

The Role of Sodium-Glucose Co-Transporter-2 Inhibitors in Heart Failure

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Abstract

Introduction: Long standing chronic conditions such as Type 2 diabetes have been a known risk factor in the development of cardiovascular disease. The Food and Drug Administration's (FDA) guidance issued in 2008 for all new antidiabetic medications to undergo large cardiovascular studies came about due to safety concerns with certain classes of diabetic agents, which prompted drug manufacturers to conduct several well-known large clinical studies evaluating safety and efficacy of these drugs in relation to cardiovascular disease and adverse effects.

Discussion: The benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors are thought to be due to its mechanism of action in promoting natriuretic and diuretic effects resulting in lowering blood pressure and reducing blood plasma volume. Clinical studies starting with the Canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) along with its sister trial CANVAS R were evaluated in the CANVAS Program, Empagliflozin in the EMPA-REG Outcome, Dapagliflozin in both the DECLARE-TIMI 58 and most recently the DAPA-HF trial showed a benefit when these agents were added to standard therapy in terms of reducing hospitalization for heart failure.

Conclusion: The recent FDA approval of dapagliflozin as an adjunct agent in patients with heart failure with reduced ejection fraction marks the first time that an antidiabetic medication has been granted an indication other than for diabetes. This certainly offers clinicians who treat patients with heart failure an additional option in optimizing medication regimens and managing symptoms. Economic factors as well as adverse events should be assessed with this class of medication when used as additional therapy. Future clinical studies evaluating SGLT2-inhibitors and its benefit in cardiovascular outcomes may continue to provide more promising options to clinicians in managing cardiovascular disorders.

Keywords: Type 2 Diabetes; Food and Drug Administration's (FDA); Sodium-Glucose Cotransporter-2 (SGLT2)

Introduction

According to the 2020 National Diabetes Statistics Report, a total of 34.2 million people are currently living with diabetes, with close to 27 million adults diagnosed and just over 7 million patients as having undiagnosed diabetes. An even more alarming figure is the number of prediabetic patients in the U.S. which equals 88 million people [1].

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In 2008, due to safety concerns regarding the use of rosiglitazone, the U.S. Food and Drug Administration (FDA) issued a draft guidance requiring all new type 2 diabetic therapies to undergo large cardiovascular outcomes trials [2]. In May 2020, the U.S. FDA approved the use of the SGLT2 Inhibitor dapagliflozin (Farxiga™) for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure. This marked the first time that a medication developed to treat type 2 diabetes gained approval for the treatment of patients with New York Heart Association's functional class II-IV heart failure with reduced ejection fraction [3]. In this article, we will review the mechanism of action of this particular class of drug in terms of its cardiovascular benefits for heart failure patients as well as the clinical studies that led to the development of dapagliflozin's newest indication.

Heart failure background

In the latest figures from the Centers for Disease Control and Prevention, there are well over 6 million adults currently in the United States (U.S.) living with heart failure [4]. It has been known that several medical conditions such as long standing hypertension, diabetes, obesity and other cardiovascular disorders can lead to the development of heart failure. The annual cost for heart failure treatment is over \$30 billion dollars which includes direct costs such as medications and costs to the health-care system as well as indirect costs such as missed days from work [5].

Heart failure is a complex clinical disorder in which the ventricles have an impaired ability to either fill with oxygenated blood or eject blood to the rest of the body. Differentiation of systolic and diastolic heart failure have now been replaced with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, respectively.

Signs and symptoms of heart failure can indicate the presence of left sided heart failure affecting the lungs such as pulmonary congestion including crackles, coughing, edema and shortness of breath or right sided heart failure which manifests as peripheral edema and systemic congestion. The American College of Cardiology (ACC) and the American Heart Association's (AHA) staging system (A, B, C, D) identifies patients either at risk of developing heart failure or those with structural heart disease based on their left ventricular ejection fraction and the presence of symptoms. The New York Heart Association (NYHA) functional classification system (I, II, III or IV) evaluates the severity of heart failure by focusing on the physical limitations that a patient may have based on activity level [6].

The management of heart failure focuses on the key drugs that have been proven in clinical studies to reduce mortality and morbidity, which include ace-inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), beta-blockers (BB), aldosterone receptor antagonists (ARA) and most recently the angiotensin-receptor neprilysin inhibitor (ARNI) which was included in the 2017 ACC/AHA Heart Failure guidelines based on the results of the PARADIGM study [6]. Other medications used in the management of heart failure such as diuretics, digoxin and Ivabradine are indicated for symptom control and to help prevent hospitalizations but do not confer any mortality reduction in this patient population. Even with the introduction and development of life saving drugs, heart failure continues to be a major problem in the U.S. with hospitalizations due to patients not being optimized on guideline directed medical therapy.

Sodium-glucose co-transporter 2 inhibition

SGLT2 is located in the proximal tubules and is the primary site where filtered glucose is reabsorbed. Through inhibition of the SGLT2, glucose reabsorption is reduced along with a lowering of the renal threshold for glucose which results in an increase in the excretion of glucose and therefore a lowering of plasma glucose concentrations. The mechanism of action of SGLT-2 inhibition and its cardiovascular effects is thought to be due to an osmotic diuretic and mild natriuretic effects. Other benefits that were observed with empagliflozin in this study were blood pressure reduction and weight loss [7]. Through this mechanism of promoting fluid loss from the kidneys, SGLT2 inhibitors have been shown to reduce preload which is beneficial in patients with hypertension and heart failure.

In recent years, large scale studies evaluating Glucagon-like peptide-1 (GLP-1) receptor agonists [8-10] and SGLT2 inhibitors have continued to emphasize the benefits of these agents in terms of cardiovascular (CV) outcomes.

There are currently four SGLT2 inhibitors available in the U.S. which include empagliflozin, canagliflozin, dapagliflozin and ertugliflozin. All four have been combined with agents from different classes of antidiabetic medications and marketed for their synergistic effects in reducing plasma glucose concentrations in diabetes.

Clinical trials evaluating SGLT2 inhibitors

Empagliflozin was the first SGLT2-inhibitor found to reduce cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease. In the EMPA-REG Outcome [11] study, patients with T2DM along with underlying CV disease were evaluated over a period of three years. Empagliflozin was added to standard of care in these patients. The primary composite outcome was death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke. Secondary composite outcomes was the primary outcome plus hospitalization for unstable angina. Results from this study of over 7000 patients included a reduction in the primary composite CV outcome and death and hospitalization from heart failure. Empagliflozin did not reduce rates of MI or stroke in this study. In terms of secondary outcomes, there was no statistically significant difference between groups.

Canagliflozin was evaluated as early as 2009, first in the Canagliflozin Cardiovascular Assessment Study (CANVAS) even before it was approved by the FDA, followed by the Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R) in 2014 which was designed to meet post-approval cardiovascular safety requirements. The CANVAS program combined both these studies in terms of assessing CV safety and efficacy of canagliflozin along with renal and other safety outcomes [12]. The primary outcome was a composite of death from CV causes, nonfatal MI or nonfatal stroke. The rate of the primary outcome was found to be lower in the canagliflozin group (26.9%) when compared to placebo (31.5%), hazard ratio (HR) 0.86; 95% confidence interval (CI) 0.75 - 0.97, $p < 0.001$ for non-inferiority and $p = 0.002$ for superiority. Secondary outcomes included death from any cause, death from CV causes, progression of albuminuria, and the composite of death from CV causes and hospitalization from heart failure. Results indicated that canagliflozin conferred a possible benefit in terms of progression to albuminuria, HR 0.73, 95% CI, 0.47 - 0.77.

Dapagliflozin was evaluated in the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes study (DECLARE-TIMI 58) [13] which evaluated 17,160 patients over a period of 4.2 years. Subjects with type 2 diabetes who either had or were at risk for atherosclerotic disease were randomized to receive dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), which the authors defined as CV death, MI, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of CV death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite ($\geq 40\%$ decrease in estimated glomerular filtration rate to < 60 mL/min/1.73m², new end stage renal disease, or death from renal or CV causes and death from any cause. In terms of primary safety outcomes, dapagliflozin met prespecified criteria for non-inferiority compared to placebo in regards to MACE, but in terms of primary efficacy outcomes, dapagliflozin (8.8%) did not result in a lower rate of MACE compared to placebo (9.4%), HR 0.93, 95% CI 0.84 - 1.03, $p = 0.17$. Dapagliflozin was found to have a lower rate of CV death or hospitalization for heart failure (4.9% vs. 5.8%), HR 0.83, 95% CI 0.73 - 0.95, $p = 0.005$. The authors concluded that this reflected a lower rate of hospitalizations for heart failure (HR 0.73, 95% CI 0.61 - 0.88).

The evidence from previous trials supporting the benefits of using an SGLT2 inhibitor in reducing heart failure hospitalizations were confirmed in the DAPA-HF study [14] which was a multicenter, double blind parallel group that evaluated 4,744 patients with NYHA Class II, III or IV heart failure and an ejection fraction of 40% or less. Patients received either dapagliflozin or placebo in addition to standard heart failure therapy. Heart failure standard of care included the following: diuretic (93%), ACE-Inhibitor (56%), Angiotensin Receptor Blocker (28%), Beta-blocker (96%), Mineralocorticoid Receptor Antagonists (71%), Angiotensin Receptor Neprilysin Inhibitors (11%) and Digoxin (19%). To ensure that there were an equal number of diabetic patients in each arm, patients were stratified based on the diagnosis of diabetes at screening. Diabetes treatment included the following: metformin (51%), sulfonylurea (23%), DPP-4 inhibitor (16%), GLP-1 receptor agonist (1%) and insulin (27%). The primary outcome was a composite of worsening heart failure (hospitalization or an

urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. Patients in this study were followed over a period of 18.2 months. The primary outcome occurred in 386 patients (16.3%) in the dapagliflozin group and in 502 patients in the placebo group (HR, 0.74; 95% CI, 0.65 - 0.85, $p < 0.001$). First worsening HF event occurred in 237 patients (10%) in the dapagliflozin group and in 326 (13.7%) in the placebo group (HR 0.70, 95% CI 0.59 - 0.83). Death from CV causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (HR 0.82, 95% CI 0.69 - 0.98). Death from any cause occurred in 276 patients (11.6%) in the dapagliflozin group and 329 patients (13.9%) in the placebo group (HR 0.83, 95% CI 0.71 - 0.97). The results were found to be similar regardless of the diagnosis of diabetes. Also, the rate of adverse events related to volume depletion, renal dysfunction and hypoglycemia did not differ between treatment groups.

The results from the DAPA-HF trial led to dapagliflozin's new FDA approved indication as a secondary agent in patients with heart failure with reduced ejection fraction who are already on guideline directed medical therapy or devices such as biventricular pacemakers or implantable cardioverter defibrillator.

Adverse events

The package labeling for canagliflozin, dapagliflozin and empagliflozin state that in general for patients with type 2 diabetes, the use of these agents is contraindicated if the estimated glomerular filtration rate is less than 30 mL/min/1.73m². Currently no recommendations exist for renal dose adjustment of dapagliflozin when used in heart failure.

In general, SGLT2 inhibitors are well tolerated but safety issues have been observed in clinical trials evaluating the use of these agents. Euglycemic diabetic ketoacidosis was observed in case reports with canagliflozin use and is defined as an elevated anion gap metabolic acidosis and an abnormally high concentration of ketones in the blood while maintaining a normal blood glucose concentration [15]. Symptoms are nonspecific due to the lack of hyperglycemia and include nausea, vomiting and malaise [16].

In the CANVAS trial, canagliflozin was found to have an increased incidence of amputations when compared to placebo (6.3 vs. 3.4 per 1000 patient years, HR 1.97, 95% CI 1.41-2.75, $p < 0.001$). In 2020, the FDA removed the black box warning with the use of canagliflozin in its package insert. The CANVAS trial also showed an association of increased skeletal fractures with canagliflozin use (15.4 per 1000 patient years vs. 11.9 per 1000 patient years) [12]. The highest risk populations for amputations included those with a history of amputations, peripheral vascular disease and lower extremity foot ulcers [17].

The most common adverse effect of SGLT2 inhibitors are genitourinary infections. Due to its mechanism of action in promoting glycosuria and providing a medium where bacteria can grow, urinary tract infections are common. For patients who experience mycotic infections, either oral antifungal or topical antifungal therapy can be initiated. For most patients this side effect does not require that the medication be stopped and more serious infections such as pyelonephritis or urosepsis are rare in patients taking SGLT2 inhibitors [16].

Conclusion

The results from clinical trials have demonstrated CV benefits with the use of SGLT2 inhibitors as a class and may offer an additional option to clinicians who may evaluate risks and benefits when assessing optimal therapies for their patients living with heart failure. In particular, prevention of hospitalizations with the use of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction can be viewed as a sign of promise when looking at the economic burden to the patient and the healthcare system as a whole. Heart failure management begins with initiation of guideline directed medication therapy at starting doses used in clinical trials with the goal of achieving target doses that showed mortality reducing benefits (ACE-I's, ARBs, ARNI, BB and ARA's). For some heart failure patients, side effects of these agents including hypotension, bradycardia, hyperkalemia and increased renal dysfunction may limit upwards titration to target doses to achieve maximum benefit.

One issue that many clinicians may encounter with the use of SGLT2 inhibitors is the cost of this medication as generic options are not available and may not be covered by most patient's insurance plans. Close monitoring of adverse events, including hypotension, volume depletion and acute kidney dysfunction is warranted when adding an SGLT-2 such as dapagliflozin to patients already on standard of care heart failure regimens.

Bibliography

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services (2020).
2. Regier E., *et al.* "More than 7 years of Hindsight: Revisiting the FDA's 2008 Guidance on Cardiovascular Outcomes Trials for Type 2 Diabetes Medications". *Clinical Diabetes* 34.4 (2016): 173-180.
3. Food and Drug Administration (FDA). FDA approves new treatment for a type of heart failure (FDA News Release) (2020).
4. Virani SS., *et al.* "Heart disease and stroke statistics-2020 update: a report from the American Heart Association". *Circulation* 141.9 (2020): e139-e596.
5. Benjamin EJ., *et al.* "Heart disease and stroke statistics-2019 update: a report from the". *American Heart Association* 139.10 (2019): e56-e528.
6. Yancy CW., *et al.* "2017ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America". *Circulation* 136 (2017): e137-e161.
7. Majewski C and Bakris GL. "Blood pressure reduction: an added benefit of sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes". *Diabetes Care* 38 (2015): 429-430.
8. Gerstein HC., *et al.* "Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double blind, randomized placebo-controlled trial". *Lancet* 394.10193 (2019): 121-130.
9. Marso SP., *et al.* "Liraglutide and cardiovascular outcomes in type 2 diabetes". *The New England Journal of Medicine* 375 (2016): 311-322.
10. Marso SP., *et al.* "Semaglutide and cardiovascular outcomes in patients with type 2 diabetes". *The New England Journal of Medicine* 375 (2016): 1834-1844.
11. Zinman B., *et al.* "Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes". *The New England Journal of Medicine* 373 (2015): 2117-2128.
12. Neal B., *et al.* "Canagliflozin and cardiovascular and renal events in type 2 diabetes". *The New England Journal of Medicine* 377 (2017): 644-657.
13. Wiviott SD., *et al.* "Dapagliflozin and cardiovascular outcomes in type 2 diabetes". *The New England Journal of Medicine* 380 (2019): 347-357.
14. McMurray JJV., *et al.* "Dapagliflozin in patients with Heart Failure and Reduced Ejection Fraction". *The New England Journal of Medicine* 381 (2019): 1995-2008.
15. Peters AL., *et al.* "Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter-2 inhibition". *Diabetes Care* 38 (2015): 1687-1693.

16. Lupsa BC and Inzucchi SE. "Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits". *Diabetologia* 61 (2018): 2118-2125.
17. Food and Drug Administration (FDA). FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) (2020).

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