Serum neutrophil gelatinase-associated lipocalin (NGAL) concentration is independently associated with mortality in patients with acute coronary syndrome

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ABSTRACT

Background: Circulating neutrophil gelatinase-associated lipocalin (NGAL) concentration increases in cardiovascular disease, but the long-term prognostic value of NGAL concentration has not been evaluated in acute coronary syndrome (ACS). We examined the association between NGAL concentration and prognosis in patients with ACS after non-ST-elevation myocardial infarction (NSTEMI) or STEMI.

Methods and Results: NGAL concentration was measured in blood from 1121 consecutive ACS patients (30% women, mean age 65 years) on the first morning after admission. After adjustment for 14 variables, NGAL concentration predicted long-term (median 167 months) mortality (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.10–1.61, $P = 0.003$) for quartile (q) 4 of NGAL concentration. NGAL concentrations also predicted long-term mortality (HR = 1.63, 95% CI 1.31–2.03, $P < 0.001$, N=741) when adjusting for Global Registry of Acute Coronary Events (GRACE) score, left ventricular ejection fraction (LVEF), and pro-B-type natriuretic peptide (proBNP) and C-reactive protein (CRP) concentrations. With these adjustments, NGAL concentration predicted long-term mortality in NSTEMI patients (HR = 2.02, 95% CI 1.50–2.72, $P < 0.001$) but not in STEMI patients (HR = 1.32, 95% CI 0.95–1.83, $P = 0.100$). In all patients, the combination of NGAL concentration and GRACE score yielded an HR of 5.56 (95% CI 4.37–7.06, $P < 0.001$) for q4/q4 for both variables.

Conclusion: NGAL concentration in ACS is associated with long-term prognosis after adjustment for clinical confounders. Measuring circulating NGAL concentration may help to identify patients—particularly those with NSTEMI—needing closer follow-up after ACS.

1. Introduction

The course of patients with acute coronary syndrome (ACS), which can range from unstable angina/non-ST-elevation myocardial infarction (NSTEMI) to STEMI, varies considerably. Identification of patients with poor prognosis may help in the optimization of therapy and outcomes. The management of these patients has improved with the development of new biomarkers such as the troponin level, scoring systems such as the Global Registry of Acute Coronary Events (GRACE), and various inflammatory markers, in particular C-reactive protein (CRP). However, the ability to predict short- and long-term outcomes remains limited [1,2]. In this study, we sought to determine the predictive value of neutrophil gelatinase-associated lipocalin (NGAL) concentration alone and in combination with the composite clinical GRACE score.

NGAL was first isolated from neutrophil granules but was later shown to be produced by a wide range of cells and tissues [3]. In addition to being a sensitive marker of distal tubular damage in acute kidney injury, NGAL is upregulated in various inflammatory disorders such as inflammatory bowel disease, chronic obstructive pulmonary disease, and heart failure (HF) [4-8]. Increased serum NGAL concentration is found in patients with coronary artery disease (CAD) and is associated with disease instability and the number of vessels involved [9,10]. Strong NGAL expression has been reported within atherosclerotic carotid lesions associated with increased matrix metalloproteinase 9 (MMP-9) activity [11]. Although MMP-9 is genome-wide significantly associated with CAD [12], the role of NGAL as a marker and potential mediator of CAD is not clear.

Previous studies have suggested that NGAL is a prognostic marker for cardiovascular (CV) disorders such as acute and chronic HF [10,13,14]. Considering its association with inflammation, matrix remodelling, renal function, and CAD severity, we hypothesized that NGAL concentration may also be a prognostic marker in ACS patients. To test this

hypothesis, we measured NGAL concentration in serum obtained from a large population of patients with ACS admitted to a Scandinavian university hospital, and we estimated its associations with long-term all-cause mortality in the entire population of ACS patients and in subgroups of STEMI and NSTEMI patients. We also estimated the predictive value of NGAL concentration compared with traditional risk factors and the composite GRACE risk score, and the relationships between NGAL concentration and MMP-9 and CRP concentrations.

2. Methods

2.1. Study design

We used frozen serum samples from the 'Prognosis and Risk in ACS in Sweden' study (PRACSIS) [15,16]. Patients admitted to the coronary care unit at Sahlgrenska University Hospital, Gothenburg, Sweden, from September 1995 to March 2001 who were diagnosed with ACS were consecutively included to reflect the general ACS population treated at this centre. The diagnosis of ACS was based on chest pain and/or other symptoms suggestive of myocardial ischaemia in combination with ECG changes, biochemical markers of myocardial necrosis, or previously recognized CAD. The upper reference levels of biochemical markers at the time of inclusion were higher than today, and a large proportion of the patients diagnosed with unstable angina would have fulfilled the current criteria for NSTEMI. We have therefore included patients with unstable angina among the NSTEMI group in this report. The main exclusion criteria were age <18 or ≥80 years, non-CAD patients with a life expectancy <1 year, residence outside the hospital's catchment area, unwillingness, or prior admission resulting in inclusion in the study. Clinical data were collected from hospital medical records and through an interview conducted by an experienced research nurse. The GRACE risk score for post-discharge death was calculated for each patient [17]. Survival confirmation and date of death were obtained from the Swedish National Population Registry,

which includes all residents of Sweden. All-cause mortality was studied during the long-term follow-up (167 months); i.e., from the index event until 1 January 2015.

The study was approved by the Ethics Committee of Gothenburg University, and all patients provided informed consent [18].

2.2. Blood sampling

Peripheral venous blood was obtained the first morning after admission. For NGAL measurement, blood was collected into sterile tubes without additives, allowed to clot at room temperature, and centrifuged (1200 *g* for 10 min) within 1 h. For high-sensitivity determination of other biomarkers, blood was collected in cold EDTA tubes and centrifuged (4 °C, 2000 *g* for 15 min) within 1 hour, and the plasma was stored. Serum and plasma samples were kept at –80 °C.

2.3. Biochemical analyses

Serum NGAL concentration was measured by enzyme immunoassay (R&D Systems, Minneapolis, MN) with a sensitivity of 0.04 ng/mL. The intra- and inter-assay variances were <5% and <10%, respectively. Although storage time differed (samples were collected between 1995 and 2001, and analysed in 2011), NGAL has been shown to be stable when stored at –80 °C, and its concentration is influenced only slightly by multiple thawing cycles [19]. The range from the minimum detectable concentration to the upper limit (without dilution) was 0.156–10 ng/mL for NGAL.

Serum troponin T (TnT) and creatine kinase (CK-MB) concentrations were measured on a modular platform (Roche Diagnostics, Mannheim, Germany). Pro-B-type natriuretic peptide $(BNP)_{3–108}$ (proBNP), high-sensitivity CRP (hsCRP), troponin I (TnI), and MMP-9 concentrations were measured using immunofluorescence assays calibrated with spiked

plasma (Biosite Inc., San Diego, CA). The ranges from the minimum detectable concentration to the upper limit (without dilution) were 0.156–10 ng/mL for proBNP and 0.3–100 mg/L for hsCRP. All samples were tested in duplicate in a blinded fashion. Serum total cholesterol, low density lipoprotein (LDL) and creatinine concentrations were measured by routine laboratory methods. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula [(140-age x weight(kg)/serum creatinine (μmol/L)] multiplied by a constant of 1.23 in men and 1.04 in women.

2.4. Echocardiography

An experienced investigator performed an echocardiographic investigation within 5 days of hospital admission. The biplane left ventricular ejection fraction (LVEF) was calculated using the disc summation method, and tracings were checked for accuracy in motion mode [20].

2.5. Statistical analysis

Categorical variables are reported as percentages, and continuous variables as median values with interquartile ranges (25^{th}–75^{th} percentile) or mean and standard deviation (SD). The associations between NGAL concentration and baseline demographic variables and CV risk factors were tested using the Mann–Whitney *U* test to compare patients with and without a specific characteristic. Spearman rank correlational analysis was used to test the associations between continuous variables and NGAL concentration. Actual individual NGAL concentration was used to calculate the *P*-values shown in Table 1.

The assumption of linearity for NGAL concentrations was checked by entering the squared transformation into the models and studying the change in –2 log likelihood. This assumption was violated even after transformation of NGAL concentrations using the natural logarithm. We decided to use NGAL concentration dichotomised at the 75^{th} percentile in all

analyses. Cox proportional-hazard regression was used to calculate the crude and adjusted HR for NGAL q4 compared with q1–3 for all deaths.

Analysis of long-term all-cause mortality included adjustments in two steps. First, we analysed the effect on the hazard ratio (HR) for the fourth quartile (q4) of NGAL versus q1–3 after adjusting for each baseline characteristic (Table 1) separately, both with and without age adjustment. Variables that altered the HR by ≥3.0%, with or without age adjustment, were defined as confounders and used in the final multivariable model. Model 1) included only confounders with <3% missing data and model 2) included all confounders.

Due to the amount of missing data for some of the variables, we also performed analysis using multiple imputation of missing data. Missing data were assumed to occur at random (MAR) and 50 imputed data sets were generated with the Markov Chain Monte Carlo (MCMC) method and the expectation-maximization (EM) algorithm. Rubin´s rules were used when pooling the results from the imputed data sets.

A second multivariable analysis included three adjustments: 1) no adjustment (n = 1121); 2) adjustment for GRACE score (based on age, history of HF, history of myocardial infarction (MI), heart rate, systolic blood pressure, ST-segment depression on admission ECG, elevated biomarkers of myocardial necrosis, baseline creatinine concentration, and no in-hospital percutaneous coronary intervention (PCI) (n = 1118); and 3) as in 2) but with hsCRP and proBNP concentrations, and LVEF in a patient subgroup with this additional information (n = 741).

To analyse the added usefulness of NGAL concentration in clinical assessment, we calculated the ‘category-less’ net reclassification improvement (NRI), integrated discrimination improvement (IDI), and difference in the area under the receiver-operating characteristic curve (AUC) after adding NGAL concentration to the models for all-cause mortality at 165 months (from last patient inclusion to 1 January 2015).

To visualize the relationship between NGAL quartiles and long-term prognosis, Kaplan–Meier plots were generated, and the log-rank test was used to compare the resulting curves.

Median follow-up was calculated using the observed follow-up times for all patients from inclusion to the date of death for those who died or to the date of last follow-up.

All tests were two-sided; *P*-values < 0.05 were considered significant. All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

NGAL concentration was measured in 1121 patients (30% women, mean age 65 years) from day 1; 43% received a final diagnosis of STEMI and 57% of NSTEMI. The median (25^{th}, 75^{th} percentile) NGAL concentrations were 298 (220, 425) and 281 (209, 388) μg/L, respectively ($P = 0.01$). Table 1 shows the characteristics at admission according to NGAL quartiles. The percentage of STEMI patients was highest in the fourth quartile. Patients with a higher NGAL concentration at baseline were older, less likely to be female, and more likely to smoke, and had higher concentrations of CK-MB, TnT, proBNP, and hsCRP, and leukocyte count. They also had lower eGFR and total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations. At admission, those with a higher NGAL level were also more likely to have Killip class II–IV, lower LVEF, and higher GRACE score. Patients with a higher NGAL concentration were more likely to have a history of MI, HF, diabetes, or hypertension. The association between NGAL concentration and PCI was inverse and reflected mainly secondary PCI undertaken after blood sampling; primary PCI was not associated with NGAL concentration.

After including all variables univariately associated with NGAL concentration in a

linear multivariable stepwise regression analysis (Table S1), eGFR, female sex, total cholesterol concentration, and 'not primary PCI' remained significantly inversely associated with NGAL concentration, whereas hsCRP concentration, smoking, and diabetes showed a significant direct association. These variables explained ~20% of the variation in NGAL concentration.

3.2. NGAL concentration and long-term prognosis

In the univariate analysis, long-term all-cause mortality was nearly twofold higher in patients in NGAL q4 compared with q1–3 (HR 1.93, 95% confidence interval [CI] 1.63–2.28, $P < 0.001$).

The influence on this relationship of each baseline characteristic in Table 1 was tested individually (results shown in Table S2). Factors affecting the relationship between long-term mortality and HR of NGAL q4 vs q1–3 by ≥3% (with or without adjustment for age) were used for multivariable adjustment. When including patients with nearly complete data (N = 1086), these were age, sex, previous MI, previous angina, previous HF, previous diabetes, current smoker, lipid-lowering drugs, systolic blood pressure <100 mm Hg at admission, eGFR, max Killip class II–IV, thrombolysis, primary PCI, and other PCI. After adjusting for these variables, the HR for NGAL q4 vs q1–3 was 1.33 (95% CI 1.10–1.61, $P = 0.003$) (Table S3 upper).

Without consideration of data completeness, proBNP, hsCRP, total cholesterol, and ln(LDL cholesterol) concentrations, and LVEF were added to the model because they also influenced the relationship of NGAL with mortality by ≥3%. The adjusted HR for NGAL q4 vs q1-3 was 1.50 (95% CI 1.16–1.94, $P = 0.002$) (N = 639) (Table S3 lower). After applying multiple imputation analysis to handle missing data, the relationship remained significant: HR = 1.31 (95% CI 1.08–1.58, $P = 0.006$). Evaluation of the interactions between NGAL (q1–3

vs. q4) and each variable in Table 1 related to long-term mortality showed that these factors interacted significantly with NGAL concentration (Table S4): high (q4) leucocyte count (stronger effect when high NGAL); Killip class II–IV at admission or at any time before discharge (stronger effect when low NGAL); and low LVEF (q1) (greater effect when low NGAL). After adjusting for age, thrombolysis also had a stronger effect on mortality in patients with high NGAL concentration.

3.3. Survival plots of long-term all-cause mortality

Kaplan–Meier estimates of long-term all-cause mortality according to NGAL quartiles are shown in Fig. 1 (upper panel). The corresponding estimates of long-term all-cause mortality according to NGAL quartiles in STEMI (middle panel) and NSTEMI (lower panel) patients are also shown in Fig. 1.

3.4. GRACE score combined with NGAL concentration

To test the prognostic value of clinical data combined with NGAL concentration, we calculated the GRACE risk score. First, we tested the influence of this composite score on the relationship between NGAL concentration and all-cause mortality. As mentioned above and shown in Fig. 2, NGAL q4 had a 93% higher mortality risk than q1–3. Adjusting for the GRACE score reduced the HR of NGAL q4 vs q1–3 to 1.55 (95% CI 1.30–1.84). In the 741 patients with data available for LVEF and proBNP and hsCRP concentrations, NGAL q4 retained a 63% increased risk ($P < 0.001$) (Fig. 2 upper panel). Adding NGAL concentration to the full model of GRACE score, LVEF, and proBNP and hsCRP concentrations yielded an NRI of 0.35 ($P < 0.001$) and IDI of 0.013 ($P = 0.002$). The change in AUC was not significant (0.819 vs. 0.813, $P = 0.10$).

Separate analyses of STEMI and NSTEMI patients are shown in Fig. 1 (survival plots) and Fig. 2 (univariate and adjusted HRs). In STEMI patients, after adjustment for GRACE

score, LVEF, and hsCRP and proBNP concentrations, the adjusted HR for the association of NGAL concentration with all-cause long-term mortality was 1.32 (95% CI 0.95–1.83, P = 0.10). In NSTEMI patients the corresponding association was significant, with HR 2.02 (95% CI 1.50–2.72, $P < 0.001$).

We next evaluated the combination of GRACE score and NGAL in all patients. The survival plot in Fig. 3 shows that this combination was a powerful prognostic indicator. The HRs for q4 NGAL/q4 GRACE were 1.49 (95% CI 1.15–1.93, $P = 0.002$) relative to q1–3 NGAL/q4 GRACE; 3.11 (95% CI 2.34–4.12, $P < 0.001$) relative to q4 NGAL/q1–3 GRACE; and 5.56 (95% CI 4.37–7.06, $P < 0.001$) relative to q1–3 NGAL/q1–3 GRACE. The AUC for long-term all-cause mortality was 0.674 (95% CI 0.650–0.698) for GRACE q4. Adding NGAL concentration increased the AUC to 0.710 (95% CI 0.682–0.737) relative to GRACE alone ($P < 0.001$).

3.5. NGAL, MMP-9, and hsCRP concentrations

MMP-9 concentration correlated with NGAL concentration (r = 0.27, $P < 0.0001$, N = 928). However, MMP-9 concentration was not a significant predictor of long-term mortality and did not add predictive value to NGAL concentration alone. Univariate analysis of MMP-9 concentration produced HRs of 1.04 (95% CI 0.85–1.28, $P = 0.70$) for q4 vs q1–3 and 1.01 (95% CI 0.82–1.23, $P = 0.96$) for q2–4 vs q1.

We have previously reported that hsCRP concentration has prognostic value in this study population [21]. In the current study, we evaluated whether hsCRP had additive value when combined with NGAL concentration or GRACE score. Supplementary Table S5 shows the results for the prediction of long-term mortality in 938 patients with available data for NGAL and hsCRP concentrations and GRACE score. NGAL concentration and GRACE score combined yielded an HR of 7.46 (95% CI 5.64–9.88, $P < 0.0001$) for q4 vs q1–3.

hsCRP concentration and GRACE score combined yielded an HR of 5.74 (95% CI 4.33–7.61, $P < 0.0001$) for q4/q4 vs q1–3/q1–3. NGAL and hsCRP concentrations combined yielded an HR of 2.80 (95% CI 2.13–3.67, $P < 0.0001$) for q4/q4 vs q1–3/q1–3.

4. Discussion

In this prospective study, NGAL concentration was strongly and significantly associated with all-cause mortality during long-term follow-up in ACS patients. Surprisingly, the association was stronger in NSTEMI than in STEMI patients. NGAL concentration is a reliable marker of kidney injury [4] and, in this ACS population, correlated strongly with eGFR. However, its association with the outcome was not explained by kidney function or other known prognostic markers such as hsCRP and proBNP concentrations, LVEF, or GRACE score. MMP-9 concentration was also not an explanatory factor despite its correlation with NGAL concentration. Our findings suggest that NGAL concentration warrants further study as a prognostic biomarker in ACS, especially NSTEMI.

NGAL concentration predicts all-cause mortality and major adverse cardiac events (MACE) in the general population [22] and MACE following coronary angiography [23]. In patients with PCI-treated STEMI, increased NGAL concentration is associated with risk of all-cause mortality or major CV events [24, 25]. However, data on long-term prognosis in the broad spectrum of ACS patients, as in our study, and in NSTEMI patients, are lacking. We included a larger study population and recorded more deaths during a longer follow-up than earlier STEMI studies [24,25]. The pathophysiology and degree of inflammation differ between types of ACS. Our findings support the recent view that different pathogenic mechanisms may underlie NSTEMI and STEMI [26].

NGAL concentration may be useful clinically for risk stratification when determining the long-term prognosis of ACS patients. This is supported by the highly significant NRI,

which suggests that reclassifying patients according to NGAL concentration may significantly improve risk classification. By contrast, adding the NGAL concentration to the model of GRACE score, LVEF, and hsCRP and proBNP concentrations did not significantly increase the AUC, possibly because the AUC was already ~0.80 and, therefore, adding other strong predictors to the model would have only a modest effect [2]. If so, this does not necessarily preclude the potential clinical value of NGAL concentration as a prognostic marker of ACS. Consistent with this idea, in the group with both high GRACE score and high NGAL concentration (q4/q4) compared with the q1–3 group, the AUC value increased significantly after adding NGAL compared with GRACE alone. This suggests that combining these variables may yield important information.

In addition to CV disease, in kidney disorders, which are known to be associated with NGAL concentration, urinary and circulating NGAL concentrations increase before the creatinine concentration increases. NGAL concentration also increases in other inflammatory conditions and cancer [4,7,27,28]. Although NGAL concentration was significantly associated with eGFR, adjusting for eGFR directly in the multivariable model did not change the association between NGAL concentration and long-term outcome. This suggests that the prognostic value of NGAL concentration did not simply reflect kidney function in these ACS patients.

The strong association between NGAL concentration and adverse outcomes in ACS patients may have several explanations. First, NGAL concentration reflects various processes that influence prognosis in ACS patients, such as impaired kidney function and inflammation (e.g., neutrophil granulocyte activation). Second, NGAL forms complexes with MMP-9 and, in this configuration, MMP-9 remains functionally active for longer than when not complexed with NGAL. NGAL and MMP-9 concentrations correlated in our study; strong associations between the two have been found in plaques at risk of rupture and between MMP-9 activity

and NGAL concentration [11]. Therefore, in addition to its role as a marker of active atherosclerotic disease, NGAL may also play a role in plaque progression and destabilization through matrix degradation, which would predispose to further CV events. Third, strong NGAL expression in atherosclerotic lesions and marked myocardial upregulation of NGAL in experimental MI [6] suggest that the association of NGAL with adverse outcomes in ACS patients reflects the role of the myocardium and atherosclerotic lesions as cellular sources of circulating NGAL during ACS.

The pathophysiology and degree of inflammation vary between types of ACS [26]. The stronger association between NGAL concentration and mortality in NSTEMI patients may provide a clue about the role and source of NGAL in ACS. One possible interpretation is that NGAL in NSTEMI patients primarily reflects plaque inflammation and/or erosion, in accordance with the more serious CAD in NSTEMI [29,30]. Neutrophils constitute an important cellular source of NGAL, which may increase MMP-9 activity by inhibiting its degradation. Given the postulated role of neutrophils and MMPs in plaque erosion, NGAL may be both a marker of pathways activated during NSTEMI and a mediator of NSTEMI development.

4.1. Limitations

The long-term follow-up of these patients means that, although a large proportion of our patients were treated according to current treatment guidelines for the management of ACS (http://dx.doi.org/10.1093/eurheartj/ehv320), the results might differ from those obtained from a cohort initiated more recently. The lack of data on high-sensitivity TnT concentration is a limitation. Another limitation is that some covariates did not have complete data; however, the association of NGAL concentration with outcome remained significant after multiple imputation analysis.

5. Conclusions

Serum NGAL concentration at admission was strongly associated with all-cause mortality during long-term follow-up in a large population of ACS patients. The association was strongest in NSTEMI patients. Our findings suggest that NGAL concentration may be a useful biomarker for risk stratification in ACS patients, especially in NSTEMI patients, and may provide additional information beyond that of traditional biomarkers (e.g., hsCRP, proBNP, and troponin concentrations) in these patients. Further mechanistic studies are needed to elucidate the role of NGAL in atherosclerotic disorders.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Biosite Inc. conducted the analyses of pro-B-type natriuretic peptide, hsCRP, MMP-9, and TnI.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/...

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Legends

Fig. 1. Kaplan–Meier estimates of long-term all-cause mortality in all patients according to NGAL quartiles for the entire study group (*upper* panel), for patients with ST-elevation myocardial infarction (*middle* panel), and patients with non-ST-elevation myocardial infarction (*lower* panel).

Fig. 2. Association between the top NGAL quartile (q4) and long-term prognosis for all-cause mortality (n = number of events/total number of patients).
* adjusted for GRACE score, and **adjusted for GRACE score, pro-B-type natriuretic peptide and high sensitivity C-reactive protein concentrations, and left ventricular ejection fraction.

Fig. 3. Kaplan–Meier estimates for the entire study population according to various combinations of NGAL concentration and GRACE score. The effects on mortality of various combinations of high (q4) and low (q1–3) NGAL concentration and GRACE score are shown.

Table 1

Baseline characteristics of the study population (N = 1121) according to NGAL quartiles.

	NGAL q1 <215 μg/L (n = 280)	**NGAL q2 215–289 μg/L (n = 282)**	**NGAL q3 290–403 μg/L (n = 279)**	**NGAL q4 >403 μg/L (n = 280)**	***P*-value***
Age (years)	63 (56, 71)	66 (57, 74)	66 (58, 73)	69 (60, 74)	<0.001
Female (%)	36	36	24	25	<0.001
Previous MI (%)	19	20	24	24	0.04
Previous angina (%)	41	46	46	47	0.16
Previous HF (%)	5	5	8	11	<0.001
Previous diabetes (%)	17	15	15	22	0.03
Previous hypertension (%)	36	40	41	44	0.02
Previous hypercholesterolaemia (%)	29	32	29	23	0.07
Current smoker (%)	25 [1]	30 [1]	33 [1]	37 [1]	0.005
Lipid-lowering drug (%)	14	18	12	11	0.12
STEMI (%)	39	41	43	48	0.01
ST elevation at admission (%)	35	39	41	43	0.02
ST depression at admission (%)	10	11	11	14	0.06
Q-wave at admission (%)	9	10	12	17	0.001
Systolic BP < 100 mmHg at admission (%)	2	2	2	4	0.25
Heart rate (beats/min)	70 (60, 84)	70 (60, 84)	77 (65, 88)	72 (61, 90)	0.004
CK-MB max (μg/L)	50 (8, 177)	48 (8, 161)	57 (8, 172)	70 (14, 232)	0.009
TnT max (μg/L)	0.8 (0.1, 2.4) [2]	0.7 (0.1, 3.9) [2]	1.0 (0.1, 4.1) [2]	1.5 (0.1, 6.9) [2]	<0.001
TnI at admission (ng/L)	4190 (360, 14740) [3]	4280 (170, 17250) [3]	5410 (540, 17450) [3]	7410 (720, 18940) [3]	0.01
Estimated GFR (mL/min/1.73 m^2)	70 (58, 87) [1]	65 (54, 84) [1]	66 (54, 81) [1]	57 (43, 74) [1]	<0.001
ProBNP (pg/mL)	1551 (550, 2941) [2]	1576 (526, 3000) [2]	1763 (748, 3393) [2]	2222 (1025, 3976) [2]	<0.001
hsCRP (mg/dL)	8.7 (3.2, 19.4) [2]	11.2 (4.3, 25.8) [2]	17.4 (7.8, 50.9) [2]	23.2 (10.3, 64.3) [3]	<0.001
Leukocytes (10^3/μL)	8.0 (6.1, 9.5) [1]	8.4 (6.6, 10.4) [1]	9.2 (7.6, 11.6) [1]	9.9 (8.0, 12.4) [1]	<0.001
Total cholesterol (mmol/L)	5.6 (4.8, 6.4) [1]	5.4 (4.6, 6.1) [2]	5.2 (4.6, 6.1) [2]	5.2 (4.3, 6.0) [2]	<0.001
LDL cholesterol (mmol/L)	3.6 (2.9, 4.3) [2]	3.4 (2.8, 4.1) [2]	3.5 (2.8, 4.1) [2]	3.2 (2.5, 4.0) [2]	0.003
BMI (kg/m^2)	25.9 (23.5, 28.4) [1]	25.9 (23.7, 29.4) [1]	25.7 (23.7, 28.3) [1]	25.4 (23.4, 27.8) [1]	0.31
Killip class II–IV (%)	2	2	9	11	<0.001
Max Killip class II–IV (%)	11	11	19	29	<0.001
Thrombolysis (%)	16	17	18	22	0.02
Primary PCI (%)	13	16	17	15	0.69

Other PCI (%)	26	22	16	13	<0.001
CABG (%)	9	10	10	8	0.42
No thrombolysis or revascularization (%)	42	40	44	48	0.06
LVEF (%)	55 (49, 63) [2]	55 (48, 61) [2]	54 (44, 60) [2]	50 (41, 60) [2]	<0.001
GRACE (risk score)	102 (83, 118)	104 (88, 123)	110 (92, 128)	118 (96, 137)	<0.001

Continuous variables are reported as median (25^{th}, 75^{th} percentile)

* Actual NGAL value used in *P*-value calculations.

[1] 1–5% missing; [2] 5–25% missing; [3] >25% missing. MI, myocardial infarction; HF, heart failure; STEMI, ST elevation myocardial infarction; CK-MB, creatine kinase MB isoform; TnI, troponin I; TnT, troponin T; GFR, glomerular filtration rate; ProBNP, pro-brain natriuretic protein; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; BMI, body mass index; PCI, percutaneous coronary intervention, CABG, coronary aortic bypass grafting; LVEF, left ventricular ejection fraction; GRACE, Global Registry of Acute Coronary Events.

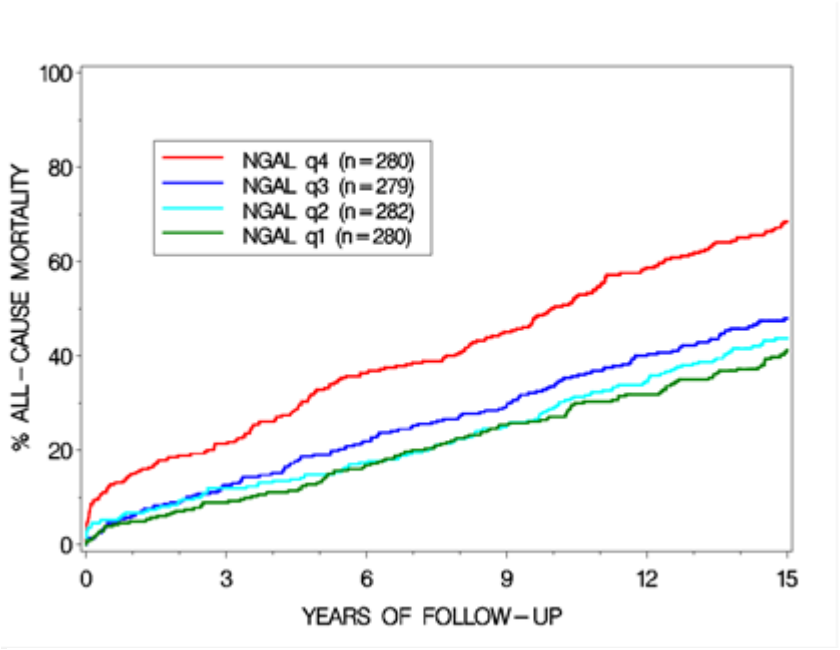
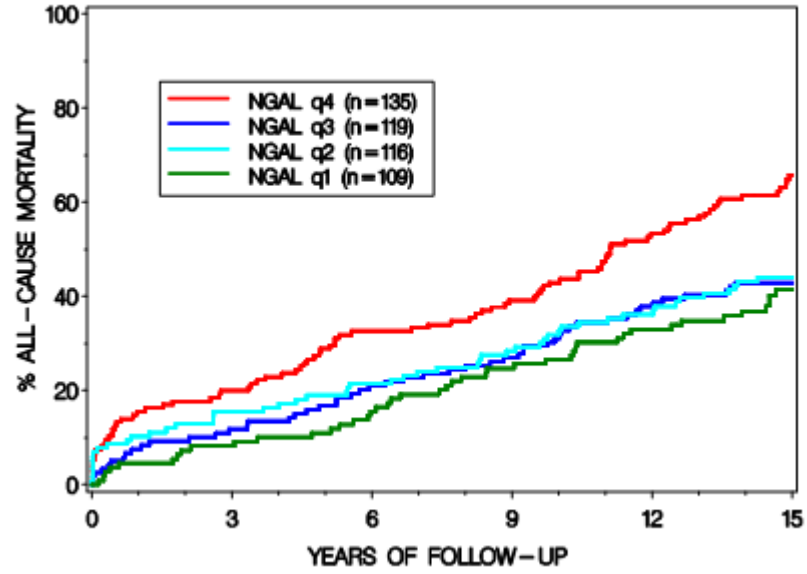
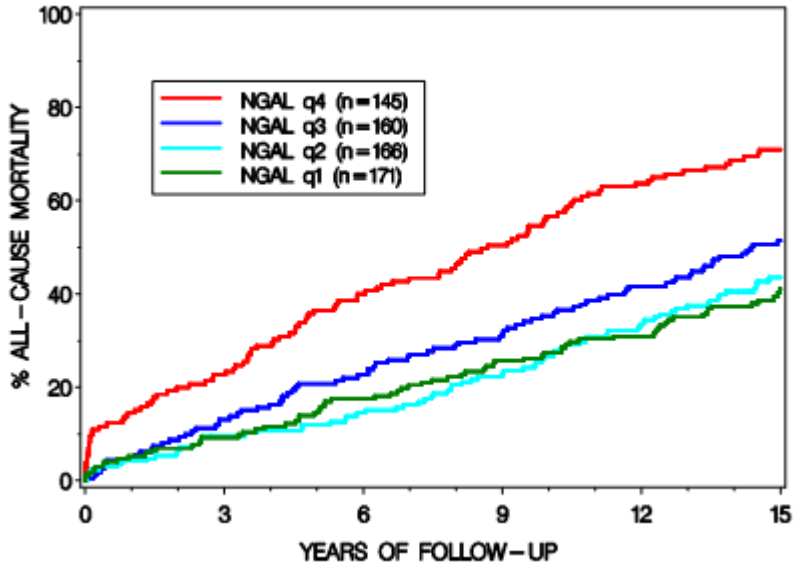

NGAL q4 (n=280)
NGAL q3 (n=279)
NGAL q2 (n=282)
NGAL q1 (n=280)
% ALL-CAUSE MORTALITY
YEARS OF FOLLOW-UP
0
20
40
60
80
100
0
3
6
9
12
15

Fig. 1


NGAL q4 (n=135)
NGAL q3 (n=119)
NGAL q2 (n=116)
NGAL q1 (n=109)
% ALL-CAUSE MORTALITY
YEARS OF FOLLOW-UP
0
20
40
60
80
100
0
3
6
9
12
15


NGAL q4 (n=145)
NGAL q3 (n=160)
NGAL q2 (n=166)
NGAL q1 (n=171)
% ALL-CAUSE MORTALITY
YEARS OF FOLLOW-UP
0
20
40
60
80
100
0
3
6
9
12
15

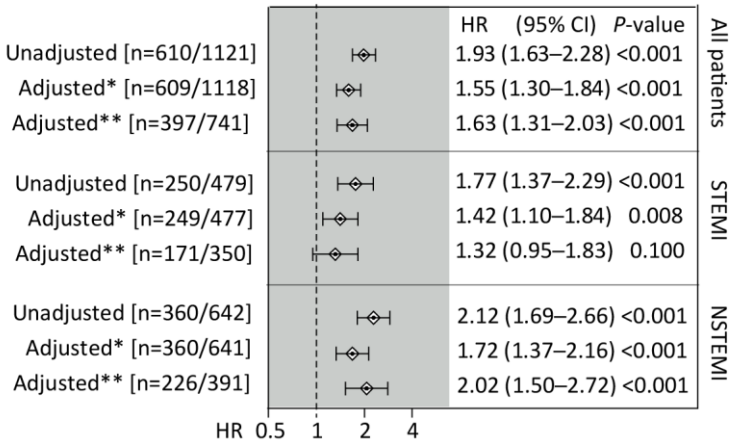

HR (95% CI) P-value
Unadjusted [n=610/1121]
1.93 (1.63–2.28) <0.001
Adjusted* [n=609/1118]
1.55 (1.30–1.84) <0.001
Adjusted** [n=397/741]
1.63 (1.31–2.03) <0.001
All patients
Unadjusted [n=250/479]
1.77 (1.37–2.29) <0.001
Adjusted* [n=249/477]
1.42 (1.10–1.84) 0.008
Adjusted** [n=171/350]
1.32 (0.95–1.83) 0.100
STEMI
Unadjusted [n=360/642]
2.12 (1.69–2.66) <0.001
Adjusted* [n=360/641]
1.72 (1.37–2.16) <0.001
Adjusted** [n=226/391]
2.02 (1.50–2.72) <0.001
NSTEMI
HR 0.5 1 2 4

Fig. 2

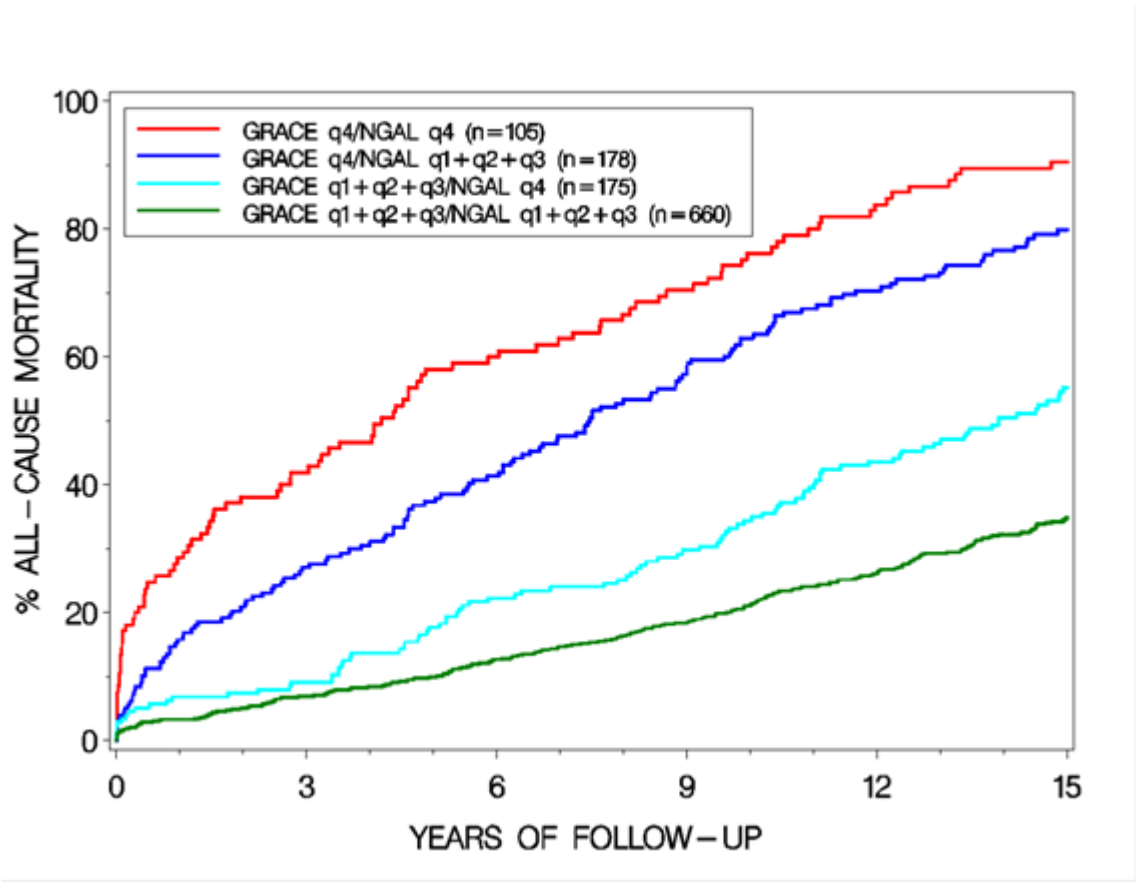

GRACE q4/NGAL q4 (n=105)
GRACE q4/NGAL q1+q2+q3 (n=178)
GRACE q1+q2+q3/NGAL q4 (n=175)
GRACE q1+q2+q3/NGAL q1+q2+q3 (n=660)
% ALL-CAUSE MORTALITY
0
20
40
60
80
100
0
3
6
9
12
15
YEARS OF FOLLOW-UP

Fig. 3

Supplementary information

Table S1

Stepwise regression model of baseline characteristics associated with the NGAL concentration.

Variable	**Beta coefficient**	***P*-value**
ln(eGFR)	–0.43301	<0.0001
Female sex	–0.19685	<0.0001
Current smoker	0.13996	<0.0001
ln(total cholesterol)	–0.13570	<0.0241
PCI, not primary	–0.09785	<0.0058
Previous diabetes	0.08402	<0.0325
Ln (hsCRP)	0.07641	<0.0001

eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; hsCRP, high-sensitivity C-reactive protein.

Table S2

Comparisons of the relationships between NGAL concentration and all-cause mortality in q4 vs q1–3 during long-term follow-up.

		Unadjusted	Covariate adjusted	Age adjusted	Age + covariate adjusted
Age	n = 1121	1.93 (1.63─2.28)	1.73 (1.46─2.05)	----------	----------
Sex	n = 1121	1.93 (1.63─2.28)	1.95 (1.65─2.31)	1.73 (1.46─2.05)	**1.70 (1.44─2.02)**
Previous MI	n = 1121	1.93 (1.63─2.28)	1.96 (1.65─2.32)	1.73 (1.46─2.05)	**1.75 (1.48─2.08)**
Previous angina	n = 1121	1.93 (1.63─2.28)	**1.96 (1.66─2.32)**	1.73 (1.46─2.05)	1.74 (1.46─2.06)
Previous HF	n = 1121	1.93 (1.63─2.28)	**1.88 (1.59─2.23)**	1.73 (1.46─2.05)	**1.67 (1.41─1.98)**
Previous diabetes	n = 1121	1.93 (1.63─2.28)	**1.89 (1.59─2.24)**	1.73 (1.46─2.05)	**1.69 (1.42─2.00)**
Previous hypertension	n = 1120	1.92 (1.62─2.27)	1.91 (1.61─2.26)	1.72 (1.45─2.04)	1.72 (1.45─2.04)
Previous hypercholesterolemia	n = 1120	1.93 (1.63─2.29)	1.93 (1.63─2.29)	1.73 (1.46─2.05)	1.75 (1.48─2.07)
Current smoker	n = 1103	1.91 (1.61─2.27)	**1.94 (1.64─2.31)**	1.71 (1.44─2.03)	**1.67 (1.40─1.99)**
Lipid-lowering drug	n = 1121	1.93 (1.63─2.28)	**1.96 (1.65─2.32)**	1.73 (1.46─2.05)	1.75 (1.48─2.07)
STEMI	n = 1121	1.93 (1.63─2.28)	1.96 (1.65─2.32)	1.73 (1.46─2.05)	1.75 (1.47─2.08)
NSTEMI	n = 1121	1.93 (1.63─2.28)	1.94 (1.64─2.29)	1.73 (1.46─2.05)	1.74 (1.46─2.06)
Adm ST elevation	n = 1119	1.93 (1.63─2.28)	1.95 (1.65─2.31)	1.73 (1.46─2.05)	1.75 (1.47─2.07)
Adm ST depression	n = 1119	1.93 (1.63─2.28)	1.91 (1.62─2.27)	1.73 (1.46─2.05)	1.72 (1.45─2.03)
Q-wave at admission	n = 1119	1.93 (1.63─2.28)	1.91 (1.61─2.26)	1.73 (1.46─2.05)	1.71 (1.44─2.03)
Adm systolic BP <100	n = 1121	1.93 (1.63─2.28)	1.92 (1.25─2.27)	1.73 (1.46─2.05)	**1.70 (1.44─2.02)**
Adm heart rate	n = 1120	1.93 (1.63─2.28)	1.92 (1.62─2.28)	1.72 (1.46─2.04)	1.70 (1.44─2.02)
CK-MB max	n = 1121	1.93 (1.63─2.28)	1.94 (1.63─2.30)	1.73 (1.46─2.05)	1.72 (1.45─2.04)
TnI	n = 801	2.14 (1.74─2.62)	2.15 (1.75─2.64)	1.94 (1.58─2.38)	1.93 (1.57─2.37)
TnT max	n = 931	2.06 (1.70─2.48)	2.03 (1.68─2.46)	1.89 (1.56─2.28)	1.87 (1.54─2.26)
Estimated GFR	n = 1104	1.89 (1.60─2.25)	**1.53 (1.28─1.82)**	1.70 (1.43─2.01)	**1.61 (1.35─1.92)**
ProBNP	n = 928	2.13 (1.76─2.58)	**1.95 (1.61─2.36)**	1.98 (1.64─2.40)	**1.89 (1.56─2.29)**
hsCRP	n = 941	2.12 (1.75─2.56)	**1.97 (1.62─2.39)**	1.98 (1.63─2.40)	**1.84 (1.52─2.24)**
Leukocytes	n = 1079	1.94 (1.63─2.31)	1.92 (1.62─2.28)	1.72 (1.44─2.04)	1.70 (1.43─2.03)
Total cholesterol	n = 1063	1.93 (1.62─2.30)	**1.87 (1.57─2.23)**	1.75 (1.47─2.09)	**1.72 (1.44─2.05)**
LDL cholesterol	n = 956	1.88 (1.57─2.27)	**1.84 (1.52─2.21)**	1.76 (1.46─2.12)	**1.73 (1.44─2.08)**
BMI	n = 1092	1.89 (1.59─2.24)	1.88 (1.58─2.23)	1.69 (1.42─2.01)	1.69 (1.42─2.01)
Adm Killip class II–IV	n = 1119	1.93 (1.63─2.29)	**1.80 (1.52─2.14)**	1.73 (1.46─2.05)	**1.66 (1.39─1.96)**
Max Killip class II–IV	n = 1119	1.93 (1.63─2.29)	**1.69 (1.42─2.00)**	1.73 (1.46─2.05)	**1.58 (1.32─1.87)**
Thrombolysis	n = 1121	1.93 (1.63─2.28)	1.94 (1.64─2.30)	1.73 (1.46─2.05)	**1.77 (1.49─2.10)**
Primary PCI	n = 1121	1.93 (1.63─2.28)	**1.96 (1.36─2.32)**	1.73 (1.46─2.05)	1.73 (1.36─2.05)
Other PCI	n = 1121	1.93 (1.63─2.28)	**1.88 (1.59─2.23)**	1.73 (1.46─2.05)	1.71 (1.44─2.03)
CABG	n = 1121	1.93 (1.63─2.28)	1.93 (1.63─2.28)	1.73 (1.46─2.05)	1.72 (1.45─2.04)
No thrombolysis/revasc	n = 1121	1.93 (1.63─2.28)	1.94 (1.64─2.30)	1.73 (1.46─2.05)	1.74 (1.47─2.06)
LVEF	n = 879	1.89 (1.56─2.29)	**1.64 (1.35─2.00)**	1.80 (1.48─2.18)	**1.64 (1.35─1.99)**
GRACE risk score	n = 1118	1.92 (1.63─2.28)	**1.55 (1.30─1.84)**	1.72 (1.46─2.04)	**1.56 (1.31─1.85)**

Hazard ratios with corresponding 95% confidence intervals. Variables significantly affecting the hazard ratio by >3% are shown in **bold**.

Abbreviations: MI─myocardial infarction; HF─heart failure; STEMI─ST-elevation MI; NSTEMI─non STEMI; Adm─admission; TnT─troponin T; GFR─glomerular filtration rate; BNP─brain natriuretic peptide; hsCRP─high sensitivity C-reactive protein; LDL─low-density lipoprotein; BMI─body mass index; PCI percutaneous coronary intervention; CABG─coronary artery bypass grafting; LVEF─left ventricular ejection fraction; GRACE─Global Registry of Acute Coronary Events.

Table S3

Multivariable analyses of the relationship between NGAL q4 vs q1–3 and all-cause long-term mortality adjusted for the variables in Table 1 with [a]nearly complete data and for [b]all variables.

[a]**Adjusted**

N = 1086	**Hazard**	**95% Confidence limits**		***P*-value**
Parameter	**ratio**	**Lower**	**Upper**	
NGAL q4 vs. q1–3	**1.333**	**1.1**	**1.614**	**0.0033**
Age	1.078	1.064	1.093	<.0001
Sex	0.831	0.689	1.001	0.0518
Previous MI	1.696	1.37	2.099	<.0001
Previous angina	1.182	0.984	1.42	0.0734
Previous HF	1.589	1.197	2.11	0.0014
Previous diabetes	1.61	1.316	1.97	<.0001
Current smoker	1.404	1.161	1.697	0.0005
Lipid-lowering drug	1.009	0.79	1.289	0.9428
SBP <100 at admission	1.675	1.047	2.678	0.0313
ln(eGFR)	0.637	0.45	0.902	0.0111
Max Killip II–IV	1.76	1.437	2.156	<.0001
Thrombolysis	0.861	0.686	1.081	0.1978
Primary PCI	0.892	0.67	1.186	0.4308
Other PCI	0.88	0.702	1.103	0.2671

[b]Adjusted

N = 639	**Hazard**	**95% Confidence limits**		***P*-value**
Parameter	**ratio**	**Lower**	**Upper**	
NGAL q4 vs. q123	**1.497**	**1.158**	**1.935**	**0.002**
Age	1.073	1.053	1.094	<.0001
Sex	0.934	0.72	1.211	0.6064
Previous MI	1.371	1.022	1.838	0.0351
Previous angina	1.417	1.106	1.817	0.0059
Previous HF	1.522	1.025	2.26	0.0371
Previous diabetes	1.568	1.19	2.067	0.0014
Current smoker	1.448	1.117	1.877	0.0051
Lipid-lowering drug	0.843	0.59	1.205	0.3499
SBP <100 at admission	2.305	1.226	4.336	0.0095
ln(estimated GFR)	0.645	0.405	1.026	0.0643
Max Killip II–IV	1.305	0.978	1.742	0.0705
Thrombolysis	0.867	0.641	1.171	0.3522
Primary PCI	0.753	0.53	1.069	0.1126
Other PCI	0.793	0.591	1.065	0.1239
ln(proBNP)	1.013	0.884	1.161	0.8495
hsCRP	1.001	0.998	1.005	0.4909
total cholesterol	1.059	0.829	1.353	0.6471
ln(LDL cholesterol)	0.493	0.204	1.191	0.116
LVEF	0.973	0.962	0.985	<0.0001

Table S4

Interactions between NGAL concentration and extended long-term mortality.

	N	NGAL q1–3	NGAL q4	*P* for interaction
Age >73 years (q4)	[a]841/280	[b]3.40 (2.77─4.18)	[b] 3.06 (2.29─4.08)	0.66
Sex	841/280	1.10 (0.90─1.35)	1.21 (0.88─1.65)	0.63
age adjusted		0.82 (0.67─1.02)	1.07 (0.78─1.46)	0.20
Previous MI	841/280	2.08 (1.68─2.57)	2.16 (1.59─2.93)	0.74
age adjusted		2.00 (1.62─2.48)	2.09 (1.54─2.85)	0.75
Previous angina	841/280	1.58 (1.30─1.92)	1.86 (1.40─2.45)	0.34
age adjusted		1.38 (1.14─1.68)	1.50 (1.13─1.98)	0.74
Previous HF	841/280	3.03 (2.20─4.16)	2.96 (1.99─4.40)	0.92
age adjusted		2.71 (1.97─3.73)	2.29 (1.54─3.40)	0.53
Previous diabetes	841/280	1.80 (1.42─2.28)	1.64 (1.19─2.27)	0.67
age adjusted		1.78 (1.40─2.26)	1.62 (1.17─2.23)	0.64
Previous hypertension	841/279	1.47 (1.21─1.78)	1.47 (1.11─1.94)	0.91
age adjusted		1.29 (1.06─1.57)	1.37 (1.04─1.80)	0.67
Previous hypercholesterolaemia	840/280	0.95 (0.77─1.18)	1.05 (0.76─1.45)	0.57
age adjusted		1.13 (0.91─1.39)	1.19 (0.86─1.65)	0.64
Current smoker	829/274	0.70 (0.55─0.88)	0.90 (0.68─1.21)	0.16
age adjusted		1.20 (0.95─1.52)	1.20 (0.89─1.62)	0.77
Lipid-lowering drug	841/280	1.34 (1.04─1.73)	1.27 (0.83─1.95)	0.91
age adjusted		1.50 (1.16─1.94)	1.25 (0.82─1.92)	0.58
STEMI	841/280	0.94 (0.77─1.14)	0.79 (0.60─1.04)	0.36
age adjusted		0.99 (0.81─1.20)	0.77 (0.58─1.02)	0.18
NSTEMI	841/280	1.06 (0.87─1.30)	1.28 (0.96─1.71)	0.33
age adjusted		1.06 (0.86─1.30)	1.32 (0.99─1.76)	0.25
ST elevation at admission	839/280	0.86 (0.70─1.06)	0.82 (0.62─1.09)	0.83
age adjusted		0.92 (0.75─1.13)	0.82 (0.62─1.09)	0.56
ST depression at admission	839/280	1.71 (1.30─2.26)	1.78 (1.23─2.56)	0.81
age adjusted		1.56 (1.18─2.06)	1.58 (1.10─2.28)	0.96
Q-wave at admission	839/280	1.11 (0.80─1.52)	1.26 (0.88─1.79)	0.53
age adjusted		1.12 (0.82─1.55)	1.19 (0.83─1.69)	0.74
Systolic BP <100 at admission	841/280	1.40 (0.77─2.55)	0.99 (0.51─1.94)	0.45
age adjusted		1.99 (1.09─3.65)	1.26 (0.64─2.45)	0.36
Heart rate at admission	840/280			
HR >86 (q4)		1.65 (1.33─2.04)	1.38 (1.02─1.86)	0.42
HR >86 (q4) age adjusted		1.76 (1.42─2.19)	1.56 (1.15─2.11)	0.60

CK-MB max	841/280			
CK-MB >184 (q4)		1.05 (0.83─1.32)	0.90 (0.67─1.22)	0.43
CK-MB >184 (q4) age adjusted		1.16 (0.92─1.46)	0.98 (0.73─1.33)	0.42
TnT max	706/225			
TnT >3.8 (q4)		1.14 (0.88─1.46)	0.94 (0.68─1.31)	0.35
TnT >3.8 (q4) age adjusted		1.03 (0.80─1.32)	0.97 (0.70─1.34)	0.78
Ln (TnI) at admission	616/185			
TnI >16.8 (q4)		1.01 (0.78─1.32)	1.00 (0.68─1.46)	0.96
TnI >16.8 (q4) age adjusted		1.07 (0.82─1.40)	1.25 (0.85─1.83)	0.41
Ln (Estimated GFR)	829/275			
eGFR <52 (q1)		2.22 (1.78─2.78)	3.00 (2.26─4.00)	0.11
eGFR <52 (q1) age adjusted		1.01 (0.79─1.28)	1.68 (1.20─2.34)	0.13
Ln (ProBNP)	718/210			
proBNP >3231 (q4)		2.33 (1.86─2.92)	2.27 (1.64─3.15)	0.96
proBNP >3231 (q4) age adjusted		1.61 (1.28─2.03)	1.55 (1.11─2.16)	0.88
hsCRP	733/208			
hsCRP >36.5 (q4)		1.47 (1.16─1.88)	1.36 (0.98─1.87)	0.75
hsCRP >36.5 (q4) age adjusted		1.47 (1.16─1.88)	1.04 (0.75─1.44)	0.12
Leukocytes	808/271			
leukocytes >11.1 (q4)		0.97 (0.76─1.24)	1.45 (1.08─1.93)	0.03
leukocytes >11.1 (q4) age adjusted		1.31 (1.02─1.68)	1.70 (1.27─2.27)	0.12
Total cholesterol	802/261			
total cholesterol <4.6 (q1)		1.56 (1.23─1.98)	1.48 (1.10─2.00)	0.86
total cholesterol <4.6 (q1) age adjusted		1.37 (1.08─1.73)	1.35 (1.00─1.82)	0.93
Ln (LDL cholesterol)	720/236			
LDL <2.77 (q1)		1.40 (1.10─1.78)	1.50 (1.10─2.04)	0.69
LDL <2.77 (q1) age adjusted		1.38 (1.09─1.76)	1.50 (1.09─2.04)	0.69
BMI	824/268			
BMI <20 or >30		1.20 (0.95─1.52)	1.02 (0.68─1.52)	0.49
BMI <20 or >30 age adjusted		1.27 (1.00─1.60)	1.09 (0.73─1.63)	0.57
Killip class II–IV at admission	839/280	3.76 (2.61─5.41)	2.09 (1.38─3.16)	<0.05
age adjusted		2.43 (1.68─3.52)	1.53 (1.00─2.32)	0.06
Max Killip class II–IV	839/280	3.01 (2.38─3.82)	1.92 (1.43─2.57)	0.03
age adjusted		2.20 (1.73─2.80)	1.45 (1.07─1.96)	0.02
Thrombolysis	841/280	1.10 (0.86─1.42)	0.76 (0.54─1.06)	0.07
age adjusted		1.00 (0.77─1.29)	0.62 (0.44─0.88)	0.02
Primary PCI	841/280	0.65 (0.48─0.89)	0.51 (0.33─0.79)	0.39
age adjusted		0.88 (0.64─1.20)	0.74 (0.47─1.14)	0.72
Other PCI	841/280	0.69 (0.53─0.89)	0.88 (0.58─1.33)	0.29
age adjusted		0.83 (0.64─1.07)	0.98 (0.65─1.49)	0.39
CABG	841/280	0.93 (0.66─1.29)	1.01 (0.62─1.66)	0.75
age adjusted		0.82 (0.59─1.15)	1.02 (0.62─1.68)	0.48
No thrombolysis/ revascularization	841/280	1.45 (1.19─1.76)	1.69 (1.28─2.23)	0.38

age adjusted		1.23 (1.01─1.50)	1.52 (1.15─2.01)	0.30
LVEF	661/218			
LVEF <45 (q1)		2.92 (2.30─3.72)	1.80 (1.31─2.49)	0.02
LVEF <45 (q1) age adjusted		2.33 (1.82─2.98)	1.65 (1.20─2.29)	0.09
GRACE risk score	838/280			
GRACE >127 (q4)		3.92 (3.19─4.83)	3.14 (2.37─4.17)	0.26
GRACE >127 (q4) age adjusted		2.01 (1.60─2.52)	1.79 (1.30─2.46)	0.23

[a]Number in q1–3/q4.

[b]Hazard ratios with corresponding 95% confidence interval.

Table S5

Comparison of hazard ratios (HR) and 95% confidence intervals (CI) between 938 patients with data for NGAL and CRP concentrations─and GRACE score.

NGAL and GRACE		**HR**	**95% CI**	***P*-value**
NGAL q1–3/GRACE q1–3	583	1		
NGAL q4/GRACE q1–3	136	1.92	1.49–2.46	<0.0001
NGAL q1–3/GRACE q4	147	3.77	3.01–4.73	<0.0001
NGAL q4/GRACE q4	72	7.46	5.64–9.88	<0.0001

hsCRP and GRACE	**N**	**HR**	**95% CI**	***P*-value**
hsCRP q1–3/GRACE q1–3	558	1		
hsCRP q4/GRACE q1–3	161	1.53	1.20–1.96	0.0007
hsCRP q1–3/GRACE q4	147	4.04	3.23–5.06	<0.0001
hsCRP q4/GRACE q4	72	5.74	4.33–7.61	<0.0001

NGAL and hsCRP	**N**	**HR**	**95% CI**	***P*-value**
NGAL q1–3/hsCRP q1–3	578	1		
NGAL q4/hsCRP q1–3	127	2.06	1.62–2.63	<0.0001
NGAL q1–3/hsCRP q4	152	1.5	1.18–1.92	0.001
NGAL q4/hsCRP q4	81	2.8	2.13–3.67	<0.0001