Original Article

Effect of a low dose of empagliflozin on short-term outcomes in type 2 diabetics with acute coronary syndrome after percutaneous coronary intervention

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ABSTRACT

الأهداف: دراسة آثار جرعة منخفضة من إمباغليفلوزين في تحسين النتائج في مرضى السكري الذين يعانون من متلازمة الشريان التاجي الحاد (ACS) بعد التدخل التاجي عن طريق الجلد (PCI).

المنهجية: أجريت هذه التجربة السريرية الخاضعة للرقابة مزدوجة التعمية على 93 مريضًا بالسكري (56 ذكرًا و 37 أنثى، متوسط العمر 56.55 عامًا) مع ACS خضعوا لـ PCI في مستشفيين جامعيين في عام 2020م، في الأهواز، إيران. قمنا باختيار المرضى بشكل عشوائي لتلقي إمباغليفلوزين (10 ملغ مرة واحدة يوميًا) أو العلاج الوهمي بجرعات مماثلة لمدة 6 أشهر بعد PCI بالإضافة إلى الرعاية الاعتياديه بعامل سكر دم آخر. قمنا بتقييم نتائج القلب والأوعية الدموية (بما في ذلك الوفيات الناجمة عن جميع الأسباب، وإعادة الأوعية التاجية، وإعادة دخول المستشفى بسبب الذبحة الصدرية غير المستقرة، والاستشفاء بسبب قصور القلب، والموت القلبي الوعائي، واحتشاء عضلة القلب غير الجنيني، والسكتة غير الجنينية) خلال فترة 6 أشهر من المتابعة بعد علاج إمباغليفلوزين.

النتائج: لم يكن هناك فرق كبير بين الجرعات المنخفضة من إمباغليفلوزين ومجموعات الدواء الوهمي بعد العلاج من حيث معدل وفيات CV (2.2% مقابل 4.2%؛ p=0.598)، إعادة دخول المستشفى بسبب الذبحة الصدرية غير المستقرة (4.5% مقابل 8.7%؛ p=0.433)، وإعادة تكوين الأوعية التاجية (2.2% مقابل 0%؛ p=0.312).

Objectives: To study the effects of low dose of empagliflozin on improving outcomes in diabetic patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI).

Methods: This double-blind controlled clinical trial was carried out on 93 diabetic patients (56 males and 37 females, mean age of 56.55 years) with ACS who underwent PCI at 2 university teaching hospitals in 2020, Ahvaz, Iran. The patients were randomly assigned to receive empagliflozin (10 mg once daily) or placebo at similar doses for 6 months after PCI. In addition, to standard treatments with another hypoglycemic agent. Cardiovascular outcomes (including all-cause mortality, coronary revascularization, rehospitalization due to unstable angina, hospitalization due to heart failure, cardiovascular death, non-fetal myocardial infarction, and non-fetal stroke) were evaluated during period of 6 months follow-up after the empagliflozin treatment.

Results: There was no significant difference between the low dose empagliflozin and placebo groups after treatment in terms of cardiovascular mortality (2.2% versus [vs.] 4.2%; p=0.598), rehospitalization due to unstable angina (4.5% vs. 8.7%; p=0.433), and coronary revascularization (2.2% vs. 0%; p=0.312).

Conclusion: The results of this study showed that adding low dose empagliflozin to standard care of ACS diabetic patients after PCI was associated with no significant reduction in negative cardiovascular outcomes during 6 months.

Keywords: empagliflozin, acute coronary syndrome, diabetes

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There are currently more than 180 million people worldwide with diabetes, and statistics show that the prevalence of diabetes mellitus is increasing worldwide.[1,2] Diabetic patients have an increased risk for cardiovascular (CV) disease, CV morbidity, and mortality due to concomitant metabolic abnormalities.[3] Cardiovascular disease is the leading cause of death in diabetic patients.[4] In addition, these patients are less likely to benefit from standard treatments for coronary artery disease.[2,5] Diabetes mellitus in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) is associated with poor clinical CV outcome and increased mortality.[1] Diabetic ACS patients have poor tolerance for ischemic complications of PCI and short- and long-term ischemic outcome; in addition, major CV events after PCI in diabetic patients is worse than those in non-diabetic patients.[6-8] Therefore, proper management of diabetic patients with ACS should focus on reducing the risk of CV events.[9] Glycemic control can affect the clinical outcome of diabetic ACS and non-ACS patients after PCI.[10,11] Hyperglycemia is also a major part of the pathophysiology of diabetes mellitus. Previous studies have revealed that glucose-lowering therapy, except insulin, has limited effects on CV outcome in diabetic ACS patients.[11-13]

Empagliflozin is a new drug in the group of sodium glucose transporter protein 2 (SGLT2) inhibitors that has recently been used clinically to improve cardiac outcomes.[17,18] Empagliflozin selectively inhibits SGLT2 and lowers blood glucose without insulin dependence. This unique mechanism of action prevents many other limitations of anti-hyperglycemic drugs such as weight gain and hypoglycemia.[17,19] In previous studies, the beneficial effects of empagliflozin on CV mortality and morbidity have been reported in diabetic patients.[20,21] In addition, a previous study showed that in diabetic patients with a history of coronary artery bypass graft (CABG), treatment with empagliflozin caused a significant reduction in mortality and CV complications.[22] However, few studies have been carried out on the effect of empagliflozin on CV outcome in diabetic ACS patients undergoing PCI.

The aim of this study was to evaluate the effects of low dose empagliflozin on improving CV outcomes in diabetic patients with ACS after PCI.

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Methods. This study was a double-blind randomized controlled clinical trial and was carried out on diabetic ACS patients undergoing PCI at 2 university teaching hospitals (namely, Golestan Hospital, Imam Khomeini Hospital), Ahvaz, Iran in 2020. This study was approved by the Vice Chancellor for Research of Ahvaz Jundishapur University of Medical Sciences (Ethics Code: IR. AJUMS. HGOLESTAN. REC. 1399.107). Informed written consent was obtained from all patients before starting treatment. In addition, the provisions of the ethics statement in the Helsinki study and the principles of patient information confidentiality were observed during all stages of this study. The required sample size was estimated to be 50 people in each group, based on confidence interval of 95% and according to the mean and standard deviation of the incidence of complications in the same study based on the sample size determination formula.[21] The diagram of the study process and the exit of the participants is shown in Figure 1. The inclusion criteria included: age over 18 years and previous diagnosis of diabetes mellitus (fasting blood sugar [FBS] ≥126 mg/dL; oral glucose tolerance test ≥200 mg/dL; hamoglobin A1C [HbA1C] ≥6.5%, classic symptoms of hyperglycemia with BS ≥200 mg/dL) with ACS (ST elevation myocardial infarction [MI], Non-STelevation MI [STEMI], unstable angina). Acute coronary syndrome diagnosis requires a clinical, biochemical, and electrocardiographic criteria associated with signs and symptoms of cardiac ischemia and common electrocardiographic abnormalities such as T-wave inversion, ST-segment elevation, or depression. In addition, patients with diabetic ketoacidosis, urinary and genital infections, type 1 diabetes, severe liver failure, any malignancy and cancer, glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, and non-adherence to treatment procedure were excluded from the study. The eGFR was calculated by MDRD formula based on serum creatinine, age, and gender of the patient: eGFR = 175 × (Serum Cr) - 1.154 × (age) - 0.203 × 0.742 (if female) × 1.212 (if the patient was black skin).

The patient's information (including age, gender, weight, smoking status, underlying diseases, medical records, and laboratory parameters) was collected at the beginning of the study. After PCI in all patients, the subjects were randomly divided into 2 groups of treatment besides standard hypoglycemic (insulin) treatments with the addition of low dose of empagliflozin or a placebo. A standard treatment to control glycaemia includes insulin administration during the first 3 days; then, this treatment is either continued or changed to an oral hypoglycemic agent according to endocrinologist consultation. Randomization was carried out using a

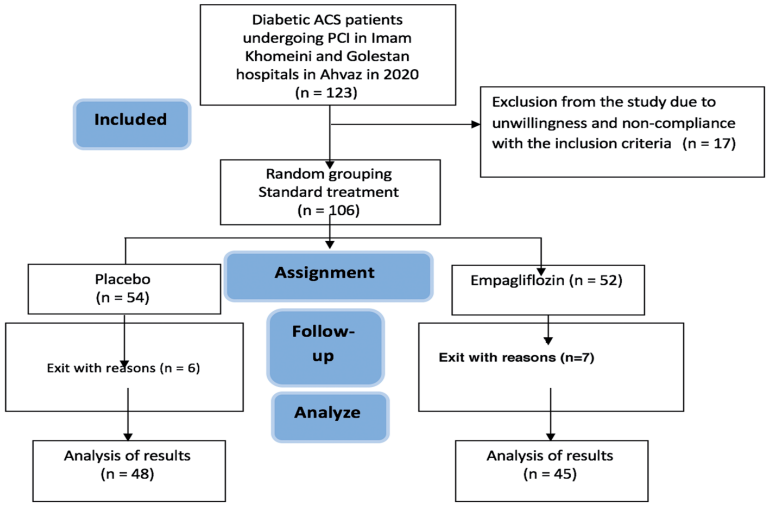

Figure 1 - Study flowchart.

permutation random method with quadruple blocks. Randomization was carried out by a person who did not interfere in the study process. In the first group, the patients received empagliflozin (10 mg once daily) for 6 months, and the placebo group received a placebo for the same period. Empagliflozin (Gloripa, Abidi Pharmaceutical Company, Iran) was provided free of charge by Abidi Pharmaceutical Company, Iran, to the patients under study. A placebo with a color, shape, and packaging similar to empagliflozin tablets was prepared by the Faculty of Pharmacy of Ahvaz Jundishapur University, Bagdad, Iran. The drugs were prescribed to patients under the supervision of an endocrinologist, and the use of drugs was fully explained to patients. Blinding was also carried out in such a way that the person who randomized and assigned individuals to the groups did not know the patients and had no information on the patient's condition. In addition, the patient and the person reviewing the results did not have information on the grouping of individuals.

The patients in both groups were followed for 6 months. Follow-up visits were carried out in the third and sixth months after treatment, and the patients were carefully evaluated for safety and drug side effects as well as CV complications. In case of non-referral, the patients were reminded by phone to follow-up. Symptoms and clinical examinations, laboratory parameters, echocardiography, electrocardiogram evaluation, as well as the incidence of major cardiovascular complications (MACE) were evaluated during follow-up visits. In addition, the patients underwent invasive or non-invasive diagnostic tests as indicated. Major adverse cardiac events are defined as coronary revascularization, non-fatal MI, all-cause mortality, transient ischemic attack (TIA), cardiac death, recurrent angina, stroke, and hospitalization due to heart failure (HF) which were carefully evaluated and recorded in all patients.[23] Any changes in metabolic parameters during the 6-month follow-up were also assessed. Finally, the collected information was statistically analyzed, and the results were compared between the 2 groups.

Statistical analysis. The Statistical Package for the Social Sciences, version 22.0 (IBMCorp, Armonk, NY, USA) was used for statistical analysis. The data were analyzed by descriptive statistics including the mean, interquartile range (IQR), frequency, and percentage. The normality of data was evaluated by Kolmogorov-Smirnov test and the homogeneity of variances was evaluated by Levene's tests. Owing to the lack of normal distribution of data, non-parametric tests were used to analyze the results in this study. The Mann-Whitney non-parametric test was used to compare quantitative variables between the 2 groups, and Chi-square (or Fisher's exact test) was used to compare qualitative variables. In this study p-value was set at p=0.05.

Results. Participants in the study included 56 (60.2%) men and 37 (39.8%) women between the ages of 30-79 years who were divided into 2 groups of treatment with empagliflozin and a placebo. The results of comparing the basic characteristics of the 2 groups are shown in Table 1.

There were 50 patients with STEMI, 6 patients with NSTEMI, and 37 with unstable angina. There was not

Table 1 - Basic characteristics of patients in both groups.

Variable	Empagliflozin (n=45)	Placebo (n=48)	*P*-value
Age (years)	55 (45.5–64)	57 (50–66.75)	0.370
Gender			
Male	27 (60.0)	29 (60.4)	0.967
Female	18 (40.0)	19 (39.6)	
Duration of diabetes (years)	6 (4-8)	6 (9-2)	0.753
Smoking	9 (20.0)	8 (16.7)	0.679
Underlying disease			
CKD	4 (8.9)	3 (6.3)	0.632
Hypertension	26 (57.8)	32 (66.7)	0.379
CVA	1 (2.2)	2 (4.2)	0.598
ACS			
STEMI	27 (60.0)	23 (50.0)	0.335
Non-STEMI	2 (4.4)	4 (8.3)	0.448
unstable angina	16 (35.6)	21 (43.8)	0.422
Number of vessels involved			
1	15 (33.3)	19 (36.6)	0.543
2	15 (33.3)	15 (31.3)	
3	15 (33.5)	14 (29.2)	

The numbers are presented as interquartile range (IQR) or frequency (percentage). Significance level: $p<0.05$. CKD: chronic kidney disease, CVA: cerebrovascular accident, ACS: acute coronary syndrome, STEMI: ST-elevation myocardial infarction

significant difference between the 2 groups in any of the different variables including age, gender, duration of diabetes, smoking, underlying disease, type of acute coronary syndrome, and number of vessels involved ($p>0.05$). A comparison of different parameters in patients before and after treatment in the 2 groups is shown in Table 2. There was no significant difference between the 2 groups in terms of weight, left ventricular ejection fraction (LVEF), systolic and diastolic blood pressure, eGFR, HbA1c, and low-density lipoprotein (LDL-C) before treatment and during follow-up 6 months after treatment ($p>0.05$). Weight change was significantly higher in the experimental group ($p=0.001$), and the amount of FBS after treatment was significantly lower in the experimental group than in the placebo group ($p=0.048$). During the 6-month follow-up, the empagliflozin group lost an average of 2 kg of weight, while the placebo group did not have any weight loss. The comparison of CV outcomes in diabetic patients under PCI in the empagliflozin and placebo groups is shown in Table 3. There was no significant difference between the 2 groups during 6 months follow-up in terms of CV death ($p=0.598$), hospitalization due to unstable angina ($p=0.433$), and

Table 2 - Comparison of different parameters in patients in both groups before and 6 months after treatment.

Variable	Empagliflozin (n=45)	Placebo (n=48)	*P*-value*
Weight (kg) – before	75 (67.5-84.5)	69.5 (65-83.75)	0.109
Weight (kg) – after	70 (66.0-79.5)	70 (65-80.5)	0.594
Weight change (kg)	2 (0-3)	0 (–1.0-1.0)	0.001
LVEF (%) – before	45 (30-50)	45 (36.25-50)	0.147
LVEF – After	50 (36.25-55)	50 (45-55)	0.318
Change of LVEF	5 (0-10)	5 (0-6.25)	0.174
SBP (mmHg) – before	130 (116.25-150)	130 (116.25-140)	0.422
SBP – After	120 (110-130)	130 (113.75-140)	0.130
DBP (mmHg) – before	80 (72.5-87.5)	75 (70-88.8)	0.564
DBP – After	75 (70-80)	75 (70-81.25)	0.311
eGFR (mL/min) – before	72 (61-83)	76 (61.25-81)	0.923
eGFR – after	70 (61-82.5)	73 (59.75-81)	0.831
HbA1c (%) – before	7.8 (7.2-8.45)	7.8 (7.1-8.05)	0.291
HbA1c – after	7.1 (6.82-8.05)	7.6 (6.75-7.9)	0.485
FBS (mg/dL) – before	178.5 (178.5-195.75)	178 (15.6–209.25)	0.799
FBS – after	148 (136-176)	173 (142–191.25)	0.048
LDL-C (mg/dL) – before	100 (78-122)	92 (73-118)	0.272
LDL-C – after	93.5 (74.25-113.5)	82.5 (68.75-109.75)	0.203

The numbers are presented as interquartile range. *Significance level: $p<0.05$. LVEF: left ventricular ejection fraction, SBP: systolic blood pressure, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, FBS: fasting blood sugar test, LDL-C: low-density lipoprotein cholesterol

Table 3 - Comparison of cardiovascular outcome of patients in both groups before and 6 months after treatment.

Variable	Empagliflozin (n=45)	Placebo (n=48)	P-value
Cardiovascular death	1 (2.2)	2 (4.2)	0.598
Hospitalized due to unstable angina	2 (4.5)	4 (8.7)	0.433
Coronary revascularization	1 (2.2)	0	0.312

The numbers are presented as frequency (percentage). Significance level: $p<0.05$.

coronary revascularization (p=0.312) after treatment. Non-fetal MI, TIA stroke, hospitalization due to HF, and all-cause mortality were not observed in either group.

Discussion. The results of this study showed that there were no statistically significant differences between the 2 groups in terms of age, gender, smoking, patient weight, duration of diabetes, underlying disease, systolic and diastolic blood pressure, LVEF, eGFR, HbA1c, FBS, and LDL-C before PCI. In addition, the frequency of STEMI, non-STEMI and unstable angina, as well as the number of vessels involved showed no significant difference between the 2 groups. These results indicate that these factors do not affect the results, the complete randomness of the samples, and the absence of bias in sample selection. The results of 6 months follow-up showed that the 2 groups of adding empagliflozin and placebo to standard regime were not significantly different in terms of systolic and diastolic blood pressure, LVEF, eGFR, HbA1c, and LDL-C. The weight loss was significantly higher in the experimental group than in the placebo group.

The amount of FBS after treatment in the experimental group was significantly lower than in the control group (p=0.048). However, average blood glucose (HbA1c) was not different between the 2 group, which was possibly due to low dose of drug usage. Empagliflozin is an SGLT2 inhibitor, which has been recently used clinically; it has been shown to improve glycemic control and cardiac outcomes.[17,18] Empagliflozin also causes weight loss, hypotension, hypoglycemia, and reducing proteinuria.[17,19,20]

Our study showed that the empagliflozin and placebo groups were not significantly different compared to the standard treatment results in terms of incidence of CV death, hospitalization due to unstable angina, and coronary revascularization after treatment; although, some positive decreasing trends were observed. Non-fetal MI, non-fetal stroke, TIA, hospitalization due to HF, and all-cause mortality were not observed in either group. In this study, side effects related to the use of empagliflozin were not observed, which is similar to other studies.[20,22]

The results of the EMPA-REG OUTCOME clinical trial[21] involving 7020 patients with type 2 diabetes mellitus and CV disease showed that 2 daily doses of 10 or 25 mg of empagliflozin compared with placebo significantly reduced major CV complications. The use of empagliflozin resulted in weight loss and reduced risk of CV death, death from any cause, and hospitalization due to HF compared to placebo.[21] The results of the study by Verma et al,[24] which reported a sub-analysis of EMPA-REG OUTCOME study, showed that in diabetic patients with a history of CABG, treatment with empagliflozin compared to placebo significantly reduced CV mortality (48.0% reduction), all-cause mortality (43.0% reduction), and hospitalization due to HF (50.0% reduction). The results of a post hoc analysis confirmed that cardio protective effect of empagliflozin was consistent regardless of the multiple baseline risk factor control.[25]

However, in previous studies, the beneficial effects of empagliflozin on CV mortality and morbidity have been reported in diabetic ischemic heart diseases patients.[20-22] There are no studies on the effect of adding empagliflozin to standard treatment on CV outcome in diabetic ACS patients undergoing PCI. Therefore, it was not possible to accurately and comprehensively compare the results of this study with other studies.

In the present study, CV complications in diabetic patients after PCI, who were treated with a low dose of empagliflozin in addition to standard treatment, were not significantly different from those in the placebo group; although, there were positive decreasing trends, but these results were not statistically significant. The obtained result may be due to the duration of treatment, use of low dose of empagliflozin, short follow-up period and significant role of PCI in improving the outcome of ACS diabetic patients, which can reduce the effect of empagliflozin, at least in the short-term clinical outcome. In the setting of acute coronary syndromes, diabetic patients are at high risk for subsequent CV events. At the same time, they derive greater benefit than non-diabetic patients from early coronary angiography and stent-based PCI.[26]

We hypothesize that long-standing diabetes and PCI intervention in this group of patients may be the reason for the absence of a significant effect of empagliflozin in reducing negative cardiovascular outcomes compared with the placebo group.[27,28] Clinical studies of the SGLT2 treatment after PCI are sparse. Patients with a history of angioplasty within 3 months were excluded

from the EMPA-REG OUTCOME study. Therefore, owing to the lack of a similar study on diabetic ACS patients after PCI and absence of a significant effect of low dose of empagliflozin in reducing CV complications in our patients, it is not possible to provide a definite conclusion.

Study limitations. The effect of a low dose of empagliflozin was evaluated only for 6 months, and the long-term effects of this drug were not evaluated. The effects of other CV risk factors (such as, inflammation, genetic factors, and socioeconomic status of patients) on the incidence of complications were not investigated. Another limitation of this study is the small number of samples studied, which was due to the COVID-19 pandemic and sampling limitations. To achieve more accurate results, multicenter studies with larger sample sizes and longer follow-up periods are recommended in diabetic patients with ACS undergoing PCI.

In conclusion, the results of this trial showed that during 6 months of follow-up, the empagliflozin and placebo groups were not significantly different in terms of the incidence of major CV complications including coronary revascularization, hospitalization due to unstable angina, and CV death; although, we observed a positive trend. A low dose of empagliflozin was not more effective than placebo (except in weight loss and FBS control) in improving the outcomes of diabetic ACS patients after PCI. Thus, it seems that the efficacy of using a low dose of empagliflozin in this group of patients is not clear. Owing to the lack of studies in this field, in addition to evaluating the effectiveness of using a low dose of empagliflozin in studies with higher sample size and longer follow-up time, it is recommended to investigate other drugs to reduce the risk of CV events in the proper management of type 2 diabetes mellitus, especially in ACS diabetic patients after PCI.

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