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RESEARCH ARTICLE

Clinical Effects of Sacubitril/Valsartan Combined with Dapagliflozin in Patients with Diabetes and ST-segment Elevation Myocardial Infarction

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Abstract

Objectives: This study was aimed at observing the clinical effects of sacubitril/valsartan combined with dapagliflozin on cardiac function and ventricular remodeling in patients with type 2 diabetes and ST-segment elevation myocardial infarction (STEMI).

Methods: Between May 2019 and May 2022, we retrospectively analyzed 57 patients with diabetes and STEMI receiving percutaneous coronary intervention: 32 patients receiving sacubitril/valsartan and dapagliflozin tablets comprised the observation group and 25 patients receiving angiotensin converting enzyme inhibition (ACEI) or angiotensin receptor blockers ARB) in combination with other hypoglycemic drugs comprised the control group. We compared the left ventricular end diastolic diameter (LVEDD), right ventricular end diastolic diameter (RVEDD), left ventricular ejection fraction (LVEF), N-terminal pro-B-type natriuretic peptide (NT-pro BNP), and noninvasive hemodynamic parameters at baseline and 3–6 months after treatment between the groups.

Results: Before treatment, the parameters were similar between the observation group and control group. However, after 3–6 months of treatment, serum NT-pro BNP levels showed a greater decline in the observation group than the control group. Moreover, the LVEDD and LVEF improved more substantially in the observation group than the control group ($P < 0.05$). RVEDD did not markedly change after treatment ($P > 0.05$). After treatment, in the observation group, the cardiac index (CI) and cardiac output (CO) were significantly higher, and the thoracic fluid conduction (TFC) and systemic vascular resistance index (SVRI) were significantly lower, than those in the control group ($P < 0.05$).

Conclusions: Sacubitril/valsartan combination with dapagliflozin exerted better effects than ACEI or ARB with other hypoglycemic drugs in improving cardiac function and ventricular remodeling in patients with diabetes and STEMI.

Keywords: sacubitril/valsartan; dapagliflozin; ventricular remodeling; noninvasive hemodynamics

Introduction

Patients usually experience cardiac dysfunction at early stages after acute myocardial infarction (AMI) because of positive regenerative cycles between ventricular remodeling and heart failure (HF). Abnormal hemodynamics and activated neuroendocrine systems, followed by myocardial necrosis, prime and expedite ventricular remodeling processes [1]. Current clinical "golden triangle" regimens – which include angiotensin converting enzyme inhibitors or angiotensin

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receptor blockers; beta receptor blockers; and aldosterone receptor antagonists – are believed to resist ventricular remodeling, thus ameliorating HF after myocardial infarction and decreasing the risk of death by 30% [2–4]. However, for patients with AMI and diabetes mellitus (DM), the fatality rates are twice those of patients with non-DM AMI [5]. Most patients with DM die from coronary artery disease, although long-term standardized management for both diseases has been implemented [6, 7]. Thus, optimized treatments are required for patients with DM and AMI. The world's first angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan, is superior to enalapril in improving outcomes in patients with chronic stable HF and acute decompensated HF [8]. Furthermore, sodium-glucose cotransporter 2 inhibitor (SGLT2i) treatment is both safe and effective in preventing and treating HF, regardless of DM status [9, 10]. Consequently, we sought to determine whether early combined treatment with sacubitril/valsartan and dapagliflozin might have advantages over the traditional "golden triangle" regimen for patients with DM with the complication of ST-segment elevation myocardial infarction (STEMI) who are at high risk of HF. Few reports have focused on this clinical issue. Therefore, we collected data on patients with DM and STEMI who underwent emergency percutaneous coronary intervention (PCI) in our hospital. We retrospectively analyzed relevant clinical indicators such as N-terminal pro-B-type natriuretic peptide (NT-pro BNP) and noninvasive hemodynamic parameters in patients jointly treated with sacubitril/valsartan sodium tablets and dapagliflozin, and investigated the effects of this combined treatment approach in ameliorating cardiac dysfunction and left ventricular remodeling.

Methods

Patients

Between May 6, 2019 and May 31, 2021, 57 patients with type 2 DM who underwent PCI for AMI at the Emergency Department of the First Hospital of Zhengzhou University (Zhengzhou, China) were retrospectively analyzed. Thirty-two patients receiving sacubitril/valsartan and dapagliflozin were included in the observation group and 25 patients receiving ACEI or ARB, with other hypoglycemic drugs were included in the control group. The inclusion criteria were as follows: (1) meeting the diagnostic criteria of the "Guidelines for the Diagnosis and Treatment of Acute ST-segment Elevation Myocardial Infarction (2019)," issued by the Cardiovascular Society of the Chinese Medical Association; (2) availability of incomplete clinical data for patients in stable condition; (3) aged between 18 and 80 years; (4) time from myocardial infarction to PCI < 12 h; and (5) taking relevant regular and standard medications after surgery.

The exclusion criteria were as follows: (1) hemorrhagic disease and severe coagulopathy; (2) malignant neoplasms; (3) chest pain for >12 h; (4) cardiac arrest or cardiogenic shock; (5) history of PCI or coronary artery bypass grafting before surgery; (6) diagnosis with type 1 diabetes; or (7) taking other SGLT2i drugs, e.g., empagliflozin (Figure 1).

Therapeutic Regimen

Both groups were administered conventional treatments including dual antiplatelet aggregation, statins, β-blockers, nitrates, and other drugs. Within 24 h after admission, patients in the observation group were administered sacubitril/valsartan sodium tablets (100 mg, Beijing Novartis, National drug approval number: H201703444) at an initial dose of 25–50 mg twice per day, which was gradually increased to the maximum tolerated dose of 100–200 mg twice per day. To control blood glucose, dapagliflozin at 5 mg–10 mg/day was taken if tolerated by patients. In the control group, patients received oral ACEI or ARB (irbesartan, enalapril, or valsartan), which were gradually increased to the maximum tolerated dose, with other hypoglycemic drugs (metformin, acarbose, vildagliptin, and glybenzcyclamide). Dual antiplatelet aggregation treatment, which includes aspirin and ticagrelor or clopidogrel, was administered for 3–12 months according to the risk assessment of hemorrhage and ischemia in patients with coronary heart disease [11].

Laboratory Indicators

At admission, general data from both groups were collected, including sex, age, smoking history, body

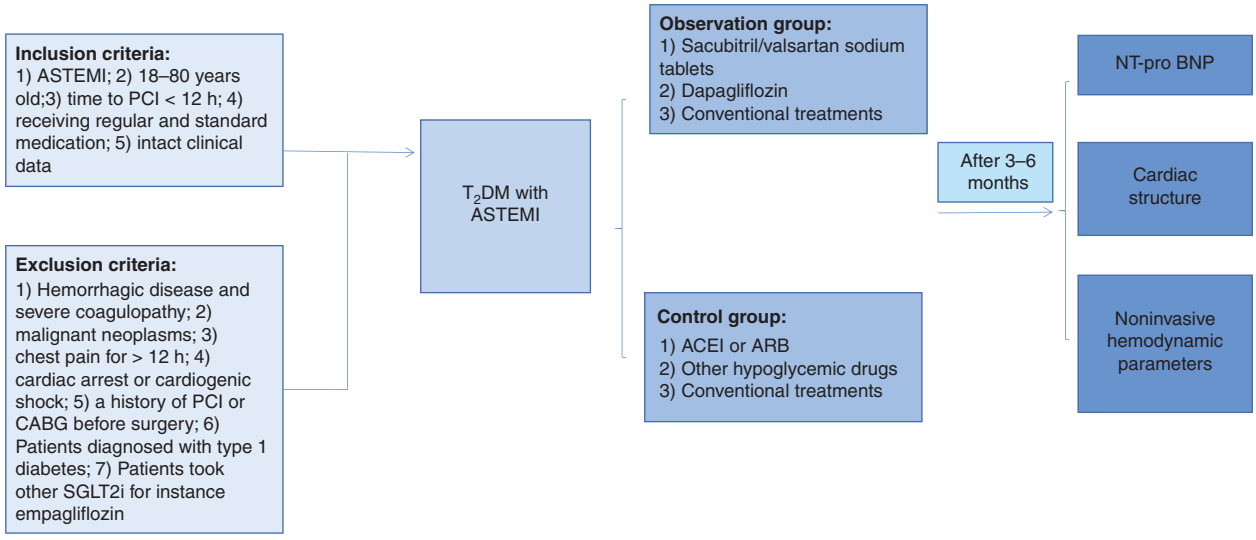

Figure 1 Flow Diagram of the Study.

mass index, hypertension, and DM. After admission, laboratory examination indicators (creatinine, troponin, NT-pro BNP, blood lipids, blood glucose, liver function, and kidney function), infarct-associated blood vessels, and time from STEMI onset to PCI were obtained. When discharged, the patients were instructed to take medication (dual antiplatelet aggregation, statins, β-blockers, nitrates, and other drugs) as directed. Their compliance was recorded. At 3–6 months after discharge, indicators such as NT-pro BNP, echocardiography findings (left ventricular end-systolic diameter, left ventricular end-diastolic diameter and ejection fraction (LVEF), and noninvasive hemodynamic parameters) were acquired and compared with the data at admission.

Statistical Analysis

All statistical analyses were performed in SPSS 27.0 software. First, the Kolmogorov-Smirnov test was used to examine the distribution of continuous variables. For normally distributed data, continuous variables are presented as mean ± standard deviation, and Student's t test was used to analyze the significance of differences. For non-normally distributed data, continuous variables are presented as the mean, and the Wilcoxon test was performed to analyze the significance of differences before and after treatment in both groups. Furthermore, generalized linear models were used to estimate the mean changes between measurements at baseline and re-evaluation with the 95% confidence interval, with the group as the study variable and baseline measurements as covariates. A P-value < 0.05 was considered to be statistically significant.

Results

Comparison of Baseline Data Between Groups

In total, 57 participants were included in our study: 25 in the control group and 32 in the observation group. The control group included 15 men (60%) with an average age of 56.40 ± 10.22 years, whereas the observation group included 21 men (65.62%) with an average age of 54.66 ± 10.09 years. In addition, 40% of patients in the control group and 43.75% of patients in the observation group had hypertension as a complication.

Other data including c-TNT, blood glucose, HbA1c, cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, blood urea nitrogen, and creatinine levels were analyzed between the groups. The results indicated no differences in the degree of myocardial injury, blood glucose levels, serum lipid levels, and renal function. Because all patients accepted PCI treatment for STEMI, surgery-associated indicators including the mean time from first medical contact to balloon expansion, infarct-associated vessels, postoperative thrombolysis in myocardial infarction flow,

and follow-up duration were collected and analyzed. The baseline data did not significantly differ between the groups ($P > 0.05$).

Before treatment, the serum NT-pro BNP levels in the observation group and control group were 669 (308.9–1408) pg/mL and 524 (123.57–1136) pg/mL, respectively. The left ventricular end diastolic diameter (LVEDD) in the observation group was 48 (46–56) mm, and that in the control group was 55 (46.5–57.5) mm. The LVEF was 59% (53%–62%) in the observation group and 51% (49%–60.5%) in the control group. The right ventricular end diastolic diameter (RVEDD) in the observation group and control group was 16 (15–17) mm and 16 (16–17) mm, respectively. No significant differences in the above variables were observed between the groups ($P > 0.05$).

Furthermore, the baseline CI and CO values in the observation group were 3.1 (2.55–3.68) L/min/m^2 and 6.05 (4.85–6.98) L/min, respectively, whereas those in the control group were 2.8 (2.45–3.65) L/min/m^2 and 5.2 (4.7–6.7) L/min, respectively. The TFC and SVRI values in the observation group were 34 (30–36) (1000 Ω) and 2786.4 (1812.63–4537.03) dyn·s/cm^5/m^2, respectively, whereas the values in the control group were 36 (31–38) (1000 Ω) and 2633.3 (1694.05–4203.45) dyn·s/cm^5/m^2, respectively. No significant differences were observed between groups ($P > 0.05$) (Table 1).

Table 1 Comparison of Clinical Baseline Data Between Two Groups of Patients.

Items	Observation (n = 32)	Control (n = 25)	P
Age (years)	54.66 ± 10.09	56.40 ± 10.22	0.522
Male (n, %)	21 (65.62%)	15 (60.00%)	0.622
Smoking (n, %)	11 (34.36%)	9 (36%)	0.898
Hypertension	14 (43.75%)	10 (40%)	0.776
CTNT (ng/mL)	0.948 ± 1.415	0.516 ± 1.012	0.204
HbA1c (%)	5.70 (5.60–6.73)	5.65 (5.40–6.58)	0.832
BS (mmol/L)	7.22 (5.89–9.71)	5.77 (5.27–7.08)	0.084
CHO (mmol/L)	4.16 ± 0.83	4.11 ± 0.87	0.826
TG (mmol/L)	1.07 (0.94–1.70)	1.78 (1.08–3.04)	0.012
HDL (mmol/L)	1.12 ± 0.28	0.98 ± 0.28	0.069
LDL (mmol/L)	2.51 ± 0.75	2.40 ± 0.69	0.571
BUN (mmol/L)	4.57 (4.03–5.59)	4.57 (3.67–5.64)	0.694
Cr (μmol/L)	63.50 (58.25–73.25)	68.00 (57.00–71.25)	0.658
NT-pro BNP (pg/mL)	669 (308.9–1408)	524 (123.57–1136)	0.254
LVEDD (mm)	48 (46–56)	55 (46.5–57.5)	0.287
RVEDD (mm)	16 (15–17)	16 (16–17)	0.886
LVEF (%)	59 (53–62)	51 (49–60.5)	0.123
CI (L/min/m^2)	3.1 (2.55–3.68)	2.8 (2.45–3.65)	0.330
CO (L/min)	6.05 (4.85–6.98)	5.2 (4.7–6.7)	0.416
TFC (1000 Ω)	34 (30–36)	36 (31–38)	0.182
SVRI (dyn·s/cm^5/m^2)	2786.4 (1812.63–4537.03)	2633.3 (1694.05–4203.45)	0.629
M to B (h)	9.00 (5.25–33.00)	9.00 (6.75–12.5)	0.897
Infarction-related			
LAD	13 (29.73%)	10 (40.91%)	0.962
LCX	8 (24.32%)	4 (22.73%)	0.312
RCA	11 (45.95%)	11 (36.36%)	0.459
Thrombolysis in myocardial infarction flow after PCI 3 grade	26 (83.78%)	20 (79.55%)	0.906
Follow-up time (m)	4.50 (3.00–5.00)	3.50 (3.00–5.00)	0.159

Comparison of NT-pro BNP and Cardiac Structure Between Groups After Treatment

After 3–6 months of treatment, lower NT-pro BNP levels were observed in patients in the observation group than the control group. The changes in NT-pro BNP in both the control and observation groups after treatment significantly differed from the baseline values ($P < 0.05$). Moreover, the improvement in the NT-pro BNP in the observation group was significantly greater than the change in the control group ($P < 0.05$, Figure 2). Similar results were observed for LVEF. Regarding the LVEDD, the variables in both groups after 3–6 months of treatment significantly improved with respect to baseline levels ($P < 0.05$). However, no significant difference was observed between groups ($P = 0.068$). Furthermore, the RVEDD was measured at admission and after treatment, but no statistical differences were observed either before or after treatment (Table 2).

Comparison of Noninvasive Hemodynamics Between the Groups After Treatment

Hemodynamic parameters were recorded with an impedance cardiogram (ICG). After 3–6 months of treatment, the CI and CO values in both groups markedly increased with respect to those before treatment ($P < 0.05$, Figure 3). Furthermore, the changes in the observation group were significantly greater than those in the control group ($P < 0.05$). Additionally, the TFC and SVRI values after treatment were significantly lower ($P < 0.05$) than those

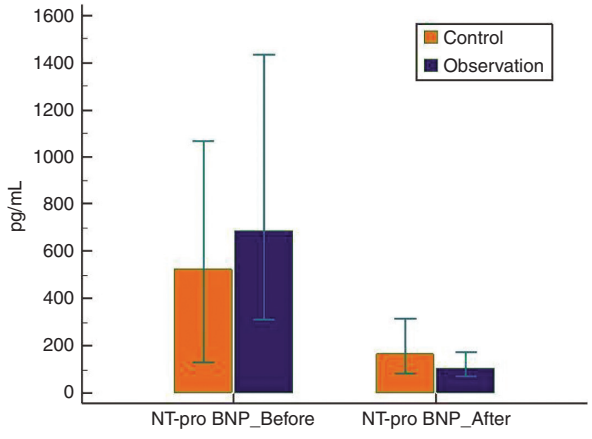

Figure 2 Comparison of NT-pro BNP Between Groups Before and After Treatment.

Table 2 Comparison of NT-pro BNP and Echocardiographic Indexes.

Items	After treatment		Reevaluation vs baseline in observation		Reevaluation vs baseline in control		Difference comparison between observation and control	
	Observation	Control	Difference	P^a	Difference	P^a	Difference	P^b
NT-pro BNP (pg/mL)	105 (72–177)	168 (86.63–327)	−521 (−1163 to −203.9)	<0.001	−216 (−720.5 to −24.12)	<0.001	−142.294 (−231.56 to −53.03)	0.002
LVEDD (mm)	44 (42–26)	55 (46.5–57.5)	−4 (−10 to −2)	<0.001	−6 (−10 to −1.5)	<0.001	−1.6 (−3.33 to 0.12)	0.068
RVEDD (mm)	16 (15–17)	16 (15–16)	−1 (−1 to 0)	0.202	0 (−1 to 0)	0.106	0.20 (−0.56 to 0.96)	0.608
LVEF (%)	58 (54.5–62)	62 (60–63)	2 (1–12)	<0.001	4 (0.5–7.5)	0.002	2.7 (0.6–4.8)	0.013

Abbreviations: NT-pro BNP: N-terminal pro-B-type natriuretic peptide, LVEDD: left ventricular end diastolic diameter, RVEDD: right ventricular end diastolic diameter, LVEF: left ventricular ejection fraction; P^a: Wilcoxon test; P^b: generalized linear model.

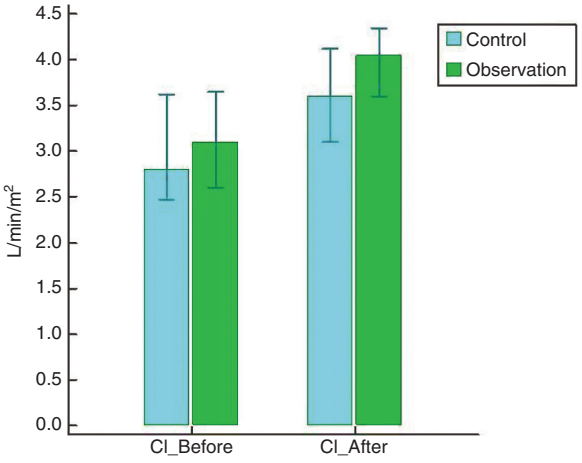

Figure 3 Comparison of CI Between Groups Before and After Treatment.

before treatment in the two groups, and the differences in the observation group were much smaller than those in the control group ($P < 0.05$) (Table 3).

Discussion

Our real-world experience suggested that alternative treatments to the conventional "golden triangle" regimen with sacubitril/valsartan sodium tablets and dapagliflozin significantly improved cardiac structure and function in patients with DM and STEMI.

Sacubitril/valsartan is a new dual-effect compound, which is composed of neprilysin inhibitors (NEPI, sacubitril) and ARB (valsartan) at a 1:1 molecular weight ratio, and exerts anti-HF activity. The compound performed better than enalapril in decreasing cardiovascular death and the hospitalization frequency of symptomatic patients with HF and low LVEF [12]. Sacubitril/valsartan is superior to ACEI or ARB in improving cardiac structure and function and reversing ventricular remodeling, because it not only decreases serum NT-pro BNP levels but also increases the LVEF [13]. Thus, the European Consensus of Current Heart Failure Experts recommend sacubitril/valsartan as an alternative to ACEI or ARB for the initial treatment of HF [14].

SGLT2i drugs (e.g., dapagliflozin) alleviate *in vivo* water-sodium retention by restraining sodium and glucose adsorption in proximal kidney tubules, thereby eliciting osmotic diuresis and antihypertensive effects. SGLT2i selectively removes fluid from

Table 3 Comparison of Noninvasive Hemodynamic Indexes.

Items	After treatment		Reevaluation vs baseline in observation		Reevaluation vs baseline in control		Difference comparison between observation and control	
	Observation	Control	Difference	P^a	Difference	P^a	Difference	P^b
CI (L/min/m²)	4.05 (3.6–4.38)	3.6 (3.1–4.15)	0.7 (0.5–1.4)	<0.001	0.5 (0.2–1.05)	<0.001	0.30 (0.02–0.58)	0.039
CO (L/min)	7.75 (6.2–8.78)	6.9 (6.0–7.8)	1.5 (0.73–2.88)	<0.001	0.9 (0.45–1.95)	<0.001	0.69 (0.04–1.34)	0.037
TFC (1000 Ω)	30 (28–32)	33 (30–36)	−3.5 (−5.75 to −2.0)	<0.001	−2.0 (−5.5 to 0.5)	0.031	−2.20 (−3.87 to −0.53)	0.010
SVRI (dyn·s/cm⁵/m²)	1376.6 (1072.35–1875.45)	1892.3 (1315.5–2398.8)	−1294.6 (−2447 to −514.53)	<0.001	−850.6 (−1886.4 to −137.35)	<0.001	−424.83 (−671.47 to −178.19)	0.001

Abbreviations: CI: cardiac index, CO: cardiac output, TFC: thoracic fluid conduction, SVRI: systemic vascular resistance index; P^a: Wilcoxon test; P^b: generalized linear model.

interstitial spaces while having minor effects on the blood volume, and it also increases organ perfusion [15]. Previous studies have indicated that in patients with type 2 diabetes mellitus, SGLT2i drugs decrease not only blood glucose levels, but also the risk of HF hospitalization and cardiovascular events [10, 16, 17]. However, whether SGLT2i drugs improve left ventricular remodeling and hemodynamics in patients with diabetes and STEMI is unclear.

NT-pro BNP is commonly used to assess myocardial injury, and its expression levels strongly correlate with the functional status of the heart. NT-pro BNP synthesis and release into the serum may be stimulated by both myocardial injury and ventricular remodeling in STEMI, and by an increased pressure burden and cardiac volume overload [18, 19]. We confirmed that, with continuous and combined sacubitril/valsartan and dapagliflozin administration, the NT-pro BNP levels were significantly lower than those after combination treatment with ACEI or ARB and other hypoglycemic drugs in patients with DM and AMI, thus suggesting mitigatory myocardial injury. Furthermore, after 3–6 months of treatment, the LVEF was significantly higher in the observation group than the control group. Interestingly, combined sacubitril/valsartan and dapagliflozin have been demonstrated to benefit left ventricular structure construction and avoid remodeling [20]. Of note, there was no significant difference in the LVEDD of the observation and control groups, possibly because of the inadequate anti-reconstruction time and the small sample size [21]. Notably, the RVEDD showed no differences between groups before or after treatment. This finding might be attributable to the smaller right ventricular diameter and the thinner right ventricular wall than left ventricle; hence the right ventricle, unlike the left ventricle, is not involved in ventricular remodeling. In addition, hemodynamic dysfunction, and even low cardiac output development (CI < 2.0 L/min/m^2), may precede the appearance of clinical symptoms in AMI [22, 23]. As a noninvasive technique, ICG enables rational and accurate measurement of hemodynamic parameters, and floating catheters can be used to optimize treatment regimens [24, 25]. Clinical studies have also confirmed the accuracy and reproducibility of ICG compared with the Swan-Ganz method [26]. In our study, we examined noninvasive hemodynamic parameters in patients with STEMI, and observed hemodynamic abnormalities in the early myocardial infarction phase. After 3–6 months of anti-remodeling therapy, ameliorative hemodynamic parameters, including higher CI and CO levels, lower TFC, and degressive SVRI, were recorded in patients receiving combined sacubitril/valsartan and dapagliflozin, compared with patients in the control group. According to our hemodynamic parameter data, the pumping ability of the heart was enhanced, and the cardiac volume load and pressure burden were dramatically diminished in the observation group, thus indicating that sacubitril/valsartan and dapagliflozin synergistically improved cardiac function in patients with diabetes and STEMI. Thus, in our patients, an angiotensin receptor-neprilysin inhibitor combined with an SGLT2i, as compared with combined ACEI or ARB and other hypoglycemic agents, was highly advantageous in alleviating HF, and ameliorating ventricular remodeling and hemodynamic dysfunction.

In terms of study limitations, this research involved a single-center retrospective analysis. Therefore, the findings might have been influenced by multiple factors, thus potentially biasing our results. Furthermore, the role of dapagliflozin alone in reversing myocardial remodeling could not be exactly demonstrated in the current experimental scheme. In the future, larger well-designed prospective clinical studies are required to confirm the improved anti-remodeling and improved hemodynamic effects of an angiotensin receptor-neprilysin inhibitor combined with SGLT2i, compared with ACEI or ARB and anti-diabetic drugs, for treatment of patients with DM and STMEI.

Ethic Statement

The study involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written or oral informed consent from all participants were obtained.

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Author Contributions

Concept: Z.W. and Z.L.; Design: Z.W., Y.H., P.W., and Z.Z.; Data curation: S.W., L.H., and Y.H.; Formal analysis: Z.W., Z.Z., and P.W.; Investigation: Z.W., Z.Z., and Y.H; Supervision: Z.L. and L.W.; Writing: Z.W., Z.L., and S.W.; Critical review: Z.L and L.W.

Conflicts of Interests

There are no conflicts of interests for all authors.

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