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Short-Term Outcomes After SGLT2 Inhibitor Initiation in a Rea
Failure Patients

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Abstract

Aims: SGLT2 inhibitors (SGLT2i) decrease mortality and risk of hosp
heart failure with reduced ejection fraction (HFrEF). SGLT2i have a n
after initiation, followed by a lasting osmotic diuretic effect. We sough
kidney injury (AKI) and therapy discontinuation with SGLT2i initiatio
HFrEF patients.

Methods: We abstracted data on 200 patients with HFrEF initiated on
setting at the University of Michigan (1/7/2016 – 2/7/2022). Our co-pr
of AKI and discontinuation of SGLT2i.

Results: A total of 200 patients were included. The majority of patient
mean LVEF of 27%. One hundred and four (52%) patients had diabete
exhibited NYHA class II (51.5%) or III (33.5%) symptoms. The major
taking an angiotensin-receptor neprilysin inhibitor. The mean daily fur
diuretic dose was 93.3 mg. AKI occurred in 22 patients and 18 patient
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SGLT2i. Yeast infection (n = 6), hypotension (n = 5), and AKI (n = 4)

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66.0 ECI 57.5-74.6). Similarly, the strongest positive models for SGLT
A1C (AUC = 81.1 ECI 74.8-87.2); baseline SCr (AUC = 67.4 ECI 58.
68.7 ECI 58.9-76.5); and furosemide equivalent diuretic dose (AUC =

Conclusions: A1C was the strongest model of AKI and SGLT2i disco
patients started on SGLT2i. Glucosuria may be related to this effect. P
SCr on higher doses of loop diuretics may be at greater risk of these o
prospective studies will be needed to further evaluate these finding
AKI and SGLT2i discontinuation to guide clinical use of SGLT2 in

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Introduction

In recent clinical trials, sodium-glucose cotransporter inhibitor
shown to reduce morbidity and mortality in patients with heart failure
fraction (HFrEF) with and without diabetes mellitus (DM). However,
on the safety of these medications outside of use in clinical trials. For
about the impact of loop diuretic dose on the risk of adverse events aft
SGLT2is have both osmotic and natriuretic diuretic effects that can co
function from a reduction in effective circulatory volume (1).

Aims

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We aimed to evaluate the safety of SGLT2i initiation in patient

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This was a retrospective cohort study of 200 adult patients with
SGLT2i between 01/07/2016 and 02/07/2022 in the University of Mich
outpatient Heart Failure Clinics. Adult (age ≥ 18 years) outpatients wi
SGLT2i and meeting the necessary 30-day follow-up laboratory evalua
Patients with heart failure with preserved ejection fraction (HFpEF) an
were initiated as an inpatient were excluded. Additionally, nineteen pa
the study due to lack of laboratory information within the established 3
primary outcomes were SGLT2i discontinuation and acute kidney inju
as an increase in serum creatinine (SCr) ≥ 0.3 mg/dL or an increase to
upon laboratory collection within the established time period (2). A re
to < 0.5 ml/kg/h for 6 hours was not utilized given the retrospective da
of real time measurement. Baseline values were obtained from laborat
a 30-day period prior to initiation of the SGLT2i. Continuous variables
and standard deviation; categorical variables were reported as a freque
curves were used to measure each model's ability to represent an outc
ability to consider error rates simultaneously with accuracy rates, capt
specificity, in addition to just modeling accuracy rates. The ROC curv

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were determined empirically by the 2.5th and 97.5th percentiles of the

statistical software (4.2.2) was utilized for data analysis (3).

Results

A total of 200 patients met inclusion criteria. The majority wer

mean age of 60.8 years and mean LVEF of 27% (Table 1). Approxima

participants were initiated on empagliflozin, and the others were starte

of 104 (52%) patients had DM with a mean A1C level of 7.4% (±1.62

was 1.16 ±0.32, and the mean 30-day SCr was 1.27±0.75. The mean d

diuretic dose was 93.3 mg.

From the cohort, 22 patients (11%) had AKI and 18 patients (9

SGLT2i. Yeast infection (33%), hypotension (28%), and AKI (22%) w

reasons for discontinuation. Fourteen patients (7%) had side effects fo

SGLT2i though did not require discontinuation of the medication. Side

hypotension (4%), gout flares (0.5%), chest pain (0.5%), and hyponatr

Using ROC curve analysis, the strongest models for AKI were

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empirical confidence interval [ECI] 66.5-83.5); baseline SCr (AUC =

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58.9-76.5); and furosemide equivalent diuretic dose (AUC = 67.2 ECI
percent of patients had changes to their diuretic dose following SGLT2
patients (9.5%) having their diuretic dose decreased and 1 patient (0.5
increase.

Discussion

This study revealed outpatient SGLT2i initiation was well toler
HFrEF. Hemoglobin A1c, baseline SCr, LVEF, and furosemide equiva
strongest models for AKI and SGLT2i discontinuation.

The rate of AKI in our study was low, though difficult to comp
randomized studies reported a composite renal endpoint (4,5). In our s
high furosemide equivalent diuretic doses contributed to AKI. Though
evaluated baseline furosemide equivalents and outcomes following SG
mean diuretic dose in this study was higher. This highlights the need t
patients on higher furosemide equivalent diuretic doses should have th
reduced prior to SGLT2i initiation.

Another factor that may impact the diuretic effect of SGLT2i

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Future studies should evaluate whether loop diuretic dose reductions a initiation among patients with higher A1c levels.

This study should be interpreted in the context of several limita size was small, and it represents a single-center study. Second, the san study was limited by the availability of electronic medical record data initiation and adverse events.

In conclusion, real-world initiation of SGLT2i in patients with Models for AKI and SGLT2i discontinuation included hemoglobin A1 furosemide equivalent diuretic dose.

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Declaration of Interest: None declared.

References:

1. Gomez-Peralta F, Abreu C, Lecube A, Bellido D, Soto A, Morales C, e Initiating SGLT2 Inhibitors in Type 2 Diabetes. Vol. 8, Diabetes Thera 2017. p. 953–62.
2. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Golds disease: Improving global outcomes (KDIGO) acute kidney injury wo practice guideline for acute kidney injury. Vol. 2, Kidney International Publishing Group; 2012. p. 1–138.
3. R Core Team. R: A language and environment for statistical computing Foundation for Statistical Computing; 2022.
4. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fra Journal of Medicine [Internet]. 2019 Nov 21;381(21):1995–2008. Ava http://www.nejm.org/doi/10.1056/NEJMoa1911303
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et a Renal Outcomes with Empagliflozin in Heart Failure. New England Jo Oct 8;383(15):1413–24.
6. Jackson AM, Dewan P, Anand IS, Bělohlávek J, Bengtsson O, de Boer and Diuretic Use in Patients With Heart Failure and Reduced Ejection Circulation. 2020 Sep 15;142(11):1040–54.
7. Ikeda Y, Ishii S, Maemura K, Oki T, Yazaki M, Fujita T, et al. Glucose relation to improvements in renal-tubular markers of sodium-glucose in hospitalized heart failure patients with diabetes. Heart Vessels. 2021

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Table 1: Baseline Characteristics

Sample Population	
Age (years), mean (SD)	
Male, n (%)	
Race	
Caucasian, n (%) Black, n (%)	
SGLT2 inhibitor	
Empagliflozin, n (%)	
Dapagliflozin, n (%)	
Cardiomyopathy type	
ICM, n (%)	
NICM, n (%)	
Diabetes, n (%)	

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I	
II	
III	
IV	
Beta blocker use, n (%)	
ACEi/ARB, n (%)	
ARNi, n (%)	
MRA, n (%)	
Diuretic use	
Bumetanide, n (%)	
Furosemide, n (%)	
Torsemide, n (%)	
Furosemide equivalent (mg), mean (SD)	
Diuretic dose change upon SGLT2i initiation	
Reduced, n (%)	
Increased, n (%)	
No changes, n (%)	

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30 day follow up potassium level (mEq/L), mean (SD)	

Abbreviations: SGLT2i = sodium-glucose cotransporter- 2 inhibitors cardiomyopathy; NICM=nonischemic cardiomyopathy; LVEF=left v fraction; ACEi=angiotensin-converting enzyme inhibitor; ARB=angi blocker; ARNi =angiotensin receptor neprilysin inhibitor; MRA=min antagonist. % = percentage calculated off total cohort.

Table 2. Outcome rates and reason for SGLT2i discontinuation

Primary Outcome	
AKI, n (%)	
SGLT2i discontinuation, n (%)	
Reason for discontinuation	
AKI, n **(%*)**	
DKA, n **(%*)**	

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Abbreviations: AKI=acute kidney injury; SGLT2=sodium-glucose c

DKA = diabetic ketoacidosis. N = total cohort, N* = patients who un

discontinuation, % = percentage calculated off total cohort, %* = per

cohort who had SGLT2i discontinuation.

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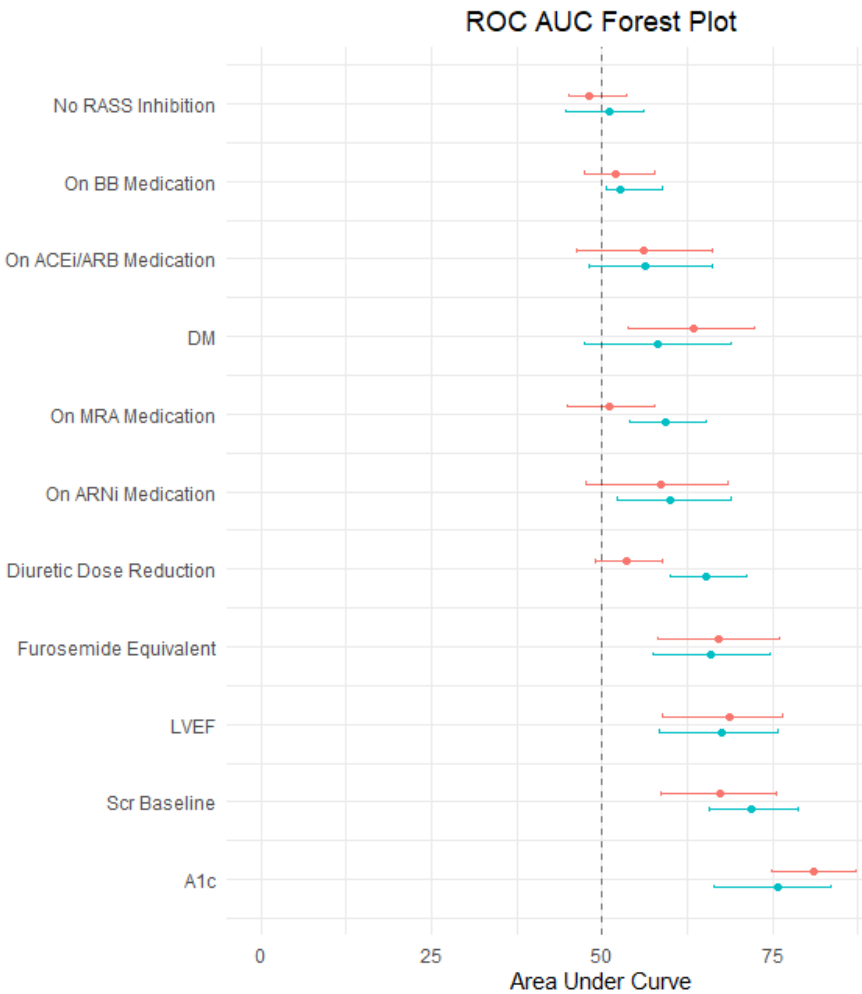


Figure 1. Models of AKI and SGLT2i discontinuation assessed with l
analysis using 1000 iterations.

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