolved fluorescence on a DELFIA fluorometer (Victor³; Perkin Elmer). The lim-

Table 1. Patients divided into quartiles (Q) according to OPG levels

Characteristics	1st Q 763–1,972 ng/l (n = 179)	2nd Q 1,973–2,837 ng/l (n = 179)	3rd Q 2,838–3,940 ng/l (n = 179)	4th Q 3,941–28,874 ng/l (n = 179)	p value
Mean age $\pm$ SD, years	58.6 $\pm$ 10.3	61.4 $\pm$ 10.8	66.1 $\pm$ 11.6	67.9 $\pm$ 13.2	<0.01
Males	84	77	72	63	<0.01
Hypertension	32	32	31	39	0.45
Diabetes	7	6	8	16	<0.01
Current smokers	51	58	50	43	0.06
Hypercholesterolemia	21	16	18	22	0.35
Previous MI	7	2	6	8	0.04
Known heart failure	2	2	2	4	0.17
Mean BMI $\pm$ SD	27.3 $\pm$ 4.0	27.2 $\pm$ 4.7	26.1 $\pm$ 4.5	26.2 $\pm$ 4.7	0.01
Peak TnI, μ g/l	89 (22–228)	100 (35–227)	110 (30–267)	89 (24–252)	0.63
CRP on admission, mg/l	3 (1–5)	3 (1–5)	4 (1–9)	6 (3–18)	<0.01
eGFR on admission	76 (64–89)	77 (62–92)	72 (58–85)	67 (50–78)	<0.01
Symptom-to-balloon time, min	180 (120–275)	200 (125–310)	195 (126–322)	225 (149–400)	0.02
LVEF, %	40 (30–50)	40 (30–50)	35 (25–50)	35 (30–45)	0.34
Multivessel disease	26	25	27	30	0.75
Lesion type					
Type A	11	17	8	13	0.31
Type B	34	37	36	37	
Type C	51	44	52	46	
Use of DES	72	74	68	69	0.66
GP IIb/IIIa inhibitors	34	24	24	22	0.06
Infarct-related artery					
LAD	51	39	47	50	0.48
RCA	37	50	42	49	
Cx	11	11	12	10	
LM	0	0.6	0.6	0.6	

Data are presented as percentages except where otherwise indicated. MI = Myocardial infarction; BMI = body mass index; TnI = troponin I; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection function; DES = drug-eluting stent; GP = glycoprotein. Figures in parentheses are median IQR.

it of detection was 15 ng/l. The intra- and interassay coefficients of variation were below 5 and 9%, respectively [28].

Follow-Up and Study Endpoints

Follow-up was 99.7% complete (2 patients were lost to follow-up due to emigration). The study endpoints were all-cause mortality, repeat MI and admission with clinical signs of heart failure (dyspnea, fatigue and edema/stasis) combined with a discharge diagnosis of heart failure. Mean follow-up time was 27 months (IQR: 22–33).

Follow-up data on mortality were collected from the National Person Identification Registry, which holds information on vital status (alive, death or emigration). Follow-up data on repeat MI and admission with heart failure were collected using hospital source data, as well as data from the highly validated Danish National Board of Health's National Patient Registry, using ICD-10 codes [29]. Repeat MI was defined as recurrent chest pain combined with significant increases in CK-MB ($>5 \mu\text{g/l}$), TnT ($>0.10 \mu\text{g/l}$) or TnI ($>0.4/0.03 \mu\text{g/l}$; kit dependent). Thus, both events with non-STEMI and STEMI were classified as repeat MI.

Statistics

OPG displayed a non-Gaussian distribution and patients were divided into quartiles. Proportions were compared using the χ^2 test, continuous Gaussian distributed variables with ANOVA and non-Gaussian distributed variables with the Kruskal-Wallis test. We tested associations between OPG and other baseline variables using univariate logistic or linear regression.

Hazard ratios (HR) were calculated by Cox proportional hazards regression analyses. The assumptions of linearity and proportional hazards in the models were assured. First-order interactions between the OPG variable and other baseline variables for endpoints were assessed in univariate models. In order to maintain a robust model, only 1 variable per 8 events were allowed in the multivariable Cox analyses of each endpoint. Variables with the lowest p value on univariate analysis were included until the maximum allowed number of variables was reached.

In the statistical tests, $p \leq 0.05$ was considered of statistical significance. SPSS for Windows (version 18.0; SPSS, Chicago, Ill., USA) was used.

Fig. 2. Unadjusted Kaplan-Meier plots for the combined endpoint of death, repeat MI (non-fatal myocardial re-infarction) and admission due to heart failure according to OPG quartiles (Q); log-rank test.

The study was approved by the local scientific ethical committee and the Danish Data Protection Agency, and complied with the Second Declaration of Helsinki.

Results

During a median follow-up time of 27 months (IQR: 22–33), 93 (13%) patients died, 51 (7%) had a repeat MI, 67 (9%) were admitted with heart failure and 186 (26%) reached the combined endpoint of death, repeat MI or admission with heart failure. Median OPG level was 2,935 ng/l (IQR: 1,973–3,940). High OPG levels were significantly associated with increased age, CRP, eGFR, diabetes, female gender and increased symptom-to-balloon time. No association between peak TnI and OPG was found (table 1).

Long-Term Follow-Up (Complete Cohort, n = 716)

No interactions between OPG and other baseline variables for endpoints were found. The log-rank test based on the Kaplan-Meier curves showed a significant association between high OPG and impaired outcome ($p < 0.001$;

fig. 2). This association was confirmed in univariate Cox analysis, where each increase in the OPG quartile led to a 65% increased risk of dying [HR: 1.65; 95% confidence interval (CI): 1.35–2.01; $p < 0.001$] and a 53% increased risk of reaching the combined endpoint (HR: 1.53; CI: 1.33–1.75; $p < 0.001$). Even after adjustment for conventional risk factors, OPG remained a significantly independent predictor of death, repeat MI, admission with heart failure and of the combined endpoint (fig. 3). The incremental prognostic value of OPG is displayed in figure 4, where χ^2 test values of different Cox models are displayed. When peak TnI levels were added to the multivariable Cox analysis (model 2), no significant increase in χ^2 test values was found ($p = 0.10$). However, when OPG was added, the χ^2 test value significantly increased ($p < 0.001$), thus confirming the incremental value of OPG (model 3).

Long-Term Follow-Up with Adjustment for LVEF (n = 450)

When the variable ‘LVEF <45%’ was included in the multivariable Cox analysis, OPG remained a significant predictor of the combined endpoint (HR: 1.34; CI: 1.11–1.61; $p < 0.001$; adjusted for: age, gender, LVEF <45%, diabetes mellitus, previous MI, known heart failure, peak TnI, CRP, eGFR, multivessel disease, complex lesions and symptom-to-balloon time). However, this association was not found in the analyses of the individual endpoints.

Discussion

In this study, we evaluated the independent impact of OPG on long-term clinical outcome in STEMI patients treated with pPCI in a real-life setting. After adjustment for conventional risk factors, OPG independently predicted death, repeat MI and admission with heart failure. In a subgroup where baseline LVEF >45% was included in the multivariable analyses, OPG still independently predicted impaired outcome.

This study confirms the association between high OPG plasma levels and impaired outcome found in previous studies. In a study by Omland et al. [19], 897 patients with acute coronary syndromes (approx. 1/3 with STEMI, 1/3 with non-STEMI and 1/3 with unstable angina), similar HR for death and heart failure were reported. In addition, OPG was also found to be a potential marker for cardiovascular mortality and clinical events in patients with MI complicated with heart failure. In a prospective study in 234 patients, high OPG levels at baseline were significant-

Fig. 3. HR plots based on multivariable Cox analyses. Median follow-up was 2.7 years. Values were adjusted for age, previous MI, complex lesion, CRP and eGFR (all values); diabetes, known heart failure, symptom-to-balloon time (all except for Repeat MI), and gender and peak TnI (Death and Combined), and multivessel disease, LAD lesion, current smoker, body mass index and use of glycoprotein IIb/IIIa inhibitor (Combined).

Fig. 4. Incremental value of OPG in predicting the combined endpoint: death, repeat MI or admission with heart failure. Model 1 includes age, gender, hypertension, diabetes mellitus, previous MI, known heart failure, peak TnI, symptom-to-balloon time, multivessel disease, complex lesion, glycoprotein IIb/IIIa inhibitor use, LAD lesion, body mass index and smoking. Model 2 includes Model 1 + peak TnI (divided into quartiles). Model 3 includes Model 1 + peak TnI and OPG.

ly associated with increased risk of cardiovascular death and all-cause mortality [18]. Recently, Andersen et al. [20] have demonstrated in 199 STEMI patients that OPG levels above the median were associated with a larger infarct size at 3 months measured by SPECT imaging.

The important information obtained from the present study is that OPG may have the potential to improve risk stratification and thus guide treatment/observation strategies in a large high-risk CAD population consisting entirely of STEMI patients treated with pPCI according to current guidelines. Only a minor proportion of our patients had a previous MI or known heart failure prior to their STEMI, and our main results were adjusted for a large number of potential confounders. These circumstances add to the importance of our findings, as they provide a very clear message regarding OPG as an independent predictor of impaired outcome.

Furthermore, this study confirms findings from previous studies showing that high levels of OPG are associated with increased age, diabetes and female gender [19, 30, 31]. If a clinical relevant cutoff point of OPG is to be implemented, these associations need to be taken into account, and studies of OPG in the general population – preferable using similar OPG-kits – would add valuable information.

Somewhat surprisingly, we could not find an association between OPG and peak TnI, and more interestingly no association between peak TnI and outcome was found. Even though troponin could be regarded as marker of

myocardial damage and thus heart failure and consequent mortality, studies of troponin as a prognostic marker have been conflicting. A number of studies have found a significant association between high troponin levels and impaired outcome [32–34]. However, other studies have clearly failed to demonstrate this association. In a study of 207 STEMI patients treated with pPCI, patients with high TnI levels had a 2% increased risk of heart failure at 1 year (HR: 1.02; CI: 1.00–1.03), but high TnI levels were unable to predict 1-year mortality or reinfarction [35]. In a similar but larger study (n = 1,237) of STEMI patients treated with pPCI, high TnT showed no association with 1-year mortality (p = 0.31) [36]. One obvious reason for this lack of association could relate to the time-dependent excretion of troponin during MI. In patients with long ‘symptom-to-balloon’ time (and thus expected poor outcome), peak troponin may not have been measured. Furthermore, in animal models it has been shown that rapid reperfusion (within 2 h) increases the amount of enzyme released from the myocytes to the plasma compared to delayed reperfusion [37]. If a similar effect is present in STEMI patients, it could partly explain the poor prognostic value of troponin.

In general practice, echocardiography is a valuable tool in risk stratification, and patients with LVEF <45% are usually treated with angiotensin-converting enzyme inhibitors and stratified to extensive follow-up in heart failure clinics. On the other hand, patients with a ‘low-risk’ profile are less likely to receive extensive treatment and close clinical control after STEMI. In our subgroup analyses where LVEF <45% was included in the multivariable analysis, OPG remained a significant independent predictor of the combined endpoint: death, repeat MI or admission with heart failure. This suggests that a risk stratification partly based on OPG levels may improve long-term outcome by optimizing clinical control, treatment and focus on patient compliance.

Study Limitations

Despite our efforts to reduce bias, the risk of unknown confounders exists in a non-randomized trial (residual confounding). We found a relatively low prevalence of diabetes, previous MI and known heart failure prior to STEMI. Validation of both baseline variables and endpoints was done in highly validated registries and in-hospital source data. However, the number of endpoints may have been slightly underestimated, although it is likely that this potential underestimation was equally distributed in all the OPG groups. The lower fraction of diabetes in our population could – to some extent – be explained by a lower background prevalence of diabetes in Den-

mark compared to the US for example. We used TnI (and in 2/3 LVEF) as surrogate markers for infarct size. It would have been preferable to have a more precise measurement such as magnetic resonance imaging. Care should be taken though, if the results are to be extrapolated to populations with very different distributions of potential risk factors and logistic facilities. Finally, our geographical and organizational conditions may not necessarily apply to other countries and regions, and our findings should not be extrapolated to settings without high-volume PCI centers.

Perspectives

In recent years, a large number of biomarkers have been examined in order to predict outcome and consequently improve patient care. Biomarkers have the obvious advantage of being relatively cheap and easy to obtain compared to more extensive and invasive diagnostic imaging procedures. Apart from providing a diagnostic tool, biomarker evaluation also provides valuable knowledge of pathophysiological mechanisms and potential targets for intervention.

Even though the association between cardiovascular disease and high OPG levels seems apparent, the cause of this association is still poorly understood and future studies need to further clarify the pathophysiological mechanisms – especially since some in vitro studies and animal studies have provided results conflicting with the findings from large human studies. If OPG is to be implemented as a prognostic biomarker, it is furthermore required that cutoff values are established. We believe that OPG is associated with CAD and that this biomarker eventually could be a valuable tool in the risk stratification of patients with different degrees of CAD.

Conclusions

After adjustment for conventional risk factors, OPG independently predicted death, repeat MI and admission with heart failure in STEMI patients treated with pPCI. In a subgroup where baseline LVEF was included in the multivariable analyses, OPG still independently predicted impaired outcome. Measurement of OPG may be useful in risk stratification and thus improve outcome in a high-risk STEMI population.

Conflict of Interest

None declared.

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