

Role of Sodium-Glucose Cotransporter-2 Inhibitors in Readmissions for Congestive Heart Failure

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ABSTRACT

Background: Patients with type II diabetes are at major risk for cardiovascular disease. Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) have demonstrated benefit for these patients. The purpose of this study is to determine whether SGLT-2 inhibitors significantly reduce heart failure readmission rates and improve outcomes in patients with congestive heart failure (CHF). **Methods:** Patient data was pulled on CHF patients with an active prescription for an SGLT-2 inhibitor, and it was analyzed using Fischer's Exact tests and two-tailed *t*-tests. The primary outcome was a 6-month hospital readmission rate due to CHF while taking SGLT-2 inhibitors. Secondary outcomes included 6-month all-cause hospital readmissions, renal function as measured by an estimated glomerular filtration rate change between admissions, mortality rates, and ejection fraction. **Results:** Of the 138 patients that met inclusion criteria for the first admission, the 6-month all-cause readmission rate for CHF patients still taking SGLT-2 inhibitors at readmission was 21 percent vs 16 percent ($p=0.6$) for the control group not

taking SGLT-2 inhibitors. The 6-month CHF readmission rate in patients taking SGLT-2 inhibitors was 7.2 percent, and a CHF specific readmission rate was not collected for the control group. In patients with an eGFR less than 90, the average eGFR for the SGLT-2 group declined slightly but was not significant between patients at first admission and those with readmission ($p=0.21$). **Conclusion:** The use of SGLT-2 inhibitors in patients with CHF did not change the overall hospital readmission rate; however, larger randomized controlled trials are needed for further evaluation of the potential benefit.

Key words: Cardiovascular Outcomes, Chronic Heart Failure, Heart Failure Hospitalization, SGLT2 Inhibition, Type II Diabetes.

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INTRODUCTION

Cardiovascular disease is the number one leading cause of death for Americans.¹ Congestive Heart Failure (CHF) is a prominent heart disease marked by progressive structural changes in the heart, resulting in inefficient filling and emptying of its chambers. An abnormality in systolic function and/or diastolic function might be the cause of CHF. Heart failure with reduced ejection fraction (HFrEF) results from a reduced systolic function whereas heart failure with preserved ejection fraction (HFpEF) is indicative of a preserved (normal) left ventricular function.² Many factors including age, gender, renal function, diabetes, and medications can affect the prognosis of patients with CHF.³

Type II diabetes is a major contributing factor to the development of heart disease as it is present as a comorbid condition in 25% to 40% of patients with CHF.^{2,4} This noninsulin-dependent diabetes is caused by β -cell dysfunction coupled with insulin resistance and defective insulin secretion related to genetics and lifestyle factors.⁵ Commonly diagnosed comorbid conditions for patients with type II diabetes are hypertension and dyslipidemia. Therefore, diabetes does not only increase the risk of CHF, but it also plays a significant role as predictor of morbidity and mortality in patients with a previously established diagnosis of CHF.^{4,6} Data demonstrates that the link between diabetes and CHF may be more pronounced than previously believed.⁷ The prevalence of heart failure and type II diabetes is expected to continue rising in the United States

(US). Currently, 29 million adults in the US have type II diabetes and 6.5 million suffer from heart failure.⁸ The pathophysiology of diabetes in HFpEF is demonstrated by an increased microvascular endothelial inflammation accompanied with hyperinsulinemia resulting in cardiomyocyte stiffness and hypertrophy. Therefore, left ventricular diastolic dysfunction worsens as a result of larger and stiffer cardiomyocytes. On the other hand, cardiomyocyte death is more commonly seen in diabetic patients with HFrEF.⁴ Since the pathophysiology of CHF and type II diabetes seem to be strongly linked, drugs that improve diabetes may also have efficacy for the treatment of CHF.

One option for treating type II diabetes is using a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, which treats this adult-onset diabetes by inhibiting the reabsorption of glucose by the kidneys, thus preventing high blood sugar levels. There is some evidence that these SGLT-2 medications may offer cardiovascular benefits. The 2021 American Diabetes Association (ADA) guidelines state that SGLT-2 inhibitors significantly reduce cardiovascular events, recommending their addition in patients with type II diabetes and atherosclerotic cardiovascular disease (ASCVD) with uncontrolled blood sugar while using metformin or lifestyle modifications.⁹

SGLT-2 inhibitors are currently recognized by the ADA to reduce cardiovascular events but are not included in heart failure guidelines as

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first-line agents. However, in the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway, SGLT-2 inhibitors are now recommended as first-line therapy for all patients.¹⁰

At the time of this study, canagliflozin and empagliflozin were the only SGLT-2 inhibitors United States Food and Drug Administration (FDA) indicated for the prevention of cardiovascular outcomes in patients with existing diabetes. Dapagliflozin has since been approved following the DAPA-HF trial. These three SGLT-2 inhibitors have been shown to offer improved outcomes in patients with HFrEF receiving guideline-directed medical therapy.^{11,12}

Empagliflozin was featured in EMPA-REG OUTCOME with a diverse patient population, of whom 65% had a medical history of myocardial infarction or stroke and all patients had greater than 12% risk for cardiovascular events in 10 years. Patients on empagliflozin demonstrated reductions in all-cause mortality, cardiovascular death, nonfatal infarcts, and nonfatal strokes. The authors concluded that empagliflozin was able to demonstrate consistent reduction in mortality and cardiovascular events despite studying a patient population with a broad range of cardiovascular histories and ASCVD risk.¹³

Among patients in the DAPA-HF trial with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than those who received placebo, regardless of the presence or absence of diabetes. Dapagliflozin is the first SGLT-2 inhibitor to be approved for patients independent of diabetes status.¹⁴

Like the authors of the DAPA-HF trial, we sought to gather data related to the impact of SGLT-2 inhibitors. Our patient population had established heart failure independent of diabetes status. Our study aimed to evaluate the efficacy of SGLT-2 inhibitors in decreasing hospital admission rates and improving the overall condition of heart failure. We also looked at the usage of first-line CHF medications in our study to determine if patients were on appropriate first-line therapy. For the established treatment of CHF, first-line therapies include angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), beta-blockers, and diuretics as needed for fluid retention.¹⁴ The aim of the present study is to investigate what benefit, if any, SGLT-2 inhibitors provide to heart failure patients with or without diabetes for the possibility of these medications becoming standard of care.

MATERIALS AND METHODS

The Institutional Review Board (IRB) of Sanford Health approved our one-center retrospective cohort study on February 6th, 2020. HIPAA authorization was waived for this approved IRB protocol #: STUDY00001918, to evaluate the efficacy of SGLT-2 inhibitors in reducing heart failure readmission rates. Patient data from 2013 to 2019 was collected and analyzed for 6 months past the first admission. The Sanford Information Technology Department pulled patient information for study inclusion criteria. Data collection took place at Sanford USD Medical Center in Sioux Falls, South Dakota, from February to March 2020. Information was de-identified and analyzed from March to April 2020. Statistical analysis was done using Fischer exact tests and two-tailed T-tests.

The primary outcome was 6-month hospital readmission rates due to heart failure while taking SGLT-2 inhibitors. Secondary outcomes included 6-month all-cause hospital readmissions, renal function as measured by eGFR change between admissions, mortality rates, and presence of HFrEF versus HFpEF while taking SGLT-2 inhibitors.

Inclusion Criteria

- Patients 18 years or older with a diagnosis of CHF (as designated by the International Classification of Diseases (ICD) 9/10 codes),

- Patients require an active prescription for an SGLT-2 inhibitor,
- Patients must have a creatinine clearance (CrCl) greater than 30 mL/min.

Exclusion Criteria

- Patients with heart failure class IV, end-stage renal disease (ESRD), and dialysis.
- Patients who discontinued their SGLT-2 inhibitor before the second admission.

At baseline, most patients were taking at least one first-line medication for heart failure, suggesting proper management. For the first admission for CHF, 138 patients met inclusion criteria. Of those, 72 patients were taking either an ACE Inhibitor or an ARB, 88 were taking beta-blockers, 71 were taking diuretics, and 18 patients were not receiving any first-line medication for CHF before hospitalization. Of those taking medications, 29 patients were taking one agent, 58 patients were taking two agents, and 34 patients were taking more than two agents, as shown in Figure 1. As a part of the inclusion criteria, all patients were taking an SGLT-2 inhibitor as shown in Figure 2. Most patients were taking canagliflozin (51), while others were taking empagliflozin (40), dapagliflozin (21), or a combination medication such as canagliflozin-metformin (7), empagliflozin-linagliptin (6), or empagliflozin-metformin (2). Due to the impact of the COVID-19 pandemic on data collection, no further patient demographics were collected.

We were able to pull a matched cohort group to our data set so we could compare readmission rates. A total of 78,000 patients with CHF from 2013 to 2019 who were not taking SGLT-2 inhibitors were included in this data set. Due to time constraints of data collection and the COVID-19 pandemic, we were unable to gather any additional information about this patient population other than readmission rates.

RESULTS

In patients taking SGLT-2 inhibitors, the 6-month all-cause readmission rate was 21%, compared to a readmission rate of 16% in those patients not taking SGLT-2 inhibitors.

Additionally, 10 of 138 patients (7.2%) taking a SGLT-2 inhibitor were readmitted for a specific diagnosis of CHF as depicted in Figure 3. A readmission rate for a specific diagnosis of CHF was not collected for the control group not taking SGLT-2 inhibitors. A Fisher Exact test comparing all-cause readmission rate of those taking SGLT-2 inhibitors to the control group produced a P-value of 0.6, which was not significantly different.

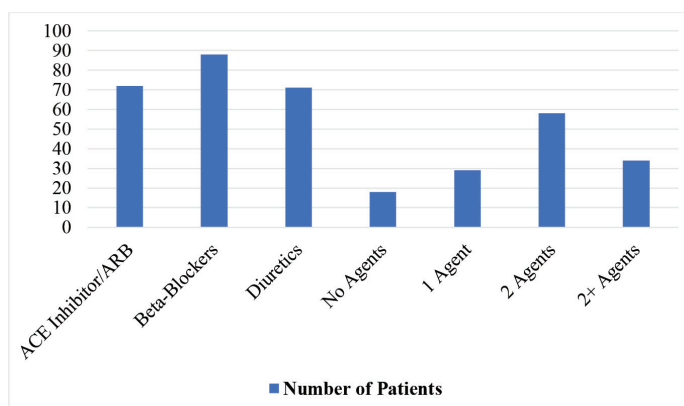


Figure 1: Baseline heart failure medication use.

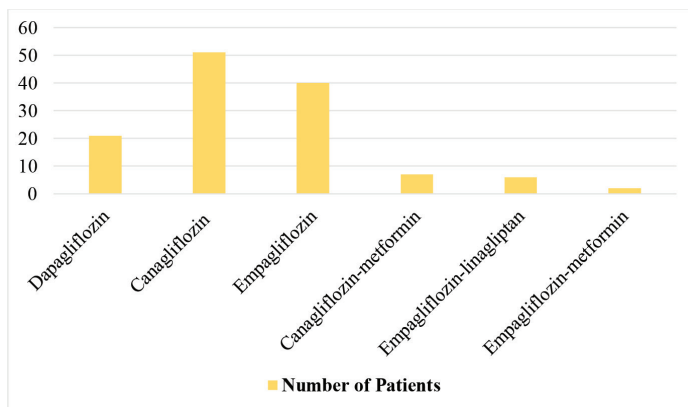


Figure 2: SGLT-2 inhibitor breakdown.

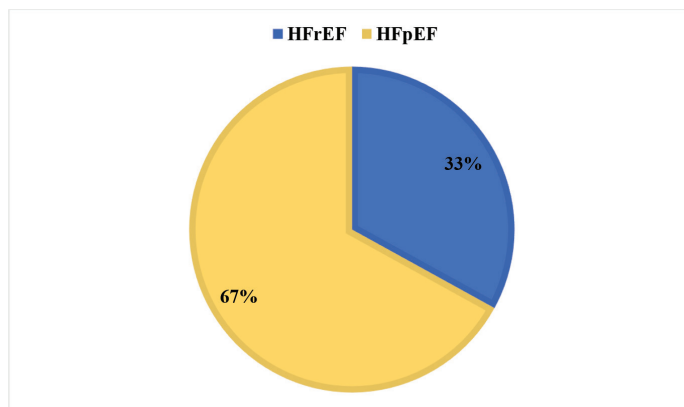


Figure 5: Prevalence of HFrEF vs. HFpEF first admission.

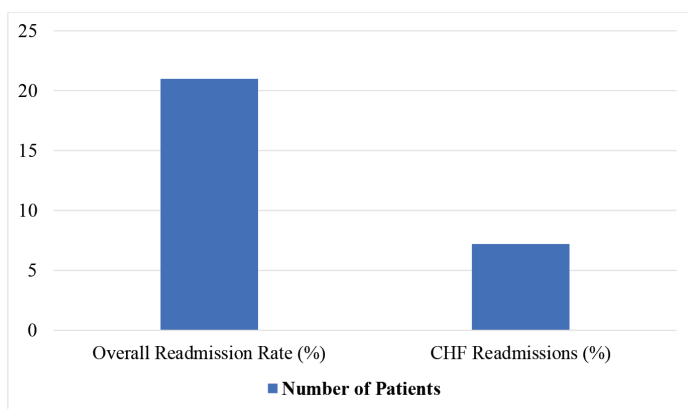


Figure 3: Readmission rates on SGLT-2 inhibitors.

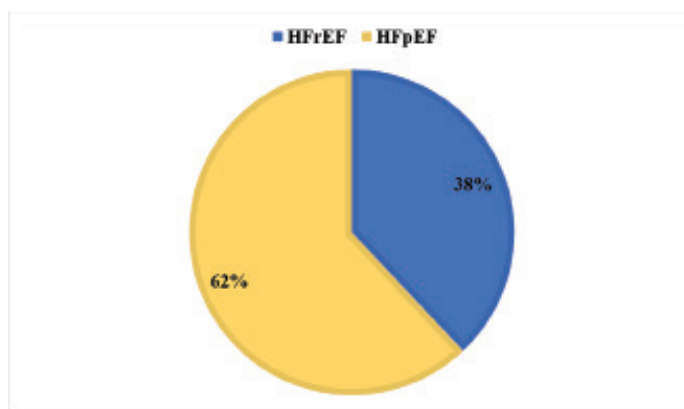


Figure 6: Prevalence of HFrEF vs. HFpEF at readmission.

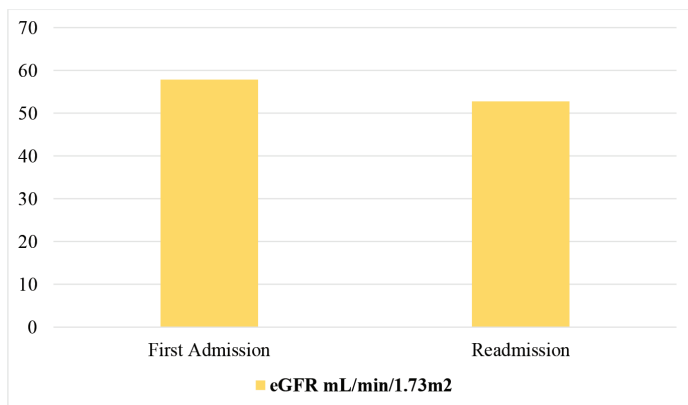


Figure 4: eGFR change between admissions. ($p=0.21$).

In patients with an eGFR less than 90, the average eGFR for the SGLT-2 group declined slightly but non-significantly from 57.9 mL/min/1.73m² to 52.8 mL/min/1.73m² between patients at first admission and those with readmission ($p=0.21$) as shown in Figure 4.

The prevalence of HFpEF and HFrEF was comparable between first admission and those with readmission, with 35 of 105 first time admits (33%) and 8 of 21 second time admits (38%) reporting HFrEF with an ejection fraction <40%. The rest of the patients with data were HFpEF, with 70 of 105 first time admits (67%) and 13 of 21 second time admits

(62%) as shown in Figures 5 and 6. These changes were not significant ($p=0.81$). Patients who did not have a recent echocardiogram within one month of admission were excluded.

During the first admission, 1 out of 131 patients did not have a diagnosis of type II diabetes. During the second admission, all 29 patients had a diagnosis of type II diabetes.

The study also evaluated mortality rate of those taking SGLT-2 inhibitors and who also were diagnosed with CHF. Patients who died after 6 months of their first admission were included in this mortality rate. At data collection, 20.3% of patients with a first admission had died. Unfortunately, similar to other endpoints, mortality rate could not be compared to a control group due to COVID restrictions.

DISCUSSION

The 6-month all-cause readmission rate for patients taking SGLT2-inhibitors was not significantly different than the readmission rate for those not taking SGLT-2 inhibitors (21% vs 16%). These 6-month readmission rates were lower than the reported statistic from the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Heart Failure Guidelines, where patients hospitalized for CHF had a 1-month readmission rate of 25% for all-cause rehospitalization.^{15,16}

The mortality rate of 20.3% in this study was similar to that reported in the 2013 American College of Cardiology Foundation (ACCF)/AHA Heart Failure Guidelines. According to the 2013 ACCF/AHA Heart Failure Guidelines, the absolute mortality rates for CHF remain approximately 50% within 5 years of diagnosis. In the ARIC study, the

30-day, 1-year, and 5-year case fatality rates after hospitalization for CHF were 10.4%, 22%, and 42.3%, respectively.¹⁷

We found no significant differences with HFrEF or eGFR, so our data cannot be used to support efficacy for renal or heart failure outcomes.

This study has some limitations. Since our data was collected using diagnostic codes, a patient might have been coded for CHF even if it was not the main cause of the admission. Therefore, to find the CHF specific readmission, we did a manual chart review to find where CHF was listed as a cause of the admission according to provider documentation, which may be subject to error.

Another major limitation of this study was small sample size. The primary outcome statistical result could be due to a type II error where we failed to find a difference although one may have existed if we had a larger sample size. Due to the small number of patients in the readmission group, we were unable to perform some of the exploratory analyses that we planned. We did not perform subgroup analysis by individual SGLT-2 inhibitor, or look at a subset analysis of patients without diabetes that were taking a SGLT-2 inhibitor.

This study also had several strengths. A strength of this study is that most patients received appropriate first-line therapy for CHF (120 of 138 patients), so we can be sure that patients were receiving some treatment for CHF. However, the effect of the other therapies for CHF on these results was not studied. Another strength was that patients were well distributed between SGLT-2 inhibitors, so we were able to look at the class benefit of SGLT-2 inhibitors.

It was also positive that there was not a significant decrease in average eGFR between readmissions. This could be interpreted as SGLT-2 inhibitors preventing a decline in renal function and a topic for future clinical research. It should be noted that those patients with eGFR >90 mL/min/1.73m² (normal renal function) were not included in the statistical analysis to prevent skewing the data. Other strengths of this study include a large health system to pull data, a matched cohort control group to compare readmission rates, and limited exclusion criteria.

For future direction, it would also have been beneficial to extend data collection for readmissions longer than 6 months to increase sample size. Finally, it is important to note that CHF is most often accompanied with a multitude of other disorders and comorbidities that can affect patients' treatment approach, morbidity, and mortality differently.

CONCLUSION

The use of SGLT-2 inhibitors in patients with CHF did not significantly change the overall hospital readmission rate; however, this study reports better readmission values than those reported in the literature. Larger randomized controlled trials are needed for further evidence of this indication. More data could help incorporate SGLT-2 inhibitors into standard care for heart failure. Now that dapagliflozin is approved as an adjunct heart failure agent, we hope that this study aids clinicians in the use of SGLT-2 inhibitors. Safety and cost are variables that would need to be addressed. Head-to-head trials of SGLT-2 inhibitors would help prescribers choose the best agent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACC: American College of Cardiology; **ACCF:** American College of Cardiology Foundation; **ADA:** American Diabetes Association; **AHA:** American Heart Association; **ASCVD:** Atherosclerotic cardiovascular disease; **CHF:** Congestive heart failure; **CrCl:** Creatinine clearance; **eGFR:** Estimated glomerular filtration rate; **ESRD:** End-stage kidney disease; **FDA:** United States Food and Drug Administration; **HF:** Heart failure; **HFrEF:** Heart failure with preserved ejection fraction; **HFrEF:** Heart failure with reduced ejection fraction; **ICD:** International Classification of Diseases; **SGLT-2 inhibitors:** Sodium-glucose cotransporter-2 inhibitors.

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