ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 17, Issue, 05, pp.32934-32941, May, 2025
DOI: https://doi.org/10.24941/ijcr.48962.05.2025

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

COMPARATIVE STUDY OF HEART FAILURE PATIENTS ON SGLT2 INHIBITORS (DAPAGLIFLOZIN) IN DIABETES AND NON-DIABETES GROUPS

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ARTICLE INFO

Article History:
Received 09th February, 2025
Received in revised form
21st March, 2025
Accepted 19th April, 2025
Published online 30th May, 2025

Key words:

Type 2 Diabetes Mellitus, SGLT-2 Inhibitors, Dapagliflozin, Heart Failure, Left Ventricular Ejection Fraction.

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ABSTRACT

Type 2 diabetes mellitus increases the risk of heart failure (HF) development, morbidity, and mortality. Mechanisms include altered myocardial substrates, mitochondrial bioenergetics, lipotoxicity, oxidative stress, advanced glycation end products, and signaling pathway changes. Sodium–glucose cotransporter-2 (SGLT-2) inhibitors, such as dapagliflozin, have shown cardiovascular benefits. Trials like DAPA-HF and EMPEROR demonstrated reductions in cardiovascular death and HF hospitalizations, but effects on diabetic versus non-diabetic HF patients remain unexplored. This is a prospective comparative cohort study was conducted from September 2022 to December 2023 at Aster CMI Hospital, Bangalore, involving 130 HF patients. The mean age was 65.35 ± 10.66 years for diabetics and 60.89 ± 7.86 years for non-diabetics. Patients were divided into two groups based on diabetic status and received dapagliflozin 10mg. Baseline characteristics included mean BMI (29.77±5.8 for diabetics, 29.90±5.9 for non-diabetics) and mean LVEF (40.40 ± 8.09 for diabetics, 44.67 ± 3.49 for non-diabetics). The primary outcome, a composite of HF hospitalization, cardiovascular events, and mortality, was assessed over 12 months. Hospitalization rates decreased from 2.43±1.29 to 0.50±0.81 in diabetics and from 2.06±1.01 to 0.47±0.72 in non-diabetics. Dapagliflozin showed similar cardiovascular outcomes in both diabetic and non-diabetic HF patients, significantly reducing HF hospitalizations and improving cardiac function, regardless of ejection fraction. Adverse effects were minimal. The findings suggest dapagliflozin's potential in enhancing myocardial function and prognosis in HF, beyond glucose control. Further research is needed to explore its use in acute HF decompensation scenarios.

Citation: Dr. Mahesh D M, MD, DM and Dr. Maheswaran Subramanian. 2025. *"*Comparative study of heart failure patients on sglt2 inhibitors (dapagliflozin) in diabetes and non-diabetes groups*". International Journal of Current Research, 17, (05), 32934-32941.*

INTRODUCTION

Heart failure (HF) is a chronic and progressive condition in which the heart muscle is unable to pump blood to meet the body's need for blood and oxygen. The burden of Heart Failure in India appears high, and estimates of prevalence range from 1.3 million to 4.6 million, with an annual incidence of 491 600–1.8 million[1]. However, reliable data is lacking because of inadequate surveillance systems. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and Heart Failure Society of America (HFSA) guidelines define HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood leading to cardinal manifestations of dyspnea, fatigue, and fluid retention[2]. Chronic heart failure describes patients with longstanding (e.g., months to years) symptoms and/or signs of HF typically treated with medical and device. Acute heart failure, previously termed acute decompensated HF, refers to the rapid onset or worsening of symptoms of HF. Most episodes of acute HF result from worsening of chronic HF, but ~20% are due to new onset HF that can occur in the setting of acute coronary syndrome, acute valvular dysfunction, hypertensive urgency or postcardiotomy syndrome[3]. The Framingham Heart Failure criteria [Table 1] diagnose heart failure based on major and minor criteria. Heart failure is diagnosed with2 major or1 major and 2 minor Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) includes angiotensin receptor neprilysin inhibitors, β-adrenergic receptor antagonists, mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 inhibitors (SGLT2i)[7]. Sodium–glucose cotransporter-2(SGLT-2) inhibitors are a class of oral glucose lowering agents with novel cardiovascular benefits. SGLT-2 inhibitors block the sodium-glucose co-transporter in the proximal convoluted tubule of the kidney, thereby halting glucose reabsorption and reducing blood glucose by increasing the excretion of urinary glucose[8]. Unlike other glucose-lowering agents, SGLT2 inhibitors offer an insulin-independent mechanism to lower blood glucose. The mechanism of dapagliflozinin cardiovascular protecting is complicated, and, in some aspect, remains unclear. The mechanism may involve improvement of ventricular loading conditions, improvement of cardiac

metabolism and bioenergetics, Na+/H+ exchange, sugar and lipid metabolism, circulatory load, cardiovascular system, and other aspects[9]. Type 2 diabetes mellitus is a risk factor for the development of HF and increases the risk of morbidity and mortality in patients with established disease. The mechanism that contribute to the development of HF includes in diabetes includes altered myocardial substrates, abnormal mitochondrial bioenergetics, lipotoxicity, oxidative stress, advanced glycation end products, G protein coupled receptor kinase 2 signaling, B2 receptor signaling, RAAS activation[10].

Dapagliflozin in patients with HF and reduced ejection fraction (DAPA HF) and Empagliflozin in heart failure with preserved ejection fraction (EMPEROR) trials showed SGLT2 inhibitors reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with HFrEF and HFpEF respectively[11,12].

No studies so far has compared the diabetic and non-diabetic groups with SGLT2 inhibitors. Either the control of hyperglycemia favors the improvement in cardiac function or the cardioprotective mechanism of SGLT2 inhibitor improves cardiac function is unknown. This study compares the heart failure patients with diabetes and non-diabetes on SGLT2 inhibitor (Dapagliflozin).

MATERIALS AND METHODOS

AIM

- Effect of SGLT-2 inhibitors (dapagliflozin) in Heart Failure patients of Diabetics and Non-Diabetic patients.

OBJECTIVE

- To compare the primary outcome in both groups
- Adverse effects observed in each groups

METHODOLOGY

STUDY DESIGN: Prospective comparative cohort study

SAMPLING METHOD: Non-randomized

SOURCE OF DATA: Department of Internal medicine, Aster CMI hospital, Bangalore, a tertiary care hospital

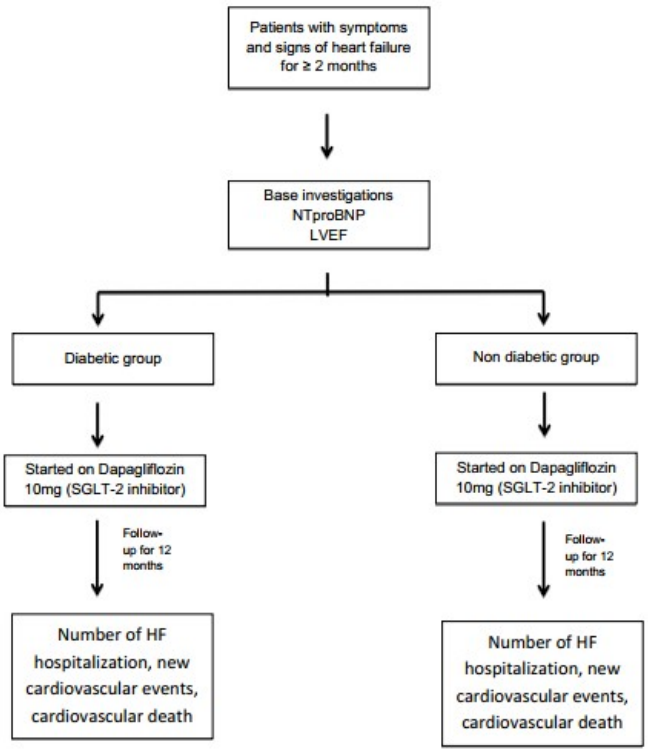
STUDY PERIOD: September 2022 to December 2023

SAMPLE SIZE: This study included 130 patients who fulfilled inclusion and exclusion criteria

METHOD OF DATA COLLECTION

- It is a comparative study in Heart failure (HF) patients in Diabetic and non diabetic groups on SGLT2 inhibitor (Dapagliflozin).
- HFrEF, HFpEF patients with elevated N-terminal pro–B-type natriuretic peptide are given Dapagliflozin.
- The primary outcome include composite of HF hospitalization, new cardiovascular events, cardiovascular death which will be compared in both groups.

SELECTION CRITERIA



Methodology

Table 1. Framingham's criteria[4]

MAJOR CRITERIA	MINOR CRITERIA
• Acute pulmonary edema • Cardiomegaly • Hepatojugular reflex • Neck vein distension • Paroxysmal nocturnal dyspnea or orthopnea • Pulmonary rales • 3rd heart sound	• Ankle edema • Dyspnea on exertion • Hepatomegaly • Nocturnal cough • Pleural effusion • Tachycardia – heart rate >120 beats per minute

INCLUSION CRITERIA

- Previously diagnosed Heart Failure (HF) patients of ≥ 2 months with Type 2 DM and without Type 2 DM

EXCLUSION CRITERIA

- Patients who are already on SGLT-2 Inhibitors treatment.
- Patients who been newly diagnosed Heart failure within 2 months of duration
- Patients with hypotension or systolic blood pressure (SBP) <95 mmHg.
- Type 1 Diabetes Mellitus, CKD, CLD patients.
- Cardiac procedures planned for the next 6 months like revascularization or any implantation.
- Pregnant women or women who is planning to become pregnant

CLINICAL PROTOCOL

- After choosing the patients based on the clinical examination and result of investigations, subjects were divided into 2 groups based on Type 2 Diabetes mellitus.

- HF patients of more than 2 months with T_2 DM and HF patients without T_2 DM are given to take SGLT-2 Inhibitor.
- Follow-up study with 12 months gap was conducted by the principle investigator, with the precise investigations to compare the outcomes in each group

SAMPLE SIZE

$$n = \frac{2\bar{P}\,\bar{Q}\,[Z_{1-\alpha/2} + Z_{1-\beta}]^2}{(P_1 - P_2)^2}$$

- $Z_{1-\alpha/2}$ = 1.96 at 95% CI
- $Z_{1-\beta}$ = 0.84 at 80% power
- P1 = Prevalence of cardiac event among Diabetic group (20%)
- P2 = Prevalence of cardiac event among Non Diabetic group (4%)

$$\bar{P} = \frac{P1+P2}{2} \qquad \bar{Q} = 1 - \bar{P}$$

$$n = \frac{2\ X\ 0.12\ X\ 0.88\ (1.96+0.84\ )^2}{(0.16)^2}$$

n = 65 per group

- Minimum required sample size is 65 per group

STATISTICAL ANALYSIS

- The collected data will be spread in Microsoft excel sheet and analyzed using SPSS version 25.
- Quantitative variables were presented as mean ± SD.
- Qualitative variables were presented as frequency and percentage.
- The primary outcome, HF hospitalization, new cardiovascular events, cardiovascular death, was assessed in a time-to-event analysis.
- Mann Whitney U test aka Wilcoxon Rank Sum Test were performed to compare the primary outcome between diabetic and non-diabetic group.
- P value <0.05 will be considered as statistically significant

RESULTS

- The abbreviation eGFR denotes estimated glomerular filtration rate, NT-proBNP
- N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association
- The body-mass index is the weight in kilograms divided by the square of the height in meters

A prospective study was carried out from September 2022 to December 2023 on 130 patients who were admitted either in ward or intensive care unit with signs and symptoms of heart failure. The baseline characteristics [Table 2]involved detailed medical history, past history, medical history, blood and radiological investigations. The patients were separated into 2 groups based on the diabetic status. Each group had been started on Dapagliflozin 10mg (SGLT-2 inhibitor) and then followed-up for 12 months for primary outcome which is composite of HF hospitalization, new cardiovascular events, cardiovascular death. The mean age was 65.35 ± 10.657 in diabetic and 60.89 ± 7.856 in non-diabetic group. The range of age of the patient was 44 to 89 years including both groups. 72.31% of the patients were male and 27.69% were females. The mean BMI were 29.77±5.8 and 29.90±5.9 in diabetic and non-diabetic group respectively.

LVEF in each group with mean value of 40.40 ± 8.087 in diabetic and 44.67 ±3.486 non-diabetic group [Figure 1].

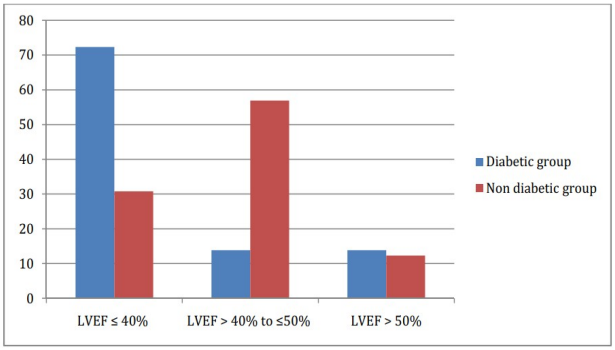


Figure 1. LVEF based on 2D echo finding in each group

ASSOCIATED COMORBID CONDITIONS IN BOTH GROUPS

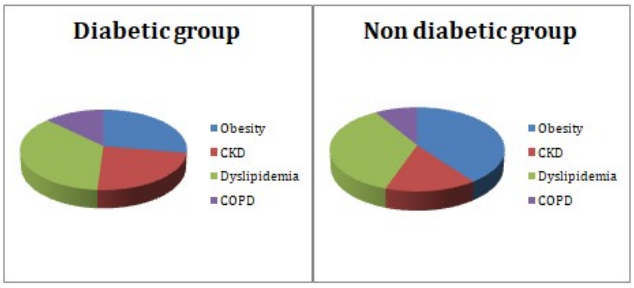


Figure 2. Associated comorbid diseases

The diabetic group had increased rate of reduced ejection fraction. Prevalence of dyslipidemia was higher in both groups which contributed 52.30% in diabetic group and 38.46% in non-diabetic group [Figure 2]. Dyslipidemia leads to development and progression of atherosclerosis and is an established risk factor for cardiovascular diseases. Other comorbid conditions included obesity, chronic kidney disease and chronic obstructive pulmonary disease. CKD increases circulating volume, worsens symptoms of HF, and results in disease progression. Obesity is both a risk factor for the development of HF and highly prevalent in patients with HF. These comorbid conditions are independent predictors of adverse outcome in heart failure. The choice of SGLT-2 inhibitors in case of CKD is preferred in addition to other anti-failure medications as SGLT-2 inhibitors were hypothesized to have renoprotective function.

PRINCIPAL CAUSES FOR HEART FAILURE

The most common etiology for heart failure was ischemic heart disease and is 47.69% in diabetic group and 55.38% in non-diabetic group. Coronary artery disease (CAD) can either acutely develop decompensated heart failure or can lead to chronic ischemic cardiomyopathy.

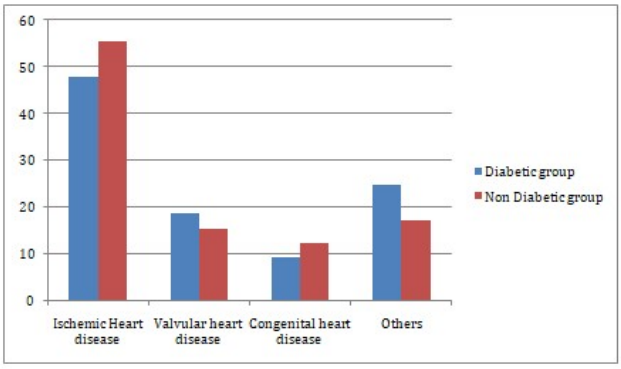


Figure 3. Etiology for heart failure

Valvular heart diseases were 18.46% in diabetic group and 15.38% in non-diabetic group. It included rheumatic heart disease complicated mitral stenosis, age related degenerative changes of aortic valve. Congenital heart diseases were 9.23% in diabetic group and 12.30% in non-diabetic group which included atrial septal defect, PDA. Other etiological factors which included restrictive cardiomyopathies, hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy and ageing were 24.62% in diabetic and 16.92% in non-diabetic group [Figure 3].

OTHER ANTI-FAILURE MEDICATION

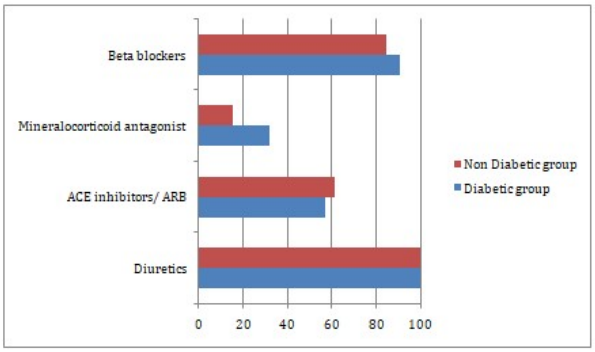


Figure 4. Other anti-failure medications

All 130 patients were on high ceiling diuretics. 90.77% in diabetic group and 84.62% in non-diabetic groups were on cardioselective beta-blockers. ACE inhibitors/ angiotensin receptor blockers (ARB) were 56.92% in diabetic group and 61.53% in non-diabetic group. Mineralcorticoid receptor antagonists (MRA) were used in 32.14% and 15.38% in diabetic and non-diabetic groups [Figure 4]. Dapagliflozin were started on patients who were included in this study irrespective of their previous medications, Among 65 patients in diabetic groups, the other oral glucose lowering agents were adjusted according to their fasting and post prandial blood sugar levels. These patients were followed for next 12 months for primary and safety outcomes.

PRIMARY AND SAFETY OUTCOMES

Primary and secondary outcomes were compared as number of events occurred in both diabetic and non-diabetic group. All patients were followed up for 12 months which was conducted from September 2022 to December 2023. In diabetic group total event of primary outcome was 31 (mean 0.50 ± 0.805) which had 24 events of hospitalization for heart failure, 4 events of new cardiovascular events and 3 events of cardiovascular death [Table 3]. In non-diabetic group total event of primary outcome was 29 (mean 0.47 ± 0.718) which had 20 events of hospitalization for heart failure, 6 events of new cardiovascular events and 3 events of cardiovascular death. The effect of dapagliflozin on the incidence of primary outcome events was similar in patients with and without diabetes [Figure 5]. The number of new cardiovascular event was higher in non-diabetic group, however as the sample size is limited, this could not besignificant.

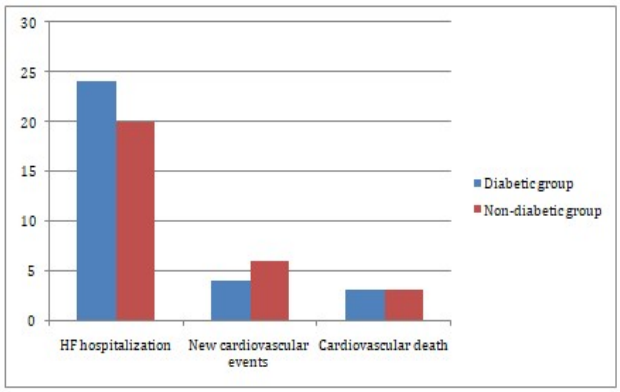


Figure 5. Primary outcome

SAFETY OUTCOME

There was no serious life threatening adverse effect leading to discontinuation of the drug. In diabetic group there were 1 events of uncomplicated urinary tract infection (UTI) and 1 event of euglycemic ketoacidosis who was already on metformin and vildagliptin. There was1 event of hypoglycemia and 3 events of UTI observed in non-diabetic group.

STATISTIC RESULT

Mann-Whitney U test was performed to compare the median no of admission between diabetic and non-diabetic group [Table 4]. It is found to be statistically not significant. Hence this shows SGLT-2 inhibitors can solely have cardioprotective role irrespective of the diabetic status. The underlying mechanism in heart failure is only hypothesized which includes diuresis/natriuresis, blood pressure reduction, erythropoiesis, improved cardiac energy metabolism, inflammation reduction, inhibition of the sympathetic nervous system, prevention of adverse cardiac remodeling, prevention of ischemia/reperfusion injury, inhibition of the Na+/H+-exchanger.

DISCUSSION

The study was conducted in the tertiary care center - Aster CMI hospital, Bangalore, Karnataka. A total of 130 cases were enrolled during the study period, i.e., from September 2022 to December 2023. Dapagliflozin had similar outcome in both groups irrespective of diabetic status and also it reduced the number of hospitalization for heart failure in both groups which is evident from reduction of mean value of hospitalization in HF from 2.430±1.289 to 0.50 ± 0.805 in diabetic group and from 2.06±1.006 to 0.47 ± 0.718 in non-diabetic group [Figure 6]. SGLT-2 inhibitors (Dapagliflozin) improved the cardiac function irrespective of the ejection fraction. Robust evidence from clinical trials and sub-studies has demonstrated that dapagliflozin reduces not only HF re-hospitalizations, but also cardiovascular mortality and all-cause death in the whole spectrum of HF, without a loss of efficacy according to ejection fraction. Our findings showed that dapagliflozin reduced the risk of cardiovascular death or

Table 2. Characteristics of the patients at baseline

Characteristic	Diabetic (n = 65)	Non Diabetic (n = 65)
Age (year) – Mean ± SD	65.35 ± 10.657	60.89 ± 7.856
Female no. (%)	20 (30.77%)	16 (24.62%)
NYHA functional classification		
• Class I	0	2
• Class II	38	42
• Class III	21	17
• Class IV	6	4
Body mass index - Mean ± SD	29.77±5.8	29.90±5.9
Heart rate - Mean ± SD	70.4±12.0	70.3±11.80
Systolic blood pressure - Mean ± SD	131.8±15.6	131.9±15.7
HbA1c - Mean ± SD	8.28 ± 1.125	5.96 ± 0.192
Left ventricular ejection fraction		
• Mean left ventricular ejection fraction - Mean ± SD	40.40 ± 8.087	41.67 ±3.486
• Left ventricular ejection fraction ≤ 40% no. (%)	47 (72.31%)	20 (30.77%)
• Left ventricular ejection fraction > 40% to ≤50% — no. (%)	9 (13.85%)	37(56.92%)
• Left ventricular ejection fraction > 50% — no. (%)	9 (13.85%)	8 (12.31%)
Median NT-proBNP (Mean ± SD)	9372.31 ± 6687.106	5344.44 ± 2278.889
Heart failure category — no. (%)		
• Ischemic Heart disease	31 (47.69%)	36 (55.38%)
• Valvular heart disease	12 (18.46%)	10 (15.38%)
• Congenital Heart disease	6 (9.23%)	8 (12.30%)
• Others	16(24.62%)	11 (16.92%)
Cardiovascular history		
• Hospitalization for HF during previous 12 months (mean±SD)	2.430±1.289	2.06±1.006
• Systemic Hypertension – no. (%)	61 (93.85%)	52 (80%)
norbids – no. (%)		
• Obesity	26 (40%)	18 (27.69%)
• Chronic Kidney Disease	22 (33.85%)	7 (10.77%)
• Dyslipidemia	34 (52.30%)	25 (38.46%)
• Chronic Obstructive Pulmonary disease	12 (18.46%)	6 (9.23%)
Mean eGFR — ml/min/1.73 m2 (Mean ± SD)	60.6±19.8	60.6±19.9
Other antifailure medications – no.(%)		
• ACE inhibitors/ ARB	37 (56.92%)	40 (61.53%)
• Diuretics	65 (100%)	65 (100%)
• Mineralocorticoid antagonist	18 (32.14%)	10 (15.38%)
• Beta-blockers	59 (90.77%)	55 (84.62%)

Table 3. Primary outcome

PRIMARY OUTCOME (NO. OF EVENTS)	HF with Diabetes (n=65)	HF without Diabetes (n=65)
1.HF hospitalization	24	20
2.New cardiovascular events	4	6
3.Cardiovascular death	3	3

Table 4. Statistical analysis

Statistics	Group	
	HF with DB (n=65)	HF without DB (n=65)
Total no of admission	31	29

Variables	HF with Diabetes (n=65)	HF Without Diabetes (n=65)	Z statistics	P value
No of admission			-0.084	0.933
Mean ± SD	0.50 ± 0.805	0.47 ± 0.718		
Median	0	0		
$Q_1 : Q_3$	0 : 1	0 : 1		
Min: Max	0 : 3	0 : 3		

hospitalization for heart failure in patients with heart failure irrespective of ejection fraction and diabetic status. Adverse drug effects were minimal to nadir in this study.

EFEECT ON PRELOAD: Dapagliflozin is a potent, competitive, reversible, highly selective and orally active inhibitor of SGLT2 receptors in the proximal renal tubule[13]. As a consequence, dapagliflozin results in a dose dependent increase in urinary glucose excretion accompanied by an osmotic diuresis and natriuresis. This reduction in preload will improve the ventricular loading conditions reducing LV wall stress. We did not see any change in LV volumes, but baseline measurements were normal which may have made any changes difficult to detect. We also did not see any significant reduction in NT-proBNP which one might expect to see with reduced preload and myocardial stretch. However,

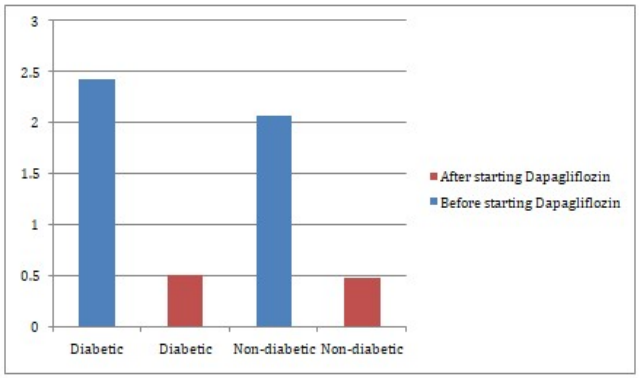


Figure 6. Comparison of mean values of Hospitalization in both groups

dapagliflozin resulted in significant weight loss in this trial which is known to result in increased natriuretic peptide concentrations which may have counteracted any reduction with reduced preload[14].

EFFECT ON ANEMIA: An alternative explanation may be an acceleration in haemoglobin production secondary to SGLT2 therapy. Inhibition of SGLT-2 transporters reduces oxygen demand in the renal proximal convoluted tubules thereby improving overall renal cortical ischemia and erythropoietin production by interstitial fibroblasts[15]. This is important as anemia has been shown to increase morbidity and mortality of patients with HF[16]. Indeed, mediation analysis showed changes in haemoglobin and haematocrit were the most important mediators of reduced CV death in the EMPA-REG OUTCOME trial[17]. This may be one of the many important differences between SGLT2 inhibitors and classic diuretics. Another difference is SGLT2 inhibitors exert their effect in the proximal tubule of the kidney. SGLT 2 inhibition therefore results in an increased delivery of sodium and chloride to the macula densa in the loop of Henle downstream which may also limit the activation of the RAAS and SNS both of which can have an adverse effect of CV remodeling and subsequent CV outcomes. Indeed, we did not observe any significant increase in heart rate during ambulatory blood pressure recording suggesting a lack of compensatory sympathetic activation. Their effect in the proximal tubule is also associated with changes in adenosine bioactivity in the afferent renal arteriole reducing intraglomerular hypertension as discussed earlier[18]. We did not measure albuminuria but studies have shown that SGLT2 inhibitors are associated with reduced progression of albuminuria and slower decline in renal function when compared with placebo[19]. The maintenance of total body salt and water homeostasis without the activation of the SNS and the inflammation associated with diabetic nephropathy may help reduce adverse LV remodeling.

EFFECT ON INSULIN: Hyperinsulinemia and insulin resistance is associated with alterations of myocardial metabolism leading to increased myocardial free fatty acids oxidation resulting in lipotoxicity and predisposition to cardiac hypertrophy and dysfunction[20,21]. Hyperinsulinemia and hyperglycemia results in the formation of AGEs. AGEs contribute to increased connective tissue crosslinking, fibrosis, cardiac stiffness and impaired diastolic relaxation.They are also involved in the production of ROS further contributing to the development of oxidative stress and subsequent inflammation and fibrosis noted in diabetic cardiomyopathy[22]. Insulin resistance may promote myocardial hypertrophy and fibrosis through several signaling pathways, including transforming growth factor, and peroxisome proliferator-activated receptor[23].In this study, dapagliflozin treatment resulted in a significant reduction in fasting glucose and glycated haemoglobin. Due to time and money constraints we did not perform a fasting insulin level.

DIRECT CARDIAC EFFECTS: Whilst dapagliflozin and other SGLT2 inhibitors can alter ventricular loading by way of blood pressure reduction, weight loss and diuresis, it may also offer novel pathways in improving HF outcomes. In addition to their modest effect on ventricular loading by way of blood pressure reduction and increased diuresis, they may also have beneficial effects on myocardial bioenergetics, ion exchange, necrosis and fibrosis pathways as well as other metabolic and biochemical effects[24,25]. These novel molecular effects may also contribute to the rapid and striking improvements in HF-outcomes seen in the large SGLT2-inhibitor CV outcome trials. In this study we did not observe any significant change in biomarker of heart failure viz NTproBNP, but we observed a significant improvement in the left ventricular ejection fraction.

CLINICAL RELEVANCE: In this study we have shown that dapagliflozin effectively improves the left ventricular function in both HFrEF and HFpEF and also independent of diabetic status of an individual. This study is highly relevant and topical following the observed CV benefits seen with SGLT2 inhibitors in the recent large CV outcome trials including most recently the DAPA-HF trial. These outcome trials were particularly noteworthy as previously trials such as the three large randomized controlled trials (RCTs) ADVANCE, ACCORD and VADT failed to demonstrate any significant effect on macrovascular events of more intensive glycemic control in patients with longstanding T2D when compared with standard medical care[26,27,28]. From a practical point of view, since SGLT2i has little impact on different clinical variables (i.e., a modest effect on blood pressure and a slightly initial effect on renal function), in contrast to other HF drugs (i.e., beta-blockers: heart rate, blood pressure; renin-angiotensin system aldosterone inhibitors: renal function, potassium levels, blood pressure), this simplifies the use of dapagliflozin in clinical practice as it can also be easily prescribed in more complex patients, such as those with low heart rate, low blood pressure, or renal dysfunction[29]. Moreover, the addition of dapagliflozin may facilitate the introduction of other HF drugs, as it may reduce the risk of adverse events (i.e., hyperkalemia with mineralocorticoid receptor antagonists is reduced with the concomitant use of dapagliflozin). On the other hand, several studies have demonstrated the cost-effectiveness of dapagliflozin in the whole spectrum of HF patients, regardless of the healthcare system of different countries[30]. In fact, the immediate initiation of dapagliflozin provides greater clinical benefits. A recent study has shown that in patients with HFrEF, dapagliflozin may be more cost-effective than empagliflozin mainly due to the specific beneficial effect of dapagliflozin on mortality. In fact, although guidelines recommend the use of SGLT2i in the management of HF, independently of ejection fraction, it seems that there could be some difference between SGTL2.

SIDE EFFECTS AND TOLERANCE OF DAPAGLIFLOZIN: Overall dapagliflozin was well tolerated in this study. No patients did have withdrawn the drug. The

incidence of common side effects reported with SGLT2 inhibitors were not excessive in this study. There were 1 episode of hypoglycemia 3 episodes of UTI in non-diabetic group, 1 episode UTI and euglycemic ketoacidosis in diabetic group. Importantly there were no reported episodes of hyponatremia/bone fracture/thromboembolism or CVA events. This may be attributed to time and sample limitation of the study.

LIMITATIONS: This was a single centered study with small number of patients. The duration of follow-up was limited and hence long term effects of dapagliflozin were not assessed. SGLT-2 inhibitors were effective in long-term management of heart failure but it warrants further trails to assess the adverse drug reactions. First, the sample size was small and single centered study. Second, this study did not include the renal parameters and hematological parameters which may also affected the outcome of heart failure.

Anyhow, this was the first study to compare the heart failure management between diabetic and non-diabetic groups. Previous real world trials have compared dapagliflozin with placebo in heart failure. This study shows there was no difference in heart failure outcome with SGLT-2 inhibitors based on diabetic status.

CONCLUSION

This study shows that dapagliflozin have equal cardiovascular outcome in heart failure in both reduced and preserved ejection fraction irrespective of diabetic status. A medication that was once utilized as an oral glucose lowering agent has been shown to improve myocardial function and improves the prognosis of heart failure in long term management. The next logical step would be to establish if SGLT2 inhibitors can be used in hospitalized patients with acute decompensation.This mechanistic study showing improvement in LVEF suggests dapagliflozin may reverse cardiac remodeling and changes in left ventricular structure which may be a potential mechanism for heart failure.

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