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The effect of empagliflozin on inflammation and oxidative stress in patients undergoing percutaneous coronary intervention, a randomized controlled trial

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Empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, has demonstrated cardioprotective effects beyond glycemic control. Empagliflozin has anti-inflammatory and antioxidant effects in long-term administration; however, current evidence on its short-term impact on inflammation and oxidative stress is limited. The purpose of this study was to investigate the rapid anti-inflammatory and oxidative effects of short-term Empagliflozin therapy in patients undergoing percutaneous coronary intervention (PCI). In this double-blind, placebo-controlled, randomized clinical trial, patients with cardiovascular disease (CVD) undergoing PCI received 10 mg Empagliflozin or placebo for three days. Biomarkers of inflammation and oxidative stress, including cystatin C, pro-oxidant–antioxidant balance (PAB), and high-sensitive C-reactive protein (hs-CRP), were measured at baseline and after treatment. The Jamovi 2.7.6 software was used for statistical analysis. A total of 121 patients, including 64 males (52.8%), were enrolled. There was no significant difference in baseline characteristics between the groups. Empagliflozin significantly reduced cystatin C and PAB levels after three days of administration compared with baseline ($p < 0.001$, $p < 0.001$, respectively). Although Empagliflozin decreased hs-CRP levels, the reduction did not reach statistical significance ($p = 0.14$). Nevertheless, the between-group difference in hs-CRP changes became significant after adjustment ($p = 0.029$). Short-term treatment with Empagliflozin significantly reduced inflammation and oxidative stress in patients undergoing PCI. Our findings indicated a rapid cardioprotective mechanism during CVD events. Although the findings revealed early anti-inflammatory and antioxidative benefits, larger and longer-term studies are warranted to confirm these effects and evaluate their impact on post-PCI outcomes and long-term cardiovascular prognosis.

Keywords Inflammation, Oxidative stress, SGLT2 inhibitor, Cardiovascular Disease (CVD)

Percutaneous coronary intervention (PCI) is a well-established minimally invasive revascularization procedure for coronary artery disease (CAD); however, it still has complications due to peri-procedural adverse events[1]. Oxidative stress and inflammation are crucial elements in the development of conditions such as contrast-

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associated acute kidney injury (CA-AKI), peri-procedural myocardial injury, and impaired microvascular reperfusion after PCI[2,3]. Contrast exposure and vascular manipulation during PCI can trigger oxidative stress pathways and inflammatory cascades, leading to endothelial cell damage, an increase in reactive oxygen species (ROS), and increase tissue injury[4,5]. Additionally, numerous studies have indicated that inflammation and oxidative stress are key components of atherosclerosis, plaque progression, and plaque rupture in CAD, which influence patients' prognosis[6,7]. Although cystatin C is primarily recognized as a biomarker of renal function, accumulating evidence suggests that it is also associated with systemic inflammation, myocardial injury, and extracellular matrix remodeling. Elevated cystatin C levels have been linked to inflammatory activity and cardiovascular events, indicating that it may reflect both renal and cardiovascular pathophysiological processes, particularly in settings involving vascular injury or contrast exposure[8,9].

Empagliflozin, a SGLT-2 inhibitor, is now recognized for its promising cardiorenal protective effects, extending beyond its glucose-lowering impact[10,11]. Potential protective mechanisms of Empagliflozin are the anti-inflammatory effect, including inhibition of the expression of proinflammatory cytokines (NLRP3, TNF-α, IL-6, and IL-1β) and other inflammatory signaling pathways, and also its antioxidant effect, such as inhibition of growth factor β/Smad pathway and activation of Nrf2/ARE signaling[12,13]. However, not all aspects are fully established.

Although recent studies have demonstrated that long-term administration of Empagliflozin could attenuate inflammation and oxidative stress, the studies evaluating short-term, peri-procedural administration of Empagliflozin to mitigate inflammation and oxidative stress around PCI are limited. In this randomized clinical trial, we aimed to assess whether short-term, peri-procedural Empagliflozin decreases inflammation and oxidative stress in patients undergoing PCI.

Method

Study design

This study is a double-blind, placebo-controlled, randomized clinical trial conducted on 121 patients who underwent PCI at Ghaem Hospital in Mashhad, Iran, between 2022 and 2023. Our research was approved by the National Institute for Medical Research Development (NIMAD) (Ethic Number: IR.NIMAD.REC.1400.160 and IRCT number: IRCT20220521054950N1, Registration date: 15/06/2022). Informed consent was obtained from all individuals before they enrolled in the study. Furthermore, the ethical guidelines of the Declaration of Helsinki were strictly followed in all phases of the study, including maintaining the confidentiality of patient information and obtaining consent for anonymous publication of the research findings. We enrolled patients over 18 who were referred for PCI for acute coronary syndrome (ACS), non-ST elevation Myocardial Infarction (NSTEMI), chronic coronary syndrome (CCS), or asymptomatic individuals. Patients with ST-elevation Myocardial Infarction (STEMI), malignancies, autoimmune, or infectious diseases were excluded. Moreover, patients using SGLT2 inhibitors, N-Acetyl Cysteine (NAC), or other anti-inflammatory drugs were excluded. Patients with a history of contrast media use in the past 10 days, alcohol consumption, or undergoing hemodialysis were also excluded. Figure 1 illustrates the study's progress and participant withdrawals and exclusions in detail. A cardiologist conducted all cardiovascular evaluations, including a detailed medical history and physical examination, as well as additional tests such as echocardiography, stress echocardiography, and electrocardiography (ECG), as needed.

A total of 600 participants underwent percutaneous coronary intervention (PCI), of whom 121 completed the study. The relatively large difference between screened and enrolled patients mainly reflects the application of strict inclusion and exclusion criteria designed to minimize confounding factors that could influence inflammatory and oxidative stress biomarkers.

Eligible patients were randomly assigned to two groups. The Intervention group, with 62 patients, received a standardized regimen of 10 mg of Empagliflozin (Gloripa, Abidi Pharmaceutical Company, Iran) once daily for 3 days, starting the day before PCI and continuing for 2 days after the procedure. The Placebo group, consisting of 59 patients, received visually identical tablets to Empagliflozin, designed by the Mashhad Faculty of Pharmacy. All patients were monitored daily by a cardiologist to ensure safety and identify any adverse reactions. Cystatin C, pro-oxidant–antioxidant balance (PAB), and high-sensitive C-reactive protein (hs-CRP) serum levels were measured from a 5 cc blood sample taken from the brachial vein after a 12-hour fasting period, before and 72 h after the intervention. The study was designed to evaluate changes in biomarkers related to inflammation and oxidative stress in the peri-procedural period. Among these biomarkers, cystatin C and PAB were considered the primary indicators reflecting inflammatory and oxidative stress responses, while hs-CRP was assessed as a secondary inflammatory marker.

Definition

The PAB is a laboratory parameter that simultaneously reflects the overall oxidative stress status by measuring the relative levels of oxidants and antioxidants in a single assay. PAB is assessed using a colorimetric assay with results expressed in arbitrary Hamidi-Koliakos (HK) units[14]. A higher PAB indicates more oxidative stress than antioxidants. hs-CRP was measured as a biomarker to assess systemic inflammation. Although cystatin C is typically used as a biomarker for renal function, it is also associated with inflammation and could be utilized as an inflammation biomarker[8,9]. Moreover, cystatin C level increases with cardiac tissue injury, playing a role in remodeling the extracellular matrix[15].

Randomization and blinding

Randomization and blinding were performed through stratified block allocation using envelopes labeled "A" for the placebo group and "B" for the intervention group. Envelopes were opened in front of participants for

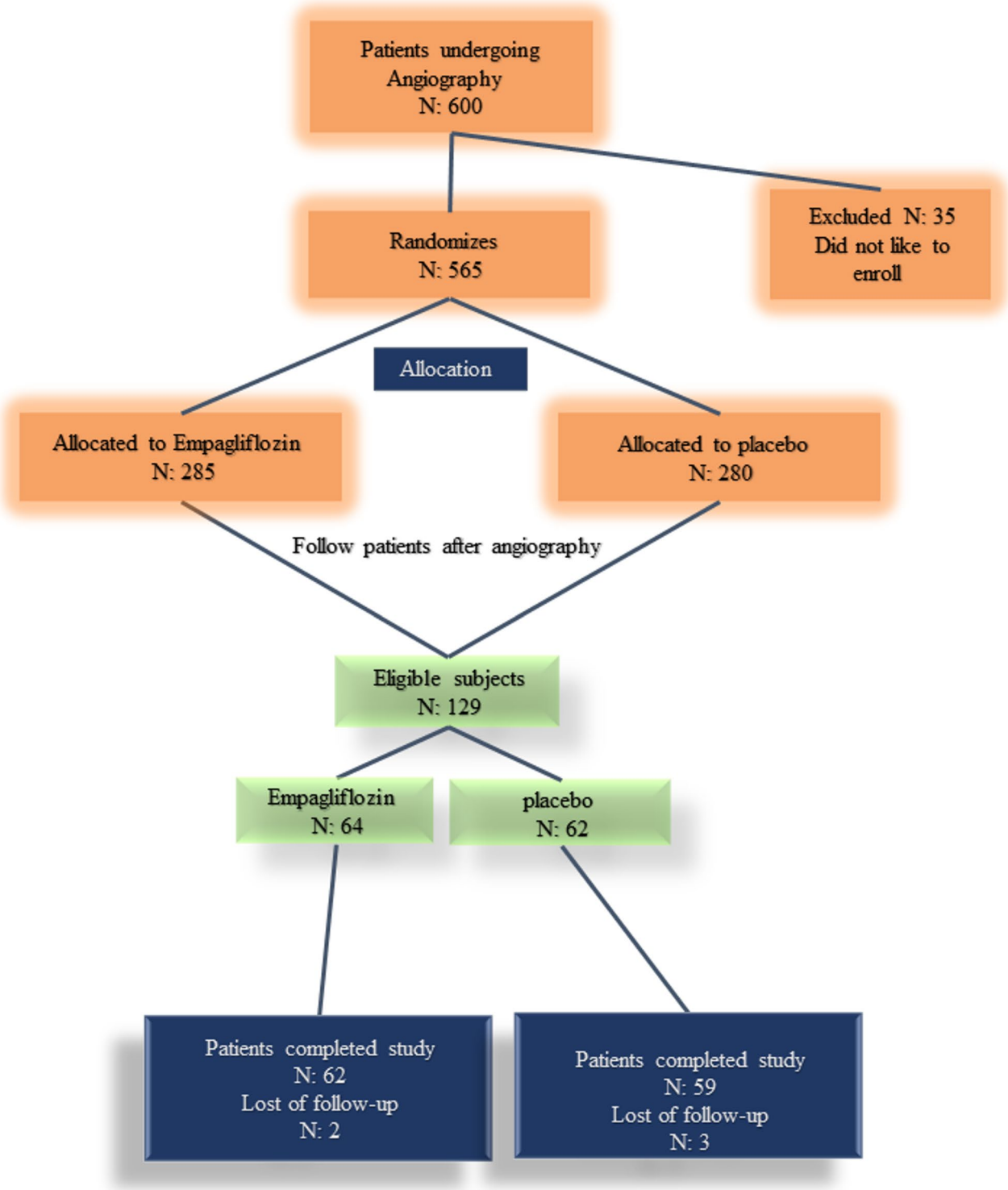


Fig. 1. Study flowchart.

transparency. The allocation list was kept secure by the faculty of Medicine, ensuring researchers remained blinded until the study's completion. More detailed protocol is discussed elsewhere[16].

Statistical analysis

We used Jamovi 2.7.6 software for data analysis. Data are presented as mean ± standard deviation or percentage. Continuous variables were analyzed using t-tests or Chi-square tests based on data distribution. ANCOVA was used to compare intervention effects between groups, adjusting for confounding factors like age, sex, and

		Total subjects		
		Empagliflozin (62)	Placebo (59)	*p*-value
Demographic and baseline characteristics				
Age, y		61.24 ± 11.83	60.86 ± 11.25	0.85
Sex	Male	32 (54.2%)	32 (51.6%)	0.77
	Female	27 (45.8%)	30 (48.4%)	
Smoking	No	34 (72.3%)	26 (59.1%)	0.42
	Former	4 (8.5%)	5 (11.4%)	
	Current	9 (19.1%)	13 (29.5%)	
Weight, kg		70.18 ± 13.17	74.39 ± 13.85	0.14
Height, m		1.64 ± 0.13	1.63 ± 0.1	0.82
BMI, kg/m^2		26.24 ± 5.9	27.98 ± 6.3	0.17
Diabetes	No	27 (60%)	29 (64.4%)	0.66
	Yes	18 (40%)	16 (35.6%)	
HTN	No	16 (34.8%)	15 (33.3%)	0.8
	Yes	30 (66.7%)	30 (65.2%)	
Dyslipidemia	No	24 (53.3%)	16 (35.6%)	0.09
	Yes	21 (46.7%)	29 (64.4%)	
CKD	No	42 (97.7%)	40 (90.9%)	0.36
	Yes	1 (2.3%)	4 (9.1%)	
Anti-hypertensive drug, yes		29 (46.8%)	27 (45.8%)	0.78
Lipid-lowering drug, yes		21 (33.9%)	24 (40.7%)	0.062
Anti-diabetic drug, yes		15 (24.2%)	13 (22%)	0.34
Contrast volume		113.56 ± 68.75	113.11 ± 57.66	0.89
Data presented as mean ± SD or number and percentage; Independent sample t-test or Chi-square test has been done				

Table 1. baseline characteristics of study population.

		Empagliflozin	*p*-value	Placebo	*p*-value	*p*-value for changes	Adjusted *p*-value and Beta (95% CI)
Cystatin C, mg/l	Before	1.15 ± 0.31	< 0.001	1.16 ± 0.58	0.3	-	-0.161 (-0.294, -0.028), p: 0.018
	After	0.91 ± 0.21		1.09 ± 0.53		-	
	Changes	-0.23 ± 0.21	-	-0.075 ± 0.55	-	< 0.001	
hs-CRP	Before	6.4 (3.45–13.6)	0.14	4.85 (3.8–7.25)	0.32	-	-3.39 (-6.47, -0.31) P: 0.029
	After	5.65 (2.68–8.2)		11.4 (5.1–12.6)		-	
	Changes	-2.35 (-5.75, 2.43)	-	4.55 (-1.88,7.72)	-	0.09	
PAB	Before	260.16 (165.78-294.42)	< 0.001	172.01 (152.12-245.02)	0.12		-12.823 (-30.623, 4.987), p: 0.29
	After	180.24 (169.6-226.32)		195.56 (164.09-249.34)			
	Changes	-18.3 (-84.8,26.3)		2.34 (-24.2,41.3)		< 0.001	
Paired sample t-test and ANCOVA were used, and the Data were adjusted by age, sex, and contrast volume							

Table 2. Comparison of the basic and post-intervention characteristics of patients across two groups.

contrast volume. A significance level of $p < 0.05$ was maintained for statistical analyses to ensure the reliability and robustness of the findings.

Result

A total of 600 participants underwent percutaneous coronary intervention (PCI), of whom 121 completed the study. The intervention group that received Empagliflozin included 62 patients with a mean age of 61.2 years, of whom 32 (54.2%) were males. The placebo group consisted of 59 patients, with a mean age of 60.8 years, and included 32 males (51.6%). There wasn't a significant difference in age, sex, smoking, weight, height, BMI, diabetes, hypertension, dyslipidemia, CKD, medications, and contrast volume between the two groups. The baseline characteristics of all patients are presented in Table 1.

The cystatin C level in the Empagliflozin group was significantly reduced after treatment (p-value < 0.001). Furthermore, the change in cystatin C level before and after treatment in the Empagliflozin group (-0.23 ± 0.21) was significantly greater than that in the placebo group (-0.075 ± 0.55), even after adjustment (p-value < 0.001 and 0.018, respectively). In the evaluation of hs-CRP levels, the Empagliflozin group showed mild improvement,

but it was not significant. Although the within-group reduction in hs-CRP in the empagliflozin group did not reach statistical significance, the adjusted between-group comparison demonstrated a significant difference (p-value: 0.029; 95% CI: -6.47, -0.31), indicating that empagliflozin attenuated the expected post-procedural inflammatory increase observed in the placebo group rather than producing a marked absolute reduction in hs-CRP levels. Our findings indicated that PAB levels were reduced considerably in the Empagliflozin group after treatment (p-value < 0.001). Although the reduction in PAB was significant within the empagliflozin group and the unadjusted between-group comparison suggested a difference, this significance was attenuated after adjustment for potential confounders (p-value < 0.001 and 0.29, respectively). Figure 2. (A, B, C) shows scatterplots with trendlines of hs-CRP, cystatin C, and PAB values pre- vs. post-intervention in Placebo and Empagliflozin groups.

Exploratory subgroup analyses were performed according to diabetes status. Among patients with diabetes, the reduction in cystatin C was significantly greater in the empagliflozin group compared with the placebo group, whereas no significant differences were observed for hs-CRP or PAB. In patients without diabetes, no statistically significant differences in biomarker changes were observed between the empagliflozin and placebo groups.

Figure 2A. (hs-CRP): Two groups show an upward inclination from pre- to post-intervention levels. However, the Empagliflozin group appeared to achieve hs-CRP that was slightly lower than in the Placebo group post-intervention, particularly at low-to-mid baseline levels.

Figure 2B. (cystatin C): A similar tendency of response can be observed, and the regression lines for both the Placebo and Empagliflozin groups are nearly parallel. The confidence intervals cross each other, suggesting that there is no significant difference between the two groups.

Figure 2C. (PAB): Men have a positive linear relationship between baseline and post-intervention measurements, as do women. The Case group also tends to have a slightly less moderate inclination than the slope of Placebo, suggesting that how much PAB had increased in the Empagliflozin group might be promoted compared with its level in the Placebo group.

Discussion

In this double-blind, randomized clinical trial, we evaluated the short-term impact of empagliflozin administration on biomarkers of inflammation and oxidative stress in patients undergoing PCI. Our findings demonstrated that empagliflozin significantly decreased cystatin C and PAB levels after three days of administration. It should also be noted that cystatin C is a well-established biomarker of renal function; therefore, the reduction observed in this study may partly reflect early renal protective effects of empagliflozin, particularly in the context of contrast exposure during PCI, in addition to its potential association with inflammatory processes. Although PAB levels decreased significantly within the empagliflozin group, the between-group difference was no longer significant after adjustment for confounders. This attenuation may be related to the relatively modest sample size, baseline variability in oxidative stress markers, and the biological variability inherent to PAB measurements. In addition, hs-CRP levels decreased in the empagliflozin group, although the within-group change did not reach statistical significance. However, the adjusted between-group comparison showed a significant difference in hs-CRP changes. These findings suggest that empagliflozin may mitigate the peri-procedural inflammatory response associated with PCI rather than producing a marked absolute reduction in hs-CRP levels. Visual inspection of the scatterplots also suggests that patients in the empagliflozin group tended to have lower post-intervention hs-CRP levels compared with the placebo group across a range of baseline values, which is consistent with the observed attenuation of the peri-procedural inflammatory response. Exploratory subgroup analyses suggested that the reduction in cystatin C was more pronounced among patients with diabetes, although these findings should be interpreted cautiously due to the limited sample size.

Overally, this finding indicated that Empagliflozin, as a member of the SGLT2 inhibitor family, could reduce inflammation and oxidative stress even with short-term treatment in patients with CVD. Our results are consistent with previous experimental and clinical evidence that SGLT2 inhibitors could have anti-inflammatory and antioxidant effects beyond glycemic control.

Recent preclinical and clinical studies have shown that Empagliflozin attenuates oxidative stress and inflammation in patients with CVD[17] through several mechanisms such as suppression of the TXNIP/NLRP3 inflammasome axis, NF-kB pathway, tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6), reactive oxygen species (ROS) production, and improves AMPK activity, thereby reducing downstream inflammatory cytokine release and vascular injury[18,19]. Additionally, endothelial and cardiac cells in animal and human models, Empagliflozin has been reported to block inflammatory and oxidative stress signaling, leading to a decrease in chemokine secretion, lowered No-Reflow phenomenon and infarct size, and improved cardiac function[20–23].

In the clinical setting, a post-hoc analysis of the EMMY trial demonstrated that Empagliflozin did not reduce inflammatory biomarkers after acute MI more than placebo after 26 weeks[24]. In contrast, a randomized trial in patients with type 2 DM and CAD reported reductions in hs-CRP and interleukin-6 and an increase in superoxide dismutase (SOD) activity, glutathione (GSH), and total antioxidant capacity (TAC) after 26 weeks of therapy[25]. In another study, long-term treatment with Empagliflozin after MI in patients with DM was associated with preventing endothelial injury and improvement in the global function of the heart[22]. Paolisso et al. reported that diabetic patients admitted with MI who were on chronic SGLT2 inhibitors had significantly reduced inflammation biomarkers and infarct size rather than other patients[26,27]. Furthermore, a recent systematic review provided strong evidence of preclinical and clinical findings suggesting that Empagliflozin has anti-inflammatory and anti-oxidative activities by numerous mechanisms in patients with CVD regardless of DM[28]. These impacts of Empagliflozin could lead to smaller infarct sizes, improved cardiac function, lower atherogenesis, and reduced plaque progression[28]. Overall, previous evidence suggests that Empagliflozin has potential cardioprotective effects that could lead to fewer complications and a better prognosis in CVD patients,

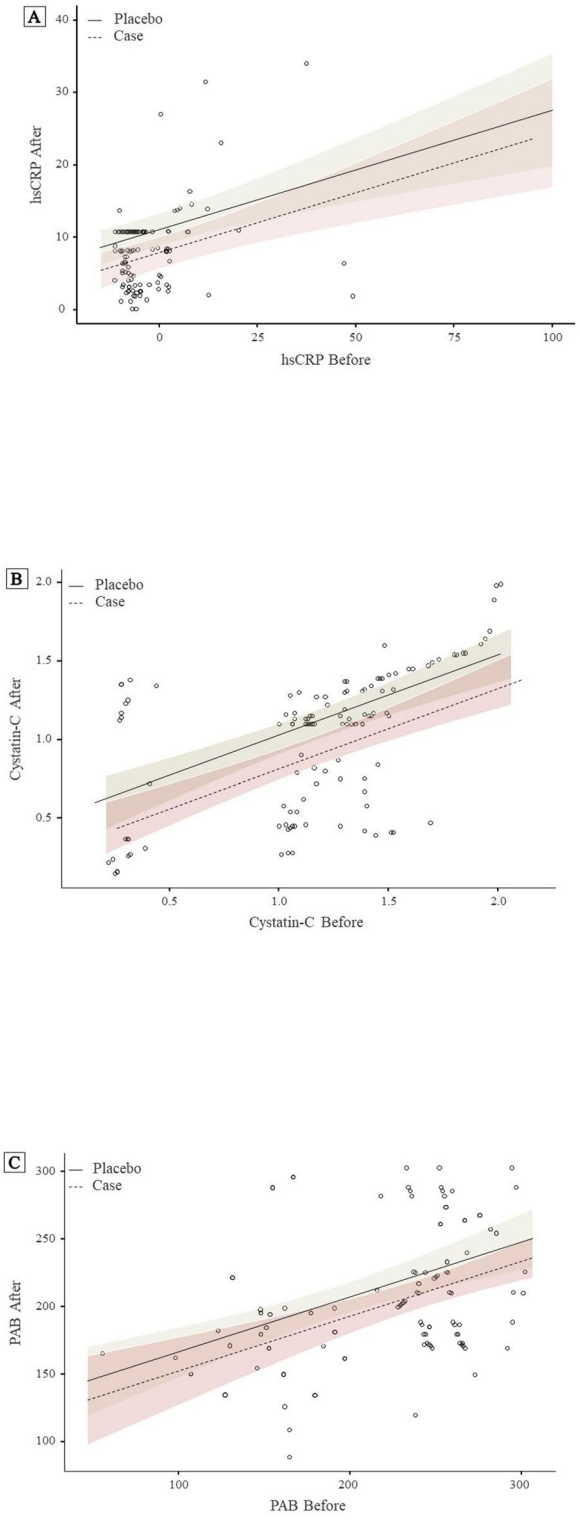


Fig. 2. Association between baseline and post-intervention levels of biomarkers in the empagliflozin and placebo groups (**A**) hs-CRP, (**B**) cystatin C, and (**C**) PAB levels showing baseline versus post-intervention values in the two study groups. Scatterplots with regression lines and confidence intervals are presented..

especially in long-term treatment. The evidence gap that our study aimed to address was whether administering Empagliflozin for three days during the peri-PCI period was effective in reducing markers of inflammation and oxidative stress, highlighting a potential rapid protective mechanism during vascular injury and reperfusion stress. Taken together, our findings provide novel evidence for the hypothesis that Empagliflozin has rapid anti-inflammatory and antioxidative benefits in patients with CVD, potentially contributing to its well-documented

cardioprotective effects. Our findings also provide novel clinical evidence suggesting that empagliflozin may exert early protective effects against inflammation and oxidative stress during PCI, which may represent a potential adjunctive strategy to reduce peri-procedural complications. Moreover, patients undergoing PCI are exposed to acute oxidative stress and inflammatory responses. Empagliflozin could possibly be considered as an adjunct therapy to minimize peri-procedural complications and improve prognosis, although larger trials are needed.

Limitations and strengths

This study has several limitations. First, it was conducted at a single center with a relatively modest sample size and short follow-up period, which may limit statistical power and generalizability. Consequently, some neutral findings, such as the lack of a significant within-group reduction in hs-CRP, should be interpreted cautiously. Second, inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) were not measured, which may have limited a more comprehensive evaluation of inflammatory pathways. Third, subgroup analyses according to different cardiovascular disease presentations were not performed. In addition, although cystatin C was used as an inflammation-related biomarker, it is also a well-established marker of renal function, and its changes may partly reflect renal effects, particularly in the context of contrast exposure during PCI. Larger studies with longer follow-up and broader biomarker panels are needed to confirm these findings and determine whether early reductions in inflammatory and oxidative stress markers translate into improved long-term cardiovascular outcomes.

Conclusion

Our study showed that short-term empagliflozin treatment was associated with a significant reduction in cystatin C levels and a within-group reduction in PAB in patients with CVD undergoing PCI. In addition, Empagliflozin decreased the hs-CRP level, but this reduction was not significant. However, the adjusted between-group difference in hs-CRP changes was significant. These findings provide new evidence of the anti-inflammatory and antioxidant effects of Empagliflozin in CVD. This suggests that empagliflozin may have long-term benefits in reducing the inflammatory and oxidative side effects of contrast-induced injury in patients candidates for angiography. Further studies are needed to assess the precise impact of the anti-inflammatory and antioxidant capacity of Empagliflozin on complications and prognosis of patients with CVD undergoing PCI.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 10 October 2025; Accepted: 11 March 2026
Published online: 14 May 2026

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Acknowledgements
The authors express their sincere gratitude to Mashhad University of Medical Sciences and Ghaem Hospital for their support in conducting this study.

Author contributions
All authors reviewed the manuscript.

Funding
This project received support from the National Institute for Medical Research Development. Funding number: 1400.160.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
Informed consent was obtained from all patients before they participated in the study. The study protocol was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD) and the Institutional Review Board of the National Institute for Medical Research Development (Ethic Number: IR.NIMAD.REC.1400.160, IRCT number: IRCT20220521054950N1).

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-026-44492-7.

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