


Retrospective analysis of SGLT2 inhibitors in heart failure with preserved ejection fraction

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Abstract

Aims Heart failure (HF) is one of the leading causes of cardiovascular morbidity and mortality. HF with preserved ejection fraction (HFpEF), or diastolic failure, accounts for half of all HF cases and differs from HF with reduced ejection fraction (HFrEF). Patients with HFpEF are typically older, female, and commonly seen with chronic kidney disease (CKD), one of the leading independent risk factors for mortality in these patients. Unfortunately, drugs that had shown significant improvements in mortality in HFrEF have not shown similar benefits in HFpEF. Recently, sodium glucose transporter 2 inhibitors (SGLT2i) have been shown to reduce cardiovascular morbidity and mortality in HFrEF patients and slow down CKD progression. This study aimed to elucidate the impact of this drug class on mortality and risk of end stage renal disease in patients with HFpEF, which is currently unclear.

Methods and results We retrospectively analysed the Research Data Warehouse containing electronic health records from de-identified patients ($n = 1\,266\,290$) from the University of Mississippi Medical Center from 2013 to 2022. HFpEF patients had an average follow-up of 4 ± 2 years. Factors associated with increased all-cause mortality during HFpEF included age, male sex, and CKD. Interestingly, the only treatments associated with significant improvements in survival were angiotensin converting enzyme inhibitors/angiotensin receptor blockers and SGLT2i, regardless of CKD or diabetes status. Additionally, SGLT2i use was also associated with significant decrease in the risk of end stage renal disease.

Conclusions Our results support the use of SGLT2i in an HFpEF population with relatively high rates of hypertension, CKD, and black race and suggests that improvements in mortality may be through preserving kidney function.

Keywords Heart failure with preserved ejection fraction; Heart failure; SGLT2 inhibitors; Antihypertensive therapy; Chronic kidney disease; End stage renal disease

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Introduction

Heart failure (HF) is growing in the United States and is estimated to have a 5 year mortality of 40%.¹ HF can present with preserved ejection fraction (HFpEF) or diastolic failure, which differs from HF with reduced ejection fraction (HFrEF) epidemiologically and mechanistically. HFpEF accounts for half of all HF cases with similar mortality as HFrEF. HFpEF patients usually present with increased myocardial stiffness, hypertension, left ventricular concentric hypertrophy, and impaired diastolic function. Further, approximately 50–60% of HFpEF patients have chronic kidney disease (CKD),² which is

a significant independent predictor of mortality in these patients.³

Hypertension is the most important attributable risk factor for diastolic dysfunction, with most of the current treatments being antihypertensive therapies. Treatments that have shown significant efficacy in HFrEF include beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), diuretics, mineralocorticoid antagonists (MRA), vasodilators, and angiotensin receptor blocker-neprilysin inhibitors (ARNI). However, these therapies have not convincingly shown a reduction in cardiovascular morbidity or mortality in HFpEF patients.

Sodium glucose transporter 2 inhibitors (SGLT2i) have been classically used as an antidiabetic drug due to its ability to increase glucose excretion and other favourable effects on body weight, blood pressure, and kidney disease progression.⁴ Indeed, SGLT2i have been shown to significantly slow renal disease and reduce the risk of end stage renal disease (ESRD) in patients with type 2 diabetes (T2D) and in HFpEF patients independent of diabetes.^{5–7} In fact, in 2021, the FDA approved the SGLT2i dapagliflozin in CKD patients, including non-diabetics, to reduce CKD progression and death.^{8,9} In the more recent EMPEROR-Preserved trial, approximately 2 years of SGLT2i treatment was shown to significantly slow down the decline in renal function and reduce HF hospitalizations in HFpEF patients.¹⁰ However, SGLT2i has not yet been shown to significantly improve mortality or risk of ESRD in patients with HFpEF, leaving the utility of this treatment and its impact on renal disease progression in this population unclear.¹⁰ Further, SGLT2i use in the black population has not been well characterized and requires further investigation. Therefore, we used a large Research Data Warehouse (RDW) containing over 1 million patients and 30 million unique encounters to investigate the impact of common HF drugs on the all-cause mortality in patients diagnosed with HFpEF. We hypothesized that SGLT2i would reduce mortality in these patients through renal protective mechanisms and that this effect persists regardless of race.

Methods

Study population

The RDW contains >45 million electronic health records (EHR) from >1 million unique patients from the University of Mississippi Medical Center (UMMC), a large academic health science centre. Patient data are de-identified and are extracted from the EHR system, Epic, and are exempt from Institutional Review Board approval.¹¹ Data from 1 January 2013 to 31 December 2021 were retrieved from patients ≥18 years old. There were 35 803 patients with an HF diagnosis with 6 016 566 unique encounters. Of these, 5569 patients had a positive diagnosis for HFpEF or diastolic dysfunction without any systolic HF or HFpEF diagnoses or record of ejection fraction <40% at baseline or throughout follow-up. Of these HFpEF patients, 2368 patients had at least 20 visits over the course of a year or longer at UMMC clinics to select patients that were dependent on UMMC for regular medical care. Clinical diagnoses for hypertension, CKD, ESRD, T2D, myocardial infarction (MI), proteinuria, and pulmonary hypertension were also queried.

HFpEF therapies of interest included BBs (carvedilol 3–6 mg; metoprolol 25–200 mg; labetalol 100–300 mg; nadolol 20–40 mg; nebivolol 2.5–20 mg; propranolol 10–60 mg;

sotalol 80 mg), ARNI (sacubitril/valsartan 24/26 mg to 97/103 mg), MRA (eplerenone 25–50 mg; spironolactone 25–100 mg), vasodilators (amlodipine 2.5–10 mg; verapamil 120–240 mg; diltiazem 30–300 mg; hydralazine 10–100 mg; minoxidil 2.5–10 mg; nifedipine 20–90 mg), diuretics (chlorthalidone 25–50 mg; chlorothiazide 250–500 mg; hydrochlorothiazide 12.5–25 mg; indapamide 2.5 mg; metolazone 2.5–10 mg), and ACEi/ARB (benazepril 10–40 mg; valsartan 40–320 mg; candesartan 4–16 mg; captopril 6–25 mg; enalapril 2.5–20 mg; irbesartan 150–300 mg; lisinopril 2.5–40 mg; losartan 25–100 mg; olmesartan 20–40 mg; quinapril 20–40 mg; ramipril 2.5–10 mg; telmisartan 40–80 mg; valsartan 40–320 mg), and SGLT2i (canagliflozin 100–300 mg; dapagliflozin 5–10 mg; empagliflozin 5–25 mg; ertugliflozin 5 mg). Patients taking a combination of the above-mentioned formulations were flagged as taking both classes. Only patients that were prescribed a drug for at least 90 days during the follow-up were considered for a given drug class.

Statistical analysis

Baseline characteristics were summarized as means ± standard deviations and compared with *t*-tests for continuous factors. Categorical factors are summarized as percentages and compared using Fisher's exact test. Survival and ESRD event curves were plotted and stratified by each drug using the Kaplan–Meier method and compared using a Cox proportional hazards regression model. Models measuring survival time were adjusted for sex, age, and race along with the presence of hypertension, T2D, and CKD. Models measuring time to first ESRD diagnosis included these same adjusters except for presence of CKD due to perfect correlation with the outcome. The proportional hazards assumption was assessed for each model fit, and results were reported in the form of hazard ratios (HRs) with their respective 95% confidence intervals (CIs) and *P*-values. Similarly, survival curves were plotted with bands representing 95% CIs. We considered *P*-values <0.05 to indicate a statistically significant difference. All statistical analyses were performed with R version 4.2.1.

Results

Of the 1 266 290 total patients in the RDW, 2368 patients had a positive diagnosis for HFpEF or diastolic HF without any systolic HF or HFpEF diagnoses or record of ejection fraction <40%. These patients were mostly female (63%), obese (35 ± 10 kg/m² body mass index) had normal ejection fraction (65%) and an average of 177 ± 196 total UMMC visits over an average follow-up of 4 ± 2 years (*Table 1*). This population was also associated with a relatively high prevalence of hy-

Table 1 Baseline characteristics of heart failure with preserved ejection fraction patients stratified by race and chronic kidney disease.

Variable	All (n = 2368)	White		Black	
		HFpEF (n = 488)	HFpEF + CKD (n = 490)	HFpEF (n = 505)	HFpEF + CKD (n = 850)
Follow-up (year)	4.0 ± 2	3.7 ± 2	3.6 ± 2	4.1 ± 2 [#]	4.4 ± 2 ^{*#}
Visits (#)	177 ± 196	125 ± 127	186 ± 187*	130 ± 119	229 ± 249 ^{*#}
Mortality (%)	16	12	23*	11	18 ^{*#}
Hospitalization (%)	75	65	82*	63	84*
Age (year)	64 ± 14	69 ± 13	70 ± 12	60 ± 14 [#]	60 ± 14 [#]
Female (%)	63	62	53*	74 [#]	63 ^{*#}
SBP (mmHg)	140 ± 24	133 ± 21	134 ± 22	144 ± 23 [#]	148 ± 25 [#]
DBP (mmHg)	76 ± 14	72 ± 13	72 ± 12	81 ± 14 [#]	79 ± 15 [#]
HR (b.p.m.)	77 ± 15	77 ± 16	75 ± 16	80 ± 15	78 ± 13
BMI (kg/m ²)	35 ± 10	32 ± 9	32 ± 9	38 ± 9 [#]	37 ± 9 [#]
EF (%)	65 ± 10	59 ± 13	65 ± 9	63 ± 11	69 ± 7
HTN drugs (#)	2.1 ± 1.5	1.6 ± 1.4	1.9 ± 1.4*	2.2 ± 1.5 [#]	2.5 ± 1.4 ^{*#}
Creatinine (mg/dL)	1.8 ± 2.2	0.9 ± 0.3	1.6 ± 1.5*	0.9 ± 2.2	3.0 ± 3.1 ^{*#}
Co-morbidities					
HTN (%)	87	74	88*	86 [#]	94 ^{*#}
T2D (%)	56	41	53*	50 [#]	71 ^{*#}
MI (%)	22	21	30*	15 [#]	22 ^{*#}
ESRD (%)	18	0	14*	0	42 ^{*#}
Proteinuria (%)	14	1	11*	3 [#]	29 ^{*#}
Pulmonary HTN (%)	19	17	19	16	23*

Note: HFpEF indicates heart failure with preserved ejection fraction. Mortality and hospitalization represent unadjusted rates for any cause. Mean ± SD are shown.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease before or during follow-up; DBP, diastolic blood pressure; EF, ejection fraction; ESRD, end stage renal disease before or during follow-up; HR, heart rate; HTN, hypertension; MI, myocardial infarction previously or during follow-up; SBP, systolic blood pressure; T2D, type 2 diabetes.

*P < 0.05 vs. HFpEF.

[#]P < 0.05 vs. White.

pertension (87%), CKD (58%), and T2D (56%). Overall mortality of the entire cohort was 16%.

As compared with White patients, Black patients with or without CKD were associated with significantly lower age, were more female, and had higher blood pressure, increased body mass index, and increased number of prescribed drugs. Black patients were also associated with higher prevalence of hypertension, T2D, and proteinuria, but lower MI prevalence. In both White and Black populations, CKD was associated with more clinical visits, higher age, and higher plasma creatinine (Table 1). This CKD population was also more likely to be hypertensive, diabetic, proteinuric, and have a MI. Table 2 reports the adjusted Cox models for variables that significantly increased the risk of all-cause mortality. These factors included age (HR 1.30 for each decade), male sex (HR 1.47), and CKD status (HR 1.68). Conversely, race, hypertension status, and diabetic status did not significantly increase the risk of death (Table 2). However, age, sex, race, hypertension status, and diabetes status all increased the risk of ESRD.

HFpEF treatments and their associated risk of ESRD development are shown in Figure 1. BB, vasodilator, and diuretic use was associated with increased risk of ESRD after adjusting for age, sex, race, hypertension status, and diabetes status (HR 1.79, 2.35, and 1.32, respectively). MRA reduced the risk of ESRD (HR 0.69 [95% CI: 0.49–0.98], P = 0.036) (Figure 1). ARNI and ACEi/ARB were not associated with significant changes in ESRD risk.

Figure 2 shows the probability of survival in patients prescribed the different treatments after adjusting for age, sex, race, and status of hypertension, diabetes, and CKD. The inclusion criteria for patients being seen at UMMC for at least 1 year are reflected in the 100% survival at 1 year (Figure 2). ACEi/ARB was associated with a 25% lower risk of death (HR 0.75 [95% CI: 0.60–0.92], P = 0.008). BB, ARNI, MRA, vasodilator, or diuretic use was not associated with any significant effects on all-cause mortality, although there was a trend for ARNI to reduce the risk of death (HR 0.37 [95% CI: 0.09–1.48]), but this did not reach statistical significance (P = 0.16) (Figure 2). After adjusting for sex, age, race, hypertension, and T2D there was an 87% lower risk of ESRD for those being treated with SGLT2i compared with those that were not (HR 0.13 [95% CI: 0.04–0.42], P = 0.007) (Figure 3). After adjusting for sex, age, race, hypertension, CKD, and T2D there was a 93% lower risk of death for those treated with SGLT2i (HR 0.07 [95% CI: 0.01–0.47], P = 0.007) (Figure 3).

As compared with White HFpEF patients, there was a significantly higher portion of Black patients prescribed SGLT2i, BB, vasodilators, and ACEi/ARB (Table 3). CKD patients were more likely to be prescribed BB and vasodilators. There were no race–drug interactions aside from a 43% reduced risk of death for Black patients that were not prescribed a BB as compared with Black patients that were prescribed a BB (Figure S1). This effect was not seen in White patients.

Table 2 Adjusted Cox models for all-cause mortality and end stage renal disease.

Variable	Death from any cause		End stage renal disease	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.03 (1.02–1.04)	<0.001	0.97 (0.97–0.98)	<0.001
Sex				
Female	-	-	-	-
Male	1.47 (1.19–1.80)	<0.001	1.57 (1.22–2.02)	<0.001
Race				
Black	-	-	-	-
White	1.20 (0.96–1.49)	0.11	0.37 (0.27–0.52)	<0.001
HTN	0.92 (0.65–1.30)	0.65	3.46 (1.63–7.37)	0.001
T2D	0.81 (0.66–1.01)	0.06	2.85 (2.09–3.89)	<0.001
CKD	1.68 (1.34–2.11)	<0.001	-	-

Note: HTN indicates hypertension diagnosis. CKD was removed from the end stage renal disease analysis. Abbreviations: CKD, chronic kidney disease; T2D, type 2 diabetes.

Discussion

Although survival for HFrEF has improved over the past 20 years, there has been no improvement in HFpEF survival.¹² Indeed, therapies that have shown a significant impact in HFrEF have not translated well in HFpEF. In a primarily Black hypertensive population, the current study demonstrated that HFpEF was associated with significantly high prevalence of hypertension, diabetes, CKD, and mortality. However, patients prescribed either ACEi/ARB or SGLT2i were associated with a significantly decreased risk of all-cause mortality (25% and 93%, respectively). This effect of SGLT2i was significantly associated with an 87% reduced risk of ESRD. These data warrant further investigation into the use of these drugs in non-diabetic HFpEF, especially in Black patients.

SGLT2i have been shown to reduce morbidity and mortality in HFrEF.¹³ However, few clinical trials have investigated this drug in HFpEF. Some believe SGLT2i should be considered for all patients with HF based on its efficacy in patients with or without CKD or T2D.¹⁴ For example, the EMPULSE trial showed in-hospital initiation of SGLT2i in patients with acute HF resulted in significant clinical benefit across all levels of ejection fraction.¹⁴ In the DELIVER trial, HFpEF patients had no significant benefit in all-cause mortality with SGLT2i use and had a 3 year mortality of around 20%, with or without the drug. In the current analysis, the all-cause mortality was slightly lower, 16% with an average follow-up of 4 years (Table 1). This may have been due to an older population (72 vs. 64 years) or inclusion of patients with previous HFrEF, which the current analysis excluded. In the EMPEROR-Preserved trial, SGLT2i reduced the risk of HF hospitalization in HFpEF patients with or without diabetes, but no direct effect was seen on mortality.¹⁰ Clearly, SGLT2i mechanism of action to increase the excretion of glucose cannot fully explain the benefits on clinical events across a broad phenotype of HF, CKD, and glucose control. Some believe that SGLT2i may improve outcomes due to direct car-

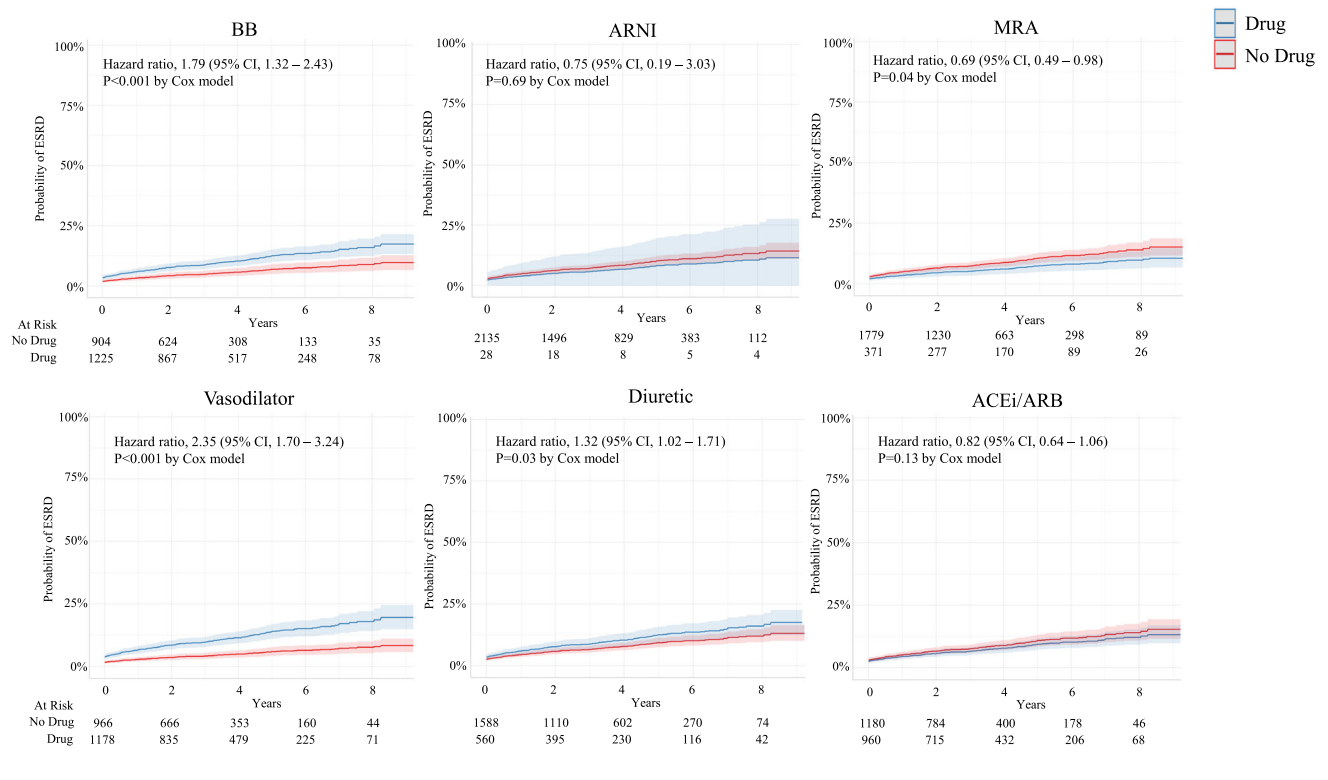
diac effects in addition to renal-mediated effects,¹⁵ but clinical evidence is lacking.

In the current study, SGLT2i significantly reduced the risk of ESRD which supports this treatment as an effective therapy to slow renal disease progression in HFpEF (Figure 3). SGLT2i have been shown to delay ESRD even in patients with advanced CKD. Indeed, recent trials suggest, these benefits persist even in patients with Stage 4 CKD (estimated GFR 15–30 mL/min/1.73 m²).¹⁶ Aside from renin-angiotensin system (RAS) inhibitors, SGLT2i has been the only drug has been shown to consistently slow CKD progression in the last 20 years.⁸ And this effect is additive in CKD patients already taking RAS inhibitors.⁹

The heart and kidney interact in a complex and tight relationship in HF. Around 60% of HF patients have CKD,¹⁷ one of the strongest independent risk factors and predictors of mortality in patients with HF, both HFpEF and HFrEF.^{18–20} Treatments that block the RAS (e.g. ACEi/ARB) are the cornerstone of effectively delaying the progression of CKD. Activation of the RAS occurs in many patients with HFpEF and most likely relates to the severity HF or renal disease.²¹ The renoprotective effects of RAS inhibitors are well established in several different populations, including T2D and CKD. RAS inhibitors have also been shown to reduce mortality in HFpEF (although this was unadjusted for confounders).²² While the current analysis did not demonstrate significant effects on incidence of ESRD with ACEi/ARB, there was a significant reduction in ESRD risk with MRA. These effects persisted after adjusting for age, sex, race, hypertension, and T2D. Studies commonly report the attenuated efficacy of RAS inhibitors in Black patients, especially during the treatment of hypertension. However, some clinical studies show beneficial effects of these drugs in Black CKD patients.²³ Similarly, our results support the use of these drugs during HFpEF, regardless of race.

National disparities in HF care and outcomes continue. Black patients are disproportionately affected by factors that are significant risk factors for HF, including hypertension, obesity, and diabetes. Black patients have the higher age-adjusted rate of incident HFrEF and HFpEF.²⁴ Interestingly, Black HFpEF patients have greater co-morbidities and increased risk of HF hospitalizations but statistically similar mortality as Whites with HFpEF.²⁵ In the current study, we found similar results in Black HFpEF patients, with similar all-cause mortality, but significantly increased risk of developing ESRD (Table 2). Blacks have also been shown to be more often affected by social determinants of health including lower income. Out of pocket expenses for SGLT2i can cost around \$900/year for Medicare patients,²⁶ and 16% of HF patients report delaying or refusing care due to financial reasons.²⁷ In the current study, Black patients with and without CKD were more often on Medicaid as compared with White patients (Table S1), which may incentivize physicians to not include SGLT2 inhibitors in the treatment plans of HFpEF. However, in the

Figure 1 Risk of end stage renal disease in heart failure with preserved ejection fraction stratified by drug class after adjusting for age, sex, race, hypertension status, and diabetes status.



current study, Black HF patients in the current study were more commonly prescribed SGLT2i, with or without CKD, as compared with Whites (Table 3). The effects of SGLT2i among minority populations, although likely, require further investigation. Unfortunately, Black patients have been poorly represented in most SGLT2i trial populations (~5%),^{7,9,10,28} warranting further investigation into the impact of this treatment in these patients. Again, our data suggest that SGLT2i improves all-cause mortality and risk of ESRD in HFpEF, regardless of race.

In the current study, most patients were prescribed BB (60%), especially in Blacks and in CKD patients (Table 3). These patients were associated with increased risk of developing ESRD, (Figure 1). Interestingly, there was a 43% reduced risk of death for black patients that were not prescribed a BB as compared with Black patients that were (Figure S1). The mechanisms for this are unknown. BB reduce all-cause mortality and are currently recommended in HFrEF; however, BB use has not been shown to improve mortality more than placebo in HFpEF patients >50%.²⁹ Similarly, a retrospective analysis of TOPCAT demonstrated, for HFpEF patients treated with MRA, BB use increased the risk of HF hospitalizations.³⁰ Surprisingly, in HFpEF patients without a previous MI, BB use actually increased the risk of all-cause mortality by 50%.³¹ These data demonstrate a lack of understanding of BB in HFpEF and highlight the need for empirical

data supporting the use of common HFrEF medications in this population. In the current study, we included all BB drug classes and did not take into consideration the differences between beta selective and beta non-selective, such as carvedilol, which has been shown to significantly reduce HFrEF mortality, but again, data demonstrating beneficial effects in HFpEF are lacking.³²

In HFrEF patients, ARNI, such as sacubitril/valsartan, have demonstrated reduced HF hospitalization, cardiovascular mortality, and all-cause mortality compared with ACEi when initiated in the outpatient setting,³³ and have rapid and significant clinical benefits among patients already hospitalized for HF.^{34,35} In HFpEF, ARNI have not shown any additional benefit in HF hospitalizations and cardiovascular mortality as compared with ARB alone but may be especially effective in CKD. For example, ARNI improved composite outcome of HF hospitalizations and cardiovascular death in HFpEF patients with an estimated GFR 30–60 mL/min/1.73 m².³⁶ Indeed, ARNI have been shown to slow the progression of CKD in HFpEF patients as compared with ARB alone.³⁷ However, the effect of ARNI in patients with advanced CKD (<30 mL/min/1.73 m²) is unknown. Unfortunately, the number of CKD patients taking ARNI in the current analysis was low ($n = 14$), making the analysis and interpretation of ARNI effects on ESRD and mortality risk difficult. Regardless, CKD patients prescribed ARNI were associated with a lower unad-

Figure 2 Risk of all-cause mortality in patients with heart failure with preserved ejection fraction stratified by drug class after adjusting for age, sex, race, hypertension status, diabetes status, and chronic kidney disease status.

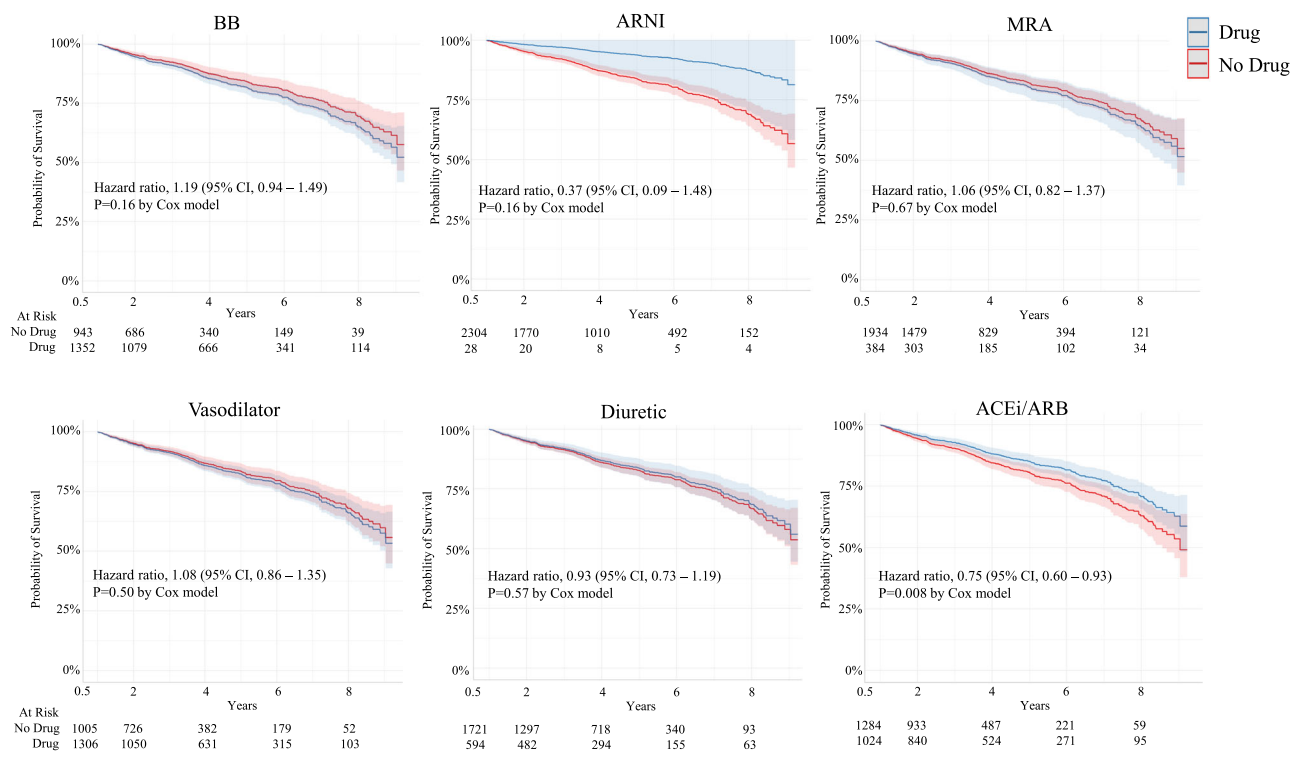
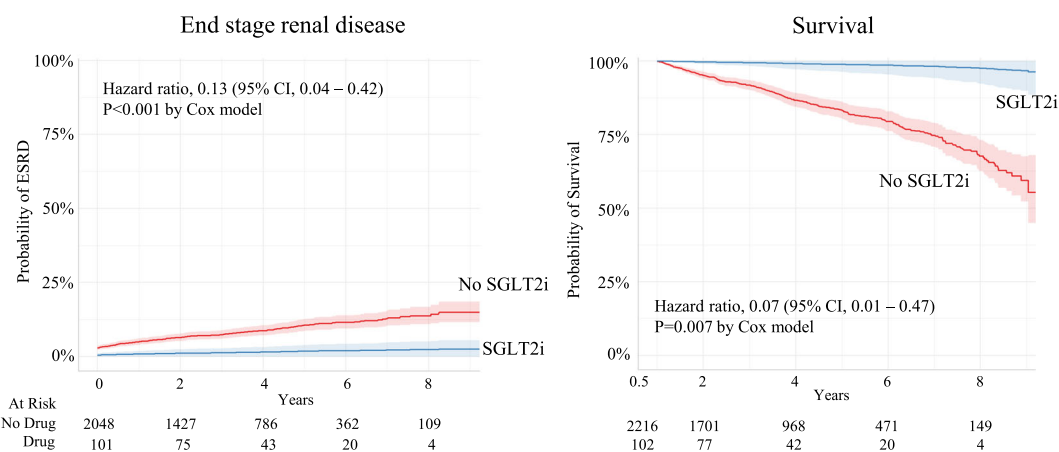


Figure 3 Risk of end stage renal disease and all-cause mortality in heart failure with preserved ejection fraction patients prescribed SGLT2i after adjusting for age, sex, race, hypertension status, and diabetes status. Kaplan–Meier curves for mortality were also adjusted for chronic kidney disease status.



justed mortality rate (7% vs. 20%) as compared with CKD patients not taking ARNI (not shown). This evidence coupled with the current data warrants further long-term studies on the impact of ARNI on the cardiovascular morbidity and mortality in HFpEF patients.

The current retrospective analysis of EHR using UMMC's RDW is a very powerful and clinically relevant tool. However, this study comes with limitations. For example, the current analysis is a single center study in Mississippi with social determinants of health that are dissimilar to most of the

Table 3 Drug prescriptions among White and Black heart failure with preserved ejection fraction patients with or without chronic kidney disease.

Variable	All (n = 2368)	White		Black	
		HFpEF (n = 488)	HFpEF + CKD (n = 490)	HFpEF (n = 505)	HFpEF + CKD (n = 850)
Drugs					
SGLT2i (%)	5	3	3	6	6 [#]
ARNI (%)	1	2	2	1	1 [#]
BB (%)	60	46	58*	56 [#]	70* [#]
Vasodilator (%)	57	40	52*	53 [#]	72* [#]
Diuretic (%)	26	15	19	34 [#]	32 [#]
ACEi/ARB (%)	45	35	40	51 [#]	50 [#]
MRA (%)	17	19	18	16	16

Note: HFpEF indicates heart failure with preserved ejection fraction. Only drugs that were prescribed for at least 90 days were considered. Abbreviations: ACEi/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CKD, chronic kidney disease before or during follow-up; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium glucose transport inhibitor.

* $P < 0.05$ vs. HFpEF.

[#] $P < 0.05$ vs. White.

United States (e.g. high proportion of poverty and black race). While this suggests that these observations may not be broadly representative, they appear consistent with other published studies. Much of the cohort had missing data on HF severity (New York Heart Association class) and specific parameters describing heart size and function (e.g. pro brain natriuretic peptide levels, mitral E/A ratio, ventricular wall thickness, and atrial diameter). While UMMC clinics have standardized echocardiography procedures for diagnosing diastolic dysfunction and HFpEF, the retrospective design does not assure that these were rigorously adhered to in routine daily practice. Further, the term 'HFpEF' was not always used for diagnosis in the RDW, and therefore, the analysis included 'diastolic HF' in addition to the diagnostic criteria. Many lifestyle factors such as diet and physical activity as well as social determinants of health like income were not recorded in our institution's data warehouse. Indeed, these factors have shown to play an important role in HFpEF. For example, in HFpEF patients with CKD, low salt diet improved diastolic function in just 3 weeks.³⁸ In the current study, treatments such as BB, vasodilators, and diuretics were associated with increased risk of ESRD but not mortality. This does not definitively exclude the beneficial effects of these drugs in HFpEF treatment but, rather, may relate to physician bias to prescribe these drugs to HF patients with more advanced HF or CKD.

Conclusions

Many treatments have shown significant benefit in HFrEF but have failed to similarly treat HFpEF. There is much clinical evidence suggesting the significant role of SGLT2i in HFrEF, with less known about HFpEF. Here, we show significant improvements in survival with SGLT2i, regardless of CKD or diabetes

status. Additionally, SGLT2i use was associated with significant decrease in the risk of ESRD. In view of the empirical data demonstrating the ability of SGLT2i to preserve kidney function paired with the common occurrence of CKD in HF, more effort is needed for exploring the patient populations that may benefit with this treatment.

Conflict of interest

The authors declare that there are no competing interests.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Survival in black and white heart failure with preserved ejection fraction patients treated with and without beta blocker therapy after adjusting for age, sex, hypertension, chronic kidney disease, and type 2 diabetes.

Table S1. Types of insurance among white and black heart failure with preserved ejection fraction patients with or without chronic kidney disease.

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