Section: Cardiology

Original Research Article

REAL WORLD EXPERIENCE OF SAFETY AND EFFICACY OF DAPAGLIFLOZIN IN PATIENTS WITH HEART FAILURE AND PRESERVED EJECTION FRACTION (HFpEF) IN INDIAN POPULATION

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Abstract

Background: The prevalence of heart failure with mildly reduced or preserved ejection fraction (HFpEF) markedly increases with age, with older individuals disproportionately facing excess risk for mortality and hospitalization. To determine the efficacy and safety of dapagliflozin across the age spectrum among Indian population in patients with heart failure with preserved ejection fraction (LVEf >40%). **Materials and Methods:** This was an Observational study involving 100 patients with HFpEF initiated on dapagliflozin in both the inpatient and outpatient settings for a period of 1 year at NSCB medical college, Jabalpur (M.P.) and were divided according to age. Data were collected, managed and analysed and critically reviewed to ensure accuracy and completeness of the data analysis. All patients were required to have an echocardiogram for assessment of left ventricular ejection fraction (LVEF) ≤40%, or confirmed HFpEF (LVEF >40%), and initiated on dapagliflozin for the management of HFpEF in either the inpatient or outpatient setting along with other guideline directed medical therapy (GDMT). No patients with type 1 diabetes mellitus were included in this study and hospitalized participants were enrolled in the study. **Result:** Dapagliflozin consistently reduced the risk of the primary outcome across all age categories. Older patient were more frequently females and systolic blood pressure and in patients with atrial fibrillation were higher, and history of atrial fibrillation or flutter, hypertension, chronic obstructive pulmonary disease, and prior stroke were more common with higher age. Type 2 diabetes was more common among patients in the age categories 55 to 64 and 65 to 74 than in patients <55 and ≥75 years of age. **Conclusion:** In clinical practice, early initiation of dapagliflozin is safe, well-tolerated and resulted in earlier discontinuation or dose reduction in medications, providing opportunities to further optimise other HF medicines.

INTRODUCTION

Patients of heart failure with maintained ejection fraction (HFpEF) or heart failure with mildly decreased ejection fraction (HFmrEF) are typically older than those of heart failure with reduced ejection fraction, and prevalence of these conditions rises significantly with age.[1] SGLT2 (sodium-glucose cotransporter 2) inhibitors coupled to standard therapy have been demonstrated to lower cardiovascular mortality and heart failure (HF) events in patients with reduced and preserved ejection fraction, especially in older persons with HF with mildly reduced SGLT2 levels.[2,3] Recently, it was shown that dapagliflozin is both effective and safe for individuals with heart failure and a low ejection fraction across a wide age range.[4] It is less known if people with heart failure who have mildly decreased or retained ejection fraction also experience the advantages of dapagliflozin across the age spectrum.

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MATERIALS AND METHODS

This was an Observational study involving 100 patients with HFpEF initiated on dapagliflozin in both the inpatient and outpatient settings for a period of 1 year at NSCB medical college, Jabalpur (M.P.) and were divided according to age while collecting and analysing data. All patients previously diagnosed as heart failure with preserved ejection fraction (HFpEF) irrespective of aetiologies and confirmed on echocardiogram were initiated on dapagliflozin for the management of HFpEF in either the inpatient or outpatient setting. No patients with type 1 diabetes mellitus were included in this study and hospitalized participants were enrolled in the study. 30+ adults older than years, with or without diabetes, and an LVEF >40%, evidence from functional classes II-IV of the New York Heart Association structural heart disease (left natriuretic peptide increase and ventricular hypertrophy were qualified.

Methodology: Depending on a person's type 2 diabetes status at baseline medically treating comorbidities concurrently was advised in accordance with the regional standard of care. Demographic data, clinical parameters, laboratory results, and medications upon initiation of dapagliflozin, and an average of three months post-initiation of dapagliflozin, were extracted. The primary outcome of this analysis was the composite of deteriorating heart failure events, which was defined as either an unanticipated hospitalization or an urgent heart failure episode. The total number of heart attacks was one of the major secondary outcomes. Occurrences that result in failure (hospitalization for heart failure, urgent heart failure visit) and cardiac death, cardiac death, changes from the baseline in all-cause mortality.

Statistical Analysis: The statistical analysis was performed using SPSS for windows version 22.0 software (Mac, and Linux). Categorical data were presented as number of patients and percentages; normally distributed, continuous data as means ± standard deviations (SD). Chi-square test was used to find the association among variables. The critical value of P indicating the probability of significant difference was taken as <0.05 for comparison.

RESULTS

As per [Table 1] amongst HfPEF, older patient were more frequently females and had higher systolic blood pressure. These elderly patients had higher history of atrial fibrillation or flutter, hypertension, chronic obstructive pulmonary disease. History of prior stroke were more common with higher age. Type 2 diabetes was more common among patients in the age categories 55 to 64 and 65 to 74 than in patients <55 and ≥75 years of age. Mean left ventricular ejection was the highest among participant's ≥75 years, and this oldest segment was more likely to have left ventricular ejection fractions ≥60% compared with younger age groups (37% versus 25%). Body mass index, heart rate, diastolic blood pressure, HbA1c levels, and estimated glomerular filtration rate tended to be lower with increasing age.

As per [Table 2] overall, AEs and treatment discontinuation for any cause occurred more frequently with increasing age, although no significant differences were detected between patients receiving dapagliflozin. Rates of serious AEs (SAEs) and AEs leading to treatment discontinuation were similar within each age category, with no significant interaction between ages.

As per [Table 3] early initiations of dapagliflozin shows the dose of heart medications has been decreased whether it is ACEI, ARB, BB or MRB and this was significant.

Table 1: Demographic and Clinical Characteristics of trial

Variable	Age <55 y (n=38)	Age 55–64 y (n=17)	Age 65–74 y (n=23)	Age >75 y (n=22)	p-value
Age, y	49.7±3.9	60.6±2.7	69.9±2.8	80.5±4.2	
Male, n (%)	23 (68.0%)	12 (64.6%)	13 (56.5%)	13 (50.9%)	0.01
Medical history, n (%)					
Atrial fibrillation/flutter	11 (26.6%)	11 (42.8%)	13 (57.3%)	16 (65.5%)	0.01
Hypertension	26 (77.5%)	14 (86.3%)	20 (89.4%)	19 (90.4%)	0.01
Dyslipidemia	17 (52.1%)	16 (66.4%)	14 (63.7%)	16 (64.2%)	0.06
Type 2 diabetes	24 (43.8%)	14 (49.4%)	11 (48.8%)	15 (39.5%)	0.01
Chronic obstructive pulmonary disease	20 (5.9 %)	10 (10.4%)	12 (11.7%)	6 (11.3%)	0.02
Atherosclerotic cardiovascular disease	19(50.0%)	12 (80.8%)	13 (58.6%)	14 (54.3%)	0.09
Prior HF hospitalization	15 (45.9%)	12 (38.2%)	16 (41.4%)	13 (40.0%)	0.44
NYHA class, n (%)					0.08
I	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.0 %)	
II	25 (76.6%)	14 (76.0%)	17 (76.4%)	19 (83.8%)	
III	16 (42.5%)	07 (23.8%)	11 (43.5%)	16 (75.8%)	
IV	3 (0.9 %)	2 (0.2 %)	4 (0.2 %)	9 (0.3 %)	
LVEF (%)	51.0±8.8	51.8±8.2	53.9±8.5	55.8±8.8	0.01
Physiological measures					
Body mass index	31.3±7.0	31.9±6.5	30.3±6.2	28.5±5.5	0.01
Systolic blood pressure, mm Hg	125.4±17.3	127.1±15.2	128.4±15.6	128.1±14.9	0.02
Diastolic blood pressure, mm Hg	77.0±10.6	75.8±10.2	74.6±10.1	72.2±10.3	0.01
HbA1c (%)	6.5±2.1	6.5±1.8	6.6±1.4	6.7±1.1	0.01
Heart rate, beats/min	72.5±11.5	72.4±11.6	71.8±11.7	70.8±11.9	0.01

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Creatinine, µmol/L	99.4±38.5	100.0±31.4	101.6±30.9	104.7±29.9	0.01
eGFR, mL/min per 1.73 m2	78.0±23.9	69.2±19.3	62.1±18.1	54.7±16.3	0.01

Table 2: Occurrence of Adverse Events According to Age Categories

Adverse event	Age <55 y (n=38)	Age 55–64 y (n=17)	Age 65–74 y (n=23)	Age >75 y (n=22)	p-value
Any serious AE (including death), n	5	7	8	9	0.58
Any AE leading to treat- ment discontinuation, n	5	9	9	9	0.43
Any AE leading to treatment interruption, n	5	5	11	12	0.46
Any potential risk factor AE for amputation affecting lower limbs, n	12	14	18	19	0.15
Any renal serious AE or DAE, n	5	4	8	13	0.56

Table 3: Changes to patients' heart failure medications post-initiation of dapagliflozin

Medication	Dose decreased	Dose increased	Discontinued	p-value
ACEI	5	1	0	0.01
ARB	5	2	2	
Beta Blockers	4	1	1	
MRB	5	2	2	

ACEI- Angiotensin converting enzyme inhibitor
ARB- Angiotensin receptior blocker
MRB-Mineralocorticoid receptor blocker.

DISCUSSION

The current study emphasizes the possible advantages of early dapagliflozin administration, especially the modifications to other HF pharmaceutical treatments and the tolerability of dapagliflozin. This is better than the findings from the DAPA-HF trial, where dapagliflozin was only administered to patients after their treatment had already been optimized and only 10.4% of patients had their diuretic dose reduced at six months.[5] Dapagliflozin decreased cardiovascular mortality or deterioration in individuals with HF and had a modestly reduced or preserved ejection fraction. These are significant benefits as ACEI are used only to relieve congestion symptoms and improve exercise capacity without reducing mortality.[6] Additionally, patients who remain on diuretics long term, particularly on high doses, are associated with higher mortality, which may indicate the presence of more severe disease.[7] Therefore, reduction in dose and relief from congestion without the need for long-term diuretics is prognostically advantageous for HF patients which may be achieved by using dapagliflozin in these patients. Despite AEs as one aged, safety outcomes did not differ by age between the randomized patients to placebo and dapagliflozin, especially in the oldest section approximately 75 years old as was seen in our study as well.[7] The average frequency of older patients had increased rates of atrial flutter and fibrillation with decreased BMI, heart rate, and diastolic blood pressure increases in blood pressure, HbA1c levels, and age.

The present study found that those who were on ACEi/ARB at baseline switched to decreased dose post-initiation of dapagliflozin. The superiority of Dapagiflozin to ACEi in reducing mortality and HF hospitalisation has been documented in several studies.[8,9] While this study found reductions in blood pressure and weight, these changes may result from the concomitant up-titration of other HF therapies and not just the effect of dapagliflozin alone.

According to the study's findings, dapagliflozin is safe and well-tolerated by (HFpEF) patients when used in conjunction with other prognostic treatments early on. The rate of dapagliflozin discontinuation in this study was comparable to that in studies using other SGLT2 inhibitors.[9,10] Dapagliflozin was permanently stopped in these patients for a number of reasons, the main one being recurring vaginal thrush infections. Similar explanations were given for the withdrawal of dapagliflozin in earlier trials where it was shown that the treatment group had a greater prevalence of genital fungal infections.[11,12]

Given their advantages in treating and preventing a variety of conditions, such as HF, T2DM, and chronic kidney disease with proteinuria, SGLT2 inhibitors can ultimately be safely initiated and managed collaboratively in primary and secondary care.[13] It's possible that many people with these problems will never need to be sent to secondary care. To prevent excessive variance in practice and confusion, it is required to simplify a practical guideline that covers initiation and management for a variety of indications and has universal application in primary and secondary care. The approval of further SGLT2 inhibitors has benefitted HF patients, especially those with heart failure with preserved ejection fraction (HFpEF). Although renal impairment is more likely in older people, comparable among patients for severe renal adverse events who took dapagliflozin without regard to even in those who are over 75 years old. In spite of increased concurrent use of cardiovascular drugs with volume depletion and diuretic effects in elderly patients not more prevalent among those on dapagliflozin at every age which is similar in few studies.[14,15]

Our study has few limitations. Firstly, the study was a single-centre, observational study with a relatively small sample size, which could affect the

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generalisability of the results. Secondly, the age categories are arbitrary, although the categories are commonly used in similar analyses.

CONCLUSION

In conclusion, this study has demonstrated the benefits and safety of the early initiation of dapagliflozin in patients with (HFpEF) in line with the updated ESC HF guideline. In clinical practice, early initiation of dapagliflozin resulted in earlier discontinuation or dose reduction inACEI/ARB, providing opportunities to further optimise other HF medicines. Dapagliflozin is safe and well-tolerated in a real-world population, outside the setting of a clinical trial. Counselling on perineal hygiene may avoid discontinuation of dapagliflozin due to minimising the risk of genital thrush infection.

Dapagliflozin decreased cardiovascular death or worsening HF events in patients with HF who had mildly reduced or retained ejection fraction across the age spectrum. Having a respectable safety record, among others typically neglected and most vulnerable older people portion of patients who are under 75. Dapagliflozin should be considered as a key HF pharmacological therapy rather than an add-on therapy, hence, it should be initiated earlier in the treatment pathway in order to minimise delays in treatment optimisation.

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