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ORIGINAL ARTICLE

Safety of Dapagliflozinin Reducing Cardiac Events and Deaths among NYHA Class II and III Cardiac Failure Patients

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ABSTRACT

Background: In last few decades, a global transition in incidence of heart failure with reduced ejection fraction from hypertension and valvular heart disease to coronary artery disease has taken place.
Aim: To assess the safety of Dapagliflozin in reducing the cardiac events and deaths among class II and class III heart failure patients. **Study design:** Randomized controlled trial.
Methodology: Cardiac patients (n=480) who belonged from class II and III with mild to moderate reduced ejection fraction were added in this study. This study was held at Cardiology Department at Mayo Hospital. All patients received sodium–glucose co-transporter-2 (SGLT2) inhibitors at a dose of 10mg once daily or matching placebo, in addition to usual therapy for eight weeks. SPSS-v25 analyzed the entered data. Mean ± SD presented age, blood pressure and eGFR level. Chi square test was used to compare the gender, NYHA class, primary composite outcome, and cardiovascular death.
Results: Dapagliflozin showed lower rates of the primary composite outcome (15.8% vs. 23.3%, p = 0.038). There was no statistically significant difference in cardiovascular death between both groups (5.8% vs. 8.8%, p = 0.219).
Practical Implication: Due to lack of research culture in our setups, common health issue like chronic heart failure remained clandestine. Present study highlighted the role of oral dapagliflozin in reducing worse cardiovascular events and deaths among NHY class II and III heart failure patients.
Conclusion: It was concluded that dapagliflozin showed significant reductions in various cardiovascular events and deaths compared to placebo thus highlighting its potential as a beneficial intervention in our population.
Keywords: Heart Failure, Reduced Ejection Fraction, NYHA Classification, Urgent Visits and Cardiac deaths.

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]. Literature review has demonstrated that Type 2 diabetes mellitus has inflicted more than 450 million adults[1]. Type-2 diabetic patients usually develop more cardiac issues like heart failure in comparison to general population[2,3] due to various abnormalities in their BMI, lipid profiles[2,3], ultimately leads to death[4]. With advancement in modern era and medical field, new drug therapies have given physicians a wide range of field to control hyperglycemia among diabetics. Although improved glycemic control has beneficial effects on micro-vascular outcomes but yet the effect on cardiovascular endpoints remains a mystery[5-8]. Hence, literature review advocated that choice of anti-diabetic treatment should be based on its ability to confer cardiovascular benefits along-with good glycemic control among patients.

SGLT-2 inhibitors are a novel class of anti-diabetic agents that improve glycemic control by inhibiting glucose re-absorption in proximal tubules thus increases urinary glucose excretion[9,10]. However, this drug is associated with one common side effect (UTI) among its users. However, its benefits overweighs its side effects among users especially with cardiac failure.

Literature review among different populations have demonstrated that treatment with empagliflozin and canagliflozin (SGLT-2) have lessened the risk of major adverse cardiovascular events as well as cardiovascular deaths among cardiac failure patients[11,12]. Similarly, another recent study showed that dapagliflozin treated patients with heart failure had cardiovascular benefits irrespective of diabetes[13]. Present study was planned to highlight the role of oral dapagliflozin in reducing worse cardiac events and deaths among NYHA class II and III heart failure patients.

METHODOLOGY

Cardiac patients (n=480) who belonged from class II and III with mild to moderate reduced ejection fraction were added in this study. This study was held at Cardiology Department at Mayo Hospital. All patients received SGLT2 inhibitors at a dose of 10mg once daily or matching placebo, in addition to usual therapy for eight weeks. Both male and female patients between older than 30years with a diagnosis of heart failure with left ventricular ejection fraction of ≤40% if they were in NYHA class II and III, evidenced by structural heart disease and elevated natriuretic peptide level were enrolled. Patients having symptoms of hypotensionor systolic blood pressure <95 mmHg, rapidly declining renal function or any malignancy were ruled out study. Calculated sample size was480 patients by keeping the power of study equal to 90%[13].

Statistical Analysis: SPSS-v25 analyzed the entered data. Mean ± SD were given for numeric data i.e., age, blood pressure and eGFR level. Categorical data i.e., gender, hypertension, dyslipidemias, NYHA class, primary composite outcome and cardiovascular death were presented as frequency. A independent sample t-test was used to compare blood pressure and eGFR levels between the two groups. Chi square test was used to compare the gender, NYHA class, primary composite outcome, and cardiovascular death. A p-value ≤0.05 was considered significant.

RESULTS

The mean age of all participants in both groups was 52.5 ± 8.4 years and 53.2 ± 9.1 years respectively as shown in figure-1.
Among both control and placebo groups, males were in majority making more than 50% of enrolled subjects. There were 57.5% males in treatment group while 54.6% males in placebo group. There were 42.5% females in treatment group while 45.4% females in placebo group. Table-1 presented baseline characteristics of patients who were divided into two groups. The distribution of patients across NYHA functional classes II and III is slightly different between the two groups. In the dapagliflozin group, 77.9% of patients are in Class II and 22.1% are in Class III, while in the placebo group, 72.9% are in Class II and 27.1% are in Class III with p-value of 0.203.Results suggested that there were no significant differences in these physiological measures between participants receiving dapagliflozin and those receiving placebo at baseline (table-1).

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Figure -1: Comparison of age between both groups

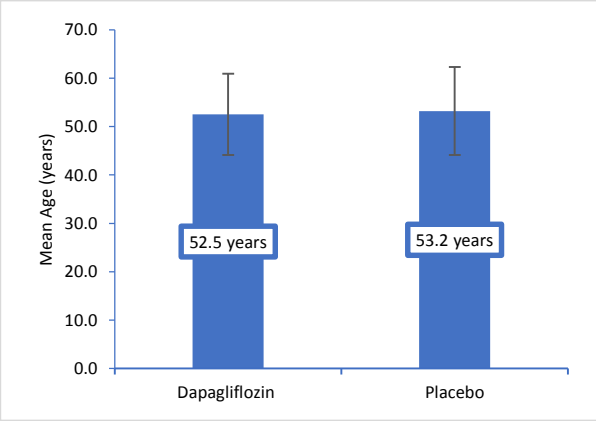


Table-2 showed that Dapagliflozin has significant benefits compared to placebo, as evidenced by lower rates of the primary composite outcome (15.8% vs. 23.3%, p = 0.038), hospitalization for heart failure alone (8.3% vs. 14.2%, p = 0.043), and urgent visits for heart failure (2.1% vs. 5.8%, p = 0.035). However, there was insignificant difference in cardiovascular death between both groups (5.8% vs. 8.8%, p = 0.219).

Table-1: Physiological measure of study participants

Parameters	Group		p-value
	Dapagliflozin	Placebo	
Hypertension	185 (77.1%)	178(74.2%)	0.457
Dyslipidemia	157 (65.4%)	163 (67.95)	0.561
Type 2 diabetes	164 (68.3%)	169(70.4%)	0.621
SBP, mmHg	133.7±18.4	132.8±19.6	0.329
DBP, mmHg	83.2 ± 9.8	80.2 ±10.4	0.360
eGFR, ml/min per 1.73m^2	71.4 ±19.2	69.8 ±20.3	0.390
NYHA Class II	187 (77.9%)	175(72.9%)	0.203
NYHA Class III	53 (22.1%)	65 (27.1%)	

Table-3 demonstrated that insignificant difference existed among groups on the basis of sex distribution for cardiovascular outcomes.

Table-4 demonstrated that significant difference existed among groups on the basis of NHYA classification for cardiovascular outcomes. Significant difference appeared among groups with patients having class II heart failure for primary composite outcome with p-value of 0.039.

Figure-2 showed causes of death according to different etiological factors between both groups.

Table-2: Adverse cardiac events among enrolled study

Parameters	Group		p-value
	Dapagliflozin	Placebo	
Primary Composite Outcome	38 (15.8%)	56 (23.3%)	0.038*
Hospitalization for heart failure	20 (8.3%)	34 (14.2%)	0.043*
Urgent visit for heart failure	5 (2.1%)	14 (5.8%)	0.035*
Cardiovascular death	14 (5.8%)	21 (8.8%)	0.219

*Statistically significant.

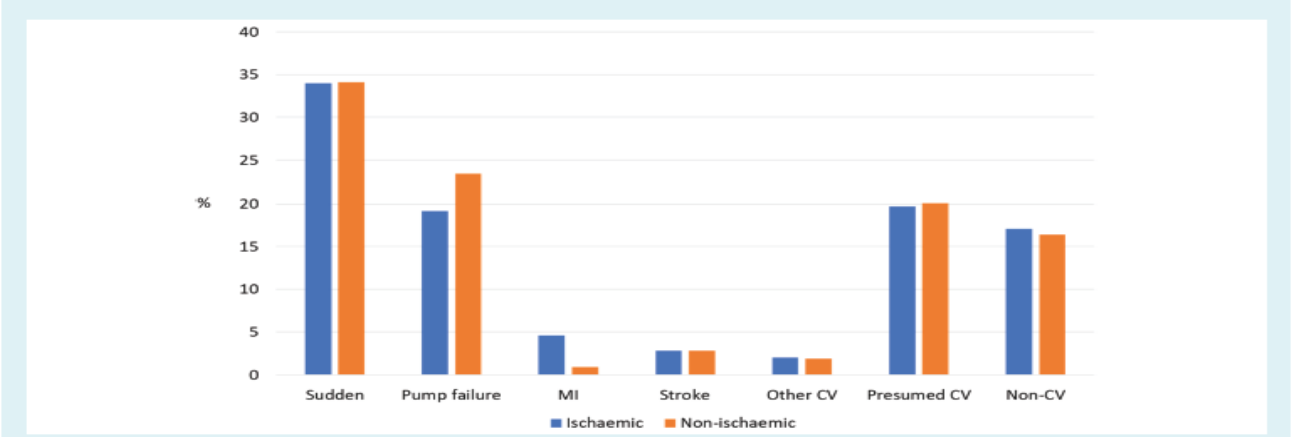
Table-3: Gender wise comparison of Cardiovascular Outcomes between both groups

Primary and Secondary Cardiovascular Outcomes	Male		p-value	Female		p-value
	Dapagliflozin (n=138)	Placebo (n=131)		Dapagliflozin (n=102)	Placebo(n=109)	
Primary Composite Outcome	23 (16.7%)	32 (24.4%)	0.115	15 (14.7%)	24 (22.0%)	0.171
Hospitalization/urgent visit for HF	16 (11.6%)	28 (21.4%)	0.030*	9 (8.8%)	20 (18.3%)	0.045*
Hospitalization for heart failure	11 (8.0%)	18 (13.7%)	0.127	9 (8.8%)	16 (14.7%)	0.188
Urgent visit for heart failure	2 (1.4%)	8 (6.1%)	0.044	3 (2.9%)	6 (5.5%)	0.357
Cardiovascular death	7 (5.1%)	12 (9.2%)	0.191	7 (6.9%)	9 (8.3%)	0.702

Table-4: Gender wise comparison of Cardiovascular Outcomes between both groups

Primary and Secondary Cardiovascular Outcomes	NYHA Class II		P value	NYHA Class III		p-value
	Dapagliflozin (n=187)	Placebo(n=175)		Dapagliflozin(n=63)	Placebo(n=65)	
Primary Composite Outcome	27 (14.4%)	40 (22.9%)	0.039*	11 (17.5%)	16 (24.6%)	0.321
Hospitalization/urgent visit for HF	17 (9.1%)	33 (18.9%)	0.007*	8 (12.5%)	15 (23.1%)	0.117
Hospitalization for heart failure	13 (7.0%)	23 (13.1%)	0.049*	7 (11.1%)	11 (16.9%)	0.344
Urgent visit for heart failure	3 (1.6%)	10 (5.7%)	0.036	2 (3.2%)	4 (6.2%)	0.425
Cardiovascular death	8 (4.3%)	11 (6.3%)	0.392	6 (9.5%)	10 (15.4%)	0.316

Figure-2: Different etiological factors of death among groups



DISCUSSION

Literature review has demonstrated that Type 2 diabetes mellitus has inflicted more than 450 million adults[1]. Type-2 diabetic patients usually develop more cardiac issues like heart failure in comparison to general population[2,3] due to various abnormalities in their BMI, lipid profiles[2,3], ultimately leads to death[4]. Due to lack of local literature, we conducted the present study in-order to review the safety of Dapagliflozin in reducing the cardiac events and deaths among class II and class III heart failure patients. Due to change in life style and modifications, incidence of coronary artery disease has increased. In our society, hakeem medications and false believes about drugs have drifted people to non compliance hence this aggravated clinical burden of disease.

Among both control and placebo groups, males were in majority making more than 50% of enrolled subjects. There were 57.5% males in treatment group while 54.6% males in placebo group. There were 42.5% females in treatment group while 45.4% females in placebo group. Literature review has shown that majority of studies have enrolled more males than females. This may be due to high incidence of cardiac issues among males due to smoking or any other factor[12-14].

Present study followed similar method of enrollment, inclusion and exclusion criteria but the duration of study was changed and increased to 8 weeks as used by previous researchers.[9]In current study, all patients received Tab. Dapagliflozin 10mg once daily or matching placebo, in addition to usual therapy for 02 continuous months. One previous study used tab. Dapagliflozin 10mg daily but only for 4 weeks[14].

Table-1 showed thatinsignificant differences in SBP (p = 0.329), DBP (p = 0.360), or eGFR (p = 0.390) between both groups. No differences in these physiological measures between participants receiving dapagliflozin and those receiving placebo at baseline were seen.Paradoxical results were demonstrated by one previous study that showed significant difference between treated group with dapagliflozin and placebo with p-value of <0.001[14].

Results in table-1 showed that percentage of patients with type-2 diabetes in the dapagliflozin group (68.3%) was slightly lower than in the placebo group (70.4%), but once more, this difference is not statistically significant (p = 0.621). The distribution of patients across NYHA functional classes II and III is slightly different between the two groups. In the dapagliflozingroup, 77.9% of patients are in Class II and 22.1% are in Class III, while in the placebo group, 72.9% are in Class II and 27.1% are in Class III with p-value0.203.Paradoxically, one previous study, enrolled patients in both groups with heart failure having NYHA class II (65%), III (34%) and IV (1.2%). They had maximum number of patients in class II followed by III and IV[15].

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-2. 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]However, there was no statistically significant difference in cardiovascular death between the dapagliflozin and placebo groups (5.8% vs. 8.8%, p = 0.219). Overall, dapagliflozin showed significant reductions in various cardiovascular events compared to placebo, highlighting its potential as a beneficial intervention in this population. Similar results were shown by many previous studies that demonstrated protective role of dapagliflozin among heart failure patients[12-15].

Table-4 demonstrated that significant difference existed among groups on the basis of NHYA classification for cardiovascular outcomes. Significant difference appeared among groups with patients having class II heart failure for primary composite outcome with p-value of 0.039. However, one previous study demonstrated insignificant difference among different classes of NYHA with respect to cardiovascular outcomes. Insignificant difference appeared among groups with patients having class II and III heart failure for primary composite outcome with p-value of 0.67[13].

CONCLUSIONS

It was concluded that dapagliflozin showed significant reductions in various cardiovascular events and deaths compared to placebo thus highlighting its potential as a beneficial intervention in our population.

Limitations: Limitations included small study duration, no genetic workup, single centre study with limited financial resources.

Author's contribution: SMA: Overall supervision and Write up and literature review.

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Conflict of interest: Nothing to be declared

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