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Research Paper

Trends in pharmacotherapy utilization among patients with heart failure with preserved ejection fraction

Munaza Riaz [a,b], Steven M. Smith [a,c], Eric A. Dietrich [d], David E. Winchester [c], Jingchuan Guo [a], Haesuk Park [a,*]

[a] Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA
[b] Lahore College for Women University, Lahore, Punjab, Pakistan
[c] Division of Cardiovascular Medicine, Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, USA
[d] Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA

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ABSTRACT

Study objective: Half of patients with heart failure have preserved ejection fraction (HFpEF). Over the years, guidelines have recommended or advised against various therapies for HFpEF management. However, there is limited evidence on the trends in utilization of the various medications. The aim of this study was to examine the trends in the use of pharmacotherapies among patients with HFpEF from 2008 through 2020.
Design: Retrospective cohort study of patients with HFpEF used MarketScan® Commercial and Medicare Supplemental Databases (2007–2020).
Participants: Patients with HFpEF.
Outcome measures: Utilization rates for angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), aldosterone receptor antagonists (ARAs), diuretics, β-blockers, calcium channel blockers (CCBs), phosphodiesterase 5 inhibitors (PDE5Is), nitrates, digoxin, and sodium glucose cotransporter-2 inhibitors (SGLT2i) within 90 days of the first HFpEF diagnosis.
Results: We identified 156,730 patients with HFpEF (mean [SD] age, 73 [13.4] years; 57 % females). From 2008 to 2020, we found increased utilization rates for ARNIs (0.02 % vs. 0.17 % of all patients, $p < 0.01$), ARBs (14.3 % vs. 18.6 %, $p < 0.01$), ARAs (7.0 % vs. 8.4 %, $p < 0.01$), CCBs (30.6 % vs. 33.4 %, $p < 0.01$), and SGLT2i (0.001 % vs. 0.021 %, $p < 0.01$). By contrast, the utilization of ACEIs (30.4 % vs. 20.5 %, $p < 0.01$), digoxin (9.5 % vs. 2.4 %, $p < 0.01$), nitrates (10.7 % vs. 4.9 %, $p < 0.01$), diuretics (54.1 % vs. 50.4 %, $p = 0.20$), and β-blockers (52.6 % vs. 51.7 %, $p < 0.01$) decreased, while utilization rates of PDE5Is remained stable (1.5 % vs. 1.1 %, $p = 0.90$) .
Conclusions: During the 13-year study period, the utilization of ARNIs, ARBs, ARAs, CCBs, and SGLT2i increased while the utilization of digoxin, nitrates, diuretics, and β-blockers decreased among patients with HFpEF.

1. Introduction

In the United States (US), 2.4 to 3.4 million people are estimated to have heart failure with preserved ejection fraction (HFpEF), a syndrome with signs and symptoms of heart failure (HF) in the context of a normal or near normal left ventricular ejection fraction. [1] HFpEF accounts for half of all HF-related healthcare resource utilization and hospitalizations in the US and has gradually increased at a rate of 10 % per decade. [1,2] HFpEF is a challenging chronic condition to treat because no single pharmacological treatment has been shown to convincingly reduce morbidity and mortality in this population until recently. [3] Hence, treating comorbid conditions has been the major focus for the management of HFpEF, as recommended by American Heart Association (AHA) guidelines. [4–6] For example, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), and β-blockers are considered

* Corresponding author at: Department of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, HPNP Building Room 3325, 1225 Center Drive, Gainesville, FL 32610, USA.
E-mail addresses: m.riaz@ufl.edu (M. Riaz), ssmith@cop.ufl.edu (S.M. Smith), dietrich@cop.ufl.edu (E.A. Dietrich), david.winchester@medicine.ufl.edu (D.E. Winchester), Guoj1@cop.ufl.edu (J. Guo), hpark@cop.ufl.edu (H. Park).

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reasonable to control blood pressure in patients with HFpEF. [6] ARBs, sodium glucose cotransporter-2 inhibitors (SGLT2i), and aldosterone receptor antagonists (ARAs) are recommended to reduce hospitalizations [5,6] By contrast, digoxin, despite being useful for treatment of heart failure with *reduced* ejection fraction (HFrEF), does not improve the quality of life for patients with HFpEF owing to different pathophysiological mechanisms. [7] Likewise, nitrates and phosphodiesterase 5 inhibitors (PDE5Is) have not been shown to improve the quality of life for patients with HFpEF, and they are thus considered ineffective for the treatment of HFpEF. [8–10] In 2016, the AHA issued a statement regarding drugs that may exacerbate HF and advised against the use of calcium channel blockers (CCBs) for patients with HF owing to their negative inotropic effects and possible risks related to cardiac events. [11,12]

A study assessing discharge prescriptions for hospitalized patients with HFpEF reported increasing trends in the utilization of β-blockers, stable trends for ARAs, and decreasing utilization trends for ACEIs/ARBs from 2005 to 2010. [13] Since then, clinical guidelines have been updated as new medications were approved by the US Food and Drug Administration and cumulative clinical evidence in pharmacotherapy treatment for HFpEF became available. However, studies assessing recent trends in pharmacotherapy use among patients with HFpEF are limited. The aim of this study was to examine the trends in pharmacotherapy utilization of HFpEF during a period of 13 years, from 2008 to 2020.

2. Methods

2.1. Data source and study design

We conducted a retrospective nationwide cohort study using IBM® MarketScan® Commercial and Medicare Supplemental Databases from July 1, 2007, to December 31, 2020. The databases contain de-identified patient-level medical and pharmacy claims data for nearly 40 million individuals annually. Data are contributed by large employers, managed care organizations, hospitals, and Medicare. The Commercial and Medicare Supplemental Databases contain the health care experiences of individuals in the US with primary or Medicare Supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. This study was approved by the University of Florida Institutional Review Board.

2.2. Study population

Patients aged ≥18 years were included if they had one in-patient or two out-patient claims with primary or secondary diagnosis codes for HFpEF using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) 428.3× or *Tenth Revision* (*ICD-10-CM*) I50.3×. These codes were validated previously with 84 % positive predictive value and 88 % specificity. [14] The first HFpEF diagnosis date was considered the index date. Patients were included only for the index year, which was defined as the year of their first HFpEF diagnosis, and they were not included any subsequent years. Patients were also required to have ≥1 electrocardiography or cardiac catheterization procedure codes (Supplemental Table S1) in the 30 days before or after the index date to ensure that patients received this procedure to aid diagnosis of HFpEF, and to be continuously enrolled in a health plan ≥6 months pre-index date (baseline period) and 90 days post-index date. Patients with any HF-related diagnosis (Supplemental Table S1), including unspecified HF, HFrEF, or combined HFrEF and HFpEF diagnoses, in the baseline period were excluded. Patients were also excluded if they had missing demographic or health plan information during the baseline period, or an unspecified HF or HFrEF diagnosis within 30 days after the index date.

2.3. Study outcomes

For each year, we determined the proportion of the patients with one or more prescription fills for 11 classes of medications for HFpEF, including ACEIs, ARBs, ARNIs, ARAs, diuretics, β-blockers, CCBs, PDE5Is, nitrates, digoxin, and SGLT2i (Supplemental Table S2). Those classes were selected because at some point they have been recommended or advised against by the Heart Failure Society of America or AHA for the management of comorbid conditions in patients with HFpEF. [4,5,15] A patient was considered a user of each class or drug in each year if they had at least one prescription fill identified through National Drug Codes from pharmacy claims within the 90-day prescription window. Annual treatment utilization was calculated by dividing the number of patients who received at least one prescription in each therapeutic class by the number of patients with HFpEF who met the inclusion/exclusion criteria in each year.

2.4. Statistical analysis

We summarized mean and standard deviation (SD) data for continuous variables, and frequency and percentage data for categorical variables. We used multivariable Poisson regression models to adjust for covariates that are known predictors or risk factors of HF and for choice of pharmacotherapy. [16,17] The following selected covariates were used: age, sex, region, health plan type, clinician specialty, procedures (implantable cardioverter-defibrillator, cardiac resynchronization therapy), and medical conditions (diabetes, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, dyslipidemia, coronary artery syndrome, renal disease, anemia, peripheral vascular disease, valvular heart disease, myocardial infarction, depression, dementia, atrial fibrillation, stroke, erectile dysfunction, and pulmonary hypertension). All analyses were performed using SAS, version 9.4 (SAS institute, Cary, North Carolina) and STATA13 (Stata Corp, College Station, TX).

2.5. Sensitivity and subgroup analysis

We conducted sensitivity analysis by changing the post-index prescription fill time window to 183 days. We performed subgroup analyses based on age, sex, and with and without comorbid obesity, diabetes, and hypertension to examine potential heterogeneity in the use of pharmacotherapy in selected subgroups of patients with HFpEF.

3. Results

We identified 156,730 patients with HFpEF between January 2008 and December 2020 (Supplemental Fig. S1). Table 1 provides the baseline characteristics of the overall cohort of patients with HFpEF. The mean (SD) age for the entire cohort was 73.1 (13.4) years, among whom 72.1 % were 65 years or older, and 57.2 % were women. In total, 45.6 % of patients had a preferred provider organization health benefit plan. The most common comorbid conditions were hypertension (77.7 %), dyslipidemia (48.2 %), diabetes (38.8 %), valvular heart disease (37.4 %), chronic obstructive pulmonary disease (36.3 %), and atrial fibrillation (33.9 %).

3.1. Overall pharmacotherapy utilization trends

Overall annual adjusted pharmacotherapy utilization trends within 90 days of the index date are shown in Fig. 1. From 2008 to 2020, diuretics, and β-blockers were the most commonly used medication classes, with approximately 45 %–55 % of patients with HFpEF receiving one of these two classes of medications in any given year. We observed increasing trends from 2008 to 2020 in the utilization of CCBs (30.6 % vs. 33.4 %, $p < 0.01$), ARBs (14.3 % vs. 18.6 %, $p < 0.01$), and ARAs (7.0 % vs. 8.4 %, $p < 0.01$) during the study period. Increased trends from

Table 1
Baseline characteristics of overall cohort with HFpEF.

Characteristic	HFpEF Cohort, No. (%) (N = 156,730)
Age, mean ± SD, years	73.1 ± 13.4
<65	43,788 (27.9)
≥65	112,942 (72.1)
Sex	
Male	67,022 (42.8)
Female	89,708 (57.2)
Index year	
2008	10,158 (6.5)
2009	13,972 (8.9)
2010	15,250 (9.7)
2011	20,369 (13.0)
2012	20,195 (12.9)
2013	18,192 (11.6)
2014	16,267 (10.4)
2015	11,967 (7.6)
2016	8568 (5.5)
2017	6697 (4.3)
2018	5677 (3.6)
2019	5687 (3.6)
2020	3731 (2.4)
US Region	
Northeast	32,210 (20.6)
North Central	53,542 (34.2)
South	50,282 (32.1)
West	17,871 (11.4)
Unknown	2825 (1.8)
Type of benefit plan	
Comprehensive	55,273 (35.3)
EPO	1005 (0.6)
HMO	16,565 (10.6)
POS	5993 (3.8)
PPO	71,525 (45.6)
POS with capitation	616 (0.4)
CDHP	3974 (2.5)
HDHP	1778 (1.1)
Comorbid conditions	
Anemia	42,802 (27.3)
Atrial Fibrillation	53,117 (33.9)
Cerebrovascular disease	31,910 (20.4)
Chronic Obstructive Pulmonary Disease	56,860 (36.3)
Coronary Artery Syndrome	36,767 (23.5)
Dementia	6110 (3.9)
Depression	17,704 (11.3)
Diabetes	60,729 (38.8)
Dyslipidemia	75,592 (48.2)
Erectile Dysfunction	1764 (1.1)
Hypertension	121,728 (77.7)
Myocardial Infarction	19,835 (12.7)
Obesity	23,003 (14.7)
Peripheral Vascular Disease	29,007 (18.5)
Pulmonary Hypertension	17,942 (11.5)
Renal Disease	33,159 (21.2)
Stroke	26,110 (16.7)
Valvular Heart Disease	58,654 (37.4)
ICD/CRT	5916 (3.8)

Abbreviations: CDHP, consumer-directed health plan; EPO, exclusive provider organization; HFpEF, heart failure with preserved ejection fraction; HMO, health maintenance organization, HDHP, high deductible health plan; ICD/CRT, implantable cardioverter-defibrillator/cardiac resynchronization therapy; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

2015 to 2020 in the utilization of ARNIs (0.02 % vs. 0.17 %, p < 0.01) were also observed. We also observed increasing utilization trends for overall SGLT2i (0.001 % vs. 0.021 %, p < 0.01) from 2013 to 2020 within 90 days after HFpEF diagnosis (Supplemental Fig. S3). Among CCB users, the utilization rate for non-dihydropyridine (non-DHP) CCBs decreased (34.8 % vs. 26.7 %), whereas the utilization rate for dihydropyridine (DHP) CCBs increased (65.2 % vs. 73.3 %) (Supplemental Fig. S2). Empagliflozin was the most utilized drug among SGLT2i (Supplemental Fig. S3-S4). Among users of SGLT2i, utilization of empagliflozin (0.000 % to 0.015 %, p < 0.01), and dapagliflozin (0.001 % to 0.005 %, p < 0.01) increased from 2014 to 2020, while the utilization of canagliflozin showed variable trends from 2013 to 2020 (Supplemental Fig. S3).

Decreasing trends were observed from 2008 to 2020 in the utilization rates of ACEIs (30.4 % vs. 20.5 %, p < 0.01), digoxin (9.5 % vs. 2.4 %, p < 0.01), nitrates (10.7 % vs. 4.9 %, p < 0.01), diuretics (54.1 % vs. 50.4 %, p = 0.20), and β-blockers (52.6 % vs. 51.7 %, p < 0.01). Among users of diuretics, utilization of thiazide diuretics increased from 2008 to 2020 (10.7 % to 15.2 %), while utilization of loop diuretics showed variable trends during this period (Supplemental Fig. S5). We observed stable utilization rates from 2008 to 2020 for PDE5Is (1.5 % vs. 1.1 %, p = 0.90).

3.2. Subgroup and sensitivity analyses

We observed different trends in the use of β-blockers and CCBs by age group (Fig. 2). Use of β-blockers modestly decreased from 2008 to 2020 (57.8 % vs. 54.2 %, p < 0.01) for patients aged <65 years but modestly increased (50.1 % vs. 52.1 %, p < 0.01) for patients aged ≥65 years. Utilization of CCBs showed an upward trend in both these age groups but was more pronounced for patients aged ≥65 years (29.9 % vs. 35.7 %, p < 0.01) than <65 years (31.1 % vs. 31.8 %, p < 0.01).

Male patients (7.6 % vs. 7.6 %, p < 0.01) showed fluctuating utilization rates for ARAs between 2008 and 2020, whereas female patients showed an increasing trend in utilization rates (6.6 % vs. 8.9 %, p < 0.01), similar to the trend observed in the main analysis (Fig. 3).

Pharmacotherapy utilization trends for patients with comorbid hypertension at baseline were consistent with the main analysis (Fig. 4) although, as expected, use of most classes was higher among patients with vs. without hypertension. CCB and ARB use increased more markedly from 2008 to 2020 among patients with hypertension (CCB: 32.2 % vs. 36.5 %, p < 0.01; ARB: 14.7 % vs. 21.3 %, p < 0.01) than among patients without hypertension (CCB: 23.1 % vs. 23.2 %, p = 0.13; ARB: 10.9 % vs. 9.7 %, p = 0.15). Similarly, CCB and ARB use increased more markedly among patients with obesity (CCB: 31.4 % vs. 35.9 %, p < 0.01; ARB: 15.4 % vs. 20.9 %, p < 0.01) than among patients without obesity (CCB: 30.3 % vs. 32.8 %, p < 0.01; ARB: 14.1 % vs. 17.9 %, p < 0.01) from 2008 to 2020.The utilization trends observed for study medications were consistent with the main analysis for patients with or without diabetes (Fig. 4).

Sensitivity analyses extending the post-index utilization time window to 183 days revealed no qualitative differences from those detected in the main analyses (Supplemental Fig. S6-S7).

4. Discussion

This large, nationwide cohort analysis examined trends in the use of various pharmacotherapies among patients with HFpEF across a 13-year study period ending in 2020. We found increasing rates in the use of ARBs, ARAs, ARNIs, CCBs, β-blockers, and SGLT2i but decreasing rates in the use of ACEIs, digoxin, nitrates, and, to a lesser extent, diuretics. PDE5Is were used infrequently across all study years.

Our findings indicated that β-blockers and diuretics were the most utilized medications by patients with HFpEF, which aligns with findings from a previous study that showed that diuretics and β-blockers were the most used cardiovascular medications during the first year after HFpEF diagnosis. [18] However, there were also some differences observed in the present study compared with prior research. For example, although a previous study also observed increased utilization of β-blockers from 2005 to 2010, [13] our study (with a start date of 2008) suggested decreased utilization between 2008 and 2010, with increased utilization thereafter through 2015. Another study using data from the Get With The Guidelines-Heart Failure registry reported decreased utilization of β-blockers between 2009 and 2016 for patients discharged from the hospital. [13,19]

Prior studies have reported decreased use and prescribing rates from 2005 to 2016 for a combined category of ACEI/ARB at hospital

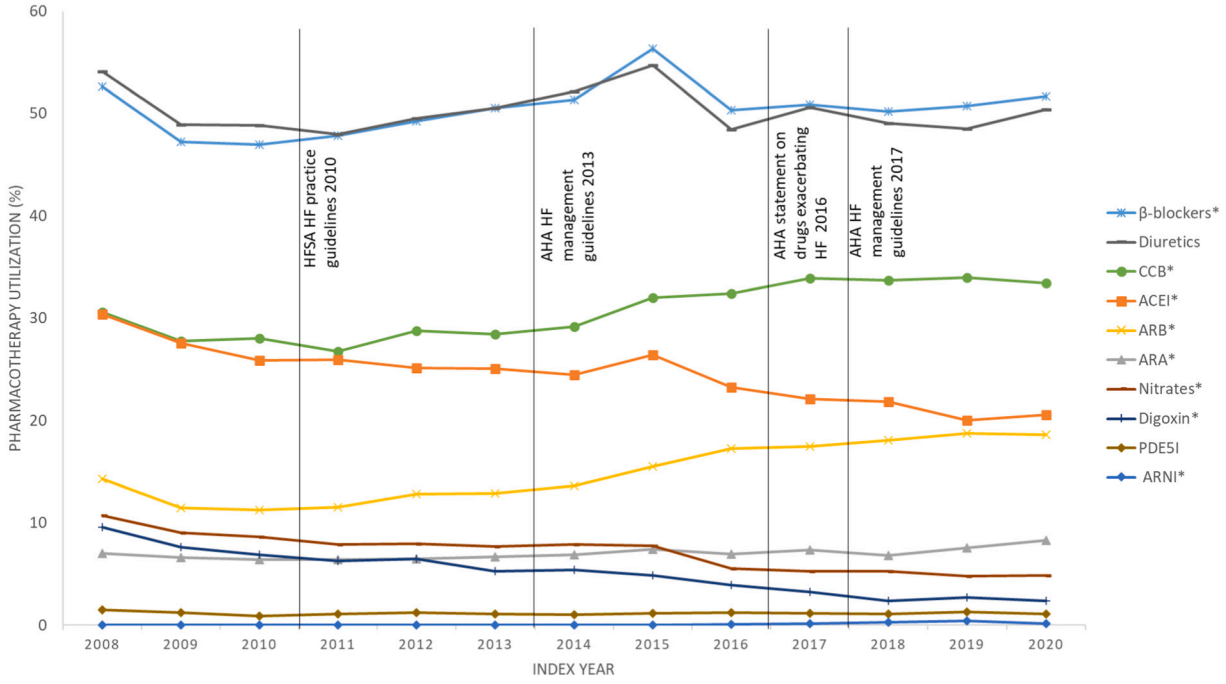

Fig. 1. Overall adjusted trends in pharmacotherapy utilization within 90 days of diagnosis of heart failure with preserved ejection fraction
ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CCB = calcium channel blocker; HF = heart failure; HFSA = Heart Failure Society of America; PDE5I = phosphodiesterase 5 inhibitor.
*$p_{trend} < 0.01$.

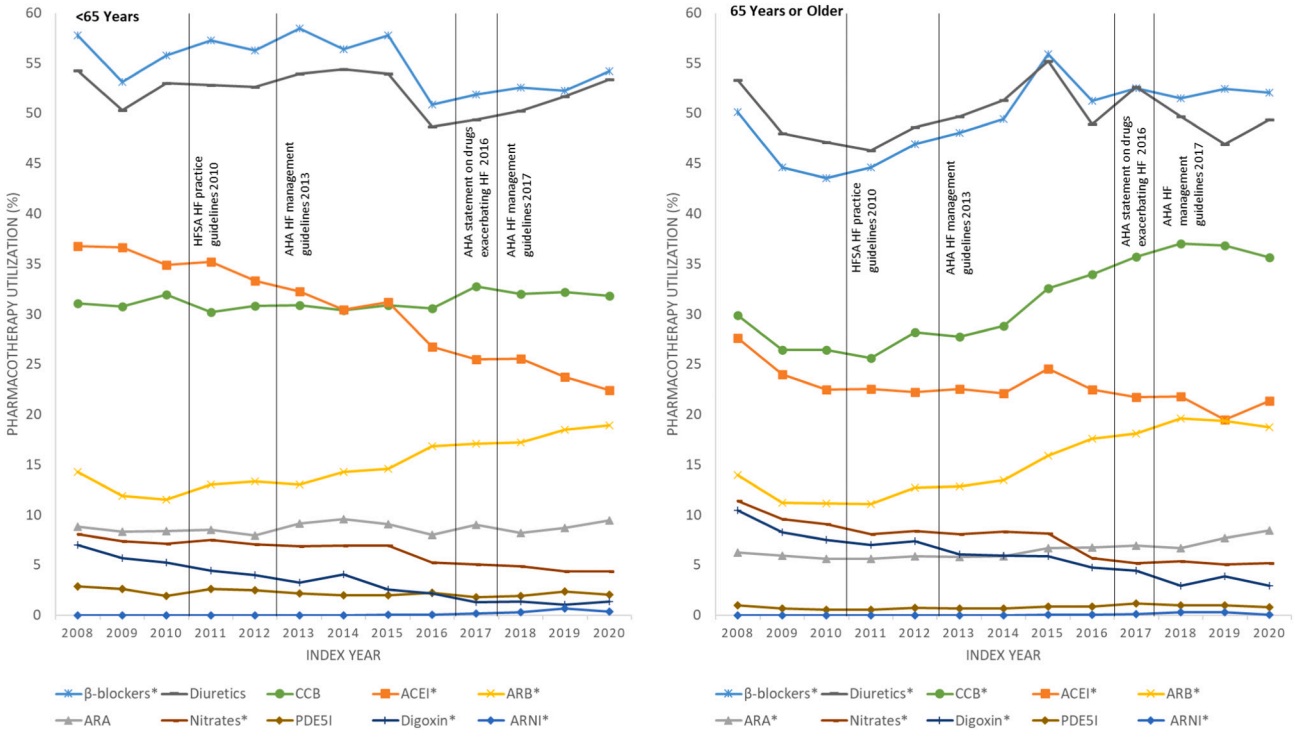

Fig. 2. Trends in pharmacotherapy utilization in subgroups based on age among patients with HFpEF
ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CCB = calcium channel blocker; HF = heart failure; HFSA = Heart Failure Society of America; PDE5I = phosphodiesterase 5 inhibitor.
*$p_{trend} < 0.01$.

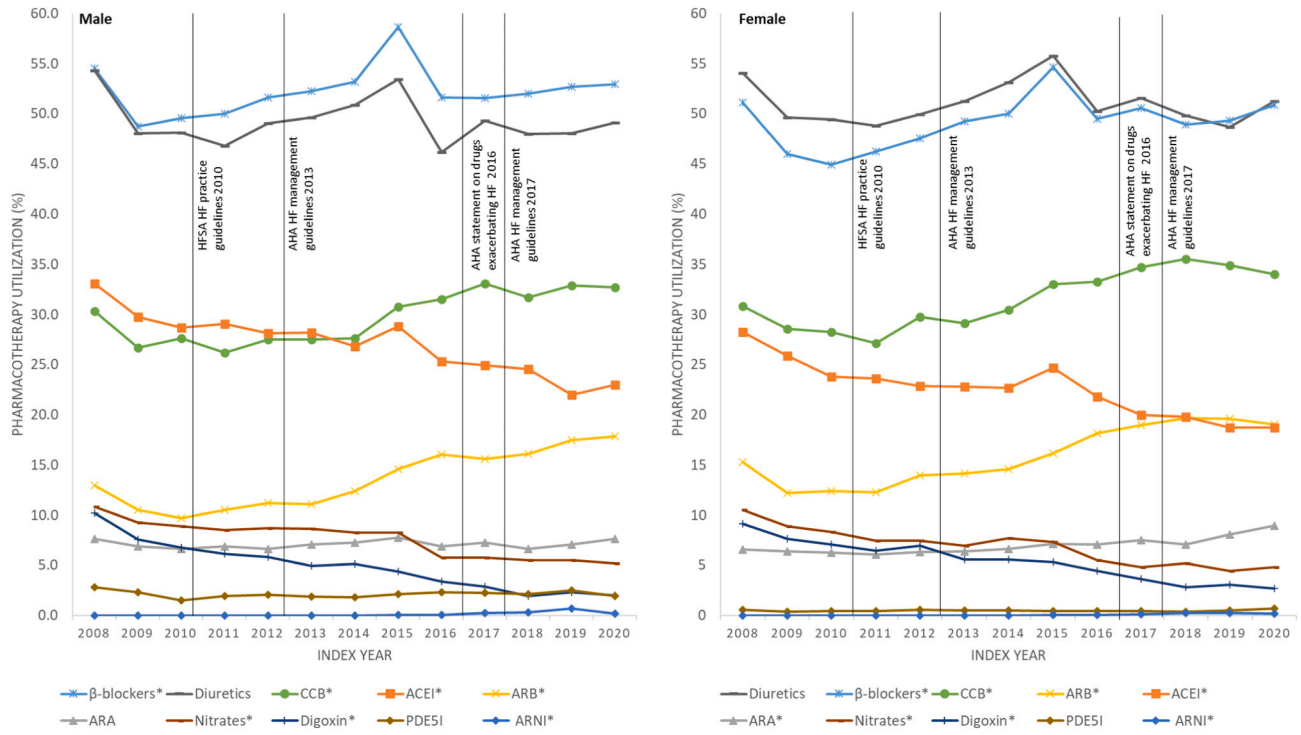

Fig. 3. Trends in pharmacotherapy utilization in subgroups based on sex among patients with HFpEF
ACEI = angiotensin-converting enzyme inhibitors; AHA = American Heart Association; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CCB = calcium channel blocker; HF = heart failure; HFSA = Heart Failure Society of America; PDE5I = phosphodiesterase 5 inhibitor.
*$p_{trend} < 0.01$.

discharge. [13,19] In the present study, we observed an increasing trend in the utilization of ARBs after 2013 but a decreasing trend in the use of ACEI; thus we analyzed these categories separately. The increasing trend in the use of ARBs may be explained by the publication of 2013 AHA guidelines for the management of HF that recommended the use of ARBs for the prevention of hospitalizations in patients with HFpEF. [4] A downward trend in the use of ACEIs may be due to switching to ARBs from ACEIs following the release of the AHA recommendations and expert opinions. [4,5,20]

We observed a modest increase in the use of ARNIs from 2015 to 2020. In 2015, sacubitril/valsartan, the first drug in the ARNI class, was approved for the management of HFrEF but was not granted an expanded indication for chronic HF (including patients with HFpEF) until 2021, after our study period. [21] In 2019, the PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) showed that sacubitril/valsartan was superior to valsartan, an ARB, for reducing morbidity and mortality in females and people of White race and ethnicity. [22] This use is expected to increase in the coming years following the release of the AHA 2022 guidelines, which recommend ARNIs for the reduction of hospitalization among patients with HFpEF. [6]

We also observed an increase in the use of SGLT2i particularly empagliflozin and dapagliflozin. In 2022, FDA approved HFpEF indication for empagliflozin based on the empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved) clinical trial and the dapagliflozin evaluation to improve the lives of patients with preserved ejection fraction heart failure (DELIVER) trial reported promising results of dapagliflozin among patients with HFpEF. [23,24] Although it was too early to assess adoption of SGLT2i in HFpEF in our study period (2008–2020), we included this class because it was recommended by AHA 2022 guidelines for management of HFpEF. [6]

We found an unexpected overall upward trend in the use of CCBs despite reports indicating that CCBs (DHP or non-DHP) may not have any morbidity or mortality benefits for patients with HFpEF. [25] In a statement in 2016, the AHA suggested that CCBs, (mainly non-DHPs and nifedipine) may exacerbate HF because of their negative inotropic effects in patients with chronic HF. [11] In the present study, utilization rates of non-DHP CCBs decreased over the study period, consistent with another observational study, [26] but DHP CCB utilization showed an upward trend, which may be a reflection of hypertension treatment trends, as evident in subgroup analyses. Further study is needed to explore the safety and the cause of this shift in the utilization of DHP and non-DHP CCBs for patients with HFpEF. Finally, similar to another study that reported an increase in the prescribing rates of ARAs among patients with HFpEF at hospital discharge, [19] we found an increase in the utilization rate of ARA across the study period.

We detected a downward trend in the use of digoxin between 2008 and 2020, which may be because digoxin has been found to be ineffective for patients with HFpEF in preventing morbidity or mortality or in improving quality of life. [7] Nitrates and PDE5Is were not recommended by 2017 AHA guidelines for the management of HFpEF. [5] We found decreasing utilization rates for nitrates but stable use of PDE5Is during the study period. The downward trend in the use of nitrates was pronounced after 2015, when the results of the NEAT-HFpEF trial (Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction) was published showing nonsignificant lower physical activity in nitrates users compared with placebo. [8]

Our study provides insights in utilization of therapeutic agents whose use has been recommended or advised against. Our findings did not provide any clinical effectiveness of specific medications to patients with HFpEF but summarized the utilization patterns of pharmacotherapies. Future studies are needed to examine effectiveness of these medications among patients with HFpEF.

Our study has several strengths. We used the MarketScan Commercial and Medicare Supplemental Databases, which are representative of

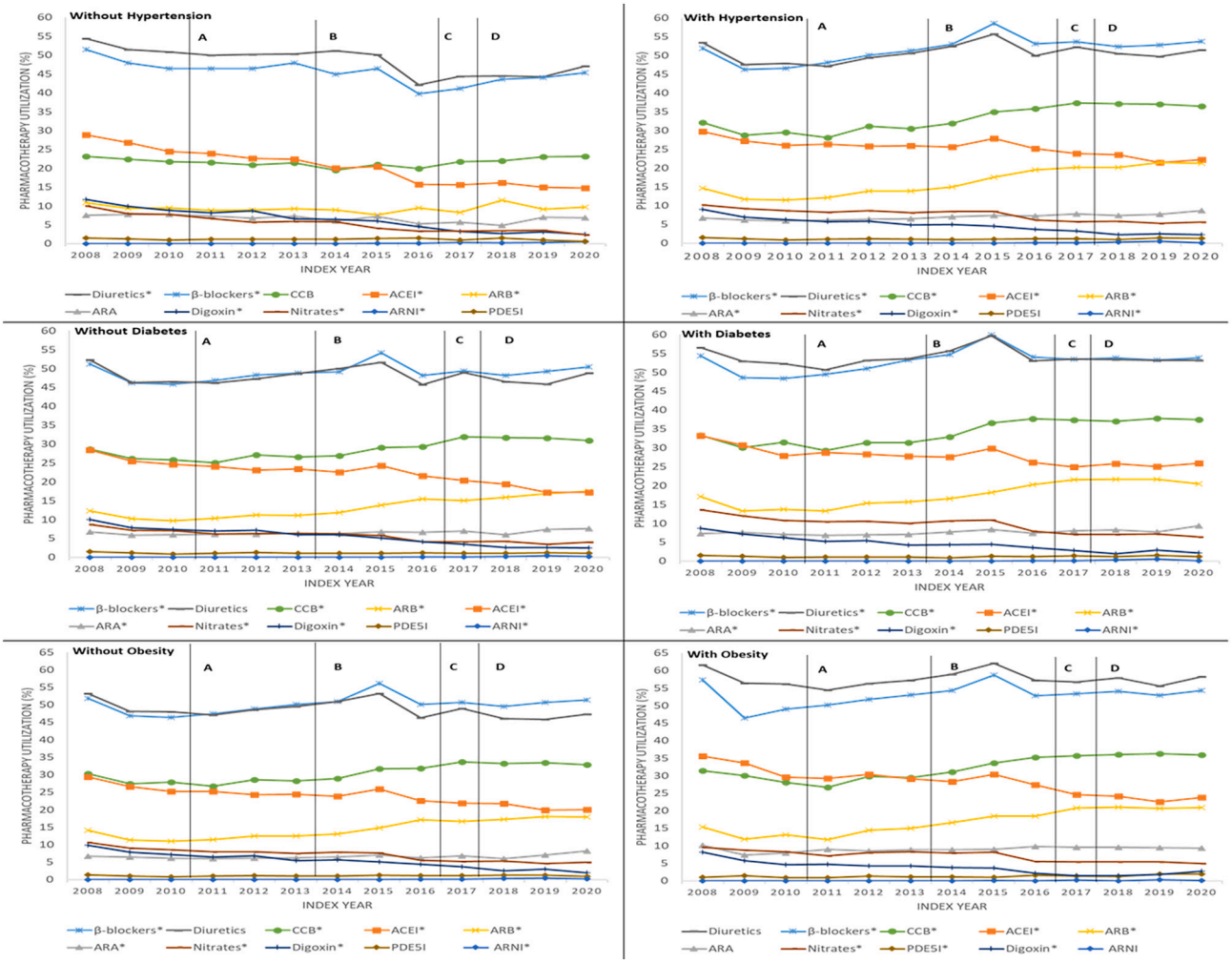

Fig. 4. Trends in pharmacotherapy utilization in subgroups based on comorbid conditions among patients with HFpEF
A = HFSA HF practice guidelines; B = AHA HF management guidelines 2013; C = AHA statement on drugs exacerbating HF 2016; D = AHA HF management guidelines 2017.
ACEI = angiotensin-converting enzyme inhibitors; AHA = American Heart Association; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CCB = calcium channel blocker; HF = heart failure; HFSA = Heart Failure Society of America; PDE5I = phosphodiesterase 5 inhibitor.
*$p_{trend} < 0.01$.

individuals enrolled in commercial health insurance across the US and allowed for longitudinal assessment of drug utilization during the 13-year study period, including for the new ARNI class, and SGLT2i, which were recently approved for HFpEF. Previous studies examined the trend from 2005 to 2016 years. We expanded the study after introduction of ARNI in the market in 2015. Our study differs from previous studies not only in the longer and more recent time period studied (2008–2020) but also in determining the trends in utilization in a study population that was not restricted to patients hospitalized with HFpEF that previous studies focused.

This study also has several limitations. We relied on *ICD-9-CM* or *ICD-10-CM* diagnostic codes recorded in claims data to identify patients with HFpEF but lacked data on the results of echocardiography or ejection fraction or laboratory tests (e.g., B-type natriuretic peptide, N-terminal pro–B-type natriuretic peptide) to corroborate these diagnosis codes. We attempted to minimize misclassification risk by using validated *ICD* code algorithms for HFpEF identification and by excluding patients with any unspecified HF- or HFrEF-related claims within 1 month of the index date. Because we used an administrative claims database for prescription fills, we were unable to determine whether patients actually consumed medications as prescribed. We cannot rule out potential unmeasured confounders, which we were unable to capture, such as race and ethnicity, socioeconomic status, or educational level, [27,28] due to the lack of records. Proportion of patients with HFpEF varied over the index years which may be due to changes in enrollees in the MarketScan data because of variations in the number of data contributors voluntarily providing their data to IBM. Although the enrollee/patient numbers have dropped, the MarketScan remains one of the largest and longer-spanning commercial claims data sources currently available in the US. The patients included in this study had private and Medicare Advantage plans; thus, our findings may not be generalizable to patients with other health insurance plans or to patients without insurance.

5. Conclusions

Our findings suggested that the utilization of ARNIs, ARBs, ARAs, CCBs, and SGLT2i increased from 2008 to 2020, while the utilization of digoxin, nitrates, diuretics, and β-blockers decreased and the use of PDE5Is remained stable among patients with HFpEF. Although the AHA 2016 statement advised against the use of CCBs in HF because of their potential to exacerbate or precipitate HF, their use during the study

years increased. Further investigation is needed to evaluate the factors contributing to this increase despite available evidence advising against their use and the availability of safer agents, such as ARBs and thiazide diuretics.

CRediT authorship contribution statement

Munaza Riaz: Conceptualization, Study Design, Data Analysis, Manuscript Writing.

Steven M. Smith: Study Design, Manuscript Review and Editing.

Eric A. Dietrich: Study Design, Manuscript Review.

David E. Winchester: Study Design, Manuscript Review.

Jingchuan Guo: Study Design, Manuscript Review.

Haesuk Park: Supervision, Study Design, Manuscript Review and Editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100259.

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