12-17-2021

SGLT2 inhibitors in the management of heart failure with reduced ejection fraction

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Abstract

Objective: to assess whether SGLT2 inhibitors significantly reduce the risk of hospitalization for heart failure (HAHF) and cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF). **Design**: systematic literature review. **Methods**: searches were conducted in PubMed with the terms “SGLT2 Inhibitors,” “heart failure with reduced ejection fraction (HFrEF),” and “hospitalization” and the following limits: publication within the last 5 years, clinical trials, meta-analyses, randomized control trials, humans, and English. These criteria determined the selected literature: randomized control trial (RCT), use of an SGLT2i compared to placebo, and outcomes including HAHF and/or cardiovascular related death. **Results:** DAPA-HF: 27% RRR in HAHF, 23% RRR of composite decrease for HAHF and cardiovascular death. NNT = 21(HAHF). EMPORER-REDUCED: 28% RRR in HAHF, 20% RRR composite decrease for HAHF and cardiovascular death. NNT = 19 (HAHF). CANVAS: 33% RRR of HAHF and 22% RRR for composite outcome of cardiovascular death and HAHF. NNT = 31 (HAHF)**.** **Conclusion:** SGLT2is modestly reduced HAHF and cardiovascular death in HFrEF patients and may be an appropriate secondary adjunct to standard treatment for secondary prevention of HAHF and cardiovascular causes of death.

Introduction

Recent medical research has shown that SGLT2i reduce HAHF and improve mortality. Heart failure is a common diagnosis in the US: between 2011 - 2014, 6.5 million Americans had HF[1]. This growing number is projected to grow to more than 8 million HF patients by 2030. Treating HF is expensive; total treatment in 2012 cost $30.7 billion,[1] and treatment in 2030 is projected to cost $69.7. HAHF is a significant cost of treatment.

Death and remodeling of the heart cause HF, which is categorized into diastolic HF or HFpEF, and systolic HF or HFrEF. Patients with Type II Diabetes Mellitus (T2DM) are at

increased risk for developing HF. SGLT2i (canagliflozin, dapagliflozin, and empagliflozin) are new T2DM drugs that inhibit glucose reabsorption in the kidney. A 2015 RCT unexpectedly showed that empagliflozin reduced the relative risk (RR) for HAHF by 35%, and this sparked research on SGLT2i in HF.[3] Currently, the mechanism by which SGLT2i improve HF outcomes is not understood. However, the emerging data show that SGLT2i improve HFrEF outcomes regardless of T2DM. This review discusses whether SGLT2i decrease HAHF and all-cause mortality in HFrEF.

Clinical Question

A.M. is a 65-year-old female with a history of hypertension (HTN), coronary artery disease (CAD), and a recent myocardial infarction (MI). She has HFrEF and her left ventricular ejection fraction (LVEF) is 30%. Would prescribing an SGLT2i to AM, in addition to standard HFrEF therapy, reduce her risk of HAHF and cardiovascular death?

Methods

An initial PubMed search performed on September 15th, 2020 with search terms “SGLT2 Inhibitors,” “heart failure with reduced ejection fraction,” and “hospitalization” yielded 88 articles. These limits reduced the number of articles to ten: publication within the last five years, clinical trials, meta-analyses, RCT, humans, and publication in English. These inclusion criteria resulted in three studies: RCT, use of an SGLT2i compared to placebo, and outcomes including decreased HAHF and/or cardiovascular related death. Exclusion criteria included patients younger than 19. A second PubMed search on October, 22nd, 2020 yielded the EMPEROR-REDUCED Trial, which had greater homogeneity than the DEFINE-HF and was therefore included in place of DEFINE-HF.

Results

Study #1 *Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. J.J.V. McMurray, et al.*[4]

Objective: To evaluate Dapagliflozin's safety and efficacy in HFrEF patients, regardless of the presence of diabetes mellitus.

Study Design: This was a double-blind, randomized, placebo-controlled trial of 4,744 patients with established New York Heart Association (NYHA) HFrEF. Table 1 summarizes the inclusion and exclusion criteria.

Table 1: DAPA-HF Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Age ≥ 18	Recent treatment with SGLT2i
EF ≤ 40%	Unacceptable side effects from SGLT2i
Symptoms of NYHA Class II-IV	Type 1 diabetes mellitus
*NT-proBNP ≥ 600pg/mL	Symptoms of hypotension or systolic blood pressure < 95 mmHg
	**eGFR < 30 ml/minute or rapidly declining renal function

*N-terminal pro--B-type natriuretic peptide, **eGFR is estimated glomerular filtration rate

In addition to SGLT2i or placebo, all patients received standard HFrEF therapy, including cardioverter-defibrillator or cardiac resynchronization therapy (or both), an angiotensin-converting enzyme-inhibitor (ACEi), an angiotensin receptor blocker (ARB) or sacubitril-valsartan plus a beta blocker. Researchers encouraged additional treatment with a mineralocorticoid receptor antagonist (MRA). All patients with DM2 were continued on their DM2 medications. Randomization was stratified by whether patients had DM2. Dapagliflozin was given in 10mg pills daily, and the control was placebo. The primary outcome was a composite of worsening HF or death from cardiovascular causes. Secondary outcomes included HAHF,

cardiovascular deaths, symptom improvement, composite worsening of renal failure or renal death, and death from any cause.

Patients were evaluated at 14 and 60 days after randomization, and then every four months; the mean follow-up was 18.2 months. Data analysis was conducted with intention to treat analysis (ITT), meaning all patients that were randomized were included in the analysis.

Study Results: The primary composite outcome of worsening HF or death from cardiovascular causes occurred in 16.3% of patients who received dapagliflozin and 21.2% of patients who received placebo (hazard ratio, 0.74; 95% CI: 0.65 to 0.85; $P < 0.001$). Additionally, 9.7% of dapagliflozin patients had HAHF and 13.4% placebo patients had HAHF (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Symptom relief was quantified using the Kansas City Cardiomyopathy Questionnaire, and patients who received dapagliflozin showed significant symptom improvement, compared to placebo (25.3% vs. 32.9%; odds ratio (OR), 0.84, 95% CI, 0.78 to 0.90; $P < 0.001$). The data demonstrated a 27% relative risk reduction (RRR) for HAHF with a number needed to treat (NNT) of 21, and a 23% RRR of composite decrease for HAHF and cardiovascular death. Researchers hypothesized that patients with Class II HFrEF may have experienced greater overall therapy response.

Study Critique: This study has several advantages. The number of subjects, 4,744, was large, and few were lost to follow up or required discontinuation of dapagliflozin. There were few exclusion criteria, and the study included 20 countries. Many researchers conducted DAPA-HF, producing extensive subgroup analysis, including glycosylated hemoglobin, creatinine, hematocrit, NT-proBNP, weight, and systolic BP. Additionally, several favorable and statistically significant results were shown, as discussed in the results section above.

This study had several limitations which reduced its application to HFrEF patients. Less than 50% of participants had eGFR ≤ 60, which is inconsistent with the low eGFR usually seen in HFrEF patients. Only approximately 5% of participants were African American, which is disproportionately fewer than the number of African Americans who have HFrEF. A high percentage of participants were male (76.6%), and the average body mass index (BMI) was

28kg/m², reducing generalization to females and patients with BMIs > 28kg/m². Approximately 67% of patients had NYHA Class II, and the DM2 patients were likely well-controlled and healthy, requiring only one or two DM2 medications. Lastly, this study was funded by AstraZeneca, the manufacturer of dapagliflozin.

Study #2: Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR-REDUCED Trial). Packer et al.[5]

Study objective: To evaluate the efficacy of empagliflozin to treat Class II-IV HFrEF. The primary outcome was a composite of cardiovascular death and HAHF.

Study design: This study was a double-blind, parallel-group, event-driven RCT performed in 520 centers across 20 countries. Inclusion criteria were NYHA Class II-IV HFrEF with EF 40% or less. Patients with EF > 30% were required to have had HAHF in the past year or have a NO-ProBNP that indicated increased risk for serious HF event. Table 2 shows further NT-ProBNP requirements for patients based on their EF.

Table 2: EMPEROR-REDUCED BNP Minimum Requirements by EF

Ejection Fraction	Minimum NT-ProBNP	Minimum NT-ProBNP in Patients with Atrial Fibrillation
< 30%	600 pg/ml	1,200 pg/ml
30% - 35%	1000 pg/ml	2,000 pg/ml
36% - 40%	2500 pg/ml	5,000 pg/ml

3,730 patients were randomly assigned to receive either daily empagliflozin (1,863 patients) or placebo. All patients were required to receive standard HF therapies (including diuretics, RAAS blockers and neprilysin inhibitors, beta-blockers, and MRAs), and ITT analysis was used.

Study results: The hazard ratios for the effect of empagliflozin on cardiovascular death and on the first HAHF were 0.92 and 0.69, respectively, for a composite HR of 0.75. During the trial

period, 19 patients would need to have received empagliflozin to prevent one primary event (95% CI, 13 to 37). Empagliflozin's effect on the primary outcome was consistent across prespecified subgroups, including patients with and without diabetes at baseline. Among the patients who were receiving sacubitril–valsartan at baseline, the hazard ratio for the comparison between empagliflozin and placebo for the primary outcome was 0.64, as compared with 0.77 among those who were not receiving sacubitril–valsartan. The total HAHF was lower among patients receiving empagliflozin, with a HR of 0.70. Overall, the data demonstrated a 28% RRR for HAHF with an NNT of 19, and a 20% RRR composite decrease for HAHF and cardiovascular death. Table 3 summarizes this trial's results.

	Table 3: EMPEROR-REDUCED Results		
	Empagliflozin Patients (N = 1863)	Placebo Patients (N = 1867)	Hazard Ratio or Absolute Risk Difference
Primary Outcome: Composite of HAHF and Cardiovascular death	361 (19.4)	462 (24.7)	0.75 (0.65 to 0.86)
HAHF	246 (13.2)	342 (18.3)	0.69 (0.59 to 0.81)
Cardiovascular death	187 (10.0)	202 (10.8)	0.92 (0.75 to 1.12)

Study critique: This was a large RCT that included several centers throughout multiple countries. Tracking NT-ProBNP enabled the researchers to analyze results according to HFrEF severity. All participants received standard HFrEF therapy which supports our clinical inquiry. EMPEROR-REDUCED replicated the findings from DAPA-HF. The fact that empagliflozin, in addition to dapagliflozin, reduced mortality indicates that the entire class of medications, SGLT2i, may reduce mortality. Limitations included a study population of predominantly white males and funding by Jardiance, the company that manufactures empagliflozin. Another concern is the research was limited to measures and evaluation of secondary prevention in

regards to HAHF. An analysis of the efficacy regarding empagliflozin in primary prevention of cardiovascular outcomes is an area that requires further investigation.

Study #3 *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. Bruce Neal, M.B., et al.*[6]

Objective: To determine how SGLT2i treat cardiovascular and renal pathologies and to researchSGLT2i safety.

Study Design: The CANVAS Program was a composite of two RCTs, the Canagliflozin Cardiovascular Assessment Study (CANVAS, 2009) and CANVAS-Renal (CANVAS-R, 2014). The aim of CANVAS, which began four years before canagliflozin received FDA approval, was to show that it was safe in terms of cardiovascular effects. CANVAS-R was designed to produce data that would be assessed together with that from CANVAS, to meet phase four cardiovascular safety requirements. As its name suggests, it was designed to study the drug's effects on renal outcomes, specifically albuminuria. In summary, the CANVAS Program, a composite of the two sister RCTs, was intended to study canagliflozin's effects on cardiovascular and renal systems, and its safety profile.

The primary outcome was a composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke. The secondary outcomes were death from any cause, death from cardiovascular causes, progression of albuminuria, and composite of death from cardiovascular causes and HAHF. Inclusion criteria included T2DM diagnosis (HbA1C 7-10.5%), age $\geq$ 30 with a history of symptomatic atherosclerotic cardiovascular disease (ASCVD), or $\geq$ 50 with two or more of the following: duration of diabetes for 10+ years, systolic blood pressure (SBP) > 140mmHg despite therapy with $\geq$ 1 antihypertensive drugs, current smoking, micro or macroalbuminuria, or HDL < 1. An eGFR < 30mL/min was the exclusion criterion.

CANVAS patients were randomly assigned to receive 300mg canagliflozin daily, or matching placebo. CANVAS-R patients were randomly assigned to receive 100mg canagliflozin

daily with the option to increase the dose to 300mg daily, or matching placebo. Patients were continued on standard pharmacotherapy to maintain glycemic control. This study was designed to show either cardiovascular non-inferiority or superiority. For canagliflozin compared to placebo, a HR < 1 indicated superiority, and < 1.3 indicated cardiovascular safety.

Study Results: A significant finding from The Canvas Program was that 5.5% of patients taking canagliflozin experienced HAHF, and 8.7% of patients taking placebo had HAHF (HR 0.67; (0.52-0.87). Additionally, canagliflozin showed benefit across all primary and secondary endpoints; 29.6% of patients taking canagliflozin and 31.5% of patients taking placebo experienced a primary outcome event (death from cardiovascular cause, nonfatal MI, nonfatal stroke). Overall, this trial demonstrated a 33% RRR of HAHF with an NNT of 31 and a 22% RRR for composite outcome of cardiovascular death and HAHF. Other notable improvements were across all secondary outcomes, and also with blood pressure, weight, and HbA1C levels.

Regarding safety outcomes, the data showed an increased risk of amputation of toes, feet, or legs among patients on canagliflozin, with a HR of 1.97. [71% of these patients had their most proximal amputation at the level of the toe or metatarsal.] Other negative outcomes higher among patients taking canagliflozin were genital infections, volume depletion, and diabetic ketoacidosis (DKA).

Study Critique: The Canvas Program was a powerful study with many advantages. It studied a large number of patients, 10,142, with an extensive duration of follow-up (mean of 188.2 weeks). Furthermore, this trial considered the effects of canagliflozin in T2DM patients only, and the mean duration of T2DM diagnosis was over 13 years, making this data applicable to the patients who may need SGLT2i the most: diabetics.

Significant weaknesses of this trial include lack of statistical significance. Due to the predetermined statistical hypothesis testing sequence, the primary and secondary outcomes, all of which canagliflozin improved, were not considered statistically significant. This is a drawback from enabling direct application to patients. Additionally, 51.6 patients per 1,000 patient years had a HgbA1C < 8%. This tight glycemic control is hard to achieve and rare among diabetics,

which may further restrict application of this data to real-world patients. Lastly, The Canvas Program was funded by the producer of Invokana, the trade brand of canagliflozin, implying possible conflict of interest. Of note, this RCT is heterogeneous to the two former RCTs, which considered SGLT2i in patients with and without T2DM, whereas this RCT considered the effects of canagliflozin in T2DM patients only.

Discussion

Heart failure contributes to 1 out of 8 deaths in the U.S. and is projected to increase in incidence each year.[7] While some aspects of standard therapies have proven beneficial in regards to all-cause mortality and survival outcomes, there is room for improvement regarding management of HFrEF patients. Recent research is focused on decreasing HAHF and minimizing cardiovascular deaths. The aggregate data from recent RCTs suggest that adding SGLT2i to standard HF therapy reduces mortality HAHF.[8]

While the outcomes of the three RCTs evaluated in this paper show a benefit with the use of SGLT2i in patients with HFrEF independent of diabetes status, the limitations of each study cannot be disregarded. All three studies were funded by major pharmaceutical companies who have a vested monetary interest in demonstrating that their products treat more than just diabetes. These medications are newer to the market and unavailable as generics, suggesting that only the affiliated companies have funding to further their research.

One limitation of the CANVAS trial was they were not initially investigating safety regarding cardiovascular and diabetic kidney disease (DKD), not HAHF. CANVAS investigated empagliflozin therapy in diabetic patients only. Further limitations included the predominant white male study populations in the DAPA-HF and the EMPEROR-REDUCED trials. A large proportion of patients suffering from HFrEF are African American. African Americans are 20% more likely to die from complications of heart disease when compared to Whites.[9] The studies showed a similar disconnect between proportion of female participants and HF prevalence.

While women tend to develop HF at an older age than men, the incidence between the sexes is similar.[10]

Currently, dapagliflozin (Farxiga) is the only SGLT2i with FDA approval to treat adults with HFrEF (NYHA class II-IV).[4] The use of dapagliflozin is recommended as a secondary adjunct agent in patients with persistent symptoms and elevated NT-proBNPs, despite current optimized standard therapy.[11]

Empagliflozin (Jardiance) recently obtained FDA approval to accelerate research into whether it can improve HFrEF outcomes after MI. However, its use for this indication is currently off-label, and costs may not be covered by insurance. Like dapagliflozin, it is indicated as an adjunct in persistently symptomatic patients who are already optimized on other therapies and is effective in patients with or without type 2 diabetes (Packer 2020).

Canagliflozin (Invokana) currently only has FDA approval to treat DKD and to reduce the risk of HAHF in patients with T2DM.[12] While data suggest that the entire class of SGLT2i can improve HFrEF outcomes, further research is required for canagliflozin to receive approval in patients without T2DM.

Approach to the Patient

Our patient is A.M., a 65-year old female with a history of HTN, CAD, an recent MI, who now has an EF of 30%. Should we prescribe an SGLT2i in addition to the standard HFrEF regimen? Since she was recently diagnosed, her NYHA Class is unknown, and she is naive to standard HFrEF therapy, we do not endorse prescribing an SGLT2i at this time. While these medications have demonstrated consistent and reproducible outcomes regarding positive cardiovascular effects and decreased HAHF in HFrEF patients, regardless of whether or not they have T2DM, they lack data demonstrating long-term safety, efficacy, and cost-efficiency.

To manage A.M., laboratory studies should be drawn at baseline and followed to monitor her response to treatment. These include NT-ProBNP, BUN and creatinine, eGFR, and

electrolytes, among others. A.M. should follow up two weeks after starting therapy, and her medications should be titrated to efficacy with manageable side effects.[5]

If she receives a NYHA Class II - IV diagnosis and experiences persistent symptoms, despite standard HFrEF management, we would discuss adding dapagliflozin. Before prescribing, we would ensure her volume status was adequate, measure her blood pressure, ensure her CrCl is > 30 ml/minan, and get a baseline NT-ProBNP and CMP. We would inform A.M. that dapagliflozin can cause a moderate decrease in weight and blood pressure and has a low occurrence of hypoglycemia. While using dapagliflozin with lisinopril is safe and requires no monitoring, its combination with bumetanide may decrease its anti-diabetic effects and precipitate a hyperglycemic state (Lexicomp). We would also notify her of the increased risk of urinary tract infections, vulvovaginal infections, hypotension, dehydration, and fractures.

Conclusion

This paper aimed to answer the following question: among HFrEF patients, does the addition of an SGLT2i to standard therapy reduce the risk of HAHF and cardiovascular death? Three large RCTs have data that begin to answer this question. DAPA-HF unexpectedly showed that SGLT2i were associated with improved cardiovascular outcomes. This novel research prompted the EMPEROR-REDUCED and CANVAS trials to examine the data and launch placebo-controlled trials to gather more information. Thus far, the accumulating research is promising for the future of HFrEF therapy. Both DAPA-HF and EMPEROR-REDUCED trials examined the effects of SGLT2i in patients with and without T2DM and showed improvements, suggesting that this class of drugs has unknown MOAs that benefit HFrEF patients, and not through glycemic control.

However, further research is needed. At this time, the only SGLT2i that is currently approved for HFrEF is dapagliflozin, and only as add-on, second-line therapy. Therefore, the current data have mainly achieved the justification of further, more conclusive and specific research into this clinical question.Further research into this question should be focused on how much SGLT2i benefit non-T2DM patients, and how they do this. While it is true that many

HFrEF patients have comorbid T2DM, many do not, but could still benefit from using an SGLT2i, pending further conclusive research.

HAHF is a negative health outcome common among HFrEF patients, and a costly expense for American healthcare. Use of SGLT2i may alleviate this unfortunate toll on our economy and wellbeing. While SGLT2i are still new drugs and therefore expensive, their prices will become more manageable, as they are already becoming widely used to treat T2DM. Thus, further research into the possible benefits of SGLT2i on HFrEF may, in time, save US healthcare millions.

An additional, fascinating area of research is the mechanism of action (MOA) of SGLT2i on the cardiovascular system. Currently, SGLT2i MOA on T2DM glycemic control is well understood. However, the untapped potential of SGLT2i to reduce morbidity and mortality in HFrEF patients will more easily become adopted and efficacious when the MOA is shown through research. In conclusion, the use of SGLT2i may be an appropriate secondary adjunct to standard treatment for secondary prevention of HAHF and cardiovascular causes of death. Further research regarding long-term efficacy, safety, and cost-effectiveness is needed.

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