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Original Article

Evaluating the limited impact of therapy with empagliflozin on primary PCI patients' outcomes: the ELITE-PCI trial

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Abstract

Objectives: Empagliflozin, a sodium-glucose co-transporter 2(SGLT2) inhibitor, has demonstrated cardiovascular benefits in various patient groups. However, its effects on patients undergoing primary percutaneous coronary intervention (PCI) have not been extensively studied. This research aims to assess the impact of empagliflozin on clinical outcomes for participants in the ELITE-PCI trial.

Methods: The ELITE-PCI trial was a prospective, single-center, randomized, triple-blind, placebo-controlled study conducted from June 8, 2023, to May 25, 2024. It included 110 patients with acute myocardial infarction (AMI) undergoing primary PCI, who were assigned to receive either 10 mg of empagliflozin or a placebo. Clinical outcomes, including major adverse cardiovascular events (MACE) and rehospitalization rates, were assessed at 12 weeks post-intervention.

Results: The study included 110 participants, with 55 in each group. The mean age was 59.9 years (±10.7) for the empagliflozin group and 58.1 years (±11.9) for the placebo group ($p = 0.392$). Both groups had a consistent sex distribution (90.9% male, $p > 0.999$). Baseline characteristics, including BMI, GFR, blood pressure, and left ventricular ejection fraction, showed no significant differences. Diabetes prevalence was 47.3% in the empagliflozin group and 43.6% in the placebo group ($p = 0.702$). At 12 weeks, MACE was absent, while the empagliflozin group had a 7.2% readmission rate, primarily due to pulmonary edema, compared to 5.4% in the placebo group($p=0.405$).

Conclusions: The findings of the ELITE-PCI trial suggest that short-term empagliflozin therapy does not have a significant impact on clinical outcomes in patients undergoing primary PCI. Nevertheless, these results highlight the necessity for further research to clarify the role of SGLT2 inhibitors within this patient population.

Keywords: Acute myocardial infarction, cardiovascular outcomes, ELITE-PCI trial, empagliflozin, primary PCI

Introduction

Acute myocardial infarction (AMI) is a leading cause of global illness and death, highlighting the urgent need for effective treatments that improve patient outcomes [1]. The introduction of sodium-glucose cotransporter-2 (SGLT2) inhibitors, especially empagliflozin, has gained attention for their potential cardiovascular benefits in patients with diabetes and heart failure [2,3]. These drugs not only help control blood sugar but also offer the added benefit of lowering cardiovascular risk, which could change how we approach treatment [4, 5]. Despite this promise, the specific effects of empagliflozin during the acute phase, particularly during primary percutaneous coronary intervention (PCI) for AMI, are not well understood [6]. Using empagliflozin in this situation is especially relevant given the unique challenges and opportunities during the early stages of a heart attack. It is essential to understand how empagliflozin might affect clinical outcomes during and after PCI to improve care for this high-risk group. The ELITE-PCI trial aims to carefully assess how empagliflozin impacts clinical results in patients undergoing primary PCI for AMI. By focusing on this specific patient group, the study seeks to close existing gaps in knowledge and determine if empagliflozin can significantly improve recovery and reduce complications after a heart attack. Ultimately, this research aims to direct clinical practice and shape future treatment approaches, helping to improve health outcomes for those affected by this serious condition.

Materials and Methods

Study Design

The ELITE-PCI trial was designed as a prospective, single-center, randomized, triple-blind, placebo-controlled investigation. Patients referred to Afshar Hospital, Yazd, Iran, with AMI who underwent primary PCI were enrolled from June 8, 2023, to May 25, 2024. Inclusion criteria encompassed adults aged 18 years or older presenting with AMI eligible for primary PCI. Exclusion criteria included prior use of empagliflozin, glomerular filtration rate (GFR) less than 30, contraindications to SGLT2 inhibitor therapy, received fibrinolytic therapy before PCI, cardiogenic shock or unstable hemodynamics, or patients who underwent an angiography more than 120 minutes after first medical contact. Figure 1 shows a summary of the method.

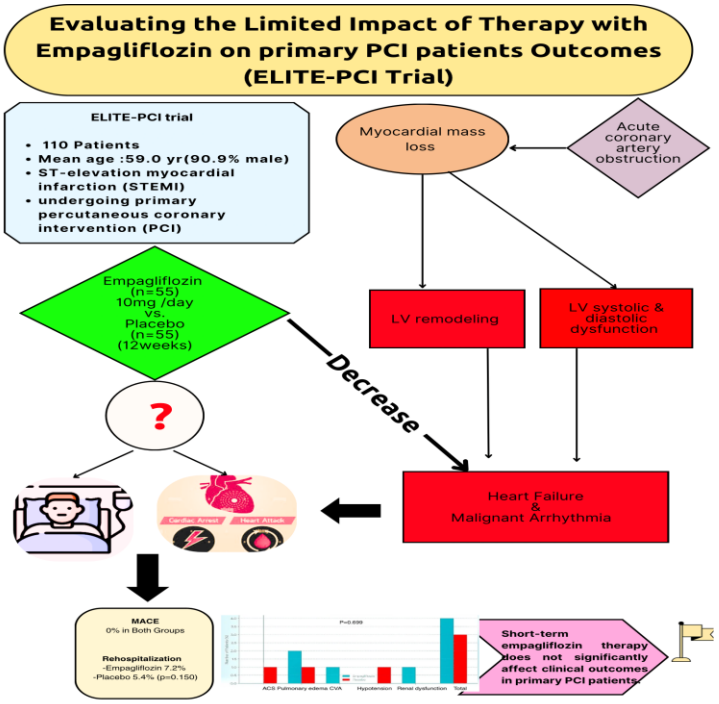

Figure1. Graphical Abstract

Ethical Considerations

The study protocol underwent rigorous review and received approval from the Institutional Review Board (IRB) at Shahid Sadoughi Medical University (IR.SSU.MEDICINE.REC.1402.273).

Informed consent was obtained from all participants before enrollment, ensuring they were fully informed about the study's purpose, procedures, potential risks, and benefits. Participants were assured of their right to withdraw from the study at any time, without any adverse effects on their medical care or treatment. Confidentiality and privacy of participants were strictly maintained throughout the study. All data collected was anonymized and securely stored, with access limited to authorized research personnel only. The trial was conducted in alignment with the principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines, prioritizing the welfare and rights of all participants. The researchers implemented continuous monitoring and oversight to keep ethical standards throughout the study.

Sample Size

The sample size was determined using Power Analysis software (G*power), with a significance level set at 5% and a target power of 95%. Based on previous findings, the required sample size was calculated to be 112 participants, which consists of 56 individuals in each group. To account for a potential dropout rate of 10%, a total sample size of 120 participants (60 per group) was planned [6]. During the follow-up, 10 patients were excluded from the study due to their unwillingness to continue participating see Figure 2.

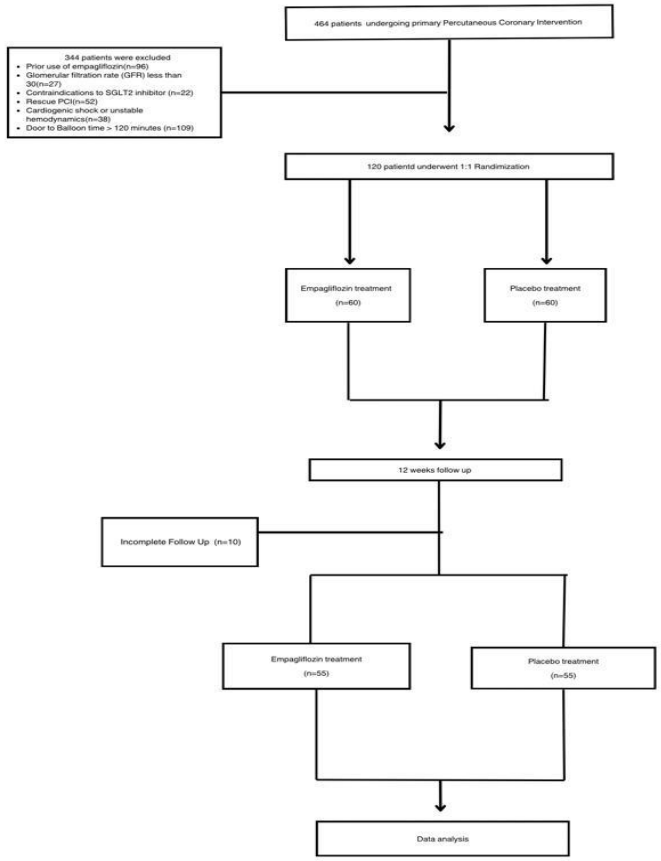

Figure 2. Enrollment, randomization, and follow-up

Participant Evaluation

The study involved patients referred to Afshar Hospital in Yazd, Iran, who had an AMI and ECG changes associated with STEMI. We excluded from the trial individuals with type 2 diabetes, diabetes treated with empagliflozin, a glomerular filtration rate (GFR) less than 30, fibrinolytic therapy, a MI with cardiogenic shock or unstable hemodynamics, or patients who underwent an angiography more than two hours after an AMI. All participants underwent thorough evaluations before randomization, which included gathering information on cardiovascular risk factors, previous medical conditions, medications, and lifestyle factors such as smoking habits and levels of physical activity. A detailed physical examination was conducted to assess vital signs, body mass index (BMI), and any physical signs of cardiovascular disease. Each participant had an ECG performed upon admission to identify any changes associated with acute myocardial infarction and to establish baseline heart rhythm and conduction patterns. Additionally, echocardiography was performed to evaluate left ventricular systolic and diastolic function.

Intervention

We randomly assigned patients in a 1:1 ratio to either receive oral empagliflozin 10 mg once daily (Gloripa, Abidi Pharmaceutical Company, Tehran, Iran) or a daily placebo within 48 hours of post-angioplasty. Both groups received other treatments prescribed for myocardial infarction according to the latest cardiovascular guidelines. To facilitate randomization, we utilized randomization software (www.random.org/sequences). Throughout the 12-week follow-up period, patients participated in regular telephone assessments, which culminated in a structured, in-person clinical evaluation at the end of week 12.

Outcome Measures

The interesting outcome of the study was the occurrence of major adverse cardiovascular events (MACE), which refers to a composite endpoint that includes cardiovascular death, non-fatal myocardial infarction, and target vessel revascularization (TVR). Additionally, the study aimed to assess secondary outcomes, which included the rates of rehospitalization.

Statistical analysis

Statistical analyses were conducted using SPSS version 26 (IBM, Chicago, USA). Descriptive statistics were employed to summarize the means and standard deviations of continuous variables. A sample t-test was used to compare the intervention and control groups for repeated outcomes. The chi-square and Fisher's exact tests were applied to assess associations between categorical variables across study groups. A p-value of ≤ 0.05 was considered statistically significant for all analyses.

Results

Baseline Characteristics

A total of 110 participants were included, with 55 in the empagliflozin group and 55 in the placebo group (Figure 1). The mean age was 59.9 years (±10.7) for the empagliflozin group and 58.1 years (±11.9) for the placebo group ($p = 0.392$). Sex distribution was consistent at 90.9% male in both groups ($p > 0.999$). BMI was similar (26.4 kg/m² vs. 26.7 kg/m², $p = 0.672$), and GFR was comparable (85.0 ml/min vs. 85.2 ml/min, $p = 0.948$). Systolic and diastolic blood pressures were 124.6 mmHg (±23.9) and 81.7 mmHg (±11.6) in the empagliflozin group, versus 121.2 mmHg (±23.9) and 77.5 mmHg (±11.0) in the placebo group (SBP: $p = 0.453$; DBP: $p = 0.059$). LVEF was also similar (34.9% ±6.8 vs. 35.8% ±4.9, $p = 0.421$). Diabetes prevalence was 47.3% in the empagliflozin group and 43.6% in the placebo group ($p = 0.702$). All participants received aspirin, with no significant differences in other medication use. Overall, no significant differences were observed across the assessed variables Table 1.

Table 1. Comparison of baseline characteristics of the patients in the empagliflozin and placebo groups

Variables	Empagliflozin group N=55	Placebo group N=55	Total	P-value
Age (years), mean±SD	59.9± 10.7	58.1 ± 11.9	59±11.3	٠.392
Sex, n (%)				
Male	50 (90.9)	50 (90.9)	100(90.9)	>0.999
Female	5 (9.1)	5 (9.1)	10(9.1)	
BMI (kg/m^2), mean±SD	26.4 ± 3.7	26.7 ± 3.9	26.6±3.8	0.672
GFR (ml/min), mean±SD	85.0 ± 15.3	85.2 ± 16.9	85.1±16.0	0.948
Blood pressure(mmHg), mean±SD				
Systolic	124.6 ± 23.9	121.2 ± 23.9	122.9±23.9	0.453
Diastolic	81.7 ± 11.6	77.5 ± 11.0	79.6±11.5	0.059
LVEF, mean±SD	34.9 ± 6.8	35.8 ± 4.9	35.4±5.89	0.421
Coronary artery disease risk factor, n (%)				
DM	26 (47.3)	24 (43.6)	50 (45.5)	0.702
HTN	33 (60.0)	26 (47.3)	59 (53.6)	0.181
HLP	10 (18.2)	10 (18.2)	20 (18.2)	>0.999
Smoking	19 (34.5)	23 (41.8)	42 (38.2)	0.432
Addiction	7 (12.7)	7 (12.7)	14 (12.7)	>0.999
Comorbidity, n (%)				
COPD	2 (3.6)	0 (0.0)	2 (1.8)	0.154
Prior MI	1 (1.8)	0 (0.0)	1 (0.9)	0.315
Prior PCI	3 (5.5)	3 (5.5)	6 (5.5)	>0.999
Prior CABG	0 (0.0)	1 (1.8)	1 (0.9)	0.315
Prior CVA	2 (3.6)	1 (1.8)	3 (2.7)	0.558
MI territory, n (%)				
Anterior				0.443
Non anterior	33(60)	28(50.9)	61(55.5)	
	22(40)	27(49.1)	49(44.5)	
Coronary territory involvement, n (%)				
Left main	0(0)	1(1.8)	1(0.9)	0.546
One vessel	19(34.5)	24(43.6)	43(39.1)	
Two vessel	19(34.5)	16(29.1)	35(31.8)	
Three vessel	17(30.9)	14(25.5)	31(28.2)	
Medication, n (%)				
Aspirin	55 (100)	55 (100)	110(100)	-
Beta Blocker	49 (89.1)	44 (80)	93(0.157)	0.187
Atorvastatin	54 (98.2)	55 (100)	109(99.1)	0.315
Clopidogrel	54 (98.2)	54 (98.2)	108(98.2)	>0.999
Ticagrelor	1 (1.8)	1 (1.8)	2(1.8)	>0.999
ACE-I / ARB	37 (67.3)	31 (56.4)	68(61.8)	0.239
Spironolactone	35 (63.6)	28 (50.9)	63(57.3)	0.177

Values are given as mean±SD and no. (%). BMI (body mass index), GFR (glomerular filtration rate), LVEF (left ventricular ejection fraction), DM (diabetes mellitus), HTN (hypertension), HLP (hyperlipidemia), COPD (Chronic obstructive pulmonary disease), MI (myocardial infarction), PCI (Percutaneous Coronary Intervention), CABG (coronary artery bypass grafting), CVA (cerebrovascular accident). The significant *p-value* is ≤0.05.

Adverse clinical outcomes

1. MACE

At the 12-week follow-up, the incidence of major adverse cardiovascular events (MACE), which included death, non-fatal myocardial infarction (MI), and repeat revascularization, was found to be zero.

2. Rehospitalization

In the empagliflozin group, there were four readmissions, representing 7.2% of the cohort, with the primary cause being pulmonary edema in two patients (3.6%). Other causes included cerebrovascular accident (CVA) in one patient (1.8%) and renal complications in another patient

(1.8%). In contrast, the placebo group experienced three readmissions, accounting for 5.4%, with causes including acute coronary syndrome (ACS) in one patient (1.8%), pulmonary edema in another patient (1.8%), and hypotension in a third patient (1.8%) see Table 2.

Table 2. Reasons for Rehospitalization in Empagliflozin and Placebo Groups

Reason	Empagliflozin group, n (%) N=55	Placebo group, n (%) N=55	p value
ACS	0 (0)	1 (1.8)	0.315
Acute pulmonary edema	2 (3.6)	1 (1.8)	0.558
CVA	1 (1.8)	0 (0)	0.315
Hypotension	0 (0)	1 (1.8)	0.315
Renal dysfunction	1 (1.8)	0 (0)	0.315
Total	4 (7.2)	3 (5.4)	0.696

Values are given as no. (%). ACS (acute coronary syndrome), CVA (cerebrovascular accident)

Drug side effects

The side effects were compared between the empagliflozin and placebo groups. Dysuria was reported in 4 participants (7.2%) in the empagliflozin group, compared to 2 participants (3.6%) in the placebo group, resulting in a p-value of 0.401. Additionally, dizziness and sweating were reported in 2 participants from the empagliflozin group, while no cases were noted in the placebo group ($p > 0.05$). Importantly, no instances of hypoglycemia were reported in either groupsee Table 3.

Table 3. Drug side effects in intervention and control groups

Side effect	Empagliflozin Group, n (%) N=55	Placebo Group, n (%) N=55	P value
Dysuria	4 (7.2)	2 (3.6)	0.401
Dizziness	1(1.8)	0 (0)	0.315
Sweating	1(1.8)	0 (0)	0.315
Total	6(10.8)	2(3.6)	0.142

Discussion

This study assessed the impact of empagliflozin on clinical outcomes in patients following acute myocardial infarction who underwent primary percutaneous coronary intervention (PCI). Our findings indicate that short-term use of empagliflozin did not provide significant clinical cardiovascular benefits when compared to placebo. SGLT2 inhibitors represent a novel class of pharmacological agents in the management of both systolic and diastolic heart failure [7.8]. These agents are noted for their safety and efficacy, having been shown to reduce mortality and readmission rates in both diabetic and non-diabetic populations [9]. As a result, they are recognized as one of the four cornerstone therapies for heart failure[10]. Recent studies have broadened the application of these medications to include cardioprotective effects in patients with myocardial infarction, primarily due to their ability to attenuate myocardial remodeling, a significant contributing factor to myocardial dysfunction [11-14]. Considerable advancements in the management of myocardial infarction, particularly in reperfusion therapy, have led to reductions in both short-term and long-term mortality rates [15, 16]. This improvement can be linked to decreases in infarct size and the incidence of heart failure, which remains the most prevalent complication following such events[17-19]. The current trial specifically focused on patients with ST-elevation myocardial infarction, all of whom underwent primary PCI. Importantly, the demographic characteristics of the patients in both study groups were well-balanced, thus ensuring robust comparative analysis. During the 12-week follow-up period, which is critical for monitoring

cardiac events, major adverse cardiovascular events (MACE) were infrequent, and no deaths were recorded. Hospital readmission rates were 7.2% in the empagliflozin group compared to 5.4% in the placebo group; however, this difference did not reach statistical significance. Similarly, the recent DAPA-MIDAPA-MIDAPA-MIDAPA-MI trial reported a low incidence of MACE, which hindered the ability to establish a statistically significant difference between the dapagliflozin and placebo groups [20]. The rarity of serious cardiac events following the initial incident can be attributed to the comprehensive treatment strategies in place, as well as the implementation of both pharmacological and non-pharmacological measures for secondary prevention. [21-23]. To fully understand the effectiveness of SGLT2 inhibitors in secondary prevention within real-world settings, further extensive and long-term studies are warranted. These medications, known for their multifaceted effects beyond glycemic control—including established cardioprotective and renal protective benefits—are positioned to play a crucial role in the primary prevention of cardiovascular events[24-26].It is expected that the widespread use of these medications may lead to a decrease in the incidence of heart disease in the future [27,28]. The adverse effects were comparable between the two groups, with dysuria being the most frequently reported side effect in the empagliflozin group, which aligns with findings from other studies. Notably, neither group experienced hypoglycemia, which is particularly significant. The low incidence of hypoglycemia is a major advantage of SGLT2 inhibitors, making them especially appealing for use in non-diabetic patients [30].

Limitations

The ELITE-PCI trial has several limitations that should be considered when interpreting its findings. One limitation is the sample size, which may be insufficient to ensure the generalizability and statistical power of the results. Additionally, the follow-up duration may not sufficiently capture the long-term effects of empagliflozin on clinical outcomes, particularly cardiovascular and renal benefits.

Furthermore, the inclusion criteria may limit the applicability of the results to a broader patient population. If the trial was conducted at a single center, local practices could influence the outcomes, limiting external validity. Moreover, the trial's focus on specific clinical endpoints may overlook other important outcomes, such as quality of life.

Conclusion

While empagliflozin has demonstrated promise in various patient populations, our findings suggest that it does not significantly enhance clinical outcomes in patients undergoing primary PCI for acute myocardial infarction. This study emphasizes the need for further research to clarify the role of SGLT2 inhibitors in acute clinical settings and to explore any potential risks associated with their use in this specific population. Future investigations should aim to elucidate these findings and assess the long-term implications of SGLT2 inhibitor therapy in patients experiencing acute coronary events.

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Authors' contribution

*****Abbas Andishmand contributed to the conception and design, critically revised the manuscript, gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy**.**
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Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this study.

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Ethical statements

The study protocol underwent rigorous review and received approval from the Institutional Review Board (IRB) at Shahid Sadoughi Medical University: (IRB.SSU.MEDICINE.REC.1402.273).

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