Research Article

Interventional Cardiology

Empagliflozin in patients with heart failure and reduced ejection fraction

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Abstract:

Background: Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors reduce the risk of a first hospitalization for heart failure in type 2 diabetics. But data regarding role of SGLT2 inhibitors in HFrEF is limited.

Methods: In this prospective small centre trial, we randomly assigned 822 patients in class II, III, NYHA and an ejection fraction of 35% or less to receive either empagliflozin or placebo, in addition to optimal medical therapy. The primary outcome was a composite of worsening heart failure or cardiovascular death.

Results: Over a period of 24months, the primary outcome occurred in 61 of 411 patients (14.8%) in the empagliflozin group and in 94 of 411 patients (22.9%) in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.87; P 0.003). Of the patients receiving empagliflozin, 40 (9.7%) were hospitalized for heart failure, as compared with 60 patients (14.6%) receiving placebo (hazard ratio, 0.67; 95% CI, 0.46 to 0.97). Cardiovascular deaths occurred in 19 patients (4.6%) who received empagliflozin and in 26 (6.3%) who received placebo(hazardratio, 0.73; 95% CI, 0.41 to 1.30). A total of 36 patients (8.75%) in the empagliflozin group and 49 patients (11.9%) in the placebo group died from any cause (hazardratio, 0.97; 95% CI, 0.97 to 1.30).

Conclusion: In patients with heart failure and a reduced ejection fraction, the risk of cardiovascular death and heart failure is lower among those who received empagliflozin compared to placebo, irrespective of their diabetic status.

Keywords: Empagliflozin . Ejection fraction . Heart attack . Placebo . Cardiovascular disorders

Introduction

Diabetes mellitus is an independent risk factor for HF [1], with studies showing that subclinical atherosclerotic and nonatherosclerotic myocardial damage occurs early in the natural history of diabetes mellitus, often before diagnosis of the condition [2]. SGLT-2 inhibitors are approved for the management of Type 2 Diabetes Mellitus (T2D) and have recently been investigated in several large, placebo-controlled trials for cardiovascular safety as well as efficacy in patients with Diabetes [3]. They have been shown to decrease the risk of first hospitalization for heart failure in DM-[2]. We designed this trial to prospectively evaluate the efficacy and safety of the SGLT2 inhibitor empagliflozin in patients with heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.

Methods

Patients

This is a prospective randomised single centre trial on HFrEF patients admitted in Ram Manohar Lohia Institute of Medical Sciences. We enrolled patients with ejection fraction of 35% or less and New York Heart Association (NYHA) class II, III, symptoms.

Patients were on optimal medical therapy including an angiotensin-converting–enzyme inhibitor, or angiotensin-receptor blocker, or sacubitril–valsartan plus a beta-blocker, and MRA and a diuretic where required. Patients with type 2 diabetes continued to take their glucose-lowering therapies, but doses could be adjusted as required.

Exclusion criteria included age less than 18, recent treatment with or unacceptable side effects associated with an SGLT2 inhibitor, type 1 diabetes mellitus, hypotension and an estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m^2

Study design

Patients with HF admitted to ICCU of RMLIMS from May 2016 to June 2018 with Ejection fraction 35% or less and NYHA Class II or III were enrolled in this study after stabilisation. All were receiving optimal medical therapy. They were randomized into two groups one received Empagliflozin 25mg over and above the OMT and the other was given a placebo.

Patients were evaluated at 15 days and 30 days for any features of heart failure, adverse events, renal function. Additional visits were planned at 3, 6 and 12 months.

Outcomes

The primary outcome was a composite of death or worsening heart failure from cardiovascular causes. A key secondary outcome was a composite of hospitalization for heart failure or cardiovascular death during the follow up period. Other secondary outcomes were total number of hospitalizations for heart failure or deaths, change in KCCQ score; deterioration in renal functions and death from any cause.

Statistical analysis

Statistical significance of differences among the groups of patients was tested using the Fischer exact or chi-square test. Odds ratios were used to measure the effect of Empagliflozin vs placebo with respect to end points. All the analysis was carried out by using SPSS 21.0 version (Chicago Inc. USA). We analyzed the total symptom score on the Kansas City Cardiomyopathy Questionnaire as a composite, rank-based outcome, incorporating patient vital status at 8 months along with a change in score from baseline to 8 months.

Results

Patients

From May 2016 to June 2018 a total of 822 HFrEF patients admitted to RMLIMS were randomly assigned to receive either empagliflozin or placebo. The patients and the therapies for heart failure were well balanced between the two groups at baseline (Table 1). About 75% patients had a history of DM-2 in both the groups. Information on vital status during the 30 day and 1 year follow-up period was available for all the patients.

Table 1: Characteristics of the patients at baseline*.

	Empagliflozin	Placebo
Characteristic	(n=411)	(n=411)
Age-year	62.2 ± 11.0	63.5 ± 10.8
Female sex-no. (%)	102(24.8)	103(25.0)
NYHA functional classification-no. (%)		
II	267(65.3)	271(66.4)
III	131(32.0)	133(32.7)
IV	13(3.0)	07(1.7)
Heart rate-beats/min	74.5 ± 12.6	75.0 ± 14.4
Systolic blood pressure-mm Hg	128 ± 12.3	127 ± 13.3
Left ventricular ejection fraction-%	30.8 ± 7.8	29.7 ± 8.5
Principal cause of heart failure-no. (%)		
Ischemic	187(45.6)	210(51.3)
Nonischemic	224(54.4)	201(48.7)
Medical history-no. (%)		
Hospitalization for heart failure	112(27.4)	112(27.5)
Atrial fibrillation	76(18.6)	76(18.0)
Diabetes mellitus	312(76.0)	308(75.0)
Estimated GFR		
Mean-ml/min/1.73 m^2	76.0 ± 19.6	74.6 ± 19.3
Diuretic	371(90.4)	376(91.5)
ACE inhibitor	244(59.3)	242(58.8)
ARB	140(34.0)	133(32.3)
Sacubitril–valsartan	64(15.5)	69(16.9)
Beta-blocker	399(97.0)	394(96.0)
Mineralocorticoid receptor antagonist	269(65..5)	265(64.6)
Digitalis	48(11.8)	51(12.6)
Glucose-lowering medication-no./total no. (%)*		
Metformin	234/312(75.2)	228/308(74.2)
Sulfonylurea	134/312(43.0)	129/308(42.0)
DPP-4 inhibitor	44/312(14.2)	46/308(15.1)
Insulin	80/312(25.6)	80/308(26.0)

*Glucose-lowering medications are listed only for the patients who had a history of diabetes at baseline

Outcomes

The primary composite outcome of worsening heart failure (hospitalization or an urgent visit) or death from cardiovascular causes occurred in 61 patients (14.8%) in the empagliflozin group and in 94 patients (22.9%) in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.48 to 0.87; P 0.003) (Table 2). Primary composite events were significantly lower in the empagliflozin arm compared to the placebo. Patients receiving empagliflozin, 40 (9.7%) were hospitalized for heart failure, as

compared with 60 patients (14.6%) receiving placebo (hazard ratio, 0.67; 95% CI, 0.46 to 0.97). Cardiovascular deaths occurred in 19 patients (4.6%) who received empagliflozin and in 26 (6.3%) who received placebo (hazard ratio, 0.73; 95% CI, 0.41 to 1.30).

The secondary composite outcome of hospitalization for heart failure or death from cardiovascular causes was significantly lower in the empagliflozin group than in the placebo group (hazard ratio, 0.77; 95% CI, 0.65 to 0.85; P<0.001) (Table 2). There were 98

Table 2: Primary and secondary cardiovascular outcomes and adverse events of special interest.

Variable	Empagliflozin (n=411) values	Placebo (n=411) values	Hazard or Rate Ratio or Difference (95% CI)	p Value
Efficacy outcomes				
Primary composite outcome-no. (%)	61 (14.8)	94 (22.9)	0.65(0.48-0.87)	0.003
Hospitalization or an urgent visit for heart failure	39 (9.0)	57 (13.9)	0.68(0.47-1.00)	0.052
Hospitalization for heart failure	40 (9.7)	60 (14.6)	0.67(0.46-0.97)	0.034
Cardiovascular death	19 (4.6)	26 (6.4)	0.73(0.41-1.30)	0.285
Secondary outcomes				
Cardiovascular death or heart-failure hospitalization-no. (%)	60 (14.5)	91 (22.1)	0.67(0.58-0.87)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	98(24)	127(31)	0.71(0.59-0.94)	<0.001
Change in KCCQ total symptom score at 8 mo	7.1 ± 14.4	2.3 ± 16.2		<0.001
Worsening renal function-no. (%)	05(1.2)	09 (2.1)	0.64(0.48-0.97)	0.057
Death from any cause-no. (%)	36 (8.75)	49 (11.9)	0.97(0.83-1.30)	0.041
Safety outcomes				
Discontinuation due to adverse event-no./total no. (%)	O5/411 (1.2)	03/411(0.7)	1.2(0.96-1.56)	NA

total first and recurrent events in the empagliflozin group and 91 total events in the placebo group, which resulting in hazard ratio 0f 0.67(95% CI, 0.58 to 0.87; P<0.001).

The improvement in the total symptom score on the Kansas City Cardiomyopathy Questionnaire was greater in the empagliflozin group than in the placebo group between baseline and month 8 (Table 2), which was statistically significant. A total of 36 patients (8.75%) in the empagliflozin group and 49 patients (11.9%) in the placebo group died from any cause (hazard ratio, 0.97; 95% CI, 0.97 to 1.30).

Safety

Adverse events rarely led to a discontinuation of treatment. 5 patients in empagliflozin and 3 patients in placebo group discontinued treatment due to adverse events.

Discussion

EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was the first cardiovascular outcomes trial (CVOT) to investigate the effects of SGLT-2 inhibition with empagliflozin on cardiovascular outcomes in T2D [4]. In patients with T2D and established atherosclerotic disease (N=7020), empagliflozin met an exploratory end point of statistically significant reduction in hospitalization for HF versus placebo. An absolute risk reduction (ARR) of 1.4% and relative risk reduction of 35% in hHF was observed in the empagliflozin group.

The DECLARE-TIMI 58 trial, published in November 2018, is the first CVOT to include hHF or cardiovascular death as 1 of its primary end points [3]. The DECLARE-TIMI 58 trial investigated the effects of dapagliflozin versus placebo in a broad population of patients (N=17160) with T2D who had either multiple cardiovascular risk factors (59.4%) or established atherosclerotic disease (40.6%) Dapagliflozin met 1 of its primary end points of a statistically significant reduction in hHF or cardiovascular death versus placebo, which was driven by a lower rate in hHF. Dapagliflozin was associated with a 0.8% ARR and 27% relative risk reduction in hHF [5,6]. Table 3 gives an overview of potential mechanisms for improved cardiac functions with SGLT2 [7,8].

Table 3: Overview of potential mechanisms of improved cardiac function with SGLT-2 inhibitors.

Potential mechanisms
1. Stimulation of natriuresis
2. Stimulation of osmotic diuresis
3. Cardiomyocyte Na+/H exchanger inhibition
4. Increased myocardial energetics (via altered myocardial substrate metabolism)
5. Reduction in left ventricular mass
6. Improved systolic and diastolic function
7. Improved cardiac filling conditions secondary to reductions in preload and afterload
8. Increased circulating proangiogenic progenitor cells
9. Increased erythropoietin
10. Improved endothelial function
11. Reduction in myocardial CaM kinase II activity
12. Improved myocardial autophagy
13. Inhibition of cardiac fibrosis

And then came the DAPA-HF trial [5] in NEJM 2019 which established that among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. Despite we being avid users of SGLT-2 data from India is limited and hence this small randomized trial of empagliflozin in patients with HFrEF. The primary outcomes of worsening heart failure or death from cardiovascular causes was lower in the empagliflozin group than in the placebo group. All the components of primary outcomes were lower in the empagliflozin arm which is quite comparable to the results of DAPA-HF trial5 and as reported by Inzucchi et al. [9] The use of empagliflozin also resulted in improved symptoms of heart failure, as measured on the KCCQ score [10,11].

As observed in DAPA-HF trial, we found that Empagliflozin was equally effective in the 25% of patients without type 2 diabetes as in those with diabetes. The cardiovascular benefits of SGLT-2 inhibitor in patients of HFrEF corroborates the findings of DAPA-HF and earlier assumptions that SGLT-2 has benefits in decreasing the incidence of heart failure apart from other pleotopic benefits.

The patients in our trial were high risk patients as they were admitted to our ICCU due to decompensation of heart failure and they were already receiving most of the heart failure medications like diuretics, ACE/ARB, beta-blockers and MRAs. Whatever benefit we observed was over and above the benefit discerned from the other therapies. Despite the use of SGLT2 there was no increase in renal dysfunction among the patients [6,10]. Overall, few patients stopped empagliflozin or placebo because of any adverse effect.

Our trial has some limitations. The number of patients in our trial is small. A large proportion of our patients were diabetics, so whether we can postulate the findings to non-diabetics is questionable. The use of ARNI [12,13], was low in our patients and this could be questioned as inability to provide optimal medical therapy. However, the postulated mechanisms of action of SGLT2 inhibition and neprilysin inhibition are distinct. So in patients with heart failure and a reduced ejection fraction, those who received the SGLT2 inhibitor empagliflozin had a lower risk of cardiovascular death and heart failure regardless of their diabetic status.

Conclusion

We can assume from the above study that in patients with heart failure and a reduced ejection fraction, the risk of cardiovascular death and heart failure is lower among those who received empagliflozin compared to placebo, irrespective of their diabetic status.

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