Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion. A post-hoc analysis of the PROTECT trial data.

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Word count: 3,191

Target journal: Circ HF

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Disclosures

Marco Metra reports personal fees and reimbursements from NovaCardia and Merck during the conduct of the PROTECT study, and personal fees from Novartis, Bayer, Amgen, Servier, Sanofi, Vifor, Trevena, and Abbott Vascular, outside the submitted work.

Gad Cotter and Beth A Davison report grants from NovaCardia and Merck during the conduct of the PROTECT study, and personal fees from Novartis Pharma AG and grants from Novartis Pharmaceuticals Corporation, Celyad (Cardio3 BioSciences), Amgen Inc., Laguna Pharmaceuticals, Inc., Singulex, Trevena, Inc., and Ventrix, Inc. outside the submitted work.

Stefanie Senger, Chris Edwards, Guillermo C Curzack, and Olga Milo report grants from NovaCardia and Merck during the conduct of the PROTECT study, and grants from Novartis Pharmaceuticals Corporation, Celyad (Cardio3 BioSciences), Amgen Inc., Laguna Pharmaceuticals, Inc., Singulex, Trevena, Inc., and Ventrix, Inc. outside the submitted work.John G Cleland - was on the Steering Committee for the study, served on the Advisory Board for MSD, and received payments for both

Piotr Ponikowski - has received honoraria from Merck.

Jon R Teerlink - has received research funds and consulting fees from Merck, the producer of rolofylline for the conduct of this study and has also received research funds and consulting fees from Abbott, Amgen, Biogen Idec, Corthera, Cytokinetics, Johnson and Johnson/ Scios, Novartis, Relypsa and Solvay for research in related areas

Michael Givertz - has received institutional research Pageh, Trevena, Vifor.

Howard Dittrich – was an employee of Merck

Daniel Bloomfield – was an employee of Merck

Christopher O'Connor . is a consultant to Merck.

Abstract

The importance of an increase in serum creatinine, traditionally considered as worsening renal function (WRF), during an admission for acute heart failure (AHF) has been recently debated, with data suggesting an interaction between congestion and creatinine changes.

Methods and results: In a post-hoc analysis, we analysed the association of WRF with length of hospital stay, 30-day death or cardiovascular (CV)/renal re-admission and 90-day mortality in the PROTECT study. Daily creatinine changes from baseline were categorized as representing WRF (an increase of 0.3 mg/dL or more) or not. Congestion scores were computed for each study day by summing the coded values of orthopnea, edema and jugular venous pressure. Of the 2033 total patients randomized, 1537 patients had both available at study day 14. Length of stay (LOS) was longer and 30-day CV/Renal readmission or death was more common in patients with WRF. However, these were driven by significant associations in patients with concomitant congestion at the time of assessment of renal function. The mean difference in LOS due to WRF was 3.51 (95% CI 1.29-5.73) more days (p=0.0019), and the hazard ratio for WRF on 30-day death or HF hospitalization was 1.49 (95% CI 1.06-2.09) times higher (p=0.0205), in significantly congested than non-significantly congested patients . A similar trend was observed with 90-day mortality although this did not reach statistical significance.

Conclusions: In patients admitted for AHF, WRF as determined by a creatinine increase of ≥0.3 mg/dL was associated with longer LOS, and worse outcomes at 30 and 90 days. However, these effects were largely driven by patients who had residual congestion at the time of renal function assessment.

Introduction

Both an increase in serum creatinine of ≥0.3 mg/dL, traditionally defined as worsening of renal function (WRF), and persistent congestion have been shown to be associated with adverse outcomes in patients admitted for acute heart failure (HF) (1-11). Further analyses have shown the importance of decongestion, measured either through clinical signs (12) or by laboratory exams, hemoconcentration or diuretic response, (13-15) as a major predictor of outcomes. Evidence has also clarified that the clinical significance of an increase in serum creatinine differs when it occurs concomitantly with decongestion, rather than in the presence of diuretic resistance. (12, 16). Lastly, retrospective analyses of randomized controlled trials have shown that a reduction, rather than an increase, in serum creatinine can be associated with worse outcomes (17-20). These last trials were characterized, however, by the enrolment of patients with severe heart failure so that a decrease in serum creatinine could have been an index of increased central venous pressure and renal venous congestion at baseline. These results further emphasise that the interpretation of serum creatinine changes is critically dependent on the patient's fluid status. Hence, the term "pseudo-WRF" has been proposed to define when an increase in serum creatinine is not associated with worsening of renal function and poorer outcomes. (21)

The PROTECT study was one of the first trials to apply serial measurements of creatinine in all patients from admission to day 6 or 7 and then at day 14 regardless of disease severity (22, 23). Analysis of data from this study has shown that creatinine changes over time, assessed as "trajectories" of change, are associated with risks of both 180-day mortality and 60-day mortality or readmission. Namely, an increase in serum creatinine >0.1 mg/dL per day was predictive of an increased risk of death, whereas stable or decreasing serum creatinine levels were associated

with reduced risk (24). These analyses seemingly contradict previous data. However, they may be caused by differences in fluid status and response to treatment. In the current post-hoc analysis of the PROTECT data we have assessed the prognostic significance of serum creatinine changes as related with the presence of congestion in patients enrolled in PROTECT.

Methods

The Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume Overload to assess Treatment Effect on Congestion and renal funcTion (PROTECT) was a randomized, double-blind, placebo-controlled trial designed to evaluate three daily 4-hour intravenous infusions of rolofylline in 2033 patients hospitalized with acute decompensated heart failure (ADHF) and mild to moderate renal impairment (20-80 mL/min) (11,12). The study was initiated as two identical trials (PROTECT-1 NCT00328692 and PROTECT-2 NCT00354458), but shortly after amended to specify a combined analysis of the two studies. Patients at centers in North America, Israel, Europe, Argentina, and Russia were enrolled between May 2007 and January 2009. ADHF was defined as dyspnea at rest or with minimal exertion and at least one sign of fluid overload: jugular venous pulse > 8 cm, pulmonary rales ≥⅓ up the lung fields not clearing with cough, or ≥2+ peripheral or presacral edema. Patients with B-type natriuretic peptide (BNP) < 500 pg/mL or N-terminal-pro-BNP < 2000 pg/mL, or systolic blood pressure <95 or >160 mmHg were excluded. Patients were randomized within 24 hours of hospital presentation. The ethics committee at each participating center approved the protocol, and all patients provided written informed consent.

Signs and symptoms of HF were assessed prior to study drug initiation (day 1), then daily while hospitalized through day 6, and then on days 7 and 14. Blood samples for central laboratory haematology and chemistry measures were taken at the same time points. Patients discharged on day 6 were not required to return at day 7. Patients were contacted by telephone at days 60 and 180. Rehospitalisation and deaths through day 60 were adjudicated by a blinded clinical events committee. The study treatment did not have a statistically significant effect on the study's primary efficacy endpoint – an ordered trichotomy defined as treatment success (based on dyspnea relief), no change (neither success nor failure), or treatment failure (death, HF readmission or in-hospital WHF, or persistent worsening renal function) – at day 7. Study treatment groups also did not differ with respect to either secondary efficacy endpoint – 60-day death or rehospitalisation for cardiovascular or renal reason or persistent renal impairment (creatinine increase $\geq$ 0.3 mg/dL at days 7 and 14) – or with respect to 180-day all-cause mortality.

Statistical methods

As no difference between the rolofylline and placebo treatment groups was found with respect to any outcome, including WRF (12, 25), the data of all patients, irrespective of drug assignment, are used in the present study.

Daily creatinine changes from baseline were categorized as representing WRF (an increase $\geq$0.3 mg/dL) or not. Congestion scores were computed for each study day by summing up the coded values of orthopnea (0= None, 1= 1 pillow, 2= 2 pillows, 3= >30°), edema (0= 0, 1= 1+, 2= 2+, 3= 3+), and jugular venous pressure (0= <6 cm, 1= 6-10 cm, 2= >10 cm), if all three parts were available, and were then dichotomized as mild ($\leq$2) or significant ($\geq$3) for each

study day, as previously described (26) and modified for this study (Rubio-Gracia 2016, unpublished). Because patients discharged on day 6 were not required to return at day 7,creatinine changes and congestion scores at day 7 were used if available and the day 6 value otherwise.

Patients were subdivided into four groups defined by the occurrence or not of a creatinine increase ≥ 0.3 mg/dL and by the presence or absence of a congestion score ≥ 3 at two time points – day 2 (24-48 hours from hospital presentation) and day 14. Groups were compared regarding baseline characteristics using ANOVA (or Kruskal-Wallis test if highly skewed) for continuous variables and chi-square test for categorical variables.

The associations with clinical outcomes of a creatinine increase ≥ 0.3 mg/dL at each study day were then evaluated by the dichotomized congestion score at the same study day. A sensitivity analysis was conducted where congestion scores from the previous day were coupled with the creatinine changes from days 3 through 6 or 7. Clinical outcomes included the time to all-cause death or cardiovascular/renal (CV/RF) rehospitalisation from the respective study day through 30 days thereafter, time to all-cause death from baseline through study day 90, and length of initial hospital stay (LOS) through study day 60 with in-hospital deaths set to a value of 61 days. Subjects who were not followed up beyond (>) the respective study day were excluded from the estimated association for that particular study day. For LOS, subjects who did not stay in hospital beyond the respective study day were also excluded. Associations, expressed as hazard ratios or mean differences respectively, were estimated using Cox proportional hazards models for time-to-event endpoints and linear regression models for LOS. Because LOS was truncated in many cases, a sensitivity analysis was performed using Cox regression for time to discharge through day 60. For each study day, the models included dichotomized creatinine

change, dichotomized congestion score, and their interaction as factors, from which, the effects (hazard ratios or mean differences) of a creatinine increase ≥0.3 mg/dL were estimated for subjects with and without significant congestion at each study day. Models were further adjusted for predictors as previously published for similar endpoints in PROTECT (27,28). Missing baseline parameters were imputed by multiple imputation with 10 imputed data sets assuming multivariate normality. Estimated effect sizes, 95% confidence intervals, and p-values were combined across the multiply-imputed datasets using Rubin's algorithm (29).

Linear regression models were used to examine whether the difference in association of creatinine increase with outcomes in patients with and without significant congestion varied over time, and to obtain an estimate of the average difference in association over time, reported as the average ratio of the HRs or average difference of the mean differences between these effects over the study period. Variances for the estimated associations of creatinine increase with outcomes (log hazard ratios or mean differences) in patients with and without significant congestion on each study day were obtained by running the models for 1000 bootstrap samples. The bootstrap estimates of the creatinine increase effect were then analysed in a single linear regression model using the bootstrap variances and including dichotomized congestion score, study day, and the interaction of congestion score and study day as factors. If the interaction of congestion and time was non-significant, the interaction term was removed from the model, and the difference in the effects of creatinine increase in patients with and without significant congestion estimated from the bootstrap results. The same analyses were conducted examining a creatinine decrease ≥ 0.3 mg/dL. Two-sided $p<0.05$ was considered statistically significant, without adjustment for multiple comparisons. SAS® 9.3 (SAS Institute, Cary, NC, USA) was used for analyses.

Results

Of the 2033 total patients randomized, 1684 patients had both creatinine change and congestion score available at study day 2, and 1537 patients had both available at study day 14. Baseline characteristics by creatinine increase and congestion score at days 2 and 14 are shown in Tables 1 and 2, respectively.

Patients with a creatinine increase of $\geq$0.3 mg/dL were more likely to have an event of death or CV/RF readmission within 30 days of the assessment if they were significantly congested at the time of assessment. Figure 1 presents multivariable-adjusted hazard ratios for a creatinine increase in patients with and without significant congestion based on estimates from individual models per study day (Supplemental Table 1a), with linear regression results from the bootstrap analysis overlaid. In the patients with a congestion score of $\leq$2, the increase in serum creatinine was never associated with worse outcomes within 30 days of the assessment; the HR estimated at day 7 from the bootstrap regression was 0.98 (95% CI 0.76-1.27, p=0.8833). In contrast, the increase in creatinine in the patients with significant congestion was associated with an almost 1.5-times higher risk of events and these hazard ratios were statistically significant with the measurements taken at days 2, 4 and 5 (the lower bound of the CI does not include 1.00) and nearly significant at the other time points (the lower 95% confidence bound was 0.97 at day 7 and 0.96 at day 14). The HR estimated at day 7 from the bootstrap regression was 1.46 (95% CI 1.12-1.90, p=0.0046) with a ratio of HRs in patients with congestion score $\geq$3 versus not of 1.49 (95% CI 1.06-2.09, p=0.0205). The effect of congestion on the association of creatinine increase with the 30-day outcome did not vary significantly over time; the ratio of HRs for a creatinine increase in patients with and without significant congestion remained constant from

day 2 (24 hours from randomization) through day 14 (congestion-by-time interaction p=0.9100). Results were similar if patients were categorized by the congestion score on the day prior to the creatinine measurement (Supplemental Table 1b, Supplemental Figure 1); the HR for a creatinine increase in patients with a congestion score ≥3 the previous day was 1.39 times the HR in those with score ≤2 (95% CI 0.94-2.05, p=0.1020).

With respect to mortality at 90 days, a creatinine increase of ≥0.3 mg/dL was associated with a higher risk of the outcome in patients significantly congested at the time of creatinine measurement (estimated at day 7 from the bootstrap linear regression: HR 1.94, 95% CI 1.43-2.63, p<0.0001) than in those with no or mild congestion (estimated at day 7 from the bootstrap linear regression: HR 1.36, 95% CI 0.94-1.96, p=0.1075), although the difference did not reach statistical significance (ratio of HRs 1.43, 95% CI 0.92-2.23, p=0.1121) (Figure 2, Supplemental Table 2a). Also in this case, the modifying effect of congestion did not vary over time, as indicated by a non-statistically-significant congestion-by-time interaction in the bootstrap linear regression (p=0.2704). Similar results were observed when evaluating modification of the creatinine increase by the previous day's congestion score (ratio of HRs 1.35, 95% CI 0.75-2.43, p=0.3121) (Supplemental Table 2b, Supplemental Figure 2).

A creatinine increase of ≥0.3 mg/dL was associated with a longer length of hospital stay especially when noted later during the admission (Figure 3, Supplemental Table 3a). Also in this case, the effect of a creatinine increase differed significantly by whether the patient had significant congestion at the time of assessment. Patients with 0-2 congestion score did not experience an appreciable increase in the LOS associated with a creatinine increase ≥0.3 mg/dL on any day through day 7 (Supplemental Table 3a); the mean change in LOS estimated at day 7 from the bootstrap linear regression (Figure 3) was 1.13 (95% CI -0.82-3.07) days (p=0.2564).

Patients with a congestion score of ≥3 had on average a 3-day greater estimated mean difference in LOS for a creatinine increase ≥0.3 mg/dL; the mean change in LOS estimated at day 7 from the bootstrap linear regression was 4.64 (95% CI 1.87-7.41) days (p=0.0010). Again, the modifying effect of congestion on the effect of a creatinine increase did not change over time for this endpoint (congestion-by-time interaction p=0.1879), with an estimated mean difference between patients with and without significant congestion of 3.51 (95% CI 1.29-5.73) days (p=0.0019). Similar patterns were observed when patients were categorized by the previous day's congestion score (Supplemental Table 3b, Supplemental Figure 3a). Analysis of the outcome as time to discharge through day 60, rather than as a continuous variable, supports this finding. A creatinine increase was associated with less likelihood of discharge through day 60 only in patients significantly congested at the time (Supplemental Table 3c, Supplemental Figure 4).

We repeated the same analysis examining the effect of a creatinine decrease of ≥ 0.3 mg/dL. Few patients experienced a creatinine decrease of such magnitude; at day 2, only 23 patients with congestion score 0-2 and 72 patients with congestion score 3 experienced such a creatinine decrease. Patients with a creatinine decrease at nearly all time points examined experienced lower rates of all three outcomes of interest (30-day CV/renal readmission or death, 90-day death, and LOS), with the estimated beneficial effects of a creatinine decrease more pronounced in patients with congestion score of 3 or more; however, as the numbers of patients were small in these subgroups the estimated effects of a creatinine decrease, differences in creatinine decrease effects between patients with and without significant congestion, and any variation in the difference between congestion groups with respect to the creatinine decrease effect over time all failed to reach statistical significance (Supplemental Figures 4-6).

Discussion

This analysis of PROTECT shows that an increase in serum creatinine is associated with poorer outcomes only in the patients with significant congestion, defined as a score of 3 or more, at the time of the serum creatinine measurements. The difference in the effect of serum creatinine increases by congestion score was significant for the composite outcome at 30 days but did not reach statistical significance when day 90 mortality was considered, likely because of insufficient events. This differential effect of a creatinine increase did not vary with respect to the time of the clinical assessment. Similar to outcomes, LOS was longer in those patients with an increase in serum creatinine and concomitant congestion but not in those with a congestion score of 0-2.

The clinical significance of serum creatinine changes in AHF is still controversial with either its increase or a reduction associated with poorer outcomes (21). Some of this heterogeneity of result may relate to the fact that when single time points are compared to the baseline assessments or the assessments are done using specific cut-offs, the result can be less significant (supllemental tables 1-3). We have previously shown using a single centre database that the importance of creatinine changes is influenced by the fluid status (12). However, this study was small and relied on creatinine measurements that were not uniformly performed at pre-defined time points. In the current post-hoc analysis of the PROTECT data base, we confirm and expand these findings. First, creatinine increases of $\geq$0.3 mg/dl are associated with adverse outcomes mainly in patients who are significantly congested at the time of creatinine measurement. This finding would suggest that creatinine “bumps” due to excessive dehydration, such as following diuretic therapy, do not necessarily carry negative prognostic implications while similar

increases in patients who have persistent congestion despite diuretic therapy, and who are likely diuretic resistant, are ominous signs. This finding is in line with clinical “common wisdom” and previous studies suggesting that patients who remain congested and display deterioration in renal function despite optimal therapy during an AHF admission, have a direr prognosis, especially when it comes to short-term events (12,13,21,30).

An interaction between the effect of increases in serum creatinine and congestion on LOS was also found in the present analysis. Patients congested at the time of serum creatinine measurements had very large increases in LOS, while little to no increase in LOS occurred in patients who were not significantly congested at the time of their measurements. These data are consistent with the poorer outcomes associated with WRF in the patients who develop worsening heart failure, and hence congestion, during hospitalization. They also confirm the finding that creatinine changes significantly affect the clinical course and outcomes of patients with AHF only when associated with significant congestion. This finding may have implications in analyzing results of intervention clinical studies, as the assumption that all creatinine increases are associated with worse outcome may not be true, and hence some creatinine changes in response to interventions may not be signifiers of future adverse outcome.

In the current analysis we did not observe an association between creatinine decreases and more adverse outcomes, a finding shown in other studies (17,20). To the contrary, we noted numerically smaller hazards for 30-day death or CV/renal readmission and 90-day mortality and shorter LOS in those patients. However, as noted above, only few patients had creatinine decreases of 0.3 mg/dL or more and none of the associations examined reached statistical significance. As with increases in creatinine, the difference between our data and those previously published may be due to chance – as none of these effects were statistically

significant – or due to ascertainment bias in other studies. In PROTECT, creatinine was measured daily systematically and hence there was no bias towards sicker patients having more creatinine measurements, enabling, possibly, a more objective assessment of the associations between creatinine changes and adverse outcomes and their interactions with congestion.

Limitations

The current analysis is a post-hoc analysis of the PROTECT study and as such should be regarded with caution and should be confirmed in larger prospective studies. Congestion scores were determined using a simple method. It is possible that the result would have benefited from better quantitative methods of congestion assessment. Analyses of the associations of creatinine increases with outcomes over time in patients with and without significant congestion were conducted on group-level data and might not be representative of individual patient trajectories.

Conclusions

In this post-hoc analysis of the PROTECT study, creatinine increases of 0.3 mg/dL or more were found to be associated with longer length of admission and higher risk of death or readmission for cardiovascular or renal reason within 30 days only in patients who at the time of creatinine measurement were significantly congested.

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Clinical perspective:

The importance of an increase in serum creatinine, traditionally considered as worsening renal function (WRF), during an admission for acute heart failure (AHF) has been recently debated, with data suggesting an interaction between congestion and creatinine changes. In a post-hoc analysis, we analysed the association of WRF with length of hospital stay, 30-day death or cardiovascular (CV)/renal re-admission and 90-day mortality in the PROTECT study. Daily creatinine changes from baseline were categorized as representing WRF (an increase of 0.3 mg/dL or more) or not. Congestion scores were computed for each study day by summing the coded values of orthopnea, edema and jugular venous pressure. We have found pts with WRF and consetsion had longer LOS - 3.51 (95% CI 1.29-5.73) more days (p=0.0019), more HF hospitalization was 1.49 (95% CI 1.06-2.09) times higher (p=0.0205), with a similar trend was observed with 90-day mortality although this did not reach statistical significance. Hence, in patients admitted for AHF, WRF as determined by a creatinine increase of ≥0.3 mg/dL was associated with longer LOS, and worse outcomes at 30 and 90 days. However, these effects were largely driven by patients who had residual congestion at the time of renal function assessment.

Table 1: Baseline characteristics by creatinine increase from baseline and congestion score at Day 2

Parameter	Creatinine increase < 0.3 mg/dL and congestion score ≤ 2 (N=386)	Creatinine increase < 0.3 mg/dL and congestion score ≥ 3 (N=1161)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≤ 2 (N=45)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≥ 3 (N=92)	P-value
Age, y	70.3 (11.83)	69.8 (11.58)	71.0 (10.19)	71.5 (10.80)	0.5081
Male gender	267 (69.2%)	768 (66.1%)	30 (66.7%)	58 (63.0%)	0.6209
White race	372 (96.4%)	1090 (94.8%)	43 (97.7%)	90 (97.8%)	0.3074
Time from presentation to randomization, h	16.40 (6.25, 21.60)	17.10 (5.40, 21.60)	16.15 (5.65, 23.35)	16.35 (5.20, 22.30)	0.9548
History of ischemic heart disease	251 (65.2%)	817 (70.5%)	31 (68.9%)	60 (65.2%)	0.2194
History of angina	64 (16.6%)	260 (22.5%)	15 (33.3%)	26 (28.3%)	0.0065
History of previous stroke or PVD	66 (17.1%)	204 (17.6%)	15 (33.3%)	22 (23.9%)	0.0228
History of diabetes mellitus	153 (39.7%)	549 (47.3%)	20 (44.4%)	33 (35.9%)	0.0199
History of respiratory disease	72 (18.7%)	240 (20.7%)	8 (17.8%)	19 (20.7%)	0.8107
History of mitral regurgitation	135 (35.0%)	401 (34.6%)	14 (31.1%)	30 (32.6%)	0.9358
History of atrial fibrillation/flutter	193 (50.3%)	642 (55.8%)	20 (44.4%)	44 (47.8%)	0.0806
History of chronic heart failure	361 (93.5%)	1122 (96.6%)	40 (88.9%)	88 (95.7%)	0.0077
History of hypertension	293 (75.9%)	932 (80.3%)	35 (77.8%)	78 (84.8%)	0.1623
History of hyperlipidemia	211 (54.7%)	598 (51.6%)	26 (57.8%)	49 (53.3%)	0.6445
History of smoking	82 (21.3%)	258 (22.3%)	9 (20.0%)	14 (15.2%)	0.4573
History of CABG or PCI	146 (38.0%)	452 (39.2%)	22 (48.9%)	30 (32.6%)	0.3094
Heart failure hospitalization in previous year	179 (46.4%)	600 (51.7%)	19 (42.2%)	43 (46.7%)	0.1855
NYHA class in previous month					
None/I/II	111 (28.8%)	215 (18.5%)	13 (28.9%)	23 (25.3%)	<.0001
III	203 (52.6%)	558 (48.1%)	22 (48.9%)	41 (45.1%)	
IV	72 (18.7%)	388 (33.4%)	10 (22.2%)	27 (29.7%)	
Body mass index, kg/m^2	26.74 (23.72, 29.40)	28.12 (24.53, 32.79)	25.95 (24.28, 28.07)	28.00 (24.98, 31.53)	<.0001
Ejection fraction, %	30.0 (23.0, 40.0)	30.0 (21.0, 40.0)	35.0 (33.0, 40.0)	27.0 (20.0, 45.0)	0.0265
Heart rate, bpm	79.3 (15.13)	80.3 (15.60)	77.6 (14.13)	81.0 (14.11)	0.4369
Systolic blood pressure, mmHg	123.1 (17.51)	123.9 (17.36)	128.2 (17.61)	126.6 (18.32)	0.1235
Diastolic blood pressure, mmHg	72.6 (11.98)	74.0 (11.39)	72.3 (11.69)	75.6 (11.85)	0.0661
Pulse pressure, mmHg	50.5 (14.96)	49.9 (15.00)	55.9 (14.83)	51.1 (15.67)	0.0590
Mean arterial pressure, mmHg	89.46 (12.171)	90.64 (11.707)	90.96 (12.065)	92.59 (12.284)	0.1083
Respiratory rate, breaths per min	20.9 (4.20)	21.3 (4.20)	19.3 (2.99)	22.2 (4.65)	0.0008
Edema					
0	125 (32.4%)	92 (7.9%)	17 (37.8%)	12 (13.0%)	<.0001
>1	114 (29.5%)	160 (13.8%)	17 (37.8%)	23 (25.0%)	
>2	130 (33.7%)	501 (43.2%)	9 (20.0%)	39 (42.4%)	
>3	17 (4.4%)	408 (35.1%)	2 (4.4%)	18 (19.6%)	
Jugular venous pressure					
<6 cm	91 (23.8%)	89 (7.7%)	11 (25.0%)	8 (8.8%)	<.0001

Parameter	Creatinine increase < 0.3 mg/dL and congestion score ≤ 2 (N=386)	Creatinine increase < 0.3 mg/dL and congestion score ≥ 3 (N=1161)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≤ 2 (N=45)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≥ 3 (N=92)	P-value
6-10 cm	209 (54.6%)	510 (44.2%)	28 (63.6%)	43 (47.3%)	
>10 cm	83 (21.7%)	556 (48.1%)	5 (11.4%)	40 (44.0%)	
Orthopnea					
None	33 (8.7%)	24 (2.1%)	6 (13.3%)	4 (4.3%)	<.0001
1 pillow	84 (22.2%)	92 (8.0%)	16 (35.6%)	6 (6.5%)	
2 pillows	165 (43.5%)	457 (39.9%)	13 (28.9%)	40 (43.5%)	
>30°	97 (25.6%)	573 (50.0%)	10 (22.2%)	42 (45.7%)	
Rales					
0	35 (9.1%)	111 (9.6%)	8 (17.8%)	10 (10.9%)	0.0971
<1/3	123 (31.9%)	350 (30.2%)	9 (20.0%)	23 (25.0%)	
1/3 to 2/3	202 (52.3%)	570 (49.2%)	26 (57.8%)	47 (51.1%)	
>2/3	26 (6.7%)	128 (11.0%)	2 (4.4%)	12 (13.0%)	
Hemoglobin, g/dL	12.87 (1.987)	12.59 (1.961)	12.61 (1.978)	12.37 (2.105)	0.0819
White blood cell count, $x10^9$/L	7.63 (6.28, 9.49)	7.32 (5.99, 9.10)	8.33 (7.27, 9.24)	7.89 (6.19, 9.93)	0.0195
Sodium, mEq/L	139.5 (3.82)	139.2 (4.18)	139.5 (3.40)	139.2 (4.27)	0.6775
Potassium, mEq/L	4.26 (0.571)	4.26 (0.580)	4.35 (0.605)	4.33 (0.545)	0.5116
Bicarbonate, mEq/L	23.9 (3.67)	24.0 (3.78)	23.2 (3.80)	23.0 (4.02)	0.0472
Creatinine, mg/dL	1.40 (1.10, 1.70)	1.40 (1.10, 1.80)	1.50 (1.20, 2.10)	1.55 (1.25, 1.90)	0.0071
eGFR, mL/min	48.95 (17.107)	49.04 (18.801)	44.61 (20.740)	41.99 (16.415)	0.0020
BUN, mg/dL	28.0 (22.0, 38.0)	29.0 (22.0, 41.0)	30.0 (23.0, 43.0)	34.0 (24.5, 48.0)	0.0283
BUN/creatinine ratio	21.93 (6.773)	22.73 (7.339)	20.63 (6.074)	22.65 (7.621)	0.0810
Uric acid, mg/dL	515.73 (150.010)	541.33 (151.949)	475.70 (112.710)	509.68 (154.683)	0.0009
Albumin, g/dL	3.94 (0.408)	3.82 (0.430)	3.92 (0.428)	3.87 (0.517)	<.0001
ALT, U/L	22.0 (15.5, 33.0)	21.0 (15.0, 30.0)	16.0 (11.0, 26.0)	20.0 (13.0, 32.0)	0.0267
Glucose, mg/dL	6.83 (5.61, 8.71)	7.02 (5.72, 9.10)	6.60 (5.38, 8.38)	6.83 (5.72, 8.38)	0.2077
Cholesterol, mg/dL	3.99 (1.193)	3.67 (1.054)	4.30 (1.082)	4.09 (1.423)	<.0001
Triglycerides, mg/dL	95.0 (66.0, 135.0)	87.0 (65.0, 118.0)	102.0 (68.0, 145.0)	75.5 (58.5, 126.5)	0.0164

ALT, alanine transferase; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; Q1, first quartile; Q3, third quartile.
Summary statistics based on subjects who were followed up beyond Day 2 and had creatinine increase from baseline and congestion score available for that study day.
Results shown are mean (standard deviation) with p-value from ANOVA (F-test) for continuous variables, median (first and third quartile) with p-value from Kruskal-Wallis test for continuous variables with skewed distributions, or prevalence (%) with p-value from Chi-squared test for categorical variables.

Table 2: Baseline characteristics by creatinine increase from baseline and congestion score at Day 14

Parameter	Creatinine increase < 0.3 mg/dL and congestion score ≤ 2 (N=902)	Creatinine increase < 0.3 mg/dL and congestion score ≥ 3 (N=281)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≤ 2 (N=249)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≥ 3 (N=105)	P-value
Age, y	69.1 (11.72)	71.2 (11.07)	72.0 (10.98)	70.5 (11.08)	0.0011
Male gender	593 (65.7%)	193 (68.7%)	159 (63.9%)	76 (72.4%)	0.3563
White race	870 (97.0%)	253 (90.7%)	240 (96.8%)	94 (90.4%)	<.0001
Time from presentation to randomization, h	17.20 (5.75, 21.70)	17.10 (5.50, 21.80)	14.35 (4.65, 20.80)	17.10 (4.75, 21.75)	0.1102
History of ischemic heart disease	610 (67.7%)	196 (69.8%)	180 (72.3%)	79 (75.2%)	0.2730
History of angina	216 (23.9%)	38 (13.6%)	56 (22.5%)	22 (21.2%)	0.0036
History of previous stroke or PVD	141 (15.6%)	54 (19.2%)	59 (23.7%)	21 (20.0%)	0.0234
History of diabetes mellitus	370 (41.1%)	164 (58.4%)	108 (43.4%)	55 (52.4%)	<.0001
History of respiratory disease	163 (18.1%)	54 (19.4%)	63 (25.3%)	30 (28.8%)	0.0094
History of mitral regurgitation	302 (33.6%)	98 (34.9%)	81 (32.5%)	34 (32.7%)	0.9461
History of atrial fibrillation/flutter	475 (53.1%)	161 (57.9%)	128 (51.6%)	59 (56.7%)	0.4127
History of chronic heart failure	861 (95.5%)	277 (98.6%)	232 (93.2%)	102 (97.1%)	0.0160
History of hypertension	694 (76.9%)	226 (80.4%)	204 (81.9%)	96 (91.4%)	0.0032
History of hyperlipidemia	416 (46.1%)	173 (61.8%)	142 (57.0%)	74 (70.5%)	<.0001
History of smoking	182 (20.2%)	68 (24.3%)	52 (21.0%)	31 (29.5%)	0.1043
History of CABG or PCI	294 (32.8%)	133 (47.5%)	108 (43.5%)	58 (55.2%)	<.0001
Heart failure hospitalization in previous year	433 (48.0%)	143 (50.9%)	119 (47.8%)	65 (61.9%)	0.0509
NYHA class in previous month					
None/I/II	172 (19.1%)	46 (16.4%)	75 (30.1%)	27 (25.7%)	<.0001
III	420 (46.6%)	166 (59.3%)	111 (44.6%)	57 (54.3%)	
IV	310 (34.4%)	68 (24.3%)	63 (25.3%)	21 (20.0%)	
Body mass index, kg/m^2	27.05 (23.99, 30.80)	29.33 (25.64, 33.64)	26.95 (23.81, 30.63)	29.98 (26.67, 34.52)	<.0001
Ejection fraction, %	30.0 (22.0, 38.0)	29.0 (20.0, 40.0)	34.5 (21.0, 45.0)	27.0 (20.0, 45.0)	0.2256
Heart rate, bpm	81.6 (15.76)	77.7 (14.91)	77.4 (14.66)	77.1 (14.03)	<.0001
Systolic blood pressure, mmHg	124.2 (16.36)	122.3 (18.27)	127.0 (18.96)	121.9 (18.51)	0.0082
Diastolic blood pressure, mmHg	74.7 (10.87)	71.8 (13.33)	73.6 (12.05)	70.5 (11.26)	<.0001
Pulse pressure, mmHg	49.4 (13.99)	50.5 (15.47)	53.5 (16.68)	51.4 (17.08)	0.0020
Mean arterial pressure, mmHg	91.20 (11.154)	88.63 (13.287)	91.39 (12.441)	87.61 (11.571)	0.0005
Respiratory rate, breaths per min	21.4 (4.13)	21.3 (3.87)	21.2 (4.20)	20.6 (3.72)	0.3898
Edema					
0	155 (17.2%)	19 (6.8%)	45 (18.1%)	4 (3.8%)	<.0001
>1	172 (19.1%)	44 (15.7%)	55 (22.1%)	15 (14.3%)	
>2	382 (42.4%)	108 (38.4%)	94 (37.8%)	39 (37.1%)	
>3	193 (21.4%)	110 (39.1%)	55 (22.1%)	47 (44.8%)	
Jugular venous pressure					
<6 cm	115 (12.9%)	19 (7.0%)	41 (16.7%)	7 (7.0%)	0.0003

Parameter	Creatinine increase < 0.3 mg/dL and congestion score ≤ 2 (N=902)	Creatinine increase < 0.3 mg/dL and congestion score ≥ 3 (N=281)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≤ 2 (N=249)	Creatinine increase ≥ 0.3 mg/dL and congestion score ≥ 3 (N=105)	P-value
6-10 cm	435 (48.9%)	120 (44.3%)	116 (47.2%)	40 (40.0%)	
>10 cm	340 (38.2%)	132 (48.7%)	89 (36.2%)	53 (53.0%)	
Orthopnea					
None	31 (3.5%)	11 (4.0%)	13 (5.3%)	3 (2.9%)	<.0001
1 pillow	118 (13.2%)	11 (4.0%)	32 (13.1%)	7 (6.9%)	
2 pillows	400 (44.6%)	110 (40.0%)	95 (38.8%)	32 (31.4%)	
>30°	347 (38.7%)	143 (52.0%)	105 (42.9%)	60 (58.8%)	
Rales					
0	77 (8.6%)	35 (12.5%)	27 (10.8%)	12 (11.4%)	0.2185
<1/3	266 (29.6%)	89 (31.8%)	67 (26.9%)	37 (35.2%)	
1/3 to 2/3	469 (52.1%)	125 (44.6%)	136 (54.6%)	48 (45.7%)	
>2/3	88 (9.8%)	31 (11.1%)	19 (7.6%)	8 (7.6%)	
Hemoglobin, g/dL	13.00 (2.024)	12.32 (1.775)	12.34 (1.839)	11.57 (1.565)	<.0001
White blood cell count, $x10^9$/L	7.48 (6.08, 9.25)	7.29 (6.04, 9.04)	7.52 (6.20, 9.06)	6.97 (5.37, 8.64)	0.0500
Sodium, mEq/L	139.6 (3.90)	138.6 (4.24)	139.8 (3.97)	138.9 (3.65)	0.0006
Potassium, mEq/L	4.29 (0.563)	4.24 (0.599)	4.20 (0.620)	4.24 (0.511)	0.1232
Bicarbonate, mEq/L	23.8 (3.62)	24.4 (3.83)	24.0 (3.72)	23.6 (4.05)	0.0729
Creatinine, mg/dL	1.30 (1.10, 1.70)	1.40 (1.20, 1.90)	1.30 (1.10, 1.70)	1.60 (1.30, 2.20)	<.0001
eGFR, mL/min	50.62 (18.756)	46.75 (17.936)	49.19 (19.600)	40.24 (14.716)	<.0001
BUN, mg/dL	27.0 (21.0, 38.0)	33.0 (23.0, 48.0)	29.0 (22.0, 38.0)	36.0 (27.0, 50.0)	<.0001
BUN/creatinine ratio	21.70 (6.513)	24.19 (8.237)	21.77 (6.704)	23.66 (8.348)	<.0001
Uric acid, mg/dL	528.04 (146.107)	551.09 (154.374)	500.03 (146.119)	575.03 (160.030)	<.0001
Albumin, g/dL	3.89 (0.439)	3.81 (0.419)	3.85 (0.413)	3.84 (0.424)	0.0430
ALT, U/L	22.0 (15.0, 34.0)	19.0 (15.0, 29.0)	20.0 (14.0, 30.0)	18.0 (12.0, 24.5)	<.0001
Glucose, mg/dL	6.99 (5.72, 8.99)	7.22 (5.86, 9.82)	6.83 (5.72, 8.52)	6.83 (5.61, 8.10)	0.0302
Cholesterol, mg/dL	3.94 (1.133)	3.47 (1.016)	3.92 (1.124)	3.41 (1.026)	<.0001
Triglycerides, mg/dL	90.0 (66.0, 125.0)	84.0 (65.0, 117.0)	89.0 (65.0, 130.0)	81.0 (62.0, 112.0)	0.1655

ALT, alanine transferase; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; Q1, first quartile; Q3, third quartile.
Summary statistics based on subjects who were followed up beyond Day 14 and had creatinine increase from baseline and congestion score available for that study day.
Results shown are mean (standard deviation) with p-value from ANOVA (F-test) for continuous variables, median (first and third quartile) with p-value from Kruskal-Wallis test for continuous variables with skewed distributions, or prevalence (%) with p-value from Chi-squared test for categorical variables.

Figure 1: Adjusted associations of creatinine increase from baseline with all-cause death or CV/RF rehospitalization through 30 days after Day x by congestion score

Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted hazard ratios for the effect of creatinine increase with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios > 0 correspond to hazard ratios > 1 and signify a harmful effect of creatinine increase. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.

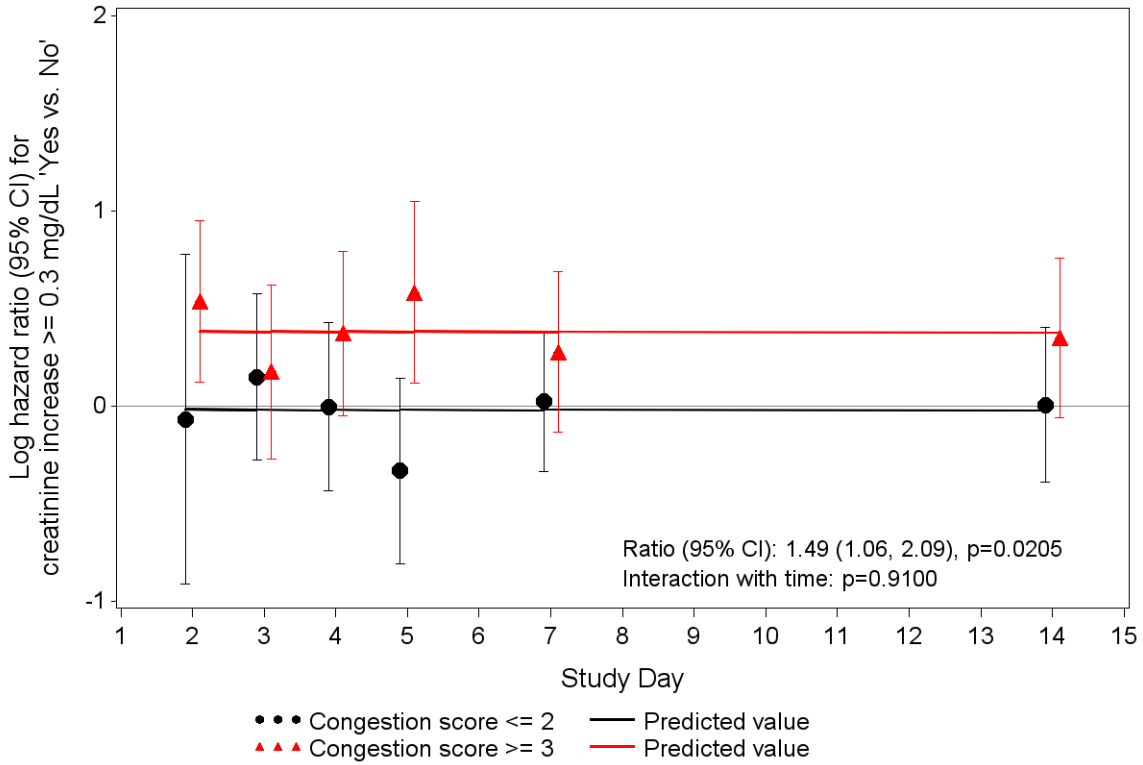


Figure 2: Adjusted associations of creatinine increase from baseline with all-cause mortality through Day 90 by congestion score

Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted hazard ratios for the effect of creatinine increase with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios > 0 correspond to hazard ratios > 1 and signify a harmful effect of creatinine increase. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.

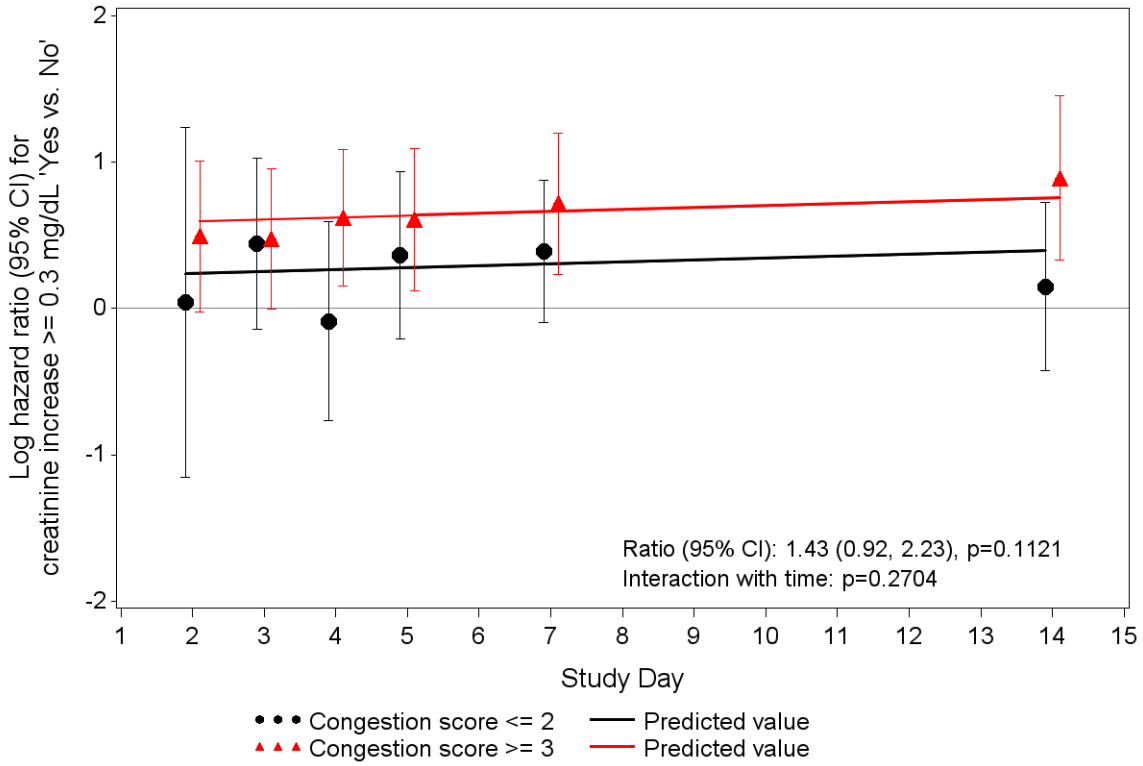
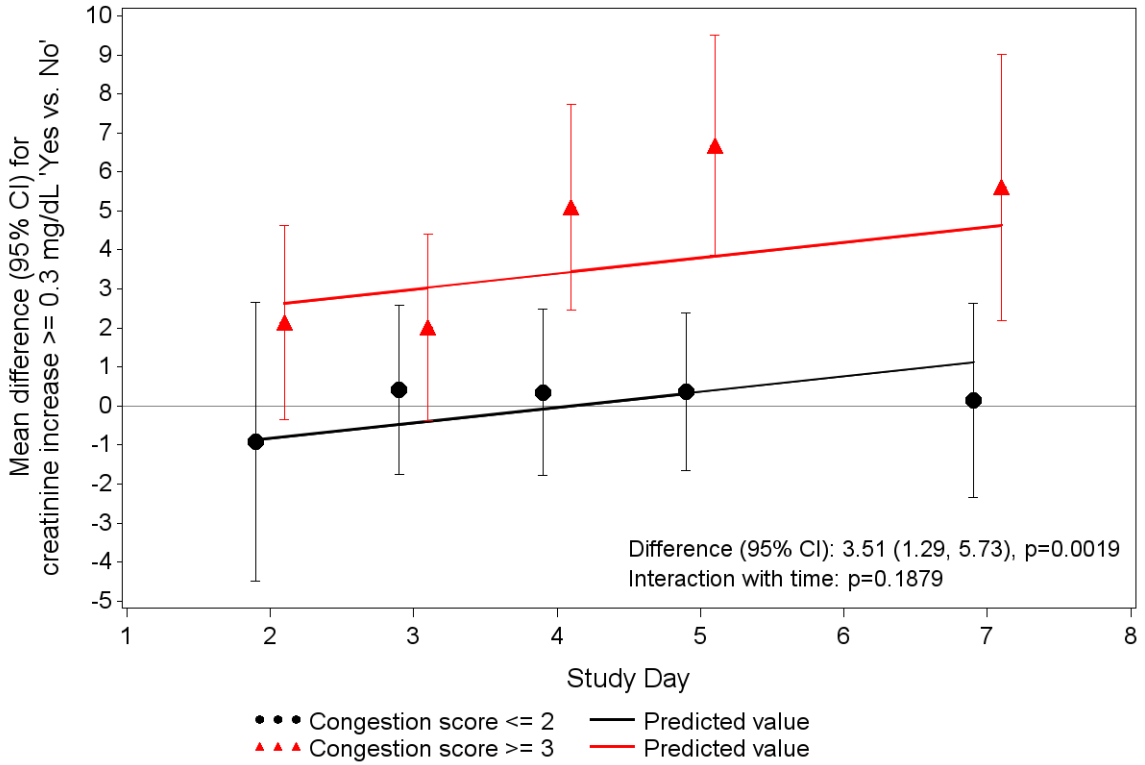


Figure 3a: Adjusted associations of creatinine increase from baseline with length of in-hospital stay through Day 60 by congestion score

Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted mean differences for the effect of creatinine increase with 95% confidence intervals were estimated from linear regression models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, or 7, respectively, and had creatinine change from baseline and congestion score available for that study day. Mean differences > 0 signify a longer LOS in patients with a creatinine increase. The difference in creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion. A post-hoc analysis of the PROTECT trial data

Supplemental Material

Supplemental Table 1a: Unadjusted and adjusted associations of creatinine increase from baseline with all-cause death or CV/RF rehospitalization through 30 days after Day x by congestion score

			Univariable model		Multivariable model †	
Parameter	**Category**	**Sample size per category / total**	**Hazard ratio (95% CI)**	**Interaction p-value #**	**Hazard ratio (95% CI)**	**Interaction p-value #**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 at Day 2	431 / 1684	0.90 (0.39, 2.09)	0.1433	0.93 (0.40, 2.18)	0.2071
	Congestion score ≥ 3 at Day 2	1253 / 1684	1.81 (1.21, 2.73)		1.71 (1.13, 2.59)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 at Day 3	805 / 1666	1.17 (0.77, 1.79)	0.8916	1.16 (0.76, 1.78)	0.9287
	Congestion score ≥ 3 at Day 3	861 / 1666	1.12 (0.72, 1.75)		1.19 (0.76, 1.86)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 at Day 4	885 / 1506	0.97 (0.63, 1.48)	0.0662	1.00 (0.65, 1.53)	0.2175
	Congestion score ≥ 3 at Day 4	621 / 1506	1.68 (1.12, 2.54)		1.45 (0.95, 2.21)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 at Day 5	863 / 1296	0.81 (0.51, 1.30)	0.0068	0.72 (0.45, 1.15)	0.0065
	Congestion score ≥ 3 at Day 5	433 / 1296	2.00 (1.27, 3.16)		1.79 (1.13, 2.85)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 at Day 6/7	1178 / 1612	1.12 (0.79, 1.60)	0.3453	1.02 (0.71, 1.47)	0.3642
	Congestion score ≥ 3 at Day 6/7	434 / 1612	1.46 (0.97, 2.18)		1.32 (0.87, 1.99)	
Creatinine increase ≥ 0.3 mg/dL at Day 14	Congestion score ≤ 2 at Day 14	1116 / 1477	1.04 (0.70, 1.54)	0.2592	1.00 (0.68, 1.49)	0.2336
	Congestion score ≥ 3 at Day 14	361 / 1477	1.44 (0.96, 2.15)		1.42 (0.94, 2.14)	

CI, confidence interval.

Results from Cox proportional hazards models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine increase from baseline and congestion score available for that study day. Hazard ratios presented for creatinine increase from baseline 'Yes vs. No'.

† Estimated effect sizes adjusted for baseline variables age, heart failure hospitalization in previous year, NYHA class in previous month, ischemic heart disease, body mass index, edema, rales, systolic blood pressure, albumin, BUN, and sodium (Cleland et al., 2014).

For the interaction of creatinine increase from baseline and congestion score.

Supplemental Table 1b: Unadjusted and adjusted associations of creatinine increase from baseline with all-cause death or CV/RF rehospitalization through 30 days after Day x by the previous day's congestion score

			Univariable model		Multivariable model †	
Parameter	**Category**	**Sample size per category / total**	**Hazard ratio (95% CI)**	**Interaction p-value #**	**Hazard ratio (95% CI)**	**Interaction p-value #**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 prior Day 2	71 / 1690	1.47 (0.41, 5.20)	0.9626	2.44 (0.68, 8.82)	0.4622
	Congestion score ≥ 3 prior Day 2	1619 / 1690	1.52 (1.03, 2.23)		1.48 (1.00, 2.19)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 prior Day 3	427 / 1660	1.12 (0.61, 2.06)	0.9186	1.18 (0.64, 2.18)	0.9708
	Congestion score ≥ 3 prior Day 3	1233 / 1660	1.16 (0.82, 1.65)		1.16 (0.81, 1.66)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 prior Day 4	703 / 1510	1.02 (0.65, 1.59)	0.1308	1.02 (0.65, 1.61)	0.2462
	Congestion score ≥ 3 prior Day 4	807 / 1510	1.60 (1.10, 2.34)		1.44 (0.98, 2.12)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 prior Day 5	753 / 1300	0.97 (0.61, 1.54)	0.1273	0.89 (0.55, 1.42)	0.1427
	Congestion score ≥ 3 prior Day 5	547 / 1300	1.59 (1.03, 2.45)		1.44 (0.92, 2.24)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 prior Day 6/7	883 / 1333	1.02 (0.68, 1.54)	0.0691	0.88 (0.58, 1.34)	0.0438
	Congestion score ≥ 3 prior Day 6/7	450 / 1333	1.78 (1.15, 2.76)		1.64 (1.05, 2.56)	

CI, confidence interval.

Results from Cox proportional hazards models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine increase from baseline and congestion score available for that study day. Hazard ratios presented for creatinine increase from baseline 'Yes vs. No'.

† Estimated effect sizes adjusted for baseline variables age, heart failure hospitalization in previous year, NYHA class in previous month, ischemic heart disease, body mass index, edema, rales, systolic blood pressure, albumin, BUN, and sodium (Cleland et al., 2014).

For the interaction of creatinine increase from baseline and congestion score.

Supplemental Table 2a: Unadjusted and adjusted associations of creatinine increase from baseline with all-cause mortality through Day 90 by congestion score

			Univariable model		Multivariable model [†]	
Parameter	**Category**	**Sample size per category / total**	**Hazard ratio (95% CI)**	**Interaction p-value [#]**	**Hazard ratio (95% CI)**	**Interaction p-value [#]**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 at Day 2	431 / 1684	0.87 (0.27, 2.87)	0.3171	1.04 (0.32, 3.45)	0.4971
	Congestion score ≥ 3 at Day 2	1253 / 1684	1.69 (1.02, 2.79)		1.64 (0.98, 2.74)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 at Day 3	805 / 1667	1.29 (0.73, 2.29)	0.6651	1.56 (0.87, 2.80)	0.9323
	Congestion score ≥ 3 at Day 3	862 / 1667	1.52 (0.95, 2.41)		1.61 (1.00, 2.59)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 at Day 4	885 / 1506	0.76 (0.39, 1.49)	0.0309	0.92 (0.46, 1.81)	0.0900
	Congestion score ≥ 3 at Day 4	621 / 1506	1.85 (1.18, 2.88)		1.86 (1.17, 2.96)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 at Day 5	864 / 1297	1.36 (0.77, 2.39)	0.3512	1.44 (0.81, 2.55)	0.5194
	Congestion score ≥ 3 at Day 5	433 / 1297	1.93 (1.21, 3.08)		1.84 (1.13, 2.99)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 at Day 6/7	1187 / 1624	1.38 (0.86, 2.23)	0.3938	1.48 (0.91, 2.40)	0.3462
	Congestion score ≥ 3 at Day 6/7	437 / 1624	1.86 (1.16, 2.98)		2.05 (1.26, 3.32)	
Creatinine increase ≥ 0.3 mg/dL at Day 14	Congestion score ≤ 2 at Day 14	1151 / 1537	1.18 (0.67, 2.07)	0.0504	1.16 (0.65, 2.06)	0.0696
	Congestion score ≥ 3 at Day 14	386 / 1537	2.59 (1.49, 4.49)		2.43 (1.39, 4.27)	

CI, confidence interval.

Results from Cox proportional hazards models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine increase from baseline and congestion score available for that study day. Hazard ratios presented for creatinine increase from baseline 'Yes vs. No'.

[†] Estimated effect sizes adjusted for baseline variables age, heart failure hospitalization in previous year, NYHA class in previous month, rales, systolic blood pressure, albumin, bicarbonate, BUN, creatinine, glucose, and sodium (Cleland et al., 2014).

[#] For the interaction of creatinine increase from baseline and congestion score.

Supplemental Table 2b: Unadjusted and adjusted associations of creatinine increase from baseline with all-cause mortality through Day 90 by the previous day's congestion score

			Univariable model		Multivariable model †	
Parameter	**Category**	**Sample size per category / total**	**Hazard ratio (95% CI)**	**Interaction p-value #**	**Hazard ratio (95% CI)**	**Interaction p-value #**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 prior Day 2	71 / 1690	0.00 (0.00, Inf.)	0.9727	0.00 (0.00, Inf.)	0.9768
	Congestion score ≥ 3 prior Day 2	1619 / 1690	1.51 (0.95, 2.40)		1.55 (0.96, 2.50)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 prior Day 3	427 / 1661	0.76 (0.29, 1.99)	0.1582	1.00 (0.38, 2.62)	0.3278
	Congestion score ≥ 3 prior Day 3	1234 / 1661	1.61 (1.09, 2.37)		1.68 (1.12, 2.52)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 prior Day 4	703 / 1510	0.88 (0.46, 1.70)	0.0958	1.12 (0.57, 2.18)	0.2823
	Congestion score ≥ 3 prior Day 4	807 / 1510	1.72 (1.12, 2.67)		1.73 (1.11, 2.70)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 prior Day 5	754 / 1301	1.70 (0.95, 3.03)	0.9886	1.76 (0.98, 3.18)	0.9794
	Congestion score ≥ 3 prior Day 5	547 / 1301	1.69 (1.08, 2.63)		1.75 (1.10, 2.76)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 prior Day 6/7	885 / 1335	1.54 (0.90, 2.62)	0.4537	1.77 (1.02, 3.06)	0.5557
	Congestion score ≥ 3 prior Day 6/7	450 / 1335	2.00 (1.28, 3.14)		2.19 (1.38, 3.48)	

CI, confidence interval.

Results from Cox proportional hazards models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine increase from baseline and congestion score available for that study day. Hazard ratios presented for creatinine increase from baseline 'Yes vs. No'.

† Estimated effect sizes adjusted for baseline variables age, heart failure hospitalization in previous year, NYHA class in previous month, rales, systolic blood pressure, albumin, bicarbonate, BUN, creatinine, glucose, and sodium (Cleland et al., 2014).

For the interaction of creatinine increase from baseline and congestion score.

Supplemental Table 3a: Unadjusted and adjusted associations of creatinine increase from baseline with length of in-hospital stay through Day 60 by congestion score

			Univariable model		Multivariable model †	
Parameter	**Category**	**Sample size per category / total**	**Mean difference (95% CI)**	**Interaction p-value #**	**Mean difference (95% CI)**	**Interaction p-value #**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 at Day 2	424 / 1669	-1.73 (-5.60, 2.14)	0.0830	-0.92 (-4.49, 2.66)	0.1679
	Congestion score ≥ 3 at Day 2	1245 / 1669	2.43 (-0.24, 5.11)		2.14 (-0.35, 4.63)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 at Day 3	724 / 1553	0.04 (-2.28, 2.35)	0.5388	0.42 (-1.75, 2.58)	0.3325
	Congestion score ≥ 3 at Day 3	829 / 1553	1.12 (-1.44, 3.68)		2.01 (-0.38, 4.40)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 at Day 4	765 / 1330	-0.26 (-2.50, 1.97)	0.0053	0.34 (-1.79, 2.47)	0.0059
	Congestion score ≥ 3 at Day 4	565 / 1330	4.80 (2.04, 7.56)		5.09 (2.45, 7.72)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 at Day 5	803 / 1217	0.02 (-2.09, 2.13)	0.0021	0.37 (-1.65, 2.39)	0.0003
	Congestion score ≥ 3 at Day 5	414 / 1217	5.68 (2.76, 8.61)		6.68 (3.87, 9.50)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 at Day 6/7	644 / 919	-0.17 (-2.70, 2.36)	0.0268	0.13 (-2.36, 2.62)	0.0111
	Congestion score ≥ 3 at Day 6/7	275 / 919	4.68 (1.22, 8.15)		5.60 (2.18, 9.02)	
Creatinine increase ≥ 0.3 mg/dL at Day 14	Congestion score ≤ 2 at Day 14	272 / 366	3.49 (-0.48, 7.46)	0.8077	2.31 (-1.61, 6.22)	0.5208
	Congestion score ≥ 3 at Day 14	94 / 366	4.32 (-1.11, 9.75)		4.43 (-0.84, 9.70)	

CI, confidence interval.

Results from linear regression models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, stayed in hospital beyond that study day, had available length of stay, and had creatinine increase from baseline and congestion score available for that study day. Mean differences presented for creatinine increase from baseline 'Yes vs. No'.

† Estimated effect sizes adjusted for region and baseline variables gender, history of angina, history of diabetes mellitus, history of chronic heart failure, body mass index, heart rate, systolic blood pressure, jugular venous pressure, orthopnea, BUN, uric acid, cholesterol, albumin, and white blood cell count (Davison et al., 2016).

For the interaction of creatinine increase from baseline and congestion score.

Supplemental Table 3b: Unadjusted and adjusted associations of creatinine increase from baseline with length of in-hospital stay through Day 60 by the previous day's congestion score

			Univariable model		Multivariable model †	
Parameter	**Category**	**Sample size per category / total**	**Mean difference (95% CI)**	**Interaction p-value #**	**Mean difference (95% CI)**	**Interaction p-value #**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 prior Day 2	71 / 1677	-2.48 (-10.68, 5.71)	0.4442	0.38 (-7.10, 7.86)	0.8693
	Congestion score ≥ 3 prior Day 2	1606 / 1677	0.84 (-1.49, 3.17)		1.03 (-1.12, 3.19)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 prior Day 3	370 / 1544	-2.27 (-5.46, 0.93)	0.0602	-1.58 (-4.54, 1.38)	0.0343
	Congestion score ≥ 3 prior Day 3	1174 / 1544	1.38 (-0.67, 3.43)		2.21 (0.30, 4.12)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 prior Day 4	610 / 1333	0.17 (-2.28, 2.61)	0.0401	0.66 (-1.68, 3.00)	0.0443
	Congestion score ≥ 3 prior Day 4	723 / 1333	3.81 (1.34, 6.27)		4.05 (1.70, 6.41)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 prior Day 5	695 / 1222	1.83 (-0.47, 4.13)	0.6379	1.73 (-0.48, 3.94)	0.2231
	Congestion score ≥ 3 prior Day 5	527 / 1222	2.67 (0.01, 5.34)		3.83 (1.25, 6.41)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 prior Day 6/7	553 / 904	-0.71 (-3.42, 1.99)	0.0085	-0.30 (-2.96, 2.36)	0.0048
	Congestion score ≥ 3 prior Day 6/7	351 / 904	4.92 (1.73, 8.12)		5.65 (2.47, 8.83)	

CI, confidence interval.

Results from linear regression models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, stayed in hospital beyond that study day, had available length of stay, and had creatinine increase from baseline and congestion score available for that study day. Mean differences presented for creatinine increase from baseline 'Yes vs. No'.

† Estimated effect sizes adjusted for region and baseline variables gender, history of angina, history of diabetes mellitus, history of chronic heart failure, body mass index, heart rate, systolic blood pressure, jugular venous pressure, orthopnea, BUN, uric acid, cholesterol, albumin, and white blood cell count (Davison et al., 2016).

For the interaction of creatinine increase from baseline and congestion score.

Supplemental Table 3c: Unadjusted and adjusted associations of creatinine increase from baseline with live discharge through Day 60 by congestion score

			Univariable model		Multivariable model [†]	
Parameter	**Category**	**Sample size per category / total**	**Hazard ratio (95% CI)**	**Interaction p-value [#]**	**Hazard ratio (95% CI)**	**Interaction p-value [#]**
Creatinine increase ≥ 0.3 mg/dL at Day 2	Congestion score ≤ 2 at Day 2	424 / 1669	1.19 (0.87, 1.63)	0.0749	1.18 (0.86, 1.61)	0.0782
	Congestion score ≥ 3 at Day 2	1245 / 1669	0.84 (0.67, 1.05)		0.83 (0.66, 1.05)	
Creatinine increase ≥ 0.3 mg/dL at Day 3	Congestion score ≤ 2 at Day 3	724 / 1553	1.00 (0.83, 1.20)	0.7581	0.87 (0.72, 1.06)	0.6735
	Congestion score ≥ 3 at Day 3	829 / 1553	0.96 (0.77, 1.18)		0.82 (0.66, 1.02)	
Creatinine increase ≥ 0.3 mg/dL at Day 4	Congestion score ≤ 2 at Day 4	765 / 1330	1.01 (0.84, 1.21)	0.0798	0.87 (0.72, 1.05)	0.0686
	Congestion score ≥ 3 at Day 4	565 / 1330	0.77 (0.61, 0.98)		0.66 (0.51, 0.83)	
Creatinine increase ≥ 0.3 mg/dL at Day 5	Congestion score ≤ 2 at Day 5	803 / 1217	1.01 (0.84, 1.20)	0.0348	0.91 (0.76, 1.09)	0.0053
	Congestion score ≥ 3 at Day 5	414 / 1217	0.71 (0.55, 0.93)		0.57 (0.44, 0.75)	
Creatinine increase ≥ 0.3 mg/dL at Day 6/7	Congestion score ≤ 2 at Day 6/7	644 / 919	1.08 (0.88, 1.32)	0.0384	1.04 (0.85, 1.28)	0.0096
	Congestion score ≥ 3 at Day 6/7	275 / 919	0.74 (0.55, 0.99)		0.64 (0.47, 0.87)	
Creatinine increase ≥ 0.3 mg/dL at Day 14	Congestion score ≤ 2 at Day 14	272 / 366	0.73 (0.52, 1.02)	0.8787	0.79 (0.56, 1.12)	0.7691
	Congestion score ≥ 3 at Day 14	94 / 366	0.76 (0.48, 1.23)		0.72 (0.44, 1.18)	

CI, confidence interval.

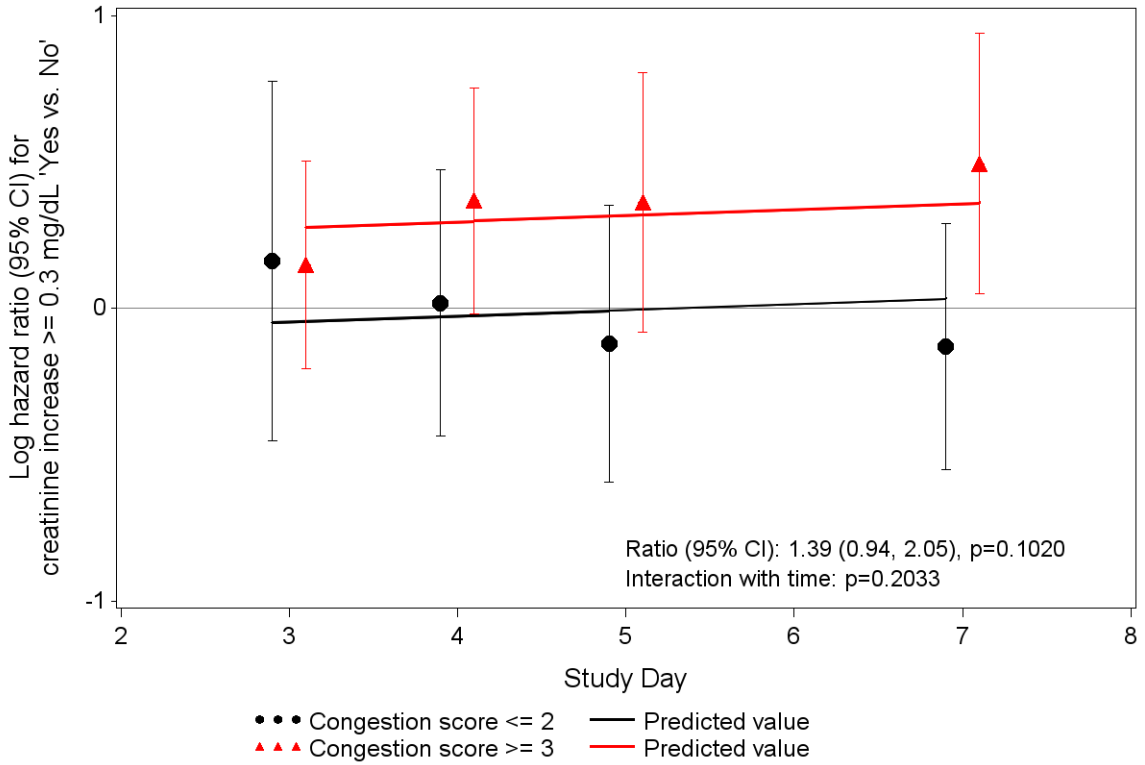
Results from Cox proportional hazards models including interaction term based on subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, stayed in hospital beyond that study day, had available length of stay, and had creatinine increase from baseline and congestion score available for that study day. Hazard ratios presented for creatinine increase from baseline 'Yes vs. No'.

[†] Estimated effect sizes adjusted for region and baseline variables gender, history of angina, history of diabetes mellitus, history of chronic heart failure, body mass index, heart rate, systolic blood pressure, jugular venous pressure, orthopnea, BUN, uric acid, cholesterol, albumin, and white blood cell count (Davison et al., 2016).

[#] For the interaction of creatinine increase from baseline and congestion score.

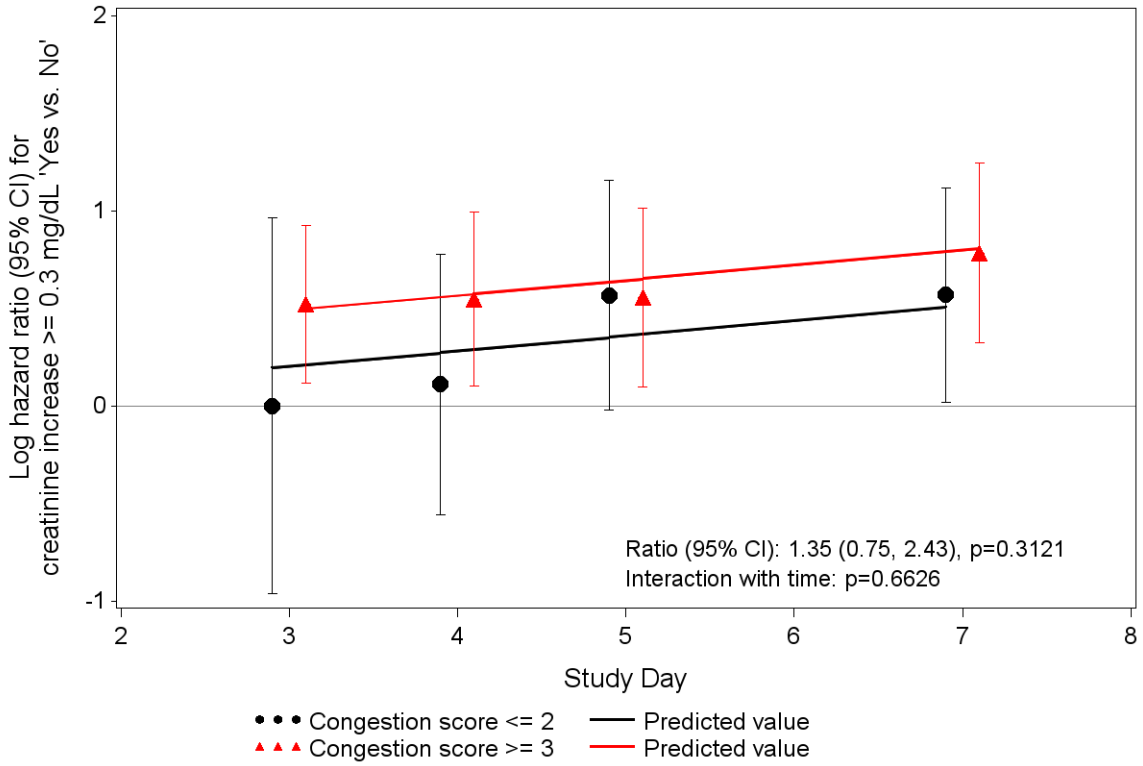
Supplemental Figure 1: Adjusted associations of creatinine increase from baseline with all-cause death or CV/RF rehospitalization through 30 days after Day x by the previous day's congestion score

Sensitivity analysis: Study day refers to the day of serum creatinine measurement (with baseline at Day 1), with patient categorized by the congestion score of the preceding visit. Adjusted hazard ratios for the effect of creatinine increase with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, or 7, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios > 0 correspond to hazard ratios > 1 and signify a harmful effect of creatinine increase. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



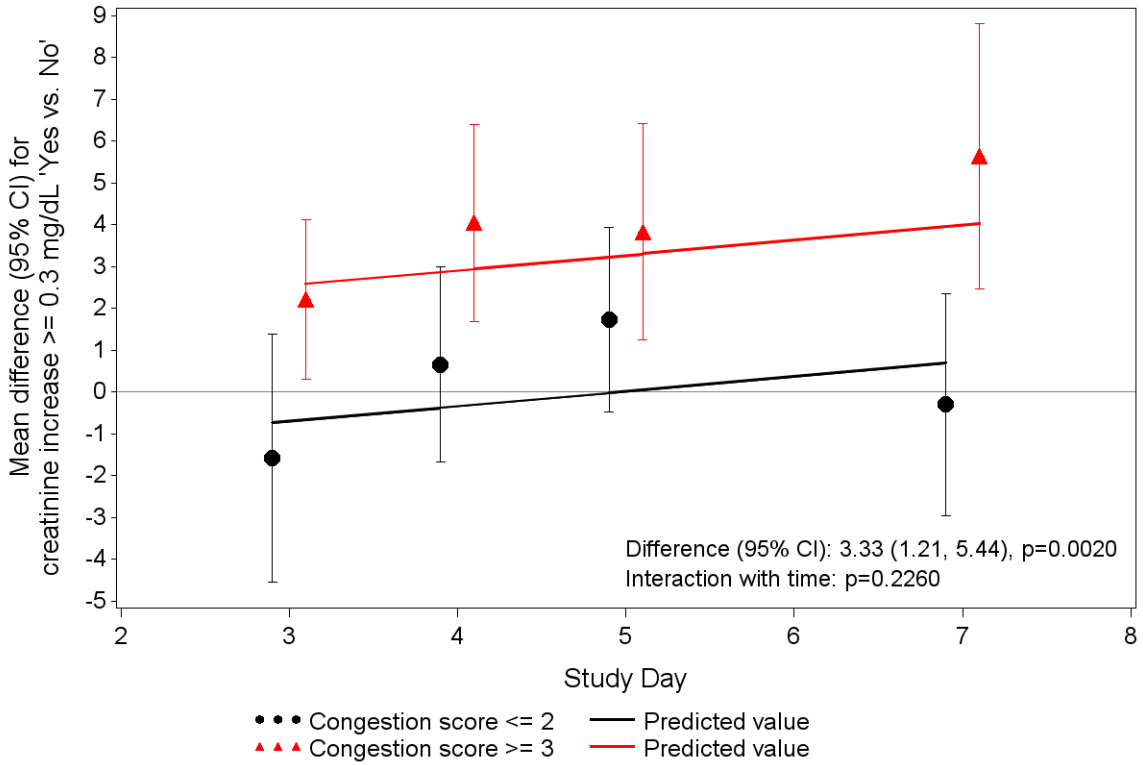
Supplemental Figure 2: Adjusted associations of creatinine increase from baseline with all-cause mortality through Day 90 by the previous day's congestion score

Sensitivity analysis: Study day refers to the day of serum creatinine measurement (with baseline at Day 1), with patient categorized by the congestion score of the preceding visit. Adjusted hazard ratios for the effect of creatinine increase with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, or 7, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios > 0 correspond to hazard ratios > 1 and signify a harmful effect of creatinine increase. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



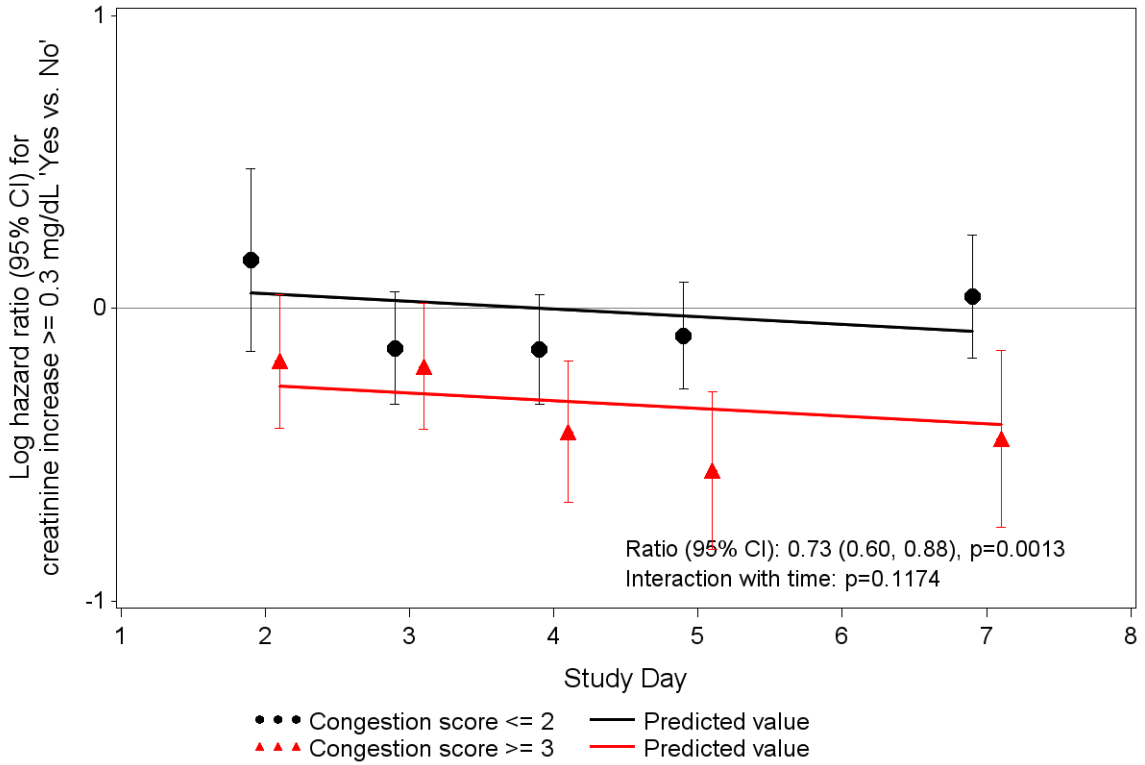
Supplemental Figure 3a: Adjusted associations of creatinine increase from baseline with length of in-hospital stay through Day 60 by the previous day's congestion score

Sensitivity analysis: Study day refers to the day of serum creatinine measurement (with baseline at Day 1), with patients categorized by the congestion score of the preceding visit. Adjusted mean differences for the effect of creatinine increase with 95% confidence intervals were estimated from linear regression models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, or 7, respectively, and had creatinine change from baseline and congestion score available for that study day. Mean differences > 0 signify a longer LOS in patients with a creatinine increase. The difference in creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



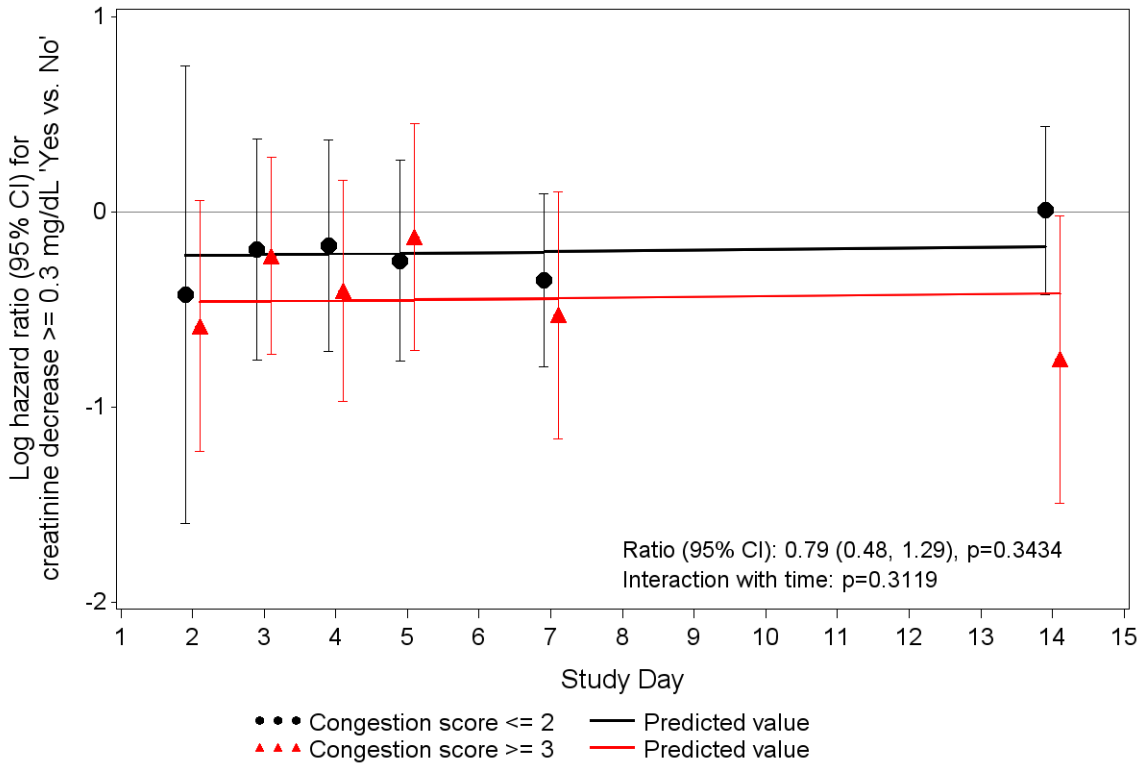
Supplemental Figure 3b: Adjusted associations of creatinine increase from baseline with live discharge through Day 60 by congestion score

Sensitivity analysis: Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted hazard ratios for the effect of creatinine increase with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine increase, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, or 7, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios < 0 correspond to longer LOS in patients with a creatinine increase. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



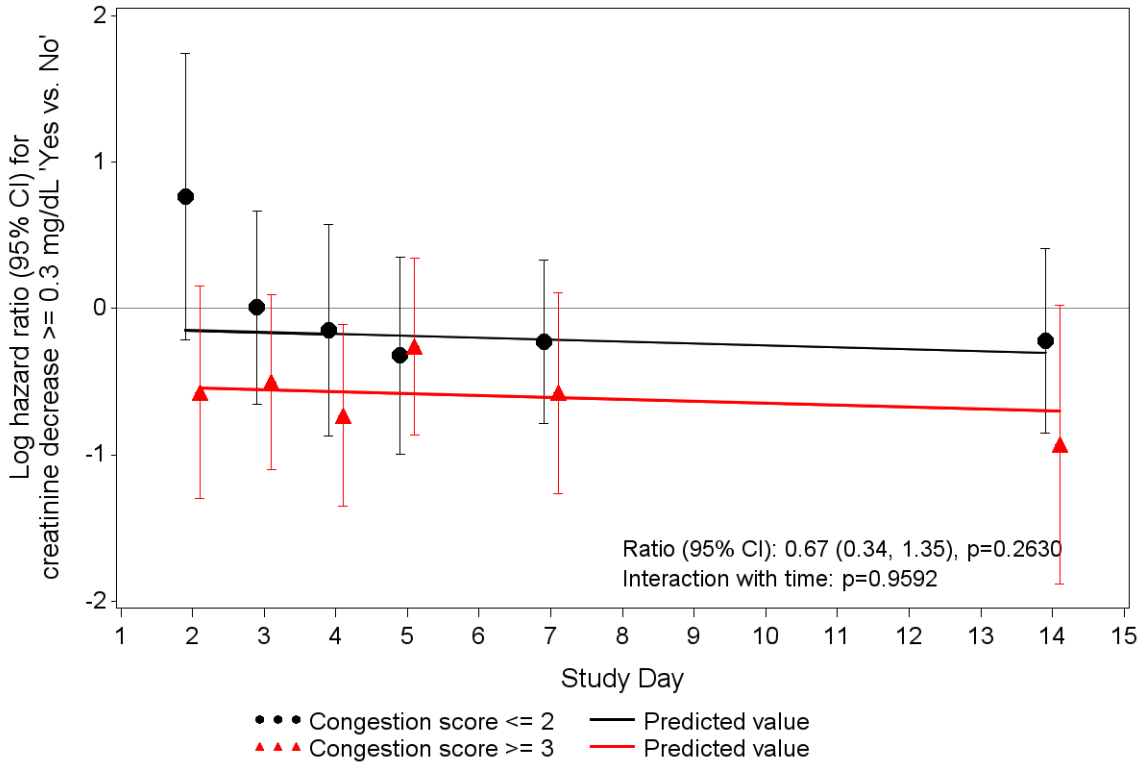
Supplementary Figure 4: Adjusted associations of creatinine decrease from baseline with all-cause death or CV/RF rehospitalization through 30 days after Day x by congestion score

Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted hazard ratios for the effect of creatinine decrease with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine decrease, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios > 0 correspond to hazard ratios > 1 and signify a harmful effect of creatinine decrease. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



Supplementary Figure 5: Adjusted associations of creatinine decrease from baseline with all-cause mortality through Day 90 by congestion score

Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted hazard ratios for the effect of creatinine decrease with 95% confidence intervals were estimated from Cox proportional hazards models for each study day that included the effects of creatinine decrease, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine change from baseline and congestion score available for that study day. Log hazard ratios > 0 correspond to hazard ratios > 1 and signify a harmful effect of creatinine decrease. The ratio of the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.



Supplementary Figure 6: Adjusted associations of creatinine decrease from baseline with length of in-hospital stay through Day 60 by congestion score

Study day refers to the day of serum creatinine measurement and congestion score assessment (with baseline at Day 1). Adjusted mean differences for the effect of creatinine decrease with 95% confidence intervals were estimated from linear regression models for each study day that included the effects of creatinine decrease, congestion category, and their interaction, in subjects who were followed up beyond Days 2, 3, 4, 5, 7, or 14, respectively, and had creatinine change from baseline and congestion score available for that study day. Mean differences > 0 correspond to longer LOS in patients with a creatinine decrease. The difference between the creatinine effects between the congestion categories was estimated based on 1000 bootstrap samples and a linear regression model including congestion score and time. The congestion-by-time interaction p-value was estimated from a model that also included the interaction effect.