Indonesian Journal of Cardiology
Indonesian J Cardiol • Vol. 47 • 2026
pISSN: 2830-3105 / eISSN: 2964-7304
doi: 10.30701/ijc.2090

**Original Article**

# Effect of Dapagliflozin Administration on the Apoptosis Levels and Myocardial Work of Patients with Acute Myocardial Infarction (DAPOPTOSIS-MI) – A Randomized Controlled Trial

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**Abstract**

**Background:** Acute myocardial infarction (AMI) is a common cardiovascular disease and a leading cause of morbidity and mortality. Cellular death during AMI involves apoptosis (80%) and necrosis (20%). Apoptosis contributes to infarct size, Left Ventricular (LV) remodeling, and heart failure post-AMI. Previous studies suggest that dapagliflozin can reduce myocardial apoptosis, marked by decreased caspase-3 levels (preclinical study) and echocardiographic parameters (preclinical and clinical studies). However, human studies evaluating the effects of dapagliflozin on caspase-3 and myocardial work (MW) in AMI patients are not yet available. This study aims to evaluate the effect of dapagliflozin administration on caspase-3 levels and MW in AMI patients.

**Methods:** This was a single-center experimental study with a double-blind randomized controlled trial (RCT) design conducted among 40 AMI patients at Dr. Moewardi General Hospital, Surakarta (September–November 2024). Patients were divided into two groups: dapagliflozin and placebo. Caspase-3 levels and MW parameters (Global Work Index [GWI], Global Constructive Work [GCW], Global Wasted Work [GWW], Global Work Efficiency [GWE]) were measured at admission before and on day 14 post-treatment. Statistical analysis was performed using independent t-tests or Mann-Whitney tests, with $p < 0.05$ considered significant.

**Results:** The mean pre-test caspase-3 levels were not significantly different between the intervention group, 51.05±36.53ng/ml, and the control group, 56.44±31.01ng/ml ($p=0.618$). However, post-test caspase-3 levels showed a significant difference: intervention group, 29.55±28.33 ng/ml, compared with control group, 51.97±31.16 ng/ml ($p=0.007$). There were no significant differences in the pre-test or post-test MW parameters between the two groups ($p>0.05$).

**Conclusions:** There was a significant reduction in caspase-3 levels in AMI patients following dapagliflozin administration compared to placebo. However, there was no significant improvement in the MW parameters.

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**Keywords:** Apoptosis, Acute Myocardial Infarction, Dapagliflozin, Myocardial Work, DAPOPTOSIS-MI.

# Introduction

Acute Myocardial Infarction (AMI) is one of the leading causes of death from cardiovascular diseases worldwide.[1] The ischemic process in acute myocardial infarction triggers cellular death through apoptosis and necrosis, with apoptosis accounting for the majority of deaths at 80%, followed by necrosis at 20%.[2] Apoptosis is closely related to Left Ventricular (LV) remodeling and heart failure post-AMI,[3] and one of the markers of apoptosis is caspase-3, which can be measured to assess the degree of apoptosis post-AMI.[4]

Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors, which were initially developed for the management of type 2 Diabetes Mellitus (DM), have emerged as a promising therapeutic class with significant cardioprotective effects. Dapagliflozin, a member of the SGLT2 inhibitor family, has demonstrated benefits in reducing heart failure hospitalizations and improving cardiovascular outcomes in patients with and without diabetes.[5] These benefits extend across a wide range of ejection fractions, making SGLT2 inhibitors a cornerstone in the management of heart failure.[6] Furthermore, their use has been advocated in DM patients with comorbid conditions such as Chronic Kidney Disease (CKD), coronary artery disease, and cerebrovascular disease.[7] However, the research for seeking the benefit of SGLT2 inhibitors in the AMI population is still under investigation and development.

The latest preclinical studies have shown that dapagliflozin can reduce myocardial apoptosis,[8] as evidenced by lower caspase-3 levels in AMI animal models.[9] It also improves myocardial systolic function,[10] Global Longitudinal Strain (GLS), and LV remodeling based on echocardiographic parameters,[11] showing significant potential benefit in the therapy of AMI patients. However, clinical studies that evaluate the effects of dapagliflozin on caspase-3 (apoptosis) and Myocardial Work (MW) in AMI patients are not yet available.

This study aims to evaluate the effect of dapagliflozin administration on caspase-3 levels (apoptosis) and MW values in patients with AMI.

# Methods

## Study Design and Intervention

The DAPOPTOSIS-MI was a single-center, double-blind, Randomized Controlled Trial (RCT) design with pre- and post-intervention assessments (NCT06615674) to evaluate the effect of treatment with Dapagliflozin (10mg tablet once daily) in patients with acute coronary syndrome. In this trial, patients were randomly assigned into two groups. The intervention group was assigned to receive Dapagliflozin (Forxiga, AstraZeneca) 10 mg once daily for 14 days in addition to standard AMI therapy, and the control group who were assigned to receive a placebo with the same dosage and duration beside standard therapy of AMI according to the 2023 European Society of Cardiology (ESC) guidelines for the management of the acute coronary syndrome.

The primary outcome of this study was the change in serum caspase-3 levels from baseline (at admission) to day 14 after treatment. Secondary outcomes included changes in MW indices, namely Global Work Index (GWI), Global Constructive Work (GCW), Global Wasted Work (GWW), and Global Work Efficiency (GWE), measured by speckle-tracking echocardiography. Serious adverse events, including death, cardiogenic shock, diabetic ketoacidosis, acute kidney injury, severe hypotension, and clinically significant infections, were specifically monitored. Safety outcomes were analyzed descriptively and compared between the two groups.

## Study Population

A total of 40 patients aged 18–70 years in the Emergency Department (ED) and Cardiovascular Centre of Dr. Moewardi General Hospital from September to November 2024 were diagnosed with AMI (including ST segment elevation myocardial infarction [STEMI] and non ST segment elevation myocardial infarction [NSTEMI]) based on clinical criteria and cardiac biomarkers according to the Fourth Universal Definition of Myocardial Infarction from the European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation and also willing to participate in the study and provide informed consent were included in the study.

Exclusion criteria included patients with cardiogenic shock (Systolic Blood Pressure [SBP] $\leq$ 80 mmHg, cold extremities, urine output <0.5 mL/kg BW/hour) <24 hours before randomization, ketoacidosis (arterial pH<7.30, serum bicarbonate <18 mEq/L, positive ketonuria), impaired renal function with an estimated Glomerular Filtration Rate (eGFR) <20 mL/min or requiring dialysis, history of chronic heart failure before AMI onset, scheduled for coronary artery bypass surgery, type 1 DM, severe valvular disease, sepsis, symptomatic acute urinary tract infection, pregnant patients and severe aortic stenosis or LV outflow tract obstruction.

### Randomization

The random allocation sequence was generated by an independent pharmacist using a simple randomization method with a 1:1 allocation ratio. The sequence was used to prepare 40 identical, opaque, sealed, and sequentially numbered envelopes, each containing a code corresponding to either dapagliflozin or placebo. The study medication and placebo were identical in appearance and packaging.

The study investigators performed participant enrollment, and group assignment was carried out by opening the next sequential envelope at the time of inclusion. This study used a double-blind design: patients, treating physicians, echocardiography operators, laboratory personnel measuring caspase-3, outcome assessors, and statisticians were all blinded to treatment allocation. The statistician performed the analysis using anonymized group codes. Each group consisted of 20 participants in the final analysis.

### Blood Caspase-3 Measurement Procedures

Blood samples were collected intravenously from all participants upon arrival at the Emergency Department of Dr. Moewardi Hospital at admission, and from the outpatient cardiovascular clinic of Dr. Moewardi Hospital, specifically collected from patients after 14 days of treatment to measure Caspase-3 levels at baseline and post-treatment. A 3 mL intravenous blood sample was drawn using a 3 mL syringe. The sample was then kept at room temperature before being transported to the clinical pathology laboratory at Dr. Moewardi Hospital.

At the laboratory, the sample was placed in a centrifuge tube and allowed to freeze. Once frozen, the blood sample was centrifuged for 5–10 minutes at 3500 rpm to separate the plasma. The plasma was then transferred to a special storage tube and frozen at -20°C before being transferred to the biomedical laboratory at the Faculty of Medicine, Universitas Sebelas Maret (UNS) for further Caspase-3 analysis. In this study, an ELISA reagent kit from Elabscience® Human CASP3 (Caspase 3) was used.

### Myocardial Work Index Measurement Procedures

Echocardiographic imaging and MW measurements were performed in the echocardiography room using GE Vivid E95 and vendor-specific software GE-AFI EchoPAC BT 13 V206, by analyzing deformation from three apical views (4-, 2-, and 3-chamber) during the end-systolic phase, as detected by the QRS complex. The longitudinal strain was automatically analyzed from 17 segments of the left ventricle. For patients with sinus rhythm, analysis was conducted over a single cardiac cycle during end-systole, while for patients with atrial fibrillation, strain was averaged over three cardiac cycles. Systolic and diastolic blood pressure values were input before the echocardiographic system performed MW analysis. All echocardiographic images were acquired by a certified sonographer, and MW analysis was conducted by an experienced cardiologist specializing in echocardiographic imaging and MW assessment.

### Sample Size

The sample size was determined using Federer's formula (1963): $(n-1)(t-1) \geq 15$, where n represents the number of samples per group, and t represents the number of groups. Based on this formula, the minimum required sample size per group was calculated to be 16, resulting in a total of 32 samples for both groups. This study is a clinical trial, and to account for the possibility of dropout, a 10% dropout rate was considered.[12] Taking into account the minimum required sample size and the dropout rate, the final sample size was set at 20 patients per group, leading to a total of 40 patients, which is sufficient and meets the required sample size calculation. This also exceeds the minimum sample size recommended for simple experimental studies, which ranges from 10 to 20 samples.[13]

### Statistical Analysis

Data were analyzed using SPSS version 22.0 for Windows. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared using the independent t-test, while non-normally distributed variables were analyzed using the Mann–Whitney U test. A p-value $<0.05$ was considered statistically significant.

The primary analysis was performed using a complete-case (per-protocol) approach, including only patients who completed the 14-day follow-up and had available outcome data. Because patients who died or were lost to follow-up did not have post-treatment measurements, no imputation of missing data was performed. Given the short follow-up period and the objective nature of the primary endpoint (serum caspase-3 levels), a complete-case analysis was considered acceptable for this exploratory clinical trial.

### Ethics

The DAPOPTOSIS-MI trial is conducted in accordance with the principles of the Declaration of Helsinki and all subsequent revisions. This study was conducted with approval from the Research Ethics

Committee of Dr. Moewardi Hospital, Central Java, Indonesia (letter number 2.226/IX/HREC/2024), and was registered at https://ClinicalTrials.gov under registration number NCT06615674. Patient consent or informed consent was obtained from the research subjects. Patient identities are kept confidential, and all research-related costs are the responsibility of the researcher.

# Results

## Characteristics of Study Subjects

From September 21, 2024, to October 30, 2024, a total of 72 AMI patients were screened for eligibility based on the study criteria. Among them, 51 patients were diagnosed with AMI and met the inclusion criteria; thus, they were randomized as study samples. Twenty-one patients were excluded: 11 declined to participate, and 10 met at least one exclusion criterion. Of the 51 randomized patients, 11 did not complete the 14-day follow-up: 9 patients (5 in the dapagliflozin group and 4 in the placebo group) were lost to follow-up, and 2 patients (1 in each group) died due to malignant arrhythmia during hospitalization. Therefore, 40 patients (20 in each group) completed the study and were included in the final analysis.

The primary and secondary outcome analyses were performed using a complete-case (per-protocol) approach, including only patients with available baseline and day-14 measurements (n = 40). The study flow is presented in Figure 1. No cases of diabetic ketoacidosis, severe hypoglycemia, severe hypotension, or acute kidney injury requiring dialysis were observed in either group. Furthermore, no adverse events were considered to be directly attributable to dapagliflozin.

The baseline characteristics of subjects in the intervention and control groups are shown in Table 1. There were no statistically significant differences between the dapagliflozin and control groups in terms of age, sex, Body Mass Index (BMI), diagnosis, Killip class, AMI onset, comorbidities (hypertension, DM, dyslipidemia, stroke, coronary heart disease, hyperuricemia), smoking history, medications (Angiotensin Converting Enzyme inhibitor [ACEi], Angiotensin Receptor Blocker [ARB], Angiotensin Receptor–Neprilysin Inhibitor [ARNI], Mineralocorticoid Receptor Antagonist [MRA], Beta Blocker [BB], statins, anticoagulants, antiplatelets, fibrinolytic, nitrates, ivabradine, and furosemide), Left Ventricular Ejection Fraction (LVEF), Tricuspid Annular Plane Systolic Excursion (TAPSE), lesion characteristics and revascularization strategies.

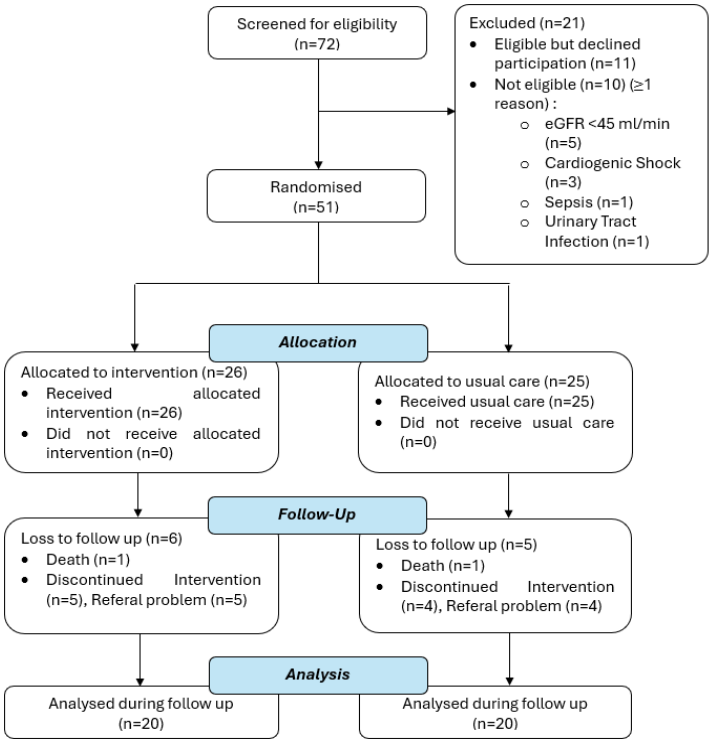


**Figure 1.** CONSORT diagram. eGFR indicates estimated glomerular filtration rate.

**Table 1.** Basic characteristics of research subjects.

| | Intervention Group (n=20) | Control Group (n=20) | P-Value |
|---|---|---|---|
| Age (mean ±SD)[a] | 53.55 ±13.46 | 57.20 ±9.05 | 0.321 |
| BMI (mean ±SD)[b] | 25.97 ±4.05 | 24.19 ±1.92 | 0.227 |
| Sex (n,%)[c] | | | 1.000 |
| Male | 15 (75.00%) | 16 (80.00%) | |
| Female | 5 (25.00%) | 4 (20.00%) | |
| Smoking History (n,%)[c] | 16 (80.00%) | 16 (80.00%) | 1.000 |
| Comorbidities (n,%)[c] | | | |
| Hypertension | 11 (55.00%) | 9 (45.00%) | 0.527 |
| Diabetes Mellitus | 10 (50.0%) | 9 (45.00%) | 0.752 |
| Dyslipidemia | 10 (50.00%) | 12 (60.00%) | 0.525 |
| Stroke | 1 (5.00%) | 0 (0.00%) | 1.000 |
| Coronary Artery Disease | 0 (0.00%) | 1 (5.00%) | 1.000 |
| Hyperuricemia | 10 (50.00%) | 12 (60.0%) | 0.525 |
| Renal Insufficiency | 4 (20.00%) | 2 (10.00%) | 0.661 |
| Infection | 3 (15.00%) | 1 (5.00%) | 0.605 |
| Diagnosis (n,%)[c] | | | 0.695 |
| STEMI | 15 (75.00%) | 17 (85.00%) | |
| NSTEMI | 5 (25.00%) | 3 (15.00%) | |
| Killip Class (n,%)[c] | | | 0.695 |
| Killip I | 17 (85.00%) | 15 (75.00%) | |
| Killip II-III | 3 (15.00%) | 5 (25.00%) | |
| MI Onset (mean ±sd) [b] | 27.50 (±31.90) | 25.25 (±29.25) | 0.903 |
| Medications (n,%)[c] | | | |
| ACE Inhibitor | 17 (85.00%) | 18 (90.00%) | 1.000 |
| ARB | 0 (0.00%) | 0 (0.00%) | 1.000 |
| ARNI | 1 (5.00%) | 2 (10.00%) | 1.000 |
| Beta-blockers | 16 (80.00%) | 16 (80.00%) | 1.000 |
| Calcium Channel Blockers | 3 (15.00%) | 0 (0.00%) | 0.231 |
| Mineralocorticoid Receptor Antagonists | 10 (50.00%) | 8 (40.00%) | 0.751 |
| Statin | 20 (100.00%) | 20 (100.00%) | 1.000 |
| Anticoagulants (IV/SC) | 20 (100.00%) | 20 (100.00%) | 1.000 |
| Dual Antiplatelet Therapy | 20 (100.00%) | 20 (100.00%) | 1.000 |
| Oral Anticoagulants | 0 (0.00%) | 2 (10.00%) | 0.487 |
| Fibrinolytics | 5 (25.00%) | 9 (45.00%) | 0.315 |
| Success | 0 (0.00%) | 1 (5.00%) | |
| Failed | 5 (25.00%) | 8 (40.00%) | |
| Nitrates | 15 (75.00%) | 12 (60.00%) | 0.311 |
| Ivabradine | 2 (10.00%) | 1 (5.00%) | 1.000 |
| Furosemide | 1 (5.00%) | 5 (25.00%) | 0.182 |
| TAPSE (n,%)[c] | | | 0.661 |
| >16 mm | 16 (80.00%) | 18 (90.00%) | |
| ≤16 mm | 4 (20.00%) | 2 (10.00%) | |
| LVEF (n,%)[c] | | | 0.153 |
| ≥50% | 5 (25.00%) | 8 (40.00%) | |
| 40-49% | 11 (55.00%) | 5 (25.00%) | |

| | | | |
|---|---|---|---|
| <40% | 4 (20.00%) | 7 (35.00%) | |
| Laboratory Results (mean ±sd) | | | |
| Hemoglobin (g/dl)[a] | 14.00±1.83 | 13.94±2.03 | 0.929 |
| White blood cell ($10^3/\mu L$)[b] | 12.72±4.56 | 13.13±3.30 | 0.310 |
| Platelets ($10^3/\mu L$)[b] | 275.95±123.92 | 258.00±67.71 | 0.829 |
| Neutrophil (%)[b] | 74.68±10.77 | 77.53±7.92 | 0.449 |
| Lymphocyte (%)[b] | 18.11±10.65 | 14.83±6.56 | 0.490 |
| eGFR ($mL/min/1.73m^2$)[b] | 75.80±32.72 | 73.65±21.52 | 0.694 |
| Hs-Troponin I (ng/L)[b] | 6425.55±10446.95 | 7199.25±14159.20 | 0.913 |
| Lesion Characteristics (n,%)[c] | | | 0.445 |
| CAD 1 VD | 13 (65.00%) | 10 (50.00%) | |
| CAD 2 VD | 2 (10.00%) | 3 (15.00%) | |
| CAD 3 VD | 1 (5.00%) | 2 (10.00%) | |
| LM Disease | 3 (15.00%) | 1 (5.00%) | |
| Non-significant Lesions | 1 (5.00%) | 4 (20.00%) | |
| Culprit lesion in LAD (n,%)[c] | 11 (55.00%) | 10 (50.00%) | 0.752 |
| Revascularization Procedure (PCI) (n,%)[c] | 16 (80%) | 14 (70%) | 0.465 |
| Complete Revascularization Procedure (n,%)[c] | 15 (75%) | 14 (70%) | 0.723 |
| Baseline (n,%) | | | |
| Caspase 3 (ng/ml)[a] | 51.05±36.53 | 56.44±31.01 | 0.618 |
| GWI (mmHg%)[a] | 996.20±455.88 | 938.85±381.50 | 0.669 |
| GCW (mmHg%)[a] | 1276.15±456.78 | 1222.50±434.55 | 0.706 |
| GWW (mmHg%)[a] | 199.80±82.55 | 206.65±88.98 | 0.802 |
| GWE (mmHg%)[b] | 84.60±7.63 | 83.65±8.61 | 0.818 |

Notes: The results of observed numerical data are described by mean ± SD, Categorical data are described using f(%), [a]Normal distribution data analyzed with independent t-test; [b]Non-normal distribution data analyzed with Mann-Whitney test; [c]Nominal categorical data analyzed with chi-square or Fisher's exact test; [d]CAD 1 VD + LM disease, CAD 2 VD + LM disease, CAD 3 VD + LM disease or isolated LM disease; BMI: Body Mass Index; STEMI: ST Elevation Myocardial Infarction ;NSTEMI: Non-ST Elevation Myocardial Infarction; MI: Myocardial Infarction; ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin Receptor Blockers; ARNI: Angiotensin Receptor-Neprilysin Inhibitor; IV: Intravenous; SC:Subcutaneous; TAPSE: Tricuspid Annular Plane Systolic Excursion; LVEF: Left Ventricular Ejection Fraction; LAD: Left Anterior Descending Artery; eGFR: Estimated Glomerular Filtration Rate; Hs-Troponin I: High-sensitivity Troponin I; GWI: Global Work Index ;GCW: Global Constructive Work; GWW: Global Wasted Work; GWE: Global Work Efficiency.

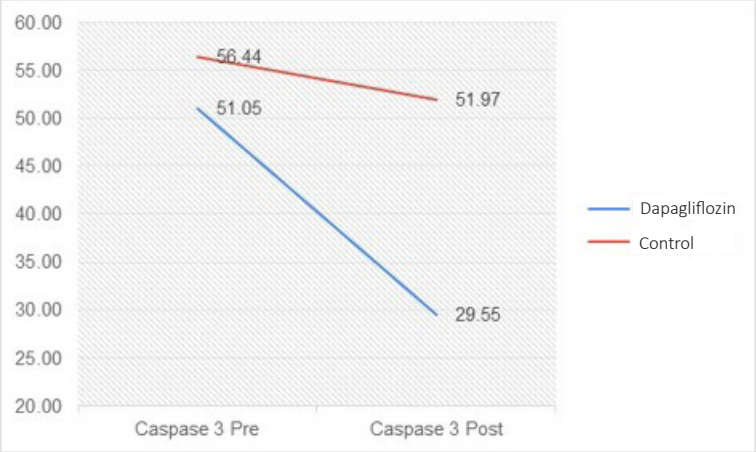


**Figure 2.** Comparison line diagram of caspase 3 changes between intervention and control group. Data shown as mean ± ng/ml (n=40 patients, n=20 patients each group). Statistical analysis performed using unpaired difference test that did not meet the normality assumption (Mann-Whitney). Statistical significance was defined as $p < 0.05$.

### Analysis of Caspase-3 Levels

Caspase-3 levels at admission (pre-test) did not differ significantly (p = 0.618), with caspase-3 levels in the intervention group at 51.05±36.53 ng/ml and in the placebo group at 56.44±31.01 ng/ml. However, a significant difference was observed post-treatment (post-test), with caspase-3 levels in the intervention group (29.55±28.33 ng/ml) being significantly lower than in the placebo group (51.97±31.16 ng/ml) (Figure 2), with a significance value of p=0.007 (Table 2).

### Analysis of Global Work Index (GWI)

In the intervention group, the pre-test GWI was 996.20±455.88 mmHg%, and the post-test GWI was 1047.30±516.66 mmHg%. In the control group, the pre-test GWI was 938.85±381.50 mmHg%, and the post-test GWI was 970.15±441.90 mmHg% (Figure 3). The post-test analysis (p=0.615) indicated a p-value >0.05, meaning no significant difference in post-treatment GWI between the intervention and control groups (Table 3). Subjects receiving dapagliflozin experienced a greater increase in GWI compared to the control group; however, the difference was not statistically significant.

### Analysis of Global Constructive Work (GCW)

In the intervention group, the pre-test GCW was 1276.15±456.78 mmHg%, and the post-test GCW was 1333.15±548.51 mmHg%. In the control group, the pre-test GCW was 1222±434.55 mmHg%, and the post-test GCW was 1252.45±460.23 mmHg% (Figure 4). The post-test analysis (p=0.617) indicated a p-value >0.05, meaning no significant difference in post-treatment GCW between the intervention and control groups (Table 3). Subjects receiving dapagliflozin experienced a greater increase in GCW compared to the control group; however, the difference was not statistically significant.

**Table 2.** Analysis of differences in Caspase 3 levels between intervention and control groups.

| | Intervention Group (n=20) | Control Group (n=20) | P-Value |
|---|---|---|---|
| Caspase 3, mean±SD | | | |
| Pre-test (ng/ml) | 51.05±36.53 | 56.44±31.01 | 0.618[a] |
| Post-test (ng/ml) | 29.55±28.33 | 51.97±31.16 | 0.007*[b] |

Notes: numerical data are described as mean±SD; [a]Unpaired difference test passes normality requirements (Independent t-test); [b]Unpaired difference test does not pass the normality requirement (Mann-Whitney); * significant at p<0.05.

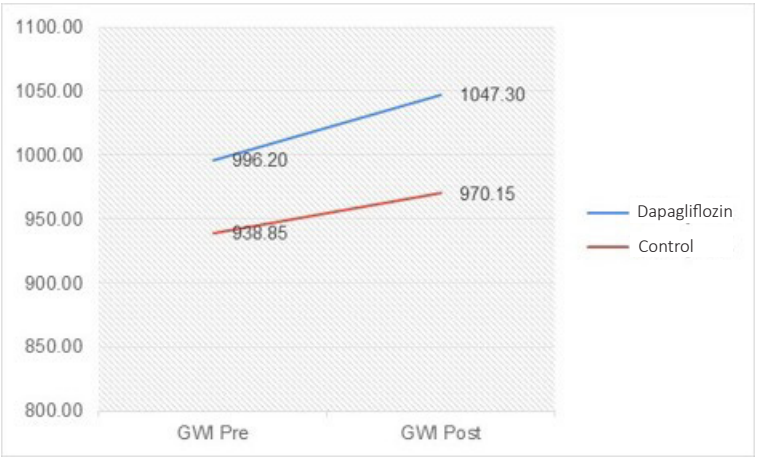


**Figure 3.** Comparison line chart of GWI changes between intervention and control group. Data shown as mean ± mmHg% (n=40 patients, n=20 patients each group). Statistical analysis performed using unpaired difference test that meet the normality assumption (Independent t-test). Statistical significance was defined as p < 0.05.

**Table 3.** Analysis of differences in myocardial work between intervention and control groups.

| | Intervention Group (n=20) | Control Group (n=20) | P-Value |
|---|---|---|---|
| GWI, mean±SD | | | |
| Pretest (mmHg%) | 996.20±455.88 | 938.85±381.50 | 0.669[a] |
| Posttest (mmHg%) | 1047.30±516.66 | 970.15±441.90 | 0.615[a] |
| GCW mean±SD | | | |
| Pretest (mmHg%) | 1276.15±456.78 | 1222.50±434.55 | 0.706[a] |
| Posttest (mmHg%) | 1333.15±548.51 | 1252.45±460.23 | 0.617[a] |
| GWW mean±SD | | | |
| Pretest (mmHg%) | 199.80±82.55 | 206.65±88.98 | 0.802[a] |
| Posttest (mmHg%) | 194.55±105.00 | 177.85±88.26 | 0.589[a] |
| GWE mean±SD | | | |
| Pretest (%) | 84.60±7.63 | 83.65±8.61 | 0.818[b] |
| Posttest (%) | 84.80±9.80 | 85.85±6.47 | 0.691[a] |

Notes: Observed numerical data are described using mean ± SD; [a]Independent sample test that meets normality requirements (Independent t-test); [b]Independent sample test that does not meet normality requirements (Mann-Whitney test);*Significant at $p < 0.05$. GWI: Global Work Index ;GCW: Global Constructive Work; GWW: Global Wasted Work; GWE: Global Work Efficiency.

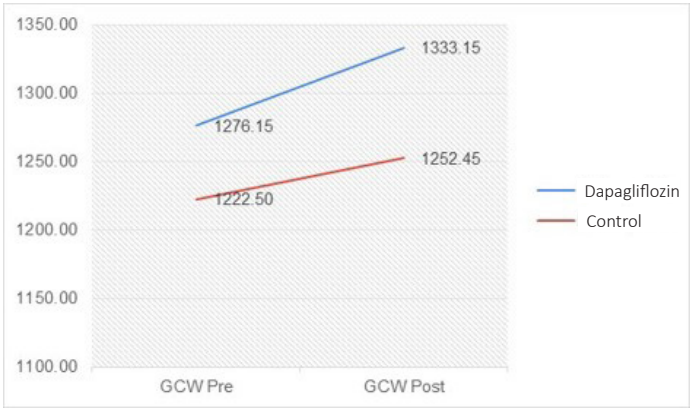


**Figure 4.** Comparison line diagram of GCW changes between intervention and control group. Data shown as mean ± mmHg% (n=40 patients, n=20 patients each group). Statistical analysis performed using unpaired difference test that meet the normality assumption (Independent t-test). Statistical significance was defined as $p < 0.05$.


**Figure 5.** Comparison line diagram of GWW changes between intervention and control group Data shown as mean ± mmHg% (n=40 patients, n=20 patients each group). Statistical analysis performed using unpaired difference test that meet the normality assumption (Independent t-test). Statistical significance was defined as p <

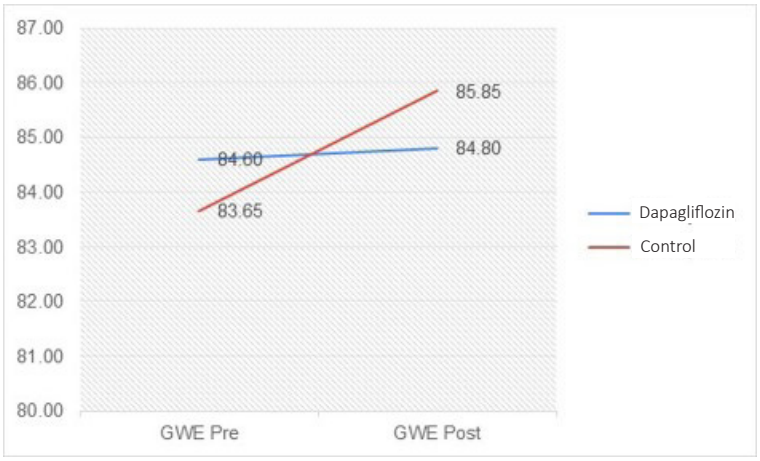


**Figure 6.** Comparison line diagram of GWE changes between intervention and control group. Data shown as mean ± mmHg% (n=40 patients, n=20 patients in each group). Statistical analysis performed using an unpaired t-test that meets the normality assumption (independent t-test). Statistical significance was defined as $p < 0.05$.

### Analysis of Global Wasted Work (GWW)

In the intervention group, the pre-test GWW was 199.80±82.55 mmHg%, and the post-test GWW was 194.55±105.00 mmHg%. In the control group, the pre-test GWW was 206.65±88.98 mmHg%, and the post-test GWW was 177.85±88.26 mmHg% (Figure 5). The post-test analysis (p=0.589) indicated a p-value >0.05, meaning no significant difference in post-treatment GWW between the intervention and control groups (Table 3). Subjects receiving dapagliflozin tended to have a smaller reduction in GWW compared to the control group; however, the difference was not statistically significant.

### Analysis of Global Work Efficiency (GWE)

In the intervention group, the pre-test GWE was 84.60±7.63%, and the post-test GWE was 84.80±9.80%. In the control group, the pre-test GWE was 83.65±8.61%, and the post-test GWE was 85.85±6.47% (Figure 6). The post-test analysis (p=0.691) indicated a p-value >0.05, meaning no significant difference in post-treatment GWE between the intervention and control groups (Table 3). Subjects receiving dapagliflozin experienced a smaller increase in GWE compared to the control group; however, the difference was not statistically significant.

## Discussion

Dapagliflozin is a type of SGLT2 inhibitor that works by preventing glucose reabsorption in the proximal renal tubules, thereby increasing glucose excretion through urine and reducing blood glucose levels.[14] Its role is no longer limited to being a therapeutic agent for DM but also extends to having broad therapeutic effects on cardiovascular diseases[15] including patients with heart failure,[6] DM with a history of coronary heart disease, stroke, or CKD, and isolated DM.[7] However, the use of SGLT2 inhibitors in AMI patients is not yet a standard therapy in the management guidelines for AMI in non-diabetic patients. Current research is actively investigating the role and benefits of this agent in AMI patients with or without DM.[16-18]

Several studies on the administration of SGLT2 inhibitors in patients with AMI have already been conducted. The AMI PROTECT cohort study demonstrated a reduction in cardiovascular mortality, hospitalization rates due to heart failure, and Major Adverse Cardiovascular Events (MACE).[16] The EMMY study reported significant improvements in echocardiographic and laboratory parameters, including LVEF, Left Ventricular Internal Diameter in Systole (LVIDs), Left Ventricular Internal Diameter in Diastole (LVIDd), and N terminal pro–B type Natriuretic Peptide (NT-proBNP) levels.[19] The Dapagliflozin in Myocardial Infarction trial (DAPA-MI) RCT (2023) showed better cardiometabolic outcomes.[17] Additionally, the EMPACT-MI study (2024) demonstrated a reduction in the risk of first hospitalization due to heart failure and total heart failure-related hospitalizations, although no significant difference was observed in all-cause mortality among AMI patients.[18]

Previous studies on human subjects have also measured the degree of cell death, but using myocardial necrosis as a mechanism, assessed by High sensitivity Troponin I (Hs-Troponin I) levels in AMI patients receiving SGLT2 inhibitors before

the onset of AMI. The results showed a significantly lower mean Hs-Troponin I level in the SGLT-2 inhibitor group compared to the non-SGLT-2 inhibitor group (635 vs. 1842 ng/L, p≤0.003), as well as a smaller infarct area, with a mean difference of 33% (95%CI 20–47%, p<0.00001). These findings highlight the strong protective effect of SGLT2 inhibitors in reducing myocardial cell death during AMI.[20]

### Effect of Dapagliflozin Administration on Caspase-3

Research on caspase-3 and apoptosis in AMI patients remains very limited. Observational studies have shown a significant increase in caspase-3 levels in AMI patients compared to healthy controls.[21] This increase in caspase-3 has been associated with enhanced endothelial permeability in blood vessels in an in-vitro study,[22] and a higher incidence of MACE in AMI patients undergoing emergency Percutaneous Coronary Intervention (PCI), aligns with other variables such as troponin I level, the presence of multivessel disease, time from onset to PCI, and the IncRNA-ZFAS1 biomarker, as reported in a case-control study.[23]

This study found that during the pre-test phase, when patient characteristics were homogeneous, caspase-3 levels were not significantly different: 51.05±36.53 ng/ml in the intervention group and 56.44±31.01 ng/ml in the control group (p=0.618,p>0.05). However, a significant difference was observed in post-test caspase-3 levels: 29.55±28.33 ng/ml in the intervention group and 51.97±31.16 ng/ml in the control group ($p = 0.007$, $p < 0.05$), suggesting an association between dapagliflozin treatment and reduced apoptotic activity in patients with AMI. Importantly, apoptosis plays a central role in infarct size expansion, adverse LV remodeling, and the subsequent development of heart failure after AMI. Therefore, the observed reduction in caspase-3 levels is not merely a biochemical finding but reflects attenuation of a key pathological process that contributes to long-term structural and functional deterioration of the myocardium. By reducing apoptosis, dapagliflozin may potentially limit myocardial injury and adverse remodeling, which are known predictors of future MACE, even though short-term functional improvement was not yet observed in this study.

Although no prior studies have specifically explored the effects of dapagliflozin administration on apoptosis activity or caspase-3 levels in AMI patients, these findings are consistent with previous preclinical studies. For example, SGLT2 inhibitors were found to reduce markers of myocardial apoptosis, such as caspase-3, in animal models of AMI. Dapagliflozin administration in animal models reduced caspase-3 levels following ischemia-reperfusion injury as early as 30 minutes of ischemia and 120 minutes of reperfusion.[24] Another study reported a significant reduction in caspase-3 levels and myocardial fibrosis area (>50%) after 4 weeks of dapagliflozin therapy.[8]

In general, during ischemia, several key events activate cell death pathways, including apoptosis, necrosis, oncosis, and pyroptosis. Anaerobic conditions lead to Adenosine Triphosphate (ATP) depletion, impairing the function of $Na^+/K^+$ ATPase channels that rely on ATP. This increases intracellular $Na^+$ levels, triggering $Na^+/Ca^{2+}$ exchangers to expel excess sodium and raise intracellular $Ca^{2+}$ levels. The influx of $Ca^{2+}$ leads to excessive intracellular calcium, activating $Ca^{2+}$-dependent proteases that damage cellular structures. Excessive calcium also opens Mitochondrial Permeability Transition Pores (MPTPs), leading to water influx (cell swelling), activation of pro-inflammatory and pro-thrombotic cascades, cytokine release, and apoptosis or necrosis. Overall, cell death occurs predominantly via apoptosis (80%) and necrosis (20%).[2]

Several mechanisms of SGLT2 inhibitors in reducing ischemic damage and apoptosis include the degradation effect on NLRP3 inflammasome, inhibition of Na+/H+ exchanger (NHE-1), reduction of intracellular Na+ and Ca2+ levels, decreased CamKII activity, reduced inflammation and oxidative stress, upregulation of STAT3 and glucose,[27] improved BAX/BCL-2 ratio,[10] inhibition of the PI3K/Akt/mTOR pathway,[26] activation of the AMPKα pathway, which increases antioxidant protein expression,[8] and increased ketone body availability as one of the energy sources in cardiomyocytes during AMI.[28] Previous studies also showed improved ATP production in SGLT-2 inhibitor-treated animal models' cardiomyocytes compared to untreated AMI models.[26]

Although large RCTs such as DAPA-MI and EMPACT-MI have not yet demonstrated a significant impact on mortality in AMI patients, the present study should be interpreted as an exploratory biomarker trial showing a short-term association between dapagliflozin use and reduced circulating caspase-3 levels. While this finding is consistent with preclinical data suggesting anti-apoptotic effects[10, 24,26,29] this study was not designed to evaluate clinical endpoints such as heart failure or MACE, and causal inferences regarding clinical

benefit cannot be drawn. Importantly, dapagliflozin was not associated with an excess of serious adverse events in this short-term study, and mortality and safety events were balanced between groups. However, the relatively small sample size and short follow-up period limit the ability to draw definitive conclusions regarding safety in the acute AMI setting.

### Effect of Dapagliflozin Administration on Myocardial Work

LV systolic dysfunction is one of the complications of AMI that occurs quite often and has a prevalence ranging from 13-32% of all post-AMI patients. The presence of LV systolic dysfunction is associated with a 2-3-fold increased risk of death and admission due to heart failure[30] and is a strong predictor of MACE.[31] In clinical practice, LV systolic function examination is measured by LVEF,[32] and recovery of LV systolic function is known to be a predictor of good prognosis and is associated with an 8-fold reduction in all-cause mortality (adjusted Hazard Ratio [aHR] 0.12, p = 0.001) and a 10-fold reduction in cardiovascular mortality (aHR 0.10,p=0.025).[33]

The measurement of systolic function with LVEF, unfortunately, has weaknesses, including being influenced by the geometric conditions of the heart (eg, hypertrophic or dilated LV), heart load conditions (load-dependent), and potentially not reflecting the actual LV contractility.[34] Meanwhile, measurements using the GLS method also still have shortcomings, namely that they are load-dependent, so they can be affected by conditions that increase preload and afterload.[35] The selection of the MW method in this study was based on recent studies that have proven that MW is more sensitive than GLS and LVEF in evaluating LV myocardial performance due to its load-independence nature.[36]

Based on the results of this study, no significant effects of dapagliflozin 10 mg daily for 14 days were observed on MW parameters, such as GWI, GCW, GWW, and GWE. However, the absence of significant changes in these parameters should be interpreted as no detectable early effect at 14 days in this small cohort, rather than definitive evidence of lack of effect. MW indices reflect structural and functional remodeling processes that typically evolve over weeks to months after AMI. Therefore, the 14-day follow-up period in the present study is likely insufficient to capture meaningful changes in these parameters, and longer-term imaging follow-up at 3–6 months may be required to test this mechanistic hypothesis more adequately.

These findings differ from previous RCTs that demonstrated improvements in LVEF and GLS after 12 weeks of dapagliflozin therapy in STEMI patients undergoing primary PCI,[11] as well as from preclinical studies showing early improvements in LVEF.[37] Although traditional parameters such as LVEF may show earlier changes, MW indices were chosen because they integrate myocardial deformation with afterload and are theoretically more sensitive to subtle changes in myocardial performance. However, this potential advantage may have been offset by the very short follow-up period in the present study, limiting the responsiveness of MW parameters to early therapeutic effects.

Factors that can influence and predict recovery of LV systolic function in post-AMI patients include non-LAD culprit lesions (Odds Ratio [OR] 1.50[1.09-2.06], 95% CI), single-vessel disease (OR 1.5 [1.13-2.06], 95% CI), Killip class I-II (OR 1.52[1.06-2.18], 95% CI), moderate systolic dysfunction (LVEF ≥30% and <45%) (OR 1.73[1.12-2.67], 95% CI), Hs-Troponin I levels which tend to be lower, namely <24,000 ng/L (OR 1.55[1.12-2.16], 95% CI), NSTEMI diagnosis (OR 1.55[1.12-2.16], 95%) and no diuretic use (OR 1.59[1.19-2.12], 95% CI).[38] In this study, the analysis of the baseline characteristics of both the intervention and control groups showed no significant differences (P>0.05), including lesion characteristics, Killip class, ejection fraction, Hs-Troponin I levels, diagnosis, and diuretic use. Therefore, these factors can be disregarded in this study, and the lack of significant MW results may still be attributable to other factors.

In this study, a significant reduction in Caspase-3 (apoptosis) without any improvement in echocardiographic parameters of MW does not align with previous research, which found that reduced apoptosis in AMI is associated with improved systolic function in AMI patients.[3] This discrepancy may be attributed to unexplored cardiomyocyte death pathways beyond apoptosis, such as necrosis, necroptosis, ferroptosis, pyroptosis,[39] and autophagy.[40] Although previous studies suggest that cardiomyocyte death is predominantly mediated by apoptosis,[2] the findings of this study raise questions about the true relative contribution of apoptosis compared to other cell death pathways in patient outcomes. Other factors, such as valvular abnormalities, pre-existing cardiomyopathy, and other conditions summarized in Table 4, may also affect the MW results. However, in this study, an assessment of LV geometry and diastolic function was not performed, and ruling out cardiomyopathy

beyond clinical history and echocardiography was challenging due to the limitations of research resources and the retrospective nature of patient data.

This study has several important limitations. First, the 14-day follow-up period is likely too short to detect meaningful changes in MW parameters, which reflect longer-term remodeling. Second, the sample size was relatively small, and the study was conducted at a single center, limiting generalizability. Third, although multiple MW indices were assessed, no adjustment for multiple comparisons was performed, increasing the risk of type I error; therefore, these secondary analyses should be considered exploratory. Finally, the study was not powered to assess clinical outcomes, and the observed reduction in caspase-3 should be interpreted as a biomarker signal rather than proof of clinical benefit. Future studies should include larger, multicenter cohorts with longer follow-up periods and incorporate serial imaging at 3–6 months to better assess the impact of SGLT2 inhibitors on myocardial remodeling. Combining MW indices with additional biomarkers of myocardial injury and remodeling may also help clarify the mechanistic and prognostic significance of early anti-apoptotic effects observed in this study.

**Table 4.** Factors influencing myocardial work values.

| Variable | GWI | GCW | GWW | GWE | References |
|---|---|---|---|---|---|
| HT | ↑ | ↑ | ↑ | ↓ | (Morbach et al., 2020)[41] |
| LVEF ↑ | ↑ | ↑ | ↓ | ↑ | (Morbach et al., 2020)[41] |
| GLS ↑ | ↑ | ↑ | ↓ | ↑ | (Morbach et al., 2020)[41] |
| E/e' ↑ | ↑ | ↑ | ↑ | ↓ | (Morbach et al., 2020)[41] |
| e' ↑ | = | = | ↓ | ↑ | (Morbach et al., 2020)[41] |
| LV Mass ↑ | = | ↑ | ↑ | ↓ | (Morbach et al., 2020)[41] |
| LA Volume ↑ | ↑ | ↑ | = | = | (Morbach et al., 2020)[41] |
| Coronary Stenosis | ↓ | ↓ | ↑ | ↑ | (Qin et al., 2021)[42] |
| HCM | ↓ | ↓ | ↑ | ↓ | (Hiemstra et al., 2020)[43] |
| Hypertensive LVH | ↑ | ↑ | ↑ | ↓ | (Zhao et al., 2022)[44] |
| DCM | ↓ | ↓ | ↑ | ↓ | (Chan et al., 2019)[45] |
| Type II Diabetes | ↓ | = | ↑ | ↓ | (Liao et al., 2022)[46] |
| Aortic Stenosis | ↑[2]/↓[1] | ↑[2]/↓[1] | ↑[2] | ↓[2] | [1](Jain et al., 2020)[47], [2](De Rosa et al., 2021)[48] |
| Aortic Regurgitation | =/↑ | =/↑ | = | = | (Meucci et al., 2022)[49] |
| Mitral Stenosis | ↓ | ↓ | ↑ | ↓ | (Rudiktyo et al., 2024)[50] |
| Mitral Regurgitation (Primary) | n/a | ↑ | ↑ | ↓ | (Pastore et al., 2024)[51] |
| Mitral Regurgitation (Secondary) | ↓ | ↓ | ↓ | ↑ | (Yedidya et al., 2021)[52] |
| Tricuspid Stenosis | n/a | n/a | n/a | n/a | n/a |
| Tricuspid Regurgitation | n/a | ↓ | ↑ | ↓ | (Berg-Hansen et al., 2024)[53] |
| Pulmonary Stenosis | n/a | n/a | n/a | n/a | n/a |
| Pulmonary Regurgitation | n/a | n/a | n/a | n/a | n/a |

Notes: n/a = no data, ↓ = decreased, ↑ = increased, '=' = no effect.

GWI: Global Work Index ;GCW: Global Constructive Work; GWW: Global Wasted Work; GWE: Global Work Efficiency; HT: Hypertension; LVEF: Left Ventricular Ejection Fraction ;GLS: Global Longitudinal Strain; E: Mitral Early Diastolic Velocity; e': Early Diastolic Mitral Annular Velocity; LV: Left Ventricle; LA: Left Atrium; HCM: Hypertrophic Cardiomyopathy; LVH: Left Ventricular Hypertrophy; DCM: Dilated

## Conclusion

In this small, single-center randomized trial, dapagliflozin was associated with a short-term reduction in circulating caspase-3 levels in patients with AMI, suggesting a potential early anti-apoptotic effect. However, no detectable early changes in MW indices were observed over the 14-day follow-up period. Larger studies with longer follow-up and clinical endpoints are required to determine whether these biomarker changes translate into meaningful improvements in myocardial remodeling and clinical outcomes.

## List of Abbreviations

| | |
|---|---|
| ACEi | Angiotensin Converting Enzyme Inhibitor |
| aHR | Adjusted Hazard Ratio |
| AMI | Acute Myocardial Infarction |
| AMI PROTECT | Acute Myocardial Infarction PROTECT Cohort Study |
| ARB | Angiotensin Receptor Blocker |
| ARNI | Angiotensin Receptor Neprilysin Inhibitor |
| ATP | Adenosine Triphosphate |
| BB | Beta Blocker |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| DAPA-MI | Dapagliflozin in Myocardial Infarction Trial |
| DAPOPTOSIS-MI | Effect of Dapagliflozin Administration on the Apoptosis Levels and Myocardial Work of Patients with Acute Myocardial Infarction |
| DM | Diabetes Mellitus |
| ED | Emergency Department |
| eGFR | Estimated Glomerular Filtration Rate |
| EMMY | Empagliflozin in Acute Myocardial Infarction Trial |
| EMPACT-MI | Trial to Evaluate the Effect of EMPAgliflozin on Hospitalisation for Heart Failure and Mortality in Patients With Acute Myocardial Infarction |
| ESC | European Society of Cardiology |
| GCW | Global Constructive Work |
| GLS | Global Longitudinal Strain |
| GWE | Global Work Efficiency |
| GWI | Global Work Index |
| GWW | Global Wasted Work |
| Hs Troponin I | High Sensitivity Troponin I |
| LV | Left Ventricular |
| LVEF | Left Ventricular Ejection Fraction |
| LVIDd | Left Ventricular Internal Diameter in Diastole |
| LVIDs | Left Ventricular Internal Diameter in Systole |
| MACE | Major Adverse Cardiovascular Events |
| MPTPs | Mitochondrial Permeability Transition Pores |
| MRA | Mineralocorticoid Receptor Antagonist |
| MW | Myocardial Work |
| NSTEMI | Non ST Segment Elevation Myocardial Infarction |
| NT-proBNP | N Terminal Pro B Type Natriuretic Peptide |
| OR | Odds Ratio |
| PCI | Percutaneous Coronary Intervention |
| RCT | Randomized Controlled Trial |
| SBP | Systolic Blood Pressure |
| SGLT2 | Sodium Glucose Cotransporter 2 |
| STEMI | ST Segment Elevation Myocardial Infarction |
| TAPSE | Tricuspid Annular Plane Systolic Excursion |

## Ethical Clearance

This study has obtained approval from the Research Ethics Committee of Dr. Moewardi Hospital, Central Java, Indonesia (letter number 2.226/IX/HREC/2024). Patient consent or informed consent was obtained from the research subjects. Patient identities are kept confidential.

## Publication Approval

All authors consent to the publication of this manuscript.

## Authors' Contributions

YY contributed to the conception and design of the study, study coordination, participant recruitment, data acquisition, data analysis and interpretation, and drafting and revision of the manuscript. TW, AY, RM, HA, AAN, and HS contributed to participant recruitment, clinical management, data acquisition, interpretation of the findings, and critical revision of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

## Acknowledgments

The authors express their gratitude to all patients for their participation in this study and to all study personnel for their invaluable assistance.

## Conflict of Interest

None.

## Availability of Data and Materials

Not applicable.

## Funding

None.

## Copyright/Permissions for Figures

Not applicable.

## Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that they did not use AI tools to generating, analyse, or interpretating data, figures, or scientific content. All text was reviewed, and edited by the authors, who take full responsibility for the content.

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