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Barriers to utilization of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction in the outpatient setting: A single center analysis

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Abstract

Background

In patients with heart failure with reduced ejection fraction (HFrEF), SGLT2 inhibitors have consistently demonstrated improved cardiovascular and renal outcomes regardless of diabetes status. However, SGLT2i remain significantly under-utilized in this patient population. We seek to study the current state of SGLT2i use and barriers to utilization using real- world data in an inner -city community hospital setting.

Methods

This is a single center retrospective analysis of patients diagnosed with HFrEF, defined as ejection fraction ≤ 40%, seen from December 2019 to December 2021, in the outpatient setting.

Results

A total of 464 patients were included in this analysis, where SGLT2 inhibitors were indicated for type 2 diabetes mellitus, chronic kidney disease (CKD), and/or heart failure. Twenty five percent of patients were on SGLT2 inhibitors, despite low frequency of absolute or relative contraindications (5%) and 14% of patients had ≥CKD4with eGFR<30ml/min/1.73m^2. History of CAD [OR 0.30; 95% CI 0.18-0.50; p<0.001], ≥CKD4 [OR 0.35; 95% CI 0.16-0.73; p=0.005] and higher ejection fraction on the spectrum of

HFrEF [OR 0.95; 95% CI 0.92-0.97; p<0.001] were significantly inversely associated with SGLT2i use.

Conclusions

There was significant under-utilization of SGLT2i in this single center analysis, despite lack of absolute and relative contraindications in the majority of our study population and the presence of multiple possible indications including concomitant type 2 diabetes and CKD. More pragmatic studies are needed emphasizing practical implementation of medical management for high-risk patient populations.

2-**Introduction**

There has been an increase in the prevalence and mortality of heart failure(HF) in the United States; [1,2] which has been accompanied by increasing investments in research focused on development of therapies to decrease morbidity and mortality of this prevalent disease. Several studies have noted the benefits of sodium glucose co-transporter 2 inhibitors (SGLT2i) in treatment of heart failure with reduced ejection fraction (HFrEF) with a consistent class effect for reduced HF hospitalizations and cardiovascular death in the large cardiovascular outcome trials with SGLT2i. [3] In November 2019, the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial [4] reported data on a total of 4,744 patients with EF of <40% who were randomly assigned to receive either dapagliflozin or placebo. The results showed that, among patients with HFrEF, those who received dapagliflozin had a lower risk of worsening heart failure or death from cardiovascular causes and better symptom scores than those who received placebo, regardless of the presence or absence of diabetes. This led to its Food and Drug Administration (FDA) approval in May 2020 for utilization in HF. In October 2020, the Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR-REDUCED) trial [5] randomized 3,730 patients with EF 40% or less to receive empagliflozin 10mg daily or placebo. The study concluded that among patients receiving recommended therapy for HF, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for HF than those in the placebo group, regardless of the presence or absence of diabetes, this in turn led to its FDA approval by February 2022 for the HF indication. Finally, a recent meta-analysis of 21,947 patients across 5 trials; with inclusion of patients in both outpatient and inpatient settings; showed that SGLT2 inhibitors significantly reduced the risk of

mortality and worsening HF; as well as improved patient symptoms and overall health status when added to standard therapy for HF. The conclusion was that these medications should be considered foundational therapy in all patients with HF, regardless of ejection fraction or care setting.[6] However, prescription of these medications may be limited by various factors including accessibility and clinical inertia. [7] We seek to study the current state of SGLT2i utilization and barriers to utilization in HFrEF using real world data in an inner-city community hospital setting.

3 - **Methods**

This is a single center retrospective analysis of patients diagnosed with HFrEF, defined as ejection fraction ≤ 40%, in the outpatient setting from December 2019 to December 2021. We obtained a list of patients with the diagnosis of heart failure with reduced ejection fraction seen in the outpatient clinic at a Community Hospital in North Philadelphia (Pennsylvania, United States). The hospital's Department of Health Information Management obtained the list by filtering the encounters of patients with diagnoses that included ICD-10 codes in the range I50.2 - I50.23, corresponding to HFrEF. A chart review was done to confirm the diagnosis. We investigated rates of SGLT2i use and factors associated with SGLT2i utilization including contraindications (history of ketoacidosis, recurrent urinary/genital tract infections, severe peripheral artery disease, GFR < 30).

Statistical methods:

Patients were stratified and analyzed according to presence or absence of SGLT2i use. Demographic and clinical variables were collected and analyzed, data were presented using frequencies or percentages. Categorical data were analyzed using chi square while continuous data were analyzed using Independent T test or Mann Whitney U test if with skewed distribution. Variables that were significantly different in the univariate analysis were incorporated into a multivariable logistic regression model to identify independent predictors of SGLT2i use. Odds ratios with 95% confidence intervals were provided as appropriate and a p value of <0.05 was considered statistically significant. All analyses were done using Stata (Version 17; Statacorp, College Station, TX).

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4 - **Results**

After screening a total of 798 encounters of patients with HFrEF seen in the outpatient setting between December 2019 and December 2021, a final sample of 464 patients with heart failure with reduced ejection fraction were included in this analysis. From the initial sample of 798 encounters, 121 were excluded due to being duplicate encounters for the same patient. From the remaining 677 patients, 212 patients were excluded due to echocardiogram showing EF > 40%. One additional patient was excluded due to absence of echocardiogram records; thus, resulting in a final sample of 464 patients (Figure 1). The majority of the patients (61%) were male, and 80% were African-American. About half of the patients (52%) had Type 2 diabetes. SGLT2I use was present in only 25% of the total patients. We also found that 71% of our patients had chronic kidney disease stages 1 to 3; however, only 28% of these patients were on SGLT2I. This was despite the fact that the contraindications noted (eGFR of <30 qualified as out of the scope of FDA label for dapagliflozin and < 20 cc/min for empagliflozin) were low (14%). Other contraindications such as history of repeated urinary/genital tract infections, severe peripheral vascular disease, ketoacidosis history were <5% (Figure 2). The subset of patients with all 3 indications (CKD eGFR30-60 + diabetes and HFrEF) was 14%, while more than half(52%) had dual indications (HF with CKD eGFR30-60 or diabetes). Insurance type was not significantly associated with SGTL2I utilization (p=0.42); of patients not on SLGT2I, 59% had private insurance, 39% had Medicare/Medicaid, and 2% were uninsured. After multivariable logistic regression, presence of Type 2 diabetes was significantly positively associated with SGLT2I use [OR 2.78; 95% CI [1.70-4.52]; p<0.001], while history of CAD [OR 0.30; 95% CI [0.18-0.50]; p<0.001], ≥CKD4 [OR 0.35; 95% CI [0.16-0.73]; p=0.005] and higher ejection fraction on the spectrum of HFrEF [OR 0.95; 95% CI [0.92-0.97]; p<0.001] were significantly inversely associated with SGLT2I use.

5-**Discussion**

In our study, we aimed to identify barriers to use of SGLT2I in patients with HFrEF in a real-world setting in an urban hospital patient practice. We found that only 25% of the patients were started on these drugs, despite a diagnosis of HFrEF and a high prevalence of comorbid Type 2 diabetes and CKD. This was despite the fact that the rates of presence of contraindications or outside the scope of existing FDA labels at the time of this analysis were low. Fourteen percent of patients had advanced CKD with GFR < 30 ml/min; and the remaining contraindications (such as history of repeated urinary/genital tract infections, severe peripheral vascular disease, prior diabetic ketoacidosis) were present in less than 5% of the patients. We found that 52% of the total number of patients had a diagnosis of diabetes mellitus; however only 31% of the diabetic patients were on SGLT2I, despite the fact that they had two indications for SGLT2i (concomitant HFrEF). We also found that 71% of our patients had chronic kidney disease stages 1 to 3; however, only 28% of these patients were on SGLT2i despite the fact that these drugs have been shown to have benefit in lowering the progression of albuminuria and substantive loss of kidney function.[8] As evidenced by our study data, as many as 14% of our patients potentially fulfill three indications(presence of diabetes, chronic kidney disease and heart failure with reduced ejection fraction) for use of this drug class while more than half had dual indications. These patients are at highest risk for poor cardiovascular outcomes, which means that they stand to benefit the most from these medications. [9] Our findings were similar to a study published in 2021 that analyzed the barriers to starting SGLT2I in patients with diabetic kidney disease. [9] The aforementioned study analyzed 3,703 consecutive outpatients with type 2 diabetes mellitus from four teaching hospitals during 6 months (from 2019 to 2020); and found out that only 32.9% of the patients with type 2 diabetes mellitus with chronic kidney disease eligible for treatment with SGLT2I were actually being treated with these medications. [10] They found that the main barriers to starting SGLT2I were clinical inertia and older patient group. In our study, the use of SGLT2i was only mentioned in only 33% of the patients (any mention of SGLT2I on medical records review). The analysis showed that the presence of type 2 diabetes mellitus was positively associated with use of SGLT2I may seem intuitive;

however the benefits of SGLT2i use in HFrEF have been approved for patients regardless of presence of diabetes. The following factors were significantly inversely associated with use of SGLT2I: history of coronary artery disease, ≥CKD4, and higher EF on the spectrum of HFrEF. The lack of any mention of these drugs on 67% of the patients' records may point to clinical inertia as a possible barrier to the use of SGLT2I in patients with heart failure with reduced ejection fraction. In 2020, a group of endocrinologists shed light on the fact that these drugs were under-utilized in patients who had indications for it; and the key barrier proposed was clinical inertia despite the increasing amount of evidence from cardiovascular outcome trials (CVOTs), that support the benefits provided by SGLT2 inhibitors. [7] One of the proposed driving factors for clinical inertia was an aversion to change with many healthcare providers having preference for medications with which they have more clinical experience. [7] It is also important to note that, in our study, insurance status was not associated with differences in SGLT2i utilization, which again points to clinical inertia as being a possible contributing factor for low prescription rates – however, this should be considered hypothesis generating as there may be other factors that may be associated with SGLT2i utilization and inertia or clinical behaviors or patterns of practice were not directly measured. It is important to raise awareness regarding the indications and benefits of these drugs, and emphasize the fact that effects of SGLT2i reduction of mortality, hospitalizations and progression of kidney disease in HFrEF patients is independent of any glucose-lowering effects, as has been consistently shown in CVOTs.[6]

Our study is limited by its single center design. There was a lack of documentation including possible insurance barriers. If there is an insurance barrier such as need for pre-authorization or peer-to-peer review for approval of a drug; this was not always documented in the electronic medical records; and this may have led to under-reported number of patients not prescribed SGLT2i due to insurance issues. Another important limitation is that our institution's outpatient center serves a patient population that is known for socio-economic disparities which can impair adherence to medication and regular follow-up. This could represent a barrier to prescription of these drugs, which may not be documented in the electronical medical

records, again leading to under-reported number of patients not prescribed SGLT2I despite having indications for being on these medications. CKD was also defined based on eGFR alone and lack of albuminuria screening may have underestimated the prevalence of this comorbidity in our population. Another important aspect is that our population is predominantly African-American (80%) which may limit generalization of study results, however, it does provide some insights as to possibility of disparities in access to healthcare. Importantly, the African-American population have been under-represented in CVOTs, as evidenced by a percentage of 4.7% of African-Americans in the DAPA-HF trial [4] as well as a percentage of 6.8% of African-Americans In the EMPEROR-Reduced trial. [5]

Conclusion

There was under-utilization of SGLT2i in our institution for no apparent reason, despite lack of contraindications in the majority of our study population and the presence of multiple possible indications including concomitant diabetes and CKD. Our hypothesis is that clinical inertia may play a role in this process. More pragmatic studies are needed emphasizing practical implementation of medical management for high-risk patient populations

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There was no funding required for this research project.

Data Availability:

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Conflict of Interest:

One of the authors receives consulting fees from Boehringer Ingelheim, directed at the author, not the

Institution. There were no other conflicts of interest.

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n (%)	On SGLT2i (n=116)	Without SGLT2i (n=348)	p-value
Age	60.1±13.7	59.5±10.5	0.67
Male gender	73(63)	212(61)	0.70
Ethnicity African American Caucasian Hispanic Other	 96(83) 2(2) 16(13) 2(2)	 276(79) 10(3) 48(14) 14(4)	0.59
CKD stage No CKD stage 1 stage 2 stage 3 stage 4 stage 5/dialysis	 11(9) 8(7) 48(41) 39(34) 10(9) 0(0)	 53(15) 13(4) 133(38) 92(26) 19(5) 38(11)	0.003
Kidney transplant	0(0)	6(2)	0.16
History of CAD	38(33)	190(55)	<0.001
History of PAD	8(7)	27(8)	0.76
History of stroke	30(26)	61(18)	0.05
Diabetes	76(66)	166(48)	0.001
Hypertension	110(95)	323(93)	0.45
Insurance Medicare/Medicaid Private No insurance	 40(34) 75(65) 1(1)	 134(39) 206(59) 8(2)	0.42
Ejection Fraction	30(20-35)	34(25-40)	<0.001

Table 1. Demographic and clinical variables

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SGLT2i use	Odds ratio	95% Confidence interval	p-value
Age	1.01	0.99 - 1.03	0.120
African American	0.77	0.41 - 1.45	0.429
Gender	1.51	0.93 - 2.44	0.091
Advanced CKD (stage 4 to HD)	0.34	0.16 - 0.73	0.005
History of CAD	0.29	0.17 - 0.49	0.000
History of Stroke	1.14	0.64 - 2.05	0.644
Presence of Diabetes Mellitus	2.77	1.70 - 4.52	0.000
Ejection Fraction	0.94	0.92 - 0.97	0.000

Table 2. Logistic Regression table on factors associated with outpatient SGLT2i use

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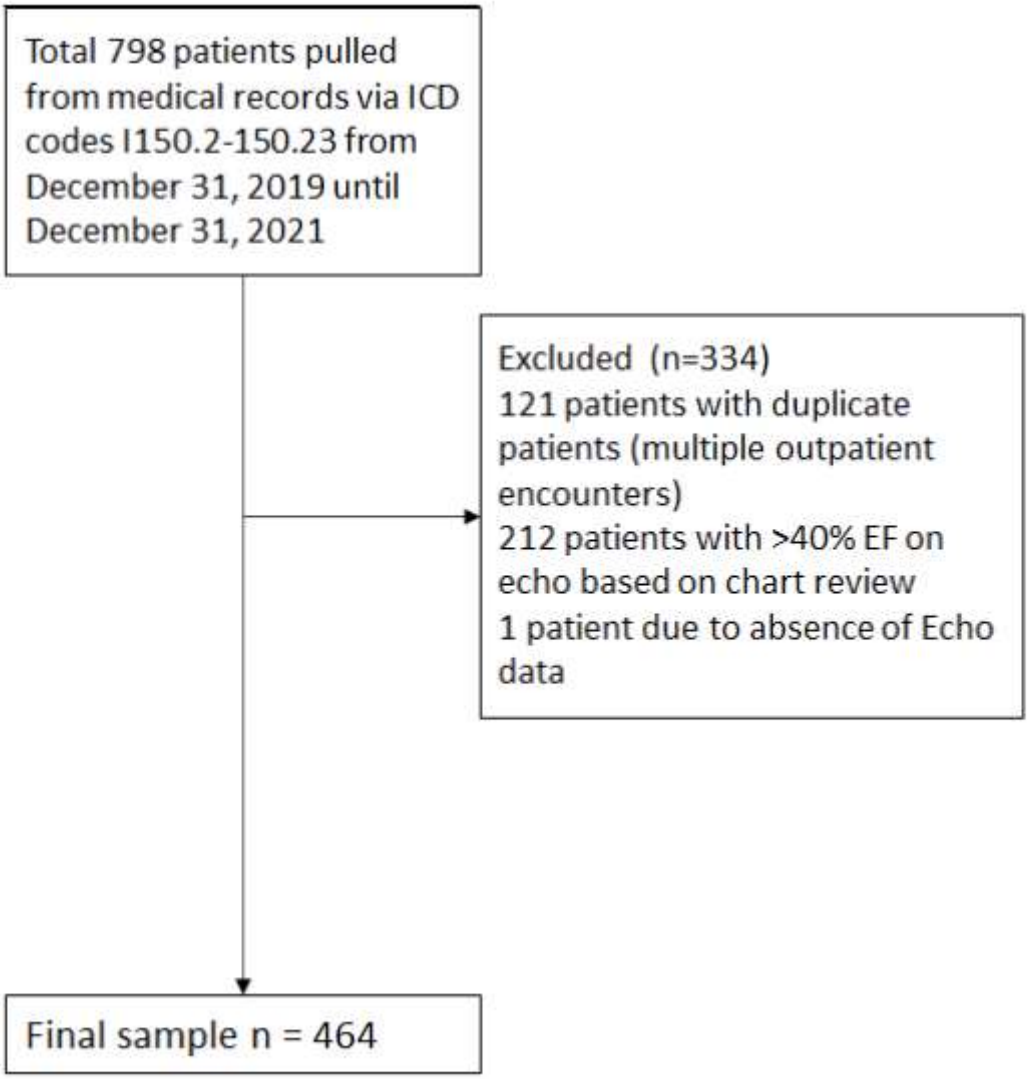

Figure 1. Final patient sample

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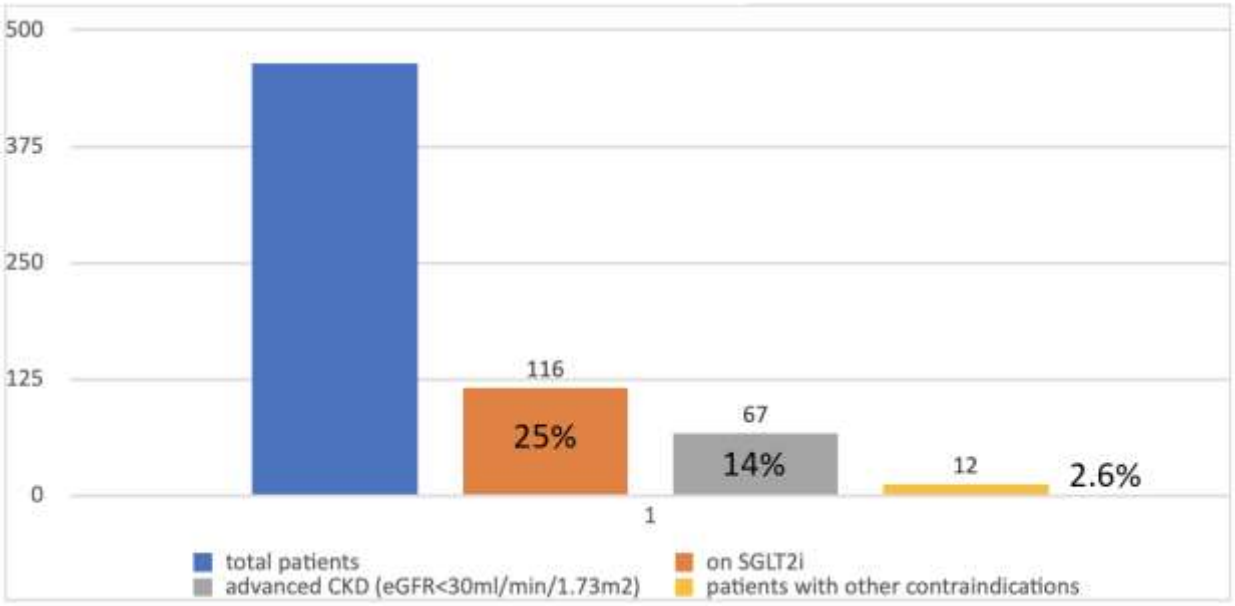

Figure 2. Frequency of contraindications to SGLT2i use