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The Risk of Death Associated with Proteinuria in Heart Failure is Restricted to Patients with an Elevated Blood Urea Nitrogen to Creatinine Ratio

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Abstract

Background—Renal dysfunction (RD) is associated with reduced survival in HF; however not all RD is mechanistically or prognostically equivalent. Notably, RD associated with “pre renal” physiology, as identified by an elevated blood urea nitrogen ratio (BUN/Cr), identifies a particularly high risk RD phenotype. Proteinuria, another domain of renal dysfunction, has also been associated with adverse events. Given that several different mechanisms can cause proteinuria we sought to investigate whether the mechanism underlying proteinuria also affects survival in HF.

Methods and Results—Subjects in the Studies Of Left Ventricular Dysfunction (SOLVD) trial with proteinuria assessed at baseline were studied (n=6,439). All survival models were adjusted for baseline characteristics and estimated glomerular filtration rate (eGFR). Proteinuria (trace or 1+) was present in 26% and associated with increased mortality (HR=1.2, 95% CI 1.1–1.3, p=0.006). Proteinuria >1+ was less common (2.5%) but demonstrated a stronger relationship with mortality (HR=1.9, 95% CI 1.5–2.5, p<0.001). In patients with BUN/Cr in the top tertile (17.3), both any (HR=1.3, 95% CI 1.1–1.5, p=0.008) and >1+ proteinuria (HR=2.3, 95% CI 1.7–3.3, p<0.001) remained associated with mortality. However, in patients with BUN/Cr in the bottom tertile (13.3), any proteinuria (HR=0.95, 95% CI 0.77–1.2, p=0.63, p interaction=0.015) and >1+ proteinuria (HR=1.3, 95% CI 0.79–2.2, p=0.29, p interaction=0.036) were not associated with worsened survival.

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Conclusion—Analogous to a reduced eGFR, the mechanism underlying proteinuria in HF may be important in determining the associated survival disadvantage.

Keywords

cardiorenal syndrome; blood urea nitrogen to creatinine ratio; heart failure; proteinuria; albuminuria

Introduction

Renal dysfunction (RD) is highly prevalent in heart failure (HF) and identifies patients at high-risk for mortality and cardiovascular events.^{1, 2} HF can precipitate RD through a number of mechanisms including increased neurohormonal activation, venous congestion and reduced perfusion.^{3, 4} However, many of the same risk factors that lead to heart failure such as diabetes and hypertension can also lead to primary intrinsic RD. Importantly, not all RD is prognostically equivalent.^{5–7} For example, the mortality risk attributable to a reduced estimated glomerular filtration rate (eGFR) is largely restricted to patients with an elevated blood urea nitrogen to creatinine ratio (BUN/Cr; serving as a surrogate for increased neurohormonal activation), whereas RD in the setting of a low BUN/Cr fails to negatively impact survival.^{8, 9}

Proteinuria is an established risk factor for mortality in cardiovascular and kidney disease and more recently has been shown to predict adverse outcomes in chronic HF.^{10–15} Notably, the survival disadvantage associated with proteinuria in HF is independent of eGFR, suggesting proteinuria may serve as a distinct metric of cardio-renal risk in these patients. Similar to a reduced eGFR, proteinuria can be caused by several different mechanisms many of which involve renal parenchymal damage from diseases such as diabetes and hypertension.¹⁶ However, a “functional” form of proteinuria secondary to factors such as increased neurohormonal activation and venous congestion is well described, providing a plausible pathophysiologic connection between HF and proteinuria.^{17–19} It is unknown whether the etiology of proteinuria influences its association with mortality.

Given that an elevated BUN/Cr provides a surrogate for neurohormonal activation and can differentiate prognostically distinct forms of RD defined by a reduced eGFR, we hypothesized that the mortality risk associated with proteinuria would be primarily restricted to patients with a neurohormonally activated “pre-renal” cause for proteinuria identified by an elevated BUN/Cr.^{8, 9, 20, 21} As such, the primary goal of this analysis was to determine if BUN/Cr modified the association between proteinuria and mortality.

Methods

The SOLVD prevention and treatment trials were placebo controlled trials investigating the effect of enalapril on patients with asymptomatic and symptomatic left ventricular dysfunction and comprise the SOLVD limited dataset.^{22, 23} Briefly, 4,228 patients were enrolled in the prevention trial and 2,569 in the treatment trial across 23 international centers for a total of 6,797 patients. An ejection fraction $\geq 35\%$ was required for inclusion in either trial. Patients who were not receiving heart failure medications and were without evidence of

overt heart failure at the end of a 3-week run-in period were eligible for the prevention trial. Eligibility for inclusion in the treatment trial required both a HF diagnosis and medical treatment for the condition. Patients with a baseline creatinine level > 2.5 mg/dL, severe or unstable coronary or valvular disease, suspected renal artery stenosis, or any other disease suspected to shorten survival and impede participation in the long-term trial were excluded. Previous use of an angiotensin converting enzyme inhibitor was not a criterion for exclusion.

The Modified Diet and Renal Disease equation was used to estimate GFR (eGFR) as per our previous analyses with this dataset.^{6, 8} RD was defined as an eGFR<60 ml/min/1.73m^{2.24} Proteinuria was assessed at baseline and 6 weeks via urine dipstick into four categories: none, trace or 1+ proteinuria, 2+ proteinuria, and 3 or 4+ proteinuria. BUN/Cr was also assessed at baseline. As the median BUN/Cr was in the normal range in the SOLVD cohort, BUN/Cr was dichotomized and comparisons were made between the top tertile (BUN/Cr >17.3) and bottom tertile (BUN/Cr<13.3) referred to as high and low BUN/Cr respectively. Patients without baseline urine dipstick (n=277) or BUN/Cr (n=81) assessment were excluded from this analysis. This manuscript was prepared using the SOLVD Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the SOLVD investigators or NHLBI. This study was deemed exempt by the institutional review boards at Medical University of South Carolina and Yale University.

Statistical analysis

Values reported are mean $\pm$ standard deviation, median (25th–75th percentile) and percentage. The independent Student t test or the Wilcoxon rank-sum test was used to compare continuous variables. The Pearson χ^2 was used to evaluate associations between categorical variables. Spearman correlation coefficients were used to examine statistical dependence between 2 variables. The primary objective of this analysis was to determine whether BUN/Cr could identify prognostically different subtypes of proteinuria. As a result, the primary outcome was the interaction between BUN/Cr and proteinuria (both any proteinuria and greater than 1+ proteinuria) on survival. Cox proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates for the multivariable models were obtained by screening clinical characteristics for an association with proteinuria, BUN/Cr or mortality at p 0.2. Using backward elimination (likelihood ratio), covariates were removed and those with a p<0.2 were retained in the final model²⁵. Stratum-specific hazard ratios (HR) were derived from the proportional hazards models of the individual strata (high vs. low BUN/Cr). The significance of the interactions was formally assessed using models incorporating the main effect of proteinuria, the main effect of high vs. low BUN/Cr, and the interaction between these variables. Adjusted survival curves for all-cause mortality were plotted to examine the effect of both any proteinuria and greater than 1+ proteinuria in patients with low BUN/Cr and in patients with high BUN/Cr. Survival curves for death from any causes were also plotted for the four combinations of groups between higher and lower BUN/Cr combined with the presence or absence of proteinuria. Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY). A two-sided p-value of <0.05 was considered statistically

significant with the exception of tests of interaction where significance was defined as a $p < 0.10$.

Results

In total, 6,439 patients were included in the analysis. Proteinuria was present in 25.8% of the population ($n=1,662$) of whom 155 patients had greater than 1+ proteinuria (2.5% of total population). Baseline characteristics of the population grouped by presence or absence of any baseline proteinuria are presented in Table 1. As expected, patients with proteinuria were more likely to have concomitant diabetes and hypertension, however; 75.4% of patients with proteinuria were without concomitant diabetes and 56.7% of patients with proteinuria were normotensive. There was no difference in etiology of heart failure, NYHA class or medication use among patients with or without proteinuria (Table 1). Markers of increased disease severity including tachycardia, hyponatremia and increased BUN were more common in patients with proteinuria (Table 1). Although RD was relatively more common in patients with vs. without proteinuria ($OR=1.49$, 95% CI 1.30–1.62, $p < 0.001$), a low eGFR was not requisite as 51.6% of patients with proteinuria did not have an eGFR < 60 ml/min/1.73m².

The mean baseline BUN/Cr of the population was in the normal range at 15.9 ± 5.18 . Baseline BUN/Cr was weakly correlated with baseline eGFR ($r=0.22$, $p < 0.001$) and baseline serum creatinine ($r=-0.13$, $p < 0.001$) yet demonstrated no correlation with baseline proteinuria ($r=0.01$, $p=0.70$). Baseline characteristics of patients with BUN/Cr in the top tertile (17.3, High) compared to BUN/Cr in the bottom tertile (13.3, Low) are shown in Table 2. Patients with high BUN/Cr were more likely to be white, to be older, more likely to be on loop and potassium-sparing diuretics and had slightly lower hemoglobin levels. Although patients with high BUN/Cr were more likely to have diabetes, they were less likely to have hypertension. Notably, there was no difference in prevalence of any or $>1+$ proteinuria between groups (Table 2).

Proteinuria and Mortality

In total, 23.3% of the population died during a median follow-up of 2.8 years. The presence of any proteinuria at baseline was associated with increased mortality ($HR=1.2$, 95% CI 1.1–1.4, $p=0.001$), an association that persisted with adjustment for baseline eGFR ($HR=1.1$, 95% CI 1.01–1.3, $p=0.034$). Although $>1+$ proteinuria was less common, it demonstrated a stronger relationship with mortality ($HR=2.5$, 95% CI 2.0–3.2, $p < 0.001$) that again remained after adjustment for baseline eGFR ($HR=2.1$, 95% CI 1.7–2.7, $p < 0.001$). Following adjustment for baseline factors significantly associated with proteinuria, BUN/Cr or mortality (age, race, sex, hypertension, diabetes, cerebrovascular disease, ischemic HF etiology, ejection fraction, New York Heart Association class, heart rate, systolic and diastolic blood pressure, beta blocker use, digoxin use, loop and potassium-sparing diuretic use, hematocrit, serum sodium, baseline eGFR and study drug) both any proteinuria ($HR=1.2$, 95% CI 1.1–1.3, $p=0.006$) and $>1+$ proteinuria ($HR=1.9$, 95% CI 1.5–2.5, $p < 0.001$) remained similarly and significantly associated with increased mortality.

Baseline BUN/Cr, Proteinuria and Mortality

A high baseline BUN/Cr demonstrated a trend toward increased mortality (HR=1.1, 95% CI 0.994–1.3, $p=0.06$), and following adjustment for baseline eGFR, this relationship strengthened significantly and became statistically significant (HR=1.3, 95% CI 1.1–1.4, $p<0.001$). Notably, there was marked effect modification by BUN/Cr on the association between both any proteinuria and >1+ proteinuria with mortality. In patients with a high BUN/Cr, both any proteinuria and >1+ proteinuria were significantly associated with increased mortality; however, in patients with a low BUN/Cr, neither any proteinuria or >1+ proteinuria demonstrated a mortality disadvantage with adjustment for baseline eGFR (Table 3). This effect modification by BUN/Cr persisted despite adjustment for baseline factors significantly associated with proteinuria, BUN/Cr or mortality (Table 3). In an adjusted model including all patients grouped by BUN/Cr and proteinuria, those with both a high BUN/Cr and proteinuria experienced the worst survival (Figure 1A). A similarly increased adjusted mortality risk was exhibited by those patients with a high BUN/Cr and >1+ proteinuria (Figure 1B).

The Effect of Enalapril on Proteinuria

In total, 5,808 patients (90.2%) had proteinuria assessed at 6 weeks. Out of the 1,495 patients with any proteinuria at baseline, 40.7% ($n=608$) experienced improvement in the degree of proteinuria. Patients randomized to enalapril were significantly more likely to improve their degree of proteinuria (OR=1.19, 95% CI 1.01–1.41, $p=0.04$). Interestingly, the likelihood of proteinuria improving with enalapril was dependent on the BUN/Cr. In those patients with an elevated BUN/Cr, enalapril treatment increased the odds of improvement in proteinuria by 50% (OR=1.51, 95% CI 1.13–2.03, $p=0.006$). However, in patients with a low BUN/Cr, enalapril was no longer significantly associated with reduction in proteinuria (OR=1.20, 95% CI 0.89–1.62, $p=0.24$, p interaction=0.078). In an exploratory analysis, patients randomized to enalapril with an elevated BUN/Cr ($n=557$) were approximately 25% more likely to survive if proteinuria improved compared to those that did not have improvement in proteinuria (HR=0.75, 95% CI 0.51–1.12, $p=0.15$), although this did not reach statistical significance.

Discussion

The primary finding of this study is that not all proteinuria in HF is prognostically equivalent. In patients with an elevated BUN/Cr, proteinuria was associated with significantly reduced survival, while in patients with a normal BUN/Cr, proteinuria failed to incur a survival disadvantage. These associations persisted despite extensive adjustment for baseline characteristics including diabetes, hypertension and eGFR, reinforcing the notion that prognostically important RD can exist despite normal filtration. Furthermore, patients with baseline proteinuria in the setting of an elevated BUN/Cr were also significantly more likely to experience improvement in proteinuria with enalapril compared to those patients with proteinuria and a normal BUN/Cr. These results provide support for the concept that the mechanism responsible for proteinuria plays a pivotal role both in the magnitude of the mortality impact and the likelihood of a meaningful response to therapy.

Abnormal amounts of protein are found in the urine in the setting of a defect in glomerular capillary integrity, or when normal or increased amounts of protein that escape the glomerulus are not reabsorbed due to proximal tubular dysfunction.²⁶ Importantly, although the development of proteinuria often occurs in parallel with a decreased GFR, glomerular or tubular damage can occur with preserved filtration, providing another dimension of renal function assessment. Increased inflammation, endothelial dysfunction and atherosclerosis are some of the pathophysiologic processes thought responsible for proteinuria, thus it is not surprising that proteinuria is highly prevalent in diseases such as diabetes and hypertension.^{10, 27, 28} Still, despite the common coexistence of these conditions in HF, the presence of diabetes or hypertension does not entirely account for the observed proteinuria in this and previous studies, suggesting other pathophysiologic processes may be a common driver for proteinuria in HF.^{12, 14, 15}

Venous congestion and increased neurohormonal activation, two mechanisms implicated in HF-induced reductions in eGFR and the cardiorenal syndrome, are potentially responsible for proteinuria in HF.^{3, 8, 13, 17} Wegria et al. demonstrated that renal vein constriction in dogs produces marked proteinuria, despite preserved renal blood flow, that resolved with restoration of normal venous pressure.¹⁸ Similarly, in patients admitted with acute decompensated HF and an elevated urine albumin to creatinine ratio, proteinuria subsequently decreased with diuresis in parallel with a decline in NT-proBNP with return to compensation.²⁹ Proteinuria following increasing doses of renin in rats is also well described, as are the abilities of angiotensin II antagonists to ameliorate these effects in both rats and humans.^{30, 31} Given the multitude of etiologies for proteinuria and their pathophysiologic differences, it is reasonable to expect that the mechanisms responsible for proteinuria (ie. HF induced vs. not) will also differentially effect outcomes, an argument supported by the marked survival disadvantage in those patients with proteinuria in the setting of an elevated BUN/Cr as presented in this analysis.

The tubular reabsorption of urea is tightly regulated by neurohormonal systems such that in states of sodium and water avidity like HF, the rate of urea excretion is decreased out of proportion to the GFR and thus creatinine.¹⁶ As a result of this dissociation between urea reabsorption and filtration, the BUN/Cr increases, providing some differentiation of “pre-renal” RD, including entities such as HF-induced RD, from intrinsic renal parenchymal disease.^{20, 21} Capitalizing on this pathophysiology, we have previously demonstrated that BUN/Cr identifies clinically distinct forms of eGFR reduction in HF, with those patients having both an elevated BUN/Cr and significant RD at the greatest risk for mortality.^{8, 9} Given the involvement of neurohormonal activation in both HF and proteinuria, the similar capacity for BUN/Cr to serve as a tool for differentiating prognostically meaningful forms of proteinuria is noteworthy. Although numerous prior analyses of proteinuria in HF have uniformly demonstrated its association with poor outcomes, this is the first to highlight minimal to no mortality risk secondary to proteinuria in those HF patients with low BUN/Cr.^{12–15} While the results of this study cannot confirm a specific mechanism behind proteinuria in HF, they do strongly support biologically distinct forms of proteinuria in those with high vs. low BUN/Cr.

The suggestion that the mortality disadvantage inherent to proteinuria in HF hinges on mechanism supports consideration of therapeutic interventions targeted at the primary pathophysiology believed responsible (increased neurohormonal activation, venous congestion etc.). In our exploratory analysis, RAAS inhibition with enalapril was more strongly associated with improvement in proteinuria at 6 weeks in those patients with an elevated BUN/Cr. Furthermore, although limited by a small number of observations and not statistically significant, patients with an elevated BUN/Cr whose proteinuria improved on enalapril tended to have a survival advantage. Still, as the mechanism responsible for proteinuria is likely more important than the proteinuria itself, intensification of therapies in proteinuric HF patients may have additional benefits that are not contingent upon proteinuria reduction. Future studies will be required to answer these important questions.

Limitations

This study was a *post hoc* analysis of a clinical trial with inherent limitations including the possibility that uncontrolled confounding exists and may have affected these results. Patients with serum creatinine > 2.5 mg/dL were excluded from the SOLVD trial limiting generalizability of these results to patients with more advanced RD. Additionally, the rigorous inclusion/exclusion criteria for a clinical trial like the SOLVD trial often produce a population that may not be representative of patients seen in clinical practice. For example, the standard of care medication therapy for heart failure has evolved since the SOLVD trial was published and patients with heart failure with preserved EF were excluded. Still, the strong relationship between proteinuria and decreased survival has been repeatedly demonstrated in both heart failure with preserved EF and more current HF populations suggesting these results are still relevant in today's practice.^{15, 32} The SOLVD trial was not originally designed to investigate associations between proteinuria and renal function and as such, physicians were not blinded to BUN, creatinine or presence of proteinuria. Moreover, non-neurohormonal factors such as protein catabolism and diet that are known to influence urea absorption may have led to uncontrolled confounding. Lastly, the urine dipstick is only semi-quantitative, dependent on urine concentration and less sensitive to lower levels of proteinuria such that patients with microalbuminuria may have been underdiagnosed in the SOLVD trial.^{33, 34} Given the above limitations, these results should be viewed as hypothesis-generating only and serve to prompt further investigation.

Conclusions

Analogous to a reduced eGFR, the mechanism underlying proteinuria may be important in determining the associated survival disadvantage. Further research is necessary to better understand and characterize different phenotypes of RD in HF and determine if targeted therapy may benefit these high-risk patients.

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References

1. McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN. Meta-analysis Global Group in Chronic Heart Failure I. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. *Circ Heart Fail*. 2012; 5:309–14. [PubMed: 22441773]
2. Dries D, Exner D, Domanski M, Greenberg B, Stevenson L. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *Journal of the American College of Cardiology*. 2000; 35:681–689. [PubMed: 10716471]
3. Testani JM, Damman K. Venous congestion and renal function in heart failure ... “It’s complicated”. *European Journal of Heart Failure*. 2013; 15:599–601. [PubMed: 23603089]
4. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation*. 2010; 121:2592–2600. [PubMed: 20547939]
5. 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. [PubMed: 20606118]
6. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic Importance of Early Worsening Renal Function After Initiation of Angiotensin-Converting Enzyme Inhibitor Therapy in Patients With Cardiac Dysfunction. *Circ Heart Fail*. 2011; 4:685–691. [PubMed: 21903907]
7. Testani JM, Damman K, Brisco MA, Chen S, Laur O, Kula AJ, Tang WH, Parikh C. A combined-biomarker approach to clinical phenotyping renal dysfunction in heart failure. *J Card Fail*. 2014; 20:912–9. [PubMed: 25152498]
8. Testani JM, Coca SG, Shannon RP, Kimmel SE, Cappola TP. Influence of renal dysfunction phenotype on mortality in the setting of cardiac dysfunction: analysis of three randomized controlled trials. *European Journal of Heart Failure*. 2011; 13:1224–1230. [PubMed: 21926073]
9. Brisco MA, Coca SG, Chen J, Owens AT, McCauley BD, Kimmel SE, Testani JM. Blood urea nitrogen/creatinine ratio identifies a high-risk but potentially reversible form of renal dysfunction in patients with decompensated heart failure. *Circ Heart Fail*. 2013; 6:233–239. [PubMed: 23325460]
10. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol*. 1997; 80:164–9. [PubMed: 9230153]
11. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation*. 2002; 106:1777–1782. [PubMed: 12356629]
12. Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, Frisinghelli A, Minneci C, Valisi M, Maggioni AP, Marchioli R, Tognoni G, Tavazzi L, Investigators G-H. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circ Heart Fail*. 2010; 3:65–72. [PubMed: 19850697]
13. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation*. 2009; 120:1577–1584. [PubMed: 19805651]
14. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ. Committees ftcIa. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet*. 2009; 374:543–550. [PubMed: 19683640]
15. Jackson CE, MacDonald MR, Petrie MC, Solomon SD, Pitt B, Latini R, Maggioni AP, Smith BA, Prescott MF, Lewsey J, McMurray JJV. for the ALiskiren Observation of heart Failure Treatment (ALOFT) investigators. Associations of albuminuria in patients with chronic heart failure: findings in the ALiskiren Observation of heart Failure Treatment study. *European Journal of Heart Failure*. 2014; 13:746–754. [PubMed: 21459891]
16. Brenner, B.; Rector, F. Brenner & Rector’s The Kidney. 9. Philadelphia: Elsevier/Saunders; 2008.

17. Addis T, Barrett E, et al. Renin proteinuria in the rat; the relation between the proteinuria and the pressor effect of renin. *Journal of Experimental Medicine*. 1949; 89:131–140. [PubMed: 18107967]
18. Wegria R, Capece NE, Blumenthal MR, Kornfeld P, Hays DR, Elias RA, Hilton JG. The pathogenesis of proteinuria in the acutely congested kidney. *J Clin Invest*. 1955; 34:737–743. [PubMed: 14367532]
19. Burack WR, Pryce J, Goodwin JF. A reversible nephrotic syndrome associated with congestive heart failure. *Circulation*. 1958; 18:562–71. [PubMed: 13573573]
20. Lindenfeld J, Schrier RW. Blood urea nitrogen a marker for adverse effects of loop diuretics? *Journal of the American College of Cardiology*. 2011; 58:383–385. [PubMed: 21757115]
21. Schrier RW. Blood Urea Nitrogen and Serum Creatinine: Not Married in Heart Failure. *Circ Heart Fail*. 2008; 1:2–5. [PubMed: 19808263]
22. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991; 325:293–302. [PubMed: 2057034]
23. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992; 327:685–691. [PubMed: 1463530]
24. Levey A, Coresh J, Greene T, Stevens L, Zhang Y, Hendriksen S, Kusek J, Van Lente F. Chronic Kidney Disease Epidemiology C. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006; 145:247–254. [PubMed: 16908915]
25. Mickey R, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol*. 1989; 129:125–137. [PubMed: 2910056]
26. Dickson LE, Wagner MC, Sandoval RM, Molitoris BA. The proximal tubule and albuminuria: really! *J Am Soc Nephrol*. 2014; 25:443–53. [PubMed: 24408874]
27. Comper WD, Hilliard LM, Nikolic-Paterson DJ, Russo LM. Disease-dependent mechanisms of albuminuria. *Am J Physiol Renal Physiol*. 2008; 295:F1589–600. [PubMed: 18579704]
28. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med*. 1984; 310:356–60. [PubMed: 6690964]
29. Koyama S, Sato Y, Tanada Y, Fujiwara H, Takatsu Y. Early evolution and correlates of urine albumin excretion in patients presenting with acutely decompensated heart failure. *Circ Heart Fail*. 2013; 6:227–232. [PubMed: 23395932]
30. Yoshioka T, Mitarai T, Kon V, Deen W, Rennke H, Ichikawa I. Role for angiotensin II in an overt functional proteinuria. *Kidney International*. 1986; 30:538–545. [PubMed: 2431191]
31. Araki S, Haneda M, Sugimoto T, Isono M, Isshiki K, Kashiwagi A, Koya D. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. *Diabetes*. 2005; 54:2983–7. [PubMed: 16186402]
32. Katz DH, Burns JA, Aguilar FG, Beussink L, Shah SJ. Albuminuria is independently associated with cardiac remodeling, abnormal right and left ventricular function, and worse outcomes in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF*. 2014; 2:586–96.
33. Constantiner M, Sehgal AR, Humbert L, Constantiner D, Arce L, Sedor JR, Schelling JR. A dipstick protein and specific gravity algorithm accurately predicts pathological proteinuria. *Am J Kidney Dis*. 2005; 45:833–41. [PubMed: 15861348]
34. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? *Ann Clin Biochem*. 2009; 46:205–17. [PubMed: 19389884]

Figure 1A

Figure 1B

Figure 1. Adjusted survival plots by high or low BUN/Cr and presence or absence of any proteinuria (Panel A) or presence or absence of greater than 1+ proteinuria (Panel B) High and low BUN/Cr defined as the top vs. bottom tertile. BUN/Cr: blood urea nitrogen to creatinine ratio.

Table 1

Baseline characteristics in those with and without proteinuria

Characteristic	Total (N=6,439)	No proteinuria (n=4,777)	Proteinuria (n=1,662)	p-value
Demographics				
Age (y)	59.4 ± 10.2	59.3 ± 10.1	59.7 ± 10.4	0.139
Male	85.8%	86.1%	84.9%	0.227
Black race	11.3%	10.8%	12.9%	0.017 *
Medical History				
Hypertension	38.6%	37.0%	43.3%	<0.001 *
Diabetes	19.2%	17.3%	24.6%	<0.001 *
Cerebrovascular disease	6.5%	6.7%	6.1%	0.371
Ischemic etiology	79.1%	79.0%	79.6%	0.580
Ejection fraction (%)	27.0 ± 6.28	26.9 ± 6.35	27.2 ± 6.09	0.061
NYHA Class I	46.0%	46.0%	46.1%	0.300
Admission Physical Exam				
Heart rate (beats/min)	76.2 ± 12.3	76.0 ± 12.1	76.6 ± 12.7	0.110
Systolic blood pressure (mmHg)	119 ± 16.8	119 ± 16.6	121 ± 17.0	<0.001 *
Diastolic blood pressure (mmHg)	77.5 ± 10.1	74.0 ± 9.81	75.0 ± 10.1	0.001 *
Medications				
β-Blocker	18.1%	17.8%	19.1%	0.244
Digoxin	32.7%	32.5%	33.2%	0.580
ACE inhibitor (Enalapril)	50.1%	50.2%	49.9%	0.867
Loop diuretic	32.2%	32.2%	32.1%	0.973
Potassium sparing diuretics	6.1%	6.3%	5.5%	0.261
Laboratory Values (Baseline)				
Serum sodium (mEq/L)	140.0 ± 3.00	140.1 ± 2.95	139.8 ± 3.10	0.002 *
Hematocrit (%)	42.7 ± 4.47	42.7 ± 4.37	42.9 ± 4.73	0.074
eGFR (mL/min)	64.8 ± 18.7	65.8 ± 18.6	61.8 ± 18.9	<0.001 *
Serum creatinine (mg/dL)	1.18 ± 0.28	1.16 ± 0.27	1.23 ± 0.32	<0.001 *
Blood urea nitrogen (mg/dL)	18.1 ± 6.40	17.9 ± 6.32	18.9 ± 6.60	<0.001 *
BUN/Cr	15.9 ± 5.18	15.9 ± 5.23	15.9 ± 5.03	0.645

NYHA: New York Heart Association; ACE: angiotensin converting enzyme; eGFR: estimated glomerular filtration rate; BUN/Cr: Blood urea nitrogen to creatinine ratio

* Significant p-value

Table 2

Baseline characteristics stratified by BUN/Cr

Characteristic	Low BUN/Cr (n=2,032)	High BUN/Cr (n=2,182)	p-value
Demographics			
Age (y)	57.4 ± 10.4	61.1 ± 9.81	<0.001 *
Male	89.9%	79.6%	<0.001 *
Black race	17.9%	7.6%	<0.001 *
Medical History			
Hypertension	37.6%	39.2%	0.287
Diabetes	13.9%	24.7%	<0.001 *
Cerebrovascular disease	6.9%	7.3%	0.670
Ischemic etiology	78.8%	78.6%	0.877
Ejection fraction (%)	27.1 ± 6.27	26.8 ± 6.32	0.138
NYHA Class I	47.3%	43.8%	<0.001 *
Admission Physical Exam			
Heart rate (beats/min)	76.8 ± 12.4	76.0 ± 12.2	0.024 *
Systolic blood pressure (mmHg)	119 ± 16.8	120 ± 16.8	0.842
Diastolic blood pressure (mmHg)	74.8 ± 9.97	73.9 ± 9.93	0.002 *
Medications			
β-Blocker	17.9%	17.0%	0.456
Digoxin	32.6%	34.1%	0.307
ACE inhibitor (Enalapril)	49.0%	51.6%	0.087
Loop diuretic	29.6%	35.3%	<0.001 *
Potassium sparing diuretics	3.8%	7.7%	<0.001 *
Laboratory Values (Baseline)			
Serum sodium (mEq/L)	140.0 ± 2.89	140.0 ± 3.07	0.510
Hematocrit (%)	43.0 ± 4.53	42.2 ± 4.48	<0.001 *
eGFR (mL/min)	61.5 ± 15.8	69.0 ± 22.0	<0.001 *
Serum creatinine (mg/dL)	1.22 ± 0.27	1.14 ± 0.30	<0.001 *
Blood urea nitrogen (mg/dL)	14.8 ± 4.59	21.7 ± 7.17	<0.001 *
Any urine protein	25.4%	25.5%	0.950
Greater than 2+ proteinuria	2.3%	3.0%	0.147

NYHA: New York Heart Association; ACE: angiotensin converting enzyme; eGFR: estimated glomerular filtration rate; BUN/Cr: Blood urea nitrogen to creatinine ratio

* Significant p-value. BUN/Cr dichotomized as top vs. bottom tertile.

Table 3

Mortality risk associated with proteinuria stratified by BUN/Cr

	Low BUN/Cr		High BUN/Cr	
	HR (95% CI)	P	HR (95% CI)	P
Any Proteinuria				
Adjusted for baseline eGFR	0.95 (0.77–1.2)	0.63	1.3 (1.1–1.5)	0.008*
Adjusted for baseline characteristics including eGFR	1.0 (0.8–1.2)	0.99	1.4 (1.1–1.6)	0.002*
Greater than 1+ Proteinuria				
Adjusted for baseline eGFR	1.3 (0.79–2.2)	0.29	2.3 (1.7–3.3)	<0.001*
Adjusted for baseline characteristics including eGFR	1.3 (0.8–2.2)	0.32	2.0 (1.4–2.8)	<0.001*

Hazard ratios represent the risk for all cause mortality comparing patients with and without any proteinuria and with and without greater than 1+ proteinuria. Adjustment for baseline characteristics included age, race, sex, hypertension, diabetes, cerebrovascular disease, ischemic HF etiology, ejection fraction, New York Heart Association class, heart rate, systolic and diastolic blood pressure, beta blocker use, digoxin use, loop and potassium-sparing diuretic use, hematoctrit, serum sodium, baseline eGFR and study drug. BUN/Cr: blood urea nitrogen to creatinine ratio; eGFR: estimated glomerular filtration rate; HR: hazard ratio

* Significant p-value. BUN/Cr dichotomized as top vs. bottom tertile.