Section: Miscellaneous

Original Research Article

ASSOCIATION OF SGLT2 INHIBITOR USE WITH CARDIAC REMODELLING AND RENAL OUTCOMES IN TYPE 2 DIABETES MELLITUS WITH HEART FAILURE: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Patients with type 2 diabetes mellitus and heart failure are at high risk of adverse cardiac remodelling and renal deterioration. This study evaluated the association of SGLT2 inhibitor use with cardiac remodelling and renal outcomes.

Materials and Methods: This prospective cohort study included 100 patients with type 2 diabetes mellitus and heart failure followed for two years at Prasad Institute of Medical Sciences, Lucknow. Patients were grouped as SGLT2 inhibitor users or non-users. Echocardiographic, renal, biochemical, and heart failure-related clinical outcomes were compared between groups.

Results: SGLT2 inhibitors were used in 58 patients, while 42 were non-users. Over 24 months, SGLT2 inhibitor users showed greater improvement in LVEF than non-users (+4.1% vs +0.6%) and greater reductions in LVEDD, LVEDV, LVESV, LVMI, and E/e′ ratio. Diastolic dysfunction improvement and favourable cardiac response were more frequent among users. Renal outcomes also favoured SGLT2 inhibitor users, with relative preservation of eGFR, smaller creatinine increase, and reduction in UACR. NYHA class improvement was more frequent among users, while heart failure hospitalization and treatment escalation were lower. SGLT2 inhibitor use remained independently associated with favourable composite cardiorenal response after adjustment for baseline LVEF, eGFR, UACR, and HbA1c.

Conclusion: SGLT2 inhibitor use was associated with favourable cardiac remodelling, renal preservation, and improved heart failure outcomes in patients with type 2 diabetes mellitus and heart failure.

Keywords: SGLT2 inhibitors; type 2 diabetes mellitus; heart failure; cardiac remodelling; renal outcomes.

INTRODUCTION

Heart failure is one of the most clinically important consequences of type 2 diabetes mellitus (T2DM), which is strongly associated with cardiovascular and renal complications. T2DM and heart failure share common metabolic, hemodynamic, inflammatory and renal abnormalities that promote adverse cardiac remodelling and progression of chronic kidney disease. This cardiorenal interaction contributes to morbidity, re-hospitalization and long-term mortality, and therapies with combined cardiovascular and renal benefit are particularly relevant in this population.

Sodium–glucose cotransporter 2 inhibitors were originally designed as glucose-lowering drugs, but they have been shown to have effects beyond glycemic control in large cardiovascular outcome trials. Empagliflozin was shown to significantly lower major cardiovascular events, cardiovascular mortality, all-cause mortality, and hospitalization for heart failure in patients with T2DM and established cardiovascular disease in the EMPA-REG OUTCOME trial.[1] A follow-up renal study of the same trial revealed that empagliflozin was also

linked to reduced progression of kidney disease in T2DM.[2] These findings changed the clinical relevance of SGLT2 inhibitors from antidiabetic therapy to cardiorenal protective therapy.

This effect of SGLT2 inhibitors in established heart failure was subsequently validated in dedicated heart failure trials. In DAPA-HF, dapagliflozin reduced worsening heart failure and cardiovascular death among patients with heart failure with reduced ejection fraction, irrespective of diabetes status.[3] Likewise, the EMPEROR-Reduced trial demonstrated that empagliflozin lowered the composite endpoint of cardiovascular death or hospitalization for heart failure and also provided renal benefit in patients with reduced ejection fraction heart failure.[4] These trials have proven that SGLT2 inhibition is a key therapeutic approach in heart failure patients, including those with T2DM.

Renal protection is especially important in patients with T2DM and heart failure, as a reduction in renal function is associated with worsening volume overload, reduced ability to optimize heart failure therapy, and higher adverse outcomes. In the DAPA-CKD trial, dapagliflozin lowered the risk of persistent kidney function decline, end-stage kidney disease, or renal/cardiovascular death in patients with chronic kidney disease, with or without diabetes.[5] These data can be used to assess renal trajectories (eGFR, serum creatinine, and albuminuria) in patients treated with SGLT2 inhibitors.

In addition to clinical outcomes, there is increasing interest in whether SGLT2 inhibitors have a direct effect on cardiac structure and function. Cardiac remodelling, which is manifested by alterations in left ventricular mass, ventricular volumes, ejection fraction, and diastolic parameters, is a major factor in the progression of heart failure. In the EMPA-HEART CardioLink-6 randomized trial, empagliflozin was shown to significantly decrease left ventricular mass index in patients with T2DM and coronary artery disease after 6 months.[6] In SUGAR-DM-HF, empagliflozin decreased left ventricular volumes in patients with HFrEF and T2DM or prediabetes, indicating potential reverse remodelling as a mechanism for better outcomes.[7]

Recent prospective remodelling data have further supported this mechanistic link. The DAPA-MODA study demonstrated that dapagliflozin therapy resulted in improvement in cardiac remodelling parameters in patients with chronic heart failure, including favourable changes in atrial and ventricular remodelling over follow-up.[8] But, there is still a lack of real-world prospective data from Indian tertiary-care centers, especially in patients with T2DM and heart failure where both cardiac remodelling and renal outcomes are evaluated simultaneously.

Thus, the present prospective cohort study was conducted at Prasad Institute of Medical Sciences, Lucknow, for two years in 100 patients to assess the relationship of SGLT2 inhibitors with cardiac remodelling and renal outcomes in patients with T2DM and heart failure. This study could offer real-world evidence of the cardiorenal effects of SGLT2 inhibitors in this high-risk population by evaluating echocardiographic remodelling parameters, renal function, and clinical heart failure outcomes.

Objectives

1. To evaluate changes in echocardiographic markers of cardiac remodelling among patients with type 2 diabetes mellitus and heart failure receiving SGLT2 inhibitors.
2. To compare renal outcomes between SGLT2 inhibitor users and non-users using eGFR, serum creatinine, and urinary albumin/protein parameters.
3. To assess heart failure-related clinical outcomes, including NYHA functional class, hospitalization, and treatment escalation.
4. To identify clinical and biochemical predictors of favourable cardiorenal response in patients with type 2 diabetes mellitus and heart failure.

MATERIALS AND METHODS

Study design and setting: This prospective cohort study was conducted at Prasad Institute of Medical Sciences, Lucknow, over a period of two years. Patients with type 2 diabetes mellitus and heart failure were followed to evaluate the association of SGLT2 inhibitor use with cardiac remodelling, renal outcomes, and heart failure-related clinical outcomes.

Study population: A total of 100 patients with type 2 diabetes mellitus and established heart failure were included. Patients were enrolled if they had documented type 2 diabetes mellitus, clinically diagnosed heart failure, baseline echocardiographic assessment, baseline renal function parameters, and available follow-up data at 24 months.

Patients with type 1 diabetes mellitus, acute decompensated heart failure at enrolment, end-stage renal disease, dialysis dependence, severe valvular heart disease requiring intervention, recent acute coronary syndrome, active malignancy, incomplete baseline data, or loss to follow-up were excluded.

Exposure classification: Patients were classified into two groups according to SGLT2 inhibitor use during routine clinical care. Patients receiving any SGLT2 inhibitor as part of their diabetes or heart failure management were included in the SGLT2 inhibitor group. Patients managed without SGLT2 inhibitors formed the non-user group. Background heart failure therapy, including ACE inhibitor, ARB, ARNI, beta-blocker, diuretic, mineralocorticoid receptor antagonist, and other antidiabetic therapy, was continued as clinically indicated.

Data collection: Baseline data included age, sex, residence, body mass index, duration of diabetes, heart failure phenotype, NYHA functional class, hypertension, coronary artery disease, chronic

kidney disease, HbA1c, renal function, albuminuria, and background heart failure medications.

Laboratory and biochemical parameters included serum creatinine, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, HbA1c, and NT-proBNP. eGFR was calculated using standard creatinine-based estimation. UACR was assessed using spot urine albumin-to-creatinine ratio.

Echocardiographic assessment: Transthoracic echocardiography was performed at baseline and at 24 months. Parameters assessed included left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular mass index, E/e′ ratio, and diastolic dysfunction grade.

Cardiac remodelling was assessed by comparing changes in these echocardiographic parameters from baseline to 24 months between SGLT2 inhibitor users and non-users.

Outcome measures: The primary outcome was change in cardiac remodelling parameters over 24 months, including LVEF, LVEDD, LVEDV, LVESV, LVMI, E/e′ ratio, and diastolic dysfunction grade.

Secondary outcomes included changes in renal parameters, including eGFR, serum creatinine, and UACR; biochemical changes in HbA1c and NT-proBNP; and heart failure-related clinical outcomes, including NYHA class improvement, heart failure hospitalization, and treatment escalation.

Favourable cardiac response was defined as improvement in left ventricular systolic or structural parameters, including increase in LVEF and/or reduction in LV volumes or LV mass, with no worsening of heart failure status. Favourable renal response was defined as stabilization of eGFR with no clinically significant renal decline and improvement or non-progression of albuminuria. Composite favourable cardiorenal response was defined as the presence of both favourable cardiac and favourable renal response during follow-up.

Statistical analysis: Continuous variables were expressed as mean ± standard deviation or median with interquartile range, and categorical variables as frequency and percentage. Baseline characteristics were compared between SGLT2 inhibitor users and non-users using t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Changes from baseline to 24 months were compared between groups for echocardiographic, renal, and biochemical parameters. Odds ratios with 95% confidence intervals were calculated for clinical outcomes. Multivariable logistic regression was used to assess the independent association of SGLT2 inhibitor use with favourable composite cardiorenal response after adjustment for baseline LVEF, eGFR, UACR, and HbA1c. A p-value <0.05 was considered statistically significant.

Ethical Considerations: The study was approved by the Institutional Ethics Committee of Prasad Institute of Medical Sciences, Lucknow. Written informed consent was obtained from all participants.

RESULTS

Study cohort and baseline characteristics: A total of 100 patients with type 2 diabetes mellitus and heart failure were followed for two years. SGLT2 inhibitors were used in 58 (58.0%) patients, while 42 (42.0%) patients were managed without SGLT2 inhibitors. Baseline characteristics are summarized in [Table 1]. The groups were broadly comparable with respect to demographic profile, heart failure phenotype, baseline functional class, and background heart failure therapy. Baseline renal function was more favorable among SGLT2 inhibitor users, whereas CKD was more frequent among non-users.

Table 1: Baseline characteristics according to SGLT2 inhibitor use

Characteristic	SGLT2 users (n=58)	Non-users (n=42)	Test statistic	p-value
Age, years	60.2 ± 8.6	63.7 ± 8.6	t(89.0)=-1.99	0.050
Male sex	36 (62.1%)	27 (64.3%)	$\chi^2(1)=0.05$	0.821
Rural residence	23 (39.7%)	24 (57.1%)	$\chi^2(1)=2.99$	0.084
BMI, kg/m²	27.2 ± 3.6	27.3 ± 2.9	t(96.4)=-0.20	0.844
Diabetes duration, years	9.2 ± 3.5	10.7 ± 5.6	t(64.7)=-1.46	0.149
HFrEF phenotype	44 (75.9%)	27 (64.3%)	$\chi^2(1)=1.59$	0.208
NYHA class III/IV	28 (48.3%)	23 (54.8%)	$\chi^2(1)=0.41$	0.522
Hypertension	48 (82.8%)	37 (88.1%)	$\chi^2(1)=0.54$	0.461
Coronary artery disease	26 (44.8%)	22 (52.4%)	$\chi^2(1)=0.56$	0.456
CKD present	31 (53.4%)	32 (76.2%)	$\chi^2(1)=5.41$	0.020
Baseline HbA1c, %	8.7 ± 0.9	8.4 ± 0.8	t(92.9)=2.04	0.045
Baseline LVEF, %	37.4 ± 8.2	40.9 ± 9.1	t(82.8)=-1.94	0.055
Baseline eGFR, mL/min/1.73 m²	65.0 ± 14.9	56.7 ± 17.4	t(80.0)=2.53	0.013
Baseline creatinine, mg/dL	1.21 ± 0.42	1.47 ± 0.49	t(79.8)=-2.73	0.008
Baseline UACR, mg/g	60.4 (18.7–169.4)	108.7 (29.0–300.0)	U=1024.5	0.178
ACEi/ARB/ARNI use	48 (82.8%)	29 (69.0%)	$\chi^2(1)=2.59$	0.108
Beta-blocker use	49 (84.5%)	34 (81.0%)	$\chi^2(1)=0.22$	0.643

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as n (%). Between-group comparisons were performed using Welch's t-test for normally distributed continuous variables, Mann–Whitney U test for skewed continuous variables, and chi-square test for categorical

variables. CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; UACR, urinary albumin-to-creatinine ratio.

Cardiac remodeling outcomes: Changes in echocardiographic parameters over the two-year follow-up are presented in [Table 2]. SGLT2 inhibitor users demonstrated a more favorable remodeling pattern, with greater improvement in LVEF and larger reductions in ventricular dimensions, volumes, LVMI, and E/e′ ratio compared with non-users. Diastolic dysfunction grade improvement and favorable cardiac response were also more frequent among SGLT2 inhibitor users.

Table 2: Echocardiographic remodeling outcomes over 24 months

Parameter	SGLT2 baseline	SGLT2 24 months	SGLT2 change	Non-user baseline	Non-user 24 months	Non-user change	Test statistic (change comparison)	p-value
LVEF, %	37.4 ± 8.2	41.5 ± 8.8	4.1 ± 3.5	40.9 ± 9.1	41.5 ± 10.0	0.6 ± 3.1	t(93.9)=5.36	<0.001
LVEDD, mm	56.0 ± 5.8	54.0 ± 5.7	-2.0 ± 1.8	56.4 ± 6.2	56.3 ± 7.0	-0.2 ± 2.5	t(69.1)=-3.98	<0.001
LVEDV, mL	156.0 ± 29.9	143.9 ± 34.5	-12.1 ± 13.7	151.2 ± 32.3	151.4 ± 35.9	0.2 ± 13.6	t(88.9)=-4.44	<0.001
LVESV, mL	98.1 ± 28.8	85.6 ± 32.0	-12.5 ± 12.7	91.0 ± 28.9	92.5 ± 32.8	1.5 ± 11.7	t(92.2)=-5.68	<0.001
LVMI, g/m²	119.8 ± 18.6	110.7 ± 20.6	-9.1 ± 6.9	121.2 ± 19.4	121.7 ± 19.4	0.5 ± 9.7	t(69.7)=-5.54	<0.001
E/e′ ratio	14.5 ± 3.8	12.4 ± 4.4	-2.2 ± 1.9	14.9 ± 3.8	14.7 ± 4.7	-0.2 ± 2.3	t(78.1)=-4.58	<0.001
Diastolic dysfunction grade improved	—	—	21 (36.2%)	—	—	7 (16.7%)	$\chi^2(1)=4.61$	0.032
Favorable cardiac response	—	—	45 (77.6%)	—	—	10 (23.8%)	$\chi^2(1)=28.46$	<0.001

Between-group comparisons are based on change from baseline to 24 months. Continuous variables are presented as mean ± SD; categorical outcomes are presented as n (%). LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index.

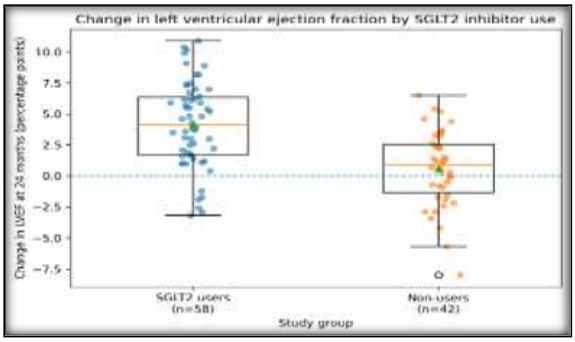

Figure 1: Change in left ventricular ejection fraction at 24 months according to SGLT2 inhibitor use.

Box-and-point plot showing the distribution of LVEF change from baseline to 24 months in SGLT2 inhibitor users and non-users. The horizontal dashed line represents no change from baseline.

Renal and biochemical outcomes

Renal and biochemical outcomes are summarized in [Table 3]. Over two years, eGFR remained relatively stable among SGLT2 inhibitor users but declined among non-users. Creatinine increased more among non-users, while UACR decreased among SGLT2 inhibitor users and increased among non-users. Improvements in HbA1c and NT-proBNP were also greater in the SGLT2 inhibitor group.

Table 3: Renal and biochemical outcomes over 24 months

Parameter	SGLT2 baseline	SGLT2 24 months	SGLT2 change	Non-user baseline	Non-user 24 months	Non-user change	Test statistic (change comparison)	p-value
eGFR, mL/min/1.73 m²	65.0 ± 14.9	64.3 ± 14.6	-0.7 ± 5.0	56.7 ± 17.4	49.0 ± 18.4	-7.6 ± 5.1	t(87.6)=6.72	<0.001
Serum creatinine, mg/dL	1.21 ± 0.42	1.23 ± 0.36	0.02 ± 0.15	1.47 ± 0.49	1.73 ± 0.71	0.26 ± 0.32	t(53.8)=-4.56	<0.001
UACR, mg/g	60.4 (18.7–169.4)	36.0 (16.5–127.8)	-18.6 (-68.0–-5.0)	108.7 (29.0–300.0)	132.1 (29.5–239.0)	7.1 (-5.8–42.6)	U=450.0	<0.001
UACR percentage change, %	—	—	-39.0 (-53.8–-12.6)	—	—	15.4 (-8.6–34.0)	U=314.5	<0.001
HbA1c, %	8.7 ± 0.9	7.9 ± 0.9	-0.8 ± 0.3	8.4 ± 0.8	8.1 ± 0.8	-0.3 ± 0.4	t(82.4)=-6.46	<0.001
NT-proBNP percentage	—	—	-31.8 (-39.7–-	—	—	-6.8 (-18.9–13.5)	U=699.0	<0.001

change, %			13.7)					
Favorable renal response	—	—	43 (74.1%)	—	—	5 (11.9%)	$\chi^2(1)=37.80$	<0.001

Between-group comparisons are based on change from baseline to 24 months. eGFR, creatinine, and HbA1c are reported as mean ± SD; UACR and percentage changes are reported as median (IQR). eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

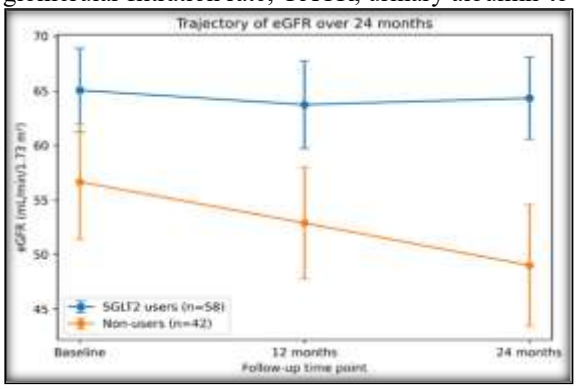

Figure 2: eGFR trajectory over 24 months according to SGLT2 inhibitor use.

Line plot showing mean eGFR at baseline, 12 months, and 24 months in SGLT2 inhibitor users and non-users. Error bars represent 95% confidence intervals.

Heart failure-related clinical outcomes: Heart failure-related clinical outcomes are shown in Table 4. NYHA class improvement was more frequent among SGLT2 inhibitor users, whereas heart failure hospitalization and treatment escalation were less frequent. A composite favorable cardiorenal response was observed in 29 (50.0%) SGLT2 inhibitor users compared with 2 (4.8%) non-users.

Table 4: Heart failure-related clinical outcomes and response endpoints

Outcome	SGLT2 users (n=58)	Non-users (n=42)	Effect estimate	Test statistic	p-value
NYHA class improvement	40 (69.0%)	14 (33.3%)	OR=4.44 (1.90–10.39)	$\chi^2(1)=12.45$	<0.001
Heart failure hospitalization	8 (13.8%)	17 (40.5%)	OR=0.24 (0.09–0.62)	$\chi^2(1)=9.25$	0.002
Treatment escalation	9 (15.5%)	19 (45.2%)	OR=0.22 (0.09–0.57)	$\chi^2(1)=10.67$	0.001
Favorable cardiac response	45 (77.6%)	10 (23.8%)	OR=11.08 (4.32–28.38)	$\chi^2(1)=28.46$	<0.001
Favorable renal response	43 (74.1%)	5 (11.9%)	OR=21.21 (7.04–63.95)	$\chi^2(1)=37.80$	<0.001
Composite favorable cardiorenal response	29 (50.0%)	2 (4.8%)	OR=20.00 (4.42–90.58)	$\chi^2(1)=23.31$	<0.001

Effect estimates are odds ratios for the outcome among SGLT2 inhibitor users compared with non-users. Values are presented as n (%).

Factors associated with favorable cardiorenal response: Clinical and biochemical factors associated with favorable composite cardiorenal response are presented in [Table 5]. After adjustment for baseline LVEF, eGFR, albuminuria, and HbA1c, SGLT2 inhibitor use remained independently associated with a higher likelihood of favorable composite response.

Table 5: Multivariable logistic regression for favorable composite cardiorenal response

Variable	Adjusted OR (95% CI)	Test statistic	p-value
SGLT2 inhibitor use	23.38 (4.80–113.94)	z=3.90	<0.001
Baseline LVEF, per 5% increase	1.03 (0.76–1.40)	z=0.22	0.826
Baseline eGFR, per 10 mL/min/1.73 m² increase	1.05 (0.76–1.46)	z=0.29	0.774
Baseline UACR, per ln-unit increase	1.42 (0.95–2.13)	z=1.71	0.088
Baseline HbA1c, per 1% increase	1.08 (0.60–1.92)	z=0.25	0.805

The dependent variable was favorable composite cardiorenal response. OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

DISCUSSION

In this prospective cohort of 100 patients with type 2 diabetes mellitus and heart failure, SGLT2 inhibitor use was linked to better cardiac remodelling, renal outcomes, and heart failure-related clinical outcomes over 24 months. SGLT2 inhibitor users experienced more improvement in LVEF (+4.1% vs +0.6%), more reduction in LVEDD, LVEDV, LVESV, LVMI, and E/e′ ratio, and more frequent favourable cardiac response compared with non-users. Renal outcomes were also better in SGLT2 inhibitor users, including relative preservation of eGFR, lower progression of creatinine, reduction in UACR, and higher rate of favourable renal response. In the clinic, SGLT2 inhibitor users experienced greater NYHA class improvement and fewer heart failure hospitalizations and treatment escalations. In adjusted analysis, SGLT2 inhibitor use was independently associated with favourable composite cardiorenal response.

The cardiovascular outcome pattern seen in the current study is similar to that seen in large diabetes cardiovascular outcome trials. The CANVAS Program, which comprised 10,142 patients with type 2 diabetes and high cardiovascular risk, demonstrated that canagliflozin lowered major cardiovascular events and exhibited favourable renal and heart failure-related signals.[9] This is consistent with our results that SGLT2 inhibitor use was linked to reduced hospitalizations for heart failure and improved overall cardiorenal response in a high-risk diabetic heart failure population. Our study, however, adds to the clinical outcome signal by showing parallel echocardiographic improvement, specifically in LVEF, LV volumes, LVMI, and filling pressure surrogate measures.

DECLARE–TIMI 58 is important as a comparator study because it included a wide spectrum of type 2 diabetes patients, including those with known atherosclerotic cardiovascular disease or multiple risk factors. Dapagliflozin did not significantly lower major adverse cardiovascular events, but did lower the composite of cardiovascular death or hospitalization for heart failure, primarily due to fewer hospitalizations for heart failure.[10] This is consistent with our study, which found that SGLT2 inhibitor users had significantly reduced heart failure hospitalization compared with non-users (13.8% vs 40.5%). The uniformity of the trial and real-world cohort data indicates that the heart failure benefit of SGLT2 inhibitors could be clinically relevant even with diverse cardiovascular risk profiles at baseline.

The VERTIS CV trial with ertugliflozin provides additional context. Ertugliflozin was non-inferior to placebo for major cardiovascular events in patients with type 2 diabetes and known cardiovascular disease, and the composite outcome of cardiovascular death or heart failure hospitalization was numerically but not statistically inferior.[11] By contrast, the current cohort showed greater clinical heart failure outcomes, such as reduced hospitalization and treatment escalation in SGLT2 inhibitor users. This difference could be due to the fact that our study population was specifically patients with established heart failure, where the clinical effects of SGLT2 inhibition might be more evident than in larger diabetes cardiovascular outcome trials.

Renal protection was a major finding in the present study. After 24 months, eGFR was virtually unchanged in SGLT2 inhibitor users but significantly reduced in non-users, and UACR was reduced in SGLT2 inhibitor users and increased in non-users. This is in line with the CREDENCE trial, in which canagliflozin reduced the risk of kidney failure and cardiovascular events in patients with type 2 diabetes and kidney disease over a median follow-up of 2.62 years.[12] The renal trajectory in our study is particularly relevant because baseline CKD was common, and non-users had worse baseline renal function. Even with this imbalance, SGLT2 inhibitor use was still independently associated with a favourable composite cardiorenal response after adjusting for baseline eGFR and albuminuria.

This renal finding is also confirmed by EMPA-KIDNEY, which assessed empagliflozin in a large chronic kidney disease population and demonstrated reduced risk of progression of kidney disease or cardiovascular death.[13] The decrease in UACR in the current cohort of SGLT2 inhibitor users and the maintenance of eGFR align with the albuminuria-lowering and kidney-protective effects seen in the large renal outcome trials. These findings are clinically relevant in diabetic heart failure as poor renal function may exacerbate congestion, restrict heart failure drug optimization, and raise the risk of hospitalization.

Phenotype diversity of heart failure should also be taken into account. While the majority of patients in our cohort were HFrEF, there was a proportion of patients with non-HFrEF phenotypes. EMPEROR-Preserved showed that empagliflozin lowered the risk of cardiovascular death or hospitalization for heart failure in patients with preserved ejection fraction.[14] In a similar fashion, DELIVER demonstrated that dapagliflozin decreased the risk of worsening heart failure or cardiovascular death in patients with mildly reduced or preserved ejection fraction.[15] These trials also help to validate the applicability of SGLT2 inhibitors throughout the heart failure spectrum and reinforce the relevance of our findings, which showed clinical improvement not only in terms of hospitalization reduction, but also in terms of NYHA class and treatment escalation.

The observed improvement in NT-proBNP and functional status in our study is similar to that seen in smaller mechanistic and patient-centered heart failure trials. DEFINE-HF demonstrated that dapagliflozin did not significantly alter mean NT-proBNP after 12 weeks, but did increase the percentage of patients with clinically meaningful improvement in heart failure health status or natriuretic peptide response.[16] In our cohort, SGLT2 inhibitor users experienced greater median percent decrease in NT-proBNP and more frequent NYHA improvement. This indicates that in the real world, biomarker and remodelling trends can be favourable and symptomatic improvement can occur, especially with a longer follow-up of 24 months.

PRESERVED-HF also supports the patient-centered relevance of SGLT2 inhibition. In that multicenter randomized trial, dapagliflozin was found to benefit symptoms, physical limitations, and exercise function in patients with HFpEF, regardless of diabetes status.[17] While our study did not employ a specific health-status scale like KCCQ, the direction of the greater NYHA class improvement among SGLT2 inhibitor users is consistent with these findings. The decrease in E/e′ ratio and improvement in diastolic dysfunction grade in our

cohort could offer an echocardiographic mechanism for the improvement in functional status, particularly in those with higher filling pressures.

The major advantage of this study is the comprehensive two-year evaluation of echocardiographic remodelling, renal function, biochemical markers, and clinical outcomes. Beyond glycemic control, SGLT2 inhibitor users demonstrated favourable changes in LV volumes, LV mass, eGFR, UACR, NT-proBNP, and NYHA status, indicating cardiorenal benefit.

There are limitations to this study. This is a non-randomized prospective cohort study, and there may be residual confounding, as baseline renal function was better in the SGLT2 inhibitor group and CKD was more prevalent in the non-SGLT2 inhibitor group. Outcomes may also have been affected by differences in drug selection, compliance, concurrent treatment, and echocardiographic measurements. However, SGLT2 inhibitor use was still independently associated with favourable composite cardiorenal response after adjusting for baseline LVEF, eGFR, UACR, and HbA1c.

In conclusion, SGLT2 inhibitors were associated with beneficial cardiac remodelling, renal protection, functional improvement, and reduced heart failure hospitalizations over 2 years, highlighting their real-world cardiorenal benefits in patients with type 2 diabetes mellitus and heart failure.

CONCLUSION

SGLT2 inhibitor use was associated with favourable cardiac remodelling, better renal preservation, improved NYHA functional status, and fewer heart failure hospitalizations over two years in patients with type 2 diabetes mellitus and heart failure. These findings support the real-world cardiorenal benefit of SGLT2 inhibitors in this high-risk population.

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