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EDITORIAL

Role of sodium-glucose co-transporter-2 inhibitors in the management of heart failure in patients with diabetes mellitus

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Abstract

Heart failure (HF) is a major complication of diabetes mellitus (DM). Patients with DM have considerably higher risk for HF than non-diabetic subjects and HF is also more severe in the former. Given the rising prevalence of DM, the management of HF in diabetic patients has become the focus of increased attention. In this context, the findings of several randomized, placebo-controlled trials that evaluated the effects of sodium-glucose co-transporter-2 inhibitors on the risk of hospitalization for HF in patients with type 2 DM represent a paradigm shift in the management of HF. These agents consistently reduced the risk of hospitalization for HF both in patients with and in those without HF. These benefits appear to be partly independent from glucose-lowering and have also been reported in patients without DM. However, there are more limited data regarding the benefit of sodium-glucose co-transporter-2 inhibitors in patients with HF and preserved left ventricular ejection fraction, which is the commonest type of HF in diabetic patients.

Key words: Heart failure; Type 2 diabetes mellitus; Sodium-glucose co-transporter-2 inhibitors; Canagliflozin; Dapagliflozin; Empagliflozin

Core tip: Sodium-glucose co-transporter-2 inhibitors substantially reduce the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus (T2DM). Accordingly, these agents should be considered in all patients with T2DM and HF with reduced left ventricular ejection fraction regardless of HbA_{1c} levels. However, more studies are needed to clarify the role of sodium-glucose co-transporter-2 inhibitors in patients with T2DM and HF with preserved left ventricular ejection fraction, which is the commonest type of HF in this population.

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EDITORIAL

During the last decades, the prevalence of diabetes mellitus (DM) worldwide has almost doubled, from 4.7% in 1984 to 9.3% in 2019[1]. Moreover, it is estimated that patients with DM will reach 300 million by 2025 and 366 million in 2030, with the majority of them living in low-income countries[2,3]. It has also been projected that the prevalence of DM globally will rise to 10.4% by 2040 and that 12% of healthcare expenditure will be dedicated to diabetic patients[4]. These trends are of great importance given the strong relationship between DM and cardiovascular disease (CVD). It is well-established that DM is a major cardiovascular risk factor[5]. Indeed, 75%-80% of patients with DM die due to CVD[6]. Accordingly, DM is one of the leading causes of death worldwide[7].

Among the manifestations of CVD in patients with DM, heart failure (HF) has become the focus of intense research in the last years. Heart failure is an important public health issue, affecting more than 23 million people all over the world and leading to excess morbidity and mortality[8,9]. Heart failure-related healthcare costs are also substantial and are mostly due to the repeated hospitalization of these patients[8,9]. Based on the left ventricular ejection fraction (LVEF), HF is categorized into HF with reduced EF (HFrEF), HF with midrange EF (HFmrEF) and HF with preserved EF (HFpEF)[10,11]. Patients with HFpEF have a higher prevalence of comorbidities including obesity, chronic obstructive pulmonary disease and DM than those with HFrEF[12,13]. Several studies showed that the incidence of HF is 2-5 times higher in diabetic patients than in those without DM[14,15]. Patients with type 1 DM also have a higher risk of developing HF[16]. In addition, diabetic patients with HF have longer HF-related hospital stays, more frequent HF-related readmissions and higher risk for cardiovascular mortality than patients with HF but without DM[17-20]. All-cause mortality and healthcare costs are also higher in the former[21-23].

In addition to atherosclerosis-related ischemic heart disease, small vessel dysfunction, renal dysfunction and a direct effect of insulin resistance on cardiomyocytes appear to play a role in the pathogenesis of HF in patients with DM[24,25]. The most profound feature of diabetic cardiomyopathy is LV diastolic impairment manifesting as HFpE whereas HFrEF is less prevalent in these patients[26,27]. Early signs of diastolic dysfunction in patients with DM include elevated LV filling pressures portrayed by reduced peak myocardial systolic velocity and reduced E/A ratio (transmittal early to late diastolic peak ratio), along with increased LV mass and wall thickness[28-31].

Given the rising prevalence of DM and its strong association with HF, the findings of several recent, randomized, placebo-controlled trials of sodium glucose co-transporter 2 (SGLT2) inhibitors might represent a paradigm shift in the management of these patients. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial [n = 7020 patients with type 2 DM (T2DM) and established CVD], treatment with empagliflozin reduced the risk of hospitalization for HF by 35% and reduced the incidence of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) by 14% during a median follow-up of 3.1 years[32]. In the Canagliflozin Cardiovascular Assessment Study (n = 10142 patients with T2DM who were either ≥ 30 years old with established CVD or ≥ 50 year-old with ≥ 2 of the following cardiovascular risk factors: T2DM duration ≥ 10 years, systolic blood pressure > 140 mmHg despite treatment with ≥ 1 antihypertensive agent, current smoking, micro- or macroalbuminuria, or high-density lipoprotein cholesterol level < 39 mg/dL), treatment with canagliflozin reduced the risk of hospitalization for HF by 33% and reduced the incidence of the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) by 14% during a mean follow-up of 3.6 years[33]. In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial [n = 4401 patients with T2DM and chronic kidney disease (estimated glomerular filtration rate 30-90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio > 300 mg/g)], treatment with canagliflozin reduced the risk for hospitalization

for HF by 39% during a mean follow-up of 2.6 years[34]. In the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE TIMI-58) trial (n = 17160 patients with T2DM and either established CVD or multiple cardiovascular risk factors), dapagliflozin reduced the risk for hospitalization for HF by 27% compared with placebo during a median follow-up of 4.2 years[35]. In an observational study in 309056 patients with DM followed-up in real-world practice, treatment with SGLT2 inhibitors also resulted in a 39% reduction in the risk of hospitalization for HF compared with other antidiabetic agents[36]. Notably, SGLT2 inhibitors appeared to reduce the risk of hospitalization for HF to a similar degree in patients with and without a history of HF[37,38]. It is therefore possible that SGLT2 inhibitors might prevent the development of HF in diabetic patients. However, it is also possible that many patients in these trials had undiagnosed HF and that SGLT2 inhibitors are also effective in patients with less severe, asymptomatic HF. It is also noteworthy that, in the DECLARE TIMI-58 trial, dapagliflozin reduced the risk of hospitalization for HF to a similar degree in patients with HFrEF and in those with HFpEF[38]. However, this analysis was based on a small number of patients and should be considered exploratory and hypothesis-generating[38].

Despite the consistently beneficial effects of SGLT2 inhibitors on the incidence of hospitalization for HF, it should be emphasized that only a small proportion of patients in these trials had HF at baseline (10%-15%)[32-35]. However, in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin reduced the risk of hospitalization for HF by 30% and reduced cardiovascular mortality by 18% compared with placebo in 4744 patients with New York Heart Association class II, III, or IV heart failure and an EF ≤ 40% during a median follow-up of 18.2 mo[39]. Therefore, the findings of this large study further support the benefits of SGLT2 inhibitors in the management of HF, particularly with reduced EF. Nevertheless, given the limited data on the effects of these agents in patients with HFpEF, more studies are needed in this important subgroup. It should also be mentioned that patients with DM (42% of the study population) experienced a similar reduction in the risk of hospitalization for HF as patients without DM[39]. This finding suggests that other actions of SGLT2 inhibitors besides glucose-lowering might play a role in the beneficial effects of these agents in patients with HF. Indeed, it has been reported that SGLT2 inhibitors promote reverse cardiac remodeling, improve myocardial energetics and filling conditions, reduce LV wall stress and mass and reduce blood pressure and arterial stiffness[40-43].

CONCLUSION

SGLT2 inhibitors substantially reduce the risk of hospitalization for HF in patients with DM. Accordingly, current guidelines recommend these agents in patients with T2DM and HFrEF regardless of HbA_{1c} levels[44]. However, more studies are needed to clarify the role of SGLT2 inhibitors in patients with T2DM and HFpEF, which is the most common type of HF in this population.

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