MEDICAL SCIENCE

Outcomes of sodium-glucose cotransporter-2 inhibitors in patients with heart failure with or without diabetes in a real-world setting: A retrospective observational study

Saleh F Alqifari[1*], **Adil B Mohammad**[2], **Eman I Anwar**[3], **Kashan Uddin Niazi**[4], **Rahaf F Aldawish**[4], **Rand Albahli**[5], **Maha A Binsaqr**[4], **Asmaa A Khojah**[4], **May R Mutlaq**[4], **Palanisamy Amirthalingam**[6], **Ahmed Aljabri**[7], **Shaimaa Ziada**[2], **Bshaier Alshaye**[2], **Salman Almokhlef**[8]

To Cite:
Alqifari SF, Mohammad AB, Anwar EI, Niazi KU, Aldawish RF, Albahli R, Binsaqr MA, Khojah AA, Mutlaq MR, Amirthalingam P, Aljabri A, Ziada S, Alshaye B, Almokhlef S. Outcomes of sodium-glucose cotransporter-2 inhibitors in patients with heart failure with or without diabetes in a real-world setting: A retrospective observational study. *Medical Science* 2023; 27: e115ms2909.
doi: https://doi.org/10.54905/disssi/v27i132/e115ms2909

Authors' Affiliation:
[1]Assistant Professor, Department of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, Tabuk, Saudi Arabia
[2]Department of Cardiology, Prince Sultan Cardiac Center, Qassim, Saudi Arabia
[3]Lecturer, Department of Clinical Pharmacology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[4]Physician, College of Medicine, Sulaiman Alrajhi University, Qassim, Saudi Arabia
[5]Physician, College of Medicine, Qassim University, Qassim, Saudi Arabia
[6]Associate Professor, Department of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, Tabuk, Kingdom of Saudi Arabia
[7]Assistant Professor, Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[8]Physician, Department of Internal Medicine, King Fahad Specialist Hospital, Qassim, Saudi Arabia

[*]**Corresponding Author**
Assistant Professor, Department of Pharmacy Practice, Faculty of Pharmacy, University of Tabuk, Tabuk,
Saudi Arabia
Email: salqifari@ut.edu.sa
ORCID: 0000-0002-0288-065X

Peer-Review History
Received: 10 February 2023
Reviewed & Revised: 12/February/2023 to 24/February/2023
Accepted: 25 February 2023
Published: 27 February 2023

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

ABSTRACT

Objectives: Sodium-glucose cotransporter 2 (SGLT2) inhibitors demonstrated a reduction in the risk of death and hospitalization for heart failure and major renal complications in recent clinical trials. However, real-world studies are still limited, especially in Saudi Arabia. This study aims to examine the clinical outcomes of SGLT2 inhibitors in heart failure patients regardless of diabetes status. *Materials and methods:* A retrospective study was conducted at a single cardiology center in Saudi Arabia. The study spanned from July 2021 to June 2022. The study included adult patients (≥18 years) diagnosed with heart failure with a prior history of using SGLT2 inhibitors for at least 3 months. *Results:* A total of 45 patients were included in the study. A significant difference was detected among the diabetic and non-diabetic patient groups in baseline diastolic blood pressure (DBP), baseline left ventricular ejection fraction (LVEF) and the use of diabetic medications with ($p= 0.008$, <0.001, 0.008), respectively. SGLT2 inhibitors use resulted in a trend toward improvements in HbA1C, LVEF and ED visits however, these findings were non-statically significant. *Conclusions:* This is the first protocol to report outcomes of SGLT2 inhibitors in Saudi heart failure patients regardless of diabetes status. We detected an improvement signal in HbA1C, ED visit frequency and LVEF in both diabetic and non-diabetic groups. Larger studies are warranted to further evaluate outcomes of SGLT2 inhibitors in this patient group regardless of diabetes.

Keywords: Heart failure, diabetes mellitus, SGLT2 inhibitors, cardiovascular outcomes, renal outcomes

1. INTRODUCTION

The World Health Organization reported that cardiovascular disease (CVD) is a leading cause of death worldwide. In 2019, around 17,000,000 fatalities were attributed to CVD, accounting for a third of fatalities around the world (Kim, 2021). According to recent trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors, which were approved in 2012 to treat type 2 diabetes mellitus (T2DM), are not used only in lowering glucose levels, but also in reducing the risk of hospitalization, major renal complications and CV death in HF with reduced ejection (HFrEF) patients (Raz et al., 2020; Anker et al., 2021; Mc-Murray et al., 2019). Other anti-hyperglycemic medications do not exhibit this benefit (Anker et al., 2021). A recent study found that SGLT2 inhibitors lower the risk of heart failure hospitalization by more than 30% (Zelniker et al., 2019). A double-blind trial conducted in 20 countries randomly assigned 3730 participants with heart failure reported that empagliflozin reduced death because of CVD or heart failure hospitalization compared to placebo, regardless of whether they had diabetes or not. The total hospitalized number of patients because of heart failure was lower with empagliflozin compared to placebo (HR, 0.70; $p<0.001$) (Anker et al., 2021).

Dapagliflozin also demonstrated comparable benefits to empagliflozin. In a trial, heart failure symptoms decreased because of dapagliflozin treatment with 55% efficacy in patients without T2DM compared to patients with T2DM. This indicates that SGLT2 inhibitors have positive effects on CVD in people without T2DM, supporting earlier claims that these medications have advantages beyond just decreasing blood sugar levels. Thus, HFrEF patients had better symptom scores and a lower risk of worsening heart failure or cardiovascular (CV) death with dapagliflozin compared to placebo (Mc-Murray et al., 2019).

Since no real-world confirmatory studies have been conducted to confirm heart failure outcomes of SGLT2 inhibitors, more data are needed. Therefore, the purpose of this study was to report real-world clinical outcomes of SGLT2 inhibitors in Saudi adult patients with heart failure regardless of T2DM status.

2. MATERIAL AND METHODS

Study design and study population

This was a retrospective cohort study of patients diagnosed with heart failure conducted in a single cardiology center in Saudi Arabia from July 2021 to June 2022. Patients who were 18 years and exposed to SGLT2 inhibitors for at least 90 days were included. We divided the patients into two main groups: Diabetic and non-diabetic. All patients who met the inclusion criteria were included in the study.

Data collection and outcomes

The data collection was done through chart review. De-identified data was stored and accessed by study personnel only. Clinical outcomes were compared between diabetic and non-diabetic groups. The clinical outcomes of interest were baseline hemoglobin A1C (HbA_1C), serum creatinine (Scr), left ventricular ejection fraction (LVEF), body weight, hospital admission and emergency department (ED) visits. The study approval was obtained from the Al-Qassim research committee. All the information was treated confidentially.

Data Analysis

The Chi-square test was used to assess the categorical variable among the characteristics of the diabetic and non-diabetic population and the parameters included hospital admission and ER visits before and after treatment for the corresponding diabetic and non-diabetic population. The remaining parameters were expressed as mean and standard deviation (SD) and blood parameters were analyzed by using the student's t-test. SPSS (version 23) was used for the statistical analysis and $p< 0.05$ was considered statistically significant.

3. RESULTS

A total of 45 patients were included. A summary of study sample characteristics is illustrated in (Table1). Our sample included 28 (62%) patients who were below 65 years and 20 (44%) who were above 65 years. Males constitute the largest proportion of patients, representing 31 patients (69%) while females were 14 (31%). In the non-diabetic group, 12 (27%) of the participants were below 65 years of age and six (13%) were over 65 years of age. Like the diabetic group, male participants were more than females, in which they constituted 11 (24%) of the sample and females were seven (16 %) in the non-diabetic group.

The Body Mass Index (BMI) varied between groups, nine (20%) of the diabetic patients had a BMI of less than 30 while six (13%) of nondiabetic participants had a BMI of less than 30. More patients in both groups had a baseline BMI above 30, constituting 18

(40%) of the diabetic group and 12 (27%) of the non-diabetic group. These differences in age, sex and BMI were statistically non-significant between groups (p= 0.615, p=0.357, p=1.000, respectively).

For baseline systolic blood pressure (SBP), around 11 (24%) in each group had baseline SBP of above 120 mmHg. Contrarily, 16 (36%) of diabetics and seven (16%) of non-diabetics had baseline SBP below 120 mmHg. No statistically significant differences have been observed between groups (p=0.180). The baseline diastolic blood pressure (DBP) was significantly lower in diabetic patients receiving SGLT2 inhibitors compared to non-diabetic participants (p= 0.008). Around 26 (58%) diabetics and 15 (33%) non-diabetics had baseline DBP ≤80 mmHg and only one (2%) diabetic and three (7%) non-diabetics had >80 mmHg DBP. Baseline heart rate (HR) didn't show any significant difference between groups (p=0.912). The differences in baseline HbA_{1c} between groups were non-significant (p=0.873).

A statistically significant difference was detected between groups in baseline LVEF (p= <0.001). Around 12 (27%) of diabetic participants and 17 (38%) of non-diabetics had LVEF ≤ 30%. On the other hand, baseline LVEF was > 30% in 15 (33%) diabetic and one (2%) non-diabetic. Regarding the use of diuretic medications, differences between groups were non-significant (p=0.313). The differences in the baseline LVEF between groups were statistically significant, p= <0.001.

The use of antihypertensive medications didn't show any significant difference between the groups (p=0.591). The Empagliflozin dose in the two groups was comparable (p=0.332). Twenty-three (51%) diabetics and 17 (38%) non-diabetics were using 10mg of empagliflozin. Empagliflozin was also used with a dose of 25mg among 4 (9%) diabetics and one (2%) non-diabetic patient.

Table 1 Characteristics of the study population

Variable	Diabetic, n (%)	Non-diabetic, n (%)	P value
Age			
< 65 years	16 (35.5)	12 (26.6)	0.615
≥ 65 years	11 (24.4)	6 (13.3)	
Gender			
Male	20 (44.4)	11 (24.4)	0.357
Female	7 (15.5)	7 (15.5)	
Baseline BMI			
< 30	9 (20)	6 (13.3)	1.000
≥ 30	18 (40)	12 (26.6)	
Baseline SBP			
> 120 mmHg	11 (24.4)	11 (24.4)	0.180
≤ 120 mmHg	16 (35.5)	7 (15.5)	
Baseline DBP			
>80 mmHg	1 (2.2)	3 (6.6)	0.008
≤80 mmHg	26 (57.7)	15 (33.3)	
Baseline Heart rate			
<60 Bpm	1 (2.2)	1 (2.2)	0.912
60-100 Bpm	25 (55.5)	16 (35.5)	
>100 Bpm	1 (2.2)	1 (2.2)	
Baseline HbA_{1c}			
< 6.5%	5 (11.1)	3 (6.6)	0.873
≥ 6.5%	22 (48.8)	15 (33.3)	
Baseline LVEF			
≤ 30%	12 (26.6)	17 (37.7)	<0.001
> 30%	15 (33.3)	1 (2.2)	
On diuretic medications			
Yes	24 (53.3)	14 (31.1)	0.313
No	3 (6.6)	4 (8.8)	
On diabetic medications			

Yes	11 (24.4)	1 (2.2)	0.008
No	16 (35.5)	17 (37.7)	
On antihypertensive medications			
Yes	24 (53.3)	15 (33.3)	0.591
No	3 (6.6)	3 (6.6)	
Empagliflozin dose			
Yes	23 (51.1)	17 (37.7)	0.332
No	4 (8.8)	1 (2.2)	

Note: Chi-square statistics; $p<0.05$ considered as statistically significant
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; LFEF, left ventricular ejection fraction

The SGLT2 inhibitors showed no significant impact on HbA_1C, Scr, LVEF, body weight, hospital admission and ED visits in our sample. However, it is important to highlight that hospitalization and ER visits didn't increase with SGLT2 inhibitors in both groups. Interestingly, there were no reported deaths due to heart failure in both groups. A comparison of the parameters before and after treatment with SGLT2 inhibitors in diabetic and non-diabetic groups is shown in (Table 2).

Table 2 Comparison of parameters before and after treatment with SGLT2 inhibitors

Variable	Diabetic (n= 27)			Non-diabetic (n= 18)		
	Before treatment	After Treatment	P value	Before treatment	After Treatment	P value
HbA_1C (%), mean (SD)	8.82 (1.85)	8.56 (1.77)	0.728*	7.43 (1.50)	6.37 (0.87)	0.101*
Scr (mmol/L), mean (SD)	102 (88)	141 (89)	0.274*	94.75 (27.43)	106.12 (47.87)	0.557*
LVEF (%), mean (SD)	22.69 (7.25)	26.92 (8.04)	0.128*	21 (8.21)	23 (15.24)	0.838*
Body weight (Kg), mean (SD)	83.43 (17.16)	82 (17.49)	0.472*	76.69 (15.95)	81.46 (3.18)	0.364*
Hospital admission (n)						
Yes	1	2	0.552**	2	1	0.546**
No	26	25		16	17	
ED visits (n)						
Yes	2	1	0.552**	3	2	0.629**
No	25	26		15	16	

Notes: *Two-tailed p-value for paired t-test; mean (SD) value between before and after treatment
** Chi-square statistics; $p<0.05$ considered as statistically significant
Abbreviations: Scr, serum creatinine; LVEF, left ventricular ejection fraction.

The spread of HbA1C levels in the diabetic group before and after the treatment with SGLT2 inhibitors (Figure 1.1). The mean value of HbA1C level was lower post-treatment compared to baseline but was not statistically significant, p=0.728. In Figure 1.2, the variability of Scr after the treatment was larger than baseline with the mean value being higher in the post-treatment diabetic group. However, the change in Scr was not statistically significant, p= 0.274. The mean level of LVEF in the post-treatment group was also higher compared to the baseline as illustrated in (Figure 1.3) but non-statistically significant, p= 0.128. Additionally, the mean body weight for the diabetic group was lower after treatment and that also was not statistically significant, p=0.472. Figure 2.1 shows that the mean level of HbA1C was lower after the treatment. Figure 2.2 and 2.3 shows that levels of Scr and LVEF increased post-treatment in non-diabetic groups respectively. On the other hand, mean body weight increased slightly in the non-diabetic group after the treatment (Figure 2.4). However, all the changes in these parameters among the non-diabetic group are non-significant and can't be relied on due to the small sample of our study and short assessment duration.

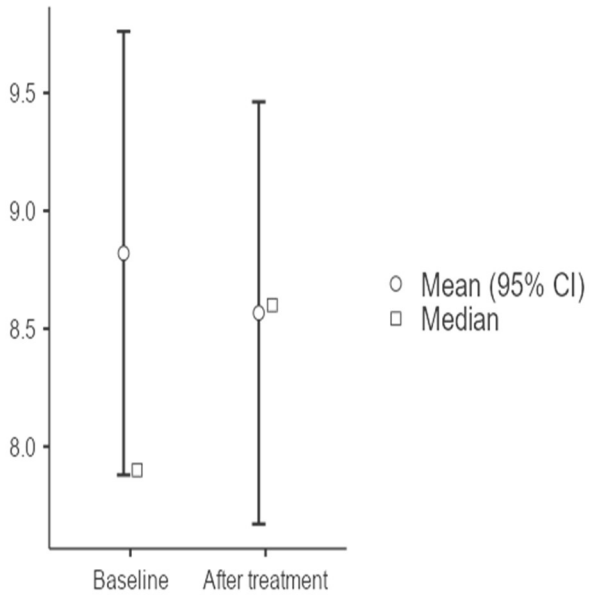

Figure 1.1 HbA1C level in the diabetic population

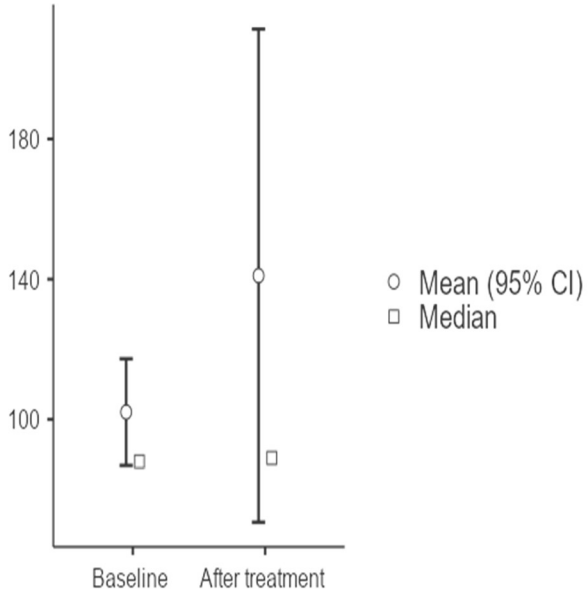

Figure 1.2 Scr level in the diabetic population

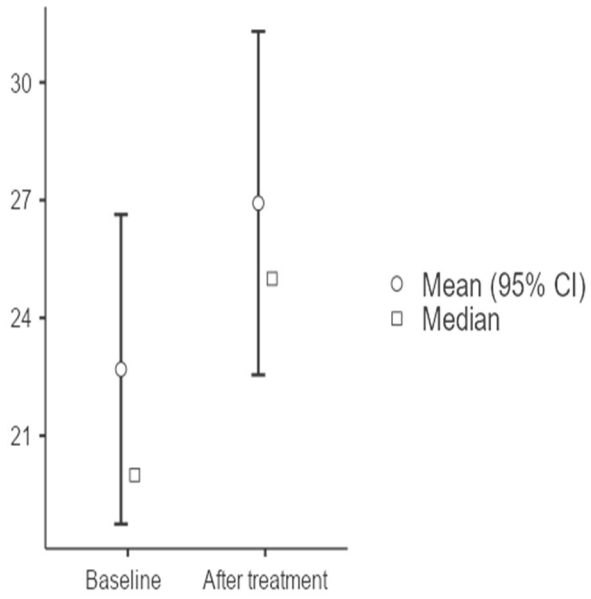

Figure 1.3 LVEF level in diabetic population

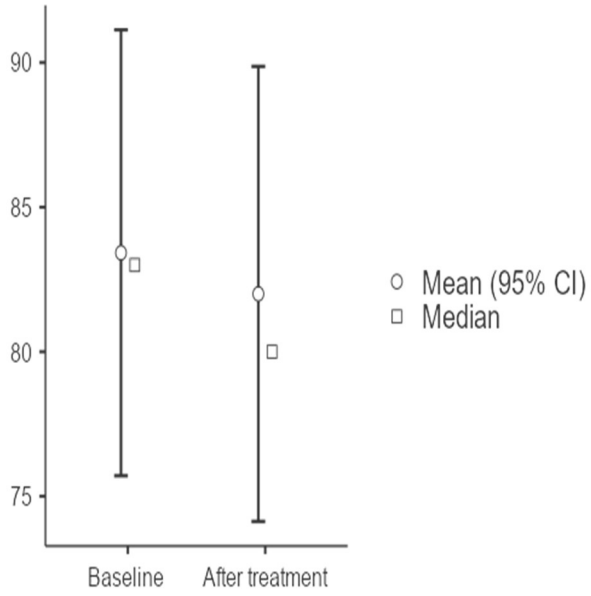

Figure 1.4 Bodyweight in diabetic population

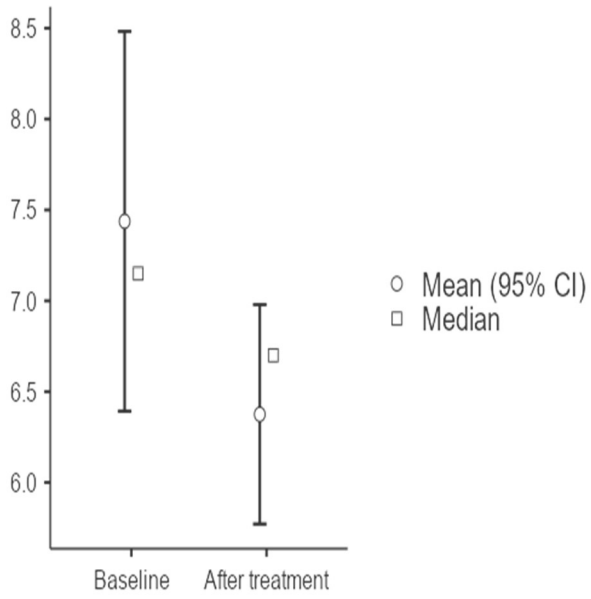

Figure 2.1 HbA1C level in non-diabetic population

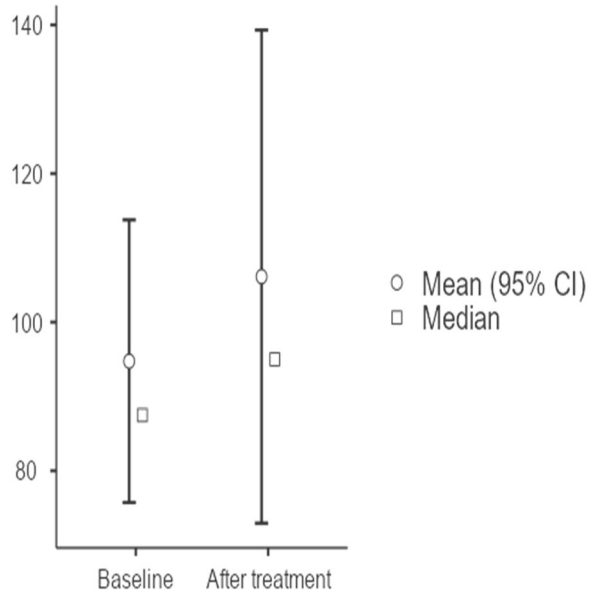

Figure 2.2 Scr level in non-diabetic population

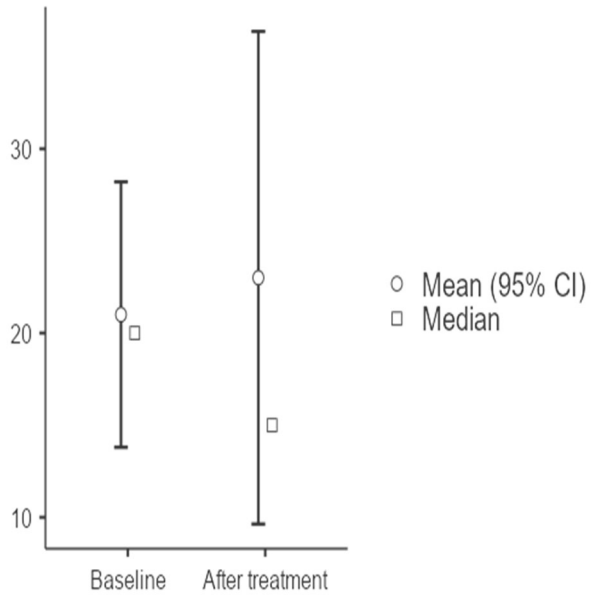

Figure 2.3 LVEF level in non-diabetic population

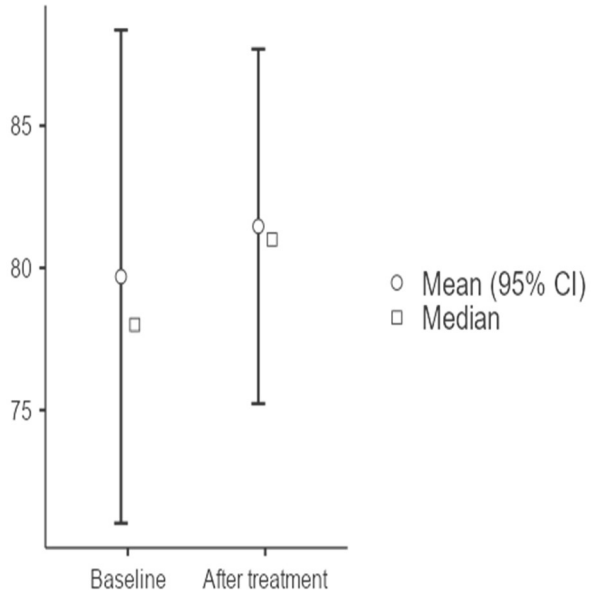

Figure 2.4 Bodyweight in non-diabetic population

4. DISCUSSION

SGLT2 inhibitors have been proven in numerous studies to provide CVD benefits in T2DM (Kyriakos et al., 2021). The rapid development of such evidence prompted additional studies exploring their possible impact on non-diabetic patients. However, limited real-world data has directly exhibited their CV and metabolic effects on non-diabetic patients, especially in Saudi Arabia. To the best of our knowledge, this is the first study that aimed to address this gap using real-world data in Saudi Arabia. In the current study, we observed that SGLT2 inhibitors were associated with a trend toward improvements in HbA1C and LVEF concurrent with decreasing ED visits irrespective of diabetes whereas change in body weight was not similar in both groups.

We analyze CV characteristics and how they differ between diabetics and non-diabetics. The only two baseline characteristics that were significant between groups were DBP and LVEF. Baseline LVEF was significantly higher in diabetic compared to non-diabetic groups. This could be explained by the fact that the majority of the sample's participants were diabetics on several antidiabetic medications; hence, some antidiabetics postulated to have cardio-protective properties that may improve LVEF, such as GLP-1 agonists which are significantly associated with improved LVEF (Zhang et al., 2020). This finding is inconsistent in direction with Ehl et al., (2011) in which diabetic patients showed a statistically significant lower LVEF compared with non-diabetic patients.

In addition, baseline DBP was significantly lower in diabetic patients compared to nondiabetic patients. Both aging and DM are presumed to have a combined effect in increasing arterial stiffness thus leading to a greater decline in diastolic blood pressure. This change in diastolic pressure induced by arterial stiffening takes place at a younger age in diabetes (Osher and Stern, 2008).

The present study detected no significant difference between groups in terms of BMI as most of our sample was obese regardless of DM status. This contrasts with the research by Shah et al., (2006) done in Nepal, which demonstrated a substantial difference in BMI between groups.

Surprisingly, most non-diabetic individuals in our sample had baseline HbA1c values above 6.5% as in diabetic patients; this discrepancy might be caused by unreported and undiagnosed DM that had not yet been treated with medication. According to an Emirati study done by Bashier et al., (2017) HbA1c was significantly reduced within 1 year using SGLT2 inhibitors. This conclusion is consistent with our observation which shows an average decline in HbA1c by 0.26 in diabetics and 1.06 in non-diabetics, however, this decline was not significant owing to the small sample.

Our study shows encouraging results with a slight reduction of body weight from a mean of 83.43 (±17.16) to 82 (±17.49) kg in the diabetic population. This favorable weight loss in diabetics may be reinforced by another anti-hyperglycemic medication like metformin. A similar highly significant change was observed when comparing baseline weight in the Emirati population (85.7 ± 17.8 kg vs. 84 ± 17.2kg, p = 0.0001) (Bashier et al., 2017).

On the other hand, body weight increased slightly after treatment in the non-diabetic group. This contrasts with the systematic review and meta-analysis by Zheng et al., (2021), which demonstrated a statistically significant reduction in body weight in non-diabetics (mean difference -1.42 kg, 95% CI: -1.70 to -1.14; p<0.00001) and BMI.

Interestingly, when comparing pre- and post-treatment Scr, there was a dramatic increase in Scr in both groups and the reason behind these changes remains unknown (most likely due to the water-wasting effect of SGLT2 inhibitors in patients on other therapies such as loop diuretics) circumstantial evidence suggests that treatment with SGLT2 inhibitors does result in a loss of muscle mass, which affects the reliability of Scr as a marker for kidney function (Post et al., 2020). Therefore, more data is needed regarding this effect.

Shi et al., (2022) systematically reviewed thirteen studies addressing the SGLT2 inhibitors on impact left ventricular function and clearly stated that this drug can significantly improve LVEF in patients with or without diabetes. Similarly, we noted that in both groups LVEF improved from a mean of 22.69 (±7.25) % pre-treatment to 26.92 (±8.04) % post-treatment in the diabetic group and from a mean of 21 (±8.21) to 23 (±15.24) % in non-diabetic.

The glucose-independent benefits of SGLT2 inhibitors have been confirmed by recently published clinical trials. According to the DAPA-HF trial, the use of dapagliflozin reduced the composite of worsening heart failure, CV death and hospitalization in heart failure patients and the results were not different between those with diabetes and those without (Mc-Murray et al., 2019). Even though our conclusion concerning this outcome was not statistically significant, it agrees with this trial. This does not necessarily indicate the lack of benefits of SGLT2 inhibitors in reducing hospitalization and ED visits and our findings should be interpreted with caution. Our results would be enough to highlight that hospitalization and ED visits didn't increase with SGLT2 inhibitors in both groups, consequently, neither group reported any mortality from heart failure.

In recent years, SGLT2 inhibitors have been gaining popularity in the treatment of heart failure regardless of diabetes. So far, our study supports the American College of Cardiology (ACC) 2022 recommendation published and presented during the Scientific Sessions in Washington which implement findings from trials including DAPA-HF and EMPEROR-HF, that previously shown the benefit of SGLT2 inhibitors dapagliflozin and empagliflozin in reducing composite CV events and mortality in patients with HFrEF among other CV and cardiometabolic outcomes (Anker et al., 2021; Mc-Murray et al., 2019).

Limitations

We attribute the lack of renal benefits in this study to the small study sample. Moreover, while the improvements in LVEF by SGLT2 inhibitors in each group were observed and supported the CV benefits of SGLT2 inhibitors, providers practicing in similar settings with a similar number of patients should expect similar benefits and lack thereof.

5. CONCLUSION

The DAPA-HF and the EMPEROR-Reduced trials showed that SGLT2 inhibitors effectively reduce heart failure hospitalizations and CV death. In both studies, the results were observed independently of the presence of T2DM. Our study is the first to evaluate the real-world clinical benefit of SGLT2 inhibitors in heart failure irrespective of whether patients have diabetes or not in Saudi

Arabia. There was a trend toward improvements in HbA1C, LVEF and ED visits in diabetics and non-diabetics. Further studies with a larger sample size are needed to confirm the results of our study.

Acknowledgment
None

Ethical consideration
Study protocol #2022-1002 was approved by the medical ethical committee in the Al-Qassim region, Saudi Arabia. All participants' data were kept confidential.

Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding
This study has not received any external funding.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES AND NOTES

1. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, Schnaidt S, Ofstad AP, Brueckmann M, Jamal W, Bocchi EA, Ponikowski P, Perrone SV, Januzzi JL, Verma S, Böhm M, Ferreira JP, Pocock SJ, Zannad F, Packer M. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: Results from the EMPEROR-reduced trial. Circulation 2021; 143(4):337-349. doi: 10.1161/CIRCULATIONAHA.120.051824
2. Bashier A, Khalifa AA, Rashid F, Abdelgadir EI, Al-Qaysi AA, Ali R, Eltinay A, Nafach J, Alsayyah F, Alawadi F. Efficacy and safety of sglt2 inhibitors in reducing glycated hemoglobin and weight in Emirati patients with type 2 diabetes. J Clin Med Res 2017; 9(6):499-507. doi: 10.14740/jocmr2976w
3. Ehl NF, Kühne M, Brinkert M, Müller-Brand J, Zellweger MJ. Diabetes reduces left ventricular ejection fraction-irrespective of presence and extent of coronary artery disease. Eur J Endocrinol 2011; 165(6):945-951. doi: 10.1530/EJE-11-0687
4. Kim HC. Epidemiology of cardiovascular disease and its risk factors in Korea. Glob Health Med 2021; 3(3):134-141. doi: 10.35772/ghm.2021.01008
5. Kyriakos G, Quiles-Sanchez LV, Garmpi A, Farmaki P, Kyre K, Savvanis S, Antoniou VK, Memi E. SGLT2 inhibitors and cardiovascular outcomes: Do they differ or there is a class effect? New insights from the EMPA-REG OUTCOME trial and the CVD-REAL Study. Curr Cardiol Rev 2020; 16(4):258-265. doi: 10.2174/1573403X15666190730094215
6. Mc-Murray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, Boer RAD, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, De-Mets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM. DAPA-HF trial committees and investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381(21):1995-2008. doi: 10.1056/NEJMoa1911303
7. Osher E, Stern N. Diastolic pressure in type 2 diabetes: Can target systolic pressure be reached without "diastolic hypotension"? Diabetes Care 2008; 31 Suppl 2:S249-S254. doi: 10.2337/dc08-s262
8. Post A, Groothof D, Eisenga MF, Bakker SJL. Sodium–Glucose co transporter 2 inhibitors and kidney outcomes: True Reno protection, loss of muscle mass or both? J Clin Med 2020; 9(5):1603. doi: 10.3390/jcm9051603

9. Raz I, Cernea S, Cahn A. SGLT2 inhibitors for primary prevention of cardiovascular events. J Diabetes 2020; 12(1):5-7. doi: 10.1111/1753-0407.13004
10. Shah A, Parthasarathi D, Sarkar D, Saha CG. A comparative study of body mass index (BMI) in diabetic and non-diabetic individuals in Nepalese population. Kathmandu Univ Med J 2006; 4(1):4-10
11. Shi FH, Li H, Shen L, Xu L, Ge H, Gu ZC, Lin HW, Pu J. Beneficial effect of sodium-glucose co-transporter 2 inhibitors on left ventricular function. J Clin Endocrinol Metab 2022; 107(4):1191-1203. doi: 10.1210/clinem/dgab834
12. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, Mc-Guire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393(10166):31-39. doi: 10.1016/S0140-6736(18)32590-X
13. Zhang DP, Xu L, Wang LF, Wang HJ, Jiang F. Effects of anti-diabetic drugs on left ventricular function/dysfunction: A systematic review and network meta-analysis. Cardiovasc Diabetol 2020; 19(1):10. doi: 10.1186/s12933-020-0987-x
14. Zheng H, Liu M, Li S, Shi Q, Zhang S, Zhou Y, Su N. Sodium-Glucose co-transporter-2 inhibitors in non-diabetic adults with overweight or obesity: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2021; 12:706914. doi: 10.3389/fendo.2021.706914