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ORIGINAL ARTICLE

Effectiveness of Dapagliflozin in Reducing Incidence of Worsening Heart Failure Events among patients with Reduced Ejection Fraction

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ABSTRACT

Background: Sodium–glucose co-transporter 2 (SGLT2) inhibitors are the groups of oral hypoglycemics that decreases the worse events among cardiac patients of chronic heart failure.
Aim: To assess the effectiveness of Dapagliflozin in reducing the incidence of worsening heart failure events among chronic heart failure patients.
Study design: Randomized controlled trial.
Methodology: This study enrolled 480 cardiac patients with mildly reduced ejection fraction. This study was held at Punjab Institute of Cardiology. All patients received dapagliflozin 10mg once daily or matching placebo, in addition to usual therapy for four weeks. The data was entered and analyzed in SPSS 25. Independent sample t-test was used to compare the mean age and body mass index between two groups. Chi square test was used to compare gender and hypertension with primary composite.
Results: There were 138(57.5%) males in Dapagliflozin group and 131(54.6%) males in placebo group. Dapagliflozin demonstrated significant benefits compared to placebo, as evidenced by lower rates of the primary composite outcome (15.8% vs. 23.3%, p = 0.038), hospitalization for heart failure or an urgent visit (10.4% vs. 20.0%, p = 0.003).
Practical Implication: Chronic heart failure with mildly reduced ejection fraction is a major problem in modern era. Present study will highlight the effect of oral hypoglycemic, dapagliflozin, in reducing worse cardiovascular events among chronic heart failure patients. As there is a lack of local literature review on this health issue so this study added information to existing literature and add new dimensions in its treatment.
Conclusion: It was concluded that dapagliflozin reduced worsening of cardiac events among heart failure patients with mildly reduced ejection fraction thus this drug is effective treatment option among cardiac failure patients in reducing hospitalization.
Keywords: Heart Failure, Reduced Ejection Fraction, Effectiveness, Urgent Visits and Hospitalization.

INTRODUCTION

In recent past according to literature review, there has been a global transition in etiology of heart failure with reduced ejection fraction (HFrEF) due to various factors.[1,2] Health issues like sedentary life styles has raised the incidence of hypertension, hyper-dyslipidemias and high BMI among individuals that leading to coronary artery disease and heart failure[3-5]. Thus, the most common cause of HFrEF is coronary heart disease[6]. It is important to make difference between the ischemic and non-ischemic cause of heart failure as many treatment options are dependant on its cause. A treatment option like bypass graft surgery is suitable only for coronary artery disease.[7-9] However, effectiveness of other treatment options like implantable cardioverter-defibrillator, cardiac resynchronization therapy, and milrinone for HFrEF may be modified by aetiology[10].

Although, less medical drugs are available to treat patients with heart failure having mildly reduced left ventricular ejection fraction thus this diverted the researchers towards the development of oral hypoglycemic that have role in cardiac failure management[5,6]. Sodium–glucose co-transporter 2 (SGLT2) inhibitors are the groups of oral hypoglycemics that decreases the worse events among cardiac patients of chronic heart failure when added to conventional guidelines recommended therapies. According to literature review they lower tha overall mortality and improve symptoms among patients with reduced ejection fraction.[11] One previous study showed that, treatment with the SGLT2 inhibitor, empagliflozin, reduced the combined risk of hospitalization for heart failure or cardiovascular death among patients with heart failure and a left ventricular ejection fraction of more than 40%. Thus their findings suggested that the benefits of SGLT2 inhibition may extend to all patients with heart failure[12].

In the light of above discussion as chronic heart failure with mildly reduced ejection fraction is a major problem till today. Due to lack of local literature, present study was planned with aim to assess the effectiveness of Dapagliflozin in reducing the incidence of worsening heart failure events among chronic heart failure patients. This study added information to existing literature and add new dimensions in its treatment.

The objective of the study was to assess the effectiveness of Dapagliflozin in reducing the incidence of worsening heart failure events among chronic heart failure patients.

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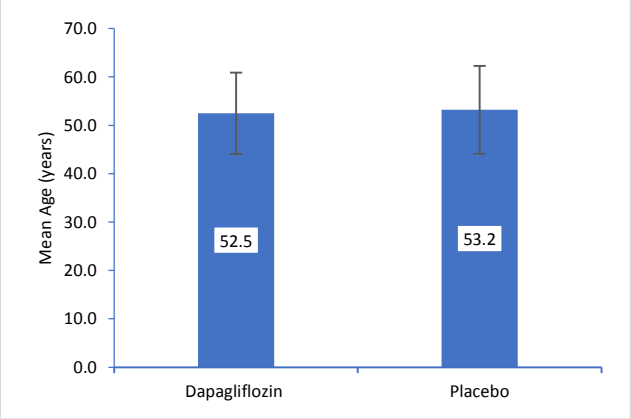
METHODOLOGY

This randomized controlled trial enrolled 480 cardiac patients with mildly reduced ejection fraction. After getting IRB permission, this study was held at Punjab Institute of Cardiology. All patients received dapagliflozin 10mg once daily or matching placebo, in addition to usual therapy for four weeks. Both male and female patients between 40-70 years having diagnosis of stable heart failure with left ventricular ejection fraction of more than 40%, evidence of structural heart disease and elevated natriuretic peptide level were included. Individuals suffering from any hepatic/renal failure or malignancy were excluded. The sample size of 240 patients in each group was calculated by the following formula keeping the power of study equal to 90% and the confidence level equal to 95% with the expected incidence rate of worsening heart failure events and cardiovascular deaths with dapagliflozin is 11.3% and 21.3% with placebo.[13]
Statistical Analysis: The data was entered and analyzed in SPSS 25. Mean ± SD were given for numeric data i.e., age, body mass index and blood pressure. The frequency and percentage were calculated for categorical data i.e., gender, hypertension and dyslipidemia. Normality of the data was assessed using Shapiro-Wilk test. Independent sample t-test was used to compare the mean age and body mass index between the two groups. Chi square test was used to compare hypertension and dyslipidemia with primary composite outcome. A p-value ≤ 0.05 was considered significant.

RESULTS

The mean age of the patients in control group was 52.5 ± 8.4 years and the mean age of the patients in placebo group was 53.2 ± 9.1. Independent sample t test was used to compare the mean age between both groups. The p-value 0.574 indicated that there was no significant difference in mean age between both groups as shown in Figure-1.

Figure -1: Comparison of age between both groups



There were 138(57.5%) males in Dapagliflozin group and 131(54.6%) males in placebo group. Chi-square revealed that there was no difference in gender distribution between both groups (p = 0.520) as shown in table-1.

Table-1: Gender distribution of study participants

Group	Male	Female	p-value
Dapagliflozin	138 (57.5%)	102 (42.5%)	0.520
Placebo	131 (54.6%)	109 (45.4%)	

Table-2 presented baseline characteristics of patients who were divided into two groups: one receiving dapagliflozin and the other receiving a placebo. The percentage of patients with hypertension in the dapagliflozin group (77.1%) is slightly higher than in the placebo group (74.2%), but this difference is not statistically significant (p = 0.457). The percentage of patients with dyslipidemia in the dapagliflozin group (65.4%) is slightly lower than in the placebo group (67.95%), but again, this difference is not statistically significant (p = 0.561). There was no statistically significant difference in mean BMI between the dapagliflozin group (32.4 ± 6.7) and the placebo group (31.6 ± 6.5) with a p-value of 0.640. Similarly, there were no significant differences in SBP (p = 0.329) as shown in table-2. The percentage of patients with type 2 diabetes in the dapagliflozin group (68.3%) is slightly lower than in the placebo group (70.4%), but once more, this difference is not statistically significant (p = 0.621).

Table 2: Characteristics of the Patients at Baseline.

Parameters	Group		p-value
	Dapagliflozin	Placebo	
Hypertension	185 (77.1%)	178(74.2%)	0.457
Dyslipidemia	157 (65.4%)	163(67.95)	0.561
Body Mass Index	32.4 ± 6.7	31.6± 6.5	0.640
Systolic Blood Pressure (mmHg)	133.7± 18.4	132.8±19.6	0.329
Type 2 diabetes	164 (68.3%)	169(70.4%)	0.621

Table-3 compared the cardiovascular outcomes in the overall population receiving dapagliflozin versus placebo. Dapagliflozin demonstrated significant benefits compared to placebo, as evidenced by lower rates of the primary composite outcome (15.8% vs. 23.3%, p = 0.038) and hospitalization for heart failure or an urgent visit (10.4% vs. 20.0%, p = 0.003) as shown in table-3.

Table-3: Comparison of Cardiovascular Outcomes between both groups

Parameters	Group		p-value
	Dapagliflozin	Placebo	
Primary Composite Outcome	38 (15.8%)	56 (23.3%)	0.038*
Hospitalization for heart failure or an urgent visit for heart failure	25 (10.4%)	48 (20.0%)	0.003*
Urgent visit for heart failure	5 (2.1%)	14 (5.8%)	0.035*

*Statistically significant.

DISCUSSION

Many previous studies have reported the role of Dapagliflozin in reducing worse cardiac events. Due to lack of local literature, present study was planned with aim to assess the effectiveness of Dapagliflozin in reducing the incidence of worsening heart failure events among chronic heart failure patients. Health issues like sedentary life styles has raised the incidence of hypertension, hyper-dyslipidemias and high BMI among individuals that leading to coronary artery disease and heart failure. We face this health issue commonly in our clinical setups. Due to various parallel treatment systems like hakeem medications and false believe about drugs drift people to non compliance hence this aggravates clinical burden.

In current study, there were 480 cases with 240 patients in each group while males were more in both groups as shown in table-1. In one previous study, number of patients were less (n=259) but similarly, males (85%) were in enrolled.[14] Thus our study was in line with previous study that enrolled both genders. Another study enrolled both females and males although sample size was quite large per group (n-3132)[12].

In current study, our method of enrollment was in line with one previous study and followed similar inclusion and exclusion criteria with mild modifications[9,12]. In current study, all patients received Tab. Dapagliflozin 10mg once daily or matching placebo, in addition to usual therapy. The percentage of patients with dyslipidemia in the dapagliflozin group (65.4%) is slightly lower than in the placebo group (67.95%), but again, this difference is not statistically significant (p=0.561). Similarly, one study documented that among their enrolled patients, majority of the patients had dyslipidemias[14].

Present study reported that tablet Dapagliflozin had significant benefits compared to placebo, as evidenced by lower rates of the primary composite outcome (15.8% vs. 23.3%, p = 0.038) and hospitalization for heart failure or an urgent visit (10.4% vs. 20.0%, p = 0.003) as shown in table-3. In one previous study it was reported that worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group while 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91)[12]. Similarly, another study showed that SGLT2i improved cardiac remodeling among patients with heart failure thus reduced cardiac adverse events[14]. These findings were in favor of our results that showed dapagliflozin as good treatment option inorder to reduce cardiac events.

Present study results showed that Dapagliflozin has significant benefits compared to placebo as urgent visits for heart failure (2.1% vs. 5.8%, p = 0.035) as shown in table-3. One previous study showed that group of patients receiving dapagliflozin in comparison to placebo had lower incidence of recurrent worsening heart failure events in the overall population (rate ratio, 0.77; 95% CI, 0.67 to 0.89; P<0.001) and among the patients with a left ventricular ejection fraction of less than 60% (rate ratio, 0.77; 95% CI, 0.65 to 0.90; P = 0.002).[12] Similarly, other studies showed dapagliflozin reduced significantly the incidence of worsening of heart failure episodes and urgent hospitalizations among whites when compared to blacks.[15,16] They therefore concluded that their findings favored the use of dapagliflozin as treatment option among HF patients in order to reduce the incidence of worsening of cardiovascular events.

Limitations: Our limitations included single centered study with small follow-up period and lack of genetic workup. There was no workup on cardiac remodeling and cardiac mortality. Hence more studies with long duration of study and different ethnic groups are recommended for production of more reliable results.

CONCLUSIONS

It was concluded that dapagliflozin reduced worsening of cardiac events among heart failure patients with mildly reduced ejection fraction thus this drug is effective treatment option among cardiac failure patients in reducing hospitalization.

Author's contribution: MA: Overall supervision and Write up and literature review, **TL:** Statistics application, analysis literature review, help in write up.

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