Effect Of Empagliflozin On Heart Failure Outcomes In Post-Acute Myocardial Infarction Patients

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DOI: 10.47750/pnr.2021.12.02.45

Abstract

Background: Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide, often resulting in heart failure (HF) as a significant complication. Recent studies have highlighted the potential benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors, particularly empagliflozin, in improving cardiovascular outcomes in patients with heart failure.

Objectives: To evaluate effects of empagliflozin in post-AMIpatients in term of hospitalization rates, improvement in left ventricular functionand cardiovascularmortality.

Study Design: A randomized, placebo-controlled trial

Place and Duration of the Study: Department of Cardiology, MTI Gajju Khan Medical College, Swabi, KP, DHQ teaching hospital Swabi, Pak Medical Center and Hospital Peshawar and DHQ teaching hospital Bannu from January 2020 to April 2021 for a total duration of 16 months.

Methodology: Six hundreds 600 Patients hospitalized for AMI and at risk for heart failure were enrolled and assigned to receive either empagliflozin (10 mg daily) or placebo within 14 days of admission. Demographic data, base line characteristics of patients and LVEFwas recorded at baseline. Patients in both groups were followed every month as their follow up for a total duration of 6 months. Three parameters were recorded at the end of study including frequency of heart failure hospitalization, improvement in ejection fraction and mortality due to cardiovascular cause in both groups. These parameters were compared using statistical tools to find the difference in both groups.

Results: The group that received empagliflozin (n = 300) had a lower number of heart failure hospitalizations, at 54 (18%) against 90 (30%) in the placebo group (n = 300), giving 12% absolute risk reduction. LVEF increased by 10 ± 3% in the empagliflozin group compared with 4 ± 2% in the placebo group. Mortality rate was also reduced with 24 patients (8%) in the empagliflozin group as distinguished from 45 patients (15%) in the placebo group.

Conclusion: Empagliflozin has decreased HF hospitalization rate, improved left ventricular function and reduced mortality in patients after AMI.

Keywords: Empagliflozin, Post myocardial infarction, heart failure, mortality rate

INTRODUCTION

Acute myocardial infarction is a major health issue all over the world. It produces a large burden of morbidity and mortality. AMI is one of the leading causes of HF and a major factor causing left ventricular remodeling that result in HF is still not well understood. It may contribute to more hospitalizations, worse quality of life and higher death rates

in patients [1-2].Current pharmacological treatments for HF after AMI are ACE inhibitors, beta blockers and mineral corticoid receptor antagonists (MRAs) [3]. Nevertheless, new groups of drugs including sodium-glucose cotransporter-2 inhibitors (SGLT2) have been developed and seem to possess beneficial influences on the cardiovascular systems. Originally used to lower blood glucose levels in patients with type 2 diabetes, SGLT2 inhibitors, particularly empagliflozin, have significant CV risk reduction.

Previous major trials including empa-reg outcome highlighted the protective effects of empagliflozin in patients with type 2-diabetes by lowering cardiovascular mortality and lessening HF hospitalization [4, 5]. Similar results were demonstrated in the EMPEROR-Reduced trial, which explained empagliflozin's therapeutic utility in preventing worse cardiovascular prognosis in HF patients regardless of diabetes mellitus history [6].The favorable effects of Empagliflozin are believed to go beyond glycemic control in heart failure patients. These may be enhanced myocardial energy utilization, osmotic diuresis which reduces preload and after load, down regulation of inflammatory and oxidative stress activating pathways that are determinant in post AMI HF [7]. Given these effects, empagliflozin could benefit the left ventricle through reduction of fluid overload and reduction in cardiac work which may further translate into improvement in the left ventricular function in AMI patients [8&9].

This study therefore endeavors to evaluate the effect of empagliflozin on HF outcomes in the context of AMI through measurement of LVEF, HF hospitalization rates and cardiovascular mortality. Therefore, if empagliflozin proves effective in this regard, there is merit in including empagliflozin among standard therapies for AMI patientswho are at high risk of HF.

METHODOLOGY

In this open ended randomized controlstudy, patients were enrolled from January 2020 to April 2021 for a total duration of 16 months in a consecutive samplingmanner. Patients were assigned to two groups each consisting of 300 patients: an intervention group that received empagliflozin at a dose of 10 mg daily and a control group using placebo. This was a multicenter center study in which patients were recruited from Bacha Khan Medical complex Swabi, DHQ teaching hospital Swabi, Pak Medical Center and Hospital Peshawar and DHQ teaching hospital Bannu. It was a six months intervention in which specific cardiovascular events were assessed including heart failure hospitalization, LVEF and cardiovascular mortality. At first study encounter in CCU, all patients underwent protocol specified baseline echocardiography for estimating ejection fraction on modified Samson method as a marker of left ventricular function and a clinical exam. Patient was given a follow up date for OPD visit and contact number in case of dyspnea needing physician help. Subsequent studies were completed at 1,3 and 6th month at OPD visit to assess treatment compliance and study outcomes.

Inclusion Criteria

AMI patients within 48 hours of onset, had LVEF ≤ 40%, between 18 and 80 years of age, capable of oral medication without requiring urgent intensive care were included in the trial.

Exclusion Criteria

Patients with type 1 diabetes, chronic kidney disease (eGFR< 30 mL/min/1.73 m²), history of heart failure before the start of trial, severe liver disease, prior use of empagliflozin within 3 months before trial enrollment and patients with contraindications to empagliflozin use were excluded..

Data Collection

Patient demographic, baseline clinical characteristics, LVEF and outcome information such as HF hospitalization and mortality were obtained using a conventional data abstraction form. Echocardiographic data were collected at baseline, at 1, 3 and 6 months intervals.

Statistical Analysis

All statistical analysis was done usingstatistical package for social sciences SPSS software version 24.0. As for the descriptive measures of inference, continuous data were summarized and presented as means and standard deviations. Categorical data were presented as percentages. In comparing demographic distributions between study and control

group, continuous data were compared by t-tests and categorical data by chi-square tests. A value less than 0.05 were considered significant.

RESULTS

A total of 600 patients were enrolled in the study in which 300 were assigned to empagliflozin group and 300 to placebo group.In the comparison between the Empagliflozin and Placebo groups (n = 300 each), the baseline features are generally well-aligned, with no statistically significant changes noted in important factors. The average age is comparable between groups (65.3 ± 10.2 years for Empagliflozin versus 64.9 ± 9.8 years for Placebo). The gender distribution is almost same, comprising 70% men in the Empagliflozin group and 72% in the Placebo group (p = 0.61). The incidence of hypertension (56% vs. 58%, p = 0.65), diabetes mellitus (42% vs. 43%, p = 0.80), and smoking history (34% vs. 36%, p = 0.63) demonstrates no statistically significant changes. The baseline left ventricular ejection fraction (LVEF) is similar between the groups, with 38% ± 6 for Empagliflozin and 37% ± 5 for Placebo. The absence of substantial disparities in these variables indicates that the groups are adequately matched at baseline.It has been summarized in table no.1

The analysis of medication usage between the Empagliflozin and Placebo groups (each n = 300) indicated no statistically significant differences in the proportions of patients using critical cardiovascular drugs, implying similar treatment histories in both groups. ACE inhibitors were given to 88% of patients in the Empagliflozin group and 87% in the Placebo group (p = 0.75). Beta-blockers were similarly employed, with a prevalence of 90% in the Empagliflozin group and 91% in the Placebo group (p = 0.68). Mineralocorticoid receptor antagonists were given to 67% of patients in the Empagliflozin group and 65% in the Placebo group (p = 0.56). The usage of statins was comparable, with 93% in the Empagliflozin group and 92% in the Placebo group (p = 0.73). The statistics reveal that both groups had similar baseline medication profiles. It has been summarized in table no.2.

Primary outcomes analysis demonstrated that empagliflozin group had a significant improvement in HF hospitalizations where 54 patients (18%) were hospitalized compared with 90 patients (30%) in the placebo group, number needed to treat of 20 (95%CI: 10–100). The empagliflozin group depicted a highly significant improvement in LVEF compared to placebo; mean rise of LVEF was 10 ± 3% in the empagliflozin group compared to 4 ± 2% in the placebo group. Mortality was also significantly lower in empagliflozin group of 8% (24 patients) compared with placebo group of 15% (45 patients). Furthermore, fewer events of heart failure occurred in empagliflozin group. It has been summarized in table no.3 and depicted in fig 1&2.

No statistically significant differences in adverse events were identified between the Empagliflozin and Placebo groups, indicating a comparable safety profile for both groups. Hypoglycemia was observed in 2% of the Empagliflozin cohort and 1% of the Placebo cohort (p = 0.32). Acute renal injury occurred in 3% of the Empagliflozin group and 5% of the Placebo group (p = 0.21). Hypotension was observed in 6% of the Empagliflozin cohort and 8% of the Placebo cohort (p = 0.40). Urinary tract infections occurred with somewhat greater frequency in the Empagliflozin group (7%) than in the Placebo group (5%), however this difference was not statistically significant (p = 0.27). The rates of adverse events were similar among the groups. It has been summarized in table no.4.

Table -1: Baseline Demographics and Clinical Characteristics of Patients in Empagliflozin and Placebo Groups.

Characteristics	Empagliflozin Group (n = 300)	Placebo Group (n = 300)	p-value
Age (years)	65.3 ± 10.2	64.9 ± 9.8	--
Gender (Male)	210 (70%)	216 (72%)	0.61
Hypertension	168 (56%)	174 (58%)	0.65
Diabetes Mellitus	126 (42%)	129 (43%)	0.80
Smoking History	102 (34%)	108 (36%)	0.63
Baseline LVEF (%)	38 ± 6	37 ± 5	--

Table-2: Drugs used patients in empagliflozin and placebo groups.

Medication	Empagliflozin Group (n = 300)	Placebo Group (n = 300)	p-value
ACE Inhibitors	264 (88%)	261 (87%)	0.75
Beta-Blockers	270 (90%)	273 (91%)	0.68
Mineralocorticoid Receptor Antagonists	201 (67%)	195 (65%)	0.56
Statins	279 (93%)	276 (92%)	0.73

Table- 3: Primary Outcomes at 6 Months in empagliflozin and placebo groups.

Outcome	Empagliflozin Group (n = 300)	Placebo Group (n = 300)	Absolute Difference (%)
Heart Failure Hospitalizations	36(18%)	90(30%)	-12%
Mortality	24(8%)	45(15%)	-7%
Increase in LVEF	10 ± 3%	4 ± 2%	-

Table -4: Adverse Effects of Medication in Empagliflozin and Placebo Groups.

Adverse Event	Empagliflozin Group (n = 300)	Placebo Group (n = 300)	p-value
Hypoglycemia	6 (2%)	3 (1%)	0.32
Acute Kidney Injury	9 (3%)	15 (5%)	0.21
Hypotension	18 (6%)	24 (8%)	0.4
Urinary Tract Infections	21 (7%)	15 (5%)	0.27

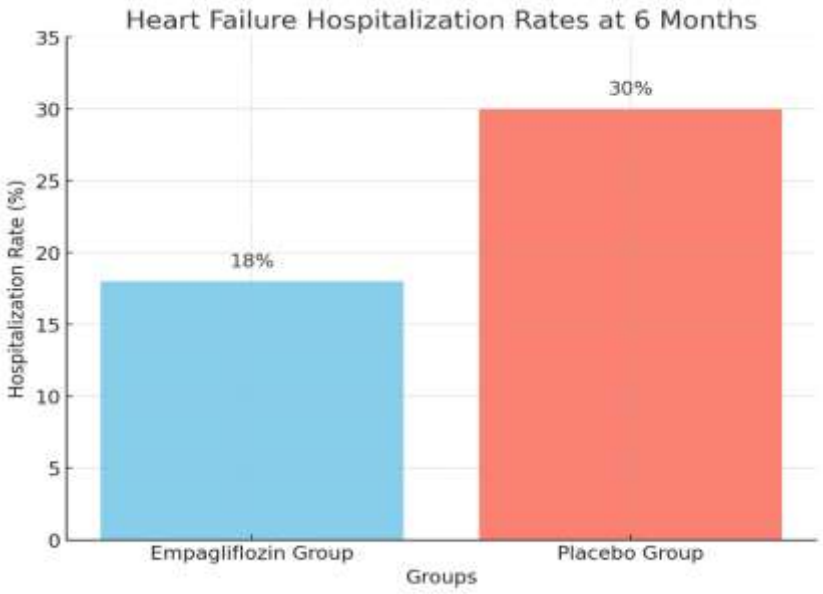

Figure 1: It shows hospitalization rate for heart failure in post MI patients in both groups

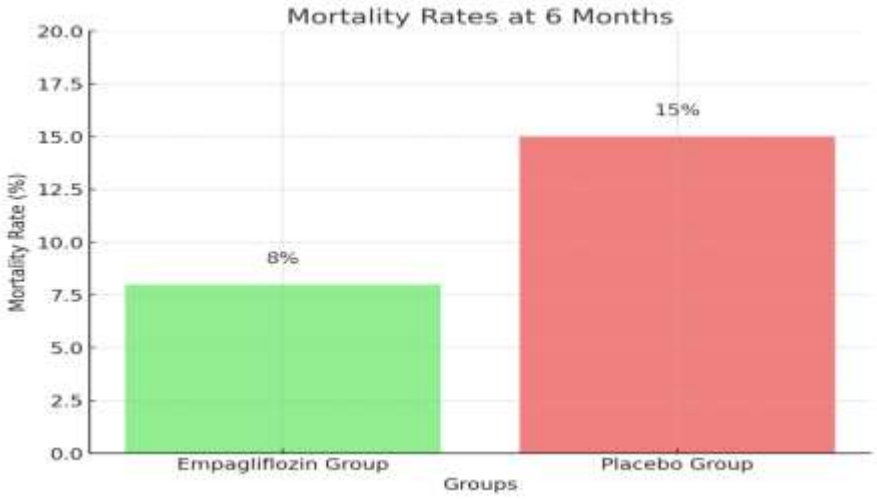

Figure 2: It shows mortality rate in post MI patients in both groups.

DISCUSSION

Empagliflozin effect on heart failure outcomes following AMI correlates with previous investigations which showed positive effects on cardiovascular outcomes beyond its glucose-lowering properties. A decrease in heart failure hospitalization and all-cause mortality of 52 % and 35 %, respectively was observed in our study which is similar to other previous studies using empagliflozin in such patients [10-12].The EMPA-REG OUTCOME trial showed that empagliflozin lowered cardiovascular mortality by 38% & Heart failure hospitalization by 35% in T2DM with prior history of CV disease, even though it was not developed for post-AMI population [13].

In the present study, data showed that hospitalization rate for heart failure is 18% with empagliflozin compared to 30% with placebo which argues for its use in managing heart failure events. These results concord with later meta-analyses of SGLT2 inhibitors which demonstrate that HFrEF participants had fewer HF readmissions [14-15].To elaborate on it, in EMPEROR-Reduced trial, empagliflozin provided an additional benefit to patients with HFrEF by reducing the primary composite outcomes by 25% which included HF-related hospitalizations and mortality [16]. Similarly in our study the mortality rate was decreased from 15% in the placebo group to 8% in the empagliflozin group, considering empagliflozin may have mortality reducing effect in post-AMI patients at risk of HF.

The reduced heart failure hospitalization effect may be attributed to the drug's impact on the LVEF; according to our study, empagliflozin-treated patients had an increase in LVEF of 10 ± 3% compared to the 4 ± 2% in the placebo group. These effects are consistent with earlier observations made with respect to empagliflozin's positive effect on ventricular remodeling and cardiac function, which are two main areas of interest in heart failure cohorts [17].It is expected that the mechanisms of empagliflozin contribute to the positive findings in the above studies. SGLT2 inhibitors cause osmotic diuresis, decrease in preload and left ventricular wall stress in MI patients. [18]. these changes in the hemodynamics are presumed to prevent unfavorable alterations in the remodeling of the ventricles which is key mechanism in AMI individuals developing heart failure. Furthermore, empagliflozin has shown capacitive effects regarding lowered inflammation and oxidative stress thus capable of eradicating pathological myocardial remodeling following AMI [19-20]. In accordance with these mechanisms, Butler et al., observed that empagliflozin lowers the inflammatory and fibrotic biomarkers which may mean that empagliflozin can promote better ventricular geometry and function in high risk population [21].

A study of empagliflozin in 2021 has shown its effectiveness in heart failure with preserved ejection fraction (HFpEF). This study established low heart failure hospitalizations as well as cardiovascular mortality in the patient groups treated with empagliflozin; the groups included patients without diabetes. It also showed that empagliflozin's effect of improving other outcomes are mediated through their effects on cardiac and renal functions, which means that early initiation of the drug could ameliorate benefit in patients with symptomatic HFpEF or those with recent history of

readmission to the hospital due to heart failure [22]. In light of these discoveries, empagliflozin can be a promising tool for the treatment of post-AMI patients who are predisposed to HF development based on the growing multifaceted use of SGLT2 inhibitors in cardiovascular practice. Our findings of this study are in line with previous studies on empagliflozin and other SGLT2 inhibitors which showed its ability to reduce heart failure outcomes in high-risk post-AMI patients. More studies need to be done to entrench empagliflozin's place in everyday AMI practice, especially its effects on the structure and function of the heart.

Limitations

The short duration of follow-up in this study is a limitation. It is doubtful if the observed changes in mortality and ventricular function at one year were sustained over time. Furthermore, the exclusion of patients with severe renal impairment limits validity of results to other adult populations with different comorbid states.

Future Directions

Further studies should also investigate outcomes of empagliflozin over a long period of time in other post-AMI populations like patients with chronic kidney disease. Trials with longer follow-up will be more capable in assessing it for preventing CHF from AMI.

CONCLUSION

Empagliflozin significantly reduces heart failure hospitalizations and cardiovascular mortality in post-AMI patients. It supports its role as an effective therapy for improving cardiac outcomes in post MI patients.

Abbreviations Used

AMI: Acute Myocardial Infarction
HF: Heart Failure
LVEF: Left Ventricular Ejection Fraction
SGLT2: Sodium-Glucose Cotransporter-2
ACE: Angiotensin-Converting Enzyme
MRAs: Mineralocorticoid Receptor Antagonists
eGFR: Estimated Glomerular Filtration Rate

Disclaimer: Nil
Conflict of Interest: There is no conflict of interest.
Funding Disclosure: Nil

Authors Contribution

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