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Article

Cardiovascular Effect of Sodium-glucose Cotransporter-2 Inhibitors: from Antidiabetic Agents to Heart Failure Medications

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Abstract:
The evolution of antidiabetic agents has been dramatic in recent decades. Since diabetic patients are at increased risks of cardiovascular diseases and heart failure, validation of cardiovascular safety had been mandatory for pharmaceutical development before acquired with marketing approval. Among these novel regimens, performance of sodium-glucose cotransporter 2 (SGLT2) inhibitors was surprisingly salutary. Accumulating evidence endorsed its beneficial efficacy on cardiovascular outcome even in nondiabetic individuals and regardless of baseline glycemic level, implying the pleiotropic effects on heart and vessels. Subsequent trials further demonstrated favorable prognosis achieved by SLGT2 inhibitors in heart failure with reduced ejection fraction. Additionally, studies are ongoing to interrogate the application of SGLT2 inhibitors toward other clinical scenarios, including but not limited to acute decompensated heart failure, its concomitant use with mechanical device therapy, and in post-transplantation status. In this review, we summarized how SGLT2 inhibitors altered cardiovascular endpoints in various trials as reference for future study design and clinical implication.

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1. Background

Type 2 diabetes mellitus (DM) has traditionally been a prevalent disease entity necessitating extensive medical intervention. The occurrence of myocardial infarction [1] and ischemic stroke [2] have all been proposed to be intertwined with DM. According to Swedish epidemiological study, DM pronouncedly elevated the risk of heart failure even after other cardiovascular risk factors being fully controlled [3]. Development of pharmaceutical industry for optimized antidiabetic agents was thereby nurtured and remained prosperous for decades. In contrary to traditional medications which acted purely on metabolic control, drugs of newer generation incidentally demonstrated pleiotropic effects to bring about cardiovascular benefits. The introduction of sodium-glucose cotransporter 2 (SGLT2)

inhibitors revolutionized the field, as this class of drug dually served as both antidiabetic agents and potentially as heart failure medications in the foreseeable future.

Although diabetic patients frequently sustained concurrent cardiovascular morbidities, minimal awareness was paid on the cardiovascular impact of antidiabetic agents until 2007 when Nissen et al pooled 42 trials of rosiglitzone and unintendedly observed significantly increased risk of myocardial infarction [4]. Despite suspicions on the statistical methodology regarding this study, it addressed the central importance of cardiovascular safety for newly-marketed glucose-lowering medications. Correspondingly, not only thiazolidinedione but also all upcoming antidiabetic agents were warranted to demonstrate cardiovascular outcome before licensing. After regulation adjustment of US Food and Drug Administration (FDA) in 2008 to nurture pharmaceutical industry, 10 times of the patients were enrolled for ensuing relevant clinical trials [5]. Still, the majority of subsequent interrogations were designed to prove the cardiac safety rather than demonstrating long-term benefits. Intriguingly, SGLT2 inhibitors demonstrated unexpectedly promising cardiovascular prognosis. Later trials further determined its role in the management of heart failure. In this review, we aimed to summarize the cardiovascular composite outcome of SGLT2 inhibitors in clinical trials and propose future directions to potentially extent their indications.

2. Composite cardiovascular outcomes in SGLT2 inhibitor trials

Cardiovascular outcome was included for investigation in the studies of SGLT2 inhibitors (Table 1) [6–8]. EMPA-REG OUTCOME trial pioneered this field in 2005. A total of 7,020 diabetic patients with preexisting cardiovascular diseases were enrolled for analysis. The study was originally carried out so as to confirm cardiovascular safety in high-risk individuals. After a median follow-up of 3.1 years, the efficacy of secondary prevention for cardiovascular diseases by empagliflozin 10 mg or 25 mg per day was promising. Modest reduction in major adverse cardiovascular event (MACE) in addition to significant decrease in cardiovascular mortality and heart failure hospitalization (HHF) were reported.

CANVAS program jumped on the bandwagon shortly. A total of 10,142 diabetic patients (65.6% with underlying cardiovascular diseases) from multi-center participated to elucidate the effects of both primary and secondary prevention. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Median followed period was 188.2 weeks after administration of canagliflozin. Similar to EMPA-REG OUTCOME trial, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo.

The third SGLT2 inhibitor study, DECLARE-TIMI 58 trial, echoed previous reports to substantiate cardiovascular benefits. A total of 17,160 diabetic patients with established cardiovascular diseases or multiple risk factors, while fair baseline renal function, were included to elucidate clinical efficacy of dapagliflozin 10 mg daily. After followed for 4.2 years, the cohort demonstrated non-inferior MACE (a composition of cardiovascular disease, myocardial infarction, and ischemic stroke), while significant efficacy on cardiovascular death and HHF.

Together, Wiviott et al meta-analyzed these aforementioned 3 trials and pooled 34,322 subjects to appreciate the magnitude of cardiovascular impact [9]. The outcome endorsed an overall 11% reduction in MACE by SGLT2 inhibitors, yet such effect was highly restricted only to those with underlying atherosclerotic comorbidity. Nevertheless, SGLT2 inhibitor brought about consistent reduction in HHF, which was independent of their clinical background. Likewise, another meta-analysis focused on 6 trials with 46,969 diabetic subjects. In addition to the amelioration of MACE, the study also proposed the most consistent and noticeable benefit was HHF reduction [10].. It gradually became more convincing that SGLT2 inhibitors might not merely act as antidiabetic agents but potentially be incorporated as heart failure medications.

3. SGLT2 inhibitors and heart failure

As encouraging cardiovascular outcomes accumulated, SGLT2 inhibitors were hypothesized not only to serve as antidiabetic agents but also to be included as one of the regimens against heart failure. In addition to similar pathophysiology of heart failure and DM, the glucosuria, natriuresis, diuretic, and metabolic effects of SGLT2 inhibitors were present regardless of diabetic status [11, 12]. Further enlightened by EMPA-REG OUTCOME trial in which the cardiovascular benefit was demonstrated independent of glucose level, subsequent trials were ambitiously designed to recruit a certain proportion of nondiabetic participants and attempted to inquire drug efficacy upon heart failure (Table. 1).

Initial attempt was executed upon patients with heart failure with reduced ejection fraction (HFrEF). The first remarkable triumph was accomplished by DAPA-HF trial [13]. On top of recommended therapy administered to 4,744 patients with HFrEF and New York Heart Association at least class II, addition of dapagliflozin 10 mg daily resulted in lower risk of heart failure deterioration (necessitating hospitalization or intravenous therapy) and cardiovascular death. Post-hoc analysis also suggested such benefit was related to neither DM status nor baseline HbA1c level [14]. Besides, the positive effect of SGLT2 inhibitor was not associated with background guideline-directed therapy [15] and thereby proposed to be linked with volume depletion. Successive study further endorsed the initiation of dapagliflozin consistently improved cardiovascular outcome on subjects with different diuretic doses [16]. Yet despite these reassurances, the clinical usage of dapagliflozin was still considerably scarce. In fact, 81.1% of the admitted patient with HFrEF would be candidate to receive dapagliflozin in observation of FDA regulation [17]. Comprehensive literacy of this novel agent will facilitate the generalization of its prescription.

Such class effect was also observed in VERTIS CV trial. A total of 8,246 patients with type 2 diabetic and atherosclerotic cardiovascular disease were engaged to receive daily ertugliflozin 5 mg, 15 mg, or placebo. Ertugliflozin numerically, although not significantly, reduced the risk of cardiovascular mortality and HHF. Although the effect was independent of baseline ejection fraction, stratified subgroup analysis pointed out those with HFrEF harbored greater benefit [18].

As for empagliflozin, EMPEROR-Reduced trial (3,730 participants with HFrEF and New York Heart Association at least class II) successfully demonstrated the reduced rate of both cardiovascular death and HHF, yet the performance of 6-minute walk remained neutral [19]. Meta-analysis of DAPA-HF and EMPEROR-Reduced studies also indicated these SGLT2 inhibitors favorably improved all-cause and cardiovascular mortality [20]. The eligibility of SGLT2 inhibitor against HFrEF even without DM was herein gradually established.

However, whether the cardiovascular efficacy of SGLT2 inhibitor would be as promising in heart failure with preserved ejection fraction (HFpEF) was still enigmatic. HFpEF was recognized in 3 phenotypes: dysregulated expression of elasticity gene, aggregation of abnormal protein, e.g. transthyretin, and inflammation of epicardial adipose tissue [21]. Correspondingly, SGLT2 inhibitor was introduced to resolve these abnormalities as literature displayed administration of SGLT2 inhibitor abated local inflammation [22] and curtailed the volume of epicardial fat [23]. EMPERIAL-Preserved trial intended to assess the improvement of exercise capacity in 315 patients with chronic HFpEF under empagliflozin 10 mg daily or placebo [24]. Preliminary data, nevertheless, adumbrated SGLT2 inhibitor failed to evince improvement in 6-minute walk test. Additionally, ongoing EMPEROR-Preserved trial aimed to examine the efficacy of empagliflozin on cardiovascular mortality and HHF in patients with chronic HFpEF [25]. In conjunction with DAPA-HF and DAPA-CKD studies, the DELIVER trial was designed to determine if introducing dapagliflozin was superior to placebo in cardiovascular death and heart failure events (HHF and urgent heart failure visit) in patients with HFpEF and New York Heart Association at least class II [26]. Additionally, DETERMINED-preserved was carried out to figure how dapagliflozin influences exercise tolerability (Kansas-City Cardiomyopathy Questionnaire-Total Symptom Score and 6-minute walk distance) in patients with HFpEF and New York Heart Association at least class II [27]. Aforementioned landmark studies of SGLT2 inhibitors were summarized (Table.

Table 1. Landmark studies of sodium-glucose cotransporter 2 inhibitors

Study	Year	Medication	Cohort	Main Findings	Ref
EMPA-REG	2005	Empagliflozin	7,020 diabetic patients (all with underlying CVD)	Reduced CV death & HHF	[6]
CANVAS	2017	Canagliflozin	10,142 diabetic patients (65.6% with underlying CVD)	Reduced CV events	[7]
DECLARE-TIMI 58	2019	Dapagliflozin	17,160 diabetic patients (with established CVD or multiple risk factors)	Reduced CV death & HHF	[8]
DAPA-HF	2019	Dapagliflozin	4,744 patients with HFrEF and NYHA at least II	Reduced CV death & HF worsening	[13]
VERTIS CV	2020	Ertugliflozin	8,242 diabetic patients with atherosclerotic cardiovascular disease	Reduced CV death & HFF (not significant), especially in HFrEF	[18]
EMPEROR-Reduced	2020	Empagliflozin	3,730 patients with HFrEF and NYHA at least II	Reduced CV death & HHF, regardless DM. No improvement in 6-minute walk.	[19]
EMPERIAL-Preserved	2020	Empagliflozin	315 patients with chronic HFpEF	No improvement in 6-minute walk	[24]
EMPEROR-Preserved		Empagliflozin	5,988 patients with chronic HFpEF	To assess CV death & HHF (ongoing)	[25]
DELIVER		Dapagliflozin	6,263 patients with HFpEF and NYHA at least II	To assess CV death and HF events (HHF or urgent HF visit) (ongoing)	[26]
DETERMINE-Preserved		Dapagliflozin	504 patients with HFpEF and NYHA at least II	To assess exercise capacity (ongoing)	[27]

* CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HHF, hospitalization for heart failure; NYHA, New York Heart Association; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection.

1). Presentation of these trials will propel our understanding upon SGLT2 inhibitor use in patients with HFpEF.

4. Unanswered questions and future perspectives

Although the protective cardiovascular effect on heart failure by SGLT2 inhibitors was well-demonstrated in aforementioned trials, the populations enrolled in these studies were carefully selected and clinical condition thereof highly controlled. Applications of the trial outcome on generalized individuals mandated more evidence. First, the effect of SGLT2 inhibitor in the setting of acute decompensated heart failure (ADHF) remained unclear. Griffen et al documented a case series of 31 previously naive admitted patients who freshly received either canagliflozin or empagliflozin in conjunction with loop diuretics during ADHF [28]. No aggravation of creatinine, potassium, and blood pressure level was observed after adding SLGT2 inhibitor, while facilitation of urine output and body weight loss was present. Nonetheless, the cardiovascular outcome and mortality benefit were untouched. EMPA-RESPONSE-AHF was the pilot study designed in attempt to answer this issue [29]. A total of 80 patients with ADHF were administered with either empagliflozin or placebo. The preliminary outcome endorsed acceptable safety and toleration of SGLT2 inhibitor use during ADHF, whilst no effect on subjective dyspnea and length of hospital stay was demonstrated. Interestingly, SOLOIST-WHF trial enrolled 1,222 participants with ADHF [30]. Composite outcome (cardiovascular death, HHF, or urgent visits for heart failure) was superior under sotagliflozin, and the positive effect held true even in those with HFpEF. The efficacy onset within the first month after drug administration and lasted until the ninth month as long as this study followed. Similarly, SOLIST trial not only

reported reduced cardiovascular endpoints but also decreased the risk of stroke [31]. These suggested SGLT2 inhibitors may serve a novel role in ADHF, yet aggregation of more clinical data is imperative to support this practice.

Post-transplantation status was one of the other debatable settings for the administration of SGLT2 inhibitors. Although initiation of SGLT2 inhibitor for renal protection after kidney transplantation was not recommended due to predisposed risk of urinary tract infection, literature showed empagliflozin significantly improved glucose profile, reduced body weight, and decreased dose of furosemide in diabetic patients after heart transplantation [32]. Some even hypothesized SGLT2 inhibitor to be capable of alleviating cardiac allograft vasculopathy due to its anti-inflammatory and anti-oxidative effects. Besides, SGLT molecule was proposed not only to be upregulated secondary to myocardial infarction but also acts as an adaptive mediator for the recovery of cardiac dysfunction after implantation of left ventricular assistive device (LVAD) [33]. However, patient with LVAD was one of the exclusion criteria in EMPEROR-Reduced trial. Currently there is also no available data to appreciate the synergistic efficacy of SGLT2 inhibitor in conjunction with mechanical devices.

5. Conclusion

DM and cardiovascular comorbidities pose increasingly heavy burden in the contemporary community. Literature not only exhibited the cardiovascular safety of SGLT2 inhibitor but also promising efficacy toward heart failure. Modern studies were designed to enroll patient with more extended clinical background, in attempt to expand their usage in broadened clinical scenario. SGLT2 inhibitors were demonstrated to improve cardiovascular outcome in patients with HFrEF but not yet in HFpEF. As the accretion of evidences and prosperous trials ongoing to validate salutary effect on cardiovascular outcome, the next clinical issue is for physicians to opt for most suitable medication and achieve individualized prescription. Besides, better appreciation on the hemodynamic and metabolic mechanism of SGLT2 inhibitors will propel the advancement of future drug development for DM and heart failure.

Conflicts of Interest:
The authors declare no conflict of interest.

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