2021

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

Rebecca R. Beyer
University of North Dakota

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

Rebecca Beyer, PA-S
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

UND School of Medicine & Health Sciences
University of North Dakota

Abstract

Heart failure remains a complex disease that affects an increasing number of patients annually. For heart failure, most of the research has focused on the hemodynamic changes of the heart chambers and the medications that slow the disease progression. 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 inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor agonists, and angiotensin receptor-neprilysin inhibitors 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 HFpEF recommended therapies.

Introduction

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?

Literature Review

Pathophysiology of HFpEF and HFrEF

- Yancy et al. (2013) published the ACC/AHA (American College of Cardiology/American Heart Association) guidelines which describe 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.
- Kusumoto (2019), heart failure has three distinct categories of pathophysiologic processes, including hemodynamic, neuro-hormonal, and cellular changes.

Pharmacokinetics of SGLT2 Inhibitors on Heart Failure

- Maejima (2020) SGLT2 blockade will suppress the sympathetic nervous system's activity, thereby decreasing blood pressure without impacting heart rate
- Bedi et al. (2016) and Bay, Kohlhaas, Maack (2013), the benefits of SGLT inhibition stem from a decrease in plasma volume, allowing for improved remodeling of the ventricle.
- Bedi et al. (2016) Suggests that SGLT2 inhibitors encourages lipolysis when fasting, generating ketone bodies, which are a more effective energy source than free fatty acids and glucose because of their ability to be more easily converted to Acetyl-CoA, especially in those susceptible to impaired oxygen supply to the cardiac myocytes, such as with heart failure.
- Kohlhaas and Maack (2010) 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.

Comparison of SGLT2 Inhibitors to Placebo

- Zinman et al. (2015) outlined the EMPA-REG OUTCOMES trial which was initially a placebo trial to test the safety and efficacy of Empagliflozin in relation to concerns of it causing an increase in 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
- Zannad et al. (2020) analyzed the trials DAPA-HF and EMPEROR-Reduced, which assessed the medications Dapagliflozin and Empagliflozin on all-cause mortality when used as treatment for heart failure in those with a reduced ejection fraction with or without diabetes
  - 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 (the need for dialysis, kidney transplant, or a ≥50% decrease in kidney function).
  - Results remained consistent regardless of age, gender, kidney function, or diabetes status.

Comparison of Guideline Directed Medical Therapy to Placebo

HFrEF Therapies

- Burnett et al. (2017) focused on the guideline-recommended therapies for patients with HFrEF
  - Supports the recommendation of initial therapy being dual therapy with an ACEI (or if intolerant, an ARB) and beta-blockers
  - Supports that second-line treatment should include adding an MRA to, followed by replacing the ACEI/ARB with an ARNI as symptoms progress.

HFpEF Therapies

- Martin, Manoharan, Thomas, Davies, & Lumbers (2018) showed minimal statistical evidence of mortality benefits using the current treatment options 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 adequate evidence for or against the use of beta-blockers in heart failure patients with a preserved ejection fraction has not yet been identified.

Discussion

HFrEF Therapies

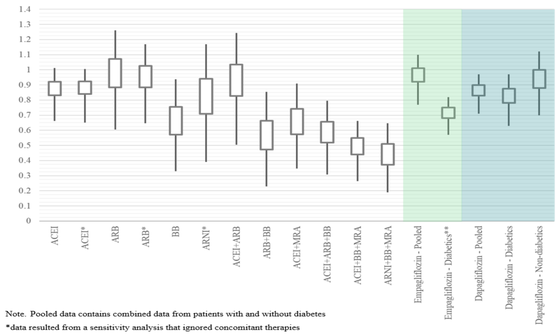
- The results of this analysis have shown that the addition of SGLT2 inhibitors in diabetic and non-diabetic patients with a reduced ejection fraction have comparable outcomes to other monotherapies, including ACEI and ARBs (see Figure 1)
- Beta-blocker monotherapy continues to demonstrate more of a 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 1).
- 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 1).

HFpEF Therapies

- Empagliflozin in the treatment for those with HFpEF when compared to current guideline-directed monotherapies including MRA, ACEI, and ARB classes, favors the SGLT2 inhbtors.All current recommended medication classes showing higher hazard ratios compared to SGLT2 inhibitors (see Figure 2 and Table 2).

Figure 1

Monotherapy and Combination Therapy 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

Table 1
Monotherapy/Combination Therapy Treatment Options of HFrEF All-Cause Mortality Ratios

	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
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

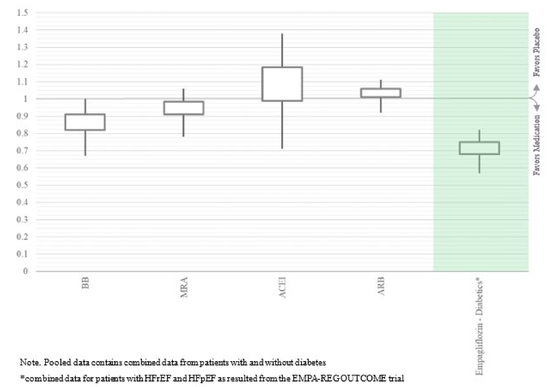
Table 2
Monotherapy Therapy Treatment Options of HFpEF All-Cause Mortality Ratios

	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
*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

Monotherapy Options of HFpEF All-Cause Mortality Ratios



Nots. Pooled data contains combined data from patients with and without diabetes
*combined data for patients with HFrEF and HFpEF as resulted from the EMPA-REGOUTCOME trial

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.

References

Heart Failure | cdc.gov. (2019). In Centers for Disease Control and Prevention. https://www.cdc.gov/heartdisease/heart_failure.htm

Kohlhaas, M., & Maack, C. (2010). Adverse bioenergetic consequences of Na+-Ca2+ exchanger-mediated Ca2+ influx in cardiac myocytes. Circulation, 122(22), 2273–2280. https://doi.org/10.1161/CIRCULATIONAHA.110.968057

Maejima, Y. (2020). SGLT2 inhibitors play a salutary role in heart failure via modulation of the mitochondrial function. Frontiers in Cardiovascular Medicine, 6, 186). https://doi.org/10.3389/fcvm.2019.00186

Martin, N., Manoharan, K., Thomas, J., Davies, C., & Lumbers, R. (2018). Beta-blockers and inhibitors of the renin-angiotensin-aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database of Systematic Reviews, 2018(6). https://doi.org/10.1002/14651858.CD012721.pub2

Packer, M., Anker, S., Butler, J., Filippatos, G., & Zannad, F. (2017). Effects of sodium-glucose co-transporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiology, 2(9), 1025–1029. https://doi.org/10.1001/jamacardio.2017.2275

Zannad, F., Ferreira, J., Pocock, S., Anker, S., Butler, J., Filippatos, G., … Packer, M. (2020). SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: A meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet, 396(10254), 819–829. https://doi.org/https://doi.org/10.1016/S0140-6736(20)31824-9

Zinman, B., Wanner, C., Lachin, J., Fitchett, D., Bluhmki, E., Hantel, S., … Inzucchi, S. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine, 373(22), 2117–2128. https://doi.org/10.1056/NEJMoa1504720

Acknowledgements

I would like to express my very great appreciation to my husband, Wyatt, and my mother, Julie, for their support throughout the scholarly project process.

Advice given by Professor Russ Kauffman MPAS, PA-C has been a great help in choosing a topic of research and for guidance throughout this project.

I wish to acknowledge the help provided by Kristen Hogan, Christina Rasanen, Samantha Simley, Traci Leitheiser, Angela Kurth, and Matthew Hoth for their input, guidance, and recommendations throughout the research process.