Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: The NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely decompensated heart failure (GALLANT) trial

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Aims	Neutrophil gelatinase-associated lipocalin (NGAL) is a measure of acute kidney injury. Renal dysfunction portends significant risk after discharge from acute heart failure (AHF). Thus, a sensitive marker of renal injury might also help to risk stratify HF patients.
Methods and results	GALLANT [NGAL EvaLuation Along with B-type NaTriuretic Peptide (BNP) in acutely Decompensated Heart Failure] was a multicentre, prospective study to assess the utility of plasma NGAL, alone and in combination with BNP, as an early risk marker of adverse outcomes. We studied 186 patients (61% male). There were 29 events (AHF readmissions and all-cause mortality) at 30 days (16%). Patients with events had higher levels of NGAL than those without (134 vs. 84 ng/mL, $P < 0.001$). The area under the receiver operating characteristic curve was higher for NGAL (0.72) than BNP (0.65), serum creatinine (0.57), or estimated glomerular filtration rate (eGFR; 0.55). In multivariable analyses, NGAL predicted events ($P = 0.001$), BNP approached significance ($P = 0.052$ and 0.070 without creatinine and GFR, respectively) while neither serum creatinine nor eGFR were significant. The addition of discharge NGAL over BNP alone improved classification by a net 10.3% in those with events and 19.5% in those without events, for a net reclassification improvement of 29.8% ($P = 0.010$). Subjects with both BNP and NGAL elevated were at significant risk [hazard ratio (HR) = 16.85, $P = 0.006$], as were subjects with low BNP and high NGAL (HR = 9.95, $P = 0.036$).
Conclusions	Plasma NGAL is a measure of kidney injury that at the time of discharge is a strong prognostic indicator of 30 days outcomes in patients admitted for AHF. Clinical trial registration number: NCT 00693745
Keywords	Renal injury • Acute heart failure • Biomarkers • BNP

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Introduction

Renal dysfunction is common in patients with acute heart failure (AHF) and is associated with significant early and late morbidity and mortality.[1,2] The fact that creatinine rise is a marker of renal function and not renal injury makes it less sensitive to early injury that might occur secondary to diuretic treatment, or other causes of decreased renal perfusion, including elevated central venous pressure.[3] This and the fact that it can take up to 2 days for creatinine to increase after an 'insult' to the renal tubules make it less appealing than a potential specific early rising marker of renal injury and, therefore, as a risk predictor in these patients.[3,4]

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin family of proteins. Neutrophil gelatinase-associated lipocalin is produced in the kidney following ischaemic or nephrotoxic injury in both animals and humans.[5-11] Dent et al.[12] demonstrated that NGAL was effective in identifying acute kidney injury (AKI) 2–3 h after cardiopulmonary bypass surgery as compared with 2–3 days for creatinine. In chronic HF urinary NGAL levels are elevated,[1] while Damman et al. demonstrated that admission serum NGAL levels were associated with heightened risk of subsequent development of worsening renal function (WRF) in patients admitted for AHF.[1,3]

B-type natriuretic peptide (BNP) is a well-established marker for the diagnosis of AHF.[13-15] Importantly, it has been clearly demonstrated that BNP levels at discharge are highly predictive of short-term outcomes.[16] Ideally if BNP, which is a marker for ventricular stretch and a surrogate for pulmonary congestion,[17] could be matched with a marker of renal injury, the combination would be quite useful for risk stratification.

The GALLANT trial was a multicentre prospective pilot clinical study to assess the utility plasma NGAL—alone and in conjunction with the BNP—as an aid to early risk assessment for HF-related adverse clinical outcomes (deaths, readmissions, and additional emergent outpatient visits) in patients presenting with acutely decompensated HF.

Methods

Patient population

We studied patients who were >18 years of age, and who presented to the emergency department (ED) or hospital with symptoms of new or decompensated HF in whom diuretics were an expected part of therapy. B-type natriuretic peptide levels were required to be ≥100 pg/mL and patients were also required to have systolic or diastolic dysfunction as documented on an echocardiogram within the past 12 months or during hospitalization. Patients were excluded if there was evidence of acute myocardial infarction or active ischaemia, cardiogenic shock, or any other clinical condition that might preclude administration of diuretics. Patients were also excluded if they had renal failure (serum creatinine ≥3.0, on dialysis (either acute or chronic) or in imminent need of dialysis). Patients who had received intravenous diuretic treatment for >90 min prior to enrolment were also excluded. Finally, patients with known or suspected infection with human immunodeficiency virus (HIV) or infectious hepatitis were excluded.

Ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood was collected for the NGAL and BNP measurements. Specimens were centrifuged (10 min at 2000 g) within 1 h of collection and the plasma was frozen at <70°C prior to analysis. Creatinine was measured on serum specimens.

Once written informed consent had been obtained, baseline demographic data were recorded and blood samples were obtained for measurements of creatinine, NGAL, and BNP. These were repeated daily for up to 5 days as well as at discharge. Discharge samples were used for the analysis of the prognostic value of NGAL and BNP for adverse HF-related outcomes. Patients were followed for 30 days following discharge for HF readmission or all-cause mortality. The combined endpoint was considered to have been met if the patient experienced AHF readmission or all-cause mortality during the follow-up period. The institutional review boards of the enrolling institutions approved this study. The five participating study centres and corresponding patient numbers are given in Table 1.

Measurements

The Triage NGAL Test (Alere Inc, San Diego, CA, USA) is an immunoassay in a single-use plastic cartridge that contains a fluorescently labelled monoclonal antibody against NGAL labelled with a fluorescent dye and NGAL. There are built-in control features, including control immunoassays, to ensure that the test performs properly and the

Table 1 Demographic and baseline characteristics

	With event (n = 29)		Without event (n = 159)		P
	Mean	SD	Mean	SD	
Age (years)	68.2	15.3	70.8	14.1	0.381
BMI	28.5	8.8	30.9	8.9	0.171
BP systolic (mmHg)	123.1	30.7	142.8	30.0	0.001
BP diastolic (mmHg)	72.2	12.8	81.8	17.7	0.006
Heart rate (bpm)	88.7	21.7	86.9	22.0	0.695
	With event (n = 29)		Without Event (n = 159)		P
	n	%	n	%	
Male	19	65.5	96	60.4	0.682
White race	17	58.6	101	63.5	0.678
Black race	7	24.1	39	24.5	1.000
Orthopnoea	16	55.2	90	56.6	1.000
PND	10	34.5	44	27.7	0.505
Dyspnoea on exertion	22	75.9	121	76.1	1.000
Dyspnoea at rest	10	34.5	51	32.1	0.831
Rales	5	17.2	28	17.6	1.000
Wheezing	5	17.2	30	18.9	1.000
S3	1	3.4	4	2.5	0.572
S4	0	0.0	1	0.6	1.000
JVP	9	31.0	34	21.4	0.335
Peripheral oedema	21	72.4	120	75.5	0.816
EF < 45%	11/20	55.0	39/77	50.6	0.729

Note: Study centres and patient numbers were as follows: San Diego VA Hospital (n = 41), Ohio State University (n = 11), New York Methodist Hospital (n = 91), University Medical Center, Groningen (n = 23), and Universitätsspital, Basel (n = 22).

reagents are functionally active. The test procedure involves the addition of several drops of whole blood or plasma to the sample port on the test device. After addition of the sample, the cells are automatically separated from the plasma via a filter. The sample reacts with fluorescent antibody conjugates within the reaction chamber and flows down the device detection lane by capillary action. The fluorescent antibody conjugates are captured on discrete solid-phase zones resulting in binding immunoassays that are specific for NGAL or the control antigens. B-type natriuretic peptide testing was also performed on the Triage platform using a standard commercially available assay (Triage Assay, Alere Inc.). Estimated glomerular filtration rate (eGFR) was calculated as MDRD as per Smilde *et al.*[16]

Statistical analysis

Continuous variables are expressed as mean (standard deviation) and compared using *t*-tests for independent groups if normally distributed; otherwise, they are expressed as medians [quartiles] and compared with Mann–Whitney *U* tests. Receiver operating characteristic (ROC) analysis was performed to evaluate individual marker prognostic utility for the combined endpoint and to ascertain cut-points yielding 80% sensitivity. The areas under the ROC curves (C-statistics) were compared using the method of DeLong *et al.*[17] Relationships between biomarkers were evaluated with Spearman rank-order correlation. Kaplan–Meier methods were employed to generate survival plots that were compared using a log-rank test. Cox proportional hazards regression was employed to evaluate survival models using biomarkers with common log transformations for NGAL and BNP to achieve normality, and using biomarker cut-points. Net reclassification improvement[20] was calculated based on risk levels of 6 and 20% as cut-points. A significance criterion of 0.05 without correction for multiple comparisons was employed throughout.

Results

There were 194 patients who met the inclusion criteria, of whom six were excluded due to loss to follow-up ($n = 3$) or withdrawal ($n = 1$), or HF not being the final diagnosis ($n = 2$). Twenty-nine subjects reached an endpoint of all-cause mortality or HF readmission by 30 days (16%). *Table 1* shows the demographics of patients with or without events. The overall sample was 61% male with a mean age of 71 $\pm$ 13.8 years. Subjects with events were not different from subjects without events with respect to age, gender, symptoms, and physical findings. Only systolic and diastolic blood pressures were significantly different between groups.

Figure 1 depicts discharge levels of NGAL, BNP, serum creatinine, and eGFR in those with and without 30 days events. Those with events had higher levels of NGAL than those without events (134 ng/mL [104–181] vs. 84 ng/mL [59–128], $P < 0.001$). Patients with events also had higher discharge BNP levels (585 pg/mL [375–1380]) than those without (384 pg/mL [172–818] $P = 0.013$). Neither discharge creatinine nor eGFR were significantly different between patients with and without events. At baseline, NGAL levels were already different for those with events than those without (112 ng/mL [75–153] vs. 72 ng/mL [60–120], $P = 0.006$) while BNP levels did not differ (837 pg/mL [500–1465] vs. 672 pg/mL [359–1350], $P = 0.180$).

Figure 2 shows the area under the ROC curve for NGAL, BNP, creatinine, and eGFR for predicting 30 days HF-related adverse events. The area under the ROC curve (or C-statistic) was higher for NGAL (0.73) than for BNP (0.65), serum creatinine (0.57), or eGFR (0.55). Comparing C-statistics, NGAL was superior to creatinine ($P = 0.004$) and eGFR ($P = 0.002$), but not to BNP ($P = 0.21$). B-type natriuretic peptide, however, was not
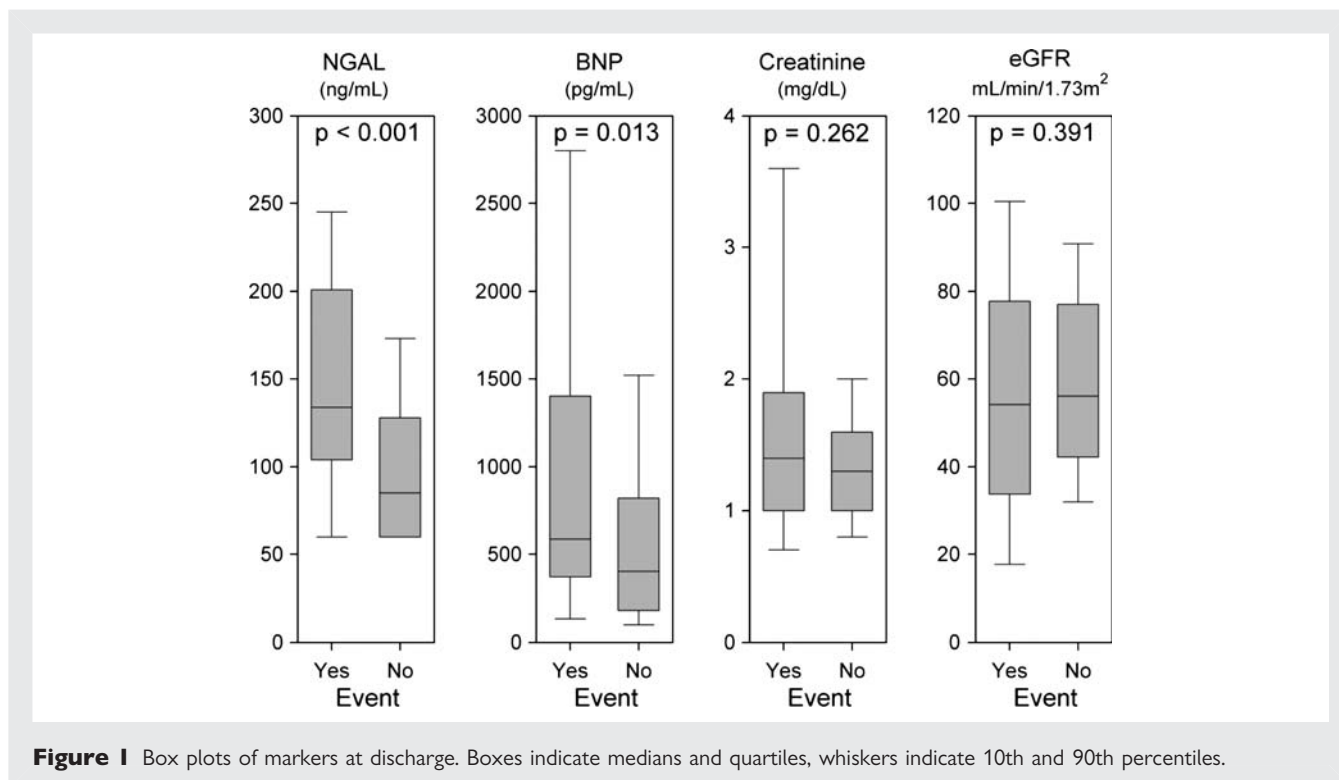

Figure 1 Box plots of markers at discharge. Boxes indicate medians and quartiles, whiskers indicate 10th and 90th percentiles.
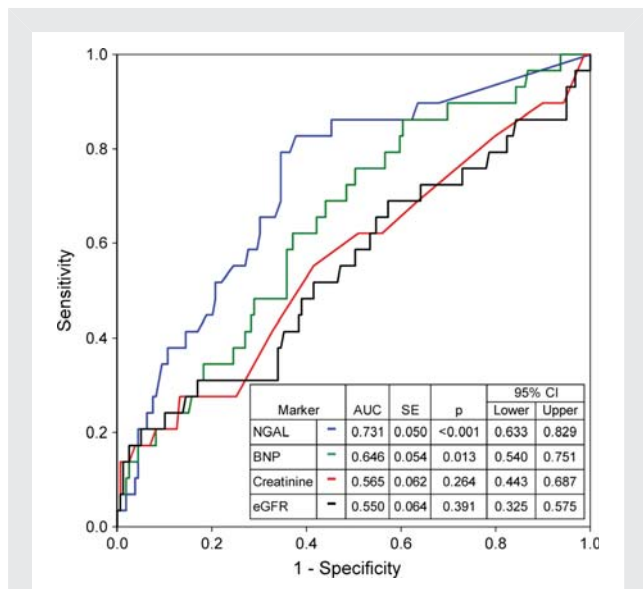
Figure 2 Receiver operating characteristic curve analysis for markers predicting heart failure re-hospitalization or all-cause mortality.

Table 2 Multivariable Cox models for risk of heart failure re-hospitalization or all-cause mortality

Biomarker	P	HR	95% CI for HR	
			Lower	Upper
Model with eGFR				
lg BNP (pg/mL)	0.052	2.47	0.99	6.14
lg NGAL (ng/mL)	0.000	29.83	5.43	163.96
eGFR (mL/min/1.73 m²)	0.284	1.01	0.99	1.02
Model with creatinine				
lg BNP (pg/mL)	0.070	2.327	0.934	5.795
lg NGAL (ng/mL)	0.001	19.912	3.472	114.189
lg creatinine (mg/dL)	0.891	1.177	0.115	12.064

significantly different to creatinine ($P = 0.33$) or eGFR ($P = 0.24$). Discharge eGFR and creatinine were also not significantly different ($P = 0.50$).

The correlation of NGAL levels was modest with creatinine ($r = 0.42$, $P < 0.001$) and eGFR ($r = 0.44$, $P < 0.001$) and weak with BNP ($r = 0.22$, $P = 0.002$). Multiple linear regression was used to predict NGAL levels from these variables.

Table 2 shows Cox regression models with either eGFR or creatinine in the model. In these multivariable analyses, neither log serum creatinine nor eGFR were significant for 30 days events, but log NGAL ($P < 0.001$ for both models) was a significant predictor of events and the log BNP values approached significance ($P = 0.052$ and 0.070). Using risk cut-points of 6 and 20%, subjects were divided into 30 days risk groups using log BNP alone or log BNP and log NGAL. The addition of NGAL to the model

Table 3 Cox models for risk of heart failure re-hospitalization or all-cause mortality in groups based on neutrophil gelatinase-associated lipocalin and B-type natriuretic peptide cut-offs

Group	P	HR	95.0% CI for HR	
			Lower	Upper
NGAL < 100, BNP < 330	0.002	1.00	reference	
NGAL < 100, BNP > 330	0.294	3.23	0.36	28.93
NGAL > 100, BNP < 330	0.036	9.95	1.16	85.19
NGAL > 100, BNP > 330	0.006	16.85	2.26	125.94

improved classification by a net 10.3% in those with events and 19.5% in those without events, for a net reclassification improvement of 29.8% ($P = 0.010$).

Using cut-points at the level of 80% sensitivity for BNP (330 pg/mL) and NGAL (100 ng/mL), subjects were sorted by high/low BNP and high/low NGAL. *Table 3* shows a Cox regression model with the four groups. As can be seen, when NGAL is low, a high BNP delineates no significant risk. However, when BNP is low, a high NGAL still portends significant risk. When both markers were elevated the risk was substantial (HR = 16.9, 95% CI = 2.3–195.9, $P = 0.006$). *Figure 3* depicts Kaplan–Meier curves for these four groups. As shown, high-BNP/high-NGAL had the worst outcomes and survival rate was high when both markers were low. While the risk in the low-BNP/high-NGAL group was significant, the high-BNP/low-NGAL group had outcomes similar to when both markers were low.

Discussion

The main finding of the present study is that plasma NGAL at the time of hospital discharge is a powerful predictor of 30 days outcome in patients with AHF. It is stronger than BNP, which is considered to be the standard for risk prediction, and is substantially superior to conventional measures of renal function such as serum creatinine and eGFR. Thus, NGAL is not only a risk predictor for renal injury but is an overall strong risk marker for cardiac events in the setting of HF.

Physicians now recognize that HF entails a disorder at the level of both the heart and the kidneys. Worsening renal function is especially common during admission for acute decompensated HF and is associated with a poor prognosis.[19–31] While the underlying causes of WRF are multifactorial, the combination of angiotensin-converting enzyme-inhibitors and intravenous diuretics likely are large contributors. The shortcomings of creatinine as a predictor of acute renal dysfunction are well known. Serum creatinine lacks the sensitivity to detect changes in GFR, as its increase is delayed by the need for accumulation once there is a reduction in GFR. Even if not present at the time of admission, kidney injury can ensue during diuresis at the tail end of the hospital period, and may not be manifest (in terms of elevated serum creatinine) at the time of discharge. While serum creatinine and eGFR are clearly
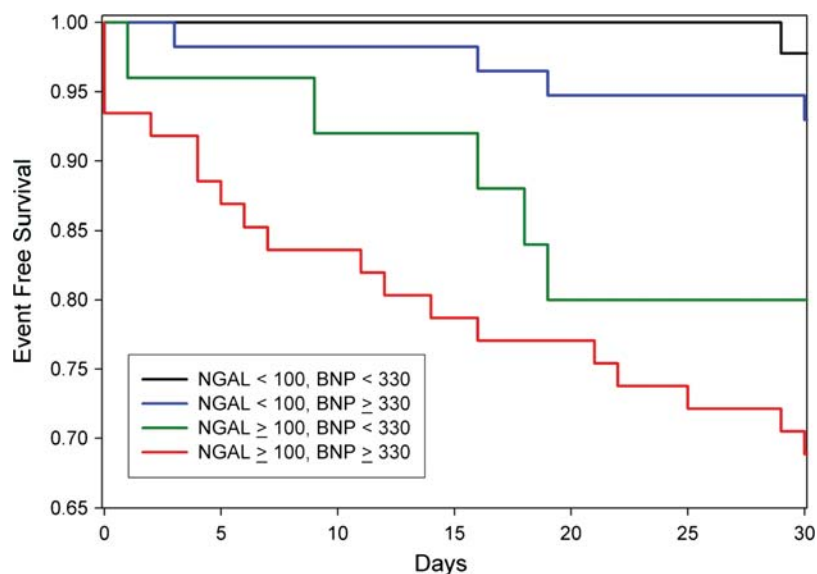
Figure 3 Kaplan–Meier plots of heart failure re-hospitalization free survival based on cut-offs of 100 ng/mL for neutrophil gelatinase-associated lipocalin and 330 pg/mL for B-type natriuretic peptide. Log rank test $P < 0.001$.

prognostic at the time of discharge, a specific marker of tubular injury that rises early should reflect the state of tubular function at the time of discharge.

Neutrophil gelatinase-associated lipocalin is one of the earliest markers produced in the kidney following ischaemic or nephrotoxic injury in animal models, and it can be detected in the blood and urine of humans soon after AKI[6–12] Several studies have confirmed these findings. In intensive care adult patients with AKI secondary to sepsis, ischaemia, or nephrotoxins, NGAL is significantly increased in the plasma and urine when compared with normal controls.[12] In children undergoing cardiopulmonary bypass, NGAL was increased significantly in plasma and urine 2–6 h after surgery in those patients who subsequently developed AKI; the rise in creatinine was not evident until 48–72 h later. In this setting, both urine and plasma NGAL were powerful independent predictors of AKI, with an outstanding area under the curve of 0.998 for 2 h urine NGAL levels and 0.91 for 2 h plasma NGAL measurement. Similar findings have been reported in adults who develop AKI after cardiac surgery, with NGAL elevation occurring 1–3 h after surgery.[6]

Neutrophil gelatinase-associated lipocalin and B-type natriuretic peptide: implications for risk stratification

Assessment of blood BNP levels is now commonly performed in the ED to aid in the diagnosis of AHF in patients presenting with acute dyspnoea. The clinical utility of assessing BNP levels in the ED has been confirmed and described in detail in the scientific literature.[13–16,30] B-type natriuretic peptide concentrations measured during hospital admission and/or at discharge in patients with HF have also been shown to provide prognostic information

about the patient's subsequent risk of death or rehospitalization.[16,17]

While BNP is a marker of ventricular stretch, and therefore a surrogate of volume overload, NGAL is a marker of renal tubular injury that is both diagnostic and prognostic. Haase *et al.*[31] recently presented a meta-analysis consisting of 1217 patients, with clinical outcomes of AKI patients according to NGAL and creatinine status. A major finding was that 41% of patients diagnosed with AKI would have been missed by creatinine alone. Neutrophil gelatinase-associated lipocalin tended to identify increased risk even when the creatinine was not significantly changed. Damman *et al.*[1] demonstrated that structural tubular damage, as measured by increased concentrations of NGAL, is highly prevalent in patients with chronic HF. While the Damman study differed from ours in that urinary NGAL was not prognostic, the acute nature of our patients and the use of blood rather than urine, may have accounted for the difference in prognostic effect observed. Thus, across the spectrum of HF and healthy controls, NGAL levels are not only associated with different indices of renal dysfunction, but also positively associated with increased levels of natriuretic peptides.

In our study, subjects with the combination of high BNP/high NGAL had the worst outcomes; survival rate was high when both markers were low. While the risk in the low BNP/high NGAL group was significant, the high BNP/low NGAL group had outcomes similar to when both markers were low. This may be due to the fact that even though the BNP was high, it likely represented, 'dry' not 'wet' BNP. Thus, at the time of discharge, two easy to measure biomarkers: one of ventricular stretch (and volume overload) and one of renal tubular injury offer powerful risk stratification. Perhaps treatments to effectively lower BNP levels to euvolaemic 'dry' states without leading to decreases in renal perfusion, subsequent tubular ischaemia, and rising NGAL

levels might offer the patient a better chance of improved survival and improved quality of life once they are discharged from the hospital. One might speculate that a high NGAL at the time of discharge might at a minimum, be a signal for early and perhaps more frequent follow-up and a judicious use of outpatient diuretics.

Funding

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