Review Article

Sodium-Glucose Co-Transporter 2 Inhibitors Should be the Standard [P1] of Care for Treatment of Most Patients with Heart Failure and Reduced Ejection Fraction Irrespective of Presence of Diabetes

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Abstract

Background: Recent well-designed trials have shown that Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors decrease Heart Failure Hospitalization (HFH) in patients with or without type 2 diabetes.

Methods: Review of literature [p2] (English, French, Spanish) from January 1990 to December 20, 2019. Key words included heart failure, sodium-glucose co-transporter 2, SGLT2 inhibitors, safety, randomized trials, and meta-analysis. Expert opinions and guidelines are also reviewed.

Results: The use of SGLT2 inhibitors in patients with type 2 diabetes was associated with significant relative reduction in HFH by [p3] 27-35%. The latter reduction is most likely a class effect and is consistent in patients with various degrees of Cardiovascular (CV) risk at baseline. In patients with Heart Failure and Reduced Ejection Fraction (HFrEF), dapagliflozin decreased risk of a composite outcome of worsening Heart Failure (HF) or CV death by 26%, as well as the secondary outcomes of HFH by 30% and death from any cause by 17%. Moreover, dapagliflozin decreased severity of symptoms of heart failure. Importantly, the amelioration of previous outcomes was similar in patients with or without diabetes. Dapagliflozin did not cause major hypoglycemia in non-diabetic patients with heart failure. However, patients with advanced HFrEF with New York Heart Association (NYHA) class IV were not included.

Conclusions: SGLT2 inhibitors should be added to the standard care [p4] in most patients with HFrEF in presence or absence of type 2 diabetes.

Keywords: Heart Failure; Sodium-Glucose Cotransporter 2; Type 2 Diabetes; Empagliflozin; Canagliflozin; Dapagliflozin [p5]

Introduction

SGLT2 inhibitors are medications approved to treat type 2 diabetes. They decrease hyperglycemia independently of insulin by lowering the renal threshold for glucose and therefore increasing urinary excretion of glucose [1]. Recent large CV trials have consistently shown that these agents decrease HFH by 27-35% compared with placebo [2-4]. HFrEF is defined as HF syndrome with Left Ventricular Ejection Fraction (LVEF) $\leq$ 40% [5]. A large randomized trial, called the DAPA-HF Trial, published in late 2019 demonstrated that dapagliflozin significantly decreased HFH and mortality in patients with HFrEF [6]. The results of previous trials were not reflected on American practice guidelines because they were published after the release of Practice guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) [7]. The Heart Failure Association of the European Society of Cardiology (ESC) Consensus published in August 2019 reports that there is sufficient evidence to consider that the ability of SGLT2 inhibitors to prevent HFH is a class effect. Yet, there is insufficient evidence to extend this observation to reductions in either CV or all-cause mortality or to patients without diabetes [8]. However, the latter Consensus was published after the release of the DAPA-HF Trial [6]. The author expects that the newer American and International guidelines will recommend SGLT2 inhibitors for standard management of most patients with HFrEF irrespective of existence of diabetes. This expectation is based on data showing that use of SGLT2 inhibitors results in first, prevention of HFH in patients with type 2 diabetes in both randomized and real-world studies, second: by effective treatment of actual HFrEF in patients with and without diabetes.

Large randomized cardiovascular trials of SGLT2 inhibitors

Upon request of the Federal Drug Administration (FDA), pharmaceutical companies are required to design large clinical trials to prove CV safety of their products. Thus, 3 large randomized double-blind trials were published to examine CV safety of the 3 SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin (Table 1) [2-4]. The primary outcome in these trials was a composite of Major Adverse CV Outcome (MACE) defined as CV death, non-

Table 1: Hospitalization due to heart failure in major randomized cardiovascular trials of SGLT2 inhibitors in patients with type 2 diabetes.

Trial	EMPA-REG [2]	CANAVAS [3]	DECLARE [4]
SGLT-2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin
Patients	n=7020, mean age 63, 28% women	N=10142, mean age 63, 35.8% women	N=17160, mean age 64, 37.5% women
Patients with *CVD at baseline	100%	65%	40%
Patients with heart failure at baseline	10.10%	14.40%	10.00%
Follow-up	Median treatment 2.6 y, median observation 3.1 y	Mean 188 wks, median 126 wk	Median 4.2 y
Relative risk reduction in **HFH (Hazard ratio, 95% CI)	0.65 (0.5-0.85), P=0.002	0.67 (0.52-0.87), P value not reported	0.73 (0.61-0.88), P value not reported

*CVD=Cardiovascular Disease
**HFH=Heart Failure Hospitalization

fatal myocardial infarction or ischemic stroke. One of the secondary outcomes of these trials was HFH [2-4]. Despite the variable baseline CV risk across the 3 trials, the relative reduction in HFH compared with placebo was robust and consistent, ranging from 27% to 35% (Table 1) [2-4]. A meta-analysis of the 3 studies estimated the overall risk reduction to be 31% (hazard ratio 0.69, 95% CI 0.61-79) [9]. The decrease in HFH was similar whether patients had established CV disease at baseline or had only CV risk factors [9]. Regarding the time course of events, the difference in rates of HFH between the SGLT2 inhibitors and placebo was evident early few months after starting treatment [2-4].

Meta-analysis of randomized trials

Yang et al [10] performed a network meta-analysis of 91 randomized trials to examine the incidence of HF among different classes of anti-diabetic agents. They found that SGLT2 inhibitors were superior in terms of risk of HF to insulin (odds ratio 0.75, 95% CI 0.62-0.91), dipeptidyl peptidase inhibitors (odds ratio 0.68, 95% CI 0.59-0.78), Glucagon-Like Peptide-1 (GLP-1) receptor agonist (odds ratio 0.65, 95% CI 0.54-0.78), and thiazolidinediones (odds ratio 0.46, 95% 0.27-0.77) [10]. In the subgroup of patients with baseline HF, SGLT2 inhibitors were also superior to metformin in reducing risk of subsequent HF (odds ratio 0.75, 95% CI 0.58-0.95) [10].

Results of real-world studies

The benefits of SGLT2 inhibitors on HFH and death were clearly shown in observational studies of real-world practice. The CVD-REAL Study is a large study comparing 154,528 patients with type 2 diabetes initiating SGLT2 inhibitor with similar number of matched patients initiating other glucose lowering drugs across 6 countries [11]. Only 13% of patients had known CVD at baseline. Compared with other anti-diabetic agents, treatment with SGLT2 inhibitors was associated with 39% relative risk reduction (hazard ratio 0.61, 95% CI 0.51-0.73) in HFH, the primary outcome, and 51% reduction (hazard ratio 0.49, 95% 0.41-0.57) in all-cause death, the secondary outcome [11]. This large study adds important information to CV benefits of SGLT2 inhibitors. First, it supports the fact that reduction in HFH is a class effect shared by various SGLT2 inhibitors. Second, it suggests that reduction in HFH and all-cause death extends to relatively young patients with type 2 diabetes (mean age was 57 y) at lower CV risk at baseline [11].

In another study using 2 commercial and one Federal data sources, Patorno et al, [12] showed that initiation of empagliflozin in real-world practice was associated with 50% reduction in HFH as compared with initiation of sitagliptin over a mean follow-up of 5.3 months, hazard ration 0.50 (95% CI 0.21-0.91) [12]. Subgroup analysis by presence of baseline CV disease, history of heart failure, and gender yielded consistent results [12].

SGLT2 inhibitors as treatment for heart failure in patients with and without diabetes

Two studies were recently published to evaluate SGLT2 inhibitors as treatment for patients with HF irrespective of presence of diabetes. The first was a small short-term randomized trial using empagliflozin 10 mg/d in patients with HFrEF (mean LVEF 26 [p6] %) [13]. After 12 weeks, significantly greater proportions of patients treated with empagliflozin experienced improvements in HF symptoms, functional status and quality of life as compared with placebo [13]. Results were the same whether patients had type 2 diabetes (166 of 263, 62%) or no diabetes (97 of 263, 38 [p7] %) [13].

The second study is a landmark randomized trial, the DAPA-HF trial, that examined the effect of dapagliflozin in 4,744 patients with HFrEF with LVEF of 40% or less (Table 2) [6]. The primary outcome was a composite of worsening HF (defined as hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death [6]. Over a median follow-up of 18.2 months, the relative reduction in primary outcome in the dapagliflozin group *versus* the placebo group was 26% (hazard ratio 0.74, 95% CI 0.65-0.85, P< 0.001) [6]. In addition, there was significant improvement in quality of life at 8 months. Importantly, results in patients without diabetes, who constitute 55% of the study population, were similar to those with diabetes [6]. Furthermore, all individual components of the primary outcome were in favor of dapagliflozin (Table 2). The DAPA-HF provides strong evidence that SGLT2 inhibitors do not only decrease incidence of HF but also may serve as actual therapy for HFrEF irrespective of presence of diabetes [6].

Mechanisms of cardiac benefits of SDLT2 inhibitors

Mechanisms underlying the reduction in HFH of SGLT2 inhibitors are not fully understood and are currently an area of active research. These mechanisms include changes in arterial stiffness and cardiac oxygen demand, and reduction in the following parameters: serum uric acid, tissue sodium, albuminuria, ambulatory blood pressure, and weight [for review see reference 14]. Regarding the relative importance of these mechanisms, several observations have to be considered. First, the fact that reduction in HFH occurred early within the first few months after administration of SGLT2 inhibitors suggests that diuresis and natriuresis by these agents may be early

Table 2: Overview and main results of DAPA-HF trial in patients with heart failure and reduced ejection fraction with or without diabetes [6].

Design	Randomized, double-blind, multi-center, 2 groups
Patients	n=4744, mean age 66 y/o, 23% females,
Patients' disease	Heart failure with ejection fraction ≤40%, NYHA Class II (67%), III (32%), IV (1%).
Percentage of patients with/without type 2 diabetes	45/55
Primary outcome	Composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death
Median follow-up	18.2 months
Intervention	Dapagliflozin 10 mg/d (n=2373), placebo (n=2371)
Risk reduction in primary outcome with dapagliflozin *vs* placebo	Dapagliflozin 16.3%, placebo 21.3%, *HR 0.74 (95% CI, 0.65-0.85), P<0.001
Death from any cause	Dapagliflozin 11.6%, placebo 13.9%, HR 0.83 (95% CI 0.71-0.97)
Death due to cardiovascular causes	Dapagliflozin 9.6%, placebo 11.5%, HR 0.82 (95% CI 0.69-0.98)
Hospitalization due to heart failure	Dapagliflozin 9.7%, placebo 13.4% HR 0.70 (95% CI 0.59-0.83)
Worsening renal function	Dapagliflozin 1.2%, placebo 1.6%, HR 0.71 (95% CI 0.44-1.16)
Percentage of patients with ≥5 increase in the KCCQ ** at 8 months	Dapagliflozin 58.3%, placebo 50.9%, odds ratio, 1.15 (95% CI 1.01-1.23)
Discontinuation of study drug due to adverse effects	Dapagliflozin 4.6%, Placebo 4.9%

*HR: hazard ratio.

** KCCQ: Kansas City Cardiomyopathy Questionnaire. Score is from 0 to 100, with higher score reflects fewer symptoms. An increase in scoring of is considered clinically important ≥5 [6].

mechanisms involved to decrease the after load. Second, it is unlikely that the mild reduction in hemoglobin A1c values (approximately 0.2-0.4% less than placebo) is a significant factor. This notion is supported by the fact that patients without diabetes had similar magnitude of cardiac benefits [6]. Third, recent data do not suggest a positive inotropic action by SGLT2 inhibitors. Thus, using cardiac magnetic resonance imaging, Verma et al [15] showed amelioration of left ventricular mass index after 6 months of empagliflozin therapy, but no significant effect on ejection fraction [15].

Safety of SGLT2 inhibitors in heart failure

Overall, SGLT2 inhibitors were well-tolerated as reflected by rates of discontinuation due to adverse effects that are close to placebo [2-4,6]. Likewise, rates of hypoglycemia, acute renal failure are either similar or less than placebo [2-4]. It was particularly reassuring that no major hypoglycemic episodes were reported among patients without diabetes [6]. However, there are 2 adverse effects shared by members of the class. First, genital fungal infections are the commonest adverse effect of SGLT2 inhibitors, particularly in women. Second, diabetic ketoacidosis occurred 2-10 times more frequently with SGLT2 inhibitors than placebo, but the absolute number of events was small. Increased risk of lower limb amputation and fractures previously reported in one large CV trial with canagliflozin [3], were not seen with empagliflozin and dapagliflozin [2,4].

Rationale [p8] for adding SGLT2 inhibitors to standard therapy of heart failure irrespective of diabetes

Based on the preceding, SGLT2 inhibitors should be included as part of management of most patients with HFrEF irrespective of presence of diabetes based on the following: first the reduction in HFH is robust and consistent across a wide range of patients' characteristics [2-4]. Second, the magnitude of decrease in HFH is substantial, was already manifest after few months, and was demonstrated on top of standard treatment of HF [6]. Third, the decrease in HFH by SGLT2 inhibitors was similar in patients with

and without diabetes [6]. Fourth, in addition to reduction in HFH and amelioration of symptoms of HF, dapagliflozin significantly reduced CV death and all-cause death [6]. Fifth, SGLT2 inhibitors did not cause major hypoglycemia in patients without diabetes [6].

Limitation for the recommendation of using SGLT2 inhibitors in all patients with HFrEF

Despite the encouraging results of dapagliflozin in reducing CV events in patients with HFrEF, patients with NYHA class IV, i.e. patients with more advanced heart failure, were not adequately studied [6]. Thus, less than 1% of patients involved in the DAPA-HF trial pertained to NYHA class IV, whereas approximately 67% and 32% of patients pertained to class II and III, respectively [6[p9]]. Therefore, use of SGLT2 inhibitors cannot be recommended in patients with HFrEF class IV until this group of patients is thoroughly evaluated in terms of efficacy and safety.

Conclusions and Current Directions

Reduction of HFH by 27-35% is a robust class effect of the 3 SGLT2 inhibitors [2-4]. The relative risk reduction in HFH by these agents emerges few months after starting treatment and is similar in patients with established CV disease and patients with only CV risk factors. In subjects with established HFrEF of NYHA class II and III, dapagliflozin significantly decreased HFH, CV death and all-cause death [6]. Moreover, these benefits extend to patients without diabetes [6]. Based on the available data, the author recommends using SGLT2 inhibitors as a standard therapy for patients HFrEF class II and III, irrespective of presence of diabetes. Randomized trials (n=17 trials) are underway to examine the effects of different SGLT2 inhibitors on clinical and safety outcomes in patients with HF. These trials include patients with and without type 2 diabetes, and with HFrEF as well as HF with preserved Ejection Fraction (HFpEF) i.e. LVEF ≥ 50% [8]. Randomized studies are needed to specifically evaluate efficacy and safety of SGLT2 inhibitors in patients with more advanced HF (i.e. NYHA class IV). The results of these ongoing trials will likely have

great impact on the pending American and International guidelines of HF practice.

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