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A Comparison of SGLT2 Inhibitors to Current Guideline Directed Medical Therapy for the Treatment of Heart Failure in Non-diabetic Patients

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Abstract

Heart failure remains a complex disease that affects a continually increasing number of patients annually. For heart failure, most of the research has focused on the hemodynamic changes of the heart chambers and the medication interventions that slow the progression of heart failure. Recent studies have investigated treatment options that may disrupt the neuro-hormonal and pathophysiologic cell changes that lead to further progression of heart failure. Although the mechanisms by which the sodium-glucose cotransporter 2 (SGLT2) inhibitors are not entirely understood, they are believed to directly affect the cardiac electrolyte imbalances that trigger the cellular changes which contribute to the altered contractility, adrenergic receptor changes, and resulting hemodynamic changes seen with heart failure.

To evaluate SGLT2 inhibitors in the treatment of heart failure in diabetic and non-diabetic patients, placebo studies for SGLT2 inhibitors and current guideline-directed therapies including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), mineralocorticoid receptor agonists (MRA), and angiotensin receptor-neprilysin inhibitors (ARNIs) were compared for each class of medications using the hazard ratios and confidences intervals of the all-cause mortality rates. The results showed that treatment with SGLT2 inhibitors in patients with heart failure with reduced ejection fraction (HFrEF) may be comparable to other guideline-directed therapies. Because of the lack of data specific to patients with heart failure with preserved ejection fraction (HFpEF), further research is needed to assess these medications' efficacy in this population. When assessing the available pooled data for HFrEF and HFpEF patients, SGLT2 inhibitors appear to be a promising area of research compared to the recommended therapies for those with HFpEF.

A Comparison of SGLT2 Inhibitors to Current Guideline Directed Medical Therapy for the Treatment of Heart Failure in Non-diabetic Patients

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were first introduced to the market in 2013 as a medication to help treat diabetes mellitus type II by effectively reducing hemoglobin A1C with the benefit of not causing hypoglycemia when used alone. Since then, several studies have outlined the benefits of these medications as being cardiac and renal protective for patients with diabetes. This literature review assesses whether this medication class's benefits extend outside the diabetic population and help those suffering from heart failure regardless of their diabetic status.

Statement of the Problem

Heart failure affects roughly 6.5 million people in the United States. In 2017, it contributed to the cause of death for one in every eight people. Many therapies for decreasing mortality in those with heart failure with reduced ejection fraction (HFrEF) have been well studied. However, heart failure with preserved ejection fraction (HFpEF) has had no standard of treatment for reducing mortality. Historically, HFpEF treatment has consisted of medical therapies directed at patients' comorbidities such as hypertension, kidney disease, or dysrhythmias. ("Heart Failure | CDC.gov," 2019)

Research Question

In diabetics and non-diabetic patients with heart failure, how does the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors compare to treatment with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs),

mineralocorticoid receptor agonists (MRA), and angiotensin receptor-neprilysin inhibitors (ARNIs) for patient survival?

Methodology

A literature review was performed by searching health science databases, medical studies, and scholarly articles by performing a comprehensive search of PubMed, Clinical Key, Dynamed, Cochrane Review, EBSCO, and ScienceDirect. With several keywords and mesh terms used, publications were reviewed that pertained to the pathophysiology and current treatment standards of heart failure, the SGLT2 inhibitor's mechanisms of action, and SGLT2 inhibitors' use non-diabetic heart failure patients. The research was refined to identify the search results focusing on comparative placebo studies for the treatment of heart failure involving beta-blockers, ACE inhibitors, ARBs, MRAs, and ARNIs. There was extensive information on the topic of these medications and their applications for treating HFrEF. Studies with reliable evidential findings for these same medication classes for managing HFpEF were less available than those of HFrEF. When searching for cardiac benefits of SGLT2 inhibitors, many studies were available that explored the cardioprotective effects for those diagnosed with diabetes mellitus. The search results were then refined to include the studies focusing on the non-diabetic population or the studies that included diabetic and non-diabetic patients. With this use of SGLT2 inhibitors being a new area of study, there was a lack of head to head comparison trials of SGLT2 inhibitors to beta-blockers, ACE inhibitors, ARBs, MRAs, and ARNIs. Studies that directly compare each medication class to placebos were used to best determine efficacy.

Literature Review

Pathophysiology of HFpEF and HFrEF

The clinical diagnosis of heart failure has been predominantly based on the signs and symptoms of only HFrEF (Nanayakkara, Patel, Kaye, 2018). ACC/AHA (American College of Cardiology/American Heart Association) describes heart failure as a syndrome with typical signs and symptoms resulting from abnormal heart structure or function involving ventricular filling or pumping of blood out of the heart. The symptoms must not be related to other comorbid conditions, including severe lung disease, renal failure, obesity, or anemia. The ACC/AHA guidelines for the diagnosis of HFpEF requires the presence of signs and symptoms of heart failure, ejection fraction (EF) ≥ 50%, and nonspecific structural remodeling. The ACC/AHA does not require patients to have LV dilation, elevated BNP, or diastolic dysfunction. With HFpEF, there are limited benefits of utilizing an echocardiogram for the diagnosis, and BNP levels are often within normal limits for these patients (Yancy et al., 2013).

According to Kusumoto (2019), heart failure has three distinct categories of pathophysiologic processes, including hemodynamic, neuro-hormonal, and cellular changes. The hemodynamic changes associated with heart failure include both systolic and diastolic dysfunction. Systolic dysfunction changes include increasing preload, increasing cardiac output associated with increased heart rate and end-systolic pressure-volume relationship, and hypertrophy of the ventricles leading to decreased diastolic pressure to volume ratio (Viau, Sala-Mercado, Spranger, O'Leary, & Levy, 2015). In cases of diastolic dysfunction, the end-systolic pressures and volumes remain unchanged due to the contractility of the myocytes remaining intact. In these cases, the diastolic pressure-volume ratio is impacted by the increased left ventricular end-diastolic pressure (LV EDP), resulting in an overall decrease in cardiac output

and symptom development. Diastolic dysfunction can result from numerous disease processes that result in a decrease of ventricular relaxation, a decrease in elastic recoil, or an increase in stiffness. In most cases of heart failure, there are components of systolic and diastolic dysfunction (Viau, 2015).

Kusumoto (2019) explains that following an injury to the cardiac tissue, there is a release of endogenous neuro-hormones and cytokines to prompt additional activation of the adrenergic and renin-angiotensin systems, which is also seen in the earliest stages of heart failure. Brown et al. (2015) and Kusumoto (2019) describe that initially, this elevation of norepinephrine levels within the blood will help compensate for the decrease in cardiac output by increasing heart rate and cardiac contractility. Kusumoto (2019) goes on to explain that with extended activation, this action will increase preload and afterload from the venous and arterial vasoconstriction, respectively, ultimately worsening heart failure. The reduction in cardiac output will also cause angiotensin II and sympathetic nervous system stimulation, triggering glomerular efferent arteriole constriction within the kidneys in an effort to maintain the glomerular filtration rate (GFR) despite the reduced blood flow. Aldosterone synthesis will also be prompted by the angiotensin II production to increase the blood pressure to better perfuse the kidneys. The aldosterone will result in renal sodium resorption, subsequently increasing water resorption and excretion of potassium in the urine (Kusumoto, 2019).

According to Kusumoto (2019), interleukins (IL) and tumor necrosis factor (TNF) are the main groups of cytokines that are often elevated and have been identified to play roles in the development and the worsening of heart failure. TNF has been found to influence the cycle of hypertrophy and apoptosis of myocytes. IL-1 has been linked to an acceleration in the rate of myocyte hypertrophy. The peptide endothelin also has a suspected role in heart failure, not only

with its known action of being a potent vasoconstrictor but also for inducing myocyte growth and collagen deposition within the interstitial matrix (Kusumoto, 2019).

Multiple cellular level changes have been identified in the heart following the development of heart failure. Reddy and Bernstein (2015) describe that these changes include dysfunction of the processes involving the shifting of calcium in and out of the cells, alterations in the expression of adrenergic receptors, and myocyte structure. The body's ability to deliver the necessary calcium supply required by the sarcomeres, the contractile units of the myocyte, is decreased in those with heart failure. Kusumoto (2019) explains that the reuptake of calcium into the sarcoplasmic reticulum is slowed, resulting in delayed relaxation of the myocyte. Adrenergic receptors become altered, with an upregulation in alpha1 receptors, contributing to the development of hypertrophy and desensitization followed by downregulation of beta1 receptors as a result of the chronic stimulation by the sympathetic nervous system. As outlined above, heart failure has known processes that contribute to cell apoptosis. As cardiac cells die off, the cells are replaced by poorly functioning tissue, thereby increasing the stress on the heart and contributing to the cycle of increasing hypertrophy, apoptosis, and collagen deposition. The deposition occurs following the activation of fibroblasts triggered by cell death, leading to stiffness of the cardiac muscle and diastolic dysfunction (Kusumoto, 2019).

Heart failure is an all-encompassing term to describe the very complex pathophysiologic changes that lead to various disease manifestations. When looking at the physiology responsible for the disease's development, it is clear why this disease process requires highly individualized management. Understanding the relationships between the hemodynamic, neuro-hormonal, and cellular changes of the heart can provide insight into identifying the most effective treatment for each patient.

Pharmacokinetics of SGLT2 Inhibitors on Heart Failure

How the SGLT2 inhibitors work on the body is only partially understood. Identifying the much-debated mechanism of action of SGLT2 inhibitors will help researchers and clinicians understand the benefits of these medications in their entirety (Maejima, 2020). Several proposed actions of SGLTs have been discussed to explain why we see benefits from the blockade of these cotransporters in those with heart failure and diabetes. Most theories pertain to benefits that have effects outside of the heart itself. According to Maejima (2020), one proposed action suggests that SGLT2 blockade will suppress the sympathetic nervous system's activity, thereby decreasing blood pressure without impacting heart rate. Some theorize that blocking SGLTs ramp up erythropoietin resulting in increased oxygen delivery to the myocardium. Conversely, other mechanisms of actions suggest that the SGLTs blockade has effects on the heart itself. These theories center around the idea that SGLT2 inhibition impacts the mitochondria in cardiac myocytes, metabolism of ketone bodies over free fatty acids glucose molecules, and more effective regulation of intracellular and intramitochondrial ions (Maejima, 2020).

Some researchers suggest that the benefit results from the blockade of SGLT2 cotransporters within the kidney's nephrons, which results in diuresis. As suggested by Bedi et al. (2016) and Bay, Kohlhaas, Maack (2013), the benefits of SGLT inhibition stem from a decrease in plasma volume, which allows for improved remodeling of the ventricle. Bay (2013) suggests that the decrease in plasma glucose and the use of ketone bodies over glucose in cardiac myocytes as an energy source are both secondary results stemming from the known action of SGLT2 inhibitors causing glycosuria. This action decreases glucose levels, and when fasting, results in decreased insulin and increased glucagon levels. These changes encourage lipolysis, generating ketone bodies. As outlined by Bedi et al. (2016), ketone bodies are a more effective

energy source than free fatty acids and glucose because of their ability to be more easily converted to Acetyl-CoA. This makes ketone bodies a more efficient energy source for oxidative phosphorylation, especially in those susceptible to impaired oxygen supply to the cardiac myocytes, such as with heart failure. In addition to these benefits, ketone bodies are thought to have anti-inflammatory effects that may further benefit those with heart failure.

As outlined by Kohlhaas and Maack (2010), the SGLTs inhibition benefits are the results of glycosuria and natriuresis, allowing for a better balance of both sodium and glucose molecules. Adequately regulated sodium is thought to impact the excitation-contraction coupling and reduce the generation of and responses driven by reactive oxygen species (ROS). The importance of SGLTs on the heart breaks down into sodium's interactions with calcium. High intracellular calcium and sodium is a known problem in those with heart failure. The intracellular sodium increases due to the increased late sodium current from the cardiac sodium channel along with the increased extracellular sodium exchange for intracellular hydrogen ions occurring at the sodium-myoinositol cotransporter 1 (SMIT1) and the sodium-hydrogen exchanger (NHE) sites. Maejima (2020) explains that the sodium/potassium pump of the cell cannot keep up with the influx due to the requirement of potassium and adenosine triphosphate (ATP) to remove the sodium from the cell. In diabetic patients, SGLT1s are upregulated, also exchanging intracellular glucose for sodium. The imbalance of increased intracellular sodium activates the sodium-calcium exchanger (NCX) and the mitochondrial sodium-calcium exchanger (NCLX) to remove the excess intracellular sodium by exchanging it for calcium. The activation of the NCX and NCLX exchanges the extracellular and intramitochondrial calcium for sodium, resulting in excess intracellular calcium and low mitochondrial calcium. The low intramitochondrial calcium results in a blunted mitochondrial response of ATP production to any increase in the energy

demand of the myocytes. SGLT2 inhibition results in SMIT1 and NHE blockade, preventing the cascade of events that lead to intracellular calcium and sodium overload (Kohlhaas & Maack, 2010).

Although there are no SGLT2s expressed on cardiomyocytes surface, the NHE-1s are believed to have an SGLT2 docking site making them structurally and functionally intertwined (Packer, Anker, Butler, Filippatos, & Zannad, 2017). This would mean that SGLT2 inhibitors work by inhibiting the NHE through the site, thereby decreasing the diminishing of the activation of the extracellular sodium exchange into the cell. Increased NHE-1 expression is a known phenomenon in diabetes and heart failure, leading to increased intracellular calcium, which eventually leads to an overload of calcium in the cell, causing cell dysfunction and, ultimately, cell death (Packer et al., 2017).

Although several of the theories align with the objective findings of heart failure, whether SGLT2 inhibitors' cardioprotective effects are secondary to indirect changes within the body or if they directly affect the heart has yet to be proven. The actual change by which these dynamics are done cannot definitively be determined; therefore, we rely only on the measured results found after administering the medications. As these medications are further researched for their use in non-diabetic patients with heart failure, the proposed mechanisms by which they benefit the heart will either be solidified or weakened, prompting further research into the matter.

Comparison of SGLT2 Inhibitors to Placebo

Several ongoing clinical trials are studying the effects of SGLT2 inhibitors in the treatment of heart failure (see Table 1). Most of these trials have been modeled after the EMPA-REG OUTCOMES trial that concluded in 2015. This placebo trial's initial intent was to test Empagliflozin's safety due to the concerns of this medication contributing to an increased risk of

cardiovascular-related deaths. Incidentally, in this trial, patients were found to have a significant decrease in heart failure hospitalizations, cardiac-related deaths, and all-cause mortality (Zinman et al., 2015). Given that the trial's intention was not to study the effects of this medication on heart failure, the researchers failed to specify whether the patients had a reduced or preserved ejection fraction. The study showed a statistically significant hazard ratio of 0.68 for all-cause mortality and 0.62 for cardiovascular-related deaths with confidence intervals of 0.57-0.82 and 0.49-0.77, respectively.

The meta-analysis by Zannad et al. (2020) analyzed the data from the two large-scale trials with available results. The meta-analysis evaluated the impact of SGLT2 inhibitors on cardiovascular and all-cause mortality when used as treatment for heart failure in those with a reduced ejection fraction with or without diabetes. The trials included were the DAPA-HF and EMPEROR -Reduced, which assessed the medications Dapagliflozin and Empagliflozin, respectively. When combined, these trials included 8,474 patients resulting in a 13% reduction in all-cause mortality. Secondary endpoints also identified a 30% reduction in the risk of being hospitalized for heart failure and a 38% reduction in severe renal complications, including the need for dialysis, kidney transplant, or a ≥50% decrease in kidney function. These resulted remained consistent regardless of age, gender, kidney function, or diabetes status.

DEFINE-HF was a study designed with primary outcomes being improved patient-reported heart failure symptoms and lowered NT-proBNP (Jensen et al., 2020). The study included only 263 patients and followed them over 12 weeks. Though the trial showed positive results between the correlation of symptom improvement due to the treatment for HFrEF in both diabetic and non-diabetic patients, it failed to reveal that there is a significant measurable improvement of NT-proBNP levels compared to placebo. One of the secondary outcomes

included all-cause mortality, which was one person per group. The small sample size made this trial statistically insignificant, leading to the results from the DEFINE-HF trials being excluded from this analysis.

Table 1

Clinical Trials on SGLT2 Inhibitors as Treatment for Heart Failure

Study Name and Year	Medication	Diabetic Status	HF Status	
2015				
EMPA-REG	Empagliflozin	Diabetes only	Both	*
2018				
EMPA-HEART	Empagliflozin	Diabetes only	HFrEF	***
2019				
DAPA-HF	Dapagliflozin	Both	HFrEF	*
Define-HF	Dapagliflozin	Both	HFrEF	***
Preserved-HF	Dapagliflozin	Both	HFpEF	**
Emperial-Reduced	Empagliflozin	Both	HFrEF	**
Emperial-Preserved	Empagliflozin	Both	HFpEF	**
Embrace-HF	Empagliflozin	Both	Both	**
NCT02920918	Canagliflozin	Both	HFrEF	**
2020				
Emperor-Reduced	Empagliflozin	Both	HFrEF	*
Emperor-Preserved	Empagliflozin	Both	HFpEF	**
2021				
Deliver	Dapagliflozin	Both	HFpEF	**
Soloist-WHF	Sotagliflozin	Diabetes only	Both	**

Note. Status of patients' LVEF being reduced or preserved is unknown for EMPA-REG OUTCOMES trial

* Data included ** Not yet completed/Results not released *** Study was not included due to insufficient data

Comparison of Current Guideline Directed Medical Therapy to Placebo

HFrEF Therapies

A meta-analysis by Burnett et al. (2017) focused on the guideline-recommended therapies for patients with HFrEF receiving outpatient treatment with one or more medication classes, including ACEI, ARB, MRA, ARNI, or beta-blockers. This analysis included 57 randomized control trials. Patients in these studies had individually defined definitions of HFrEF based on the New York Heart Association (NYHA) classification system and ejection fraction ranges. The majority of patients studied were NYHA classes II and III at baseline, with some studies including either NYHA class I or class IV, but not both within the same study. All available baseline ejection fraction averages for each study fell within the range of 15-40%. Four of the included studies either did not use or did not disclose their patients' NYHA classes, and 3 of the studies did not include their data for their average baseline ejection fractions; none of these 7 failed to provide both. All participants were either on one or more medications outlined in the recommended treatment guidelines from the ACCF/AHA 2013 report for the recommended management of heart failure or taking a placebo. Most of the studies that were included were multi-center, double-blind, placebo-controlled studies. The number of participants varied between studies from 28 to 8,399 people with durations for follow-up ranging from eight weeks to as long as four years.

In comparisons against single medication class studies versus placebos for all-cause mortality rates, beta-blockers showed the most significant reduction in risk, followed closely by ACEI and ARNI, respectively. When each class of medication was compared to other classes, beta-blockers were found to be a better choice for monotherapy over ACEI and ARB. For those taking a combination of two medication classes, the combinations of ACEI and beta-blockers

were most favorable when compared to placebo for all-cause mortality. This combination was very closely followed by the combination of ACEI taken with an MRA and the combination of an ARB with a beta-blocker. Interestingly, when ACEI/beta-blocker dual therapy was compared ARB/beta-blocker therapies head to head, the beta-blocker therapy paired with an ARB was slightly more beneficial than the ACEI. Therapy in which the use of beta-blockers and an MRA was used in combination with either an ARNI or an ACEI was the most effective treatment form when considering all-cause mortality (Burnett et al., 2017).

The data analysis results by Burnett et al. (2017) support the current suggested guidelines for the treatment of HFrEF. This includes initial therapy recommendation for HFrEF being dual therapy with an ACEI and beta-blocker, or an ARB if the patient is intolerant to an ACEI. It also supports that second-line treatment should include adding an MRA to the regimen, followed by replacing the ACEI or ARB with an ARNI as symptoms progress. The meta-analysis also provides head-to-head treatment comparisons that have not yet been tested in head to head trials. Because of these findings, it can be suggested that the benefits of combination therapy, which includes beta-blockers and MRA, the addition of an ARNI would be more efficacious than the use of an ACEI (Burnett et al., 2017).

HFpEF Therapies

In the meta-analysis performed by Martin, Manoharan, Thomas, Davies, and Lumbers (2018), 39 randomized control trials, including a total of 18,311 patients comparing the current guideline-directed therapies in the treatment of heart failure with a preserved ejection fraction (HFpEF). Of these 39 studies, the classes of medications evaluated included beta-blockers, mineralocorticoid receptor agonists (MRA), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and angiotensin receptor neprilysin inhibitors (ARNI). All

the studies included a comparison of the active agents against placebos or a group with no intervention in randomized controlled trials.

The results of the meta-analysis showed minimal statistical evidence of benefits in those with HFpEF. Some low-quality evidence was identified, supporting that the use of beta-blockers in these patients may improve cardiac mortality, but further investigation into these findings needs to be done. This class has shown to have high rates of treatment discontinuation due to patient intolerance of the medication. Adequate evidence for or against the use of beta-blockers in heart failure patients with a preserved ejection fraction has not yet been identified (Martin et al., 2018).

It was found that patients treated with an MRA had a reduced risk of hospitalization related to their heart failure. Although hospitalizations were reduced, there was no significant impact identified for reducing cardiovascular or all-cause mortality rates. The data on ACE inhibitors showed no improvement in hospitalization rates or mortality rates, including cardiovascular-related and all-cause. ARBs were shown to have little evidence to suggest the impact of the quality of life, heart failure hospitalizations, or mortality rates. Some data may suggest that this class does not significantly impact the time until the first hospitalization, but it may decrease the number of recurrent heart failure-related hospitalizations. Data involving the treatment of HFpEF with an ARNI was found to have inadequate and incomplete data and therefore had to be excluded (Martin et al., 2018).

The current guideline-directed heart failure therapies fail to identify any medication intervention that adequately proves improved outcomes and symptom relief for patients with HFpEF. Although several medication classes would benefit from either more extensive studies

with greater sample sizes or extended follow up time, all fail to show motivating results with their current investigational studies.

Discussion

To most accurately perform direct comparisons of the SGLT2 inhibitors' efficacy to the current guideline-directed treatments for heart failure, the hazard ratios and confidence intervals were collected from various studies and clinical trials. The hazard ratios collected were based on the specified treatment versus placebo for all-cause mortalities. The confidence interval used was 95%. Unsurprisingly, in every medication class, the hazard ratio favored the treatments regardless of the class. Few of the high confidence intervals exceeded 1.0, indicating that, in some cases, the treatment would not be more beneficial than the placebo.

Table 2

Monotherapy Treatment Options of HFrEF All-Cause Mortality

	Hazard Ratios	Confidence Intervals (95%)	
		Low	High
ACEI	0.83	0.66	1.01
ACEI*	0.84	0.65	1.01
ARB	0.88	0.61	1.26
ARB*	0.88	0.65	1.17
BB	0.57	0.33	0.94
ARNI*	0.71	0.39	1.17
Empagliflozin – Pooled	0.92	0.77	1.10
Empagliflozin – Diabetics**	0.68	0.57	0.82
Dapagliflozin – Pooled	0.83	0.71	0.97
Dapagliflozin – Diabetics	0.78	0.63	0.97
Dapagliflozin – Non-diabetics	0.88	0.70	1.12

Note. Pooled data contains combined data from patients with and without diabetes

*data resulted from a sensitivity analysis that ignored concomitant therapies

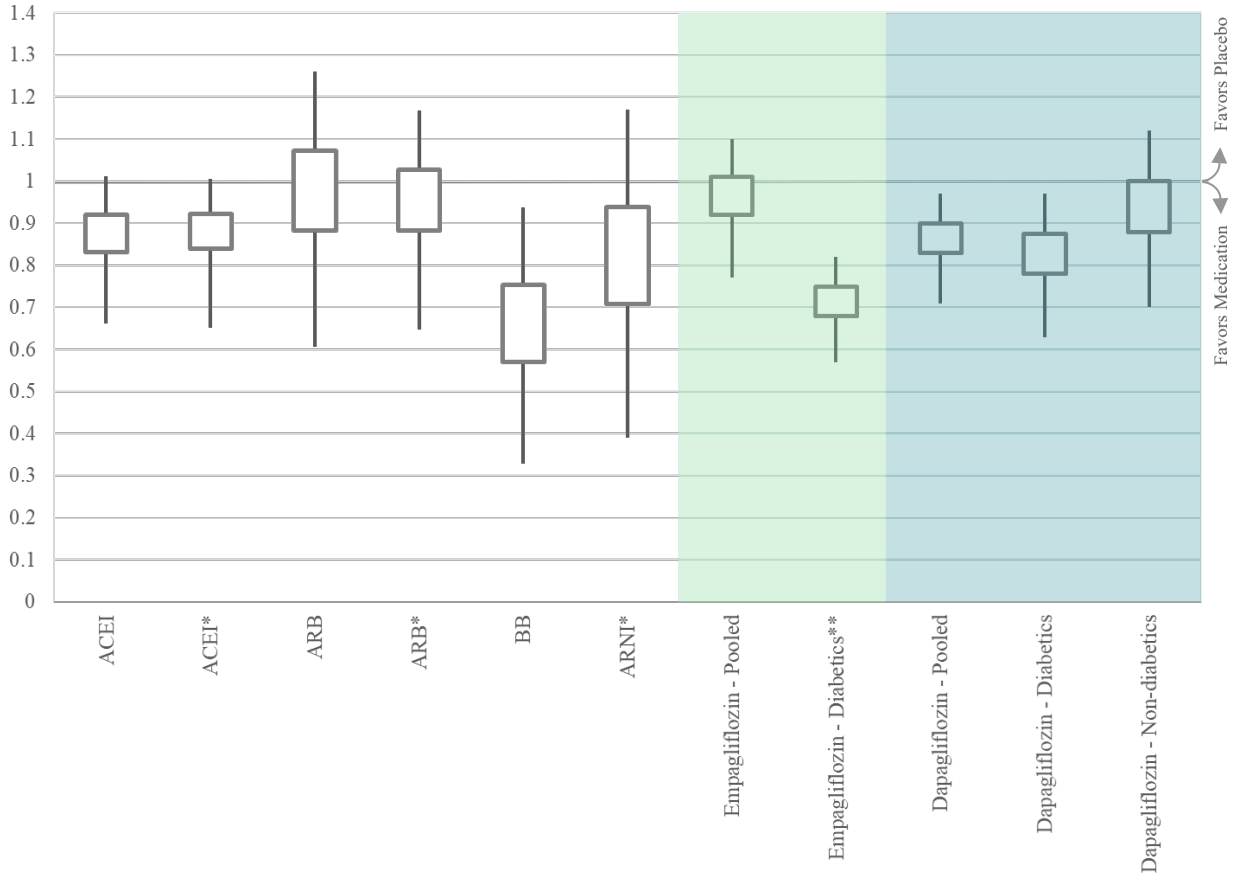
**combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REG OUTCOME trial

SGLT2 Inhibitors in Treatment of HFrEF Compared to Guideline-Directed Therapies

The results of this analysis have shown that the addition of SGLT2 inhibitors in diabetic and non-diabetic patients with a reduced ejection fraction have comparable outcomes to other monotherapies, including ACEI and ARBs (see Figure 1). Beta-blocker monotherapy continues to demonstrate more of a benefit in all-cause mortality to this group of patients. All other combination therapies show improved mortality rates compared to SGLT2 inhibitor therapy, except for ACEI and ARB combination therapy (see Figure 2).

Figure 1

Monotherapy Treatment Options of HFrEF All-Cause Mortality Ratios



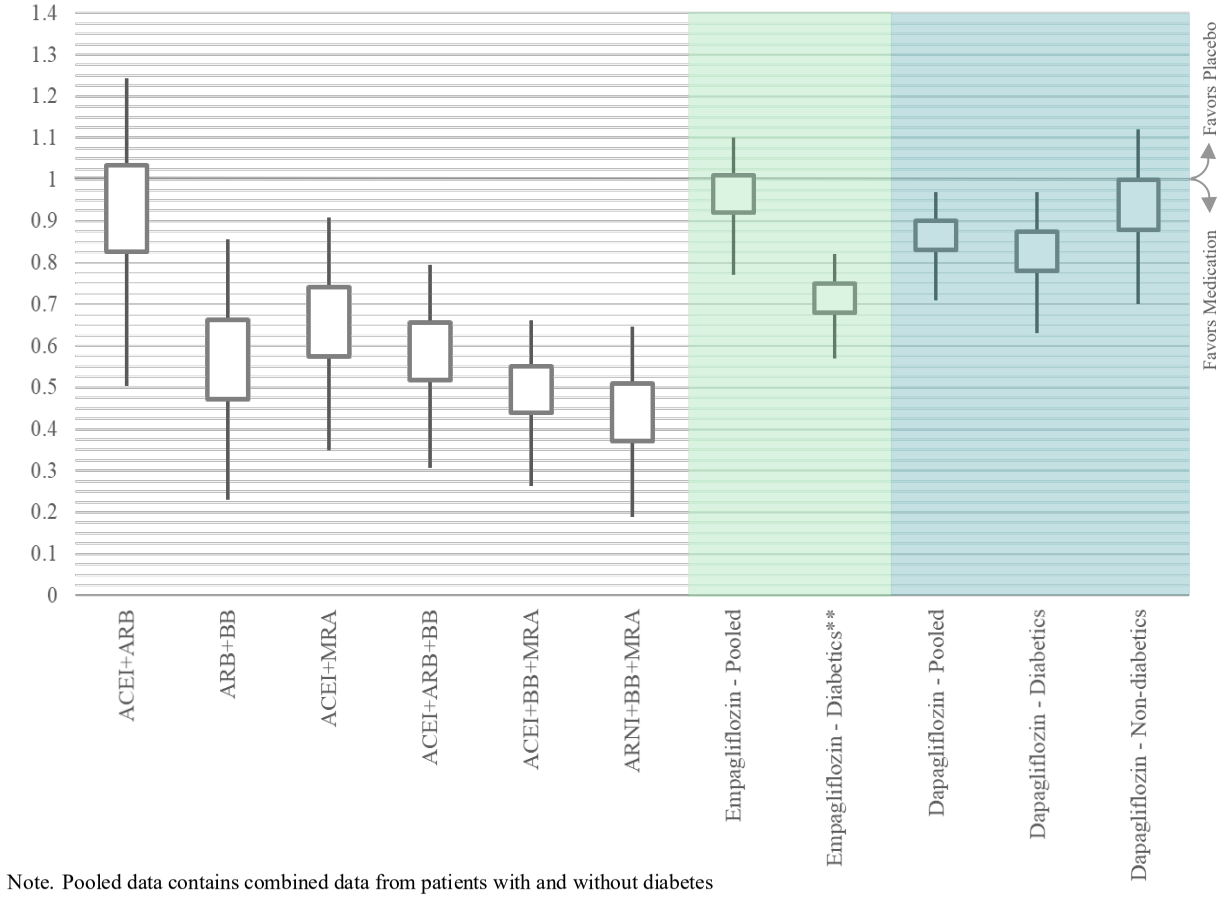
Note. Pooled data contains combined data from patients with and without diabetes

*data resulted from a sensitivity analysis that ignored concomitant therapies

**combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REG OUTCOME trial

Figure 2

Combination Therapy Treatment Options of HFrEF All-Cause Mortality Ratios



Note. Pooled data contains combined data from patients with and without diabetes

**combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REG OUTCOME trial

Of the studies looking at the all-cause mortality of the SGLT2 inhibitors, the hazard ratios and confidence intervals were comparable to those of the current guideline-directed therapies (see Table 2). The DAPA-HF and EMPEROR-Reduced were two large clinical trials looking at SGLT2 inhibitors' effects on heart failure with reduced ejection fraction in patients with and without diabetes. The DAPA-HF trial suggested an improvement in all-cause mortality for both diabetics and non-diabetics. In this study, statistics showed that those with diabetes had a hazard ratio of 0.78 with a confidence interval of 0.63-0.97. Those without diabetes had a hazard ratio of

Table 3

Combination Therapy Treatment Options of HFrEF All-Cause Mortality

	Hazard Ratios	Confidence Intervals (95%)	
		Low	High
ACEI+ARB	0.83	0.51	1.24
ARB+BB	0.47	0.23	0.86
ACEI+MRA	0.57	0.35	0.91
ACEI+ARB+BB	0.52	0.31	0.80
ACEI+BB+MRA	0.44	0.26	0.66
ARNI+BB+MRA	0.37	0.19	0.65
Empagliflozin – Pooled	0.92	0.77	1.10
Empagliflozin – Diabetics*	0.68	0.57	0.82
Dapagliflozin – Pooled	0.83	0.71	0.97
Dapagliflozin – Diabetics	0.78	0.63	0.97
Dapagliflozin – Non-diabetics	0.88	0.70	1.12

Note. Pooled data contains combined data from patients with and without diabetes

*combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REG OUTCOME trial

0.88 with a confidence interval of 0.70-1.12. The EMPEROR-Reduced trial failed to release the breakdown of the statistics for a comparison of diabetic to non-diabetic patients. The pooled information for the all-cause mortality hazard ratio for patients with reduced ejection fractions with or without diabetes was 0.92, with a confidence interval of 0.77-1.10.

SGLT2 Inhibitors in Treatment of HFpEF Compared to Guideline-Directed Therapies

With the available data, Empagliflozin appears to be a promising treatment for those with HFpEF when compared to current guideline-directed monotherapies (see Figure 3). The hazard ratio of Empagliflozin was 0.68, with a confidence interval of 0.57-0.87. The closest comparable class for treatment efficacy would be beta-blockers with a hazard ratio of 0.82 with a confidence interval of 0.67-1.0 (see Table 4). The MRA, ACEI, and ARB classes all show significantly higher hazard ratios (0.91, 0.99, and 1.01, respectively), with their high confidence intervals all exceeding 1.0.

Table 4

Monotherapy Treatment Options of HFpEF All-Cause Mortality

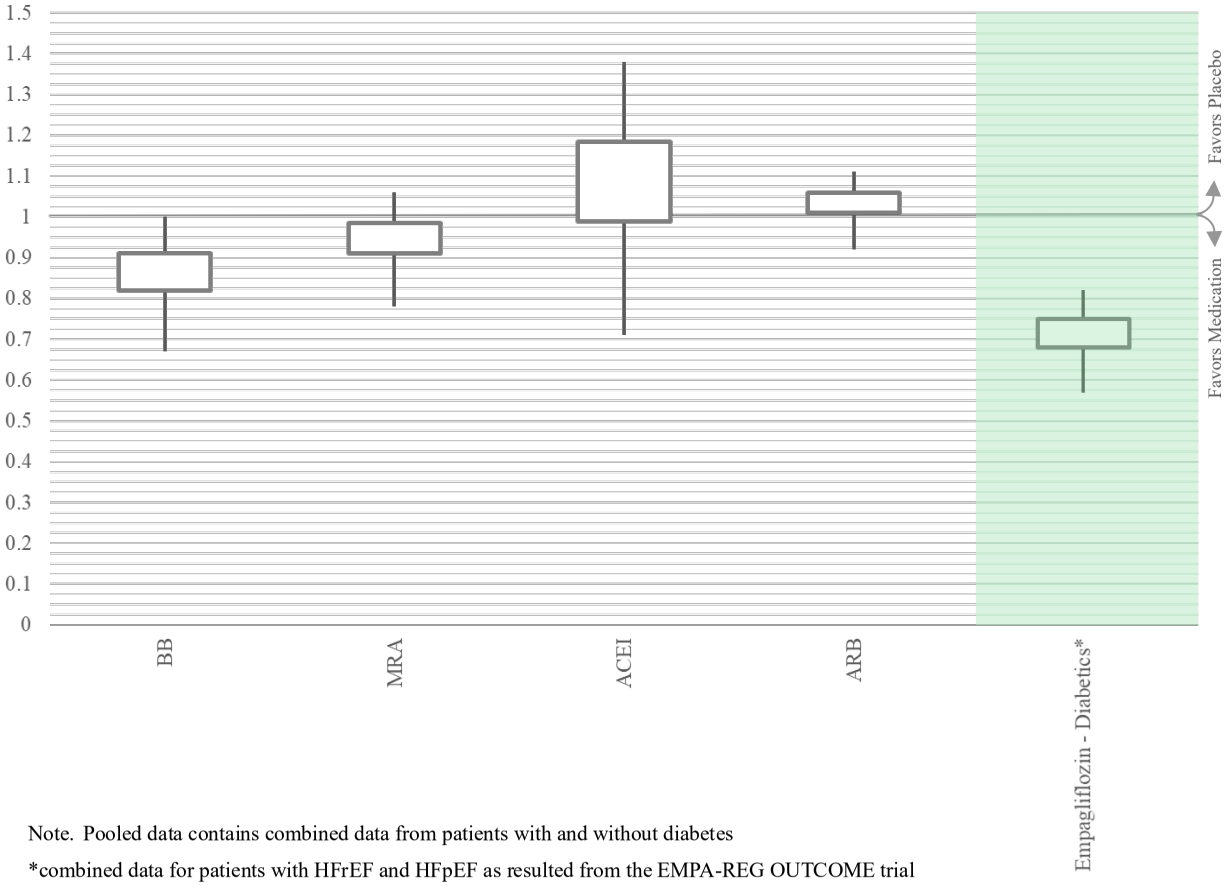
	Hazard Ratios	Confidence Intervals (95%)	
		Low	High
BB	0.82	0.67	1
MRA	0.91	0.78	1.06
ACEI	0.99	0.71	1.38
ARB	1.01	0.92	1.11
Empagliflozin – Diabetics*	0.68	0.57	0.82

Note. Pooled data contains combined data from patients with and without diabetes

*combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REG OUTCOME trial

Figure 3

Monotherapy Options of HFpEF All-Cause Mortality Ratios



Note. Pooled data contains combined data from patients with and without diabetes

*combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REG OUTCOME trial

Research Limitations

Although the data above suggests that SGLT2 inhibitors have potential benefits to those with HFrEF with and without diabetes, patients with diabetes have demonstrated an increase in benefits when compared to those without diabetes. Although the data collected showed similar hazard ratios for SGLT2 inhibitors compared to ACEI and ARBs, the studies failed to show statistical support forSGLT2 inhibitor monotherapy when evaluating the all-cause mortality. Many of these patients were on guideline-directed therapies prior to study enrollment for the treatment of their heart failure.

As expected, the data pertaining to the treatment of heart failure with a preserved ejection fraction were far scarcer and with data that was more difficult to compare directly. There were no placebo comparison trials for angiotensin receptor-neprilysin inhibitors (ARNI) in the treatment of HFpEF so that data could not be adequately assessed. For the other classes of medications, the data was obtained from placebo comparison studies contained the risk ratio. In all other aspects of this review, hazard ratios with the associated confidence intervals. The data should not be impacted by this difference as the information used for studies on the guideline-directed therapies had study follow-up ranging from 6 months to 4.4 years compared with EMPEROR-Reduced, DAPA-HF, and EMPA-REG OUTCOMES trials being 16 months, 18 months, and 4.6 years, respectively. It should also be noted that the data used for comparison for HFpEF treatment in the SGLT2 inhibitors group is a pooled patient population that includes data collected from both reduced and preserved ejection fraction patients. The data contains only that of the EMPA-REG OUTCOMES trials; therefore, it also contains only patients with type II diabetes due to it being a retrospective study done on the unintended finding of the benefit of

Empagliflozin on heart failure patients. There are ongoing trials to study the effects of SGLT2 inhibitors, specifically on HFpEF.

Conclusion

Based on these data and recent studies, SGLT2 inhibitors should be a strong consideration for initial heart failure therapy in diabetic patients. In non-diabetics, this class could also be considered given that the data has shown to have similar all-cause mortality benefits compared to other monotherapies. Further data on its benefits towards the treatment of HFpEF need to be studied before determining this class's efficacy on the disease. Clinical studies on this subject will be resulting as early as next year.

These theories would suggest that the inhibition of SGLT2s would reduce the inflammatory state that leads to the development and worsening of heart failure. Theoretically, if this were the case, the decrease in inflammation would show considerable benefits in those with HFpEF.

Applicability to Clinical Practice

After reviewing the information, SGLT2 inhibitors may be considered for treatment in non-diabetic patients with HFpEF or HFrEF. In the future, they may be acknowledged as a standard of care for those with HFpEF due to their benefits and the current lack of standardization set for the treatment of this disease. Due to their well-established clinical application for diabetes mellitus type II, these medications may be a new treatment option that is more affordable for patients.

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