Prognostic Value of Plasma Neutrophil Gelatinase–Associated Lipocalin for Mortality in Patients With Heart Failure

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Background—In patients with heart failure, renal dysfunction is associated with a poor outcome. We aimed to assess the prognostic value of plasma neutrophil gelatinase–associated lipocalin (NGAL), a novel marker of renal tubular damage, in patients with heart failure with or without renal dysfunction, and compare it with 2 frequently used biomarkers of chronic kidney disease.

Methods and Results—Plasma NGAL, estimated glomerular filtration rate (eGFR), and cystatin C were assessed in 562 patients with heart failure. Chronic kidney disease was defined as eGFR<60 mL/min per 1.73 m^2. Outcome was all-cause mortality at 36 months. Mean age was 71±11 years, 61% were men, and 97% were in New York Heart Association functional class II/III. Mean baseline eGFR was 54±20 mL/min per 1.73 m^2, mean cystatin C was 11.2 (7.7–16.2) mg/L, and median plasma NGAL was 85 (60–123) ng/mL. Higher plasma NGAL levels were independently associated with an increased risk of all-cause mortality, in patients with and without chronic kidney disease (hazard ratio [per SD increase in log NGAL]=1.45 [1.22–1.72]; P<0.001 and hazard ratio=1.51 [1.06–2.16]; P=0.023, respectively). Similarly, both in patients with high and low cystatin C (median cut-off), higher plasma NGAL levels were independently associated with an increased risk of all-cause mortality. Moreover, when NGAL was entered in the multivariable risk prediction model, eGFR (P=0.616) and cystatin C (P=0.937) were no longer associated with mortality.

Conclusions—Plasma NGAL predicts mortality in patients with heart failure, both in patients with and without chronic kidney disease and is a stronger predictor for mortality than the established renal function indices eGFR and cystatin C. **(*Circ Heart Fail*. 2014;7:35-42.)**

Key Words: heart failure ■ NGAL protein, human ■ prognosis

Moderate to severe chronic kidney disease (CKD), mainly expressed by estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2, is strongly associated with increased mortality among patients with heart failure, whereas these findings are far less established in the presence of mild impaired renal function.[1,2]

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Interestingly, serum creatinine is relatively insensitive to changes in the GFR, and kidney disease is not only reflected by GFR. In patients with intrinsic kidney failure, tubulointerstitial damage is an established marker for renal disease as well.[3] In different pathogenesis of kidney failure, tubulointerstitial hypoxia seems to be an early marker for the development of kidney failure.[4–13] Several studies showed that tubular markers are increased before an increase of creatinine is observed.[14–17]

We recently demonstrated that urinary markers of tubular damage, such as N-acetyl-β-D-glucosaminidase, kidney injury molecule 1, and neutrophil gelatinase–associated lipocalin (NGAL), were elevated in patients with heart failure.[3,18] In addition, the tubular markers, urinary N-acetyl-β-D-glucosaminidase and kidney injury molecule 1, were related to a poor prognosis, independent of eGFR.[19] Also, in a much larger sub-study of the GISSI-HF (The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure Study) trial, urinary NGAL levels were independently associated with cardiovascular outcome.[19] Few studies in patients with heart failure have indicated that higher plasma markers of tubular damage are also related to an increased risk of mortality.[20–24]

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However, the prognostic value of plasma tubular damage in patients with normal or mildly impaired renal function has been less well described.[23] The aims of this study were first to assess the role and performance of the tubular marker plasma NGAL as a prognostic marker of mortality in patients with heart failure with both normal and impaired renal function. Second, we aimed to compare the prognostic value of plasma NGAL with 2 frequently used biomarkers of CKD.

Methods

Patient Population

This is a retrospective analysis of the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH), a multicenter, randomized, open trial, designed to compare usual care, basic support, and intensive support in patients with heart failure, conducted between 2002 and 2007 in The Netherlands.[25,26] Patients were included just before discharge of their hospitalization for acute decompensated heart failure. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the locally appointed ethics committees. All patients provided written informed consent for the main study. Of all 1023 patients from the COACH, 562 patients had baseline plasma available for this analysis. Demographic and clinical data were collected from chart review.

Renal Function

We calculated eGFR (mL/min per 1.73 m^2) using the simplified modification of diet in renal disease formula ($186.3\times(\text{serum creatinine [mg/dL]})^{-1.154}\times\text{age}^{-0.203}\times[0.742 \text{ if women}]$)[27] at discharge and after 6 months. Cystatin C was measured using a Luminex assay by Alere San Diego (R&D). Plasma NGAL was measured using a simultaneous ELISA developed in-house at Alere San Diego. The primary antibody was biotinylated and bound to a neutravidin plate. The secondary antibody was labeled with fluorescein, which serves as a hapten for an antifluoroscein antibody labeled with alkaline phosphatase. All other liquid handling steps were performed with a Beckman Biomek FX. Intra-/interassay variability were 15.8%/15.7% for 27 ng/mL, 13.5%/13.7% for 280 ng/mL, and 17.1%/17.1% for 860 ng/mL, respectively. The analysis was performed independent of the data analysis.

Other Biomarkers

To account for the possible inflammatory association of NGAL, C-reactive protein was measured using a bead-based immunoassay performed in microtiter plates. The primary antibody was conjugated to modified paramagnetic Luminex beads obtained from Radix Biosolutions; purified C-reactive protein was biotinylated.

B-type natriuretic peptide (BNP) was measured using a bead-based immunoassay performed in microtiter plates. The primary antibody was conjugated to modified paramagnetic Luminex beads obtained from Radix Biosolutions; the secondary antibody was biotinylated. Fluorescent signals were generated using Streptavidin-R-Phycoerythrin (SA-RPE: Prozyme PJ31S).

Outcome

The extended outcome of the COACH trial consisted of mortality assessed at 36 months, for which additional ethical committee approval was obtained.

Statistical Analyses

Patients were divided into 2 groups according to the value of eGFR: the CKD group (eGFR<60 mL/min per 1.73 m^2 by modification of diet in renal disease equation) and the non-CKD group (eGFR≥60 mL/min per 1.73 m^2). Because previous research suggests a difference in risk curves for CKD and non-CKD heart failure patients, the analyses were conducted separately by the presence of CKD.[2] Data are presented as mean±SD when normally distributed, as median and interquartile range when non-normally distributed, and as frequencies and percentages for categorical variables. Differences between baseline variables were evaluated by Student *t* test, Kruskal–Wallis test, Mann–Whitney *U* or χ^2 tests where appropriate. For the Kaplan–Meier curves, CKD classification and medians of plasma NGAL and cystatin C were used as cut-off points.

Cox proportional hazard analysis was used to assess whether plasma NGAL is a predictor of prognosis. NGAL showed a log-linear functional shape with the response variable and was transformed to a log scale. In consecutive models, plasma NGAL was adjusted for age and sex, eGFR and finally for the final model, consisting of diastolic blood pressure, pulse pressure, history of stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, previous hospitalization, serum sodium, BNP, and treatment (fully adjusted model).[28] For confirmatory analysis, BNP was replaced with N-terminal pro-BNP. Interactions between plasma NGAL and both eGFR and cystatin C were tested. To evaluate predictive use of plasma NGAL, eGFR and cystatin C, Harrell's C-statistics and corresponding 95% confidence interval (CI) generated by an approximate Jackknife method were calculated using the somersd package from STATA. Furthermore, we calculated the incremental value of plasma NGAL by means of the integrated discrimination index and net reclassification index for the model of all significant variables versus this model plus plasma NGAL. Cut-off values of mortality were arbitrarily set at 10% and 30%.

A *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using R Statistics (version 2.13.2) and STATA (version 10, College Station, TX).

Results

A total of 562 patients were available for this analysis. These patients did not differ significantly from the 461 excluded patients that originally participated in COACH (Table in the Data Supplement). Mean age was 71±11 years, 61% were men, 97% were in New York Heart Association functional class II or III, and 53% had been hospitalized previously because of heart failure. Mean baseline eGFR was 54±20 mL/min per 1.73 m2, mean cystatin C was 11.2 (7.7–16.2) mg/L, and median plasma NGAL was 85 (60–123) ng/mL.

Table 1 shows the baseline characteristics of the patients according to CKD and non-CKD. Patients with CKD were older, were in a higher New York Heart Association functional class, were less likely to receive an angiotensin-converting enzyme inhibitor, had higher levels of cystatin C and NGAL, lower levels of hemoglobin (all *P*<0.001), and had more comorbidities. C-Reactive protein did not differ between the CKD and non-CKD groups (*P*=0.093) nor was C-reactive protein correlated with plasma NGAL (*r*=0.073; *P*=0.14).

Plasma NGAL, eGFR, and Prognosis

After a follow-up of 3 years, 232 (41%) patients died. After 3 years, mortality in patients with CKD was 49% (n=175/357) compared with 28% (57/205) in the non-CKD-group (hazard ratio, 2.09; 95% CI, 1.55–2.81; *P*<0.001).

Figure 1 shows the Kaplan–Meier curves for the occurrence of all-cause mortality. Curves are shown for 4 groups (CKD and non-CKD, and high and low NGAL). There was a gradual increase in risk with more evidence of kidney disease (CKD or high NGAL). NGAL above the median was associated with increased risk of mortality in both CKD (hazard ratio, 1.97; 95% CI, 1.41–2.77; *P*<0.001) and non-CKD (hazard ratio, 2.05; 95% CI, 1.20–3.50; *P*=0.008).

Table 1. Baseline Characteristics of Patients According to CKD and Non-CKD

	All Patients (N=562)	CKD (n=347)	Non-CKD (n=205)	*P* Value
Age, y	71±11	74±10	66±11	<0.001
Sex (% women)	39	42	33	0.005
LVEF, %	32±14	33±14	32±15	0.493
NYHA, %				<0.001
2	47	39	59	
3	50	57	39	
4	3	4	2	
Systolic BP, mm Hg	118±21	119±22	116±20	0.067
Diastolic BP, mm Hg	69±12	68±12	70±12	0.122
Heart rate, beats per minute	74±13	74±13	75±13	0.43
Medical history, %				
Hypertension	42	49	31	<0.001
Peripheral arterial disease	16	18	12	0.009
Myocardial infarction	41	45	34	0.044
Atrial fibrillation	45	49	40	0.014
Stroke	15	18	11	0.061
COPD	28	31	24	0.084
Laboratory				
Cystatin C, mg/L	11.2 (7.7–16.2)	12.6 (8.7–19.2)	8.8 (7–12.6)	<0.001
NGAL, ng/mL	85 (60–123)	104 (72–151)	65 (51–85)	<0.001
Creatinine, mg/dL*	1.30 (1.03–1.64)	1.56 (1.32–1.89)	0.98 (0.87–1.14)	<0.001
Hemoglobin, g/dL	13±2	12.8±1.9	13.7±2	<0.001
BNP, pg/mL	454 (202–904)	480 (214–997)	416 (185–785)	0.078
CRP, mg/L	2.3 (0.9–5.1)	2.3 (1–5.5)	2.3 (0.8–4.9)	0.093
Medication use, %				
ACE inhibitor	72	68	79	<0.001
Angiotensin receptor blocker	11	12	10	0.699
β-Blocker	67	64	71	0.207
Diuretic	95	96	95	0.238
Statin	39	39	38	0.576
Calcium antagonist	14	13	15	0.645

ACE indicates angiotensin-converting enzyme; BNP, brain-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NGAL, neutrophil gelatinase–associated lipocalin; and NYHA, New York Heart Association functional class.

*For μmol/L multiply by 88.4.

Overall, higher plasma NGAL levels were independently associated with increased mortality. In all consecutive models (plasma NGAL adjusted for age and sex, adjusted for eGFR, and finally for the fully adjusted model with BNP), higher plasma NGAL levels were independently associated with an increased risk of all-cause mortality (hazard ratio, 1.44 per SD increase in log NGAL; 95% CI, 1.22–1.69; *P*<0.001; Table 2). The prognostic values (C-statistics) of plasma NGAL and eGFR are shown in Table 3. Integrated discrimination index improved significantly adding NGAL to the fully adjusted model (0.029; *P*<0.001), whereas net reclassification index showed a trend toward a significant improvement (0.062; *P*=0.054). When BNP was replaced with N-terminal pro-BNP, results remained consistent.

Divided into CKD and non-CKD, plasma NGAL levels remained significantly associated in the consecutive models with 3-year mortality, in patients with CKD and in non-CKD patients, whereas eGFR was only univariate associated with mortality in patients with CKD. Furthermore, eGFR was no longer significantly associated with mortality in patients with CKD when plasma NGAL was introduced in the crude, age and sex adjusted, and fully adjusted model (Table 2).

Plasma NGAL, Cystatin C, and Prognosis

In accordance with eGFR, we divided cystatin C into 2 groups. Figure 2 shows the Kaplan–Meier curves for the occurrence of all-cause mortality (high and low cystatin C, and high and low

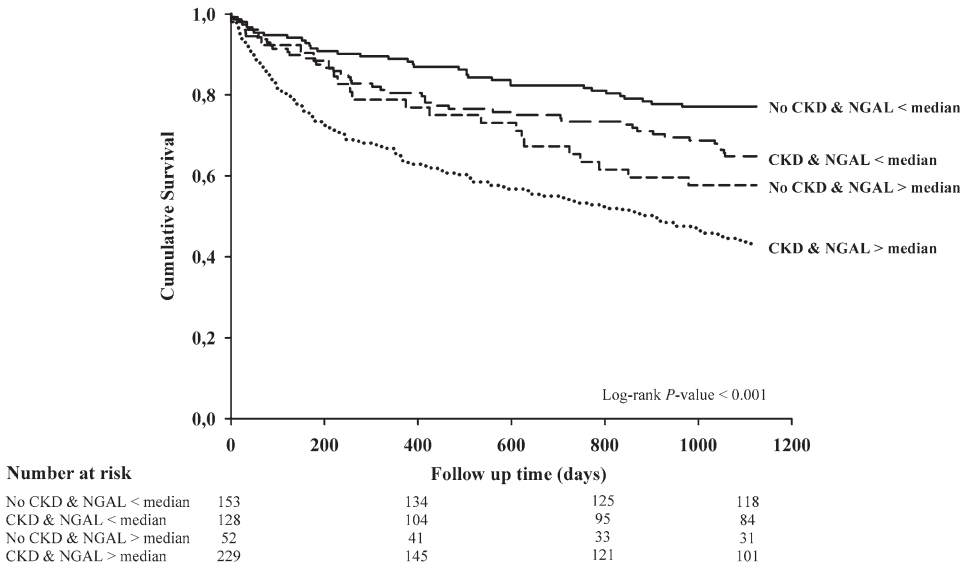

Figure 1. Three-year mortality (chronic kidney disease [CKD] and non-CKD vs low/high neutrophil gelatinase–associated lipocalin [NGAL])-Kaplan–Meier curves showing the association between all-cause mortality and low/high estimated glomerular filtration rate (cut-off point, 60 mL/min per 1.73 m^2) and low/high NGAL (cut-off point, 84.62 ng/mL). Hazard ratio vs no CKD/NGAL<median for CKD/NGAL<median, 1.65; 95% confidence interval (CI), 1.01 to 2.56; *P*=0.027; for no CKD/NGAL>median, 2.05; 95% CI, 1.20 to 3.49; *P*=0.009; and for CKD/NGAL>median, 3.26; 95% CI, 2.24 to 4.74; *P*<0.001.

NGAL). Within the groups of NGAL, there was no difference in mortality between the 2 cystatin C groups.

Again, higher plasma NGAL levels were independently associated with increased mortality, in all consecutive models (adjusted for age, sex, and cystatin C, and finally for the fully adjusted model with cystatin C; Table 2). The prognostic value of plasma NGAL including cystatin C (measured by C-statistic) for the total group was higher compared with cystatin C without NGAL (Table 3). Integrated discrimination index improved significantly adding NGAL to the fully adjusted model (0.027; *P*<0.001), whereas net reclassification index did not show improvement in discrimination (–0.025; *P*=0.409). When BNP was replaced with N-terminal pro-BNP, results remained consistent. The discrepancy in significance could be explained because integrated discrimination index can be seen as the continuous version if net reclassification index with probability differences used instead of categories.

Divided into high and low cystatin C groups, plasma NGAL levels remained significantly associated in the

Table 2. Risk Models of the Predictive Value of Plasma NGAL, eGFR, and Cystatin C in Patients With Heart Failure With and Without CKD

	All Patients		CKD		Non-CKD	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
eGFR alone (per SD increase)	1.50 [1.30–1.72]	<0.001	1.54 [1.19–1.98]	<0.001	1.02 [0.66–1.56]	0.938
eGFR, age and sex adj.	1.41 [1.21–1.64]	<0.001	1.51 [1.17–1.96]	0.002	0.93 [0.60–1.43]	0.726
eGFR, fully adjusted	1.28 [1.10–1.49]	0.001	1.26 [0.94–1.67]	0.121	1.04 [0.62–1.77]	0.858
eGFR, fully adjusted with NGAL	1.04 [0.88–1.24]	0.616	0.87 [0.63–1.21]	0.413	1.00 [0.60–1.67]	0.993
Cyst C alone (per SD increase)	1.15 [1.02–1.30]	0.020	1.04 [0.90–1.19]	0.623	1.24 [0.96–1.62]	0.100
Cyst C, age and sex adj.	1.11 [0.98–1.26]	0.093	1.04 [0.90–1.20]	0.573	1.18 [0.91–1.55]	0.217
Cyst C, fully adjusted	1.09 [0.96–1.23]	0.208	1.07 [0.92–1.24]	0.406	1.08 [0.82–1.44]	0.572
Cyst C, fully adjusted with NGAL	0.99 [0.87–1.14]	0.937	0.98 [0.84–1.15]	0.836	1.03 [0.77–1.38]	0.844
NGAL alone (per SD increase)	1.61 [1.42–1.83]	<0.001	1.48 [1.27–1.72]	<0.001	1.62 [1.17–2.23]	0.003
NGAL, age and sex adj.	1.51 [1.32–1.72]	<0.001	1.44 [1.23–1.68]	<0.001	1.44 [1.03–2.00]	0.033
NGAL, fully adjusted	1.47 [1.27–1.69]	<0.001	1.45 [1.22–1.72]	<0.001	1.51 [1.06–2.16]	0.023
NGAL, fully adjusted with eGFR	1.44 [1.22–1.69]	<0.001	1.51 [1.24–1.85]	<0.001	1.51 [1.06–2.16]	0.024
NGAL, fully adjusted with cyst C	1.47 [1.27–1.70]	<0.001	1.45 [1.22–1.74]	<0.001	1.50 [1.04–2.16]	0.026

Fully adjusted model: adjusted for age, sex, diastolic blood pressure, pulse pressure, history of stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, previous hospitalization, serum sodium, B-type natriuretic peptide, and treatment allocation. CI indicates confidence interval; CKD, chronic kidney disease; cyst C, cystatin C; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and NGAL, neutrophil gelatinase–associated lipocalin.

Table 3. C-Statistics of Models Comparing the Prognostic Value of eGFR and NGAL in Patients With Heart Failure With and Without CKD

	All Patients	CKD	Non-CKD
eGFR	0.614 (0.578–0.650)	0.569 (0.525–0.613)	0.520 (0.436–0.604)
eGFR, fully adjusted	0.730 (0.698–0.762)	0.723 (0.686–0.761)	0.701 (0.632–0.770)
Cyst C	0.554 (0.517–0.591)	0.511 (0.467–0.555)	0.581 (0.505–0.657)
Cyst C, fully adjusted	0.725 (0.693–0.757)	0.721 (0.684–0.758)	0.703 (0.634–0.771)
NGAL	0.644 (0.609–0.680)	0.615 (0.573–0.657)	0.616 (0.543–0.689)
NGAL, fully adjusted	0.740 (0.708–0.772) *P*=0.099 vs eGFR fam *P*=0.030 vs cystatin C fam	0.739 (0.701–0.777) *P*=0.027 vs eGFR fam *P*=0.031 vs cystatin C fam	0.716 (0.648–0.784) *P*=0.248 vs eGFR fam *P*=0.290 vs cystatin C fam
NGAL, fully adjusted with eGFR	0.740 (0.708–0.772) *P*=0.570 vs NGAL fam	0.740 (0.701–0.778) *P*=0.379 vs NGAL fam	0.716 (0.648–0.784) *P*=0.685 vs NGAL fam
NGAL, fully adjusted with cyst C	0.740 (0.708–0.772) *P*=0.598 vs NGAL fam	0.740 (0.702–0.777) *P*=0.401 vs NGAL fam	0.716 (0.648–0.784) *P*=0.958 vs NGAL fam

Fam: adjusted for age, sex, eGFR, diastolic blood pressure, pulse pressure, history of stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes mellitus, left ventricular ejection fraction, previous hospitalization, serum sodium, B-type natriuretic peptide, and treatment allocation. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; Fam, fully adjusted model; and NGAL, neutrophil gelatinase–associated lipocalin.

consecutive models with 3-year mortality, whereas cystatin C was not significantly associated with mortality in both groups. Furthermore, cystatin C was no longer significantly associated with mortality in patients with CKD when plasma NGAL was introduced in the crude, age and sex adjusted, and fully adjusted model (Table 2).

Discussion

This study shows that plasma NGAL predicts mortality in patients with heart failure, both in patients with and without CKD. Moreover, plasma NGAL is a stronger predictor for mortality than the frequently used biomarkers of impaired renal function eGFR and cystatin C.

Plasma NGAL and Prognosis

NGAL is a 25-kDa lipocalin-superfamily glycoprotein that is considered to play a role in acute kidney injury in a diverse range of settings.[16,29] In normal circumstances, only small amounts can be found in plasma and urine. However, during and after acute kidney injury, NGAL levels rise quickly and massively.[30]

In the present study, we found that plasma NGAL is independently associated with mortality. This confirms our recent study in which we found that tubular damage in heart failure was prevalent in chronic heart failure and related to impaired survival, independent of GFR and albuminuria.[18] In this small study, we were unable to establish the prognostic value of

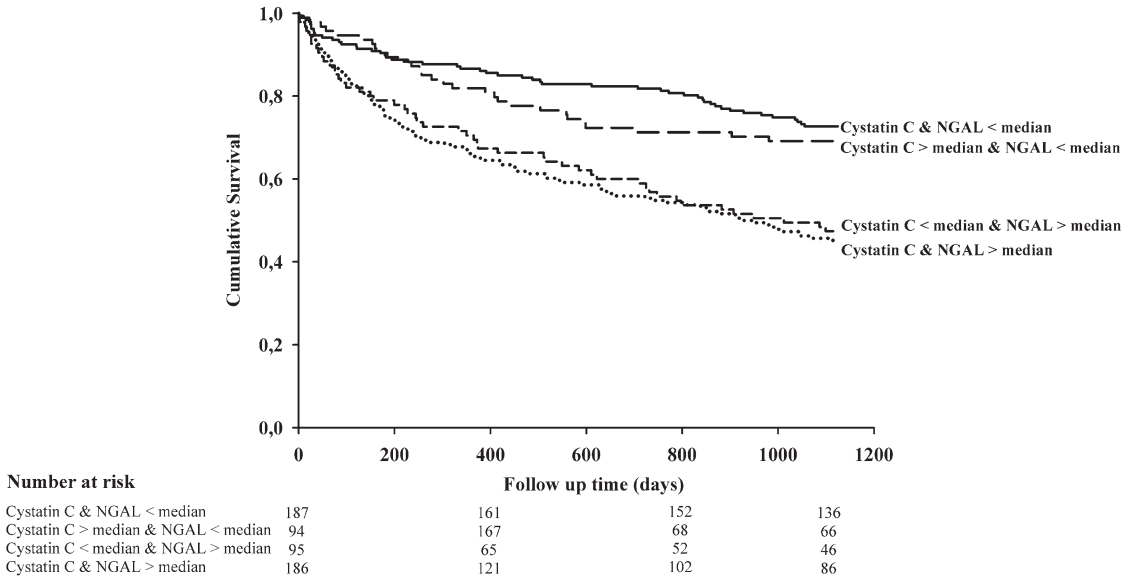

Figure 2. Three-year mortality (low/high cystatin C vs low/high neutrophil gelatinase–associated lipocalin [NGAL])-Kaplan–Meier curves showing the association between all-cause mortality and low/high cystatin C (cut-off point, 11.2 mg/L) and low/high NGAL (cut-off point, 84.62 ng/mL). Hazard ratio vs cystatin C and NGAL<median for cystatin C>median/NGAL<median, 1.17; 95% CI, 0.74 to 1.85; *P*=0.50; for cystatin C<median/NGAL>median, 2.35; 95% CI, 1.59 to 3.47; *P*<0.001; and for cystatin C and NGAL>median, 2.53; 95% CI, 1.81 to 3.54; *P*<0.001.

urinary NGAL in chronic heart failure. However, in a much larger sub-study of the GISSI-HF trial, urinary NGAL levels were independently associated with outcome.[19]

Bolignano et al[20] found prognostic significance of plasma NGAL levels in 46 patients with chronic heart failure. In 3 confirmative smaller studies, serum NGAL, measured at admission for acute heart failure, predicted death only when NGAL was dichotomized by an optimally taken cut-off point.[21,22]

In the CORONA (Controlled rosuvastatin multinational study in heart failure) study, with 1415 patients with chronic heart failure of ischemic pathogenesis, plasma NGAL was an univariate predictor of all-cause mortality, cardiovascular death, and hospitalization. However, plasma NGAL was no longer a significant predictor when adjusted for GFR and N-terminal pro-BNP.[23] In contrast, Alvelos et al[22] showed that plasma NGAL was an independent predictor of increased risk of short-term death and readmission in patients with acute heart failure. In the recent NGAL EvaLuation Along with B-type NaTriuretic Peptide trail, in which plasma NGAL was measured in 186 patients with acute heart failure at discharge, plasma NGAL was an even better prognostic indicator compared with BNP.[24]

Plasma NGAL in Non-CKD Patients

This study shows that plasma NGAL predicts mortality in patients with heart failure, even in non-CKD patients. Taking into consideration that creatinine is a marker of kidney function and NGAL is a marker of kidney injury, there are several arguments why tubular damage in patients with heart failure is associated with prognosis, whereas glomerular function in the mild impaired renal function ranges is not.

First, in patients with heart failure, decreased perfusion may be a key deleterious factor for the kidneys. Because the tubulus is more vulnerable to hypoxic damage,[4–12] it is possible that small declines in renal function result in tubular damage where the renal cortex stays intact, maintaining GFR.[4,31] Therefore, tubular damage might better reflect a decreased perfusion than eGFR.[30]

Second, in the acute setting, tubular markers are increased, whereas creatinine is still normal.[14–17] A possible mechanism is that decreased renal perfusion in heart failure leads to compensatory glomerular hyperfiltration.[32] In fact, renal blood flow can decrease by 30% to 40% without apparently affecting functional GFR.[31] Notably, tubular markers reflect renal injury, instead of renal function. Tubular markers, such as plasma NGAL, are therefore likely to be more sensitive than creatinine.

Third, creatinine levels are dependent of muscle metabolism, weight, age, and sex. Although formulas partly overcome this limitation, creatinine is still actively secreted by the proximal tubule, especially when GFR is low, making creatinine less useful in extremes of true GFR.

Plasma NGAL Compared With eGFR and Cystatin C

We show that plasma NGAL is a more powerful predictor of mortality than eGFR. The results of the incremental value of plasma NGAL over eGFR are almost similar when compared with the results of a more sensitive glomerular marker cystatin C.[33,34] Although eGFR is regularly used in daily practice, cystatin C can be seen as a more accurate reflection of glomerular function. In acute settings, creatinine is known to be a slower marker.[33,34] Creatinine-based formulas are less accurate in extremes of true eGFR,[27] and this is one of the factors why cystatin C is superior to creatinine.[35–38] Moreover, cystatin C is less dependent on body mass, decreased muscle mass, and cachexia, which are present in patients with chronic heart failure.[39–42]

Nevertheless, even when related to and adjusted for cystatin C, plasma NGAL remained to have a better prognostic value. This might indicate that in patients with heart failure, tubular damage might better reflect an impaired hemodynamic status as compared with glomerular function.

Limitations

Recognizing the importance of renal biomarkers in heart failure for improving risk stratification, there are several concerns in analyzing different biomarkers. It would be best to approach the accuracy of risk prediction with a multi-marker approach.[43,44]

Primary renal disease was not excluded at baseline in this study. Therefore, the observed relationships could have been affected by underlying renal disease, where associations among tubular damage, glomerular function, and outcome can be different. Larger studies are required to confirm our results, preferably with a specific intervention to investigate effects rather than associations. Also, we do not have information on cause of death.

Kidney disease is not only identified by low GFR and tubular damage. Unfortunately, we do not have sufficient data on albuminuria in the COACH cohort.

We assessed plasma NGAL, rather than urinary NGAL, which may be more affected by specific confounders, such as bacterial infection, presence of cancer or chronic obstructive pulmonary disease, and inflammation,[30] although C-reactive protein was not correlated with plasma NGAL in the present study. Plasma levels of NGAL still increase markedly (≤16-fold) in the setting of renal tubular injury. Plasma NGAL also has the advantage of easy collection because plasma is already collected in the clinical setting.[30]

Conclusions

The present study shows the incremental prognostic value of plasma NGAL in patients with heart failure with and without renal dysfunction. Moreover, plasma NGAL is a stronger predictor for mortality than frequently used biomarkers of CKD.

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CLINICAL PERSPECTIVE

Moderate to severe chronic kidney disease, mainly expressed by estimated glomerular filtration rate <60 mL/min per 1.73 m^2, is strongly associated with increased mortality among patients with heart failure, whereas these findings are far less established in the presence of mild impaired renal function. In different pathogenesis of kidney failure, tubulointerstitial hypoxia seems to be an early marker for the development of kidney failure. Several studies showed that tubular markers are increased before an increase of creatinine is observed. Neutrophil gelatinase–associated lipocalin (NGAL) reflects renal tubulointerstitial damage. Neutrophil gelatinase–associated lipocalin is an established renal marker in patients with intrinsic kidney failure along with other tubular markers. The novelty of this article is related to the predictive value of neutrophil gelatinase–associated lipocalin for mortality in patients with a normal renal function. Moreover, plasma neutrophil gelatinase–associated lipocalin was a stronger predictor for mortality than the established renal function indices estimated glomerular filtration rate and cystatin C.

Prognostic Value of Plasma Neutrophil Gelatinase–Associated Lipocalin for Mortality in Patients With Heart Failure

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SUPPLEMENTAL MATERIAL

Supplemental Table.

	NGAL not available n = 461	NGAL available n = 562	*P*-value
Age (years)	71 ± 12	71 ± 11	0.455
Gender (% female)	37	38	0.693
LVEF (%)	34 ± 15	32 ± 14	0.174
NYHA (%)			0.012
2	56	47	
3	41	50	
4	3	4	
Systolic BP (mmHg)	119 ± 21	118 ± 21	0.733
Diastolic BP (mmHg)	68 ± 12	69 ± 12	0.311
Heart rate (bpm)	75 ± 14	74 ± 13	0.325
Medical history (%)			
Hypertension	44	42	0.687
Peripheral arterial disease	17	16	0.826
Myocardial infartion	45	41	0.226
Atrial fibrillation	42	46	0.155
Stroke	17	15	0.483
COPD	24	28	0.093
Laboratory			
Cystatin C (mg/l)	NA	11.2 (7.7 - 16.2)	-
Creatinine (µmol/l)*	110 (90 - 141)	115 (91 - 145)	0.063
Hemoglobin (g/dl)	13.1 ± 1.9	13.2 ± 2	0.862
BNP (pg/ml)	1340 (738 - 2144)	1409 (810 - 2144)	0.91
CRP (mg/l)	NA	2.3 (0.9 - 5.1)	-
Medication use (%)			
ACE inhibitor	73	72	0.807
Angiotensin receptor bl	13	11	0.324
Beta blocker	65	67	0.588
Diuretic	96	96	0.666
Statin	37	39	0.53
Calcium antagonist	18	14	0.058

* for mg/dL divide by 88.4. Abbreviations: ACE: Angiotensin Converting Enzyme; BNP: Brain-type Natriuretic Peptide; Bpm: beats per minute; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; NGAL: Neutrophil Gelatinase Associated Lipocalin; NYHA: New York Heart Association functional class.