

## Early Efficacy of Empagliflozin in Addition to Optimal Medical Treatment of Heart Failure with Reduced Ejection Fraction

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### Abstract

**Introduction:** Heart failure with reduced ejection fraction (HFrEF) is a life-threatening condition that can lead to unfavorable clinical outcomes. It is recommended to add a sodium-glucose cotransporter 2 (SGLT2) inhibitor to previous mortality-reducing pharmacological therapy. Full treatment access may be limited by costs in many countries, and early benefits with guideline-directed medical therapy must be proven and reinforced.

**Objective:** We aimed to analyze the short-term impact of empagliflozin on HFrEF patients concerning functional capacity, quality of life and left ventricle remodeling.

**Methods:** Prospective observational study that analyzed patients with HFrEF on triple therapy and were indicated to use SGLT2 inhibitor. A six-month follow-up was conducted for patients who adhered to empagliflozin use with no interruptions or complications. To compare the initial and final periods, patients performed the six-minute walk test (6MWT), the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and echocardiograms. The chi-square test, the Fisher's test and the paired Student's t-test were used for comparative analyses before and after treatment for six months, with a significance level of 0.05.

**Results:** Thirty patients were analyzed, mean age  $61.9 \pm 7.1$ , 30% female, 40% diabetic. The distance walked in the 6MWT raised from  $372 \pm 89$ m to  $402 \pm 53$ m ( $p=0.034$ ); quality of life improved from  $36.4 \pm 24$  points to  $21.4 \pm 17$  points in the MLHFQ ( $p=0.0002$ ); left ventricular ejection fraction raised from  $30.4 \pm 6\%$  to  $40.3 \pm 13\%$  ( $p=0.0001$ ); left ventricular systolic diameter reduced from  $49.7 \pm 7$ mm to  $45.3 \pm 11$ mm ( $p=0.014$ ). Mean left ventricular diastolic diameter was  $58.7 \pm 9$ mm at inclusion and  $56.9 \pm 9$ mm at the end of six months ( $p=0.29$ ).

**Conclusion:** There was an improvement in functional capacity, quality of life, cardiac function and left ventricle remodeling on echocardiogram after six months of empagliflozin use added to triple therapy in HFrEF.

### Keywords

Heart failure, SGLT2 inhibitors, Empagliflozin, Reduced ejection fraction.

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## Introduction

Heart failure (HF) is a severe cardiac disease that affects more than 23 million people worldwide. It is characterized by signs and symptoms resulting from reduced cardiac output and/or filling pressures, with several structural and functional causes. The syndrome can be classified according to the left ventricular ejection fraction (LVEF) into: preserved (50% or above), mildly reduced (40-49%) or reduced (below 40%). It is also classified according to the severity of its symptoms by the New York Heart Association (NYHA) classification, with worsening symptoms from class I to class IV [1].

The basic treatment for heart failure with reduced ejection fraction (HFrEF) is a combination of drugs that act on mechanisms related to HF. In general, beta-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, aldosterone antagonists, and sodium-glucose co-transporter 2 (SGLT2) inhibitors are used together [1-4]. SGLT2 inhibitors, the latest class to be recommended as a mortality-reducing drug in HFrEF, have shown significant additional benefits in the treatment of HF, regardless of the presence of type 2 Diabetes Mellitus (T2DM), having their efficacy demonstrated in several clinical trials [5]. They are currently considered one of the cornerstones of the treatment of HFrEF [2-4]. Their early action occurs mainly in the proximal convoluted tubules of the nephrons, promoting greater elimination of sodium and glucose in the urine, which leads to an increase in diuresis and a consequent reduction in blood volume [5].

A meta-analysis carried out by the DAPA-HF and EMPEROR-Reduced studies corroborates the adoption of SGLT2 inhibitors as an important component in the treatment of HFrEF. It showed a significant reduction in cardiovascular death and hospitalization for HF in patients with LVEF <40% and NYHA class III/V symptoms, thus demonstrating the positive impacts of incorporating these drugs into the established treatment [6]. However, local studies may be necessary to further prove remodeling efficacy and to quantify its impact on HF outcomes. This study aims to evaluate the clinical impact of adding empagliflozin to the previously optimized treatment of HFrEF, regarding functional capacity, quality of life (QoL) and left ventricular remodeling.

## Methods

### Study Design and Population

This is a prospective observational cohort study that analyzed clinical data of HF patients followed up in the outpatient Cardiology Department of a teaching hospital in Brazil. Inclusion criteria were patients diagnosed with HFrEF and with an indication to use a SGLT2 inhibitor in addition to the usual previous drugs. All patients were prescribed empagliflozin and were recommended to maintain the standard treatment already in use. The recruitment period was between July 2022 and December 2022, with a six-month clinical follow-up after inclusion.

Patients over the age of 18 with a diagnosis of HFrEF (with the last LVEF < 40% as documented by Simpson's method on

transthoracic echocardiogram) and classified as NYHA functional class II to IV were included. For inclusion, patients had to be under clinical treatment with beta-blockers, spironolactone, and RAAS inhibitors (angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers [ARBs] or sacubitril-valsartan). No run-in period was done before actual inclusion in the study.

Patients were initially excluded if they presented any of the following criteria: creatinine clearance <20 mL/min, current use of any SGLT2 inhibitor including empagliflozin, absence from medical appointments for the last six months, history of poor adherence to drug and non-drug treatment, low life expectancy (expected survival <1 year), decompensated clinical condition and inability to fully perform the tests applied in the study. During and after follow-up, patients were also excluded if they had poor medication adherence, important clinical events (hospitalization for decompensated HFrEF or death), loss to follow-up or inability to perform the study tests within 30 days after the six-months follow-up.

The dose of empagliflozin used was 10mg orally once a day. However, for diabetic patients with glycated hemoglobin  $\geq 7.0\%$ , despite the use of metformin and sulfonylurea, the dose administered was 25mg orally once a day. Patients were instructed to return to the clinic if they had an adverse reaction that could be attributed to the medication. Since this was a single-arm prospective cohort study, initial data of all patients were compared with data collected after six months of follow-up.

### Analyzed Variables and Outcomes

Data were collected at the time of inclusion, i.e., before the patient started using empagliflozin, and after six months of optimized treatment, including its addition. The last transthoracic echocardiogram performed before inclusion was considered, compared with a new one performed after six months of empagliflozin use, observing LVEF (preferably by Simpson's method), left ventricular systolic diameter (LVSD) and left ventricular diastolic diameter (LVDD).

The six-minute walk test (6MWT) was performed at inclusion and at the end of the six months. It assessed the distance walked in a 30-meter corridor along six minutes, encouraging the patient to walk as far as possible. During the test, heart rate and oxygen saturation were monitored using a digital oximeter, as well as clinical evaluation checking for the occurrence of symptoms. Participants were instructed to stop, if necessary, especially if they presented dyspnea or severe fatigue, and encouraged to continue if symptoms subsided sufficiently. The test could be stopped if the patient wished or if symptoms such as chest pain, severe dyspnea, severe loss of balance, intense sweating, cyanosis, or severe oxygen desaturation occurred.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to assess QoL on the day of inclusion and after six months. The MLHFQ consists of 21 items, graded on a scale of 0

to 5, with zero being the absence of impairment to QoL and five being the maximum impairment. The overall score ranges from 0 to 105 points, with the higher the score, the lower the QoL. The questionnaire addresses issues relating to physical and emotional difficulties, financial conditions, side effects of medication and lifestyle.

In addition, information was collected on gender, age, comorbidities (hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, heart failure, coronary artery disease), medications and doses, serum creatinine and creatinine clearance (CKD- EPI), to analyze the outcome of death and hospitalizations in patients with HFrEF.

### Statistical Analysis

The Statistical Package for the Social Science (SPSS) software version 25.0 was used to statistically analyze the data. Categorical variables are described as absolute frequency and percentage. Continuous variables were described as mean and standard deviation when they showed a normal distribution, and as median and interquartile range when they showed an abnormal distribution. Comparisons were made between time zero and at six months of follow-up for the same group of included patients.

The Kolmogorov-Smirnov test was used to define the normality of the data. The chi-square test, the Fisher's test and the paired Student's t-test were used to carry out comparative analyses before and after treatment for six months, with p-values of less than 0.05 being considered statistically significant. Sample size calculation presumed the analysis of 28 patients, expecting an improvement of LVEF in five percentage points after six months of empagliflozin use, with a target alpha 5% and beta 20%. We estimated that the inclusion of 50 patients would lead to a loss to follow-up of 10%, poor adherence in 10%, impossibility of performing the follow-up tests within 30 days after completion of the six-months follow-up in 10%, and hospitalizations for decompensated HF in 10%, resulting in 30 patients completely analyzed until the end of the study.

### Ethical Aspects

This study was developed according to ethical principles from the Declaration of Helsinki and followed the recommendations of Resolution 466/2012 of the Brazilian National Health Council. Ethical approval was obtained from the Ethics Committee for Research with Human Beings of the institution, under the number 5,496,084 in June 28<sup>th</sup>, 2022. The authors have full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript.

### Results

Among 218 patients screened, 55 were initially included, and 25 were excluded from the final analysis: 10 due to poor medication adherence, three due to hospitalization for decompensated HFrEF, two due to requests to change medication, six due to loss to follow-up, two due to inability to perform the 6MWT, and one death, resulting in a final sample of 30 patients. Among the 30 patients

included in the analysis, nine patients (30%) were female and 21 (70%) were male, with a mean age of  $61.9 \pm 7.1$  years. Table 1 shows the main comorbidities found in our sample.

**Table 1:** Most common comorbidities found in patients with heart failure with reduced ejection fraction included in the study.

Comorbidity	N (%)
Hypertension	26 (86.7%)
Dyslipidemia	22 (73.3%)
Type 2 diabetes mellitus	12 (40.0%)
Chronic obstructive pulmonary disease	2 (6.7%)

The most frequent etiology of HFrEF was ischemic, although a high number of undefined or idiopathic etiology was found. The distribution of etiologies of HFrEF in our sample is shown on Table 2.

**Table 2:** Etiology of heart failure with reduced ejection fraction among patients included in the study.

Etiology of heart failure with reduced ejection fraction	N (%)
Ischemic	14 (46.7%)
Chemotherapy-induced cardiotoxicity	3 (10.0%)
Alcoholic	2 (6.7%)
Hypertensive	1 (3.3%)
Idiopathic/Unknown	10 (33.3%)

After the six-month follow-up, improvements were observed in functional capacity, QoL, and left ventricular remodeling, as seen in Table 3. A total of 26 patients (86.7%) showed an increase in the distance walked on 6MWT, 23 (76.7%) had better (lower) QoL results on MLHFQ, 22 (73.3%) had an increase of LVEF on echocardiogram, 16 (53.3%) had a lower value of LVSD measurement, and 17 (56.7%) had a lower value of LVDD measurement.

**Table 3:** Comparison outcomes (functional capacity, quality of life and left ventricular remodeling) at the moment of inclusion and after six months on empagliflozin.

Outcome	Initial result (inclusion)	Final result (six months)	p-value
Six-minute walk test (distance in meters, mean $\pm$ SD)	372 $\pm$ 89	402 $\pm$ 53	0.034
Minnesota Living with Heart Failure Questionnaire (points, mean $\pm$ SD)	36.4 $\pm$ 24	21.4 $\pm$ 17	0.0002
LVEF on echocardiogram (percentage, mean $\pm$ SD)	30.4 $\pm$ 6%	40.3 $\pm$ 13%	0.0001
LVSD on echocardiogram (milimeters, mean $\pm$ SD)	49.7 $\pm$ 7	45.3 $\pm$ 11	0.014
LVDD on echocardiogram (milimeters, mean $\pm$ SD)	58.7 $\pm$ 9	56.9 $\pm$ 9	0.29

SD: standard deviation; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; LVDD: left ventricular diastolic diameter.

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## Discussion

This single-arm cohort study showed a highly positive impact of the SGLT2 inhibitor empagliflozin on functional capacity, QoL and left ventricular remodeling for patients with HFrEF. Even though all outcomes of our study can be considered surrogate endpoints, an impressive increase of LVEF was seen after only six months of empagliflozin added to an initially optimized treatment using the other three recommended drugs for HFrEF.

The hypothesis that SGLT2 inhibitors could be beneficial for HFrEF was confirmed for the first time in 2019 with the publication of the DAPA-HF study [6], showing that dapagliflozin added to optimized therapy for HFrEF reduced HF hospitalizations and cardiovascular mortality. In 2020, this evidence was reinforced by the publication of the EMPEROR-Reduced trial [7], showing that empagliflozin added to optimized therapy for HFrEF mainly reduced HF hospitalizations. Both studies established SGLT-2 inhibitors as the fourth pillar of prognosis-modifying therapy for HFrEF, added to the gold standard of HFrEF treatment [8].

Initially designed as a diabetes drug [9], SGLT2 inhibitors have been one of the most studied pharmacological classes for cardiovascular conditions [10-13]. Clinical benefits of SGLT2 inhibitors in HFrEF are expected also in patients without diabetes [14]. Empagliflozin has effects that go beyond glucose reduction, resulting in improved cardiac function and quality of life even in non-diabetic patients [15]. In our study, most patients were non-diabetic. Although it would be troublesome to make a comparison between diabetic and non-diabetic patients in our sample, this condition most likely had little impact on our results. The early positive results on 6MWT, echocardiographic parameters, and MLHFQ suggest that the introduction of empagliflozin for patients with HFrEF is a highly recommended approach as soon as HFrEF is diagnosed. This aggressive combined approach in medical therapy is superior to a stepwise approach in reducing HF-related outcomes [1,16]. Our study showed an impressive 10 percentage points raise of LVEF after full medical treatment for HFrEF. This is a positive remodeling evidence that can strongly impact prognosis, since LVEF has been considered one of the most relevant prognostic markers in HFrEF.

Functional capacity may progressively worsen in HFrEF natural history. Whilst it may be difficult to quantify functional limitation, the 6MWT is an effective and unexpensive tool to objectively address functional capacity [17]. Although the increase of approximately 30 meters in the distance covered in our study may seem small at first sight, it is noteworthy to consider that there was an increase of almost 10% in only six months, especially knowing that few patients actually adhere to lifestyle and physical activity advices [18]. Our result of increased quality of life after empagliflozin may reflect this improved functional capacity, since these parameters are associated [19]. Although relevant, our study has limitations. Patients who presented hospitalizations for decompensated HF were excluded, which might have influenced the results. The exclusion of patients with this complication probably selected

patients who had a better chance for positive remodeling of the left ventricle. Besides, our small sample size and the endpoints we used allow no extrapolations concerning clinical outcomes. Therefore, our results strongly reinforces our theory of early remodeling in HFrEF with intensive guideline-directed medical therapy, and further research is needed to assess hard clinical endpoints in the long term, for different HF patients.

## Conclusion

Empagliflozin proved to be effective in improving functional capacity, quality of life, and echocardiographic parameters, including – and mainly – LVEF, even in the short term. These outcomes have the potential benefit of lowering clinically relevant events related to HFrEF, such as hospitalizations and death. It is paramount to highlight the relevance of SGLT2 inhibitors in the treatment of HFrEF since its diagnosis, as well as the importance of its widespread and easy access to the HFrEF population.

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