The risk of sudden cardiac death and use of SGLT2 inhibitors in patients with heart failure and effect on major outcomes with respect to etiology of cardiomyopathy : a meta analysis of pivotal randomi ...

Berntsen, Julia Kitty

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Julia Kitty Berntsen

THE RISK OF SUDDEN CARDIAC DEATH AND USE OF SGLT2 INHIBITORS IN PATIENTS WITH HEART FAILURE AND EFFECT ON MAJOR OUTCOMES WITH RESPECT TO ETIOLOGY OF CARDIOMYOPATHY: A META ANALYSIS OF PIVOTAL RANDOMIZED CONTROLLED TRIALS

Diploma thesis

Academic year:
2022/2023

Mentor:
Josip A. Borovac, MD, PhD

Split, July 2023

TABLE OF CONTENTS

First and foremost I want to thank my mentor Josip A. Borovac MD, PhD, for his support and help during the writing of this diploma thesis. Thank you for being available and understanding during this whole process.

A huge thanks goes to my dear family for constant support and for always believing in me.

I want to thank all my friends for being there for me.

LIST OF ABBREVIATIONS

ACC/ AHA – The American College of Cardiology and American Heart Association

ACEi – Angiotensin-converting enzyme inhibitors

AdHF – Acute decompensated heart failure

AHF – Acute heart failure

ANP – Atrial natriuretic peptide

ARBs – Angiotensin receptor blockers

ARNIs – Angiotensin receptor-neprilysin inhibitors

BNP – Brain natriuretic peptide

BP – Blood pressure

CAD – Coronary artery disease

DCMi – Chronic inflammatory dilated cardiomyopathy

CHF – Chronic heart failure

CKD – Chronic kidney disease

COPD – Chronic obstructive pulmonary disease

CVD – Cardiovascular disease

CRT – Cardiac resynchronization therapy

CRT-D - cardiac resynchronization therapy with defibrillator

CRT-P - Cardiac resynchronization therapy pacemaker

DCM – Dilated cardiomyopathy

DM – Diabetes mellitus

ECG – Electrocardiogram

EDV – End diastolic volume

EVP – End diastolic pressure

GDMT – Guideline-directed medical therapy

GI – Gastrointestinal

GWW – Global wasted work

HCM – Hypertrophic cardiomyopathy

HF – Heart failure

HFA/ ESC – Heart Failure Association of ESC

HFmrEF – Heart failure with mildly reduced ejection fraction

HFpEF – Heart failure with preserved ejection fraction

HFrEF – Heart failure with reduced ejection fraction

HHD – Hypertensive heart disease

HR – Heart rate

hoHF – High output heart failure

HTN – Hypertension

HRQoL – Health-related quality of life

ICD – Implantable cardioverter defibrillator

ICM – Ischemic cardiomyopathy

IHD – Ischemic heart disease

IHF – Ischemic heart failure

IL-1 β – Interleukin 1-Beta

IL-18 – Interleukin-18

JHFS – The Japanese Heart Failure Society

JVP – Jugular venous pressure

KCCQ – Kansas City Cardiomyopathy Questionnaire

loHF – Low output heart failure

LVEF – Left ventricular ejection fraction

MI - Myocardial infarction

MRAs – Mineralocorticoid receptor antagonist

MRI – Cardio magnetic resonance imaging

NICM – Non-ischemic cardiomyopathy

NO – Nitric oxide

NT-proBNP – N-terminal pro-brain natriuretic peptide

NLRP3 – Nucleotide-binding domain, leucine-rich-containing family, pyrin domain – containing-3

NYHA – New York Heart Association

OMT – Optimal medical therapy

QOL – Quality of life

QRS - Q, R, and S waves of an ECG

RAAS – Renin-angiotensin- aldosterone system

RCM – Restrictive cardiomyopathy

RCT – Randomized controlled trial

RV = Right ventricle

RHD – Rheumatic heart disease

SCD – Sudden cardiac death

SGLT2i – Sodium-glucose cotransporter 2 inhibitor

SNS – Sympathetic nervous system

SV – Stroke volume

SVR – Systemic vascular resistance

TRP – Total peripheral resistance

VF – Ventricular fibrillation

VHD – Valvular heart disease

VT – Ventricular tachycardia

1. INTRODUCTION

1.1. History and definitions of heart failure

Ancient civilizations such as the Egyptian, Greek, Indian, and Chinese had descriptions of symptoms related to heart failure (HF), but they did not have a complete understanding of the underlying pathophysiology of the condition (1). Hippocrates, a Greek physician from the 4th century B.C., described symptoms of HF such as dyspnea, peripheral edema, and crepitations over the lung fields (2). It wasn't until the 19th and 20th centuries that medical knowledge advanced enough to begin to diagnose and treat HF on a rational foundation. In the early 20th century, physicians began to use the term "heart failure" to describe a clinical syndrome characterized by symptoms such as dyspnea and edema, along with physical signs such as jugular venous distension and pulmonary rales (3). Today, a better understanding of the pathophysiology of HF has led to the development of additional treatment options such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs), as well as the use of implantable cardiac devices such as pacemakers and implantable cardioverter defibrillator (ICD) (3).

Heart failure (HF) is a complex clinical syndrome with different etiologies, cardiometabolic and hemodynamic disturbances as opposed to a specific disease (3,4). Definitions of HF differ significantly across medical literature, contemporary guidelines, and medical practice. These range from “textbook” definitions of HF which are primarily focused on the pathophysiology to case definitions such as the Framingham criteria which are more commonly used in research. The classic textbook definition of HF is often described as a “*condition in which the heart cannot pump enough blood to meet the body’s needs”,* or an *“abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate that is equivalent with the requirements of the metabolizing tissues”* (4). However, these definitions are complex, impractical, and not verified in practice and only pertain to a specific group of HF patients. In clinical practice, other diagnostic measures such as the assessment of plasma natriuretic peptides are essential for accurately diagnosing HF. Despite the differences in definitions, the current practice guidelines from ACC/AHA, HFA/ESC, and JHFS recognize HF as a clinical syndrome with cardinal symptoms like dyspnea, edema, fatigue, activity intolerance, and exercise limitation including some form of structural and/or functional heart disease (4). Some guidelines also detail a reduced cardiac output and, or increased intracardiac pressures at rest or during stress. Essentially, HF definitions include evidence of structural heart disease, typical HF symptoms, and observable/objective clinical signs (4). Some of the more common disease etiological pathways resulting in HF include ischemia-related myocardial dysfunction, adverse ventricular remodeling, and increased hemodynamic overload (in terms of volume and intracardiac pressure) (5).

Heart failure (HF) defined accordingly to the time of onset can be categorized as acute and chronic (6). Acute heart failure typically presents as rapid onset of new or worsening signs and symptoms of

HF, usually with pulmonary edema or with fluid retention requiring urgent intervention (7). However, the symptoms of chronic heart failure (HF) usually happen gradually and tend to be linked to several comorbidities (7). Most chronic HF patients have undergone medical treatment and typically present with a few symptoms at rest (6). If chronic HF leads to a worsening clinical picture, either suddenly or slowly the episode can be described as "*decompensated*" chronic HF or worsening HF (7).

Heart failure (HF) can be further functionally classified with respect to the degree of cardiac output (CO) into high and low-output heart failure (4). High output (HoHF) is described as the heart's inability to sufficiently supply blood and oxygen for the body's demand (4). This type of cardiac dysfunction can be indicated by high CO, echocardiographic evidence of right ventricular dilation or dysfunction, and increased circulating levels of natriuretic peptides (6). These patients can have signs of decreased systemic vascular resistance and can be accompanied by pulmonary congestion (4). HoHF tends to arise as a response to extracardiac causes including arteriovenous shunts, thiamine deficiency, anemia, thyroid or liver disease (4,8). Low output heart failure (LoHF), is a clinical condition characterized by reduced CO and insufficient blood flow to the body's organs marked by significant end-organ hypoperfusion (9). LoHF is not the commonest form of HF and is more frequent in post-surgery HF patients (9). This clinical condition signals an advanced stage of HF with significant morbidity and mortality outcome (9). LoHF usually has a multifactorial and a complex etiology and may be the result of right ventricle (RV) or systemic ventricle (single ventricle anatomy) dysfunction and can include systolic and/or diastolic dysfunction (9).

1.2. Clinical classification of heart failure

Numerous classification systems aim to categorize heart failure (HF) into specific groups (6). These include the New York Heart Association (NYHA) functional class, ejection fraction categories, and classifications based on the etiology of HF. These classifications are important as they significantly affect prognosis predictions (6). Moreover, they are useful in clinical trials as entry criteria influencing product labeling and guideline recommendations. Essentially, these classifications aid in determining the appropriate treatment approach for individual patients.

Heart failure (HF) has traditionally been classified into different subtypes and is defined according to HF phenotype based on left ventricular ejection fraction (LVEF) and signs of HF, which is represented in **figure 1** (10). The 2013 ACC/AHA guidelines utilize the term "*HFpEF borderline*" for patients with heart failure (EF) between 41% and 49% (10). They use "*HFpEF improved*" for those whose EF is >40% classifying these patients under the HFpEF category (10). JHFS and HFA/ESC guidelines have implemented a third category of HF with mid-range EF, also known as HFmrEF or mildly reduced ejection fraction for patients with an LVEF between 41% and 49% (10). However, this category is not accepted by all guidelines (10).

Society Name	HF Classification According to LVEF	LVEF	Additional requirements
ACCF/AHA (2013)[3]	Heart failure with reduced ejection fraction (HF*r*EF)	≤40%	Symptoms and signs
	Heart failure with preserved ejection fraction (HF*p*EF)	≥50%	Symptoms and signs
	HF*p*EF, borderline	41%–49%	Symptoms and signs
	HF*p*EF, improved	>40%	Symptoms and signs
ESC (2016)[4]	Heart failure with reduced ejection fraction (HF*r*EF)	<40 %	Symptoms and signs
	Heart failure with mid-range ejection fraction (HFmrEF)	40-49%	Symptoms and signs, elevated levels of natriuretic peptides and ≥1 additional criterion of relevant structural heart disease (LVH or LAE) or diastolic dysfunction
	Heart failure with preserved ejection fraction (HF*p*EF)	≥50%	Symptoms and signs, elevated levels of natriuretic peptides and ≥1 additional criterion of relevant structural heart disease (LVH or LAE) or diastolic dysfunction
JCS/JHFS (2017)[5]	Heart failure with reduced ejection fraction (HF*r*EF)	<40%	
	Heart failure with mid-range ejection fraction (HFmrEF)	40% to <50%	
	Heart failure with preserved ejection fraction (HF*p*EF)	≥50%	
	Heart failure with preserved ejection fraction, improved (HF*p*EF improved) or heart failure with recovered EF (HFrecEF)	≥40%	

Figure 1. Current heart failure classifications according to left ventricular ejection fraction in Contemporary Clinical Practice Guidelines.

Figure unmodified from work by Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure. J Card Fail. 2021;4:387–413 (10).

Abbreviations: LVH = left ventricular hypertrophy; LAE = left atrial enlargement; ACC/AHA= American College of Cardiology Foundation/American Heart Association; ESC= European Society of Cardiology; HF= heart failure; JCS= Japanese Cardiology Society; JHFS= Japanese Heart Failure Society.

The latest European Society of Cardiology (ESC) guidelines from 2021 continue to emphasize the importance of the left ventricular ejection fraction (LVEF). This classification is presented in **table 1.** Heart failure with reduced ejection fraction (HFrEF) is now defined as LVEF up to 40%, as opposed to the previous threshold of LVEF of less than 40%. The term "*Heart Failure with mid-range Ejection Fraction"* has now been changed to *"mildly reduced"* designated by an LVEF between 41% and 49% (11). Those presenting with symptoms and signs of heart failure (HF), along with structural and/or functional changes and/or elevated natriuretic peptides and maintain an LVEF of 50% or above, are classified as having heart failure with preserved ejection fraction (HFpEF) (6).

Table 1. Definition of HFrEF, HFmrEF and HFpEF according to the 2021 European Society of Cardiology guidelines.

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

Table unmodified from work by McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726 (6).

Abbreviations: HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejec-tion fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

The American College of Cardiology and the American Heart Association stages (ACC/AHA) are provided in **table 2.** refer to a classification system categorizing the progression of heart failure (HF) (12). The goal of therapeutic interventions varies depending on the stage of HF. In stage A, interventions aim to treat risk factors and structural heart disease that may lead to HF in the future. In stage B, the focus is to reduce symptoms. Additionally, stage C and D, aims to reduce symptoms, morbidity and mortality associated with HF (12).

Table 2. Stages of heart failure according to American College of Cardiology and American Heart Association.

Stages	Definition and Criteria
Stage A **At risk for HF**	At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury (patients with HTN, atherosclerotic CVD, diabetes, metabolic syndrome, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy).
Stage B **Pre-HF**	Patients with evidence of increased filling pressure or risk factors such as increased natriuretic peptide levels or persistent elevated cardiac troponin in the absence of competing diagnosis, resulting in biomarker elevation (coronary syndrome, pulmonary embolus, or myopericarditis).
Stage C **Symptomatic HF**	Established structural heart disease with current or previous symptoms of HF.
Stage D **Advanced HF**	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite optimized GDMT.

Table modified from work by Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:895-1032 (12).

Abbreviations: HF = heart failure; HTN = hypertension; GDMT= guideline-directed therapy; CVD= cardiovascular disease.

The New York Heart Association (NYHA) functional classification system is the simplest terminology used to assess the functional status and symptom severity in heart failure (HF) patients (6). It is a subjective measurement made by a clinician and can change over time as the condition progresses. NYHA functional classification serves as an independent predictor of mortality in HF patients (12). The classification is based on a scale of I to IV, with each class representing a different level of functional impairment, demonstrated in **table 3**. Unlike ACC/AHA classification, it is possible to go back to a lower degree of NYHA classification if the patient's symptoms improve, since this classification depends on symptoms alone (6). For instance, a patient in NYHA class III can enter NYHA class II upon functional improvement, however a patient from stage C HF per ACC/AHA classification cannot move back to stage B HF.

Table 3. New York Heart Association functional classification based on the severity of symptoms and physical activity.

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

Table unmodified from work by McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726 (6).

Despite the availability of evidence-based therapies, some patients with heart failure (HF) will progress to advanced stages of the disease. The updated HFA-ESC definition of advanced HF include the following (13):

- New York Heart Association (NYHA) class III or IV with persistent and severe HF symptoms
- Left ventricular ejection fraction (LVEF) <30% with significant cardiac dysfunction, isolated right ventricle (RV) failure, severe inoperable heart valve or congenital defects, persistently high or increasingly high cardiac biomarkers (BNP, NT-proBNP) accompanying severe diastolic dysfunction.
- Incidents of pulmonary or systemic congestion or episodes of low output state requiring medications, or dangerous arrythmias leading to more than one unplanned hospitalization or visit during a period of 12 months.
- Significant decrease in exercise tolerance attributed to heart problems, low 6-minute walk test distance (<300m), or low peak oxygen uptake (<12-14mL/kg/min).

The distinction between advanced heart failure (HF) and end-stage HF is often based on the response to available therapies, which may include medications and mechanical support devices such as ventricular assistance devices or heart transplantation (8).

1.3. Prognosis in heart failure

Heart failure (HF) is a chronic and progressive disease with a poor prognosis that can lead to hospitalizations, reduced quality of life and increased mortality even with the best available therapy (6). The increasing prevalence, long-term management and end-of-life care (palliative care) for patients with HF greatly depend on primary care as a central pillar in their healthcare journey. When discussing prognosis it is important to differentiate between chronic heart failure (HF) and acute heart failure since evidence-based studies usually recruit from either stable "chronic" or those admitted with an "acute" episode of chronic HF (14). Several cohort studies conducted worldwide have investigated the prognosis of patients with chronic HF, who are either managed in the community or outpatient setting. These studies have reported a survival rate of approximately 80-90% over a period of one year, compared to 97% in the general population (14). The survival rate for chronic HF patients at 5 years is similar, with the survival of approximately 50-60% in contrast to the 85% survival rate in the general population (14). While a high number of patients can experience symptom stability in extended periods, the disease could also progress and rapidly lead to death.

A highly influential factor linked to unfavorable outcomes in heart failure (HF) patients is advancing age (14). Several other factors linked to a poor prognosis in HF patients include elevated levels of natriuretic peptides and N-terminal pro-brain natriuretic peptide (NT-proBNP), hyponatremia, anemia, acute kidney injury, chronic kidney disease, prior stroke, smoking, male sex, previous myocardial infarction, peripheral vascular disease and high or low body mass index (14). Based on the AHEAD registry by Parencia et al. the five factors on admission exhibiting the greatest hazard ratios for one-year mortality included: NYHA score of III-IV, brain natriuretic peptide (BNP) levels over 2000 pg/ml or NT-proBNP levels under 10,000 pg/ml, the use of diuretics, creatinine exceeding 145 uumol/l or a creatinine clearance rate less than 40 ml/min and age above 70 years (15, 16).

The underlying cause of heart failure (HF) with reduced ejection fraction (HFrEF) is linked to coronary heart disease in the majority of patients (16). It is important to differentiate between ischemic and nonischemic causes of HF as prognosis varies (16). Ischemic causes of HFrEF patients typically have a poorer prognosis compared to nonischemic patients diagnosed with HFrEF (16). Patients with ischemic cardiomyopathy (ICM) usually have more comorbidities like coronary artery disease and diabetes, where idiopathic HF and hypertension are the most common causes of nonischemic cardiomyopathy (NICM) (8). These patients can benefit from medications such as

angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRIs) and SGLT1 inhibitors. However, these medications, with the exception of SGLT2i do not appear to improve survival rates in heart failure with preserved ejection fraction (HFpEF) (18).

Several factors have been proposed as potential causes for heart failure with preserved ejection fraction (HFpEF) including hypertension (HTN) and diabetes mellitus (DM) (19). HTN and HFrEF may contribute to diastolic dysfunction, ventricular stiffening, and chronotropic incompetence (19). HFpEF is a common condition, especially observed in the elderly and among women (20). With regard to sex distribution, women are two times more likely than men to develop HFpEF (21). As the prevalence of HTN, obesity, atrial fibrillation and diabetes continues to rise, coupled with the growing population of older adults, the incidence of HFpEF is expected to increase in the future (20). The prognosis and symptom burden of HFrEF appears to be worse compared to HFpEF, although there are varying outcomes reported in different studies. In addition to suboptimal use of proven treatments for HFpEF, patients with HF often have multiple comorbidities that affect their prognosis. Addressing these comorbidities should also be a focus in the management.

OPTIMIZE-HF trial led by Fonarow et al. showed that mortality during hospital admission was lower in patients diagnosed with heart failure with preserved ejection fraction (HFpEF) compared to heart failure with reduced ejection fraction (HFrEF) patients (22). However, there was no significant difference in long-term mortality between these two conditions (15, 22). The AHEAD registries encompassed patients hospitalized due to acute heart disease (AHF) (15). Their conclusion highlighted that patients with HFpEF had a higher survival rate at 1 and 3 years compared to those with HFrEF (15).

HFpEF patients have a better prognosis, but these patients may have limited access to specialized services and have comorbidities that require significant primary care management (14). TIME-CHF trial led by Rickenbacher et al. along with the CHART-2 studies by Tsuji et al. demonstrated that HFmrEF is more similar to HFrEF rather than HFpEF in terms of disease burden and the benefits from NT-proBNP guided treatment (23, 24). A single-center propensity score-matched analysis conducted by Borovac et al. showed that HFmrEF phenotype was linked to poorer overall survival rate in a timespan of one year after hospital discharge compared to those with HFpEF (25). HFmrEF phenotype exhibit significantly improved outcomes in terms of mortality and heart failure (HF) related hospital admissions when compared to HFrEF (23–25). Consequently, this could imply that HFmrEF is a milder form of systolic dysfunction (25).

Acute heart failure (AHF) is associated with a bad prognostic factor and frequent hospital visits (26). A multicenter study by Harjola et al. investigated the mortality of hospitalized AHF patients at 3 months and 1 year (26). The results showed that the mortality rate after discharge was lower in

patients who experienced first incidence of AHF, in comparison to those with acutely exacerbated chronic heart failure (HF) (26). One-year mortality rate was highest in patients with cardiogenic shock, while patients with hypertensive HF recorded the lowest one-year mortality rate. Factors such as older age, history of myocardial infarction (MI), elevated creatinine levels, and lower plasma sodium levels were independently linked to mortality throughout the entire follow-up period. Conditions like diabetes, anemia, and chronic (HF) were linked with worse long-term survival, in contrast to patients with a history of cerebrovascular disease (CVD) who were associated with a worse short-term outcome (26).

Patients with heart failure (HF) are at an increased risk of cardiac events, cardiac death, and sudden cardiac death (SCD) compared to those without HF (27). Cardiac causes of death other than HF include arrhythmias and myocardial infarction (MI). Non-cardiovascular cases of death include respiratory disease and cancer, the latter being the most common causes of non-cardiovascular death in patients with chronic (HF) (28, 29). People of older age diagnosed with HF, especially in heart failure with preserved ejection fraction (HFpEF) often die due to a non-cardiovascular disease (27). In other words, while HF poses a significant risk for cardiovascular mortality, it is important to recognize that patients may still die from other conditions as well (30).

Progress in both pharmaceutical and device-based therapies has been liked to improved prognoses and enhanced survival rates in heart failure (HF) (28). Age-standardized rates due to HF have been shown to drop by 40% in seven European nations from 1987 to 2008 (28). A comprehensive study of all patients in Scotland hospitalized with a first incidence of HF between 1986 and 2003 showed a relative decline in short to medium-term mortality rates, between 40- 50% in men and between 20-25% in females (28). These improvements in mortality among HF patients coincided with significant increases in the usage of angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers during this period. However, in recent times, there has been little to no progress with only slight enhancements in terms of survival rates (14). Despite advancements in healthcare, individuals diagnosed with HF still have lower survival rates compared to individuals with various types of cancers, making HF even worse than some of the common cancers in both men and women (28). With the aging population and the increasing prevalence of cardiovascular disease (CVD), the number of people with HF is expected to rise in the coming years (3).

1.4. Epidemiology

From an epidemiological perspective, heart failure (HF) imposes a significant burden on individuals and society (21). The epidemiology of HF has been a subject of interest ever since it was identified as a new epidemic in 1997 (21). The global financial strain of HF is substantial. Back in 2012, HF management accounted for an estimated $30.7 billion of healthcare expenses in the United States, predicted to reach approximately $69.8 billion by 2030 (31). This would lead to a total cost of $244 per American adult in 2030 (31). According to new numbers from European Heart Journal (ESC), HF affects more than 64 million people worldwide (31). The condition has a high overall prevalence of 1-3% in the general adult population with increasing prevalence in the older population (31). This includes 10% of males and 8% of females (5). The incidence of HF is 1-20 cases per 1,000 person-years or per 10,000 population (31). This suggests that the wave of HF first noticed as an epidemic in 1997, is still not under control (21). The increasing prevalence of advanced HF is due to the aging of the population, better treatment options, and the growing number and survival of HF patients (6).

The ESC-HF-LT study by Chioncel and colleagues showed that 60% of heart failure (HF) patients were classified as heart failure with reduced ejection fraction (HFrEF), 24% as heart failure with mildly reduced ejection fraction (HFmrEF), and 16% as heart failure with preserved ejection fraction (HFpEF) (19). This suggests that HFrEF is the most prevalent phenotype of HF (19). However, data are limited due to data sources frequently lacking information regarding patient's ejection fraction (EF) status (31). G-CHF Investigators, a multinational HF registry examined the differences in HF etiology, treatment, and outcomes between countries of different levels of economic development (32). This study showed that combined guideline-directed medications (GDM) for HFrEF patients, were most frequently prescribed in high-income countries (32). Conversely, low to middle-income countries reported a twofold increase in mortality compared to high-income countries (32). Additionally, in low-income countries, deaths were reported more frequently than hospitalizations (32). Moreover, the short-term mortality risk associated with hospitalization in these countries were 3 to 5 times higher than in high-income countries (32). The age-standardized prevalence shows considerable variation across different countries and regions. In 2017, Central Europe, North Africa, and the Middle East recorded the highest prevalence of HF, with rates between 1133 to 1196 per 100,000 individuals (31). On the other hand, Eastern Europe and Southeast Asia reported lower numbers, within the range of 498 to 595 per 100,000 people (31).

Ischemic heart disease (IHD) is the most common risk factor for developing heart failure (HF) (3). The population-attributable risk linked to IHD is 65% for men and 48% for women (31). In 2017 IHD was globally responsible for 26.5% of the age-standardized prevalence rate of HF, with a higher likelihood of affecting individuals with higher income (31). Studies have shown that IHD is the

leading cause of HF in the developed world, including the United States and Western Europe (31). This is largely due to the increased prevalence of risk factors such as smoking, physical inactivity, and unhealthy diets, which contribute to the development of atherosclerosis and CAD (31,33). However, valvular heart disease (VHD) and arrhythmias are also frequent causes. Rheumatic heart disease (RHD) and infectious diseases may be more prevalent in certain regions, particularly in developing countries (31). However, the global burden of RHD has decreased over a period of 25 years, likely due to better living conditions and the increased use of antibiotics (31).

1.5.Common heart failure etiologies

Heart failure (HF) is a complex syndrome with multiple potential causes, leading to a common set of symptoms. (32). The commonest etiologies of HF are listed in **table 4**. The causes of HF can differ depending on geographic location and it is not unusual for more than one specific cause to contribute to the onset of this clinical condition (31). When discussing HF, it is importance to mention that there is a variability in HF patients receiving medical therapy across different parts of the world. This can influence the prognosis of HF since it is well established that evidence-based pharmacotherapy will improve the symptoms of HF (32).

Cardiomyopathy is a term used to describe a group of heart diseases that affect the structure and function of the heart muscle. Ischemic cardiomyopathy (ICM) is a major risk factor to develop heart failure (HF) and remains the commonest cause of HF in Western World (31). ICM is caused by a reduced blood supply to the myocardium caused by blockage of one or more coronary arteries (34). This can lead to damage to the heart muscle and reduced function of the heart. The primary cause of ischemic heart disease (IHF) is arteriosclerosis, a process in which cholesterol and other substrates build up in the inner lining of arteries (34). This can lead to the formation of plaques that can obstruct the blood flow. According to data from G-CHF Investigators, coronary artery disease can manifest itself through various means, such as acute myocardial infarction (MI), chronic ischemia, arrhythmia, and asymptomatic, occult disease (32). Other causes of IHF include coronary artery spasms, embolic events, and arteritis.

Non-ischemic cardiomyopathy (NICM) is less common and refers to heart muscle damage and dysfunction, with no clinical or electrocardiographic evidence of coronary artery disease (CAD) (35). Some classical nonischemic causes that represent prevalent cardiovascular conditions that can induce heart failure (HF) include hypertension (HTN), valvular heart disease (VHD) and arrhythmias (17). The three main types of NICM are hypertrophic, dilated and restricted (34). Hypertrophic cardiomyopathy (HCM) is characterized by thickening of the heart muscle which ultimately can make it harder for the heart to pump blood effectively. In 50% of HCM cases, mutations have been identified in the genes encoding sarcomere proteins leading to idiopathic LV hypertrophy (36). HCM

often follows an autosomal inheritance and is considered the most frequent cause of sudden death in young adults, especially athletes (36). Dilated cardiomyopathy (DCM) is a condition affecting the heart muscle, characterized by the enlargement and dilation of one or both ventricles accompanied by impaired contractility which is defined as a left ventricular ejection fraction (LVEF) below 40% (37). Patients with DCM typically have systolic dysfunction and may or may not display obvious symptoms of heart failure (HF) (37). DCM can be classified as either primary or secondary. Primary DCM is categorized as idiopathic and the diagnosis can only be confirmed after excluding secondary causes (37). Secondary causes encompass conditions like infectious myocarditis (e.g., viral, Chagas disease, Lyme disease), ischemic disease, HTN, drug-induced cardiomyopathy (e.g., anthracyclines), or infiltrative diseases (37). Restrictive cardiomyopathy (RCM) is characterized by a stiffening of the heart muscle, which can make it difficult for the heart to relax and fill blood properly (38). This type of cardiomyopathy is also the least common type of the aforementioned cardiomyopathies (38).

Hypertensive heart disease (HHD) is the most common cause of HF in developing countries (31). HHD is a constellation of abnormalities including an enlarged left ventricle (LVH), systolic and diastolic dysfunction and associated clinical symptoms such as arrhythmias and heart failure (HF). In response to elevated blood pressure, the left ventricular wall thickens as a compensatory response to reduce wall stress (40). Isolated systolic hypertension accounts for over 90% of all patients with hypertension (3).

Heart failure (HF) can be caused by or result from valve dysfunction, with most cases attributable to acquired valvular diseases (17). Valvular disease refers to any dysfunction or disease of the heart valves - mitral, aortic, tricuspid and pulmonary valves accordingly (17). Valvular disease can be classified as stenosis and regurgitation. Stenosis is characterized as a narrowing of the valve opening leading to inhibition of blood flow, in comparison to regurgitation which results in an abnormal backflow of blood (17). Rheumatic valvular disease (RVD) is the most common cause of HF in developing countries (17). Alterations in heart rate such as tachycardias, bradycardias, and arrhythmias are common in patients with HF (13). Atrial fibrillation (AF) is both a cause and consequence of HF and associated with a three-fold increased risk of developing HF (41). AF is characterized by rapid and irregular heartbeats, and can cause impaired systolic and diastolic function not present in sinus rhythm (41). Myocarditis is a rare but important cause of HF and is characterized by the inflammation of the heart muscle. Myocarditis can be caused by viral infections, bacteria, protozoa, fungi, autoimmune diseases, and exposure to certain medications or toxins (42). It is worth noting that up to 20% of individuals with myocarditis may subsequently develop a chronic inflammatory dilated cardiomyopathy (42).

Table 4. Causes of heart failure and the common modes of presentation.

Cause	Examples of presentation
CHD	Myocardial infection, chronic ischemia, arrhythmias
HTN	HF with preserved systolic function. Malignant HTN/acute pulmonary edema
Valvular disease	Primary valve disease e.g., aortic stenosis Secondary valve disease e.g., functional regurgitation. Congenital valve disease
Arrhythmias	Atrial tachyarrhythmias, ventricular arrhythmias
Cardiomyopathy	Dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy. Peripartum. Toxins: alcohol, cocaine, iron, copper
Infective	Viral myocarditis, Chagas disease, HIV, Lyme disease
Iatrogenic	Anthracyclines, Abstruzimab
Infiltrative	Amyloid, Sarcoidosis, Neoplastic
Storage disorders	Haemochromatosis, Fabry disease, Glycogen storage disorders
Endomyocardial disease	Radiotherapy, Endomyocardial fibrosis/eosinophilia, Carcinoid
Pericardial disease	Calcification, Infiltrative
Metabolic	Endocrine disease, Nutritional disease (thiamine and selenium deficiency), Autoimmune disease
Neuromuscular disease	Friedreich's ataxia, Muscular dystrophy
High-output	Anemia, thyrotoxicosis, A-V fistulae, Paget's disease.

Table modified from work by McDonagh TA, Gardner RS, Clark AL, Dargie H, editors. Oxford Textbook of Heart Failure. 1st ed. Oxford University Press; 2011. p. 30. & from work by McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726.

Abbreviations: MI = myocardial ischemia; HTN = hypertension; PE = pulmonary edema; HIV = human immunodeficiency virus; CHD = coronary heart disease

1.6.Pathophysiology of heart failure

Heart failure (HF) is a complex condition with a multifactorial pathophysiology that is subject of intense research (3). It is characterized by a series of events or underlying conditions that lead to a decrease in the heart's ability to pump blood effectively (43). The development and progression of cardiac dysfunction leading to HF primarily originate from factors such as neurohormonal activation, increased hemodynamic overload and ventricular remodeling (3). Additionally, evidence indicates that the activation of immune regulatory and inflammatory responses is major contributor to the underlying pathogenesis of HF (44). Stroke volume (SV) refers to the volume of blood being pumped out from the left ventricle (LV) during each systolic cardiac contraction and relies on preload, afterload, and the heart's ability to contract (45). Preload is defined as the stretching of the cardiac myocytes before contraction, afterload as the amount of pressure that the heart needs to exert to eject blood during ventricular contraction and contractility is the inotropic state of the heart (45). As myocardial contractility declines, there is a subsequent decrease in SV and a rise in end diastolic volume and end-diastolic pressure. In HF, the sympathetic nervous system (SNS) becomes dysregulated (46). This is evident through the functionality of baroreceptor and chemoreceptor reflexes. As well as an overflow of catecholamines in the nervous system and the bloodstream (46). This leads to a diminished parasympathetic response and increased sympathetic activity toward the heart, kidneys and skeletal muscles (46). When these effects which stimulate the cardiovascular system are chronically present, a vicious cycle of progressive heart failure is sustained. Such SNS dysregulation is associated with apoptosis of the cardiomyocyte, maladaptive vascular and ventricular remodeling, arrhythmias and poor prognosis in patients diagnosed with HF (46).

Several compensatory mechanisms occur as the failing heart attempts to maintain adequate function. Activation of the renin-angiotensin-aldosterone system leads to increased absorption of sodium and water by the kidneys (3). This results in increased blood volume and venous return, peripheral vasoconstriction as well as increased total peripheral resistance and preload (3). Angiotensin and aldosterone can cause harmful outcomes by stimulating the growth of fibrous tissue through collagen deposition, cardiac myocyte hypertrophy and can trigger cellular apoptosis and necrosis (17). The production of vasoactive substances ANP, BNP, and NO leads to a vasodilation which attempts to correct TRP and maintain afterload (17). The elevated production of norepinephrine and epinephrine from nerve endings and the adrenal gland increases the heart's ability to pump leading to enhanced contractility (46). In the early stages of HF, compensatory mechanisms such as Frank-Starling mechanism, myocardial hypertrophy, and hypercontractility help the heart adapt (47). However, with increased wall stress the myocardium undergoes eccentric remodeling which leads to a worsening of the already damaged heart (48). In other words, compensatory mechanisms are initially beneficial but can eventually lead to a vicious cycle of worsening HF

including systolic ventricular dysfunction and arrhythmias such as ventricular tachycardia and ventricular tachycardia, and ultimately leading to death (48, 49).

1.7.Clinical picture of heart failure

The clinical symptoms regardless of heart failure (HF) etiology remain almost uniform (6). Symptoms include difficulty breathing (breathlessness/dyspnea), leg and abdominal swelling, coughing and wheezing (6). Common signs and symptoms are presented in **table 5**. Patients may also experience nausea, lack of appetite and worsening dyspnea when laying down (5). Gastrointestinal (GI) congestion can cause upper quadrant pain, bloating and indigestion. Peripheral edema in the lower extremities is a common finding in volume-overloaded HF and hepatojugular reflux may also be observed in patients with right heart failure (50). The underlying cause of these symptoms is the hearts inability to handle and circulate blood efficiently. When this occurs in the left ventricle, blood will start to accumulate in the interstitium and/or alveoli and precipitate lung edema. As the disease progress, diaphoresis, sinus tachycardia at rest and peripheral vasoconstriction in the form of cool extremities may develop. Encephalopathy can happen in the end stage of the disease due to poorly regulated blood flow to the brain thus decreased cerebral perfusion (51).

Table 5. Typical signs and symptoms of heart failure.

Symptoms	Signs
Dyspnea	Elevated jugular venous pressure
Orthopnea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third and fourth heart sound
Fatigue	Displaced apex
Reduced exercise tolerance	

Table reproduced from work by McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726 (6).

1.8.Sudden cardiac death in heart failure

Sudden cardiac death (SCD) is a major cause of mortality in patients with heart failure (HF) compared to the general population, with up to 50% of death in HF patients being sudden and unexpected (52). In the past the definition of SCD was originally defined as death within one hour of the onset of new cardiac symptoms (29). The definition was developed to identify the event in general population without any previous or identified heart disease. Currently, SCD is only recognized if the patient was anticipated to survive for many months or years, and if death was unexpected (29). Common causes of SCD are shown in **figure 2** (53).

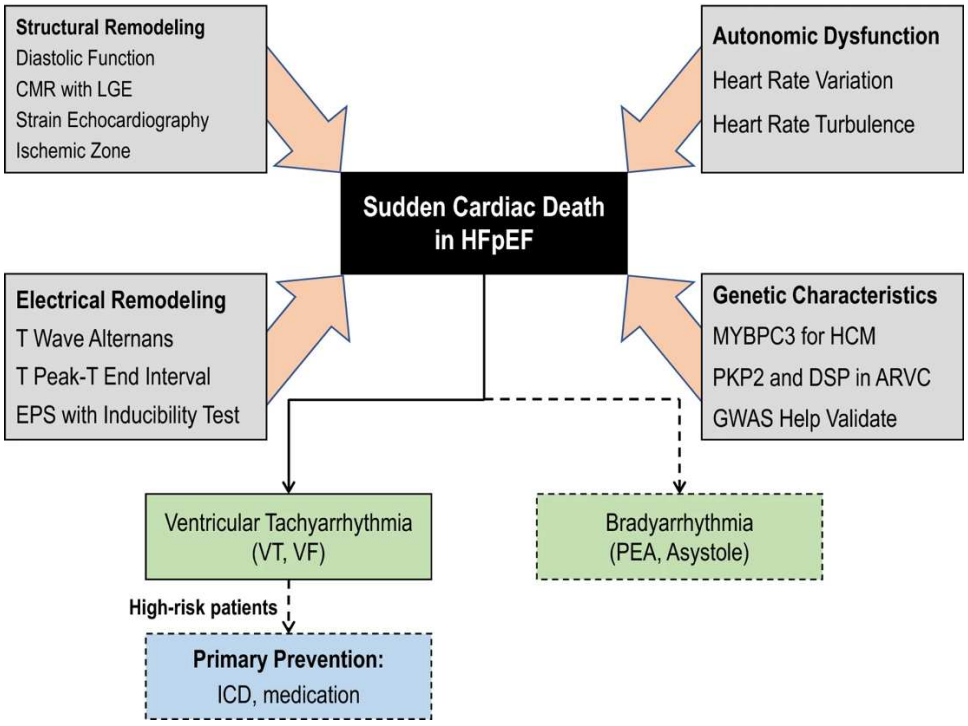

Figure 2. Common causes of sudden cardiac death in patients with HFpEF.

Figure obtained from work by Wu SJ, Hsieh YC. Sudden cardiac death in heart failure with preserved ejection fraction: an updated review. Int J Arrhythmia. 2022;1:7 (53).

Abbreviations: HFpEF= heart failure with preserved ejection fraction; CMR= cardiac magnetic resonance); LGE (late gadolinium enhancement; HCM= hypertrophic cardiomyopathy; ARVC= arrhythmogenic right ventricular cardiomyopathy; GWAS= genome-wide association studies; VT = ventricular tachycardia; VF= ventricular fibrillation; ICD= implantable cardioverter-defibrillator; PEA= pulseless electric activity

The slow but steady process of heart remodeling in heart failure (HF) which is characterized by a gradual loss of cardiomyocytes, stretching of ventricular chamber walls and ongoing cardiac fibrosis, may lead to sudden cardiac death (SCD) (29). SCD may have an identifiable trigger such as myocardial infarction, catecholamine surges or electrolyte imbalances, although in many cases there are no clear precipitating factor (6). This theory refers to a phenomenon where a slowly progressive process can end suddenly and unexpectedly in the absence of an acute precipitating event (29).

The majority of sudden cardiac death (SCD) events are predominantly due to undiagnosed cardiovascular disease (CVD). Congenital heart defects are more common causes of SCD in younger individuals, while coronary artery disease (CAD) is the leading cause in those over 35 years of age (54). CAD is responsible for 80% of SCD cases and it is the most prevalent cause with cardiomyopathies and genetic channelopathies being other significant contributors (54). SCD pathologies related to patient age are listed in **table 6**.

Heart failure (HF) is associated with changes in the electrical function of the heart which predispose patients to potentially lethal cardiac arrhythmias with the most frequent type being ventricular tachycardia (VT) and ventricular fibrillation (VF), which can be treated with implantable cardioverter defibrillator (ICD) (55). It is important to note that pulseless electrical activity and bradyarrhythmia may also result in sudden cardiac death (SCD) (54, 56). Acute coronary ischemia is typically the predominant cause of VF, while patients with structural heart disease and channelopathies are at an increased risk of VT. A myocardial scar from a post-infarction is the principal cause of sustained monomorphic VT in patients with structural heart disease and typically results in VF (54). Cardiac fibrosis is related to the initiation of the endogenous neurohormonal system leading to the activation of norepinephrine, angiotensin II, and neprilysin. Inhibition of these mechanisms reduces the development of heart remodeling and its harmful effects can be minimized (29). Persistent ventricular tachyarrhythmias unresponsive to ICDs may also indicate mechanical failure, highlighting the complex nature of SCD mechanisms (29).

Metabolic imbalance and oxidative stress, particularly during myocardial ischemia can participate sudden cardiac death (SCD). This dysfunction disrupts ionic balance in the cells of the heart causing heart rhythm disturbances. Preceding a myocardial infarction, the biggest risk of SCD include tachyarrhythmias, re-infarction, and myocardial rupture, though this risk diminishes over time (54). Non-ischemic cardiomyopathies that contribute to SCD include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and left ventricular non-compaction which is a rare condition caused by unusual heart muscle formation in the early stages of embryonic development (54).

Table 6. Sudden cardiac death pathologies related to patient's age.

Age	Primary pathology
From birth to 13 years	A congenital abnormality such as Teratology of Fallot
14 to 34 years	Hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, congenital coronary anomalies, genetic channelopathies, Wolf-Parkinson-White syndrome, and Marfan syndrome.
Over 35 years	Coronary artery disease

Table unmodified from work by Kumar A, Avishay DM, Jones CR, Shaikh JD, Kaur R, Aljadah M, et al. Sudden cardiac death: epidemiology, pathogenesis and management. Rev Cardiovasc Med. 2021;1:147-158 (54)

The use of an implantable cardioverter defibrillator (ICD), with or without biventricular pacing has demonstrated protection against sudden cardiac death (SCD) (57). In the OPTIMIZE-CHF study by Felker et al. it was established that prophylactic implantation of an ICD reduced the risk of SCD and all-cause-mortality in heart failure with reduced ejection fraction (58). As per ESC 2021 guidelines ICDs are recommended for patients with NYHA functional class II or III symptoms and a left ventricular ejection fraction of 35% or less, irrespective of the etiology of the condition (6). The DEFINITE trial by Kadish and colleagues showed fewer SCD instances in non-ischemic cardiomyopathy patients with an implanted ICD, however, the study did not demonstrate a significant difference in overall mortality (59).

An analysis including over 40,000 patients from 12 pivotal heart failure (HF) trials by Shen and colleagues demonstrated a 44% decrease in sudden cardiac death (SCD) rates from 1995 to 2015 (60). This can largely be attributed to advancements in heart failure (HF) treatments. **figure 3** show the trends in the rate of SCD across trial groups over time. Therapies such as beta-blockers, mineralocorticoid receptor antagonist (MRAs), sacubitril/valsartan, and cardiac resynchronization therapy (CRT) has shown to lower the risk of SCD (6). Recently three new medications have been introduced and shown to significantly improve survival rates, these drugs are ARNIs, also known as sacubitril/valsartan, SGLT2i, and vericiguat (57).

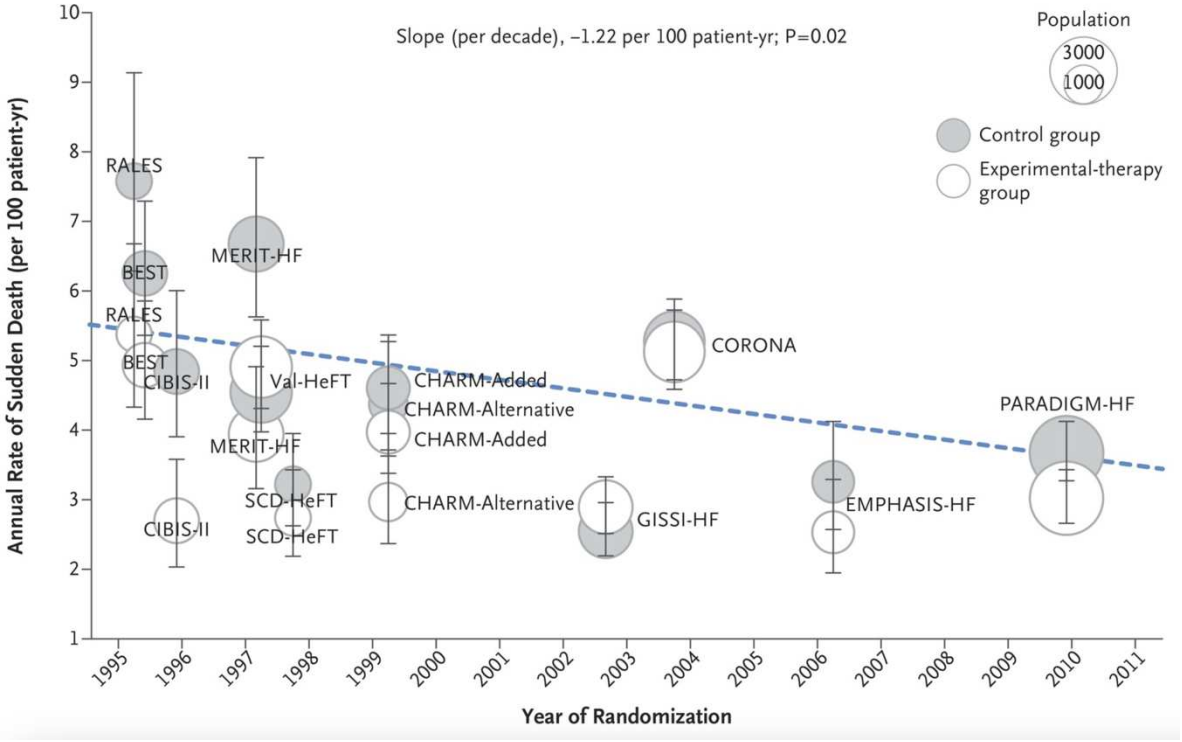

Figure 3. Changes in the rate of sudden cardiac death (SCD) across trial groups over time. The figure shows annual SCD rates per 100 patient years. Data are shown according to the start dates of each trial. Each circle stands for a trial group; control groups are shaded, while experimental-therapy groups are not.

Figure unmodified from work by Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, et al. Declining Risk of Sudden Death in Heart Failure. N Engl J Med. 2017 Jul 6;1:41–51 (60).

1.9.Diagnosis of heart failure

Diagnostic work-up of heart failure typically includes most of the following components:

- Comprehensive medical history assessment
- Blood tests (complete blood count, electrolytes, BUN, creatinine, hepatic enzymes, urinalysis).
- Genetic testing
- Physical examination
- Cardiac biomarkers
- Electrocardiogram (ECG)
- Chest x-ray
- Cardiac ultrasound (US)
- CT coronary angiography
- Cardiac magnetic resonance imaging (MRI)

The diagnostic algorithm according to ECS guidelines are shown in **figure 4**. The clinical history elicits the symptoms that are commonly presented in patients with heart failure (HF) and typically include dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and fatigue (6). Laboratory tests can provide valuable information such as electrolyte imbalances, kidney function, liver function and blood counts (12). Genetic testing is available to look for mutations in genes known to cause cardiomyopathy such as hypertrophic cardiomyopathy or amyloidosis. Common signs on physical examination may include elevated jugular venous pressure (JVP), pulmonary rales, peripheral edema, and an enlarged liver (3). JVP elevation is often indicative of elevated left-sided filling pressures. Studies have suggested that an elevated JVP has a sensitivity of about 70% and a specificity of 79% (3).

N-terminal pro–B-type natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are two cardioselective circulating biomarkers that are commonly used to diagnose and to assess the severity and prognosis of heart failure (HF) (3). These biomarkers are released from the cardiac myocytes in response to cardiac stretch. Elevated levels of these biomarkers are indicative of HF, and their values are highly precise assays as patients with normal natriuretic peptide (NP) concentrations are unlikely to have HF. The threshold levels for diagnosing HF using BNP and NT-proBNP vary in chronic and acute scenarios (61). For outpatients suspected of having HF, a BNP level below 35 pg/mL and an NT-proBNP level below 125 pg/mL can rule out the condition. Conversely, in an emergency department setting, the respective cutoff values increase to 100 pg/mL and 300 pg/mL (62). However, it is important to note that the reference values and cutoffs for these biomarkers may vary depending on the specific assay used and the laboratory performing the test. Overall, NT-proBNP and BNP are useful biomarkers for the diagnosis and management, but their results should always be interpreted in the context of the patient's clinical history and other diagnostic tests (6). The PRIDE and ICON studies suggest optimal age-adjusted thresholds for diagnosing acute heart failure (AHF) using NT-proBNP those proposed are 450, 900, and 1,800 pg/ml for age groups under 50 and 75, and over 75 years old respectively (63). Alongside these age-specific thresholds there is a universal age-independent NT-proBNP cutoff level of 300 pg/mL which generally rules out AHF (63). However, they deviate significantly from the FDA-approved cutoffs for NT-proBNP, which are 125 and 450 pg/ml for people under 75 and 75 years or older, which are primarily aiming to exclude ambulatory HF in outpatient setting (63).

An electrocardiogram can help detect arrhythmias and pathologies of the heart chambers, with special emphasis on left ventricular hypertrophy (LVH) (6). Sinus tachycardia due to sympathetic nervous system activation is often seen in advanced heart failure (HF) or during episodes of acute decompensation (3). The presence of atrial arrhythmia may provide clues as to the underlying cause of HF. Arrhythmias themselves can induce HF and this is also known as "*tachycardia-induced*

cardiomyopathy". The finding of increased QRS voltage may suggest LVH. However, without a previous history of hypertension, the underlying cause might be valvular disease or hypertrophic cardiomyopathy (HCM). On the other hand, low QRS voltage may be indicative of an infiltrative disease such as neoplasia, sarcoidosis and amyloidosis or due to pericardial effusion. The presence of Q waves may suggest that HF is due to ischemic heart disease, while new, dynamic, or reversible ST segment changes may point towards an acute coronary ischemia (3).

Chest X-ray is an important diagnostic modality when examining a patient with established or suspected heart failure (HF) as it may reveal an enlarged heart, pulmonary edema, or other signs of congestion such as pleural effusions or vascular congestion. The classic "butterfly" pattern of interstitial and alveolar opacities bilaterally to the periphery of the lungs can also be seen on chest X-rays in patients with pulmonary edema, and is a common finding in HF (3). Transthoracic 2-D ultrasound with color Doppler is a non-invasive imaging modality that uses high-frequency sound waves to produce images of the heart in real-time. It is a cost-effective tool and widely used for evaluating the size of the heart chambers, eccentric or concentric left ventricular hypertrophy, wall motion abnormalities, valvular and right ventricular function (6, 64). CT coronary angiography is a minimally invasive imaging procedure that is commonly used to assess the patency of coronary arteries (65). It uses a CT scanner to produce detailed images of the heart and surrounding blood vessels, which can be used to diagnose and evaluate coronary artery disease (12). Cardiac magnetic resonance imaging is considered the gold standard for the assessment of heart anatomy, particularly in cases of infiltrative diseases and myocardial scarring (66).

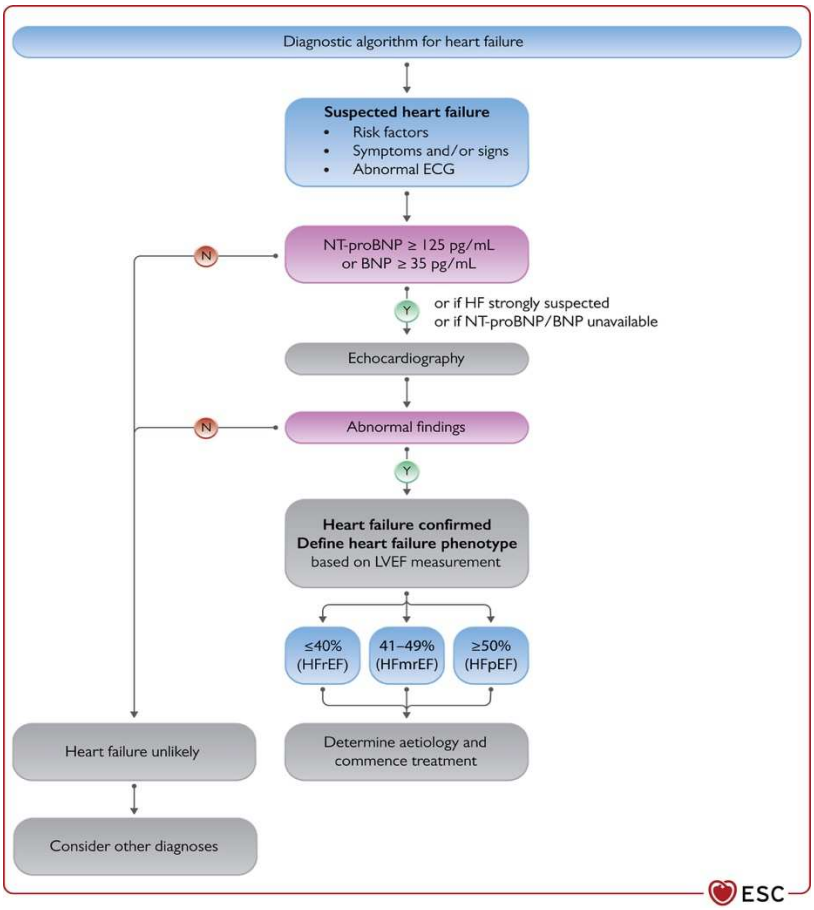

Figure 4. Diagnostic heart failure algorithm according to the 2021 European Society of Cardiology guidelines.

Figure reproduced from work by McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726 (6).

Abbreviations: BNP = Brain natriuretic peptide; ECG = electrocardiogram; HFeEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction.

1.10. Treatment modalities for heart failure

The primary objective in managing patients with heart failure (HF) is to enhance their overall prognosis by reducing mortality and morbidity rates, preventing recurrent hospitalizations, improving their clinical condition and addressing any comorbidities that may be contributing to their poor prognosis (6,67). Treatment modalities in patients with heart failure with reduced ejection fraction are shown in **figure 5.**

Following pharmacological agents should be used depending on precipitating factors and symptoms or signs of congestion:

Beta-blockers act on the β_1-adrenergic receptor receptors located in the heart, resulting in a negative chronotropic and inotropic effect (68). This means that they slow down the heart rate and

decrease the strength of the heart's contractions. By doing so, they help to prevent ventricular remodeling that is often promoted by the stimulation of the renin-angiotensin-aldosterone system and the sympathetic nervus system. Beta-blockers have demonstrated a reduction in morbidity, symptom control, and death due to HF in patients with reduced ejection fraction (6). They are considered as a first line, IA level of recommendation for treatment of heart failure, as per ESC 2021 guidelines (6).

Angiotensin-converting enzyme inhibitor (ACEi) are used for their neurohormonal stimulatory actions, which promote vasodilation and improve left ventricular ejection fraction function. They work by decreasing total peripheral vascular resistance and reducing afterload by inhibiting the conversion of angiotensin I to angiotensin II. Cough is the most common adverse effect of ACEi probably due to the suppressed activity of kininase II leading to buildup of substance P and prostaglandins (69). CONSENSUS trial study group demonstrated that ACEi reduce cardiovascular mortality, and morbidity and improve symptom control among patients with congestive heart failure (70). As per 2021 ESC guidelines ACEi are recommended in heart failure with preserved ejection fraction and an in heart failure with reduced ejection fraction to reduce hospitalizations and death (6).

Angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin-aldosterone system by blocking the binding of angiotensin II to its receptor, -this prevents release of aldosterone and leads to vasoconstriction. The mechanism of ARBs is similar to angiotensin-converting enzyme inhibitors (ACEi). However, this drug does not inhibit kinase and does not lead to increased incidence of cough compared to ACEi (68). The CHARM-Alternative trial by Granger and colleagues demonstrated that the use of ARBs decreased hospitalization admissions and cardiovascular deaths in chronic heart failure patients (68, 71). The current 2021 ESC guidelines for HF states that ARBs can be used as alternatives for ACEi or angiotensin receptor neurolysin inhibitors when these drugs are not tolerated due to serious side effects (6,12). Additionally, these guidelines advice the use of ARB in patients with heart failure with mildly reduced ejection fraction and in heart failure with reduced ejection fraction, with the aim to reduce the risk of heart failure with heart failure related hospitalization and mortality.

Angiotensin receptor neurolysin inhibitor (ARNIs) are medications that function as both an angiotensin receptor blocker and a neprilysin inhibitor. By inhibiting neprilysin, the breakdown of the natriuretic peptide is prevented. This leads to a decrease in blood pressure and prevents vasoconstriction (68). In the PARADIGM-HF trial led by McMurray et al. sacubitril/valsartan, demonstrated a reduction in hospitalizations for worsening heart failure (HF) when compared in patients receiving enalapril (72). Furthermore, additional benefits shown were improved QOL (72). As per 2021 ESC guidelines sacubitil/valsartan is recommended as a replacement therapy for an angiotensin-converting enzyme inhibitor in heart failure with reduced ejection fraction to reduce the risk of HF hospitalizations and mortality (6)

Mineralocorticoid receptor antagonist, also known as aldosterone receptor antagonists (MRAs). Aldosterone, an endogenous steroid hormone work by binding to mineralocorticoid receptor promoting sodium retention and the magnesium/potassium wasting, potentially leading to myocardial fibrosis, vascular damage, and baroreceptor dysfunction which contributes to the progression of heart failure (HF) (73). Studies conducted by Pitt et al. and Zannad et al. investigated the effects of eplerenone and findings showed reduced hospitalizations, mortality and morbidity among patients with heart failure with reduced ejection fraction (HFrEF) (74, 75). It is recommended that all patients with HFrEF take MRAs in combination with an angiotensin-converting enzyme inhibitor and a beta-blocker as per 2021 ESC guideline. This combination has been shown to decrease mortality and the likelihood of hospital admission due to HF (6,74,75).

Digoxin is a medication that blocks the Na+-/K+ exchanger in the heart, increasing the concentration of calcium within the heart muscle cells (6) This in turn causes an increase in the strength of the heart's contractions (positive ionotropic effect) and suppressing neurohormonal effects, which include reducing the activity of the sympathetic nervous system and renin-angiotensin-aldosterone system. As per the 2021 ESC guidelines, the administration of digoxin might be a viable option for patients with atrial fibrillation exhibiting a rapid ventricular rate of over 110 beats per minute, irrespective of ongoing beta-blocker therapy (6) Furthermore, for heart failure patients with reduced ejection fraction in sinus rhythm, digoxin can be considered due to its potential to decrease the likelihood of hospitalization (6). Additionally, the initial use of digoxin may be considered in patients with severe symptoms not responding to guideline-directed medical therapy (6).

Diuretics are used in patients with signs and symptoms of fluid overload to help mobilize and excrete the excess fluid. In heart failure (HF) patients who are experiencing fluid retention, diuretics are advocated to alleviate congestion, improve symptoms, and prevent exacerbation as per ESC 2021 HF guidelines. Loop diuretics are typically the preferred choice in HF patients, due to rapid onset of action and effectiveness, however, thiazides may be used in patients with hypertension along with HF and mild fluid retention (12,44). Intravenous injection of diuretics are the primary choice in managing acute heart failure patients as this patient group usually experience symptomatic fluid overload and congestion (6). It’s worth mentioning that angiotensin receptor neurolysin inhibitors, mineralocorticoid receptor antagonists and SGLT2 inhibitors may also exhibit diuretic effects (6). A meta-analysis by Faris et al. concluded that patients with heart failure with reduced ejection fraction (HFrEF) receiving loop or thiazide diuretics had reduced the risk of worsening (HF) and showed improved exercise tolerance (6, 76). However, the quality of evidence on diuretics for treating HFrEF is inadequate, and their impact on morbidity and mortality hasn't been properly studied through randomized controlled clinical trials (6). Not only thiazide diuretics are an adjunct, but this is also acetazolamide for the acute decompensated heart failure. Acetazolamide inhibits the reabsorption of

sodium in the proximal tubules of the kidney. ADVOR trial by Mullens and colleagues studied patients with acute decompensated HF and volume overload who had been treated with acetazolamide added to a loop-diuretic (77). The results showed that patients receiving acetazolamide experienced faster decongestion and shorter hospital stays. Additionally, a greater proportion of these patients were leaving the hospital free of residual congestion (77).

In addition to pharmacological therapies, interventions can be used to manage heart failure (HF), including **implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy (CRT)** and **heart transplantation (61).** CRT is a specialized form of pacing therapy that involves the placement of two or three leads under the skin of the chest to monitor heart rhythm and deliver an electric shock to restore a normal rhythm if a dangerous arrhythmia is detected. CRT has been shown to reduce symptoms, mortality rates and hospitalizations in heart failure (HF) in appropriately selected patients (6). Based on the 2021 ESC HF guidelines, CRT is advised for symptomatic HF patients with a QRS duration > 150 ms, LBBB QRS morphology and LVEF of 35% or less. This is despite receiving optimal medical therapy to achieve symptom improvement and reduction in morbidity and mortality (6). It is preferred over right ventricular (RV) pacing for heart failure with reduced ejection fraction requiring ventricular pacing for high degree AV block, including those with atrial fibrillation. Additionally, CRT may be considered for patients with non-LBBB QRS morphology, or with a QRS duration of 130-149 ms and LBBB QRS morphology (6). Patients with LVEF of 35% or less who developed worsening heart failure (HF) after receiving a conventional pacemaker or ICD, and have significant RV pacing should also consider switching therapy to CRT (6).

Implantable cardioverter defibrillators (ICDs) are recommended in patients with heart failure (HF) who are at high risk of sudden cardiac death (SCD), including those with heart failure with reduced ejection fraction and a history of cardiac arrest or sustained ventricular tachycardia (61). The evidence concerning the mortality benefit associated with the use of ICD in cases of nonischemic cardiomyopathy presents inconsistencies (78). Research indicates that the use of an ICD, with or without biventricular pacing, serves as a preventive measure against SCD for patients with heart failure with reduced ejection fraction (HFrEF) (57). The 2021 ESC guideline outline separate recommendations for the use of ICD in patients with HF, categorizing them under primary and secondary prevention measures (6). In primary prevention an ICD is recommended to reduce the risk of SCD and overall-cause mortality in patients exhibiting NYHA class II-III, with underlying ischemic etiology. This recommendation is applicable for patients whose left ventricular ejection fraction is below 35%, despite adherence to optimal medical therapy for over 3 months and if they are expected to survive considerably longer than one year as well as maintain good functional status. Similarly, for patients presenting NYHA class II-III of non-ischemic origins. In the context of

secondary prevention, an ICD is recommended in patients who have survived from a ventricular arrhythmia causing hemodynamic instability (6). Such an intervention is advised if patients are predicted to survive over a year maintaining a good functional status, in the absence of reversible causes, or if an episode of ventricular tachycardia has not occurred within 48 hours post-myocardial infarction (6). An ICD can lower the risk of SCD secondary to an arrhythmic event and can also prevent bradycardia in case of transvenous system (6). The IN-TIME trial by Hindricks et al. showed that telemonitoring via ICD with, or without biventricular pacing can lead to better composite clinical scores regarding all-cause mortality, hospital admission for HF, changes in NYHA class and alterations in patients' global self-assessment (57, 79). The mechanism behind these improvements was believed to be due to early identification of new or progressing ventricular and atrial tachyarrhythmias, early detection of inadequate device functionality and patient interviews triggered by telemonitoring which occasionally uncover symptomatic worsening or noncompliance to drugs (57).

Heart transplantation is a surgical procedure in which a diseased heart is replaced with a healthy heart from a donor (3). Heart transplantation is a viable option for selected patients with advanced heart failure (HF) who have failed medical therapy and other interventions (6). Heart transplantation is the main treatment option for patients with advanced or end-stage HF in the absence of contraindications. However, it is restricted by the limited availability of donor hearts and the geographic location may impact eligibility (6). It is considered the optimal therapy for treatment resistant HF, leading to improved survival, functional capacity, and quality of life (6). The survival rate one year after a transplant is approximately 90%, with an average survival period of 12.5 years (6).

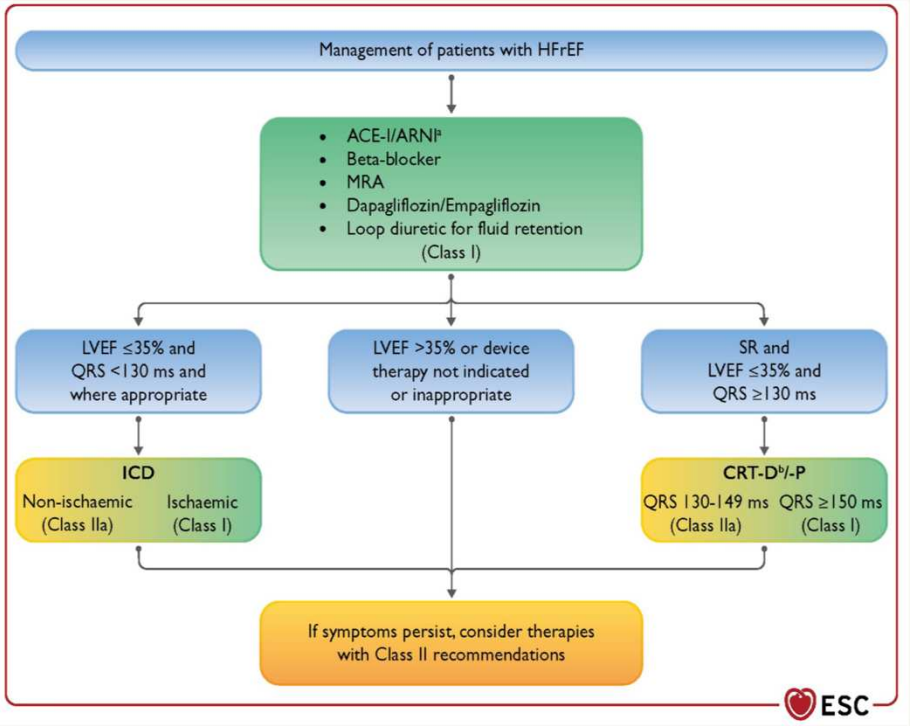

Figure 5. Treatment modalities in patients with HFrEF according to the 2021 European Society of Cardiology guidelines.

Figure is obtained from work by McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726 (6).

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D =cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves of an ECG; SR = sinus rhythm.

1.11. SGLT2 inhibitors

Sodium-glucose co transporter 2 inhibitors (SGLT2i) like empagliflozin and dapagliflozin were originally investigated as an oral anti-diabetic drug for patients with diabetes mellitus (DM) (80). However, cardiovascular outcome trials showed unexpected benefits on cardiovascular outcome and reduction in HF hospitalization in patients who used these agents thus SGLT2 inhibitors have emerged as a promising therapeutic option for heart failure (HF), beyond their initial indication for type 2 DM (80). The SGLT2 is a transporter in the proximal convoluted tubules of the nephron that mediates the absorption of around 90% of filtered glucose, happening simultaneous as the reabsorption of sodium (44). SGLT2 inhibitors leads to increased excretion of glucose thus lowering blood glucose levels. SGLT2 inhibitors also play a significant role in cardiac hemodynamics, functioning to enhance HF management and diminish the risk of sudden cardiac death (SCD). They exhibit a diuretic effect that promotes the clearance of fluid from interstitial spaces rather than the circulation. This potentially leads to the alleviation of congestion with a minimal effect on blood volume, arterial filling, and organ perfusion (57). Additionally, other positive cardiovascular outcomes associated with SGLT2i, are attributed to their impact on multiple mechanisms involved in HF, including inflammation, oxidative stress, cardiac metabolism and energetics, demonstrated in **figure 6** (44). The mechanisms behind this reduction in inflammation are still being investigated. Current research on the liver and kidney suggests that SGLT2 inhibitors can decrease organ inflammation and occurs through the suppression of nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome of the kidney. NLRP3 inflammasome is a group of regulatory proteins that initiate an inflammatory response leading to the secretion of proinflammatory cytokines like interleukin1-β (IL-1 β) and IL-18. High levels of cholesterol can enhance the vulnerability of arterial walls to atherosclerosis. Numerous investigations in both animal models and human subjects have demonstrated that SGLT2i can lower serum cholesterol and triglyceride levels in the bloodstream (81).

A study conducted by Spallone and colleagues is among numerous research investigations suggesting that SGLT2 inhibitors can potentially modulate the cardiovascular autonomic nervous system, hence reducing the risk of cardiac arrhythmias (82). The DAPA-HF trial substudy has recently revealed that SGLT2i may reduce the incidence of ventricular arrhythmias and sudden cardiac death in heart failure (HF) patients. This may be explained by a shortening of the cardiac action potential by reduction of the late sodium current, a decrease in the cytosolic calcium-concentration during diastole, and a reduction of cardiac remodeling leading to less fibrosis (44). Cardiac metabolism and energetics are also important factors in the pathogenesis of HF. The heart primarily relies on fatty acids and glucose as energy sources, however in HF there is a shift towards glucose metabolism (44). SGLT2 inhibitors improve cardiac metabolism and energetics, particularly

through the promotion of ketone body utilization by decreasing insulin to glucagon ratio (83). Verma et al. demonstrated that SGLT2i enhances cardiac energy metabolism by promoting energy production from glucose and fatty acid oxidation, thereby improving the energy supply to a "deprived, weakened heart" (84).

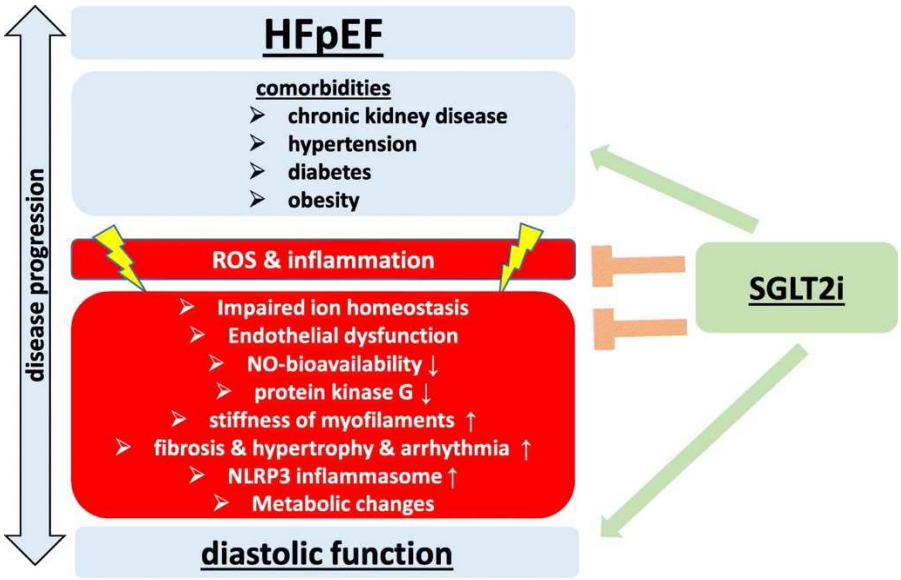

Figure 6. Mechanisms of SGLT2 inhibitors on heart failure with reduced ejection fraction (HFpEF).

This figure summarizes the pathophysiology of heart failure with preserved ejection fraction (HFpEF) and the potential therapeutic impact of sodium-glucose-cotransporter 2 inhibitors (SGLT2i). It highlights the beneficial effects of SGLT2i on common HFpEF comorbidities such as hypertension, diabetes, and obesity, as well as its direct influence on heart abnormalities associated with HFpEF.

This figure is obtained from the work by Dyck JRB, Sossalla S, Hamdani N, Coronel R, Weber NC, Light PE, et al. Cardiac mechanisms of the beneficial effects of SGLT2 inhibitors in heart failure: Evidence for potential off-target effects. J Mol Cell Cardiol. 2022;167:17–31 (44).

Abbreviations: ROS= reactive oxygen species.

Several placebo-controlled clinical trials were conducted to evaluate the effects of SGLT2 inhibitors and SGLT2 inhibitors (SGLT2i) in the chronic heart failure (HF) population with and without diabetes mellitus type 2 (DM2). DAPA-HF led by McMurray et al. and EMPEROR-Reduced led by Packer et al. are pivotal trials that studied patients with heart failure with reduced ejection fraction (HFrEF), while EMPEROR-Preserved led by Anker et al. evaluated patients with heart failure with preserved ejection fraction (HFpEF) (18,85,86). In all three trials, it was found that

patients who were treated with SGLT2i showed a 20%-25% decrease in the combined outcome of hospitalization due to heart failure (HF) or cardiovascular death, compared to those who were given a placebo (80). Across the three trials, empagliflozin was found to significantly improve Health-related quality of life (HRQoL) as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The therapeutic advantages of the treatment remained consistent, regardless of HRQoL, presence or absence of DM2, and chronic kidney disease (CKD). The EMPEROR-preserved trial showed robust outcomes and established SGLT2i as the first effective therapy for treating HFpEF. The trial also revealed a reduction in hospitalization for HF compared to placebo. The pivotal trial SOLOIST-WHF led by Bhatt et al. investigated the effect of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, in type 2 diabetes mellitus patients with recently worsening HF (87). The trial showed a reduction in total HF hospitalization or cardiovascular death by 33% over a follow-up of 9 months. This effect was consistent in patients with HFrEF and HFpEF and patients with and without CKD (32,34). According to KCCQ, sotagloflozin also resulted in a statistically significant improvement in the worsening of the HF population. Based on the foundation of several different studies including the aforementioned; dapagliflozin or empagliflozin are recommended in patients with HF who do not have any contraindications, in addition to optimal medical therapy with an ACEi/ARNi, a beta blocker and an mineralocorticoid receptor antagonists (MRA) for patients with HFrEF regardless of diabetes status. Additionally, the use of SGLT2i may reduce the need for other diuretics such as loop diuretics, which are commonly used in HF management (67,80).

Due to the lack of data and uncertainties regarding the potential effects of SGLT2 inhibitors on the reduction of sudden cardiac death (SCD) as one of the key drivers of mortality in heart failure (HF), the aim of the present MD thesis was to examine the effects of SGLT2 on SCD event reduction in cohorts of patients with HF that were derived from pivotal heart failure trials. For this purpose, a qualitative and quantitative synthesis of available data was performed and meta-analysis was undertaken to ascertain these effects. Similarly, we sought to determine if SGLT2i exhibits differential impact in reduction of primary composite outcome with respect to the underlying etiology of HF (ischemic vs. non-ischemic cardiomyopathy) -a question that has not been adequately addressed in the literature this far.

2. OBJECTIVES

2.1. Aims of the study

As the principal objective of the present thesis, we aimed to investigate the effect of SGLT2 inhibitor treatment (10 mg empagliflozin once daily or 10 mg dapagliflozin once daily or 200 to 400 mg sotagliflozin once daily) vs. placebo in patients with chronic heart failure and across the spectrum of left ventricular ejection fractions concerning the occurrence of sudden cardiac death (SCD) events during the designated follow - up of respective studies. Secondary objective was to determine if the use of SGLT2 inhibitors would have a different impact on principal composite outcome across selected randomized clinical trials with respect to the etiology of heart failure (ischemic vs. non-ischemic cardiomyopathy). All of the trials defined primary outcome as a composite of adjudicated cardiovascular death or hospitalization for heart failure, usually analyzed as the time to first event. For this scientific undertaking, we analyzed pivotal and practice-changing double-blinded, placebo-controlled, randomized clinical trials that investigated the efficacy of SGLT2 inhibitor on important clinical outcomes in the setting of chronic heart failure or recent worsening of chronic failure.

2.2.Hypothesis of the study

Concerning the prespecified objectives of this thesis, we proposed the following hypotheses:

a) Use of SGLT2 inhibitors will be associated with a significant reduction of sudden cardiac death events among patients with chronic heart failure, compared to placebo
b) SGLT2 inhibitors will show greater reduction of primary events among patients with chronic heart failure and non-ischemic cardiomyopathy compared to those with ischemic cardiomyopathy.

3. PATIENTS AND METHODS

3.1.Study design

This MD thesis was envisioned as a systematic review of the literature and meta-analysis of pivotal, large-scale, double-blinded, placebo-controlled, randomized controlled trials (RCTs) examining the impact of SGLT2 inhibitor administration in patients with established chronic heart failure (including those with reduced, mildly reduced and preserved ejection fraction) on the occurrence of SCD, compared to placebo. Secondarily, within the cohort of HF patients that received SGLT2 inhibitor, we aimed to investigate its impact in patients with ischemic etiology of HF, compared to patients with non-ischemic etiology of HF, with respect to the primary outcome (cardiovascular death or HF-related hospitalizations). No prespecified protocol was registered for this analysis and no Ethics Committee approval from the University of Split School of Medicine was required for the study that was designed in this way. This study was carried out under the Department of Pathophysiology, University of Split School of Medicine.

3.2.Search strategy

The search strategy was devised by the student mentor (JAB) while the search of electronic databases was independently carried out by the student (JB) and student mentor (JAB). Electronic databases that were searched included the National Library of Medicine–PubMed, Ovid MEDLINE, Cochrane Central Register of Controlled Trials, Ovid Journals (full text), and SCOPUS. These databases were manually searched to obtain full records of original articles (RCTs) that investigated the use of SGLT2 inhibitor (empagliflozin, dapagliflozin, or sotagliflozin) in patients with established chronic heart failure. The search was limited to records published in relevant peer-reviewed journals in the English language from 2019 (when first major trial in human subjects with heart failure using an SGLT2 inhibitor was published-DAPA-HF) until May of 2023. All trials had to include adult human subjects. The date of the last search was performed on May 13th, 2023. We did not perform any search of grey literature because we wanted to capture the most important and most robust clinical trials that have shaped the clinical practice in terms of HF management and use of SGLT2 inhibitors for such indication. Moreover, both the student (JB) and mentor (JAB) independently carried out the literature search, deleted duplicate records, screened available titles and abstracts for relevance , and classified studies as „excluded“ or requiring further inspection as these studies were labeled as „potential for inclusion“. Finally, prespecified eligibility and exclusion criteria were applied consistently for each examined study. If there was a discrepancy between the two investigators concerning the search strategy, this was resolved by the joint discussion involving the opinion of the third investigator from the Department of Pathophysiology, University of Split School of Medicine.

3.3.Inclusion and exclusion criteria, Patients/Intervention/Comparison/Outcome/Study design (PICOS)

In order to be included in the qualitative and quantitve studies, selected studies had to fulfill the following inclusion criteria according to PICOS questions, as outlined below:

a) Patient population: outpatients with established chronic heart failure or with recent worsening event of chronic heart failure regardless of ejection fraction (the whole spectrum of LVEF was considered, including HFrEF, HFmrEF, and HFpEF patients).

b) Intervention: patients with HF in the intervention group had to receive a once - daily, peroral dose of SGLT2 inhibitor on top of the guideline-directed medical therapy and other standards of care that are established for heart failure treatment, according to international guidelines. The established doses of SGLT2 inhibitor had to be *empagliflozin* 10 mg once daily OR *dapagliflozin*10 mg once daily OR *sotagliflozin* 200 to 400 mg once-daily (depending on individual patient tolerability in the trial.

c) Comparison: patients in the control group would need to not receive an SGLT2 inhibitor and would need to be administered a placebo pill in addition to established standard of care

d) Outcome: the primary outcome of interest was the event of sudden cardiac death (SCD) occurring at any time during the designated study follow-up and duration. For the secondary goal of the study, we analyzed the primary composite outcome in these studies that consisted of cardiovascular death or first HF - related hospitalization with respect to if the SGLT2 inhibitor was administered to HF patients with ischemic vs. non-ischemic cardiomyopathy.

e) Study design: it was mandatory for the potential study to be conducted as a double-blind, placebo-controlled, and randomized controlled trial.

We excluded potential studies in the following circumstances:

a) If the study had a non - RCT design (i.e. observational and/or non-randomized study) or was not double-blinded accordingly

b) If the study did not report on any of the two prespecified outcomes of interest or if the study did not provide basic data on study length, description of the main baseline characteristics relevant for the syndrome of HF such as age, sex, type of treatment and doses that were administered, left ventricular ejection fraction, functional classification as per NYHA class, renal function, important comorbidities such as diabetes mellitus, arterial hypertension, atrial fibrillation, etc.

c) If the study enrolled patients with acute heart failure or acutely decompensated heart failure.

d) If the study enrolled patients that were not naive to SGLT2 inhibitor treatment. e)If the potential study was a duplicate report without additional or updated outcome data.

3.4.Data extraction

Study data were extracted independently by both the mentor (JAB) and student (JB) and for this, pre-designed, piloted extraction forms in the MS Excel format were used. These forms contained baseline study information such as author's first and last name, study name or study acronym, type of study design, duration (timeframe) of the study, study location, the total number of patients randomized, and broken down by the treatment allocation, drug dosing, sex distribution in the SGLT2i and placebo group as well as the mean age of SGLT2i and placebo group. Furthermore, relevant variables such as NYHA functional classification, etiology of HF, mean or median LVEF, mean systolic and diastolic blood pressure, and mean estimated glomerular filtration rate were recorded for each study. HF - related pharmacotherapy and device therapy at baseline was recorded for each study and encompassed diuretics, ACE inhibitors, ARBs, ARNis, beta-blockers, MRAs, digoxin, as well as ICD and CRT use. We also extracted the prevalence of comorbidities including arterial hypertension, diabetes mellitus, and atrial fibrillation as well as the history of recent hospitalizations for HF. Finally, major outcomes of interest were separately recorded for each study and included hospitalization for heart failure, cardiovascular death, and the prevalence of the adverse events.

3.5. Risk of Bias (RoB) assessment

Cochrane's Risk of Bias 2 (RoB2) tool, as recommended by the Cochrane Collaboration has been used to assess the individual risk of bias of each included study across the set of fixed domains of bias. These potential biases are classified into 5 domains and are separately graded for each study. These domains include: potential biases arising from the randomization process (D1), deviations from the intended intervention (D2), missing outcome data (D3), discrepancies in outcome measurements (D4), and selection bias (D5) with respect to reported results. By combining individual grades from each domain, the overall judgment for each study is provided classifying it as either low risk of bias, high risk of bias or some concerns regarding the risk of bias.

Risk of Bias (RoB) (88) was assessed by using RoB 2 tool (revised tool for Risk of Bias in randomized trials), available on the following link:
https://www.riskofbias.info/welcome/rob-2-0-tool

RoB2 assessment was independently performed by the student (JB) and mentor (JAB) while potential incongruencies were resolved by consultation with the third investigator from the Department of Pathophysiology, University of Split School of Medicine.

3.6.Statistical analysis

Data analysis was performed by proposed Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (89).

In the meta-analysis only dichotomous outcomes were analyzed (sudden cardiac death-YES/NO and composite outcome of cardiovascular death and HF-related hospitalization-YES/NO) and outcome measures were expressed as risk ratio (RR) with 95% confidence intervals (95% CI). Due to the low heterogeneity of included studies, fixed-effects model with Mantel-Haenszel algorithm was applied. Meta-analysis was performed by using Review Manager software (RevMan, version 5.4, The Cochrane Collaboration, 2020).

Chi-square test of heterogeneity and Higgins I^2 statistic of non - consistency were used to assess heterogeneity across included studies. Studies with an 1^2 statistic <15% were considered to have no heterogeneity, 15% to <35% were considered to have low heterogeneity; >35% to 75% -moderate heterogeneity, and those with 1^2 statistic >75% were considered as exhibiting high heterogeneity. Publication bias was assessed by visually inspecting the obtained funnel plots and formal Egger's test calculation-P-values <0,05 indicated significant publication bias across included studies. All P-values reported were two-tailed and results were considered statistically significant if P <0,05 at all instances.

4. RESULTS

A total of 7 randomized controlled trials were studied in the final analysis. **Table 7** provides essential details about each study, including the total number of participants, study period, study location and if the study was multicentric or single - center.

Table 7. Basic characteristics of studies included in the main analyses

Authors of the study and year	Number of patients	Study period	Study location	Multicentric or single-centre study	Study type
DAPA-HF McMurray et al. 2019	2373 receiving dapagliflozin *vs.* 2371 receiving placebo	February 2017 - August 2019	USA, Germany, Spain, etc.	Multicentric	Randomized controlled trial
DECLARE-TIMI 58 Kato ET et al. 2019	8582 receiving dapagliflozin *vs.* 8578 recieving placebo	April 2013 – September 2018	North America, Europe, Latin America, Asia Pacific etc.	Multicentric	Randomized double-blind trial
DEFINE-HF Nassif ME et al. 2019	131 receiving dagaliflozin *vs.* 132 receiving placebo	N/A	USA	Multicentric	Randomized, double blind controlled trial
DELIVER Trial Solomon SD et al. 2022	3131 receiving dapagliflozin *vs.* 3132 receiving placebo	August 2018 – December 2020	North America, Latin America, Europe, Asia, Saudi Arabia	Multicentric	Randomized double-blind controlled trial
EMPEROR-Preserved Anker SD et al. 2021	2997 receiving empagliflozin *vs.* 2991 receiving placebo	March 2017 – April 2020	North America, Latin America, Europe, Asia etc.	Multicentric	Randomized, double blind, parallell-group, event driven trial
EMPEROR-Reduced Packer M et al. 2020	1863 receiving empagliflozin, 1867 receiving placebo	April 2017 – November 2019	North America, Latin America, Europe, Asia etc.	Multicentric	Randomized, double-blind, paralell-group, event driven trial
SOLOIST-WHF Bhatt DL et al. 2020	608 receiving sotagliflozin *vs.* 614 receiving placebo	2018 – March 2020 (ended early due to loss of funding)	North America, Latin America, Europe etc.	Multicentric	Double-blind, randomized, event driven, controlled trial

Table 8 provides a detailed summary of the baseline characteristics of the study participants, including their average age, gender distribution, HF severity, LVEF, average systolic blood pressure, heart rate, kidney function, HF ethology and average NT - proBNP levels. Pharmacotherapy and device therapy of patients randomized to control arms are shown in **table 9.** The major comorbidities and major outcomes of patients enrolled in the meta-analysis are presented in **table 10** and **table 11**, respectively.

Table 8. Baseline patient characteristics across included studies.

Authors of the study and year	**Mean age,** (years)	**Female sex, N** (%)	**NYHA II functional class** (%)	**NYHA III functional class** (%)	**Mean or median LVEF** (%)	**Mean ± SD SBP** (mmHg)	**Mean ± SD HR** (bpm)	**Mean ± SD eGFR** (mL/min./1.73 m^2)	**Ischemic etiology of HF** N (%)	**Mean or median NT-proBNP** (pg/mL)
DAPA-HF McMurray et al. 2019	66,3	23,4%	67,6%	31,6%	31%	121,8	71,5	65,8	56,4%	1437
DECLARE-TIMI 58 Kato ET et al. 2019	64	29,3%	56,2%	8,5%	46,5%	N/A	N/A	84,5	56,5%	N/A
DEFINE-HF Nassif ME et al. 2019	61,3	26,7%	65,4%	34,2%	26,5%	123,6	72	69	52,9%	1136
DELIVER Trial Solomon SD et al. 2022	71,7	43,9%	75,3%	24,5%	54,2%	N/A	N/A	61	N/A	N/A
EMPEROR-Preserved Anker SD et al. 2021	71,9	44,7%	81,5%	18,1%	54,3%	131,9	70,4	60,6	35,4%	970
EMPEROR-Reduced Packer M et al. 2020	66,9	24%	75,1%	24,4%	27,5%	122	71,3	62	51,8%	1907
SOLOIST-WHF Bhatt DL et al. 2020	69,5	33,7%	45,2%	45,8%	35%	122	N/A	49,9	58,3%	1779

Table 9. Pharmacotherapy and device therapy across studies included in the analyses

Authors of the study and year	Diuretic, N (%)	ACE inhibitor, N (%)	ARB, N (%)	Sacubitril-Valsartan, N (%)	Beta-blocker, N (%)	MRA, N (%)	Digitalis, N (%)	ICD, N (%)	CRT, N (%)
DAPA HF McMurray et al. 2019	93,5%	56,1%	27,6%	10,7%	96,1%	71%	18,7%	26,2%	7,5%
DECLARE-TIMI 58 Kato ET et al. 2019	65%	86,6% (ARB and ACE inhibitors reported together)		N/A	82,5%	22%	N/A	N/A	N/A
DEFINE-HF Nassif ME et al. 2019	85,6% (loop diuretic)	59,3% (ARB and ACE inhibitors reported together)		32,4%	96,6%	61%	17,5%	62%	25,9%
DELIVER Trial Solomon SD et al. 2022	76,8% (loop diuretic)	36,6%	36,3%	4,8%	82,7%	42,6%	N/A	N/A	N/A
EMPEROR-Preserved Anker SD et al. 2021	N/A	80,7% (ACE inhibitors, ARB or sacubitril-valsartan reported together)			86,3%	37.5%	9,3%	N/A	N/A
EMPEROR-Reduced Packer M et al. 2020	N/A	69,7% (RAS inhibitor without neprilysin inhibitor)		19,5%	94,7%	71,4%	N/A	31,4%	11,9%
SOLOIST-WHF Bhatt DL et al. 2020	95% (loop diuretic)	40,6%	42,2%	16,8%	92,1%	64,5%	N/A	20,3% (ICD and CRT reported together)	

Abbreviations: ACE inhibitor= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist; ICD= implantable cardioverter- defibrillator; CRT= cardiac resynchronization therapy.

Table 10. Major comorbidities of heart failure patients across included studies

Authors of the study and year	**Arterial hypertension,** N (%)	**Atrial fibrillation,** N (%)	**Diabetes mellitus,** N (%)	**Hospitalization for HF,** N (%)
DAPA-HF McMurray et al. 2019	N/A	38,3%	41,8%	47,5%
DECLARE-TIMI 58 Kato ET et al. 2019	91,5%	N/A	100%	N/A
DEFINE-HF Nassif ME et al. 2019	N/A	40,3%	63,1%	79,5%
DELIVER Trial Solomon SD et al. 2022	88,7%	56,7% (atrial fibrillation or flutter)	44,8%	40,6%
EMPEROR-Preserved Anker SD et al. 2021	90,6%	51,1%	49,1%	22,9% (during <12 months)
EMPEROR-Reduced Packer M et al. 2020	72,4%	36,7%	49,8%	30,9% (during <12 months)
SOLOIST-WHF Bhatt DL et al. 2020	N/A	47,1% (atrial fibrillation or flutter)	100%	N/A

Table 11. Major outcomes of interest (HF-related hospitalization and cardiovascular mortality) across included studies.

Authors of the study and year	SGLT2 Hospitalization for heart failure N (%)	Placebo Hospitalization for heart failure N (%)	SGLT2 Cardiovascular death N (%)	Placebo Cardiovascular death N (%)	SGLT2 Adverse events N (%)	Placebo Adverse events N (%)
DAPA-HF McMurray et al. 2019	9,7%	13,4%	9,6%	11,5%	35,7% (any serious adverse events, including events with outcome= death)	40,2% (any serious adverse events, including events with outcome= death)
DECLARE-TIMI 58 Kato ET et al. 2019	13,2%	17,8%	15%	14,4%	34,1% (serious adverse events)	36,2% (serious adverse events)
DEFINE-HF Nassif ME et al. 2019	7,6%	6%	0,8%	0,8%	22,9% (serious adverse events)	18,2% (serious adverse events)
DELIVER Trial Solomon SD et al. 2022	10,5%	13,3%	7,4%	8,3%	43,5% (serious adverse events)	45,5% (serious adverse events)
EMPEROR-Preserved Anker SD et al. 2021	8,6%	11,8%	7,3%	8,2%	47,9% (serious adverse events)	51,6% (serious adverse events)
Emperor-Reduced Packer M et al. 2020	13,2%	18,3%	10%	10,8%	76,2%	78,5%
SOLOIST-WHF Bhatt DL et al. 2020	40,4%	63,9%	10,6%	12,5%	69,4% (treatment emergent adverse event)	67,4% (treatment emergent adverse event)

4.1. Impact of SGLT2 inhibitors on the rate of SCD events in patients with heart failure

As shown in **figure 7**, the addition of SGLT2 inhibitors on top of optimal medical therapy was associated with a 20%, relative risk reduction of the SCD event, compared to placebo, among unselected population HF patients, regardless of baseline ejection fraction (RR 0,80, 95% CI 0,65-0,98; *P*=0,030). This finding was based on the cumulative data from 6 RCTs, encompassing 21,637 patients with HF. This calculation was based on the evidence that showed n heterogeneity across studies (I^2=0%; *P*=0,952). No publication bias was detected (**figure 8**).

Figure 7. Relative risk of sudden cardiac death with respect of treatment with SGLT2 inhibitor *vs.* placebo, in patients with heart failure.

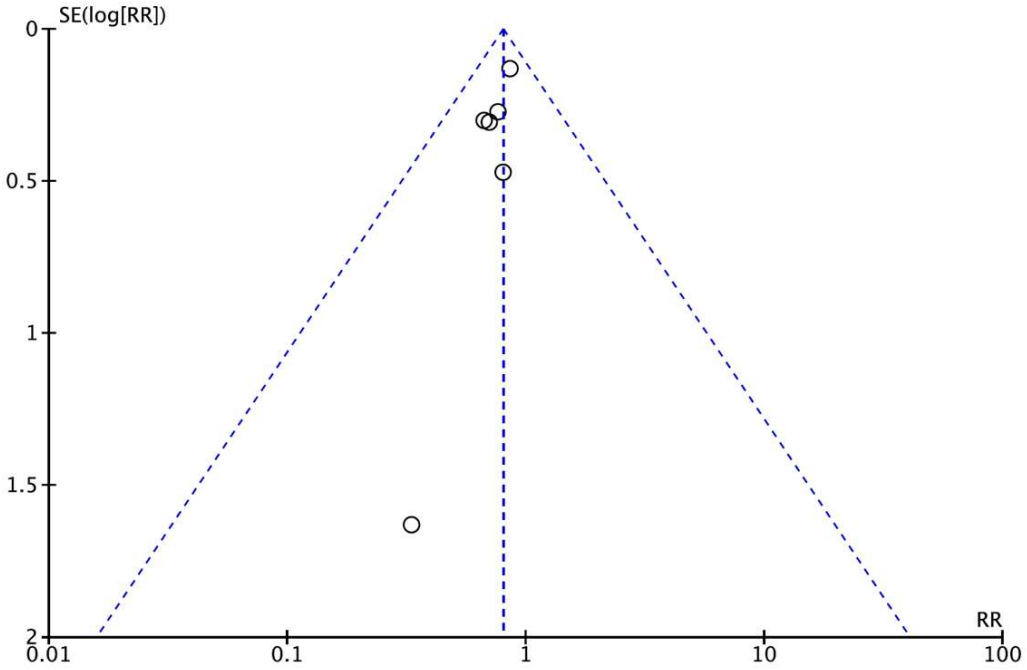

Figure 8. Publication bias across included studies for the outcome of sudden cardiac death.

4.2. Impact of SGLT2 inhibitor on the primary composite outcome (cardiovascular death or hospitalizations for HF) with respect to etiology of HF (ischemic *vs.* non-ischemic cardiomyopathy)

As shown in **figure 9** the addition of SGLT2 inhibitor on top of optimal medical therapy was associated with a 12% relative risk reduction of primary composite outcome, among heart failure patients with non-ischemic compared to ischemic cardiomyopathy (RR 1,12, 95% CI 1,01-1,25; *P*=0,031). This finding was based on the cumulative data from 3 RCTs, encompassing 7232 patients with heart failure (3378 with ischemic and 3854 with non-ischemic cardiomyopathy). This calculation was based on the evidence that showed no heterogeneity across studies (I^2=0%; *P*=0,693). No publication bias was detected (**figure 10**).

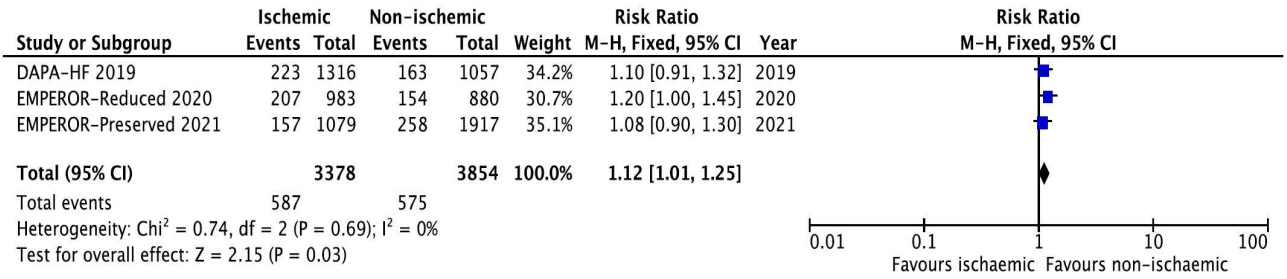

Figure 9. Relative risk of composite outcome with respect of the etiology of cardiomyopathy in patients with heart failure treated with the SGLT2 inhibitor.

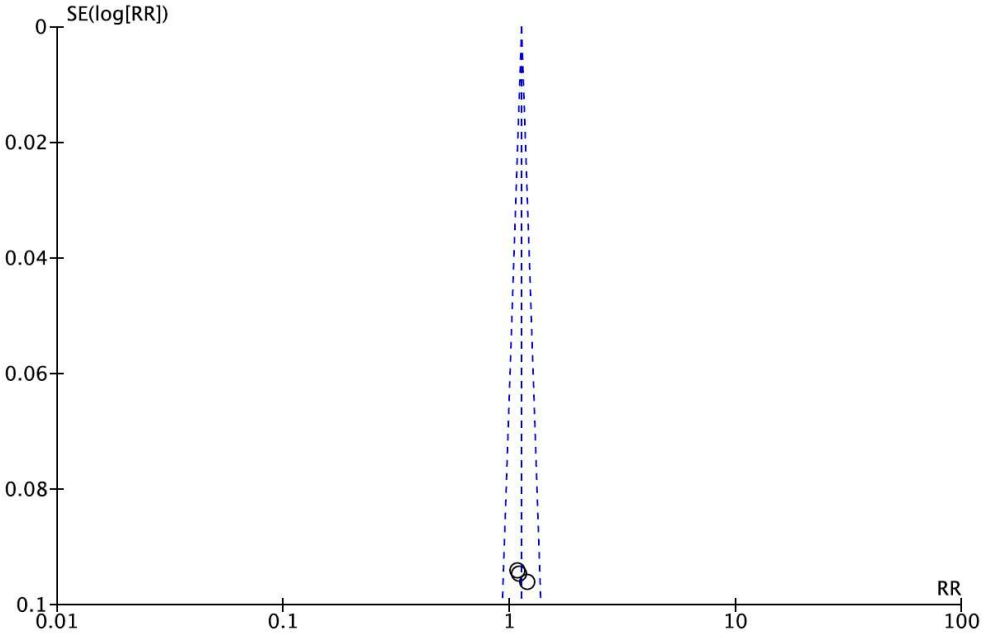

Figure 10. Publication bias across included studies for the composite outcome of cardiovascular death or hospitalizations for heart failure.

4.3. Risk of bias (RoB) of included randomized controlled trials

In general, both investigators adjudicated, independently of each other, that included randomized controlled trials showed low risk across all five examined bias domains (bias due to randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome and selection of the reported result). The RoB 2 summary is shown in **figure 11** below.

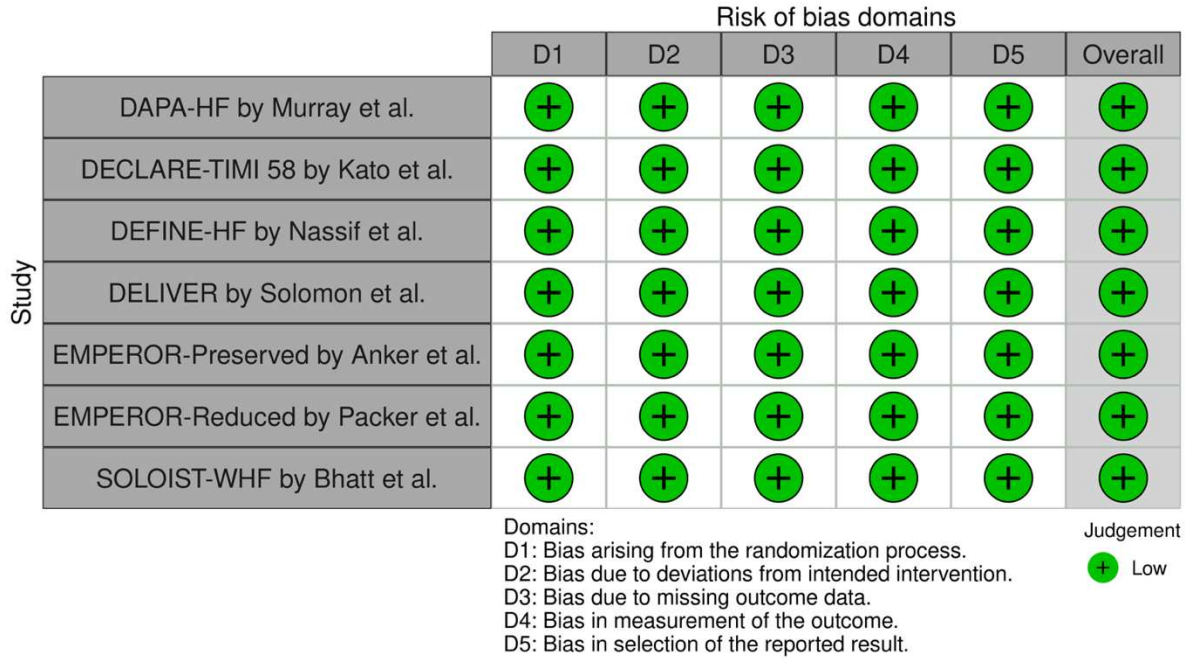

Figure 11. Risk of bias across included trials (N=7) concerning five bias domains.

5. DISCUSSION

In this meta-analysis of pivotal randomized controlled trials, we elucidated the potential benefits of SGLT2 inhibitors (SGLT2i) with respect to migration of sudden cardiac death (SCD) events and important clinical outcomes related to heart failure (HF) of different etiologies. A total of 36,248 individuals with HF enrolled in seven randomized controlled trials published between 2013 and 2020 were eligible for the analysis. These studies in total enrolled 19,685 patients receiving SGLT2i and 16,563 receiving placebo.

Our principal finding of the present thesis is that addition of SGLT2 inhibitors (SGLT2i) to optimal medical therapy (OMT) for heart failure significantly decreased sudden cardiac death (SCD) events and conferred a 20% relative risk reduction of SCD among a diverse population of heart failure (HF) patients, including heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction, and heart failure with reduced ejection fraction. This finding was based by accumulating available data from six studies. Secondary main finding revealed that SGLT2i in addition on top of OMT for HF reduced the main composite outcome by 12% among patients with non-ischemic cardiomyopathy compared to those with ischemic cardiomyopathy. Although this additional protective effect in non–ischemic subgroup was modest, it was statistically significant. This conclusion was based from three studies, as the remaining studies did not report on this specific outcome. Therefore, such finding of our analysis should be interpreted with caution since the effect size measured was rather small and 95% confidence intervals were wide.

Several studies have suggested that SGLT2 inhibitors (SGLT2i) offer a range of cardiac benefits, however, the influence of SGLT2i on the risk of sudden cardiac death (SCD) in these patients have remained uncertain. The first signal that SGLT2i might be beneficial for these endpoints was provided in the post hoc subanalysis of pivotal DAPA-HF trial by Curtain and colleagues (90). This study focused on analysis of serious adverse event reports that included events such as ventricular arrhythmias, cardiac arrest and adjudicated SCD. This study showed that use of dapagliflozin among patients with heart failure with reduced ejection fraction was associated with 21% relative risk reduction in the composite of aforementioned outcomes. When we look specifically at SCD in isolation, this analysis showed lower SCD event rate in dapagliflozin arm compared to placebo (2,7 vs. 3,3 events per 100 person-years. What is staggering from this analysis was also the observation that out of 500 cardiovascular deaths, 206 or 41% were adjudicated as sudden death thus emphasizing the importance of this mode of death among patients with heart failure and reduced ejection fraction. For these reasons and owing to inspiration received from the subanalysis of seminal DAPA-HF trial, we decided to execute this analysis.

Similar signal benefit was confirmed very recently in the meta-analysis conducted by Connor et al. reporting that SGLT2 inhibitor (SGLT2i) therapy was linked to a significant reduction of sudden cardiac death (SCD) between heart failure patients receiving SGLT2i therapy in contrast to patients

receiving placebo (relative risk reduction of as much as 32% with RR of 0,68 and 95% Cl of 0,48 to 0,95) (91). This meta–analysis concluded that SGLT2i treatment was associated with a significantly diminished risk of SCD in patients with heart failure across ejection fraction (EF) spectrum that were concomitantly treated with contemporary OMT. In the light of this new evidence, we can conclude that these finding strongly correlate with the main result that is currently presented in our meta-analysis.

Our findings are in alignment with other studies and substantiate the potential of SGLT2 inhibitors (SGLT2i) as potent therapeutic agents in the management of cardiovascular diseases, particularly in their role in reducing hospitalizations and mortality in heart failure (HF). Scheen, and Savarese et al. 2022, demonstrated that patients treated with SGLT2 inhibitors had a reduced risk of HF hospitalization, mortality, and major adverse cardiovascular events compared to placebo, both in patients with type 2 diabetes (T2DM) and in those diagnosed with HF who were non diabetic (93, 92). Important studies by Vasiliadis el al. and Singh et al. revealed that around 50% of cardiovascular-related deaths in T2DM patients was attributed to sudden cardiac death. (94, 95)

Even though both heart failure (HF) and diabetes are recognized risk factors for cardiac arrhythmias, the exact mechanistic pathway through which SGLT2 inhibitors (SGLT2i) reduce arrhythmia burden, and the extent of their effect, are not fully elucidated (96). In the EMBODY trial led by Shimizu et al. conducted among patients with type 2 diabetes and acute myocardial infarction, it was shown that empagliflozin modulated cardiac sympathetic and parasympathetic activity by improving heart rate variability and heart rate turbulence (97). Given that lethal ventricular arrhythmias can be potentiated by autonomic nervous system and this can, in turn, lead to sudden cardiac death (SCD) it is plausible that this might be a viable hypothetical explanation for some of the arrhythmogenic properties of SGLT2i. Similarly, a study led by Spallone and colleagues confirmed that SGLT2 inhibitors can potentially modulate the cardiovascular autonomic nervous system, hence reducing the risk of cardiac arrhythmias (82). A prolonged QT interval duration is strongly associated with the risk of developing *torsade de pointes*, a type of ventricular tachycardia that can progress into ventricular fibrillation and lead to SCD (98). Dapagliflozin and empagliflozin, even when administered at doses exceeding the therapeutic range, do not lead to QT interval prolongation, as evidenced by comprehensive QT/QTc studies conducted in healthy individuals (101, 102). Koev et al. suggests that by supplementing contemporary HF treatments with SGLT2i, ARNI and vericiguat, there could be a substantial improvement in the left ventricular ejection fraction (LVEF), and these enhancements might be sustainable over durations longer than proposed in the current guidelines (57). These advantageous effects may potentially also lead to significant shifts in the decision-making process regarding cardioverter defibrillator implantation for primary prevention in patients with heart failure with reduced ejection fraction (HFrEF). However, in regard to

established "*train of thought"*, prophylactic implantation of ICDs in patients with ischemic HFrEF has been consistently associated with reduced risks of SCD and all-cause mortality (58). On the other hand, the effectiveness of such prophylactic implantations in non-ischemic HFrEF remains a contentious point of debate. Moreover, cardiac resynchronization therapy, when applied in cases of HFrEF caused by non-ischemic HF, may result in more significant enhancements in left ventricular function than in patients with ischemic etiology of HF (86).

One of our main findings is that SGLT2 inhibitors (SGLT2i) showed marginal, but significant additional protective effect in patients with non–ischemic compared to ischemic etiology of heart failure (HF) with respect to cardiovascular death and hospitalizations for HF. These findings has not been previously confirmed in the sub-analysis of large-scale heart failure trials. Consequently, there is currently not enough data to substantiate this finding. However, a small prospective study led by Mustapic and colleagues showed that patients with HF and non-ischemic cardiomyopathy prospectively treated with an SGLT2i (mostly empagliflozin) had a greater numerical improvement in echocardiographic myocardial work parameters, compared to patients with ischemic cardiomyopathy, although these observations did not reach statistical significance (101). However, same study revealed that there was less global wasted work (GWW) in patients with non-ischemic cardiomyopathy *vs.* those with ischemic cardiomyopathy and this result reached statistical significance (P=0,023) thus suggesting greater improvement of functional efficiency in this patient subgroup.

Recently, a retrospective study by Silverdal et al. demonstrated, in a real-world cohort of patients with recent-onset heart failure with reduced ejection fraction (HFrEF), that those who had non-ischemic cardiomyopathy responded better to optimal medical therapy compared to those with ischemic etiology of heart failure (HF) (102). However, this study did not evaluate the effect of SGLT2i separately neither did it include patients with an SGLT2i, likely due to the fact that the study was initiated and mostly carried out during the time before SGLT2i is received an indication for the use in HF. In contrast, Khan et al. did not find differential effect of guideline-directed therapies with varying HF etiologies (16). Some of the putative explanation for potentially higher efficacy of SGLT2 inhibitor in non-ischemic cardiomyopathy vs. ischemic cardiomyopathy might be provided. For instance, patients with an ischemic cause of HF are typically older and more likely to have more advanced or complex cardiac pathology and comorbidities including diabetes mellitus, coronary artery disease and potentially multiple previous myocardial infarctions (16). The existence of myocardial scarring and loss of cardiac contractility due to death of cardiomyocytes, could potentially hinder the effectiveness of any guideline-directed therapy for HF, including SGLT2 inhibitors. In contrast to this, patients with non-ischemic cardiomyopathy are often younger , have less traditional risk factors for ischemic heart disease and may have heterogeneous underlying causes of

cardiomyopathy, some of which might be reversible with proper therapeutic management (such as myocarditis or atrial fibrillation-induced cardiomyopathy). We believe that it would be interesting, from a scientific standpoint, to specifically and prospectively analyze effects of SGLT2 inhibition with respect to underlying substrate of heart failure as this might allow for the more personalized and individual-tailored approach in therapeutic decision-making.

There are some limitations regarding the results presented in this thesis that should be acknowledged. Although all studies had low risk of bias and no heterogeneity was detected across studies, these findings should be interpreted with caution since the outcome analysis with respect to etiology of heart failure (HF) provided a modest effect size and produced a wide confidence interval. Similarly, studies involving both HFrEF and HFpEF/HFmrEF patients were analyzed together and it has been previously well-known that these HF phenotypes respond differently to guideline-directed medical therapies used in HF and also have substantially different pathophysiology that drives cardiac dysfunction and such facts might limit the conclusiveness of our results. Furthermore, the event of sudden cardiac death was not specifically adjudicated by the investigators in all studies which might present a bias given that some events registered as sudden deaths might not have necessarily be cardiac in origin and vice-versa. Finally, not all of the studies reported on both outcomes of interest, therefore, it is plausible that these results might have been different if all studies presented required data regarding the outcomes of interest.

Taken together, our findings highlight the potential benefit of SGLT2i in reducing sudden cardiac death (SCD) events in a wide population of patients with heart failure (HF), irrespective of baseline left ventricular ejection fraction. Our findings not only assert the beneficial role of SGLT2 inhibitors in reducing SCD but also suggest a possible differential response to SGLT2i therapy based on the underlying etiology of HF. The appeared enhanced efficacy of SGLT2 inhibitors in non-ischemic HF patients might present an intriguing avenue for future research and for expanding our understanding of the factors that might influence the effectiveness of this therapy. Our study lays the groundwork for further investigation into the mechanisms behind these observed differential effects. It also highlights the need for personalized treatment strategies considering underlying causes of HF.

6. CONCLUSION

Based on the meta-analytic synthesis of obtained data derived from pivotal, large-scale, double-blinded, placebo-controlled, randomized controlled trials, examining the impact of SGLT2 inhibitor administration in patients with established chronic heart failure of various etiologies and ejection fractions, we provide the following conclusions:

1. SGLT2 inhibitor addition on top of optimal medical therapy was associated with a 20% relative risk reduction in the risk of sudden cardiac death, compared to placebo, among a wide population of patients with heart failure encompassing HFpEF, HFmrEF, and HFrEF phenotypes.

2. Administration of an SGLT2 inhibitor showed greater efficacy among patients with non-ischemic *vs.* ischemic etiology of heart failure as it reduced the relative risk of a composite outcome of cardiovascular death and HF-related hospitalizations by 12%. However, this reduction should be considered modest due to the relatively small effect size and wide confidence interval approaching the value of 1.

3. These findings were based on data exhibiting no heterogeneity across included trials while trials in general were adjudicated as high quality with low risk of bias.

7. REFERENCES

1. Ferrari R, Balla C, Fucili A. Heart failure: an historical perspective. Eur Heart J Suppl. 2016;18:G3–10.
2. Cheng TO. Hippocrates and cardiology. Am Heart J. 2001;2:173–83.
3. Libby P, Bonow R, Mann D, Tomaselli G, Bhatt D, Solomon S, editors. In: Braunwald's heart disease: a textbook of cardiovascular medicine. 12th ed. Philadelphia: Elsevier; 2021. p. 933–1154.
4. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;3:352–80.
5. Inamdar A, Inamdar A. Heart Failure: Diagnosis, Management and Utilization. J Clin Med. 2016;7:62.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;36:3599–726.
7. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, et al. Acute heart failure. Nat Rev Dis Primer. 2020;1:16.
8. Reddy YNV, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-Output Heart Failure. J Am Coll Cardiol. 2016;5:473–82.
9. Albakri A. Low-output heart failure: A review of clinical status and meta-analysis of diagnosis and clinical management methods. Clin Med Investig. 2019. doi: 10.15761/CMI.1000179.
10. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure. J Card Fail. 2021;4:387–413.
11. Pascual Figal D, González-Juanatey JR, Bayes-Genis A, Cobo M, Delgado J, Diaz-Molina B, et al. Comments on the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Rev Esp Cardiol Engl Ed. 2022;6:458–65.
12. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2022. doi: /10.1161/CIR.0000000000001063.
13. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European

Society of Cardiology: Advanced heart failure: HFA position statement. Eur J Heart Fail. 2018;11:1505–35.
14. Jones NR, Hobbs FR, Taylor CJ. Prognosis following a diagnosis of heart failure and the role of primary care: a review of the literature. BJGP Open. 2017. doi: 10.3399/ bjgpopen17X101013.
15. Parenica J, Spinar J, Vitovec J, Widimsky P, Linhart A, Fedorco M, et al. Long-term survival following acute heart failure: The Acute Heart Failure Database Main registry (AHEAD Main). Eur J Intern Med. 2013;2:151–60.
16. Khan MS, Butler J, Anker SD, Filippatos G, Ferreira JP, Pocock SJ, et al. Impact of Empagliflozin in Heart Failure With Reduced Ejection Fraction in Patients With Ischemic Versus Nonischemic Cause. J Am Heart Assoc. 2023;1:e027652.
17. McDonagh TA, Gardner RS, Clark AL, Dargie H, editors. Oxford Textbook of Heart Failure [Internet]. 1st ed. Oxford University Press; 2011. p. 5-529
18. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;16:1451–61.
19. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry: Analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;12:1574–85.
20. Andersson C, Vasan RS. Epidemiology of Heart Failure with Preserved Ejection Fraction. Heart Fail Clin. 2014;3:377–88.
21. Roger VL. Epidemiology of Heart Failure: A Contemporary Perspective. Circ Res. 2021;10:1421–34.
22. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, Treatments, and Outcomes of Patients With Preserved Systolic Function Hospitalized for Heart Failure. J Am Coll Cardiol. 2007;8:768–77.
23. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF): Heart failure with mid-range ejection fraction: a distinct clinical entity? Eur J Heart Fail. 2017;12:1586–96.
24. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study: Characterization of HFmrEF. Eur J Heart Fail. 2017;10:1258–69.
25. Borovac JA, Novak K, Bozic J, Glavas D. The midrange left ventricular ejection fraction

(LVEF) is associated with higher all-cause mortality during the 1-year follow-up compared to preserved LVEF among real-world patients with acute heart failure: a single-center propensity score-matched analysis. Heart Vessels. 2019;2:268–78.
26. Harjola V, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, et al. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail. 2010;3:239–48.
27. Lee DS, Gona P, Albano I, Larson MG, Benjamin EJ, Levy D, et al. A Systematic Assessment of Causes of Death After Heart Failure Onset in the Community: Impact of Age at Death, Time Period, and Left Ventricular Systolic Dysfunction. Circ Heart Fail. 2011;1:36–43.
28. Mamas MA, Sperrin M, Watson MC, Coutts A, Wilde K, Burton C, et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland: Outcomes in heart failure and cancer. Eur J Heart Fail. 2017;9:1095–104.
29. Packer M. What causes sudden death in patients with chronic heart failure and a reduced ejection fraction? Eur Heart J. 2020;18:1757–63.
30. Pons F, Lupón J, Urrutia A, González B, Crespo E, Díez C, et al. Mortality and Cause of Death in Patients With Heart Failure: Findings at a Specialist Multidisciplinary Heart Failure Unit. Rev Esp Cardiol Engl Ed. 2010;3:303–14.
31. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;17:3272–87.
32. G-CHF Investigators, Rasmussen M, Prado A, Hominal MA, Zaidman CJ, Cursack G, et al. Global Variations in Heart Failure Etiology, Management, and Outcomes. JAMA. 2023;19:1650-1661.
33. Rajadurai J, Tse HF, Wang CH, Yang NI, Zhou J, Sim D. Understanding the Epidemiology of Heart Failure to Improve Management Practices: An Asia-Pacific Perspective. J Card Fail. 2017;4:327–39.
34. Jensen RV, Hjortbak MV, Bøtker HE. Ischemic Heart Disease: An Update. Semin Nucl Med. 2020;3:195–207.
35. Seferović PM, Polovina MM, Coats AJS. Heart failure in dilated non-ischaemic cardiomyopathy. Eur Heart J Suppl. 2019. doi: 10.1093/eurheartj/suz212
36. Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ Res. 2017;7:749–70.
37. Mahmaljy H, Yelamanchili VS, Singhal M. Dilated Cardiomyopathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK441911/

38. Brown KN, Pendela VS, Ahmed I, Diaz RR. Restrictive Cardiomyopathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537234/
39. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. The Lancet. 2014;9921:999–1008.
40. Drazner MH. The Progression of Hypertensive Heart Disease. Circulation. 2011;3:327–34.
41. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? Eur Heart J. 2015;36:ehv513
42. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of Myocarditis-Related Cardiomyopathy in Adults. Circ Res. 2019;11:1568–83.
43. Faucine A, Longo D, Hauser S, Jameson L, Loscalzo J. Harrison's principles of internal medicine. Vol. 19. 2015. p. 96-299.
44. Dyck JRB, Sossalla S, Hamdani N, Coronel R, Weber NC, Light PE, et al. Cardiac mechanisms of the beneficial effects of SGLT2 inhibitors in heart failure: Evidence for potential off-target effects. J Mol Cell Cardiol. 2022;167:17–31.
45. Bruss ZS, Raja A. Physiology, Stroke Volume. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK547686/
46. Borovac JA, D'Amario D, Bozic J, Glavas D. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. World J Cardiol. 2020;8:373–408.
47. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol. 2012;5:365–71.
48. Azevedo PS, Polegato BF, Minicucci MF, Paiva SAR, Zornoff LAM. Cardiac Remodeling: Concepts, Clinical Impact, Pathophysiological Mechanisms and Pharmacologic Treatment. Arq Bras Cardiol [Internet]. 2016 [cited 2023 Mar 14]; Available from: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2016000100062.
49. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021;1:263–76.
50. Chua Chiaco JMS, Parikh NI, Fergusson DJ. The jugular venous pressure revisited. Cleve Clin J Med. 2013;10:638–44.
51. MacVicar BA, Newman EA. Astrocyte Regulation of Blood Flow in the Brain. Cold Spring Harb Perspect Biol. 2015;5:a020388.
52. Tomaselli GF, Zipes DP. What Causes Sudden Death in Heart Failure? Circ Res. 2004;8:754–63.
53. Wu SJ, Hsieh YC. Sudden cardiac death in heart failure with preserved ejection fraction: an

updated review. Int J Arrhythmia. 2022;1:7.
54. Kumar A, Avishay DM, Jones CR, Shaikh JD, Kaur R, Aljadah M, et al. Sudden cardiac death: epidemiology, pathogenesis and management. Rev Cardiovasc Med. 2021. doi: 10.31083/j.rcm.2021.01.207.
55. Scheen AJ. Dissecting the reduction in cardiovascular death with SGLT2 inhibitors: Potential contribution of effects on ventricular arrhythmias and sudden cardiac death? Diabetes Epidemiol Manag. 2022. doi: /10.1016/j.deman.2022.100107.
56. Mulder BA, Veldhuisen DJ, Rienstra M. Sudden cardiac death in heart failure: more than meets the eye. Eur J Heart Fail. 2021;8:1361–3.
57. Koev I, Yarkoni M, Luria D, Amir O, Biton Y. Sudden cardiac death prevention in the era of novel heart failure medications. Am Heart J Plus Cardiol Res Pract. 2023. doi: 10.1016/j.ahjo.2023.100281.
58. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, et al. Heart failure etiology and response tomilrinone in decompensated heart failure. J Am Coll Cardiol. 2003;6:997–1003.
59. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NAM, Anderson KP, et al. Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy. N Engl J Med. 2004;21:2151–8.
60. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, et al. Declining Risk of Sudden Death in Heart Failure. N Engl J Med. 2017;1:41–51.
61. Authors/Task Force Members:, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;1:4–131.
62. Alcidi G, Goffredo G, Correale M, Brunetti ND, Iacoviello M. Brain Natriuretic Peptide Biomarkers in Current Clinical and Therapeutic Scenarios of Heart Failure. J Clin Med. 2022;11:3192.
63. Januzzi JL, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, et al. N-Terminal Pro–B-Type Natriuretic Peptide in the Emergency Department. J Am Coll Cardiol. 2018;11:1191–200.
64. Khan UA, Aurigemma GP. Cardiac Ultrasound Imaging in Heart Failure: Recent Advances. Curr Heart Fail Rep. 2012;2:154–61.
65. Busse A, Cantré D, Beller E, Streckenbach F, Öner A, Ince H, et al. Cardiac CT: why, when, and how: Update 2019. Radiol. 2019;S1:1–9.

66. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;1:129.
67. Tamargo J, López-Sendón J. Novel therapeutic targets for the treatment of heart failure. Nat Rev Drug Discov. 2011;7:536–55.
68. Shah A, Gandhi D, Srivastava S, Shah KJ, Mansukhani R. Heart Failure: A Class Review of Pharmacotherapy. P T Peer-Rev J Formul Manag. 2017;7:464–72.
69. Overlack A. ACE Inhibitor???Induced Cough and Bronchospasm: Incidence, Mechanisms and Management. Drug Saf. 1996;1:72–8.
70. The Consensus Trial Study Group*. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. N Engl J Med. 1987;23:1429–35.
71. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. The Lancet. 2003;9386:772–6.
72. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014;11:993–1004.
73. Weber KT. Aldosterone in Congestive Heart Failure. N Engl J Med. 2001;23:1689–97.
74. Zannad F, McMurray JJV, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;1:11–21.
75. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. N Engl J Med. 2003;14:1309–21.
76. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol. 2002;2:149–58.
77. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med. 2022;13:1185–95.
78. Kolben Y, Hirsh Raccah B, Koev I, Luria D, Amir O, Biton Y. Implantable cardioverter defibrillator for primary prevention in patients with non-ischemic cardiomyopathy in the era of novel therapeutic agents- meta-analysis. Front Cardiovasc Med. 2023;10:1192101.
79. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised

controlled trial. The Lancet. 2014;9943:583–90.
80. Anker SD, Usman MS, Butler J. SGLT2 Inhibitors: From Antihyperglycemic Agents to All-Around Heart Failure Therapy. Circulation. 2022;4:299–302.
81. Pahud de Mortanges A, Salvador Jr. D, Laimer M, Muka T, Wilhelm M, Bano A. The Role of SGLT2 Inhibitors in Atherosclerosis: A Narrative Mini-Review. Front Pharmacol. 2021:12:751214.
82. Spallone V, Valensi P. SGLT2 inhibitors and the autonomic nervous system in diabetes: A promising challenge to better understand multiple target improvement. Diabetes Metab. 2021. doi: 10.3389/fphar.2021.751214.
83. Saucedo-Orozco H, Voorrips SN, Yurista SR, de Boer RA, Westenbrink BD. SGLT2 Inhibitors and Ketone Metabolism in Heart Failure. J Lipid Atheroscler. 2022;1:1.
84. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, et al. Empagliflozin Increases Cardiac Energy Production in Diabetes. JACC Basic Transl Sci. 2018;5:575–87.
85. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;21:1995–2008.
86. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;15:1413–24.
87. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;2:117–28.
88. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;l4898.
89. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;n71.
90. Curtain JP, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Køber L, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J. 2021;36:3727–38.
91. Oates CP, Santos-Gallego CG, Basyal B, Kawamura I, Musikantow D, Turagam M, et al. Mp-453091-3 sglt2 inhibitors reduce risk of sudden cardiac death in patients with heart failure: a meta-analysis of randomized clinical trials. Heart rhythm. 2023:5:109–10.
92. Savarese G, Butler J, Lund LH, Bhatt DL, Anker SD. Cardiovascular effects of non-insulin glucose-lowering agents: a comprehensive review of trial evidence and potential cardioprotective mechanisms. Cardiovasc Res. 2022;10:2231–52.
93. Scheen AJ. Counteracting heart failure with diabetes drugs: a review into the pharmacokinetic and pharmacodynamic properties. Expert Opin Drug Metab Toxicol. 2022;6:381–

93.
94. Vasiliadis I, Kolovou G, Mavrogeni S, Nair DR, Mikhailidis DP. Sudden cardiac death and diabetes mellitus. J Diabetes Complications. 2014;4:573–9.
95. Singh KB, Nnadozie MC, Abdal M, Shrestha N, Abe RAM, Masroor A, et al. Type 2 Diabetes and Causes of Sudden Cardiac Death: A Systematic Review. Cureus [Internet]. 2021 Sep 20 [cited 2023 Jun 23]; Available from: https://www.cureus.com/articles/66483-type-2-diabetes-and-causes-of-sudden-cardiac-death-a-systematic-review
96. Attachaipanich T, Chattipakorn SC, Chattipakorn N. Potential roles of sodium-glucose co-transporter 2 inhibitors in attenuating cardiac arrhythmias in diabetes and heart failure. J Cell Physiol. 2022;5:2404–19.
97. Shimizu W, Kubota Y, Hoshika Y, Mozawa K, Tara S, Tokita Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. Cardiovasc Diabetol. 2020;1:148.
98. Gallego M, Zayas-Arrabal J, Alquiza A, Apellaniz B, Casis O. Electrical Features of the Diabetic Myocardium. Arrhythmic and Cardiovascular Safety Considerations in Diabetes. Front Pharmacol. 2021;12:687256.
99. Carlson GF, Tou CKP, Parikh S, Birmingham BK, Butler K. Evaluation of the effect of dapagliflozin on cardiac repolarization: a thorough QT/QTc study. Diabetes Ther. 2011;3:123–32.
100. Ring A, Brand T, Macha S, Breithaupt-Groegler K, Simons G, Walter B, et al. The sodium glucose cotransporter 2 inhibitor empagliflozin does not prolong QT interval in a thorough QT (TQT) study. Cardiovasc Diabetol. 2013;1:70.
101. Mustapic I, Bakovic D, Susilovic-Grabovac Z, Borovac JA. Left Ventricular Systolic Function After 3 Months of SGLT2 Inhibitor Therapy in Heart Failure Patients with Reduced Ejection Fraction. J Cardiovasc Transl Res [Internet]. 2023 May 8 [cited 2023 Jul 2]; Available from: https://link.springer.com/10.1007/s12265-023-10389-3
102. Silverdal J, Bollano E, Henrysson J, Basic C, Fu M, Sjöland H. Treatment response in recent-onset heart failure with reduced ejection fraction: non-ischaemic vs. ischaemic aetiology. ESC Heart Fail. 2023;1:542–51.

8. SUMMARY

Objectives: The present study aimed to examine the impact of SGLT2 inhibitor added to optimal medical therapy on the rates of sudden cardiac death (SCD) events among outpatients with heart failure, compared to placebo. Furthermore, we sought to investigate the potential differential impact of SGLT2 inhibitor with respect to etiology of heart failure (ischemic *vs.* non-ischemic cardiomyopathy) in HF patients treated with SGLT2 inhibitor.

Patients and methods: Meta-analysis examined data from seven pivotal, large-scale, double-blinded, placebo-controlled, randomized controlled trials conducted among HF outpatients. The primary outcome of interest was the impact of SGLT2i administration in patients with HF on the occurrence of SCD events, compared to placebo. Secondary goal was to assess the impact of SGLT2 inhibitor on the composite outcome of cardiovascular death or hospitalization for HF with respect to etiology of HF. Principal outcome measures were reported as a risk ratio (RR) with 95% confidence intervals (95% CI). Due to low heterogeneity across included studies, a fixed effects method with Mantel-Haenszel algorithm was used.

Results: A total of 7 randomized clinical trials were included in the final analysis enrolling 21,637 outpatients with heart failure. The results of the present meta-analysis demonstrate that the addition of SGLT2 inhibitor to optimal medical therapy was associated with a relative risk reduction of SCD occurence by 20% (RR 0,80, 95% CI 0,65-0,98; *P*=0,030) when compared to placebo. Furthermore, the meta-analysis encompassing 7,232 patients from 3 studies revealed that among HF outpatients using SGLT2 inhibitor, on top of optimal medical therapy, occurence of the composite outcome including cardiovascular death and heart failure hospitalizations was reduced by 12% among patients with HF and non-ischemic cardiomyopathy compared to those with ischemic cardiomyopathy (RR 1,12, 95% CI 1,01-1,25; P=0,030). Both main results were derived from clinical trials that exhibited a low degree of heterogeneity (I^2=0%). All included studies showed low risk of bias, as adjudicated independently by two investigators.

Conclusion: The use of SGLT2 inhibitor, on top of optimized background therapy for heart failure, among heart failure outpatients, was associated with a 20% relative risk reduction in the occurrence of sudden cardiac death, compared to placebo. Similarly, SGLT2 inhibition appears to be more effective in heart failure patients with non-ischemic etiology of cardiomyopathy *vs.* those with ischemic etiology, although this effect should be cautiously interpreted due to the small effect size and wide confidence intervals.

9. CROATIAN SUMMARY

Naslov rada: Rizik iznenadne srčane smrti i korištenje SGLT2 inhibitora u bolesnika sa zatajivanjem srca te utjecaj istih na velike ishode s obzirom na etiologiju kardiomiopatije: meta-analiza pivotalnih randomiziranih kontroliranih studija.

Ciljevi: Ciljevi ovog rada su istražiti utjecaj dodatka SGLT2 inhibitora optimalnoj medicinskoj terapiji na pojavnost događaja iznenadne srčane smrti među vanbolničkim bolesnicima sa zatajivanjem srca u usporedbi s placebom. Nadalje, istražili smo potencijalni diferencijalni efekt SGLT2 inhibitora s obzirom na etiologiju srčanog zatajivanja (ishemijska naspram neishemijskoj kardiomiopatiji) u bolesnika sa zatajivanjem srca koji su liječeni sa SGLT2 inhibitorima.

Pacijenti i metode: Ova meta-analiza je obradila podatke iz sedam pivotalnih, velikih, dvostruko zaslijepljenih, placebom kontroliranih, randomiziranih kontroliranih studija koje su provedene u vanbolničkih bolesnika sa zatajivanjem srca. Primarni ishod od interesa je bio učinak korištenja SGLT2 inihbitora u odnosu na placebo, a s obzirom na pojavnost događaja iznenadne srčane smrti. Sekundarni cilj je bio istražiti utjecaj SGLT2 inhibitora na kompozitni ishod koji se sastojao od kardiovaskularne smrtnosti ili hospitalizacija zbog zatajivanja srca, a s obzirom na etiologiju zatajivanja srca. Glavne mjere ishoda koje su korištene je omjer rizika (RR) sa 95% intervalima pouzdanosti (95% CI). Zbog utvrđene niske heterogenosti uključenih studija, statistička metoda fiksnih učinaka sa Mantel-Haenszelovim algoritmom je korištena za generiranje rezultata meta-analize.

Rezultati: Ukupno je u analizu uključeno 7 randomiziranih kliničkih studija koje su uključile ukupno 21,637 bolesnika sa zatajivanjem srca. Glavni rezultat ukazuje na to da je dodatak SGLT2 inhibitora optimalnoj medicinskoj terapiji povezan sa značajnim smanjenjem relativnog rizika za pojavnost iznenadne srčane smrti za 20%, u usporedbi sa placebom (RR 0,80, 95% CI 0,65-0,98; *P*=0,030). Nadalje, meta-analitičko združivanje rezultata 7,232 bolesnika iz 3 studije je pokazalo da je SGLT2 inhibitor, povrh optimalne medicinske terapije smanjio relativni rizik za pojavnost kompozitnog ishoda kardiovaskularne smrti ili hospitalizacije zbog zatajivanja srca za 12% kod bolesnika sa neishemijskom kardiomiopatijom u odnosu na bolesnike sa ishemijskom kardiomiopatijom (RR 1,12%, 95% CI 1,01-1,25; *P*=0,030). Oba glavna rezultata su postignuta analizom studija za koje se pokazalo da imaju nizak stupanj heterogeneosti (I^2=0%). Sve navedene studije su imale nizak rizik od pristranosti prema neovisnoj procjeni dvoje istraživača.

Zaključci: Uporaba SGLT2 inhibitora pored ostale optimizirane terapije za zatajivanje srca, među vanbolničkim bolesnicima, bila je povezana sa smanjenjem relativnog rizika iznenadne srčane smrti za 20% u odnosu na placebo. Slično tomu, naši rezultati sugeriraju da su SGLT2 inhibitori bili efikasniji u redukciji pojavnosti kompozitnog ishoda kardiovaskularne smrti ili hospitalizacija zbog zatajivanja srca u bolesnika sa neishemijskom naspram ishemijske etiologije zatajivanja srca.

Međutim, opisani učinak je potrebno interpretirati sa posebnim oprezom s obzirom na relativno malu veličinu efekta i širok raspon intervala pouzdanosti.