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EDITORIAL

Heart Failure with Preserved Ejection Fraction and Obstructive Sleep Apnea: A Novel Paradigm for Additional Cardiovascular Benefit of SGLT2 Inhibitors in Subjects With or Without Type 2 Diabetes

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ABSTRACT

After examining the complex interplay between heart failure (HF) in its various clinical forms, metabolic disorders like nonalcoholic fatty liver disease (NAFLD), and obstructive sleep apnea (OSA) syndrome, in this mini-review we described possible favorable effects of sodium–glucose cotransporter 2 inhibitors (SGLT2is) on HF with preserved (i.e., $\geq$ 50%) ejection fraction (HFpEF) through enhanced cardiorenal function and visceral-subcutaneous body fat redistribution. In greater detail, on the basis of pathophysiological mechanisms underlying OSA onset and the direct positive SGLT2i effect on renal function benefiting chronic kidney disease, we emphasized the promising role of SGLT2is in prevention, rehabilitation, and treatment of patients with OSA regardless of coexisting type 2 diabetes (T2DM). Indeed, SGLT2is enhance lipolysis and fatty acid beta-oxidation. These phenomena might prevent OSA by reducing the size of visceral and subcutaneous

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adipose tissue and, as proven in humans and animals with T2DM, counteract NAFLD onset and progression. The aforementioned mechanisms may represent an additional SGLT2i cardioprotective effect in terms of HFpEF prevention in patients with OSA, whose NAFLD prevalence is estimated to be over 50%.

Considering the close association between OSA and HFpEF, SGLT2is might also be promising for OSA prevention, treatment, and rehabilitation regardless of coexisting T2DM, as well as for the often-associated NAFLD when T2DM is present.

Keywords: Heart failure; Preserved ejection fraction; Obstructive sleep apnea; SGLT2is; T2DM; NAFLD; Cardiorenal protection; Rehabilitation

Key Summary Points

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 40–50% of incident HF, and is associated primarily with hypertension, coronary heart disease, chronic kidney disease, type 2 diabetes mellitus (T2DM), and nonalcoholic fatty liver disease (NAFLD).

The prevalence of NAFLD is up to 50% in patients with HFpEF.

Moreover, obstructive sleep apnea (OSA) may be a significant risk factor for HFpEF.

The putative mechanism underlying the association between OSA and HFpEF seems to be the intermittent hypoxia-induced autonomic nervous system stimulation mediated by oxidative and endoplasmic reticulum stress.

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) proved effective in reducing cardiovascular events in patients with HFpEF and improving renal function independently of T2DM.

SGLT2is also proved active against NAFLD in T2DM.

Heart failure (HF) encompasses a broad spectrum of disorders involving myocardial dysfunction with typical signs and symptoms. The European Society of Cardiology (ESC) guidelines include echocardiographic parameters, i.e., left ventricular ejection fraction (EF), for subclassification of this complex clinical entity: heart failure with reduced EF (HFrEF; EF < 40%), mid-range EF (HFmrEF; EF 41–49%), and preserved EF (HFpEF ≥ 50%) [1].

HFpEF accounts for approximately 40–50% of incident HF overall [2], and is associated with many cardiovascular risk factors, like arterial hypertension (AH) [2] and coronary heart disease (CAD) [3]. Other comorbidities are associated with HFpEF. They include obesity, atrial fibrillation (AF), metabolic syndrome, diabetes, chronic obstructive pulmonary disease, chronic kidney disease (CKD), and transthyretin-related amyloidosis [4–6]. Other parameters for the diagnosis of HFpEF are evidence of either diastolic dysfunction or structural heart disease, signs or symptoms of heart failure, and elevated natriuretic peptides [1].

According to a recent hypothesis, obstructive sleep apnea (OSA) may be a significant risk factor for HFpEF [7]. Frequent episodes of apnea characterize OSA during sleep due to upper airway obstructions, which might be either total (consisting of the cessation of respiratory flow for a period greater than 10 s) or partial (so-called hypopneas, consisting of a reduction of respiratory flow by more than 50% of normal) [8, 9].

The gold standard for diagnosing OSA involves simultaneous monitoring of sleep and

breathing, so-called polysomnography (PSG) [10], providing two clinically relevant indices: the apnea–hypopnea index (AHI; i.e., the mean number of episodes of apnea and hypopnea per hour of sleep) and the oxygen desaturation index (ODI; i.e., the mean number of oxygen desaturations of at least 3–4% below baseline per hour of sleep) [11].

The third edition of the International Classification of Sleep Disorders (ICSD-3) defines OSA as a PSG-determined obstructive respiratory disturbance index (RDI) $\geq$ 5 events per hour of sleep associated with the typical symptoms of OSA (e.g., unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with a gasping or choking sensation, loud snoring, or witnessed apneas), or an obstructive RDI $\geq$ 15 events for an hour of sleep (even in the absence of symptoms) [12]. Another index called RERAs (respiratory effort-related arousals) is also critical for the clinical evaluation of OSA [13, 14].

The diagnosis of sleep apnea/hypopnea syndrome (OSA syndrome, OSAS) refers to the association of OSA with utmost, unexplained daytime sleepiness or two or more of the following unexplained symptoms: sleep-time choking or gasping, recurrent awakenings, unrefreshing sleep, daytime fatigue, and impaired concentration [15, 16]. According to the so-called Chicago criteria [17], its severity is given by the AHI value as follows: absent (< 5), mild (5–14), moderate (15–29), and severe ($\geq$ 30) [9].

A study on 252 patients with HF found an 86%, 86%, and 62% prevalence of sleep-disordered breathing (SDB) ($p = 0.001$) in those with HFrEF, HFmrEF, and HFpEF, respectively. OSA was present in 48% and central sleep apnea (CSA) in 22% of those patients. The prevalence of OSA among the three groups was 42%, 47%, and 49%, respectively ($p = 0.708$), while the prevalence of CSA among the three groups was 44%, 40%, and 13% ($p < 0.001$) [18]. So, the prevalence and severity of SDB in patients with HFrEF and HFmrEF were significantly higher than in those with HFpEF and were mainly related to the high prevalence of CSA. In contrast, OSA was more prevalent in HFpEF [18].

Another prospective, cross-sectional, case–control study on 25 patients with HFpEF and 25 controls also showed a higher SDB prevalence in the former group (64% vs.12%; odds ratio [OR] = 12.2, 95% confidence interval [CI] = 2.83–52.74; $p < 0.001$) [19]. AHI severity significantly correlated with diastolic dysfunction degree ($r = 0.67$; $p < 0.001$). Among patients with HFpEF and SDB (16/25), 13 had OSA, and only three had central sleep CSA, thus confirming the higher prevalence of OSA in patients with HFpEF [19].

The putative mechanism underlying the association between OSA and HFpEF seems to be the intermittent hypoxia-induced stimulation of the sympathetic nervous system and renin–angiotensin–aldosterone system (RAAS). The latter causes a systemic inflammatory state, mediated by tumor necrosis factor (TNF)-alpha and transforming growth factor (TGF) beta-1 [20], with oxidative stress and endoplasmic reticulum stress, mediated mainly by the activation of hypoxia-inducible factor 1 transcription factor [21].

Until recently, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers alleviating symptom burden and reducing mortality in patients with HFrEF did not prove equally effective in HFpEF [22–26]. The randomized, double-blind TOPCAT study, which aimed to determine the effect of spironolactone on mortality in patients with HFpEF, showed that it did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF [27]. In addition, despite being superior to enalapril against risks of death and hospitalization for patients with HFrEF in the PARADIGM trial [28], according to the following PARAGON-HF trial, the sacubitril–valsartan combination could not reduce the rate of either HF-related hospitalizations or cardiovascular death [29].

Initially, only statins were supposed to reduce HFpEF mortality [30]. Then, the randomized, double-blind placebo-controlled EMPEROR–Preserved trial clearly showed the glucose-lowering sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin to reduce the combined risk of cardiovascular death, HF-related hospitalization, and

emergency/urgent HF visits requiring intravenous treatment in such patients. This great achievement was independent of diabetes (432 patients on empagliflozin vs. 546 on placebo; hazard ratio, 0.77 [95% CI 0.67–0.87]; $p < 0.0001$) [31].

On the basis of pathophysiological mechanisms underlying OSA onset-related and renal SGLT2 effects, we already suggested SGLT2is as promising for prevention, rehabilitation, and treatment of patients with OSA regardless of coexisting diabetes. This approach would expand their indications beyond current ones, including glucose, lipids, uric acid, blood pressure, body weight control, and chronic HF, and kidney disease prevention [32]. This hypothesis finds further support in the previously mentioned EMPEROR-Preserved trial because of the close association between OSA and HFpEF [7, 33]. Indeed, OSA is associated with an increased risk of hospital admission for HFpEF [34]. In addition, taking into account that HFpEF is more frequent in women [35], it is noteworthy that HFpEF is significantly more frequent in patients with SDB [36].

Moreover, a clear benefit of SGLT2is has been recently proven in chronic kidney disease (CKD) in patients with and without diabetes, mediated by a direct improvement of renal function [37, 38] and by the ability to prevent the associated cardiovascular autonomic neuropathy from further self-sustaining kidney function impairment [39, 40], and by the ability to reduce the associated increased albumin urinary excretion [41].

The relationship between OSA and CKD is likely bidirectional [42], even in the early stage of the disease [43, 44]. So, considering that OSA is associated with accelerated loss of kidney function [45] and is a risk factor for incident end-stage renal disease [46], the proven benefit for CKD further supports the use of SGLT2is for patients with OSA independently of coexisting diabetes.

Further evidence of the favorable effect on OSA pathophysiology comes from the proven effect of SGLT2is on visceral and subcutaneous adipose tissue [47–49]. As shown in animal models of T2DM and metabolic syndrome, the latter depends on the increased lipolysis and beta-oxidation of fatty acids [50–52] caused by a shift in energy substrates from carbohydrates to lipids [53]. SGLT2is proved active against liver steatosis in humans and animals with T2DM [54–58]. Canagliflozin, an SGLT2i, reduced epicardial fat accumulation [59], which is closely associated with coronary heart disease [60, 61].

Moreover, the lipolytic activity and the beneficial effects on nonalcoholic fatty liver disease (NAFLD) [62] may represent an additional SGLT2i cardioprotective mechanism in patients with OSA [63], who, in fact, often suffer from NAFLD [64, 65], obesity, and metabolic syndrome [66]. Indeed, some HFpEF phenotypes seem to be cardiac manifestations of NAFLD, thus supporting the novel concept of a pathophysiological continuum between NAFLD and HFpEF. Such a view is supported by multiple shared pathophysiological mechanisms that rely on increased systemic inflammation [67] and contribute to the associated endothelial dysfunction [67]. Indeed, NAFLD and nonalcoholic steatohepatitis (NASH) favor the accumulation of epicardial fat secreting proinflammatory adipocytokines, thus causing microvessel dysfunction and adjacent myocardium fibrosis. All the above leads to HFpEF and an increased risk of AF [68]. Also, a recent clinical prospective study on 181 patients followed as part of the University of Michigan HFpEF outpatient clinic reported a higher NAFLD prevalence (up to 50%) in patients with HFpEF than in those with HFrEF [69].

All the above further supports the hypothesis of cardiovascular and neurological (polysomnographic parameters) SGLT2i benefits in OSA independently of diabetes [32].

SGLT2is have also been supposed to elicit positive effects in patients with OSA through an intriguing yet controversial effect [70], i.e., hindered activation of leptin [71], whose levels are high in OSA [72, 73], Indeed, in support of this hypothesis, a recent meta-analysis of ten randomized controlled trials showed that SGLT2is treatment was associated with decreased circulating leptin and increased adiponectin levels in patients with T2DM [74].

In conclusion, the putative favorable effect of SGLT2is in patients with OSA is likely due to the ability to reduce cardiovascular events in

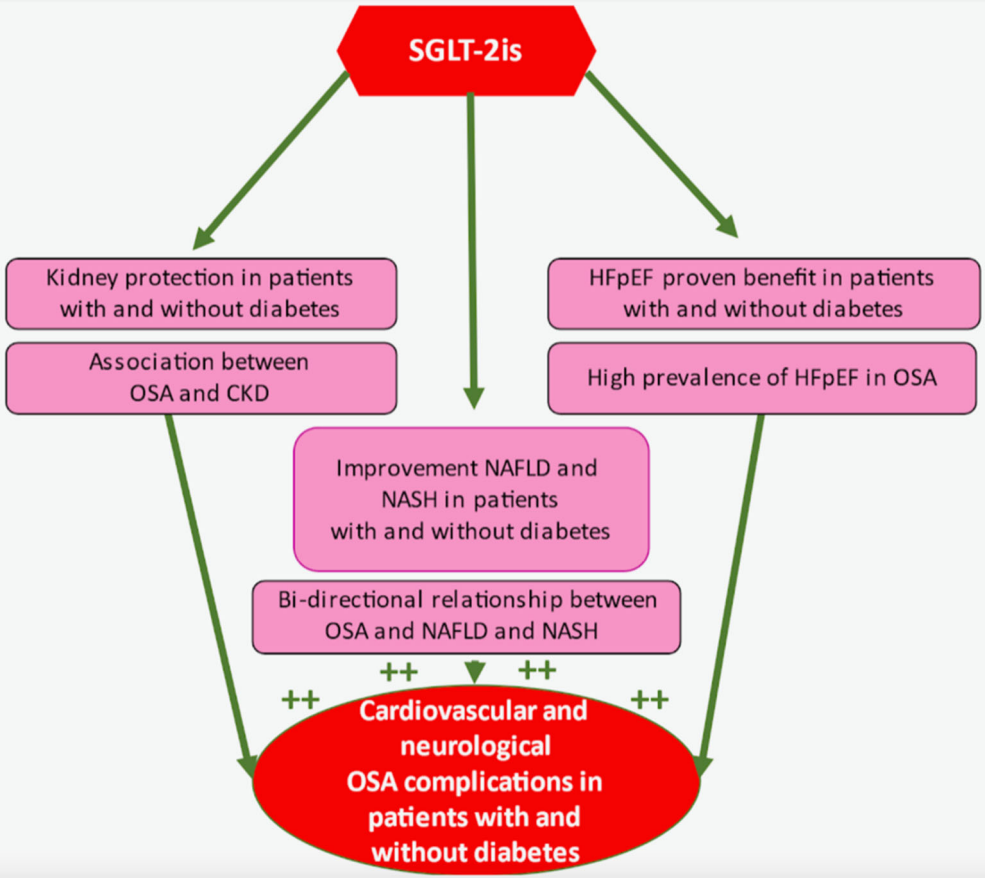

Fig. 1 Putative mechanisms of the benefit of SGLT2is in patients with OSA with and without diabetes. *SGLT2is* sodium–glucose cotransporter 2 inhibitors, *CKD* chronic kidney disease, *HFpEF* heart failure with preserved ejection fraction, *NAFLD* nonalcoholic liver disease, *NASH* nonalcoholic steatohepatitis

patients with HFpEF [31] and improve renal function independently of diabetes [37, 38]. OSA is an independent risk factor for cardio- and cerebrovascular events independently of diabetes [75, 76] and has a high prevalence especially in patients with obesity resistant to antihypertensive therapy [77]. This points to the need for effective OSA screening, diagnosis, and treatment to decrease cardiovascular risk [78, 79] besides improving the polysomnographic parameters and the quality of life [66, 80].

On the basis of all the above considerations, we feel it necessary for the scientific community to set up additional studies in order to expand the favorable extraglycemic effects of SGLT2is to patients with OSA with and without diabetes, as depicted in Fig. 1.

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Compliance with Ethics Guidelines. This study does not take into consideration data from directly observed diabetic patients, but is limited to analyzing data deriving from the literature.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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