Burden and Outcomes of Heart Failure Hospitalizations in Adults With Chronic Kidney Disease

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ABSTRACT

BACKGROUND Data on rates of heart failure (HF) hospitalizations, recurrent hospitalizations, and outcomes related to HF hospitalizations in chronic kidney disease (CKD) are limited.

OBJECTIVES This study examined rates of HF hospitalizations and re-hospitalizations within a large CKD population and evaluated the burden of HF hospitalizations with the risk of subsequent CKD progression and death.

METHODS The prospective CRIC (Chronic Renal Insufficiency Cohort) study measured the estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR) at baseline. The crude rates and rate ratios of HF hospitalizations and 30-day HF re-hospitalizations were calculated using Poisson regression models. Cox regression was used to assess the association of the frequency of HF hospitalizations within the first 2 years of follow-up with risk of subsequent CKD progression and death.

RESULTS Among 3,791 participants, the crude rate of HF admissions was 5.8 per 100 person-years (with higher rates of HF with preserved ejection fraction vs. HF with reduced ejection fraction). The adjusted rate of HF was higher with a lower eGFR (vs. eGFR >45 ml/min/1.73 m^2); the rate ratios were 1.7 and 2.2 for eGFR 30 to 44 and <30 ml/min/1.73 m^2 (vs. >45 ml/min/1.73 m^2), respectively. Similarly, the adjusted rates of HF hospitalization were significantly higher in those with higher urine ACR (vs. urine ACR <30 mg/g); the rate ratios were 1.9 and 2.6 for urine ACR 30 to 299 and ≥300 mg/g, respectively. Overall, 20.6% of participants had a subsequent HF re-admission within 30 days. HF hospitalization within 2 years of study entry was associated with greater adjusted risks for CKD progression (1 hospitalization: hazard ratio [HR]: 1.93; 95% confidence interval [CI]: 1.40 to 2.67; 2+ hospitalizations: HR: 2.14; 95% CI: 1.30 to 3.54) and all-cause death (1 hospitalization: HR: 2.20; 95% CI: 1.71 to 2.84; 2+ hospitalizations: HR: 3.06; 95% CI: 2.23 to 4.18).

CONCLUSIONS Within a large U.S. CKD population, the rates of HF hospitalizations and re-hospitalization were high, with even higher rates across categories of lower eGFR and higher urine ACR. Patients with CKD hospitalized with HF had greater risks of CKD progression and death. HF prevention and treatment should be a public health priority to improve CKD outcomes. (J Am Coll Cardiol 2019;73:2691–700) © 2019 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACR = albumin-to-creatinine ratio

CKD = chronic kidney disease

EF = ejection fraction

eGFR = estimated glomerular filtration rate

ESRD = end-stage renal disease

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

Heart failure (HF) is one of the leading causes of morbidity and mortality in the United States. HF is the primary diagnosis in >1 million hospitalizations annually, and the rates of hospitalizations for HF continue to increase (1,2). The total cost of HF care in the United States exceeds $30 billion annually (1). Hospitalization for HF represents a sentinel prognostic event in the course of many patients with a high risk for recurrent hospitalization (e.g., 50% at 6 months), and a 1-year mortality rate of approximately 30% (3,4).

The risk of HF is even greater in patients with chronic kidney disease (CKD) (5-8). Previous studies have estimated that patients with CKD have a 3-fold increased risk of incident HF (6). It is also well known that patients with CKD, in particular those with end-stage renal disease (ESRD) who require dialysis, have higher rates of hospitalizations (9). Data from the U.S. Renal Data System indicate that, on average, ESRD patients are hospitalized twice a year and approximately 30% have an unplanned re-hospitalization within 30 days (10). However, there are limited published data on rates of HF hospitalizations, recurrent hospitalizations, and outcomes related to HF hospitalizations specifically in patients with CKD, which may help prioritize research and health care policy initiatives. Therefore, we examined rates of HF hospitalizations and re-hospitalizations within a large, multicenter CKD population and evaluated the association between burden of HF hospitalizations and subsequent progression of CKD and all-cause death.

METHODS

STUDY POPULATION. We studied 3,939 individuals with mild to severe CKD enrolled in the CRIC (Chronic Renal Insufficiency Cohort) study. The CRIC study recruited participants with mild to severe CKD, defined as an estimated glomerular filtration rate

(eGFR) of 20 to 70 ml/min/1.73 m², between June 2003 and August 2008 at 7 clinical centers across the United States (Ann Arbor/Detroit, Michigan; Baltimore, Maryland; Chicago, Illinois; Cleveland, Ohio; New Orleans, Louisiana; Philadelphia, Pennsylvania; and Oakland, California) (11,12). All study participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites. Detailed inclusion and exclusion criteria were previously described (11). Participants on maintenance dialysis or with a kidney transplant were not included at cohort entry. CRIC also excluded participants with advanced HF, defined as New York Heart Association functional class III or IV, on cohort entry. All participants enrolled in the study had annual in-person study visits when detailed interviews were conducted, brief physical examinations performed, laboratory measures done, and cardiovascular testing performed. In addition to the annual study visits, all CRIC participants were contacted every 6 months to obtain updated information on medication use and interim updates to medical history and/or hospitalizations.

For the present study, we excluded 148 participants who were missing urine albumin-to-creatinine ratio (ACR) measurements at the baseline study visit, which left a final analytical cohort of 3,791 participants.

MEASURES OF KIDNEY FUNCTION AND DEFINITION OF CKD PROGRESSION. We evaluated 2 measures of kidney function, eGFR and urine ACR, which were measured via standardized methods at annual research study visits. Serum creatinine was measured using an enzymatic method on an Ortho Vitros 950 (Ortho Clinical Diagnostics, Raritan, New Jersey) at the CRIC central laboratory and standardized to isotope dilution mass spectrometry traceable values (13,14). eGFR was calculated using serum creatinine and the CKD-EPI equation (15) and categorized as ≥45, 30 to 44, and <30 ml/min/1.73 m² (16). Urine ACR was quantified from 24-h urine samples and categorized as <30, 30 to 299, or >300 mg/g (16).

CKD progression was defined as either 50% decline in eGFR or progression to ESRD. All eGFR measures

were calculated from serum creatinine obtained at annual study visits. ESRD was defined as undergoing long-term dialysis or a kidney transplantation and was identified through participant self-report, medical records review, and data from the U.S. Renal Data System.

HF HOSPITALIZATIONS. Hospitalizations for HF were adjudicated from study entry through May 2014. Hospitalizations for HF were identified by asking study participants semi-annually if they were hospitalized, and electronic health records from selected hospitals or health care systems were also queried for qualifying encounters. The first 30 discharge codes were identified for all hospitalizations, and codes relevant to HF resulted in retrieval of medical records by study personnel for centralized adjudicated review. At least 2 study physicians reviewed all possible HF events and deaths using medical records and adjudicated for clinical HF based on clinical symptoms, radiographic evidence of pulmonary congestion, physical examination of the heart and lungs, and, when available, central venous hemodynamic monitoring data and echocardiographic imaging. HF was confirmed when both reviewers agreed upon a "probable" or "definite" occurrence of HF based on modified clinical Framingham criteria (17).

In addition to quantifying the number of HF hospitalizations, we also evaluated the number of HF readmissions within 30 days during all available CRIC follow-up. In addition, we evaluated the total number of HF hospitalization days during CRIC follow-up. This was calculated from length of stay data available for each HF hospitalization.

In secondary analyses, we stratified the outcome of HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). HFpEF was defined as an ejection fraction (EF) ≥40% and HFrEF was defined as EF <40%. EF was ascertained from echocardiograms performed during the index hospitalization for clinical purposes. If an echocardiogram was not performed during the index hospitalization, we used the EF quantified from an ambulatory CRIC research echocardiogram ≤1 year before or after the index HF hospitalization. Research echocardiograms in CRIC were performed at multiple time points, including years 1, 4, and 7, as well as when the participant progressed to eGFR <20 ml/min/1.73 m². Our previous work showed that EFs in the CRIC study were generally stable over time (18,19). Among a total of 1,774 first (during CRIC follow-up) or recurrent HF hospitalizations, 1,127 (64%) had EFs available through either a clinical echocardiogram during the index hospitalization or a CRIC research echocardiogram.

ALL-CAUSE MORTALITY. Death was ascertained from study entry through May 2014. Deaths were identified from reports from next of kin, retrieval of death certificates or obituaries, review of hospital or outpatient records, and searching Social Security Death vital status and state death certificate files, if available.

COVARIATES. At the baseline study visit, participants provided information on their sociodemographic characteristics, medical history, medication usage, and lifestyle behaviors. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other. History of cardiovascular disease was determined by self-report and included history of HF, myocardial infarction, coronary revascularization, or stroke. Anthropometric measurements and blood pressure were assessed using standard protocols (20). Body mass index was calculated as weight in kilograms divided by height in meters squared. Diabetes mellitus was defined as a fasting glucose of >126 mg/dl, a nonfasting glucose of >200 mg/dl, or use of insulin or other antidiabetic medication. Cardiovascular medications, including diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and β-blockers, were ascertained by detailed review with participants at baseline.

STATISTICAL ANALYSES. All analyses were performed using R 3.4.0 (R Foundation for Computing, Vienna, Austria). We first described characteristics of study participants across categories based on number of HF hospitalizations per year. We then calculated the crude rates (per 100 person-years) of HF hospitalizations and 30-day HF re-hospitalizations overall and by categories of eGFR and urine ACR individually and collectively; 95% confidence intervals (CIs) were obtained using bootstrap methods. Participants were censored at death, loss to follow-up, study withdrawal, or end-of-study follow-up (through May 2014). Rate ratios for HF hospitalizations and 30-day re-hospitalizations were calculated using Poisson regression models with Huber-White robust SEs. We serially adjusted for age, sex, race/ethnicity in model 1; adjusted for diabetes, history of cardiovascular disease, use of statins, current smoking, systolic blood pressure, and body mass index in model 2; and adjusted for use of cardiovascular medications (diuretics, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, and β-blockers) in model 3. In secondary analyses, we repeated these analyses by examining rates and rate ratios for HFrEF and HFpEF among participants who had available data on EFs.

TABLE 1   Baseline Characteristics, by Annual HF Hospitalization Rate Among Participants With CKD

	No HF Events/Year (n = 3,115)	>0-1 Event/Year (n = 607)	> 1 Event/Year (n = 69)
Age, yrs	57.2 ± 11.1	60.2 ± 9.5	61.6 ± 9.2
Women	1,425 (46)	265 (44)	25 (36)
Race/ethnicity			
Non-Hispanic white	1,383 (44)	207 (34)	14 (20)
Non-Hispanic black	1,230 (39)	305 (50)	45 (65)
Hispanic	374 (12)	78 (13)	8 (12)
Other	128 (4)	17 (3)	2 (3)
eGFR, ml/min/1.73 m^2	45.6 ± 15.1	38.4 ± 13.0	38.4 ± 13.4
Urine albumin to creatinine ratio, µg/mg	37.3 (7.3–335.4)	309.6 (33.4–1405.1)	210.6 (42.6–944.9)
Diabetes mellitus	1,348 (43)	434 (71)	48 (70)
Previous cardiovascular disease	872 (28)	346 (57)	51 (74)
Previous heart failure	191 (6)	140 (23)	38 (55)
Previous atrial fibrillation	433 (14)	177 (29)	32 (46)
Current smoker	399 (13)	83 (14)	13 (19)
Body mass index, kg/m^2	31.6 ± 7.6	34.3 ± 8.4	32.9 ± 7.1
Systolic blood pressure, mm Hg	126.7 ± 21.4	136.0 ± 23.3	133.7 ± 24.4
Diastolic blood pressure, mm Hg	71.7 ± 12.4	70.0 ± 13.8	69.8 ± 15.6
Hemoglobin, g/dl	12.8 ± 1.7	12.0 ± 1.8	11.9 ± 1.7
LDL cholesterol, mg/dl	103.4 ± 34.8	98.7 ± 36.5	96.2 ± 40.3
HDL cholesterol, mg/dl	48.0 ± 15.7	45.4 ± 14.3	44.2 ± 13.2
ACE inhibitor/ARBs	2,076 (67)	463 (76)	49 (71)
Diuretics	1,710 (55)	478 (79)	57 (83)
Loop diuretics	1,001 (32)	374 (62)	55 (80)
Thiazide diuretics	905 (29)	155 (26)	8 (12)
Beta-blockers	1,387 (45)	412 (68)	52 (75)
Calcium-channel blockers	1,173 (38)	320 (53)	33 (48)
Aldosterone receptor antagonists	105 (3)	33 (5)	16 (23)
Statins	1,621 (52)	412 (68)	47 (68)
FGF-23, RU/ml	134.2 (90.9–212.6)	207.7 (133.9–346.5)	289.6 (148.4–456.2)
Serum phosphorus, mg/dl	3.7 ± 0.6	3.9 ± 0.8	3.9 ± 0.6
Total parathyroid hormone, pg/ml	50.1 (33.0–82.6)	72.9 (45.8–120.0)	87.7 (47.5–120.5)
Left ventricular ejection fraction, %	55.2 ± 7.5	50.2 ± 11.0	43.9 ± 14.2
Left ventricular mass index, g/m^2	49.0 ± 12.5	61.4 ± 15.0	68.9 ± 16.7
NT−pro-BNP, pg/ml	109.1 (39.3–285.7)	432.2 (175.5–972.8)	808.1 (428.9–2,675.6)
High sensitive troponin T, pg/ml	13.1 (8.0–22.7)	25.4 (15.7–41.4)	35.0 (18.1–50.2)

Values are mean ± SD, n (%) and median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; FGF = fibroblast growth factor; HDL = high-density lipoprotein; HF = heart failure; LDL = low-density lipoprotein; NT−pro-BNP = N-terminal pro-B-type natriuretic peptide.

Cox regression was used to model the association of the number of HF hospitalizations within the first 2 years of study follow-up with subsequent risk of CKD progression (defined as eGFR decline by 50% or progression to ESRD) and all-cause mortality. Participants were censored at death, lost to follow-up, study withdrawal, or at the end-of-study follow-up (through May 2014), whichever came first. For these analyses, time to follow-up started at year 2 and only included participants who did not experience the event within the first 2 years of the study or were not censored during this time (n = 2,978 for CKD progression; n = 3,582 for mortality). These models were adjusted for the same covariates as described previously.

In a secondary analysis, we examined the total number of HF hospital days as a predictor. We calculated crude rates and rate ratios of HF hospital days across eGFR and urine ACR categories (similar to the primary analysis). We then used Cox models to examine the association of number of HF hospital days within the first 2 years of study follow-up with subsequent risks of CKD progression and all-cause mortality.

RESULTS

STUDY POPULATION. A total of 1,774 HF hospitalizations during follow-up were observed among 3,791 participants (range 0 to 17 per participant per year), of

CENTRAL ILLUSTRATION Heart Failure in Chronic Kidney Disease

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Unadjusted rates of heart failure (HF) admissions across by level of kidney function among participants with chronic kidney disease (CKD). eGFR = estimated glomerular filtration rate; uACR = urine albumin-to-creatinine ratio.
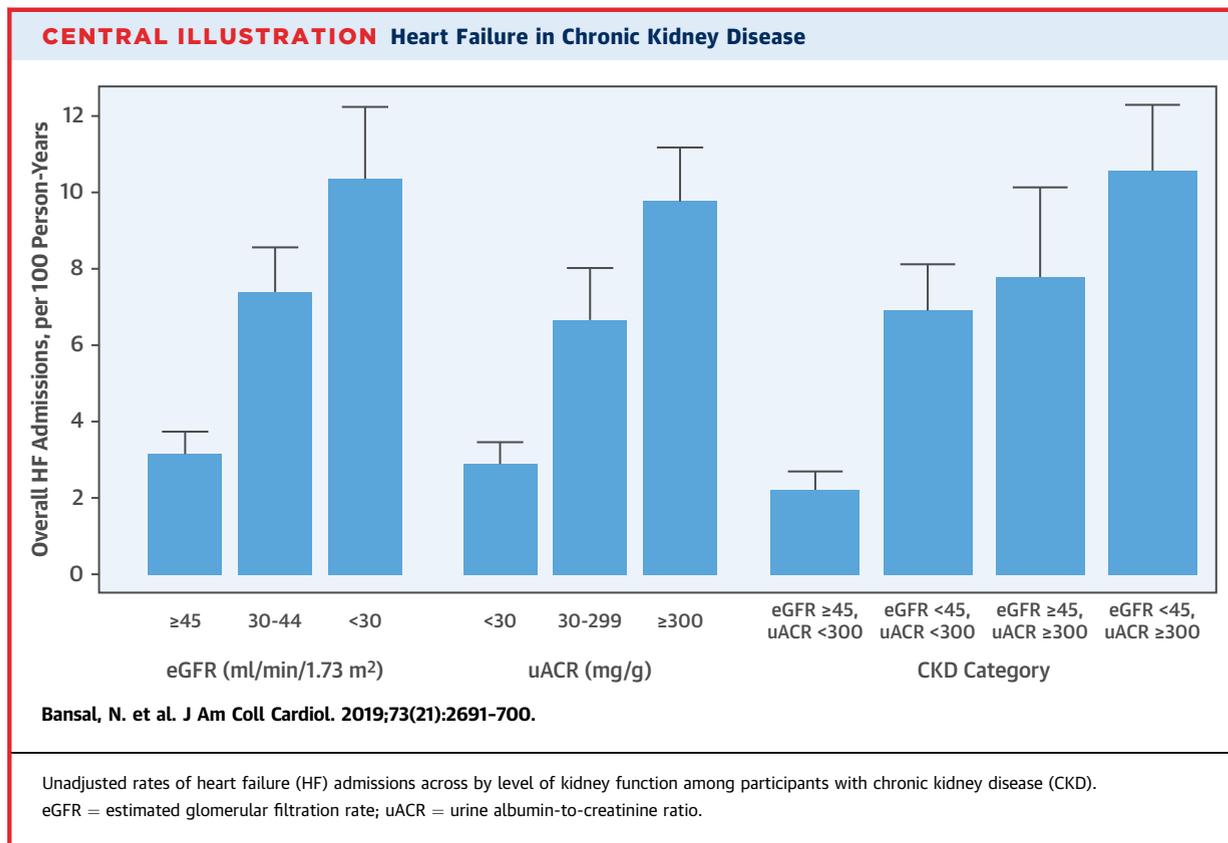
which 702 episodes were incident HF and 1,072 were among participants with known HF. Among study participants, 607 participants had an annual HF hospitalization rate of >0 to 1 HF hospitalization per year, whereas 69 had an annual HF hospitalization rate of >1 HF hospitalizations per year. Compared with participants who remained HF free during CRIC follow-up (n = 3,115), those who had a HF hospitalization were more likely to be older, men, black, have lower baseline eGFR and higher proteinuria, more likely to have diabetes, prevalent HF and a history of cardiovascular disease (including atrial fibrillation), have higher blood pressure, and were more likely to be taking cardiovascular medications (Table 1).

RATES OF HF ADMISSIONS OVERALL AND BY eGFR AND URINE ACR CATEGORIES. Median follow-up for participants who experience at least 1 HF hospitalization was 7.8 years (interquartile range: 5.6 to 9.2 years). The overall crude rate of HF admissions was 5.8 (95% CI: 5.2 to 6.4) per 100 person-years, with higher rates in those with lower baseline eGFR and higher urine ACR (Central Illustration). After adjustment for demographic characteristics, the rate of HF was 2.1- and 2.9-fold higher for participants with eGFRs of 30 to 44 and <30 ml/min/1.73 m², respectively (Table 2). These associations remained robust

with adjustment for cardiovascular risk factors and medication use; rate ratios were 1.7 (95% CI: 1.3 to 2.2) and 2.2 (95% CI: 1.7 to 2.9) for participants with eGFRs of 30 to 44 and <30 ml/min/1.73 m² (vs. >45 ml/min/1.73 m²), respectively.

The crude rate of HF hospitalizations was also higher across categories of higher urine ACRs, with a rate of 9.7 (95% CI: 8.3 to 11.2) among participants with a urine ACR ≥300 mg/g (Central Illustration). In models adjusted for demographic characteristics, the rate of HF hospitalizations was significantly higher among participants with urine ACRs of 30 to 299 or ≥300 mg/g versus urine ACRs <30 mg/g (Table 2). Even after additional adjustment for cardiovascular risk factors and medication use, the rates of HF hospitalization remained significantly higher in those with higher baseline urine ACRs (vs. urine ACR <30 mg/g); they had rate ratios of 1.9 (95% CI: 1.5 to 2.6) and 2.6 (95% CI: 1.9 to 3.5) for urine ACRs 30 to 299 and ≥300 mg/g, respectively.

RATES OF HFrEF AND HFpEF HOSPITALIZATIONS OVERALL AND BY CATEGORIES OF eGFR AND URINE ACR. There were 1,127 participants for whom HF subtype was determined. The rate of the first HF hospitalization during CRIC follow-up was 8.3 (95% CI: 7.1 to 9.5) per 1,000 person-years (213 events)

TABLE 2 Rates and Rate Ratios of HF admissions Across Levels of Kidney Function Among Participants With CKD

	No. at Risk (Total No. of Events)	Crude Rate, per 100 Patient-Years (95% Bootstrapped CIs)	Rate Ratio (95% CI)		
			Model 1	Model 2	Model 3
Overall	3,791 (1,706)	5.8 (5.2–6.4)			
eGFR stage, ml/min/1.73 m²					
eGFR ≥45	1,714 (437)	3.1 (2.5–3.7)	1.0 (ref)	1.0 (ref)	1.0 (ref)
eGFR 30–44	1,379 (766)	7.4 (6.2–8.6)	2.1 (1.7–2.7)	1.9 (1.5–2.4)	1.7 (1.3–2.2)
eGFR <30	698 (503)	10.3 (8.4, 12.2)	2.9 (2.2–3.8)	2.5 (1.9–3.3)	2.2 (1.7–2.9)
Albuminuria, mg/g					
uACR <30	1,629 (383)	2.9 (2.3–3.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
uACR 30 to <300	1,001 (510)	6.6 (5.3–8.0)	2.3 (1.8–3.1)	1.9 (1.4–2.6)	1.9 (1.5–2.6)
uACR ≥300	1,161 (813)	9.7 (8.3–11.2)	3.8 (3.0–4.9)	2.6 (2.0–3.5)	2.6 (1.9–3.5)
CKD category					
eGFR ≥45, uACR <300	1,401 (253)	2.2 (1.7–2.7)	1.0 (ref)	1.0 (ref)	1.0 (ref)
eGFR <45, uACR <300	1,229 (640)	6.9 (5.7–8.1)	2.7 (2.0–3.6)	2.5 (1.9–3.4)	2.3 (1.7–3.0)
eGFR ≥45, uACR >300	313 (184)	7.7 (5.4–10.1)	4.1 (2.8–6.1)	2.9 (1.9–4.4)	2.9 (1.9–4.4)
eGFR <45, uACR >300	848 (629)	10.6 (8.8–12.3)	4.6 (3.5–6.2)	3.2 (2.3–4.4)	3.0 (2.2–4.1)

All rate ratios with p < 0.05. Model 1: age, sex, and race/ethnicity. Model 2: model 1 + diabetes, history of cardiovascular disease, use of lipid-lowering medications, smoking, systolic blood pressure, and body mass index. Model 3: model 2 + use of diuretics, ACE inhibitors/ARBs and, β-blockers.

CI = confidence interval; uACR = urine albumin-to-creatinine-ratio; other abbreviations as in Table 1.

for HFrEF and 11.2 (95% CI: 9.9 to 12.5) per 1,000 person-years for HFpEF (288 events). The rates of all (first and recurrent) HFrEF hospitalizations were 19.4 (95% CI: 16.3 to 22.5) per 1,000 person-years (568 events), and rates for HFpEF hospitalizations were 17.8 (95% CI: 15.6 to 20.0) per 1,000 person-years (522 events).

After accounting for differences in demographic characteristics, cardiovascular risk factors, and medication use, there were graded, higher adjusted rates of both HFrEF and HFpEF hospitalizations with lower eGFRs and higher urine ACRs, with similar rate ratios in the primary analysis (Online Tables 1 and 2).

THIRTY-DAY READMISSIONS FOR HF. Among 702 participants with incident HF during CRIC follow-up, 67 (9.5%) were readmitted for HF within 30 days compared with 179 (16.7%) of 1,072 participants with prevalent HF. Rates of recurrent HF hospitalizations increased across categories of lower eGFRs and higher urine ACRs (Online Figure 1, Table 3). In models that adjusted for demographic characteristics, cardiovascular risk factors, and medication use, the rate ratio for re-hospitalization within 30 days was 2- to 3-fold higher in participants with the lowest eGFR and highest urine ACR; the rate ratios were 2.6 (95% CI: 1.4 to 4.7) for eGFR <30 ml/min/1.73 m² and 3.6 (95% CI: 1.8 to 7.3) for urine ACR ≥300 mg/g.

NUMBER OF HF HOSPITALIZATIONS WITHIN 2 YEARS AND SUBSEQUENT CKD PROGRESSION. There were 884 participants who experienced a 50% decline in eGFR or developed ESRD during follow-up. In fully-adjusted models, participants who experienced HF hospitalization within the first 2 years of follow-up had higher adjusted rates of subsequent CKD progression (1 hospitalization: HR: 1.93; 95% CI: 1.40 to 2.67; ≥2 hospitalizations: HR: 2.14; 95% CI: 1.30 to 3.54) (Table 4).

NUMBER OF HF HOSPITALIZATIONS WITHIN 2 YEARS AND SUBSEQUENT ALL-CAUSE MORTALITY. A total of 819 participants died during follow-up. After adjustment for potential confounders, participants who experienced a HF hospitalization during the first 2 years of follow-up had a graded, higher risk of subsequent all-cause death. Participants with 1 HF hospitalization had a >2-fold increased adjusted rate of death (HR: 2.20; 95% CI: 1.71 to 2.84) and those with ≥2 HF hospitalizations had a 3-fold higher adjusted rate (HR: 3.06; 95% CI: 2.23 to 4.18) (Table 4).

NUMBER OF HF HOSPITALIZATION DAYS AND CLINICAL OUTCOMES BY eGFR AND URINE ACR. In secondary analyses, we evaluated burden of HF hospitalization (based on number of hospital days) and outcomes by level of kidney function and damage. The overall rate of HF hospital days was 36.9 (95% CI: 32.2 to 41.7) per 100 person-years. Lower baseline eGFRs and higher baseline urine ACRs were associated with graded, increased rates of HF hospital days (Online Figure 2). The rate of HF hospital days was highest for participants with both low eGFRs and higher urine ACRs (60.6 per 100 person-years; 95% CI: 48.8 to 72.4). In models adjusted for demographics, there was a 2- to 4-fold increase in rate

TABLE 3 Rates of 30-Day HF Re-Hospitalizations Across Level of Kidney Function Among Participants With CKD

	No. of Participants	No of HF Hospitalizations	Total No. of 30-day HF Rehospitalizations	Crude Rate, per 100 Patient-Years (95% CI)	Model 1	Model 2	Model 3
Overall	3,791	1,706	238	0.8 (0.6-1.0)			
eGFR stage, ml/min/1.73 m²							
eGFR ≥45	1,714	437	53	0.4 (0.2-0.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
eGFR 30-44	1,379	766	111	1.1 (0.7-1.4)	2.5 (1.5-4.1)	2.2 (1.3-3.6)	1.9 (1.2, 3.1)
eGFR <30	698	503	74	1.5 (0.8-2.2)	3.4 (1.9, 6.2)	3.0 (1.6, 5.6)	2.6 (1.4, 4.7)
Albuminuria, mg/g							
uACR <30	1,629	383	43	0.3 (0.2-0.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)
uACR 30 to <300	1,001	510	80	1.0 (0.6-1.5)	3.2 (1.8-5.5)	2.7 (1.5-4.7)	2.7 (1.5, 4.8)
uACR ≥300	1,161	813	115	1.4 (0.9-1.9)	4.6 (2.7-7.7)	3.6 (1.8, 7.1)	3.6 (1.8, 7.3)
CKD category							
eGFR ≥45, uACR <300	1,401	253	29	0.2 (0.1-0.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)
eGFR <45, uACR <300	1,229	640	94	1.0 (0.7-1.4)	3.4 (1.9-6.1)	3.2 (1.8-5.7)	2.8 (1.6, 4.9)
eGFR ≥45, uACR >300	313	184	24	1.0 (0.4-1.6)	4.5 (2.1-9.7)	3.6 (1.6-8.2)	3.8 (1.6, 8.7)
eGFR <45, uACR >300	848	629	91	1.5 (0.9-2.2)	5.5 (3.0-10.2)	4.2 (2.0-8.8)	3.8 (1.8, 8.1)

All rate ratios with p < 0.05. Model 1: age, sex, and race/ethnicity. Model 2: model 1 + diabetes, history of cardiovascular disease, use of lipid-lowering medications, smoking, systolic blood pressure, and body mass index. Model 3: model 2 + use of diuretics, ACEi/ARB, and β-blockers.

Abbreviations as in **Tables 1 and 2**.

of HF hospital days across categories of lower eGFRs and higher urine ACRs (Online Table 3). These associations persisted after further adjustment for cardiovascular risk factors and medication use; the rate ratios were 1.7 (95% CI: 1.2 to 2.4) and 2.3 (95% CI: 1.6 to 3.3) for participants with eGFRs 30 to 44 and <30 ml/min/1.73 m² (vs. >45 ml/min/1.73 m²), respectively. Similarly, the rates of HF hospital days remained significantly higher in those with higher urine ACRs (vs. urine ACRs <30 mg/g); the rate ratios were 1.9 (95% CI: 1.4 to 2.6) and 2.5 (95% CI: 1.8 to 3.5) for urine ACRs 30 to 299 and ≥300 mg/g, respectively (Online Table 3).

When we examined the total burden of HF hospitalization days in the first 2 years of follow-up with clinical outcomes, we found a strong association of a higher number of HF hospital days with higher subsequent risk of CKD progression and all-cause mortality (Online Table 4). Compared with participants with no HF hospital days in the first 2 years of follow-up, participants who had ≥8 HF hospital days had a 90% higher rate (HR: 1.90; 95% CI: 1.15 to 3.15) and nearly 3-fold higher rate (HR: 2.91; 95% CI: 2.17 to 3.90) of CKD progression and death, respectively, in fully-adjusted models (Online Table 4).

TABLE 4 Association of Number of HF Episodes in the First 2 Years of Follow-Up With Risk of CHD Progression and All-Cause Mortality Among Participants With CKD

			HR (95% CI)			
No. of HF Events, Years 0-2	No. at Risk	No. of Events	Unadjusted	Model 1	Model 2	Model 3
Decline in eGFR by 50% or progression to ESRD						
0	2,868	827	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1	80	41	3.27 (2.39- 4.48)	2.61 (1.90-3.59)	1.98 (1.43-2.73)	1.93 (1.40-2.67)
≥ 2	30	16	3.77 (2.30-6.19)	3.41 (2.08-5.60)	2.32 (1.41-3.83)	2.14 (1.30-3.54)
All-cause mortality						
0	3380	698	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
1	135	74	3.48 (2.74-4.43)	3.41 (2.68-4.35)	2.35 (1.83-3.03)	2.20 (1.71-2.84)
≥ 2	67	47	6.03 (4.48-8.11)	5.81 (4.31-7.83)	3.38 (2.48-4.61)	3.06 (2.23-4.18)

All hazard ratios (HRs) with p < 0.05. Model 1: age, sex, and race/ethnicity. Model 2: model 1 + diabetes, history of cardiovascular disease, use of lipid-lowering medications, smoking, systolic blood pressure, and body mass index. Model 3: model 2 + use of diuretics, ACE inhibitors/ARBs, and β-blockers.

ESRD = end-stage renal disease; other abbreviations as in **Tables 1 and 2**.

DISCUSSION

In this large, prospective cohort of adults with CKD, the overall rate of HF hospitalizations was high at 5.8 hospitalizations per 100 person-years of follow-up and even higher among participants with eGFRs <30 ml/min/1.73 m^2 or urine ACRs ≥300 mg/g (Central Illustration). The rate of first hospitalization for HFpEF was higher than that of HFrEF, but the rates of all hospitalizations were similar between HFpEF and HFrEF. Overall, >1 in 5 patients were readmitted for HF within 30 days. Greater burden of HF hospitalizations or HF hospital days in the first 2 years of follow-up was associated with a 2- to 3-fold increased risk of CKD progression and death. Collectively, these data provided unique and comprehensive evidence of the tremendous burden of HF in CKD and the independent association of HF with subsequent renal outcomes and survival.

In our study, participants with CKD experienced 3 to 10 HF hospitalizations per 100 person-years, depending on levels of eGFR and urine ACR, which were substantially greater than that seen in the general population. In the Nationwide Inpatient Sample, the rates of primary HF hospitalizations were 0.5 per 100 person-years and 1.5 per 100 person-years for secondary diagnosis of a HF hospitalization in 2009 (21). Among Medicare beneficiaries, the rates of HF hospitalizations were 0.4 per 100 person-years in 2004, which was a significant increase over the previous 25 years (22). Although data from U.S. Renal Data System reported that the rate of hospitalization for any cardiovascular cause was 46 per 100 person-years for ESRD patients (10), limited data exist for HF-specific hospitalizations in those with CKD. Our study provided novel data on this important public health burden in CKD.

There are fewer data on the rates of HF subtypes in patients with CKD. We found that the rates of first hospitalization during follow-up in CRIC participants was higher for HFpEF than the rates for HFrEF. However, the rates of all hospitalizations for HFpEF and HFrEF were similar, which suggested that although HFpEF might be more prevalent in CKD, HFrEF patients might be more likely to have recurrent HF hospitalizations. In the Framingham Heart Study of participants with and without CKD, microalbuminuria was only associated with HFrEF, and low eGFR was associated with HF overall, but was not associated with HFpEF or HFrEF (23). In a study of patients from multiple health care delivery systems who participated in the Cardiovascular Research Network, the association of eGFR with risk of a HF hospitalization or mortality was similar among patients with known HFpEF or HFrEF (24). Because of the different pathophysiology of HFrEF versus HFpEF and the lack of proven therapies for HFpEF, our findings supported the need to identify more effective treatment strategies for both HFrEF and HFpEF in patients with CKD.

Rates of 30-day readmissions for HF were also high at 20.6% overall and 27% among participants with known HF. The observed rates seen in our CKD population were greater than those observed in the general population. In a study of the ARIC (Atherosclerosis Risk In Communities) cohort, approximately 8% of participants with known HF were rehospitalized for HF within 30 days (25). Among Medicare fee-for-service beneficiaries age 65 years or older, the median 30-day readmission rate for any cause (not specifically for HF as in our study) was 24.4% after HF admission (26). Previous studies tested strategies to decrease rates of recurrent hospitalizations, such as earlier physician visits postdischarge, target education about medication and diet adherence, and support from an ambulatory HF care team (27-30). These strategies have not been specifically tested in patients with CKD and may be able to reduce the excessive burden of recurrent HF hospitalizations in this high-risk population.

Our study also found that a higher number of HF hospitalizations and HF hospital days was independently associated with a greater risk of CKD progression. Of participants hospitalized for HF, 52% experienced significant CKD progression. In a previous study of patients with CKD in Canada, rates of ESRD were 4- to 14-fold higher among patients with previous HF hospitalizations (31). In a study of patients with normal kidney function, HF was associated with a 2-fold greater risk of incident CKD (32). Our findings supported and materially expanded on these associations in a large U.S. population of patients with CKD. There are several possibilities to explain these findings. HF leads to hemodynamic changes, endothelial injury, inflammation, and other processes that may further injure the kidneys (33-35). Thus, further studies are needed to explore therapies to help preserve kidney function after an acute HF hospitalization.

We found a graded, strong association between greater burden of HF and the risk of death. Among participants with ≥2 HF hospitalizations, the risk of all-cause death was 3-fold higher compared with participants who did not experience HF. Among participants in our study who experienced a HF hospitalization, 60% died during follow-up. A previous study using data from Medicare fee-for-service beneficiaries reported that all-cause mortality rates after

a HF hospitalization was 11.7% overall (36). Another study from the same population found that reductions in rates of HF hospitalizations were associated with a reduction in post-discharge mortality (37). Because of the even higher proportion of post-HF hospitalization deaths in patients with CKD, interventions to improve post-HF care should also be prioritized in this high-risk population.

These findings have important implications in the management of patients with CKD. Primary and secondary treatment of HF in CKD should be a public health priority. The high burden of HF hospitalizations in CKD likely contributes to the higher cost of care observed for the treatment of CKD and cardiovascular disease. Therefore, there is a need to improve treatment of HF in patients with known disease. Strategies should include better implementation of current therapies that may often be withheld in patients with CKD (e.g., renin-angiotensin-aldosterone system inhibitors), development of novel therapies that may target CKD-specific HF risk factors, incentives to improve the transition between inpatient and outpatient HF care in CKD to reduce the risk of readmissions, and improved patient education about HF in CKD.

STUDY STRENGTHS AND LIMITATIONS. Our study had several strengths. We studied a large, multicenter, well-characterized, U.S.-based CKD population to study cardiovascular complications with extensive longitudinal follow-up. All HF hospitalizations that occurred during CRIC follow-up were adjudicated using standardized criteria. We recognized a few limitations as well. We were not able to determine whether acute kidney injury occurred during the HF hospitalizations, which might have contributed to subsequent CKD progression. EF data to determine HF subtype were not available in all participants. Kidney biopsy data on the cause of the CKD were not available in all participants; however, we did control for primary contributors of CKD (e.g., diabetes) in our statistical models. We did not have detailed data on whether certain medications (e.g., renin-angiotensin-aldosterone system inhibitors or diuretics) were held or doses adjusted after the

hospitalization because medication use was ascertained every 6 months per the CRIC study protocol. Although the CRIC adjudication process was known to capture >90% of hospitalizations, it was possible that some HF hospitalizations were missed. This was a clinic-based population of research volunteers, so the results might not be generalizable to all CKD patients. Because this was an observational study, we could not determine causality, and we could not exclude reverse causality.

CONCLUSIONS

In a large U.S. CKD population, the rates of HF hospitalizations and 30-day re-hospitalization were high, with even higher rates across categories of lower eGFR and higher urine ACR. HF hospitalizations were independently associated with 2- to 3-fold higher rates of CKD progression and death. Prevention and treatment of HF should be a major priority to improve clinical outcomes in patients with CKD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Compared with patients with preserved renal function, those with CKD (defined as eGFR <45 ml/min/1.73 m^2) or microalbuminuria (urine ACR >30 mg/g) hospitalized with HF are at high risk of recurrent HF, re-admission for HF, and death within 2 years.

TRANSLATIONAL OUTLOOK: Additional research is needed to improve outcomes of HF in patients with CKD.

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