



# Assessing the early prognosis of heart failure after acute myocardial infarction using left ventricular pressure-strain loop: a prospective randomized controlled clinical study

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**Background:** The left ventricular pressure-strain loop (LV-PSL) technique, which is noninvasive and independent of pressure load, is more sensitive than is left ventricular speckle tracking imaging in detecting subtle changes in myocardial function. This study evaluated the improvement in cardiac function after application of LV-PSL in patients with heart failure with reduced ejection fraction (HFrEF) after acute myocardial infarction (MI) treated with sacubitril/valsartan plus dapagliflozin as compared to treatment with sacubitril/valsartan monotherapy.

**Methods:** This prospective, multicenter, open-label study recruited 60 MI survivors with HFrEF between March 2021 and June 2022. The patients were randomly assigned in 1:1 groups, as stratified by center. Patients were randomly categorized into either an observation group [n=30; conventional treatment + 100 mg (49/51 mg) of sacubitril/valsartan, + 10 mg of dapagliflozin] or a control group [n=30; conventional treatment + 100 mg (49/51 mg) of sacubitril/valsartan]. Patients were assessed at three time points: 1 month after discharge (T1), 3 months after discharge (T3), and 6 months after discharge (T6). Two-dimensional ultrasound images were routinely collected, two-dimensional speckle tracking imaging was applied to calculate the left ventricular global longitudinal strain (LV-GLS) rate for both groups, and LV-PSL analysis was used for the assessment of myocardial work, including global work index (GWI), global constructive work (GCW), global wasted work, and global work efficiency. The results at the three follow-up visits were compared with the predischARGE results (baseline, T0).

**Results:** Compared with the values at T0, the LV-GLS and left ventricular myocardial work index (LVMWI) values increased in both the observation and control groups at T1, T3, and T6, with GWI and GCW showing significantly greater improvement in the observation group at T6 (GWI: 1,204±336 vs. 987±417 mmHg%, P=0.03; GCW: 1,401±348 vs. 1,206±356 mmHg%, P=0.04). Survival analysis revealed that the overall incidence of major adverse cardiovascular events (MACEs) in the observation group was significantly lower than that in the control group (P=0.03). In a multivariate logistic regression analysis including GCW, GWI, GLS, and left ventricular ejection fraction (LVEF), GCW emerged as the only independent predictor of

occurrence of MACEs (odds ratio =1.08; 95% CI: 0.63–0.93;  $P < 0.001$ ).

**Conclusions:** Sacubitril/valsartan and dapagliflozin combination therapy led to a moderate improvement of cardiac function in patients with post-MI heart failure (P-MI-HF) compared to treatment with sacubitril/valsartan alone. Moreover, LV-PSL analysis can be used to assess the early prognosis of patients with P-MI-HF.

**Keywords:** Left ventricular pressure-strain loop (LV-PSL); angiotensin receptor-neprilysin inhibitor (ARNI); sodium-glucose cotransporter 2 inhibitor; heart failure with reduced ejection fraction (HFrEF)

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## Introduction

Acute myocardial infarction (AMI) is a common and critical disorder in emergency departments worldwide. In recent years, with the establishment of chest pain centers, the concept of “time is life and time is heart” has gained popularity. However, some patients still fail to receive timely treatment to relieve blockage and eventually develop serious complications. Several factors, such as recurrent myocardial infarction (MI), ventricular remodeling, mechanical MI complications, and stunned or hibernating myocardium, lead to post-MI heart failure (P-MI-HF) (1). Studies have shown that the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan improves myocardial remodeling-related indices in animal models of heart failure (HF) with reduced ejection fraction (HFrEF), patients with hypertension, and patients with AMI (2-5). It is particularly important to implement drug intervention measures in the early stage of MI. Although the recent PARADISE-MI study demonstrated suboptimal efficacy of sacubitril/valsartan in patients with AMI (6), several studies have reported the beneficial effect of sacubitril/valsartan in improving cardiac function in patients with P-MI-HF (5,7). Moreover, the European Society of Cardiology recommends the use of sacubitril/valsartan in patients with stable acute HFrEF (8). Previously, dapagliflozin, a sodium-glucose cotransporter 2 inhibitor, was primarily used for regulating blood glucose in patients with diabetes (9). However, a growing number of studies have shown its benefits in both cardiovascular and renal diseases (10-12). Most notably, the combination of sacubitril/valsartan and dapagliflozin has proven effective in reducing the risk of cardiovascular events in patients with HFrEF (13). However, this combination has not been studied adequately in the treatment of P-MI-HF.

Russel *et al.* proposed a new method, left ventricular pressure-strain loop (LV-PSL), for the noninvasive

measurement of LV myocardial work. In this approach, the intraventricular pressure curve is estimated by combining the peripheral arterial pressure (used as maximal intraventricular pressure) and the valve events (aortic and mitral valve opening and closure) to adapt the standard intraventricular pressure curve to the specific patient. The strain curve is separately calculated using the two-dimensional (2D) speckle tracking technique (STE). The combination of both curves results in the pressure-strain loop (PSL). The area of this loop is the global myocardial work index. The combination of segmental myocardial strain obtained by STE and the estimated LV pressure curve overcomes the load dependence of LV ejection fraction (LVEF) and STE. This allows for a more accurate assessment of myocardial function (14). Moreover, myocardial work assessed by LV-PSL correlates well with that measured by invasive cardiac catheterization, as demonstrated in animal and human studies (14,15). Notably, LV-PSL is superior to other echocardiographic parameters, including global longitudinal strain (GLS) rate and LVEF, for predicting coronary artery disease, with good reproducibility of the LV myocardial work index (LVMWI) (16). LV-PSL has thus become an area of intense research in the field of cardiac ultrasonography in recent years (17). We therefore aimed to evaluate the early prognosis of patients with P-MI-HF using LV-PSL following treatment with either sacubitril/valsartan plus dapagliflozin or sacubitril/valsartan alone. We present this article in accordance with the CONSORT reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1079/rc>).

## Methods

### Study population

The study enrolled patients with ST-elevation MI who were

treated for primary percutaneous coronary intervention (PPCI) from March 2021 to June 2022 at the cardiology departments of the Affiliated Brain Hospital of Nanjing Medical University, Nanjing Pukou Hospital of Traditional Chinese Medicine, and Lujiang County People's Hospital. These patients were enrolled after they were deemed to meet the following inclusion criteria: (I) a diagnosis of P-MI-HF based on the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) Guidelines for the management of HF (2); (II) age 18–80 years; (III) <12 hours between the onset of P-MI-HF and emergency coronary angiography (CAG); (IV) significant preoperative chest pain; (V) thrombolysis in MI (TIMI) score 0 with no collateral circulation of reverse perfusion distal to the infarcted vessel; (VI) postoperative LVEF <40%; and (VII) no history of HF. The exclusion criteria were as follows: (I) patients with poor image quality on transthoracic speckle tracking echocardiography; (II) acute non-ST-segment elevation MI; (III) complications such as previous MI, cardiogenic shock, septal perforation, mitral tendon cord, or papillary muscle rupture; (IV) heavy thrombus load, with lesion anatomy unsuitable for PPCI; (V) CAG showing a TIMI  $\geq 1$  for lesion vessel flow or distal grade or distal reverse perfusion of the collateral circulation; (VI) allergy to sacubitril/valsartan or dapagliflozin; and (VII) inability to undergo follow-up.

### Treatments

All patients received 300 mg of aspirin (Bayer, Leverkusen, Germany) and 180 mg of Tegretol (AstraZeneca, Cambridge, Britain) orally before PPCI. In addition, patients were administered anticoagulant therapy intraoperatively and postoperatively; moreover, they were administered the standard drug regimen for HF postoperatively. Emergency interventions were performed by experienced senior physicians in the departments.

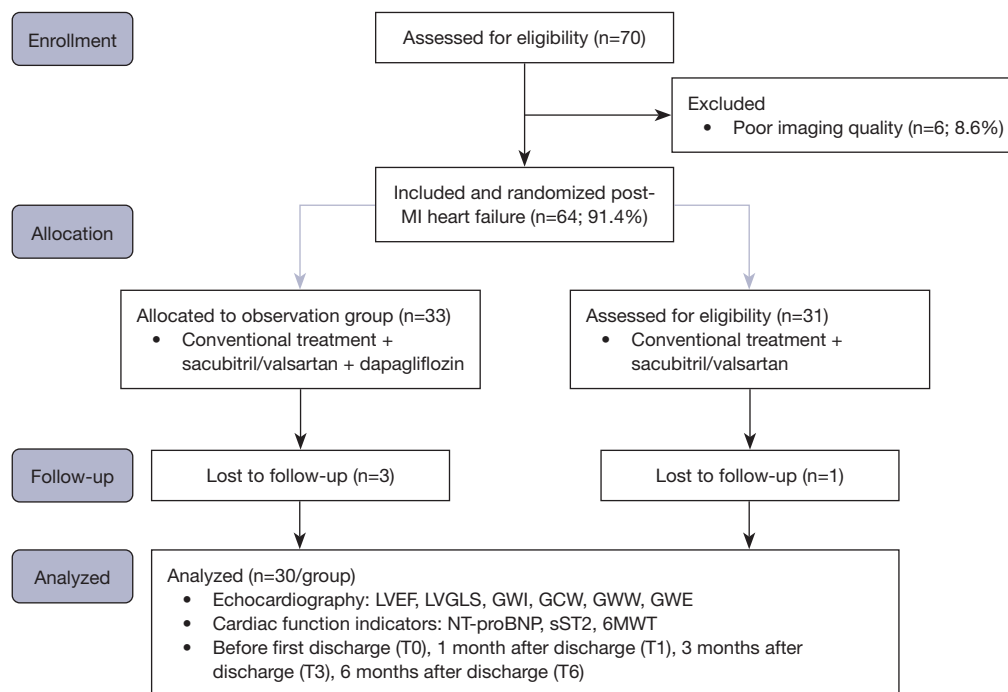
The standard postoperative treatment for HF comprised a  $\beta$ -blocker and an aldosterone receptor antagonist. Patients in the observation group received standard treatment for HF along with sacubitril/valsartan plus dapagliflozin. Sacubitril/valsartan [100 mg (49/51 mg)] was administered orally, initially at a dose of 50 mg twice a day, which was followed by an increment of 50 mg at 2-week intervals to a maximum dose of 200 mg/dose twice a day. Dapagliflozin (10 mg; AstraZeneca) was administered at an initial dosage of 5 mg once daily, which was then increased to 10 mg once

daily, based on individual requirements. In contrast, patients in the control group received the standard treatment along with sacubitril/valsartan only (dosing similar to that in the observation group). Both groups received treatment for 6 months.

### Assessment indicators

All patients underwent transthoracic 2D echocardiography in the left lateral position to measure LV end-diastolic diameter (LVEDD), LV end-systolic internal diameter (LVESD), and LVEF using the biplane Simpson method in accordance with the current guidelines (18). Ultrasound images were acquired before (T0), 1 month after (T1), 3 months after (T3), and 6 months after (T6) discharge from the hospital. An ultrasound diagnostic device (Vivid E95 R4, GE Healthcare, Chicago, IL, USA) with an M5Sc-D heart probe was used for imaging at a frame rate of >40/s and a frequency of 154.6 MHz. All images were obtained in the three apical views (four-chamber, two-chamber, and three-chamber views) and were quantified for global longitudinal strain (GLS) analysis in the EchoPAC workstation (GE HealthCare). The system automatically outlines the endocardial and epicardial boundaries based on the dynamic images of the apical three-, four- and two-chamber cardiac views to manually correct poorly tracked endocardial edges, resulting in the final LV-GLS data. The myocardial work analysis mode was used to mark the aortic valve closure as well as determine the isovolumic relaxation, ejection, and isovolumic contraction via the spectrograms of antegrade flow from the aortic valve. After obtaining the cardiac dynamic images, we immediately instructed the patient to remain seated, after which we measured the blood pressure in the patient's right arm using a cuffed sphygmomanometer. The peak LV pressure was estimated from the obtained blood pressure values, and the standardized LV pressure reference curve was adjusted according to the different phases of the cardiac cycle. The adjusted standardized LV pressure curve was combined with the longitudinal strain curve obtained from 2D speckle tracking to obtain a PSL. The area within the PSL was defined as the global work index (GWI).

To assess other cardiac function indicators, 5 mL of venous blood was collected before the start of the therapy and at different timepoints during follow-up treatment and centrifuged. Subsequently, the serum was separated for determining the level of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) using colloidal



**Figure 1** Patient recruitment. LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble growth stimulator 2 protein; 6MWT, 6-minute walk test.

gold immunochromatography and the level of soluble growth stimulator 2 protein (sST2) using enzyme-linked immunosorbent assay. In addition, a 6-minute walk test (6MWT) was performed before treatment and after 1, 3, and 6 months of treatment to measure the distance walked on a flat surface before and after 6 minutes of treatment in both groups. At all timepoints, the same nurse assisted patients in the 6MWT.

### Study design

We conducted a prospective, randomized, open-label, multicenter study across multiple centers. Based on prior research (3,10), it was anticipated that using conventional treatment in combination with sacubitril/valsartan would lead to around a 26% discrepancy in GWI improvement rates among the patients with HFrEF. Conversely, using conventional treatment combined with sacubitril/valsartan and dapagliflozin resulted in an approximately 48% difference in GWI improvement values in patients with HFrEF. The standard deviation was 2% and 0.5%,  $\alpha$  was set at 0.05, power was set at 0.9, and a sample size of 28 cases was necessary for each group. With an expected dropout

rate of 20%, the study aimed to include 70 patients, 35 in each group. However, four patients were lost to follow-up and six patients had poor image quality, resulting in a 14% dropout rate. The participants were stratified by centers and then randomly allocated into two groups at a 1:1 ratio within centers.

The recruitment of patients is shown in *Figure 1*. Based on conventional HF treatment, the observation group was treated with dapagliflozin (SGLT2 inhibitor) + sacubitril/valsartan (ARNI), and the control group was treated with the treatment regimen of ARNI alone. There was one more drug used in the observation group. Therefore, the study was designed as a nonblinded, open-label study. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Nanjing Pukou Hospital of Traditional Chinese Medicine (TCM) (Nanjing, China; approval No. 20210021). Patients at each center were informed of the study's details and provided their consent to participate. All participating hospitals were informed of and agreed with the study protocol. The clinical trial was not registered at the start of the study due to an oversight by the investigator. The registration process is currently underway. The

registration number will be provided upon completion of the review process, which is expected to be lengthy.

### Statistical methods

All statistical analyzes were performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA). For normally distributed data, the mean  $\pm$  standard deviation was determined using the single-sample Kolmogorov-Smirnov normality test. For statistically significant data, the least significant difference (LSD) test was used for pairwise comparison. The median (interquartile range) was used for assessing data that were not normally distributed. Enumeration data are expressed as fractions, and the  $\chi^2$  test was used for comparisons between groups. Continuous data were assessed using Pearson correlation analysis. Kaplan-Meier analysis was used to conduct survival analysis with the incidence of major adverse cardiovascular events (MACEs) being the endpoint. Logistic regression analysis was performed to assess independent correlates of cardiac function parameters and occurrence of MACEs. The hazard ratio (HR) with the 95% confidence interval (CI) was estimated. Receiver operating curve (ROC) analysis was performed to test the parameters associated with cardiac function and occurrence of MACEs. Results with a P value  $<0.05$  were considered significant.

## Results

### Clinical data

In total, 60 patients were included and grouped (1:1) using the random number table method. The observation group received conventional treatment + sacubitril/valsartan + dapagliflozin [n=30; 18 males; mean age  $63\pm 12.2$  years; onset to treatment time 2–12 hours (mean  $5.3\pm 1.4$  hours)]. The control group received conventional treatment + sacubitril/valsartan [n=30; 16 males; mean age  $64\pm 12.4$  years; onset to treatment time 2–12 hours (mean  $5.7\pm 1.5$  hours)]. The baseline characteristics were comparable between the two groups ( $P>0.05$ ) and are provided in *Table 1*.

### Comparison of echocardiography indicators before and after treatment between the two groups

At T0, there were no statistically significant differences in echocardiography indices [LVESD, LVEDD, LVEF, LVGLS, GWI, global constructive work (GCW), global

wasted work (GWW), and global work efficiency (GWE)] between the two groups.

At T1, there were no significant differences in the LVESD, LVEDD, LVEF, LVGLS, GWI, GCW, GWW, or GWE indices compared with those at T0. Moreover, at T1, these parameters did not differ significantly between the observation and control groups.

LVESD and LVEDD were lower in both the observation and control groups at T3 than at T0. In contrast, LVEF was higher at T3 than at T0, but not significantly so. The LVGLS, GWI, GCW, and GWE indices were higher at T3 in both groups than at T0. However, a lower GWW value was observed at T3 than at T0, although this difference was not significant ( $P>0.05$ ). In addition, none of the indices differed significantly between the observation and control groups.

At T6, LVESD and LVEDD values decreased further in both groups compared to T0. LVEF was significantly higher at T6 than at T0 ( $P<0.05$ ). Compared with the control group, the observation group had higher LVEF, but without a statistically significant difference. LVGLS, GWI, and GCW values were significantly higher while the GWW value was significantly lower at T6 than at T0 ( $P<0.05$ ). LVGLS was higher in the observation group than in the control group, but not significantly so. GWI and GCW were significantly increased in the observation group as compared to the control group ( $P<0.05$ ) (*Table 2*). *Figures 2,3* present examples of the PSL from T0 to T6 in patients with HFrEF after AMI was treated with sacubitril/valsartan plus dapagliflozin or sacubitril/valsartan monotherapy, respectively.

Results of intra- and interobserver variability of global strain and work parameters in 15 randomly selected patients with P-MI-HF are shown in *Table 3*. The intraclass correlation coefficients for both intra- and interobserver measurements indicated good reliability for all parameters.

### Comparison of other cardiac function indicators between the two groups before and after treatment

At T0, there were no statistical differences in NT-proBNP or sST2 levels and 6MWT results between the two groups. At T1, NT-proBNP levels significantly decreased compared to the levels at T0 in the observation group (T0 vs. T1:  $3,678.4$  vs.  $2,998.7$  pg/mL;  $P<0.001$ ) and the control group (T0 vs. T1:  $3,534.9$  vs.  $2,876.5$  pg/mL;  $P<0.001$ ). The NT-proBNP levels at T3 decreased significantly from T0 to T1 in the observation group (T1 vs. T3:  $2,998.7$  vs.  $1,117.8$  pg/mL;

**Table 1** Comparison of clinical baseline data

Parameters	Observation group (n=30)	Control group (n=30)	t/ $\chi^2$ value	P value
Age (years)	63±12.2	64±12.4	0.32	0.75
Males/females (n)	18/12	16/14	0.27	0.60
Time from onset to treatment (hours)	5.3±1.4	5.7±1.5	1.07	0.29
BMI (kg/m <sup>2</sup> )	25.9±2.2	25.1±2.7	1.20	0.24
Killip classification ≥ class II	12 (40.0)	10 (33.3)	0.29	0.59
Heart rate (bpm)	92.1±8.1	88.2±9.2	1.74	0.09
NT-proBNP (pg/mL)	1,470.2 [361.0, 2,780.0]	1,514.7 [369.7, 2,937.2]	0.76	0.84
sST2 (ng/mL)	88.4±11.7	93.1±10.1	1.67	0.1
Creatinine (μmol/L)	94.9±21.5	96.3±22.6	0.25	0.81
Total cholesterol (mmol/L)	4.3±1.4	4.2±1.5	0.27	0.79
Low-density lipoprotein (mmol/L)	2.8±0.3	2.9±0.4	1.1	0.28
Hypertension	22 (73.3)	24(80.0)	0.37	0.54
Diabetes	11 (36.7)	13 (43.3)	0.28	0.60
Cerebral infarction	6 (20.0)	5 (16.7)	0.11	0.74
History of smoking	16 (53.3)	13 (43.3)	0.60	0.44
History of drinking	11 (36.7)	14 (46.7)	0.62	0.43
Affected coronary artery				
LAD	15 (50.0)	17 (56.7)	0.27	0.61
LCX	3 (10.0)	4 (13.3)	–	0.88
RCA	5 (16.7)	5 (16.7)	–	0.94
LM or two or more branches	7 (23.3)	4 (13.3)	1.00	0.32

Data presented as the mean ± SD, n (%), or median [interquartile range]. BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble growth stimulator 2 protein; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LM, left main artery.

**Table 2** Follow-up data of echocardiography

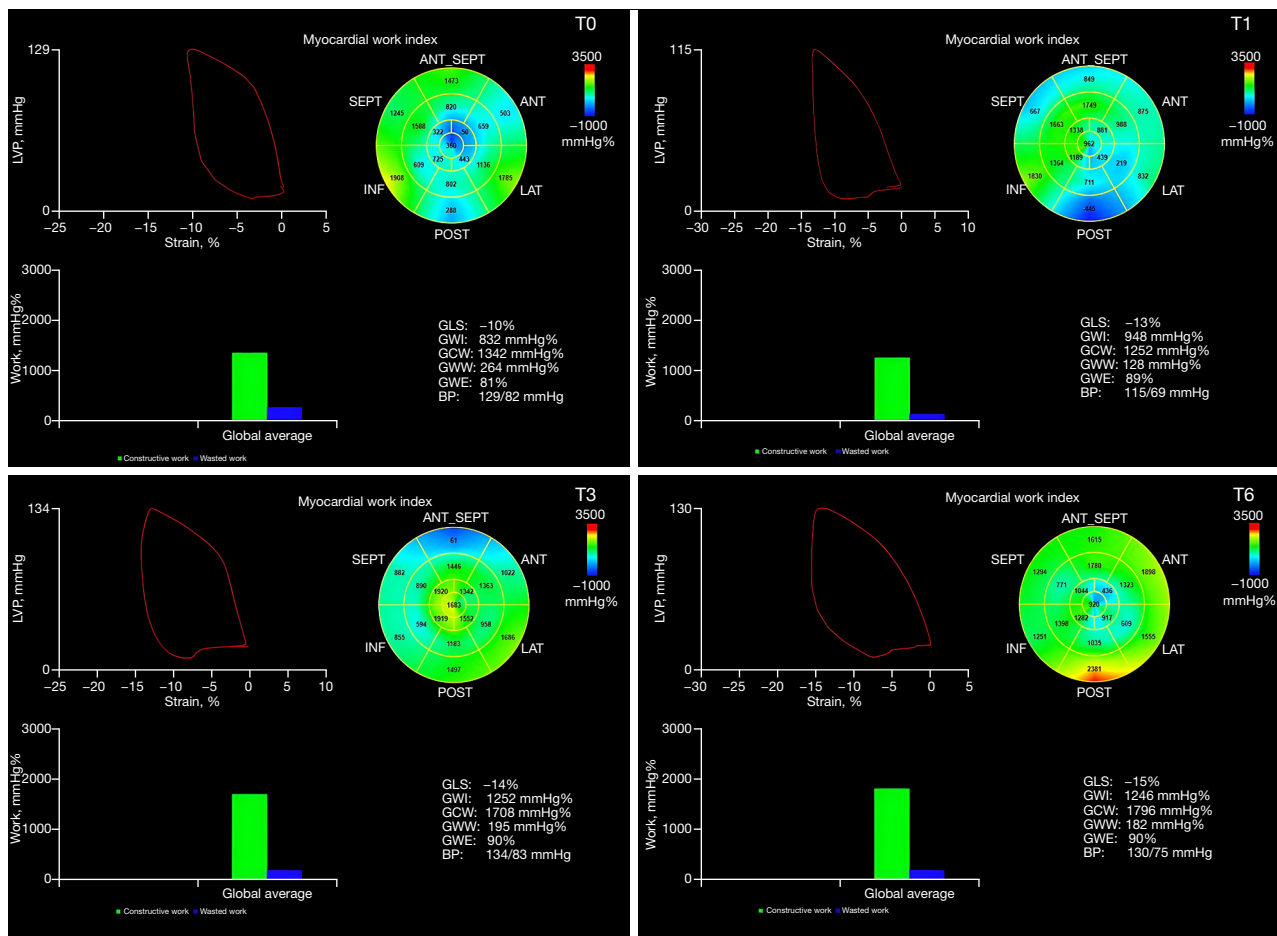
Parameters	Follow-up time (months)	Observation group (n=30)	Control group (n=30)	P value
LVEDD (mm)	T0	67.8±10.3	68.0±11.4	0.93
	T1	64.8±12.3	63.2±13.8	0.62
	T3	62.3±15.7	62.1±14.6	0.97
	T6	61.7±14.6*	61.4±11.0*	0.93
LVESD (mm)	T0	56.8±8.5	57.3±8.9	0.85
	T1	54.1±6.3	54.4±7.5	0.84
	T3	53.6±11.1	54.1±9.4	0.85
	T6	51.1±9.5*	51.0±10.7*	0.96
E/A	T0	0.43±0.19	0.46±0.16	0.51
	T1	0.47±0.21	0.48±0.19	0.85
	T3	0.54±0.27	0.53±0.31	0.89
	T6	0.63±0.32*	0.59±0.29*	0.51

**Table 2** (continued)

Table 2 (continued)

Parameters	Follow-up time (months)	Observation group (n=30)	Control group (n=30)	P value
Average E/e'	T0	17.5±4.3	18.1±5.2	0.63
	T1	17.3±4.5	17.9±4.9	0.62
	T3	16.4±5.5	16.1±5.7	0.84
	T6	14.4±7.2*	14.6±7.8*	0.92
2D LVEF (%)	T0	32.5±5.2	30.9±4.8	0.23
	T1	33.9±8.8	32.8±5.9	0.55
	T3	35.1±9.7	34.5±8.3	0.79
	T6	38.4±9.5*	37.9±10.7*	0.86
SBP (mmHg)	T0	98.6±7.5	97.2±6.9	0.46
	T1	99.4±7.6	98.3±6.9	0.56
	T3	104.1±7.9*	102.1±7.2*	0.31
	T6	110.5±9.5*	106.9±8.7*	0.13
DBP (mmHg)	T0	63.4±4.3	61.7±3.8	0.11
	T1	64.7±4.9	63.5±4.6	0.33
	T3	64.3±5.2	62.3±4.8	0.13
	T6	67.6±5.9*	66.8±5.1*	0.58
LVGLS (%)	T0	-9.3±1.5	-9.0±2.0	0.44
	T1	-9.9±1.9	-9.0±3.5	0.23
	T3	-11.8±2.9*	-11.3±3.0*	0.44
	T6	-15.4±1.9*	-14.4±2.5*	0.07
GWI (mmHg%)	T0	788±364	783±365	0.96
	T1	797±388	792±354	0.96
	T3	943±416	896±373	0.65
	T6	1,204±336*	987±417*	0.03
GCW (mmHg%)	T0	1,083±443	1,095±396	0.91
	T1	1,085±394	1,107±373	0.83
	T3	1,198±439	1,196±416	0.99
	T6	1,401±348*	1,206±356	0.04
GWW (mmHg%)	T0	261 [201, 386]	272 [232, 398]	0.87
	T1	226 [177, 354]	233 [164, 377]	0.99
	T3	187 [127, 349]	194 [132, 366]	0.93
	T6	132 [89, 316]*	167 [94, 345]*	0.80
GWE (%)	T0	63 [52, 81]	61 [50, 83]	0.99
	T1	64 [56, 83]	65 [49, 81]	0.99
	T3	71 [57, 91]	68 [56, 88]	0.98
	T6	79 [64, 94]	74 [61, 89]	0.98

Data are presented as mean ± standard deviation or median [interquartile range]. \*, P<0.05 compared with T0. T0: before first discharge; T1: 1 month after discharge; T3: 3 months after discharge; T6: 6 months after discharge. LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; E/A, the ratio of the rate of blood flow for rapid ventricular filling in early diastole to the rate of blood flow in mid- to late diastole; E/e', the ratio of peak early diastolic mitral flow velocity E to peak early diastolic mitral annular velocity e'; 2D, two-dimensional; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVGLS, left ventricular global longitudinal strain; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency.



**Figure 2** An example of pressure-strain loop from the observation group. The pressure-strain loop is represented as a 17-segment bull's eye, and all myocardial work parameters are listed from baseline (T0) to 6 months after discharge (T6) in patients with heart failure with reduced ejection fraction after acute anterior wall myocardial infarction treated with sacubitril/valsartan plus dapagliflozin. The region enclosed by the red circle depicts the work done in the left ventricle. LVP, left ventricle pressure; ANT, anterior wall; SEPT, septal wall; INF, inferior; POST, posterior wall; LAT, lateral anterior wall; GLS, global longitudinal strain; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; BP, blood pressure.

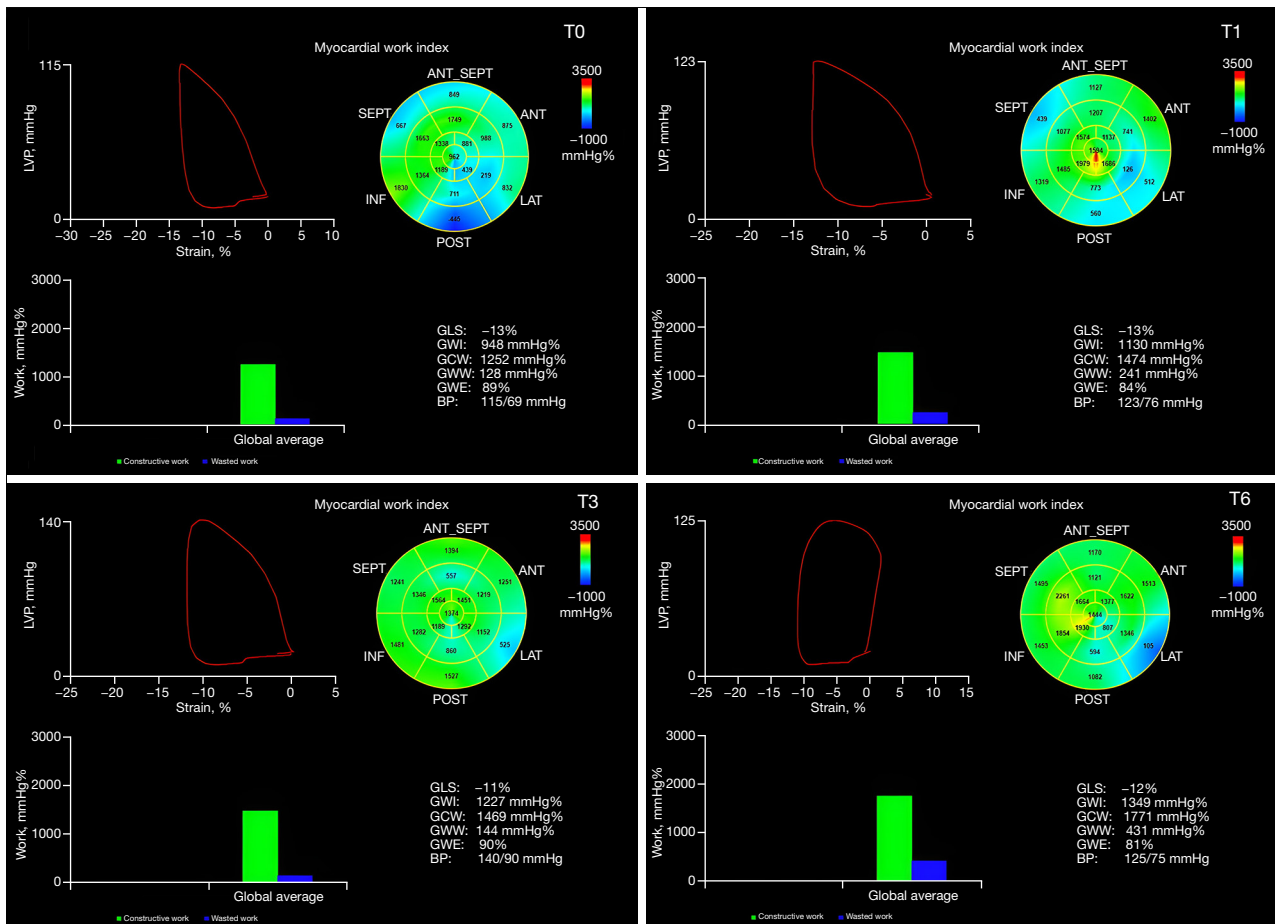
$P < 0.001$ ) and the control group (T1 *vs.* T3: 2,876.5 *vs.* 1,289.5 pg/mL;  $P < 0.001$ ). At T6, the NT-proBNP levels continued to decrease in the observation group (T3 *vs.* T6: 1,117.8 *vs.* 1,087.4 pg/mL;  $P = 0.480$ ), demonstrating slightly lower levels than the control group (T3 *vs.* T6: 1,289.5 *vs.* 1,215.7 pg/mL;  $P = 0.074$ ) (Figure 4).

The sST2 level at T1 was significantly lower than at T0 in the observation group (T0 *vs.* T1: 84.3 *vs.* 71.1 ng/mL;  $P < 0.001$ ) and the control group (T0 *vs.* T1: 88.5 *vs.* 73.6 ng/mL;  $P < 0.001$ ). Similarly, this parameter showed significantly lower values in T3 than in T0 and T1 for the observation group (T1 *vs.* T3: 71.1 *vs.* 49.3 ng/mL;  $P < 0.001$ )

and control group (T1 *vs.* T3: 73.6 *vs.* 51.2 ng/mL;  $P < 0.001$ ). In addition, sST2 levels further were significantly decreased at T6 compared to at T0, T1, and T3 in the observation group (T3 *vs.* T6: 49.3 *vs.* 43.2 ng/mL;  $P = 0.0003$ ) and the control group (T3 *vs.* T6: 51.2 *vs.* 45.9 ng/mL;  $P = 0.0026$ ). Moreover, the sST2 levels were lower in the observation group than in the control group at T0 (84.3 *vs.* 88.5 ng/mL;  $P = 0.106$ ), T1 (71.1 *vs.* 73.6 ng/mL;  $P = 0.276$ ), T3 (49.3 *vs.* 51.2 ng/mL;  $P = 0.295$ ), and T6 (43.2 *vs.* 45.9 ng/mL;  $P = 0.072$ ) (Figure 5), but these differences were not significant.

Compared with the 6MWT results at T0, those at T1





**Figure 3** An example of the pressure-strain loop from the control group. The pressure-strain loop is represented as a 17-segment bull’s eye, and all myocardial work parameters are listed from baseline (T0) to 6 months after discharge (T6) in patients with heart failure with reduced ejection fraction after acute inferior wall myocardial infarction treated with sacubitril/valsartan monotherapy. LVP, left ventricle pressure; ANT, anterior wall; SEPT, septal wall; INF, inferior; POST, posterior wall; LAT, lateral anterior wall; GLS, global longitudinal strain; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; BP, blood pressure.

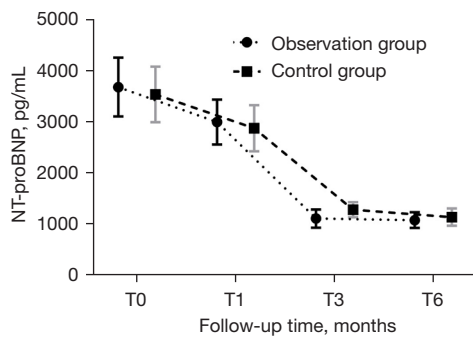
**Table 3** Follow-up results of patients

Parameters	Observation group (n=30)	Control group (n=30)	P value
Rehospitalization rate	5 (16.7)	7 (23.3)	0.52
All-cause mortality	1 (3.3)	3 (10.0)	0.57
Incidence of MACES	6 (20.0)	14 (46.7)	0.03*

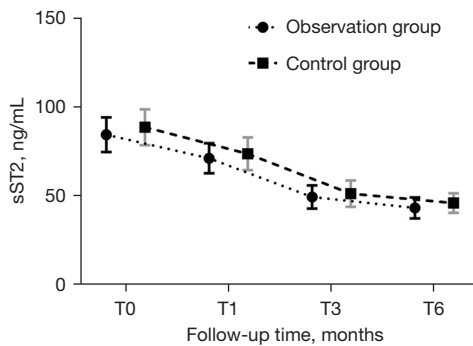
Data are presented as n (%). \*, P<0.05 compared with the control group. An MACE is defined as recurrent angina, acute myocardial infarction, severe dysrhythmia, heart failure, or death due to coronary heart disease. MACE, major adverse cardiovascular event.

were improved in the observation group (T0 vs. T1: 241.7 vs. 256.7 m; P=0.076) and the control group (T0 vs. T1: 245.4 vs. 258.6 m; P=0.210), but not significantly so. At T3, the 6MWT results were significantly better than those at

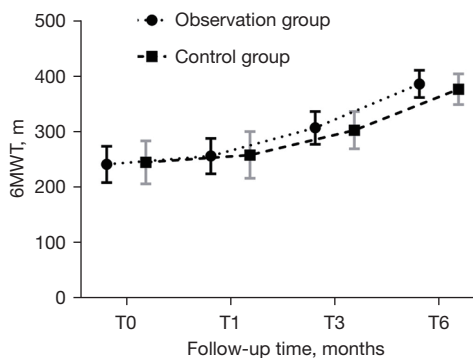
T0 and T1 in the observation group (T1 vs. T3: 256.7 vs. 307.5 m; P<0.001) and the control group (T1 vs. T3: 258.6 vs. 303.3 m; P<0.001). Similarly, at T6, the 6MWT results were significantly improved compared to those at T0, T1, and



**Figure 4** Follow-up data of NT-proBNP. NT-proBNP, N-terminal pro-B-type natriuretic peptide.



**Figure 5** Follow-up data of sST2. sST2, soluble growth stimulator 2 protein.



**Figure 6** Follow-up data of the 6MWT. 6MWT, 6-minute walk test.

T3 in the observation group (T3 *vs.* T6: 307.5 *vs.* 386.4 m) and in the control group (T3 *vs.* T6: 303.3 *vs.* 376.8 m;  $P < 0.001$ ). In addition, there were no significant differences in the 6MWT results between the observation and control groups at T0 (241.7 *vs.* 245.4 m;  $P = 0.690$ ), T1 (256.7 *vs.*

**Table 4** Intra- and interobserver variability of global strain and myocardial work assessment

Parameters	Absolute difference	ICC
Intraobserver variation		
LVEDD (mm)	1.9±0.73	0.95 (0.89–0.98)
LVESD (mm)	1.8±0.92	0.96 (0.87–0.97)
2D LVEF (%)	3.14±1.74	0.84 (0.69–0.94)
LVGLS (%)	−7±1.17	0.95 (0.87–0.98)
GWI (mmHg%)	1.24±0.94	0.92 (0.83–0.96)
Interobserver variation		
LVEDD (mm)	2.3±0.77	0.90 (0.78–0.95)
LVESD (mm)	2.4±0.96	0.89 (0.75–0.96)
2D LVEF (%)	5.32±2.34	0.81 (0.62–0.91)
LVGLS (%)	−12±0.79	0.88 (0.73–0.95)
GWI (mmHg%)	1.46±0.86	0.83 (0.66–0.92)

Data are presented as the mean ± standard deviation and ICC (95% CI). ICC, intraclass correlation coefficient; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; 2D, two-dimensional; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; GWI, global work index; IC, confidence interval.

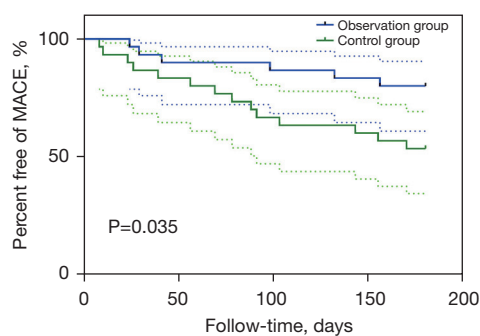
258.6 m;  $P = 0.844$ ), T3 (307.5 *vs.* 303.3 m;  $P = 0.607$ ), or T6 (386.4 *vs.* 376.8 m;  $P = 0.163$ ) (Figure 6).

#### Follow-up outcomes for both groups

There were no adverse events caused by the study in this trial. The incidence of MACEs in the observation group was significantly lower than that of the control group ( $P = 0.035$ ), and the observation group had a lower rate of rehospitalization for P-MI-HF and all-cause mortality (Table 4). Kaplan-Meier survival curves were drawn with MACE as the endpoint and were analyzed using the log-rank test. The results indicated that overall outcome of P-MI-HF treatment was better in the observation group than in the control group (observation group *vs.* control group: HR, 0.37; 95% CI: 0.15–0.86;  $P = 0.035$ ) (Figure 7).

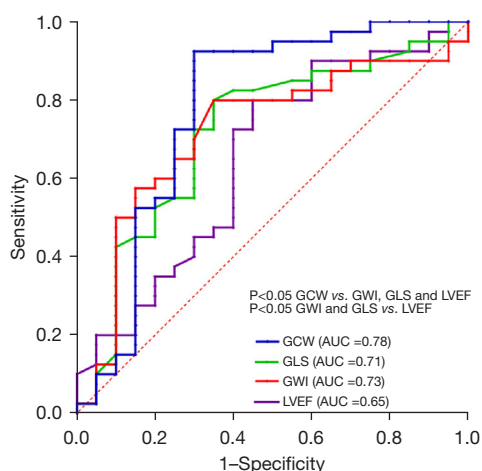
#### Prediction of the occurrence of MACE

In the comparison of ROC curves, GCW had a significantly higher area under the curve (AUC) as compared to GWI, GLS, and LVEF (all  $P$  values  $< 0.05$ ; see Figure 8). The best



Number at risk:	0	50	100	150	200
Observation group	30	27	26	25	0
Control group	30	25	20	18	0

**Figure 7** Kaplan-Meier survival curves according to the occurrence of major adverse cardiovascular events in both groups. MACE, major adverse cardiovascular event.



**Figure 8** A comparison of ROC curves of cardiac function parameters in predicting the occurrence of MACEs. GCW, global constructive work; GWI, global work index; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic; MACE, major adverse cardiovascular event.

cutoff of GCW for predicting the occurrence of MACEs was  $>1,092$  mmHg% ( $P<0.001$ ). In a multivariate logistic regression analysis including GCW, GWI, GLS, and LVEF, GCW emerged as the only independent predictor if MACE occurrence (OR =1.08; 95% CI: 0.63–0.93;  $P<0.0005$ ).

The GCW (blue line in *Figure 8*) had the better AUC for predicting the occurrence of MACEs (AUC =0.78) when compared with GWI (red line; AUC =0.73;  $P<0.05$ ), GLS (green line; AUC =0.71;  $P<0.05$ ), and LVEF (purple line; AUC =0.65;  $P<0.05$ ).

## Discussion

The 2022 AHA/ACC/HFSA guidelines for the management of HF highlight the role of dapagliflozin in all phases of treatment. Accordingly, dapagliflozin has become the first-line agent recommended in the full phase of HF (2). Moreover, it was the first drug to be recommended for use in all phases of HF. However, relatively few studies have assessed the role of dapagliflozin in the treatment of P-MI-HF (19,20). Thus, we conducted this study to assess the early prognosis of patients with P-MI-HF treated with dapagliflozin plus sacubitril/valsartan *vs.* sacubitril/valsartan alone using the LV-PSL technique. The results demonstrated the superiority of sacubitril/valsartan plus dapagliflozin in the treatment of patients with P-MI-HF.

One clinical trial assessed the safety of adding dapagliflozin to mineralocorticoid receptor antagonists or ARNIs in 6,263 patients with HF with midrange EF/HF with preserved EF. The results confirmed that dapagliflozin had no interaction with the other therapeutic agents (21). In another study by Karabulut *et al.* (22), the effect of dapagliflozin plus sacubitril/valsartan on long-term cardiac mortality in patients with HFrEF was assessed. This retrospective study confirmed the long-term benefit of dapagliflozin in combination with sacubitril/valsartan (22). These findings are consistent with those of our study, which confirmed that combination therapy of dapagliflozin plus sacubitril/valsartan can provide additional benefits to patients with HFrEF. However, finding a more sensitive screening tool is critically important and was one of the focuses of our study. Moreover, we found that compared with 2D ultrasound LVEF and STE, LV-PSL is more sensitive for the assessment of early changes in cardiac function, particularly GWI and GCW. In clinical settings, LVEF is widely used to evaluate LV systolic function and the prognosis of patients with AMI. However, as 2D M-mode ultrasound is dependent on cardiac morphology, it is an unreliable tool in patients with segmental ventricular wall motion abnormalities occurring after MI. The biplane Simpson method is another method for assessing cardiac function. Although it is less affected by abnormal cardiac morphology, it requires accurate identification of the intima-media borders, which is often not achieved. Therefore, LVEF has poor accuracy in evaluating LV function in patients with AMI. Moreover, LVEF only allows the evaluation of the overall systolic function, making it difficult to localize myocardium with segmental ventricular wall motion abnormalities in patients with AMI (23). The GLS obtained using 2D STE is more accurate than is LVEF and facilitates the detection of subtle

LV systolic dysfunction; moreover, it has a high sensitivity for identifying segments with damaged myocardia (24,25).

First proposed by Russell *et al.*, the novel noninvasive LV-PSL technique is a method that can provide a more comprehensive assessment of LV myocardial function. The technique integrates STE and load effects and combines myocardial deformation with noninvasively measured LV pressures (14). Studies have demonstrated that LV-PSL can accurately assess cardiac workup as efficiently as can invasive cardiac catheterization (14,15). Thus, LV-PSL could be a potentially efficient and novel predictor of clinical status, which can help explore the clinical significance of the underlying cardiomyopathies and their related mechanisms (26,27).

In this study, we used LV-PSL in patients with P-MI-HF to determine if dapagliflozin plus sacubitril/valsartan was more effective than sacubitril/valsartan monotherapy. In addition, 2D ultrasound images (including 2D data such as LVEDD, LVESD, and LVEF), data on myocardial markers (NT-proBNP and sST2), and 6MWT results were obtained. These indicators showed a significant difference between baseline and each timepoint. However, no such differences were observed between the two groups in proving the superior efficacy of sacubitril/valsartan plus dapagliflozin over sacubitril/valsartan monotherapy. Notably, GWI and GCW, determined using LV-PSL, showed intergroup variability, indicating the utility of this technique in detecting subtle changes in myocardial contractile function. Meanwhile, we performed multiple regression analysis of the correlation of GCW, GWI, GLS, and LVEF—which are the important parameters of cardiac function assessment—with the occurrence of MACEs and found that GCW was independently correlated with the occurrence of MACEs. Compared with the other three parameters, GCW had a significantly larger AUC. The results also demonstrated the importance of GCW in LV-PSL, which provides valuable guidance for the prognosis of P-MI-HF. In addition, an analysis of readmission rates for HF, all-cause mortality, MACE incidence, and survival data over 6 months revealed that the observation group had a better prognosis than did the control group.

As one of its strengths, this study enrolled patients from three medical centers, with a relatively large population size; thus, the findings of this study can guide treatment in clinical settings. Moreover, this study provides a reference for clinicians treating patients with AMI for prognostic testing of cardiac function and can serve as a guide for further studies on the quantitative assessment of myocardial

function. However, there are certain limitations to this study. The myocardial work index assessed using the noninvasive LV-PSL technique still only provides an estimate of myocardial work, unlike the myocardial parameters measured via cardiac catheterization. Myocardial work parameters rely on software models that are currently only available from a single company, GE HealthCare; as a result, there is no comparator available for testing the results. Moreover, the sample size was relatively small, with a short follow-up period. Thus, future studies with larger sample sizes and longer follow-ups are required to verify the benefits of sacubitril/valsartan plus dapagliflozin combination therapy *vs.* sacubitril/valsartan monotherapy in patients with P-MI-HF.

## Conclusions

This study confirmed the advantages of dapagliflozin in combination with sacubitril/valsartan in the treatment of patients with P-MI-HF and demonstrated the sensitivity of LV-PSL in detecting myocardial motion abnormalities in LV systolic function.

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## Footnote

*Reporting Checklist:* The authors have completed the CONSORT reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1079/rc>

*Trial Protocol:* Available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1079/tp>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1079/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are 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. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Nanjing Pukou Hospital of TCM (Nanjing, China) (approval No. 20210021). Informed consent was obtained from each patient. All participating hospitals/institutions were informed of the study protocol and agreed with the study.

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