Brief Report

Spironolactone Utilization among Patients with Reduced and Preserved Ejection Fraction Heart Failure

Efe Eworuke [1,*], Austin Cosgrove [2], Qoua Liang Her [2], Jennifer G. Lyons [2], Dave Martin [3] and Sruthi Adimadhyam [2]

1   Division of Epidemiology II, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA
2   Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA 02215, USA
3   Statlog Econometrics, Quebec, QC G1Y 3M9, Canada
*   Correspondence: efe.eworuke@fda.hhs.gov; Tel.: +1-240-402-3972; Fax: +1-301-796-9850

Abstract: Background: Spironolactone is a mineralocorticoid receptor antagonist indicated for the management of heart failure with reduced ejection fraction (HFrEF). In a previous clinical trial, spironolactone significantly lowered the incidence of heart failure (HF) hospitalizations among HF patients with preserved ejection fraction (HFpEF). Real world utilization of spironolactone in HFrEF and HFpEF is unknown. Methods: We conducted a retrospective cohort study using data from FDA's Sentinel System. We identified patients with HFrEF or HFpEF using diagnosis and procedure codes from a previously validated algorithm. We required patients to be continuously enrolled in the 183 days prior to HF diagnosis. Follow-up started on the day of HF diagnosis and ended at the earliest occurrence of a spironolactone dispensing, disenrollment, death, or end of data. We calculated the proportion of spironolactone utilization, and for those initiating treatment, we estimated the dose and duration of the first continuous treatment episode. Results: Among 2,009,529 HFrEF patients, 57.8% were male, and mean age was 73.8 ± 12.1 years. Among 9,257,514 HFpEF patients, 42.7% were male, and mean age was 73.0 ± 12.1 years. The proportion of spironolactone utilization following HFrEF diagnosis was 20.7% versus 7.6% after HFpEF. The median time (days) to initiation of spironolactone after HFrEF diagnosis was 90 (IQR: 19–385) versus 286 (IQR: 57–851) after HFpEF diagnosis. The median duration (days) of first treatment episode in HFrEF patients was 120 (IQR: 44–321) and 114 (IQR: 32–301) for HFpEF patients. The median dose was similar (25 mg/day) for both HF cohorts. Conclusion: Findings of low real-world utilization of spironolactone from our large, geographically, and demographically diverse multi-site study in the US are consistent with reports from smaller studies in the literature. Similar spironolactone dosing and duration were observed in both the HFpEF and HFrEF cohorts. Future research characterizing spironolactone treated and untreated HFpEF cohorts will be needed to identify treatment gaps.

Keywords: heart failure; medication utilization; real-world evidence

1. Introduction

In the United States, about 40–50% of patients with heart failure (HF) have relatively normal left ventricular ejection fraction [1,2]. Heart failure patients with preserved ejection fraction (HFpEF) appear to experience morbidity and mortality at rates comparable to HF patients with reduced ejection fraction (HFrEF) [3]. Despite the clinical burden, treatment options for patients with HFpEF are limited.

Spironolactone is a mineralocorticoid receptor antagonist indicated for the management of HFrEF. Mineralocorticoid receptor antagonists, including spironolactone, are effective at reducing overall mortality and hospitalizations for patients with HFrEF [4] and those with myocardial infarction (MI) complicated by HF [5]. Despite evidence demonstrating the effectiveness of spironolactone in patients with chronic heart failure, it is an

underutilized therapeutic option [6]. Studies show that a third of eligible HF patients in the US receive spironolactone.

Among patients with HFpEF, spironolactone has been associated with improved myocardial contractile function and some parameters of diastolic function [7]. Long-term blockade of the aldosterone receptor by spironolactone has been shown to improve left ventricular diastolic function among patients with HFpEF [8]. More recently, findings from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial showed that among patients with HFpEF, there was a significant reduction in the incidence of HF hospitalization (hazard ratio, 0.83; 95% CI, 0.69 to 0.99, $p = 0.04$) with spironolactone compared to placebo; although there was no association between spironolactone and the primary endpoint (composite outcome of death from cardiovascular causes, aborted cardiac arrest and HF hospitalization) [9]. Interestingly, the results stratified by region showed significant reductions in the primary outcome in the Americas, but not in Russia or Georgia. The differences in study entry criteria have been discussed as a plausible explanation [10]. Eastern European patients were selected based on HF hospitalization while US patients met natriuretic peptide level entry criteria and had a higher event rate [10]. Nonetheless, the findings from the TOPCAT trial led the American Heart Association/American College of Cardiology Committee to recommend spironolactone for selected patients with HFpEF to decrease HF hospitalizations [11].

Real-world utilization of spironolactone among patients with HFrEF and HFpEF, especially in the context of presumed benefits reported among HFpEF, remains unknown. Thus, we sought to examine the real-world utilization of spironolactone in patients with HFrEF and HFpEF separately using a large demographically and geographically diverse database.

2. Results

2.1. HF Cohort Characteristics

For the study period, we identified 2,009,529 HFrEF patients, 9,257,514 HFpEF patients. The mean age (approximately 73 years) was similar across the HF cohorts, with almost 80% of the patients aged 65 years and older (Table 1). There were more males in the HFrEF cohort (57.8%) compared to the HFpEF cohort (42.7%). The majority of HFrEF patients (87.8%) had an index-defining systolic HF diagnosis, while most HFpEF patients (71.6%) had an unspecified HF diagnosis. HFrEF patients used more cardiovascular-related medications during the baseline period (Angiotensin-Converting Enzyme Inhibitors (ACEI), antiarrhythmics, beta blockers, digoxin, hydralazine, loop diuretics, nitrates, potassium sparing diuretics and other mineralocorticoids) compared to HFpEF patients. On the other hand, HFpEF patients used Angiotensin II Receptor Blockers (ARBs) and thiazide diuretics more than HFrEF patients. A high proportion of HFrEF also had history of HF-related comorbidities compared to HFpEF patients (Table 1).

Table 1. Demographic and Clinical Characteristics of HFrEF and HFpEF Patients in the Sentinel Distributed Database between July 2010 and September 2018.

	HFrEF	HFpEF
Characteristic [1]	**%/Std Dev** [2]	**%/Std Dev** [2]
Number of unique patients	2,009,529	9,257,514
Demographics		
Mean Age	73.8 ± 12.1	73.0 ± 12.1
Age: 0–17	<0.1	<0.1
Age: 18–44	2.4	3.0
Age: 45–64	17.7	18.2
Age: 65+	79.9	78.8
Gender (Female)	42.2	57.3
Gender (Male)	57.8	42.7
Race (American Indian or Alaska Native)	0.5	0.4

Table 1. *Cont.*

Characteristic [1]	HFrEF %/Std Dev [2]	HFpEF %/Std Dev [2]
Race (Asian)	1.5	2.3
Race (Black or African American)	13.5	12.5
Race (Native Hawaiian or Other Pacific Islander)	0.1	0.1
Race [3] (Unknown)	12.6	17.5
Race (White)	71.7	67.2
Hispanic Origin	2.3	2.9
Recorded on heart failure index diagnosis:		
Diastolic heart failure	–	33.7
Left heart failure	12.2	–
Systolic heart failure	87.8	–
Unspecified heart failure	11.0	71.6
Spironolactone use in the prior 183 days:		
Spironolactone dispensing	5.7	1.4
History of cardiovascular-related medication use in the prior 183 days:		
Angiotensin-converting enzyme inhibitors	43.0	33.7
Angiotensin II receptor blockers	21.1	23.6
Antiarrhythmics	12.8	4.9
Beta blockers	71.3	48.8
Digoxin	12.0	4.0
Hydralazine	7.5	4.2
Loop diuretics	53.9	27.9
Mineralocorticoid receptor antagonists (eplerenone)	0.8	0.1
Nitrates	20.9	10.0
Potassium-sparing diuretics	9.7	4.8
Thiazide diuretics	16.4	25.6
History of heart failure related comorbidities in the prior 183 days:		
Anemia	45.9	30.4
Atrial fibrillation or flutter	47.0	20.9
Cardiomyopathy	66.7	0.0
Chronic obstructive pulmonary disease	36.1	21.6
Coronary artery bypass graft	2.7	0.5
Depression	20.5	16.6
Diabetes mellitus	49.9	40.7
Endocarditis	2.0	0.7
Heart transplant	0.9	0.3
Human immunodeficiency virus	0.5	0.4
Hyperkalemia	12.0	4.5
Hyperlipidemia	72.6	61.6
Hypertension	88.7	81.8
Hypertensive nephropathy	32.5	13.7
Hypotension	18.1	5.9
Implantable cardioverter defibrillator	20.7	0.0
Ischemic stroke or transient ischemic attack	23.6	15.9
Myocardial infarction	34.7	3.6
Nephropathy	54.4	30.0
Obesity	20.5	15.9
Other dysrhythmias	48.4	19.0
Psychosis	8.3	6.2
Pulmonary hypertension	17.6	5.3

Table 1. *Cont.*

Characteristic [1]	HFrEF %/Std Dev [2]	HFpEF %/Std Dev [2]
Renal disorders	40.4	21.4
Rheumatic heart disease	16.4	4.9
Sleep apnea	15.2	10.2
Smoking	15.3	8.3
Stable angina	12.0	5.7
Unstable angina	18.0	7.2
Valve disorders	20.7	7.8

[1] All metrics are based on total number of episodes per group, except for sex and race which are based on total number of unique patients. [2] Value represents standard deviation where no % follows the value. [3] Race data may not be completely populated at all data partners; therefore, data about race may be incomplete.

2.2. Spironolactone Use following HF Diagnosis

Overall, a greater proportion of patients with HFrEF had a dispensing of spironolactone following HF diagnosis (20.7%) compared to patients with HFpEF (7.6%). Among HFrEF patients, males had a higher proportion of spironolactone use compared to females and the highest proportion of spironolactone use was among the 18–44-year olds, followed by 45–64-year olds (Figure 1). In patients with HFpEF, females had a higher proportion of spironolactone use compared to males and use increased steadily as patients aged. When stratified by calendar year of cohort entry, we observed declining use of spironolactone over the study period for both HFrEF and HFpEF cohorts (Figure 2).
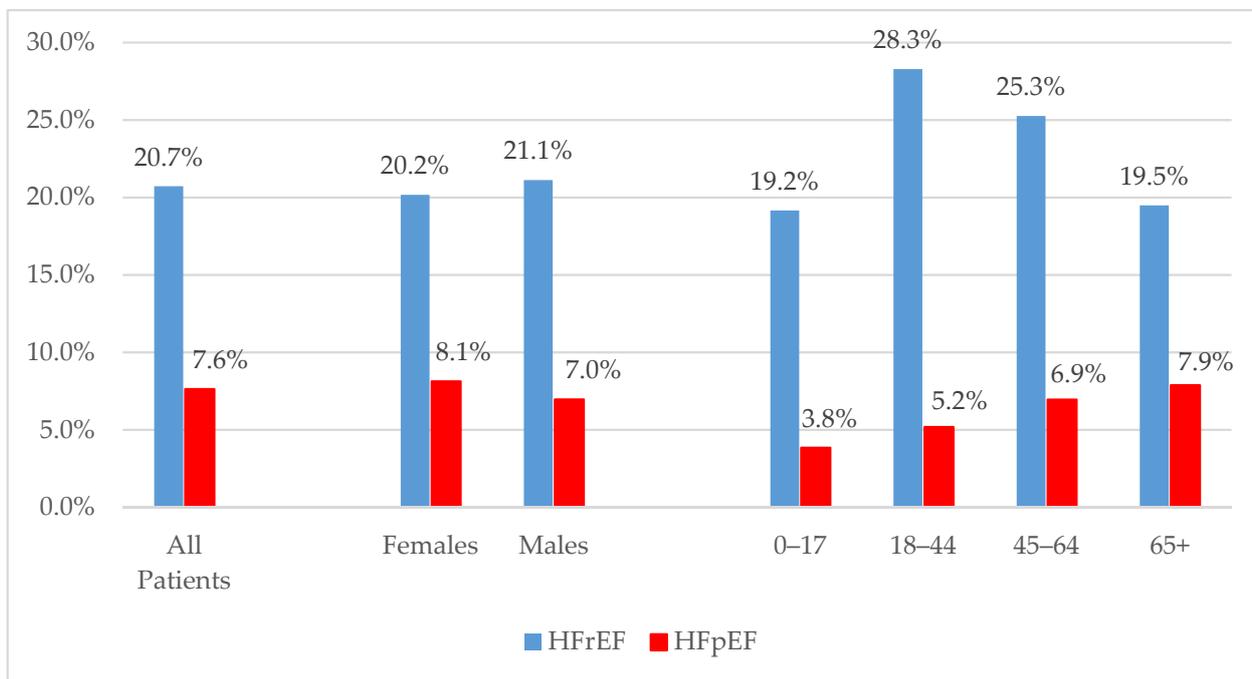

Figure 1. Spironolactone Initiation following Heart Failure Diagnosis in the Sentinel Distributed Database between July 2010 and September 2018 *. * Spironolactone initiation occurred at any point after HF diagnosis. We did not identify any HFs after September 2018, but the last observed initiation occurred in September 2019.
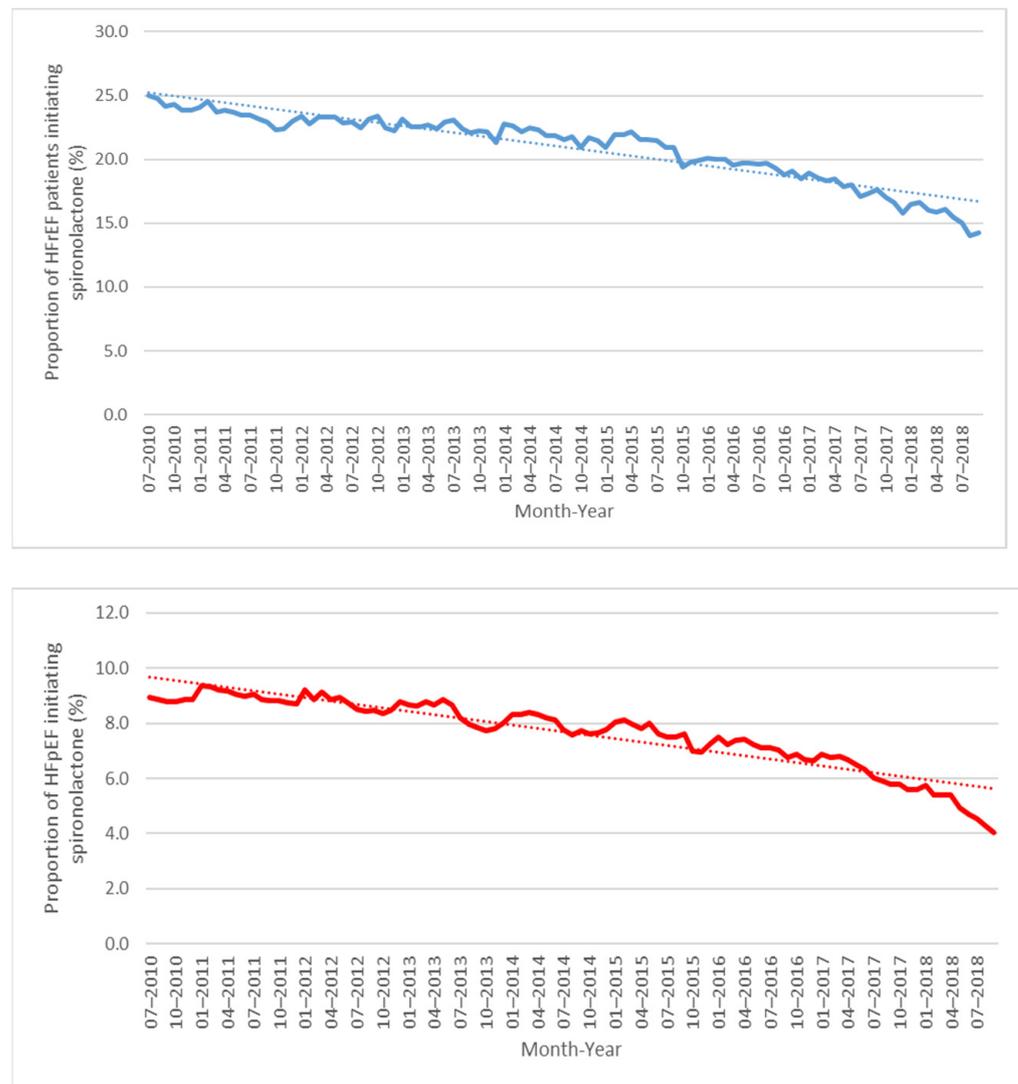
Figure 2. Spironolactone Initiation following Heart Failure Diagnosis between 1 July 2010 and 30 September 2018 *. * Study period was truncated to 30 September 2018 due to varying end dates from the data partners.

2.3. Time to Spironolactone Initiation following HF Diagnosis

Most HFrEF patients had a dispensing for spironolactone within 1 month of the index HF diagnosis (Table 2). Within six months, 62% of the HFrEF patients had a spironolactone dispensing. For HFpEF patients, we observed a delayed onset of spironolactone treatment. Overall, the time to spironolactone dispensing was longer for the HFpEF cohorts (mean: 565 days; median: 286 days) compared to the HFrEF cohort (mean: 307; median: 90 days).

Table 2. Spironolactone Utilization following Heart Failure Diagnosis in the Sentinel Distributed Database between July 2010 and September 2018.

Time to First Spironolactone Dispensing Following HF Diagnosis (in Days)		
	HFrEF	**HFpEF**
Mean	307	565
Median	90 (IQR: 19–385)	286 (IQR: 57–851)
<1 month (%)	30.8	17.4
1–<6 months	31.4	24.5
6 months–<1 year (%)	11.9	13.0
1–<2 years (%)	11.9	16.3
2–<3 years (%)	6.2	10.2
3+ years (%)	7.8	18.7
First Continuous Treatment Episode (in Days) of Spironolactone Dispensing		
	HFrEF	HFpEF
Mean	262	250
1–<3 months (%)	39.6	40.2
3–<6 months (%)	16.1	16.1
6 months–<1 year (%)	16.8	16.5
1+ years (%)	22.0	20.7
<1 month (%)	5.6	6.4
Median	120 (IQR: 44–321)	114 (IQR: 32–301)
Average Daily Dose * (mg per Day) in the First Continuous Treatment Episode of Spironolactone		
	HFrEF	HFpEF
Mean	28	34
Median	25 (IQR: 25–25)	25 (25–45)
<15 mg/day (%)	18.1	11.3
15–<30 mg/day (%)	64.5	59.3
30–<45 mg/day (%)	3.4	4.3
45–<75 mg/day (%)	11.4	18.7
75–<100 mg/day (%)	0.7	1.5
100+ mg/day (%)	1.9	4.9

* We calculated average daily dose for only those treatment episodes (99.7%) in which the amount supplied divided by days supply for all dispensings was ≥0.25 and ≤8. We calculated average daily dose for only exposed time within the first continuous treatment episode. That is, bridged gap days (≤30 days) were removed from the calculation.

2.4. Duration of Continuous Spironolactone Treatment following HF Diagnosis

We observed a slightly longer duration of spironolactone use among HFrEF patients (mean: 262; median: 120 days) compared to HFpEF patients (mean: 250; median: 114 days) (Table 2). However, most spironolactone episodes were 1–<3 months in duration for both HFrEF and HFpEF patients. We observed no differences in the distribution of the length of spironolactone episodes by age or gender (data not shown). Calendar-time trends for the duration of first treatment episode were consistent throughout the study period for both HFrEF and HFpEF cohorts.

2.5. Average Daily Dose of Spironolactone Treatment following HF Diagnosis

Overall, we observed a slightly higher mean dose for HFpEF (34 mg/day) compared to HFrEF (28 mg/day) patients, but both cohorts with median dose of 25 mg/day (Table 2). Most HFpEF and HFrEF patients had an average spironolactone dispensing of 15–<30 mg/day. However, for HFpEF patients there was a higher proportion of patients who had an average dose of 45–<75 mg/day compared to HFrEF patients (19% compared to 11%). We also did not observe any differences in dose distributions by age or gender (data not shown).

2.6. Sensitivity Analyses

We observed differences in coding between the ICD-9 and ICD-10 eras. More HFpEF patients had rheumatic heart failure, hypertensive heart disease, or hypertensive heart disease with kidney disease in the ICD 10-era compared to the ICD 9-era; more HFrEF patients had left HF diagnosis in the ICD 9-era compared to 10-era (Supplementary Table S2). HFpEF patients were also older in the ICD-10 era compared to the ICD-9 era, suggesting aging rather than an influx of new patients. For instance, for the HFrEF cohorts, the proportion of 18–44 and 45–64 year olds decreased from 2.5% and 17.8% to 2.3% and 17.5%; while the 65+ year olds increased from 79.7% to 80.3%. Similarly, the proportion of 18–44 and 45–64 year olds decreased from 3.2% and 18.7% to 2.0% and 15.7% respectively; while the proportion of 65+ year olds increased from 78.0% to 82.3% for the HFpEF cohort (Supplementary Table S2). Utilization of spironolactone also varied slightly across ICD-9 and 10 eras with 22.7% of HFrEF patients diagnosed in the ICD-9 era initiating spironolactone as compared to 18.0% in the ICD-10 era. Similarly, 8.5% HFpEF patients diagnosed in the ICD-9 era initiated spironolactone as compared to 6.3% in the ICD-10 era.

Patient characteristics and spironolactone utilization in the HFpEF cohort that excluded MI at baseline were similar to the HFpEF cohort without MI exclusion (Results not shown).

3. Methods

3.1. Data Sources

We used the FDA's Sentinel System [12], a distributed network of 16 participating health plans (i.e., sites) across the United States with varying dates of data availability. The Sentinel Distributed Database is a curated data source; the health plans included large national insurers, integrated delivery care networks, a state Medicaid, and the 100% Medicare fee-for-service plan. Each plan regularly updates and transforms their enrollment, demographic, medical, and pharmacy data, including inpatient and outpatient diagnoses and procedures, and retail and mail order prescription records, into standardized formats to facilitate routine querying [13]. This study was conducted as part of public health surveillance activities and therefore not under the purview of Institutional Review Boards [14].

3.2. Cohort Definitions

We classified patients into cohorts of HFrEF or HFpEF based on characteristics that were most predictive of ejection fraction class in a previously validated algorithm [15]. Cardiomyopathy, left HF, systolic HF, myocardial infarction (MI), prior congestive heart failure (CHF) hospitalizations and implantable cardioverter defibrillator were most predictive of HFrEF while unspecified HF (defined as rheumatic HF, hypertensive HF, or hypertensive HF with chronic kidney disease) and diastolic HF were most predictive of HFpEF.

HFrEF patients were identified as patients with at least one diagnosis of left HF (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 428.1, International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM): I50.1) or systolic HF (ICD-9: 428.2×, ICD-10: I50.2×) and no co-occurring diagnosis of diastolic (ICD-9: 428.3×, ICD-10: I50.3×) or combined diastolic and systolic HF (ICD-9: 428.4×, ICD-10: I50.4×). We also excluded patients that were diagnosed with left and systolic HF on the same day consistent with the definition used in the validated algorithm [15]. In addition, we required HFrEF patients to have a diagnosis of cardiomyopathy or MI or an implantable cardioverter during the 183 days prior to HF diagnosis (baseline period) as these factors were deemed most predictive of rEF in the validated algorithm. In the HFpEF cohort, patients were required to have at least one diagnosis of diastolic HF or unspecified HF (defined as rheumatic HF (ICD-9: 398.91, ICD-10: I09.81), hypertensive HF (ICD-9: 402.××, ICD-10: I11.0, I11.9), or hypertensive HF with chronic kidney disease (ICD-9: 404.××, ICD-10: I13.0, I13.1×, I13.2)) and no co-occurring diagnosis of left, systolic, or combined diastolic and systolic HF (Supplementary Table S1 for operational definitions). We excluded HFpEF patients who had a diagnosis of

cardiomyopathy or an implantable cardioverter during the baseline period as these factors were deemed most predictive of rEF in the validated algorithm.

The cohort selection period spanned 1 July 2010 to 30 September 2018. We defined the index date as the date of the HF diagnosis in the respective cohorts and followed patients until the first occurrence of a dispensing of spironolactone, disenrollment, death, or end of available data for the health plan (Figure 3). For those initiating spironolactone, we described their medication utilization.
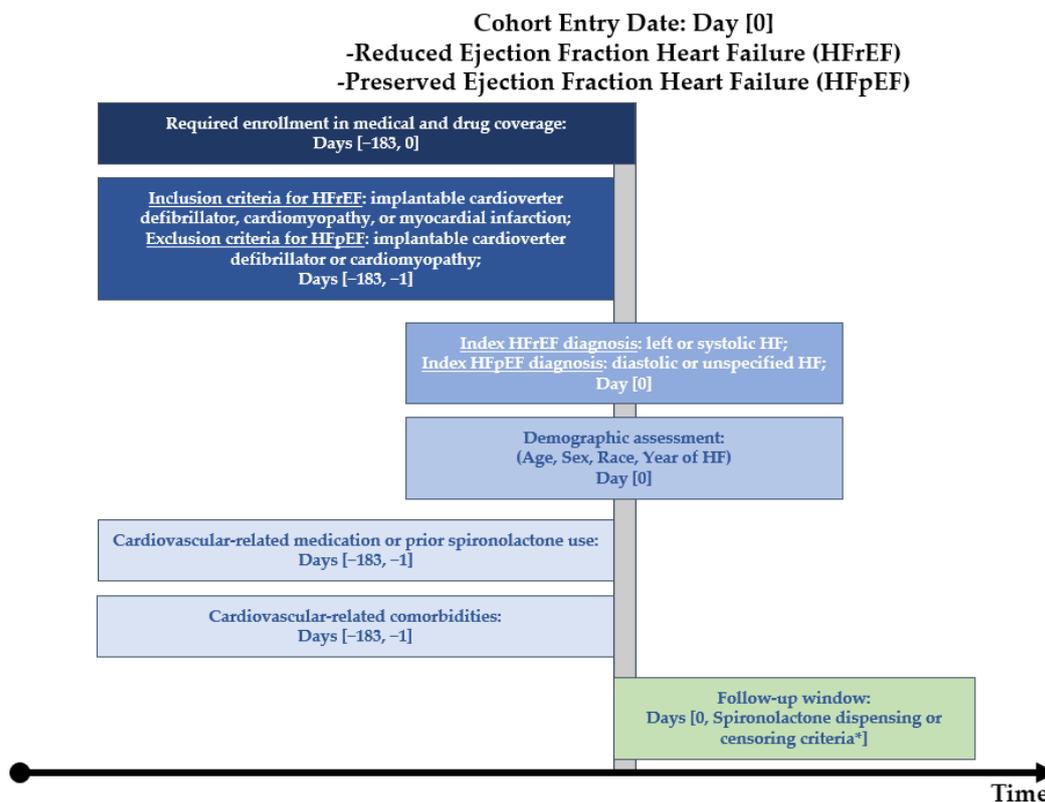
Figure 3. Study Design Schematic. * We censored follow-up at the first occurrence of the following: spironolactone dispensing, disenrollment, Data Partner end date, or death.

The analytic process was completed using the Sentinel Query Request Package, version 9.0.1, a pre-tested, validated analytic program [16].

3.3. Spironolactone Utilization

We created continuous spironolactone treatment episodes bridging a maximum gap of 30 days between adjacent dispensings after index HF. We examined the time from index HF to spironolactone initiation and the duration of the first continuous spironolactone episode. We also calculated the average daily dose for the first spironolactone episode, using only exposed time not including the bridged ≤ 30-day gaps between dispensings. Average daily dose (mg/day) was calculated by multiplying the total amount (pills) supplied and the product strength (mg) divided by the total number of days of exposed time. We calculated average daily dose in spironolactone treatment episodes where every dispensing had a ratio of amount to days supplied <0.25 or >8 pills per day to account for any extreme values. Average daily dose was not calculated for 0.3% of all spironolactone treatment episodes due to suspected extreme values in days and/or amount supplied.

3.4. Descriptive Analyses

We examined the initiation of spironolactone use following HF diagnosis among HFrEF and HFpEF patients separately. For each cohort, we presented patient demographics

on index date, including age, gender, and race and other baseline characteristics including cardiovascular-related medications and comorbidities observed in the prior 183 days. We examined the proportion of spironolactone initiation after index HF diagnosis; the distributions of time until spironolactone dispensing, duration of the first continuous spironolactone treatment episode after HF diagnosis and the average daily dose of the spironolactone treatment episode overall and by month-year. We stratified results by age, gender, and calendar time of cohort entry.

3.5. Sensitivity Analyses

The HF algorithm was constructed using diagnosis codes from the ICD-9 era which were mapped to pertinent ICD-10 diagnosis codes in our study. Thus, we examined the utilization of spironolactone separately for HFs diagnosed in the ICD-9 (1 July 2010– 30 September 2015) and ICD-10 eras (1 April 2016–30 September 2018) due to the potential for differences in the performance of the HF algorithm in ICD-9 vs. ICD-10 eras. In the validation study [14], among correctly classified HFpEF patients, there was a low proportion (26.2%) of patients with MI diagnosis compared to incorrectly classified HFpEF patients (68.6%). Thus, we performed another sensitivity analysis where we examined the utilization of spironolactone in an HFpEF cohort that was required to have no evidence of MI during the baseline period.

4. Discussion

In this large observational study, we observed a higher prevalence of HFpEF patients compared to HFrEF, consistent with published reports [1,3]. While we did not have ejection fraction values to categorize patients into HFrEF and HFpEF, we used factors most predictive of ejection fraction class in a previously validated algorithm to classify patients as HFrEF vs. HFpEF. Our study HF cohorts displayed similar patient characteristics in the validated HF cohorts [15]. HFrEF patients were more likely diagnosed with systolic HF, while HFpEF patients were likely diagnosed with unspecified HF. HFrEF patients also were dispensed more HF-related medications and had more cardiac-related comorbidities during the baseline period.

Spironolactone, a mineralocorticoid receptor antagonist (MRA), is recommended in patients with class II-IV HF who have ejection fraction of 35% or less [17]. In our study, HFrEF patients were more likely to initiate spironolactone after HF diagnosis and did so much earlier than HFpEF patients. Consistent with prior literature, we see low (21%) utilization of spironolactone in our cohort of patients with HFrEF, 80% of whom were ≥65 years. Concerns regarding polypharmacy, comorbidities, and adverse reactions, especially in the older population, have been previously noted as barriers to the adoption of mineralocorticoid receptor antagonists in HF [18]. By comparison, 32.5% of eligible HF patients treated at hospitals participating in the Get With The Guidelines-HF (GWTG_HF) registry in the United States between 2005–2007 were discharged with a prescription for an aldosterone antagonist [6]. We observe a lower utilization (21%) than what was observed in the GWTG-HF registry (32.5%). Age may in part explain this difference. In the GWTG-HF registry, eligible patients receiving an aldosterone antagonist were on average 64 years old whereas those that did not receive the medication were on average 68 years old. Younger patients were more likely to be prescribed an aldosterone antagonist. The average age in our population of HFrEF patients was 74 with 80% of our HFrEF cohort being ≥65 years old. Another plausible explanation is that the hospitals participating in the GWTG-HF registry were undergoing a quality improvement program to increase adherence to guideline based treatment, whereas our database is representative of the broader prescribing community.

Spironolactone and other MRAs have also been of interest in the management of HFpEF due to their effects on interstitial fibrosis, myocardial stiffness, extracellular matrix expansion and vascular function, which play a role in the pathogenesis of HFpEF [19]. However, available evidence on the efficacy of spironolactone in HFpEF is limited. Short-comings of available evidence (low sample size, trial eligibility criteria, and inconsistent

effects) have been discussed elsewhere [10]. Nonetheless, guidelines based on xpert consensus recommend the use of spironolactone in selected patients with HFpEF [11]. Despite presumed benefits, our real-world utilization study revealed much lower use of spironolactone among HFpEF patients compared to HFrEF patients. The absence of a mortality benefit for spironolactone or other mineralocorticoid antagonists found in clinical trials and the need for careful monitoring of potassium and renal function could be deterring use in HFpEF management. We also observed declining use of spironolactone following HFrEF and HFpEF diagnosis. It is possible that HF patients receive other treatment options with less monitoring, since careful monitoring of potassium, renal function and diuretic dosing is necessary with spironolactone use.

In our study, both HFrEF and HFpEF patients had similar average dose and duration of spironolactone use, shortly after the HF diagnosis. This finding suggests similar treatment patterns for both HF cohorts. Clinicians are likely following the recommended treatment regimen for chronic HF for the management of both HFrEF and HFpEF patients [17]. The 2013 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines recommends HF patients are initially started at 12.5–25 mg orally once daily, to a maximum dose of 50 mg once daily if clinically indicated and as tolerated. The average daily dose of 25 mg/day shortly after HF diagnosis is observed in our study, and likely reflects the initial dosing patterns for HF management. In the TOPCAT trial [9], HFpEF patients were initially started at 12.5 mg once daily, titrated every four weeks to 25 to 50 mg daily. Our data did not find the use of spironolactone at this lower dose among HFpEF patients.

HFpEF represents more than half of the HF population and the incidence of HFpEF continues to increase [1,3]. Despite the poor prognosis, similar morbidity and mortality as HFrEF, the management of HFpEF is controversial and there is no therapy that has been shown to reduce all-cause and cardiac-related mortality. Spironolactone appears to improve diastolic function, induce reverse left ventricular remodeling, and even reduce cardiac hospitalizations, although there is no definitive beneficial effect of spironolactone on all-cause and cardiac mortality in patients with HFpEF [9,20]. Thus, spironolactone can be considered a therapeutic option for HFpEF. The low utilization of spironolactone found in this study highlights the need for future research to evaluate the effectiveness of spironolactone in HFpEF and identify any subgroups of patients with HFpEF that are most likely to benefit from spironolactone.

Our study is the first study to analyze a large, demographically and geographically diverse database of U.S. healthcare claims to examine the use of spironolactone among HF patients. The use of a modified validated HF-identification algorithm allowed for evaluation of spironolactone utilization by HF subtypes. We were also able to examine average daily dosing and duration of first use of spironolactone after HF diagnosis. Despite the study strengths, there are limitations. Although we relied on a validated algorithm to classify patients into HFrEF and HFpEF categories, there is still potential misclassification of HF categories due to the lack of EF values in administrative data. However, it is reassuring that the clinical characteristics of the HFrEF and HFpEF patients presented in this study are similar to those in the validation study. We used pharmacy dispensing data to ascertain treatment initiation and to calculate dosing and duration of use, these estimates are also subject to potential inaccuracies in administrative billing data.

5. Conclusions

Our study suggests lower initiation of spironolactone following HFpEF compared to HFrEF diagnosis. Over time, the initiation of spironolactone after HF diagnosis declined in both HF cohorts. Similar spironolactone dosing and duration were observed in both the HFpEF and HFrEF cohort. Future studies should examine appropriateness of spironolactone utilization and utilization of other therapeutic agents available for the management of HF. Research evaluating effectiveness of spironolactone and characterizing spironolactone

treated and untreated HFpEF cohorts will also be needed to identify treatment strategies and gaps in this population.

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