THE RATE AND OUTCOMES OF REDUCING RE-HOSPITALIZATIONS WITH A TREATMENT REGIMEN INCLUDING DAPAGLIFLOZIN IN HEART FAILURE WITH REDUCED EJECTION FRACTION WITHOUT DIABETES PATIENTS

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ABSTRACT

Background: *Heart failure, a cardiovascular disease with a substantial disease burden, often leads to frequent hospitalizations for acute episodes. The readmission rate is estimated to be around 30-50%, resulting in high costs for both pharmacological and non-pharmacological treatments. Additionally, heart failure is associated with a considerable mortality rate, ranging from 48-57%.* ***Objectives:*** *To describe the rate and outcomes of reducing hospital readmissions for heart failure in non-diabetes patients and with heart failure featuring reduced ejection fraction, through the use of Dapagliflozin at Can Tho University of Medicine and Pharmacy Hospital.* ***Materials and methods:*** *A cross-sectional descriptive study was conducted 44 non-diabetes and heart failure with reduced ejection fraction patients who were examined and treated at Can Tho University of Medicine and Pharmacy Hospital.* ***Results:*** *The average age of patients was 67.3 ± 13, with male patients representing 65.9%. Shortness of breath was the most common symptom (77.3%). Other frequently observed symptoms included distended neck veins, peripheral edema, and rales in the lungs. The average ejection fraction was 36.65 ± 8.16%. In terms of functional classification, NYHA III represents the highest proportion at 54.5%. The median NT-proBNP concentration was 8757 pg/mL (ranging from a minimum of 604 pg/mL to a maximum of 35.000 pg/mL). The observed improvement rate in NYHA classification after treatment was 13.6%. The rate of rehospitalization for heart failure before treatment was 27.3%, decreasing to 11.4% after treatment (p=0.118 but the analysis suggests that there were no independent risk factors contributing to rehospitalization for heart failure in patients with reduced ejection fraction without diabetes.****Conclusions:*** *Dyspnea was the most common symptom in patients with heart failure with reduced ejection fraction and non-diabetes. The rate of rehospitalization for heart failure after 12 weeks of Dapagliflozin treatment was lower than before treatment, but this difference was not statistically significant.*

Keywords: *Heart failure with reduced ejection fraction, Diabetes, Dapagliflozin.*

I. INTRODUCTION

Heart failure represents a global health challenge, with its incidence steadily rising in both developed and developing nations [1]. Among the various subtypes of heart failure, heart failure with reduced ejection fraction constitutes 45-70% of cases [2]. Despite active treatment with numerous medications, heart failure remains a cardiovascular disease with a substantial disease burden. Patients frequently experience hospitalizations due to acute heart failure, with a readmission rate of approximately 30-50% [3]. During periods of decompensation, patients face work incapacity, and the associated care costs are high, encompassing both pharmacological and non-pharmacological treatments. Additionally, there is a notable mortality rate ranging from 48-57% [4].

Dapagliflozin, a novel medication, has demonstrated efficacy in heart failure treatment. Numerous global studies have affirmed the drug's effectiveness in reducing the rates of heart failure rehospitalization and cardiovascular-related deaths, irrespective of the presence of diabetes mellitus [5]. However, in clinical practice, disparities persist in the recommended and actual treatment of patients with heart failure with reduced ejection fraction, and the effectiveness of Dapagliflozin in Vietnamese subjects is not well-documented. Therefore, the objective of describing the rate and outcomes of reducing hospital readmissions for heart failure in patients with heart failure featuring reduced ejection fraction without diabetes using Dapagliflozin.

II. MATERIALS AND METHODS

2.1. Research subjects: Patients diagnosed with heart failure and reduced ejection fraction and non-diabetes sought examination and treatment at Can Tho University of Medicine and Pharmacy Hospital from May 2023 to December 2023.

Sample selection criteria

Patients satisfy all of the following criteria:

Age: Participants must be aged 18 years or older.

Heart failure diagnosis: Patients diagnosed with heart failure and reduced ejection fraction according to VNHA 2022 standards for more than 3 months before the start of participation [6].

Diabetes status: Patients must not meet the criteria for diagnosing diabetes according to ADA 2021 [7].

Medical Therapy: Patients should be actively using reduced ejection fraction heart failure medical therapy according to VNHA 2022, which includes a full range of drugs such as ACE inhibitors/ARNI, beta blockers, and aldosterone antagonists [6].

Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

Current use of Dapagliflozin: Individuals currently using dapagliflozin to treat any other condition at the time of study participation.

Symptomatic hypotension: Participants experiencing symptomatic hypotension or having a systolic blood pressure <95 mmHg in two consecutive measurements.

Reduced kidney function: Individuals with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2.

2.2. Research Methods

Study design: A cross-sectional descriptive study.

The sampling method: patients in this study is convenience sampling.

2.3. Data collection

General characteristics of patients with heart failure and reduced ejection fraction: this includes age, gender, and medical history.

Clinical and paraclinical characteristics in patients with heart failure and reduced ejection fraction.

Rate and outcomes of reduced rehospitalization for heart failure with Dapagliflozin treatment: The treatment regimen for study subjects is based on VNHA 2022 heart failure treatment recommendations [6]. Drug classes, indications, and dosages adhere to these recommendations. Dapagliflozin, marketed as Forxiga, with a content of 10 mg, was administered at a dose of 1 tablet/day. The pre-treatment readmission rate was assessed by

reviewing medical records or conducting interviews covering the 12 weeks before admission. Readmission for heart failure was treated as a qualitative variable, recorded when the patient exhibits symptoms or signs of new or worsening heart failure. This information was gathered through interviews with the patient, their relatives, or by reviewing the patient's discharge papers. Improvement in NYHA (New York Heart Association) class was also recorded as a qualitative variable, noting instances where the patient decreases at least one level on the NYHA scale.

2.4. Statistical Analysis: The data were processed and analyzed using SPSS 22.0 software. Qualitative variables are presented as frequencies and percentages, while quantitative variables are reported as mean ± standard deviation for normally distributed variables or as median, maximum value, and minimum value for variables with a non-normal distribution. The McNemar test was utilized to assess differences between two related groups when the measured variable in the paired t-test was binary.

2.5. Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Can Tho University of Medicine and Pharmacy (protocol code 23. 035.GV/PCT-HĐĐĐ in 2023).

III. RESULTS

3.1. Baseline Subject Characteristics

Table 1. Baseline characteristics of the study population

Parameter	n	%
Male	29	65.9%
Age group		
< 60	12	27.3%
≥ 60	32	72.7%
Mean ± SD	67.3 ± 13	
Medical history		
Hypertension	32	72.7%
Coronary artery disease	19	43.2%
Heart valve disease	11	25,0%
Cardiomyopathy	8	18.2%
Arrhythmias	6	13.6%

A higher proportion of patients in the study are male, constituting 63.3%, while female patients make up the remaining percentage. Among the patients, those aged 60 years and older represent the largest subgroup, accounting for 72.7% of the total. The average age of the patients is 67.3, ranging from the youngest at 40 to the oldest at 93. Notably, a history of hypertension is prevalent, representing the highest rate at 72.7% (Table 1).

Table 2. Clinical and paraclinical characteristics of research subjects

Symptoms at admission	n	%
Shortness of breath	34	77.3
Dry cough	13	29.5
Weakness and fatigue	17	38.6
Peripheral edema	28	63.6
Enlarged liver	5	11.4
Distended neck veins	30	68.2

Symptoms at admission	n	%
Lung rales	25	56.8
T3	1	2.3
NYHA Classification		
II	20	45.5%
III	24	54.5%
Paraclinical		
Ejection fraction (EF) (%)		
EF: 31-40%	9	20.5%
EF: ≤30%	35	79.5%
Mean± SD	36.65 ± 8.16	
NT- pro BNP (pg/mL)		
Median	8757	
Min	604	
Max	35000	

Heart failure patients with reduced ejection fraction and non-diabetes, upon hospital admission, commonly presented with symptoms such as shortness of breath, dry cough, and weakness. Notably, Shortness of breath as the most prevalent symptom, affecting 77.3% of patients. Physical manifestations include distended neck veins observed in 68.2% of patients, peripheral edema in 63.6% of patients, and pulmonary rales in 56.8% of patients. Additional physical symptoms, such as hepatomegaly, were noted in 11.4% of patients, and a S3 heart sound was present in 2.3% of patients. Ejection fraction analysis revealed that 79.5% of patients had severely reduced EF, while 20.5% had moderately reduced EF. The mean EF was 36.65 ± 8.16. In terms of functional classification, NYHA III represents the highest proportion at 54.5%. The median NT-proBNP concentration was 8757 pg/mL (ranging from a minimum of 604 pg/mL to a maximum of 35.000 pg/mL) (Table 2).

3.2. The hospital readmission rate and outcomes of reducing readmissions with Dapagliflozin.

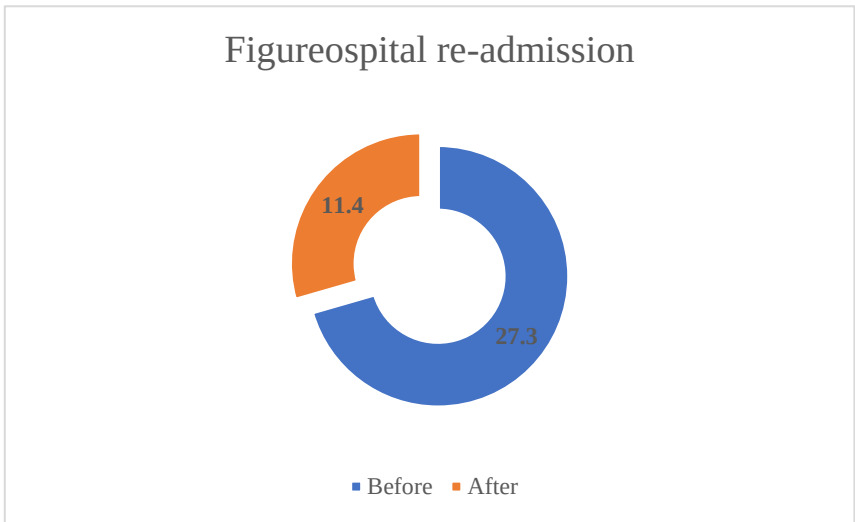

Figure 1. The hospital readmission rate before and after treatment with the regimen including Dapagliflozin

The observed readmission rate for heart failure following Dapagliflozin treatment was 11.4% (Figure 1).

Table 3. The NYHA and a reduction in the hospital readmission rate after 12 weeks of treatment.

Characteristics		Treatment				p
		Before		After		
		n	%	n	%	
Hospital readmission	Yes	12	27.3	5	11.4	0.118
	No	32	72.7	39	88.6	
NYHA	II	20	45.5	25	56.8	0.063
	III	23	52.3	19	43.2	
NYHA Improvement	Yes	-		6	13.6	
	No			38	86.4	

The readmission rates for heart failure before and after Dapagliflozin treatment were 27.3% and 11.4%, respectively. Notably, this difference did not reach statistical significance (p = 0.118). The observed improvement rate in NYHA classification after treatment was 13.6% (Table 3).

Table 4. Multivariable logistic regression between readmission for heart failure and independent risk variables.

Risk factors	OR	95%CI		p
Age≥ 60	5.4	0.7	42	0.1
Male	2.5	0.4	15.2	0.32
Hypertension	8.4	0.9	77.2	0.06
Coronary artery disease	10.1	0.5	205.9	0.13
Heart valve disease	0.4	0.01	18	0.67
Cardiomyopathy	0.3	0.01	8.1	0.48
Arrhythmias	1.1	0.3	31.1	0.9
NYHA III	1.6	0.3	9.1	0.57
EF ≤ 30%	5.5	0.4	70.1	0.19
NT-proBNP >20000 (pg/mL)	2.4	0.24	25.9	0.45

There were no independent risk factors contributing to rehospitalization for heart failure in patients with reduced ejection fraction non-diabetes (Table 4).

IV. DISCUSSION

Through our research, we observed that the percentage of patients in the age group ≥ 60 was higher than that in the age group < 60, constituting 72.7% and 27.3%, respectively. The average age of patients with diverse heart failure and reduced ejection fraction and non-diabetes was 67.3 ± 13. This finding aligns with the study conducted by Nguyen Hai Nguyen (2014), where the age group ≥ 60 accounted for 75%, with an average age of 69.3 ± 16.1 [8]. In our study, the proportion of male patients was 65.9%, resembling the gender distribution found in Nguyen Duy Toan's study in 2018, where the proportions were 72.0% for men and 28% for women [9]. Middle-aged and elderly male often exhibit multiple risk factors, including smoking, alcohol consumption, and high protein intake. These factors collectively contributed significantly to the development of heart disease and impact treatment outcomes. Clinically, dyspnea was the predominant symptom in most patients,

occurring at a rate of 77.3%. Other prevalent symptoms include distended neck veins (68.2%), peripheral edema (63.6%), and lung rales (56.8%). These findings closely resemble the results of Nguyen Thi Thuy Trang's study, which reported similar rates of 100%, 78.45%, 62.09%, and 52.59% for these symptoms, respectively [10].

The average ejection fraction was 36.65 ± 8.16, a result consistent with Nguyen Van Thu's study, which reported 31.16 ± 6.05 [11]. In our study, the serum concentration of NT-proBNP was notably high, with a median of 8757 pg/mL (ranging from 604 pg/mL to 35,000 pg/mL). This finding closely resembles the results of a study conducted by Author Tsutsui H and colleagues in Japan (2021) [10]. Regarding treatment outcomes, the rate of rehospitalization for heart failure after 12 weeks of Dapagliflozin treatment was lower than that before treatment (11.4% compared to 27.3%). However, this difference did not achieve statistical significance ($p = 0.118$). In the DAPA-HF study involving 4744 patients, with a median follow-up of 18.2 months, the hospitalization rate for heart failure after Dapagliflozin treatment was 10%, compared to 13.7% before treatment. The difference in the DAPA-HF study was statistically significant ($p < 0.05$) [5]. In our study, although the difference was not statistically significant, there was a lower rate of rehospitalization for heart failure after Dapagliflozin treatment during the follow-up period. Further research with a larger sample size and a longer follow-up period is needed to establish the statistical significance of Dapagliflozin's effectiveness.

V. CONCLUSION

In our study, the average age of patients with heart failure and reduced ejection fraction and non-diabetes was 67.3 ± 13, with male comprising 65.9% of the participants. The most prevalent symptom reported by patients was shortness of breath (77.3%), accompanied by other common symptoms such as distended neck veins, peripheral edema, and lung rales. The average ejection fraction was 36.65 ± 8.16%, and the median concentration of NT-proBNP was 8757 pg/ml. Following 12 weeks of Dapagliflozin treatment, the hospital readmission rate decreased to 11.4% from the pre-treatment rate of 27.3%. However, this reduction was not statistically significant.

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