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Clinical Efficacy of Dapagliflozin in Patients wth Type 2 Diabetes and Heart Failure with Reduced Ejection Fraction Associated with Coronary Artery Disease

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Abstract

Objective To study the clinical efficacy of Dapagliflozin in patients with coronary heart disease (CHD) combined with Heart Failure with Reduced Ejection Fraction (HFrEF) and type 2 diabetes mellitus (T2DM). **Methods** A retrospective analysis of 202 patients with CHD and T2DM who were hospitalized in our department of cardiovascular medicine and/or underwent PCI treatment from November 2019 to November 2022 was conducted. Patients were divided into two groups according to whether they received Dapagliflozin treatment: the Dapagliflozin group (n=100) and the control group (n=102). A subgroup analysis was performed on the 80 HFrEF patients in the total population, which was also divided into two groups: the Dapagliflozin group (n=44) and the control group (n=36). The incidence of major adverse cardiovascular events (MACE) during hospitalization and the median follow-up period (224.5 days) was recorded and analyzed in both the total population and the subgroup. **Results**The results of the analysis of the total patient population showed no statistical differences between the two groups in baseline data and related clinical treatment conditions (P>0.05). The follow-up period events analysis showed that the overall MACE event rate in the Dapagliflozin group was lower than that in the control group (6.00% vs. 17.65%), but not statistically significant (P=0.071). The COX regression analysis of MACE events showed that the use of Dapagliflozin was an independent protective factor for MACE events [HR=0.166, 95% CI (0.026-0.953), P=0.047]. In the HFrEF subgroup analysis, there was no significant difference between the two groups in the baseline data analysis (P>0.05). The COX regression analysis in the subgroup analysis showed that the use of Dapagliflozin was a strong protective factor for the HFrEF subgroup during the follow-up period [HR=0.250, 95% CI (0.017-0.518), P<0.001]. Further analysis using the Kaplan-Meier method showed that the event rate in the Dapagliflozin group was significantly lower than that in the control group. **Conclusion** The use of Dapagliflozin in patients with CHD combined with HFrEF and T2DM may be effective in reducing the incidence of MACE.

Keywords: Dapagliflozin; Coronary Heart Disease; Type 2 Diabetes; Heart Failure with Reduced Ejection Fraction.

As the aging trend of the population in our country becomes increasingly serious, the incidence and mortality rates of chronic diseases such as coronary heart disease, hypertension, and type 2 diabetes mellitus (T2DM) are also increasing year by year, and it is well known that diabetes and coronary heart disease have clinical correlations [1]. Compared to non-diabetic patients, diabetic patients have an increased risk of developing coronary artery disease, and diabetes is also an important risk factor for poor outcome in coronary heart disease [2]. Therefore, for patients with both diabetes and coronary heart disease, clinical medical workers need to take more active and effective intervention measures to reduce the clinical risk of patients. Although subcutaneous insulin injections and oral metformin are currently the main treatment drugs for most T2DM patients in clinical practice, when T2DM is combined with cardiovascular risk, it is urgent to use antidiabetic drugs that also have cardiovascular protection advantages for treatment.

Represented by dapagliflozin, sodium glucose co-transporter 2 (SGLT2) inhibitors is a new type of oral antidiabetic drug that reduces glucose levels by a mechanism independent of insulin. They can reduce glucose reabsorption in the renal proximal tubules and increase glucose excretion in urine, thereby reducing blood glucose.

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They not only do not cause the low blood glucose risk commonly seen with traditional antidiabetic drugs, but also many studies have confirmed that dapagliflozin can provide cardiovascular benefits beyond glycemic control in patients with T2DM and cardiovascular disease [3-5]. In addition, many studies have also observed that using SGLT2 inhibitors in T2DM patients can lead to additional benefits of blood pressure and weight reduction, which exceed the clinical benefits of simple glycemic control [6-8]. The DAPA-HF study has confirmed that for heart failure with reduced ejection fraction (HFrEF), dapagliflozin has additional benefits for reducing cardiovascular morbidity and mortality compared to placebo, which are beyond the benefits of glucose control alone [9-10].

However, for patients with confirmed diagnosis of coronary artery disease who are concomitantly diagnosed with T2DM, it is currently unknown whether Dapagliflozin is still capable of improving the clinical outcomes of these patients, and whether patients with HFrEF may have additional benefits. Due to these uncertainties, we designed this retrospective study aimed at exploring the clinical efficacy of Dapagliflozin in patients with concurrent coronary artery disease and T2DM with HFrEF.

Methods

1. Study population

A retrospective analysis was conducted on 202 patients with concurrent coronary artery disease and type 2 diabetes (T2DM) who were diagnosed through clinical presentation, electrocardiogram (ECG), and coronary angiography or coronary computed tomography angiography (CTA) between November 2019 and November 2022 at Anqing Municipal Hospital's cardiovascular department. All patients received standard treatment for coronary artery disease or post-PCI, and were guided by endocrine specialists in standardized T2DM treatment. The decision on whether to use dapagliflozin as second-line treatment for T2DM to control blood glucose was made by the cardiovascular physician and endocrine physician in collaboration. All eligible patients were divided into two groups based on T2DM treatment: the Dapagliflozin group (n=100) and the control group receiving conventional T2DM treatment (n=102). In the HFrEF subgroup analysis, 80 patients with EF<40% were included based on echocardiography results, these patients were then divided into two groups based on whether they received dapagliflozin treatment: the Dapagliflozin group (n=44) and the control group receiving conventional T2DM treatment (n=36).

2. Clinical Data Collection

The eligible study subjects will be recruited. General patient information (age, gender, personal history, etc.) and medical history will be recorded. Laboratory examination data during hospitalization will be recorded, including blood cell analysis, cardiac enzyme spectra, N-terminal B-type natriuretic peptide (NT-pro BNP), liver and kidney function, etc. Clinical drug use information will be recorded, including use of statins, calcium channel blockers, beta receptor blockers, diuretics, and angiotensin receptor-neprilysin inhibitors (ARNIs) among others.

3. Coronary Angiography(CAG) and Percutaneous Coronary Intervention(PCI)

The procedure is performed via the radial or femoral artery, with multiple positional and angulated projections to fully visualize the disease vessel. According to the number of diseased coronary vessels with stenosis≥50%, it is classified into single or multiple vessel disease. The type and degree of calcification of the lesions are observed. When necessary, PCI is performed, and the specific method and medication used during the operations are determined by the surgeon.

4. Evaluation Indicators

The endpoint of this study is the incidence of re hospitalization during follow-up, all-cause mortality, and MACE events (cardiac death, non-fatal myocardial infarction, heart failure exacerbation, anginal episode requiring revascularization, and in stent thrombosis or rest enosis for patients undergoing PCI).

5. Statistical Analysis

All statistical analyses in this study will be performed using SPSS 26.0 software. Normally distributed continuous data will be presented as mean ± standard deviation and will be compared between groups using analysis of variance (ANOVA). Non-normally distributed continuous data will be presented as median (inter quartile range) and will be compared between groups using the Wilcox on rank-sum test. Count data will be presented as number and percentage and will be compared between groups using Pearson's chi-square test or Fisher's exact test.

Independent risk factors for endpoint events during follow-up will be analyzed using Cox regression. The overall event rate during follow-up in the two groups will be analyzed using the Kaplan-Meier method. The cut-off for entry and removal of variables in the multivariate analysis is 0.1 and 0.05, respectively. A two-tailed P value of less than 0.05 is considered statistically significant.

Results

1. Comparison of Clinical Baseline Data between Two Groups

There were no statistical differences between the two groups in terms of age, gender composition, and comorbidities (P > 0.05). After admission, there were also no significant differences between the two groups in terms of myocardial enzyme spectra, NT-pro BNP, liver and kidney function, and other laboratory test results (P > 0.05). In terms of medication usage, the proportion of ARNI use was higher in the Dapagliflozin group than in the control group (26.00% vs. 11.76%), and the proportion of diuretic use was also higher in the Dapagliflozin group than in the control group (26.00% vs. 13.73%), although both comparisons indicated significant differences (P > 0.05), suggesting that patients treated with dapagliflozin may have more severe sodium retention. There were no statistically significant differences between the two groups in terms of other medications, including mineral corticoid receptor antagonists, β receptor blockers, etc. (P > 0.05) .Table 1

2. Comparison of Follow-Up Conditions of Two Groups

All patients completed 180-day follow-up (median follow-up time is 224.5 days) and clinical events were classified and counted. During the follow-up period, 4 cases (3.92%) in the control group experienced cardiac death, while no death cases occurred in the Dapagliflozin group. There was no statistically significant difference between two groups (P=0.495). The incidence of recurrent heart failure in the control group was higher than that in the Dapagliflozin group (4.00% vs. 9.8%, P=0.436), and the incidence of re-myocardial infarction was also higher than that in the latter one(1.96% vs. 0, P=1.000), but both of them showed no statistically significant. Both groups had one case receiving revascularization therapy, and there was no significant difference between the two groups (2.00% vs. 1.96%, P=1.000). Integrating all event situations during the follow-up period, the overall MACE event rate in the Dapagliflozin group was lower than that in the control group (6.00% vs. 17.65%, P=0.071), but has no statistically significant.Table 2

3. COX regression

A COX regression analysis was conducted on the time parameters of related factors including the use of dapagliflozin, gender, diagnosis of ACS, presence of multi-vessel disease, use of ACEI/ARB and ARNI in drug treatment, and history of hypertension and the establishment of HFrEF diagnosis. The results showed that the use of dapagliflozin was a protective factor for MACE events [HR=0.166, 95%CI (0.026-0.953), P=0.047], while other factors did not showed protective or harmful significance to the overall event (P>0.05). Table 3

4. Comparison of Clinical Baseline Data in HFrEF Subgroup Analysis.

In the baseline data analysis of HFrEF subgroup, there was no statistically significant difference between the two groups of patients in terms of age, gender composition, prior comorbidities, related laboratory tests and clinical medication after admission (P > 0.05). At the same time, there was no significant difference in the number of concomitant vascular lesions and implanted stents between the two groups (P > 0.05). Table 4

5. COX regression in HFrEF Subgroup.

The COX regression analysis was conducted on the combined time parameters of relevant factors including the use of dapagliflozin, gender, diagnosis of ACS, multiple vessel lesions, use of ACEI/ARB and ARNI in drug treatment, and prior history of hypertension in the HFrEF subgroup. The results showed that the use of dapagliflozin was a protective factor for MACE events [HR=0.250, 95%CI (0.017-0.518), P < 0.001], while other factors were not associated with event occurrence (P > 0.05). Table 5

6. Survival analysis during follow-up in HFrEF Subgroup.

The occurrence of MACE events during the 180-day follow-up period was analyzed using the Kaplan-Meier method and compared between the two groups. The event rate in the Dapagliflozin group was significantly lower compared to the control group [HR=0.131, 95%CI (0.031-0.820), log-rank P=0.028]. Figure 1

Discussion

As a therapeutic agent that has been highly innovative in the treatment of diabetes in recent years, the SGLT2 inhibitor dapagliflozin has gained much attention since its introduction. As early as 2010, the Lancet journal revealed that combining dapagliflozin with metformin effectively reduced hemoglobin.

A1c levels did not increase the risk of hypoglycemia in patients with poor glycemic control on monotherapy with metformin [11]. Subsequent research has shown that dapagliflozin provides additional benefits to patients with T2DM and cardiovascular disease [8, 12]. The DECLARE-TIMI 58 study analyzed 17,160 patients with a median follow-up of 4.2 years and showed that dapagliflozin significantly reduced the composite endpoint of heart failure

hospitalization or cardiovascular death by 17% compared to placebo [4.9% vs. 5.8%; HR=0.83, 95% CI (0.73-0.95), P=0.005]. The decline in heart failure hospitalization or cardiovascular death was also sustained in the overall patient population. Dapagliflozin also demonstrated a reduction in major adverse cardiovascular events (MACE), but no statistically significant difference was observed in this study [dapagliflozin 8.8% vs. placebo 9.4%; HR=0.93, 95% CI (0.84-1.03), P=0.17][3].

This study included a total of 202 patients with T2DM and coronary heart disease, and the results of the full cohort analysis showed that the use of dapagliflozin did not demonstrate statistical differences in baseline data, medication, laboratory tests, etc. Although the overall MACE events during the follow-up period did not show statistical significance (P=0.071), the occurrence rate of MACE events in the Dapagliflozin group was already demonstrated to be lower than that in the control group (6.00% vs 17.65%). The results of the multivariate Cox regression analysis showed that the use of dapagliflozin was an independent protective factor for MACE events [HR=0.166, 95%CI (0.026-0.953), P=0.047]. This conclusion is similar to the results of many other studies, including the DECLARE-TIMI 58 study. Although simple correlation analysis did not show the contribution of dapagliflozin to reducing MACE events, after adding a time variable in the Cox regression analysis, dapagliflozin was found to be an independent protective factor for MACE events.

In subsequent HFrEF subgroup analysis, we also conducted a Cox regression analysis of multiple risk factors, and the results showed that the use of dapagliflozin was a protective factor for long-term (180 days) MACE events in HFrEF patients with concomitant T2DM [HR=0.250, 95% CI (0.017-0.518), P<0.001]. Subsequently, the Kaplan-Meier method also showed a significant clinical benefit of dapagliflozin in these patients [HR=0.131, 95% CI (0.031-0.820), log-rank P=0.028]. The DAPA-HF study published in NEJM in 2020 aimed to evaluate the clinical trial efficacy of dapagliflozin for HFrEF patients. The results showed that compared to the heart failure standard treatment group, adding dapagliflozin to heart failure standard treatment could reduce the relative risk ratio of the primary endpoint by 26% [HR=0.74, 95% CI (0.65-0.85), P=0.00001]. The risk of cardiovascular death was significantly reduced by 18% [HR=0.82, 95% CI (0.69-0.98), P=0.03], and the proportion of risk reduction in heart failure deterioration was also 30% [HR=0.70, 95% CI (0.59-0.83), P<0.001]. Bergg et al. found in a study of dapagliflozin treatment for HFrEF that included 4744 samples showed that dapagliflozin could significantly reduce short-term (within 28 days) clinical endpoint events [HR=0.51, 95% CI (0.28-0.94), P=0.03], and with longer follow-up time, dapagliflozin demonstrated a greater advantage compared to the control group [13]. Similar to these study results, our study results also showed the superiority of dapagliflozin in the HFrEF patient population. However, unlike previous studies, the population included in our study was more severe (patients with T2DM who have confirmed coronary heart disease). Heerspink et al. believed that the unique mechanism of SGLT2 inhibitors increasing glucose excretion makes SGLT2 inhibitors also a therapeutic option for heart failure patients[7]. The DAPA-HF study further confirmed this finding, providing a new treatment option for HFrEF patients.

Conclusion

Our study results show that dapagliflozin is a protective factor for patients with coronary heart disease and T2DM, particularly in effectively reducing the incidence of long-term MACE events in patients with HFrEF, CHD and T2DM. However, it should be noted that this study is a retrospective single-center study with a limited sample size, especially in the subgroup of HFrEF patients. Further multi-center, large-scale, and prospective studies are needed to verify the conclusions of this study.

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Author contributions

XZ, RQ designed the research;. XJX, AJS, YXZ conducted the research. CHG and XZ analyzed the data. CHG wrote the manuscript. CHG and CJ critically revised the manuscript. All authors reviewed the manuscript.

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Availability of data and materials

The data that support the fndings of this study are available from the co-responding author, Xin Zhao, upon reasonable request. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance to relevant guidelines and regulations. The ethical committee of Anqing Municipal Hospital, approved the study protocol. Written informed consent was obtained from all participants at the beginning of the study .

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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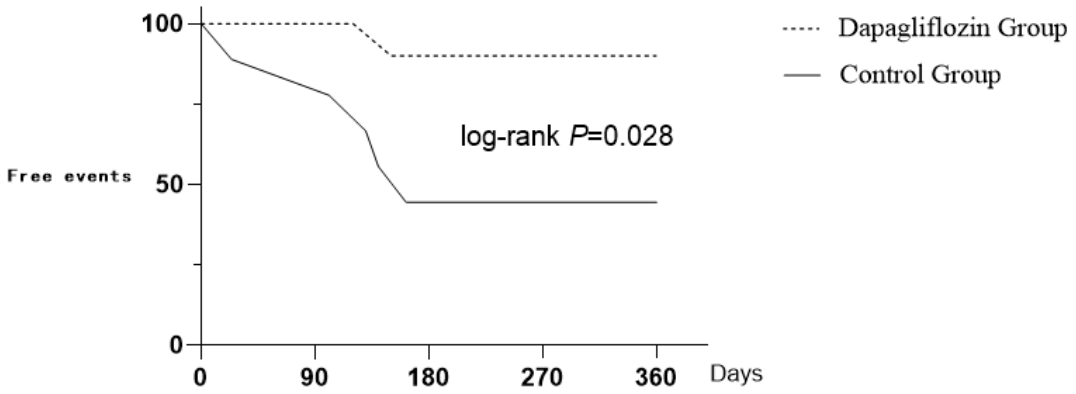

Figure 1. K-M Curve for HFrEF-subgroup

Table1.Baselin Characteristics

	Dapagliflozin n=100	Control n=102	t/χ^2/Z	*P*
Age (year, x±s)	63.18±10.04	61.00±9.33	1.131	0.261
ACS[n(%)]	64（64.00）	66（64.71）	0.005	1.000
Female[n(%)]	40（40.00）	24（23.53）	3.164	0.075
Smoking[n(%)]	28（28.00）	40（39.22）	1.422	0.233
Alcohol[n(%)]	18（18.00）	6（5.88）	3.541	0.060
HTN [n(%)]	66（66.00）	56（54.90）	1.300	0.254
CKD[n(%)]	0	4（3.92）	2.000	0.495
Stroke [n(%)]	14（14.00）	14（13.73）	0.002	0.968
Cancer[n(%)]	2（2.00）	0	1.030	0.495
PAD[n(%)]	10（10.00）	8（7.84）	0.145	0.741
SBP (mmHg, x±s)	137.74±20.50	132.12±18.09	1.462	0.147
DBP (mmHg, x±s)	86.06±12.30	83.51±11.25	1.088	0.279
HR (bpm, x±s)	82.30±18.27	82.90±18.40	0.165	0.869
Scr (μmol/L, x±s)	75.82±20.52	71.33±25.43	0.975	0.332
K+(mmol/L, x±s)	4.26±1.52	4.10±0.29	0.742	0.460
Na+ (mmol/L, x±s)	139.10±3.59	140.36±3.65	1.748	0.084
PLT($\times10^9$/L, x±s)	175.60±68.23	166.02±54.93	1.619	0.438
WBC ($\times10^9$/L, x±s)	9.50±3.30	8.74±4.19	1.021	0.310
Hb (g/L, x±s)	129.62±19.59	130.80±17.99	0.316	0.752
TC (mmol/L, x±s)	4.34±1.37	4.13±1.18	0.842	0.402
TG[mmol/L, M(Q3-Q1)]*	2.16（2.47）	1.82（2.21）	1.015	0.313

ALT [mmol/L, M(Q3-Q1)]*	26.34（41.28）	26.98（36.06）	0.155	0.877
AST [mmol/L, M(Q3-Q1)]*	62.68（57.11）	45.37（63.29）	1.059	0.292
LDL-C (mmol/L, x±s)	2.20±0.92	2.14±1.07	0.335	0.738
Glucose (mmol/L, x±s)	9.96±3.95	8.60±3.80	-1.771	0.080
Peak-CK [U/L, M(Q3-Q1)]*	507.09（463.24）	572.53（402.53）	0.336	0.738
Peak-CK-MB [U/L, M(Q3-Q1)]*	50.17（64.27）	67.82（54.38）	0.066	0.948
Peak-TNT [ng/L, M(Q3-Q1)]*	1664.01（2316.76）	1523.75（2201.33）	0.221	0.826
Peak-NT-proBNP[μg/L, M(Q3-Q1)]*	1764.56（2554.01）	1939.85（2667.68）	0.212	0.833
LVEF (%, x±s)#	56.46±12.41	59.16±10.34	1.188	0.238
HFrEF [n(%)]	22（22.00）	18（17.65）	0.301	0.583
Medication [n(%)]				
Diuretics（%）	26（26.00）	14（13.73）	2.395	0.122
MRA（%）	24（24.00）	16（15.69）	1.099	0.295
CCB（%）	24（24.00）	22（21.57）	0.085	0.771
βRB（%）	46（46.00）	62（60.78）	2.218	0.136
ACEI/ARB	50（50.00）	40（39.22）	1.189	0.276
Statins	100（100.00）	98（96.08）	0.000	0.989
ARNI	26（26.00）	12（11.76）	3.350	0.067

*Means nonnormally distributed continuous variables. ACS. Acute Coronary Syndrome; HTN. Hypertension; CKD. Chronic kidney disease; PAD.Peripheral arterial disease; SBP. Systolic blood pressure; DBP. Diastolic blood pressure; HR. Heart rate;Scr. Serum creatinine;PLT. Platelets;WBC. White blood cells; Hb. Hemoglobin; TC.Total Cholesterol; TG.Triglycerides; ALT. Alanine aminotransferase;AST. Aspartate aminotransferase; LDL-C. Low-density lipoprotein cholesterol;CK. Creatine kinase; CK-MB. Creatine kinase-myocardial band; TNT. Troponin T;NT-proBNP. N-terminal Pro-Brain Natriuretic Peptide; LV. Left ventricular; EF. Ejection fraction; HFrEF. Heart Failure with Reduced Ejection Fraction; MRA. Mineralocorticoid receptor antagonist; CCB. Calcium channel blocker; βRB. β-receptor blocker; ACEI. Angiotensin-converting enzyme inhibitor; ARB. Angiotensin II receptor antagonist.ARNI.Angiotensin Receptor-Neprilysin Inhibitor;

Table 2. follow-up of two groupspatients

	Dapagliflozin n=100	**Control n=102**	**$t/\chi^2/Z$**	***P***
Total MACE[n(%)]	6（6.00）	18（17.65）	3.271	0.071
Cardiac death[n(%)]	0	4（3.92）	2.000	0.495
HF Rehospitalization[n(%)]	4（4.00）	10（9.80）	1.318	0.436
Re-myocardial infarction[n(%)]	0	2（1.96）	0.990	1.000
Revascularization[n(%)]	2（2.00）	2（1.96）	0.000	1.000

Table 3.COX regression

Risk Factors	**HR**	**95% CI**	***P*值**
Dapagliflozin	0.166	0.026-0.953	0.047
Fremale	0.180	0.015-2.151	0.175
ACS	1.176	0.196-7.055	0.859
MVD	4.077	0.819-20.296	0.086
βRB	1.812	0.303-10.850	0.515
ACEI/ARB	1.475	0.180-12.078	0.717
ARNI	6.906	0.630-75.686	0.114
HTN	1.231	0.237-6.390	0.804
HFrEF	3.387	0.715-16.037	0.124

Table 4. HFrEF-subgroup Baselin Characteristics

	Dapagliflozin n=44	Control n=36	t/χ^2/Z	*P*
Age (year, x±s)	63.36±12.05	63.89±11.53	0.099	0.922
ACS[n(%)]	32 (72.72)	28 (77.78)	0.067	1.000
Female[n(%)]	20 (45.45)	24 (66.67)	0.900	0.406
Smoking[n(%)]	8 (18.18)	12 (33.33)	0.606	0.617
Alcohol[n(%)]	4 (9.09)	0	0.861	1.000
HTN [n(%)]	28 (63.63)	16 (44.44)	0.737	0.391
CKD[n(%)]	0	0	-	-
Stroke [n(%)]	4 (9.09)	8 (22.22)	0.669	0.566
Cancer[n(%)]	0	0	-	-
PAD[n(%)]	0	0	-	-
SBP (mmHg, x±s)	120.91±20.89	113.89±11.45	-0.901	0.380
DBP (mmHg, x±s)	81.55±13.00	73.67±8.29	-1.527	0.133
HR (bpm, x±s)	84.55±19.51	89.44±26.84	0.473	0.642
Scr (μmol/L, x±s)	72.82±21.45	84.33±44.06	0.766	0.454
K+(mmol/L, x±s)	4.54±0.39	4.61±0.31	0.999	0.320
Na+ (mmol/L, x±s)	139.99±2.94	139.97±4.45	-0.015	0.988
PLT($\times10^9$/L, x±s)	173.64±61.24	190.89±83.80	0.532	0.601
WBC ($\times10^9$/L, x±s)	8.36±2.41	12.70±13.01	1.090	0.290
Hb (g/L, x±s)	129.73±18.67	136.11±12.15	0.882	0.389
TC (mmol/L, x±s)	3.83±0.84	4.20±2.18	0.532	0.601
TG[mmol/L, M(Q3-Q1)]*	1.39 (2.17)	2.18 (2.34)	1.516	0.147
ALT [mmol/L, M(Q3-Q1)]*	36.55 (37.65)	31.11 (32.36)	-0.455	0.655
AST [mmol/L, M(Q3-Q1)]*	94.64 (72.13)	101.67 (90.85)	0.113	0.911
LDL-C (mmol/L, x±s)	1.99±0.82	2.10±1.90	0.161	0.874
Glucose (mmol/L, x±s)	10.74±4.22	9.23±4.17	-0.801	0.433
Peak-CK [U/L, M(Q3-Q1)]*	823.13 (513.22)	1122.56 (798.38)	0.468	0.647
Peak-CK-MB [U/L, M(Q3-Q1)]*	61.04 (53.78)	98.71 (76.41)	0.938	0.362
Peak-TNT [ng/L, M(Q3-Q1)]*	2848.32 (2143.46)	2325.13 (2278.19)	-0.288	0.780
Peak-NT-proBNP[μg/L, M(Q3-Q1)]*	3529.20 (2336.97)	4852.37 (3376.52)	0.447	0.663
LVEF (%, x±s) #	33.27±6.42	34.67±4.61	1.261	0.210
Medication [n(%)]				
Diuretics（%）	32 (72.73)	24 (66.67)	0.087	1.000
MRA (%)	28 (63.63)	24 (66.67)	0.020	1.000
CCB (%)	0	0	-	-
βRB（%）	36 (81.82)	16 (44.44)	3.039	0.160
ACEI/ARB	20 (45.45)	12 (33.33)	0.606	0.617
Statins	40 (90.91)	36 (100.00)	0.861	1.000
ARNI	28 (63.64)	12 (33.33)	1.818	0.370

Table 5.COX regression in HFrEF-subgroup

Risk Factors	**HR**	**95% CI**	***P***
Dapagliflozin	0.250	0.017-0.518	＜0.001
Fremale	0.506	0.389-5.336	0.647
ACS	4.608	0.144-147.618	0.388
MVD	2.068	0.183-23.342	0.557
βRB	1.812	0.303-10.850	0.515
ACEI/ARB	0.375	0.022-6.348	0.497
ARNI	0.643	0.068-6.056	0.699
HTN	0.278	0.037-2.092	0.214