Long-Term Care Updates

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SGLT-2 Inhibitors in the Management of Heart Failure

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Introduction

Heart failure (HF) is common among elderly American adults, and cases are predicted to trend upward over the next years. At this time, a 40-year-old American has a 20% lifetime risk of developing HF with the risk for development increasing with age. Over 650,000 new cases of HF are diagnosed in America each year, with non-Hispanic black men having the highest risk and white women having the lowest risk.[1] Common causes of HF in American adults are myocardial infarction (MI) and long-standing hypertension, but can also include endocrine and metabolic causes (i.e., obesity or diabetes), toxins such as alcohol and some medications, tachycardia, and inflammation involving the heart. Common symptoms include dyspnea, fatigue, and edema (both pulmonary and peripheral).[1]

HF occurs when the heart is unable to supply enough oxygen-rich blood to the body due to structural or functional changes. HF can be divided into two categories: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Those with HFpEF have an ejection fraction ≥ 50%. Once <40% of the left ventricle ejection fraction remains, patients are diagnosed with reduce ejection fraction. Those with left ejection fraction of 40-49% are considered borderline preserved ejection fraction. HF is further classified into stages based on presence and severity of HF symptoms.[1] There are two main classification systems used: the New York Heart Association (NYHA) functional classification and the ACC/AHA Stages. The two are compared in Table 1 to the right.

Table 1. Heart failure classification

ACC/AHA Stage	NHA Functional Class
A: At risk, but no structural heart disease	None
B: Structural heart disease but without signs/symptoms of HF	I - No physical limitations or symptoms with normal daily activities
C: Structural heart disease with prior or current symptoms of HF	I - No physical limitations or symptoms with normal daily activities
	II - Slight limitation of physical activity in the form of moderate exertion; comfortable at rest
	III - Marked limitation of physical activity in the form of minimal exertion; comfortable at rest
	IV - Inability for any physical activity due to symptoms, or symptoms at rest
D: Refractory disease requiring specialized intervention	IV - Inability for any physical activity due to symptoms, or symptoms at rest

The HF classification systems not only provide insight into the severity of the patient's disease; medication therapy is selected based on their classification. Medications in HF are used for one of two reasons: to provide morbidity/mortality benefits or to relieve HF symptoms. Medications that decrease mortality in all HF patients include: ACE inhibitors (ACEI)/Angiotensin receptor blockers (ARBs), angiotensin recepor-neprilysin inhibitors (ARNIs), beta-blockers (BB), and aldosterone receptor antagonists. Hydralazine and nitrates decrease mortality in non-Hispanic black patients with class III or IV HF. Medications used for symptom management, but provide no mortality benefit, include: loop diuretics, digoxin, and ivabradine. Treatment guidelines for HFrEF stage C and D can be found as Figure 2 in the 2017 Focused Update.[2]

SGLT-2 Inhibitors

Sodium glucose co-transporter 2 (SGLT-2) inhibitors are known for their proven efficacy in type 2 diabetes mellitus (T2DM) management. These medications work by decreasing glucose reabsorption via inhibiting the transport of glucose back into the blood, increasing urinary excretion of glucose, and decreasing plasma glucose concentration. There are several medications within this class that are on the market: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. These medications are known to have renal and cardiovascular (CV) benefits in diabetic patients. The CV outcomes data in diabetics with HF led researchers to examine the effects of SGLT-2 inhibitors in non-diabetics with HF. Dapagliflozin was the first SGLT-2 inhibitor on the market to evaluate patients with and without T2DM and found a reduction in the risk of CV death and hospitalization for HF in patients with HFrEF class II-IV.[3] These results led to an FDA-approval of this medication for this indication in May 2020 on top of approval for use in T2DM with HF to reduce the risk of hospitalizations for HF which was received in October 2019.[4,5] Additional studies have been or are being conducted to determine if this is a class effect.

Dapagliflozin

"Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction" (DAPA-HF) was one of the first trials to study the effect of an SGLT-2 inhibitor on HF in patients with and without diabetes. This phase 3, placebo-controlled trial used stratified randomization based on T2DM diagnosis at baseline to assign 4744 patients with NYHA class II, III, or IV HFrEF to received 10mg of dapagliflozin daily or placebo in addition to the recommended therapy. The primary outcome was a composite of worsening HF or CV death. The baseline characteristics similar between groups with 66 as the mean age, 76% male, 70% white, 42% diabetics, median LVEF was 32%, and about 67.6% of patients were NYHA class II. Monitoring occurred 14 days, 60 days, and 4 months after randomization, then every 4 months thereafter. At these times, patients were assessed for HF and volume status, adverse events, renal function, potassium levels, and need for treatment discontinuation (i.e., if the patient became pregnant or experienced diabetic ketoacidosis).

The primary outcome, the composite of worsening HF or CV death, occurred in 16.3% of dapagliflozin patients and in 21.2% of placebo patients (HR = 0.74; 95% CI 0.65-0.85) after 24 months of treatment showing a statistically significant decline in HF progression in patients using dapagliflozin. The primary outcome could be broken into three components, all of which also yielded statistically significant results. The number needed to treat to prevent one primary event during the trial period was 21 (95% CI 15-38). Secondary outcomes, including symptom assessment, also showed that dapagliflozin had a favorable effect. HF hospitalizations and CV death were lower in the dapagliflozin group and the total symptom assessment showed more dapagliflozin patient's had significant symptom improvements. Serious adverse events were rare in both treatment groups. While it was thought that the SGLT-2 inhibitor may have worse renal events than placebo, those treated with dapagliflozin had fewer reported

cases of volume depletion and serious renal adverse events than those treated with placebo (1.2% v. 1.7%, P=0.23; 1.6% v. 2.7%, P=0.009). The outcomes of this trial demonstrated that dapagliflozin had cardiovascular protection in patients regardless of diabetes status. The results were consistent across all subgroups except for one which suggested less benefit in NYHA class III or IV compared to class II. The trial has been critiqued for lacking generalizability due to having a younger, "healthier" sample population with few black patients (<5%) and very elderly patients with multiple coexisting illnesses. However, the study results are groundbreaking as they showed the benefits of dapagliflozin in non-diabetics with HF who were also more at risk for hospitalizations for HF or CV death than in previous studies.[3]

Empagliflozin

In the EMPA-REG OUTCOME trial, a randomized controlled trial to evaluate cardiovascular outcomes, empagliflozin showed a 35% decreased risk of HF hospitalizations *(HR 0.65, 95% CI 0.50 – 0.85, p=0.002)*. However, this was a secondary outcome, and thus minimal clinical impact can be drawn.[6]

Empagliflozin's latest cardiovascular outcomes study, the EMPRISE (Empagliflozin Comparative Effectiveness and Safety) study, was a propensity-score matched retrospective review aimed to evaluate empagliflozin's efficacy, safety, and overall utilization in routine care via claims data from August 2014 through September 2016. The risk of hospitalization of HF was investigated, comparing empagliflozin to sitagliptin, a dipeptidyl peptidase-4 inhibitor. Data from 2 commercial and 1 Medicare source provided 16,443 propensity-score matched patient pairs with type 2 diabetes initiating empagliflozin or sitagliptin. Pairs were matched on over 140 characteristics, with particular care paid to indicators of diabetes severity and complications. Incidence of HF hospitalization was identified via discharge diagnoses. Patients had an average age of 59 years, 54% were male, 25% of patients had existing cardiovascular disease and 5% had existing HF diagnoses. There was a slight but non-significant difference in A1c at baseline between the empagliflozin and sitagliptin groups (8.60% vs 8.46%, p = 0.08). Compared to sitagliptin, initiation of empagliflozin decreased the risk of primary HF hospitalizations by 50% (HR = 0.50; 95% CI 0.28 - 0.91) and the risk of hospitalizations including HF concerns by 49% (HR = 0.49; 95% CI 0.39-0.68) over a follow-up period of 5.3 months. These results were consistent when subgroup analysis of baseline cardiovascular disease, history of HF, sex and empagliflozin daily doses were evaluated.[7]

The EMPEROR HF Trials are expected to produce positive HF results. Boehringer Ingelheim (BI) and Eli Lilly received Fast Track designation to empagliflozin for the reduction of the risk of cardioavascular death and hospitalization for HF in people with chronic HF for these trials.[8] In December of 2019, Lilly and BI announced the results of the EMPERIAL-Reduced and EMPERIAL-Preserved trials. These trials enrolled 312 and 315 patients, respectively, regardless of type 2 diabetes status. These trials demonstrated a non-significant difference in the primary endpoint, which was the change from baseline to week 12 in exercise ability as measured by distance walked in six minutes. While disappointing, these results align with the results of the DEFINE-HF trial of Farxiga.[9]

Canagliflozin

While the manufacturers of dapagliflozin and empagliflozin have aimed to focus on HF outcomes of late, the research group behind canagliflozin has decided to pursue kidney outcomes data over HF outcomes. Therefore, data on canagliflozin's HF hospitalization reductions are pulled from a subanalysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS). The CANVAS and CANVAS-R trials were randomized, double-blind, multicenter studies designed to evaluate cardiovascular and renal benefits and risks from using canagliflozin. Patient inclusion criteria of interest for HF outcomes included A1c between 7% and 10.5%, age 18 and older, and either be over the age of 30 with history of symptomatic atherosclerotic cardiovascular disease or be over the age of 50 with 2 risk factors for cardiovascular

disease. Patients were excluded if they had NYHA Class IV HF at time of inclusion. After a 2-week, single-blind, placebo run-in period, patients were randomized 1:1:1 to placebo, canagliflozin 100mg or canagliflozin 300mg. Mean follow-up was 188.2 weeks for their cohort of 10,142 patients. Compared to placebo, canagliflozin showed a significant reduction in hospitalization rates in patients with a history of HF (HR 0.72, 95% CI 0.33 - 0.78), but not in patients with no history of HF at baseline. Canagliflozin also showed a statistically significant reduction in all-cause mortality in patients with a history of HF (HR 0.790, 95% CI 0.51-0.96) but not in patients without a history of HF. There was no evidence that this effect varied by dose.[10]

Ertugliflozin

Ertugliflozin, the fourth SGLT-2 inhibitor available in the United States, received FDA approval in December 2017.[11] Given its recency to market, its complete cardiovascular outcomes trial has not been published. The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS-CV) completed data collection on December 27, 2019 and has yet to release data on the outcomes observed. Of note, the VERTIS-CV trial enrolled the highest number of patients with HF at 23% of total patients. However, on April 28, 2020, Merck's CEO announced preliminary results. Ertugliflozin met its primary MACE endpoints of non-inferiority. However, unlike the other SGLT-2 inhibitors, ertugliflozin failed to demonstrate superiority on any of the key secondary outcomes. Importantly, unlike the other CV outcome trials, VERTIS CV evaluated patients with existing cardiovascular disease. Of interest to this article, a reduction in HF hospitalizations was noted, but was not powered for statistical testing.[12]

Table 2. Heart failure trials summary.[3,6,9,10,12,13]

Trial	SGLT-2 Inhibitor	Main Findings
CANVAS; CANVAS R	Canagliflozin	Canagliflozin showed significant reductions in hospitalization rates and all-cause mortality in patients with a history of HF, but not in patients with no history of HF; NNT= 315.
DAPA-HF	Dapagliflozin	Dapagliflozin 10mg daily provided benefit to patients with HFrEF class II-IV with and without T2DM. NNT = 21
EMPA-REG OUTCOME	Empagliflozin	Empagliflozin showed a 35% decrease in HF hospitalizations in patients with diabetes and HF. NNT = 72
EMPRISE	Empagliflozin	Compared to sitagliptin, empagliflozin decreased risk of primary HF hospitalizations by 50%
VERTIS-CV	Ertugliflozin	Ertugliflozin was shown to be noninferior for secondary prevention of CV outcomes. Trial was not adequately powered to evaluate HF outcomes

Future studies

Table 2 details a few of the many upcoming clinical trials investigating the impact of SGLT-2 inhibitors in patients with HF, regardless of their diabetes diagnosis.

Table 2. Ongoing heart failure-related SGLT-2 inhibitor trials.[14-16]

Drug	Trial Name	Population	Primary Outcome	Completion Date
Canagliflozin	Canagliflozin: Impact on health status, quality of life, and functional status in HF	Clinically stable HF (n=1,900)	HF symptom score	February 2021
Dapagliflozin	Randomized, open-label study of dapagliflozin in patients with type 2 diabetes admitted with acute HF	Patients with diabetes and decompensated HF (n=250)	Body weight	August 2021
	Effects of dapagliflozin on biomarkers, symptoms and functional status in patients with preserved ejection fraction HF	NYHA class II-IV preserved HF (n=320)	NTproBNP	February 2021
	DAPA ACT HF-TIMI 68	Patients hospitalized due to HF (n=2,400)	Time to first occurrence of cardiovascular death or worsening HF	October 2022
Empagliflozin	EMPEROR HF – Preserved	HF with preserved ejection fraction (n=5,988)	Time to first event of cardiovascular death or hospitalization for HF	November 2020
	EMPEROR HF – Reduced	HF with reduced ejection fraction (n=3,730)	Time to first event of cardiovascular death or hospitalization for HF	July 2020
	EMPULSE	Current hospitalization for HF, regardless of ejection fraction (n=500)	Composite - time to death, number of HF events, time to first HF event, change in symptom score	July 2021
	EMPACT – MI	HF post-acute MI (n=3,300)	All-cause mortality and hospitalization for HF	Unknown
Ertugliflozin	ERADICATE-HF	Type 2 diabetes and NYHA class II – III HF (n=36)	Proximal sodium reabsorption	March 2021

Despite the existing studies evaluating HF outcomes as secondary outcomes, additional studies are needed evaluating HF hospitalizations as primary outcomes. The Empagliflozin Outcome Trial in patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-REDUCED) and the Empagliflozin Outcome Trial in patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-PRESERVED) will attempt to evaluate the effect of exercise abilities. As double-blinded phase III trials, there is a large amount of hope that these trials will show efficacy and safety in patients with chronic HF, particularly in preserved ejection fraction patients who lack medications that improve mortality.[13]

Future studies may focus on the exact mechanism of action that provides benefit for HF patients. The benefit is likely separate from SGLT-2 inhibitors' effects on blood sugar, as dapagliflozin showed reduction in HF hospitalizations in patients without diabetes. The list below lists the most compelling potential mechanisms of SGLT-2 inhibitors that correlate to improved cardiac function.[17]

1. Stimulation of natriuresis
2. Stimulation of osmotic diuresis
3. Cardiomyocyte Na+/H exchanger inhibition
4. Increased myocardial energetics (via altered myocardial substrate metabolism)
5. Reduction in left ventricular mass
6. Improved systolic and diastolic function
7. Improved cardiac filling conditions secondary to reductions in preload and afterload
8. Increased circulating proangiogenic progenitor cells
9. Increased erythropoietin
10. Improved endothelial function
11. Reduction in myocardial CaM kinase II activity
12. Improved myocardial autophagy
13. Inhibition of cardiac fibrosis
14. Increased cardiac output, HR, oxygen consumption, coronary blood flow mediated by increased levels of circulating glucagon

Despite these varied theories, no definitive mechanism has been established. SGLT-2 inhibitors also provide renal benefits independent of their blood glucose benefits. The renal-preserving benefits likely play a role in the reduction of hospitalizations and other cardiovascular benefits. In the EMPA-REG, CANVAS and DECLARE-TIMI 58 trials, a greater reduction in HF hospitalizations were seen in patients with worse baseline renal function.[17]

Conclusion

Although these agents are not included in recent cardiovascular guidelines, it would appear that most SGLT-2 inhibitors provide benefit for the reduction of HF hospitalizations. Dapagliflozin was shown to reduce the worsening of HF and cardiovascular death in patients with and without diabetes, and many experts believe this benefit will be seen in all SGLT-2 inhibitors. However, ertugliflozin's unimpressive initial cardiovascular trial data may indicate it will not carry the same CV benefits. Future research and guideline updates will continue to clarify the role of SGLT-2 inhibitors in the management of HF.

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