ORIGINAL RESEARCH

Effect of Dapagliflozin on Ventricular Remodeling and Prognosis in Patients with Coronary Atherosclerotic Heart Disease Undergoing Percutaneous Coronary Intervention

Lu Ye, BM; Kun Wang, BM; Hui Sheng, BM; Xiajun Shi, MM; Ling Yan, MM

ABSTRACT

Objective • Acute coronary syndrome (ACS) is a common cardiovascular complication in patients with type 2 diabetes mellitus (T2DM) and significantly increases the risk of disability and death in T2DM patients. Dapagliflozin inhibits blood glucose reabsorption, improves insulin resistance, and reduces the occurrence of long-term adverse cardiovascular events, indicating the importance of Dapagliflozin as a drug for type 2 diabetes patients and its close relationship with coronary atherosclerotic heart disease. At present, there are few studies on the effects of Dapagliflozin intervention on ventricular remodeling and myocardial microperfusion in patients with ACS combined with T2DM after PCI.

Methods • Between January 2019 and August 2023, a total of 35 patients diagnosed with Coronary atherosclerotic heart disease and T2DM were chosen as the observation group using a multi-stage cluster sampling method. Concurrently, 35 patients with similar age, height, weight, and healthy physical examination results were selected as the control group during the same time frame. We collected demographic data, symptoms and underlying diseases of the two groups Before enrollment and 6 months after discharge and compared the data between the two groups. Subsequently, multivariate logistic regression analysis was employed to identify indicators with statistically significant differences and to summarize the potential risk factors that could impact ventricular remodeling in patients with Coronary atherosclerotic heart disease and T2DM.

Results • There was significant difference in LDL-C between the two groups, and the difference was statistically significant ($P < .05$). After treatment, the levels of hs-CRP, FBG, HbA_{1c} and IL-6 in both groups were significantly decreased, and the decrease was more obvious in the observation group, with statistical significance ($P < .05$). These results indicated that Dapagliflozin intervention could significantly inhibit postoperative inflammation in patients with ACS combined with T2DM after PCI. LVMI of Observation group patients was significantly higher than Comparison group, LVEDD and ESVI of Observation group patients were significantly lower than Comparison group. The difference was statistically significant ($P < .05$). These results indicated that Dapagliflozin intervention could significantly inhibit the improvement of blood glucose index, ventricular remodeling and myocardial microperfusion in patients with ACS combined with T2DM after PCI. After treatment, TIMI Flow Count Frame Count (CTFC) level and Myocardial Perfusion (TMPG) level in the observation group were significantly lower than those in the comparison group, and the difference was statistically significant ($P < .05$). These results indicated that Dapagliflozin intervention could significantly inhibit ventricular remodeling and improve myocardial microperfusion in patients with ACS combined with T2DM after PCI.

Conclusion • Dapagliflozin intervention can significantly inhibit inflammatory indexes in patients with Coronary atherosclerotic heart disease combined with T2DM after PCI, promote the improvement of blood glucose indexes, ventricular remodeling and myocardial microperfusion, and reduce the risk of occurrence. (*Altern Ther Health Med.* 2024;30(4):204-208)

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INTRODUCTION

Coronary atherosclerotic heart disease is mainly caused by rupture of atherosclerotic plaque, exposure of subcutaneous collagen and lipid-rich core, and subsequent thrombosis.[1] Platelet-rich thrombus mainly forms in human coronary arteries.[2] In Coronary atherosclerotic heart disease, the rupture or surface ulceration of unstable atherosclerotic plaques exposes the subcutaneous matrix and binds to the receptor on the surface of platelets, thereby activating platelets, and the activated platelets act as initiating factors to form white thrombus through adhesion, aggregation and release.[3] In the clinical setting, patients with combined Coronary atherosclerotic heart disease and Type 2 Diabetes Mellitus often undergo Percutaneous Coronary Intervention (PCI) in conjunction with the administration of Dapagliflozin, a medication used for the treatment of these conditions. However, it should be noted that conventional hypoglycemic drugs primarily focus on reducing blood sugar levels and

have limited efficacy in enhancing cardiac function among these patients.[4]

We reviewed the relevant literature and found that Dapagliflozin mainly achieved hypoglycemic effects by inhibiting blood glucose reabsorption, improving insulin resistance (IR), and promoting the increase of glucagon level, indicating the importance of Dapagliflozin as a drug for patients with type 2 diabetes.[5] Dapagliflozin can regulate cardiomyocyte energy metabolism and inhibit collagen synthesis, thereby alleviating cardiac fibrosis.[6] Dapagliflozin has a more important role in protecting the heart and reducing the occurrence of long-term adverse cardiovascular events, indicating a close relationship with coronary atherosclerotic heart disease.[7] Studies have found that Dapagliflozin can also promote the improvement of cardiac function in patients by inhibiting Ca2+ overload of cardiomyocytes.[8] At present, there are few studies on the effect of Dapagliflozin intervention on ventricular remodeling and myocardial microperfusion in ACS patients with T2DM after PCI.[9] This study aims to solve this research gap.[9]

Patients with ACS combined with T2DM have both hypoglycemic and myocardial microperfusion problems, while Dapagliflozin can reduce blood glucose, improve ventricular remodeling, improve myocardial microperfusion, and reduce the risk of cardiovascular diseases. So, we hypothesized that Dapagliflozin could inhibit markers of inflammation in patients. Improve ventricular remodeling and myocardial microperfusion, and reduce the risk of cardiovascular disease.Therefore, we investigated the effects of Dapagliflozin on ventricular remodeling and prognosis in patients with Coronary atherosclerotic heart disease combined with T2DM after PCI, providing a basis for formulating prevention and treatment strategies for Coronary atherosclerotic heart disease combined with T2DM.

PATIENTS AND METHODS

Research object

According to the epidemiological and demographic characteristics, the formula was calculated according to the sample size (n = 0.25 Z 2/d.[10] Z is the confidence interval (0.3-0.7), n is the sample size, and d is the sampling error range (0.2-0.8). Estimate the sample size we selected and increase the estimated sample size by 30% to account for the possibility of no response. We used multi-stage cluster sampling from January 2019 to June 2023 to obtain 35 patients with Coronary atherosclerotic heart disease combined with T2DM as the observation group. During the same period, 35 patients with matched age, height and weight and healthy physical examination were selected as the Comparison group.

PCI indication standards

PCI indications[11]: Patients have hemodynamic Dapagliflozintability or cardiogenic shock, patients have intractable angina, and patients have malignant arrhythmia or cardiac arrest. The patient developed myocardial infarction with mechanical complications and acute heart failure with refractory angina pectoris and ST segment changes. Patients with recurrent ECG ST-T dynamic evolution, especially patients with intermittent ST segment pickup. Patients showed elevated troponin and dynamic ST-T changes. STEMI symptoms appeared <12h. Severe heart failure or cardiogenic shock. Thrombolysis is contraindicated and ischemic symptoms <12h. Clinical and/or electrocardiogram evidence of persistent ischemia 12 to 24h after the appearance of the disc. High-risk patients whose symptoms resolve within 12-24 hours. Direct PCI was performed on non-infarct-associated vessels under hemodynamic stability.

Inclusion criteria

Patients have low activity tolerance with recurrent episodes of angina pectoris or myocardial ischemia or with adequate medication. The patient had elevated blood myocardial enzymes and new ST segment depression. Patients developed heart failure or mitral regurgitation or deterioration of the original regurgitation and hemodynamic Dapagliflozintability. Patients had persistent supraventricular tachycardia or had received interventional therapy within 6 months.

Exclusion Criteria

The patient had unmanageable, severe hypertension (SBP > 180 mmHg),a history of stroke or active intracranial disease, and a history of cerebrovascular disease within one year. The patient had a history of trauma or prolonged (>10 min) cardiopulmonary resuscitation within 2 weeks.

Methods

Patients in the comparison group who met the trial's inclusion and exclusion criteria were given conventional medication: dual antiplatelet aggregation (Bay Aspirin enteric-coated tablets 100mg1/day and clopidogrel (Polivir) 75mg1/day. Low molecular heparin anticoagulation, statin lipid-lowering, nitrate coronary expansion, β-blockers to reduce myocardial oxygen consumption, ACEI/ARB/ARNI drugs to inhibit ventricular remodeling, as appropriate, diuretics are given as appropriate, and positive inotropes such as digitalis are prohibited. The observation group was given Dapagliflozin (AstraZeneca Pharmaceuticals Co. Ltd. National Pharmaceutical License J20170040),10mg 1/day on the basis of the appeal routine treatment.

Statistical analysis

All the data of middle-aged women included in our study were established in a database using EpiData 3.02, and double-entry real-time verification was carried out. SPSS 26.0 statistical software was used, and the counting data were expressed as integers or percentages. The χ^2 test was used for comparison between groups of categorical variables, and the rank sum test was used for ordered variables. The measurement data were represented by mean ± standard deviation, and *t* test was applied when the patient's age, BMI, SDS total score and LES score were normally distributed. $P < .05$ was considered statistically significant.

Table 1. Comparison of clinical data between the two groups ($\bar{x} \pm s$, n)

project	Observation group (n = 35)	Comparison group (n = 35)	t/χ^2	*P* value
Age (years)	54.53±2.72	54.49±2.29	0.080	.937
Gender (Male/female)	33/17	32/18	0.044	.834
Infarct site (n)			0.675	.879
forearm	21	22		
underwall	16	15		
High sidewall	6	8		
Extensive anterior wall	7	5		
History of hypertension (n)	45	46	0.122	.727
Diabetes history (n)	21	22	0.041	.840
Systolic pressure (mmHg)	136.69±10.74	135.66±11.51	0.468	.641
Heart rate (times /min)	74.11±4.70	75.56±5.54	1.411	.161
Creatinine (μmol/L)	75.57±10.75	78.21±9.73	1.287	.201
LDL-C (mmol/L)	2.53±0.42	2.33±0.45	2.297	.024
CTnT (ng/ml)	4.23±1.70	4.24±1.90	0.028	.978

RESULTS

Comparison of clinical data

There were no significant differences in age, BMI, gender, infarct site, history of hypertension, history of diabetes, systolic blood pressure, heart rate, creatinine,CTnT and other general data between the two groups ($P > .05$). There was a significant difference in LDL-C between the two groups, and the difference was statistically significant ($P < .05$). See Table 1**.**

Comparison of clinically relevant indicators

Before treatment, there was no statistically significant difference in clinically relevant indicators between the two groups, $P < .05$. After treatment, the BMI of patients in the comparison group increased significantly, the BMI of patients in the Observation group decreased significantly, and the BMI of patients in the Observation group was significantly lower than that in the comparison group. After treatment, the levels of hs-CRP, FBG and HbA_{1c} were significantly decreased in both groups, and the decrease was more significant in the Observation group ($P < .05$). See Figure 1.

Comparison of ventricular remodeling indexes

The Comparison of ventricular remodeling indexes between the two groups showed that before treatment, there was no statistically significant difference between the Observation group and the Comparison group in ventricular remodeling indexes $P = .012$. After treatment,LV of the Observation group patients was significantly higher than the Comparison group,EF and FS of the Observation group patients were significantly lower than the Comparison group. The difference was statistically significant ($P = .029$). See Figure 2**.**

Comparison of myocardial microperfusion indexes

Before treatment, there was no significant difference in myocardial microperfusion indexes between the two groups ($P = .017$). After treatment, CTFC level and TMPG levels in the Observation group were significantly lower than those in the comparison group, and the difference was statistically significant ($P = .021$). See Figure 3**.**

Figure 1. Comparison of clinically relevant indicators: Measurement data were represented by mean ± standard deviation, and independent sample *t* test was used when clinically relevant indicators of patients followed normal distribution. Before treatment, there was no statistically significant difference in clinical relevant indicators between the two groups ***$P < .05$, after treatment, the BMI of patients in the comparison group increased significantly, the BMI of patients in the Observation group decreased significantly,and the BMI of patients in the Observation group was significantly lower than that in the comparison group. After treatment, the levels of hs-CRP,FBG and HbA_{1c} were decreased significantly in both groups,and the decrease was more obvious in Observation group, with statistical significance ***$P < .05$.

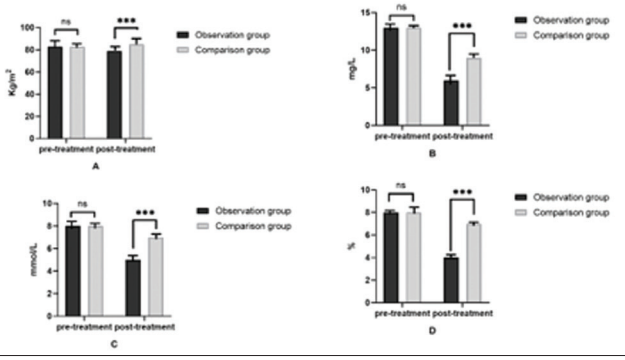
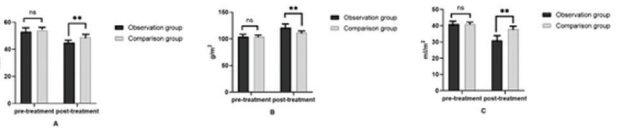


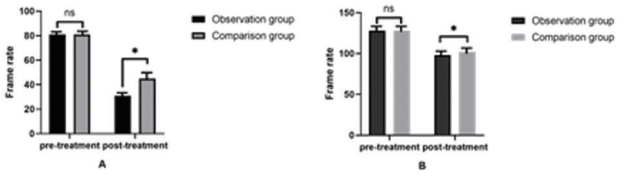
Figure 2. Comparison of ventricular remodeling indexes:(A) The vertical coordinate represents EF level,and the horizontal coordinate represents pre-treatment and post-treatment,and this statistical graph reveals that after treatment,The EF level of Observation group patients was significantly lower than that of Comparison group,and the difference was statistically significant **$P < .05$. (B) The vertical coordinate represents LV level,and the horizontal coordinate represents pre-treatment and post-treatment. This statistical chart reveals that after treatment, LV level of Observation group patients was significantly higher than that of Comparison group,and the difference was statistically significant **$P < .05$. (C) The vertical coordinate represents FS level,and the horizontal coordinate represents pre-treatment and post-treatment.This statistical chart reveals that after treatment,the FS level of Observation group patients is significantly lower than that of Comparison group.The difference was statistically significant **$P < .05$.



DISCUSSION

T2DM is a high incidence disease in Chinese residents, with an incidence of about 11.6%.[12] Currently, it is believed that long-term hyperglycemia in T2DM patients can enhance vascular endothelial damage and promote platelet activation,

Figure 3 . Comparison of myocardial microperfusion indexes:(A) The vertical coordinate represents the Frame rate of CTFC level, and the horizontal coordinate represents pre-treatment and post-treatment.This statistical graph reveals that after treatment, The CTFC level of the Observation group was significantly lower than that of the comparison group, and the difference was statistically significant *$P < .05$. (B) The vertical coordinate represents the Frame rate of TMPG level, and the horizontal coordinate represents pre-treatment and post-treatment. This statistical chart reveals that after treatment, The TMPG level of the Observation group was significantly lower than that of the comparison group, and the difference was statistically significant *$P < .05$.



making the risk of ACS higher than that of non-T2DM patients.[13] Dapagliflozin is often used for hypoglycemic treatment in ACS patients with T2DM after PCI, but it is very easy to cause hypoglycemia and can promote the increase of patients' BMI, but the effect is limited.[14] Currently, it is believed that SGLT2 is the main carrier of glucose reabsorption and plays an important role in blood glucose regulation.[15] Dapagliflozin belongs to SGLT2 inhibitor, which can significantly reduce blood glucose level and improve liver sensitivity to Dapagliflozin, while not increasing the risk of hypoglycemia, with good safety.[16] By clarifying the effects of Dapagliflozin intervention on ventricular remodeling and myocardial microperfusion after PCI, relevant evidence can be provided for the treatment of ACS patients with T2DM.[17]

Our study found that after treatment, the levels of hs-CRP, FBG, HbA_{lc} and IL-6 of patients in the two groups were significantly decreased, and the decrease was more obvious in the observation group, and the comparison difference was statistically significant. This may be due to the fact that Dapagliflozin can enhance urinary glucose excretion and promote body fat consumption, thereby contributing to weight reduction and further improvement of FBG and HbAlc in patients. The study found that Dapagliflozin in the treatment of ACS patients with T2DM can effectively promote the weight loss of patients with good safety. The treatment of Dapagliflozin in ACS patients with T2DM may be carried out by inhibiting the levels of hs-CRP, FBG, HbA_{lc}, IL-6 and other inflammatory factors, but the specific mechanism still needs to be further studied. Dapagliflozin can significantly reduce Na+ inflow and Ca^{2}+ overload during myocardial ischemia, and promote the improvement of patients' cardiac function.[27] In addition, Dapagliflozin can also reduce the oxidative stress response of the body through Nfr2/ARE and other pathways, thus preventing myocardial fibrosis and ventricular hypertrophy, improving myocardial diastolic function, promoting myocardial remodeling and improving myocardial microperfusion.[28] The increase of blood lipid level can promote abnormal glucose and lipid metabolism in the body, strengthen vascular endothelial damage, and promote the formation of intravascular microthrombi.[29] Uric acid can promote the expression of inflammatory factors by enhancing the body's oxidative stress response.[30] Dapagliflozin can promote urinary sugar excretion, enhance the body's decomposition of fat, reduce blood uric acid level, and then reduce inflammation and oxidative stress response, thus achieving the effect of inhibiting microvascular disease and enhancing plaque stability.[31] Currently, it is believed that Dapagliflozin can significantly improve the levels of triacylglycerol and blood uric acid in the body, promote the increase of high-density lipoprotein levels, and thus achieve the effect of improving the body's glucose and lipid metabolism.[32] The study found that Dapagliflozin significantly improved cardiovascular outcomes in patients with angina and T2DM without increasing the risk of complications such as reproductive system infection. Other studies have also found that Dapagliflozin can significantly improve macrophage infiltration, inhibit the expression of inflammation-related genes, and reduce the degree of arteriosclerosis in type 1 diabetic mice.[33]

Our study found that LVMI of Observation group patients was significantly higher than Comparison group, and LVEDD and ESVI of Observation group patients were significantly lower than Comparison group. CTFC and TMPG levels in the observation group were significantly lower than those in the control group, and the difference was statistically significant. These results indicated that Dapagliflozin intervention could significantly inhibit inflammatory indexes in patients with ACS combined with T2DM after PCI, promote the improvement of blood glucose indexes, ventricular remodeling and myocardial microperfusion, and reduce the risk of occurrence. The reasons are as follows: The therapeutic indication of Dapagliflozin has changed, and it is not only a hypoglycemic drug, but also suitable for the treatment of heart failure.[18] According to the results of animal experiments and large-scale clinical trials, the currently known protective mechanisms of Dapagliflozin on patients with heart failure may include: osmotic diuresis, moderate blood pressure reduction, weight loss, reduction of cardiac load before and after, and inhibition of ventricular remodeling.[19] Dapagliflozin can promote myocardial energy metabolism, and the patient has difficulties in glucose uptake. After 5 weeks of diabetes treatment with DAPagliflozin, significant changes in metabolism were found, including increased fat oxidation, improved 24-hour energy metabolism, and increased insulin sensitivity of liver and fat.[20] By inhibiting Na+-H+ exchange protein, it can eventually increase the mitochondrial Cat, and inhibit myocardial fibrosis and apoptosis of cardiomyocytes. It has also been found in pig model experiments that it can inhibit inflammation by inhibiting adrenal medulla hormone.[21] After heart failure, the heart will activate self-protection mechanisms, including the activation of the

natriuretic peptide system.[22] Among them, NT-ProBNP is a commonly used index to predict the severity of HF in clinical practice. It is a series of 76 amino acid fragments that have lost biological activity and are formed by the cleavage of BNP by the neutral peptide chain enzyme, and are mainly cleared by the kidney.[23] Recently, Dapagliflozin was found to improve cardiac structure and function and inhibit inflammatory cytokines and cardiomyocyte apoptosis in a simulated non-diabetic mouse myocardial infarction model.[24] So far, there are few clinical data on the effects of Dapagliflozin on patients with myocardial infarction.[25] Dapagliflozin has a better therapeutic effect. Multiple experimental studies have found that the decrease of NT-ProBNP may be related to the inhibition of VR by Dapagliflozin.[26] The results of the above literature study are consistent with our research results.

There are some limitations to our study. The sample size we included was limited and there may be some bias. The duration of our study is relatively short, and it cannot be comprehensively evaluated over a long period of time. These limitations affect the generality of the results. In summary, Dapagliflozin intervention can significantly inhibit postoperative inflammatory indicators in patients with ACS combined with T2DM after PCI, promote the improvement of blood glucose indicators, ventricular remodeling and myocardial microperfusion, and reduce the risk of occurrence. Prospective studies with large samples and long-term follow-up should be increased in the future.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of Tongling People's Hospital of Anhui Province.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

LYe and LYan designed the study and performed the experiments, KW and HS collected the data, KW and XS analyzed the data, LYe and LYan prepared the manuscript.All authors read and approved the final manuscript.

FUNDING

This work was supported by the Ningbo Medical and Health Brand Discipline (No.PPXK2018-02).

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