Nesiritide, Renal Function, and Associated Outcomes During Hospitalization for Acute Decompensated Heart Failure

Results From the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF)

Vincent M. van Deursen, MD, PhD; Adrian F. Hernandez, MD, MPH; Amanda Stebbins, MS; Vic Hasselblad, PhD; Justin A. Ezekowitz, MBBCh, MSc; Robert M. Califf, MD; Stephen S. Gottlieb, MD; Christopher M. O'Connor, MD; Randall C. Starling, MD; W.H. Wilson Tang, MD; John J. McMurray, MD; Kenneth Dickstein, MD; Adriaan A. Voors, MD, PhD

Background—Contradictory results have been reported on the effects of nesiritide on renal function in patients with acute decompensated heart failure. We studied the effects of nesiritide on renal function during hospitalization for acute decompensated heart failure and associated outcomes.

Methods and Results—A total of 7141 patients were randomized to receive either nesiritide or placebo and creatinine was recorded in 5702 patients at baseline, after infusion, discharge, peak/nadir levels until day 30. Worsening renal function was defined as an increase of serum creatinine >0.3 mg/dL and a change of ≥25%. Median (25^{th}–75^{th} percentile) baseline creatinine was 1.2 (1.0–1.6) mg/dL and median baseline blood urea nitrogen was 25 (18–39) mmol/L. Changes in both serum creatinine and blood urea nitrogen were similar in nesiritide-treated and placebo-treated patients (P=0.20 and P=0.41) from baseline to discharge. In a multivariable model, independent predictors of change from randomization to hospital discharge in serum creatinine were a lower baseline blood urea nitrogen, higher systolic blood pressure, lower diastolic blood pressure, previous weight gain, and lower baseline potassium (all P<0.0001). The frequency of worsening renal function during hospitalization was similar in the nesiritide and placebo group (14.1% and 12.8%, respectively; odds ratio with nesiritide 1.12; confidence interval, 0.95–1.32; P=0.19) and was not associated with death alone and death or rehospitalization at 30 days. However, baseline, discharge, and change in creatinine were associated with death alone and death or rehospitalization for heart failure (all tests, P<0.0001).

Conclusions—Nesiritide did not affect renal function in patients with acute decompensated heart failure. Baseline, discharge, and change in renal function were associated with 30-day mortality or rehospitalization for heart failure.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00475852.

(*Circulation*. 2014;130:958-965.)

Key Words: heart failure ■ nesiritide ■ renal insufficiency

Nesiritide is recombinant B-type natriuretic peptide (BNP)[1–4] approved for use in patients with acute heart failure, because of its ability to reduce pulmonary-capillary wedge pressure and improve dyspnea.[3,5] Yet after approval, it was suggested that nesiritide might cause renal toxicity and increase mortality. Specifically, in a meta-analysis of 5 randomized studies with 1269 acute heart failure patients compared with placebo, intravenous nesiritide increased the rate of worsening renal function by 50%, although confidence intervals around this estimate were wide.[6,7] These concerns led to a marked decrease in the use of nesiritide.[8]

Editorial see p 936
Clinical Perspective on p 965

The Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) was conducted to re-evaluate the efficacy and safety of nesiritide, compared with placebo, added to standard of care in 7141 acute

Received April 4, 2013; accepted June 30, 2014.

From the Department of Cardiology, University Medical Center Groningen, University of Groningen, The Netherlands (V.M.v.D., A.A.V.); Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (A.F.H., A.S., V.H., C.M.O., R.C.S.); Mazankowski Alberta Heart Institute, Edmonton, Canada (J.A.E.); Duke Translational Medicine Institute, Durham, NC (R.M.C.); University of Maryland Hospital, Division of Cardiology, Baltimore, MD (S.S.G.); Cleveland Clinic Foundation, Cleveland, OH (W.H.W.T.); British Heart Foundation Cardiovascular Research Centre, Glasgow, Scotland, UK (J.J.M.); and Central Hospital Cardiology Division, Stavanger, Norway (K.D.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.003046/-/DC1.

Correspondence to Adriaan A. Voors, MD, PhD, Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands. E-mail a.a.voors@umcg.nl

decompensated heart failure (ADHF) patients. Overall, compared with placebo, nesiritide did not improve (or worsen) clinical outcomes and nesiritide did not increase the risk of worsening renal function (predefined as >25% decrease in estimated glomerular filtration rate).[9]

Our study was a retrospective analysis of ASCEND-HF, in which we examined the detailed effects of nesiritide on renal function, clinical predictors of changes in creatinine, and the relationship between changes in renal function and outcomes.

Methods

ASCEND-HF was a randomized, double blind, placebo-controlled trial of nesiritide in addition to standard of care.[10] The trial was conducted from May 2007 through August 2010 at 398 international centers. Patients were included if they were hospitalized for heart failure occurring within 24 hours before they received their first intravenous treatment for heart failure, or if they had received a diagnosis of ADHF <48 hours after hospitalization for another cause, and underwent randomization within 24 hours after intravenous treatment. Patients were excluded if they had a high risk of hypotension (systolic pressure <100 mm Hg or 110 mm Hg with the use of intravenous nitroglycerin), other contraindications for vasodilators, persistent uncontrolled hypertension, normal levels of BNP or N-terminal proBNP (NT-proBNP), chronic or intermittent renal support therapy (ie, hemodialysis, ultrafiltration, or peritoneal dialysis), or clinically significant anaemia.[10] Eligible patients were randomly assigned in a 1:1 ratio to receive nesiritide or placebo, in addition to standard therapy. After a recommended (but optional) intravenous bolus of nesiritide, at a dose of 2 μg per kilogram, nesiritide was administered as a continuous infusion of 0.010 μg per kilogram per minute for 24 hours or more, for up to 7 days.

The ASCEND-HF study was approved by each participating center's ethics committee or institutional review board, and all participants provided written informed consent (ClinicalTrials.gov #: NCT00475852).

Patients for Analyses

A total of 7141 patients underwent randomization; of these, 7007 (98%) received the study drug and were included in the modified intention-to-treat analysis. The study groups were well-balanced and similar to the intention-to-treat group.[9] Our retrospective analysis of ASCEND-HF focuses on the 5702 patients who had both baseline and inpatient peak creatinine measurement available for review (Table I in the online-only Data Supplement).

Worsening Renal Function

Worsening renal function was defined as an increase of serum creatinine >0.3 g/dL (26.5 μmol/L) and ≥25% change.[11,12] Creatinine was measured at baseline and at discharge.

End Points

The primary end point of interest in this study is the composite of rehospitalization for heart failure and death from any cause within 30 days postevent. The other end point of interest was the separate outcome of rehospitalization for heart failure or death from any cause within 30 days. The following criteria were required for hospitalization events to be classified as attributable to heart failure: typical clinical manifestations of worsening heart failure and the addition of (or increase in) treatment specifically for worsening heart failure with an intravenous pharmacological agent, or mechanical or surgical intervention or ultrafiltration, hemofiltration, or dialysis specifically for the management of persistent or worsening heart failure.

Statistical Analyses

Change in creatinine was defined as the change from baseline to peak during hospitalization (Table 1, which displays 2 groups, those changes ≤0.3 mg/dL and those >0.3 mg/dL).[13,14] Presenting factors, baseline medications, and medical history information is reported as counts and frequencies for discrete factors and either the mean with standard deviation or 50th, 25th, and 75th percentiles for continuous. A Wilcoxon rank-sum test was performed for continuous factors, and a χ^2 test was performed for binary measurements.

Cox proportional hazards regression modeling was generated to assess the association between prespecified baseline factors and change in creatinine (from randomization to discharge). To verify modeling assumptions, plots were generated to view the residuals of each independent predictor. Outliers of creatinine measurements ≥10 mg/dL were excluded. The blood urea nitrogen (BUN), BNP, and NT-proBNP were modeled using log transformations. A test for normality was evaluated. The stepwise variable selection procedure was applied using a P value of 0.05 for to enter and stay in the model. Interactions between treatment and baseline factors were reviewed.

Analyses on the prognostic value of serum creatinine were separated into 2 cohorts. The first and most valuable cohort consisted of all patients having baseline values of serum creatinine as well as one or more other serum creatinine values. Of all serum creatinine values during hospitalization, the highest value was taken as peak serum creatinine value. Change in creatinine values was calculated as peak value minus baseline value. The second smaller cohort consisted of patients having baseline and discharge values of creatinine, ignoring other serum creatinine values during hospitalization.

Baseline, discharge, peak, and change from baseline to each creatinine measurement were modeled univariably as predictors of 30-day mortality and 30-day mortality or rehospitalization for heart failure. These same measurements were also added to previously generated multivariable models for 30-day mortality and 30-day mortality or rehospitalization for heart failure. The 30-day mortality model includes age, sodium, systolic blood pressure, dyspnea, BNP, and NT-proBNP. The combination end point of 30-day mortality and rehospitalization includes age, cerebrovascular disease, chronic respiratory disease, depression, hospitalization within the past year, sodium, qualifying jugular venous pressure episode, systolic blood pressure, weight, BNP, and NT-proBNP. Each creatinine term was added individually to assess the measurement's importance after adjusting for these baseline characteristics. The baseline, peak, and discharge measurements were modeled using the log transformation. The log of creatinine is also analyzed using each measure in a time-dependent covariate analysis unadjusted and adjusted for the prespecified baseline confounders. This time-dependent analysis provided updated assessments of creatinine measures over time. The time-dependent variable is initially set to the baseline measure. As follow-up time matches the date that a new creatinine measurement is observed, the time-dependent variable is changed to the updated value. Creatinine and BUN measurements are displayed at different time points in Figure 1. The cumulative distribution of creatinine measurements by treatment at the end of treatment and discharge are displayed in Figure 2. Kaplan–Meier plots were generated to display the relationship of worsening renal failure and 30-day mortality.

SAS version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

Baseline characteristics (as presented in Table 1) of the 5702 patients who were included in the present study did not clinically differ from the 1439 patients who were excluded because of missing creatinine data (data not shown). Patients who were excluded were 66.3±14.6 years old (versus 65.3±14.0, P=0.002 for the included patients), 33% were female (versus 34%, P=0.437), and had similar systolic and diastolic blood pressures (122 versus 123 mm Hg [P=0.198] and 73 versus 75 mm Hg [P=0.001], respectively). Although excluded patients had modestly higher baseline weight (80 versus 77 kg, P<0.001) they had a similar drop in weight during hospitalization (−2.2 versus −2.3 kg, P=0.829). Excluded patients

Table 1. Clinical Characteristics (Split by >0.3 mg/dL Change in Creatinine [Peak From Baseline])

		WRF status		
	Total	No	Yes	*P* Value
Number of patients	5702	4041	1661	
Nesiritide*†	2871 (50%)	1974 (49%)	897 (54%)	<0.001
Placebo	2831 (50%)	2067 (51%)	764 (46%)	
Age, y (SD) †	65.3 (14.0)	64.3 (14.2)	67.6 (13.3)	<0.001
Female sex†	1964 (34%)	1319 (33%)	645 (39%)	<0.001
Median weight, kg	77 (64, 94)	76 (62, 92)	82 (68, 99)	<0.001
Median SBP†	123 (110, 140)	120 (110, 137)	130 (114, 145)	<0.001
Median DBP†	75 (67, 84)	75 (68, 83)	75 (65, 84)	0.517
Median heart rate†	82 (72, 96)	84 (72, 96)	80 (70, 93)	<0.001
Race†				<0.001
White	3090 (54%)	2070 (51%)	1020 (61%)	
Black	863 (15%)	570 (14%)	293 (18%)	
Asian	1512 (26%)	1244 (31%)	268 (16%)	
Other	236 (4%)	156 (4%)	80 (5%)	
Medical history				
HF-PEF	15.2%	12.8%	21.1%	<0.001
Myocardial infarction†	34.4%	33.8%	35.9%	0.122
Atrial fibrillation	36.7%	34.9%	41.0%	<0.001
Hypertension	71.6%	68.3%	79.7%	<0.001
Diabetes mellitus†	41.8%	39.5%	47.3%	<0.001
Loop diuretic in first 24h†	89.2%	88.9%	90.2%	0.145
Medication use (prerandomization)				
ACEI/ARB	60.9%	60.4%	62.2%	0.201
Aldosteron antagonist	28.0%	29.1%	25.3%	0.004
Beta blockers	56.5%	54.8%	60.8%	<0.001
Loop diuretics	62.2%	60.9%	65.4%	0.001
Oral/topical nitrates	23.0%	21.6%	26.2%	<0.001
Digoxin	26.4%	27.5%	23.8%	0.005
Hydrazaline	6.4%	4.7%	10.6%	<0.001
Anticoagulant	22.6%	21.4%	25.6%	0.001
Inotropes	4.4%	5.2%	2.4%	<0.001
Vasodilators	15.7%	15.7%	15.9%	0.847
Baseline laboratory				
eGFR (mL/min/m^2)	62±25	63±24	59±27	<0.001
Creatinine (mg/dL) †	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.3 (1.0, 1.6)	<0.001
BUN (mmol/L)†	25 (18, 38)	25 (18, 38)	26 (18, 39)	0.113
Hemoglobin (g/dL)‡	12.7 (11.4, 14.1)	12.8 (11.5, 14.1)	12.5 (11.1, 13.9)	<0.001
BNP (pg/mL)†	990 (539, 1865)	1010 (538, 1943)	928 (542, 1696)	0.076
NT-proBNP (pg/dL)	4357 (2019, 9082)	4240 (2002, 8955)	4642 (2094, 9550)	0.075
Sodium†	139 (136, 141)	138 (136, 141)	139 (137, 142)	<0.001
Potassium†	4.1 (3.7, 4.5)	4.1 (3.7, 4.4)	4.1 (3.7, 4.5)	0.316
Median LVEF	30 (20–36)	28 (20, 35)	30 (24, 40)	<0.001
Median change in SBP	−8 (−20, 3)	−7 (−20, 4)	−10 (−25, 1)	<0.001
Median change weight†	−2.3 (−5.0, −0.6)	−2.1 (−4.8, −0.6)	−2.7 (−5.3, −0.6)	0.034

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, b-type natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; h, hour; HF-PEF, heart failure–preserved ejection fraction; kg, kilograms LVEF, left ventricular ejection fraction; NT, N-terminal; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; and WRF, worsening renal function.

*There was no difference between nesiritide and placebo in quintiles of change in creatinine

†All prespecified factors included in the stepwise model of Table 2, including respiration rate, orthopnea, dyspnea, peripheral edema, pulmonary congestion on x-ray, paroxysmal nocturnal dyspnea, rales, elevated jugular venous pressure or S3, NYHA class, heart failure hospitalization in previous year, chronic respiratory disorder, baseline troponin, and body mass index.

‡For mg/dL divide by 88.4.

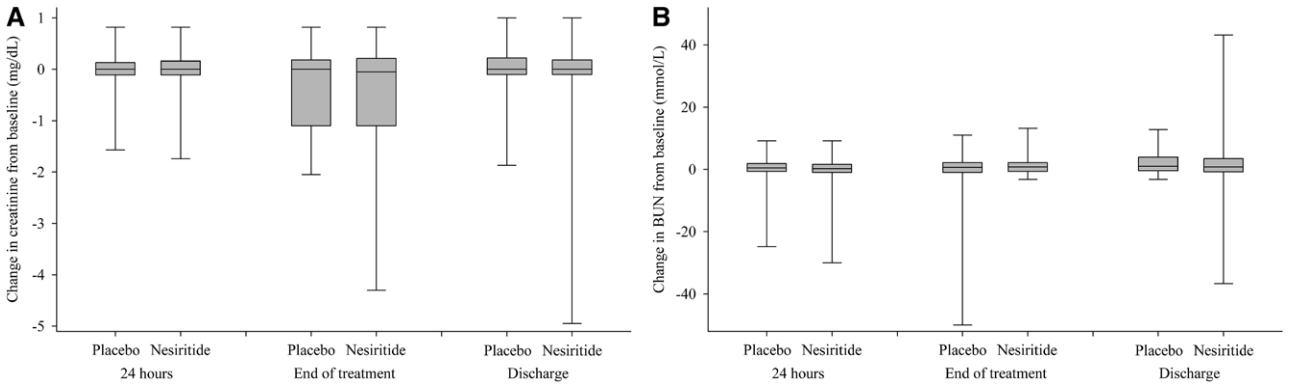

Figure 1. Patients randomized to either nesiritide or placebo. This figure displays the changes in (**A**) serial creatinine levels and (**B**) BUN levels in patients randomized to either nesiritide or placebo. BUN indicates blood urea nitrogen.

had similar rates of worsening renal function (12.1% versus 13.7%, *P*=0.265), although excluded patients more often died within 30 days (6.3% versus 3.2%, *P*<0.001).

Table 1 shows the baseline characteristics of the patient population in this study. In short, median age was 65±14 year, and 34% were female. Nesiritide treatment was given to 50% of the included patients. A history of hypertension was present in 72% of patients, and 34% had a history of myocardial infarction. Median weight was 77 (64–94) kg with a median change in weight of −2.3 (−5.0 to −0.6) kg during hospitalization. Loop diuretics were administered in 89% of all patients within the first 24 hours.

Change in Renal Function

Median creatinine concentration increased from 1.2 (1.0–1.6) mg/dL at baseline to a maximum of 1.4 (1.1–1.8) mg/dL during hospitalization. Median BUN concentration increased from 25 (18–38) mmol/L at baseline to a maximum of 33 (23–50) mmol/L during hospitalization. The change from randomization to hospital discharge in both serum creatinine and BUN was similar in nesiritide- and placebo-treated patients (*P*=0.20 and *P*=0.41, respectively) as shown in Figure 1 and supported by the cumulative distribution curves shown in Figure 2.

As shown in Table 1, patients were split by those with a change in creatinine >0.3 mg/dL between baseline and peak. Patients with worsening renal function were older; more often female; and more often had diabetes mellitus, higher left ventricular ejection fraction, higher baseline systolic blood pressure, more cardiovascular comorbidities, a higher weight at baseline, and a larger decrease in weight during hospitalization.

Worsening renal function at any time from randomization through discharge occurred in 13.5% of the patients, and the frequency was similar in the nesiritide and placebo groups (14.1% and 12.8%, respectively; odds ratio [OR] with nesiritide, 1.12; 95% confidence interval [CI], 0.95–1.32; *P*=0.19), regardless of the degree of baseline renal insufficiency (OR, 1.01; 95% CI, 0.79–1.28; *P*=0.955 in patients with baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2, and OR, 1.24; 95% CI, 0.98–1.57; *P*=0.076 in patients with baseline estimated glomerular filtration rate ≥60 mL/min/1.73 m^2).

Using a multivariable stepwise model, we defined characteristics that were related to changes in creatinine (Table 2). All prespecified factors included in the stepwise model are identified in Table 1 with a "†" symbol. In summary, a lower baseline BUN (log β = −0.091, *P*<0.0001), a higher systolic blood pressure (β = 0.002, *P*<0.0001), a lower diastolic blood pressure (β = −0.002, *P*<0.0001), a lower baseline potassium (β = −0.040, *P*<0.0001), and previous weight gain (β = 0.039, *P*<0.0001) were all significantly related to an increase in serum creatinine. Treatment with nesiritide did not have a significant relation to a change in creatinine (β = 0.001, *P*=0.89).

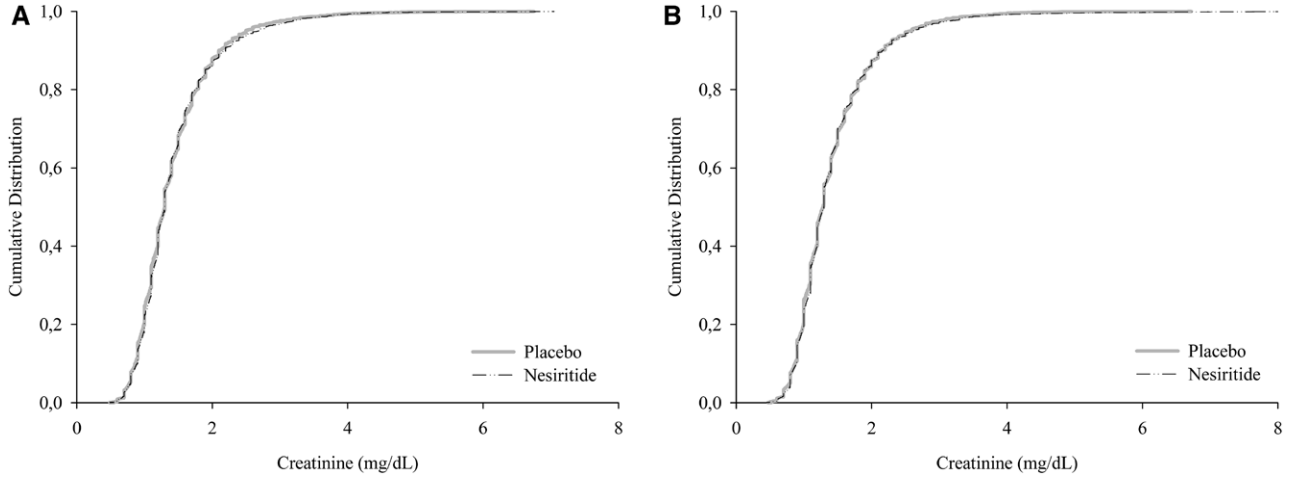

Figure 2. Cumulative distribution curve. This figure displays the cumulative distribution curves of both nesiritide and placebo on (**A**) creatinine at end of treatment and (**B**) discharge/d 10.

Table 2. Multivariable Model of Changes in Creatinine

	Parameter Estimate	Standard Error	*P* Value
Intercept	0.32977	0.05367	<0.0001
Randomization allocation*	0.00127	0.00939	0.8921
Log BUN	–0.09123	0.00874	<0.0001
SBP measurement in standard units	0.00230	0.00028	<0.0001
Baseline DBP (mm Hg)	–0.00183	0.00041	<0.0001
Baseline potassium (mmol/L)	–0.04013	0.00818	<0.0001
Prior weight gain	0.03898	0.00992	<0.0001

BUN indicates blood urea nitrogen; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Placebo is used as the reference group.

Predictive Value of Creatinine in Relation to Clinical Outcomes

The prognostic value of serum creatinine and change in serum creatinine at different time points is shown in Tables 3 and 4. In the subset of patients who had creatinine values measured at baseline and discharge, we found that both creatinine measures had strong associations with 30-day mortality (multivariable, $P<0.001$). Change in creatinine was also predictive of 30-day mortality ($P<0.001$; Table 3). In the set of patients with measures of both baseline and peak creatinine values, creatinines remained significant for 30-day mortality after adjusting for potential confounders, as did the change from baseline to peak ($P=0.003$, $P=0.003$, and $P=0.01$, respectively). The multivariable statistical significance of the evaluation of all creatinine values, updated across the hospitalization, was similar to that of the updated changes from baseline across time ($P<0.001$). Table 4 shows creatinine at discharge, peak, and across all values. All had strong associations with the combined end point of 30-day mortality or rehospitalization, even after adjusting for baseline covariates ($P<0.001$).

Table 3. Prognostic Value of Serum Creatinine for 30-Day Mortality

	Univariable		Multivariable	
	HR	*P* Value	HR	*P* Value
Discharge creatinine	n=4732		n=4290	
Baseline*	1.62	<0.001	1.44	<0.001
Discharge*	1.82	<0.001	1.70	<0.001
Change†	1.31	<0.001	1.38	<0.001
Peak creatinine	n=5607		n=5043	
Baseline*	1.63	<0.001	1.40	0.003
Peak*	1.51	<0.001	1.37	0.003
Change†	1.09	0.0453	1.14	0.013
Time-dependent creatinine				
Creatinine*	1.81	<0.001	1.7	<0.001
Change†	1.21	<0.001	1.2	<0.001

HR indicates hazard ratio.

*HR is for 1.5 increase in creatinine.

†HR is for 0.3 increase in change in creatinine.

Discussion

In the present renal retrospective analysis of the ASCEND-HF trial, we found that nesiritide did not have any effect on changes in creatinine during hospitalization in patients with ADHF. By any point in time during hospitalization, renal function as measured by creatinine was associated with 30-day death and 30-day death or rehospitalization including baseline, discharge, peak, change, or the most recent measure.

Worsening Renal Function

Renal dysfunction is prevalent in patients with both chronic and acute heart failure, and may influence patients' treatments and outcomes.[15,16] Approximately 20% to 40% of patients with acute heart failure have an increase in creatinine, which is generally defined as worsening renal function.[15] We also found that the prevalence of diabetes mellitus was higher in patients with worsening renal function, which confirms previous studies.[17,18]

In our study, we found that baseline renal function was mildly impaired and further deteriorated during hospitalization. Predictors of a decline in renal function (measured using creatinine on a continuous scale) included higher systolic and lower diastolic blood pressure, lower potassium levels, more previous weight gain, and lower BUN levels. Similar predictors were found in previous studies.[12,19–21]

Nesiritide

In a meta-analysis of 5 randomized studies that included 1269 ADHF patients, the frequency of worsening renal function was found to be 50% more prevalent in the nesiritide group.[6] Therefore, the neutral effects of nesiritide on renal function in the present study are markedly different from the meta-analysis. There are several potential explanations for this difference. First, in 3 of the 5 studies, detailed data could not be obtained because they have not been published.[22] In the remaining 2 studies, nesiritide was not compared with placebo (as in ASCEND-HF), but was compared with either dobutamine[23] or nitroglycerin[3]; we cannot exclude the possibility that these agents may have had a positive effect on renal function. Second, ASCEND-HF excluded patients with high risk of hypotension (systolic pressure <100 mm Hg or 110 mm Hg with the use of intravenous nitroglycerin), whereas the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) and Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) trials had less strict exclusion criteria for hypotension (90 mm Hg and 85 mm Hg, respectively). Finally, in the meta-analysis, the confidence intervals around the estimate were wide, suggesting that larger studies were needed. Also, publication of meta-analysis data from another study suggested that nesiritide might even improve renal function.[23] Given the large sample size, ASCEND-HF had definitive power to demonstrate a meaningful difference in renal function between placebo and nesiritide, yet no difference was found.[9]

The present retrospective analysis of ASCEND-HF presents a more detailed report on the associations between nesiritide and other clinical predictors on changes in creatinine and BUN during hospitalization, as well as the drug's association with clinical outcomes. We demonstrated that there was not a significant relationship between nesiritide and change in renal function when corrected for clinical characteristics and other laboratory measurements.

Table 4. Prognostic Value of Serum Creatinine for 30-Day Mortality or Rehospitalization

	Univariable		Multivariable	
	HR	*P* Value	HR	*P* Value
Discharge creatinine	n=4646		n=4267	
Baseline*	1.62	<0.001	1.51	<0.001
Discharge*	1.66	<0.001	1.66	<0.001
Change†	1.15	<0.001	1.15	<0.001
Peak creatinine	n=5467		n=4986	
Baseline*	1.53	0.003	Not included	
Peak*	1.52	0.003	1.40	<0.001
Change†	1.10	0.013	1.13	<0.001
Time-dependent creatinine				
Creatinine*	1.56	<0.001	1.34	<0.001
Change†	1.10	<0.001	1.10	<0.0001

HR indicates hazard ratio.
*HR is for 1.5 increase in creatinine.
†HR is for 0.3 increase in change in creatinine.

Because hypotension is related to worsening renal function in ADHF,[24] there was some concern that patients with hypotension had a higher rate of renal impairment compared with those without hypotension. We found this concern to be true in the overall group, as well as within each treatment group. Importantly, the overall relative risk of increased serum creatinine was the same within both treatment groups. So despite there being some correlation between hypotension and renal dysfunction, there was no evidence of a stronger correlation when using nesiritide.

Outcomes

The conclusions on prognostic value of serum creatinine were drawn from the cohort of patients having baseline values, as well as ≥1 other creatinine values during hospitalization at any time. Importantly, we have also reported the results that were generated when ignoring creatinine values not being measured at discharge. Although the significance of the prognostic values may be attributable to ascertainment bias, we believe that in the setting of a randomized, clinical trial with standardized measurement times of creatinine, it is more likely that the difference in *P* values is attributable to a different sample size of the 2 cohorts. We suggest measuring creatinine values more than once during hospitalization, for it is important to understand that the time of ascertainment of creatinine values can yield differences in the association with outcomes.

Both serum creatinine at baseline and serum creatinine at discharge had a strong association with both 30-day mortality and with the combined end point of 30-day mortality or rehospitalization. Because change in renal function is a function of the baseline and discharge measures, it is not surprising that it, too, was also associated with short-term outcomes. Likewise, when examining the most recent measure of renal function, it is strongly associated with clinical outcomes.

A large number of studies reported an association between in-hospital worsening renal function and short-term outcomes in patients with ADHF.[11,12,25–32] However, others did not show such an association,[33] perhaps because of patients having a good diuretic response, developing a transient rise in creatinine, but having a good clinical outcome. In contrast, patients with a poor diuretic response and developing worsening renal function have a poor clinical outcome.

Differences in outcomes of studies relating worsening renal function in acute decompensated heart failure to outcome might also be caused by a measurement bias. Most studies do not measure creatinine routinely, so in those that did, there was probably a reason, which perhaps means that these patients were more likely to have worsening of symptoms or nonresponse to diuretics[34–36] related to clinical outcomes. This theory of measurement bias is supported by a recent study composed of 599 patients who had their serum creatinine levels routinely measured.[32] The authors of this study concluded that worsening renal function is not an independent predictor of outcomes in patients with ADHF. Interestingly, they found that worsening renal function was prognostic in patients with persistent signs of congestion, suggesting a differential effect of worsening renal function. This may explain, at least to a degree, the strong significance noted in the models which used all creatinine measures updated over time compared with the model with discharge or peak only.

Limitations

Our study had several limitations. First, our study was a retrospective analysis. Second, our study has a possible selection bias inherent in clinical trial populations. For example, our population largely consisted of North American patients, possibly limiting the generalizability of our findings. Third, treatment bias could have occurred because concurrent medication could have been altered as a result of changes in creatinine. Finally, 1439 patients did not have serial creatinine values during the inpatient stay, which could have potentially biased the finding that worsening renal function did not predict patient outcomes. For example, patients who lacked serial creatinine values could have developed worsening renal function in-hospital and died before their serial creatinine was measured. Nevertheless, because of the design of ASCEND-HF, this study is more likely to have missing data because of less specific reasons, whereas other studies are more likely to have missing values because patients had no clinical suspicion to have worsening renal function or worse clinical outcomes.

Conclusions

In the present renal retrospective analysis of ASCEND-HF patients who were hospitalized with ADHF, nesiritide did not affect renal function. In addition, baseline, discharge, and change in renal dysfunction were associated with higher 30-day mortality and rehospitalization for heart failure.

Sources of Funding

This work was supported internally by the Duke Clinical Research Institute. The ASCEND-HF trial was supported by Scios Inc.

Disclosures

Dr Hernandez reports research funding from Johnson & Johnson, Amylin, and Portola; honorarium from Corthera and Cytokinetics. All conflicts can be found at www.dcri.org. Dr Hasselblad reports research funding from Bioheart, Eli Lilly & Company, Glaxo Smith Kline (GSK), Medicure, Merck Group, and Scios Inc (all significant). All conflicts can be found at www.dcri.org. Dr Ezekowitz

reports modest research support from Scios Inc and Johnson and Johnson, in conjunction with the ASCEND-HF trial for his role as a member of the Steering Committee. Dr Califf reports research funding from Amylin, Johnson & Johnson-Scios, Merck/Schering Plow, Novartis, and Bristol Myers Squibb Foundation (all significant); consulting from Johnson & Johnson-Scios, Novartis, Bayer, Roche, Pfizer, Bristol-Myers Squibb Foundation (all modest); equity in NITROX LLC (modest). All conflicts can be found at www.dcri.org. Dr Gottlieb reports payment from the DCRI for serving on the Steering Committee. Dr O'Connor reports consulting fees/honoraria from Amgen (significant), Actelion Pharmaceuticals Ltd (modest); ownership/partnership/principal from Biscardia, LLC (modest); research grants from Otsuka, Astellas, Gilead, BG Medicine, Roche Diagnostics, Critical Diagnostics (all significant), and ResMed (modest). Full disclosures can be viewed at cardiosource.org. Dr Starling reports consulting fees/honoraria from Medtronic, BioControl, and Novartis (all modest); ownership/partnership/principal from Cardiomems (modest); research/research grants from National Institutes of Health (significant), Medtronic (modest), Biotronik (modest), Thoratec (none), Novartis (none); other financial benefit from the American Board of Internal Medicine (modest). Full disclosures can be viewed at cardiosource.org. Dr Voors was member of the steering committee of ASCEND-HF and received consultancy fees from Johnson and Johnson. Also, he received consultancy fees and/or research grants from: Alere, Bayer, Cardio3Biosciences, Celladon, Ceva, Novartis, Servier, Torrent, Vifor. Dr Voors is Clinical Established Investigator of the Dutch Heart Foundation (2006T37), is supported by a grant from the Dutch Heart Foundation entitled "Approaching Heart Failure by Translational Research of RNA mechanisms" (ARENA), and is leader of a project funded by the European Commission (FP7-242209-BIOSTAT-CHF), entitled "a systems BIOlogy Study to TAilered Treatment in Chronic Heart Failure (BIOSTAT-CHF). The other authors report no conflicts.

References

1. Clarkson PB, Wheeldon NM, Macleod C, Coutie W, MacDonald TM. Brain natriuretic peptide: effect on left ventricular filling patterns in healthy subjects. *Clin Sci (Lond)*. 1995;88:159–164.
2. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagoner LE, Givertz MM, Liang CS, Neibaur M, Haught WH, LeJemtel TH. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med*. 2000;343:246–253.
3. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531–1540.
4. Zellner C, Protter AA, Ko E, Pothireddy MR, DeMarco T, Hutchison SJ, Chou TM, Chatterjee K, Sudhir K. Coronary vasodilator effects of BNP: mechanisms of action in coronary conductance and resistance arteries. *Am J Physiol*. 1999;276:H1049–H1057.
5. Bueno H, Ross JS, Wang Y, Chen J, Vidán MT, Normand SL, Curtis JP, Drye EE, Lichtman JH, Keenan PS, Kosiborod M, Krumholz HM. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. *JAMA*. 2010;303:2141–2147.
6. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation*. 2005;111:1487–1491.
7. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA*. 2005;293:1900–1905.
8. Hauptman PJ, Schnitzler MA, Swindle J, Burroughs TE. Use of nesiritide before and after publications suggesting drug-related risks in patients with acute decompensated heart failure. *JAMA*. 2006;296:1877–1884.
9. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Wilson WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:32–43.
10. Hernandez AF, O'Connor CM, Starling RC, Reist CJ, Armstrong PW, Dickstein K, Lorenz TJ, Gibler WB, Hasselblad V, Komajda M, Massie B, McMurray JJ, Nieminen M, Rouleau JL, Swedberg K, Califf RM. Rationale and design of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF). *Am Heart J*. 2009;157:271–277.
11. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail*. 2007;13:599–608.
12. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol*. 2000;85:1110–1113.
13. Testani JM, McCauley BD, Kimmel SE, Shannon RP. Characteristics of patients with improvement or worsening in renal function during treatment of acute decompensated heart failure. *Am J Cardiol*. 2010;106:1763–1769.
14. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WH. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. *Eur J Heart Fail*. 2013;15:433–440.
15. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J*. 2012;33:2135–2142.
16. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol*. 2008;51:1268–1274.
17. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.
18. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, Moye L, Pfeffer MA, Solomon SD. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol*. 2006;17:2886–2891.
19. de Silva R, Nikitin NP, Witte KK, Rigby AS, Goode K, Bhandari S, Clark AL, Cleland JG. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. *Eur Heart J*. 2006;27:569–581.
20. Khan NA, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, Levin A. Kidney function and mortality among patients with left ventricular systolic dysfunction. *J Am Soc Nephrol*. 2006;17:244–253.
21. Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ; COACH investigators. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). *Eur J Heart Fail*. 2009;11:847–854.
22. Scios Inc. NDA 20–920 Cardio-Renal Advisory Committee Briefing Document. United States Food and Drug Administration web site. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3749B2_01_Scios-1999.pdf. Updated January 11, 1999. Accessed April 2, 2013.
23. Burger AJ, Horton DP, LeJemtel T, Ghali JK, Torre G, Dennish G, Koren M, Dinerman J, Silver M, Cheng ML, Elkayam U; Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. *Am Heart J*. 2002;144:1102–1108.
24. Voors AA, Davison BA, Felker GM, Ponikowski P, Unemori E, Cotter G, Teerlink JR, Greenberg BH, Filippatos G, Teichman SL, Metra M; Pre-RELAX-AHF study group. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. *Eur J Heart Fail*. 2011;13:961–967.
25. Voors AA, van Veldhuisen DJ. Cardiorenal effects of recombinant human natriuretic peptides. *J Am Coll Cardiol*. 2010;55:1852–1853.
26. Klein L, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF Jr, Califf RM, Gheorghiade M; OPTIME-CHF Investigators. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a

Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail*. 2008;1:25–33.
27. Butler J, Chirovsky D, Phatak H, McNeill A, Cody R. Renal function, health outcomes, and resource utilization in acute heart failure: a systematic review. *Circ Heart Fail*. 2010;3:726–745.
28. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J*. 2004;147:331–338.
29. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002;8:136–141.
30. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.
31. Breidthardt T, Socrates T, Noveanu M, Klima T, Heinisch C, Reichlin T, Potocki M, Nowak A, Tschung C, Arenja N, Bingisser R, Mueller C. Effect and clinical prediction of worsening renal function in acute decompensated heart failure. *Am J Cardiol*. 2011;107:730–735.
32. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;5:54–62.
33. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805.
34. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122:265–272.
35. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J*. 2014;35:1284–1293.
36. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol*. 2013;61:1973–1981.

CLINICAL PERSPECTIVE

Nesiritide is recombinant B-type natriuretic peptide approved for use in patients with acute heart failure, because of its ability to reduce pulmonary-capillary wedge pressure and improve dyspnea. Yet after its approval, it was suggested that nesiritide might cause renal toxicity and increase mortality. These concerns led to a marked decrease in the use of nesiritide. The Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) was conducted to re-evaluate the efficacy and safety of nesiritide, compared with placebo, added to standard of care in 7141 acute decompensated heart failure (ADHF) patients. Overall, compared with placebo, nesiritide did not worsen clinical outcomes. In the present renal retrospective analysis of the ASCEND-HF trial, we found that nesiritide did not have any effect on changes in creatinine during hospitalization in patients with ADHF. Furthermore, we examined the clinical predictors of changes in creatinine, and the relationship between changes in renal function and outcomes. At any time point during hospitalization, renal function as measured by creatinine was associated with 30-day death and 30-day death or rehospitalization including baseline, discharge, peak, change, or the most recent measure. We suggest measuring creatinine values more than once during hospitalization, for it is important to understand that the time of creatinine value ascertainment can yield differences in the association with outcomes.

Nesiritide, Renal Function, and Associated Outcomes During Hospitalization for Acute Decompensated Heart Failure: Results From the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF)

Vincent M. van Deursen, Adrian F. Hernandez, Amanda Stebbins, Vic Hasselblad, Justin A. Ezekowitz, Robert M. Califf, Stephen S. Gottlieb, Christopher M. O'Connor, Randall C. Starling, W.H. Wilson Tang, John J. McMurray, Kenneth Dickstein and Adriaan A. Voors

Circulation. 2014;130:958-965; originally published online July 29, 2014;
doi: 10.1161/CIRCULATIONAHA.113.003046
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Total number of patients reported in table 1, 3 and 4.

Total number of patients reported in Table 1:	5702
Death before discharge:	73
Total number of baseline measurements equal to zero:	1
Total number of peak values greater than or equal to ten:	9
Total number of patients missing thirty day mortality status:	12
Total number of patients reported peak in Table 3:	5607

Total number of patients reported in Table 1:	5702
Death before discharge:	73
Total number of baseline measurements equal to zero:	1
Total number of peak values greater than or equal to ten:	9
Total number of patients missing thirty day mortality status:	152
Total number of patients reported peak in Table 4:	5467

Total number of patients reported baseline/DC values in Table 3:	4732
Total number of patients missing thirty day mortality rehospitalization:	90
Total number of patients reported baseline/DC values in Table 4:	4646