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Comparative Assessment of Short-Term Adverse Events in Acute Heart Failure With Cystatin C and Other Estimates of Renal Function

Results From the ASCEND-HF Trial

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ABSTRACT

OBJECTIVES The purpose of this study was to investigate the predictive values of baseline and changes in cystatin C (CysC) and its derived equations for short-term adverse outcomes and the effect of nesiritide therapy on CysC in acute decompensated heart failure (ADHF).

BACKGROUND Newer renal biomarkers or their derived estimates of renal function have demonstrated long-term prognostic value in chronic heart failure.

METHODS CysC levels were measured in sequential plasma samples from 811 subjects with ADHF who were enrolled in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) biomarker sub-study (randomized to nesiritide therapy vs. placebo), and followed for all-cause death (180 days) and recurrent hospital stay (30 days).

RESULTS Median CysC levels were 1.49 (interquartile range [IQR]: 1.20 to 1.96) mg/l at baseline, 1.56 (IQR: 1.28 to 2.13) mg/l at 48 to 72 h, and 1.58 (IQR: 1.24 to 2.11) mg/l at 30 days. Higher baseline (but not follow-up) CysC levels were associated with increased risk of 30-day adverse events and less improvement in dyspnea after 24 h as well as 180-day mortality, although not incremental to blood urea nitrogen. Worsening renal function (defined as a 0.3 mg/l increase in CysC) occurred in 161 of 701 (23%) patients, but it was not predictive of adverse events. Changes in CysC levels were similar between the nesiritide and placebo groups.

CONCLUSIONS Our findings confirmed the prognostic value of baseline CysC levels in the setting of ADHF. However, worsening renal function based on CysC rise was not predictive of adverse events. Nesiritide did not worsen renal function compared with placebo. (J Am Coll Cardiol HF 2015;3:40–9) © 2015 by the American College of Cardiology Foundation.

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Renal insufficiency and worsening renal function (WRF) are prevalent in acute decompensated heart failure (ADHF), and they often coincide with diuretic unresponsiveness and inability to relieve congestion (1,2). This situation translates into worse outcomes associated with renal insufficiency and WRF. Hence, preservation of renal function is an important therapeutic goal in the treatment of acute heart failure. Although tubular functions are likely important as well, renal function has traditionally been quantified by its glomerular filtration rate (GFR). As the most frequently used marker of GFR, serum creatinine and its derived equations have thus become the mainstays of renal assessment in guiding management and risk stratification. However, because of variable production, dietary influence, dependence on muscle mass, and tubular secretion, the reciprocal relationship of serum creatinine with GFR has well-known limitations.

Cystatin C (CysC) is a small 13-kDa cysteine protease inhibitor that is ubiquitously produced at a fairly constant rate in all nucleated cells. It is freely filtered and neither secreted nor reabsorbed into the bloodstream. The general consensus has been that CysC is a more sensitive marker of early renal insufficiency (3,4). Several studies have suggested the prognostic role of baseline CysC levels in long-term adverse outcomes in the setting of ADHF (5,6), as well as in chronic stable heart failure (7–10). Meanwhile, newer estimates of GFR have also used CysC to achieve better prognostication in various stable clinical settings (8,11–13). As a result, there has been a strong emphasis on using CysC and CysC-derived equations in clinical practice, including the ADHF setting, in which renal dysfunction is common. However, prospective evaluations of clinical utility of serial CysC measurements or CysC-derived GFR estimates and their responses to therapeutic interventions have been less well established.

The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; NCT00475852) biomarker substudy creates a unique opportunity to investigate these questions (14). Herein, we test the hypothesis that elevated CysC (and its derived GFR estimate) is associated with poor short- and intermediate-term prognosis. In particular, we aim to describe the prevalence and time course of CysC elevations in acute heart failure, the relationship of prevalent and incident CysC elevation to dyspnea response, 30-day clinical outcomes, and nesiritide response.

ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure

BUN = blood urea nitrogen

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

CysC = cystatin C

GFR = glomerular filtration rate

WRF = worsening renal function

METHODS

STUDY POPULATION. The design and primary results of the main ASCEND-HF study have been described elsewhere (14,15). Briefly, ASCEND-HF was a multicenter randomized, double-blind, placebo-controlled trial of nesiritide, a recombinant B-type natriuretic peptide with vasodilatory properties, compared with placebo in 7,141 patients admitted to the hospital with ADHF. Patients with clinical evidence of acute coronary syndrome or baseline troponin level >5 times the upper reference limit at the local clinical laboratory were excluded from the trial. The biomarker sub-study enrolled 811 subjects who underwent serial venous blood sampling at baseline, 48 to 72 h following initiation, and at 30-day follow-up visit as previously described (16). Eighty-five percent of patients in the biomarkers sub-study were enrolled in North America. Blood samples were collected in ethylenediaminetetraacetic acid plasma, immediately centrifuged, and stored at −80°F for subsequent analysis at core laboratory.

CYSTATIN C MEASUREMENT. Plasma CysC level was determined with a particle-enhanced immunoturbidimetric immunoassay on the Architect ci8200 platform (Abbott Laboratories, Abbott Park, Illinois). Briefly, latex particles are coated with anti-human CysC antibody and agglutinate with CysC present in the patients' sample. The result is a change in absorbance that is proportional to the amount of CysC present in the sample. The analytic range spans 0.05 mg/l to the highest calibration point. Intra-assay and interassay coefficients are 3.1% and 6%,

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respectively. Baseline, 24-h, and end-of-treatment serum creatinine levels were measured at local laboratories. Estimated glomerular filtration rates (eGFR) were estimated by the 4-variable Modification of Diet in Renal Disease (MDRD) equation and by arbitrarily determining subjects as having either preserved (eGFR ≥60 ml/min/1.73 m^2) or impaired (eGFR <60 ml/min/1.73 m^2) renal function at baseline. When quantitatively comparing the prognosis of renal indices among different models, we used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for serum creatinine, CysC, and both biomarkers (17). Blood urea nitrogen (BUN) values measured at local laboratory were collected as part of the ASCEND-HF study.

CLINICAL ENDPOINTS. Co-primary endpoints were improvement in dyspnea at 6 or 24 h as measured by a 7-point Likert scale and the composite endpoint of hospital stay for heart failure or death at 30 days. For analysis of the relationship between CysC and dyspnea response, dyspnea was dichotomized as moderately or markedly improved at 6 and 24 h relative to the time of randomization. The composite of persistent or worsening heart failure and death from any cause was a secondary endpoint. Events were adjudicated up to 180 days.

STATISTICAL ANALYSES. Clinical characteristics were presented as percentage (%) for categorical variables, mean ± SD for normally distributed continuous variables, and median (interquartile range [IQR]) for non-normally distributed continuous variables. The Cochran-Armitage test was used to test for trend in baseline characteristics in increasing tertiles of baseline CysC. Levels of CysC and changes therein were compared between patients receiving nesiritide and placebo by using Wilcoxon rank sum test or Student *t* test. A 2-sided probability value of <0.05 was considered statistically significant. The association between CysC and outcomes was performed using both univariate and multivariate logistic regression analysis (30 days mortality) or Cox proportional hazards analysis (for length of stay and 180 day mortality). CysC was slightly skewed. Both log-normal transformation and nontransformation were tested, and the results had no difference. Results here are presented by nontransformation. To identify the association between baseline CysC and dyspnea improvement at 6 or 24 h, logistic regression was used. Odds ratio (OR) and hazard ratio (HR) represent the risk per unit increase in CysC. The clinical endpoints of interest were: 1) 30-day mortality; 2) the composite of 30-day mortality and recurrent hospital stay for heart failure; 3) 180-day mortality; 4) dyspnea improvement at 6 and 24 h; 5) death or worsening HF before discharge; and 6) length of stay for the index hospital stay. We confirmed that the proportional hazards assumption was met for the Cox regressions for length of stay and 180-day mortality. When comparing the prognostic value between creatinine and CysC, we use the area under the curve (c-statistic) from receiver operator characteristic curve. For the multivariable analysis, we adjusted the covariates identified from the overall ASCEND-HF study population (Online Table 1). Death at 180 days was evaluated by Kaplan-Meier survival analysis. Differences between groups were calculated with the log-rank test. The Net reclassification index (NRI) for evaluating the improvement in prediction performance gained by adding renal indices to base covariates model was calculated according to the Pencina method (18). All statistical analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

STUDY POPULATION. The ASCEND-HF biomarker sub-study population was similar to the overall study population with the exception that 88% of patients were enrolled in North America (43% in the main trial). The median CysC level at baseline was 1.49 (IQR: 1.20 to 1.96) mg/l. **Table 1** illustrates the baseline characteristics of our sub-study cohort, stratified by baseline CysC levels. Subjects with higher CysC levels were more likely to be older, with history of coronary artery disease, diabetes mellitus, and atrial fibrillation, and with higher left ventricular ejection fraction.

SERIAL CYSTATIN C LEVELS. Of the 811 patients with baseline CysC levels, 701 and 598 had available 48- to 72-h and 30-day levels, respectively. As compared with baseline, CysC was higher at 48 to 72 h (1.56 [IQR: 1.28 to 2.13] mg/l, $p < 0.01$ compared with baseline) and at 30 days (1.58 [IQR: 1.24 to 2.11] mg/l, $p < 0.01$ compared with baseline). **Figure 1** demonstrates that no difference in CysC evolution occurred as a function of treatment randomization (placebo vs. nesiritide). Both placebo and nesiritide groups demonstrated similar increases in CysC levels from baseline to 48 to 72 h (+0.14 ± 0.30 mg/l vs. +0.11 ± 0.33 mg/l, $p = 0.47$), as well as from baseline to 30 days (+0.12 ± 0.41 mg/l vs. +0.15 ± 0.43 mg/l, $p = 0.17$). The ratios of follow-up to baseline CysC were higher in the placebo group than in the nesiritide group at 48 to 72 h (1.78 ± 0.6 vs. 1.74 ± 0.7, $p = 0.31$) and at 30 days (1.78 ± 0.7 vs. 1.70 ± 0.7, $p = 0.08$), but their differences did not reach

TABLE 1 Baseline Characteristics

		Cystatin C (mg/l)			
	Total (N = 811)	Tertile 1 0.58–1.28 (N = 268)	Tertile 2 1.29–1.80 (N = 275)	Tertile 3 1.81–4.20 (N = 268)	p Value*
Age (yrs)	65.75 ± 14.94	58.83 ± 15.72	66.47 ± 14.23	71.93 ± 11.62	<0.01
Male (%)	562 (69.30)	191 (72.27)	196 (71.27)	175 (65.30)	0.13
Race (white, %)	550 (67.82)	157 (58.58)	192 (69.82)	201 (75.00)	<0.01
Systolic BP (mm Hg)	127.12 ± 20.03	127.24 ± 20.82	126.04 ± 18.44	128.11 ± 20.79	0.61
Heart rate (beats/min)	80.26 ± 16.47	84.71 ± 16.46	81.11 ± 16.15	74.94 ± 15.33	<0.01
Atrial fibrillation (%)	338 (41.68)	91 (33.96)	116 (42.18)	131 (48.88)	0.001
Hypertension (%)	631 (77.81)	194 (72.39)	215 (78.18)	222 (82.84)	0.004
BUN (mg/dl)	10.31 ± 6.08	6.84 ± 2.93	8.97 ± 3.89	15.12 ± 7.14	<0.01
Creatinine (μmol/l)	128.54 ± 52.08	96.85 ± 23.65	114.40 ± 31.00	174.75 ± 57.75	<0.01
Cystatin C (mg/l)	1.64 ± 0.61	1.07 ± 0.16	1.51 ± 0.15	2.35 ± 0.47	<0.01
Sodium (mEq/l)	138.63 ± 3.87	138.20 ± 3.93	138.41 ± 3.74	139.29 ± 3.87	<0.01
LVEF (%)	26 (20, 40)	25 (15, 35)	27 (20, 40)	30 (20, 45)	<0.01
Time from presentation to randomization (h)	18.03 (8.08, 22.60)	17.69 (7.69, 22.42)	17.58 (8.85, 22.55)	18.54 (7.97, 22.93)	0.38
Ischemic etiology (%)	493 (60.79)	128 (47.76)	162 (58.91)	203 (75.75)	<0.01
Beta-blockers (%)	613 (75.59)	194 (72.39)	207 (75.27)	212 (79.10)	0.07
ACEI or ARB (%)	524 (64.61)	179 (66.79)	183 (66.55)	162 (60.45)	0.13
MRA (%)	198 (24.41)	68 (25.37)	76 (27.64)	54 (20.15)	0.16

Values are mean ± SD, n (%), or median (Q1, Q3). *p value from test of trend.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; BUN = blood urea nitrogen; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.

statistical significance. There were good correlations between CysC and creatinine levels at their respective time points (baseline r = 0.70; 48 to 72 h r = 0.6 with 24-h creatinine and r = 0.69 with end-of-treatment creatinine).

ASSOCIATION OF BASELINE AND FOLLOW-UP CYSTATIN C AND OUTCOMES. Figure 2 shows Kaplan-Meier curves for all-cause death after 180 days according to baseline as well as 48- to 72-h CysC tertiles. A total of 25 (3.1%) and 95 (11.9%) deaths occurred at 30 days and 180 days of follow-up, respectively. The composite of death or recurrent hospital stay for heart failure at 30 days occurred in 98 patients (12.3%). Table 2 illustrates the associations among baseline CysC levels, dyspnea scores, and clinical outcomes. In univariate analysis, higher baseline CysC levels were associated with more adverse events (all p values < 0.01), longer length of stay, and less improvement in dyspnea score at 24 h (p = 0.03). Apart from dyspnea improvement at 24 h, all these associations persisted after multivariable adjustment (adjusted model 1). However, when BUN and creatinine values were included in these models (adjusted model 2), none of the significant associations persisted. Furthermore, higher follow-up (48 to 72 h) CysC levels conferred higher risk of adverse outcomes in the unadjusted model, and higher follow-up (48 to 72 h) CysC levels were not associated with more adverse events after adjustments even without BUN and creatinine included (Table 2). There were also no statistically significant differences between the 180-day death endpoint using baseline CysC and changes in creatinine (log-transformed, c-statistics 0.72 vs. 0.73, p = 0.63). We further evaluated the incremental prognostic value of CysC when considering baseline estimates of renal function and observed that the prognostic value of CysC was negated in a similar fashion whether it was BUN or estimates of GFR using CKD-EPI equations that used creatinine, CysC, and both (Table 3). Among the various renal indices, the highest AUC and NRI achieved were adding BUN to ASCEND-HF covariates to CysC. In addition, higher CysC levels at 30 days predicted 180-day all-cause mortality (tertiles 1 vs. 2 vs. 3: 3.5% vs. 8.2% vs. 12.6%, p = 0.002), and even after adjusting for baseline BUN, baseline CysC, age, systolic blood pressure (adjusted HR: 2.07; 95% confidence interval [CI]: 1.17 to 3.64, p = 0.01).

ASSOCIATION OF CHANGE IN CYSTATIN C AND OUTCOMES. To assess the clinical significance of CysC changes, outcomes were compared between patients with a ≥0.3 mg/l increase in CysC (signifying WRF) and patients without such an increase. After 48 to 72 h, 161 of 701 patients (23.0%) experienced

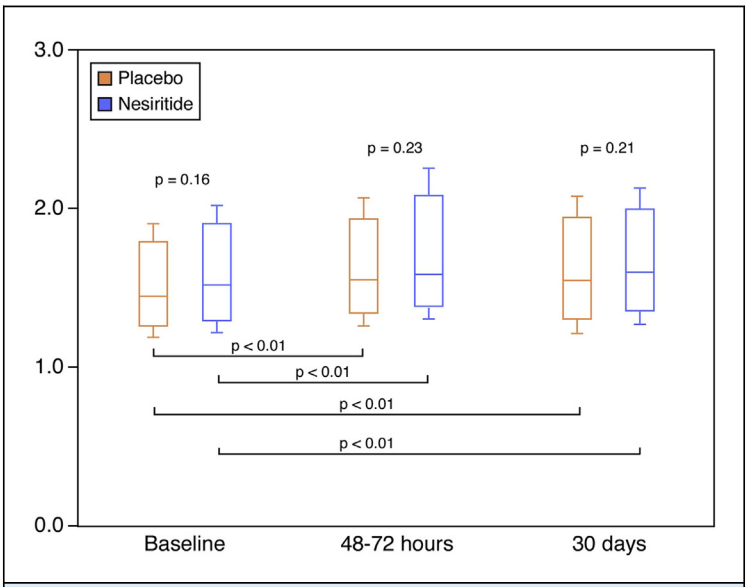

FIGURE 1 Cystatin C Levels Stratified by Treatment Groups (Placebo vs. Nesiritide) at Baseline, 48 to 72 h, and 30 Days After Randomization

WRF. Interestingly, changes in CysC correlated only modestly with changes in creatinine from baseline to 24 h ($r = 0.25$) or to end of trial ($r = 0.38$). Outcomes were not different between those with or without WRF (Table 4, Figure 3), or when stratified according to an increase or decrease in CysC of ≥0.3 mg/l versus unchanged (Online Table 2). Higher changes in CysC at 30 days did not predict 180-day all-cause mortality when adjusted for baseline BUN, baseline CysC, age, and systolic blood pressure (HR: 1.43, 95% CI: 0.76 to 2.67, $p = 0.27$). We further observed that patients with abnormal ranges of baseline CysC levels (>1.4 mg/l) had higher 30-day and 180-day mortality rates. Interestingly, lowering CysC levels from abnormal range at baseline back to the normal range at 48 to 72 h was associated with lower 30-day or 180-day mortality. For changes from baseline to 30 days, only those patients with persistently elevated CysC demonstrated the highest mortality risk at the 180-day visit. In contrast, differences between groups regarding hospital stay for heart failure were not as consistent (Online Table 3).

Patients with dynamic renal function (increase or decrease in CysC of ≥0.3 mg/l) were also compared with patients who had stable renal function, and no difference in the 180 day all-cause death rate was observed (Figure 3). Furthermore, there were no statistically significant differences between the nesiritide versus placebo groups in patients with high baseline CysC or low baseline CysC (stratified at the median CysC level) for the development of WRF (either defined as change in CysC ≥0.3 mg/l at 72 h or at 30 days), urine volume at 24 h, or any clinical events. As expected, patients with higher baseline CysC experienced less urine output at 24 h after randomization when compared with patients with lower CysC (within the nesiritide group: median 2.4 l vs. 2.9 l, $p = 0.002$; within the placebo group: median 2.4 l vs. 3.0 l, $p = 0.029$). However, higher baseline CysC levels have no impact on the incidence of WRF compared with low baseline CysC at 30 days (23.1% vs. 26.6%, $p = 0.322$), even though a higher incidence of WRF was observed at 48 to 72 h (19.3% vs. 26.6%, $p = 0.021$) (Figure 4).

DISCUSSION

The key findings of this study are as follows: 1) baseline CysC is a strong predictor of adverse events in patients admitted with ADHF; 2) the predictive ability of CysC (or its GFR estimates) is independent of many other risk factors but not of other standard measures of renal function such as BUN; 3) changes in CysC during treatment or follow-up (48- to 72-h level) do not seem to have predictive ability for intermediate or long-term all-cause mortality; and 4) nesiritide has no significantly favorable or detrimental effect on renal function as judged by serial CysC levels. Based on our findings using a more sensitive marker of glomerular filtration, we conclude that CysC or CysC-derived GFR estimates do not provide incremental clinical insights into clinical course of ADHF beyond traditional renal indices such as BUN, they do not predict responses to nesiritide therapy.

Several studies performed in the last decade convincingly showed the importance of renal function as a predictor of adverse events in patients with (AD)HF (2). As a result, preservation of renal function has become a separate goal during treatment of acute heart failure, going from the premise that renal-sparing therapies will translate into overall better outcomes. Although the kidney has a tubular and endocrinologic function as well, its function is almost invariably judged by quantifying GFR. Traditionally, serum creatinine and derived equations are used for this purpose, although several reports have pointed toward CysC as an improved marker of GFR, in patients both with and without heart failure (8,17). Recent derivations of CysC-based equations have further provided evidence to support the notion that these improved estimates of GFR can provide more precise and accurate prediction of adverse events in populations with chronic heart failure (13,17,19). Although higher baseline CysC portends poorer short-term and long-term prognosis and identifies a

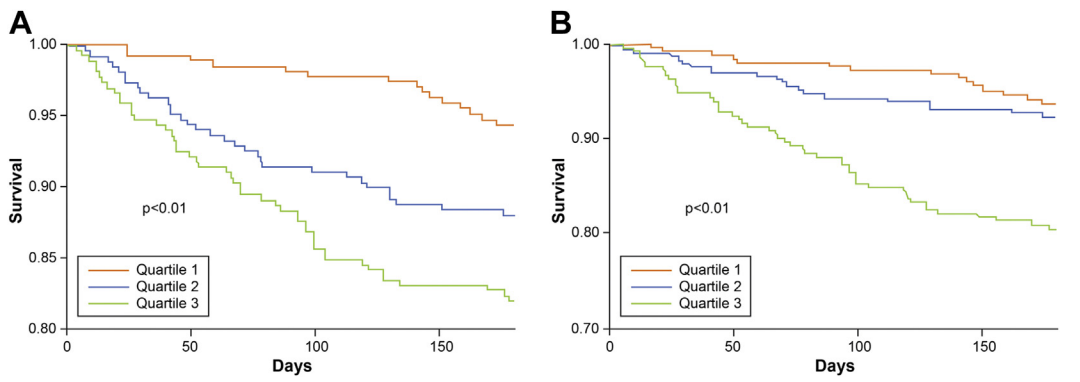

FIGURE 2 Kaplan-Meier Analysis of 180-Day All-Cause Death Stratified by Cystatin C Tertiles

(A) Baseline cystatin C levels. **(B)** Cystatin C tertiles at 48 to 72 h.

subgroup of patients with less robust diuretic responses to medical therapy, we did not observe increments above and beyond traditional renal indices in the setting of ADHF. There may be several potential explanations. First, derivations of CysC and GFR equations that use CysC or creatinine were based on measurements in stable patients with chronic kidney disease in whom glomerular filtration is the primary determinant of renal function. In the setting of ADHF, dysregulated central and renal hemodynamics as a result of volume overload or following aggressive decongestion may confound such derivations, as some investigators have suggested (20). Second, inflammatory and endothelial cell activation in response to venous congestion (21,22) may also generate counterregulatory CysC production above and beyond myocardial dysfunction (6). The finding that BUN, rather than CysC or any GFR estimates, achieved the greatest incremental prognostic value in a head-to-head comparison beyond standard clinical predictors of adverse clinical outcomes may directly challenge the broad acceptance of these newer measurements to predict the clinical course of renal dysfunction in ADHF.

TABLE 2 Baseline and Follow-Up (48- to 72-h) Cystatin C levels and Intermediate- and Long-Term Outcomes

	Unadjusted		Adjusted Model 1*		Adjusted Model 2†	
Endpoint	**OR/HR**	**p Value**	**OR/HR**	**p Value**	**OR/HR**	**p Value**
Baseline Cystatin C						
Death at 30 days	2.46	<0.01	2.14	0.01	1.44	0.42
Death/recurrent hospital stay at 30 days	1.61	<0.01	1.74	<0.01	0.81	0.49
Death at 180 days	2.07	<0.01	1.70	<0.01	0.86	0.59
Improved dyspnea at 6 h	0.86	0.26	0.96	0.84	0.98	0.93
Improved dyspnea at 24 h	0.70	0.03	0.72	0.16	0.77	0.40
Death or worsening heart failure prior to discharge	2.09	<0.01	2.28	<0.01	1.04	0.93
Length of stay‡*	0.74	<0.01	0.75	<0.01	0.85	0.10
Length of stay‡* (high vs. low)	1.88	<0.01	1.86	<0.01	1.45	0.08
Follow-up (48- to 72-h) Cystatin C						
Death at 30 days	2.63	<0.01	2.91	0.13	2.25	0.26
Death/recurrent hospital stay at 30 days	1.65	<0.01	1.31	0.45	1.27	0.53
Death at 180 days	2.07	<0.01	1.37	0.33	1.30	0.43
Length of stay‡*	0.81	<0.01	1.05	0.68	1.02	0.91
Length of stay‡* (high vs. low)	1.63	<0.01	0.93	0.79	1.00	0.99

*Adjusted model 1 = covariates derived from overall ASCEND-HF population excluding BUN and creatinine. †Adjusted model 2 = covariates derived from overall ASCEND-HF population including BUN and creatinine. ‡For length of stay, numerically lower hazard ratio equates to high risk for increased length of stay.

ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; BUN = blood urea nitrogen; HR = hazard ratio; OR = odds ratio.

TABLE 3 Prognostic Value of Adverse Outcomes According to Model Adjusted for Renal Indices

Incremental Adjustment to Model*		Cystatin C	BUN	GFR_{CysC}	GFR_{Cr}	$GFR_{Cr/CysC}$
Death at 30 days	OR	2.14 (1.17–3.90)†	1.06 (1.01–1.12)†	0.97 (0.94–1.00)	0.97 (0.95–0.99)†	0.97 (0.94–0.99)†
	AUC	0.77	0.76	0.77	0.76	0.77
	NRI	55.9%‡	44.8%‡	28.4%‡	41.3%‡	33.0%‡
Death/recurrent hospital stay at 30 days	OR	1.74 (1.22–2.46)‡	1.03 (0.98–1.07)	0.98 (0.97–0.99)‡	0.98 (0.97–0.99)‡	0.98 (0.97–0.99)‡
	AUC	0.66	0.68	0.65	0.67	0.67
	NRI	26.6%‡	44.1%‡	23.7%‡	35.0%‡	29.9%‡
Death or worsening heart failure before discharge	OR	2.28 (1.37–3.79)‡	1.06 (1.00–1.12)	0.97 (0.95–0.99)‡	0.97 (0.95–0.99)‡	0.97 (0.95–0.99)‡
	AUC	0.74	0.74	0.73	0.72	0.74
	NRI	58.5%‡	60.9%‡	33.9%‡	46.8%‡	56.1%‡
Death at 180 days	HR	1.70 (1.28–2.27)‡	2.49 (1.70–3.64)‡	0.98 (0.97–0.99)‡	0.98 (0.97–0.99)‡	0.98 (0.97–0.99)‡
	AUC	0.71	0.72	0.71	0.71	0.72
	NRI	32.3%‡	44.5%‡	29.8%‡	40.2%‡	39.4%‡

*Base model = covariates derived from overall ASCEND-HF population excluding BUN and creatinine. †$p < 0.05$. ‡$p < 0.01$.

ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; AUC = area under the curve; BUN = blood urea nitrogen; Cr = creatinine; CysC = cystatin C; GFR = glomerular filtration rate; NRI = net reclassification index; OR, odds ratio.

The clinical utility of single time-point versus serial measurements of renal indices has been debated in recent years, after its initial endorsements as an important prognostic determinant. Lassus et al. (23) previously reported their findings in 292 subjects of the FINN-AKVA (Finnish Acute Heart Failure) study with available baseline and 48-h CysC levels. The investigators proposed a 0.3 mg/l increase in CysC as a sensitive and clinically meaningful threshold for the prediction of adverse events (3). There are some important differences in the study populations: patients in the FINN-AKVA study were on average 10 years older and were more likely to be female and with history of hypertension. In addition, they had a higher left ventricular ejection fraction and were included even if they were admitted with an acute coronary syndrome. Our data, containing more than twice as many patients with careful endpoint adjudication and largely from North American sites, could not confirm the predictive ability of this definition of WRF. The absence of an association between WRF and adverse outcomes is likely not caused by the biomarker or the exact cut-off point itself, but it may reside in the way WRF is defined or other extrarenal factors. Some studies identified subgroups of patients experiencing WRF with either improved (hemoconcentration) or impaired (tubular injury) survival (24,25). Clearly, the notion that WRF measured by changes in serum creatinine may represent detrimental end-organ injury and damage remains controversial. Nevertheless, we did not observe any difference in outcomes even when we characterized our study population with respect to stable versus dynamic renal function (**Figure 3B**). These observations did not clarify the complexity of renal insufficiency related to ADHF therapy, but it is at best reassuring to note that baseline CysC did not influence long-term changes in CysC. Further investigations to examine the pathophysiologic underpinnings of such fluctuations in serum creatinine levels in this patient population are warranted.

Our current analysis also consolidates the safety profile of nesiritide, thereby challenging initial reports of the detrimental effect of this drug on renal function, as highlighted in previous reports. These findings are concordant with recent reports of similar urine output between nesiritide and placebo in the overall ASCEND-HF study cohort (26). In general, CysC levels were somewhat higher after 48 to 72 h and 30 days compared with that of baseline, but these changes were not significantly different between those treated with placebo and those receiving nesiritide. This finding is in spite of a higher incidence of symptomatic and asymptomatic hypotension (a potential WRF-inducing factor) in the nesiritide-treated group (14). However, these findings are in contrast with recent reports of fewer changes in CysC with administration of serelaxin versus

TABLE 4 Outcomes for Patients With or Without Worsening Renal Function (≥0.3 mg/l Rise in Cystatin C at 48–72 h)

Endpoint	Cystatin C Increase ≥0.3 mg/l at 48–72 h		
	No (n = 540)	Yes (n = 161)	p value
Death at 30 days	13 (2.4%)	6 (3.7%)	0.41
Death or recurrent hospital stay at 30 days	64 (12.1%)	21 (13.0%)	0.76
Death at 180 days	61 (11.4%)	18 (11.5%)	0.97

Values are n (%).

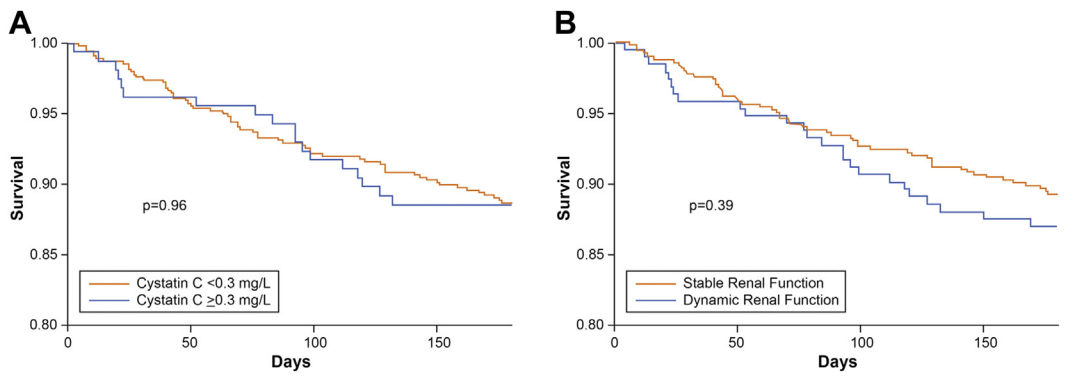

FIGURE 3 **Kaplan-Meier Curves for 180-Day All-Cause Mortality Comparing Patients With or Without Short-Term (48- to 72-h) Changes in Renal Function**

(A) Worsening renal function (≥0.3 mg/l increase in cystatin C at 48 to 72 h). **(B)** Dynamic renal function (≥0.3 mg/l increase or decrease in cystatin C at 48 to 72 h).

placebo in the RELAX-AHF (Relaxin for the Treatment of Acute Heart Failure) study, in which serelaxin was associated with less rise in CysC compared with placebo (27).

It is important to highlight in the ASCEND-HF biomarker sub-study cohort that short-term changes in CysC in our relatively large cohort did not confer any long-term prognostic value. The recently published ROSE (Renal Optimization Evaluation Strategies) study used changes in serial CysC levels as 1 of the 2 co-primary endpoints to evaluate potential incremental benefit of 2 intravenous interventions (low-dose dopamine and low-dose nesiritide) over standard therapy in ADHF (28). Although the neutral results based on the primary endpoint still tracked concordantly with the 90-day clinical outcome

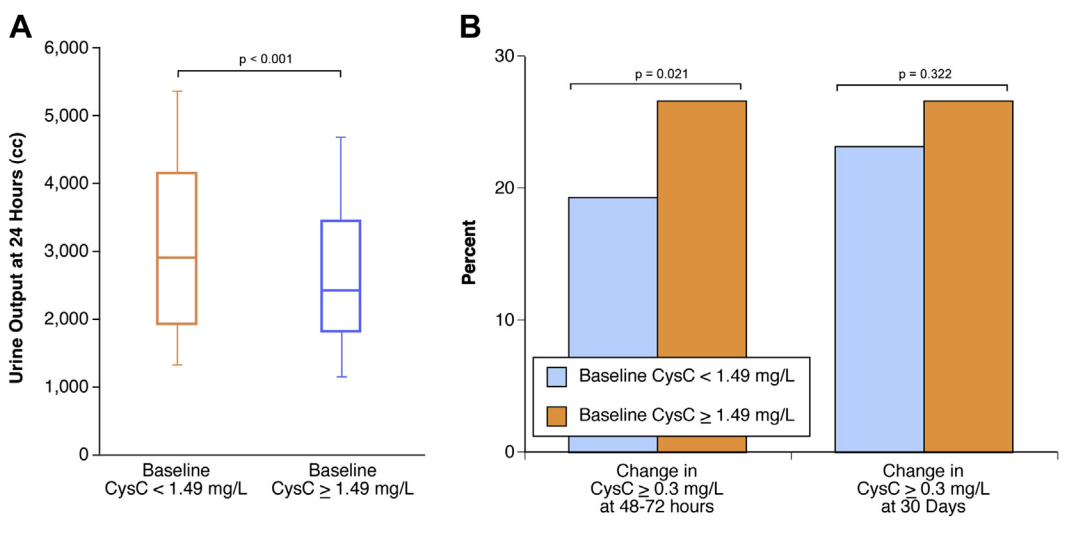

FIGURE 4 **Comparison Between High and Low Baseline CysC Levels on Renal Function Defined by Urine Output at 24 h and Worsening Renal Function**

(A) Urine output at 24 h. **(B)** Worsening renal function. Cystatin C (CysC) levels stratified according to median level of 1.49 mg/L. Worsening renal function defined by changes in CysC levels from baseline to 48 to 72 h as well as to 30 days.

measures, the serial CysC comparisons were practically equivalent, whereas the outcome measures trended nonsignificantly, particularly in the nesiritide-treated group. Hence, whether changes in serial CysC levels can serve as reliable surrogates for subsequent long-term adverse outcomes remained to be determined.

STUDY LIMITATIONS. The most obvious limitation of this study is that there is no direct measurement of GFR. However, good evidence exists, even in patients with heart failure, that CysC reflects GFR accurately. Other major limitations include the absence of available follow-up creatinine and BUN values taken at exactly the same time points as the CysC draws (48 to 72 h and 30 days of research blood draw analyzed in core laboratory versus clinical blood draw for creatinine levels at baseline, 24 h, and at the end of treatment) and the absence of urine output data beyond the first 24 h. In our biomarker substudy, there were only 4 incidents of "orthostatic hypotension" and 19 incidents (18 patients) of "hypotension." Coupled with the small number of patients with changes in CysC over time, there were too few events to determine the relationship between baseline and changes in CysC and hypotension (known adverse effect of nesiritide). We also did not have the data to separate the different contributors to renal insufficiency in the setting of decompensated heart failure from pharmacotherapy. Nevertheless, the findings are reassuring regarding the renal safety of nesiritide, and they further suggest that pre-existing or persistently elevated renal biomarkers such as CysC provide more prognostic insights than their transient changes during aggressive decongestive therapy.

CONCLUSIONS

Higher admission levels of CysC, but not short-term rise in CysC, are associated with adverse events in ADHF. Changes in CysC levels were not different between nesiritide-treated and placebo-treated groups.

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KEY WORDS acute heart failure, cystatin C, nesiritide, renal insufficiency

APPENDIX For supplemental tables, please see the online version of this paper.