ORIGINAL ARTICLE

A Comparison of the Effects of SGLT2 Inhibitors in Heart Failure Patients with Diabetes Versus Non-diabetic Patients

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ABSTRACT

Aim: To evaluate the effects of dapagliflozin in patients with HFrEF with and without diabetes.
Methodology: A case-control study was conducted at the department of Cardiology, Liaquat University Hospital, Hyderabad between February 2020 to August 2020 for a duration of six months. A dose of 10 mg of dapagliflozin were added to the standard therapeutic regimes of all patients. Primary outcome was the composite of an attack of worsening heart failure, or death due to cardiovascular causes. SPSS v 26 was used to run data analysis.
Results: The rate of cardiovascular death, hospitalization for heart failure (HHF), or an urgent heart failure visit in patients with DMT2 was 20% which was higher than the group without diabetes (13.3%). The rate of hospitalization for heart failure in patients with DMT2 was 13.33% which was higher than the group without diabetes (7.5%). The rate of cardiovascular death in patients with DMT2 was 14 (11.67%) while in the group without DMT2 10 (8.33%) patients died because of cardiovascular complications during the study period. Number of first and recurrent hospitalizations for heart failure and cardiovascular death were significantly higher in individuals with diabetes compared to those without i.e. 37 (30.83%) vs 22 (18.33%) with a p=0.025.
Conclusion: The impact of dapagliflozin on the primary and secondary outcomes did not significantly alter in patients with and without diabetes mellitus type 2. However, SGLT2 inhibitor - dapagliflozin caused significantly lower rates of first and recurrent heart failure hospitalizations and cardiovascular death in individuals without diabetes in comparison to those with diabetes.
Keywords: Dapagliflozin, SGLT2 inhibitors, heart failure, diabetes mellitus type 2

INTRODUCTION

Patients with Type 2 diabetes mellitus (T2DM) are at an increased risk for developing cardiovascular complications. It is associated with increased morbidity and mortality among patients[1,2]. Until a few decades ago, the medications used to manage T2DM did not offer additional cardiovascular or nephrology related benefits. Furthermore, the side effects of these drugs were often undesirable and deleterious. Some of the side effects include, proliferative retinopathy, edema, and cardiovascular complications, and hypoglycemia with insulin, thiazolidinediones and sulfonylureas, respectively[3-5]

In 2008, the Food and Drug Administration (FDA) made it compulsory for companies to provide cardiovascular outcomes trials (CVOTs) of any novice antihyperglycemic drug to provide insight into any harmful cardiovascular effects associated with the drug. [6] This was done to ensure that any novel drug for the treatment of diabetes mellitus did not increase the risk of cardiovascular adverse events[7,8] SGLT2 inhibitors are a class of FDA-approved antihyperglycemic medicines that in combination with dietary modification and increased physical activity are used to lower blood sugar in adults with type 2 diabetes[9]. Drugs in the SGLT2 inhibitor group include canagliflozin, dapagliflozin, and empagliflozin.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors play a role in the management of type 2 diabetes by inhibiting the reabsorption of the filtered glucose load at the proximal tubule[10]. Additionally, it enhances the process of sodium excretion via urine, causing reduction in the intravascular volume and altering the renal hemodynamics, contributing to the beneficial effects on blood pressure and body mass index. Several trials have reported SGLT2 inhibitors' role in reduced adverse cardiovascular or renal events[11-12]. However, there is no consistency about the cardiovascular and renal outcomes of SGLT2 inhibitors among these trials and metaanalysis. In the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) trial, which included 17,160 patients who were either at risk or had a cardiovascular disease. However, the majority of the patients did not have an established cardiovascular disease. The study did not report any significant reduction of major cardiovascular events in patients who were on dapagliflozin compared to those who were on placebo[13].

There is a scarcity of local literature on the subject. As to the knowledge of the authors, no study has been conducted in Pakistan on the additional benefits of SGLT2 inhibitors including the cardiorenal effects. Hence, the current study was conducted to evaluate the cardiovascular outcomes of dapagliflozin - an SGLT2 inhibitor in patients with or without diabetes.

METHODS AND MATERIALS

A case-control study was conducted at the department of Cardiology, Liaquat University Hospital, Hyderabad between February 2020 to August 2020 for a duration of six months. The study was first approved by the ethical committee. After securing an informed written consent, patients were enrolled in the study using non-probability convenience sampling technique.

A total of 120 patients, sixty in each category were enrolled in the study. All patients irrespective of gender, aged above 45 years of age, with New York Heart Association classification II to IV with an ejection fraction less than or equal to 40% and elevated plasma N-terminal pro B-type natriuretic peptide were eligible to take part in the study[14]. Patients with ejection fraction of above forty were not included in the study.

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Patients with a congenital heart disease or familial hyperlipidemia were also excluded from the study.

Patient data was recruited from the patient files after taking informed consent from the patients and proper permission from the hospital administration. At baseline, all demographic and clinical characteristics of patients were recorded. A dose of 10 mg of dapagliflozin were added to the standard therapeutic regimes of all patients. The patients were requested to maintain a chart of any side effects and report at each follow-up visit. Primary outcome was the composite of an attack of worsening heart failure, or death due to cardiovascular causes. The secondary composite outcomes included, cardiovascular death or hospitalization for heart failure, number of first and recurrent hospitalizations for heart failure and cardiovascular death, worsening kidney function, and an all-cause mortality. All data were recorded by the principal author in a predefined pro forma. These outcomes were analyzed in two groups i.e. Patients with Diabetes Mellitus Type 2 and those without DMT2. Patients with diabetes had a glycated Hemoglobin of equal to or more than 5.7% whereas, the patients without DMT2 had HbA1c of less than 5.7%.

Data were entered and analyzed using SPSS version 26.0. Mean±SD were computed for age and mean HbA1c. Frequency and percentage were computed for all the categorical variables including gender, NYHA classification, primary and secondary outcomes. Chi-Square test was applied to find out the association between dapagliflozin and outcome of study in patients with DMT2 and those without. A P-value<0.05 was considered statistically significant.

RESULTS

The mean age of patients in the non-diabetes group was 65.6±10.7 years while in the group with diabetes, 65.9 ± 9.5 years. The other sociodemographic characteristics including the gender, NYHA functional classification, and vitals were similar in individuals with diabetes and those without. The mean ejection fraction in patients without diabetes mellitus type 2 was 30.9±6.7 whereas it was 31.3 ± 6.5 in patients with DMT2. The baseline glycated hemoglobin (%) in patients with DMT2 was 7.5± .5% while in patients without DMT2, the HBA1c was less than 5.7% (Table 1).

Upon assessing the primary composite outcomes of dapagliflozin in patients with or without diabetes mellitus type 2, it was found that the rate of cardiovascular death, hospitalization for heart failure (HHF), or an urgent heart failure visit in patients with DMT2 was 20% which was higher than the group without diabetes (13.3%). However, the difference was not statistically significant (p>0.05).

Similarly, the rate of HHF or an urgent HF visit in patients with DMT2 was 13.33% which was higher than the group without diabetes (7.5%). However, the difference was not statistically significant (p>0.05).

When primary outcomes were assessed individually, it was found that the rate of hospitalization for heart failure in patients with DMT2 was 13.33% which was higher than the group without diabetes (7.5%). The rate of cardiovascular death in patients with DMT2 was 14 (11.67%) while in the group without DMT2 10 (8.33%) patients died because of cardiovascular complications during the study period.

Number of first and recurrent hospitalizations for heart failure and cardiovascular death were significantly higher in individuals with diabetes compared to those without i.e. 37 (30.83%) vs 22 (18.33%) with a p=0.025. See table 2 for details.

Table 1: The sociodemographic and clinical characteristics of study population (n=120)

Characteristics	Non-diabetes group	Diabetes Mellitus type 2 group	p-value
Age (years)	65.6 ± 10.7	65.9 ± 9.5	0.819
Gender			
Female	29 (24.17%)	27 (22.50%)	0.760
Male	91 (75.83%)	93 (77.50%)	
NYHA functional classification			
II	86 (71.67%)	74 (61.67%)	0.246
III	33 (27.50%)	44 (36.67%)	
IV	1 (0.83%)	2 (1.67%)	
Heart rate/min	71.2 ± 12.1	72.4 ± 11.4	0.43
Systolic blood pressure, mm Hg	121.3 ± 15.9	123.5 ± 16.4	0.292
Left ventricular ejection fraction	30.9 ± 6.7	31.3 ± 6.5	0.639
Hemoglobin A1c, %	5.6 ± 0.5	7.5 ± 1.5	<0.001
BMI	26.8 ± 6.2	29.4 ± 5.8	<0.001
Principal cause of heart failure, No. (%)			
Ischemic	61 (50.83%)	73 (60.83%)	0.293
Nonischemic	47 (39.17%)	38 (31.67%)	
Unknown	12 (10.00%)	9 (7.50%)	
Heart failure medication at randomization visit			
β-blocker	113 (94.17%)	115 (95.83%)	0.323
Diuretic	109 (90.83%)	111 (92.50%)	
ACE inhibitor	69 (57.50%)	65 (54.17%)	
Angiotensin receptor blocker	34 (28.33%)	33 (27.50%)	
Sacubitril-valsartan	13 (10.83%)	11 (9.17%)	

Table 2: Frequency of Outcome variables among Study Groups (diabetes vs non-diabetes)

Primary composite outcome and individual components	No Diabetes	Diabetes	P value
Cardiovascular death, hospitalization for heart failure, or an urgent heart failure visit	16 (13.33%)	24 (20%)	0.166
Hospitalization for heart failure or an urgent heart failure visit	9 (7.50%)	16 (13.33%)	0.139
Hospitalization for heart failure	9 (7.50%)	16 (13.33%)	0.139
Urgent heart failure visit	1 (0.83%)	1 (0.83%)	1.000
Cardiovascular death	10 (8.33%)	14 (11.67%)	0.389
Secondary outcomes			
Cardiovascular death or hospitalization for heart failure	17 (14.17%)	24 (20.00%)	0.229
No. of first and recurrent hospitalizations for heart failure and cardiovascular death	22 (18.33%)	37 (30.83%)	0.025
Worsening kidney function	1 (0.83%)	3 (2.50%)	0.313
Death from any cause	13 (10.83%)	16 (13.33%)	0.552

DISCUSSION

We evaluated the primary and secondary outcomes of SGLT2 inhibitor - dapagliflozin in patients with diabetes and those without. The current study reported that SGLT2 inhibitors did not significantly alter the primary or secondary outcomes in patients with diabetes mellitus type 2 compared to those

without DMT2. There was however a significantly increased number of first and recurrent heart failure associated hospitalizations and cardiovascular death among patients with diabetes compared to those who did not (p=0.02).

Zelniker et al., performed a meta-analysis of cardiovascular outcomes trials on glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i). Eight studies with 34 322 (44.4%) patients on SGLT2 inhibitors were evaluated. It was concluded that SGLT2 inhibitors reduce the incidence of major adverse cardiovascular events (MACE) by 11 percent (HR, 0.89; 95% CI, 0.83-0.96; P=0.001) which is comparable to the GLP1-RA which reduce the occurrence of MACE by 12 percent.[15]

Studies have suggested that the benefits of SGLT2 inhibitors are not restricted to individuals with diabetes mellitus type 2 but are applicable to individuals with prediabetes or patients with heart failure concomitant with reduced ejection fraction, irrespective of their glycemic status[16-17].

For instance, in a metaanalysis, it was revealed that in the individuals without diabetes, dapagliflozin reduced the primary outcome occurrence in both non-diabetes group (normal glycated hemoglobin < 5.7%) and those with prediabetes (glycated hemoglobin of more than or equal to 5.7%)[16].

Kato et al., analyzed the data from DECLARE outcome trial. The authors revealed that dapagliflozin when administered to patients with heart failure with reduced ejection fraction significantly reduced heart failure hospitalization and over all cardiovascular death and all-cause mortality[18]. In our study, the all-cause mortality in patients with diabetes and those without was 16 (13.33%) and 13 (10.83%), respectively. The effect of SGLT2 inhibitors on the all-cause mortality did not significantly differ between the diabetes and non-diabetes group.

John J.V. McMurray and colleagues revealed that dapagliflozin substantially affected the primary cardiovascular outcome in form of composite worsening of heart failure or cardiovascular death, irrespective of diabetes status of the patients[19]. The findings presented by McMurray coincides with our study.

Keeping the current findings and previous literature into consideration, we can conclude that dapagliflozin - an FDA approved SGLT2 inhibitor has beneficial cardiovascular and renal effects irrespective of the presence or absence of diabetes mellitus type 2.

There are some limitations of the current study. First of all, the current study did not have a placebo group due to which we could not compare the cardiovascular outcomes in patients with heart failure with or without diabetes who were administered dapagliflozin and those who were administered a placebo. Secondly, the sample size was limited. A large diversified sample size is needed for further adequate exploration into the beneficial effects of dapagliflozin in addition to providing glycemic control in patients with diabetes mellitus type 2.

CONCLUSION

The impact of dapagliflozin on the primary and secondary outcomes did not significantly alter in patients with and without diabetes mellitus type 2. However, SGLT2 inhibitor - dapagliflozin caused significantly lower rates of first and recurrent heart failure hospitalizations and cardiovascular death in individuals without diabetes in comparison to those with diabetes. However, large cohort studies and randomized trials are required to ascertain the effect of SGLT2 inhibitors like dapagliflozin on cardiovascular and renal outcomes.

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