Drugs - Real World Outcomes (2022) 9:53–62
https://doi.org/10.1007/s40801-021-00277-0

ORIGINAL RESEARCH ARTICLE

# Sodium-Glucose Cotransporter-2 Inhibitor Use is Associated with a Reduced Risk of Heart Failure Hospitalization in Patients with Heart Failure with Preserved Ejection Fraction and Type 2 Diabetes Mellitus: A Real-World Study on a Diverse Urban Population

**Weijia Li[1] · Adarsh Katamreddy[1] · Rachna Kataria[2] · Merle L. Myerson[3] · Cynthia C. Taub[2,3]**

Accepted: 10 August 2021 / Published online: 3 September 2021


## Abstract

**Background** Limited evidence-based therapies exist for the management of heart failure with preserved ejection fraction (HFpEF). Sodium-glucose cotransporter-2 inhibitor (SGLT2i) use in patients with systolic heart failure (HFrEF) and type-2-diabetes mellitus (T2DM) is associated with improved cardiovascular (CV) and renal outcomes.

**Objective** We sought to examine whether there is an association of SGLT2i use with improved CV outcomes in patients with HFpEF.

**Patients and methods** We conducted a single-center, retrospective review of patients with HFpEF and T2DM. The cohort was divided into two groups based on prescription of a SGLT2i or sitagliptin. The primary outcome was heart failure hospitalization (HFH); secondary outcomes were all-cause hospitalization and acute kidney injury (AKI).

**Results** After propensity score matching, there were 250 patients (89 in the SGLT2i group, 161 in the sitagliptin group), with a mean follow-up of 295 days. Univariate Cox regression analysis showed that the SGLT2i group had a reduced risk of HFH versus the sitagliptin group (hazard ratio (HR) 0.13; 95% confidence interval (CI) (0.05–0.36); $p < 0.001$). The SGLT2i group had a decreased risk of all-cause hospitalization (HR 0.48; 95% CI (0.33–0.70); $p < 0.001$) and SGLT2i had a lower risk of AKI (HR 0.39; 95% CI (0.20–0.74); $p = 0.004$).

**Conclusions** The use of SGLT2is is associated with a reduced incidence of HFH and AKI in patients with HFpEF and T2DM.

## 1 Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF), also known as diastolic heart failure, is characterized by abnormalities of ventricular relaxation and compliance, resulting in decreased cardiac output and compromised organ perfusion [1]. More than 8 million Americans live with all forms of HF and the total medical expenditure

**Key Points**

Patients with both heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (T2DM) who were started on SGLT2 inhibitors (SGLT2is) are less likely to be hospitalized for heart failure exacerbation.

SGLT2i use is associated with a lower risk of developing acute kidney injury among patients with T2DM and HFpEF.

General internal medicine physicians are prescribing SGLT2is for T2DM and HFpEF patients more often than cardiologists.

✉ Cynthia C. Taub
cynthia.c.taub@hitchcock.org

[1] Department of Medicine, Jacobi Medical Center/Albert Einstein College of Medicine, The Bronx, NY, USA

[2] Division of Cardiology, Montefiore Medical Center/Albert Einstein College of Medicine, The Bronx, NY, USA

[3] Section of Cardiovascular Medicine, Dartmouth-Hitchcock Medical Center, Geisel School of Medicine, 1 Medical Center Drive, Lebanon, NH 03756, USA

for HF is projected to reach US$53.1 billion in 2030, with 80% of the costs attributed to hospitalization [2]. Up to a half of the patients with HF have HFpEF, which is defined as left ventricular ejection fraction of ≥ 50% with defined echocardiographic features and/or clinical evidence of congestion [3]. However, while evidence-based therapies are available for heart failure with reduced ejection (HFrEF), similar therapies for HFpEF are unknown [4, 5]. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) are a novel class of cardiometabolic drugs, which have not only shown conclusive benefits in patients with HFrEF [6–8], but have also shown some promise in the management of HFpEF [9]. The US Food and Drug Administration (FDA) currently approves SGLT2is for type 2 diabetes mellitus (T2DM) patients as an add-on therapy to metformin [10]. The blood pressure-lowering, weight-reducing, and anti-inflammatory effects of SGLT2is are postulated to benefit HFpEF patients independent of a glucose-lowering effect [11]. Subgroup analysis of the recently published Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial showed a consistent benefit of SGLT2is in the total number of deaths from cardiovascular causes, hospitalizations, and urgent visits for heart failure patients with left ventricular ejection fraction (LVEF) less than and greater than 50%. However, only 21% of the cohort had LVEF greater than 50%, and the trial was terminated earlier than planned due to funding issues [12]. While the results of this trial provided the first evidence for the potential clinical benefit of SGLT2is in patients with HFpEF, there remains a lack of definitive evidence on the clinical benefits of SGLT2is in patients with HFpEF [13].

Another co-morbidity common in patients hospitalized for heart failure is acute kidney injury (AKI), and is associated with worse clinical outcomes [14]. SGLT2is are associated with improved renal outcomes, including progression to end-stage kidney disease, doubling of serum creatinine, and renal death in patients with established diabetes mellitus and chronic kidney disease (CKD) [15]. However, AKI has not been assessed as a clinical outcome for the effects of SGLT2is in patients with HFpEF and T2DM.

Therefore, we sought to assess the clinical impact of SGLT2i use in patients with HFpEF and T2DM on hospitalizations for heart failure, all-cause hospitalizations, and AKI incidence. While medication regimens for patients with HFpEF and T2DM vary, we chose patients who were prescribed sitagliptin (and not an SGLT2i) as a comparator group while noting other relevant medications that were background therapy for participants.

## 2 Material and Methods

### 2.1 Study Design and Patient Population

This retrospective observational cohort study was conducted at Montefiore Medical Center, an inner-city tertiary academic center with three main campuses. We included patients older than 18 years of age, with a diagnosis of HFpEF (ICD-10-CM I50.3 diastolic heart failure, I50.30 unspecified diastolic heart failure, I50.31, acute diastolic heart failure, I50.32 chronic diastolic heart failure, I50.33 acute on chronic diastolic heart failure) with left ventricular ejection fraction more than 50% and T2DM. All patients were divided into two groups: the SGLT2i group and the control group. The SGLT2i group included eligible patients who were prescribed one of the FDA-approved SGLT2is (canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin) between 1 January 2016 and 1 January 2020. The control group included patients who were prescribed sitagliptin without any SGLT2i prescriptions during the same period. Sitagliptin, an oral hypoglycemic agent for patients with T2DM, was used as the control group due to its neutral effect on cardiovascular outcomes in randomized clinical trials while having similar glucose-lowering efficacy to that of SGLT2is [16, 17]. Additionally, sitagliptin has been used as the control group in prior studies of SGLT2is in HFrEF patients [18, 19]. Index date was set at the date of first prescription of SGLT2is or sitagliptin.

Patients were excluded if the transthoracic echocardiogram (TTE) closest to the index date showed a left ventricular ejection fraction less than 50% or the prescription date of the SGLT2is or sitagliptin was before 1 January 2016. Patients diagnosed with chronic kidney disease (CKD) stage 5 or end-stage renal disease (ESRD) on dialysis before the index date were excluded. Moreover, patients who were prescribed both SGLT2i and sitagliptin were excluded.

Baseline characteristics including age at the time of inclusion in the study; gender; race/ethnicity; body mass index (BMI); estimated glomerular filtration rate (eGFR); and co-morbidities including hypertension, hyperlipidemia, coronary artery disease, chronic kidney disease, and cerebrovascular accident were collected. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20]. Mean hemoglobin a1c (HbA1c) was shown to have a predictive value for HFH in prior studies and therefore included in our study [21]. Medications commonly used in HFrEF (angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNi), beta-blockers (BBs), and spironolactone) and T2DM (metformin and

insulin) were collected as possible confounding variables. In the SGLT2i group, patients' insurance information and SGLT2i prescriber information were collected. The follow-up period was set as 300 days after the index date. Patients were selected based on eligibility criteria with the help of the Clinical Looking Glass (CLG, Streamline Health, Atlanta, GA, USA), which is a user-friendly software that can help clinical researchers navigate through electronic medical records (EMRs) and select cohorts of eligible patients [22].

The institutional review board of Albert Einstein College of Medicine approved the study.

### 2.2 Data Extraction

Two researchers (WL, AK) independently reviewed each patient's EMR to extract and document relevant information in a pre-designed data extraction sheet. The follow-up was available until the time of death or 300 days from the index date. Subjects who reached clinical outcomes (hospitalization, acute kidney injury) were censored when the first event occurred during the follow-up period. If the index date was during hospitalization, subjects were censored when the first hospitalization occurred after hospital discharge or the time of death or 300 days after index date for hospitalization outcomes.

### 2.3 Outcome and Statistical Analysis

The primary outcome was the first occurrence of hospitalization for acute decompensated heart failure, as first heart failure hospitalization has been found to be predictive of future events [23]. The secondary outcomes were all-cause hospitalization and acute kidney injury. Acute kidney injury as defined by KDIGO (Kidney Disease Improving Global Outcomes)—"An absolute increase in serum creatinine at least 0.3 mg/dL within 48 h or by a 50% increase in serum creatinine from baseline within seven days, or a urine volume of less than 0.5 mL/kg/h for at least 6 h"—was used [24]. Heart failure hospitalization was defined as acute decompensated heart failure resulting in hospitalization. Continuous variables were described as mean ± standard deviation. Categorical variables were reported as absolute numbers and percentages. The standardized mean difference (SMD) is calculated to assess the difference between the two groups [25]. Propensity score matching using nearest neighbor matching with a caliper of 0.1 standard deviation of the logit of the propensity scores was conducted to improve the comparability between the two groups. The baseline characteristics including, age, gender, race/ethnicity, hypertension, hyperlipidemia, coronary artery disease, chronic kidney disease, cerebrovascular accident, eGFR, mean BMI, mean hemoglobin A1c, and other confounding medications, were incorporated into the propensity score matching. Age, gender, and race/ethnicity have been found to be significant sociodemographic risk factors for heart failure hospitalization [26, 27]. Coronary artery disease, chronic kidney disease, and cerebrovascular disease were included due to association with the risk of heart failure hospitalization [28, 29]. Mean hemoglobin A1c was included to offset the glycemic effects related to heart failure adverse events [30]. Hypertension, hyperlipidemia, and obesity are common co-morbidities associated with HFpEF [27]. Confounding medications are either part of established guideline-directed medical therapy (GMDT) for HFrEF or common medications used in type 2 diabetes mellitus. One-to-two ratio matching was adopted to preserve sample size. An SMD less than 0.1 is considered well matching between the two groups. Univariate Cox regression was performed individually for each study outcome: HFH, all-cause hospitalization, and AKI risk between the SGLT2i group and the sitagliptin group. Cox regression results were provided as the hazard ratio (HR) with the 95% confidence interval (CI) and two-sided *p*-values. The time-to-outcome analysis was performed using the Kaplan-Meier method and the log-rank test was used. The threshold of statistical significance was $p < 0.05$. All analyses were conducted using R 3.6.3 version (RStudio software, RStudio, Inc.).

## 3 Results

A total of 845 patients were eligible for study enrollment; after screening there were 149 patients in the SGLT2i group and 696 patients in the sitagliptin group. After further exclusion and propensity score matching, the SGLT2i group contained 89 patients, and the sitagliptin group consisted of 161 patients (Fig. 1). The matched cohorts were balanced for age, gender, race/ethnicity, clinical co-morbidities such as HTN and HLD, eGFR, mean BMI, and mean HbA1c, and prescriptions of other medications with SMDs less than 0.10 (Table 1).

### 3.1 Primary Outcome: Heart Failure Hospitalization

A total of 4.5% (4/89) patients in the SGLT2i group and 29.8% (48/161) patients in the sitagliptin group were hospitalized for acute decompensated heart failure during a mean follow-up of 295 days. Univariate Cox regression analysis showed that the SGLT2i group had a significantly lower occurrence of heart failure hospitalization compared to the sitagliptin group within the study period (HR 0.13; 95% CI (0.05–0.36); $p < 0.001$) (Fig. 2).

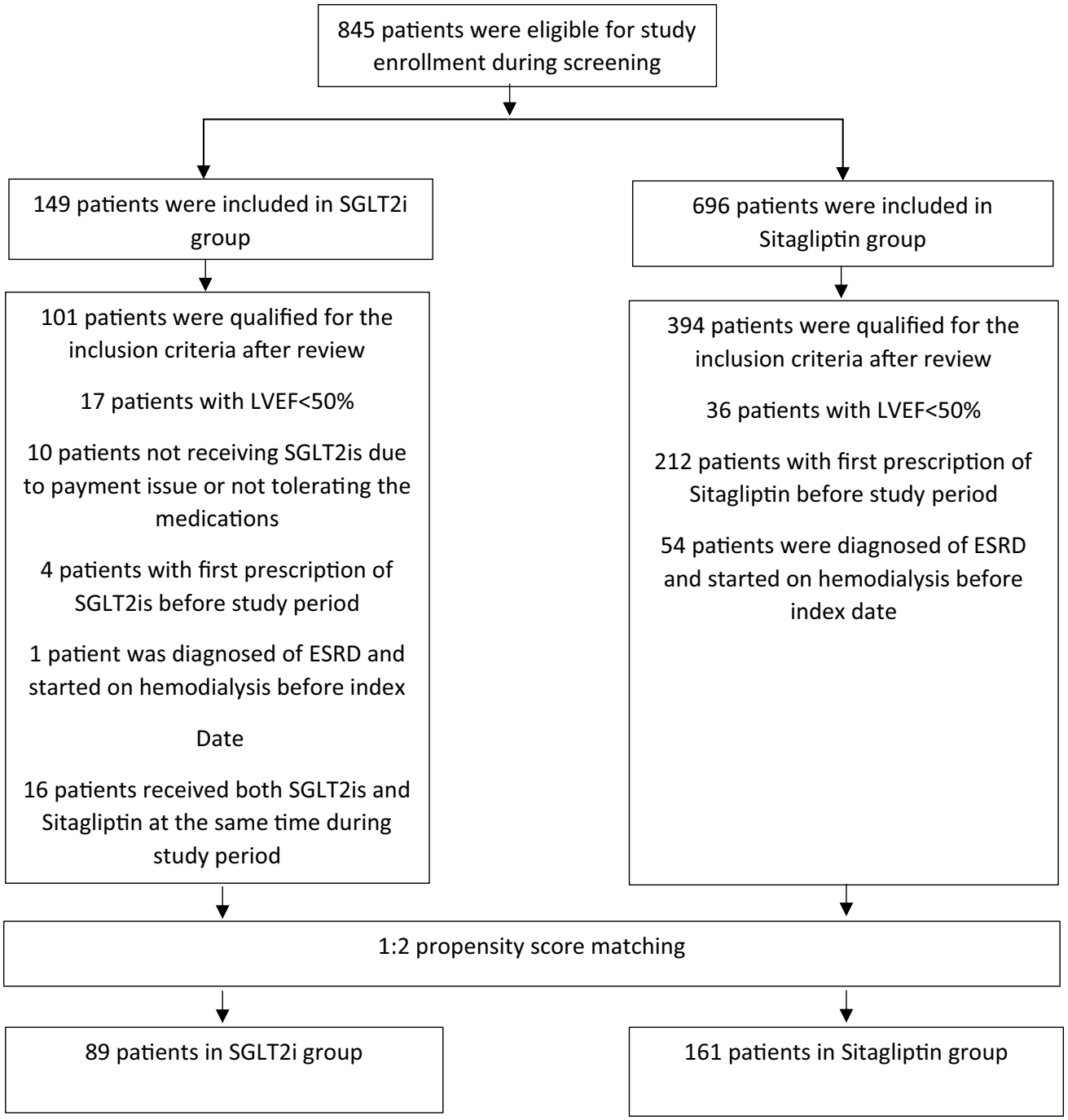


**Fig. 1** Flow chart showing patient selection and propensity score matching

## 3.2 Secondary Outcomes

### 3.2.1 All-Cause Hospitalization

In the SGLT2i group, 39.3% (35/89) of patients were hospitalized, while 65.8% (106/161) of patients in the sitagliptin group were hospitalized during a mean follow-up period of 295 days. Univariate Cox regression analysis showed that the SGLT2i group had a significantly lower occurrence of all-cause hospitalization than the sitagliptin group within the study period (HR 0.48; 95% CI (0.33–0.70); $p < 0.001$) (Fig. 2).

**Table 1** Baseline demographic and clinical co-morbidities between the sodium-glucose cotransporter-2 inhibitor (SGLT2i) group and the sitagliptin group

| | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| | SGLT2i group | Sitagliptin group | SMD | SGLT2i group | Sitagliptin group | SMD |
| Number of patients | 101 | 394 | | 89 | 161 | |
| Age [mean (SD)] | 66 (12) | 72 (13) | 0.440 | 68 (12.2) | 69 (13.3) | 0.093 |
| Male gender (%) | 36 (35.6) | 143 (36.3) | 0.014 | 31 (34.8) | 55 (34.2) | 0.014 |
| Race/ethnicity (%) | | | 0.304 | | | 0.045 |
| Asian | 13 (12.9) | 18 (4.6) | | 7 (7.9) | 11 (6.8) | |
| African American | 35 (34.7) | 138 (35.0) | | 32 (36.0) | 57 (35.4) | |
| White | 16 (15.8) | 74 (18.8) | | 16 (18.0) | 30 (18.6) | |
| Hispanic | 37 (36.6) | 164 (41.6) | | 34 (38.2) | 63 (39.1) | |
| BMI ($kg/m^2$) | 33.9 (8.3) | 32.0 (9.2) | 0.218 | 33.8 (8.6) | 33.3 (9.4) | 0.064 |
| eGFR ($mL/min/1.73\ m^2$) | 65.9 (23.0) | 55.7 (26.2) | 0.414 | 64.8 (23.4) | 62.6 (26.4) | 0.087 |
| Hypertension (%) | 101 (100.0) | 380 (96.4) | 0.271 | 89 (100.0) | 161 (100.0) | <0.001 |
| Hyperlipidemia (%) | 77 (76.2) | 306 (77.7) | 0.034 | 69 (77.5) | 129 (80.1) | 0.064 |
| Coronary artery disease (%) | 50 (49.5) | 202 (51.3) | 0.035 | 45 (50.6) | 79 (49.1) | 0.030 |
| Chronic kidney disease (%) | 43 (42.6) | 250 (63.5) | 0.428 | 42 (47.2) | 80 (49.7) | 0.050 |
| Cerebrovascular accident (%) | 11 (10.9) | 58 (14.7) | 0.115 | 10 (11.2) | 18 (11.2) | 0.002 |
| Mean hemoglobin A1c | 8.6 (1.4) | 8.3 (1.9) | 0.187 | 8.6 (1.4) | 8.8 (2.1) | 0.068 |
| ACEi/ARB/ARNi (%) | 66 (65.3) | 206 (52.3) | 0.268 | 56 (62.9) | 101 (62.7) | 0.004 |
| Beta blocker (%) | 57 (56.4) | 228 (57.9) | 0.029 | 51 (57.3) | 98 (60.9) | 0.073 |
| Spironolactone (%) | 23 (22.8) | 34 (8.6) | 0.396 | 17 (19.1) | 25 (15.5) | 0.095 |
| Metformin (%) | 42 (41.6) | 130 (33.0) | 0.178 | 37 (41.6) | 64 (39.8) | 0.037 |
| Insulin (%) | 65 (64.4) | 170 (43.1) | 0.435 | 56 (62.9) | 100 (62.1) | 0.017 |
| Follow-up time (d) | 296.0 (23.9) | 284.6 (55.8) | 0.265 | 295.4 (25.4) | 295.8 (28.4) | 0.016 |

*BMI* body mass index, *eGFR* estimated glomerular filtration rate, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ARNi* angiotensin receptor-neprilysin inhibitor

#### 3.2.2 Acute Kidney Injury

Among patients taking SGLT2is, 12.4% (11/89) developed acute kidney injury (AKI) during a mean follow-up of 295 days, and 29.2% (47/161) of the patients taking sitagliptin developed AKI. Univariate Cox regression demonstrated that within study period, acute kidney injury occurred significantly less in the SGLT2i group compared with the sitagliptin group (HR 0.39; 95% CI (0.20–0.74); $p = 0.004$) (Fig. 2).

### 3.3 Prescriber and Insurance Information of Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is)

Empagliflozin was the most commonly prescribed SGLT2i used in our cohort [58.4% (52/89)]. Other SGLT2is were dapagliflozin 19.1% (17/89) and canagliflozin 22.5% (20/89). All patients in the SGLT2i group had insurance coverage, with 87.6% of patients having government-issued insurance under the supervision of the Center of Medicare and Medicaid (CMS). Most of the patients (46.1%) in the SGLT2i group had Medicaid, a public health insurance for people with low income. The majority of the SGLT2is were prescribed by general internal medicine physicians (50.6 %), followed by endocrinologists (27.0%) and cardiologists (12.4%) (Fig. 3).

## 4 Discussion

The main findings of our retrospective cohort study of HFpEF patients with T2DM are as follows: (1) Patients started on SGLT2is are 87% less likely to be hospitalized for heart failure exacerbation compared to those started on sitagliptin during the first 300 days after initiation of these medications. (2) SGLT2i use is associated with a lower risk of developing AKI among patients with T2DM and HFpEF. (3) General internal medicine physicians are prescribing SGLT2is in T2DM and HFpEF more often than cardiologists.

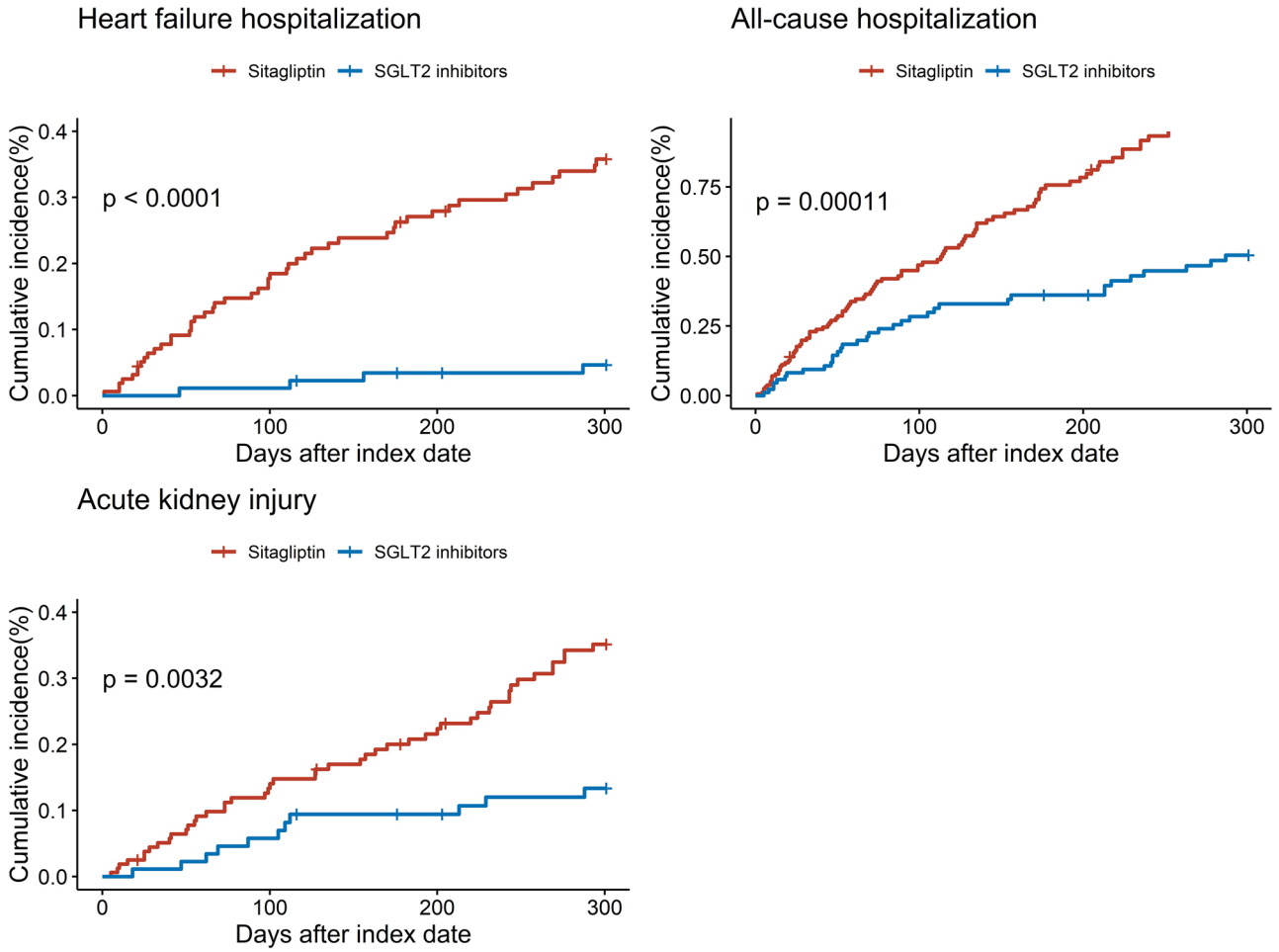


**Fig. 2** Comparison of cumulative incidence of primary and secondary outcomes between SGLT2i group and sitagliptin group

HFHs are associated with decreased quality of life, higher mortality, and increased economic burden on the healthcare system [31]. The association between SGLT2i use and reduced hospitalization risk in our study has a potential clinical and economic impact. HFpEF-associated heart failure hospitalizations continue to increase in the USA [32]. Unlike HFrEF, there is a lack of GDMT to reduce the hospitalization rate for patients with HFpEF. Since large-sized randomized clinical trials have demonstrated the positive effects of SGLT2is on the reduction of hospitalization in patients with HFrEF, SGLT2is might help HFpEF patients as well [6, 19]. SGLT2is inhibit the reabsorption of sodium and glucose from the proximal convoluted tubule, resulting in reduced fluid overload [33]. It is also proposed that SGLT2is can reduce left ventricular mass and improve diastolic function by inhibiting cardiac fibrosis [34]. Fluid overload is associated with increased heart failure hospitalization and cardiovascular mortality in HFpEF patients. SGLT2is could reduce fluid overload by causing diuresis in combination with loop diuretics, especially in patients with diabetes [35]. Studies have suggested that SGLT2is can have an even stronger diuresis effect than loop diuretics since two-thirds of filtered sodium were reabsorbed through the proximal convoluted tubules [36, 37]. Furthermore, the theoretical benefits of SGLT2is may be the reason behind the clinical outcomes seen in our study.

AKI is common in heart failure patients, and an increased number of AKI episodes increases hospitalization risk [38]. Our study revealed that in patients with HFpEF and T2DM, the use of SGLT2is was associated with a lower AKI risk. A meta-analysis by Neuen et al. reported that SGLT2i use was associated with a reduced incidence of AKI in patients with T2DM [39]. Our study has demonstrated that in patients suffering from both HFpEF and T2DM, SGLT2is can still achieve such benefits. Furthermore, multicenter randomized controlled trials suggested SGLT2i use is associated with a slower decline in kidney function and progression to end-stage kidney disease [40]. The renal protective effect of SGLT2is is likely multifactorial. SGLT2is are theorized to decrease intraglomerular pressure, suppress inflammation,

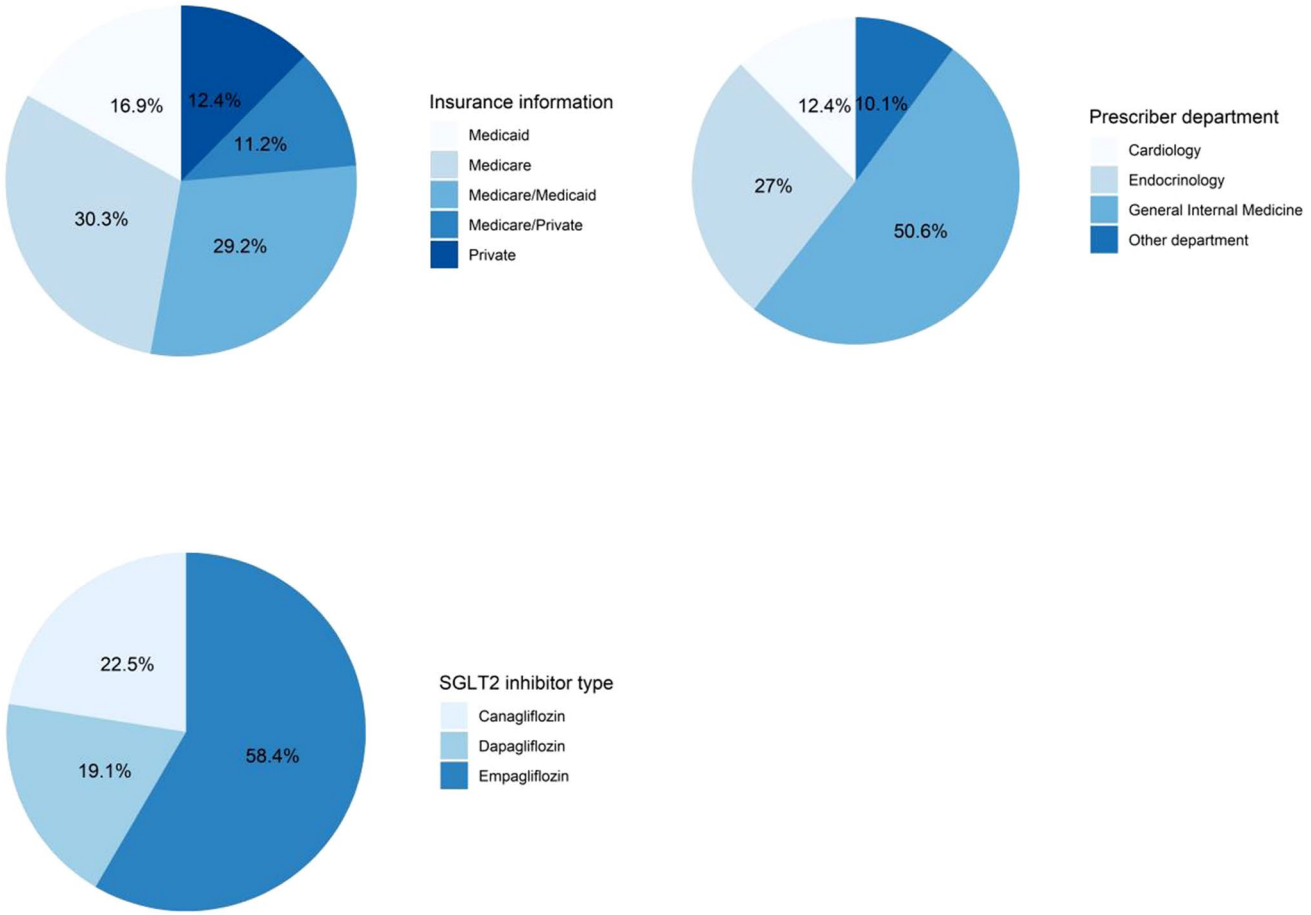


**Fig. 3** Insurance and prescriber information for SGLT2is

reduce oxidative stress, and improve the energy consumption of the kidney [41]. These possible mechanisms may likely explain our findings.

With this new group of medications that overlap disease categories, the question of who should or who is best to prescribe these is relevant. Current studies indicate internists or endocrinologists but not cardiologists are the most common prescribers of SGLT2is. The prescription of SGLT2is among cardiologists has been low, and only 4.5% of total annual prescriptions of SGLT2is in a retrospective study conducted at a multicenter health system came from cardiologists [42]. Our study found a similar prescription pattern of SGLT2is in patients with both T2DM and HFpEF (Fig. 3). This might be related to unfamiliarity with the expanded applications of the SGLT2is and concerns of possible side effects of SGLT2is such as euglycemic diabetic ketoacidosis and urinary tract infections. An increase in awareness of the benefits of SGLT2is in cardiac patients could improve prescription patterns of SGLT2is among cardiologists.

Lastly, most of the patients in our cohort receiving SGLT2is were either Medicare or Medicaid beneficiaries (Fig. 3). As a novel class of medications, patients who are Medicare or Medicaid beneficiaries could face high out-of-pocket charges despite coverage as well as other obstacles to obtaining these medications [27, 43]. Our study shows that the part of Medicare or Medicaid beneficiaries who received SGLT2is successfully had their associated clinical benefits. Our findings should encourage future prescriptions of this class of drugs to all patients and possible healthcare coverage reform.

Our study added to the current literature that SGLT2is could not only decrease hospitalization for heart failure patients with reduced ejection fraction [6, 7], but also for those with preserved ejection fraction, which is an increasingly prevalent clinical syndrome with a growing number of hospitalizations annually [44].

The main strengths of our study include its strict methodology with propensity score matching of possible confounding factors, careful selection of patient cohort, and robust analysis. Our patient population is truly diverse and mainly consisted of racial and ethnic minorities, with Black and Hispanic participants forming

a majority—groups who can be under-represented in randomized multicenter studies. In addition, studies have shown that Black patients have a significantly higher rate of HFH [45]. Representation of this population in our study is therefore relevant and complements the results of randomized controlled trials.

On the other hand, we would like to acknowledge a few limitations of our study, mainly associated with its observational nature. Since SGLT2is are a novel class of medications, patients in the SGLT2i groups can be early adopters with other hidden unadjusted confounding variables. Our study is limited by its relatively small sample size, lacking sufficient power to detect the difference in mortality outcome between the SGLT2i group and the sitagliptin group. We also note that a few patients in the SGLT2i group were on GLP1 receptor agonists as well.

While there are many agents in the SGLT2i class of medications, we feel that there is a class effect whereby the mechanisms of interest are sufficiently similar to consider them as one group [6, 7, 9, 10].

While not a randomized clinical trial, we sought a control group that would allow for statistical comparison to further support our findings. Sitagliptin is also a relatively newer drug with a different mechanism to SGLT2is. Unlike the other dipeptidyl peptidase-4 (DPP-4) inhibitors such as saxagliptin and alogliptin, sitagliptin has not been found to be associated with increased risk of HFH [16, 46].

Our study is hypothesis-generating and provides information that can help with the development of future randomized prospective studies with a large-size sample of patients. Randomized clinical trials such as the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) study of empagliflozin and Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) study of dapagliflozin for HFpEF are in progress with the aim of improving our clinical practice in HFpEF patients [47, 48].

## 5 Conclusion

The use of SGLT2is is associated with significantly reduced hospitalization and fewer events of AKI in a diverse population of patients with heart failure with preserved ejection fraction and T2DM. The prescription of SGLT2is for heart failure with preserved ejection fraction from cardiologists remains low.

## Declarations

**Funding** None.

**Conflicts of interest** No relevant conflicts of interest to declare.

**Ethics approval** The study was approved by the institutional review board of Albert Einstein College of Medicine. Consents have been waived due to the retrospective nature of the study.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and material** The data used in this study are not publicly available.

**Code availability** Not applicable.

**Author contributions** WL and AK contributed to the initial study conception and design, data collection and analysis, and manuscript preparation. RK, MM, and CT contributed to manuscript review and revision. All authors read and approved the final manuscript.



## References

1. Gazewood JD, Turner PL. Heart failure with preserved ejection fraction: diagnosis and management. Am Fam Phys. 2017;96:582–8.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6:606–19. https://doi.org/10.1161/HHF.0b013e318291329a.
3. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14:591–602. https://doi.org/10.1038/nrcardio.2017.65.
4. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–92. https://doi.org/10.1056/NEJMoa1313731.
5. Solomon SD, McMurray JJV, Committee, P.-H.S.; Investigators. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. Reply. N Engl J Med. 2020;382:1182–3. https://doi.org/10.1056/NEJMc2000284.

6. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303.
7. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190.
8. Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program. Circulation. 2018;138:458–68. https://doi.org/10.1161/CIRCULATIONAHA.118.034222.
9. Petrie MC, Lee MMY, Docherty KF. Sodium-glucose co-transporter 2 inhibitors-the first successful treatment for heart failure with preserved ejection fraction? Eur J Heart Fail. 2021. https://doi.org/10.1002/ejhf.2108.
10. Simes BC, MacGregor GG. Sodium-glucose cotransporter-2 (SGLT2) inhibitors: a clinician's guide. Diabetes Metab Syndr Obes. 2019;12:2125–36. https://doi.org/10.2147/DMSO.S212003.
11. Petrie MC, Lee MMY, Docherty KF. SGLT2 inhibitors—the first successful treatment for HFpEF? Eur J Heart Fail. 2021. https://doi.org/10.1002/ejhf.2108.
12. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384:117–28. https://doi.org/10.1056/NEJMoa2030183.
13. Moses RG, Round E, Shentu Y, Golm GT, Neill EA, Gantz I, Engel SS, Kaufman KD, Goldstein BJ. A randomized clinical trial evaluating the safety and efficacy of sitagliptin added to the combination of sulfonylurea and metformin in patients with type 2 diabetes mellitus and inadequate glycemic control. J Diabetes. 2016;8:701–11. https://doi.org/10.1111/1753-0407.12351.
14. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018;137:2016–28. https://doi.org/10.1161/CIRCULATIONAHA.117.030112.
15. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–306. https://doi.org/10.1056/NEJMoa1811744.
16. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373:232–42. https://doi.org/10.1056/NEJMoa1501352.
17. Cornel JH, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, Engel SS, Lopes RD, McGuire DK, Riefflin A, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes From TECOS. Diabetes Care. 2016;39:2304–10. https://doi.org/10.2337/dc16-1415.
18. Carbone S, Billingsley HE, Canada JM, Bressi E, Rotelli B, Kadariya D, Dixon DL, Markley R, Trankle CR, Cooke R, et al. The effects of canagliflozin compared to sitagliptin on cardiorespiratory fitness in type 2 diabetes mellitus and heart failure with reduced ejection fraction: the CANA-HF study. Diabetes Metab Res Rev. 2020;36: e3335. https://doi.org/10.1002/dmrr.3335.
19. Patorno E, Pawar A, Franklin JM, Najafzadeh M, Deruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M, et al. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. Circulation. 2019;139:2822–30. https://doi.org/10.1161/CIRCULATIONAHA.118.039177.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
21. Kishimoto I, Makino H, Ohata Y, Tamanaha T, Tochiya M, Kada A, Ishihara M, Anzai T, Shimizu W, Yasuda S, et al. Hemoglobin A1c predicts heart failure hospitalization independent of baseline cardiac function or B-type natriuretic peptide level. Diabetes Res Clin Pract. 2014;104:257–65. https://doi.org/10.1016/j.diabres.2014.02.009.
22. Pirvulescu I, Suciu S, Andrei M, Lupu A, Diculescu M. The influence and prevalence of nonalcoholic steatohepatitis in chronic hepatitis B. Rev Med Chir Soc Med Nat Iasi. 2011;115:91–6.
23. Malik A, Gill GS, Lodhi FK, Tummala LS, Singh SN, Morgan CJ, Allman RM, Fonarow GC, Ahmed A. Prior heart failure hospitalization and outcomes in patients with heart failure with preserved and reduced ejection fraction. Am J Med. 2020;133:84–94. https://doi.org/10.1016/j.amjmed.2019.06.040.
24. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-184. https://doi.org/10.1159/000339789.
25. Zhang Z, Kim HJ, Lonjon G, Zhu Y, written on behalf of, A.M.E.B.-D.C.T.C.G. Balance diagnostics after propensity score matching. Ann Transl Med. 2019;7:16. https://doi.org/10.21037/atm.2018.12.10.
26. Nieminen MS, Harjola VP, Hochadel M, Drexler H, Komajda M, Brutsaert D, Dickstein K, Ponikowski P, Tavazzi L, Follath F, et al. Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II. Eur J Heart Fail. 2008;10:140–8. https://doi.org/10.1016/j.ejheart.2007.12.012.
27. Yoon S, Eom GH. Heart failure with preserved ejection fraction: present status and future directions. Exp Mol Med. 2019;51:1–9. https://doi.org/10.1038/s12276-019-0323-2.
28. Lamblin N, Meurice T, Tricot O, de Groote P, Lemesle G, Bauters C. First hospitalization for heart failure in outpatients with stable coronary artery disease: determinants, role of incident myocardial infarction, and prognosis. J Card Fail. 2018;24:815–22. https://doi.org/10.1016/j.cardfail.2018.09.013.
29. Bansal N, Zelnick L, Bhat Z, Dobre M, He J, Lash J, Jaar B, Mehta R, Raj D, Rincon-Choles H, et al. Burden and outcomes of heart failure hospitalizations in adults with chronic kidney disease. J Am Coll Cardiol. 2019;73:2691–700. https://doi.org/10.1016/j.jacc.2019.02.071.
30. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. Circulation. 2001;103:2668–73. https://doi.org/10.1161/01.cir.103.22.2668.
31. Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. Risk Manag Healthc Policy. 2017;10:63–70. https://doi.org/10.2147/RMHP.S130341.
32. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC, Get With the Guidelines Scientific Advisory, C.; Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126:65–75. https://doi.org/10.1161/CIRCULATIONAHA.111.080770.
33. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure:

potential mechanisms, clinical applications, and summary of clinical trials. Circulation. 2017;136:1643–58. https://doi.org/10.1161/CIRCULATIONAHA.117.030012.
34. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. J Am Heart Assoc. 2019;8: e013389. https://doi.org/10.1161/JAHA.119.013389.
35. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure. Circulation. 2020;142:1713–24. https://doi.org/10.1161/CIRCULATIONAHA.120.048739.
36. Grodin JL, Tang WHW. Sodium-glucose cotransporter-2 inhibitors and loop diuretics for heart failure: priming the natriuretic and metabolic reserve of the kidney. Circulation. 2020;142:1055–8. https://doi.org/10.1161/CIRCULATIONAHA.120.048057.
37. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab. 2018;20:479–87. https://doi.org/10.1111/dom.13126.
38. Holgado JL, Lopez C, Fernandez A, Sauri I, Uso R, Trillo JL, Vela S, Nunez J, Redon J, Ruiz A. Acute kidney injury in heart failure: a population study. ESC Heart Fail. 2020;7:415–22. https://doi.org/10.1002/ehf2.12595.
39. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019;7:845–54. https://doi.org/10.1016/S2213-8587(19)30256-6.
40. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375:323–34. https://doi.org/10.1056/NEJMoa1515920.
41. Bonora BM, Avogaro A, Fadini GP. Extraglycemic Effects of SGLT2 Inhibitors: A Review of the Evidence. Diabetes Metab Syndr Obes. 2020;13:161–74. https://doi.org/10.2147/DMSO.S233538.
42. Vaduganathan M, Sathiyakumar V, Singh A, McCarthy CP, Qamar A, Januzzi JL Jr, Scirica BM, Butler J, Cannon CP, Bhatt DL. Prescriber patterns of SGLT2i after expansions of U..S Food and Drug Administration Labeling. J Am Coll Cardiol. 2018;72:3370–2. https://doi.org/10.1016/j.jacc.2018.08.2202.
43. Luo J, Feldman R, Rothenberger SD, Hernandez I, Gellad WF. Coverage, formulary restrictions, and out-of-pocket costs for sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists in the medicare part D program. JAMA Netw Open. 2020;3: e2020969. https://doi.org/10.1001/jamanetworkopen.2020.20969.
44. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251–9. https://doi.org/10.1056/NEJMoa052256.
45. Nayak A, Hicks AJ, Morris AA. Understanding the complexity of heart failure risk and treatment in black patients. Circ Heart Fail. 2020;13: e007264. https://doi.org/10.1161/CIRCHEARTFAILURE.120.007264.
46. Son JW, Kim S. Dipeptidyl peptidase 4 inhibitors and the risk of cardiovascular disease in patients with type 2 diabetes: a tale of three studies. Diabetes Metab J. 2015;39:373–83. https://doi.org/10.4093/dmj.2015.39.5.373.
47. Williams DM, Evans M. Dapagliflozin for heart failure with preserved ejection fraction: will the DELIVER study deliver? Diabetes Ther. 2020;11:2207–19. https://doi.org/10.1007/s13300-020-00911-0.
48. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019;21:1279–87. https://doi.org/10.1002/ejhf.1596.