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Prognostic Utility of Neutrophil Gelatinase-Associated Lipocalin in Predicting Mortality and Cardiovascular Events in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

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Objectives The aim of this study was to investigate the prognostic role of neutrophil gelatinase–associated lipocalin (NGAL) in a large population of patients with ST-segment elevation myocardial infarction.

Background NGAL is a glycoprotein released by damaged renal tubular cells and is a sensitive maker of both clinical and subclinical acute kidney injury. New data have demonstrated that NGAL is also stored in granules of mature neutrophils, and recent data suggest that NGAL may also be involved in the development of atherosclerosis. NGAL is significantly increased in patients with myocardial infarction compared with patients with stable coronary artery disease and healthy subjects. However, the prognostic value of NGAL has never been studied in patients with myocardial infarction.

Methods We included 584 consecutive ST-segment elevation myocardial infarction patients admitted to the heart center of Gentofte University Hospital, Denmark, and treated with primary percutaneous coronary intervention, from September 2006 to December 2008. Blood samples were drawn immediately before primary percutaneous coronary intervention. Plasma NGAL levels were measured using a time-resolved immunofluorometric assay. The endpoints were all-cause mortality (n = 69) and the combined endpoints (n = 116) of major adverse cardiac events (MACE) defined as cardiovascular mortality and admission due to recurrent myocardial infarction or heart failure. The median follow-up time was 23 months (interquartile range, 20 to 24 months).

Results Patients with high NGAL (>75th percentile) had increased risk of all-cause mortality and MACE compared with patients with low NGAL (log-rank test, $p < 0.001$). After adjustment for confounding risk factors chosen by backward elimination by Cox regression analysis, high NGAL remained an independent predictor of all-cause mortality and MACE (hazard ratio: 2.00; 95% confidence interval: 1.16 to 3.44; $p = 0.01$ and hazard ratio: 1.51; 95% confidence interval: 1.00 to 2.30; $p = 0.05$, respectively).

Conclusions High plasma NGAL independently predicts all-cause mortality and MACE in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. (J Am Coll Cardiol 2012;60: 339–45) © 2012 by the American College of Cardiology Foundation

Neutrophil gelatinase–associated lipocalin (NGAL) is a glycoprotein stored in granules of mature neutrophils (1). Furthermore, it is released by renal tubular cells in response to inflammation, is an early and specific marker of tubular damage and acute kidney injury (AKI), and is related to poor outcome (2). However, it was recently demonstrated that NGAL is also expressed in endothelial

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

AKI = acute kidney injury

AMI = acute myocardial infarction

CAD = coronary artery disease

CRP = C-reactive protein

CV = cardiovascular

eGFR = estimated glomerular filtration rate

MACE = major adverse cardiovascular event(s)

NGAL = neutrophil gelatinase–associated lipocalin

PCI = percutaneous coronary intervention

pPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

cells, smooth muscle cells, and macrophages in atherosclerotic plaques (3) and that NGAL may be involved in the development of atherosclerosis via endothelial dysfunction, inflammatory processes, and matrix degradation (3–5), leading to atherosclerotic plaque instability by modulating the activity of metalloproteinase 9 (4). Plasma NGAL is significantly increased in the presence of coronary artery disease (CAD) and correlates with its severity (6); furthermore, plasma NGAL is significantly higher in patients with acute myocardial infarction (AMI) compared with stable CAD (7). This leads to the hypothesis that NGAL, a widely accepted renal marker, may be a prognostic marker in patients with AMI. We therefore investigated the prognostic utility of NGAL in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI).

Methods

Study population. From September 2006 through December 2008, we prospectively enrolled 584 STEMI patients treated with pPCI at Gentofte University Hospital, Copenhagen, Denmark. Inclusion criteria were patients admitted due to a suspected STEMI with the presence of chest pain for >30 min and <12 h, and persistent ST-segment elevation ≥2 mm in at least 2 contiguous precordial electrocardiography leads or ≥1 mm in at least 2 contiguous limb electrocardiography leads or a newly developed left bundle branch block. Exclusion criteria were a nonsignificant troponin I increase (≤0.5 μg/l), percutaneous coronary intervention (PCI) was not performed (no stenoses on coronary artery angiography or coronary artery bypass surgery was elected instead) or missing NGAL values. A total of 1,030 patients met the inclusion criteria. However, 446 patients were excluded due to exclusion criteria, thus ending up with 584 STEMI patients.

Gentofte University Hospital is a high-volume center at which >1,500 PCIs are performed yearly. A description of the PCI setting and procedure at Gentofte University Hospital was previously published (8). Subsequent medical treatment included aspirin 75 mg daily, clopidogrel 75 mg daily (for 12 months), lipid-lowering drugs (statins), and β-receptor antagonists.

Information on both height and weight was collected for all patients to calculate the body mass index and estimated glomerular filtration rate (eGFR). We defined hypertension as use of blood pressure–lowering drugs on admission. Patients were considered to have type 2 diabetes mellitus if they were being treated with glucose-lowering drugs at the time of admission or had a fasting plasma glucose concentration ≥7 mmol/l or a nonfasting plasma glucose concentration ≥11.1 mmol/l. Patients were considered to have hypercholesterolemia if they were being treated with cholesterol-lowering drugs at the time of admission. Multivessel disease was defined as 2- or 3-vessel-disease and complex lesions such as type C lesions. Severe hemodynamic stress was defined as the need for vasopressors or an intra-aortic balloon pump, and severe bradyarrhythmia or cardiac arrest treated with basic life support and/or defibrillation. Echocardiography was performed by specialists at our institution in 305 patients (52%) using Vivid 7 or E9 (GE Vingmed Ultrasound, Horten, Norway) 1 to 2 days after admission. The left ventricular ejection fraction was visually estimated by expert interpreters guided by strain analyses and wall motion index. The accuracy of this method was documented previously (9).

Endpoints were all-cause mortality and major adverse cardiovascular events (MACE) defined as cardiovascular (CV) mortality or admission due to recurrent AMI or heart failure.

Follow-up information with regard to the endpoints was obtained after 23 months (interquartile range, 20 to 24). Information was obtained for all 584 patients from the National Person Identification Registry, hospital sources, and data from the highly validated Danish National Board of Health's National Patient Registry (10). The study was approved by the local scientific ethical committee and The Danish Data Protection Agency and complied with the second revision of the Declaration of Helsinki.

Laboratory methods. Blood samples were drawn from the femoral sheath before the pPCI procedure (baseline values). Serum was centrifuged within 30 min and plasma stored at −80°C for subsequent analysis.

Plasma NGAL was determined using an in-house time-resolved immunofluorometric assay based on NGAL antibodies and recombinant NGAL from R&D Systems (Abingdon, United Kingdom) (11). Samples and controls were diluted 1:100 and analyzed in duplicate. Intra-assay coefficients of variation of standards, controls, unknown samples, and nonspecific background controls averaged <5%. Interassay coefficients of variation averaged <9% based on standards, nonspecific background controls, internal controls, and repeated samples. Plasma NGAL concentrations were determined using a 5-parameter standard curve fit implemented in the WorkOut 2.5 Data Analysis software (Perkin Elmer Inc., Waltham, Massachusetts). Mean values were calculated and used for statistical analyses.

Other blood tests including C-reactive protein (CRP), troponin I, and creatinine were assayed by routine laboratory methods. Troponin I was measured at baseline and after 6 and 12 h. Creatinine was measured at baseline. In patients remaining at our institution for post-PCI treatment (53%, n = 309),

creatinine was measured again on the second and third days and again if deemed necessary. eGFR was estimated on the basis of serum creatinine (at baseline), age, sex, and weight using the Cockcroft-Gault formula (12).

Statistical analysis. Plasma NGAL concentrations were positively skewed and therefore logarithmically transformed in the statistical analysis where appropriate. In Table 1, comparisons between groups were performed using the χ^2 test for dichotomous variables, the Student *t* test if Gaussian distributed, and Mann-Whitney *U* test if non-Gaussian distributed. Kaplan-Meier curves according to high versus low NGAL (cutoff at the 75th percentile) were constructed and compared by the log-rank test. The association of NGAL with endpoints was examined by Cox proportional hazards regression analyses both in univariate and multivariate models including selected variables identified using backward elimination. Variables were entered as listed in Table 1. To maintain a robust model, only 1 variable for each 10 events was allowed in the final models. Evaluation of first-order interactions was done after selecting the final model, and interactions were tested both in models containing 1 variable and NGAL and in a model containing all the selected variables. Deviation from linearity was assessed by simultaneous assessment of linear and quadratic effects. Misspecification of the functional form of the covariates and the assumption of proportional hazards were evaluated by plots of the cumulative martingale residuals. For the statistical analysis, p values ≤0.05 were considered of statistical significance. SPSS for Windows version 20.0 (SSPS Inc., Chicago, Illinois) and SAS software (SAS for Windows, version 9.2, SAS Institute Inc., Cary, North Carolina) were used.

Results

Distribution of NGAL and baseline characteristics. During follow-up (median, 23 months; interquartile range, 20 to 24 months), all-cause mortality was 12% (n = 69), including 7% (n = 38) from CV causes. Six percent of patients (n = 36) were admitted to the hospital with a new AMI and 9% (n = 55) due to heart failure. Nineteen percent (n = 116) reached the combined endpoint of MACE.

The plasma level of NGAL was (geometric mean [5th to 95th percentiles]) 134.2 μg/l (range, 44.9 to 400.6 μg/l). High NGAL was significantly associated with age, current smoking, CRP, creatinine, and severe hemodynamic stress and inversely associated with eGFR (Table 1). No interactions between NGAL and baseline variables with regard to endpoints were found.

Table 1 Baseline Clinical Characteristics of STEMI Patients Treated by pPCI Stratified According to High NGAL (>75th Percentile) Versus Low NGAL

	Low NGAL <170.1 μg/l (n = 438)	High NGAL >170.1 μg/l (n = 146)	p Value
Age, y	62 ± 12	66 ± 13	0.002
Male, %	73	73	0.95
Hypertension, %	32	36	0.38
Diabetes, %	8	13	0.08
Current smoker, %	54	42	0.02
Hypercholesterolemia, %	16	23	0.06
Previous myocardial infarction, %	6	8	0.16
Body mass index, kg/m^2	26.6 ± 4.6	26.4 ± 6.7	0.64
Peak troponin I, μg/l	114 (31–244)	94 (30–283)	0.47
C-reactive protein, mg/l	3 (1–8)	6 (3–18)	<0.001
Serum creatinine, μmol/l	91 ± 30	137 ± 99	<0.001
Estimated glomerular filtration rate, ml/min	78 ± 21	59 ± 26	<0.001
Further increased serum creatinine during admission, %	26	21	0.09
Increase in serum creatinine during admission in patients with further increased creatinine during admission, μmol/l	11 (5–20)	18 (4–28)	0.40
Symptom-to-balloon time, min	195 (130–310)	195 (135–315)	0.74
Left ventricular ejection fraction (available in 52% [n = 305])	40 (30–50)	35 (28–45)	0.07
Complex lesion, %	49	51	0.63
Multivessel disease, %	26	30	0.33
LAD lesion	44	50	0.21
Glycoprotein IIb/IIIa inhibitor	29	23	0.22
Severe hemodynamic stress before PCI	9	24	<0.001

Values are % for categorical variables, mean ± SD for Gaussian, and median and interquartile range for non-Gaussian distributed variables.
LAD = left anterior descending coronary artery; NGAL = neutrophil gelatinase–associated lipocalin; PCI = percutaneous coronary intervention; pPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevated myocardial infarction.

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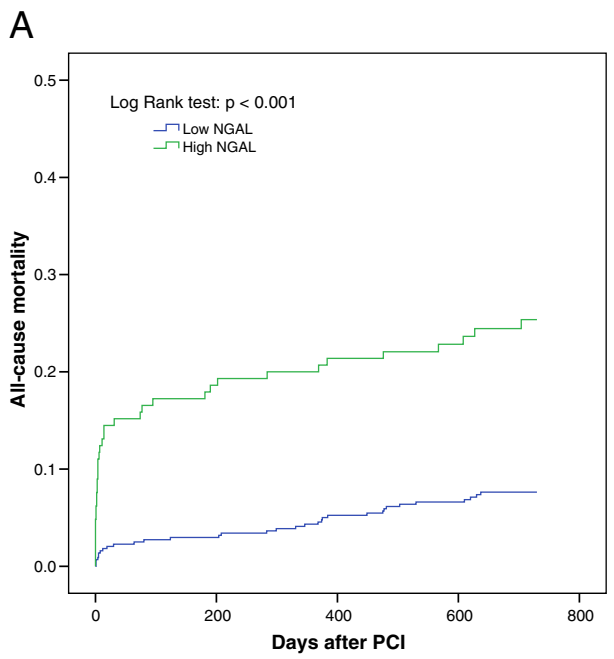

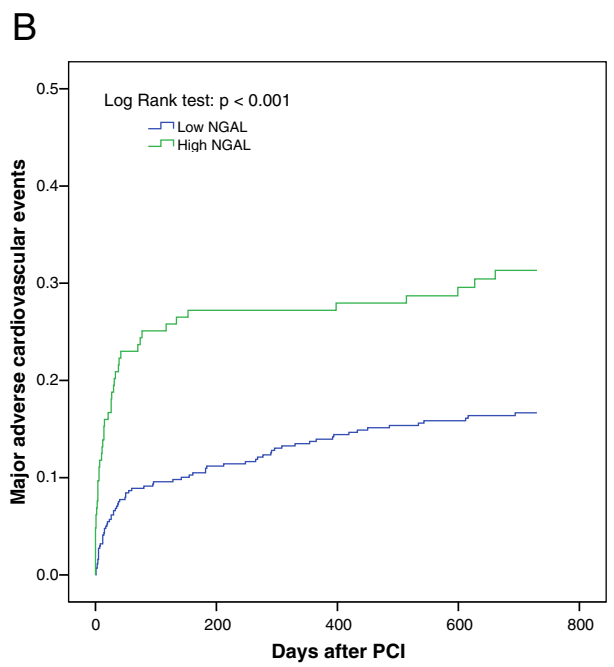

Figure 1 NGAL and All-Cause Mortality and MACE

(A) Kaplan-Maier plots of all-cause mortality dependent on neutrophil gelatinase-associated lipocalin (NGAL) stratified as high (>75th percentile) versus low. **(B)** Kaplan-Maier plot of major adverse cardiac events (MACE) for NGAL stratified as high versus low. PCI = percutaneous coronary intervention.

NGAL and mortality/MACE. The log-rank test based on the Kaplan-Meier curves showed a significant association between high NGAL (>75th percentile) and all-cause mortality ($p < 0.001$) (Fig. 1A) and MACE ($p < 0.001$) (Fig. 1B). After adjustment for selected baseline variables (listed in Table 2), using Cox regression analyses, high NGAL remained a significantly independent predictor of all-cause mortality and MACE (Table 2).

As seen in Figure 1B, a large proportion of the CV events occurred in the first 30 days after the STEMI. This is in accord with previous studies of patients with STEMI (13). Patients with early events had higher NGAL than patients with events occurring after 30 days (geometric mean [5th to 95th percentiles]: 192.2 μg/l (range, 48.2 to 764.4 μg/l) vs. 132.7 μg/l (range, 50.4 to 349.3 μg/l) ($p < 0.001$).

NGAL, kidney function, and AKI. Two patients were treated with long-term hemodialysis before their STEMI; no other patients were treated with dialysis during admission. Patients with high NGAL had increased creatinine and decreased eGFR at admission. In patients with high NGAL, increasing creatinine during admission did not occur more frequently and creatinine did not increase significantly during admission compared with patients with low NGAL (Table 1), although this might be difficult to interpret due to the fact that nephrotoxic contrast was used during the PCI, possibly influencing an increase in creatinine during admission.

Increased NGAL is associated with the occurrence of both clinical and subclinical AKI, and the increase occurs before creatinine making adjustment for AKI difficult (14,15).

However, to reduce the influence of potential AKI, we adjusted the Cox regression analyses for severe hemodynamic stress before the PCI. As seen in Table 2, high NGAL remained an independent predictor of both all-cause mortality and MACE after this adjustment.

Furthermore, we evaluated the impact of increased creatinine during admission with respect to endpoints. In univariate models, increased creatinine during admission was associated with all-cause mortality ($p = 0.04$) but not MACE ($p = 0.56$). When included in the multivariate Cox regression analyses, increased creatinine during admission did not predict all-cause mortality ($p = 0.67$) or MACE ($p = 0.50$). In fact, the variable was eliminated early by backward elimination, and when it was included in the model, increased creatinine levels did not affect the prognostic value of NGAL.

Table 2 Multivariable Cox Analyses Estimating HR for High NGAL (Upper Quartile [170.1 μg/l])

	HR	95% CI	p Value
All-cause mortality (n = 69), adjusted forage, BMI, CRP, eGFR, peak TnI, and severe hemodynamic stress	2.00	1.16–3.44	0.01
MACE (n = 116), adjusted for age, previous AMI, BMI, CRP, eGFR, peak TnI, symptom-to-balloon time, multivessel disease, use of glycoprotein IIb/IIIa inhibitor, and severe hemodynamic stress	1.51	1.00–2.30	0.05

BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NGAL = neutrophil gelatinase–associated lipocalin; TnI = troponin I; MACE = major cardiovascular event(s); AMI = acute myocardial infarction.

Table 3 Cox Models for Risk of All-Cause Mortality in Groups Based on NGAL and CRP

All-Cause Mortality	HR	95% CI	p Value
NGAL <170.1, CRP <10 (n = 363)	1.00	—	
NGAL <170.1, CRP >10 (n = 76)	2.48	1.20–5.12	0.014
NGAL >170.1, CRP <10 (n = 86)	3.63	1.93–6.84	<0.001
NGAL >170.1, CRP >10 (n = 59)	6.46	3.50–11.95	<0.001

Abbreviations as in Table 2.

NGAL and CRP. There were no interactions between NGAL and CRP with regard to reaching the endpoints. Using a cutoff at the 75th percentile for NGAL (170.1 μg/l) and the upper limit of normal of CRP (10 mg/l) (16), patients were stratified by high/low NGAL and high/low CRP. Table 3 shows a Cox regression analysis for all-cause mortality including the 4 groups. When both markers were high, risk was significantly increased (hazard ratio: 6.6; 95% confidence interval: 3.5 to 12.2; $p < 0.001$). Figure 2A shows Kaplan-Meier curves for the 4 groups. As shown, patients with high NGAL/high CRP had the poorest outcome, whereas low NGAL/low CRP had the best. Likewise, Figure 2B shows that the risk of MACE was high when NGAL was high regardless of CRP, whereas the risk was low when NGAL was low.

Discussion

The present study demonstrates for the first time that high NGAL is an independent predictor of all-cause mortality and CV events in patients with STEMI treated with pPCI, even after adjusting for conventional risk factors, renal function, and other significant baseline values. We were able to confirm previous findings of an association between NGAL and CV risk factors such as age and current smoking (17). However, we did not find an association between NGAL and the number of affected coronary arteries, which was previously described (6).

The primary cause of coronary artery thrombosis and acute coronary syndrome (ACS) (including STEMI) is rupture of atherosclerotic plaque (18,19). Inflammation plays a role in the pathogenesis of atherosclerosis and plaque instability and thus ACS (20). It has been demonstrated that CRP and neutrophil leukocytes increase in the event of ACS and that neutrophils infiltrate the atherosclerotic plaques and is involved in the inflammatory process leading to plaque rupture (21–23). Expression of NGAL is also increased in atherosclerotic plaques (3), and in combination with the correlation with the CV risk factors, age, hypertension, and smoking (17), NGAL may be directly involved in the development and progression of atherosclerosis and CAD. Indeed Zografos et al. (6) found that NGAL was independently associated with the presence and severity of CAD in 73 patients undergoing coronary angiography. This was also found by Choi et al. (24) in a study of 49 patients with CAD compared with 42 age- and sex-matched controls. In a study of 128 patients with CAD (37 stable CAD, 37 non-STEMI, 53 STEMI), NGAL was higher in patients with AMI compared with stable CAD (7).

The prognostic value of NGAL is well established in renal disorders (25), but it has not been investigated in patients with AMI until now. Recent data have demonstrated that in the instance of acute heart failure, NGAL

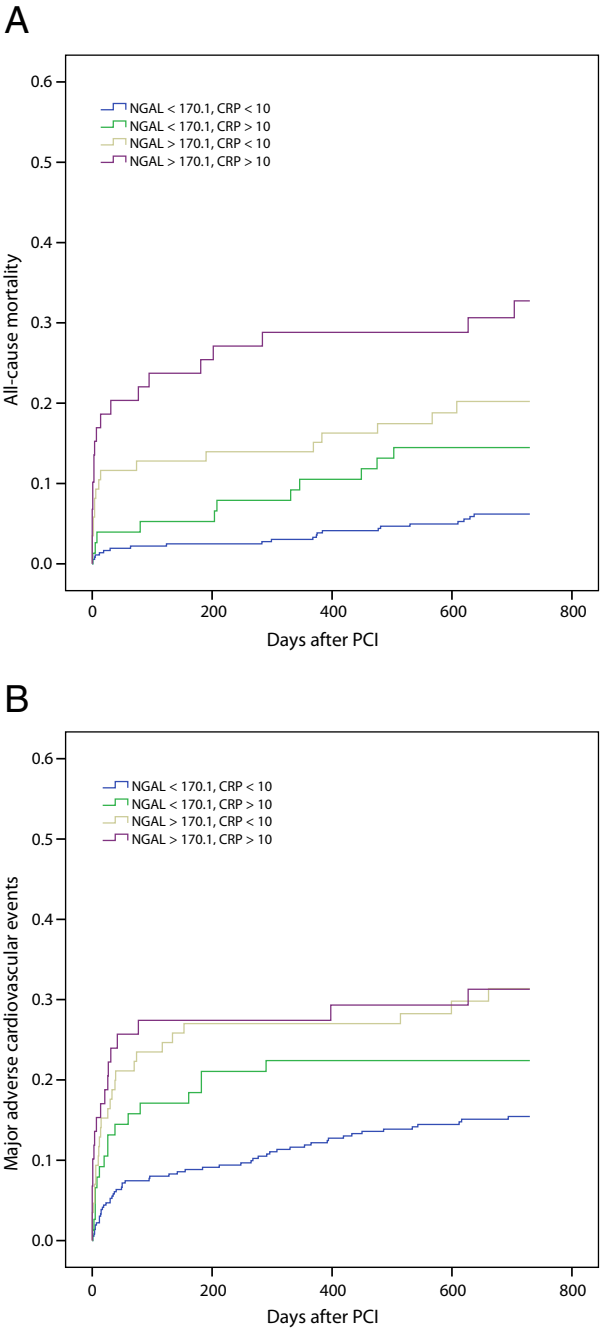

Figure 2 All-Cause Mortality and MACE Based on NGAL and CRP

Kaplan-Meier plots of all-cause mortality **(A)** and MACE **(B)** based on cutoffs of 170.1 μg/l for NGAL and 10 mg/l for C-reactive protein (CRP). Abbreviations as in Figure 1.

was a strong predictor of 30-day heart failure rehospitalization and all-cause mortality, far more than brain natriuretic peptide, creatinine, and eGFR (26). This association was also found by Alvelos et al. (27) in a study of 121 patients with acute heart failure. We were able to extend the prognostic value of NGAL to patients with AMI (STEMI).

It is tempting to speculate that part of the prognostic information of NGAL is related to its association with inflammation, as Ramos-Mozo et al. (28) have shown that NGAL is a marker of thrombus activity, but the prognostic value could likely be explained by the well-established relationship between increased NGAL and AKI (29) because AKI is common in critically ill patients (30).

In a large multicenter analysis of critically ill patients, Haase et al. (30) demonstrated that increased NGAL was associated with both poorer outcomes and increased need for renal replacement therapy and therefore likely represents subclinical AKI. Several other studies have also shown that increased NGAL is associated with AKI, although sensitivity and specificity were only moderate (14,15).

The relationship between increased NGAL and AKI is also evident in the present study in which high NGAL is strongly associated with increased creatinine, reduced eGFR, and more frequent severe hemodynamic stress before admission and thus likely AKI.

We found no association between high NGAL and increased creatinine during admission; however, creatinine is an insensitive marker of AKI (30), and the use of nephrotoxic contrast during PCI makes interpretation difficult. Therefore, elevated NGAL levels may still represent subclinical AKI.

To demonstrate a possible association between NGAL and endpoints independent of AKI, we adjusted our analyses for both eGFR, further increased creatinine during admission, and severe hemodynamic stress before the pPCI (and thus likely AKI). That high NGAL remained an independent predictor of all-cause mortality and MACE could suggest a nonrenal contribution to plasma NGAL. However, due to limitations in the study design, this adjustment may be insufficient.

NGAL exists in different molecular forms and Cai et al. (31) suggested that monomeric and heterodimeric forms are the predominant forms produced by tubular epithelial cells, whereas the dimeric form primarily originates from neutrophils. Further investigation is therefore needed before firm conclusions about the origin of NGAL can be drawn.

CRP is involved in vascular inflammation by its inhibition of nitric oxide (32) and was previously shown to predict mortality in patients with ACS (33). In this study, patients with increased CRP and probably vascular inflammation had increased mortality. However, the combination of high CRP/high NGAL significantly conferred the highest mortality, whereas low CRP/low NGAL conferred the lowest mortality; thus, NGAL conferred additional prognostic information. Of interest, patients with high NGAL/low CRP had a higher risk of mortality compared with patients with low NGAL/high CRP, thus indicating that NGAL possesses better prognostic value compared with CRP. With regard to MACE, patients with high NGAL had significantly increased risk regardless of CRP.

NGAL was higher in patients with early events compared with patients with events occurring later. This could indicate a relationship with vascular inflammation, but this point needs to be investigated further.

Study limitations. The present study demonstrates an independent prognostic value of NGAL in patients with STEMI; however, it cannot prove a causal relationship with CAD. Therefore, investigations of the source(s) and specific molecular forms of increased NGAL in patients with ACS are warranted. Timing of blood samples is an issue in the few studies investigating NGAL and CAD. We measured NGAL just before the invasive procedure to prevent contamination with contrast fluid and increase in NGAL due to direct tissue damage of the kidney (i.e., ischemia-reperfusion injury caused by the pPCI) (34). However, we only measured NGAL and other inflammatory markers once. It is possible that additional blood sampling as inflammation peaked would have provided a more accurate correlation with other inflammatory markers, as done by Sahinarslan et al. (7). In contrast, Choi et al. (24) measured NGAL 3 months after coronary angiography. To evaluate the prognostic value of NGAL independently of AKI, baseline creatinine levels before admission would be needed to make a true assessment of AKI. Furthermore, urine NGAL levels compared with plasma NGAL levels would have been useful. Finally, this study was conducted as a single-center study.

Conclusions

High NGAL independently predicts all-cause mortality and MACE after AMI. Whether this is caused by AKI, increased inflammation, or both and whether plaque rupture contributes as well remain to be elucidated.

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