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Effect of Renal Function on Prognosis in Chronic Heart Failure

Adrián I. Löffler, MD[a,*], **Thomas P. Cappola, MD, ScM**[b], **James Fang, MD**[c], **Scott J. Hetzel, MS**[a], **Andrew Kadlec, BA**[a], **Brad Astor, PhD, MPH**[a], and **Nancy K. Sweitzer, MD, PhD**[a]

[a]University of Wisconsin, Department of Cardiovascular Medicine, 600 Highland Ave, Madison, WI, 53705, USA

[b]University of Pennsylvania, Department of Cardiology, 3400 Spruce St, Philadelphia, PA 19104, USA

[c]Case Western Reserve University, Department of Cardiology, 11100 Euclid Ave, Cleveland, OH 44106, USA

Abstract

Renal dysfunction (RD) is associated with increased mortality in heart failure (HF). The aim of this study was to identify whether worsened or improved renal function during mid-term follow-up is associated with worsened outcomes in chronic HF patients. 892 participants from a multicenter cohort study of chronic HF were followed over 3.1±1.9 years of enrollment. Worsened and improved renal function were tested with multivariable models as independent predictors of HF hospitalization and mortality. While 12% of subjects experienced a ≥25% decrease in estimated glomerular filtration rate (eGFR), 17% experienced a ≥25% increase in eGFR, and there was stability of kidney function observed in the cohort as a whole. The quartile with the worst RD at any point in time had increased risk of HF hospitalization and mortality. Worsened eGFR was associated with HF outcomes in the unadjusted (HR=1.71 (95%CI 1.04-2.81), p=0.035), but not the adjusted analysis. Improvement in eGFR was not associated with outcome (p=0.453). In chronic HF, the severity of RD predicts risk of poor outcome better than changes in renal function during mid-term follow-up. This suggests that in patients with appropriately treated chronic HF, worsening renal function in itself does not yield useful prognostic information and may not reflect poor outcome.

Keywords

worsening; improved; renal function; hospitalization; death

[*]Address for Correspondence: Adrián I. Löffler, MD, Internal Medicine Resisdency Program, PO Box 800696, University of Virginia Health System, Charlottesville, VA 22908, Phone: +011 (434) 924-5725 Fax: +011 (434) 982-4413, adrian.i.loffler@gmail.com.

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Introduction

Heart failure (HF) affects approximately 6 million people in the United States.[1] Comorbidities clearly impact HF prognosis. Over the last two decades, the number of comorbidities and medications in the average HF patient has increased substantially, renal failure being among those.[2] Given the high cost of HF hospitalization, identifying risk factors that increase its likelihood is useful. Renal function is considered to be a sensitive marker of decreased organ perfusion and is commonly thought to deteriorate in HF due to chronic hypoperfusion.[3] Recently, several studies have reported an association between worsening renal function (WRF) during inpatient treatment for acute decompensated HF and poor clinical outcomes. [4-11] In chronic HF, reduced renal perfusion may occur over a long period, and patients may experience few symptoms related to the declining renal function.[3] Several studies have found an association of WRF with mortality in the ambulatory setting. [12-17] Most studies have included only patients with heart failure with reduced ejection fraction (HF*r*EF), and follow-up has typically been short, investigating changes in renal function over no more than a 6 month interval from baseline. Our aim was to assess how kidney function changed during mid-term follow-up in HF patients, and whether WRF predicts all-cause mortality and HF hospitalization in patients medically treated for chronic HF. We also examined risk factors for WRF and whether improvement in renal function was associated with improved outcomes.

Methods

Subjects were enrolled in the multicenter Penn Heart Failure Study (PHFS). The PHFS began in 2003 at the University of Pennsylvania and subsequently expanded into a multi-center study. This is a prospective observational cohort study of over 2,000 subjects with heart failure followed in HF specialty clinics. The study was approved by institutional review committees and the subjects gave informed consent. Detailed patient information was collected at baseline and patients followed every six months to measure predefined endpoints (hospitalization, change in therapy and death). Patients were either seen in clinic or called at six month intervals. Inclusion criteria in this analysis were an available baseline measurement of creatinine (at time of enrollment) and at least one follow-up value. At the beginning of the study follow-up kidney function was not routinely collected, and therefore only the subset of patients in whom this information was available was included in this analysis. The primary outcome measures were death or HF hospitalization (primary composite outcome) and death alone. Ten subjects underwent heart transplantation and were counted in the death endpoint. This was done since the assumed outcome without transplantation is death. HF hospitalization was based on primary discharge diagnosis. Patients with a clinical diagnosis of HF were considered to have HF*r*EF based on an EF <=40% as defined in current guidelines.[18] The remaining patients were classified as HF with preserved EF (HF*p*EF).

eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.[19] Change in eGFR was calculated by subtracting the most recent follow-up eGFR from baseline eGFR. For patients with a primary outcome, the most recent eGFR prior to reaching the primary outcome was used. We used previously defined criteria for WRF: a ≥25%

decrease in eGFR[20,21] or an increase in SCr≥0.3 mg/dL.[22-24] Improvement in renal function was defined as a ≥ 25% increase in eGFR or a decrease in SCr≥0.3 mg/dL.

Participants were divided into quartiles of baseline eGFR. Comparisons between baseline eGFR groups were made with one-way ANOVA, Kruskal-Wallis tests, or Chi-square tests based on distribution and normality assumptions. Univariate Cox proportional hazards (Cox PH) models were used to assess the relationship between time to a primary outcome and baseline or follow-up eGFR/SCr. WRF status and time to primary composite outcome were also assessed with univariate Cox proportional hazards model. Similarly, univariate Cox models were used for the mortality outcome. To assess for linearity in the coefficients of the Cox model over the entire range of follow-up SCr and eGFR, each group was divided into quartiles and hazard ratios calculated using the lowest SCr quartile and highest eGFR quartile as the reference.

Multivariate Cox proportional hazards models were developed by compiling a list of 39 baseline variables of clinical importance and that did not have large numbers of missing values. Univariate Cox models of each baseline variable were created for time to primary composite outcome. Candidate variables were considered to be baseline variables that had chi-square p-values less than 0.05. Backwards and forwards stepwise models of the candidate variables were run to determine final variables for inclusion in multivariate models. To test for robustness, models were rerun excluding variables that might over-correct the model, such as New York Heart Association (NYHA) Class. This led to no significant changes in the predictive value of the variables in the model, so the best iteration is presented. The above analysis was repeated for HF*r*EF and HF*p*EF separately.

Results

The analysis cohort included 892 patients. Fifty-two (5.7%) of the 892 subjects were missing data for at least one candidate variable in the multivariate analysis. Table 1 illustrates baseline characteristics across eGFR quartiles. The average age was 56 years and 2/3 were men. HF*r*EF was present in 61% of patients. Most patients had NYHA Class II or III symptoms. More than a third (36%) of the study population had experienced a hospitalization in the 12 months prior to enrollment into PHFS. Older patients, those with an ischemic etiology, and those with comorbidities such as diabetes, hypertension, and stroke were more likely to have lower baseline eGFR. NYHA class and the Minnesota Living with Heart Failure Questionnaire score[25] were greater in patients with lower baseline eGFR, indicating higher symptom burden. Mean EF (37%) was not different between groups, nor were blood pressure, heart rate, BMI, or serum sodium. Loop diuretics, aldosterone antagonists, aspirin, hydralazine, long acting nitrates, and statins were more commonly prescribed in patients with worse baseline renal function. ACE inhibitor use was more common in those with better baseline renal function.

There are 2767 patient-years of follow up in the cohort, with a median follow up time of 2.9 years, and mean follow-up of 3.1±1.9 years. A regression analysis of creatinine values versus time was created for each subject. The mean change in creatinine over time was 0.0074±0.43 mg/dL increase in creatinine per year; the slope of this regression line was not

statistically different from zero. Similarly, estimated GFR did not deteriorate over time in the cohort as a whole. Stage 3 or greater CKD was present at baseline in 309 (35%) of the 892 subjects. 322 (36%) subjects had Stage 3 or greater CKD at the most recent follow-up visit or just prior to reaching a primary outcome. A total of 109 (12%) subjects experienced WRF during follow-up using eGFR, 110 (12%) using SCr. A total of 152 (17%) subjects experienced improved eGFR; 108 (12%) had improved SCr. A total of 674 (76%) subjects had stable eGFR. Mean baseline SCr in the worsening eGFR group was 1.56±1.18mg/dL and was 1.27±0.81mg/dL in the stable group (p=0.015). There was a trend toward WRF in patients with lower baseline eGFR, but this did not reach statistical significance (p=0.076). 110 subjects (12%) had a primary outcome; 26 (2.9%) died. Of 840 subjects with complete data in the multivariate analysis, 107 (12%) had a primary outcome, of whom 26 (3.1%) died, and of whom 10 (1.2%) underwent heart transplant.

Table 2 includes the univariate analysis results for the 14 candidate variables and 4 pre-selected variables (age, sex, diabetes, and ischemic status). Of the pre-selected variables, only sex did not have a statistically significant association with the primary composite outcome of death or HF hospitalization (p=0.906). As illustrated in Table 3, baseline and follow-up renal function demonstrated significant associations with the primary composite outcome in both the unadjusted and adjusted analysis. Separate analyses of HF*r*EF (HR=1.05 (95%CI 1.00-1.09) and 1.21 (95%CI 1.10– 1.32), p=0.05, <0.001 for baseline SCr and eGFR respectively) and HF*p*EF (HR=1.09 (95%CI 1.02- 1.16) and 1.20 (95%CI 1.01–1.42), p=0.009, 0.038 for baseline SCr and eGFR respectively) showed the same association with the primary outcome in unadjusted analysis but not in the adjusted analysis. Figure 1 demonstrates that risk of the primary outcome rises markedly in the group with most impaired renal function at baseline. The association between follow-up renal function and the primary composite outcome was even stronger.

There was an association between WRF and the primary composite outcome and death alone in the unadjusted analysis, however not in the adjusted analysis. Improvement in renal function showed no association with primary composite outcome in the adjusted analysis. As shown in table 4, diabetes and age were predictors of WRF (using either SCr or eGFR). Loop diuretic and hydralazine use were predictors of worsening SCr but not change in eGFR. Importantly, EF and NYHA class did not predict WRF.

Discussion

The results of this study highlight significant facts about kidney function in an aggressively treated cohort of outpatients with heart failure. Our study confirmed the high prevalence of chronic renal dysfunction in chronic HF patients. However we did not find any evidence of deterioration of kidney function over time in participants, despite over 2700 patient-years of follow-up. There was a statistically significant independent association between kidney function at multiple time points and the primary composite outcome of HF hospitalization or death. Follow-up measures of renal function were most strongly associated with outcomes, suggesting that perhaps optimization of hemodynamics with therapy in HF clinics unmasked intrinsic renal dysfunction and thus predicted outcomes most effectively. It has previously

been suggested that severity of renal dysfunction rather than its change over time appeared to be the most important determinant of outcome,[12] similar to our findings.

In this analysis, 12% of patients had WRF (using eGFR). While the degree of renal insufficiency measured at single points in time showed associations with the primary outcome variables in this study, the change in renal function over time was not related to the primary outcome in the multivariate analysis. This suggests that worsening renal function in a heart failure patient may be a marker of progression of HF, but is not independently prognostic.

Several studies have shown an association of WRF with increased mortality in patients with chronic heart failure.[12-17,19-22] A recent meta-analysis showed that in chronic HF, WRF occurring without treatment strongly correlated with poor outcome but in other clinical settings may not.[26] WRF in a cohort of elderly patients receiving 6 months of intensive medical therapy was associated with mortality only when SCr increased by ≥ 0.5 mg/dL.[17] These elderly patients received high doses of loop diuretics and spironolactone. The authors suggested that the higher doses of loop diuretics may have played a causal role instead of being a surrogate marker of more severe HF. They also proposed that WRF in the elderly may reflect initiation of aggressive treatment. Two studies assessing WRF in the setting of ACE inhibitors did not demonstrate a correlation with poor outcome.[12,27] Measuring WRF over shorter periods may be misleading, especially during initiation of medical treatment. ACE inhibitors are known to cause an acute decline in GFR while preserving kidney function over time.[28] At the time of enrollment, 92% of patients in this cohort were on an ACE inhibitor or ARB. It is thus useful to measure WRF over longer follow-up periods to determine whether an association with outcomes exists in chronic HF. Renal dysfunction attributable to normal aging in the HFrEF population has been shown to have limited risk on mortality.[29] These findings suggest that the clinical setting in which WRF occurs may be important in evaluating its significance. Our results expand previous findings in chronic HF patients to include HF*p*EF. Although we suffered from loss of power, the separated analyses in HF*r*EF and HF*p*EF demonstrated qualitatively similar results, with WRF not associated with outcome in either group.

Table 4 shows that mean baseline SCr and eGFR were significantly higher in the WRF group compared to the stable group, indicating that the presence of intrinsic renal dysfunction was associated with WRF. Age, coronary artery disease, diabetes, loop diuretic and hydralazine use (SCr definition only) were also independently associated with WRF. The WRF with hydralazine may reflect the absence of renin-angiotensin system blockade in this group, but may also be confounding by indication, as ACE inhibitors are routinely withheld from those with elevated creatinine

In this analysis, more patients (17% using eGFR) had improvement in renal function over time than had WRF. One study has reported decreased risk of all-cause mortality with improved SCr over the initial 6 month follow-up period (HR 0.8, CI 0.6-1.0).[12] In contrast, in our study, improved renal function was not associated with improved long-term outcome in either the univariate or the multivariate analysis. This was unexpected as we had hypothesized that improved renal function with medication optimization would result in

fewer HF hospitalizations and better outcomes. This may suggest that improvement in renal function accompanying HF therapy may result in improved volume status but does not appear to alter disease trajectory.

WRF due to low cardiac output is rare. Our study suggests that, while commonly coexisting, heart failure and renal failure are two separate processes. Patients with heart failure who have significant intrinsic renal disease have a poorer prognosis than those without renal disease. Having heart failure in and of itself does not worsen kidney function in HF outpatients. Clinicians should not alter management of chronic HF patients based solely on change in renal function. An inexorable decline in kidney function is not an obligatory accompaniment to a HF diagnosis suggesting that WRF should alert providers of coexistent significant kidney disease.

Our cohort was comprised of patients seen in tertiary HF clinics. Patients in this study were younger, had more systolic dysfunction, more severe symptoms, and less CAD than chronic HF patients in population-based studies.[1] It is notable that the referral nature of this cohort provides both strengths and limitations. The population spanned a full spectrum of diseases, heart failure etiologies, and severity. This permits us to evaluate findings from such subgroups using data from three US centers in order to make interferences about differences in disease pathophysiology and outcome. Interferences are likely to be generalizable to similar populations but may not be extrapolated to the general heart failure population. Additionally, HF*r*EF are more likely to be referred to tertiary specialty centers than HF*p*EF, thus resulting in a higher proportion of HF*r*EF patients in this cohort than in the general population. The HF*p*EF group was too small to make meaningful conclusions however there were not substantial qualitative differences between the two groups when analyzed separately. More study is needed to determine the true differences between HF*r*EF and HF*p*EF with regard to change in kidney function with outpatient treatment.

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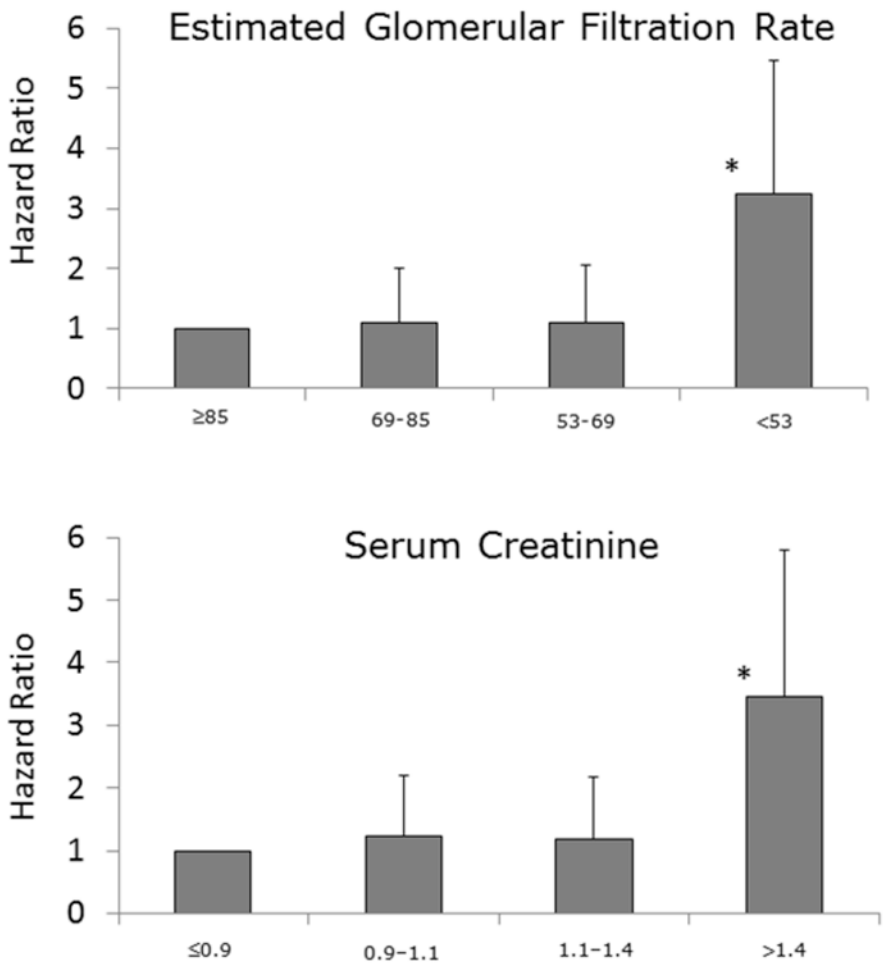

Figure 1.

The relation between baseline renal function, expressed as estimated glomerular filtration rate (mL/min/1.73m^2) or creatinine (mg/dL), and the hazard ratio for death or heart failure hospitalization. The risk of the outcome rises markedly in the group with the most impaired renal function at baseline. * = $p < 0.001$.

Table 1

Baseline characteristics by baseline eGFR quartiles

	Quartile					
Variable	**1 (n=223)**	**2 (n=223)**	**3 (n=223)**	**4 (n=223)**	**Total Cohort (n=892)**	***P***
eGFR (mL*min^{-1}*1.73m^{-2})						
median (minimum, maximum)	95 (85, 628)	76 (69, 84)	62 (53, 69)	40 (6, 53)	69 (6, 628)	…
Age (years)	48 (14)	54 (13)	59 (14)	64 (12)	56 (15)	< 0.01
Male	154 (69%)	138 (62%)	135 (61%)	128 (57%)	555 (62%)	0.07
White Race	155 (71%)	165 (76%)	182 (83%)	151 (70%)	653 (73%)	< 0.01
Black Race	58 (27%)	50 (23%)	32 (15%)	58 (27%)	198 (22%)	
Ischemic origin	33 (15%)	47 (21%)	70 (32%)	78 (36%)	228 (26%)	< 0.01
Systolic heart failure	114 (52%)	130 (58%)	121 (55%)	121 (55%)	486 (55%)	0.57
Hospitalization in prior 12 months	68 (30%)	83 (37%)	84 (38%)	91 (41%)	326 (37%)	0.14
Diabetes mellitus	44 (20%)	49 (22%)	49 (22%)	86 (39%)	228 (26%)	< 0.01
Hypertension	11 (50%)	121 (54%)	131 (59%)	166 (74%)	529 (59%)	< 0.01
Stroke	3 (1%)	16 (7%)	10 (4%)	21 (9%)	50 (6%)	< 0.01
Follow-up time, years, median (IQR)	3.0 (1.6, 5.0)	2.9 (1.8, 4.8)	3.0 (1.7, 4.4)	2.5 (1.3, 3.7)	2.9 (1.5, 4.5)	< 0.01
New York Heart Association Class						
II	122 (55%)	123 (55%)	116 (52%)	113 (52%)	472 (53%)	
III	31 (14%)	43 (19%)	45 (20%)	71 (33%)	190 (22%)	< 0.01
IV	1 (0%)	0 (0%)	6 (3%)	6 (3%)	13 (1%)	
Ejection Fraction (%)	37 (16)	36 (17)	38 (17)	39 (18)	37 (17)	0.53
Body Mass Index (kg/m^2)	30 (7)	30 (8)	31 (7)	32 (9)	31 (8)	0.11
Heart rate (beats per minute)	73 (13)	72 (13)	73 (14)	72 (13)	72 (13)	0.78
Systolic blood pressure (mm Hg)	117 (21)	116 (21)	117 (22)	119 (25)	118 (22)	0.59
MLHFQ* score, median (IQR)	19 (2, 51)	18 (4, 45)	24 (6, 50)	34 (9, 59)	24 (4, 52)	0.01
Serum creatinine (mg/dL)	0.9 (0.1)	1.0 (0.1)	1.2 (0.2)	2.1 (1.4)	1.3 (0.9)	< 0.01
Serum sodium (mEq/L)	139 (3)	140 (2)	139 (3)	139 (4)	139 (3)	0.19
Potassium-sparing diuretics	2 (1%)	3 (1%)	7 (3%)	2 (1%)	14 (2%)	0.25
Loop diuretics	118 (53%)	135 (61%)	138 (62%)	168 (75%)	559 (63%)	< 0.01
ACE inhibitors	161 (72%)	163 (73%)	149 (67%)	138 (62%)	611 (68%)	0.04

	Quartile					
Variable	**1 (n=223)**	**2 (n=223)**	**3 (n=223)**	**4 (n=223)**	**Total Cohort (n=892)**	***P***
Aldosterone antagonist	59 (26%)	64 (29%)	61 (27%)	87 (39%)	271 (30%)	0.01
Angiotensin receptor blockers	48 (22%)	50 (22%)	59 (26%)	56 (25%)	213 (24%)	0.58
Aspirin	114 (51%)	122 (55%)	123 (55%)	145 (65%)	504 (57%)	0.02
β-Blockers	195 (87%)	198 (89%)	194 (87%)	198 (89%)	785 (88%)	0.91
Digoxin	63 (28%)	58 (26%)	57 (26%)	70 (31%)	248 (28%)	0.5
Hydralazine	14 (6%)	9 (4%)	9 (4%)	36 (16%)	68 (8%)	< 0.01
Long acting nitrate	19 (9%)	21 (9%)	21 (9%)	54 (24%)	115 (13%)	< 0.01
Statin	89 (40%)	127 (57%)	128 (57%)	143 (64%)	487 (55%)	< 0.01

Continuous variables are reported as mean (SD) unless otherwise noted.

Categorical variables are reported as frequency (%).

P-values for continuous variables are from one-way ANOVA or Kruskal-Wallis tests.

P-values for categorical variables are from Pearson chi-square test or Fisher's exact test.

* Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Table 2

Baseline variables associated with primary outcome

Baseline characteristic	Hazard Ratio	95% CI	P-value	Number (%)	Events (%)
New York Heart Association class				882 (99)	109 (99.1)
I	reference	--	--		
II	3.21	1.46 - 7.09	0.004		
III	9.89	4.47 - 21.91	< 0.001		
IV	13.47	3.93 - 46.2	< 0.001		
Race				867 (97.3)	108 (98.2)
Caucasian	reference	--	--		
Black	1.63	1.07 - 2.48	0.022		
Other	0.54	0.07 - 3.86	0.536		
Gender				892 (100)	110 (100)
Female	reference	--	--		
Male	0.94	0.64 - 1.40	0.747		
Age (years)	1.019	1.01 - 1.03	0.007	892 (100)	110 (100)
Ischemic origin	1.47	0.98 - 2.21	0.060	876 (98.3)	109 (99.1)
Hospitalization in prior 12 months	1.22	1.14 - 1.32	< 0.001	892 (100)	110 (100)
Diabetes	1.52	1.01 - 2.28	0.043	892 (100)	110 (100)
Hypertension	2.07	1.37 - 3.12	0.001	892 (100)	110 (100)
Hyperlipidemia	1.65	1.12 - 2.42	0.010	892 (100)	110 (100)
Ejection fraction	0.973	0.96 - 0.99	< 0.001	886 (99.4)	110 (100)
Heart rate, beats per minute	1.017	1.00 - 1.03	0.021	877 (98.4)	108 (98.2)
Systolic blood pressure (mm Hg)	0.989	0.98 - 1.00	0.026	884 (99.2)	110 (100)
MLHFQ score	1.017	1.01 - 1.02	< 0.001	892 (100)	110 (100)
Loop diuretic	2.82	1.78 - 4.47	< 0.001	892 (100)	110 (100)
Aldosterone antagonist	2.08	1.42 - 3.03	< 0.001	892 (100)	110 (100)
Hydralazine	3.13	1.76 - 5.55	< 0.001	892 (100)	110 (100)
Long acting nitrate	3.04	1.96 - 4.71	< 0.001	892 (100)	110 (100)
Digoxin	1.57	1.07 - 2.31	0.020	892 (100)	110 (100)

Univariate Cox proportional hazard modes were used to assess the relationship between 14 candidate variables and the 4 pre-selected variables to control for (age, sex, diabetes and ischemic status) with primary outcome. Frequency for each variable is reported by number and % out of 892 subjects studied.

Table 3

Relationship between renal parameters and primary outcome

	Unadjusted Analysis			Adjusted Analysis*		
Primary Composite	**HR†**	**95% CI**	***P***	**HR†**	**95% CI**	***P***
Baseline SCr	1.06	1.02 – 1.10	0.002	1.04	0.99 – 1.09	0.091
Baseline eGFR	1.20	1.11 – 1.30	< 0.001	1.11	1.02 – 1.21	0.017
Follow-Up SCr	1.05	1.02 – 1.08	0.002	1.05	1.00 – 1.10	0.040
Follow-Up eGFR	1.24	1.15 – 1.33	< 0.001	1.16	1.07 – 1.26	< 0.001
Stable SCr	ref.					
≥ 0.3 mg/dL ↓SCr‡	2.02	1.20 – 3.40	0.008	1.11	0.64 – 1.93	0.713
≥ 0.3 mg/dL ↑SCr‡	2.21	1.36 – 3.57	0.001	1.27	0.76 – 2.13	0.368
Stable eGFR	ref.					
≥ 25% ↑eGFR‡	1.32	0.81 – 2.15	0.269	0.88	0.53 – 1.47	0.624
≥ 25% ↓eGFR‡	1.71	1.04 – 2.81	0.035	0.92	0.53 – 1.58	0.759
Death	HR	95% CI	P	HR	95% CI	*P*
Baseline SCr	1.03	0.95 - 1.13	0.424	0.96	0.85 - 1.07	0.433
Baseline eGFR	1.21	1.05 - 1.39	0.009	1.05	0.90 - 1.23	0.514
Follow-Up SCr	1.05	1.00 – 1.11	0.052	1.03	0.94 - 1.14	0.477
Follow-Up eGFR	1.33	1.17 - 1.52	< 0.001	1.23	1.04 - 1.44	0.014
Stable SCr	ref.					
≥ 0.3 mg/dL ↓SCr‡	1.92	0.72 - 5.14	0.192	0.81	0.28 - 2.31	0.689
≥ 0.3 mg/dL ↑SCr‡	3.1	1.41 - 6.82	0.005	1.48	0.61 - 3.57	0.387
Stable eGFR	ref.					
≥ 25% ↑eGFR‡	1.03	0.39 - 2.73	0.956	0.53	0.19 - 1.52	0.239
≥ 25% ↓eGFR‡	2.26	1.00 – 5.10	0.050	1.03	0.42 - 2.55	0.941

*Cox proportional hazards model controlling for the following baseline characteristics: age, sex, race, ejection fraction, NYHA class, ischemic etiology, systolic blood pressure, long acting nitrate, hypertension, MLHFQ, diabetes, and loop diuretic.

†Hazard ratio (HR) calculated per 0.3 mg/dL increments in serum creatinine (SCr) and per 10 mL/min decrements in eGFR.

‡Improved renal function, defined as a decrease in SCr ≥ 0.3 mg/dL; and an increase in eGFR ≥ 25%.

Worsening renal function, defined as an increase in SCr ≥ 0.3 mg/dL; and a decrease in eGFR ≥ 25%.

Table 4

Multivariable analysis of factors associated with worsening renal function

≥ 0.3 mg/dL ↑SCr	Stable† (n=782)	Worsened‡ (n=109)	Odds Ratio*	95% CI	P-value
Age – 5 year increments	55.5 (14.5)	60.8 (14)	1.12	1.04 – 1.21	0.005
Coronary artery disease	17 (2.2%)	9 (8.3%)	3.13	1.27 - 7.28	0.01
Diabetes	185 (23.7%)	43 (39.4%)	1.59	1.02 – 2.46	0.04
Baseline creatinine	1.27 (0.81)	1.56 (1.19)	1.22	1.00 - 1.46	0.04
Hydralazine use	50 (6.4%)	18 (16.5%)	2.53	1.34 – 4.62	0.003
Loop diuretic use	473 (60.5%)	85 (78%)	1.82	1.12 – 3.04	0.02
≥ 25% ↓eGFR	Stable (n=783)	Worsened‡ (n=109)	Odds Ratio	95% CI	P-value
Age – 5 year increments	55.7 (14.7)	59.3 (13.6)	1.08	1.00 – 1.17	0.05
Coronary artery disease	17 (2.2%)	9 (8.3%)	3.23	1.32 - 7.42	0.01
Baseline eGFR	69.5 (31.3)	70.0 (25.5)	1.01	1.00 - 1.01	0.08
Diabetes	186 (23.8%)	42 (38.9%)	1.71	1.09 – 2.64	0.007
Loop diuretic use	477 (60.9%)	82 (75.2%)	1.77	1.13 – 2.87	0.02

*Odds ratio from logistic regression model while controlling for the other factors in each respective list.

†Reported as group mean (SD) or frequency (%).

‡Worsened renal failure, defined as an increase in SCr ≥ 0.3 mg/dL; and a decrease in eGFR ≥ 25% from baseline to last creatinine follow-up or last creatinine follow-up prior to composite event.