Universitat de Girona
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EFFECTS OF EMPAGLIFLOZIN ON CARDIAC FUNCTION

FINAL DEGREE PROYECT

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1. ABBREVIATIONS

ACSs	Acute Coronary Syndromes
ADA	American Diabetes Association
AMI	Acute myocardial infarction
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
CVA	Cerebrovascular Accident
DALYs	Disability-Adjusted Life Years
DM	Diabetes Mellitus
EU	European Union
FDA	Food and Drug Administration
GF	Glomerular Filtration
HbA1c	Hemoglobin A1c
HBP	High Blood Pressure
HF	Heart Failure
HDL	High Density Lipoprotein
IR	Insulin Resistance
LDL	Low Density Lipoprotein
LV	Left Ventricle
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
SGLT	Sodium-glucose linked transporter

2. ABSTRACT

***Background*:** Heart failure and diabetes are diseases with extremely high prevalence in Spain, what implies a high economic cost for the health system and a great loss of quality-adjusted life years. So far, any antidiabetic drug had shown a clear decline in hospitalizations due to heart failure (neither in cardiac mortality). Empagliflozin surprisingly demonstrated these results in the EMPA-REG study, it has led to its recommendation by the European and American Guidelines for diabetic patients with high cardiovascular risk. Despite this, little is known about the mechanism by which it is achieved, and about which patients can benefit more from this drug.

***Objectives*:** The main aim is to determine if Empagliflozin produces changes in cardiac function that may justify its cardiovascular benefit in heart failure. Thus, we intend to achieve the improvement in the optimization of this treatment.

***Design*:** A quasi-experimental, prospective, pre-post, longitudinal follow-up, open without a control group, in which each patient will be their own control. It will be carried out in Hospital Santa Caterina of Girona between November 2017 and February 2021.

***Participants*:** Patients between 18 and 85 years old, with poor control of type 2 Diabetes Mellitus and heart failure, who are in follow-up in the cardiology consultations of Hospital Santa Caterina.

***Method*:** A non-probabilistic consecutive sampling will be used in this study; we will evaluate cardiac function through echocardiographic parameters and evolution of heart failure though NT-proBNP values.

***Keywords*:** Type 2 Diabetes Mellitus. Heart Failure. Empagliflozin. Cardiac function.

3. INTRODUCTION

3.1 DIABETES

3.1.1 Definition, diagnosis and prevalence of Diabetes

Type 2 diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to a combined insulin resistance with a progressive production deficit of this. This type accounts for 85-95% of DM cases. (1)

DM diagnostic is based on American Diabetes Association (ADA) criteria exposed in Table 1.

Table 1 ADA criteria for DM (2)

FPG>/= 126mg/dl. Fasting is defined as no caloric intake for at least 8h*
OR
2h PG >/=200mg/dl during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water*
OR
A1C>/= 6,5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >/=200 mg/dl.
***In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.**
FPG: fasting plasma glucose; PG: plasma glucose; OGTT: oral glucose tolerance test; DCCT: Diabetes Control and Complications Trial

In Spain, prevalence is estimated at 2.8-3.9% It increases with age, reaching 20% in >80 years. (3)

3.1.2 Importance of Diabetes Mellitus in cardiovascular diseases

Dealing with our topic, cardiovascular morbidity in these patients is 2-4 times higher than in the non-diabetic population. (3,4) Furthermore, about two third parts of deaths in diabetic patients are due to acute myocardial infarction, cerebrovascular accident and /or

congestive heart failure (in order of frequency). While mortality from cardiac disease has decreased during the last years in the non-diabetic population, in type 2 DM it has not decreased significantly despite glycemic control, which suggests other influential factors. Life expectancy of patients with DM2 and high risk of cardiovascular diseases decreases around 12 years. (5–8)

Diabetic patients have, a higher incidence of atherosclerotic cardiovascular disease (ASCVD), defined by the following pathologies: acute coronary syndromes, history of previous myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin. ASCVD is the leading cause of morbidity and mortality for these individuals and is the largest contributor to the direct and indirect costs of diabetes. In addition, the vessels show greater degrees of stenosis with lesions of greater severity and extension. (5) Approximately 40% to 50% of patients with coronary heart disease have DM2, so it should be taken into account when studying those patients and their comorbidities.(9)

Others mayor risk factors of ASCVD are: smoking, high blood pressure (HBP), and hypercholesterolemia. Besides, hypertension and dyslipidemia, added to renal insufficiency, are common conditions coexisting with type 2 diabetes and also risk factors for it.(2,3) These risk factors are very frequent in the population, and therefore, they are account for a very important part of cases of cardiovascular diseases (CVD) in the Spanish population. Other predisposing risk factors can be added to the ones mentioned previously, such as obesity and sedentary lifestyle, which exert their action through intermediate, causal or conditional risk factors. (10)

Heart Failure (HF) is caused by coronary injury and cardiomyopathy, although the mortality only increases at the expenses of the ischemic cause. Many studies support the high incidence of heart failure in DM, with a risk x2 in men and x5 in women, compared to the non-diabetic population, matched by age and sex. Hospitalization for heart failure are doubled in diabetic patients too. Isolated left ventricular dysfunction, called diabetic cardiomyopathy (without coronary lesions), is typical of DM. This is initially characterized by diastolic dysfunction with early decrease of diastolic filling and thinning of the evolutive ventricular wall until systolic dysfunction. Beyond 50% of diabetic individuals with HF also have coronary artery disease.

Conversely, the possibility that the Cardiovascular diseases (CVD) favors the development of insulin resistance and even DM has been suggested. (5)

3.1.3 Pathophysiology; how diabetes causes cardiac pathology

Regarding the pathophysiology of ASCVD, hyperglycemia leads to the formation of end products of glycation in the arterial wall, which damages protein structures due to their oxidative potential. Hypercoagulability, which is more frequent in Diabetes, can contribute to vascular risk through high production of procoagulant proteins (fibrinogen, factor VII, von Willebrand factor), high concentrations of inflammatory cytokines or suppression of fibrinolysis due to increased concentrations of PAI (Plasminogen activator inhibitor). Finally, DM can directly damage the myocardium, in the default of coronary disease, through hypertrophy of the myocyte, interstitial fibrosis, microvascular changes, or functional defects (alteration of calcium channels). (5)

As a conclusion, DM is a public health problem of great dimension, due to its high and increasing prevalence, as well as its cardiovascular consequences.

3.2 CARDIOVASCULAR DISEASES

3.2.1 Cardiovascular deaths and causes of these

Nowadays, more than 125,000 deaths are produced in Spain related to cardiovascular diseases; which is the 34% of all deaths. Furthermore, there are more than 5 million hospital stays for cardiovascular diseases per year. Thus, CVD is the leading cause of death and hospitalization in the Spanish population.

Ischemic heart disease and cerebrovascular disease are the two CVD that produce a greater number of cardiovascular deaths, with a 60% of total cardiovascular mortality. Also, these two CVD are, respectively, the third and fourth causes of loss of life adjusted for disability (disability-adjusted life years, DALYs) in Spain. (10)

The third major CVD as cause of death is ***heart failure***. Heart failure is defined as a heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic need of the body. Heart failure can be caused by structural defects, functional abnormalities (ventricular dysfunction), or a sudden overload beyond its capacity. Chronic heart failure is more common than acute heart failure which results from sudden insult to cardiac function, like a heart attack, although the term HF is commonly used to refer just to chronic HF.

Diastolic HF is caused by abnormal myocardial relaxation during diastole, leading to defect cardiac filling; and systolic HF is caused by abnormal contraction during systole, leading to defective cardiac emptying. Both HF have similar prevalences. However, systolic HF is the most studied, and more is known about its physiopathology and its treatment. (11)

After all that has been said, we consider that more research on this area could help in reducing deaths and hospitalization rates.

3.2.2 Cost of cardiovascular diseases

The CVD were a cost to the health care systems of the European Union (EU) of approximately 105,000 million euros in 2003. This represents a cost per capita of 230 euros per year, around 12% of the total health care spending across the EU. From the total cost of CVD to the health care systems, up to 57% is at the expense of hospitalization while drugs are only represented around 27%

CVD is the complication of diabetes that more direct cost implies. That is, it accounts for more than half of the cost related to mortality.

Hospitalizations account for half of the total expenses of the total DM cost. (12)

Because of this, we believe that we should focus our efforts on reducing cardiovascular complications and the number of hospitalizations. If these reductions could be achieved with a drug treatment it would be cost-effective.

3.3 CARDIOVASCULAR SAFETY OF NON-INSULIN ANTIDIABETICS.

The treatment of DM2 until now has not shown to be able to reduce mortality or cardiovascular morbidity (except for controversial data regarding metformin, which I will comment later). Besides, in some cases, it can aggravate it. Regarding this, the meta-analysis of Nissen represented a turning point in the cardiovascular safety of antidiabetic drugs.

3.3.1 Glitazone

In the meta-analysis of Nissen 2007, treatment with rosi**glitazone** was associated with a significant increment in the risk of presenting myocardial infarction, and with an increased tendency of death of cardiovascular cause. This caused that, first the FDA (Food and Drug Administration) in the year 2008 and, later, the European Agency of the Medicine, established that, in order for a new antidiabetic drug to be approved, its cardiovascular safety had to be demonstrated. (13,14)

The data found about pioglitazone, the other **glitazone** used as an antidiabetic treatment, has not shown an increment in AMI, but it has shown an increase in hospitalization due to HF. For this reason, they are contraindicated in this condition. (4,14)

3.3.2 Dipeptidyl peptidase-4 inhibitors

So far, the results of 2 clinical trials have been published following this regulation. In the SAVOR-TIMI 53, saxagliptin (a Dipeptidyl pentidase-4 inhibitor), added to the habitual antidiabetic treatment, did not increase the risk of cardiovascular death, myocardial infarction or ischemic stroke compared to placebo. However, more cases of hospitalization due to heart failure were described.

In the EXAMINE study, alogliptin (another drug of the same group) was also not associated with an increase in the risk of death of cardiovascular cause, nonfatal myocardial infarction or non-fatal stroke compared to placebo.

The results of those studies warned about the possible increment in the risk of heart failure when treated with drug from this pharmacological group. The Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS) was expected to confirm or deny the possible drugs class effect. In this study, non-inferiority of the drug was established with respect to placebo, but also non-superiority. (15)

The subanalysis of Zannad et al. carried out to assess the risk of HF and alogliptin, founded no association. There are more studies about **dipeptidyl peptidase-4 inhibitors,** but they have dubious statistical significance. Thus, the only conclusion that can be obtained is that they are not harmful in the cardiovascular field according to these data, but also they do not produce any benefit beyond glycemic control. (4,13)

3.3.3 Metformin

Most studies about **metformin** have been done before the FDA restriction of 2008. The UKPDS study showed that metformin monotherapy in obese newly diagnosed was related with reduction in sudden death, myocardial infarction and all-cause mortality. A subsequent metanalysis showed that metformin reduced adverse cardiovascular events (MI, stroke, peripheral artery disease and cardiovascular death) versus placebo/no therapy, but not against active-comparators. Therefore, the cardiovascular benefit of metformin is doubtful, and although it is not contraindicated in HF, it does not show any benefit in this high percentage of patients. (2,4)

3.3.4 Sulfonylureas

The **sulfonylureas** are the oldest and most widely prescribed oral anti-diabetic agents. The UGDS study first reported that DM patients who received tolbutamide (sulfonylurea) had increased cardiovascular mortality compared with placebo or insulin. Several subsequent observational studies supported an association between sulfonylurea use and increased cardiovascular mortality. A review of 115 randomized trials found a 22% increased risk of all-cause mortality with sulfonylurea therapy compared with placebo or other anti-diabetic drugs, although the overall incidence of major adverse cardiovascular events appeared to be unaffected. Recent meta-analyses reported inconsistent findings. Therefore, only a harmful or null effect on cardiovascular safety can be expected from this group of drugs. (4)

3.3.5 Megliptinides

In NAVIGATOR, after a median follow up of 5 years, no differences between nateglinide (a drug of this group) and placebo in the sum of cardiovascular deaths, AMIs, strokes and heart failure hospitalizations were found. About this last objective, a reduction was found, but without statistical significance. (2,4)

3.3.6 Sympatholytic D2 dopamine agonist

Bromocriptine is a **Sympatholytic D2 dopamine agonist,** in *Cycloset study* we could find contradictory outcomes about this drug. There was difference without statistical significance in the number of general adverse events between the placebo group and the Cycloset group. However, a higher percentage of patients treated with bromocriptine experienced a specific cardiovascular event (outcomes with signification statistical significance). But comparing mayor adverse cardiac events, the risk was reduced in Cycloset group compared with placebo group.

We cannot draw a solid affirmation about its cardiovascular safety with these outcomes. Therefore, we shouldn't recommend to people with a high cardiac risk. (16,17)

3.3.7 Alpha glucosidase inhibitors

There are no long-term studies examining the effect of Alpha Glucosidase Inhibitors on cardiovascular disease or mortality in DM2 patients. Acarbose treatment (an alpha glucosidase inhibitors) was associated with a reduction in the outcome of cardiovascular events even though the study was not initially driven to draw conclusions about cardiovascular outcomes. Despite of this, we don't have long-term studies to obtain conclusion about its cardiovascular safety.(4)

To the surprise of the clinicians, different drugs seem to be showing a certain beneficial effect beyond the control of HbAc1 in the cardiovascular field. This is producing an increase of interest in the investigation of these in recent years. In fact, redGDPS (group of primary care physicians with special interest in improving the care of people with DM2) recommends, based on the Standards of Medical Care in Diabetes 2018, the use of glucagon-like peptide-1 agonists or sodium-glucose cotransporters-2 inhibitors in patients with DM2, high cardiovascular risk and poor glycemic control with metformin treatment and lifestyle improvement.(18) The Canadian Diabetes Association also recommends any of these two pharmacological groups with a level 1A in patients with cardiovascular disease and poor glycemic control. (19)

3.3.8 Glucagon-like peptide-1 agonists

Glucagon−like peptide−1 agonists cardiovascular safety was examined in some studies such as LEADER (for liraglutide, one of this group) and SUSTAIN-6 (studying semaglutide effects, another of these drugs), providing significative data in favor of a decrease in cardiovascular risk. Others, such as CNODES, did not have statistical significance. On the other hand, ELIXA did not find differences. Therefore, their cardiovascular safety has yet to be studied, but these results seem promising. (4,20,21)

3.3.9 Sodium glucose cotransporter-2 inhibitors

Finally, we will focus on the drug on which this work is based: Empagliflozin, which belong to the family of **Sodium glucose cotransporter-2 inhibitors.** Canagliflozin and Daplagliflozin are also in this drug group.

3.3.9.1 Working of Sodium glucose cotransporter-2 inhibitors

This group of drugs blocks the receptor that is in the proximal tubule and reabsorbs 97% of the urinary glucose (SGLT2, Sodium-glucose linked transporter 2). Tubular glucose that escapes SGLT2 is subsequently reabsorbed by SGLT1 in more distal tubular segments. Therefore, Empagliflozin increases glycosuria without interfering with the function of pancreatic beta cells, which implies a low risk of hypoglycemia. Studies have also shown that SGLT2 expression is increased in hyperglycemic conditions, likely representing an adaptive response to increased plasma glucose filtration, and paradoxically increasing the threshold for urinary glucose excretion in patients with diabetes mellitus. The ability to lower blood glucose and glycated hemoglobin (HbA1c) levels is limited by the filtered load of glucose and the osmotic diuresis that is caused by this therapy. Moreover, although the currently developed SGLT2 inhibitors block almost completely proximal tubular glucose reabsorption, the measured inhibition is less than 50

percent based on urine glucose excretion. This could suggest an incomplete inhibition by pharmacological SGLT2 blockade, insufficient target concentration, or a compensatory increase in SGLT1 expression/activity when SGLT2 is blocked. (9)

3.3.9.2 Benefits of Sodium glucose cotransporter-2 inhibitors

Sodium glucose cotransporter-2 inhibitors produce a significant decrease in systolic and diastolic blood pressure without an increase in heart rate, partly due to this osmotic diuresis.

It reduces HbA1c, improves insulin sensitivity, reduces glucose toxicity and promotes weight loss of 2-3 kg over 12 weeks. It has a modest beneficial effect on the lipid profile through an increase in high-density-lipoprotein cholesterol and low-density-lipoprotein cholesterol (despite this last fact, in EMPAREG study, patients did not need a higher dose of lipid-lowering drugs) and decrease in triglycerides, waist circumference, uric acid level. Empagliflozin also has favorable effects on markers of arterial stiffness, vascular resistance and albuminuria. (4,6,8,9,22)

3.3.9.3 Cardiovascular safety of Sodium glucose cotransporter-2 inhibitors

In *EMPA-REG OUTCOMES* study 7020 patients were followed during 3.1 years between 2010 and 2013 with the aim of assessing the cardiovascular safety of Empagliflozin. These patients had suffered at least one cardiovascular event (any ASCVD). Therefore, these results are only extrapolated as secondary cardiovascular prevention in diabetic patients, and all the patients also had their standard treatment for their pathologies (statin, fibrate, acetylsalicylic acid agent, blockers of the renin-angiotensin system, beta-blockers and calcium channel blockers; Sulfonylureas, metformin, insulin in monotherapy or in combination were added in the cases that were necessary to control glycaemia). Although there were no significant differences in the number of non-fatal AMI and CVA, it showed

a significant decrease in death from any cause, in death due to cardiovascular causes, by AMI and by CVA and hospitalization by HF. (23)

Empagliflozin has two doses marketed, 10mg and 25mg and the use of one or the other did not influence the cardiovascular results, but it did influence the control of blood glucose. All results were stratified by weight, HbA1c, region and renal function. (6)

These were shocking results because no hypoglycemic drug has shown cardiovascular benefits in this type of patients. In fact, only 39 patients need to be treated for 3 years to prevent a death. Furthermore, it is the first antidiabetic that demonstrates a reduction of hospitalization by heart failure. (4,6,7,24)

Driven mainly by these results, a meta-analysis of data from regulatory submissions and published trials (CVOTs, 2nd Cardiovascular Outcome Trial) suggested net protection of SGLT-2 inhibitors against cardiovascular outcomes and death and highlighted the great importance of HF occurrences. (4,25)

The FDA recently added the new indication for Empagliflozin to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors have the same effect in high-risk patients or Empagliflozin and other SGLT2 inhibitors have a similar effect in lower-risk patients with diabetes remains unknown. (2) However the recent published results of the study CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R supported the theory that this cardiovascular benefit is an effect of the whole group of drugs. Patients treated with Canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation. This was obtained in both trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease. This decrease risk of cardiovascular events was assessed as either death from cardiovascular causes, nonfatal

myocardial infarction, or nonfatal stroke (the primary outcome). The results also showed that patients treated with Canagliflozin had lower risk of hospitalization for heart failure, progression of albuminuria, and substantive loss of kidney function than patients who received placebo, although on the basis of the prespecified hypothesis testing sequence these findings are not considered statistically significant. (26)

Currently there are ongoing studies with dapagliflozin: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58 study) with completion scheduled for April 2019. This study has a large percentage of patients in treatment as primary prevention that can shed light on these results. (24)

3.3.9.4 Hypothesis about the cause of cardiovascular benefits

Since the surprising results of Empagliflozin a very interesting debate has started around the cause of these cardiovascular benefits.

There are multiple mechanisms that may be involved in this benefit such as the decrease in blood pressure (BP), the greatest known benefit of which is the decrease in CVA but it was not observed in the study. (24)

Regarding its possible action on the arteriosclerosis, it seems to be unlikely, as three years is a short period to produce benefits on it; besides, there was no decrease in AMI or CVA in the group of empagliflozin.

The most plausible hypothesis to explain these results seems to be the hemodynamic changes. Natriuresis and osmotic diuresis produced by empagliflozin could improve both heart failure and possible cardiac dysfunction, and this could contribute to start seeing the benefit after three months of treatment. Plasma volume contraction–mediated decreases in myocardial stretch may have reduced cardiac arrhythmogenesis, another mechanism plausibly responsible for the reduced mortality observed. However, when we treat this

type of patients with diuretics (which were more used in the placebo group), we do not obtain these benefits.

SGLT2 inhibitors have been associated with suppression of proinflammatory and profibrotic pathways. Most of these studies have either been in vitro or have looked at effects in kidney tissue. Less is known about these effects in the heart, and nothing to date has been reported in humans. In the heart, epicardial adipose tissue has been related to cardiac fibrosis, reduced contractility, arrhythmias, and heart failure. If SGLT2 inhibitors reduce epicardial fat in addition to decreasing adipose tissue in other areas of the body, this could provide a mechanism which links Empagliflozin and the cardiovascular effects observed. (9)

Another possible option postulated is changes in arterial stiffness, demonstrated by pulse wave velocity and pulse pressure.

As possible causes, the following have increased their relevance: the improvement of kidney function (including reductions in hyperfiltration, proteinuria, glomerular hypertrophy, mesangial expansion and effects of blood pressure and weight lost), reduction of uric acid and visceral fat.

Differences regarding glycemic control, lipid or weight do not seem determinant.

Rather than simplistically attributing the clinical impact of Empagliflozin to one pathway versus another, perhaps the results observed in EMPA-REG OUTCOME were instead attributable to an overall beneficial profile: reduced BP and plasma volume, weight loss, and modest antihyperglycemic and uric acid–lowering effects. (9,24)

3.4 NEUROHUMORAL ACTIVATION AND ECHOCARDIGRAPHY IN HEART FAILURE

3.4.1 NT-proBNP

3.4.1.1 Function and formation of BNP and NT-proBNP

The B-type natriuretic peptide (BNP) is a hormone that constitutes a part of the vasodilator system, with effects on the heart, kidneys, vascular and central nervous system. BNP produces natriuresis, diuresis, lusitropic actions and vasodilation (by inhibiting cardiac sympathetic traffic and renin-angiotensin-aldosterone activity); it also has a certain antifibrotic effect on cardiomyocytes. (27–29)

In normal conditions, the transcription of the BNP gene and the production of pro-hormone (NT-proBNP, N-terminal prohormone of brain natriuretic peptide) occurs predominantly in the auricles. Under pathological conditions (volume overload or left ventricle pressure), the transcription and translation of BNP are up-regulated in ventricular myocytes (converting the ventricles into the predominant source of BNP production). Peptide levels are higher in patients with left ventricular hypertrophy and are even higher in subjects with left ventricular hypertrophy and clinical heart failure. They also reflect left atrial size and left atrial volume and are inversely related to LV ejection fraction.

The right ventricle also contributes to plasma levels of NT-proBNP and BNP. Levels of this peptide correlate with measures of right ventricle size and function, rising with greater dilatation and systolic dysfunction, and with increasing right ventricle pressure estimated.

NT-proBNP and the BNP have the same diagnostic value, and both vary the blood levels equally, but the first is more stable than the second. Because of that, NT-proBNP usually is used by the analysis . (27,28)

3.4.1.2 Significance and use of high NT-proBNP levels

As we have already commented, an elevated BNP level is a marker of increased LV filling pressures and LV dysfunction; these high levels of NT-proBNP aid the diagnosis of systolic and diastolic dysfunction. BNP or NT-proBNP levels are higher in heart failure with impaired LV systolic function than when LV ejection fraction is preserved, consistent with greater wall stressing (that is the strongest correlation with NT-proBNP). However, peptide levels have limited accuracy in differentiating these two entities.(29)

Thus, it can aid to diagnose Congestive heart failure (CHF), with a sensitivity of 75% and a negative predictive value of 99%. In fact, these were highly correlated with increasing CHF symptoms. Some studies support the theory that NT-proBNP may be most useful for detecting early LV dysfunction without overt clinical CHF (but with echocardiographic or structural LV heart disease). (27,29)

Left ventricular geometry is also important; dilated ventricles secrete more peptide for a given filling pressure due to greater wall stress and chamber mass.

Plasma levels of BNP and NT-proBNP increase with age, as we can see in European Society of Cardiology guides and are lower in men than in women. These levels are inversely related to body mass index and lean mass and directly related with worsening glomerular filtration rate. Even in stable subjects, peptide levels vary with repeat testing as a consequence of assay characteristics and biological variation. Relative variation is greater in normal subjects, in whom absolute levels are low. In disease states, absolute levels are higher and relative variation is lower. In stable heart failure subjects, changes

of more than 23% for NT-proBNP or 43% for BNP are likely to indicate a change beyond that due to background biological variation. (29,30)

For all these, we believe that it can be a good way to assess the cardiac changes that can be produced in the heart.

3.4.2 Echocardiogram

Dealing with the role of echocardiography in systolic and diastolic heart failure as the most useful test, it is effective not only in diagnosis (that is especially helpful in patients who present with resting or / and exertional symptoms of heart failure) but also as a tool to provide insights into the pathophysiological mechanism of various etiologies of heart failure (despite having symptoms, for an optimal management strategy). 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.

It is important to obtain objective evidence of structural or functional abnormalities to explain patient’s symptoms of heart failure, since 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. (31)

Ventricular remodeling caused by heart failure, or an acutest failure such as a heart attack, produces hemodynamic changes that determine survival in this type of patients. So, echocardiography is useful to evaluate the prognostic. (32)

Others important echocardiographic parameters that determine survival in HF are: ejection fraction of the LV, volume/dilatation/ hypertrophy of the ventricle, alteration of intracardiac geometry, deceleration time of early mitral diastolic inflow velocity, restrictive pattern and shortening of the deceleration time. (31,32)

These should be evaluated at the moment of the diagnostic of HF and it should be regularly assessed to control the patients' evolution and adjust their treatments.

Everything said confirms that echocardiogram is an excellent tool to evaluate HF, to classify it in systolic or diastolic and to evaluate the changes that take place throughout the disease or if morphological changes occur with the taking of a drug.

Echocardiography and the B-type natriuretic peptides provide powerful incremental assessment of cardiac function, clinical status, and outcome across the spectrum of cardiac disease. There is strong evidence to support their integrated use in the diagnosis and management of cardiovascular disease.

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. (29)

4. JUSTIFICATION

Empagliflozin, as well as Canagliflozin, (which belongs to the family of Sodium glucose cotransporter-2 inhibitors, a new group of oral non-insulin antidiabetics) has been shown to reduce hospitalizations of HF and deaths rate of others cardiovascular diseases in the studies performed; this discovery has been of great importance and amazement for clinicians since in the current field this had not been demonstrated by any antidiabetic drug. (6,7,22)

It is unknown the physiological mechanism by which is produces this benefit, postulated as a possible single cause or more likely added to others, changes in cardiac function. Likewise, it is not established if all patients with ventricular dysfunction can benefit or if it depends on the degree of dysfunction, or if there are differences depending on whether the dysfunction is systolic or diastolic. (9,24)

Given the high prevalence of DM2, HF and others cardiovascular diseases in diabetic patients, the DALYs that removes these diseases, and the resources and economic expenditure that supposes, we consider it important to evaluate if there is a relationship between the improvement of cardiovascular morbidity and mortality in patients treated with Sodium glucose cotransporter-2 inhibitors and changes in cardiac morphology, which we can identify through echocardiography and changes in neurohumoral activation; in measurements of Pro-BNP levels, to be able to get the most out of this therapy.

The study of the effect of these drugs on ventricular function should allow us to identify which patients with DM2 and HF can obtain more benefit from the use of these drugs, and develop new drugs taking advantage of this knowledge.

5. HYPOTHESIS

The hypothesis of this study is that Empagliflozin produces changes in cardiac function that can be evidenced by echocardiography and by improving the value of NT-proBNP in diabetic patients with heart failure that justifies its beneficial effects.

6. OBJECTIVES

The ***main objective*** of this study is to determine the effect of Empagliflozin on echocardiographic variables and neurohumoral activation; that is, to determine if it produces morphological changes in the heart that justify its benefits in diabetic patients with heart failure.

Secondary objective:

- Treatment optimization; Defining the profile of patients with HF in which the benefit of the drug is greater.

7. SUBJECTS AND METHODS

7.1 STUDY DESIGN

This study will be a quasi-experimental, pre-post, longitudinal follow-up, prospective, open without a control group, in which each patient will be their own control. It will be carried out in Hospital Santa Caterina of Girona.

We are going to use this type of study because we are trying to get the highest level of evidence, and this is obtained through a clinical trial, but we cannot use it due to it won't be ethical use a control group without antidiabetic treatment (it will increase the patients' morbimortality).

7.2 SUBJECTS SELECTION

The population of interest for this study includes all patients with type 2 DM and who are currently suffering HF. All participants have to be monitored in Hospital Santa Caterina.

We have defined the population of this study as follows:

7.2.1 Inclusion criteria

- Patients diagnosed with DM2 according to the ADA criteria (without changes in the 2017 revision) and those older than 18 years.

- They must be diagnosed with heart failure, with no changes in the last month.

- Patients with NT-proBNP levels ≥ 600 pg/ml. *(It is the level at which the usual variations are smaller, therefore the changes will more likely indicate a morphological difference. Furthermore, in subjects with normal LV ejection fraction, elevated NT-proBNP (>600 pg/ml) are the strongest independent predictors of severe diastolic dysfunction).*(33)

- Patients with HbAic > 7% in the last analysis. *This means, patients with poor control of diabetes with their current hypoglycemic treatment.*

- Patients who agree to participate in the study by understanding and signing the informed consent form.

7.2.2 Exclusion criteria

- Patients with diastolic HF and atrial fibrillation (since diastolic function cannot be determined by echocardiogram).

- Patients whose ventricular dysfunction is caused by severe valvular disease.

- Patients who do not sign the consent form.

- Patients whose creatinine level, age or others specials conditions contraindicate to take Empagliflozin (despite results obtained in the EMPA-REG OUTCOME study that shows benefits in patients with important kidney failure - <60ml/min and including 30 ml/min -, the Spanish Government don't recommends use this drugs in these patients for the risk of dehydration, hypovolemia and hypotension; for the same problem it is not recommended in people with more than 85 years.) (6,8,9)

7.3 SAMPLE

After consulting with the computer service of Santa Caterina Hospital and checking the codified diagnoses, we calculated that approximately 300 to 400 patients a year could meet the criteria to participate in our study (who attend external consultations of cardiology in the Hospital Santa Caterina).

In a bilateral contrast, with an alpha risk of 5% and a power (1-beta) of 80%, finite population (Hospital Santa Caterina) and assuming maximum indeterminacy and drop-out of 15%.

326 patients will be needed for an accuracy of 5%, 154 patients for an accuracy of 8%, and 103 patients for an accuracy of 10%. Accuracy is the difference in percentage that we want to detect as a minimum, in this study we will remain with 154 patients accepting an accuracy of 8%. The calculations have been made with the prof Marc Saez's software, based on the pwr package of the free statistical environment R (version 3.4.2).

A non-probabilistic consecutive sampling will be used in this study. The patients will be selected once they arrive to the cardiologist visit in Hospital Santa Caterina, and the specialist decides that he or she is a good candidate to benefit from this drug. If they have not any contraindication or exclusion criteria, they meet the inclusion criteria and sign the consent, it will proceed to perform the necessary tests to they participate in the study.

We have calculated approximately one year for the recruitment of patients, but if the 154 patients for the sample are recruited before then, the recruitment phase will be closed.

7.4 VARIABLES

7.4.1 Independent variable

-Empagliflozin treatment, is a qualitative dichotomous variable, it will be expressed as before treatment and after treatment.

7.4.2 Dependent variables

- Echocardiographic variables: *will be evaluated from a previous echocardiogram (maximum 3 months before) to the inclusion in the study. If the patient meets the inclusion criteria and wishes to participate in the study, even if he does not have a recent echocardiogram, it will be made prior to taking the drug.*

We will measure the following echocardiographic variables: end-diastolic and end-systolic diameter of Left Ventricle (LV), LV ejection fraction, LV mass, LV mass index, mitral E / A ratio, mitral E-wave deceleration time, LV isovolumic relaxation time, e'septum and lateral, E / e' ratio by tissue Doppler, volume index of the left atrium, maximum velocity of tricuspid regurgitation. These variables are continuous quantitative and normal values can be seen in the ANNEX 1.

- Analytical variable: *it will be obtained from a blood analysis taken at most one month before the patient begins to take de drug. If the patient meets the inclusion criteria and wishes to participate in the study, even if he does not have a recent blood analysis, it will be made prior to the commencement of the study.*

NT- proBNP: is a continue quantitative variable expressed in pg/ml

7.4.3 Covariates

- *Demographic and clinical variables: the information of these variables will be collected at the moment the patient begins to participate in the study (the screening day or de check-in day; ANNEX 3).*

Age: will be expressed in quintiles and it is measured in years; it is a continue quantitative variable.

Gender: will be expressed as categories woman and man; it is a dichotomous qualitative variable.

Race/ ethnicity: as a nominal qualitative variable.

Time of evolution of DM: is a continue quantitative variable; it will be measured in years.

Diagnosis of arterial hypertension: is a dichotomous qualitative variable, expressed as yes or no, based on clinical history.

Diagnosis of dyslipidemia: is a dichotomous qualitative variable expressed by yes or no, based on clinical history.

Tobacco use: will be expressed by smoked, non-smoked or former smoker due to it is a nominative qualitative variable, it will be asked on the spot of the study starts. We will define as former smokers those who have not smoke during a year.

History of cardiovascular events: includes any ASCVD at any time of their life. It is a dichotomous qualitative variable, and it will be expressed by yes or no and then we will specify which type of ASCD is each one (acute coronary syndromes, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin).

Number of admissions for HF in the last year: is a discrete quantitative variable.

Usual treatment: we should specify the patients' treatment; not only anti-diabetic treatment but also treatment for arterial hypertension, secondary prevention of ASCVD…

- *Analytical variables*: *all these variables will be obtained from a blood analysis done at most one month before of introduction of patients in the study (as with NT-proBNP values).*

HbA1c (Hemoglobin A1c): is a continue quantitative variable expressed as a percentage.

LDL (Low Density Protein): is a continue quantitative variable measured in mg/dL.

HDL (High Density Protein): is a continue quantitative variable measured in mg/dL.

Glomerular filtration: is a continue quantitative variable, it will be calculated using the CKD- EPI equation (which consider age, sex, serum creatinine expressed mg/dl and race/ethnicity and it will be expressed in ml/min/1,73m^2.

- *Physical variables*: *These variables will be measured by the doctor or the nurse in Hospital Santa Caterina the day which the patient will be included in the population study. The normal values for analytical and physical variables can be consulted in the ANNEX 2.*

Systolic and diastolic blood pressure: is a continue quantitative variable which will be measured in millimeters of Mercury(mmHg) with a sphygmomanometer and a stethoscope; the patient should be sitting (at least 5 min before the measurement).

Weight: will be expressed in kg and measured with a scale; it is a continue quantitative variable.

Height: is a continue quantitative variable and we are going to measure it in meters.

BMI: is expressed like $kg/m^{2.}$

Abdominal perimeter: will be measured with a metric tape expressed in cm.

These last variables (physical variables) are important because Empagliflozin show a reduction of them.

7.5 STUDY INTERVENTION

In this study we will perform the addiction of Empagliflozin to patients with HF and poor control of type 2 DM with their current treatment. This drug is approved and recommended by the FDA, Canadian Diabetes Association and the European Guidelines for this type of patients, with high cardiovascular risk (and it is subsidized by the Spanish Health System).(2,4,25,30) It will be prescribed in its minimum dose for all the patients, 10mg / day, and will be evaluated in subsequent controls (3 and 6 months later) the need to increase the dose for glycemic control (25mg/ day).

7.6 DATA COLLECTION

7.6.1 Data collection circuit

All information regarding data collection will be collected in the database with the help of the schedule of events (ANNEX 3). Information will be entered directly into the database, either from the echocardiogram, the blood analysis, the clinical history or the physical measurements taken at the time of the clinical consultation. Each patient will be assigned a number in the database to ensure confidentiality.

At Hospital Santa Caterina, patients come from Salt, Girona and other parts of the province of Girona to control their HF in outpatient cardiology. Patients who come there, with a correct diagnosis of this pathology and who suffer from DM2 (diagnosed correctly by the ADA criteria) will be studied by the clinician to see if they meet the criteria to participate in the study. This will be done by evaluating the patients' medical history and previous tests and, if they apparently meet the criteria and they do not have exclusion criteria. In the case the patient agrees to participate in the study, after informed consent is signed, we will proceed to perform the **initial echocardiogram and analysis** before starting Empagliflozin treatment in order to evaluate the baseline heart function, if they

really meet the inclusion criteria and know the general baseline condition of the patient needed to be able to correctly evaluate the variables of our study.

If some non-compatible information is found with the study criteria once these tests are performed, this patient would be excluded from the study and would not proceed with the following steps.

In the case in which the patient has an analytical and echocardiography done recently (period described previously) that includes all the necessary parameters to evaluate, it will not be necessary to carry out this part of the program.

Once this process has been completed and the results of the tests analyzed, patients who can continue in the study will go to the Santa Caterina Hospital in order to have **the physical variables measures and received the prescription of Empagliflozin.** The treatment will be added to their basal medication (hypoglycemic, beta blockers, diuretics...) and at the minimum dose of 10mg.

The patients will have a first control after one month of treatment to assess the tolerance of the drug and the **undesirable effects, and measures of the physical variables** will be taken in this medical appointment.

There will be a second control at 3 months and a third control at 6 months where **a blood analysis** extracted the previous week, will be evaluated to assess glycemic control (with HbAc1, to increase the dose of Empagliflozin treatment at 25mg/day if it is necessary), and the others analytical parameters. The **physical variables** will be collected again. In both consultations patients will be asked again about **undesirable effects.**

The next appointment will be 12 months after treatment, at the end of which **a second echocardiography and a new analysis** will be done to the patients to determine the differences in the proposed objectives (all the previous parameters will be evaluated again to analyze them together and stratify the results).

7.6.2 Echocardiogram and blood analysis

Echocardiogram

The echocardiogram will be performed by a cardiologist specialized in echocardiographic imaging and trained for the study, who will perform all the measurements and as many times as necessary to ensure correct values in each test. It is important that both echocardiograms (before and after Empagliflozin treatment) are done by the same specialist since the inter-professional variability in this type of tests is higher than intra-professional variability.

Blood analysis

The blood analysis will be extracted by collaborating nurses with the study at the Hospital Santa Caterina (in the corresponding special tubes that are necessary to correctly analyze all the parameters) early in the morning, so that all the variables are equally valuable. The blood drawn will be studied by a clinical analyst at the Hospital Santa Caterina.

8. STATISTICAL ANALYSIS

8.1 DESCRIPTIVE ANALYSIS

Dependent variables, echocardiographic variables and NT-proBNP, descriptions using means (standard deviations) and medians (interquartile range), depending on the distribution of their frequencies are symmetric or asymmetric respectively, before and after the intervention.

This descriptive will be stratified by the covariates; I will categorize quantitative covariables (in quintiles).

8.2 BIVARIATE INFERENCE

I will test the differences in means, and in medians before and after the intervention by means of the Student's T and the Mann-Whitney's U, respectively.

I will repeat those contrast stratifying by the covariates. Again, if the variables are quantitative I will categorize them.

8.3 MULTIVARIATE ANALYSIS

As the response variables are continuous, the intervention will be assessed in linear regression models. The dependent variable will be the response variable, the variable of interest will be an indicator of the intervention (0 before, 1 after). In all cases, I will adjust for the covariates, categorized if it was the case.

9. WORK PLAN

9.1 SCHEDULE

Main researches: 1 cardiologist

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

Phase 0: Preparation and coordination phase (4 months)

During this first phase of the project, a detailed protocol will be elaborated with the help of the main investigator and collaborators; the hypothesis, objectives, variables and methods will be discussed.

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

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 and an authorization of the "Generalitat de Catalunya".

First phase: Study conduct (24 months)

Patients' recruitment:

Patients diagnosed with heart failure and type 2 Diabetes Mellitus, who meet the inclusion criteria for the study and who are in flow-up at Hospital Santa Caterina will be recruited if they want it, after signing the informed consent form.

Echocardiogram and blood analysis:

Blood analysis: this assignment will consist in the collection of blood samples for further analysis. The first sample will be collected at the time when it is thought that the patient can participate in the study (This part is dispensable if the patient has a blood test done in the last month in which all the parameters that we evaluate in our study have been analyzed). In this sample all analytical variables will be evaluated, including NT-proBNP for later comparison with the value of this after treatment with Empagliflozin.

A second blood test will be performed 3 months after starting treatment with our hypoglycemic agent to evaluate the glycemic control and the rest of the analytical variables (if necessary, the dose of Empagliflozin will be increased).

The next sample will be extracted after 6 months of treatment with the same function as the previous analytic.

The last blood test will be performed after one year been treated with Empagliflozin, including the analysis of NT-proBNP value (as explained in the data collection chapter).

Echocardiogram: the measurement of the echocardiographic variables will be done twice as well. The first time will be when the specialist considers that the patient could enter our study (being able to avoid this test, if the patient has an echocardiogram performed in the last 3 months with the variables that we are going to analyze). And the second time will be after one year of treatment with Empagliflozin.

While the study takes place, the data collected from each patient will be register in our database, with the help of our schedule of events with the intention of being as meticulous as possible (so as not to forget any step) (ANNEX 3).

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

During this period, a pilot test will be conducted in order to depurate data procedures and detect possible errors.

Second phase: Data analysis (3 months)

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

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, publication and dissemination of the results (9 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, the European Congress of Cardiology and the Europrevent.

9.2 CHRONOGRAM

	ASSIGNMENT	STAFF	CALENDAR												
				Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
PHASE 0	◆Study protocol development ◆Presentation to the CEIC ◆Coordination meetings	All research team	2017												
			2018												
			2019												
			2020												
			2021												
PHASE 1	◆Patients recruitment ◆Performance of echocardiogram and blood analysis ◆Register in database	Cardiologist Clinical analyst Nurse Staff	2017												
			2018												
			2019												
			2020												
			2021												
PHASE 2	◆Data analysis	Statistician	2017												
			2018												
			2019												
			2020												
			2021												
PHASE 3	◆Interpretation and study writing ◆Publication and dissemination	Cardiologist	2017												
			2018												
			2019												
			2020												
			2021												

10. LEGAL AND ETHICAL ASPECTS

This research protocol will be presented to the Clinical Research Ethical Committee (**CEIC**) of Hospital Santa Caterina in Girona for its assessment and approval. Moreover, the recommendations given by the committee will be considered to carry out the study.

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

The **confidentiality** of personal and clinical information of all participants involved in the study will be guaranteed, according to the "Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal". All the information will be only used for the research and it will be treated in an homogeneous and **no-discriminative** way, preserving the ethical principle of justice. Patients will always be allowed to modify or destruct any of their collected data study.

According to the "Ley 41/2002 Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica" and the Helsinki Declaration, all participants interested on being part of the study, will be asked to sign voluntarily the **informed consent**. Before being included in it, they will receive all the appropriate information about the study (the trial's objectives, the tests, interventions and implications, risks, contact number to answer questions…), through a personal conversation with the researchers and using the information sheet. (ANNEX 4 AND ANNEX 5)

This study will respect biomedical regulation according to "Real Decreto Legislativo 1/2015 de 24 de julio, Artículo 2" for drugs.

It is considered, despite being a quasi-experimental study, a clinical trial of low level of intervention (since to a diabetic patient, a new antidiabetic drug is added with the participation of the specialist in the decision). Therefore, it will respect the "Real Decreto 1090/2015", this implies that we will need an authorization from the center's management, an authorization of the "Generalitat de Catalunya" and a civil responsibility policy (which already has the health center).

The study will be clasificated by the "Asociación Española de Medicamentos y Productos Sanitarios".

This quasi-experimental study will also preserve the principles of **non-maleficence** and **beneficence.** There is not much data available about the results that we will obtain with the treatment under study, and our hypothesis is not yet proven, but our thinking, regarding all the previous studies, is that we would reduce more efficiently the rate of hospitalization of heart failure. Previous studies confirmed, also, the absence of increased cardiovascular risk of Empagliflozin, so we assume that it is a **safe and beneficial** treatment for our patients. Nevertheless, **we will be in alert for any adverse effect** that may appear.

We declare no conflict of interest of any kind.

11. LIMITATIONS

Due to our study design and the study target population, there are a few undeniable and identifiable limitations such as:

- The sample size of this study could be considered small, but it is reasonable for our hospital patients' income. If a larger sample was needed, we could consider engaging other hospitals into the study and designing a multicenter study.
- The study design does not include a control group without treatment, but the patient is evaluated before and after treatment, so the patient is used as a control. It is done in this way because it would not be ethical to leave a group of patients with diabetes and heart failure and who had no contraindication to take Empagliflozin without a treatment that has been shown to be beneficial to them.
- Our results cannot be extrapolated to patients with other cardiac pathologies and type 2 diabetes mellitus as severe valvopathies or diastolic HF and atrial fibrillation.
- Another possible limitation is the fact that the risk factors that usually accompany type 2 diabetes such as hypertension, nephropathy, hypercholesterolemia, obesity... can progress over time and can deteriorate cardiac function and act as confounding factors. To avoid it, all patients will follow their prescribed treatment for these pathologies, so they should be controlled. Part of our objective by collecting all these is to try these factors to influence as little as possible our study.

- It is important to assume that our study might have a measurement bias, this bias is related to the observer bias. This occurs when the researcher makes more detailed measurements of the group variables due to the fact that he knows these patients are under treatment. This can happen when the echocardiographic variables are collected, as they will be measured by the same specialist who carries out the clinical control of the patient, who will follow up on his pathology and prescribe the treatment.

12. FEASIBILITY

Our research will take place between November 2017 and February 2021 in the Hospital Santa Caterina in Girona.

Study staff

In this quasi-experimental study, we are going to work with a diverse group of professionals. Before the start of the study, two informative meetings with all the components involved will be organized. In these two appointments, the main researcher will explain the objectives of the study, data that will be collected and how to do it, remarking the importance of gathering these data into a uniform database.

We consider that with two meetings it will be sufficient, since the research group is not very large and the tests necessary for the study are usually done in clinical practice, and the professionals are already accustomed to their management.

The personnel whom are going to be part of this study are well trained and has experience on this field.

Available resources

We assume that, as the tests we are going to carry out (echocardiogram and blood analysis) are the same as we will do to patients affected with HF for their usual review, regardless of their participation in the trial, materials, staff and rooms will be ready and available to receive and treat our patients.

The only difference will be the addition of Empagliflozin treatment. It is true that several controls are performed (one month after treatment, another after 3 months of treatment and another after 6 months of treatment), but this number of controls is usual when a drug is added to control its efficacy and undesirable effects.

Take into account that these people are patients with poor diabetic control with their current treatment, thus either this treatment or another, we would have to add an antidiabetic and perform this initial control anyway.

Patients

Regarding the recruitment of the patients, we have estimated that we will collect data over the course of one year to reach the desired sample size of the research. The recruitment of patients will stop when the sample size is reached, and the follow -up when the last recruited makes a year since the starting of the treatment. In that sense, we expect to carry out a clinical trial feasible regarding the time, personnel and material resources.

13. IMPACT ON THE NATIONAL HEALTH SYSTEM

As previously it has been discussed, cardiovascular pathology is considered one of the main causes of death in our country in addition to producing a large decline in the quality of life. Diabetes participates as a risk factor and aggravating of these diseases in turn.

The cardiovascular pathology in diabetic patients produces a great economic cost to the health system both in the pharmacological cost and interventionism, as well as in hospitalization (most of the cost).

The fact that this drug has been shown to reduce cardiovascular death and especially hospitalization for HF is a great step forward in reducing all this cost and DALYs.

If the results obtained in this study are relevant and our hypothesis is validated, showing changes in cardiac function after treatment with Empagliflozin, we will have made an important step towards the optimization of this treatment, since stratifying all the data we could see what type of patient responds to this drug (or which one responds better). Especially around the echocardiographic parameters since we believe that we can clarify if this sodium glucose cotransporter-2 inhibitor is beneficial for both types of heart failure or only for one, or if it only changes certain variables. Also observing which variables improve, we can prescribe this drug with better evidence according to the morphological alterations that the patient has in their hearts.

This new information can be used for the development of new drugs for this type of patients, improving their life expectancy and their quality of life and reducing the costs that these diseases imply to the health system.

14. BUDGET

All staff members that will visit and attend participants during the study, the follow-up appointments, blood analysis and material for these, and echocardiogram annual, 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 nursing staff, clinical analyst and the cardiologist need for the use of the database will be considered in the budget.

EXPENSES	***COSTS (€)***
SERVICIES AND MATERIAL	
Statistician 35€/h x 100h	*3.500€*
Nurse, clinical analyst or doctor 35€/h x 80h	*2.800€*
Creation of database	*3.000€*
Information sheet and informed consent printing (0,30€/unit x 4units x 154patients)	*184,8€*
Treatment (55,45€/unit x 13units x 154 patients)	*111.010,9€ → 0€*
PUBLICATION AND DISEMINATION EXPENSES	
Journal Publication	*2000€*
National Congress of Cardiology costs (registration, travelling, accommodation, diets…)	*1000€*
TOTAL	**123.495,7€ →12.484,8€**

The cost in the treatment would amount to 110,010.9€. Given the benefit that this study will represent for the pharmaceutical company if our hypothesis is confirmed, we will ask the laboratory that markets Empagliflozin in Spain, the necessary amount of this drug to perform the study. Thus, this part of the budget would be reduced to 0€. This will be accepted as long as it does not involve changing any part of the study, any change in the publication or any extra requirements.

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16. ANNEXES

ANNEX 1. NORMAL VALUES OF ECHOCARDIOGRAPHIC VARIABLES (34)

TWO-DIMENSIONAL ECHOCARDIGRAM:

1. *End-diastolic diameter of LV:*

   Longitudinal parasternal axis: 48 (36-54mm)

   Apical plane of 4 cameras: 47 mm (38-62mm)

2. *End-systolic diameter of LV:*

   Longitudinal parasternal axis: 31 (23-39mm)

   Apical plane of 4 cameras: 28 mm (21- 39 mm)

3. *Ejection fraction of LV:* 50-70%

DOPPLER ECHOCARDIOGRAM:

4. *Mitral E-wave deceleration time: 179 (150-240mseg)*
5. *Mitral E/A ratio:* 1.62 (1.31-1.93)
6. *LV isovolumic relaxation time*: 76 (60-110mseg)

M MODE:

7. *LV mass:*

   Calculated with Mode M:
   134g / m2 in men (143g / m)
   110g / m2 in women (120g / m)
   Calculated with Simpson:
   148 ± 26 g in men (76 ± 13 g / m2)
   108 ± 21 g in women (66 ± 11 g / m2)

8. *LV mass index:* 125g/m2 in men
   110g/m2 in women

9. *Volume index of the left atrium:* 16-34 ml/m^2

TISSUE DOPPLER:

10. *E / e' ratio by tissue Doppler:* 7,7 ± 3
11. *e'septum:*11.6 ± 2.03
12. *e'lateral:*15.1 ± 3.2
13. *Maximum velocity of tricuspid regurgitation:*

ANNEX 2. VALUES OF ANALYTICAL VARIABLES AND PHYSICAL VARIABLES

A. ANALYTICAL VARIABLES

HbA1c:

Table 2: Values of HbA1c (35)

Classification	***Percentage of saturation***
Normal value	<5.7%
Prediabetes	5.7-6.4%
Diabetes	≥6.5%

LDL:

Table 3: Levels of LDL (36)

Level	***Value***
Optimal level	<100mg/dL
Close to the optimal level	100-129mdg/dL
High limit of normality	130-159mg/dL
High level	160-189mg/dL
Very high level	≥190mg/dL

→ *In patients with a very high cardiovascular risk, the optimal option is less than 70mg/dL.*
Patients with diabetes and a high risk of heart disease
People with a medium or high risk of heart disease
Diabetic patients and aged between 45 and 70 years old

HDL:

Table 4: Levels of HDL (36)

Level	***Value***
Low level	<40mg/dL
Normal level	40-60mg/dl
High level	≥60mg/dL

Glomerular filtration:

Table 5 Stage of Glomerular filtration (37)

Stage	***Description***	***GF (ml/min/1,73m$^{2)}$***
1	Normal GF	≥ 90
2	slight decrease of GF	60-89
3	moderate decrease of GF	30-59
4	serious decrease of the GF	15-29
5	Kidney Failure	<15

B. PHYSICAL VARIABLES

Systolic and diastolic blood pressure:

Table 6: Classification of blood pressure (38)

Classification	*Systolic blood pressure (mmHg)*	*Diastolic blood pressure (mmHg)*
Optimum blood pressure	90-120	60-80
Normal blood pressure	<130	<85
High normal blood pressure	130-139	85-89
Stage 1 of hypertension	140-159	90-99
Stage 2 of hypertension	160-179	100-109
Stage 3 of hypertension	179	>109

BMI:

Table 7: classification of weight according to BMI (39)

Classification	*BMI (kg/m$^{2)}$*
Insufficient weight	<18,5
Normal weight	18,5-24,9
Overweight	25-29,9
Obesity type 1	30.0-34,9
Obesity type 2	35-39,9
Obesity type 3	≥40

Abdominal perimeter:

In women, the abdominal perimeter should be less than 88 cm (in case there is no pregnancy). If a woman has an abdominal perimeter greater than 88 cm, she has abdominal obesity.

In men, the abdominal perimeter should not exceed 102 cm. If a man has an abdominal perimeter greater than 102cm, he has abdominal obesity. (40)

ANNEX 3. SCHEDULE OF EVENTS

Procedures	**Screening**	**Check-in**	**On-Treatment Visits**					
			Days					**Final visit**
Study Day	Day <-30/-90	Day 0	Day 30	Day 83	Day 90	Day 173	Day 180	Day 365
Study Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographic information	X	X						
Medical History	X	X						
Physical Examination		X	X		X		X	
Blood analysis	**X**			**X**		**X**		**X**
Echocardiogram	**X**							**X**
Adverses Effects Reporting			XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX					
Endpoints Reporting			XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX					
Glycemic control evaluation	X				X		X	
Prior and Concomitant Medication	X	X	X		X		X	X
Study drug initial prescription		X						
Drug dispensing control			X		X		X	X

ANNEX 4. HOJA DE INFORMACIÓN AL PACIENTE.

Estudio: "Effects of Empagliflozin on cardiac function"

Promotor: Dr. Marco Paz Bermejo

Investigador del estudio: Sandra Pérez Motos

INTRODUCCIÓN:

Nos dirigimos a ustedes para informarles sobre un estudio que va a realizarse acerca de un nuevo fármaco antidiabético en personas con Diabetes Mellitus tipo 2 e insuficiencia cardíaca, 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 un mal control con su tratamiento antidiabético actual e insuficiencia cardiaca, como es su caso, si la adicción del tratamiento con Empagliflozina produce cambios en la función cardíaca.

DESCRIPCIÓN DEL ESTUDIO:

En este estudio participarán más de 150 pacientes y se realizará exclusivamente en el Hospital Santa Caterina. Una vez otorguen el consentimiento para participar, se les realizará un ecocardiograma y una analítica sanguínea 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 si ha sido realizada 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 medirá la tensión arterial, el peso, la altura y el perímetro abdominal, y se les prescribirá el fármaco y se les dará las indicaciones de como tomarlo.

Todos los pacientes recibirán el tratamiento con Empagliflozina.

Tendrán un control médico al mes de tratamiento, para evaluar si ha podido aparecer algún efecto indeseado, y un control a los 3 meses y a 6 meses médico y analítico para evaluar el control de la glucemia (para modificar la dosis de Empagliflozina a una mayor si fuese necesario) y nuevamente se medirán la tensión arterial, el peso y el perímetro abdominal.

A los 12 meses de tratamiento se les realizará nuevamente un ecocardiograma y una analítica sanguínea y se tomarán las medidas físicas de nuevo (peso, perímetro abdominal y tensión arterial).

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 1 año, con las visitas médicas al mes, a los tres meses, a los seis meses y al año 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 15/99 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 esta disminución es a causa de un cambio en la función cardiaca, 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 periodo 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.

FULL D'INFORMACIÓ AL PACIENT

Estudi: "Effects of Empagliflozin on cardiac function"

Promotor: Dr. Marc Paz Bermejo

Investigador de l'estudi: Sandra Pérez Motos

INTRODUCCIÓ:

Ens dirigim a vostès per informar-los sobre un estudi que se realitzarà sobre un nou fàrmac antidiabètic en persones amb Diabetis Mellitus tipus 2 i insuficiència cardíaca, en què se'ls convida a participar-hi. L'estudi ha estat aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Santa Caterina.

La nostra intenció és que vostès rebin la informació correcta i suficient perquè puguin avaluar si volen participar en l'estudi. Per això, llegeixin aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que en puguin sorgir. A més, poden consultar amb les persones que considerin oportunes.

OBJECTIU:

El principal objectiu d'aquest estudi és avaluar, en persones amb un mal control amb el seu tractament antidiabètic actual i insuficiència cardíaca, com és el cas, si l'addicció del tractament amb Empagliflozina produeix canvis en la funció cardíaca.

DESCRIPCIÓ DE L'ESTUDI:

En aquest estudi hi participaran més de 150 pacients i es realitzarà exclusivament a l'Hospital Santa Caterina. Un cop atorguin el consentiment per a participar, se'ls farà un ecocardiograma i una analítica sanguínia abans de començar amb el tractament (si vostès tenen un ecocardiograma realitzat en els últims 3 mesos amb les variables que s'avaluaran en l'estudi no serà necessari repetir-o. Passarà el mateix amb l'analítica si ha estat realitzada en l'últim mes i posseeix tots els paràmetres que estudiarem).

Si vostès segueixen complint els criteris per participar a l'estudi, tindran una altre visita mèdica on se'ls mesurarà la tensió arterial, el pes, l'alçada i el perímetre abdominal, i se'ls prescriurà el fàrmac i se'ls donaran les indicacions de com prendre'l.

Tots els pacients rebran el tractament amb Empagliflozina.

Tindran un control mèdic al mes de tractament, per avaluar si ha pogut aparèixer algun efecte indesitjat, i un control als 3 mesos als 6 mesos mèdic i analític per avaluar el control de la glucèmia (per modificar la dosi de Empagliflozina a una major si fos necessari) i novament es mesuraran la tensió arterial, el pes i el perímetre abdominal.

Als 12 mesos de tractament se'ls realitzarà novament un ecocardiograma i una analítica sanguínia i es prendran les mesures físiques de nou (pes, perímetre abdominal i tensió arterial).

PARTICIPACIÓ VOLUNTÀRIA:

La seva participació en aquest estudi és totalment voluntària i en cas que decideixin no fer-ho, no ha de donar explicacions i la seva decisió no implicarà cap diferència pel que fa a la qualitat assistencial que han de rebre.

DURADA DE LA PARTICIPACIÓ:

L'estudi durarà 1 any, amb les visites mèdiques al mes, als tres mesos, als sis mesos ia l'any de tractament. Finalitzat aquest temps, seguiran els seus controls mèdics habituals.

CONFIDENCIALITAT:

Tota la informació que es reculli i que es guardi (mitjançant un sistema informàtic) i l'anàlisi de fer un estadístic (amb un sistema informàtic també) serà estrictament confidencial i seguirà la normativa vigent a Espanya (Llei 15/99 de Protecció de dades de caràcter personal).

Els seus documents mèdics podrien ser revisats només per persones dependents de les autoritats sanitàries, membres de comitès ètics independents i altres persones designades per llei per comprovar que l'estudi s'està duent a terme correctament.

BENEFICIS I RISCOS ESPERATS:

S'espera una disminució d'hospitalitzacions per insuficiència cardíaca i de la mort per causa cardiovascular, benefici ja demostrat prèviament. De l'estudi es podrà concloure si aquesta disminució és a causa d'un canvi en la funció cardíaca, quins canvis produeix i en quin tipus de

pacients. A través dels resultats si, com s'espera, són satisfactoris, podrem aconsellar a les autoritats sanitàries sobre com implementar l'eficàcia d'aquest tractament.

Entre els riscos més freqüents que apareixen amb aquest fàrmac es troben la hipoglucèmia (sobretot quan s'usa amb una sulfonilurea o insulina), pruïja generalitzat i exantema, i infeccions genitals a dones. Altres riscos molt menys freqüents són angioedema, cetoacidosi diabètica, trastorns renals i elevació de l'hematòcrit.

TRACTAMENTS ALTERNATIUS:

Hi ha altres tractaments alternatius, que podran consultar-li a l'especialista.

PUBLICACIÓ:

En cas de publicació dels resultats de l'estudi a través de publicacions i / o congressos, ja sigui a les autoritats sanitàries o a la comunitat científica, sempre es farà de forma global i mai de forma individualitzada, de manera que no serà possible la identificació dels participants.

CONTACTE:

Si vostès tenen qualsevol dubte durant el període de l'estudi poden contactar amb l'investigador principal.

Telèfon: 972412200

Hospital Santa Caterina. Servei de Cardiologia.

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

Gràcies per llegir aquest full. Si tenen algun dubte o pregunta sobre l'estudi, si us plau feu-lo saber.

No dubteu a preguntar a l'investigador o col·laboradors. En cas que decideixin participar en l'estudi intentin mantenir aquesta informació per als seus registres fins al final del procés. Si estan disposats a participar, poden seguir llegint i signar el consentiment informat.

ANNEX 5. CONSENTIMIENTO IMFORMADO DEL PACIENTE

Estudio "Effects of Empagliflozin on cardiac function"

Promotor: Dr. Marco Paz Bermejo

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 SANDRA PÉREZ MOTOS

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 …../……../……	Fecha …../……/……
Nombre:	Nombre:
Firma del paciente	Firma del médico

CONSENTIMENT IMFORMAT DEL PACIENT

Estudi "Effects of Empagliflozin on cardiac function"

Promotor: Dr. Marc Pau Bermejo

Jo, ... (Nom i cognoms del pacient)

- He llegit el full d'informació que se m'ha lliurat.
- He rebut suficient informació sobre l'estudi.
- He pogut fer preguntes sobre l'estudi
- He parlat amb SANDRA PÉREZ MOTOS

Comprenc que puc retirar-me de l'estudi:

1) Quan vulgui

2) Sense haver de donar explicacions

3) Sense que això repercuteixi en les meves cures mèdiques

Presto lliurement la meva conformitat a l'estudi i dono el meu consentiment per a l'accés i utilització de les meves dades en les condicions detallades en el full d'informació.

Aquest consentiment, d'acord amb la llei 15/1999 i RD 1720/2007 és revocable, pel que puc exercir el dret d'accés, rectificació i cancel·lació dirigint-me a l'investigador.

Data ... ../ ... . /	Data ... ../ ..... / .....
Nom:	Nom:
Signatura del pacient	Signatura del metge