Diploma Thesis

OUTCOMES OF HEART FAILURE THERAPY IN PATIENTS WITHOUT DIABETES TREATED WITH SGLT2-INHIBITORS

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Graz, 09.06.2022.

Statutory Declaration

I hereby declare that I have written this diploma thesis on my own, and without help of any third party. Moreover I have fully acknowledged by name all of the individuals and source materials that have contributed to this thesis, cited or by content from the sources.

Graz, 09.06.2022. Farah Džanković eh.

Acknowledgement

I would like to express my graditude for the guidance throughout the writing process during very challenging times of global pandemic that I received from my supervisor Univ.-Prof. Priv.-Doz. Dr.med.univ. Harald Sourij. The idea for this work came from two years experience of working in the diabetes outpatient clinics in Graz which I consider an incredibly enriching experience in my life. The people I met there, the patients and colleagues, will always have a special place in my heart.Another thank you is dedicated to my family and friends for their perpetual support and encouragement that they have been giving me since the first day of my studies. I am happy to have you.

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ABBREVATIONS AND ACRONYMS

HFrEFI.....Heart failure with reduced ejection fraction

HFpEFI.....Heart failure with perserved ejection fraction

CHFI.....Chronic heart failure

CHF.....Congestive heart failure

NT-proBNP.....N-terminal proBrain Natriuremic Peptide

AF.....Atrial fibrilation

ECG.....Electrocardiogram

BMI.....Body Mass Index

HbA1c.....Glycated Haemoglobin

LDL.....Low-density lipoprotein

HDL.....High-density lipoprotein

AKI.....Acute kidney injury

NYHA.....The New York Heart Association

FDA .....The Food and Drug Administration

MACE.....Major adverse cardiovascular events

ARNI.....Angiontensin Receptor Neprilysin Inhibitor

GFR.....Glomerular filtration rate

ARR.....Absolute risk reduction

HHF.....Hospitalisation for heart failure

NNT.....Number needed to treat; yrs, years

AF.....Atrial fibrillation

HF.....Heart failure

LVEF.....Left ventricular ejection fraction

IRR.....Incidence rate ratio

CO.....Cardiac output

COPD.....Chronic obstructive pulmonary disease

MI.....Acute myocardial infarction

CAD.....Coronary artery disease

EF.....Ejection fraction

ESC.....European Society of Cardiologists

CT.....Computerized Tomography

SPECT.....Single-photon emission computerized tomography

PET .....Positron emission tomography scan

eGFR.....Estimated glomerular filtration rate

KCCQ .....Kansas City Cardiomyopathy Questionnaire

CSS.....Clinical Summary Score

NDMVD.....Non-degenerative mitral valve disease

MRA.....Mineralocorticoid Receptor Antagonists

MRI.....Magnetic resonance imaging

DPP 4.....Dipeptidyl peptidase-4 inhibitor

CVD.....Cardiovascular disease

CMR.....Cardiac magnetic resonance

CREDENCE.....Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

UTI.....Urinary tract infection

HF.....Heart failure

RAAS.....The Renin-Angiotensin-Aldosterone-System

SGLT2i.....Sodium-glucose cotransporter 2 inhibitors

ACE.....Angiotensin-converting enzyme

ECMO .....Extracorporeal membrane oxygenation

TAH .....Total artificial heart

VADs .....Ventricular assist devices

CI..... Confidence interval

HR..... Hazard ratio

eGFR.....Glomerular filtration rate

DAPA-HF.....Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure

EMPEROR.....Reduced Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction

EMPEROR-Preserved.....Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction

CANVAS .....Canagliflozin Cardiovascular Assessment Study

CKD KIDNEY.....Chronic kidney disease

T2D.....Type two diabetes

IHD.....Ischaemic heart disease

ONOO.....Oxygen-Nitrogen-Oxygen-Oxygen; Peroxynitrite ion

NO.....Nitrite oxide

VCAM.....Vascular cell adhesion molecule

sGC.....Soluble guanylate cyclase

cGMP.....Cyclic guanosine monophosphate

PKG.....Protein kinase G

IL-6.....Interleukin 6

TNF.....Tumor Necrosis Factor

sST2.....Serum Soluble Suppression of Tumorigenicity 2

CRT.....cardiac resynchronization therapy

ICD.....Implantable cardioverter-defibrillators

CABG.....Coronary artery bypass grafting

PCI.....Percutaneous coronary intervention

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Zusammenfassung

Einführung: Die chronische Herzinsuffizienz ist eine globale Erkrankung mit Prävalenz von ca. 2% der gesamten Bevölkerung. Sie ist sowohl mit einer hohen Mortalität, als auch hohen finanziellen Ausgaben verbunden. Die medikamentöse Therapie der Herzinsuffizienz ist primär auf eine Verbesserung der Auswurfleistung und Senkung der Herzfrequenz gerichtet.

Methoden: Die vorliegende Diplomarbeit ist Ergebnis einer Literaturrecherche. Literatur vorhanden in Lehrbüchern, Studien und Reviews wurde in Anspruch genommen. Die Studienergebnisse wurden über die Forschungsplattform PubMed® aufgerufen.

Ergebnisse: Die recherchierten Studien haben gezeigt, dass SGLT2-Hemmer erhebliche kardiale und metabolische Vorteile bei Patient*innen mit Herzinsuffizienz haben. Darüber hinaus waren die Vorteile bezüglich Gewicht, Blutdruck, Hämatokrit, eGFR und NT-proBNP unabhängig vom Diabetesstatus der Patient*innen. Aus diesem Grund sind diese Medikamente in den Leitlinien zur Behandlung von Herzinsuffizienz aufgeführt. Die Häufigkeit unerwünschter Ereignisse unterschied sich zwischen Patient*innen mit und ohne Diabetes nicht signifikant. Es ist wichtig zu betonen, dass zum Studienbeginn bei keiner Person ohne Diabetes eine signifikante Hypoglykämie oder diabetische Ketoazidose auftrat. Das ist ein starker Beweis dafür, dass SGLT2-Hemmer eher in der kardioprotektiven als blutzuckersenkenden Therapie eingesetzt werden sollten.

Schlussfolgerung: Kürzlich wurden SGLT2-Inhibitoren als vielversprechende Therapie für Patient*innen mit Herzinsuffizienz mit sowohl reduzierter als auch erhaltener Ejektionsfraktion vorgestellt. Überzeugende Daten aus klinischen Studien bei Menschen mit Herzinsuffizienz, mit oder ohne Diabetes, gaben dieser Medikamentenklasse einen herausragenden Platz in der Therapie der Herzinsuffizienz. Die Studien, die ihre Auswirkungen auf die Nieren untersuchen, sind noch im Gange.

Abstract

Introduction: Chronic heart failure poses a global disease with a prevalence of up to 2% in the general population. It comes with a high mortality rate, and is bound to a great financial burden, including extensive treatment costs.The pharmacological treatment of heart failure aims to improve the ejection fraction and lower the heart rate.

Methods: This Diploma Thesis constitutes the result of Literature Research, using literature contained in Textbooks, different clinical studies and their reviews. Furthermore, the trial outcomes were accessed from research platform PubMed®.

Results: The studies have shown that SGLT2-inhibitors have significant cardiac and metabolic benefits on patients with heart failure. Moreover, the benefits concerning weight, blood pressure, haematocrit, eGFR, and NT-proBNP were independent of diabetes status of patients. As a result of that, they are listed under guidelines for treatment of heart failure. The rate of adverse events did not differ significantly in those with and without diabetes. It is important to emphasize that significant hypoglycaemia or diabetic ketoacidosis did not present in any patient without diabetes at baseline. This is strong evidence that SGLT2-Inhibitors instead as glucose-lowering drugs, should rather be used in cardioprotective therapy.

Conclusion: Recently, SGLT2 inhibitors presented as promising therapy for patients with heart failure, with both reduced and perserved ejection fraction. Compelling data from clinical trials in people with heart failure, with or without diabetes, gave this class of drugs a prominent place in heart failure therapy.The studies exploring their renal impact are still ongoing.

1. INTRODUCTION

1.1 Heart failure

Heart failure is a progressive, multifactorial, and chronicle clinical condition that arises from cardiac overload due to structural or functional heart disorder. (1) It represents a significant risk for mortality among the general population. (1) The mean problem of this condition is that the heart cannot meet its systemic needs because of impaired filling of ventricles and decreased ejection fraction.(1) The most frequent causes include vascular or metabolic disorders pathological changes in the three layers of the heart wall and heart valves. *(2)*

With an estimated 64.3 million people living with heart failure worldwide, it is considered an epidemic disease in the modern world. (3)

Furthermore, in developed countries, the prevalence of known heart failure is generally estimated at 1% to 2% of the general adult population (4), with standing variances in diagnostic criteria. (4) It is estimated that over 50% of patients with HF have a preserved LVEF and that this proportion shows an increasing trend. (5,6)

1.2 Epidemiology of heart failure

Heart failure was seen as a condition predominantly affecting older people. It has been shown in recent studies that **heart failure among young people might be increasing**. (7) One study performed in Denmark compared the incidence of hospitalization due to heart failure from 1995 and 2012(7), where a significant decline in hospitalization rate was shown. At the same time, the primary age of onset of heart failure declined by double. (7)

Another study done in Sweden linked hospital discharges and several deaths between 1987 and 2006 among people between 18 and 34, and 35 and 44 years.(8) It turned out that the heart failure incidence increased by 50% and 43% during these five years. (8) One possible explanation could be the ever-increasing obesity trend, and thus obesity-correlated diseases such as diabetes type 2, hypertension, and atrial fibrillation, (7) and an increase of patients with less common causes of heart failure such as Chagas disease, amyloidosis, or rheumatic disease.(7) That being said, it is expected in the future, that heart failure will become an even more significant burden for the public hearth if this trend continues. (9)

In general, women are less prevalent in the population with heart failure; however, more than half of the patients with HFpEF are women, in contract with HFrEF, where about 29% of patients are women. (10) That would suggest that women are more predisposed for HFpEF than HFrEF. (11,12) The factor that should also be considered is age distribution as women tend to live longer. (13,14) Framingham Study gave us another useful insight, that female gender was not directly linked to a higher incidence rate of HFpEF (15), but rather lower risk than HFrEF.(15) In pooled data from the Multi-Ethnic Atherosclerosis Study and Cardiovascular Health Study, the long-term risk for HFrEF was higher in the male than female population (respectively 10.7% versus 5.9%).(16) In contrast, the risk for HFpEF did not differ much in the female and male population. (16)

There is a possible correlation between obesity and the incidence of HFpEF, because women tend to be more obese than men. (17,18). Based on the collected data of the Framingham Heart Study, the male patients with diabetes, aged between 45 and 74 years, had twice as much chance of developing heart failure, in contrast with the female population with the same comorbidity, where that risk was five times higher. (19) Meta analysis of 47 cohort studies, which included 12 million participants, showed that the relative risik was 0.95 (95% CI 1.70–2.22) in women and 1.74 (95% CI 1.55–1.95) in men, with a pooled men-to-women ratio of the relative risks of 1.09 (95% CI 1.05–1.13), indicating a significant difference. (20) Female patients with T2D experienced more pronounced left ventricular remodeling, in the direction of concentric hypertrophy.(21) They reported lower life quality and worse outcomes than males with type 2 diabetes, even when BMI and glucose were in the normal range. (21,22)

Around 40% of HFrEF and 45% of the HFpEF patients have T2D. (23). Moreover, diabetes and obesity influence left ventricular function, even when coronary artery disease and hypertension are absent. (24,25) There is a positive correlation between diabetes and heart failure, which goes in both directions. (26) Lifestyle of patients with diabetes often leaves heart failure unrecognized in the early stages due to lack of physical activity and exercise. (27)

1.3 THE PATHOPHYSIOLOGY

There are numerous neurohormonal systems linked to HF, the main ones being the sympathetic nervous system and renin-angiotensin-aldosterone system, and endogenous natriuretic mechanisms. (28)

Angiotensin- II, and aldosterone are activated and produced over the RAAS system when the body recognizes the lack of water in the cells. (29) They promote the retention of water and sodium ions. (29) This physiological mechanism can turn pathological in case of decompensated heart failure with edema, causing hypertrophy and fibrosis of heart tissue. . (29,30,31) The natriuretic peptide system counteracts this system by detecting the enlargement of heart chambers. It then promotes natriuresis and lowers blood pressure. (29,30,31)

When the heart muscle is injured due to hypertension, atherosclerosis, or ischemic heart disease, these compensatory pathways are initially trying to maintain regular blood pressure and preserve the kidneys' normal function.(32) However, over time, chronic activation increases LV afterload and promotes remodeling of the heart and vessels and thus the further progression of the disease. (32)

Another neurohormonal mechanism with probable relevance to heart failure might include endothelin-1, the major endothelin isoform in the cardiovascular system.(33,34,35) It works in synergy with RAAS and SNS, promoting vasoconstriction, myocardial remodeling, and renal dysfunction. (33,34,35) Endothelin-1 levels in plasma correlate strongly with mortality and morbidity in patients with HF. (36)

Other potent mechanisms might include neurotensin-II, adrenomedullin, bradykinin, and serotonin.(37-40) Even though their role in pathophysiology remains incompletely understood, according to some sources, they might act as neprilysin inhibitors since their metabolites have a chemically similar structure to that of neprilysin. (41,42,43)

The interaction between sympathetic nerve fibers and the cardiovascular system is of interest when further exploring the pathophysiology of HF. (44-47) As sympaticus is activated and catecholamines are released, the number of beta-adrenergic receptors declines and loses its function over time, thus deteriorating the condition of patients with HF. (44-47) Although initially unlisted from therapy guidelines, beta-adrenergic receptor antagonists (beta-blockers) represent an important building block of the current medical treatment of HF based on results from clinical trials. (48,49,50)

As the failing heart tries to maintain and re-establish normal function, another compensatory mechanism is important to mention.(51) It is namely the Frank-Starling mechanism, which acts on remodeling ventricles by increasing their volume and wall thickness in order to maintain tissue perfusion.(51) Although beneficial in the early stage, these compensatory systems eventually lead to a vicious cycle of the worsening condition of heart failure. (51)

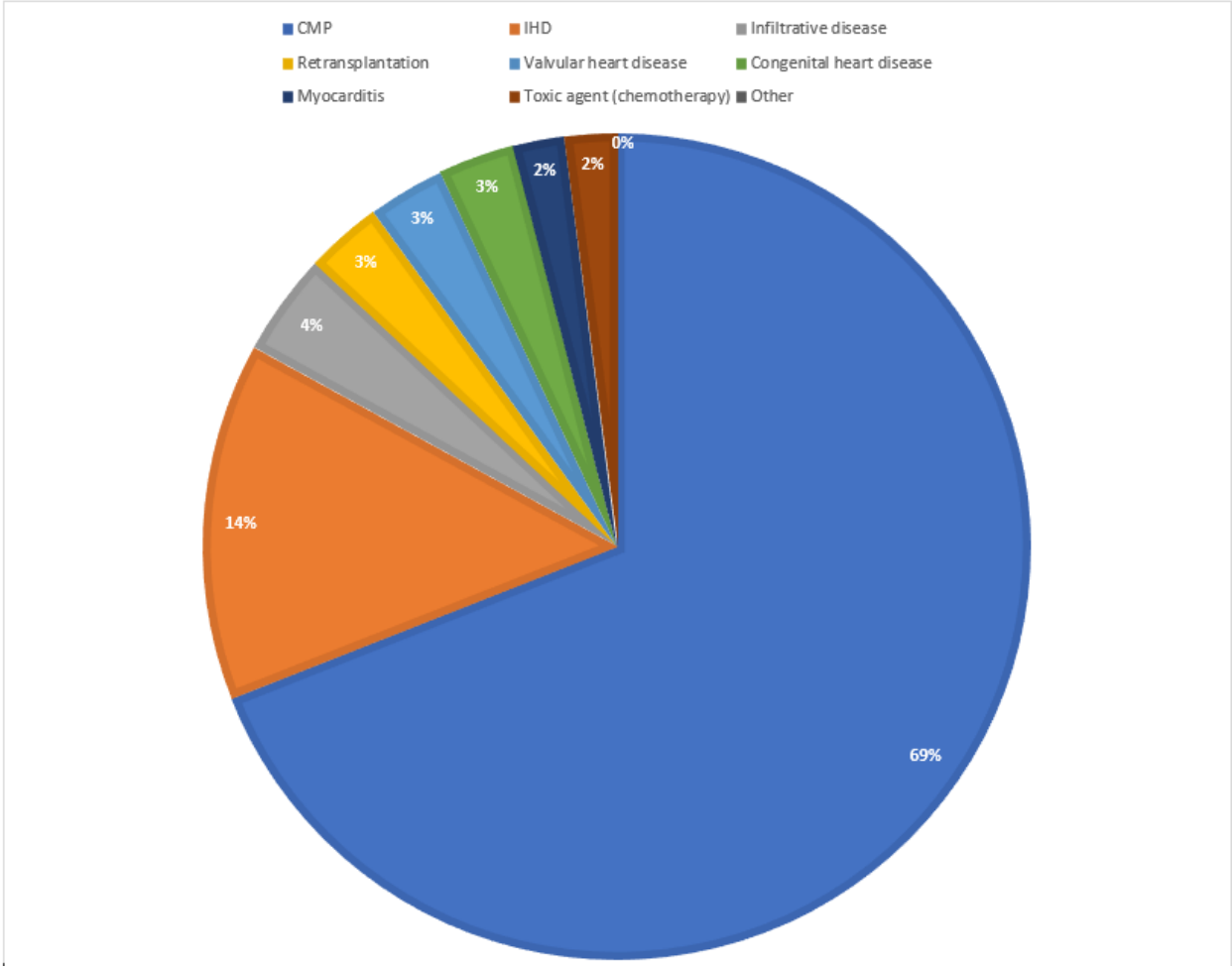

Figure 1. Causes of cardiomyopathy in heart failure (51); *IHD-ischaemic heart disease;* Image modified from (51);

1.3.1 The most common causes of heart failure

The most frequent (in)direct causes of heart failure include (51) :

- Hypertension, where increased pressure on myocardial walls leads to arterial stiffening and myocardial hypertrophy, finally resulting in myocardial dilation and heart (52)

- Congenital heart abnormalities represent a group of inborn defects in the formation of heart anatomy and vasculature.(53) The manifestation of symptoms varies from asymptomatic to problems with breathing, central cyanosis, inability to gain weight, and tiredness. (53) The risk factors include certain infections during pregnancy, such as rubella, drugs, alcohol, or tobacco. (54,55) Other risks may include parents genetically closely related, one or both parents with congenital abnormalities, poor nutritional status, or obesity during pregnancy. (54,55,56) The genetic conditions associated with heart defects are Down syndrome, Turner syndrome, and Marfan syndrome. (54)
  This lead to fibrosis and hypertrophy of the myocardial tissue, often in combination with arrhythmias. (57)

- *Heart valve disease*, where the blood flow is distorted, is caused by congenital heart diseases, autoimmune disease, atherosclerosis, and infection.(58) The pathophysiologic mechanism is again like in any cardiomyopathy-dilation and stiffening of heart walls due to volume overload or/and high pressure in blood vessels. (pulmonary artery) (58)

- Coronary artery disease (CAD) develops due to atherosclerosis and manifests in stiffening of coronary arteries and myocardial remodeling and scar formation.(59) This stiffening impairs the heart's ability to contract and relax(systole and diastole) and decreases overall cardiac output. (59) Especially prevalent in this group of patients are rhythm irregularities, such as atrial fibrillation or flutter and ventricular tachycardia. (59) For that speak the data that approximately 70% of patients with HF have coronary artery disease. (59) That may suggest revascularisation as an essential milestone in the therapy of HF.(60)

- Myocardial infarction (MI) causes irregular contractions of affected heart segments by necrosis the heart tissue and damaged heart valves, which further worsens heart failure.(60)

- Chronic obstructive pulmonary disease (COPD) causes pulmonary hypertension, which increases the pressure in the right side of the heart(so-called cor pulmonale), and eventually right heart failure. (61)

- *Myocarditis* is inflammation of heart muscle, primarily viral genesis, with additional causes such as fungi, bacterias, and protozoa, as well as toxins and drugs. As a consequence, the patients often develop systolic dysfunction, arrhythmia, and lastly, heart failure. (62)

- *Heart Arrhythmias*, like irregular heart rhythms, are caused by changes in electrophysiology of the heart, predominantly originating in the sinoatrial and atrioventricular node, as well as hormone levels, including ACE and potassium. (63) Supraventricular arrhythmias are decreasing cardiac output and deteriorating heart failure. (63) The therapy consists of frequency control with beta-blockers, cardioversion with electricity or Amiodaron, and catheter ablation. *(63)*

- Chronic diseases such as HIV, and metabolic diseases like hyperthyroidism, hypothyroidism, hemochromatosis, or amyloidosis, also may contribute to heart failure. (64)

A systemic literature review of a few community-based cohorts, which included 30 000 individuals and 1800 incident HFpEF (LVEF > 45%) and HFrEF (LVEF ≤ 45%) diagnoses, found correlation between different risk factors and HF subtypes. (65)
Here are few significant findings:

- **Age** correlates positively with HFpEF, whereas smoking, myocardial infarction, left ventricular hypertrophy, and left bundle branch block were more strongly associated with HFrEF (51)

- Obesity and obesity-related comorbidities, especially among women, are more strongly associated with HFpEF than HFrEF. In general, it was noticed that a higher number of comorbidities correlates positively with preserved ejection fraction.(66,67,68,69,70) This might possibly be explained by age, although this trend

held even after the age adjustment. In an Italian cohort study based on reports from more than 2000 patients, there was a strong correlation between hypertension and obesity with HfpEF. (71,72)

- In general, there is a positive correlation between non-cardiac comorbidities and incidence of death and hospitalization due to heart failure. (72) The risk of unfavorable outcomes increases with the number of comorbidities, irrespective of LVEF.(72)

1.3.2 Diabetes and heart failure

Type 2 diabetes (T2D) is among many diseases causing heart and end-organ damage, predisposing in that way HF and causing all related complications, including death.(72) These risks are further compounded in the presence of diabetic nephropathy, highlighting an important interaction between T2D, CKD, and HF.(24) Over the past decade of research, heart anatomy and function, intercellular communication had a significant role in HFpEF. (24) A new hypothesis for etymology and development of HFpEF is therefore proposed, which identifies a systemic proinflammatory state induced by comorbidities as the cause of myocardial structural and functional alterations. (24)

The new paradigm presumes the following sequence of events in HFpEF (72): 1) a high prevalence of comorbidities such as obesity, DM, COPD, and hypertension which leads to systemic inflammation(71); 2) inflammation further causes inflammation of endothelial of coronary arteries(71); 3) this inflammation reduces the bioavailability of nitric oxide, cyclic guanosine monophosphate content and protein kinase G activity (71); 4) low PKG favors hypertrophy development (72) and 5) both stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic left ventricular (LV) stiffness and heart failure development. (72) All taken together, it is not unusual to see heart failure patients being treated

first and foremost with medications treating metabolic comorbidities, antidiabetic medications such as metformin, statins, and recently SGLT2 inhibitors. (74)

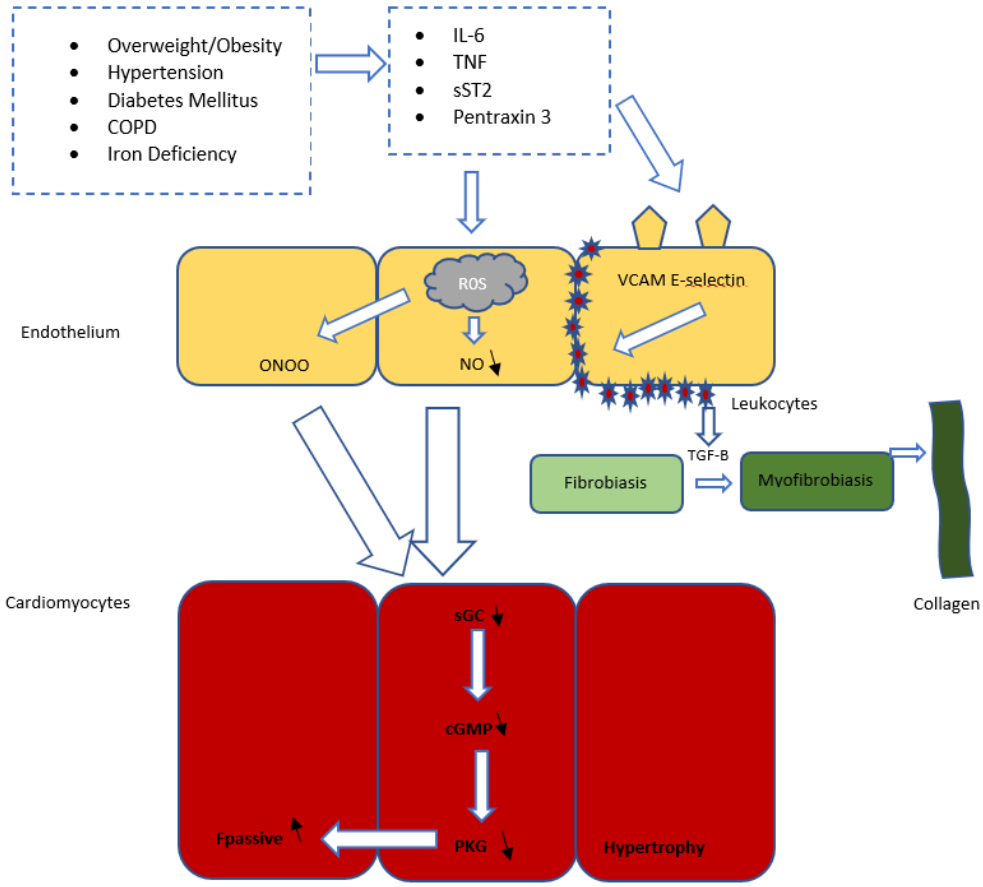

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Figure 2. Comorbidities Drive Myocardial Dysfunction and Remodeling in HFpEF (74); ONOO- Peroxynitrite ;NO-nitrite ocxide, VCAM- Vascular cell adhesion molecule; sGC-Soluble guanylate cyclase;cGMP-Cyclic guanosine monophosphate; PKG-protein kinase G ; IL-6-Interleukin 6 ; TNF-Tumor Necrosis Factor; sST2-Serum Soluble Suppression of Tumorigenicity 2 *Image modified from (74)*

1.4 Types of heart failure

There are two main types of heart failure; right-sided heart failure and left-sided heart failure. (with preserved and reduced ejection fraction) (52)

1.4.1 Left-sided heart failure

Heart failure is caused by dysfunction of the left ventricle, which results in reduced ejection fraction, where the value of LVEF is 40% or less; known as HFrEF. (1) This definition is still a point of discussion, and there has still not been found one version, so according to some textbooks, different numbers could be found, such as LVEF equal or less to 35%, less than 40%, equal or less than 40%.(1) In routine clinical practice, however, many clinicians consider EF less than 45% as significant systolic dysfunction and label it as HFrEF.Current ESC definition of HFrEF is<40 %, 40-50% is mildly reduced and >50% with HF symptoms represents HFpEF. (1)

Preserved ejection fraction heart failure (HFpEF) is mainly classified as that one where ejection fraction equals 40% or more, according to some begins only from 45%, or 50%, or even 55% ejection fraction. (1) The term HFpEF is used because these patients do not meet the criteria for „normal ejection fraction“, but also do not have reduced ejection fraction. (1)

There is additionally a new class of HF, introduced in 2016, by ESC guidelines for heart failures diagnosis and management; heart failure with mildly reduced EF (HFmrEF) – also known under the name HFpEF-borderline or heart with mildly reduced ejection fraction.(1) The criteria for this category is EF from 41% to 49% according to European guidelines and 40 to 49% according to the US guidelines. (1) This class represents the middle ground between HFpEF and HFrEF. (1)

For these patients, routine check-ups are advisable, especially with multiple risk factors which ought to be monitored and treated preventively according to guidelines, just like in the case of HFrEF.(1)

1.4.2 Right-sided heart failure

In this condition, there is a distorted blood flow from the right ventricle to the lungs due to pulmonary hypertension, usually caused by untreated left heart failure. (73) This causes leg and ankle edema, as well as ascites. Often, patients have left- and right-sided CHF at the same time. (73)

1.5 The symptoms of CHF

Symptoms	Signs
Typical	**More specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss (in advanced HF)
Bloated feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac mrmur
Confusion (especially in the elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmionary crepitations
Palpitations	Reduced air entry and dullness to
Dizziness	percussion at lung bases (pleural
Syncope	effusion)
Bendopnea	Tachycardia
	Irregular pulse
	Tachypnoea
	Cheyne Stokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

HF=Heart failure

Figure 3: Symptoms of heart failure; modified after ESC guidelines on heart failure management 2016 guidelines (78) *Image modified from (78)*

In the first stages of CHF, it is hard to notice any changes in health. However with time, there is a wide range of symptoms, varying from edema in lower extremities to breathlessness, loss of appetite, palpitations, and syncope.(76) It can be especially difficult to recognize heart failure in infants and young children. Symptoms may include **poor feeding**, **excessive sweating**, **difficulty breathing**. (76)

1.6 Clinical classification

Variety and type of symptoms are used in the classification of severity of heart failure and monitoring the response to treatment. (77) The classification of the New York Heart Association (NYHA) is used worldwide, although the outcome in heart failure is best determined not only by symptoms (NYHA class) but also by echocardiographic criteria. (77) According to the European Society of Cardiology's guidelines for the diagnosis of heart failure, essential features of heart failure are actively presented symptoms such as breathlessness, fatigue, edema, and objective evidence of cardiac dysfunction (at rest). (77) Non-essential features include response to treatment directed towards heart failure (in cases where the diagnosis is in doubt). (77)

The following four categories according to **NYHA Classification**(78) are:

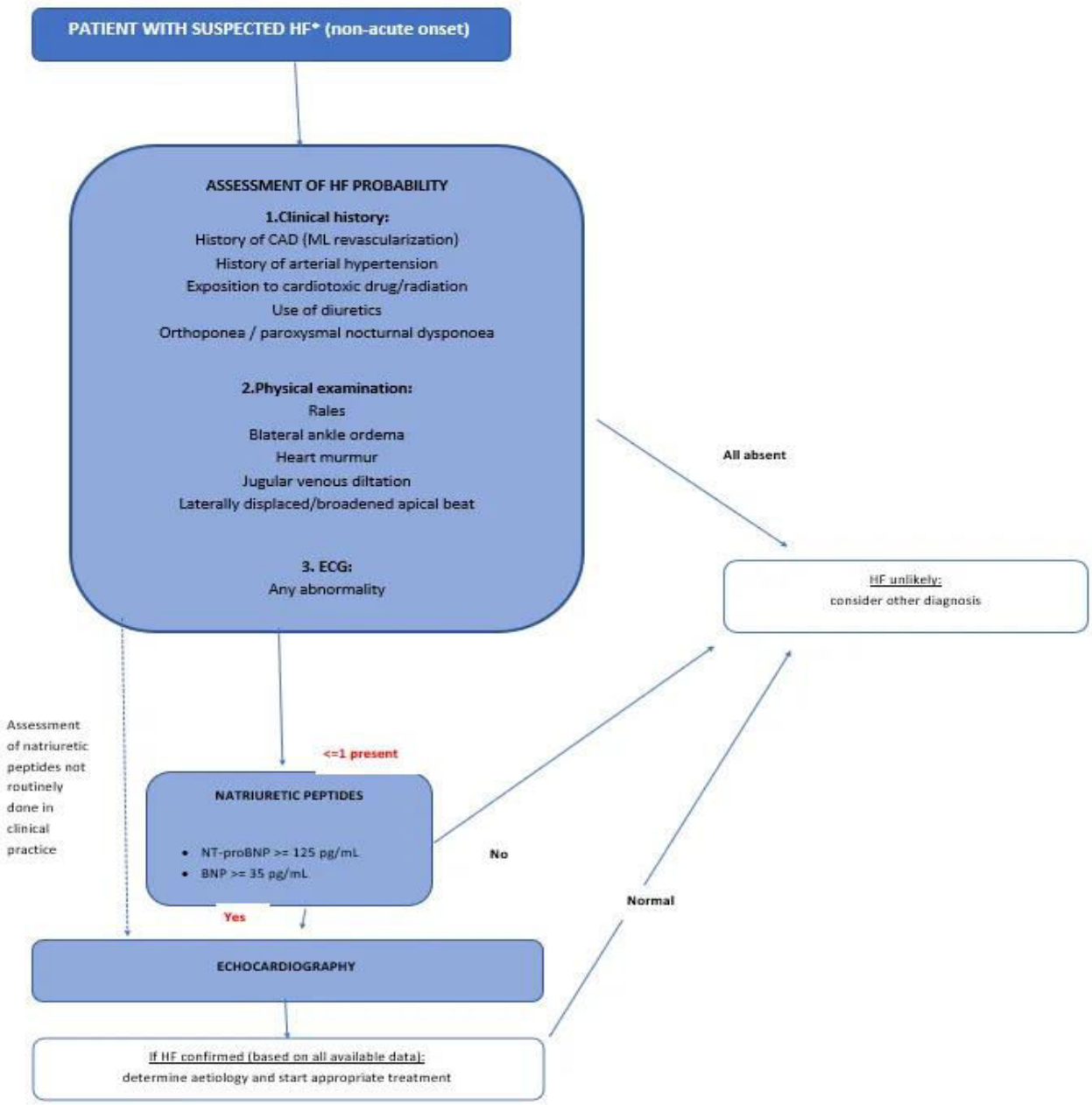
Class I (Mild) There are no limitations to the usual lifestyle. Patients do not feel discomfort, chest pain, dyspnoea while performing ordinary physical activities. *(78)*

Class II (Mild) Patients might experience symptoms such as tiredness, palpitation, dyspnea, or anginal pain while performing physical activities. At rest, these symptoms disappear. *(78)*

*Class III (*Moderate) In this stage, the symptoms are the same but more severe and experienced earlier or by smaller physical activity. This results in mild to moderate limitation of ordinary activities *(78)*

Class IV (Severe) Symptoms and discomfort are present even at rest, although more severe during physical activity. There is a severe limitation in terms of lifestyle. *(78)*

Figure 4. Diagnostic Algorithm according to ESC Guidelines (78) *;* NT-proBNP-N-terminalpro B-type natriuretic peptide, BNP- B-type natriuretic peptide; Image modified from (78)



1.7 Diagnosis

Symtopms and signs of HF need to be identified, with particular attention to evidence of congestion. (75) In monitoring the symptoms, it is important to look for stability or persistence over certain amount of time. There are many possible steps presented with algorithm below, depending on the stage of the condition.(75)

If the symptoms are presenting for the first time, good taking of history if crucial in the diagnosis of HF. It is important to look/ask for coronary artery disease (CAD), arterial hypertension, use of diuretics, presenting symptoms (e.g., orthopnoea), as well as detailed physical examination, with emphasis on clues such as bilateral edema, increased jugular venous pressure and displaced apical beat. (79) Resting ECG is also to be performed. If all elements are standard, HF is unlikely, and other diagnoses need to be evaluated. If at least one of these components is present, NPS levels in plasma are to be measured to identify those who meet the criteria for echocardiography. (79)

The next step comprises an advanced workup in case of initial evidence of HFpEF/HFmrEF. (79) It consists of an objective demonstration of structural and functional alterations of the heart as the underlying cause for the clinical presentation. (79) These include; electrocardiogram, chest-x-ray, blood test, stress transthoracic echocardiogram, cardiac magnetic resonance, CT SPECT; PET; Coronary Angiography, and Endomyocardial Biopsy. (79)

1.8 Therapy

Medical care for heart failure includes several non-pharmacologic, pharmacologic, and invasive strategies to limit and reverse its manifestations. (79) Depending on the severity, non-pharmacologic therapies include lifestyle changes, such as dietary regimes; sodium and fluid restriction; physical activity, and attention to weight gain.(90) On the other side,

pharmacological therapies include the use of diuretics, vasodilators, inotropic agents, anticoagulants, beta-blockers, and digoxin.(79,90,91)

Dependent on the pathophysiology , various interventions such as CRT, pacemakers and ICDs can be benefit patients with arrhythmia. (79) In case when revascularization procedures are needed, possible treatment options include CABG and PCI. (79); Lastly, there is also a new treatment providing artificial heart to the patients; EKMO, or smaller procedures with anatomical valve replacement or repair, and ventricular restoration. (79-95) All of these surgical procedures play a key role in preventing sudden death in emergency cases.(79-95)

In the case of progressive end-stage heart failure with a poor prognosis, there is no alternative but heart transplantation despite maximal therapy. (79,90, 95) In bridging the patient to transplantation, mechanical devices such as VADS and TAHs are used (90). In addition, VADs are increasingly being used as permanent therapy. (90)

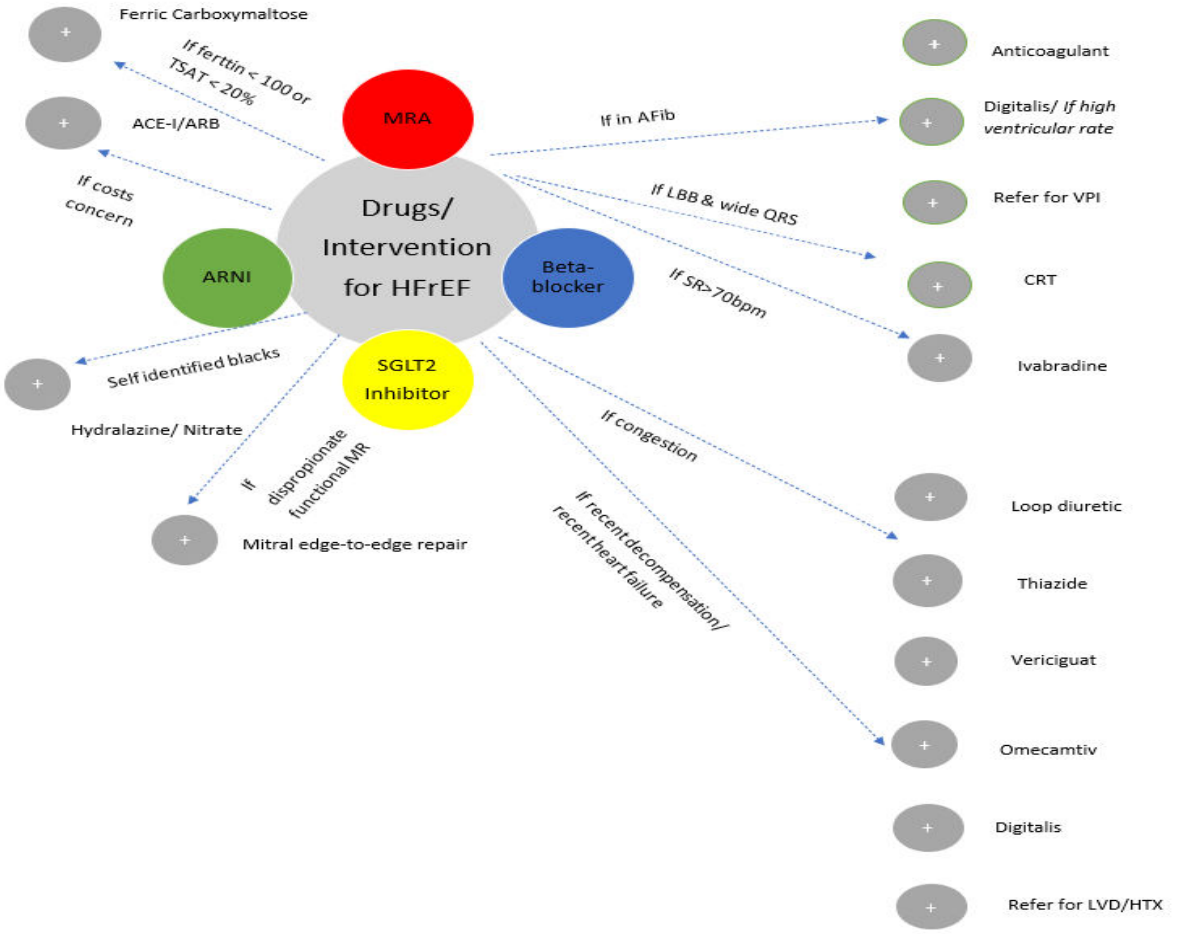


Figure 5. Pharmacological and interventional treatment options for HfrEF; according to ESC Guidelines (97); VPI- Vasopeptidase inhibitors, CRT- Cardiac Resynchronization Therapy; *Image modified from (97)*

Furthermore, HFrEF requires treatment that combines several medications to improve symptoms and prognosis of the disease. (96) Medications like angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors /neprilysin inhibitors, sacubitril/valsartan, known as ARNIs (97), then beta-blockers (97), and mineralocorticoid receptor antagonists(97) provide incremental benefit with a significant reduction in all-cause mortality, cardiovascular mortality(97), hospitalizations for heart failure, as well as overall-hospitalization. (97) Despite obvious cardiovascular benefits, the patients face adverse collateral effects, including hypotension, kidney dysfunction, and electrolyte abnormalities.

(97) Therefore, new therapeutic strategies to improve symptoms, reduce mortality, and recurrent hospitalization are critical to advance outcomes in HF patients. (98)

Previous standards of care for HF patients with HFrEF included β-blockers, RAAS inhibitors, ARNI, diuretics, and digoxin, worked to suppress neurohormones, reduce volume overload and improve cardiac contractility. (98) However, recently another drug was introduced into guidelines for treating patients with HF with reduced and recently also preserved EF.(99,100) It is essential to say that conventional diuretics only provide symptomatic relief for HF patients but do not impact mortality. (100) Despite benefits, currently available HF therapies, such as RAAS inhibitors and diuretics, increase the risk of adverse effects due to hypotension, volume depletion, and SNS activation, highlighting the urgent need for safe, novel therapies. (101,216)

Other medications which might be beneficial :

- Anticoagulants are used to treat heart failure in case of atrial fibrillation. (102)

- Cholesterol-lowering drugs (statins) decrease the level of cholesterol in the blood and thus act as preventive information for plaques. (102)

- Digoxin reduces the risk of hospitalization in the case of symptomatic heart failure with reduced ejection fraction and sinus rhythm. (102) The digoxin results in patients with HFrEF and AF have not been studied in randomized controlled trials. (102) “Still, recent studies suggested a potentially higher risk of mortality and HF hospitalization in patients with AF receiving digoxin”. (103-107) However, this remains controversial, as another recent meta-analysis concluded that digoxin has no adverse effect on mortality in patients with AF and concurrent HF, most of whom had HFrEF.(102-107)

Recently, SGLT2 inhibitors; dapagliflozin and empagliflozin showed a significant reduction in mortality and hospitalizations due to HF and overall improvement of quality of life when added to the current standard therapy HFrEF. (103) The exact mechanisms of these medications will be discussed in detail later on. (103)

The recent studies in diabetic cardiology and HFrEF showed that ARNIs and SGLT2 inhibitors should not be given separately but rather together. (108)

1.9 SGLT2- INHIBITORS

Sodium-glucose cotransporters SGLT1 (also known under SLC5A1) and SGLT2 (SLC5A2) are important endothelial mediators in glucose transport. While SGLT1 acts primarily in dietary uptake of glucose in the gastrointestinal tract, SGLT2 is largely responsible for the glucose reuptake in the tubules of the kidney. (108) Accordingly, mutations in the SGLT1 gene cause glucose malabsorption, while mutations in SGLT2 are associated with glucosuria. (108)

There have appeared thirty years ago, and since then, we have gathered knowledge about their exact mechanism in the human body, where phlorizin plays a significant role. Phlorizin is in nature-occurring competitive inhibitor of SGLT1 and SGLT2 receptors.(109) The problems scientists encountered were side effects in the gastrointestinal tract and their short decay in the human organism.(109) It was a breakthrough for their development, and since they were approved by the FDA, SGLT2 inhibitors are currently in guidelines for the treatment of heart failure, and their potential renal benefits are yet to be fully explored. (109)

1.9.1 How do they work?

SGLT2 inhibitors are medications that are unique in terms of their mechanism that lowers glucose level, independent of the function of β-cells and insulin secretion. (110)

As their name suggests, they block SGLT2 channel proteins, making them potent antidiabetic medications, given that renal function is preserved. (110) Sodium-glucose cotransporter-2 proteins are expressed in the proximal convoluted tubule of the kidneys. (110) These transporters are responsible for over 90% of overall glucose reabsorption and are therefore suitable in targeting diabetes. (110)

1.9.2 Phlorizin

Research in the last 150 years found a connection between glucosuria and naturally occurring plant extract phlorizin, which was later identified as a non-specific inhibitor of SGLT proteins. (111) The interesting part about these proteins is that they function independently of insulin excretion.(111) It becomes obvious why they are such an attractive concept for the treatment of diabetes if we take into account their positive impact on the metabolism of carbohydrates. (112,113,114)

1.9.3 Current Selective SGLT2 Inhibitors

There are currently five SGLT2 selective inhibitors approved by the FDA as single, dual, or triple therapy. These are: Canagliflozin (Invokana®), Dapagliflozin (Farxiga®), Empagliflozin (Jardiance®) and Ertugliflozin (Steglatro®). (109,115)

In terms of their selectivity, empagliflozin has the greatest selectivity, whereas canagliflozin is the least selective. *(116)*

FDA-approved SGLT2 inhibitors

Generic agent (brand)	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
Initial dose (maximum dose)	100 mg/d if eGFR is 45 to <60 and 300 mg/d if eGFR ≥60	5 mg/d (10 mg/d)	10 mg/d (25 mg/d)
Renal dosage adjustments	Discontinue if eGFR is persistently <45 (Contraindicated if eGFR <30)	Do not administer/discontinue with eGFR <60	Do not initiate/discontinue with eGFR persistently <45 (Contraindicated if eGFR < 30)
Hepatic dosage adjustments	No adjustement for mild to moderate impairment; not recommended in servere impairment (has not been)		None to note
Drug interactions	If receiving concurrent UGT enzyme inducers and eGFR is 45 to <60, consider alternative antihyperglycemic therapy	None to note	
Administration	Administer prior to first meal	Administer in the morning without regard to food	
Common adverse effects	Genital mycotic infections, urinary tract infections, volume-related effects such as dizziness and hypotension		
Available combination products, generic (brand)	Canagliflozin + metformin (Invokamet)	Dapagliflozin + metformin ER (Xigduo)	Empagliflozin + metformin (Synjardy) empagliflozin + linagliptan (Glyxambi)

Table 1.FDA-approved SGLT2 inhibitors (289) ; eGFR-estimated glomerular filtration rate (reported in mL/minute/1.73 m2); UGT-uridine 5'-diphospho-glucuronosyltransferase enzyme inducers (eg, rifampin, phenytoin, phenobarbital, ritonavir) ;*Table modified from (289)*

1.10 Benefits of SGLT2 Inhibitors

1.10.1 Glucose Control

SGLT2-Inhibitors proved very efficient in lowering glucose levels, although correlated with mild hypoglycemic risks, similar to those of Metformin and DPP-4 inhibitors.(117) In 2014, a meta-analysis showed that other factors play a role, such as lower mean age, duration of diabetes, and higher baseline of BMI, fasting glucose, and HbA1C. (117) These factors were directly proportional to HbA1C Reduction.(117) Recent clinical trials showed that Reduction in HbA1c compared to placebo reached its maximum at six months and is stayed the same up to almost a year (52 weeks). (117) SGLT2 inhibitors have demonstrated numerous metabolic benefits and no inferiority compared to other anti-diabetic medications. (118) Moreover, when combined with other medications and insulin, SGLT2 Inhibitors showed additional benefits to therapy. In one trial, dapagliflozin was added to patients already taking metformin and sulfonylurea. (118) This resulted in an HbA1C level decrease by 0.87% compared to 0.17% reduction in the placebo group during 24 weeks. (119)
Previously,it is vital to ensure that the estimated glomerular function (eGFR) is below 60 mL/min before initiating the treatment with SLGT2 Inhibitors.(120) Once initiated, however, the SGLT2 inhibitors were to be continued down to an eGFR of 45 mL/min before discontinuation (the lower doses of canagliflozin, empagliflozin, and ertugliflozin can be prescribed if eGFR falls below 60). (120) That being said, renal function check-ups are done at least once a year and even more frequently if eGFR is <60 mL/min (120).

In short, lower the eGFR, the less potent the glucose lowering effect is.Recenty, the eGFR limit has been lowered however, as the cardiovascular and renal effects of SGLT2 remains unchanged by it.

1.10.2 Other Metabolic Effects

1.10.2.1 Weight loss

In a clinical trial with SGLT2 inhibitors, the average weight loss was 1 to 4 kg for 104 weeks. (121) This is associated with glucose regulation and has metabolic benefits and a positive impact on blood pressure. (121)

1.10.2.2 Blood Pressure

All studies with SGLT2 inhibitors have found a significant reduction in blood pressure, with numbers being even more significant in systolic (1.66 to 6.9mmHg) than diastolic (0.88 to 3.5mmHg) blood pressure. (122)
Interestingly, the reduction in blood pressure was independent of eGFR.(122) Participants with eGFR of 40 mL/min/1.73 m2 experienced the same benefits without developing hyponatremia as many do with diuretics.(122) The initial reductions in BP were believed to be due to the diuretic-like volume depletion effects. (123) However, longer-term effects may be linked to metabolism, weight loss, and RAAS system *inhibition.* SGLT2 inhibitors are therefore suitable for patients with T2D and hypertension. (123)

1.10.2.3 Lipids

Clinical trials have shown a small rise in both LDL and HDL levels without significant changes in triglycerides. (122)

1.10.3 Cardiovascular Benefits

The cardiovascular benefits of SGLT2i include hemodynamics, metabolism, and mechanisms of inflammation and oxidative stress, which all interact and are codependent on each other. (282)

During the HF, the heart muscle cells are losing energy and need an alternative supply, which changes energy resources from oxidation of **free fatty acids** to that of **glucose**.(123) In the first case, more ATP molecules are produced, although fatty acids have lower oxygen efficiency than glucose. (124,125). This switch lowers the energy available to cardiomyocytes and lowers the work efficiency of the heat pump.(126), As an additional energy supply, ketone bodies (β-hydroxybutyrate) are used. They classify as the best molecules in oxygen efficiency and producing ATP, with low oxygen demand (124,125,126). SGLT2i-induced glycosuria reduces blood glucose brings the body in similar state to **the fasting**, including an energetical shift from glucose to fats and ketone bodies. Lipolysis is made faster, and there is an increased concentration of ketone bodies in plasma. (126, 128). This energetic switch increases cardiac energy, diminishes remodeling, and maintains LV systolic function (129).

There is an increase in **hematocrit** as plasma volume decreases and erythropoietin level increases. (131). This is beneficial to cardiac metabolism since the oxygen delivery is enhanced (132). Although this was expected to be especially beneficial in patients with coronary artery disease, in the DAPA-HF trial, "there was no difference in the magnitude of benefit of dapagliflozin in patients with or without ischemic cardiomyopathy". (132) So it was concluded that an increase in hematocrit produced by" erythropoietin-mimetic agents" in patients with heart failure, "does not have favorable effects on the course of the disease". (133). Ketone bodies attenuate oxidative stress and systemic inflammation by inhibiting the "Nod-like receptor protein 3" (NLRP3) inflammasome (134, 135) and by "activating G-protein coupled receptor 109" and "hydroxycarboxylic acid receptor 2". (136). Since SGLT2i elevate ketone levels in plasma (137,138), they are associated with a mild increase in developing **diabetic ketoacidosis** (138,140,141).

1.10.3.1 Inhibition of cardiac Na+/H+ exchanger

"Increased cardiac Na+/H+ exchanger activity is found during developing HF". (142, 143). SGLT2i direct inhibits Na+/H+ exchanger in the myocardial and decreases the concentration of sodium and calcium(144), and at the same time increases calcium concentration in

the mitochondria, necessary for myocardial contractibility. (144,145) According to the sodium hypothesis, increased sodium concentration will reduce the activity of enzyme dehydrogenases during the Krebs cycle by enabling their regeneration and is essential in providing more energy supply to the cells. (149)
To sum up, the inhibition of the Na+/H+ exchanger prevents myocardial hypertrophy and HF symptoms. (146,147) by increasing mitochondrial calcium concentrations, enhancing cardiac work, and reducing the risk of remodeling and fibrosis sudden cardiac death (148).

1.10.3.2 Reduction in uric acid serum level

Urine represents the final product in the metabolism of purine." Uric acid stimulates the proliferation of smooth muscle cells and harms HF, as it causes further hypertrophy of the myocardium". (154). "Uric acid is also connected to hypertension (159), atrial fibrillation (160), and HF" (161).
"It further promotes oxidative stress inside the cell (155), depletes nitric oxide (156), activates the renin-angiotensin system in the vascular system (157), and induces inflammation ".(158). SGLT2i-induced glycosuria leads to increased uric acid excretion and reduced plasma urine levels. (150,151,152). "In a meta-analysis of 60 clinical studies with patients who had diabetes type 2, there was a significant decrease of plasma uric acid, which had a rapid onset and was maintained for a long time. "(153).

1.10.3.3 Improvements in cardiac function and structure

As far as we know today, there are no SGLT2 in the human heart (162), so "the effect of SGLT2 inhibitors is based on hemodynamic, neurohormonal, and metabolic mechanisms". "In animal studies with mice, SGLT2 inhibitors showed a reduction in the expression of fibrotic proteins and reduced deposition of collagen (both I and III) in the heart interstitium: this reduced cardiac fibrosis and hypertrophy and improved diastolic function." (165, 163). In rats with MI, SGLT2 inhibitors" inhibit myocardial fibrosis by activating the so-called STAT3 or transcription pathway and reducing the release of superoxides and nitro-

tyrosine" (164). Additionally, in a "non-diabetic pig model with heart failure, SGLT2i appeared to attenuate the remodeling of the myocardium, have a positive impact on cardiac metabolism, and improve the overall systolic function of the heart". (134).Many clinical studies using imaging such as MRI and echocardiography proved that SGLT2i are improving diastolic function and reducing left ventricular volume and mass. (166-169). However, most studies did not include individuals with advanced LV remodeling, so it is unclear if these medications would have had the same effect on those patients. (128)

1.10.3.4 Attenuation of inflammation response

Inflammation of tissue plays a vital role in the formation of atherosclerosis, and it comes with an increased risk of cardiovascular disease (170,171,172)." Many studies have indicated that SGLT2i can slightly decrease inflammatory factors, such as interleukin-6, high-sensitivity C-reactive protein, and tumor necrosis factor gamma and alpha". (173-175). "Furthermore, SGLT2i reduce M1 macrophage accumulation and polarizes M2 macrophages in fat and liver". (176).

1.10.4 Other possible mechanisms

Macula densa is part of **the juxtaglomerular apparatus** in the kidney. When it detects increased sodium concentrations, it reduces the release of renin, which leads to inhibition of the RAAS system. An animal study showed a similar effect, where SGLT2i suppressed renal RAAS (178,179). "However, another clinical study in diabetes type 2 suggested that SGLT2i enhances the plasma renin activity, turning it to baseline after three months". (177).The exact mechanism of SGLT2i on the RAAS system remains incompletely understood.(177)

1.10.4.1 Role of calcium

Even patients without diabetes can develop ventricular dysfunction, which is, in that case, called diabetic cardiomyopathy. (235) Calcium plays the leading role in that mechanism due to calcium overload in cardiomyocytes and its function in the relaxation and contraction of the heart muscle.SGLT2 Inhibitors decrease the level of sodium in the cytoplasm, followed by decreased concentration of calcium as well. (235). Seven days of treatment with empagliflozin was proven to alter calcium level, and restore the heart's ability to contract and relax, independent of the glycolytic capacity of cardiomyocytes.(234)

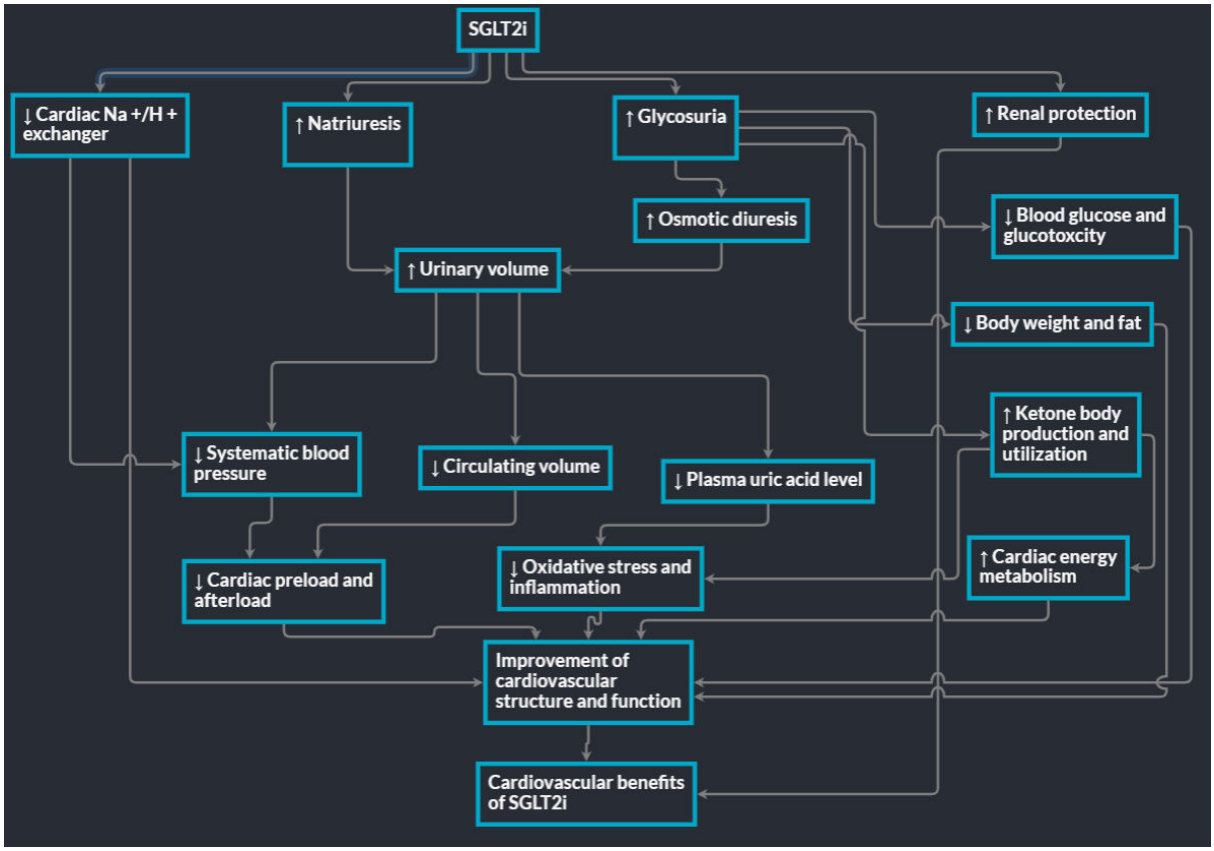


Figure 6. Cardiovascular protection mechanisms of SGLT2 inhibitors (282);Image modified from (282)

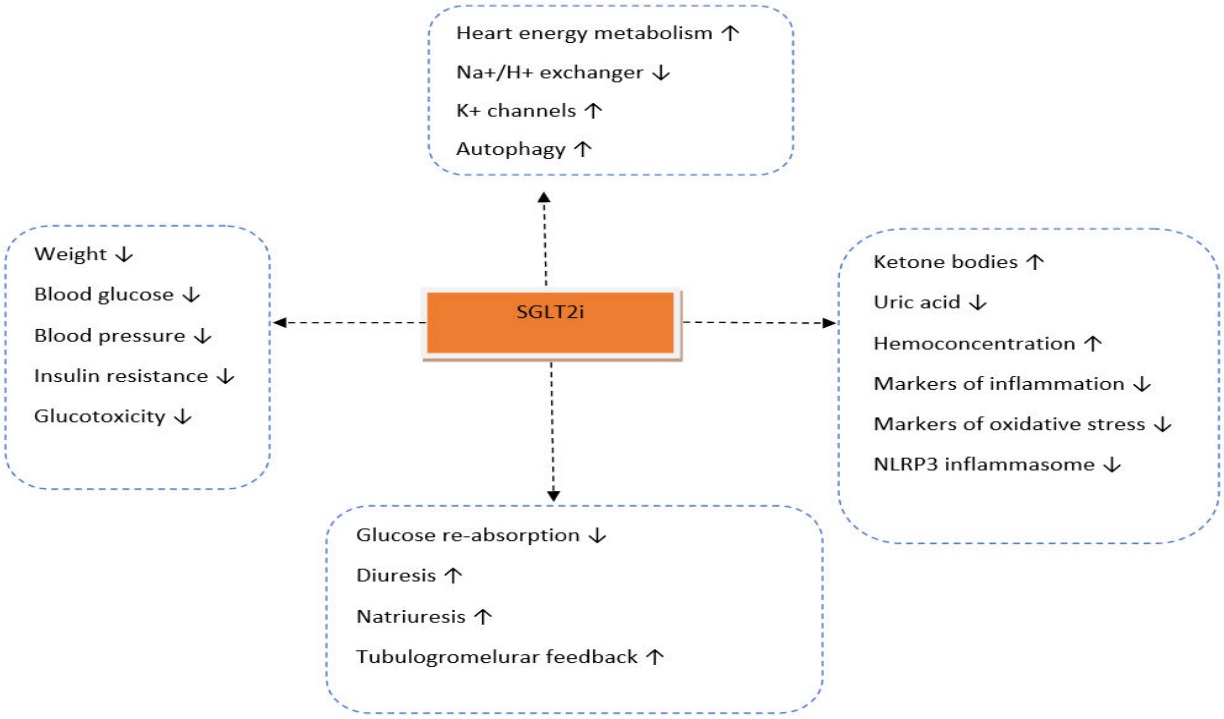


Figure 7. Role of SGLT2 inhibitors in formation of atherosclerosis:from pharmacology to pre-clinical and clinical implementation (283) ;Image modified from (283)

Regarding general renal function under usage of SGLT2 inhibitors, the slight decrease in eGFR (reversible on discontinuation) occurs at the beginning, but over the longer term, renal function stabilizes and falls less compared to that of a placebo(180), and the progression of albuminuria is slowed down as well. (180)

There is further evidence for renal benefits under the SGLT2 therapy. The CVOTs for empagliflozin, canagliflozin, and dapagliflozin all included a composite renal endpoint as a secondary outcome(181), which included progression of albuminuria, reduction in eGFR/doubling of serum creatinine, the need for dialysis, or death from a renal cause. (181) In all three trials, substantial reductions in the composite renal outcomes were seen in people with T2D (including those without established cardiovascular disease), consistent

with a renoprotective effect (181). The CREDENCE study was a double-blind, randomized controlled trial investigating the effect of canagliflozin on people with T2D and albuminuric diabetic kidney disease (204). The primary outcome was a composite of end-stage renal disease, doubling of serum creatinine, and death from renal or cardiovascular causes. (181) All 4401 participants enrolled in the study had an eGFR in the range of 30–90 mL/min/1.73 m2 and were already undergoing treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). (181) A significant 30% relative risk ratio for the primary outcome was shown.(181)

The mechanism of **renoprotection** is thought to be based on vasoconstriction of the afferent glomerular arteriole and subsequent reduction in intraglomerular pressure, which has a protective effect on the glomerular basement membrane, thus reducing albuminuria (181). So it can be said that the effect of SGLT2 inhibitors has a similar renoprotective effect as ACE inhibitors and ARBs, which operates via vasodilation of the efferent arteriole of the glomerulus *(182)*

SGLT2i bind to SGLT2 in the proximal tubule of the kidneys and induce natriuresis, which means that the delivery of sodium to macula densa is increased.(183) That activates tubuloglomerular feedback, vasoconstriction of afferent vessels, and decreases glomerular pressure. (183,184,185) These alone accounts for up to 40% reduction in albuminuria observed with empagliflozin, dapagliflozin, and canagliflozin. (186) The hemodynamic effects of SGLT2 inhibition occur even when kidneys are not completely functional, preventing volume overload and complications related to diuretic resistance. (187) That points to natriuresis as likely a major factor leading to cardiovascular and renoprotective effects observed with empagliflozin and canagliflozin. (188,189)

1.10.5 SGLT2 and atherosclerosis

Type I and type II diabetes represent risk factors for coronary artery diseases and other related comorbidities such as MI and stroke(190,191,192).The most prevalent pathophysiological complication is the nonenzymatic glycosylation of proteins and lipids. (190-192) They form molecules known as AGEs, which initiate oxidative reactions that promote the formation of oxidized LDL(193), which damage the vessels and contribute to atherosclerosis.[193]. SGLT2 inhibitors are further reducing the preload, thereby lowering ventricular

filling pressure.(193) Afterload reductions may occur through blood pressure and arterial stiffness lowering, thereby improving subendocardial blood flow. (61,194)

1.10.6 Adverse Side Effects and Warnings

1.10.6.1 Genitourinary infection

The glycosuria induced by SGLT2 inhibitors represents predisposing factor to genital fungal and urinary tract infection (UTI). (195) A meta-analysis, where trials comparing SGLT2 inhibitors with placebo or other medications for patients with type 2 diabetes were analyzed, showed that the class was associated with a five-fold increase in genital mycotic infections and a more modest 40% increase in UTIs (195.).

Other relatively common side-effects that are generally easily treated with topical(e.g., miconazole or clotrimazole cream for several days) or oral (e.g., fluconazole stat dose) antifungal agents were candidal vulvovaginitis and balanitis.(194) The major risk factors here included being female and having a previous history of infection (194). Recurrent and/or severe fungal infections may necessitate cessation of SGLT2 inhibitor therapy, although in some cases, it was wise to take prophylactic treatment (e.g., fortnightly fluconazole) in order to preserve the benefits achieved with SGLT2 inhibition. (182)

These symptoms of infection are increased urinary frequency, thirst, and sometimes orthostatic hypotension. Risk factors are age above 75 years, GFR below 60 mL/min, and use of loop diuretics. (196) The majority of urinary infections are mild to moderate in severity (except upper UTIs) and respond very well to standard therapy.(196) Fournier's gangrene, as another possible side-effect, is one extremely rare but life-threatening bacterial infection of the tissue under the skin that surrounds nerves, muscles, fat, and blood vessels of the perineum. (196) Diabetes was always known as one of the risk factors for Fournier's gangrene, but recently SGLT2i are also on the same list of risk factors.(196) In the FDA data, few cases of Fournier's gangrene were identified in the period between

1st March 2013 and 31th January 2019, among patients treated with SGLT2 inhibitors. (197)

1.10.6.2 Diuretic side-effects

The glycosuria induced by SGLT2 inhibitors leading to more frequent urination may be problematic for older people for practical reasons and as a possible cause of dehydration and postural hypotension. (196) Due to these complications, it is advisable to avoid dapagliflozin among people younger than 75 years and empagliflozin among those below 85 years of age. (196) Thus, combining SGLT2 inhibitors with diuretics must be done carefully and is generally to be avoided (if possible). (196)

One of the most serious complication under treatment with SGLT2 Inhibitors was amputation. In the CANVAS study, patients treated with canagliflozin had more chances for amputations compared to placebo. (6.3 vs. 3.4 events per 1000 person-years) (199) „Risk factors for amputation were prior history of amputation, peripheral vascular disease, and neuropathy.“(199) Numbers say that 71% of those affected had the highest amputation at the level of the toe or metatarsal (140).). Higher risks for amputations were not demonstrated in the other cardiovascular outcome trials. (198)

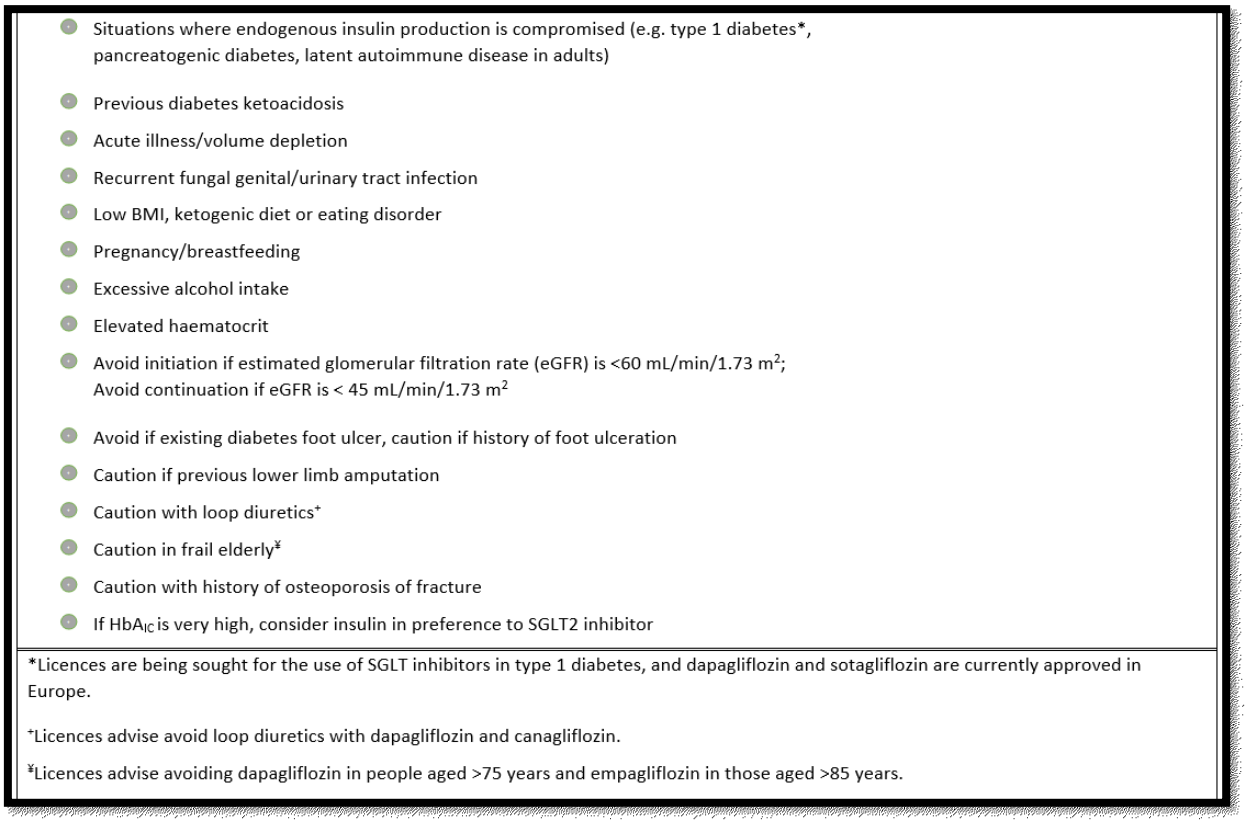


Figure 8. When to avoid SGLT2 Inhibitors (182); Image modified from (182)

Due to alternative energy pathways, including ketone bodies, there is an elevated risk of **diabetic ketoacidosis** (DKA). (215) Typically for SGLT2i is the so called euglycaemic ketoacidosis with blood sugar levels of approximately 250 mg/dl. (215) Overall the frequency in people with T2D is very small.(215) Although there have been some warnings around DKA from the European Medicines Agency [EMA] in 2016, it was concluded that the metabolic benefits such as weight loss outweigh the risks in this case. (182)

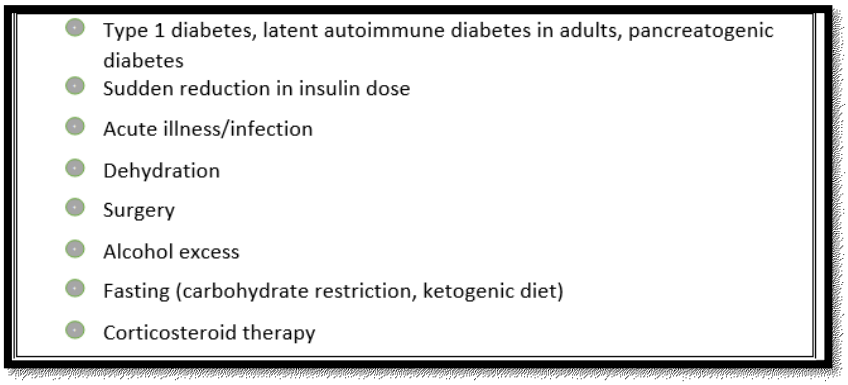


Figure 9.SGLT inhibitors and ketoacidosis (182); Image modified from (182)

1.10.7 When to use SGLT inhibitors in type 1 diabetes as off-label therapy?

Considering that DKA is a potentially life-threatening condition, prescribing SGLT2 inhibitors with type one diabetes should be especially carefully considered, and acknowledging that this may occur at relatively low levels of glycemia(even lower than 14 mmol/L). (182) That is why ketone monitoring is strongly advisable. Patients should also be very selectively chosen, where the previous history of DKA, as well as poor compliance with insulin regime, should be taken as eliminatory factors. (182)

2. METHODS

The present Diploma Thesis represents the result of Literature Research. Utilized literature was found in textbooks, studies and other significant study reviews available online. Moreover, research was conducted using scientific data of the medical research platform PubMed. For the purpose of this systemic review, three major studies were used: EMPEROR-Reduced, EMPEROR-Preserved and DAPA-HF.These studies included results of heart failure with reduced and preserved ejection fraction, as well as various other metabolic and cardiovascular diseases.

2.1 Clinical Trials Overview

All SGLT2-Inhibitors Studies were required to have a CVOT in order to receive sustainable market authorisation. These studies, which involved patients with type two diabetes, are summed up in the table below:

Trial	Study drugs	Cohort	Primary endpoints and results	Secondary CV endpoints (significant results)
EMPA-REG OUTCOME	Empagliflozin 10 mg or 25 mg vs Placebo	T2D and established CVD; n=7020	Composite of CV death, non fatal MI or non-fatal stroke (HR=0.86;CI=0,74-0,99)	CV death (HR=0,62;CI=0,49-0,77) All-cause death (HR=0,68;CI=0,57-0,82) HHF (HR=0,65;CI=0,50-0,85)
CANVAS	Canagliflozin 100 mg or 300 mg vs placebo	T2D and established CVD (66%) or ≥2 CVD risk factors (33%) n=10142	Composite of CV death, non fatal MI or non-fatal stroke (HR=0.86;CI=0,75-0,97)	HHF(HR=0,67;CI=0,52-0,87)
DECLARE-TIMI, 58	Dapagliflozin 10mg vs. placebo	T2D and established CVD (41%) or ≥2 CVD risk factors (59%) n=17160	Composite of CV death, non fatal MI or non-fatal stroke (HR=0.93;CI=0,84-1,03; difference non-significant	HHF(HR=0,73);CI=0,61-0,88)
VERTIS CV	Ertugliflozin 5mg or 15 mg vs placebo	Study ongoing	Study ongoing	Study ongoing
Ci=95% confidence interval; CV=cardiovascular; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; HHF=hospitalisation for heart failure; HR=hazard ration; MI=myocardial infraction; T2D=type 2 diabetes				

Table 2. The most significant studies researching cardiovascular benefits of SGLT2-Inhibitors (182) ; Table modified from (182)

Based on the working mechanisms of SGLT2 Inhibitors, many cardiovascular protective effects were expected apart from the obvious metabolic ones, which were later confirmed in a few studies shown above. (290) The EMPA-REG Trial was the pioneering study that confirmed these effects on over 7000 selected patients with CVD.(290) The primary outcome was a composite of 3 major cardiovascular events(nonfatal MI, nonfatal stroke, and death due to cardiovascular causes); (290) which was reduced by 14%, while the total hospitalization for heart failure was reduced by 35%.(290,200) It should be said that there was no significant change in the incidence of strokes and that the reduction in of the primary outcome was largely driven by a reduction in death due to cardiovascular reasons.(200) Compared with placebo, empagliflozin also showed slower progression in renal disease. (200,201).

Another important study that showed a statistically significant reduction in 3-MACE events was CANVAS Trial, where patients were treated with canagliflozin or placebo. (202) Similarly, no big benefits were demonstrated for MI or stroke.(202) The renal endpoint showed a reduction of 27%. (202) another significant study may as well be the CREDENCE Trial which focused on renal outcomes of patients treated with canagliflozin(203), including end-stage kidney disease, creatinine serum, renal and cardiovascular deaths. (203,204)

Two significant trials where patients were treated with dapagliflozin are DAPA-HF and DECLARE-TIMI 58.(204,205) Both showed that dapagliflozin reduced the risk of heart failure, and the composite renal endpoint was reduced by 24% (204,205).
The DECLARE–TIMI 58 trial included patients with T2D, 40 years of age or older, and with established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease**.**(207,208)

The trial showed that the dapagliflozin was noninferior to placebo with respect to the primary safety outcome of MACE.(209) The MACE rate was not considerably lower, but the rate of cardiovascular death or hospitalization for heart failure was significantly lower than placebo(209), with additional possible lower rate of adverse renal outcomes.(209)

The VERTIS-CV study included 8246 patients with diabetes type 2 and peripheral/coronary/cerebral artery disease, which were treated with ertugliflozin. (209) Although the risk of HHF was reduced (209), no significant reduction in incidence for 3-point MACE was found.(209) Furthermore, there was a decrease in ischemic heart disease with those using SGLT2i, compared to placebo, which was partially caused by lower systolic pressure. (210)

To sum up, empagliflozin and canagliflozin had protective effects on major cardiovascular events (211). All medications mentioned above showed a reduction in hospitalization rate due to heart failure.(212,213)

2.2 Cardiovascular outcome trials in heart failure

After all the cardiovascular benefits shown among patients with diabetes, there was a question of whether the same medication group would have a similar effect on the patients without diabetes. The recent findings are represented in the results of three most important studies- two of them tackled heart failure with reduced ejection fraction: EMPEROR-Reduced and DAPA HF, and one concerning preserved ejection fraction; EMPEROR-Perserved. (1)

Heart failure with reduced ejection fraction is present when the left ventricle's muscle is not pumping the blood sufficiently and where the ejection fraction is 40% or less.(1)

3. RESULTS

3.1 Heart failure with reduced ejection fraction

3.1.1 EMPEROR-Reduced Study

EMPEROR-Reduced was a „multionational, multicenter,double-blind, randomized, controlled trial“, which investigated the effect of Empagliflozin on cardiovascular outcomes among over 3700 patients with and without diabetes. (214,215) This was a second large-scale heart failure trial, but compared to DAPA-HF, it included more serious cases of LV systolic dysfunction.(215,216)

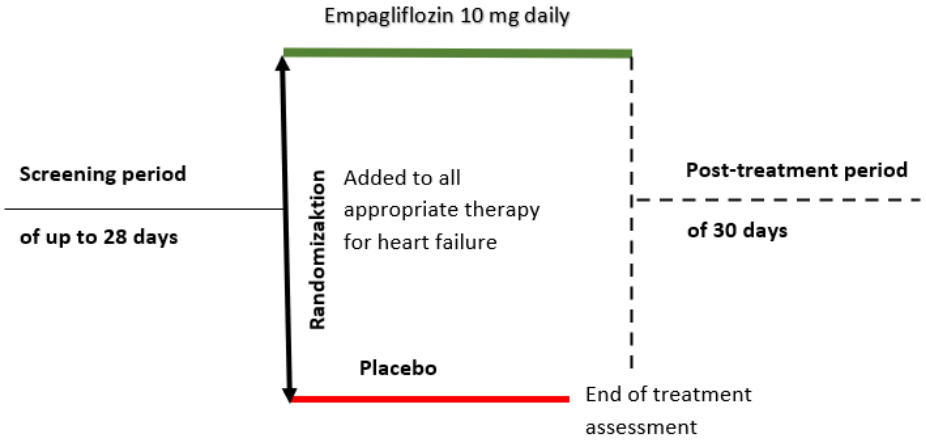


Figure 10. : Emperor-Reduced Study design (215); *image modified from (215)*

EMPEROR REDUCED	
Inclusion criteria	**Exclusion Criteria**
· Age 18 years or older	· Uncontrolled hyperglycemia (>13 mmol/L = 234 mg/dL)
Chronic HF, New York Heart Association (NYHA) functional class II/III/IV Left ventricular EF (LVEF) ≤40%	· ACS/TIA/Stroke within last 2 months.
HF hospitalization within 12 months	· eGFR < 30 mL/min.
N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥600 pg/ml if EF ≤30%; ≥1000 pg/ml if EF 31-35%; ≥2500 pg/ml if EF >35%; If concomitant atrial fibrillation, then above thresholds were doubled)	· pre-menopausal women with birth control, and alcohol or drug abuse within 3 months of study
· Body mass index ≤45 kg/m2	· steroid therapy
· Glomerular filtration rate (GFR) >30	· thyroid dysfunction within 6 weeks of starting study
· Established cardiovascular disease (225)	· myocardial planned cardiac surgery within 3 months
Appropriate dose of medical therapy for HF consistent with prevailing local and international CV (Cardiovascular) guidelines, stable for at least 1 week prior to Visit 1	· Systolic blood pressure (SBP) ≥ 180 mmHg, symptomatic hypotension and/or SBP ≤ 100 mmHg
Appropriate use of medical devices such as cardioverter defibrillator (ICD) or a cardiac resynchronization therapy (CRT) consistent with prevailing local or international CV guidelines	· treatment with weight loss medications for the past 3 months
Signed and dated written ICF (Informed Consent Form)	· heart transplant bariatric surgery within 2 years
	· any GI surgery that induces chronic malabsorption,
	· eGFR < 20 ml/min/1.73 m2 or requiring dialysis
	· known hypersensitivity or allergy to empagliflozin
	ketoacidosis
	pregnancy

Table 3. Inclusion and exclusion criteria for EMPEROR-Reduced Trial (216,217);
eGFR- Estimated glomerular filtration rate ;Table modified from (216,217)

3.1.1.2 Outcomes

The primary endpoint was represented by cardiovascular death(such as stroke or myocardial infarction) or hospitalization due to heart failure, analyzed as first time occurring event. (218) The primary-secondary endpoint was the occurrence of all **hospitalizations** for heart failure, even recurring ones. The secondary endpoint was the rate of e**GFR**.(218)

3.1.1.3 Primary outcomes

· The **cardiovascular** death or hospitalization due to heart failure occurred in 19,5% of patients or 361 patients in the group treated with empagliflozin and in almost 25% or 462 patients in the placebo group (hazard ratio, 0.75; 95% confidence interval, 0.65 to 0.86; P<0.001).(218) The number of patients who need to be treated with empagliflozin to prevent one of these primary outcomes is 19 (95% CI, 13 to 37).(218)
The empagliflozin effect on the primary endpoint was consistent across all subgroups, regardless of their diabetes status. (218) Among the patients who were taking ARNIs as a baseline, the hazard ratio was 0,64 compared to 0,77 for those who were not receiving the sacubitril-valsartan(218), so there was no significant difference when taking ARNIs. (218)

3.1.1.4 Secondary outcomes

Empagliflozin proved to have a beneficial effect on both main secondary outcomes- total number of hospitalization and renal disease. The total number of hospitalizations for heart failure was lower in the empagliflozin group (388 events) compared to the placebo group (553 events) (HR 0.9, 95% CI p < 0.001). (219) Renal endpoints(hemodialysis, kidney transplantation, eGFR reduction) were 1.6 in the empagliflozin group vs. 3.1 in the placebo group, with (HR 0.5, 95% CI, p < 0.001).(219) All-cause mortality was 13.4% compared to placebo 14.2% (HR 0.92, 95% CI 0.77-1.10, p > 0.05). (219) Newly diagnosed type 2 dia-

betes among patients with prediabetes was 11.2% vs. placebo 12.6% ($p > 0.05$).(219) The decrease of systolic blood pressure differed -2.4 compared to. -1.7 mm Hg ($p > 0.05$). (219) The confirmed hypoglycemic event were similar; 1.4% vs. 1.5% in the placebo group. (219)

Intensification of diuretics were respectively 16% and 22% ($p < 0.0001$). (222) Need for intravenous treatment due urgent HF visit was 6.8% vs. 9.9% ($p = 0.0004$). (222-231) Hospitalization due to heart failure requiring cardiac care at intensive care unit care was 5% vs. 6% (222-231)

3.1.1.5 Interpretation

The results showed the superiority of empagliflozin compared to placebo in overall improvement of heart failure status and cardiovascular outcomes among patients with reduced heart failure (EF ≤40%), regardless of whether they had diabetes or not.(222,223) The primary benefit was **the reduction in hospitalizations due to heart, which was related to other non-cardiac reasons**.(222-231) There was an early and sustained benefit according to *CSS* of the *KCCQ*, which represents the patient's perception of their health status, including heart failure symptoms, and impact on physical and social function, as well as the overall quality of life. (223-231) There was also a benefit for the kidneys in terms of eGFR. The use of MRAs did not influence the effect of empagliflozin on clinical outcomes.(222-231) Some slight regional and racial differences in efficacy were noted. (222-231)

3.1.1.6 Side-effects

Regarding side-effects under empagliflozin, uncomplicated genital tract infections were more frequently compared to the placebo group.(220) Regarding other known complications with SGLT2 inhibitors, such as bone fracture, hypoglycemia, and even amputations, no significant difference was noted between the two groups(220,221) Other concerns that have been often associated with previous medication combinations for heart failure, such as hypotension, volume depletion, kidney dysfunction, bradycardia, and hyperkalemia, were not observed with empagliflozin in the EMPA-Reduced trial.(220,222)

3.1.1.7 Limitations of the analysis

This post-hoc analysis did not assess the effect of empagliflozin in all subgroups of cardio-vascular diseases, nor the effect in even smaller subgroups such as the five categories of eGFR. (219) Although the benefits on the kidney outcome were based on more than one event and with fair significance, as seen by the confidence intervals,(219) the magnitude of these study findings of a benefit on kidney outcomes is still very similar to that seen in large-scale trials patients with diabetes and chronic kidney disease.(219)

Regarding the EMPEROR-Reduced study, it is significant to notice that the number of people on an ARNI were still limited and this has to be investigated further.

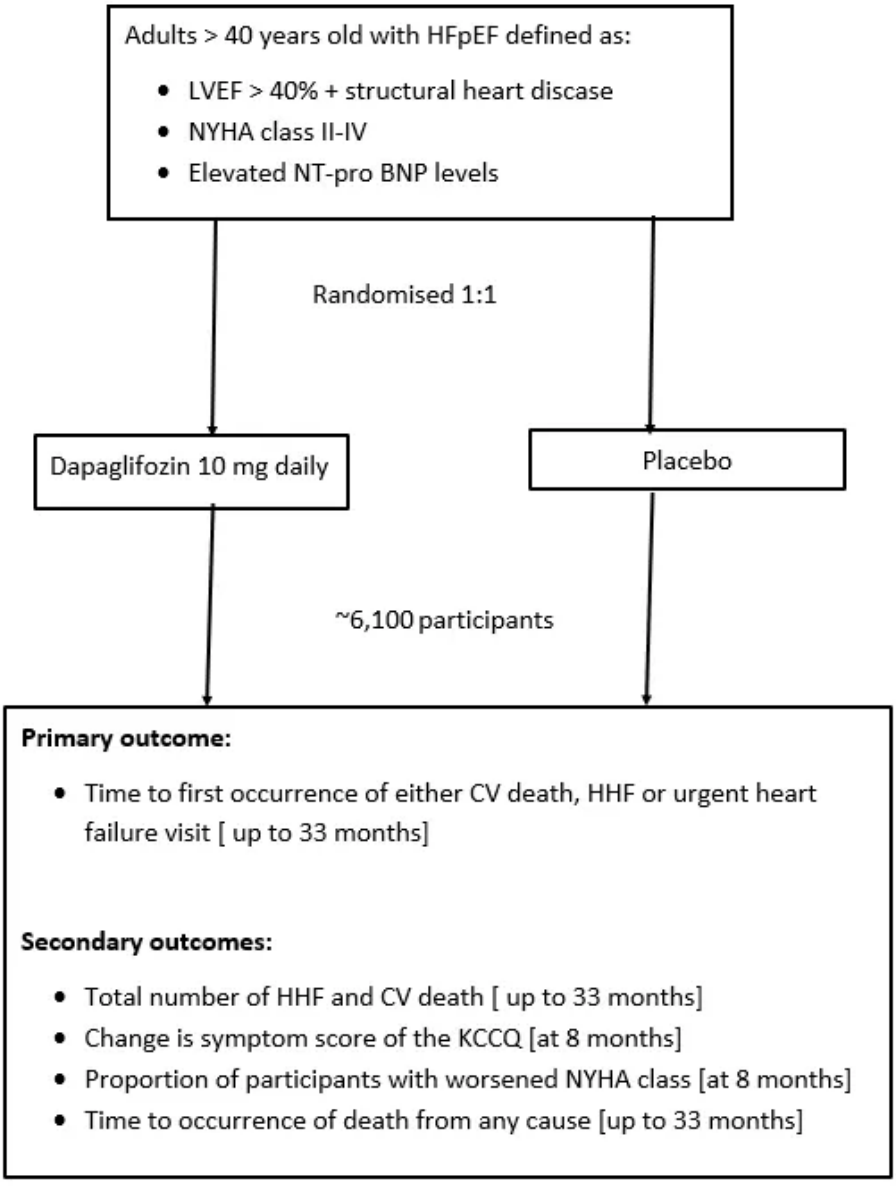
3.1.2 DAPA-HF

DAPA-HF was a randomized, double-blind, placebo-controlled trial in patients with HfrEF(108), which the goal of assessing the efficacy and safety of dapagliflozin by adding 10 mg to standard care once daily, compared with a matching placebo. (108) The inclusion and exclusion criteria are represented in the table below.

DAPA-HF	
Inclusion Criteria:	**Exclusion Criteria**
Male or female, aged ≥18 years	Receiving therapy with an SGLT2 inhibitor within 8 weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor
Established documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV), which has been present for at least 2 months	Type 1 diabetes mellitus
LVEF≤40%	Symptomatic hypotension or systolic BP <95 mmHg at 2 out of 3 measurements either at visit 1 or visit 2
NYHA Class II, III, or IV symptoms Plasma NT-proBNP level of: ≥600pg/mL OR ≥400pg/mL if they were hospitalized for HF within the past 12 months OR ≥900pg/mL if patient had atrial fibrillation/flutter on baseline ECG.	Current acute decompensated HF or hospitalization due to decompensated HF <4 weeks prior to enrolment
Patients should receive background standard of care for HFrEF and be treated according to locally recognized guidelines	MI, unstable angina, stroke or transient ischemic attack within 12 weeks prior to enrolment
eGFR ≥30 mL/min/1.73 m^2 (CKD-EPI formula) at enrolment (visit 1) (262)	Unacceptable side effects associated with SGLT2i

Table 4. Inclusion and exclusion criteria for DAPA-HF Trial (246,247); MI-myocardial infarction, LVEF- left ventricular ejection fraction**;** eGFR- Estimated glomerular filtration rate ; *Table modified from (246,247)*

Figure 11.DAPA-HF Design (108); KCCQ- Kansas City Cardiomyopathy Questionnaire; LVEF- Left ventricular ejection fraction; *Image modified from (108)*



3.1.2.1 Trial outcomes

The primary endpoint was worsening heart failure (hospitalization or an urgent IV therapy) or CV death(102) . Over 18.2 months, the primary endpoint occurred in 386 out of 2,373 patients (16.3%) with patients taking dapagliflozin and in 502 out of 2,371 patients (21.2%) who were in the placebo group (HR 0.74, 95% CI [0.65–0.85], and p<0.001). (102) CV death causes occurred in 9.6% of the dapagliflozin group and 11.5% of the placebo group (HR 0.82; 95% CI [0.69–0.98]).(102) Hospitalization due to heart failure happened in 9.8% of the dapagliflozin and in 13.5% of the placebo group. (HR 0.71; 95% CI [0.59–0.83]; p<0.001) (255) Both first and recurrent hospitalizations for HF were significantly reduced in the group treated with dapagliflozin compared with placebo.(255) The effect of dapagliflozin on the primary endpoint showed the same trend in all subgroup analyses, including in patients without diabetes.(255) However, the patients in NYHA functional class III or IV appeared to benefit less than those in the second class.(255) A total of 276 patients (11.5%) in the group treated with(102), and 329 patients (13.9%) in the placebo group died from any cause (hazard ratio, 0.83; 95% CI [0.71 to 0.97]). (102)

3.1.2.2 Interpretation

This was a randomized, placebo-controlled trial including only patients with HFrEF, with and without diabetes.(253) It was observed that the risk of the previously defined primary endpoint was significantly lower in the treated group than in the placebo one. (253) Further, the total hospitalization and deterioration of HF were lower than in the placebo group. (253) Under therapy with dapagliflozin, there were fewer symptoms of heart failure, as measured in the Kansas City Cardiomyopathy Questionnaire.(253-259) These benefits occurred early after randomization and regardless of the patients' therapy for HF.(diuretics, ARNIs, mineralocorticoid receptor antagonist).(253-259) Especially among patients using MRA and diuretics, there was a risk of volume depletion since most had chronic kidney disease.(253-259) But it turned out the renal adverse events happened in less than 5% of participants in both groups. (253) Dapagliflozin was as effective in 55% of patients with-

out, as in those with diabetes type 2. That suggests this medication has benefits other than just glucose lowering.(253-259) Thus; these findings extended the role of dapagliflozin in treating patients without diabetes and with CV diseases.(253-259)
Major adverse events such as hypoglycemia and diabetic ketoacidosis were rare and only present in patients with diabetes.(253-259)

3.1.2.3 The limitations

The limitations of the trial was that it included only 5% black participants and primarly patients with mild symptoms, corresponding to NYHA class II. (260) Moreover, the use of sacubitril–valsartan as baseline alone reduced the incidence of hospitalization and death due to HF, being more effective than renin-angiotensin system blockade (260) However, the mechanisms of action of SGLT2i and ARNIs are distinct, and in a post subgroup analysis, the benefits were similar for both patients treated with sacubitril–valsartan and among those who did not receive that treatment.(261,262) Lastly, urinary infections caused by discontinuation of SGLT2i in early staged of this trial, were not documented. (248)

3.2 Heart failure with preserved ejection fraction

3.2.1 EMPEROR-Perserved Study or Study with HFpEF

Emperor-perserved was a double-blind, randomized trial, including 5988 patients with HF class II-IV and preserved ejection fraction. (263) The primary endpoint was worsening and hospitalization of HF and CV death, with follow-ups every 24 months and post-treatment period of 30 days.(264,265)

Patients were randomized in a 1:1 to empagliflozin 10 mg (2,997 participants) or placebo (2,991 participants). (263) There was stratification by geographic region, diabetes status estimated glomerular filtration rate (eGFR), and left ventricular ejection fraction (LVEF; <50%/≥50%).(263) All the patients were receiving additional treatments if needed for heart failure. (263) Inclusion, exclusion criteria are represented in the table below. (267)

EMP-PRESERVED	
Inclusion criteria	**Exclusion criteria**
Age ≥18 years	Acute coronary syndrome, stroke, or transient ischemic attack within 90 days
Chronic HF, New York Heart Association (NYHA) functional class II/III/IV	Listed for orthotopic heart transplantation (OHT) or OHT recipient
Preserved LVEF (EF >40%)	Acute decompensated HF
HF hospitalization within 12 months	Systolic blood pressure BP ≥180 mm Hg
N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml without atrial fibrillation (AF), >900 pg/ml with AF	Symptomatic hypotension or SBP ≤100 mm Hg
Structural heart disease within 6 months or documented HF hospitalization within 12 months	Liver or kidney disease (eGFR <20 ml/min/1.73 m^2)
Stable dose of oral diuretics, if prescribed	Current use or prior use of a sodium-glucose co-transporter (SGLT)-2 inhibitor or combined SGLT-1 and -2 inhibitor tp

Table 5. Inclusion and exclusion criteria for EMPEROR-Preserved Trial (267); BP-blood pressure, SBP-systolic blood pressure, eGFR- Estimated glomerular filtration rate ; *Table modified from (267)*

3.2.2 Study outcomes

During period of 26.2 months, a primary endpoint event occurred in 415 of 2997 patients (or 13.8%) in the group treated with empagliflozin and in 511 of 2991 placebo patients (17.1%) (hazard ratio 0.79; 95% , CI [0.69 to 0.90],P<0.001). (263) The total number of CV deaths was 7,3% of study participants in the placebo group, compared to 8,2% in the treated group. (HR 0.91, 95% CI [0.76-1.09]).(263)The main observation was reduced risk of HF hospitalization in the group with empagliflozin therapy, regardless of diabetes. In total, the number of HF hospitalizations was significantly lower in the empagliflozin than in placebo participants (407 vs. 541; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; and P<0.001).(263)The benefit appeared somewhat attenuated among patients with EF ≥60%. (263) The reported side-effects were uncomplicated genital and urinary tract infections and hypotension, which were more prevalent in the empagliflozin group.(263)
Regarding secondary outcomes,the number of all hospitalizations was 407 vs. 541 ($p < 0.001$) for empagliflozin and placebo repectively. (267) Change in mean eGFR observed was: -1.25 vs. -2.62 ($p < 0.001$), and the composite renal outcome occurred in 3.6% compared to placebo 3.7% ($p > 0.05$).(267) All-cause mortality was calculated to be 13.4% in the group treated with empagliflozin and 14.2% in placebo group (HR 0.92, 95% CI 0.77-1.10, $p > 0.05$). (267) Newly diagnosed type 2 diabetes among patients with existing prediabetes occured in 12.0% of patients treated with empagliflozin compared to 14.0% in the placebo group. ($p > 0.05$). (267-272)

3.2.3 Interpretation

In the EMPEROR-Preserved trial, the two most significant findings were that empagliflozin reduces the risks for the combined endpoint of heart failure hospitalization and CV death and the that the Kaplan-Meier curves start to separate quickly after the initiation of the empagliflozin. (271) Patients with empagliflozin showed stable improvement of clinical symptoms and were also less likely to show deterioration of general health status. (271) These findings matched with those from EMPEROR-Reduced Trial, which enrolled patients with HFrEF(HF was less than 40%) (271)

Other small studies have assessed the health status in patients with HFpEF who participated in this study.(273-279) In the treatment of HFpEF with an Aldosterone Antagonist(TOPCAT Trial) including 3400 patients with baseline KCCQ-Score from 54.8, showed a 1.36-point improvement over the placebo group in a period of 4 months.(273) Similarly, the Prospective Comparison of ARNI With ARB Global Outcomes in HFpEF(Paragon-HF) Trial included patients with a baseline health status.(271-280), which was similar to that in EMPEROR-Preserved (where mean KCCQ-CSS score was 74.2) and showed an improvement in KCCQ-CSS with sacubitril/valsartan by 1.0 point compared with placebo after eight months. (274)

3.3 Results with patients without diabetes type two

To further strengther theory according which, SGLT2 Inhibitors have positive effect on patients with cardiovascular diseases, even without diabetes, studies and sub-group analysis were performed. Among them the most significant are the EMPA-TROPISM study and subgroup analysis of DAPA-HF.(243)

3.3.1 EMPA-TROPISM

This was a double-blind, randomized study with 84 patients with reduced ejection fractions.(243) The inclusion criteria involved being over 18, having HFrEF- NYHA II or III class, LVEF under 50%, and stable symptoms and medical therapy within the last three months.(243) The exclusion criteria were diabetes mellitus, acute cardiac events or surgery

in the last three months, GFR under 30 ml/kg/min, parental inotropic agents, systolic blood pressure lower than 90mmHg, CMR compatible cardiac devices, and pregnancy. (236) The primary endpoint was a significant change in diastolic and systolic volume in the left ventricle, assessed by cardiac magnetic resonance.(236) The secondary ones included change in the mass, ejection fraction in the left ventricle, results of 6 minutes walk test, quality of life scale, and the peak of oxygen consumption during the cardiopulmonary exercise test. (236) These parameters were necessary because of the pathophysiology of heart failure. LV remodeling is characterized by dilation, were often due to volume increase, sphericity, and hypertrophy (231-236), which worsens ejection fraction and heart failure. Reversing these changes is an essential factor in reducing mortality and morbidity in patients with HF.(237,238)

Five visits over six months were performed, and two additional visits at 1 and 3 months post-randomization included an interview, drug dispensation, and blood and urine tests for safety and tolerability.(239,240) At the final visit, all baseline anthropometric measurements were performed again.(239,240)

As a main result, significant regression of left ventricular hypertrophy and mass was observed under empagliflozin treatment. (249) The decrease in volume was supported by a reduction in N-terminal pro-B type natriuretic peptide levels in plasma. There was a significant difference (240)

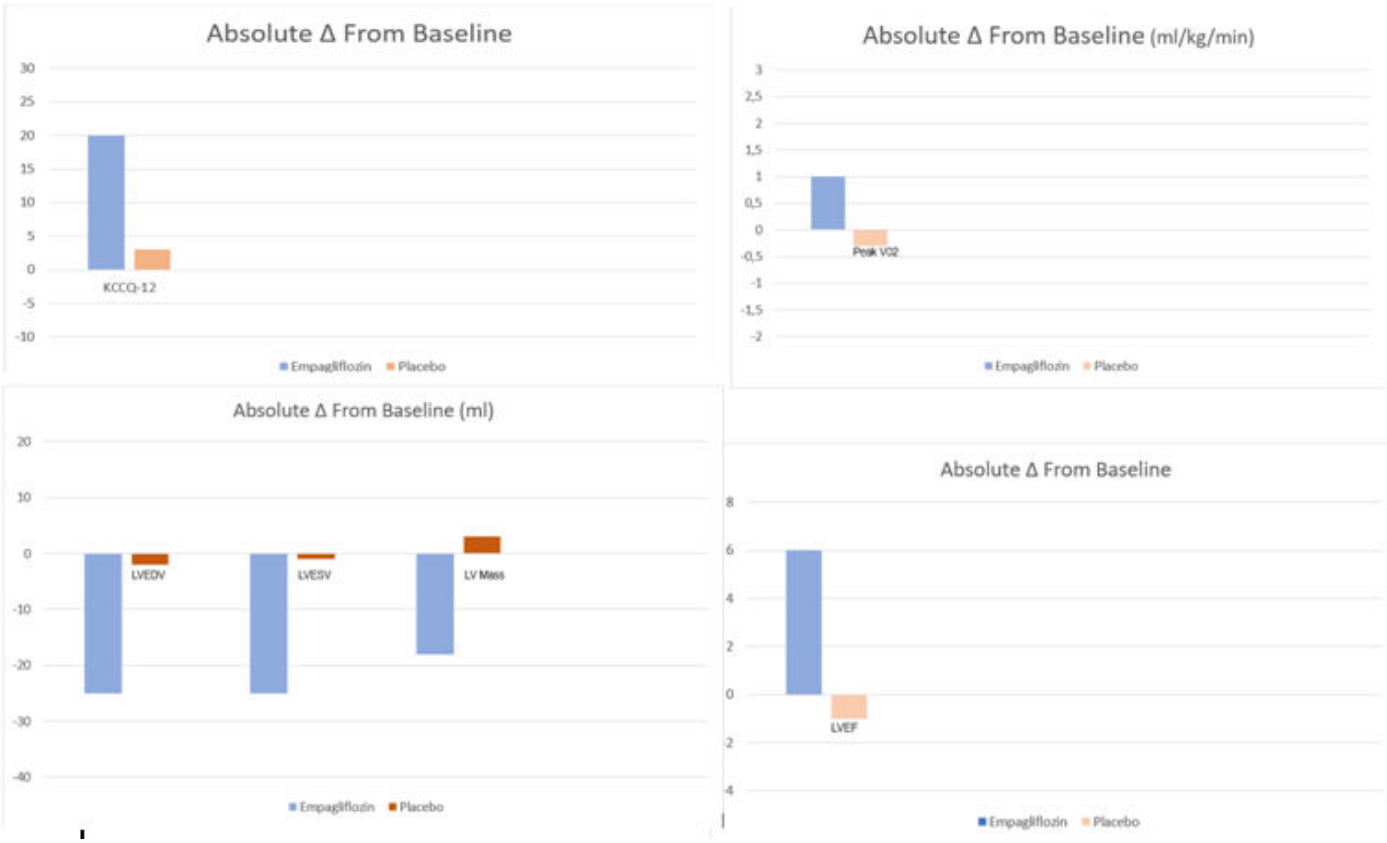


Figure 12. Empagliflozin in patient without diabetes and HFrEF(236); LVEF- left ventricular ejection fraction, KCCQ- Kansas City Cardiomyopathy Questionnaire Peak; V02- peak volume of oxygen**;** *Image modified from (236)*

in all six primary clinical endpoints of this study compared to placebo. So apart from LV volume and ass, there was significantly less change in hearts geometry in terms of sphericity and remodeling, which are usually correlated to worse heart failure outcomes. (241). There was also increased cardiopulmonary capacity noted (242), as well as better systolic and diastolic function,(243) function(contractions, EF), and reduced sympathetic drive(242,243). This was the first study that demonstrated that empagliflozin improves the geometry of LV in HF patients without diabetes. This improvement has been confirmed in the rat model with HFrEF (245,246,247), so both the human and the animal data point towards the enhanced performance of LV in HFrEF with SGLT2 inhibitors treatment.(246)

3.3.2 Subanalysis of DAPA-HF and EMPEROR-Reduced

2139 (45%) patients with diabetes type 2 participated in the DAPA-HF study.(8) Although the overall risk of events was higher among patients with diabetes, the relative risk reduction of the primary outcome did not differ between patients with (HR 0.75; 95% CI [0.63–0.90]) and without diabetes at baseline (HR 0.73; 95% CI [0.60–0.88]), (233,239). A similar risk reduction was observed in secondary outcomes, involving the total number of HF hospitalizations and CV deaths; 23% among those with diabetes type 2 at baseline vs. 25% among those without diabetes.(HR 0.77; 95% CI [0.63–0.94 and HR 0.73; 95% CI [0.59–0.91]) compared with placebo.(252)

The subgroup analysis of EMPEROR-Reduced suggests the same result as shown in the graph below:

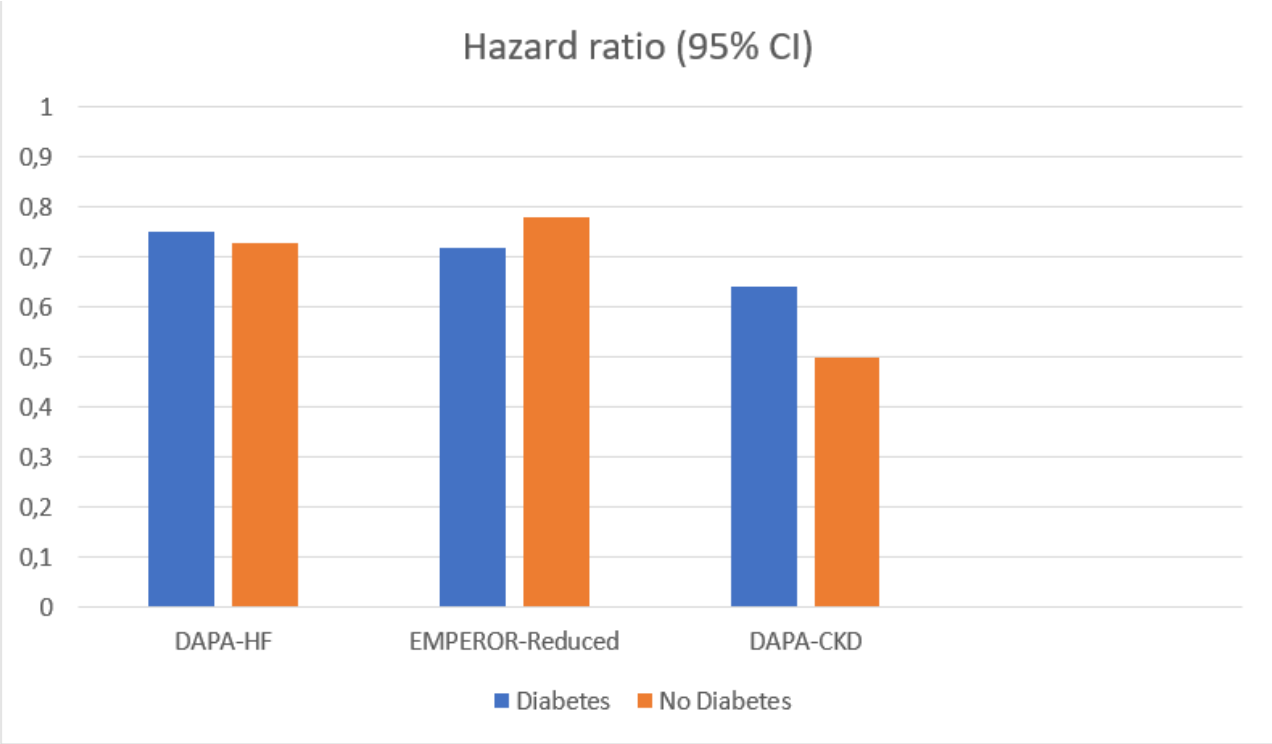


Figure 13: SGLT2i and CV deaths among patients with HF without diabetes (282); Image modified from (282)

A status subanalysis of DAPA-HF was performed to understand better the link between health benefits of SGLT2 Inhibitors and diabetes. (266) All the patients were divided based on their diabetes status, and their glycated hemoglobin level was measured ina laboratory at enrollment visit, then again at visit 2, after 14 to 21 days. (266) The patients had diabetes if they had a positive diabetes history and if their glycated hemoglobin level was at least 6.5% (equal or more than 48 mmol/mol) at visits oneand two.(266) Patients with glucose levels less than 5.7% (39 mmol/mL) were considered normal glycated hemoglobin.(266,281)

4. DISCUSSION

An estimated 1-2%of the general adult population worldwide have heart failure (1), resulting in reduced quality of life, increased risk of mortality, and high financial costs. (1) Despite many cardiovascular benefits, the previous standard HF therapy included renin-angiotensin-aldosterone system inhibitors, angiotensin receptor blockers or neprilysin inhibitors, and beta-blockade (283,284), patients still had an increased risk for multiple morbidities and mortality. (284) Among the most common comorbidities is diabetes type two, causing end-organ damage and increasing the risk of HF-related complications, including the heart. (285,286,287). SGLT2 inhibitors represent a novel drug class, which have been developed in the first line as glucose-lowering medications for patients with diabetes type two, but in recent years proved to reduce hospitalization and other unwanted events due to heart failure, and to have a cardioprotective benefit, even among the patients without diabetes. (285)

This literature review aimed to summarize clinical evidence and theoretical knowledge on heart failure, diabetes type 2, and SGLT2 inhibitors to explore further and strengthen their position in heart failure guidelines among patients without diabetes.

Mechanism of action of SGLT2 inhibitors are multifunctional. They include glucose lowering, reduce fibrosis and inflammation, volume regulation, nephron hemodynamics or the influence of Na+/H+ exchangers. (142) This class of medication showed multifactorial benefits on cardiovascular and renal outcomes, mainly through mechanisms on the renal system, primarily nephron.(288,289,290)

Numerous clinical studies have confirmed the hypothesis that SGLT2i are safe and beneficial for people with heart failure, both, with and without diabetes.

Two major trials, DAPA-HF and EMPEROR-Reduced, showed a positive effect of SGLT2i on HFrEF by significantly lowering the risk of cardiovascular deaths and heart failure events.(291) Emperor-Preserved demonstrated the same effect on patients with HFpEF and extended further the usage of these medications. (291)

Uncomplicated urinary infections, genital fungal infections, hypoglycemia and more rarely diabetic ketoacidosis or Fournier gangrene are known adverse events, that need to be considered when using this drug. (266)

The clinical evidence arising from these trials threw a completely new light on the approach of HF management, which will continue to impact future medical practice.(292) Since the results came out, a new standard of therapy in HFrEF was introduced and currently consists of four building blocks: Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, Angiotensin receptor-neprilysin inhibitors/ARNIs, Aldosterone receptor antagonists, and SGLT2 inhibitors.(292)

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