Original Article

Empagliflozin's Effects on Carotid Ultrasound Parameters in Type 2 Diabetes Patients Post-ST-Elevation Myocardial Infarction: A Randomized Controlled Trial

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What's Known

- Sodium-glucose transporter 2 inhibitors reduce cardiovascular events in patients with type 2 diabetes and established cardiovascular disease. However, their effects on early carotid intima-media thickness changes after acute myocardial infarction are not well established.

What's New

- In this study, 3 months of empagliflozin therapy was associated with a reduction in carotid intima-media thickness in patients with type 2 diabetes after ST-elevation myocardial infarction, suggesting early favorable vascular changes.

Abstract

Background: Patients with type 2 diabetes (T2D) and recent ST-elevation myocardial infarction (STEMI) face accelerated atherosclerosis and a high risk of recurrent cardiovascular events. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), particularly empagliflozin, offer proven cardioprotection in T2D. This study investigated the 3-month effects of empagliflozin on carotid intima-media thickness (CIMT) and Doppler hemodynamic parameters (resistive index [RI] and pulsatility index [PI]) in T2D patients post-STEMI.

Methods: In this randomized clinical trial, 80 patients with T2D and a recent STEMI from Ayatollah Mousavi Hospital, Zanjan, Iran (from July to December 2025), were randomized in a 1:1 ratio to empagliflozin 10 mg daily or an identical placebo, in addition to standard therapy. The primary endpoint was the change in CIMT at 3 months, assessed using B-mode ultrasound. Secondary endpoints included changes in RI and PI, measured via Doppler ultrasound.

Results: Follow-up data were available for 78 patients (two deaths in the intervention arm, both unrelated to the study drug). In the primary intention-to-treat analysis (n=80), empagliflozin was associated with a significant reduction in left CIMT compared with controls (median change=-0.13 mm vs. -0.01; within-group P=0.002; between-group ΔCIMT P=0.004; ANCOVA-adjusted P<0.001) versus controls (-0.01 mm). A smaller though statistically significant difference was also observed for right CIMT (ΔCIMT, P=0.021; ANCOVA-adjusted P=0.006). These findings remained consistent in the per-protocol analysis. After Bonferroni correction, the reduction in left CIMT remained significant, whereas the effect on right CIMT became more modest. No significant changes were observed in RI or PI.

Conclusion: Short-term empagliflozin suggested favorable changes in CIMT in high-risk T2D patients post-STEMI, without detectable effects on RI or PI.

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Keywords ● Sodium-glucose transporter 2 inhibitors ● Carotid intima-media thickness ● Ultrasonography ● Diabetes mellitus ● Myocardial infarction

Introduction

Cardiovascular events are among the most common non-communicable diseases and represent the leading cause of mortality worldwide. Numerous risk factors are associated with cardiovascular events. Type 2 diabetes (T2D) is one of the most significant risk factors, and individuals with T2D are, on average, twice as likely to develop cardiovascular diseases.[1] Importantly, those who experience an acute myocardial infarction constitute a particularly high-risk subgroup for recurrent cardiovascular events. Studies indicated that among patients undergoing primary percutaneous coronary intervention (PCI), underlying T2D increased the risk of recurrent cardiovascular events more than hypertension alone, and even more than the presence of both T2D and hypertension together.[2, 3]

Atherosclerosis is a predictor of future vascular events such as heart attacks and strokes.[4] It begins early in life and progresses through endothelial damage and gradual intimal thickening, remaining silent until plaque formation occurs.[5] Early identification of subclinical atherosclerosis is therefore critical for cardiovascular risk stratification and secondary prevention. Various diagnostic modalities exist for assessing vascular atherosclerosis. The standard diagnostic method is angiography, which detects arterial narrowing.[6, 7] However, this technique fails to accurately assess atherosclerotic plaque burden, is invasive and expensive, involves X-ray exposure, and is not used in the early stages of atherosclerosis. Therefore, alternative methods are required for evaluating asymptomatic individuals.[8]

Ultrasound is widely used as a non-invasive, cost-effective method for assessing early structural changes in the carotid arteries, including atherosclerotic plaques and increased carotid intima-media thickness (CIMT). CIMT reflects early arterial wall remodeling and precedes overt plaque formation, which typically appears at more advanced stages of atherosclerosis.[9] The resistive index (RI) is a hemodynamic parameter easily assessed using Doppler ultrasound, indicating vascular resistance. In addition, the pulsatility index (PI) reflects arterial compliance and downstream resistance.[10] Given the correlation between atherosclerotic plaques, IMT, PI, and RI with vascular events, these radiological parameters are highly suitable for diagnosing early atherosclerosis before clinical symptoms emerge.[11, 12]

Typically, CIMT is measured using B-mode ultrasound in different sections of the carotid artery, providing a safe and accessible approach for detecting hidden plaque formation. According to the 2011 Mannheim carotid intima-media thickness and plaque consensus, CIMT should be assessed at the posterior wall of plaque-free arterial segments, preferably in the distal one centimeter of the common carotid artery (CCA) proximal to the bifurcation, where measurements are most reproducible.[9]

Empagliflozin is a selective sodium-glucose co-transporter 2 inhibitor (SGLT2i) that prevents hyperglycemia by reducing renal glucose reabsorption and increasing glucose excretion. Beyond its glucose-lowering effects, empagliflozin has demonstrated significant cardiovascular benefits in high-risk patients with T2D, including reductions in cardiovascular morbidity and mortality.[13-15] Several mechanisms have been proposed to explain these outcomes, including anti-inflammatory effects, improvements in endothelial function, reduction in oxidative stress, and modulation of arterial stiffness.[16-18] However, despite growing evidence supporting its cardioprotective effects, the impact of empagliflozin on structural markers of atherosclerosis remains inconsistent across studies and has been insufficiently explored in the early post-ST-elevation myocardial infarction (post-STEMI) period.

Previous investigations evaluating sodium-glucose cotransporter 2 inhibitors in stable T2D populations reported mixed findings. Empagliflozin has been associated with favorable reductions in CIMT or related vascular markers over short-to-medium treatment durations in some studies,[19, 20] whereas other agents within this drug class, including ipragliflozin and tofogliflozin, have demonstrated neutral effects on CIMT progression over longer follow-up periods.[21, 22] These inconsistencies highlighted the need for context-specific evaluation of empagliflozin, particularly in clinical settings characterized by heightened vascular vulnerability.

Patients with T2D in the early post-STEMI phase represent a uniquely vulnerable subgroup with residual inflammation, endothelial dysfunction, and accelerated atherosclerotic remodeling. This period constitutes a critical window during which early vascular interventions may exert measurable and clinically relevant effects.[23, 24] Despite the prognostic importance of CIMT and carotid Doppler indices, the short-term vascular impact of empagliflozin in the acute post-infarction setting has not been adequately investigated.

Therefore, the present study aimed to evaluate short-term changes in CIMT and carotid Doppler ultrasound parameters in patients

with T2D and STEMI undergoing primary percutaneous coronary intervention, comparing empagliflozin therapy with placebo. By focusing on the early post-myocardial infarction phase, this study aimed to provide exploratory evidence regarding the potential early vascular effects of empagliflozin in a high-risk population.

Materials and Methods

Study Design and Population

This study was conducted as a double-blind, randomized, placebo-controlled clinical trial in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study protocol was approved by the Research Ethics Committee of Zanjan University of Medical Sciences (code: IR.ZUMS.REC.1402.100). The trial was prospectively registered in the Iranian Registry of Clinical Trials (IRCT code: IRCT20230727058945N1). Written informed consent was obtained from all participants prior to enrollment.

The study population consisted of patients with T2D admitted with acute STEMI to Ayatollah Mousavi Hospital, Zanjan, Iran, between July 2025 and December 2025. All patients initially received insulin therapy during hospitalization according to standard clinical practice for acute myocardial infarction. After hemodynamic stabilization and prior to hospital discharge, eligible patients were transitioned to oral antidiabetic therapy. Only patients who, according to the most recent clinical practice guidelines, were appropriately treated with metformin in combination with sulfonylurea as their background antidiabetic regimen were included in the study. Patients previously treated with older-generation sulfonylureas were switched to newer-generation sulfonylureas in combination with metformin upon discharge to standardize background therapy. Guideline-directed medical therapy (including high-intensity statins, dual antiplatelet therapy, angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARBs], and beta-blockers) was optimized and balanced between groups at baseline and maintained throughout, with no significant differences in concomitant medications.

Randomization, Blinding, and Intervention

Eligible participants were randomly assigned in a 1:1 ratio to the intervention or control group using a computer-generated random sequence with a four-block randomization technique (block size=4). The randomization sequence was generated by an independent statistician not involved in patient recruitment, treatment allocation, or outcome assessment. Allocation concealment was ensured through centralized medication coding and packaging. Study medications were coded, packaged, and labeled by Abidi Pharmaceutical Company (Iran). Throughout the study period, participants, treating cardiologists, nursing staff, and the outcome assessor (radiologist) were all blinded to group allocation.

Participants in the intervention group received standard oral antidiabetic therapy plus empagliflozin 10 mg orally once daily for 3 months. Participants in the control group received standard oral antidiabetic therapy plus a placebo tablet identical in appearance, size, color, and packaging to empagliflozin, containing inert excipients only and manufactured by the same pharmaceutical company. Medication adherence was monitored via pill counts at follow-up visits and patient self-reporting, with adherence defined as taking >80% of prescribed doses.

Sample Size calculation and Eligibility Criteria

We assumed a moderate effect size of 0.65 (based on the change in CIMT reported by Ardahanlı and colleagues, 2021).[19] Using a two-sided alpha of 0.05, 80% power, G*Power software (version 3.1.9.7),[25] and allowance for dropout, the required sample size was 40 participants per group.

Patients were excluded if they had intolerance to the study medication, major drug-related adverse effects, loss to follow-up, cardiogenic shock, severe hypoglycemia, diabetic ketoacidosis, prior coronary artery bypass graft surgery, type 1 diabetes mellitus, severe hepatic failure, advanced malignancy, severe renal impairment (defined as an estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73 m²), end-stage renal disease or dialysis, hypovolemia, active inflammatory disease, advanced heart failure, pregnancy, or age younger than 18 years.

Ultrasound Assessment and Outcomes

All participants underwent carotid ultrasound examinations at two time points: within the first 7 days of hospitalization after hemodynamic stabilization and prior to initiation of the study medication, and again at the end of the 3-month follow-up period. Ultrasound examinations were performed by a single experienced radiologist blinded to clinical data and treatment allocation, using a SuperSonic Imagine ultrasound system with a linear SL15-4 probe (SuperSonic Imagine, France).

CIMT was measured using B-mode ultrasonography in accordance with the 2011

Mannheim carotid intima-media thickness and plaque consensus recommendations.[9] Measurements were obtained from the far wall of the distal 1 cm of the CCA in plaque-free segments. Doppler ultrasonography was used to assess the RI and PI of the common and internal carotid arteries, as well as the presence of atherosclerotic plaques. The primary outcome was the change in CIMT from baseline to 3 months. Secondary outcomes included changes in RI and PI.

Statistical Analysis

Statistical analysis was performed using SPSS software version 22 (IBM Corp., United States). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were presented as mean±SD, whereas non-normally distributed continuous variables were presented as median (interquartile range: Q1–Q3). Categorical variables were reported as numbers and percentages. The primary analysis was conducted according to the intention-to-treat (ITT) principle, including all randomized participants (N=40). For participants who died before follow-up ultrasound assessment, baseline CIMT values were carried forward. A per-protocol (PP) analysis was performed as a sensitivity analysis.

Baseline characteristics were compared between groups using the Chi square test for categorical variables and the Mann–Whitney U test for continuous variables. Within-group changes were assessed using the Wilcoxon signed-rank test. Between-group P values were corrected for multiple comparisons using the Bonferroni method. Adjusted P values were obtained from analysis of covariance (ANCOVA), with adjustment for baseline value of the respective outcome, sex, current smoking status, and left circumflex artery involvement. All tests were two-sided, and a P value of less than 0.05 was considered statistically significant.

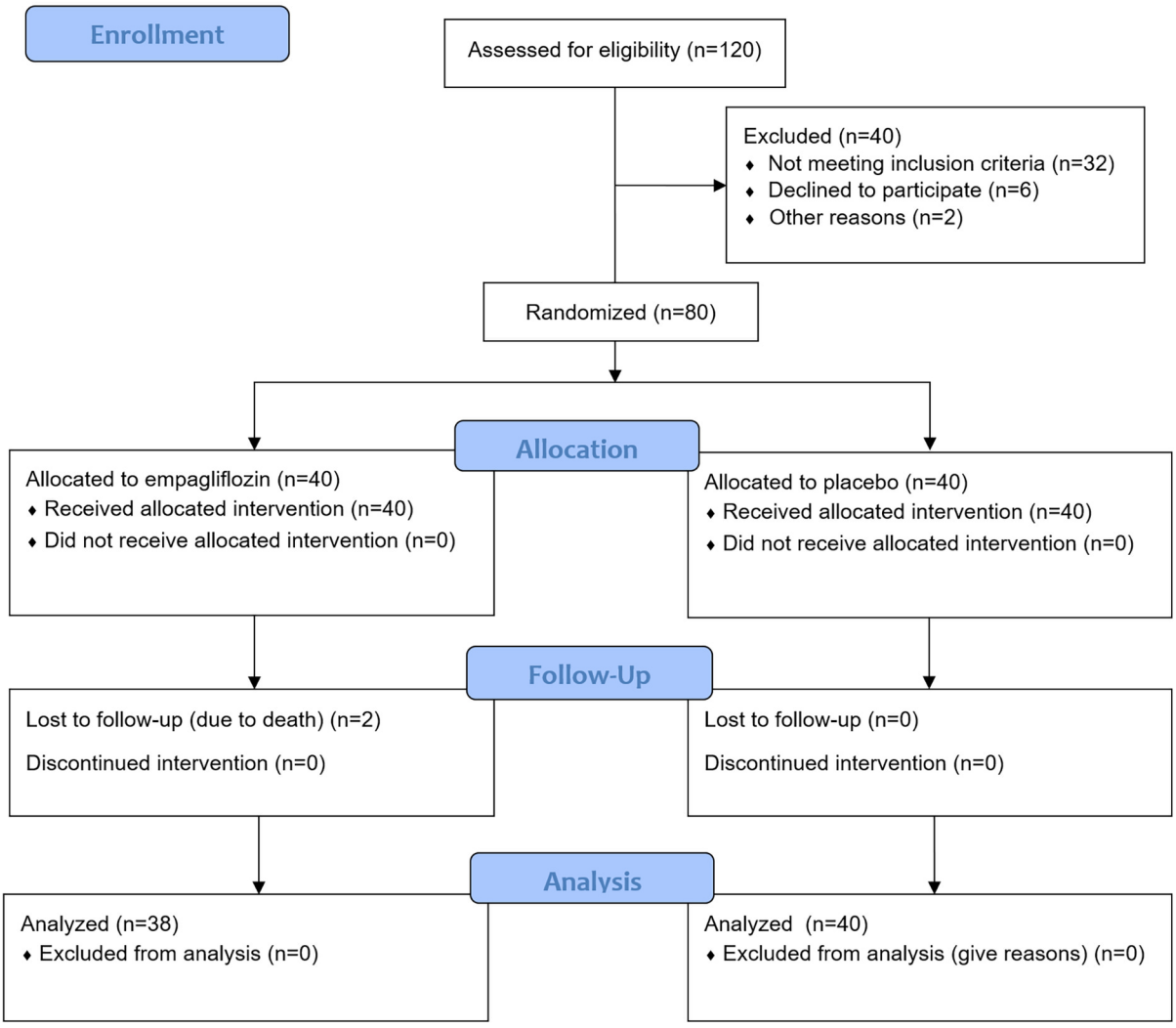

Figure 1: This figure presents the CONSORT flow diagram illustrating the progress of participants through the enrollment, randomization, allocation, follow-up, and analysis phases of the study.

Results

A total of 80 patients with T2D and STEMI were randomized equally to the intervention group (empagliflozin plus standard oral diabetes medication) and the control group (placebo plus standard oral diabetes medication). All patients received the assigned treatment and underwent baseline ultrasound assessments.

During the 3-month follow-up period, two patients in the intervention group died (all-cause mortality: 5% in intervention vs. 0% in control). One patient died 4 weeks after randomization due to recurrent STEMI complicated by cardiogenic shock. The second patient was readmitted 1 week after study initiation due to hospital-acquired pneumonia and sepsis and died 4 weeks later despite intensive care management. Both events were reviewed by the study investigators and were not considered related to the study medication. Consequently, follow-up ultrasound data were missing for these two individuals, and 38 patients in the intervention group and 40 in the control group completed the study with full follow-up assessments (figure 1).

Table 1 presents the baseline demographic, clinical, and ultrasound characteristics of the study participants. The two randomized groups were largely comparable, with no significant differences in age, CIMT, RI, PI, or most angiographic parameters. However, the empagliflozin group included a higher proportion of current smokers (P=0.03) and a numerically higher proportion of females (P=0.06), along with a significantly greater involvement of the left circumflex artery (P=0.04). These imbalances, while not unexpected in a trial of this size, were considered potential confounders and were addressed using appropriate statistical methods.

Table 2 presents the changes in CIMT at baseline and after 3 months of treatment, using both ITT and PP analyses. In the primary ITT analysis, empagliflozin was associated with a statistically significant attenuation of CIMT progression compared with placebo, particularly on the left side (median change:-0.13 mm; within-group P=0.002, between-group ΔCIMT P=0.004; ANCOVA-adjusted P=0.006) and, to a lesser extent, on the right (ΔCIMT P=0.021; ANCOVA-adjusted P=0.006).

Table 1: Baseline Characteristics of Study Participants

Characteristic		Control group (n=40)	Intervention group (n=40)	P value
Demographics				
Age, years		64.4±9.5	63.0±10.5	0.480
Sex, n (%)	Male	30 (75.0)	21 (52.5)	0.063
	Female	10 (25.0)	19 (47.5)	
Current smoker, n (%)		22 (55.0)	32 (80.0)	0.032
Coronary angiography findings				
Number of carotid plaques	0	13 (32.5)	7 (17.5)	0.250
	1	16 (40.0)	15 (37.5)	
	2	11 (27.5)	17 (42.5)	
	3	0 (0.0)	1 (2.5)	
Extent of coronary disease				
SVD		4 (10.0)	11 (27.5)	0.090
2VD		13 (32.5)	17 (42.5)	0.490
3VD		21 (52.5)	12 (30.0)	0.070
Vessel involvement, n (%)				
RCA		16 (40.0)	24 (60.0)	0.120
LAD		18 (45.0)	25 (62.5)	0.180
LCX		14 (35.0)	24 (60.0)	0.040
OM		1 (2.5)	7 (17.5)	0.060
Carotid ultrasound parameters				
CIMT–Right, mm		1.05 (0.85–1.30)	0.99 (0.80–1.20)	0.131
CIMT–Left, mm		1.02 (0.82–1.25)	1.05 (0.85–1.30)	0.281
RI–Right		0.87 (0.80–0.94)	0.84 (0.77–0.91)	0.230
RI–Left		0.81 (0.72–0.90)	0.79 (0.70–0.88)	0.534
PI–Right		1.55 (1.30–1.85)	1.45 (1.20–1.70)	0.168
PI–Left		1.62 (1.40–1.85)	1.55 (1.30–1.80)	0.250

SVD: Single-vessel disease; 2VD: Two-vessel disease; 3VD: Three-vessel disease; RCA: Right coronary artery; LAD: Left anterior descending; LCX: Left circumflex; OM: Obtuse marginal; CIMT: Carotid intima-media thickness; RI: Resistive index; PI: Pulsatility index. Data are presented as mean±SD for continuous variables, n (%) for categorical variables, and median (Q1-Q3) for non-normal variables. P values were calculated using the Mann-Whitney U test for continuous variables and the Chi square test for categorical variables. P<0.05 was considered statistically significant.

Table 2: Changes in Carotid Intima-Media Thickness (CIMT)

Parameter	Analysis	Intervention group (n=40 ITT/n=38 PP)	Control group (n=40)	P value between-group ΔCIMT	Adjusted P value
Right CIMT (mm)					
Baseline	ITT/PP	0.99 (0.80–1.20)	1.05 (0.85-1.30)	0.131	—
Follow-up	ITT	1.02 (0.82–1.25)	1.15 (0.92-1.35)	0.008	0.006
	PP	1.00 (0.80–1.23)	1.15 (0.92-1.35)	0.008	0.006
Change (Δ)	ITT	-0.03 (-0.12–0.06)	+0.05 (-0.05–0.15)	0.021	0.006
	PP	-0.05 (-0.15–0.05)	+0.05 (-0.05–0.15)	0.006	0.006
Within-group P value	ITT	0.31	0.06	—	
	PP	0.18	0.06	—	
Left CIMT (mm)					
Baseline	ITT/PP	1.05 (0.85–1.30)	1.02 (0.82–1.25)	0.281	
Follow-up	ITT	0.92 (0.72–1.15)	1.01 (0.80–1.22)	0.009	0
	PP	0.90 (0.70–1.12)	1.01 (0.80–1.22)	0.032	0
Change (Δ)	ITT	-0.13 (-0.25– -0.02)	-0.01 (-0.10–0.08)	0.004	0
	PP	-0.15 (-0.28–-0.03)	-0.01 (-0.10–0.08)	0	0
Within-group P value	ITT	0.002	0.11	—	—
	PP	0.001	0.11	—	—

ITT: Intention-to-treat analysis; PP: Per-protocol analysis; CIMT: Carotid intima-media thickness. Data are presented as median (Q1-Q3). Change (Δ) represents the follow-up value minus the baseline value. Between-group P values were calculated using the Mann-Whitney U test and corrected for multiple comparisons using the Bonferroni method. Within-group P values were determined using the Wilcoxon signed-rank test. Adjusted P values were obtained from analysis of covariance (ANCOVA), adjusted for baseline CIMT, sex, current smoking status, and left circumflex artery involvement. P<0.05 was considered statistically significant.

Table 3: Changes in Resistive Index (RI) of the Carotid Arteries

Parameter	Analysis	Intervention group (n=40 ITT/n=38 PP)	Control group (n=40)	P value between-group ΔRI	Adjusted P value
Right RI					
Baseline	ITT/PP	0.84 (0.77-0.91)	0.87 (0.80–0.94)	0.230	—
Follow-up	ITT	0.84 (0.77-0.91)	0.88 (0.80–0.96)	0.206	0.312
	PP	0.83 (0.76-0.90)	0.88 (0.80–0.96)	0.206	0.312
Change (Δ)	ITT	0.00 (-0.05–0.05)	+0.01 (-0.04–0.06)	0.700	0.312
	PP	-0.01 (-0.06–0.04)	+0.01 (-0.04–0.06)	0.700	0.312
Within-group P value	ITT	0.610	0.513	—	—
	PP	0.610	0.513	—	—
Left RI					
Baseline	ITT/PP	0.79 (0.70–0.88)	0.81 (0.72–0.90)	0.534	—
Follow-up	ITT	0.81 (0.72–0.90)	0.83 (0.74–0.92)	0.456	0.521
	PP	0.82 (0.73–0.91)	0.83 (0.74–0.92)	0.456	0.521
Change (Δ)	ITT	+0.02 (-0.03–0.07)	+0.02 (-0.04–0.08)	0.580	0.521
	PP	+0.03 (-0.02–0.08)	+0.02 (-0.04–0.08)	0.580	0.521
Within-group P value	ITT	0.281	0.380	—	—
	PP	0.281	0.380	—	—

ITT: Intention-to-treat analysis; PP: Per-protocol analysis; RI: Resistive index. Data are presented as median (Q1-Q3). Change (Δ) represents the follow-up value minus the baseline value. Between-group P values were calculated using the Mann-Whitney U test and corrected for multiple comparisons using the Bonferroni method. Within-group P values were determined using the Wilcoxon signed-rank test. Adjusted P values were obtained from analysis of covariance (ANCOVA), adjusted for baseline RI, sex, current smoking status, and left circumflex artery involvement. P<0.05 was considered statistically significant.

These between-group differences remained significant after Bonferroni correction and adjustment for baseline CIMT, sex, smoking status, and left circumflex artery (LCX) involvement. Within-group reductions were more pronounced in the empagliflozin group (left P=0.002), whereas the control group showed no meaningful change. The PP sensitivity analysis revealed a stronger treatment effect.

Table 3 presents the changes in the RI of the common and internal carotid arteries over the 3-month intervention period. Baseline RI values were comparable between groups and fell within the expected upper-normal range for patients with T2D and recent MI. Neither the ITT nor PP analysis demonstrated any clinically or statistically significant within-group or between-group differences in ΔRI or follow-up values for either carotid artery (all P≥0.206 after Bonferroni correction). Adjustments for baseline covariates using ANCOVA did not alter the null findings.

Table 4: Changes in Pulsatility Index (PI) of the Carotid Arteries

Parameter	Analysis	Intervention group (n=40 ITT/n=38 PP)	Control group (n=40)	P value between-group ΔPI	Adjusted P value
Right PI					
Baseline	ITT/PP	1.45 (1.20–1.70)	1.55 (1.30–1.85)	0.168	—
Follow-up	ITT	1.42 (1.18–1.68)	1.55 (1.30–1.85)	0.028	0.120
	PP	1.40 (1.15–1.65)	1.55 (1.30–1.85)	0.028	0.120
Change (Δ)	ITT	-0.03 (-0.20–0.15)	0.00 (-0.18–0.18)	0.760	0.120
	PP	-0.05 (-0.22–0.12)	0.00 (-0.31–0.18)	0.760	0.120
Within-group P value	ITT	0.310	0.650	—	—
	PP	0.310	0.650	—	—
Left PI					
Baseline	ITT/PP	1.55 (1.30–1.80)	1.62 (1.40–1.85)	0.250	—
Follow-up	ITT	1.48 (1.20–1.75)	1.55 (1.30–1.80)	0.130	0.820
	PP	1.47 (1.18–1.72)	1.55 (1.30–1.80)	0.130	0.820
Change (Δ)	ITT	-0.07 (-0.25–0.11)	-0.07 (-0.25–0.11)	0.500	0.820
	PP	-0.08 (-0.28–0.12)	-0.07 (-0.25–0.11)	0.500	0.820
Within-group P value	ITT	0.072	0.240	—	—
	PP	0.072	0.240	—	—

ITT: Intention-to-treat analysis; PP: Per-protocol analysis; PI: Pulsatility index. Data are presented as median (Q1-Q3). Change (Δ) represents the follow-up value minus the baseline value. Between-group P values were calculated using the Mann-Whitney U test and corrected for multiple comparisons using the Bonferroni method. Within-group P values were determined using the Wilcoxon signed-rank test. Adjusted P values were obtained from analysis of covariance (ANCOVA), adjusted for baseline RI, sex, current smoking status, and left circumflex artery involvement. P<0.05 was considered statistically significant.

Table 4 presents the changes in PI of the carotid arteries before and after treatment. Baseline PI values were within the anticipated range for this high-risk population and did not differ significantly between groups. In the primary ITT analysis, no significant between-group differences emerged in ΔPI or follow-up values for either artery (all P≥0.125 after Bonferroni correction). A borderline within-group reduction was observed in left PI in the empagliflozin arm (P=0.072). However, it was not accompanied by a significant treatment effect compared with controls. The isolated lower post-treatment right PI in the intervention group (P=0.028) was not supported by a significant change from baseline (ΔPI P=0.760) and did not persist after statistical adjustment. The PP analysis indicated similar conclusions, reinforcing the absence of hemodynamic impact of empagliflozin over the 3 months.

Discussion

In this randomized controlled trial, empagliflozin (10 mg daily) added to standard therapy for 3 months suggested favorable changes in left CIMT, with a median reduction of 0.13 mm in the primary ITT analysis (within-group P=0.002; between-group ΔCIMT P=0.004) in patients with T2D and recent STEMI, with a smaller though statistically significant effect on the right side (ITT between-group ΔCIMT P=0.021). No meaningful changes were observed in the RI or PI.

CIMT is a well-validated surrogate marker of systemic atherosclerosis and cardiovascular risk.[26, 27] In 2020, Willeit and colleagues conducted a meta-analysis of 119 randomized controlled trials including 100,667 patients to evaluate whether changes in CIMT predict cardiovascular disease (CVD) risk reduction. Results showed that for every 10 μm/year reduction in CIMT progression, the relative risk of CVD decreased by 9% (RR=0.91; 95% CI:0.87–0.94). The study concluded that slower CIMT progression reliably predicts lower CVD risk.[27] In our study, the observed reduction in CIMT over just 3 months, particularly lateralized to the left, suggested preliminary evidence of early favorable vascular remodeling with empagliflozin, potentially consistent with its anti-inflammatory and plaque-stabilizing properties.[28-30] However, the short 3-month duration limited generalization to long-term clinical outcomes. It is noteworthy that not all SGLT2i uniformly reduce CIMT. While empagliflozin demonstrated consistent CIMT regression in multiple studies,[17, 19, 29] ipragliflozin had a neutral effect on the CCA IMT status in the PROTECT study,[22] tofogliflozin had a neutral effect on mean, left, and right grey-scale median CCA values in the UTOPIA trial,[21] and ipragliflozin failed to alter CIMT after 52 weeks of treatment in Japanese patients with T2DM in the FUSION study.[31] This discrepancy might reflect differences in drug-specific pleiotropic effects, patient demographics, baseline vascular burden, or study duration. The selective CIMT benefit observed with empagliflozin in our cohort further supported its unique vascular profile within the SGLT2i class.[32]

Numerous indicators of arterial stiffness exist, including pulse pressure, pulse wave velocity (PWV), RI, and PI.[33] RI reflects downstream microvascular resistance and is typically stable in large conduit arteries such as the CCA. Reports indicated that the normal RI in vessels supplying vital organs ranged from 0.55 to 0.70.[34] However, in patients with diabetes or post-MI vasculopathy, values rise due to microvascular stiffness and endothelial dysfunction.[33, 35] In our study, baseline RI values fell within this elevated range, consistent with the high-risk profile. The trivial changes observed (<0.03 units) were not statistically significant. Given the CCA diameter of approximately 6-8 mm,[36] a 0.15 mm change in wall thickness represented less than 2-3% of luminal caliber, insufficient to meaningfully alter flow velocity or resistance in a vessel of this size over 3 months. Thus, the absence of RI change was physiologically expected and did not negate the structural benefit observed in CIMT.

The PI index integrates both resistance and arterial compliance.[37] Our baseline PI was within the expected range for this population. The isolated post-treatment reduction in right PI without a corresponding between-group ΔPI significance likely represented statistical noise rather than a true hemodynamic shift, especially given the short treatment duration and minimal absolute change. As with RI, a 0.1-0.15 mm wall thinning in a 6-8 mm vessel would not be anticipated to substantially modify pulsatile flow dynamics within 3 months. Operator-dependent Doppler angle alignment further contributed to variability in PI/RI measurements, which we have mitigated through protocol standardization, though we cannot fully eliminate it.

PWV is considered the non-invasive gold standard measurement of arterial stiffness.[38] Although we did not measure PWV, our findings might indirectly relate to it. The SGLT2i, particularly empagliflozin, was shown to reduce central and peripheral PWV in T2DM patients.[39] The lack of RI/PI changes does not preclude PWV benefits, as Doppler indices reflect local resistance, while PWV assesses global stiffness. The null findings in RI and PI were mechanistically plausible due to the brief intervention period, the modest structural change relative to vessel caliber, and the measurement limitations of Doppler ultrasound. Future studies combining CIMT and PWV could confirm if short-term empagliflozin-induced CIMT reduction predicts improved arterial compliance post-STEMI.

The study's design, with a small sample size (n=80), short 3-month follow-up, and unexplained laterality of CIMT changes (predominantly left-sided), restricted definitive conclusions. Baseline imbalances might have been confounding, although statistical adjustment did not alter primary results. The absence of plaque characterization, pulse wave velocity, or longer-term clinical endpoints further restricted interpretation. Finally, the two deaths in the intervention arm (adjudicated as unrelated to study drug) were conservatively handled via ITT with last observation carried forward (LOCF), but this might have slightly attenuated effect estimates.

Conclusion

In this double-blind, randomized, placebo-controlled trial, 3 months of empagliflozin therapy in patients with T2D following STEMI was associated with a modest reduction in CIMT, particularly in the left carotid artery. These findings were consistent across ITT and PP analyses, although effect sizes were smaller in the ITT analysis. Overall, this study suggested that empagliflozin might be associated with early, favorable vascular changes during the vulnerable post-myocardial infarction period in patients with T2D. Larger, adequately powered randomized trials with longer follow-up and comprehensive safety assessment are required to confirm these observations.

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Authors' Contribution

H.S.S.: Conceptualization, investigation, methodology, data curation, and writing of the original draft preparation. Sh.A.: Writing-review and editing, submission, correspondence, and project administration. S.K.: Conceptualization, supervision, and writing-review and editing. R.M.: Supervision, validation, and writing review and editing. Z.K.: Contributed to methodology, investigation, data curation, and writing of the original draft preparation. A.A.M.: Contributed to methodology, investigation, data curation, and writing of the original draft preparation. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of AI

The authors disclose the use of Grok (XAI) as an artificial intelligence-assisted technology for language refinement and English polishing of the manuscript. Grok was not used for study design, data analysis, interpretation of the results, or generation of original content. All scientific content and conclusions are the sole responsibility of the authors.

Conflict of Interest: None declared.

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