Heart Failure Increases the Risk of Adverse Renal Outcomes in Patients With Normal Kidney Function

BACKGROUND: Heart failure (HF) is associated with poor cardiac outcomes and mortality. It is not known whether HF leads to poor renal outcomes in patients with normal kidney function. We hypothesized that HF is associated with worse long-term renal outcomes.

METHODS AND RESULTS: Among 3 570 865 US veterans with estimated glomerular filtration rate (eGFR) ≥60 mL min^{-1} 1.73 m^{-2} during October 1, 2004 to September 30, 2006, we identified 156 743 with an *International Classification of Diseases*, *Ninth Revision*, diagnosis of HF. We examined the association of HF with incident chronic kidney disease (CKD), the composite of incident CKD or mortality, and rapid rate of eGFR decline (slopes steeper than −5 mL min^{-1} 1.73 m^{-2} y^{-1}) using Cox proportional hazard analyses and logistic regression. Adjustments were made for various confounders. The mean±standard deviation baseline age and eGFR of HF patients were 68±11 years and 78±14 mL min^{-1} 1.73 m^{-2} and in patients without HF were 59±14 years and 84±16 mL min^{-1} 1.73 m^{-2}, respectively. HF patients had higher prevalence of hypertension, diabetes mellitus, cardiac, peripheral vascular and chronic lung diseases, stroke, and dementia. Incidence of CKD was 69.0/1000 patient-years in HF patients versus 14.5/1000 patient-years in patients without HF, and 22% of patients with HF had rapid decline in eGFR compared with 8.5% in patients without HF. HF patients had a 2.12-, 2.06-, and 2.13-fold higher multivariable-adjusted risk of incident CKD, composite of CKD or mortality, and rapid eGFR decline, respectively.

CONCLUSIONS: HF is associated with significantly higher risk of incident CKD, incident CKD or mortality, and rapid eGFR decline. Early diagnosis and management of HF could help reduce the risk of long-term renal complications.

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WHAT IS NEW?

- This article describes an association between heart failure (HF) and a high risk of new-onset chronic kidney disease and rapid decline in kidney function among a large cohort of patients with normal baseline estimated glomerular filtration rate.
- The risk of the composite end point of incident chronic kidney disease or mortality was also significantly higher in patients with HF.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Both patients and their treating physicians need to be aware that HF could hasten the development of chronic kidney disease and could lead to faster decline in kidney function even in patients with normal estimated glomerular filtration rate.
- It is thus important that kidney function be monitored closely in patients with HF, and potentially nephrotoxic exposures (eg, nonsteroidal anti-inflammatory medications, radiocontrast agents) are minimized or avoided.
- Although this observational study shows increased risk for chronic kidney disease and rapid decline in renal function in patients with HF, prospective studies are required to look into the effects of early renoprotective strategies in these patients.

Concurrent renal dysfunction and heart disease is an interdependent phenomenon secondary to (among others) changes in hemodynamics[1,2] and is associated with increased mortality and morbidity.[3,4] Heart failure (HF) and acute myocardial infarction increase the risk of 30-day readmission,[5,6] progression to end-stage renal disease,[7] and mortality in patients with chronic kidney disease (CKD).[8] Of all HF patients admitted to a hospital, those with worsening kidney function on follow-up have higher mortality and recurrent hospital admissions.[9,10] Several studies have evaluated the effects of HF in patients with CKD,[11–13] but to the best of our knowledge, the risk of incident CKD and progressive loss of kidney function in patients with HF and normal kidney function has not been examined, and it is unclear whether interventions aimed at preventing or treating HF in patients with normal kidney function could be useful to prevent the development of de novo CKD. We hypothesized that HF in patients with normal baseline kidney function is associated with higher risk of long-term adverse renal outcomes.

METHODS

Cohort Definition

Our study used data from a cohort study examining risk factors and outcomes in patients with incident CKD (RCAV study [Racial and Cardiovascular Risk Anomalies in CKD]), as previously described.[14–16] In brief, we identified 3 570 865 US veterans with estimated glomerular filtration rate (eGFR) of ≥60 mL min^{-1} 1.73 m^{-2} during October 1, 2004 to September 30, 2006, calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[17] Out of this cohort, 156 743 patients with a diagnosis of congestive heart failure were identified during the same time period using International Classification of Diseases, Ninth Revision, diagnostic codes (Figure 1). Cohort entry was defined as the first date of eGFR ≥60 mL min^{-1} 1.73 m^{-2} during October 1, 2004 to September 30, 2006. Baseline characteristics—income level, body mass index, blood pressure, International Classification of Diseases, Ninth Revision, code for personal history of noncompliance with medical treatment, service connection (a measure indicating whether one or more of a patient's comorbidities were caused by their military service, resulting in certain privileges, such as preferential access to care and lower copayments), comorbid conditions, and laboratory characteristics—were obtained as previously described.[18,19] Medication compliance was estimated as the percentage of days a subject had medication available (proportion of days covered) based on medication dispensation records from any Veteran Administration (VA) pharmacy. Proportion of days covered was calculated as the ratio of the total number of pills and the number of days between the first fill of the medication and the end of the evaluation period.[19] Information about race was supplemented from Medicare through the VA–Medicare data merge project. Data on medication exposure throughout the entire follow-up period were collected from VA pharmacy dispensation records. Data on mortality were obtained from the VA Vital Status Files, which contain dates of death or last medical/administrative encounter from all sources in the VA system with sensitivity and specificity of 98.3% and 99.8%, compared with the National Death Index as gold standard.[20]

Outcomes

We defined 3 different outcomes: (1) incident CKD, (2) composite of incident CKD or mortality, and (3) rate of kidney function decline. Incident CKD was defined as two eGFR values of <60 mL min^{-1} 1.73 m^{-2} occurring ≥3 months apart and a decrease from baseline eGFR of at least 25%.[21,22] The 25% drop was measured from the baseline eGFR to the second of the two eGFR values used to define CKD. A rapid rate of eGFR decline was defined as slopes of longitudinal eGFR (calculated by ordinary least squares regressions for individual patients from minimum of three eGFR values steeper than –5 mL min^{-1} 1.73 m^{-2} y^{-1}).[21]

Statistical Analysis

Descriptive analyses were performed, and skewed variables were log transformed. Data were summarized using proportions, means (±SD), or medians (25th–75th percentile) as appropriate. Because of the large sample size, traditional comparisons were all statistically significant, and we hence determined significance based on biologically relevant differences. The association of HF with incident CKD and with the composite of incident CKD or mortality was assessed using unadjusted and multivariable-adjusted Cox

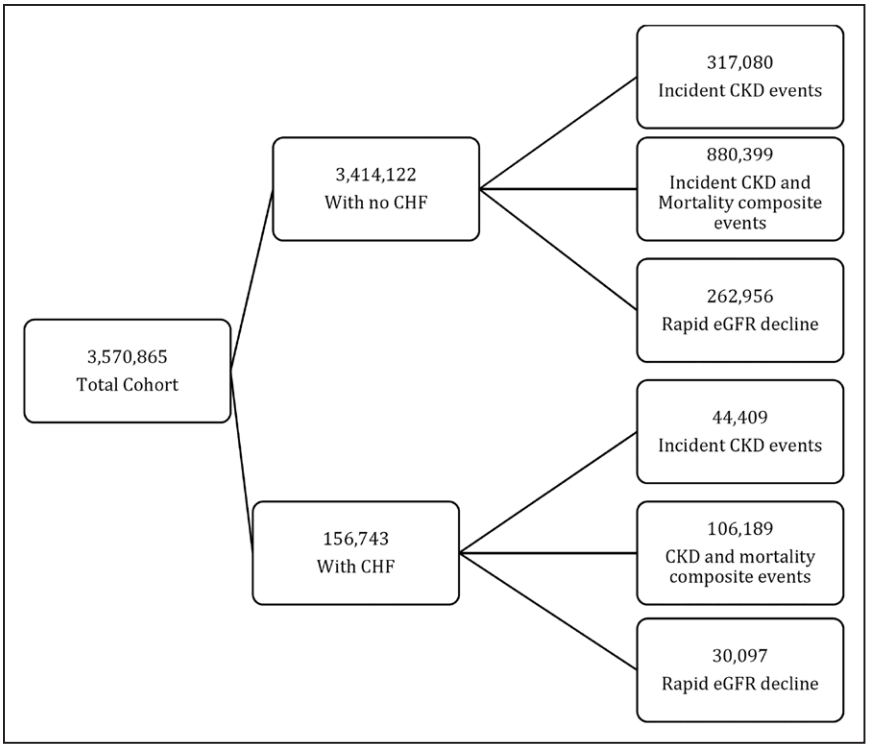

Figure 1. Flow chart of patient selection.
CKD indicates chronic kidney disease; and eGFR, estimated glomerular filtration rate.

proportional hazard models, and the association of HF with rapid decline in eGFR was assessed using unadjusted and multivariable-adjusted logistic regression models (for slope as a categorical variable) and linear regression models (for slope as a continuous variable). All models were adjusted sequentially for the following confounders based on a priori considerations: model 1: unadjusted; model 2: age, sex, and race/ethnicity; model 3: model 2 variables and marital status, income level, service connection, and noncompliance; model 4: model 3 variables and diabetes mellitus, hypertension, cardiovascular disease, peripheral arterial disease, lung disease, and malignancy; model 5: model 4 variables and body mass index, systolic and diastolic blood pressure; and model 6: model 5 variables and eGFR. Medications which could be initiated in response to HF (angiotensin-converting enzyme inhibitors, statins, β-blockers, calcium channel blockers, vasodilators, thiazide diuretic, loop diuretic, potassium-sparing diuretics, anticoagulants, antiplatelet agents, digoxin, and inotropes), and which could act as effect mediators, were not included in the main multivariable analyses, but adjustment for these medications was performed in sensitivity analyses (model 7).

In the final multivariable model, 78.5% of patients had complete data for analysis. Missing data were not imputed.

Analyses were repeated in subgroups of patients divided by age, race, presence or absence of diabetes mellitus and cardiovascular disease, systolic blood pressure level, use of inotropes, anticoagulants, and loop diuretics. Statistical analyses were performed using STATA MP Versions 13 and 14 (STATA Corporation, College Station, TX). The study protocol with waiver of informed consent was approved by the Institutional Review Boards at the Memphis and Long Beach VA Medical Centers and complied with Declaration of Helsinki.

RESULTS

Baseline Characteristics

Baseline characteristics of patients categorized by HF status are shown in Table 1. HF patients were older, had lower baseline eGFR, and higher prevalence of various comorbid conditions. Medication use was higher, and medication compliance was lower in HF patients.

Incident CKD

A total of 361 488 incident CKD events occurred at an event rate of 16.04/1000 patient-years (PY; 95% confidence interval (CI), 15.98–16.09) over a median follow-up of 7.6 years. The CKD incidence in HF patients was higher at 68.90/1000 PY (95% CI, 68.22–69.51) compared with 14.48/1000 PY (95% CI, 14.43–14.53) in patients without HF.

The crude and multivariable-adjusted hazard ratios of incident CKD associated with HF were 4.30 (95% CI, 4.26–4.35) and 2.12 (95% CI, 2.10–2.14), respectively (Table 2). The association of HF with higher risk of incident CKD was present in all examined subgroups (Figure 2). The association between HF and incident CKD was attenuated, but remained significant after adjustment for medication use (Table 2).

Composite of Incident CKD or Mortality

A total of 986 588 composite events of CKD or mortality were identified. The incidence of the composite

Table 1. Baseline Characteristics of HF Patients and Patients Without HF

	HF (n=156 743)	No HF (n=3 414 122)
Demographics		
Age, y	68±11	59±14
Sex (% male)	98	93
Race (% black)	16	17
Marital status		
Married (%)	54	56
Single	7	11
Divorced	26	26
Widowed	13	7
Income ($)*	19 859 (11 225–31 460)	23 129 (11 752–36 490)
Service connection (%)	36	40
Medication use (%)		
Statin	68	53
ACEI/ARB	87	50
β-blocker	84	42
CCB	44	31
Vasodilator	14	4
Thiazide	33	32
Loop diuretic	79	16
Potassium-sparing diuretic	32	8
Anticoagulation	37	17
Antiplatelet agents	16	9
Digoxin	35	4
Inotropic agent	3	0
Comorbidities (%)		
Medication compliance	89	94
Hypertension	82	58
Diabetes mellitus	45	23
CVD	42	10
CVA	15	6
PAD	16	5
Chronic lung disease	43	17
Dementia	2	1
Rheumatologic disease	2	1
Liver disease	2	1
Malignancy	16	10
HIV	0	1
Depression	9	9
Vital signs		
SBP, mm Hg	129±15	133±14
DBP, mm Hg	71±9	76±9
BMI, kg/m^2	30.4±7.2	29.1±5.6
Laboratory findings		
eGFR, mL min^{-1} 1.73 m^{-2}	78±14	84±16
Serum BNP, ng/L*	262 (84–728)	15 (1–74)
Serum cholesterol, mg/dL	163±38	183±38
Serum sodium, mmol/L	139±3	139±3
Serum potassium, mmol/L	4.3±0.3	4.3±0.4
Serum bicarbonate, mmol/L	28±3	28±3
Serum BUN, mg/dL	19±8	15±5

Data presented as mean±SD or *median and interquartile range. Because of the large sample size, traditional comparisons were all statistically significant, and we hence determined significance based on biologically relevant differences. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blocker; CVA, cerebrovascular accident; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HIV, human immunodeficiency virus; PAD, peripheral arterial disease; and SBP, systolic blood pressure.

end point in HF patients was higher at 164.66/1000 PY (95% CI, 163.67–165.65) compared with 40.20/1000 PY (95% CI, 40.12–40.29) in patients without HF.

The crude and multivariable-adjusted hazard ratios of the composite outcome associated with HF versus no HF were 3.96 (95% CI, 3.94–3.99) and 2.06 (95% CI, 2.05–2.08), respectively (Table 2). The association of HF with the composite outcome remained significant in all the studied subgroups (Figure 3). The association between HF and the composite of incident CKD or mortality was attenuated, but remained significant after adjustment for medication use (Table 2).

Rapid Decline in eGFR

The prevalence of rapid eGFR decline was 9.12%. Among patients with and without HF, 21.69% and 8.56% had a rapid decline in eGFR, respectively. The crude and adjusted odds ratios of rapid decline in eGFR were 2.96 (95% CI, 2.92–3.00) and 2.13 (95% CI, 2.10–2.17), respectively (Table 2). The association of HF with rapid decline in eGFR remained significant in all examined subgroups (Figure 4). The association between HF and the risk of rapid loss of kidney function was attenuated, but remained significant after adjustment for medication use (Table 2).

DISCUSSION

We describe an association between HF and a significantly higher risk of new-onset CKD (incident CKD) and rapid decline in kidney function among a large cohort

Table 2. Multivariable-Adjusted Models, Showing the Risk of Various Outcomes Associated With Congestive Heart Failure Status

Model number (n)	Incident CKD (HR, 95% CI)	Incident CKD or Mortality (HR, 95% CI)	Rapid Decline in eGFR (OR, 95% CI)	Slopes of eGFR (Coefficient, 95% CI)
Model 1 (3212315)	4.30 (4.26 to 4.35)	3.96 (3.94 to 3.99)	2.96 (2.92 to 3.00)	−1.53 (−1.51 to −1.56)
Model 2 (2941052)	3.21 (3.18 to 3.24)	2.79 (2.78 to 2.81)	2.55 (2.52 to 2.59)	−1.28 (−1.26 to −1.31)
Model 3 (2693381)	3.00 (2.96 to 3.03)	2.65 (2.63 to 2.67)	2.45 (2.42 to 2.49)	−1.22 (−1.20 to −1.25)
Model 4 (2693381)	2.13 (2.10 to 2.15)	2.07 (2.05 to 2.08)	2.02 (1.99 to 2.06)	−1.01 (−0.99 to −1.03)
Model 5 (2599864)	2.14 (2.12 to 2.17)	2.06 (2.05 to 2.08)	2.06 (2.03 to 2.09)	−1.03 (−1.01 to −1.06)
Model 6 (2599864)	2.12 (2.10 to 2.14)	2.06 (2.05 to 2.08)	2.13 (2.10 to 2.17)	−1.09 (−1.07 to −1.11)
Model 7 (2599864)	1.34 (1.32 to 1.36)	1.41 (1.39 to 1.42)	1.41 (1.39 to 1.44)	−0.62 (−0.59 to −0.64)

Model 1: unadjusted; model 2: baseline age, sex, and race/ethnicity; model 3: model 2 variables and marital status, income level, service connection, and noncompliance; model 4: model 3 variables and diabetes mellitus, hypertension, cardiovascular disease, peripheral arterial disease, lung disease, and malignancy; model 5: model 4 variables and body mass index, systolic blood pressure and diastolic blood pressure; model 6 (main multivariable model): model 5 variables and eGFR; model 7 (adjustment for medication use): model 6 variables and use of ACE inhibitors, statins, β-blockers, calcium channel blockers, vasodilators, thiazide diuretic, loop diuretic, potassium-sparing diuretics, anticoagulants, antiplatelet agents, digoxin, and inotropes. ACE indicates angiotensin-converting enzyme; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

of patients with normal baseline eGFR. The risk of the composite end point of incident CKD or mortality was also significantly higher in patients with HF.

There are several potential biological explanations for the association between HF and kidney disease. Among patients with preexisting CKD, the presence of HF has been linked with poorer outcomes, including significant worsening of kidney function.[23–28] HF is characterized by numerous pathophysiologic abnormalities, which could lead to long-term kidney damage. In addition to hemodynamic mechanisms, such as low cardiac output and increased renal venous pressure, complex neurohormonal changes, such as activation of the sympathetic nervous system and the renin–angiotensin system, increased oxidative stress, and inflammatory activation can affect renal blood flow and glomerular perfusion.[29,30] Further contributing to potential renal damage are recurrent episodes of acute kidney injury[31] and potential direct nephrotoxicity of medications received during the course of HF.[32] Much less is known about the effects of HF on long-term kidney function in patients with normal eGFR, but the above-mentioned pathophysiologic changes postulated to cause poorer renal outcomes in those with preexisting CKD could also be instrumental in engendering new-onset kidney damage and incident CKD. It is thought that the elevated renal G protein–coupled receptor [G protein βγ (GPCR-Gβγ)] signaling and endothelin system expression seen in HF may cause renal tissue damage, fibrosis, and inflammation, which can manifest as acute renal failure and cardiorenal syndrome 2.[33]

The concomitant presence of HF and CKD has also been associated with a higher risk of mortality.[13,27,34] The putative pathophysiological mechanism for the increased mortality is similar to the ones responsible for kidney damage, including exaggerated neurohormonal activation and oxidative stress[30]; these, along with diffuse atherosclerosis especially in cases of ischemic cardiomyopathy and vascular calcification, can result in increased risk of cardiovascular events and mortality.[35,36]

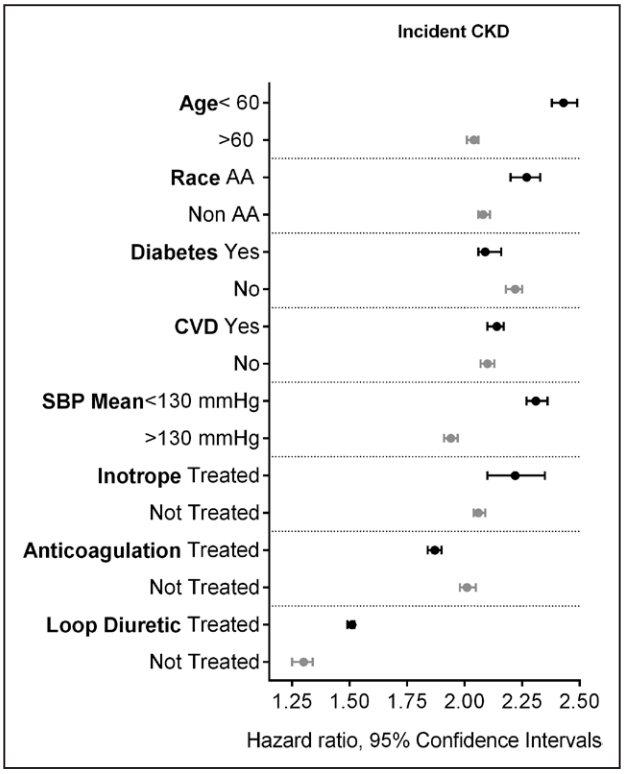

Figure 2. Association between heart failure and the risk of incident chronic kidney disease (CKD) in various subgroups.
Adjusted for baseline age, sex, race/ethnicity, marital status, income level, service connection and noncompliance, diabetes mellitus, hypertension, cardiovascular disease (CVD), peripheral arterial disease, lung disease and malignancy, body mass index, systolic blood pressure (SBP) and diastolic blood pressure, and estimated glomerular filtration rate (eGFR). The light and dark markers denote the hazard ratio and 95% confidence intervals of 2 categories of the same variable. AA indicates African American.

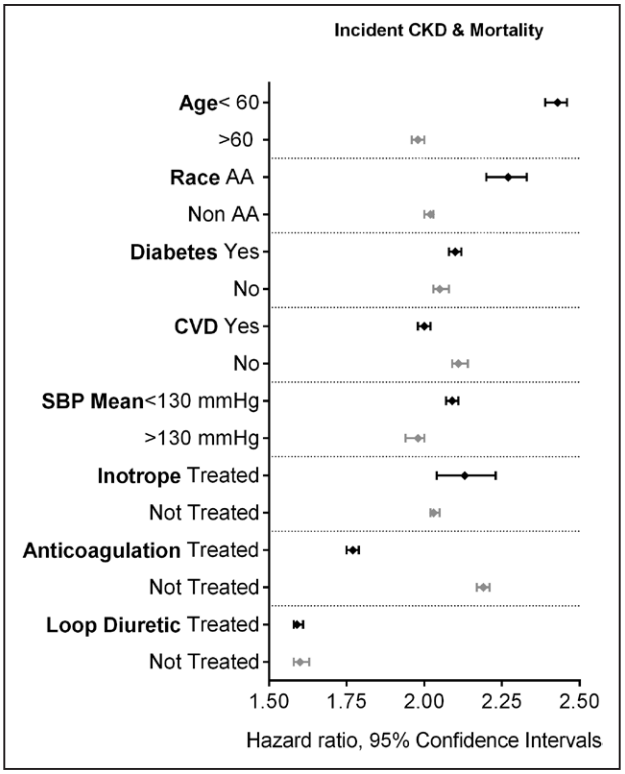

Figure 3. Association between heart failure and the risk of the composite end point of incident chronic kidney disease (CKD) or mortality in various subgroups.
Adjusted for baseline age, sex, race/ethnicity, marital status, income level, service connection and noncompliance, diabetes mellitus, hypertension, cardiovascular disease (CVD), peripheral arterial disease, lung disease and malignancy, body mass index, systolic blood pressure (SBP) and diastolic blood pressure, and estimated glomerular filtration rate (eGFR). The light and dark markers denote the hazard ratio and 95% confidence intervals of 2 categories of the same variable. AA indicates African American.

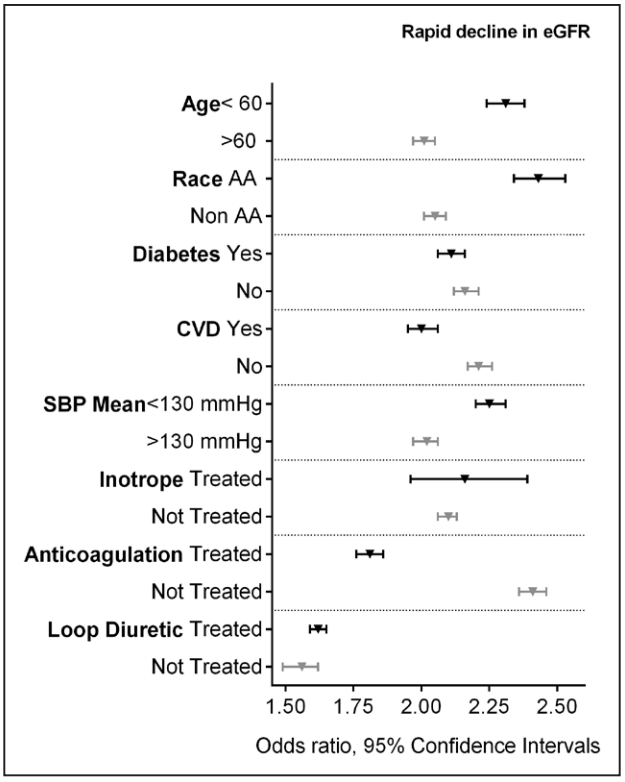

Figure 4. Association between heart failure and the risk of rapid decline in estimated glomerular filtration rate (eGFR; ≥5 mL min−1 1.73 m−2 y−1) in various subgroups.
Adjusted for baseline age, sex, race/ethnicity, marital status, income level, service connection and noncompliance, diabetes mellitus, hypertension, cardiovascular disease (CVD), peripheral arterial disease, lung disease and malignancy, body mass index, systolic blood pressure (SBP) and diastolic blood pressure, and eGFR. The light and dark markers denote the odds ratio and 95% confidence intervals of 2 categories of the same variable. AA indicates African American.

Treatment strategies aimed at preventing and treating HF may prevent worsening kidney function and mortality in these patients. Angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and aldosterone inhibitors have been shown to reduce the risk of mortality in patients with HF in numerous studies,[24,37–41] but the renoprotective effect of these agents in this population is not well validated. Slight worsening of kidney function is often seen at the initiation of therapy with renin–angiotensin–aldosterone system inhibitors, but the progressive decline in kidney function and the severity of proteinuria are mitigated on the continuation of these medications.[42] It is therefore possible that early interventions aimed at treating HF could also help prevent the development of CKD and progressive loss of kidney function. Although we cannot make practical recommendations on the beneficial effect of early treatment based on our study, this should stimulate further research. This hypothesis will have to be proven in dedicated randomized controlled clinical trials.

Strengths and Limitations

The strength of this study is in its scale and rigorous follow-up in a closed patient care system and the inclusion of veterans from the entire United States. Our study also has limitations. This being an observational study, we can only report associations, and we cannot claim that HF was indeed the cause of the worse renal outcomes. In addition, models could only be adjusted for confounders for which we had available data, and we cannot rule out residual confounding from unobserved variables. The study population consisted of mostly male patients; hence, the results may not be generalizable to females. We used International Classification of Diseases, Ninth Revision, diagnostic codes to define

HF and hence may have misclassified patients with HF who did not have a diagnostic code entered in their record. However, such misclassification would have biased results toward the null. We did not have access to information about the severity of HF (New York Heart Association class), cause of HF, presence of cardiac resynchronization therapy or implantable cardiac defibrillator device, average 24-hour ambulatory heart rate or blood pressure readings, heart transplant status, left ventricular assist device support, and the baseline left ventricular ejection fraction. Hence, we could not assess the presence or absence of a graded relationship between its severity and the various outcomes and more importantly the differential impact of HF with preserved or reduced left ventricular ejection fraction on the outcomes. Finally, we did not have information about proteinuria, hematuria, or evidence of structural or pathological changes in kidneys; consequently, the diagnosis of CKD is less accurate, and patients with proteinuria and normal eGFR (eGFR ≥60 mL min^{-1} 1.73 m^{-2}) may be misclassified as not having CKD.

Conclusions

HF is associated with significantly higher risk of incident CKD, incident CKD or mortality, and more rapid GFR decline. Early diagnosis and management of HF or its risk factors may have the potential to reduce the risk of long-term renal complications. The benefits of such strategies will have to be examined in randomized clinical trials.

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DISCLOSURES

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FOOTNOTES

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