

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Reduced Ejection Fraction: A Real-World Study

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Abstract

Aims: We aimed to observe the improvements in cardiac function indexes and the occurrence of adverse events in patients with heart failure with reduced ejection fraction (HFrEF) after dapagliflozin administration in a real-world setting.

Methods: We retrospectively included 201 patients with HFrEF who were treated at a tertiary hospital in Zhengzhou and started to take dapagliflozin (10 mg/d) from March 2020 to June 2021. Their New York Heart Association (NYHA) functional class, cardiac ultrasound indexes, laboratory indexes, and vital signs between baseline and the last follow-up visit were compared, and their adverse events during the follow-up period were recorded.

Results: The follow-up period was 173 (67–210) days. The cardiac function indexes of patients at follow-up, compared with baseline, indicated significant improvement (proportion of NYHA functional class I and II: 40.8% vs. 56.2%; left ventricular ejection fraction: $28.4 \pm 5.3\%$ vs. $34.7 \pm 5.9\%$; left ventricular end-diastolic diameter: 70.1 ± 6.4 mm vs. 64.7 ± 5.6 mm; N-terminal pro-B-type natriuretic peptide: 5421.9 ± 2864.4 pg/mL vs. 2842.8 ± 1703.4 pg/mL at baseline vs. at follow-up; all $P < 0.05$). The rates of hypotension, deterioration of renal function, and genital infection during the follow-up period were 6.5%, 4.0%, and 3.5%, respectively.

Conclusions: We believe that dapagliflozin is safe and effective in patients with HFrEF in the real world.

Keywords: Dapagliflozin; Heart failure with reduced ejection fraction; Real world

Introduction

The DAPA-HF trial [1] has suggested that the oral hypoglycemic agent dapagliflozin may improve the prognosis of patients with heart failure with reduced ejection fraction (HFrEF), regardless of whether they have diabetes mellitus. In clinical work, physicians are increasingly including dapagliflozin in the

treatment plans for HFrEF. Therefore, in this study, we observed the improvements in cardiac function indexes and the occurrence of adverse events in patients with HFrEF after dapagliflozin administration in a real-world setting.

Methods

Study Population

In this single-center, single-arm, retrospective clinical study, we included 201 patients who were

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treated at a tertiary hospital in Zhengzhou and started to take dapagliflozin (10 mg/d) from March 2020 to June 2021. These patients had the following characteristics: (1) left ventricular ejection fraction (LVEF) <40%; (2) New York Heart Association (NYHA) functional class II–IV; and (3) follow-up period >1 month.

Study Design

We used the electronic medical record system to collect the baseline data for the patients, including demographic characteristics, causes of HFrEF, co-morbidities, and treatments for HFrEF. Their NYHA functional class, cardiac ultrasound indexes, laboratory indexes, and vital signs at the baseline and at the last follow-up visit were compared, and their adverse events during the follow-up period were recorded.

Study Indexes

The cardiac ultrasound indexes included LVEF, left ventricular end-diastolic diameter (LVEDD), and right ventricular end-diastolic diameter (RVEDD). The laboratory indexes included N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine, and serum potassium. The vital signs included systolic blood pressure, diastolic blood pressure, and heart rate. The adverse events included hypotension, deterioration of renal function, hyperkalemia, hypokalemia, genital infection, and urinary tract infection. Hypotension was defined by systolic blood pressure <90 mmHg; deterioration of renal function was defined by an increase in serum creatinine >26.5 $\mu\text{mol/L}$ or 25% from baseline; hyperkalemia was defined by serum potassium >5.5 mmol/L; and hypokalemia was defined by serum potassium <3.5 mmol/L.

Statistical Analysis

Continuous variables are expressed as mean \pm standard deviation or median (interquartile range), and categorical variables are expressed as numbers (percentages). Comparisons between the baseline and the follow-up were performed with paired samples t-test or Pearson chi-square test. $P < 0.05$ was considered statistically significant.

Results

Baseline Data

The follow-up period of this study was 173 (67–210) days. Two hundred and one patients were 65.4 ± 13.8 years of age; 126 (62.7%) were male and 75 (37.3%) were female; and 179 (89.1%) had diabetes mellitus. The numbers of patients taking angiotensin receptor neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), beta-blockers, and aldosterone receptor antagonists were 96 (47.8%), 52 (25.9%), 9 (4.5%), 173 (86.1%), and 149 (74.1%), respectively (see Table 1).

Data at Baseline and Follow-Up

Compared with those at baseline, several cardiac function indexes of the patients showed significant

Table 1 Baseline Data.

| Variables | Study population (<i>n</i> = 201) |
|------------------------------------|---------------------------------------|
| Demographic characteristics | |
| Age, year | 65.4 \pm 13.8 |
| Male, <i>n</i> (%) | 126 (62.7) |
| Female, <i>n</i> (%) | 75 (37.3) |
| BMI, kg/m ² | 26.6 \pm 3.5 |
| Causes of HFrEF, <i>n</i> (%) | |
| Ischemic | 152 (75.6) |
| Non-ischemic | 49 (24.4) |
| Co-morbidities, <i>n</i> (%) | |
| Atrial fibrillation | 37 (18.4) |
| Hypertension | 89 (44.3) |
| Diabetes mellitus | 179 (89.1) |
| Treatments for HFrEF, <i>n</i> (%) | |
| ARNI | 96 (47.8) |
| ACEI | 52 (25.9) |
| ARB | 9 (4.5) |
| Beta-blocker | 173 (86.1) |
| Aldosterone receptor antagonist | 149 (74.1) |
| ICD | 0 (0.0) |
| CRT | 0 (0.0) |

BMI: body mass index; HFrEF: heart failure with reduced ejection fraction; ARNI, angiotensin receptor neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ICD, implantable cardioverter-defibrillator; CRT, cardiac-resynchronization therapy.

Table 2 Data at Baseline and at Follow-up.

| Variables | At baseline (<i>n</i> = 201) | At follow-up (<i>n</i> = 201) | P |
|--|-------------------------------|--------------------------------|--------|
| NYHA functional class I and II, <i>n</i> (%) | 82 (40.8) | 113 (56.2) | 0.002 |
| Cardiac ultrasound indexes | | | |
| LVEF, % | 28.4 ± 5.3 | 34.7 ± 5.9 | <0.001 |
| LVEDD, mm | 70.1 ± 6.4 | 64.7 ± 5.6 | <0.001 |
| RVEDD, mm | 21.6 ± 3.5 | 19.8 ± 2.7 | <0.001 |
| Laboratory indexes | | | |
| NT-proBNP, pg/mL | 5421.9 ± 2864.4 | 2842.8 ± 1703.4 | <0.001 |
| Serum creatinine, μmol/L | 96.1 ± 18.7 | 93.5 ± 15.1 | 0.090 |
| Serum potassium, mmol/L | 3.9 ± 0.6 | 4.4 ± 0.6 | <0.001 |
| Vital signs | | | |
| Systolic blood pressure, mmHg | 121.9 ± 18.7 | 115.4 ± 14.6 | <0.001 |
| Diastolic blood pressure, mmHg | 69.2 ± 11.3 | 66.8 ± 10.2 | <0.001 |
| Heart rate, beats/min | 86.5 ± 10.9 | 67.7 ± 7.5 | <0.001 |

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; RVEDD: right ventricular end-diastolic diameter; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

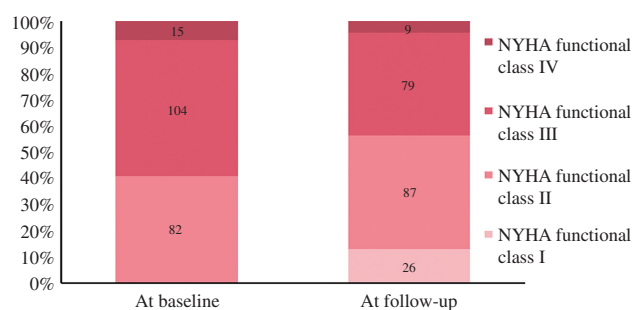


Figure 1 NYHA Functional Class at Baseline and at Follow-up.
NYHA: New York Heart Association.

improvement at follow-up. The proportion of NYHA functional class I and II increased from 40.8% to 56.2% ($P = 0.002$); the LVEF increased from $28.4 \pm 5.3\%$ to $34.7 \pm 5.9\%$ ($P < 0.001$); the LVEDD decreased from 70.1 ± 6.4 mm to 64.7 ± 5.6 mm ($P < 0.001$); and the NT-proBNP decreased from 5421.9 ± 2864.4 pg/mL to 2842.8 ± 1703.4 pg/mL ($P < 0.001$; see Table 2 and Figure 1).

Adverse Events During Follow-Up

During the follow-up period, the rates of hypotension, deterioration of renal function, and genital infection were 6.5%, 4.0%, and 3.5%, respectively (see Table 3).

Table 3 Adverse Events During Follow-up.

| Variables | Study population (<i>n</i> = 201) |
|---|------------------------------------|
| Hypotension, <i>n</i> (%) | 13 (6.5) |
| Deterioration of renal function, <i>n</i> (%) | 8 (4.0) |
| Electrolyte disorders, <i>n</i> (%) | |
| Hyperkalemia | 3 (1.5) |
| Hypokalemia | 31 (15.4) |
| Genitourinary infections, <i>n</i> (%) | |
| Genital infection | 7 (3.5) |
| Urinary tract infection | 2 (1.0) |

Twenty-eight (13.9%) patients were hospitalized for heart failure, and 9 (4.5%) patients died of cardiovascular causes.

Discussion

The DAPA-HF trial [1] is a placebo-controlled trial that has substantially influenced the treatment of HFrEF. In that study, a total of 4744 patients (approximately 40% of whom had diabetes mellitus) at 410 centers in 20 countries were randomly assigned to receive either dapagliflozin or placebo, and the results suggested that dapagliflozin significantly decreased the risk of worsening heart failure or death from cardiovascular causes in patients with HFrEF [1]. We believe that dapagliflozin is safe and effective in patients with HFrEF in the real world.

By reviewing the medical records of the patients in this study, we found the following: (1) The patients had poor cardiac function, with LVEF of only $28.4 \pm 5.3\%$, LVEDD as high as 70.1 ± 6.4 mm, and NT-proBNP as high as 5421.9 ± 2864.4 pg/mL. (2) The proportions of patients with atrial fibrillation, hypertension, and diabetes mellitus were relatively high, at 18.4%, 44.3%, and 89.1%, respectively. Dapagliflozin not only ameliorated HFrEF and diabetes mellitus, but also decreased blood pressure, thus potentially providing multiple benefits to some patients. (3) Rational and effective treatment plans were needed: 1) Although the mean systolic blood pressure was not high, the standard deviation was large, thus suggesting that the blood pressure control of some patients was insufficient. 2) The heart rate was relatively fast, reaching 86.5 ± 10.9 beats/min, thus potentially requiring high doses of beta-blockers and/or ivabradine. 3) Patients with HFrEF often have ventricular tachycardia, ventricular fibrillation, and left bundle branch block, which may require device therapy. In this study, none of the patients were treated with an implantable cardioverter-defibrillator (ICD) or cardiac-resynchronization therapy (CRT), possibly because of the relatively high cost of device therapy.

LVEF not only reflects the pumping function of the heart but also has predictive value for prognosis [2, 3]. In this study, at the follow-up, the LVEF of the patients had significantly increased, from $28.4 \pm 5.3\%$ to $34.7 \pm 5.9\%$. In addition, other cardiac function indexes improved to different degrees. The proportion of NYHA functional class I and II increased from 40.8% to 56.2%; the LVEDD decreased from 70.1 ± 6.4 mm to 64.7 ± 5.6 mm; and the NT-proBNP decreased from 5421.9 ± 2864.4 pg/mL to 2842.8 ± 1703.4 pg/mL. These results suggested that sodium-glucose cotransporter-2 (SGLT2) inhibitors might improve cardiac remodeling and quality of life in patients with HFrEF in the real world, in agreement with findings from previous studies [4, 5].

Comparisons of different doses of SGLT2 inhibitors have been investigated in many studies, primarily in patients with diabetes mellitus. A meta-analysis [6] of 51 randomized clinical trials has suggested that the occurrence of adverse events is not significantly higher with high than low doses of SGLT2 inhibitors. Another meta-analysis [7] has suggested that high doses of SGLT2 inhibitors have a stronger hypoglycemic effect than low doses. In fact, whether

differences exist in the efficacy and safety of 10 mg and 5 mg of dapagliflozin in HFrEF remains unclear. The 201 patients in this study had taken 10 mg of dapagliflozin for as many as 173 (67–210) days, thus suggesting that dapagliflozin might be well tolerated in patients with HFrEF in the real world.

Dapagliflozin has an osmotic diuretic effect, thus potentially leading to inadequate renal perfusion and subsequent elevation of blood urea and/or creatinine. A randomized, double-blind trial [8] has suggested that dapagliflozin causes an acute and reversible decrease in the measured glomerular filtration rate. However, hypovolemia may also lead to symptomatic hypotension. In this study, 13 (6.5%) and 8 (4.0%) patients experienced hypotension and deterioration of renal function, respectively. On the basis of our clinical experience, we believe that these adverse events were more associated with the diseases themselves and/or ARNI/ACEI/ARB, and that the hypotension and deterioration of renal function in these patients might improve after dose adjustment of ARNI/ACEI/ARB.

SGLT2 inhibitors decrease blood glucose by elevating urine glucose, thus potentially contributing to the development of genitourinary infections. Although the conclusions of prior studies [9, 10] are not entirely consistent, many physicians believe that SGLT2 inhibitors are more associated with genital infection than urinary tract infection. In this study, genital infection and urinary tract infection occurred in seven and two patients, with occurrence rates of 3.5% and 1.0%, respectively.

This study was a single-center retrospective study with some limitations, such as a short follow-up period and the absence of a control group. More future in-depth studies are needed to address these issues.

Conclusion

We believe that dapagliflozin is safe and effective in patients with HFrEF in the real world.

Conflicts of interest

None.

Funding

None.

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