



Intersection Between Diabetes and Heart Failure: Is SGLT2i the “One Stone for Two Birds” Approach?

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Abstract

Purpose of Review Diabetes mellitus (DM) is a major comorbidity of heart failure (HF). Comparing the similarities and differences in disease characteristics and treatment between the HF patients with and without DM, this review was to investigate whether and how the novel class of sodium-glucose transport protein 2 inhibitors (SGLT2i) would benefit both populations.

Recent Findings Despite the obviously different clinical profiles, patients of HF with reduced ejection fraction (HFrEF) should be treated the same with guideline directed medical therapy, irrespective of DM status. Upon the mounting evidence that supported its use in diabetic patients at high risk of HF, recent large clinical trials demonstrated that SGLT2i could further reduce HF hospitalization or cardiovascular mortality and improve quality of life in diabetic and non-diabetic HFrEF patients who were optimally managed.

Summary SGLT2i expands the foundation of HFrEF therapy. Whether it is equally effective in HF with preserved ejection fraction awaits more evidence.

Keywords Heart failure · Diabetes mellitus · Sodium-glucose transport protein 2 inhibitors

Introduction

Diabetes mellitus (DM) is a common comorbidity in heart failure (HF) patients, occurring in 20–40% of patients with HF with reduced ejection fraction (HFrEF) and more frequently in HF with preserved ejection fraction (HFpEF) [1–3]. Besides diabetic cardiomyopathy which displays two distinct phenotypes as metabolism-mediated restrictive HFpEF phenotype and autoimmune-mediated dilated HFrEF phenotype [4], DM drives a fourfold higher prevalence of

HF via its combined atherogenic effect with hypertension and dyslipidemia [5]. Conversely, HF patients are predisposed to DM through dysregulated neurohormonal system [6], HF medication, and reduced physical activity [7]. This review will focus on the special patient population of HF with DM and compare to the HF population without DM for similarities and differences in terms of disease profile, clinical impact, as well as the implication of medical therapy by the novel class of anti-diabetic drugs, the sodium-glucose transport protein 2 inhibitors (SGLT2i).

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HF Patients With or Without DM: Are They Different?

Clinical Profile

HF patients with DM are younger, have higher body mass index (BMI), experience worse symptoms, and have a prevalent background of ischemic heart disease both in HFrEF and HFpEF [2, 8–10]. In addition to a greater burden of hypertension, chronic kidney disease, hyperlipidemia, anemia, and chronic obstructive pulmonary disease [2, 8, 11], DM was associated with a 34% higher risk of atrial

fibrillation (AF) [12]. Diabetic patients with AF were more symptomatic who had markedly increased adverse cardiovascular (CV) outcomes [13], including a 70% increased relative risk of thromboembolic stroke events [14].

Biomarkers in Subtypes of HF

The Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial found a significantly higher N-terminal pro-brain natriuretic peptide (NT-proBNP) level in HFrEF patients with undiagnosed DM at baseline, compared to the prediabetic and normoglycemic group, but not in those with diagnosed DM [15]. However, the link between NT-proBNP and DM in patients with HFpEF was less consistent across studies which may partially explained by different inclusion criteria: Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial showed higher NT-proBNP in patients with DM [9]; Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction (RELAX) trial found similar NT-proBNP between DM and non-DM cohorts [16]; the Get With The Guidelines (GWTG)-HF registry, however, showed lower NT-proBNP in patients with DM [11]. Furthermore, Foustieris et al. demonstrated an increased soluble ST2 (sST2) in patients with DM, which was more pronounced in the presence of left ventricular diastolic dysfunction [17]. A similar trend was observed in both HFrEF [18] and HFpEF cohorts [19]. In the RELAX trial, diabetic patients with HFpEF had higher levels of galectin-3 (Gal-3) [16]. Alanso et al. showed an elevated Gal-3 level, rather than sST2, in ambulatory HF patients with DM; after adjusting for age, sex, BMI, and estimated glomerular filtration rate (eGFR), the correlation attenuated [20]. Note that the relationship between Gal-3 and DM might be complicated by renal dysfunction [21].

Myocardial Imaging

Either eccentric (dilated/HFrEF) or concentric (restrictive/HFpEF) remodeling is typical structural and functional alterations [22]. Decreased myocardial compliance extensively presents in both phenotypes, as evidenced by higher early mitral inflow velocity and mitral annular early diastolic velocity (E/e') ratio [2, 9, 16, 23]. DM is associated with smaller left ventricles, greater LV mass, and thicker ventricular wall in HFpEF [16, 23], whereas it only leads to mildly enlarged left ventricular end-diastolic volume index in HFrEF [2, 16, 24, 25]. Despite similar left ventricular ejection fraction (LVEF) between DM and non-DM cohorts, Tanaka et al. demonstrated that global longitudinal strain (GLS) was significantly lower in patients with dilated cardiomyopathy

with DM than those without [26]. Cardiac magnetic resonance (CMR) adds more information on DM-related changes of the heart, though they have not been investigated in HF patients. Wong et al. found that DM raised extracellular volume fraction (ECV) in patients with underlying CV diseases and comorbid hypertension referred for clinical CMR [27]. In a Western cohort, patients with prediabetes and DM had lower ECV, higher cell volume, and greater burden of late gadolinium enhancement (LGE) [28]. Paiman et al. found that ECV increased in South Asian but not European patients with DM [29]. Levelt et al. detected increased myocardial triglyceride content and phosphocreatine-to-ATP ratio using ^1H and ^{31}P magnetic resonance spectroscopy in patients with DM [30], indicating a potential role of cardiac steatosis in LV concentric remodeling [30, 31]. DM also impaired myocardial perfusion reserve but had an inconsistent correlation with cardiac dysfunction [32, 33].

Mortality and HF Hospitalization

Undoubtedly, HF patients with DM are at greater risk of death and HF hospitalization, which exaggerates in younger women [2, 8, 9, 34–36]. However, limited data have suggested the differential impact of DM on patients with HFpEF and HFrEF. Candesartan in Heart failure-Assessment of Reduction in Mortality and Morbidity (CHARM) study showed that DM conferred more adverse effects on patients with HFpEF by increasing the risk of the combined outcome of CV death and HF hospitalization [8]. In contrast, an analysis from Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) found no interaction between DM and subtype of HF in HF hospitalization [2]. Ather et al. also demonstrated that DM was associated with a similarly increased risk of all-cause mortality in HFrEF and HFpEF patients [3].

HF Patients With or Without DM: Shall Treatment Be Different?

Effects of Anti-HF Therapy on DM Subgroup

HF medications had comparable survival benefits between patients with and without DM, which was delicately concluded in a recent American Heart Association (AHA)/Heart Failure Society of American (HFSA) statement [37]. Briefly, angiotensin converting enzyme inhibitor (ACEI) (captopril [38] and trandolapril [39]), angiotensin receptor blocker (ARB) (valsartan [40, 41], losartan [42], and candesartan [8]), sacubitril-valsartan [15], mineralocorticoid receptor antagonist (MRA) (eplerenone [43]), and ivabradine [44] were equally effective according to the secondary analyses of the pivotal trials, respectively. Treatment effect was concluded to be the same for beta-blocker (carvedilol,

metoprolol succinate, and bisoprolol) and enalapril in a meta-analysis [45]. Combined with renin-angiotensin system blockades, carvedilol has more favorable metabolic effects when compared to metoprolol [46]. Notably, sacubitril-valsartan exhibited an extra glucose-lowering effect when compared to enalapril, favoring its use in patients with HF and DM [47]. Device therapy with implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) also showed consistent benefit in both DM and non-DM patients [48–51].

Goal of Glucose-lowering Treatment

The optimal range for blood glucose control in patients with HF is not well defined. In Diabetes Mellitus and Diastolic Dysfunction (DADD) study, Jarnert et al. observed no improvement in myocardial diastolic dysfunction and perfusion reserve by implementing strict glycemic control in DM [52]. Multiple studies illustrated a “U” shape relationship between the mortality risk and hemoglobin A_{1c} (HbA_{1c}) in patients with HF, where the lowest point occurred with HbA_{1c} levels of 7.0–7.9% [46, 53, 54]. Despite the lack of consensus, a general target of HbA_{1c} lower than 7.0% is well-accepted. For patients with advanced HF and more serious comorbidities, a lenient glycemic control with a HbA_{1c} level of <8.5% should be considered [37, 55].

Recent studies have demonstrated that glycemic variability was a more potent prognostic factor [56]. In a secondary analysis from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a relative 10% increase or decrease in HbA_{1c} was associated with 32% and 55% higher risks of HF in patients with DM [57]. Echouffo-Tcheugui et al. found that a greater visit-to-visit variability of fasting blood glucose increased the mortality risk in patients free of CV diseases at baseline [58].

Choice of Metformin or SGLT2i as the First-line Glucose-lowering Agent

Metformin has been the most widely used oral anti-diabetic drug for decades [59]. Since 2006, it was recommended as the first-line glucose-lowering agent for its CV protective effects [60]. There were initial concerns for lactic acidosis when treated patients with HF. Two large observational studies, however, demonstrated that metformin significantly reduced the risk of death and hospitalization compared to sulfonylurea monotherapy in patients with HF, without causing additional metabolic acidosis. In response to these results, FDA removed the warning for HF patients in 2006 [61–63]. A systematic review involving 9 observational studies and 34,000 patients with HF and DM further confirmed its efficacy and safety, showing decreased risks of mortality and all-cause hospitalization and a similar risk

of lactic acidosis when compared with the control group (mostly treated with sulfonylurea) [64]. Thus, metformin became the first-line drug for glycemic control in patients with HF according to the 2016 European Society of Cardiology (ESC) guidelines on HF management (class IIa, level of evidence C), but is contraindicated in patients with severe renal or hepatic impairment [65]. However, all the data were generated from observational studies. The ongoing Metformin in Patients with Chronic Heart Failure and Diabetes or Insulin Resistance Trial (Met-HeFT) will be the largest randomized study to date powered to address the effects of metformin on clinical outcomes in chronic HFrEF patients [66].

Recently, SGLT2i, a novel class of anti-diabetic agents, exhibited unexpected CV benefits in the CV outcome trials (CVOTs) mandated by FDA since 2008. SGLT2i blocks the reabsorption of glucose by inhibiting SGLT2 in the proximal tubule. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG Outcome) (2015) [67] and the Canagliflozin Cardiovascular Assessment Study (CANVAS) (2017) [68] showed a decreased risk of hospitalization for HF in SGLT2i versus placebo in diabetic patients with CVD [empagliflozin, hazard ratio (HR) 0.65, 95% confidence interval (CI) 0.50–0.85; canagliflozin, HR 0.67, 95% CI 0.52–0.87]. Similar effects were observed with dapagliflozin [Dapagliflozin Effect on Cardiovascular Events (DECLEAR-TIMI 58), 2019] [69] and ertugliflozin [Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV), 2020] [70, 71]. Accordingly, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) [72], AHA [37], and Canadian Cardiovascular Society (CCS) [73] recommended SGLT2i for those at high risk or with index HF. But the debate about SGLT2-i or metformin as the first-line choice persists. A recent retrospective multi-institution cohort study enrolled 41,020 DM patients with either SGLT2i or metformin as the first-line therapy. During the 1-year follow-up, patients on SGLT2i had lower risks of HF hospitalization (HR 0.47; 95% CI 0.41–0.54), and all-cause mortality (HR 0.49, 95% CI 0.44–0.55), but a higher risk for ischemic stroke (HR 1.21, 95% CI 1.10–1.32) [74].

Despite the mounting evidence that supported the use of SGLT2i in diabetic patients with HF, higher cost, limited experience, a lack of head-to-head study with metformin, and inconsistent recommendations from different communities hinder its application. In 2019, ESC presented a “major paradigm shift,” which proposes prescribing SGLT2i to diabetic patients at high risks of CV diseases and HF or with index CV diseases, before the initiation of metformin [55]. However, ADA/EASD still advocates metformin for its established pharmacological effects and safety profile,

whereas SGLT2i (empagliflozin, canagliflozin, and dapagliflozin) is included in the add-on regimen for diabetic patients with HF or chronic kidney disease irrespective of HbA_{1c} [72, 75, 76].

HF Patients With or Without DM: Not Different in the Era of SGLT2i?

SGLT2i Reduces Mortality and Hospitalization in Chronic HFrEF

Although the CVOTs of SGLT2i revealed a robust reduction in HF hospitalization and mortality in patients with DM, no more than 20% patients enrolled had established HF, and the characteristics of HF were not well established. It was not confirmed whether the benefit of SGLT2i could extrapolate to HF patients without DM, until recent announcement of two late-breaking randomised control trials (RCTs) known as the Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) [77••] and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) [78••] which enrolled both diabetic and non-diabetic HF patients (with LVEF ≤ 40%). The trials examined the add-on efficacy of dapagliflozin or empagliflozin versus placebo in patients with HFrEF who had already received guideline-directed medical therapy, respectively. Regardless of mild differences in baseline characteristics, i.e. patients in EMPEROR-Reduced had lower LVEF (27.2% vs. 30.9%) and eGFR (62.2 vs. 65.5 mL·min⁻¹·1.73 m⁻²) and had more patients with DM (49.8% vs. 41.8%), HF hospitalization (HHF) in previous 12 month (30.7% vs. 27.4%), angiotensin receptor-neprilysin inhibitor (ARNI) (20.7% vs. 10.9%) and CRT (11.9% vs. 6.9%) treatment, but few ischemic cardiomyopathy (50.7% vs. 57.3%), the two trials showed a similar risk reduction in primary outcome of CV death or hospitalization for worsening HF (DAPA-HF: HR 0.74, 95% CI: 0.65–0.85; EMPEROR-Reduced: HR 0.75, 95% CI: 0.65–0.86) [79–81]. In the pooled patient-level data analysis of these two trials including 8,474 patients, it reconfirmed that the reduction in relative risk of combined CV death or first hospitalization for HF by using SGLT2i was 26% and 25% in patients with and without DM, respectively ($p < 0.0001$). The pooled treatment effects showed consistent benefits for predefined subgroups of age, gender, background ARNI therapy, and baseline eGFR [82].

SGLT2i Improves Quality of Life in Chronic HFrEF

The DAPA-HF trial also revealed that patients treated with dapagliflozin had greater improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ)-total symptom score,

clinical summary score, and overall summary score at 8 months (2.8, 2.5, and 2.3 points higher versus placebo; $p < 0.0001$ for all) [83]. Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure (DEFINE-HF) was an investigator-initiated, multicenter RCT that investigated the effect of dapagliflozin on biomarkers, symptoms, and functional status in patients with HFrEF. A total of 263 HFrEF patients (63% DM) were randomized to dapagliflozin or placebo treatment for 12 weeks. Dapagliflozin was attributable to both higher proportions of patients with ≥ 5-point improvement in KCCQ overall summary score (42.9 vs. 32.5%, adjusted OR 1.73, 95% CI 0.98–3.05) and ≥ 20% reduction in NT-proBNP (44.0 vs. 29.4%, adjusted OR 1.9, 95% CI 1.1–3.3), which were consistent among patients with or without DM [84]. A substudy of the DEFINE-HF measured lung fluid volumes by remote dielectric sensing and found more patients in the dapagliflozin group who experienced improvement in lung fluid volumes (52.6% vs. 36.8%, $p = 0.04$) [85].

SGLT2i Benefits in Acute HF or HFpEF Awaits for More Evidence

Ibrahim et al. conducted a RCT to assess the addition of dapagliflozin to furosemide in managing patients with admitted decompensated HFrEF and DM. One hundred patients were randomized into study arm (dapagliflozin plus furosemide) and control arm (furosemide alone). At discharge, the study arm displayed a lower mean total dose of furosemide (597 mg vs. 855 mg), a higher percent in weight loss (5% vs. 3.4%), more patients without dyspnea (34% vs. 16%), and a tendency of fewer patients with worsening renal function (16% vs. 28%, $p = 0.148$) [86]. Another exploratory RCT also observed in a small group with DM and acute decompensated HF ($n = 59$) that empagliflozin as an add-on therapy was associated with reduced levels of NT-proBNP and hematocrit but without an increased risk of worsening renal function [87].

Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) is a trial designed to examine the safety and efficacy of sotagliflozin (an SGLT2i that also provides some gastrointestinal SGLT1 inhibition) in DM patients who were recently hospitalized for worsening HF with a full spectrum of LVEF. The study was ended early due to loss of funding in the COVID-19 crisis. Clinically stabilized patients were randomly assigned to receive sotagliflozin or placebo either before or within 3 days after discharge, who were followed up for a median of 9 months. The sotagliflozin was associated with 33% reduction in primary end-point of CV death, HF hospitalization and urgent visits for HF (first and subsequent events), including 16% reduction in death from CV causes, and 18% in death from

any cause. More impressively, the effects on primary outcomes were similar between subgroups of age, gender, and HF phenotypes (HFrEF and HFpEF). However, sotagliflozin also led to increased risks of diarrhea (6.1% vs. 3.4%) and severe hypoglycemia (1.5% vs. 0.3%) [88].

Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure (EMPA-RESPONSE-AHF) was the first randomized, double-blind, placebo-controlled, multicenter pilot study on the effects of empagliflozin in acute HF (AHF) patients irrespective of LVEF classification and comorbid DM ($n = 80$) [89]. No difference was observed in VAS dyspnea score, diuretic response, length of stay, or change in NT-proBNP between empagliflozin and placebo. However, empagliflozin induced more urinary output during the first 4 days [difference 3,449 (95% CI 578–6,321) mL; $p < 0.01$] with no recorded adverse effects on blood pressure or renal function. More importantly, empagliflozin reduced a combined endpoint of in-hospital worsening HF, rehospitalization for HF, or death at 60 days compared with placebo (10% vs. 33%, $p = 0.014$). Currently, other SGLT2i trials in AHF are underway, which include Efficacy and Safety of Dapagliflozin in Acute Heart Failure (DICTATE-AHF), Ertugliflozin in Acute Heart Failure, A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE), Effects of Empagliflozin on Diuresis and Renal Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF), and Effect of Empagliflozin on Cardiac Output in Patients With Acute Heart Failure (EMPA Acute Heart Failure).

In vitro studies demonstrated that SGLT2i could improve left ventricular diastolic function, relieve wall stress, reduce preload, and diminish tissue fibrosis [90]. A number of clinical trials are ongoing to testify mortality or exercise capacity benefits of SGLT2i in patients with HFpEF, such as Dapagliflozin in Preserved Ejection Fraction Heart Failure (PRESERVED-HF), Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER), Dapagliflozin Effect on Exercise Capacity Using a 6-min Walk Test in Patients With Heart Failure With Preserved Ejection Fraction (DETERMINE-preserved), and Empagliflozin outcome trial in Patients With chronic heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved).

SGLT2i Emerges as an Anti-HF Drug in the “Fantastic Four” [91]: Call for Action

Real-world studies are useful to examine the degree to which extent the results from RCTs could apply to patients outside the trials and also to assess long-term response and safety. The Comparative Effectiveness of Cardiovascular Outcomes

in New Users of SGLT-2 Inhibitors (CVD-REAL) study enrolled more than 300,000 patients with DM and newly initiated on any SGLT2i or other glucose-lowering drugs from six countries in the USA or Europe. Patients treated with SGLT2i in CVD-REAL were younger (56.9 vs. 63.1 vs. 63.3 years), had more females (43.3 vs. 28.8 vs. 35.8%), and fewer established CVD (13.1 vs. 99 vs. 65.6%) than patients in EMPA-REG Outcome and CANVAS. However, the CVD-REAL revealed similar results that SGLT2i was associated with a 39% relative risk reduction in HF hospitalization, 51% in all-cause mortality when compared to other glucose-lowering drugs after propensity score matching to account for potential confounding factors [92]. The results were consistent across countries, regardless of the use of specific SGLT2i (predominantly canagliflozin in the USA; dapagliflozin in Europe), suggesting a class effect rather. Subsequently, the CVD-REAL2 study conducted in over 400,000 patients from Asia Pacific (South Korea, Japan, Singapore, and Australia), Middle East (Israel), and North America (Canada) demonstrated the benefits of SGLT2i over other oral glucose-lowering drugs, with a 49% relative risk reduction in death, 36% in HFrEF, 19% in myocardial infarction and 32% in stroke. The results were consistent across countries and patient subgroups, including those with and without CV diseases [93]. Unfortunately, the real-world data are not available yet to examine whether the findings of the DAPA-HF and EMPEROR-Reduced trials could be extrapolated to routine HFrEF patient care.

Despite solid evidence and strong recommendation by guidelines, the use of SGLT2i in DM patients with indications is much fewer than expected. In a Denmark cohort study of 41,733 patients with a new diagnosis of DM and CVD, the 1-year cumulative user proportions of SGLT2i increased from 0.2% in 2012 to only 8.7% in 2018 [94]. Another real-world use of new agents with CV benefits was examined in a cohort of 21,173 patients with DM and CVD [95], which revealed a slow increase in SGLT2i initiation (5 new prescriptions in the first half of 2014 to 83 new prescriptions in the first half of 2019) and a very low prescription rate of SGLT2i (in 1.4% patients only). Primary care physicians accounted for 53.4% of SGLT2i prescriptions, endocrinologists for 30.3%, and cardiologists for 6.0% [95]. Although no data is available for the use of SGLT2i in real-world HF population, a cohort of 154,714 hospitalized patients with HFrEF (LVEF $\leq 40\%$) in the GWTG-HF registry identified that four in five patients (irrespective of DM status) would be candidates for dapagliflozin based on the 2020 FDA approval of dapagliflozin for patients with HFrEF to reduce risk of CV death and HFrEF [96].

Although the mechanisms underlying cardioprotection of SGLT2i has not completely clarified (the proposed hypotheses cover decrease in arterial stiffness and cardiac remodeling, reduction in blood pressure [97], inhibition of

cardiac Na⁺/H⁺ exchanger [98], suppression of cardiac fibrosis [99], natriuresis, and osmotic diuresis [100]), this will not stop SGLT2i from becoming the fourth drug class (following ARNI/ACEI/ARB, beta-blocker, and MRA) that fulfills the goals of HFrEF management independent of glycemic effect. In recently released 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment, dapagliflozin or empagliflozin representative of SGLT2i is now a followed add-on therapy for HFrEF patients with or without diabetes after ARNI/ACEI/ARB and beta-blocker treatment have started [101].

Conclusion

HF and DM are the two apparently separate disease entities from pathophysiology, diagnosis, and treatment. With the increase in incidence and prevalence of the two conditions, cardiologists and endocrinologists now encounter a crossing path of patient management. The cumulating evidence supports the reduction of HHF for DM patients treated with SGLT2i and recently extended late-breaking evidence of reducing HHF and improving quality of life by SGLT2i in HFrEF patients with and without DM. Such findings not only shifted the paradigm for the foundation of HFrEF therapy, but also pushing into revision of the HF treatment guidelines. Whether SGLT2i is equally effective in HFpEF awaits further multicenter clinical trials.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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