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Research Article

Safety and Efficacy of Remogliflozin in Patients with Type 2 Diabetes Mellitus Hospitalized For Acute Decompensated Heart Failure (RemoSafe AHF)

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Abstract

Background: Acute Decompensated Heart Failure (ADHF) is one of the leading causes of hospital admissions world-wide, with a post-discharge mortality and re-hospitalization risk as high as 20-30% within the first 3 to 6 months. This Investigator initiated study was aimed to find out the safety and efficacy of Remogliflozin in patients with type 2 diabetes mellitus (T2DM) admitted for ADHF.

Methods: In this open-label, parallel-group study, ADHF patients having N-terminal pro-brain natriuretic peptide (NT-proBNP) >1400 pg/ml and Ejection Fraction (EF) < 40% were included for a follow-up duration of 12 weeks. Among 35 randomized patients who were prospectively analysed, 17 patients were allocated to Remogliflozin 100 mg BID along with the conventional therapy group and 18 patients to the conventional therapy group which also included other SGLT2i (Dapagliflozin/Empagliflozin).

Results: All the baseline demographic, glycaemic, cardiac, and renal parameters were comparable between the two groups (P >0.05). There was significant improvement in mean NT-proBNP level in both Remogliflozin and conventional therapy groups, however, no significant difference was seen between the two groups. The mean NT-proBNP (pg/ml) level improved from 3863.76 ± 2533.00 at baseline to 1802.31 ± 1138.21 at week 12 in Remogliflozin group (P = 0.0031) and from 4626.46 ± 3458.86 at baseline to 2564.94 ± 2736.90 at week 12 in conventional therapy group (P = 0.0479). The echocardiography results showed that the Left Ventricular Ejection Fraction (LVEF) % improved from 29.8% at baseline to 33.2% at week 12 and LV mass improved from 145.2gm at baseline to 143.6 gm at week 12 in the Remogliflozin group whereas LVEF improved from 29.8 % at baseline to 36.4 % at week 12 and LV mass improved from 154.1gm at baseline to 153.2gm at week 12 in conventional therapy group. The mean eGFR (ml/min/1.73m2) was 68.53 ± 37.41 at baseline and 64.35 ± 37.23 at week 12 in Remogliflozin group and 66.06 ± 30.20 at baseline and 60.54 ± 29.84 at week 12 in the conventional therapy group. Similarly, there was a significant diuretic response weight reduction in both groups. There was also similar improvement in heart rate, blood pressure reduction (systolic/

diastolic), and improvement in glycemic parameters (Fasting Blood Sugar and Post Prandial Blood Sugar) over week 12 of treatment in both groups. Also, no Serious Adverse Event (SAE), in-hospital worsening Heart Failure (HF), re-hospitalization for HF, or death till the study duration was reported in either group.

Conclusions: Initiation of Remogliflozin in ADHF patients did not increase the incidence of acute kidney injury, hypotension or hypoglycaemia. NT proBNP levels improved significantly in both groups but the percentage decline observed with Remogliflozin was larger than conventional therapy group both at discharge and at week 12. Hence, in patient with acute decompensated failure and reduced ejection fraction (HFrEF) Remogliflozin was well tolerated without any significant adverse effects.

Introduction

Type 2 Diabetes Mellitus (T2DM) has reached epidemic proportions worldwide, projected to impact over 592 million people worldwide by 2035 [1]. As per the recently published ICMR-INDIAB 17 study, the prevalence of diabetes and prediabetes in India is 11.4% and 15.3% respectively [2]. Adding complexity, adults with diabetes face a 2 to 3-fold higher chance of getting heart attacks, complicating the intricate association between HF and T2DM [3,4]. Acute Decompensated Heart Failure (ADHF) is a sudden worsening of symptoms in individuals diagnosed with Heart Failure (HF), marked by a rapid onset of breathlessness, fatigue, and fluid retention [5]. HF presents a major health challenge across the globe, with approximately 64.3 million individuals affected globally [6]. In India, where HF prevalence is estimated at 1%, global registries, and local studies reveal concerning trends, with higher rates of mortality and re-hospitalization among individuals experiencing ADHF, compounding the burden of HF. Nearly one in five individuals with Acute Heart Failure (AHF) experience readmission within 30 days of discharge, and over three in five patients face readmission within a year [7]. The one-year mortality rate varies between 10% and 30%, with the greatest risk observed within the first 30 days following the initial hospitalization [8-10]. Epidemiological data reveals a prevalent coexistence of diabetes in HF cohorts, ranging from 10% to 47%, with rates exceeding 40% in hospitalized HF patients [11]. The prognosis for individuals with ADHF and diabetes is poor with a high rate of re-hospitalization and mortality, demanding targeted and timely interventions to improve outcomes. Delayed treatment initiation in these patients can lead to rapid deterioration, therefore, prompt and effective therapeutic strategies are required.

Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors have demonstrated promising results in individuals with HF and kidney disease, regardless of whether diabetes is present or not [12]. By decreasing the circulating levels of glucose, SGLT2 inhibitors stimulate lipolysis in adipose tissue, leading to an elevation in ketone body formation. Ketone bodies are a favourable source of energy due to the ease with which they can be converted to acetyl Co-A, a process that is more efficient compared to the conversion of fatty acids or glucose to acetyl-CoA. Recent studies have reported that SGLT2 inhibitors benefit patients with cardiovascular disease and reduce hospitalization due to HF-related causes [12,13].

Remogliflozin etabonate is the prodrug form of remogliflozin, which is a potent and selective SGLT2 inhibitor. Unlike other SGLT2 inhibitors, like dapagliflozin, canagliflozin, and empagliflozin, remogliflozin has a shorter elimination half-life [14]. Consequently, it requires to be administered twice daily (BID) to achieve sustained glucose control over 24 hours [8]. Remogliflozin offers several advantages, including a potentially improved safety profile and a rapid onset of action, which can be important for conditions like ADHF. A short-term comparative RCT study between remogliflozin and dapagliflozin indicates that remogliflozin exhibits comparable efficacy alongside a similar adverse effect profile in patients with T2DM [1].

The use of SGLT2 inhibitors in chronic HF patients is now well established and a recent study has demonstrated the use of empagliflozin in ADHF patients was safe, with beneficial effects on the combined risk of worsening heart failure, re-hospitalization, and death [15]. However, no study has explored the effectiveness of Remogliflozin in patients of T2DM with ADHF. Hence, it was of interest to study the role of Remogliflozin in management of T2DM among patients hospitalized for ADHF.

Methods

Study design and settings

A randomized, Investigator initiated, open-label, parallel-group study was conducted at Spandan Heart Institute and Research Centre in Nagpur, India, following the study protocol, ethical principles of the Declaration of Helsinki, International Council of Harmonization Good Clinical Practice (GCP) guidelines, and all relevant local regulations. Patients admitted to the hospital with acute HF and meeting eligibility criteria were randomized to receive Remogliflozin 100 gm BID in addition to conventional therapy for a period of 12 weeks (Group A) or only conventional therapy with other SGLT2i (Group B) and administered at least one concomitant medication. The concomitant medications mostly included ACE inhibitors, Angiotensin Receptor Blockers (ARBs), Angiotensin Receptor Neprilysin Inhibitors (ARNI), Beta-Blockers

(BB), Calcium Channel Blockers (CCB), Mineralocorticoid Receptor Antagonists (MRA), diuretics, digoxin, long-acting nitrates, statins, antiplatelets, anticoagulants, amiodarone, anti-diabetics including Dapagliflozin and Empagliflozin and a few non-cardiovascular medications. Patients were subjected to follow-up evaluations at 1 month and 3 months post-discharge.

Group A: Remogliflozin on top of conventional therapy (BB, ACEi, ARB, ARNI, MRA, Diuretics)

Group B: Conventional therapy (BB, ACEi, ARB, ARNI, MRA, Diuretics), and oral hypoglycaemic agents including Dapagliflozin or Empagliflozin.

Eligibility criteria

Patients of both genders aged ≥18 years with T2DM with plasma glucose levels between 120 and 350 mg/dl, irrespective of their HbA1c level, upon admission to the hospital for acute HF, were enrolled in the study. Patients also required an NT-proBNP level of 1,400 pg/ml with sinus rhythm or, for those with atrial fibrillation, ≥ 2,000 pg/ml. Additionally, they must not have been exposed to SGLT2 inhibitors in the previous 30 days. Baseline assessment comprised complete hemograms, liver function tests, serum levels of urea and creatinine, sodium, potassium, NT-proBNP, insulin, glucose levels (fasting, random, and postprandial), TSH, body weight, serum and urine levels of ketones, troponin, free fatty acids, and amino acid. Patients with active malignancy, cardiogenic shock, systolic blood pressure < 100 mmHg, ongoing therapy with inotropes, NT-proBNP > 10,000 pg/ml, serum creatinine > 3.0 mg/dl or EGFR < 30 ml/min/1.73m^2, signs of active infection, recent Covid-19 infection < 4 weeks, known significant primary valvular disease, acute HF caused by high rate AF or other significant arrhythmias, acute coronary syndrome diagnosed < 30 days before study initiation, troponin ≥ 5 times of ULN (upper limit of normality) were not included in the study.

Randomization was achieved by employing sequentially numbered sealed envelopes generated from a computer-generated randomization sequence. Study flow diagram is presented in **Figure 1.**

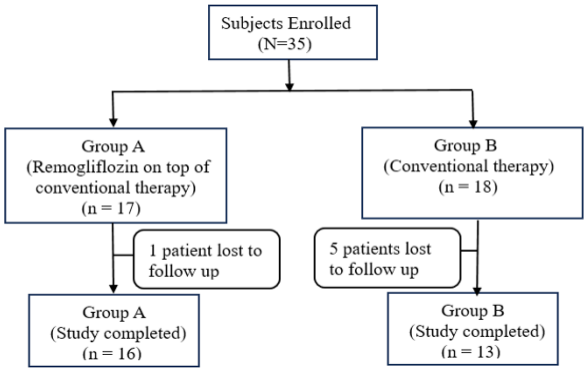

Figure 1: Study Flow Diagram.

Study outcome

The primary outcome was safety evaluation in terms of the total number of adverse events, adverse events needing treatment discontinuation, and in-hospital death.

The secondary outcome efficacy evaluation as the combination of an episode of the rate of worsening of HF/ re-hospitalization for HF or death at week 12. In addition, decrease in NT-proBNP levels upon discharge and week 12: diuretic response/ weight change at discharge, change in dyspnoea score, worsening renal function compared to baseline and at week 12.

Data Analysis

Data analysis was conducted by employing SPSS software (version 16). Descriptive statistics were applied to elucidate quantitative variables within the study. Paired t-tests were utilized to evaluate the mean difference in quantitative data pre- and post-treatment. A probability value < 0.05 was deemed statistically significant.

Results

The study enrolled a total of 35 participants. Among 35 patients, 17 were assigned to Remogliflozin on top of conventional therapy (Group A) and 18 were assigned to conventional with other SGLT2i therapy (Group B). The mean (±SD) age of patients in Group A was 64.29 ± 7.85 years, while in Group B, it was 61.44

± 11.14 years. Most of the patients in both groups were male, with 58.8% in Group A and 66.7% in Group B. The mean (±SD) BMI of patients was 24.86 ± 5.33 kg/m^2 in Group A and 25.64 ± 3.34 kg/m^2 in Group B. The clinicodemographic characteristics of the patients, as well as the therapies for heart failure, were evenly distributed between Group A and Group B. **Table 1** provides the detailed clinical and demographic characteristics of the participants.

Variables	Group A (N=17)	Group B (N=18)
	Mean ± SD	**Mean ± SD**
Age in year	64.29 ± 7.85	61.44 ± 11.14
Gender		
Male	10 (58.8%)	12 (66.7%)
Female	7 (41.2%)	6 (33.3)
BMI(Kg/m^2)	24.86 ± 5.33	25.64 ± 3.34
Weight (Kgs)	62.03 ± 12.81	66.39 ± 8.22
Haemoglobin (gm %)	11.60 ± 1.78	12.39 ± 2.38
Total leukocyte count (/µL)	8.31 ± 2.29	8.60 ± 2.63
Platelet count (/µL)	2.95 ± 0.83	2.95 ± 1.02
Creatinine (mg/dL)	1.12 ± 0.27	1.21 ± 0.31
eGFR (ml/min)	68.53 ± 37.41	66.06 ± 30.20
Sodium (mmol/L)	133.71 ± 5.58	131.00 ± 5.70
Potassium (mmol/L)	3.99 ± 0.89	4.40 ± 0.59
FBS (mg/dL)	169.88 ± 53.11	155.83 ± 45.22
RBS (mg/dL)	221.76 ± 99.23	198.22 ± 74.68
PPBS (mg/dL)	263.35 ± 106.79	225.35 ± 56.12
NT pro BNP (pg/mL)	3863.76 ± 2533.0	4626.46 ± 3458.86
Heart Rate (beats/min)	88.94 ± 15.35	95.67 ± 22.68
Blood Pressure		
Systolic (mmHg)	125.47 ± 19.43	126.44 ± 21.78
Diastolic (mmHg)	76.71 ± 10.44	79.56 ± 13.25
Dyspnoea Grade NYHA		
I	0	0
II	8	8
III	9	9
IV	0	1
Concomitant medication- Number (%)		
ACE inhibitor	7 (41.2)	4 (22.2)
ARB	7 (41.2)	6 (33.3)
BB	16 (94.1)	16 (88.9)
ARNi	10 (58.8)	17 (94.4)
CCB	1 (5.9)	3 (16.7)
Aldosterone antagonist	6 (35.3)	4 (22.2)
Diuretics	17 (100)	18 (100)

Digoxin	5 (29.4)	8 (44.4)
Nitrate	5 (29.4)	5 (27.8)
Statins	17 (100)	16 (88.9)
Antiplatelet	17 (100)	17 (94.4)
Anticoagulant	12 (70.6)	7 (38.9)
Amiodarone	1 (5.9)	7 (38.9)
Non-CV medication	9 (52.9)	13 (72.2)
Antidiabetic medication- no (%)		
Biguanides + Sulfonylurea	15 (88.2)	16 (88.9)
Alpha Glucosidase Inhibitors + Biguanides	1 (5.9)	1 (5.6)
DPP4 Inhibitors + Biguanides	3 (17.64)	4 (22.23)

Table 1: Clinico-demographic characteristics of participants.

Safety

During the study period, 1 adverse event (Hyperglycemia) with mild severity was reported in Remogliflozin group. The outcome of the event was reported as resolved without sequelae. Ketosis was not observed in either Remogliflozin on top of conventional therapy or conventional therapy group. There was also no significant drop in blood pressure (BP), eGFR or urine output in either group. No SAE, in-hospital worsening HF, re-hospitalization for HF or death till study duration were reported in either group.

Efficacy

In Group A, the mean NT-pro level was 3863.7 ± 2533.0 pg/ml at baseline. At week 12 follow-up visit, it decreased to 1802.3 ± 1138.2 pg/ml, and this difference was statistically significant (P=0.003). Similarly, in Group B, NT-pro levels decreased from 4626.4 ± 3458.8 pg/ml at baseline to 2564.9 ± 2736.9 pg/ml at week 12 (P=0.047). The details of the reduction of NT-proBNP level are presented in **Figure 2.** Though a major decline in NT-proBNP level was seen in both the groups, however, the percentage decrease in NT-proBNP was more pronounced in Group A. Specifically, Group A exhibited a 32.8% decrease in NT-proBNP levels at discharge and a further decrease to 53.3% at week 12. In contrast, Group B demonstrated a 23.2% drop in NT-proBNP at the time of discharge, with a subsequent reduction to 44.5% at week 12.

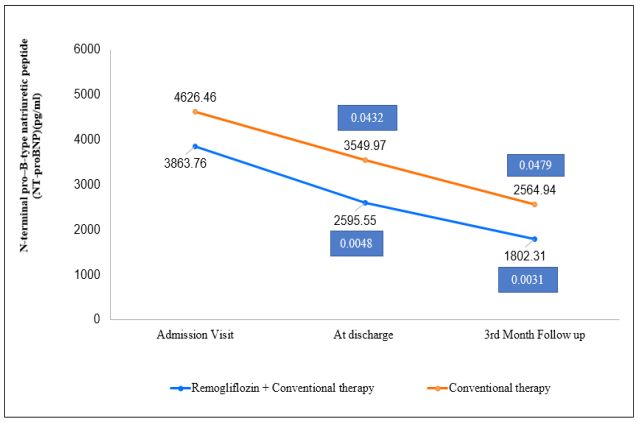

Figure 2: Mean reduction of NT pro BNP level.

In group A, the mean Left Ventricular Ejection Fraction (LVEF) showed an improvement from 29.88% at baseline to 33.25% at week 12. Group B exhibited an increase in LVEF from 29.85% at baseline to 36.46% at week 12. Left Ventricular (LV) mass improved in the Remogliflozin group from 145.2gm at baseline to 143.6gm at the 3 month follow-up. In the other SGLT2i group, LV mass improved from 154.1gm at baseline to 153.2gm at the 3 monthfollow-up. Additionally, both groups demonstrated comparable improvements in heart rate, blood pressure reduction (systolic/diastolic), and glycaemic parameters (FBS, PPBS) over

the 12-week treatment period. Initiating Remogliflozin in AHF did not increase the incidence of acute kidney injury, hypotension, or hypoglycaemia.

In group A, 23.53% of patients (n=4) exhibited serum creatinine levels exceeding 0.3 mg/dl at the time of discharge, while this proportion decreased to 11.76% (n=2) during the week 12 follow-up visit. In Group B, 22.22% (n=4) of patients showed serum creatinine levels >0.3 mg/dl at discharge, and it decreased to 11.11% (n=2) during the 12 week follow-up visit. The mean (±SD) eGFR was 68.53 ± 37.41 ml/min at baseline, showed a slight decrease at 48 hours, and returned to 65.19 ± 38.28 ml/min at week 12 in group A. Group B showed a continuous decrease in eGFR from admission to discharge, persisting below baseline levels at 3 months **(Figure 3).**

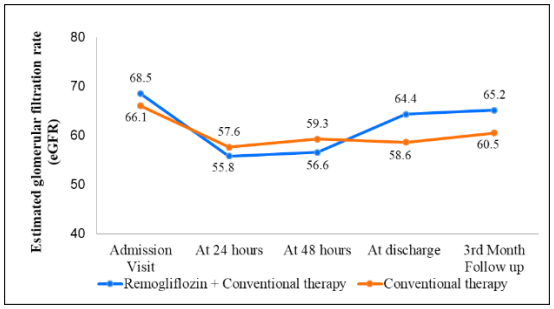

Figure 3: Summary of mean change in eGFR.

Regarding weight change/ diuretic response, in Group A, the mean weight on admission was 62.03 ± 12.8 kg, and at 3 month , it was 58.47 ± 9.26kg. A statistically significant difference (P=0.008) was identified between these values. Similarly, a significant change in mean weight from baseline (66.39 ± 8.22 kg) to 3 month (62.93 ± 8.58) was reported in patients of Group B (P=0.001). The mean diuretic response/weight reduction from baseline to study completion for both groups is presented in Table 2.

Weight change (Kgs)	n	Group A Mean (± SD)	n	Group B Mean (± SD)
Admission	17	62.03 ± 12.81	18	66.39 ± 8.22
1st month follow-up	15	60.71 ± 10.33	13	62.97 ± 8.89
3rd month follow-up	14	58.47 ± 9.26	13	62.93 ± 8.58

Table 2: Diuretic response weight change at 1 month and 3 months from baseline.

In Group A, 76.47% of patients experienced a change in NYHA dyspnoea by at least 1 grade. Among them, 29.41%, 5.88%, and 48.18% demonstrated improvements, transitioning from grade II to I, grade III to I, and grade III to II, respectively. In Group B, 77.78% of patients exhibited a change in dyspnoea by at least 1 grade. Within this group, 22.22% of patients showed improvements, transitioning from grade III to I, and an additional 22.2% of patients transitioning from grade II to I. The specific details of dyspnoea score changes are presented in **Table 3**.

Dyspnoea NYHA class	Group A n (%)	Group B n (%)
Change	13 (76.47)	14 (77.78)
II-I	5 (29.41)	4 (22.22)
III-I	1 (5.88)	4 (22.22)
III-II	7 (48.18)	5 (27.78)
IV-II	0	1 (5.56)
IV-III	0	0
No change	4 (23.53)	4 (22.22)

Table 3: Change in dyspnoea assessed by NYHA class during hospitalization.

Discussion

SGLT2 inhibitors consistently demonstrated in numerous studies to reduce the incidence of Heart Failure (HF)-related outcomes in individuals with T2DM who have either pre-existing cardiovascular disease or several cardiovascular risk factors [12,13,16]. Subsequent to these findings, there has been extensive clinical investigation into the outcomes of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction (HFrEF), irrespective of whether they have T2DM or not.

In our study, none of the patients reported worsening of HF, re-hospitalization for HF, or death. A study investigating the effects of dapagliflozin on individuals with established HFrEF revealed that the primary composite outcome, comprising worsening heart failure or cardiovascular-related death, was lowered in comparison to placebo (16.3% of patients in dapagliflozin group and 21.2% in placebo group) [12]. In contrast, there were no differences reported in the primary endpoints of the trial, such as the duration of hospitalization, or in-hospital deaths between empagliflozin and non-empagliflozin [17]. Another study by Lim et al. also reported no substantial differences in treatment outcomes, including composite ischemic events, hospitalization for HF, renal events, and the combination of HF and renal events, between dapagliflozin and empagliflozin [18].

Although we noted a significant improvement in NT-proBNP from the initial days of hospital admission to discharge and up to week 12 follow-up in both groups, the percentage of reduction was more pronounced in the remogliflozin group. In a recently published meta-analysis in chronic heart failure, SGLT-2 inhibitors demonstrated a superior effect in achieving a ≥20% decline in NT-proBNP, with 37.1% (114 out of 307) of patients in the treatment

group reaching this outcome compared to 27.1% (83 out of 306) in the placebo group [19]. Additionally, the REMIT HF study, which investigated the effects of remogliflozin in T2DM patients with chronic HF and reduced ejection fraction (HFrEF), demonstrated significant improvements in NT-proBNP levels, glycemic control, and other cardiac biomarkers. The study also reported reductions in heart rate, blood pressure, weight, left atrial volume, pulmonary artery pressures, and HbA1c levels, with no significant adverse events observed [20]. In our study, the mean LVEF and NYHA class improved in both groups which is indicative of effective management of patients with ADHF, as it is associated with improved health status and a reduced risk for future clinical cardiac events [21]. There was a significant reduction in glycemic parameters (FPG and PPG) from baseline to week 12 in both the groups. There was also similar improvement in heart rate, blood pressure and weight over 12 weeks of treatment.

Also, both the groups reported significant reduction in body weight. While loop diuretics continue to be the primary therapeutic option for acute HF, numerous drugs have been explored in research but have not shown improvements in clinical outcomes for acute HF patients [19,22]. Many of these studied drugs exhibited significant alterations in blood pressure and/or kidney function [19,23]. The EMPULSE trial comparing empagliflozin to placebo reported that empagliflozin demonstrated early, effective, and sustained decongestion, which was associated with clinical benefit at week 12 [24]. In the DICTATE AHF trial, dapagliflozin did not demonstrate a significant decrease in weight-based diuretic efficiency, however, it did show evidence of improved diuresis among AHF patients [25]. The notable improvement in renal functional parameters in both groups is an important finding, as it underscores the effectiveness of both drugs in the commonly seen, complex interplay between DM, HF and Chronic Kidney Disease (CKD).

Limitations

Firstly, the small sample size necessitates consideration of this study as a pilot study. Hence, careful interpretation of the results is warranted. Secondly, we screened a larger number of patients than those recruited in the study for various reasons. Consequently, the generalizability of the findings to the typical acute heart failure patient may be affected. As our study sample is less, hence a multicentric study with a higher sample size is required to support our findings.

Conclusions

Initiation of remogliflozin in individuals with T2DM and ADHF (HFrEF) did not result in an increased occurrence of acute renal injury, hypotension, or hypoglycaemia. Furthermore, NT-proBNP showed significant improvement in both groups, however, the percentage reduction found with remogliflozin was greater than that in the conventional therapy group, both at discharge and at week 12. Therefore, remogliflozin may be considered as one of the therapeutic options in the treatment of T2DM patients hospitalized for acute HF.

Conflict of Interest: Sumit Bhushan, Abhishek Mane, Rujuta Gadkari, Sanjay Choudhari, Saiprasad Patil and Hanmant Barkate are employees of Glenmark. All other investigators/authors have no conflicts of interest that are directly relevant to the content of this article.

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Ethical standards: The work presented in this study was in accordance with the study protocol, the New Drugs and Clinical Trials Rules 2019 issued by the Government of India, the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and all applicable local regulatory requirements. Informed consent was obtained from all the study subjects who took part in the trial. Ethic committee approval was obtained from all respective sites and study was registered in CTRI (CTRI/2021/08/035354).

References

1. Kenny HC, Abel ED (2019) Heart failure in type 2 diabetes mellitus: impact of glucose-lowering agents, heart failure therapies, and novel therapeutic strategies. Circulation Research 124: 121-141.
2. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. (2011) The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study: methodological details. Journal of Diabetes Science and Technology 5: 906-14.
3. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, et al. (2015) Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC: Heart Failure 3: 136-45.
4. Nichols GA, Hillier TA, Erbey JR, Brown JB (2001) Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care 24: 1614-9.
5. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, et al. (2020) Acute heart failure. Nature Reviews Disease Primers 6: 16.
6. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GM, Coats AJ (2022) Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovascular Research 118: 3272-87.

7. Khan MS, Sreenivasan J, Lateef N, Abougergi MS, Greene SJ, Ahmad T, et al. (2021) Trends in 30-and 90-day readmission rates for heart failure. Circulation: Heart Failure 14: e008335.

8. Buddeke J, Valstar G, Van Dis I, Visseren F, Rutten F, Den Ruijter H, et al. (2020) Mortality after hospital admission for heart failure: improvement over time, equally strong in women as in men. BMC Public Health 20: 1-10.

9. Bytyçi I, Bajraktari G (2015) Mortality in heart failure patients. Anatolian Journal of Cardiology 15: 63-8.

10. Shiraishi Y, Kohsaka S, Sato N, Takano T, Kitai T, Yoshikawa T, et al. (2018) 9□year trend in the management of acute heart failure in Japan: a report from the National Consortium of Acute Heart Failure Registries. Journal of the American Heart Association 7: e008687.

11. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, et al. (2019) Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation 140: e294-e324.

12. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. (2019) Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine 381: 1995-2008.

13. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang C-E, Tereshchenko S, et al. (2020) Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation 141: 100-111.

14. Dharmalingam M, Aravind S, Thacker H, Paramesh S, Mohan B, Chawla M, et al. (2020) Efficacy and safety of remogliflozin etabonate, a new sodium glucose co-transporter-2 inhibitor, in patients with type 2 diabetes mellitus: a 24-week, randomized, double-blind, active-controlled trial. Drugs 80: 587-600.

15. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. (2021) Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction. Circulation 143: 326-36.

16. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. (2021) The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nature Medicine 27: 1954-60.

17. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. (2021) Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine 385: 1451-61.

18. Lim J, Hwang I-C, Choi H-M, Yoon YE, Cho G-Y (2022) Comparison of cardiovascular and renal outcomes between dapagliflozin and empagliflozin in patients with type 2 diabetes without prior cardiovascular or renal disease. PLoS One 17: e0269414.

19. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, et al. (2010) Rolofylline, an adenosine A1− receptor antagonist, in acute heart failure. New England Journal of Medicine 363: 1419-28.

20. Sengupta S, Balagopalan JP, mehta a, Suryavanshi SC, Jamwal N, Bhushan S, et al. (2023) Effect of remogliflozin on biomarkers compared to empagliflozin inpatients of type 2 diabetes mellitus with chronic heart failure. Journal of the American College of Cardiology 81: 316.

21. Wilcox JE, Fang JC, Margulies KB, Mann DL (2020) Heart failure with recovered left ventricular ejection fraction: JACC Scientific Expert Panel. Journal of the American College of Cardiology 76: 719-34.

22. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, et al. (2007) Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 298: 2009-19.

23. Metra M, Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, et al. (2019) Effects of serelaxin in patients with acute heart failure. New England Journal of Medicine 381: 716-26.

24. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. (2022) The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature Medicine. 28: 568-74.

25. Cox ZL, Collins SP, Hernandez GA, McRae III AT, Davidson BT, Adams K, et al. (2024) Efficacy and safety of dapagliflozin in patients with acute heart failure. Journal of the American College of Cardiology 83: 1295-1306.