Universitat de Girona
Facultat de Medicina

ASSOCIATION OF SGLT2I TREATMENT WITH FUNCTIONAL CAPACITY IN PATIENTS WITH OR WITHOUT TYPE 2 DIABETES MELLITUS WITH HEART FAILURE AND REDUCED EJECTION FRACTION.

FINAL DEGREE PROJECT

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Girona, January 2022.

I would like to thank Dr. Marco Paz for guiding me in this work, for offering me his help and knowledge and for making it possible. I would also like to thank Dr. Elisabeth Pujol for her selfless help and involvement in the work.

To the entire Cardiology Service of the Hospital Santa Caterina in Girona, for the welcome and treatment received during my clinical internship. I have learned a lot about Cardiology thanks to them.

I would also like to thank Dr. Abel López for his involvement and effort. For guiding and advising me in the realization of the work, he has been a fundamental piece. Thanks also to Marc Sáez, for his patience and generosity.

Gracias a mis padres, por hacer posible esta etapa de mi vida, por su sacrificio y por su apoyo incondicional. Gracias familia y amigos por acompañarme durante estos 6 años.

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ABBREVIATIONS

HF	Heart failure
SGLT2i	Sodium-glucose cotransporter type 2 inhibitor
LV	Left ventricle
LVEF	Left ventricular ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure mildly reduced ejection fraction
PTE	Pulmonary thromboembolism
COPD	Chronic obstructive pulmonary disease
NYHA	New York Heart Association
AHA	American Heart Association
BMI	Body mass index
HbA1c	Glycosylated haemoglobin
GFR	Glomerular filtration rate
AF	Atrial fibrillation
ADH	Antidiuretic hormone
MI	Myocardial infarction
T2DM	Type 2 Diabetes Mellitus
AHT	Arterial hypertension
CKD	Chronic kidney disease
CHF	Chronic heart failure
NPs	Natriuretic peptides
NSAIDs	Non-steroidal anti-inflammatory drugs

ACE-I	Angiotensin-converting enzyme inhibitors
ARNI	Angiotensin receptor-neprilysin inhibitor
MRA	Mineralocorticoid receptor antagonists
CV	Cardiovascular
ESC	European Society of Cardiology
FFA	Free fatty acids
FC	Functional capacity
MET	Metabolic equivalent of task
RER	Respiratory exchange rate
VT	Ventilatory thresholds
CPET	Cardiopulmonary exercise stress test
VO2	Oxygen volume
FVC	Forced vital capacity
FEV1	Maximum exhaled volume
PETO2	
and PETCO2	Tele expiratory partial pressure
BNP	Brain natriuretic peptide
MLHFQ	Minnesota living with heart failure questionnaire
HRQL	Health related quality of life
LA	Left atrium

ABSTRACT

Background: Heart failure (HF) is a serious and common condition in clinical practice. The estimated prevalence of HF in developed countries in the adult population is 2% and increases to 10% in the elderly. HF is the leading cause of hospitalization in the United States and Europe. It implies a high economic cost for the health system and a great loss of quality of life. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially developed for the treatment of diabetes mellitus due to their hypoglycaemic activity. Around 40% of HF patients have type 2 Diabetes Mellitus (T2DM). SGLT2i show metabolic and hemodynamic effects, which justify their efficacy in T2DM and HF treatment. They have shown, in several studies like DAPA-HF or EMPEROR-reduced, to reduce cardiovascular and all-cause mortality and HF hospitalization in diabetic and non-diabetic patients. So, they have become a first-line treatment in HF with reduced ejection fraction (HFrEF) according to the ESC Guidelines 2021. The cardiorenal benefits cannot be explained by an action of SGLT2 inhibitors to lower blood glucose, since similar effects have not been seen with other antidiabetic drugs that have greater antihyperglycemic actions. Some of the hypothetic mechanisms are the osmotic diuresis they generate and the reduction of interstitial oedema in a secondary way, together with direct mechanisms on the myocyte at the level of the NHE-1 cotransporter, among others.

Objectives: The main objective is to assess changes in the exertional capacity or functional capacity of patients by ergospirometry, studying the change in the values of ventilatory thresholds, O2 consumption and VE/VCO2 slope, after SGLT2i treatment. Thus, we intend to achieve the improvement in the optimization of this treatment.

Design: A longitudinal, observational, descriptive and prospective study, without a control group, will be performed to describe the association between SGLT2i and functional capacity and cardiac function in patients with HF and reduced left ventricular ejection fraction (LVEF). It will be carried out in Hospital Santa Caterina of Girona between February 2022 and April 2022.

Participants: Patients > 18 years old, with a diagnosis of HF with reduced LVEF (<40%), with or without type 2 DM, who are in follow-up in the cardiology consultations of Santa Caterina Hospital of Girona.

Methods: a non-probabilistic consecutive sampling will be used in this study, with a sample of 196 patients. We will study functional capacity by ergospirometry and a quality of life questionnaire (Minnesota) and cardiac function by echocardiogram and NT-proBNP values.

Keywords: Functional capacity, cardiac function, heart failure, type 2 DM, SGLT2i.

1.INTRODUCTION

1.1 HEART FAILURE

1.1.1 DEFINITION

Heart failure (HF) is defined as the **inability of the heart to meet the metabolic demands of the body or, if it does, it is at the expense of elevated ventricular filling pressures** (1). It consists of the failure of the pump function of the heart and its clinical manifestations depend on the hemodynamic repercussion in other organs.

It is due to a structural or functional abnormality that results in elevated intracardiac pressure and/or inadequate cardiac output during exercise and/or at rest.

Heart failure is not a diagnosis of a single pathology, but rather a **clinical syndrome** that is composed of several main symptoms that may be accompanied by signs. **Cardinal symptoms are breathlessness, ankle swelling and fatigue; the signs are pulmonary crackles, elevated jugular venous pressure and peripheral oedema**.(2)

Other **typical symptoms** are orthopnoea and reduced exercise tolerance. Less typical are nocturnal cough, wheezing, loss of appetite, confusion, palpitation or depression. Some of the **more specific signs** are hepatojugular reflux, third heart sound (gallop rhythm) and laterally displaced apical impulse. Less specific are pleural effusion, tachycardia, irregular pulse, tachypnoea, Cheyne-Stokes respiration, hepatomegaly, ascites and oliguria (2).

Patients with extracardiac pathology, such as anaemia, thyroid, renal, pulmonary or hepatic pathology, may have symptoms similar to those of HF, but in the absence of heart failure. They may coexist with HF and exacerbate acute HF (2).

The most important point is to identify the aetiology of the underlying cardiac dysfunction in the diagnosis of HF, since the specific cause will determine the subsequent treatment. There are multiple causes of HF, most frequently is due to myocardial dysfunction (systolic, diastolic or both). But there are other pathologies of

the pericardium, endocardium, valvular heart disease, arrhythmias and conduction abnormalities that can also contribute to HF.

1.1.2 TYPES

Based on the measurement of left ventricular ejection fraction (LVEF), we can divide HF into reduced, mildly reduced and preserved left ventricular ejection fraction. (2)

- **Reduced LV ejection fraction** is defined as **≤ 40%.** They are those who have a significant reduction in LV systolic function. It is designated as **HFrEF**.

  HF is secondary to systolic dysfunction when it is due to decreased pump function of the heart. There is a deficit of myocardial contractility, due to direct injury to the myocardium or secondary to an overload imposed on the heart. Some causes may be: myocardial infarction, dilated cardiomyopathy, valvular heart disease or long-standing hypertension (1).
- **Mildly reduced LV ejection fraction** include patients with a LVEF **between 41% and 49%** (HFmrEF). According to studies, these may benefit from therapies aimed at reduced LVEFs, and are therefore referred to as moderately reduced.(2)
- **Preserved LV ejection fraction** includes those who have LVEF **≥50%**, symptoms and signs of HF, with evidence of structural or functional abnormalities and/or raised NT-proBNP (2). The most frequently cause is diastolic dysfunction. The result is an alteration in ventricular distensibility and relaxation that hinders filling of the ventricle and increases ventricular stiffness (1). The contractile function is preserved. The most frequent causes are restrictive cardiomyopathy, hypertrophic cardiomyopathy and arterial hypertension. It is more prevalent among the elderly, women, and individuals with systemic hypertension and diabetes mellitus.

Heart failure can also be produced due to right ventricular dysfunction. Although the main aetiology is LV dysfunction-induced pulmonary hypertension, there are multiple causes of pulmonary hypertension such us pulmonary thromboembolism (PTE) or chronic obstructive pulmonary disease (COPD), which can also produce right HF.

Other common terminology is the division into **chronic or acute heart failure**. Chronic HF is defined as a more gradual onset of symptoms, whereas acute HF begins more suddenly. In chronic HF that worsens or requires hospitalization or intravenous treatment, we will call it decompensated.(2)

To describe the **severity** of HF, we use the New York Heart Association (NYHA) functional classification. There are 4 degrees (I-IV), ranging from no limitation in physical activity to inability to perform any activity and having symptoms at rest (2). It is used in combination with the AHA classification of disease progression, which has 4 stages (A-D) and is complementary to the NYHA (ANNEX 5).

1.1.3 EPIDEMIOLOGY

Heart failure (HF) is a serious and **common condition in clinical practice** (3). The estimated **prevalence** of HF in developed countries in the adult population is **2%**. This figure **increases to 10% in the elderly**. These rates are expected to increase due to the aging of the population and the better treatment of the acute phases of cardiovascular disease. So, reflecting that, the age-adjusted **incidence** of HF may be falling, but, due to ageing, the overall incidence is increasing. The incidence of HF is about 3/1000 persons-year in all age groups and about **5/1000 in adults**. (2)

HF is the **leading cause of hospitalization** in the United States and Europe and the risk of death increases significantly with each hospitalization. Fortunately, in recent years new drugs such as sacubitril-valsartan or SGLT2i have appeared, which reduce the complications of HF.(3)

Atrial fibrillation (AF), a higher body mass index (BMI) and a higher glycosylated hemoglobin (HbA1c), as well as a higher glomerular filtration rate (GFR) are strong predictors of HF hospitalizations (2).

1.1.4 PHYSIOPATHOLOGY

With the decrease in cardiac output in HF, a series of compensatory mechanisms are activated so that the heart can maintain an adequate cardiac output, at least at rest.

The first compensatory mechanism that is activated is the increase in preload **(Frank Starling's law**), so that the greater residual volume and the increase in end-diastolic pressure increase the force of contraction and the ejection volume of the next beat. This produces retrograde congestion.

Other mechanisms are compensatory **neurohumoral mechanisms** such as increased sympathetic tone and activation of the renin-angiotensin-aldosterone system. The vessels maintain systemic pressure and preferentially distribute blood flow to vital areas. An increase in sympathetic activity tends to increase cardiac contractility and heart rate and produces peripheral vasoconstriction (1). Angiotensin II activates the release of aldosterone, responsible for Na+ and water retention, and interacts with the sympathetic system to increase vascular tone.

There is also an activation of ADH (antidiuretic hormone) which retains water.

To compensate for the vasoconstriction, natriuretic peptides with vasodilator effect are released.

The **natural history** of HF is a progressive worsening, with time these compensatory mechanisms worsen ventricular function.

1.1.5 DIAGNOSIS

Symptoms and signs lack sufficient accuracy to be used alone to make the diagnosis of HF, so **it is necessary the objective evidence of cardiac dysfunction**. In patients with a history of myocardial infarction (MI), hypertension (AHT), diabetes mellitus (DM), alcohol abuse, chronic kidney disease (CKD) or those with a family history of sudden death, among others, it is more likely to be diagnosed with chronic HF.

In case of suspect of CHF, we can perform the following **tests to reach a diagnosis**(2):

1) **Electrocardiogram (ECG):** which may reveal abnormalities such as AF, Q waves, LV hypertrophy and an enlarged QRS complex, that increase the likelihood of a HF diagnosis and may also guide treatment.
2) **Measurement of NPs levels**. There are 3 types of Natriuretic Peptide (NPs): A plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-

proBNP) <125 pg/mL, B-type natriuretic peptide (BNP) <35 pg/mL or mid-regional pro-atrial natriuretic peptide (MR-proANP) <40 pmol/L make a diagnosis of HF unlikely.

3) It is also recommended that **blood analysis** includes serum urea and electrolytes, creatinine, complete blood count, liver function tests and thyroid function tests, fasting glucose, HbA1c and iron status, to differentiate HF from other diseases, to provide prognostic information, and to guide possible treatment.
4) **Echocardiography**: is the key investigation for the study of cardiac function. We can determine the LVEF and other parameters like the chamber size, eccentric or concentric LVH, RV function, pulmonary hypertension, valvular function, markers of diastolic function and motion abnormalities.
5) A **chest x-ray** is recommended to rule out other causes of breathlessness such as lung disease. We can also check for cardiomegaly or pulmonary congestion.

Then, depending on the form of presentation and the suspected aetiology, we will perform more specific tests.

As important as the recognition of the underlying heart disease is the identification of the triggering causes of HF (1). There are cardiopathies that may be accompanied by few clinical manifestations, which may become evident at the same time as **any acute intercurrent process**. This process **causes overload of the previously injured myocardium**. They can be arrhythmias, infections, AHT, PTE, anaemia, non-steroidal anti-inflammatory drugs (NSAIDs), MI, pregnancy, treatment abandonment or dietary transgression (1,2).

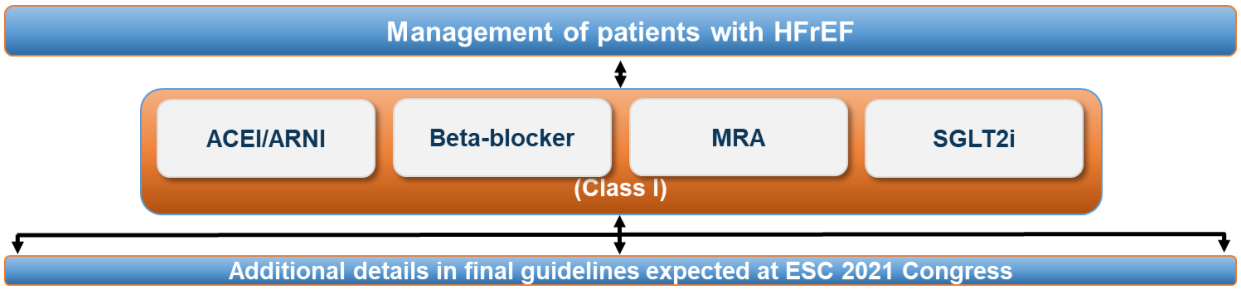
1.2 TREATMENT IN HFrEF

The main objectives of treatment are the **reduction of mortality, prevention of recurrent hospitalizations due to worsening HF and improvement of functional capacity and quality of life**. Treatment will be both pharmacological and non-pharmacological (2).

Treatment with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. (2)

The **sodium-glucose co-transporter 2 (SGLT2) inhibitors** dapagliflozin and empagliflozin **added to therapy with ACE-I/ARNI/betablocker/MRA reduced the risk of CV death and worsening HF in patients with HFrEF**. Unless contraindicated or not tolerated are **recommended for all patients with HFrEF with this previous treatment**, regardless of whether they have diabetes or not (2). So, Dapagliflozin is recommended as first-line therapy for all patients with HFrEF in the ESC 2021 HF Guidelines (Figure 1).

It is not only important to prescribe the **right treatment**, but to do so **at an early stage** in order to obtain the greatest possible benefit. We must bear in mind that HF is a progressive disease, in which there is a continuous adverse remodeling, as a consequence of neurohormonal activation and inflammatory mediators, which makes the potential recovery capacity of the myocardium increasingly lower. In the most recent HF clinical trials, the benefit of the new treatments, compared with standard therapy, was superior in patients in functional class II of the New York Heart Association (NYHA) than those in NYHA III/IV.(3) Therefore, an approach with early optimization of treatment and the **use from the beginning of those with the greatest proven efficacy**, such as dapagliflozin, should be adopted (3).



Drugs recommended in all patients with HFrEF	Class[a]	Level[b]
ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

Figure 1. Treatment in HFrEF (2).

1.3 ISGLT2

1.3.1 DEFINITION AND STUDIES

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially developed for the treatment of diabetes mellitus due to their hypoglycaemic activity (4,5). Type 2 diabetes mellitus (T2DM) is currently one of the most prevalent health problems in the western world due to its high incidence and impact on cardiovascular disease**. Around 40% of heart failure (HF) patients have T2DM** (4).

In patients with T2DM, SGLT2i reduce the risk of hospitalization for heart failure and the risk of serious adverse renal events, benefits that are not seen with other antihyperglycemic drugs (6).

In 2015, **the EMPA-REG OUTCOME** clinical trial showed us for the first time that empagliflozin reduces CV and all-cause mortality, in addition to major CV events, HF hospitalization, and progression of kidney disease **in diabetic patients**. (4) Subsequent studies with drugs such as canagliflozin and dapagliflozin (CANVAS and DECLARE-TIMI)

corroborate the existence of cardiovascular benefits associated with the mechanism of action of this drugs.

Given the benefits found in these pivotal studies of patients with diabetes and HF, new studies were designed to assess the efficacy of these drugs in patients with HF, including both with type 2 DM and non-DM.

The **DAPA-HF trial** included 4.744 HFrEF patients **with or without T2D** followed over a median of 18.2 months. It was demonstrated that dapagliflozin 10 mg daily significantly reduced the primary composite endpoint of worsening HF (including HHF or urgent HF visits) and CV death in a population highly treated with background disease-modifying HF therapies, either in patients with or without diabetes (7). It showed greater treatment benefit in class II patients, compared with class III or IV, like we said before. The occurrence of adverse events was low and similar between dapagliflozin and placebo. So, it showed a robust benefit in patients with heart failure with reduced LVEF, regardless of the presence or absence of diabetes.

The **EMPEROR-reduced** double-blind trial included a total of 3.730 patients followed for an average of 16 months. Half of the patients were diabetic, 73% had an **LVEF < 30%** and 79% had an NT-proBNP > 1,000 pg/ml, with 18.3% of patients being treated with sacubitril/valsartan. 48% had an eGFR < 60 mL/min/1.73 m2. They received empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a reduction in the composite of cardiovascular death or hospitalization for worsening heart failure, **regardless of the presence or absence of diabetes** (6).

The **SOLOIST-WHF** study with **Sotagliflozin** was a multicenter, double-blind trial in which patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure were randomly assigned to receive sotagliflozin or placebo(8). A total of 1.222 patients were followed for a median of 9 months. Sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.

As previously mentioned, based on this solid scientific evidence, SGLT2i has become first-line treatment in patients with HF and reduced LVEF, regardless of whether or not they have DM.

1.3.2 MECHANISM OF ACTION:

SGLT2i show metabolic and hemodynamic effects, which justify their efficacy in T2DM and HF treatment. They slow down harm mechanisms leading to left ventricular remodelling and pathophysiological mechanisms associated with HF development and progression (9,10).

SGLT is a family of **sodium glucose cotransporters**, and its better-known isoforms are SGLT1 and SGLT2. SGLT2 is expressed nearly exclusively in the kidney, while SGLT1 is also present in the intestine and heart (5).

SGLT2 is localized in the **first proximal convoluted tubule segment (S1) of the kidney**. It transports glucose against gradient, in the peritubular capillaries, exploiting the energy of the Na+/K+ ATPase pump and **it allows the uptake of 90% of the reabsorbed glucose** (Figure 2). In the following proximal convoluted tubules segments is localized the SGLT1 cotransporter, which reabsorbs the other 10% of glucose (5). So, these drugs increase glycosuria without interfering with the function of pancreatic beta cells, which implies a low risk of hypoglycemia.

SGLT2 is located close to the Na+/H+ exchanger 3 (NHE3), which allows sodium reuptakes in proximal tubule. **These two transporters act together**, so, for this reason, SGLT2 can directly affect natriuresis. In **HF**, NHE3 and NHE1 (which is in the myocardium) **activity is increased**, and that determine the diuretic and endogenous natriuretic peptide resistance and intracellular sodium and calcium overload, respectively. SGLT2i inhibits that (5).

The glycosuria-induced osmotic diuretic effect results in volume decrease. A moderately preserved renal function is required for urinary glucose excretion, thus, **Dapagliflozin and Empagliflozin, may be administered efficacy and safely up to an estimated glomerular filtration rate (eGFR) of 20–25 ml/min/1.73 m2**. (5).

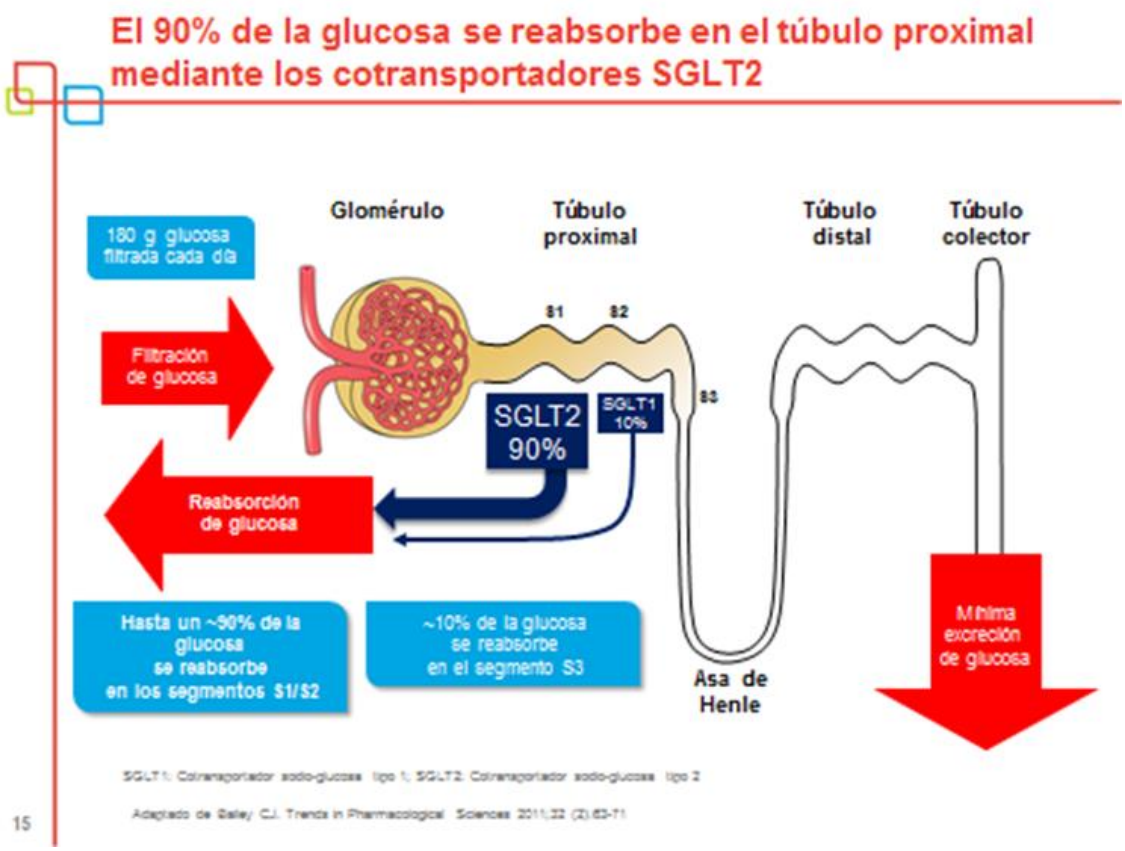


Figure 2. Mechanism of action of SGLT2i, adapted from (11).

Although impressive results have been achieved with SGLT2i, there is a lack of knowledge of the mechanisms associated with the observed benefits(7). The cardiorenal benefits cannot be explained by an action of SGLT2 inhibitors to lower blood glucose, since similar effects have not been seen with other antidiabetic drugs that have greater antihyperglycemic actions (6,12).

Some of **the hypotheses** (Figure 3) about the different mechanisms are (7,9):

→ The myocardium utilizes preferentially free fatty acids (FFA) for energy production, which yield substantial amounts of energy in the form of adenosine triphosphate (ATP) molecules, albeit at the expense of higher oxygen consumption. Ketone bodies may also be used as the most energy efficient fuel source, with the lowest oxygen expense. In the diseased myocardium, there is an increased uptake of glucose and FFA into the cytosol, but this becomes uncoupled and there is less uptake and oxidation in the mitochondria, leading

to an accumulation of metabolic intermediates and toxicity. The glycosuria induced by SGLT2i results **in lower plasma glucose and insulin levels,** and increased glucagon plasma levels, which increases lipid mobilization. All of these stimulate ketogenesis in the liver. SGLT2i cause a mild but persistent increase in the production of ketone bodies, which along with FFA, become the main substrates for ATP production in the myocardium, in detriment of glucose. Ketone bodies are more efficient, so that **improves the energetic efficiency of the heart and reduces cytotoxicity.**

→ SGLT2i binds to **and inhibits the sodium-hydrogen exchangers (NHE) in the heart and kidney** and may offer cardio-renal benefits by these mechanisms. The NHE1 isoform is the predominant isoform expressed in the heart. NHE3 expression is limited to epithelial cells of the gut and kidney. As we explained before, in HF, the activity of NHE1 in cardiomyocytes is markedly increased, and that leads on higher Na+ concentrations in the cytosol which, in turn, triggers an increase in intracellular Ca2+ and ultimately lead to cardiomyocyte injury and cardiomyopathy. SGLT2i directly bind to NHE1 transporter in cardiomyocytes, reducing cytoplasmic Na+ and Ca2+ levels. NH3 expression is also increased in HF as a result of the upregulation of mineralocorticoids, leading to fluid retention and peripheral oedema. SGLT2i may also downregulate the activity of NH3 in the proximal tubule.

→The benefits of this treatment are in part due to their **diuretic effects**. SGLT2i have **unique diuretic properties** whereby they modulate the function of the proximal tubule, leading **to natriuresis, glycosuria and ensuing osmotic diuresis**. The consequent sodium and volume reductions would result in lower preload and afterload, leading to **improved cardiac loading conditions**. Natriuretic effect act as stimuli for tubule-glomerular feedback, resulting in afferent arteriolar vasoconstriction, thus lowering glomerular hypertension, and likely causing an antiproteinuric effect. It has been also proposed that SGLT2i have the ability to selectively **reduce interstitial fluid**, a property unique

to this class, which may be particularly relevant for patients with congestive HF and interstitial oedema.

This differs from the drastic reduction in intravascular volume observed with loop diuretics, which may lead to compensatory mechanisms and neurohormonal activation, associated with deleterious effects.

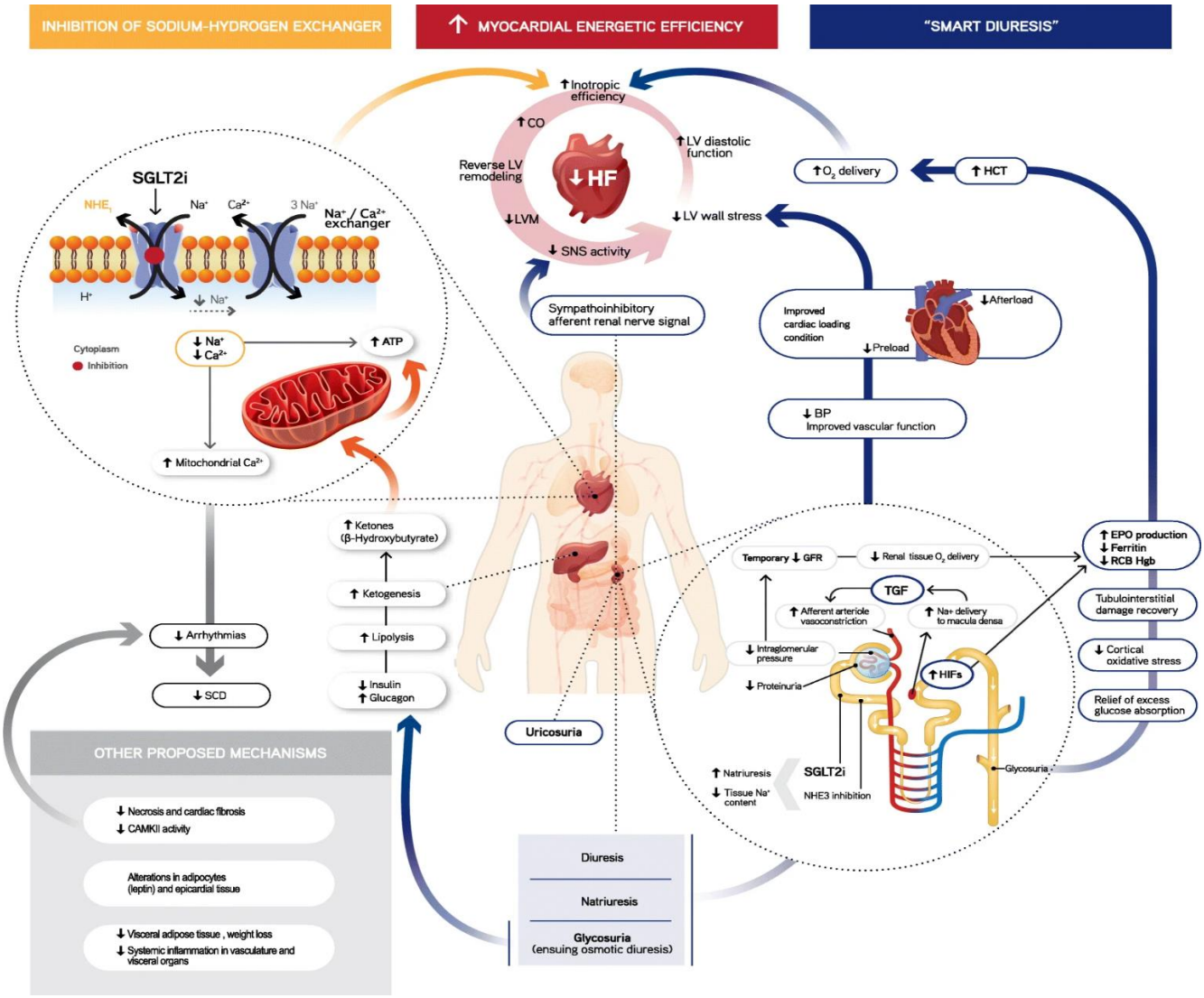


Figure 3. Hypothesis about improvement of cardiorenal function by SGLT2i (7).

1.4 ERGOSPIROMETRY

Ergospirometry is a **cardiorespiratory stress test** that non-invasively and globally **studies the body's response to exercise**. It does this through a rational analysis of the respiratory, cardiovascular, hematopoietic, neuropsychology and muscle-skeleton systems. It is also known as cardiopulmonary exercise stress test (CPET), exercise test with exhaled gas analysis, metabolic test, and maximal oxygen consumption test (13).

This test allows us, through the analysis of exhaled respiratory gases during the application of physiological stress, to determine with accuracy and reproducibility the **functional capacity (FC)** of the subject evaluated, as well as to identify probable latent myocardial ischemia or other existing pathological conditions. Its allows us to prescribe with certainty a physical exercise program that rigorously complies with the fundamental physiological principles that will make it effective (13). Moreover, the assessment of the aerobic exercise response allows for the manifestation of physiologic abnormalities that are not readily apparent during the collection of resting data (14).

Therefore, is an **useful tool** in the **functional assessment and prognostic stratification of patients with cardiovascular and respiratory diseases**. And it is essential in the evaluation of the cardiac patient undergoing a cardiac rehabilitation program.

Physical exercise plays a fundamental role in cardiovascular prevention and rehabilitation, and the **evaluation of functional capacity is an essential component in primary and secondary prevention programs, which is objectively determined by ergospirometry.** Due to several factors, when we evaluate FC by methods such as the conventional stress test, some parameters like exercise time, maximum workload achieved or the METs (metabolic equivalent of task) assumed, among others, may not be fully reproducible.

Ergospirometry is considered the **"gold standard" for the evaluation of functional capacity** in healthy and sick subjects, in athletes, as well as for prognostic stratification, both in patients with cardiovascular diseases and with other conditions, including HF.

Its **indications** are the evaluation of the maximum tolerance to physical exercise, the evaluation of patients with cardiovascular disease, including the functional, prognostic evaluation and the response to treatment of patients with **heart failure**; and also in patients with respiratory diseases (13).

In addition, it has **diagnostic value** when differentiating, in patients with breathlessness, which is the most relevant alteration, which can be cardiac, pulmonary or mixed.

Variables used are those measuring functional capacity, those measuring pulmonary response and those measuring cardiovascular response (15).

In the case of **HF**, the **most important variables** are (15):

1) **Aerobic variables** (which inform about functional class):
   - VO2 peak and VO2 at first threshold (VT1)*:* the highest VO2 value reached during exercise and O2 value at VT1.
   - O2 pulse: it is obtained by dividing VO2 by HR. Represents the volume of oxygen extracted from tissues per cardiac cycle and it is directly related to systolic volume.
2) **Ventilatory variables:**
   - Spirometry: FVC, FEV1, FEV1/FVC will be measured.
   - VE/VCO2 slope: is the quotient between ventilation per minute and CO2 elimination and indicates the ventilatory class.
   - O2 and CO2 equivalents: liters of air we must ventilate to provide 1L O2 or remove 1L CO2. If we need to ventilate less liters of air, the respiratory efficiency will be better.
   - PETO2 and PETCO2: partial pressure of O2 and CO2 measured at the end of each exhalation.
   - Oscillatory response of respiration: with high-frequency and repetitive. When they appear in patients with HF, they are a sign of poor prognosis and may be related to low cardiac output.

In the **main objective of this study**, we will include **three main variables** for measuring functional capacity. The rest of the variables can be found in the ANNEX 1.

<u>Oxygen consumption (VO2)</u> is the value that best assesses the functional capacity, giving an objective value of the same (15). The maximal oxygen uptake (VO2 max) represents the maximum capacity of the organism to extract, transport and use oxygen from the inspired air in a situation of maximum effort (13). It is expressed in ml/min, ml/kg/min or percentage of the predicted value for the patient's age, sex, weight and height. Therefore, VO2 max rate is an **objective measure of exercise capacity**. VO2 ≥ 85% of predicted VO2 is considered normal (15).

Any healthy person at rest has an O2 consumption of 3.5 ml/min/kg. This is considered a metabolic equivalent (MET). At the end of every measure, we can get the METs consumption dividing the achieved VO2 by 3.5 (15).

The following graphic (Figure 4) represents the **relationship between workload and oxygen consumption** (13). During exercise, the workload increases over time and the VO2 increases in direct proportion, until there comes a moment in which the load continues to increase, but the VO2 stops increasing, reaching a plateau. At this point the subject is said to have reached the VO2 max level, the limit of aerobic power.

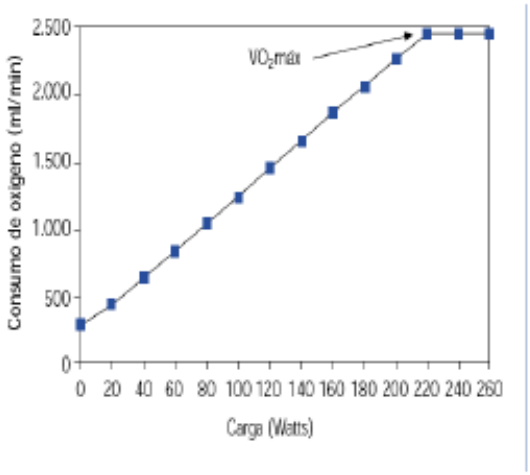


Figure 4. Relation between workload and O2 consumption (13).

When the person is not able to reach VO2max, we speak of peak VO2, the highest VO2 value reached during exercise, without reaching the plateau.

In the case of our study, patients with **chronic heart failure** present exercise intolerance due to multiple factors. These include low oxygen supply secondary to

cardiac muscle incompetence, ventricular dysfunction, alterations in blood flow, abnormalities of muscle metabolism and ventilatory system. Usually, the peak VO2 value is lower (13).

With this study, we want to see the **association between increased functional capacity and O2 consumption and SGLT2i intake**, in patients with HF with reduced LVEF, with or without T2DM.

To stratify the **prognosis of HF patients based on VO2 value**, the Weber classification may be used (15), in which A has the best prognosis and D the worst:

- *Class A*: >20ml/min/kg.
- *Class B*: 16-20 ml/min/kg.
- *Class C*: 10-15 ml/min/kg.
- *Class D*: <10 ml/min/kg.

Ventilatory thresholds (VT) correspond to the level of exercise in which aerobic energy production is supplemented by anaerobic mechanisms and is reflected by an increase in blood lactate (13). First, there is an aerobic stage, in which energy is obtained from fatty acids through the Krebs Cycle. Then, as exercise intensity increases, anaerobic glycolysis begins, which increases acidity and CO2 levels. This transition stage between aerobic and anaerobic phases would be **the first ventilatory threshold (VT1)**, in which compensatory mechanisms occur. When the anaerobic pathway becomes predominant, **second ventilatory threshold (VT2)** is reached. Wasserman calls the first **anaerobic threshold** and the second **respiratory compensatory point**. Therefore, he included two concepts: metabolic compensation by buffer systems and compensation by increased ventilation (15).

VE/VCO2 slope is the slope resulting from the **quotient between ventilation per minute and CO2 elimination** and is a **marker of ventilatory efficiency**. This slope is constant until the second ventilatory threshold, at which point it becomes steeper. It measures how many liters of air must be ventilated to remove 1L of CO2 (15).

The normal value of the slope angle in sedentary people without pathology should be between 20 and 25 degrees. Above 30 degrees it is pathological. Its prognostic value worsens as the slope increases. It is one of the variables with **the greatest prognostic**

value in the appearance of severe cardiovascular events, in patients with **HF** and its value is comparable to the prognostic value of VO2 (15).

Based on this variable, a classification was developed, called "Ventilatory Class", which establishes the prognosis of patients with HF according to the value of the VE/VCO2 slope. There are **4 ventilatory classes** (15):

- *Class 1*: slope <30 and 97,2% event free at 2 years.
- *Class 2*: slope between 30 and 35,9 and 85,2% event free at 2 years.
- *Class 3*: slope between 36 and 44,9 and 72,3% event free at 2 years.
- *Class 4:* slope ≥45 and 44,2 % event free at 2 years.

1.5 NATRIURETIC PEPTIDES

Brain natriuretic peptide (BNP) is a **protein secreted by the ventricular musculature in response to volume or pressure overload**. Natriuretic peptide (B-type NP (BNP), N-terminal proBNP (NT-proBNP), and midregional proANP (MR-proANP)) concentrations are **quantitative plasma biomarkers** for the presence and severity of haemodynamic cardiac stress and heart failure (HF) (16). While in the normal human heart ANP is secreted mainly by atrial myocytes, BNP is produced by both atria and ventricles. In normal subjects, plasma BNP concentrations are lower than those of ANP. However, compared with ANP and NTproANP, BNP and NT-proBNP reach much higher proportions in the case of disease. (17)

They form part of the **vasodilator system**, and have effects on the heart, kidney, vascular and central nervous system. They have diuretic, natriuretic and vasodilator properties. They will always **be useful together with the other clinical data**. The dominant triggers seem to be the intracardiac filling pressures, intracardiac volumes and end-diastolic wall stress. In **all patients presenting symptoms suggestive of HF** such as dyspnea, fatigue or edema, **should be measured**, so that its use allows an early diagnosis and prognosis.

NPs have **very high diagnostic accuracy** in discriminating HF from other causes of dyspnoea: the higher the NP, the higher the likelihood that dyspnoea is caused by HF

(16). NPs cannot identify the underlying cause of HF and, therefore, if elevated, must always be used **in conjunction with cardiac imaging.**

NT-proBNP and the BNP have the same diagnostic value, and both vary their blood levels equally, but the first is more stable than the second, it has lower variability and longer half-life. Because of that, NT-proBNP is used by the analysis (17).

In recent years, the determination of brain natriuretic peptide values (BNP, NT-proBNP) has demonstrated a high yield in **HF screening**, as well as **an important role in the prognostic for death and HF hospitalization** (18). So, the screening with NPs for the early detection of relevant cardiac disease including left ventricular systolic dysfunction in patients with cardiovascular risk factors may help to identify patients at increased risk, therefore allowing targeted preventive measures to prevent HF.

However, it should be noted that there are **many causes** of an elevated NP **that might reduce their diagnostic accurac**y, both CV and non- CV (1). Some of these causes are AF, increasing age, acute or chronic kidney disease, anaemia or severe infections. We should also bear in mind that in obese patients the concentrations are usually disproportionately low.

Moreover, monitoring of this hormone can guide the intensification of drug treatment (18).

The upper limits of normal in the non-acute setting are 35 pg/mL for BNP, and **125 pg/mL** for NT-proBNP (1). It has a **high negative predictive value**.

1.6 ECHOCARDIOGRAM

Echocardiogram is the **most useful test in systolic and diastolic heart failure**, not only in **diagnosis**, but also as a tool to provide insights into the pathophysiological mechanism of different aetiologies of heart failure. It is useful in **monitoring the patient's response** to various treatment options and select the most suitable patients for each therapy, and as a tool to help us develop innovative new therapies for heart failure (19,20).

ESC guidelines state that echocardiography is the single most useful test in the diagnosis of heart failure since structural abnormality, systolic dysfunction, diastolic dysfunction, or a combination of these abnormalities needs to be documented in patients who present with resting or/and exertional symptoms of heart failure to establish a definitive diagnosis of heart failure (2,19). These symptoms are not specific, and more than a third of patients with a clinical diagnosis of heart failure may not actually have heart failure symptoms. Moreover, even when someone presents with typical symptoms of heart failure, **an echocardiography examination is required to establish the underlying aetiology for an optimal management strategy, classifying them according to the LVEF** (19).

Ventricular remodeling caused by heart failure produces hemodynamic changes that determine survival in this type of patients. So, echocardiography is useful to evaluate the **prognostic** (20).

Echocardiographic parameters should be regularly assessed to control the patients' evolution and adjust their treatments. We wil asses:

LV end-diastolic and end-systolic diameters, LVEF, LV mass, aortic diameter, right ventricular systolic function, Left atrial diameter and area and the relationship between early ventricular filling wave and atrial contraction (21).

Combined assessment of peptides and echocardiography provides more powerful stratification of risk across all stages of heart failure, and the integrated use of both tests may identify subjects with greatest risk for progression and guide decision-making for timely intervention (2,16).

1.7 QUALITY OF LIFE

The **health-related quality of life** (HRQL) assesses the subjective influence of health status, health care, prevention and health promotion activities on the individual's ability to achieve and maintain a level of functioning that allows the achievement of life goals and is reflected in overall well-being. The fundamental dimensions are physical, psychological-cognitive and social functioning.

The **Minnesota Living with Heart Failure Questionnaire (MLHFQ)** (ANNEX 4), developed in the United States, is a self-administered questionnaire that contains 21 items, a total score and two dimensions: physical (8 items) and emotional (5 items). The response options range from 0, indicating unaffected quality of life, to 5, indicating maximum impact on quality of life. The overall score of the of the questionnaire, both the overall (0-105) and dimensions (physical, 0-40; emotional, 0-25), is obtained by summing the responses to each of the items (22). Is the most widely used instrument for the assessment of quality of life in patients with heart failure.

2.JUSTIFICATION

In a few years, **SGLT2i** have gone from being indicated treatments for the control of T2DM to being postulated as **first-line drugs in the management of HFrEF** and CKD.

In the context of HF, in the **DAPA-HF** study, Dapagliflozin reduced mortality and morbidity in patients with HF and LVEF <40%, **in both diabetic and non-diabetic** patients (7). In the **EMPEROR-reduced** study, Empagliflozin showed a significant **reduction** in the combined risk of **cardiovascular death or hospitalization for HF**, in patients with and without T2DM. An improvement in the functional capacity of patients was also reported in the first study (6).

According to the European Guidelines for the diagnosis and treatment of HF, SGLT2i are considered first-line drugs in the treatment of HF with reduced LVEF, with Class I A evidence, since they reduce morbidity and mortality (2).

The SGLT2i show metabolic and hemodynamic effects, and their **cardiorenal benefits** have been explained by different mechanisms that are not entirely clear, among them the **osmotic diuresis** they generate and the **reduction of interstitial oedema** in a secondary way, together with direct mechanisms on the myocyte at the level of the **NHE-1** cotransporter, among others.

HF is a common problem in clinical practice and **greatly affects the functional capacity** of patients. Due to the **high prevalence of DM and HF**, it is important to take therapeutic measures to improve quality of life. To this end, this study will be carried out to determine the association between SGLT2i drugs and the improvement of cardiac function and functional capacity of patients. So, this study will allow us to identify in **which profile of patients**, with and without T2DM, there is an **improvement in functional capacity** and through which mechanisms. This knowledge may help to identify which patients with HF and non-reduced LVEF may benefit from SGLT2i treatment, in order to plan more precise future clinical trials in heart failure.

For this purpose, we will conduct a descriptive observational study, since it is not possible to perform a clinical trial and prove its effect, because it would be unethical to deny this first-line treatment to a patient.

3.HYPOTHESIS

Treatment with **SGLT2i** in patients with **heart failure and reduced ejection fraction** will be associated with **improved functional capacity and cardiac function** in both diabetic and non-diabetic patients.

4.OBJECTIVES

4.1 MAIN OBJECTIVE

- To assess changes in the exertional capacity or functional capacity of patients by ergospirometry, studying the change in the values of **ventilatory thresholds, O2 consumption and VE/VCO2 slope after SGLT2i treatment**.

4.2 SECONDARY OBJECTIVES

- To assess changes in **LV systolic-diastolic function**, measured by echocardiogram-Doppler, before and after SGLT2i treatment.
- To assess the change in **NT-proBNP values** before and after treatment.
- To assess changes in functional capacity based on the **Minnesota questionnaire**, before and after treatment.
- To establish **differences** in the above parameters in patients **with and without T2DM.**

5.SUBJETCS AND METHODS

5.1 STUDY DESIGN

A **longitudinal, observational, descriptive and prospective study**, without a control group, will be performed to describe the association between SGLT2i and functional capacity and cardiac function in patients with HF and reduced LVEF.

The highest level of evidence would be obtained with a clinical trial, but we cannot carry it out because it would be unethical to deny a patient a treatment with SGLT2i, since it has been proven to be a first-line treatment in patients with HF and reduced LVEF, which reduces morbidity and mortality. Therefore, it would be unethical to have a control group without this treatment.

5.2 SUBJECTS SELECTION AND SETTING

The study population will be patients from the province of Girona with **HF and reduced LVEF, with or without DM**, who are treated at Santa Caterina Hospital. The study will be performed at **Santa Caterina Hospital**.

5.2.1 INCLUSION CRITERIA

- Age >18 years old.
- LVEF < 40%.
- Symptoms of HF with functional class II-IV (NYHA).
- Optimal medical treatment (use of the treatment which has demonstrated a decrease in morbidity and mortality at the maximum tolerated dose) with beta-blockers, ACEI/ARA II/sacubitril-valsartan and mineralcorticoid receptor antagonists.
- Ability to perform ergospirometry.

5.2.2 EXCLUSION CRITERIA

- Patients who do not meet any of the inclusion criteria.

- Patients who do not sign informed consent
- Patients with glomerular filtration rate < 25ml/min.
- Patients with intolerance or allergy to ISGLT2.

5.3 SAMPLE

We will use a non-probabilistic consecutive sampling in this study.

In a bilateral test, with an alpha equal to 5%, a statistical power of 80%, and assuming a 25% change in the values of O2 consumption after SGLT2i treatment, we would need 178 subjects. However, assuming a **drop-out rate of 10% we would finally need 196 subjects.**

Computations were carried out with the Prof. Marc Saez' software based on the package 'pwr' of the free statistical environment R (version 4.1.2).

5.4 VARIABLES

5.4.1 MAIN VARIABLES

- **SGLT2i treatment**: dichotomous qualitative.
- **Ergospirometry-derived variables**: quantitative variables useful for measuring functional capacity. As we explained at the "Introduction chapter", we will do a pilot study, in which we will study three main variables that measure functional capacity, and consider the rest, measuring pulmonary and cardiovascular response, for future study (ANNEX 1).
    - O2 consumption: it is expressed in ml/min, ml/kg/min or percentage of the predicted value for the patient's age, sex, weight and height. We can get the METs consumption dividing the achieved VO2 by 3.5. The maximal oxygen uptake (VO2 max) represents the maximum capacity of the organism to extract, transport and use oxygen from the inspired air in a situation of maximum effort.

    - Ventilatory thresholds: level of exercise in which aerobic energy production is supplemented by anaerobic mechanisms, and lactate begins to accumulate. The renal compensatory mechanism takes place (VT1), followed by the respiratory mechanism to increase ventilation (VT2).
    - VE/VCO2 slope: is the slope resulting from the quotient between ventilation per minute and CO2 elimination and is a marker of ventilatory efficiency. It measures how many liters of air must be ventilated to remove 1L of CO2.
- **NT-proBNP value**, or brain natriuretic peptide, produced by ventricular myocardial cells upon elevation of diastolic pressures, measured in blood analysis. Quantitative variable.
- **Echocardiographic variables**: quantitative variables measured by Doppler echocardiogram before and after treatment withISGLT2i. We will measure:
    - LV end-diastolic and end-systolic diameters.
    - LVEF.
    - LV mass.
    - Aorta diameter.
    - TAPSE (tricuspid annulus plane systolic displacement, assesses right ventricular systolic function).
    - Diameter and area of LA.
    - Mitral E/A: relationship between early ventricular filling wave and atrial contraction.
- **Functional capacity by Minnesota questionnaire:** discrete quantitative. Is the ability to perform activities of daily life without supervision or assistance, the ability to perform tasks and roles in daily life. Functional capacity can be measured by the Minnesota quality of life questionnaire (21 items). It is a less objective but also a quantitative way of measuring functional capacity.

5.4.2 COVARIATES

The following will be obtained from the patient's medical history.

- **Age**: measured in years, continuous quantitative.
- **Sex**: qualitative, measured in categories male, female or undefined.
- **Country of birth**: categorized in Europe, Africa, Asia, North America, South America, other. Qualitative nominal.
- **Socioeconomic level**: proxied by occupation and last academic year completed.
- **Tobacco**: nominal qualitative. The categories will be smoker, non-smoker or former smoker. We will define as non-smoker those who have not smoked during the last year.
- **Usual treatment**: we should specify the patients' treatment; anti-diabetic treatment, treatment for arterial hypertension, usual treatment for HF (B-blockers, ACE inhibitors//ARA II, Sacubitril-Valsartan, mineralocorticoid receptor antagonists). Qualitative polytomous.
- **AHT**: qualitative dichotomous.
- **Type 2 DM**: qualitative dichotomous.
- **Dyslipemia**: qualitative dichotomous.
- **History of any cardiovascular event**: qualitative dichotomous.

5.5 DATA COLLECTION

All the information will be stored in the database, from the echocardiogram, ergospirometry or blood test, as well as from the clinical history and physical examination at the time of consultation. Each patient will be assigned a number to ensure confidentiality.

5.5.1 PATIENT RECRUITMENT

Patients from different parts of the province of Girona **with the diagnosis of heart failure**, who come to Santa Caterina Hospital for being attended in cardiology

consultations. Patients who come with a correct diagnosis of heart failure, regardless of the presence or absence of type 2 DM, must be examined by a clinician to check whether they meet the inclusion criteria in order to be included in the study. This will be done by evaluating the clinical history of each patient and previous tests, and verifying that they do not have any exclusion criteria.

In the case that the subject has the profile to participate in this study, he/she will be provided with the **informed consent form** for signature (ANNEX 7).

5.5.2 INVESTIGATIONS

A **blood test, echocardiogram, ergospirometry and a quality of life questionnaire (Minnesota questionnaire)** will be performed at the first visit, prior to drug administration, to assess the patient's baseline situation.

If any information is found that is not compatible with the inclusion criteria once the tests have been performed, this patient will be excluded from the study and will not complete the next steps.

If the patient has had any of the above tests done recently, it will not be necessary to repeat them and perform this step.

Once we have completed this process and the results of the first tests have been analysed, the patients who can continue in the study will go to the Hospital and will receive the prescription of **Dapagliflozin** (SGLT2i). This treatment will be added to their baseline medication at the dose of 10mg.

After one month, we will schedule a follow-up visit to assess tolerance to the study drug (SGLT2i) and the appearance of adverse effects.

After three months, another visit will be scheduled to verify the objective of the study, that is, the association between treatment with SGLT2i in patients with HF with LVEF<40% and improvement in functional capacity and cardiac function, regardless of the presence or absence of type 2 DM. This will be assessed by repeating a new ergospirometry, an echocardiogram, a blood test to assess NT-proBNP levels and the

Minnesota quality of life questionnaire. Physical variables will be collected at each visit.

ECHOCARDIOGRAM

The echocardiogram will be performed by a single Cardiologist specialized in echocardiographic imaging and trained for the study, repeated measurements of some variables will be taken (those are echocardiogram variables explained in the section of "main variables") and the mean of three congruent measurements for each variable will be analysed. It is important that the pre-treatment test and the post-treatment test should be performed by the same specialist, due to the high interprofessional variability. Different parameters of cardiac function will be assessed. Normal values are listed in ANNEX 3.

ERGOSPIROMETRY

It will also be carried out by a cardiologist specialized in this type of test. It combines a spirometry with a stress test or ergometry, and makes it possible to evaluate whether the cause of the pathology present is of cardiac, respiratory or mixed origin. A series of cardiorespiratory parameters will be measured (explained in "main variables" section) and the patient's effort capacity or quality of life will be evaluated. It will be carried out by the same specialist, before and after the treatment under study. Normal values are listed in ANNEX 2.

BLOOD TEST

It will be taken by a nurse collaborating with the study at Santa Caterina Hospital, and the NT-proBNP level will be measured before and after treatment. The blood collected will be studied by clinical analysis of the Hospital. The upper limit of normal range is **125 pg/mL.**

QUALITY OF LIFE QUESTIONNAIRE

The Minnesota questionnaire will be completed at the first visit and at the last visit, three months after treatment. It is a 21-item questionnaire that measures the quality of life of patients with HF (ANNEX 4).

6.STATISTICAL ANALYSIS

In order to carry out the statistical analysis we will use SPSS version 27.1. P value of<0.05 will be considered statistically significant.

6.1 DESCRIPTIVE ANALYSIS

Variables corresponding to the primary objective (O2 consumption, VE/VCO2 slope and ventilatory thresholds) as well as the variables corresponding to secondary objectives 1 (LV systolic-diastolic function), 2 (NT-proBNP levels) and 4 (differences in patients with and without DM), being quantitative continuous variables, will be summarized using the mean, standard deviation (and additionally median and interquartile range).

The functional capacity based on the Minnesota questionnaire (objective secondary 3), being a discrete quantitative variable will be summarized using the median and the interquartile range (in addition mean and standard deviation).

Bivariate descriptive analyses before and after the treatment with SGLT2 (main objective and secondary objectives 1 to 3) and with and without DM2 (secondary objective 4) will also be done.

In addition, all the analyses will be stratified by the covariates. Age will be categorized in quintiles.

6.2 BIVARIATE INFERENCE

The difference of means before and after the treatment (for the dependent variables corresponding with the main objective and secondary objectives 1, 2 and 4) will be tested using paired Student's t.

For the secondary objective 4 the difference of means with and without DM will be tested using (an independent samples) Student's t.

In the case of the variable corresponding to the secondary objective 3, we will test the difference of medians using the Wilcoxon's test (the same as Mann-Whitney's U but for paired data).

As above, these analyses will be stratified by the covariates.

6.3 MULTIVARIATE ANALYSIS

To assess the differences before and after in the dependent variables corresponding to the main objective and secondary objectives 1, 2 and 4, linear regressions including and indicator of before and after the treatment and controlling for the covariates will be used. We will consider the paired nature of the data.

We will include in these regressions the indicator of having or not DM.

In the case of secondary objective 3, a Poisson regression will be estimated, again with the indicator before/after the treatment and of having or not DM. The paired nature of data will be also taken into account.

7.WORK PLAN

7.1 SCHEDULE

Main researchers: 2 cardiologists.

Collaborations: nursing staff, a clinical analyst, a statistician.

Phase 0: Preparation and coordination phase (3 months)

During this first phase of the project, a detailed protocol will be elaborated with the help of the main investigators and collaborators. That include the discussion of the hypothesis, the objectives, variables and methods.

All suggestions will be taken in consideration and discussed with the team; therefore, coordination meetings will be arranged to identify and solve any problems or doubts regarding the protocol.

Once the protocol is ready, it will be presented to the Ethical Committee for its evaluation and approval. The suggestions will be considered and modified in the protocol. We will apply for an authorization from the center's management.

First phase: Study conduct (3 months)

- **Patients' recruitment**:

  Patients in the province of Girona with HF and reduced LVEF, with or without DM, who are treated at Santa Caterina Hospital and who meet the inclusion criteria, could be included in the study, after signing the informed consent form.

- **Investigations**:

  1) Echocardiogram: the measurement of the echocardiographic variables will be done twice. The first, before SGLT2i treatment, when the specialist considers that the patient could enter our study; an echocardiogram performed in the last 3 months prior to the inclusion in our study, with the

variables that we are going to analyse, will be admitted. The second measurement will be after 3 months with this treatment.

2) Ergospirometry: A series of cardiorespiratory parameters will be measured, and the patient's effort capacity or quality of life will be evaluated. It will be done twice as well. The first one, when the patient is included in the study, before treatment with SGLT2i, and the second will be after 3 months of treatment. As previously mentioned, we could avoid this test if the patient has an ergospirometry performed in the last 3 months with the variables that we are going to analyse.
3) Blood analysis: This assignment will consist in the collection of blood samples for further analysis. It will be taken by a nurse collaborating with the study. The first sample will be collected at the time the patient is included in the study. The NT-proBNP level will be measured and we will comparate its value before and after 3 months with SGLT2i treatment, as we explained in the Data Collection chapter.
4) Quality of life questionnaire (Minnesota): This test consists of answering a 21-item questionnaire that measures the quality of life in patients with heart failure. It will be carried out twice, like the other assessments. The first will be when the patient enters the study and the second after 3 months with SGLT2i treatment.

While the study takes place, the data collected from each patient will be registered in our database.

This collected data will be evaluated and analysed by an external collaborator to control if the protocol is being followed.

Second phase: Data analysis (2 months)

After processing the database and using the statistical tests described in the “Study and Methods” chapter, all data will be analysed by our statistician.

The final results will be sent to the main investigator, who will then proceed to their interpretation and discussing, elaborating the conclusions of the study.

Third phase: Interpretation and publication of the results (3 months)

The main researcher will interpret the results and write and edit a scientific paper with the conclusions with publishing intention in order to disseminate the results and expose them to the National Congress of Cardiology and the European Congress of Cardiology.

7.2 CHRONOGRAM

YEAR	***2021***		***2022***								
MONTH	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
PHASE 0: Study protocol, presentation to the CEIC, coordination meetings. **Staff**: All research team.											
PHASE 1: Patient's recruitment, investigations, register in database. **Staff:** Cardiologist, Clinical analyst and Nurse Staff.											
PHASE 2: Data analysis. **Staff**: Statistician.											
PHASE 3: Interpretation and study writing, publication and dissemination of results. **Staff**: Cardiologist.											

8.LEGAL ANG ETHICAL ASPECTS

This research protocol will be submitted to the Clinical Research Ethics Committee of the Santa Caterina Hospital of Girona for its assessment and approval, and the recommendations given by the Committee will be taken into account in order to carry out the study.

This study will be conducted in accordance with the Human Rights and Ethical Principles established by the World Medical Association in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (last updated October 2013).

All participants interested in taking part in the study will be asked to voluntarily sign the informed consent form, in accordance with the Basic Law 41/2002 Regulating Patient Autonomy and the Rights and Obligations Regarding Clinical Information and Documentation (23). Through a personal conversation with the investigators and using the information sheet (ANNEX 6), before being included in the study, patients will receive all the appropriate information about the study: the objectives, the investigations, the risks and the contact number to resolve doubts.

To guarantee the confidentiality of the personal and clinical data of all the participants in the study, the Organic Law 3/2018 on Personal Data Protection (24) will be followed. This information will be used only for research purposes and will be treated in a homogeneous and non-discriminatory manner, preserving the ethical principle of justice.

This study will respect the biomedical regulation according to the Royal Legislative Decree 1090/2015 for medicines (25).

This descriptive study will also respect the principles of beneficence and nonmaleficence. Based on all previous studies, SGLT2i is a drug that reduces morbidity and mortality and hospitalizations due to HF, as well as all-cause mortality, being first-line in the treatment of HF, according to the European Guidelines. Therefore, it is a safe and beneficial drug for our patients. However, we should be alert to any adverse effect that may occur.

9.LIMITATIONS

Due to the study design, we could have the following limitations:

- The study does not include a control group without this treatment, because it is unethical not to provide it since it is first line treatment. The patient is evaluated before and after treatment, and is used as his own control.
- Based on the inclusion and the exclusion criteria, the results of this study cannot be extrapolated to other cardiac diseases.
- Associated cardiovascular risk factors, other than T2DM (such as AHT, dyslipidaemia, smoking, obesity) can impair cardiac function and act as confounding factors. All patients should have their CVRFs controlled to avoid this.
- Observer bias may occur in echocardiography, the evaluator should not know whether or not patients have T2DM, because it may influence the search for specific alterations in the diagnostic test.

10.HEALTH IMPACT

Cardiovascular pathology is considered one of the main causes of death and hospitalization in our country and is also considered an important **factor with influence in worsening of quality of life** (2,3). There are several risk factors, such as DM, dyslipidaemia, smoking, obesity, among others, that favor its development and at the same time can aggravate it.

This cardiovascular pathology produces a great economic cost to the health system, pharmacological, interventional and hospitalization costs.

The drug under study (**Dapagliflozina**, belonging to SGLT2i group) has been shown to **reduce cardiovascular mortality, hospitalization for HF, and all-cause mortality** (7). This assures us that the use of this drug is a great advance in reducing the overall cost of this pathology.

If the objective of this study is achieved and our hypothesis is validated, the association between treatment with SGLT2i and the improvement of functional capacity or exercise capacity and cardiac function in patients with HF and reduced LVEF, an important step will be taken to **optimize this treatment**, which is already first line, but it will bring us closer to the patient profile that would benefit the most from this treatment.

This study may be used as a basis for future research. Determining the profile of patients with HF and reduced LVEF who benefit most from SGLT2i treatment from a clinical point of view and identifying the mechanisms that justify it, may help to select the **profile of patients with HF with preserved or slightly reduced LVEF in whom such treatment may be effective and in whom, at present, scientific evidence is limited**.

11.BUDGET

All staff members that will visit and attend participants during the study, the follow-up appointments, blood analysis and material for these, echocardiogram and ergospirometry, are not considered in this estimated budget because they are part of the National Health System.

On the other hand, the extra hours that the research nurse, clinical analyst and statistician need for the use of the database will be considered in the budget.

	COSTS	*QUANTITY*	*SUBTOTAL*
STAFF			
Research Nurse	35 €/h	30h	1.050€
Statistician	35 €/h	50h	1.750€
Clinical Analyst	35 €/h	50h	1.750€
PUBLICATION AND DISSEMINATION			
Journal Publication	1.000€	1	1.000€
National Congress of Cardiology	1.500€	1	1.500€
TOTAL			7.050€

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13.ANNEXES

ANEXO 1: ADDITIONAL ERGOSPIROMETRY DERIVED VARIABLES FOR FUTURE STUDY.

FUNCTIONAL CAPACITY AND EFFORT	CARDIOVASCULAR RESPONSE	PULMONARY RESPONSE
Exercise time	CF	Forced Vital Capacity (FVC)
Load achieved (watts, km/h, incline)	BP	FEV1
O2 consumption in exertion and recovery phase	O2 pulse	Tiffenau Index (FEV1/FVC)
O2 consumption efficiency slope (OUES)		Respiratory reserve
Ratio between VO2 and workload		Vt/IC ratio
RER respiratory quotient		PETCO2 (tele-expiratory CO2 pressure) at baseline and at VT1
Ventilatory thresholds (VT1 and VT2)		Slope VE/VCO2

- Forced Vital Capacity (FVC): maximum volume of air exhaled, with the maximum possible effort, starting from a maximum inspiration. It is expressed as volume (in ml) and is considered normal when it is greater than 80% of its theoretical value.
- FEV1: maximal expiratory volume in the first second of forced expiration.
- Tiffenau's Index (FEV1/FVC).
- Exercise time.
- Initial heart rate and at maximum effort.
- Initial BP and at maximum effort.

- O2 saturation at baseline and at maximum effort.
- Peak VO2 (PVO2): maximum amount of oxygen extracted from the inspired air per unit of time, during the effort at the maximum tolerated intensity. It is expressed in ml / kg / min. Absolute value and percentage of the predicted.
- VO2 at VT1: the VO2 reached at the first ventilatory threshold (or anaerobic threshold), expressed as a percentage.
- Peak O2 pulse and percentage of predicted O2 pulse.
- The respiratory quotient or respiratory exchange rate (RER) is the ratio between the volume of CO2 eliminated and O2 consumption and refers to the state of fatigue of metabolic processes. It is directly related to the substrate used (fats or carbohydrates). It allows to know if the patient has made a maximum effort (O2/CO2).
- RR (respiratory reserve): to ensure/assess whether there are any respiratory conditions that prevent good exercise.
- Vt/VC quotient: for the same reason as above. It means tidal volume/ inspiratory capacity and measures the fraction of inspiratory capacity used in respiration. In restrictive pattern Vt can reach 100% of inspiration to obtain sufficient O2 supply in ventilation (normal value < 80%).
- PETCO2 (tele-expiratory CO2 pressure) basal and at VT1.
- OUES (oxygen uptake efficiency slope): represents the increase in VO2 in response to a given VE (ventilation). It is an index of the effectiveness with which O2 is extracted from the ambient air and transported to the organism. It is a marker of ventilatory efficiency and is a submaximal and objective measure of FC.

ANEXO 2: NORMAL VALUES OF ERGOSPIROMETRY VARIABLES.

VARIABLE	REPOSO	VT1 (AT)	VT2 (RCP)	PICO
FC (% predicho)				> 90
VO_2 (ml/kg/min)	3,5			
VO_2 (% predicho)		> 40%		≥ 85%
VCO_2 (% predicho)				≥ 85%
GC (l/min)	4 - 5			20 - 25
Pulso O_2 (ml O_2/latido)				> 10 (mujeres) > 15 (varones)
Pulso O_2 (% predicho)				> 80%
Δ FC/ΔVO_2				Δ 10 lat / 3,5 ml
Δ VO_2/ΔWR (ml/min/watt)				8,5 - 11
RER (VCO_2/VO_2)	< 0,8			> 1,1
TA (mmHg)	< 140/90			< 220/90
SpO_2 (%)	≥ 95%			≥ 95%
Gradiente (A-a) O_2	<10 - 20 mmHg			< 35 mmHg
VE (l/min)	6 - 7,5			100 -120
V_E/VO_2	23 - 25	Empieza a aumentar		≤ 40
V_E/CO_2	25 - 30	< 34	Empieza a aumentar	< 36-40
$P_{ET}O_2$ (mmHg)	95 - 100	Empieza a aumentar		
$P_{ET}CO_2$ (mmHg)	36 - 42	Δ 3 - 8	Empieza a disminuir	
VE/VCO_2 (pendiente)				< 30
OUES (% predicho)				> 80%
Bf (resp/min)	8 - 15			< 60

VARIABLE	REPOSO	VT1(AT)	VT2(RCP)	PICO
Vt (litros)	0,5			2-2,5
Vt/IC (%)				<80%
BR (%)				>20%
Vd/Vt (%)	<40			<28(<30 si > 40 años)
Vt max/CV				0,53
C (a-v) O2 (ml/100ml)	4-6	10,5-12		15-17,5
Escala Borg (sobre 20)				15-18
Lactato (mmol/l)		2	4	>8

ANEXO 3: NORMAL VALUES OF ECHOCARDIOGRAM VARIABLES.

- **LV end-diastolic diameter**: **<56mm**.
- **LV end-systolic diameter**: **<36mm.**
- **LVEF: ≥50%.**
- **LV mass:** male **<102g/m2**, female **<88g/m2.**
- **Aorta diameter**: **<37mm.**
- **TAPSE** (tricuspid annulus plane systolic displacement, assesses right ventricular systolic function): **>15 mm.**
- **Diameter and area of LA**: diameter: **<40mm**, area: **<20mm2**.
- **Mitral E/A:** relationship between early ventricular filling wave and atrial contraction: **>1.**

ANNEX 4: MINNESOTA QUALITY OF LIFE QUESTIONNAIRE

¿Durante el Último Mes su Problema Cardiaco le Impidió de Vivir como a Usted le gustaría? ¿Por Qué?

		Pre	6m	12m	18m	24m	36m	48m
1.	Le ha provocado hinchazón de los tobillos y piernas	( )	( )	( )	( )	( )	( )	( )
2.	Usted ha tenido necesidad de sentarse o acostarse para descansar durante el día	( )	( )	( )	( )	( )	( )	( )
3.	Su marcha y subida de escaleras se han vuelto difíciles	( )	( )	( )	( )	( )	( )	( )
4.	Sus tareas del hogar se han vuelto difíciles	( )	( )	( )	( )	( )	( )	( )
5.	Sus salidas de casa se han vuelto difíciles	( )	( )	( )	( )	( )	( )	( )
6.	Tener una buena noche de sueño se ha vuelto difícil	( )	( )	( )	( )	( )	( )	( )
7.	Sus relaciones o actividades con familiares y amigos se han vuelto difíciles	( )	( )	( )	( )	( )	( )	( )
8.	Su trabajo para ganar la vida se ha vuelto difícil	( )	( )	( )	( )	( )	( )	( )
9.	Sus entretenimientos, deportes y diversión se ha vuelto difíciles	( )	( )	( )	( )	( )	( )	( )
10.	Su actividad sexual se ha vuelto difícil	( )	( )	( )	( )	( )	( )	( )
11.	Sus ganas de comer las comidas que a usted le gusta más se ha disminuido	( )	( )	( )	( )	( )	( )	( )
12.	Ha sentido falta de aire	( )	( )	( )	( )	( )	( )	( )
13.	Le ha dejado cansado, fatigado o con poca energía	( )	( )	( )	( )	( )	( )	( )
14.	Le ha obligado a quedar hospitalizado	( )	( )	( )	( )	( )	( )	( )
15.	Le ha hecho gastar dinero con cuidados médicos	( )	( )	( )	( )	( )	( )	( )
16.	Las medicaciones le han provocado reacciones adversas	( )	( )	( )	( )	( )	( )	( )
17.	Usted ha sido un incómodo para sus familiares y amigos	( )	( )	( )	( )	( )	( )	( )
18.	Usted ha sentido falta de tener el autocontrol de su vida	( )	( )	( )	( )	( )	( )	( )
19.	Usted se ha preocupado últimamente	( )	( )	( )	( )	( )	( )	( )
20.	Concentrarse o acordarse de las cosas se ha vuelto difícil para usted	( )	( )	( )	( )	( )	( )	( )
21.	Usted se ha sentido deprimido	( )	( )	( )	( )	( )	( )	( )

NO	MUCHO POCO				DEMASIADO
0	1	2	3	4	5

ANNEX 5: NYHA FUNCTIONAL CLASSIFICATION AND ACCF/AHA CLASSIFICATION

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

NYHA classification from European Society of Cardiology Guidelines.

STAGE A	High risk of HF, but without structural alterations or symptoms. Not equivalent to any NYHA grade.
STAGE B	Structural heart disease, but without symptoms or signs of HF. Equivalent to NYHA grade I.
STAGE C	Structural heart disease, but with previous or current symptoms of HF. It includes NYHA grades I to IV.
STAGE D	Refractory HF requiring specialized procedures. Equivalent to NYHA grade IV.

ACCF/AHA classification from ACCF/AHA Heart Failure Guidelines.

ANNEX 6: PATIENT INFORMATION SHEET

HOJA DE INFORMACIÓN AL PACIENTE

Estudio: "Association of SGLT2i (sodium-glucose cotransporter type 2 inhibitors) treatment with functional capacity in patients with or without type 2 Diabetes Mellitus with heart failure and reduced ejection fraction".

Promotor: Dr. Marco Paz Bermejo.

Investigador del estudio: Dolores María Rico Morales.

INTRODUCCIÓN:

Nos dirigimos a ustedes para informarles sobre un estudio que va a realizarse acerca de un fármaco antidiabético en personas con insuficiencia cardíaca, independientemente de la presencia o no de Diabetes Mellitus tipo 2, en el que se les invita a participar. El estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Hospital Santa Caterina.

Nuestra intención es que ustedes reciban la información correcta y suficiente para que puedan evaluar si quieren participar en el estudio. Para ello, lean esta hoja informativa con atención y nosotros le aclararemos las dudas que puedan surgir. Además, pueden consultar con las personas que consideren oportunas.

OBJETIVO:

El principal objetivo del presente estudio es evaluar, en personas con tratamiento previamente establecido de insuficiencia cardíaca, como es su caso, cómo la adición del tratamiento con Dapagliflozina produce cambios en la capacidad funcional y función cardíaca y cuáles son.

DESCRIPCIÓN DEL ESTUDIO:

En este estudio participarán 196 pacientes y será llevado a cabo exclusivamente en el Hospital Santa Caterina. Una vez otorguen el consentimiento para participar, se les realizará un ecocardiograma, una ergoespirometría, una analítica sanguínea y un cuestionario antes de comenzar con el tratamiento (si ustedes poseen un ecocardiograma realizado en los últimos 3 meses con las variables que se evaluarán en el estudio no será necesario repetirlo, ocurrirá lo mismo con la analítica y la ergoespirometría si han sido realizadas en el último mes y posee todos los parámetros que estudiaremos).

Si ustedes siguen cumpliendo los criterios para participar en el estudio, tendrán otra visita médica donde se les prescribirá el fármaco y se les dará las indicaciones de como tomarlo. Todos los pacientes recibirán el tratamiento en estudio.

Tendrán un control médico al mes de tratamiento, para evaluar si ha podido aparecer algún efecto indeseado. A los 3 meses de tratamiento se les realizará nuevamente un ecocardiograma, una ergoespirometría, una analítica sanguínea y un cuestionario de calidad de vida.

PARTICIPACIÓN VOLUNTARIA:

Su participación en este estudio es totalmente voluntaria y en caso de que decidan no hacerlo, no tiene que dar explicaciones y su decisión no implicará ninguna diferencia con respecto a la calidad asistencial que ustedes van a recibir.

DURACIÓN DE LA PARTICIPACIÓN:

El estudio durará 3 meses, con la visita médica al mes y a los 3 meses de tratamiento. Finalizado este tiempo, seguirán sus controles médicos habituales.

CONFIDENCIALIDAD:

Toda la información que se recoja y que se guarde (mediante un sistema informático) y cuyo análisis realizará un estadístico (con un sistema informático también) será estrictamente confidencial y seguirá la normativa vigente en España (Ley 3/2018 de Protección de datos de carácter personal).

Sus documentos médicos podrían ser revisados sólo por personas dependientes de las Autoridades Sanitarias, miembros de comités éticos independientes y otras personas designadas por ley para comprobar que el estudio se está llevando a cabo correctamente.

BENEFICIOS Y RIESGOS ESPERADOS:

Se espera una disminución de hospitalizaciones por insuficiencia cardiaca y de la muerte por causa cardiovascular, beneficio ya demostrado previamente. Del estudio se podrá concluir si se produce una mejoría la función cardiaca y capacidad funcional, qué cambios produce y en qué tipo de pacientes. A través de los resultados si, como se espera, son satisfactorios, podremos aconsejar a las autoridades sanitarias sobre cómo implementar la eficacia de este tratamiento.

Entre los riesgos más frecuentes que aparecen con este fármaco se encuentran la hipoglucemia (sobre todo cuando se usa con una sulfonilurea o insulina), prurito generalizado y exantema, e infecciones genitales en mujeres. Otros riesgos mucho menos frecuentes son angioedema, cetoacidosis diabética, trastornos renales y elevación del hematocrito.

TRATAMIENTOS ALTERNATIVOS:

Existen otros tratamientos alternativos, que podrán consultarle al especialista.

PUBLICACIÓN:

En caso de publicación de los resultados del estudio a través de publicaciones y/o congresos, ya sea a las autoridades sanitarias o a la comunidad científica, siempre se hará de forma global y nunca de forma individualizada, de modo que no será posible la identificación de los participantes.

CONTACTO:

Si ustedes tienen cualquier duda durante el período del estudio pueden contactar con el investigador principal.

Teléfono: 972412200

Hospital Santa Caterina. Servicio de Cardiología.

Calle del Dr. Castany, s/n, 17190 Salt, Girona.

Gracias por leer esta hoja. Si tienen alguna duda o pregunta sobre el estudio, por favor hágala.

No dude en preguntar al investigador o colaboradores. En caso de que decidan participar en el estudio intenten mantener esta información para sus registros hasta el final del proceso. Si están dispuesto a participar, pueden seguir leyendo y firmar el consentimiento informado.

ANNEX 7: INFORMED CONSENT

CONSENTIMIENTO INFORMADO DEL PACIENTE

Estudio: Association of SGLT2i (sodium-glucose cotransporter type 2 inhibitors) treatment with functional capacity in patients with or without type 2 Diabetes Mellitus with heart failure and reduced ejection fraction.

Promotor: Dr. Marco Paz Bermejo. Servicio de Cardiología. Hospital Santa Caterina.

Yo, …….(Nombre y apellidos del paciente)

- He leído la hoja de información que se me ha entregado.

- He recibido suficiente información sobre el estudio.

- He podido hacer preguntas sobre el estudio

- He hablado con…..Dolores María Rico Morales.

Comprendo que puedo retirarme del estudio:

1) Cuando quiera

2) Sin tener que dar explicaciones

3) Sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

Este consentimiento, de acuerdo con la ley 15/1999 y RD 1720/2007 es revocable, por lo que puedo ejercer el derecho de acceso, rectificación y cancelación dirigiéndome al investigador.

Fecha ……/……/……..

Día mes año

Nombre:

Firma del paciente Firma del médico