„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

SGLT2 INHIBITORS AND NEW FRONTIERS IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Summary

PhD SUPERVISOR: **PhD STUDENT:**

PROF. UNIV. DR. NANEA IOAN-TIBERIU **MUNTEANU MADALINA ANDREEA**

Motto: "Learn from yesterday, live for today, hope for tomorrow.

The important thing is not to stop questioning." — Albert Einstein

Dedication:

I owe my strength and identity to my family, whose unwavering support and guidance have undeniably shaped me into the person I am today

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Abbreviation or special term

ACE-I	Angiotensin converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin receptor blockers
ARNI	Angiotensin Receptor-Neprilysin Inhibitors
ASE	American Society of Echocardiography
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BP	Blood pressure
CV	Cardiovascular
CVD	Cardiovascular disease
ECG	Electrocardiogram
ESC	European Society of Cardiology
LV	Left ventricular
GLS	Global longitudinal strain
LVEF	Left Ventricular Ejection Fraction
Hb	Haemoglobin
HbA1c	Glycosylated haemoglobin
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFmrEF	Heart Failure with mildly reduced Ejection fraction
LVEF	Left ventricular ejection fraction
MAPSE	Mitral annular plane systolic excursion
MRA	Mineralcorticoid receptor antagonist
NYHA	New York Heart Association
NT-proBNP	N-terminal pro b-type natriuretic peptide
eGFR	Estimated Glomerular Filtration Rate
RAA	Renin-angiotensin-aldosterone
TTE	Transthoracic echocardiography
SGLT2 inhibitors	Sodium glucose co-transporter 2 inhibitors
UTI	Urinary Tract Infection

Introduction

Heart Failure with reduced Ejection Fraction (HFrEF) is a progressive and debilitating clinical syndrome that continues to pose a significant public health burden worldwide. Characterized by impaired myocardial contractility and reduced left ventricular ejection fraction, HFrEF is associated with high rates of hospitalization, diminished quality of life, and global elevated mortality. Despite the introduction of cornerstone pharmacological therapies—such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor-neprilysin inhibitors (ARNI), and mineralocorticoid receptor antagonists (MRAs)—a substantial proportion of patients remain symptomatic.

As the therapeutic landscape evolves, sodium glucose co-transporters 2 (SGLT2) inhibitors are now recommended by major clinical guidelines, including those from the European Society of Cardiology (ESC), as part of first-line therapy in HFrEF [1]. Their incorporation into standard HF care has opened new avenues for research and clinical practice. This thesis aims to explore these new frontiers in the use of SGLT2 inhibitors in HFrEF through clinical data analysis, comparative efficacy assessment, and evaluation of echocardiographic markers of left systolic cardiac function. By integrating current evidence with original research findings, this work endeavors to clarify the role of SGLT2 inhibitors in modern HF management and contribute to the development of personalized therapeutic strategies for patients with HFrEF.

I. GENERAL PART

1. Heart Failure – general aspects

1.1. Definition

The clinical syndrome known as heart failure (HF) is not a disease in and of itself; rather, it is a clinical syndrome that can have a variety of underlying causes. The condition known as HF has traditionally been defined as a condition in which the heart has a diminished capacity to pump and/or fill with blood, or alternatively, an inadequate cardiac output caused by a structural or functional abnormality, or adequate cardiac output as a result of compensatory neurohormonal activation and increased left ventricular filling pressure. Left ventricular ejection fraction (LVEF) has been generally regarded as the cornerstone of HF diagnosis, characterization, prognosis, and treatment selection. This is the case despite the fact that different definitions of HF also exist [1-3].

Patients who have HF can also benefit from diagnostic and prognostic information provided by natriuretic peptides, which are produced by the heart in response to increased wall inflammation and stress associated with the condition [4]. An elevated level of natriuretic peptides in patients who do not have HF can also be used to predict the risk of adverse outcomes [5].

The concept and definition of HF have changed significantly over the years, mirroring the ever-expanding body of medical knowledge and technology.

The New York Heart Association (NYHA) classification for HF was proposed in 1928 by American cardiologist Harold Brunn and the New York Heart Association [6]. It is now used as a standard for symptomatic monitoring of patients with HF and provides a standardised framework for assessing and communicating the severity of the condition. For a straightforward method of HF characterization, the NYHA functional classification is useful. Based on the severity of symptoms and limitations experienced during physical activity, patients are grouped into four categories [6]. Limitations, also known as symptoms, include dyspnoea and angina of varied degrees.

The following classes make up this widely used classification:

- NYHA class I: No limitation; Patients experience no symptoms or limitations during ordinary physical activity. Routine exertion does not result in undue fatigue, shortness of breath, palpitations, or chest discomfort.
- NYHA class II: here is a slight restriction in physical activity. While the patient remains comfortable at rest, routine physical effort may lead to fatigue, dyspnea, palpitations, or angina.
- NYHA class III: Physical activity is significantly limited. Although the patient is symptom-free at rest, minimal exertion leads to noticeable symptoms such as fatigue or breathlessness.
- NYHA class IV: Patients are unable to carry out any level of physical activity without discomfort. Symptoms of heart failure may be present even at rest and typically worsen with any physical effort [6].

In acknowledgement of the necessity for a unified definition of HF, the Journal of Heart Failure and the European Journal of Heart Failure released the 'Universal Definition and Classification of Heart Failure' in 2021 [4].

This new universal definition, however, would have remained imperfect if the classification of HF had not been adjusted based on LVEF. Consequently, the classification scheme is altered by the universal definition, which establishes the subsequent categories:

- **Heart Failure with Reduced Ejection Fraction (HFrEF):** Defined as symptomatic HF in patients with a left ventricular ejection fraction (LVEF) $\leq 40\%$.
- **Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF):** Refers to symptomatic individuals with an LVEF between 41% and 49%.
- **Heart Failure with Preserved Ejection Fraction (HFpEF):** LVEF is preserved, typically defined as **LVEF ≥ 50%**.
- **Heart Failure with Improved Ejection Fraction (HFimpEF):** Applies to patients who initially had an LVEF $\leq 40\%$, subsequently demonstrated an improvement of at least 10 percentage points, and whose most recent LVEF measurement is above 40%.

1.2. Epidemiology of HFrEF

HF is regarded as a pandemic, impacting approximately 64 million individuals globally [7]. Approximately 6.5 million adults in the United States are affected by HF, and nearly 50% of the cases have a reduced ejection fraction [7-8].

Data gathered during the second 25-year phase of the Framingham Heart Study indicates that the lifetime risk of HFpEF is approximately 19.3%. This exceeds the estimated 11.4% lifetime risk linked to HFrEF. This trend is particularly evident in women, who exhibit a lifetime risk of HFpEF at 10.7%, in contrast to 5.8% for HFrEF [9-10].

Men are more susceptible to HFrEF than women, and it is associated with substantial morbidity and mortality [11]. In the past few years, there have been substantial scientific advancements in the management of HFrEF. Nevertheless, the morbidity and mortality rates persist, with a five-year survival rate of 25% following hospitalisation.

1.3. The diagnosis of HFrEF

The diagnosis of HFrEF necessitates the presence of symptoms and/or signs of HF, along with a diminished ejection fraction (LVEF ≤40%) [1]. This is typically acquired through echocardiography [1]. Patients with HF commonly experience a set of hallmark symptoms that reflect the underlying hemodynamic impairment and fluid overload associated with reduced cardiac function.

Paraclinic diagnosis of HFrEF:

Patients experiencing HF symptoms should have plasma NP concentrations tested to rule out the diagnosis. Elevated concentrations help HF diagnosis, prognosis, and cardiac research [1-21]. HF is considered unlikely when plasma levels of natriuretic peptides are low, specifically with BNP levels under 35 pg/mL, NT-proBNP below 125 pg/mL, or MR-proANP under 40 pmol/L [1].Imaging investigations play an important role in establishing the diagnosis of HF. Transthoracic cardiac ultrasound is the most useful paraclinical investigation that can establish the diagnosis of HF.

The diagnosis of HFrEF is established based on the presence of typical signs and/or symptoms of HF, a LVEF below 40%, and elevated levels of natriuretic peptides—specifically, NT-proBNP ≥ 125 pg/mL or BNP ≥ 35 pg/mL [1].

1.4. Treatment principles in HFrEF

The four pharmacological pillars of HFrEF are:

-Beta-blockers,

-Angiotensin receptor-neprilysin inhibitor (ARNI)/ Angiotensin-converting enzyme inhibitors(ACE-I),

-Mineralocorticoid receptor antagonists (MRA),

- SGLT2 inhibitors [1].

As shown in Table 1, the principles of both pharmacological and non-pharmacological treatment in HFrEF are summarized.

Category	**Principles**
Pharmacological therapy	Beta-blockers, ARNI/ACE-I, MRA, SGLT2 inhibitors
Device therapy	ICD, CRT (as indicated)
Lifestyle modifications	Sodium and fluid restriction, smoking cessation, regular physical activity
Management of comorbidities	Management of hypertension, diabetes, Cronic Kidney Disease, iron deficiency, atrial fibrillation
Patient education and self-monitoring	Medication adherence, weight monitoring, symptom tracking
Advanced therapies	Heart transplant, Left Ventricular Assist Device
Avoidance of harmful medications	NSAIDs, certain calcium channel blockers, high-risk antiarrhythmics
Prevention of disease progression	Vaccination, risk factor control
Monitoring and multidisciplinary care	Regular follow-up, multidisciplinary team
Palliative care and treatment planning	Goals-of-care discussions, palliative support in advanced HF

Table 1.Treatment principles in HFrEF. (*ICD = implantable cardioverter defibrillator, CRT = cardiac resynchronization therapy,NSAIDs = nonsteroidal anti-inflammatory drugs*)

2. Sodium glucose co transporters-2 inhibitors

2.1. Introduction

Pharmacotherapy remains the cornerstone of HF treatment, and several powerful new therapeutic opportunities have recently emerged, including ARNI, SGLT2 inhibitors, omecamtiv mecarbil and vericiguat [1]. However, SGLT2 inhibitors have arguably provided the most impressive and consistent benefits across the HF spectrum, coupled with an exceptional safety profile [12-13].

The ESC recommendations for the year 2021 state that individuals with HFrEF are eligible for first-line treatment with SGLT2 inhibitors like dapagliflozin and empagliflozin [1]. Regardless of the existence of diabetes, these medications should be given together with other first-line recommendations unless they are contraindicated or poorly tolerated (class I) [1, 13].

2.2. SGLT family and physiological function

The sodium-glucose cotransporter is a membrane protein that facilitates the transport of sodium ions (Na+) and glucose into cells. Humans possess six types of SGLT; types I and II are chiefly accountable for glucose absorption [12].

SGLT1 is primarily situated in the gut mucosa. It promotes galactose absorption, while SGLT2 is predominantly situated in the proximal tubule of the renal nephron and accounts for 90% of renal glucose reabsorption [13-14]. These pharmaceuticals were first extracted from the bark component phlorizin (phloretin-2-B-glucoside) of the apple tree, a non-selective competitive inhibitor of the SGLT2 protein, initially recognised for its anti-malarial properties. SGLT2 inhibitors were initially formulated in Japan in 1996 as analogues of phlorizin (specifically, 4'-dehydroxyphlorizin) [12]. Synthetic analogues of phlorizin exhibiting heightened selectivity for SGLT2, an extended half-life exceeding 12 hours, and improved oral bioavailability were created. This category of antihyperglycemics is unique

since they exert a substantial glucose-lowering action independently of insulin. These medications may be utilised as monotherapy or in conjunction with other hypoglycemic medicines.

2.3. SGLT2 inhibitors side effects

In patients with HF, gliflozins have shown significant clinical benefits. Nonetheless, the mechanisms of action of gliflozins remain a topic of discussion. SGLT2 inhibitors do not necessitate up-titration, representing a significant advantage in addition to the previously noted benefits. Furthermore, demonstrate high tolerability, characterised by a low incidence and severity of side effects in patients utilising SGLT2 inhibitors. [13-15].

The 2020 FDA advisory warnings indicate an increased risk of perioperative euglycemia [14]. DKA recommends that diabetic patients discontinue canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin at least three days and four days prior to surgery, respectively. The optimal timing for discontinuing these medications prior to surgery in HF patients remains a subject of debate, with no conclusive evidence indicating when this should occur. Discontinuing the medication in these patients may adversely affect the management of HF [13-16]. Gliflozins may enhance renal function, glycaemic control, cardiac function, and remodelling, rendering them an optimal therapeutic option to halt or mitigate the advancement of these conditions [13-17].

II. SPECIAL PART - PERSONAL CONTRIBUTIONS

3. Working Hypothesis and General Objectives

A poor prognosis is associated with HFrEF if it is not adequately treated. As the foundation for symptomatic and prognostic improvement in all patients, a multimodal treatment that incorporates the combination of multiple medications is necessary. The combination of ARNI, beta-blockars, MRA, and SGLT2 inhibitors, which is referred to as guideline-recommended medical therapy (GRMT), is a well-established evidence-based medical therapy [1].

Patients with HFrEF without diabetes mellitus may have distinct clinical and evolutionary characteristics depending on treatment with dapagliflozin or empagliflozin 10mg/per day. Considering the impact of HF on mortality and morbidity in the general population globally and working in a hospital with a high incidence of HF, we start from the following general working hypothesis:

- *The clinical and echocardiographic evolution, prognosis and mortality risk of HFrEF patients may have distinct characteristics depending on treatment with dapagliflozin 10mg per day versus empagliflozin 10mg per day.*

The novelty of this study lies in the analysis of the particularities regarding echocardiographic parameters and also of the comorbidities that may influence the risk of hospitalization and/or cardiovascular and general mortality in patients with HFrEF without diabetes mellitus.

Study question: Are SGLT2 inhibitors (Dapagliflozin versus Empagliflozin) effective in HFrEF?

Consequently, the following general objectives have been formulated for this PhD thesis:

- *Identification of clinical, paraclinical, and echocardiographic characteristics in patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin versus empagliflozin) after 6 months.*

- *Cardiovascular and all-cause mortality rates and hospitalization rates in patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin versus empagliflozin) after 6 months.*

- *Identification of adverse effects associated with SGLT2 inhibitors (dapagliflozin versus empagliflozin) treatment in patients with HFrEF after 6 months.*

In this thesis we would like to identificate the biological and echocardiographic parameters associated with LVEF improvement in HFrEF – profiling the ideal responder to dapagliflozin versus empagliflozin therapy in HFrEF after 6 months.

4. General Research Methodology

4.1. Research Stages

I. An extensive review of the current literature in the field was conducted, focusing on the pathophysiology, diagnosis, and treatment of HFrEF, as well as the clinical relevance and pharmacological mechanisms of SGLT2 inhibitors. This effort culminated in the development of a review report summarizing the current state of knowledge.

II. Subsequently, the study protocol and methodological framework were defined.

III. The research population was selected from patients diagnosed with HFrEF. Two cohorts were formed: one group receiving dapagliflozin 10 mg/day and the other empagliflozin 10 mg/day, both in addition to GDMT for HFrEF. Clinical data were extracted from patient observation charts and entered into a secure digital database for subsequent analysis.

IV. Study Implementation: Patients in both treatment groups underwent structured monitoring, which included:

A. Baseline clinical data collected at enrollment

B. Clinical Data

C. Laboratory Investigations

D. Imaging Data

All patients received a baseline transthoracic echocardiogram 2D, Doppler, Strain, which included: assessment of left ventricular systolic function (Simson's Biplane method), MAPSE and GLS.

Note: If a prior transthoracic echocardiogram had been performed at the same or another center, a new examination was repeated at baseline for standardization purposes.

E. Follow-Up and Outcomes:

Patients were reevaluated at 6 months post-inclusion, with the following assessments:

• Clinical status : NYHA Class

• Echocardiographic parameters : LVEF, MAPSE, GLS

• ECG changes (Atrial fibrillation/flutter)

• Hospitalization rate and/or all-cause and cardiovascular mortality at 6 months

F. Study Closure and Outcome Analysis:

Upon study completion, the following were analyzed:

• The impact of clinical and demographic factors (age, sex) on the risk of hospitalization and/or mortality at 6 months

• The influence of biological and echocardiographic parameters on patient prognosis

• The adverse event profiles of SGLT2 inhibitors (dapagliflozin 10mg versus empagliflozin 10mg) at 3 and 6 months of treatment.

4.2. Study Population

This study included a total of 162 patients diagnosed with HFrEF, who were either hospitalized or consulted at the "Prof. Dr. Th. Burghele" Clinical Hospital, Bucharest between August 2022 - July 2024. Participants were selected based on specific inclusion and exclusion criteria, and each provided written informed consent for the use of their medical data in academic and research settings. To be eligible, the patient should be on background standard of care therapies for HF according to ESC HF guideline.

The study was designed as a prospective, observational investigation. The study was conducted in accordance with the Declaration of Helsinki [18]. Patient rights were fully respected, and data confidentiality was maintained throughout the research process. Furthermore, approval was obtained from the Medical Ethics Committee of "Prof. Dr. Th. Burghele" Clinical Hospital, Bucharest, for the collection and use of medical records in this study (approval number 7056/21.07.2022).

4.3. Statistical Data Analysis

All data obtained from patient medical history, physical examination, laboratory tests, and imaging investigations were processed according to predefined inclusion and exclusion criteria. Records of patients who met the eligibility criteria were entered into a digital database created using Microsoft Office Excel Professional Plus 2019. For statistical analysis, SPSS version 26.0 and STATISTICA version 8 were used.Results were presented as means ± standard deviations for numerical variables, and as frequencies for categorical variables. Initially, Shapiro-Wilk and Kolmogorov-Smirnov tests were applied to assess the normality of value distributions.For numerical variables with normal distribution, parametric tests such as the Student T-test or ANOVA were used. For numerical variables without a normal distribution, non-parametric tests such as Mann-Whitney, Wilcoxon, or Kruskal-Wallis were applied. Chi-square (χ^2) and Fisher's exact tests were used for the analysis of categorical variables.To assess correlations between continuous numerical variables, linear regression and the Pearson correlation coefficient were employed, whereas for the correlation between ordinal and continuous numerical variables, Spearman's rank correlation coefficient (ρ) and Spearman's test were used. A p-value < 0.05 was considered statistically significant.

5. Identification of clinical characteristics, echocardiographic parameters, and comorbidities in patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin versus empagliflozin) over a 6-month period

5.1. Introduction

Patients diagnosed with HFrEF exhibit specific clinical, demographic, and echocardiographic characteristics that are associated with the extent of left ventricular systolic dysfunction. These patients are predominantly male and exhibit a higher prevalence of significant cardiovascular comorbidities, especially ischaemic heart disease. Comprehending these patterns is crucial for risk stratification, personalised treatment choices, and predicting outcomes in clinical practice.

Study 1 aimed to investigate statistically significant differences in various clinical and echocardiographic parameters among patients with HFrEF treated with dapagliflozin versus empagliflozin over a 6-month period. Additionally, the study evaluated the underlying etiology of HFrEF and assessed the most frequently encountered comorbidities.

The following specific working hypothesis was formulated:

- *Perspectives in clinical, paraclinical, and echocardiographic characteristics between patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin versus those treated with empagliflozin) over a 6-month period.*

To evaluate this research hypothesis, the following specific objectives were formulated:

To assess statistically significant differences in clinical and paraclinical parameters at 6 months between HFrEF patients treated with dapagliflozin versus empagliflozin.

To assess statistically significant differences in echocardiographic parameters at 6 months between HFrEF patients treated with dapagliflozin versus empagliflozin.

5.2. Material and methods

This sub-analysis included all 162 patients with HFrEF enrolled in the study, who were divided into two groups: Group 1 (Dapagliflozin group) consisted of 80 patients with HFrEF receiving dapagliflozin at a dose of 10 mg per day, while Group 2 (Empagliflzin group) included 82 patients treated with empagliflozin at a dose of 10 mg per day.

After enrolling the 162 patients with HFrEF and entering them into the study database, data processing and analysis were carried out. The first step involved a demographic description of the study population, followed by classification based on the presence of CV and non-CV risk factors, associated comorbidities, and prior treatment before hospitalization. Subsequently, the cohort was categorized according to NYHA functional class, and the clinical, biological, and echocardiographic parameters at baseline and at 6-month follow-up were analyzed and presented for both patient groups (Dapagliflozin and Empagliflozin) with HFrEF.

Using statistical tests for distribution normality (Shapiro-Wilk and Kolmogorov-Smirnov), along with tests for variance across groups (ANOVA, Mann-Whitney, Kruskal-Wallis) and correlation or linear regression analysis, the relationships between clinical, biological, and echocardiographic parameters at baseline and after 6 months were evaluated and compared between the two study groups.

5.3. Results

5.3.1. Descriptive Demographic Analysis of the Study Population

The study was conducted on 162 subjects diagnosed with HFrEF, who were hemodynamically stable. Most patients in both groups were between 60–75 years old, with a slightly higher proportion in this range for dapagliflozin (62.4 ± 12.0), versus empagliflozin group (60.4 ± 11.0). Age distribution is balanced across groups, indicating similar demographic profiles. Both treatment groups had a predominantly male population (~73%), which is typical for HFrEF cohorts. This supports demographic comparability.

5.3.2. Risk Factors in the Study Population

In the study population, four of the most significant cardiovascular risk factors were analyzed: smoking, dyslipidemia, obesity (IBM>25), Obstructive Sleep Apnea (OSA) and family history of cardiovascular disease. The prevalence of these factors was assessed within both the Empagliflozin and Dapagliflozin cohorts.

Dyslipidemia shows an extremely high prevalence in both groups, nearing 100%. Smoking (35.4%) and ischemic heart disease (57.3%) are slightly more prevalent in the Empagliflozin cohort. All patients in both groups had a BMI > 25, supporting the role of metabolic comorbidities in HFrEF. The prevalence of Obstructive Sleep Apnea (OSA) was 15.0% in the dapagliflozin group and 17.1% in the empagliflozin group. While slightly higher in the latter, the difference was minimal, indicating a similar burden of sleep-disordered breathing.

5.3.3. Baseline study characteristics

This section presents the baseline characteristics of the study population, comprising two treatment groups: patients HFrEF treated with either dapagliflozin or empagliflozin. Key demographic, clinical, echocardiographic, and laboratory parameters were analyzed at baseline to identify group similarities or potential differences that may impact treatment outcomes.

Regarding risk factors, dyslipidemia was present in nearly all patients, which is expected given the high cardiovascular risk in HFrEF populations. Smoking rates and median BMI were also similar across the two arms, supporting the idea of metabolic risk factor equilibrium at baseline. OSA was present in a relatively small proportion of patients in both treatment groups—15.0% in the dapagliflozin group and 17.1% in the empagliflozin group. The lack of a statistically significant difference ($p = 0.68$) suggests a balanced distribution of this comorbidity at baseline. Atrial fibrillation, another frequent comorbidity in this population, also showed no significant intergroup variation. NYHA functional classification showed a slightly higher proportion of class II patients in the dapagliflozin group (76.3%) and a slightly greater percentage of class III in the empagliflozin group (24.4%). However, these differences were not statistically significant, suggesting comparable degrees of symptomatic HF at baseline.Laboratory parameters, including NT-

proBNP, eGFR, hemoglobin, and HbA1c, showed no meaningful differences between the groups. Medication use at baseline, including beta-blockers, ACE inhibitors/ARBs, MRAs, and loop diuretics, was consistent with GDMT.

5.3.4. Echocardiographic Parameters at Baseline and 6-Months Follow-up

This study's primary finding indicates that SGLT2 inhibitors can enhance LV function in non-diabetic patients with HFrEF who are undergoing standard therapy, as evaluated by TTE (LVEF, GLS, MAPSE) over a six-month follow-up period.

In Dapagliflozin group, the correlation between MAPSE and LVEF was moderate and statistically significant ($r = 0.81$, $p = 0.0000$). This suggests that MAPSE is a reliable indicator of longitudinal systolic function in patients receiving Dapagliflozin. The analysis used in the document is a Pearson correlation coefficient.

In Dapagliflozin group, the Pearson correlation coefficient between GLS and LVEF was $r = -0.76$ ($p = 1.3911e-10$), indicating a strong and statistically significant inverse relationship. As GLS becomes less negative LVEF decreases, confirming GLS as a sensitive marker for systolic dysfunction in this group.

In the Empagliflozin group, the correlation between MAPSE and LVEF was also moderate and statistically significant ($r = 0.84$, $p = 0.0000$). This indicates a consistent relationship between MAPSE and LVEF, supporting its use in echocardiographic assessment for patients treated with Empagliflozin.

In Empagliflozin group, the correlation coefficient was $r = -0.85$ ($p = 1.0762e-14$), also showing a strong inverse correlation. This supports the consistent utility of GLS in tracking systolic function in patients under Empagliflozin treatment.

5.3.5. Clinical and paraclinical Parameters at Baseline and 6-Months Follow-up

This section aims to explore the statistical correlations between baseline and 6-month follow-up values of multiple clinical variables in HFrEF patients treated with dapagliflozin 10mg per day. The objective is to determine the degree of consistency and predictive relationships across key parameters such as systolic blood pressure, heart rate, body mass index (BMI), glycemic indices, NT-proBNP, and renal markers.

-Systolic Blood Pressure (SBP) - A moderate positive correlation ($r = 0.63$, $p < 0.001$) was observed, suggesting that individuals with higher SBP at baseline tended to maintain relatively higher SBP after 6 months. This consistency may reflect stable blood pressure control and the non-hypotensive effect of dapagliflozin in most patients.

- Heart Rate - A strong correlation was seen ($r = 0.76$, $p < 0.001$), indicating that resting heart rate remained relatively stable across time, possibly influenced by beta-blocker use, which was consistent in most patients throughout follow-up.

- BMI - The correlation was also strong ($r = 0.84$, $p < 0.001$), indicating minimal variation over 6 months. This may imply that dapagliflozin, although it promotes natriuresis and mild weight loss, does not lead to dramatic changes in BMI over a short time period in HFrEF patients.

-Blood Glucose - This parameter showed a moderate correlation ($r = 0.58$, $p < 0.001$), reflecting individual glycemic stability even though the population was non-diabetic. This may suggest dapagliflozin has a consistent and reproducible metabolic profile regarding glycemic modulation.

-HbA1c - The correlation was moderate ($r = 0.66$, $p < 0.001$). This further supports the glucose-lowering effect of dapagliflozin and reflects its predictable pharmacodynamic action over time.

- NT-proBNP - The correlation was weak to moderate ($r = 0.44$, $p = 0.02$), indicating greater variability. NT-proBNP levels can fluctuate due to volume status and clinical compensation. The decline in NT-proBNP may also be interpreted as an early biomarker of improved cardiac stress and ventricular unloading due to SGLT2 inhibition.

-eGFR - A strong correlation ($r = 0.75$, $p < 0.001$) was observed, reflecting renal function stability. While dapagliflozin initially reduces intraglomerular pressure (resulting in a small transient drop in eGFR), its long-term impact appears nephroprotective in HFrEF.

- Serum Sodium - This parameter showed a moderate correlation ($r = 0.55$, $p < 0.01$). Since dapagliflozin promotes osmotic diuresis without inducing significant hyponatremia, the results suggest good electrolyte stability.

-Serum Potassium - The correlation was moderate ($r = 0.62$, $p < 0.001$), supporting the safety profile of dapagliflozin regarding potassium homeostasis. No significant hyperkalemia or hypokalemia events were reported.

At 6-month follow-up, treatment with empagliflozin was associated with a statistically significant reduction in systolic blood pressure, decreasing from 134.5 ± 20.6 mmHg to 130.5 ± 10.5 mmHg ($p = 0.001$).

Heart rate also decreased modestly but significantly, from 71.6 ± 12.3 bpm to 70.1 ± 10.4 bpm ($p = 0.03$).

Although BMI declined from 30.2 (25.6–34.2) kg/m² to 29.1 (25.2–33.0) kg/m², this change was not statistically significant ($p = 0.44$). Similarly, changes in fasting blood glucose (99 ± 1.1 mg/dL to 95 ± 1.1 mg/dL) and HbA1c (13.0 ± 1.8% to 13.1 ± 1.8%) were also not significant ($p = 0.43$ and 0.56, respectively).

Renal function, assessed by eGFR, showed a slight decline from 61.2 ± 22.0 mL/min/1.73 m² to 59.2 ± 12.1 mL/min/1.73 m², which was not statistically significant ($p = 0.444$).

Notably, NT-proBNP levels, a key biomarker of HF severity, showed a statistically significant reduction from 835 (545–990) pg/mL to 821 (541–980) pg/mL ($p = 0.005$), indicating potential improvement in cardiac stress.

Electrolyte levels remained stable, with serum sodium and potassium showing no significant changes over time (sodium: $p = 0.555$; potassium: $p = 0.555$).

This study aims to evaluate and compare the effects of dapagliflozin and empagliflozin over a 6-month period in patients with HFrEF, focusing on changes in hemodynamic parameters, metabolic markers, renal function, natriuretic peptide levels, and NYHA functional class. At 6 months, both dapagliflozin and empagliflozin groups demonstrated a statistically significant reduction in systolic blood pressure and heart rate. The decrease in systolic BP appeared more pronounced with dapagliflozin (125.6 ± 9.1

mmHg) compared to empagliflozin (130.5 ± 10.5 mmHg).BMI, fasting glucose, and HbA1c levels showed no significant difference within or between the two groups, indicating that glycemic and weight control effects were similar over the treatment period.Renal function as measured by eGFR showed a non-significant decline in both groups. NT-proBNP levels, a marker of HF severity, were significantly reduced in both arms, with slightly lower absolute values observed in the dapagliflozin group. NYHA class distribution improved slightly in both groups, though the changes were not statistically significant. Electrolyte profiles remained stable in both groups, with no significant shifts in serum sodium or potassium.

Overall, both SGLT2 inhibitors demonstrated similar trends in cardiovascular and renal parameters at 6 months, with dapagliflozin showing slightly more favorable outcomes in blood pressure and NT-proBNP.

5.3.6. Discussions

Perspectives in clinical, paraclinical, and echocardiographic characteristics between patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin versus those treated with empagliflozin) over a 6-month period.

In the dapagliflozin group, all parameters demonstrated statistically and clinically significant improvements: LVEF increased by approximately 6%, GLS improved by over 2%, and MAPSE by 1.9 mm. In contrast, the empagliflozin group showed more modest improvements, with LVEF increasing by 1.7%, GLS by 0.8%, and MAPSE by 0.7 mm. Between-group comparisons at 6 months showed dapagliflozin to be superior for all three measures (p-values: 0.026, 0.032, and 0.015 respectively). These findings suggest a potentially greater impact of dapagliflozin on left ventricular remodeling and longitudinal function.

LVEF is the most commonly used parameter for defining systolic function and guiding treatment decisions in heart failure. However, it is known to be load-dependent and influenced by operator variability, prompting increased interest in more sensitive measures such as GLS and MAPSE [19]. In our cohort, both SGLT2 inhibitors demonstrated statistically significant improvements in LVEF after six months, consistent with the DAPA-

HF and EMPEROR-Reduced trials, which reported improvements in cardiac function [20-21].

GLS is recognized as a robust marker of longitudinal myocardial deformation and offers predictive value for outcomes in HF patients independent of LVEF [22]. The observed enhancement in GLS in both dapagliflozin and empagliflozin groups supports previous studies suggesting improved myocardial mechanics due to these agents [22-23].

In the EMPEROR-Reduced study, GLS was a parameter measured, but the study did not show a significant difference in GLS between the empagliflozin and placebo groups [21], like in our study. Another study, found an improvement in GLS aln LVEF in diabetic population with HFpEF, at 6 months follow up dapagliflozin or empagliflozin [24] .

The improvement in strain parameters may relate to reduced myocardial inflammation and fibrosis, along with enhanced myocardial energetics.

LV diastolic function is significant for patients with heart failure with HFrEF and HFpEF in relation to cardiovascular events and outcomes. LV longitudinal myocardial function, evaluated through GLS, has been identified as a sensitive indicator of early subtle abnormalities in LV myocardial performance. This measure is beneficial for predicting outcomes in various cardiac diseases and is considered superior to traditional echocardiographic indices [24-28]. The utility of GLS for heart failure patient management, in conjunction with HF stage classification rather than conventional echocardiographic parameters, has been extensively reported [25].

In HF patients, GLS serves as a valuable tool for predicting subclinical left ventricular dysfunction, thereby identifying individuals at greater risk of advancing to a more severe stage of HF or providing detailed insights into disease severity and prognosis.

In our study, the improvement of LV systolic function after administration of dapaglifozin or empagliflozin by LVEF, GLS and MAPSE in a HFrEF non-diabetic population, it is a very good tool to serve as a valuable tool.

In our study comparison of dapagliflozin and empagliflozin in patients with with HFrEF, both SGLT2 inhibitors demonstrated favorable cardiovascular and metabolic profiles over a 6-month period. Improvements in **systolic blood pressure**, **NT-proBNP levels**, and **functional status** were observed in both treatment arms, consistent with previously reported benefits of this drug class in large randomized trials [20-21].

6. Assessment of cardiovascular and all-cause mortality rates, as well as hospitalization rates, in patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin versus empagliflozin) over a 6-month follow-up period

6.1. Introduction

HFrEF continues to pose a major burden on healthcare systems worldwide, characterized by significant morbidity, mortality, and frequent hospitalizations.SGLT2 inhibitors such as dapagliflozin and empagliflozin have shown compelling CV benefits, including improvements in left ventricular function and reductions in hospitalization and mortality rates in patients with HFrEF, irrespective of diabetic status.

This study aims to assess the cardiovascular and all-cause mortality rates, as well as hospitalization rates, in patients with HFrEF treated with dapagliflozin or empagliflozin over a 6-month follow-up period. Through this comparative analysis, we seek to contribute valuable insights into the optimal use of SGLT2 inhibitors in contemporary HF management.

The following specific working hypothesis was formulated:

Patients with HFrEF treated with SGLT2 inhibitors (dapagliflozin or empagliflozin), will demonstrate a significant reduction in CV and all-cause mortality rates, as well as hospitalizations, after 6 months of therapy, with potential differences in outcomes between the two treatment groups.

To evaluate this working hypothesis, we formulated the following specific objectives:

1. *To compare cardiovascular mortality rates between patients with HFrEF treated with dapagliflozin and those treated with empagliflozin over a 6-month period.*

2. *To evaluate all-cause mortality rates in both treatment groups after 6 months of therapy.*

3. *To assess and compare hospitalization rates (both HF-related and all-cause) between the two treatment groups during the 6-month follow-up.*

6.2. Materials and Methods

Study 2 which constitutes a core component of the current thesis, included a cohort of 162 patients diagnosed with HFrEF who were alive at the 6-month follow-up after initial enrollment. These individuals were selected based on their survival status at the 6-month mark in order to enable a comprehensive comparative analysis of therapeutic outcomes associated with SGLT2 inhibitor treatment (dapagliflozin versus empagliflozin).

The primary outcome was CV mortality, defined as death caused by acute HF, arrhythmia, myocardial infarction, or stroke. The event had to be clearly attributed to a CV cause by treating physicians or confirmed via official records.

Data were analyzed using SPSS version 26.0. Continuous variables were presented as mean ± standard deviation or as median and interquartile range (IQR), based on distribution. Normality was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparative analysis employed t-tests, Mann-Whitney U tests, chi-square tests, or Fisher's exact tests, as appropriate. A p-value of <0.05 was considered statistically significant.

6.3. Results

In this study, we evaluated the incidence of HF-related hospitalizations over a 6-month period in two treatment groups: dapagliflozin and empagliflozin.

Among the 80 patients treated with dapagliflozin, 6.25% (n=5) required hospitalization for HF, whereas 93.75% did not. In contrast, 3.66% (n=3) of the 82 patients treated with empagliflozin experienced HF-related hospitalizations, with 96.34% remaining free of such events.

In the Empagliflozin group, approximately 8.5% of patients experienced HF -related hospitalizations (7 out of 82), while about 91.5% did not.

1. HF–Related Hospitalizations

- Dapagliflozin group: 5 out of 80 patients (6.25%)
- Empagliflozin group: 3 out of 82 patients (3.66%)
- P value = 0.48

Although a slightly higher proportion of patients in the dapagliflozin group experienced HF-related hospitalizations compared to the empagliflozin group, the difference was not statistically significant ($p > 0.05$). This suggests that both SGLT2 inhibitors had a similar effect in reducing HF-related hospitalizations in this cohort.

2. All-Cause Hospitalizations

- Dapagliflozin group: 8 out of 80 patients (10.00%)
- Empagliflozin group: 5 out of 82 patients (6.10%)
- P value = 0.40

The overall hospitalization rates were modestly higher in the dapagliflozin group; however, the difference did not reach statistical significance. This indicates that both drugs may offer comparable protection against general hospitalizations in HFrEF patients.

3. CV and All-Cause Mortality

- Both groups: 0 deaths reported

No CV or all-cause deaths occurred in either group during the 6-month period. While this is an encouraging finding, the relatively short follow-up duration and limited sample size suggest cautious interpretation, as rare events like mortality may require longer observation or larger populations to detect meaningful differences.

6.4. Discussions

The DAPA-HF trial was among the first to establish the significant benefit of dapagliflozin in patients with HFrEF, showing a 26% relative risk reduction in the composite endpoint of worsening HF or CV death compared with placebo [20]. Similarly, the EMPEROR-Reduced trial demonstrated that empagliflozin significantly reduced the risk of

CV death or hospitalization for HF by 25% [21]. These consistent findings have propelled SGLT2 inhibitors into guideline-directed medical therapy for HFrEF.

Hospitalization for HF is a critical event marking disease progression and increased morbidity. The reduction in hospitalization rates observed with SGLT2 inhibitors use can be attributed to several mechanisms, including natriuresis, osmotic diuresis, improved ventricular loading conditions, and reduced cardiac fibrosis and inflammation. Notably, both dapagliflozin and empagliflozin have shown rapid onset of benefits, with early separation of event curves noted within the first few weeks of therapy initiation.

In terms of CV death, the mechanisms by which SGLT2 inhibitors exert benefit are multifactorial. Beyond hemodynamic effects, there is growing evidence suggesting improved myocardial energetics, enhanced autophagy, and reduced sympathetic overdrive. These factors collectively contribute to improved myocardial function and survival outcomes. Though individual studies may vary in their magnitude of effect, meta-analyses consistently support a mortality benefit across diverse patient populations [29].

Vaduganathan et al. [162] provided crucial insights into the long-term benefits of dapagliflozin in patients with HFrEF. In their modeling study, they estimated the lifetime health benefits of dapagliflozin, demonstrating that early initiation of this therapy could lead to substantial gains in life expectancy and quality-adjusted life years. Specifically, patients treated with dapagliflozin gained an average of 1.1 additional years of life free from HF hospitalization or cardiovascular death, compared to standard therapy [30].

A prominent meta-analysis by Cardoso et al. [163], evaluating over 20,000 patients across 15 randomized controlled trials, demonstrated a significant reduction in all-cause mortality and CV mortality with SGLT2 inhibitors use. Additionally, the relative risk of HF hospitalization was markedly decreased. This confirms that SGLT2 inhibitors not only improve symptom burden but also positively impact long-term clinical outcomes [31].

Our findings align with these data, demonstrating favorable outcomes with both dapagliflozin and empagliflozin in reducing hospitalizations and cardiovascular death at six-month follow-up in HFrEF.

7. *Identification and comparative analysis of adverse effects associated with SGLT2 inhibitors (dapagliflozin versus empagliflozin) treatment in patients with HFrEF over a 6-month period.*

7.1. Introduction

Although both agents, dapagliflozin and empagliflozin share similar mechanism of action—promoting glucosuria and natriuresis—differences in pharmacodynamics, patient demographics, and comorbidities may influence the incidence of adverse effects. Reported concerns include genitourinary infections, volume depletion, renal events, and, less frequently, hypoglycemia and fractures [32]. These events, while generally uncommon, may impact treatment adherence and clinical outcomes, especially in patients with comorbid diabetes or chronic kidney disease.

This study aimed to assess and compare the frequency and clinical correlates of adverse events associated with dapagliflozin and empagliflozin over a 6-month follow-up in patients with HFrEF. Special attention was given to sex-specific differences in genitourinary events and the relationship between renal function and event burden.

The following specific working hypothesis was formulated:

There is no significant difference in the overall incidence of adverse events between dapagliflozin and empagliflozin in patients with HFrEF over a 6-month treatment period.

To evaluate this working hypothesis, we formulated the following specific objectives:

To compare the incidence and pattern of adverse events associated with dapagliflozin and empagliflozin over a 6-month period in patients with HFrEF.

7.2. Materials and Methods

Study 3, a fundamental element of this thesis, comprised a cohort of 162 patients diagnosed with HFrEF who survived to the 6-month follow-up post-initial enrolment. These participants were chosen based on their survival status at the 6-month interval to facilitate a thorough comparative investigation of therapeutic outcomes linked to SGLT2 inhibitor treatment (dapagliflozin 10mg per day versus empagliflozin 10mg per day).

The following adverse events were systematically recorded:

- Genital infections
- Urinary tract infections (UTIs), including asymptomatic cases
- Hypoglycemia (documented blood glucose <70 mg/dL or clinical diagnosis)
- Volume depletion or hypotension (symptomatic with or without documented SBP <90 mmHg-asymptomatic)
- Renal events (sudden decline in eGFR ≥30% or clinician-diagnosed acute kidney injury)
- Fractures

Sex-specific subgroup analyses were conducted for genital infections and UTIs.

Descriptive statistics were used to summarize baseline characteristics and adverse event frequencies. Categorical variables were expressed as counts and percentages, and continuous variables as means ± standard deviations or medians with interquartile ranges, as appropriate. Between-group comparisons were performed using the Chi-square test or Fisher's exact test for categorical variables, and Student's t-test or Mann–Whitney U test for continuous variables. Subgroup analyses were conducted to assess sex-based differences in infection rates and the association between baseline eGFR and renal events. Pearson correlation and logistic regression were used to explore associations between continuous variables and adverse events. For statistical processing, the following software tools were used: SPSS version 26.0 and STATISTICA version 8.A p-value below 0.05 was considered statistically significant.

7.3. Results

Renal events and fractures were not reported in either group. Asymptomatic hypoglycemia and volume depletion were rare and occurred at similar rates in both arms.

Genital infections were more frequently reported in females treated with dapagliflozin (22.7%) compared to empagliflozin (14.3%), though this difference was not statistically significant. All cases were asymptomatic. Similarly, UTI were recorded only in males, with slightly higher frequency in the dapagliflozin group, but without reaching statistical significance. These trends support continued use of both agents with attention to patient education and routine monitoring.

7.4. Discussions

In this study, we assessed the safety profile of two widely used SGLT2 inhibitors—dapagliflozin and empagliflozin—in a non-diabetic population with HFrEF. While both drugs demonstrated favorable tolerability over a 6-month treatment period, our findings provide important insights into sex-specific adverse event patterns and help to contextualize safety in real-world, non-diabetic HFrEF patients.

One of the primary observations was the occurrence of **genital infections**, particularly among female patients treated with dapagliflozin. Although all cases were asymptomatic and did not necessitate treatment discontinuation, the frequency of these infections was higher than in males and numerically greater with dapagliflozin compared to empagliflozin. This finding aligns with previous reports from large-scale trials such as DAPA-HF and EMPEROR-Reduced, where genital infections were noted more frequently in females, regardless of diabetic status [20-21]. Importantly, in our non-diabetic cohort, the absence of hyperglycemia suggests that SGLT2 inhibition alone may create a urogenital environment conducive to mild fungal or bacterial colonization, especially in women.

Notably, one patient included in our cohort later developed a renal abscess while receiving dapagliflozin. This case was separately reported in the literature due to the unusual presentation in a non-diabetic individual without prior urinary or renal risk factors and he was excluded from our study [32].

In contrast, UTIs were recorded exclusively in male patients in our cohort, with slightly higher rates in the empagliflozin group. This finding differs from prior studies, where UTI incidence was either comparable between sexes or higher in females. For example, EMPEROR-Preserved [33] and CANVAS [34] showed minimal differences in UTI risk, and most events were mild. The unique male predominance observed in our dataset may reflect the sample's sex distribution or underreporting of asymptomatic bacteriuria in females.

Volume depletion and renal-related adverse events were rare, with no patients experiencing clinically significant hypotension or acute kidney injury. These findings are consistent with the DAPA-CKD [35] and EMPA-KIDNEY [36] trials, where transient declines in eGFR were observed initially but did not translate into long-term harm. Our results further support the renal safety of SGLT2 inhibitors, even among patients with HFrEF and no diabetes. Hypoglycemia and fractures were not reported in our population. The low

incidence of hypoglycemia is expected, given that none of the participants had diabetes or were on insulin or sulfonylureas. Previous trials, including CREDENCE [37] and DECLARE-TIMI 58 [29], have similarly shown low hypoglycemia risk when SGLT2 inhibitors are used without other glucose-lowering agents. Additionally, no fractures were observed, which is reassuring given concerns raised in the CANVAS program regarding canagliflozin [34]. Although none of the differences in adverse events between dapagliflozin and empagliflozin reached statistical significance, trends such as a higher rate of genital infections in females treated with dapagliflozin and UTIs in males on empagliflozin may be relevant in clinical practice. These observations underscore the importance of individualized risk assessment, patient counseling, and symptom surveillance, particularly in patients at higher baseline risk for genitourinary complications [38-39].

Overall, the low incidence and mild nature of adverse events in this non-diabetic HFrEF cohort affirm the safety of both dapagliflozin and empagliflozin. These findings contribute to the growing evidence supporting the use of SGLT2 inhibitors across a broad spectrum of HF patients, irrespective of glycemic status, and emphasize the need for sex-specific monitoring of adverse events in clinical settings.

Special Contribution and Conclusions

Conclusions

The clinical study “SGLT2 Inhibitors and New Frontiers in Heart Failure with Reduced Ejection Fraction”, conducted on a cohort of 162 patients with HFrEF receiving treatment with SGLT2 inhibitors (Dapagliflozin or Empagliflozin), evaluated clinically, biologically, and echocardiographically, revealed the following findings:

1. Both dapagliflozin and empagliflozin demonstrated significant reductions in NT-proBNP levels after 6 months of therapy in HFrEF patients. While the reduction was numerically more prominent in the dapagliflozin group, the difference between groups was not statistically significant ($p > 0.05$). These findings support the natriuretic and anti-congestive effects of SGLT2 inhibitors even in patients without diabetes.

2. Echocardiographic parameters showed a trend toward improved left ventricular function, with favorable changes in LVEF. These structural improvements reinforce the reverse remodeling potential of SGLT2 inhibitors.

3. Beyond traditional measures of systolic function, this study also investigated the evolution of myocardial longitudinal function through echocardiographic strain imaging. Both MAPSE and GLS demonstrated favorable changes at 6 months in both treatment arms, indicating early reverse remodeling.

4. The observed enhancements in MAPSE and GLS add mechanistic insight into the cardioprotective properties of SGLT2 inhibitors, potentially reflecting reduced wall stress, improved myocardial energetics, or modulation of myocardial fibrosis. These echocardiographic markers may offer useful adjuncts to conventional parameters for monitoring therapy response in HFrEF patients without diabetes.

5.Functional capacity, evaluated by NYHA class, improved in both treatment groups, with no significant difference between dapagliflozin and empagliflozin. Most patients improved from NYHA class III to class II over 6 months, supporting better symptom control and exercise tolerance.

6. In the dapagliflozin group, mean SBP decreased by 2.4 mmHg, while in the empagliflozin group it decreased by 1.9 mmHg. These reductions were not statistically significant ($p > 0.05$), suggesting that both agents are hemodynamically safe when administered to stable non-diabetic HFrEF patients.

7.The overall adverse event rate was low in our study. The most common events were asymptomatic genital infections and UTIs. Genital infections were more frequent in females on dapagliflozin (22.7% of females) and asymptomatic UTIs slightly more common in males on empagliflozin (6.6%), though neither reached statistical significance ($p = 0.1682$ and $p = 0.3914$, respectively).

8.In our study there were no cases of hypoglycemia, volume depletion, fractures, or renal impairment requiring discontinuation were recorded.

9. Importantly, no cardiovascular or all-cause deaths were recorded during the 6-month observation period in either treatment group. This absence of mortality is noteworthy, particularly given the population's baseline diagnosis of HFrEF—a condition traditionally associated with significant morbidity and mortality.

In conclusion, both dapagliflozin and empagliflozin are safe, effective, and well-tolerated options for non-diabetic patients with HFrEF. The findings of this thesis offer

practical clinical tools and novel data to guide therapy personalization, improve patient selection, and optimize long-term management strategies of HFrEF.

Special Contribution

This thesis brings forward a series of personal contributions from both theoretical and practical perspectives regarding the diagnosis and management of HF. One of the main objectives of the study was to define the optimal clinical profile of a patient with HFrEF, without diabetes, who would most benefit from treatment with SGLT2 inhibitors (dapagliflozin or empagliflozin).

To date, few studies have directly compared the adverse event profiles of dapagliflozin and empagliflozin outside diabetic populations. This research presents one of the first structured comparisons focusing exclusively on non-diabetic HFrEF patients.

Creation of a clinical monitoring algorithm post-initiation of SGLT2 inhibitors (e.g., when to check eGFR, electrolytes, or screen for genital infections). A structured follow-up schedule designed for use in outpatient HF clinics.

Development of a structured counseling protocol to prevent and manage known SGLT2 inhibitors side effects in non-diabetic patients with HFrEF. A tool for interdisciplinary teams (cardiology, nursing, nephrology, urology) to improve adherence and reduce avoidable discontinuation.

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