Heart failure with reduced ejection fraction of ischaemic and non-ischaemic aetiology

Clinical characteristics, prognosis and factors associated with outcome

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ABSTRACT

BACKGROUND: Ischaemic heart disease (IHD) is common in heart failure (HF) and is often considered to infer a worse prognosis. Following treatment improvements and the increased survival in both IHD and HF, patients are generally older and increasingly multimorbid. The current impact of IHD on mortality in HF and on short-term response to initiated treatment in HF with reduced ejection fraction (HFrEF) is uncertain. Dilated cardiomyopathy (DCM) is one of the most important causes of non-ischaemic HFrEF. Even so, contemporary data on outcomes and prognostic factors are scarce.

AIMS: To evaluate the impact of IHD on mortality in HF over time and on short-term response to initiated treatment in HFrEF. To study the influence of duration on outcomes and comorbid burden in DCM, with further analyses of temporal changes and prognostic factors.

METHODS AND RESULTS: Swedish Heart Failure Registry data were analyzed in the three first studies. *In the first study*, we evaluated the impact of IHD on mortality in 31,000 patients with non-valvular HF during 2000–2012. We found that IHD was associated with higher mortality in the whole cohort, in all age groups, in both men and women, in both HF duration < 6 and ≥ 6 months, and in all groups of left ventricular ejection fraction (LVEF) < 50%. IHD was associated with increased risk during the entire study period. *In the second study*, we studied the characteristics, comorbid burden and outcomes in 3,700 patients with DCM. All outcomes were more frequent in long-standing HF (≥ 6 months) than in recent-onset HF. Irrespective of HF duration, the risk factors for mortality, heart transplantation and HF hospitalizations were: older age, lower blood pressure, lower functional capacity, lower LVEF, left bundle branch block and diabetes. Male sex was adverse in recent-onset HF only, whereas renal dysfunction, atrial fibrillation and loop diuretic use were adverse only in long-standing HF. The age-adjusted number of comorbidities increased with increasing HF duration. *In the third study*, we studied the temporal changes in the clinical characteristics, outcomes and prognostic factors in 7,900 patients with DCM during 2003–2015. Over time, the mean age and the proportion of women increased, LVEF improved, and the patients were less symptomatic. The prevalence of prognostically adverse comorbidities was stable. The risk for one-year mortality and hospitalizations diminished gradually during the study period. *In the fourth study*, we assessed the response to initiated treatment in 317 patients with new-onset HFrEF of ischaemic- and non-ischaemic aetiology hospitalized at the Sahlgrenska University Hospital during 2016–2019. Patients with non-ischaemic aetiology showed a better response over a 28-week follow-up, evaluated with a clinical composite outcome. Re-hospitalizations were half as frequent, and a higher proportion showed improvement in LVEF and a decrease in natriuretic peptides.

CONCLUSIONS: Despite improvements in the treatment of HF and IHD, the latter still entails higher mortality in a broad spectrum of patients with HF and subnormal LVEF. In new-onset HFrEF, the treatment response is better in patients with non-ischaemic- than with ischaemic aetiology. In DCM, longer HF duration is associated with increased comorbidity and worse prognosis. Most known adverse prognostic factors are similar in patients with recent-onset and long-standing HF. During 2003–2015, the overall survival gradually improved, although the changes in the cohort composition and the adverse prognostic factors were small.

KEYWORDS: Heart failure, systolic; Ischemic Heart Disease; Cardiomyopathy, dilated; Prognosis; Mortality; Risk factors

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Silverdal J, Sjöland H, Bollano E, Pivodic A, Dahlström U, Fu M. Prognostic impact over time of ischaemic heart disease vs. non-ischaemic heart disease in heart failure. *ESC Heart Fail.* 2020;7(1):264-273.

II. Silverdal J, Sjöland H, Pivodic A, Dahlström U, Fu M, Bollano E. Prognostic differences in long-standing vs. recent-onset dilated cardiomyopathy. *ESC Heart Fail.* 2022;9(2):1294-1303.

III. Sjöland H, Silverdal J, Bollano E, Pivodic A, Dahlström U, Fu M. Temporal trends in outcome and patient characteristics in dilated cardiomyopathy, data from the Swedish Heart Failure Registry 2003-2015. *BMC Cardiovasc Disord.* 2021;21(1):307.

IV. 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. *Accepted for publication in ESC Heart Fail.*

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Hjärtsvikt är en folksjukdom. Ungefär var tionde person över 75 års ålder drabbas och bland de äldre är hjärtsvikt den vanligaste orsaken till sjukhusvård. Kärlsjukdom är överlag vanligt hos personer med hjärtsvikt och den vanligaste orsaken till hjärtsvikt med nedsatt pumpfunktion. Till följd av framgångsrik behandling av kärlsjukdom och hjärtsvikt har överlevnaden successivt ökat. Hjärtsviktspatienter är därmed generellt allt äldre och mer ofta drabbade av andra sjukdomar vilket kan ha förändrat betydelsen av enskilda faktorer, så som kärlsjukdom. Dilaterad kardiomyopati är en annan vanlig orsak till nedsatt pumpfunktion men kunskapen om påverkande faktorer och betydelsen av sjukdomsduration för samsjuklighet och prognos är bristfällig.

Målsättning

Att undersöka i vilken grad kärlsjukdom påverkar överlevnad vid hjärtsvikt, och förbättring efter inledd behandling vid hjärtsvikt med nedsatt pumpfunktion. Att studera betydelsen av sjukdomsduration och påverkande faktorer vid dilaterad kardiomyopati.

Metoder och resultat

De tre första studierna baserades på det svenska hjärtsviktsregistret RiksSvikt. *I den första studien* studerades 31 000 patienter med hjärtsvikt utan klaffsjukdom. Vi fann att samtidig kärlsjukdom medförde ökad risk för död hos patienter med nedsatt pumpfunktion, i alla åldersgrupper, likartat för män och kvinnor och oberoende av sjukdomsduration. Risken var därtill ökad under hela den studerade perioden 2000–2012. *I den andra studien* studerades 3 700 patienter med dilaterad kardiomyopati. Vi fann att patienter med längre sjukdomsduration ($\geq$ 6 månader) hade högre samsjuklighet också när man tagit hänsyn till ålder, samt ökad risk för död och sjukhusvård. Högre ålder, lägre blodtryck, lägre funktionsgrad, sämre pumpfunktion, vänstersidigt skänkelblock och diabetes medförde ökad risk för död, hjärttransplantation eller sjukhusvård oavsett sjukdomsduration. Endast hos de med kort sjukdomsduration var manligt kön ogynnsamt, medan förmaksflimmer och nedsatt njurfunktion var ogynnsamt hos de med längre. *I den tredje studien* analyserades förändring av bakgrundsvariabler, betydelsefulla faktorer och utfall hos 7 900 patienter med dilaterad kardiomyopati under 2003–2015. Över tid noterades en viss ökning av medelåldern och andelen kvinnor. Pumpfunktionen och patienternas övergripande funktion förbättrades något. Andelen patienter med högt blodtryck ökade men förekomsten av de flesta samtidiga sjukdomar var oförändrade. Förändring av faktorer av betydelse för prognos var diskret, men årlig förbättrad överlevnad noterades. *I den fjärde studien* undersöktes förloppet efter påbörjad behandling hos 317 patienter sjukhusvårdade på Sahlgrenska Universitetssjukhuset för nyupptäckt hjärtsvikt med nedsatt pumpfunktion. Vi fann att patienter med bakomliggande kärlsjukdom överlag svarade sämre på behandling, baserat bland annat på dubblerad förekomst av återkommande sjukhusvård, mindre frekvent återhämtning av pumpfunktion och hjärtsviktsrelaterade blodprover under 28 veckors uppföljningstid.

Sammanfattning

Trots framgångsrik behandling medförde kärlsjukdom vid hjärtsvikt fortsatt ökad risk för död hos patienter med någon grad av nedsatt pumpfunktion, hos unga liksom hos äldre och likartat för män och kvinnor. Vid nyupptäckt hjärtsvikt med nedsatt pumpfunktion förbättrades inte heller patienter med bakomliggande kärlsjukdom i samma utsträckning som patienter med hjärtsvikt av andra skäl, med betydelsefulla följder redan under det första halvåret. Vid dilaterad kardiomyopati var samsjukligheten högre och prognosen sämre för de med längre sjukdomsduration. Överlevnaden förbättrades under perioden 2003–2015. De försämrande faktorerna var överlag kända och endast små förändringar av bakgrundsvariabler noterades över tid.

CONTENTS

ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation/flutter
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CV	Cardiovascular
DCM	Dilated cardiomyopathy
GDMT	Guideline-directed medical therapy
HF	Heart failure
HFimpEF	Heart failure with improved left ventricular ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
I-DCM	Idiopathic dilated cardiomyopathy
IHD	Ischaemic heart disease
IHF	Heart failure with reduced ejection fraction of ischaemic aetiology
IQR	Interquartile range
LDCM	Long-standing dilated cardiomyopathy
LVEF	Left ventricular ejection fraction
LBBB	Left bundle branch block
MRA	Mineralocorticoid receptor antagonist
Non-IHD	Heart failure without ischaemic heart disease
Non-IHF	Heart failure with reduced ejection fraction of non-ischaemic aetiology
NP	Natriuretic peptides
NPR	Swedish National Patient Register
NT-proBNP	Amino-terminal pro B-type natriuretic peptide
NYHA class	New York Heart Association functional class
OR	Odds ratio
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
RODCM	Recent-onset dilated cardiomyopathy
RR	Risk ratio
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SGLT2	Sodium-glucose co-transporter 2
SwedeHF	Swedish Heart Failure Registry
Tx	Transplantation

INTRODUCTION

Definition of heart failure

"Heart failure is […] a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise".

- European Society of Cardiology, 2021.[1]

"Heart failure is a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion."

- Universal Definition and Classification of Heart Failure, 2021.[2]

Epidemiology of heart failure

The reported incidence of heart failure (HF) varies substantially. The overall incidence in Europe and North America is approximately 0.2–0.3%, higher for men than for women and higher with increasing age.[3] In the Region Västra Götaland, Sweden, our group has demonstrated a yearly incidence of approximately 0.5%, increasing dramatically with age to 7.0% and 5.7% among men and women ≥85 years of age, respectively. During 2008–2017 the incidence decreased yearly by 3%, consistent with reports of a decreasing incidence in developed countries over the last two decades.[3-7] The prevalence of established HF is approximately 1–3% in Sweden and the western world.[3, 8-10] Data from South America and Africa are scarce but many developing countries are in the midst of a rapid epidemiological transition from diseases related to infections and nutritional deficiencies to chronic diseases such as cardiovascular (CV) disease and HF. The prevalence increases with age, affecting approximately 10% of persons 75 years or older.[11] Due to reduced HF-related mortality and an ageing and increasing population, the prevalence of HF in the USA is expected to increase by 23% from 2012 to 2030, resulting in an expected 46% increase in the number of people living with HF.[12] Prospective population-based cohort studies have appreciated the lifetime risk for developing HF in the middle-aged and elderly to be approximately 20–30%, similar in men and women.[11, 13]

Heart failure classification

HF is a complex multifaceted syndrome. Common classifications are based on left ventricular ejection fraction (LVEF; describing the proportion of the left ventricular volume ejected in each stroke), HF stage, symptom severity and aetiology.

Heart failure classification by left ventricular ejection fraction

Historically, HF was termed congestive, describing the notable signs of fluid retention. Following the findings of increased mortality for HF patients with LVEF <45%,[14]

most studies as from the 1990s restricted inclusion to patients with systolic impairment. In patients with more or less preserved systolic function as measured by LVEF, ventricular relaxation (diastolic function) was noticeably impaired, and the dichotomization in systolic and diastolic HF has been used for many years. Systolic- and diastolic dysfunction are, however, not uncoupled. Patients with systolic HF display evidence of diastolic dysfunction, and various measures of systolic function are abnormal in patients with diastolic HF, which has led to the current LVEF-based terminology. LVEF is most commonly assessed by two-dimensional echocardiography, the normal range being 52–72% in men and 54–75% in women.[15]

Over the years, the LVEF-based definition has been subjected to changes. The former systolic HF approximated the current HF with reduced ejection fraction (HFrEF), whereas the terminology for patients with no or mild LVEF reduction has varied. In 2016, European HF guidelines introduced the term HF with mid-range LVEF (HFmrEF, LVEF 40–49%) in recognition of the relative lack of data regarding this group of patients.[16] Acknowledging the better prognosis for patients whose LVEF increased with treatment,[17-19] American guidelines include HF with improved LVEF (HFimpEF), describing patients with HFrEF improving to LVEF >40%.[20] Although previously recognized by the European Society of Cardiology, HFimpEF was not mentioned in the 2021 European guidelines presenting the current classification: HFrEF (LVEF $\leq$ 40%), HF with mildly reduced LVEF (HFmrEF; LVEF 41–49%) and HF with preserved EF (HFpEF; LVEF $\geq$ 50%).[1]

As patients with HFpEF do not exhibit LVEF reduction, evidence of structural or functional abnormalities (diastolic dysfunction or increased levels of natriuretic peptides [NPs]) is required for a diagnosis. NPs are released from the cardiac myocytes following muscle stretch and stimuli by neurohormones and cytokines. By proteolysis, the inactive propeptide is cleaved into an inactive amino-terminal part and the active NP which reduces myocardial fibrosis and increases vasodilatation, myocardial relaxation and diuresis. B-type NP (BNP) is the NP of the main focus in the clinical context of HF, but due to short circulating half-life, the more stable amino-terminal pro B-type NP (NT-proBNP), is preferably used. A low plasma concentration of NT-proBNP <125 pg/mL for ambulatory patients or <300 pg/mL in the acute setting makes a diagnosis of HF unlikely.[1, 21]

Heart failure classification by stage

To emphasize the importance of risk factor intervention and the progressive nature of HF, the American College of Cardiology/American Heart Association classifies HF by stage, where modifiable risk factors and structural heart disease constitute the early stages preceding clinical HF.[20]

Stage A At risk for HF but without symptoms, structural heart disease or elevated cardiac biomarkers of stretch or injury.

Stage B Pre-HF. No symptoms or signs of HF but evidence of either 1) structural heart disease, 2) evidence for increased filling pressures, or 3) risk factors and increased levels of B-type natriuretic peptides or persistently elevated cardiac troponin.

Stage C Symptomatic HF. Structural heart disease with current or previous HF symptoms.

Stage D Advanced HF. Marked HF symptoms that interfere with daily life. Recurrent hospitalizations despite attempts to optimize guideline-directed medical therapy (GDMT).

Heart failure classification by symptoms and functional capacity

The New York Heart Association (NYHA) classification is a four-graded scale based on symptoms and functional capacity limitation. The NYHA classification was presented in 1921[22] and is still widely used in daily clinical practice and studies.

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.

Heart failure classification by aetiology

In HF, there is significant heterogeneity regarding aetiology, and many cases are likely multifactorial. The division into ischaemic- and non-ischaemic HF is frequent in daily clinical practice and studies.

Ischaemic heart failure

Ischaemic heart disease (IHD) is the result of coronary artery disease (CAD) reducing coronary perfusion, leading to myocardial hypoxia (ischaemia) and necrosis, either progressively or by an abrupt flow reduction with subsequent myocardial infarction. IHD is the cause of more than 60% of HFrEF cases.[23, 24]

Non-ischaemic heart failure

The most common causes of non-ischaemic HF are hypertension, valvular heart disease and cardiomyopathies[23].

Hypertension

Hypertension is a common condition worldwide, with an overall prevalence of around 30–45% in adults and > 60% in people > 60 years of age.[25] A systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 100 mmHg increases the long-term risk of developing HF by at least two-fold compared to normotension.[13] Chronic hypertension involves both pressure and volume overload, resulting in either concentric- or eccentric LV hypertrophy, which is associated with the development of HFpEF and HFrEF, respectively.[26]

Valvular heart disease

Stenotic aortic valvular disease increases left ventricular afterload and typically induces HFpEF, but may in late stages present as HFrEF. Contrary to aortic stenosis, aortic regurgitation or mitral regurgitation results in LV volume overload eventually resulting in LV dilatation and HFrEF. Although patients with valvular HF need medication for symptom relief, long-term treatment requires invasive procedures.[1] Patients with significant valvular disease are excluded from the studies of this thesis.

Dilated cardiomyopathy

According to the 2008 position statement from the European society of cardiology working group on myocardial and pericardial diseases, dilated cardiomyopathy (DCM) is defined by the presence of LV dilatation and systolic dysfunction in the absence of abnormal loading conditions (e.g. hypertension and valve disease) or CAD sufficient to cause global systolic impairment.[27] The present definition is thus less precise than the 2000 definition specifying a stenosis of > 50% in a major coronary artery and LVEF ≥ 45% criteria for exclusion.[28] The prevalence of DCM is frequently described as 36.5 in 100,000 (≈ 1 in 2,700) originally reported in an American study from 1975–1984;[29] however, different methods of estimating the true prevalence of DCM indicate much higher prevalence, up to 1 in 250–400.[30] DCM is one of the major non-ischaemic causes of HFrEF, the proportion of DCM ranging from 12–44% in HFrEF trials.[31-35] Many different conditions may lead to DCM and the term is a phenotypic description more than a specific disease. Genetic disorders, arrhythmias, toxic therapeutic or recreational drugs, inflammation due to infection or systemic diseases and several other less common conditions may all cause the hypokinetic state. Excessive intake of alcohol has been a proposed contributing factor in up to 40% of patients.[36] It is unclear why some, but not all, patients in any of these situations develop DCM. The prevalence of genetic variants associated with DCM is increased in patients with peripartum cardiomyopathy, alcohol-induced cardiomyopathy and DCM attributed to previous chemotherapy, suggesting an underlying cardiac susceptibility.[37-39] Without an identified trigger, the condition is labelled idiopathic. Genetic forms account for approximately 40% of cases[30] but the frequency of familial disease varies considerably between studies, in part due to incomplete penetrance. A meta-analysis of studies most often evaluating cardiac phenotype found that 23% of the patients with idiopathic DCM (I-DCM) had hereditary disease.[40] More than 60 identified genes are implicated in the development of DCM.[41] Compared with ischaemic heart disease, DCM affects younger patients and is the most common cause of HF leading to heart transplantation (heart Tx).[42]

Treatment for heart failure with reduced ejection fraction

In HFrEF, biological compensatory mechanisms are activated for the restoration of cardiac output, but the long-term effects of the sustained up-regulated neuro-hormonal state are detrimental. Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA) are all agents counteracting different aspects of the up-regulated systems, reducing morbidity and mortality.[32, 34, 43-48] By combining an ARB with the neprilysin inhibitor sacubitril (angiotensin receptor-neprilysin inhibitor, ARNI), inhibition of the up-regulated renin-angiotensin system is upheld while countering the effects of the

neuro-hormonal overactivation by reducing the turnover of natriuretic peptides. ARNI reduces morbidity and mortality and is recommended instead of ACEI in medically optimized but still symptomatic patients, but is safe to use in ACEI naïve patients and may be considered as first-line treatment.[1, 49] Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce CV death and worsening HF and are recommended in all patients with HFrEF since 2021.[50, 51] For patients still symptomatic despite otherwise optimized treatment, ivabradine should be considered for patients with sinus rhythm and resting heart rate > 70 beats per minute,[52, 53] and the guanylate cyclase stimulator vericiguat may be considered to reduce CV mortality/HF hospitalization.[54] The myosin activator omecamtiv mecarbil has been shown to reduce the risk for CV mortality/worsening HF in HFrEF,[55] but is yet to be approved for treatment. Furthermore, device treatment is indicated in symptomatic patients with persistently reduced LVEF < 35% despite optimized medical treatment; chronic resynchronization therapy (CRT) in patients with electrocardiographic wide QRS and branch blocks,[56] and implantable converter-defibrillators (ICD) for the prevention of sudden cardiac death (SCD).[1]

Trials of beta-blockers[44], ACEI[43], MRA[47, 48], ARNI[35] and SGLT2 inhibitors[50] have shown beneficial effects of morbidity/mortality in both ischaemic- and non-ischaemic HFrEF and/or DCM, and the recommended pharmacological treatment in chronic HFrEF does not vary with aetiology.

The treatment recommendations for HFrEF changed during the study periods of this thesis.[16, 57-59] The cornerstones for all patients were ACEI (ARB in case of ACEI-intolerance) and beta-blockers. MRA was initially advocated for patients in NYHA class III–IV but is recommended for all patients since 2012. Ivabradine is recommended since 2012 and ARNI since 2016. The recommendation for the use of diuretics to reduce signs and symptoms of congestion has been constant.

Prognosis of heart failure

The survival in HF has improved over the last 50 years. A systematic review of survival in ambulatory HF patients report that the five-year survival increased from 29% in 1970–1979 to 60% in 2000–2009.[60] The prognosis is however worse in patients in need of in-hospital care,[61] and the overall five-year mortality is approximately 50%, equal to or higher than that of common malignancies like breast-, prostate- and colorectal cancer.[60, 62] Besides the continuously high mortality, the morbidity in HF is considerable. HF is the most common cause of hospitalization in patients over the age of 65 years.[63] All-cause re-hospitalization is frequent, similar for HFrEF and HFpEF. Approximately 20% are re-admitted within 1 month and 60–65% within 1 year, with the majority of re-admissions occurring within the first three months of discharge after HF hospitalization.[64-66] To date, no pharmacological treatment has demonstrated overall mortality reduction in HFpEF, and the noted increase in overall survival in HF is most likely the result of improved treatment of HFrEF, in which IHD is the major underlying cause. The prognosis in DCM has likewise improved remarkably. Acknowledging variability in patient inclusion, studies from the 1960s and the 1970s reported median survival of less than 2–3 years,[67, 68] compared to one-year mortality event rates as low as 1–3% for patients with I-DCM in recent years.[69, 70] Long-term studies of I-DCM have shown lower mortality and less severe phenotypes in recent years, despite overall older cohorts, possibly secondary to improved treatment, more

extensive diagnostic work-up and earlier diagnosis.[69, 70] It remains uncertain if this holds true for DCM in general. Along with improved survival in DCM, the risk for patients to develop comorbidities increases which in turn could affect prognosis. Patients with DCM are also in general older than patients with I-DCM and the impact of comorbidity on outcome in patients with DCM in a wider sense is inadequately studied.

Prognostic factors

The variables used for HF classification provide prognostic information. During a long period of time, the studies were mainly focused on HFrEF, but alongside the increased understanding of the high prevalence, morbidity and mortality also in HFpEF, the number of studies has increased in the last two decades. Compared with HFrEF, patients with HFpEF are overall characterized by higher age, a higher proportion of women, lower prevalence of CAD and higher prevalence of valvular heart disease, atrial fibrillation (AF) and hypertension.[71-73] Mortality in HFpEF is half to two-thirds compared to HFrEF.[74, 75] Higher BNP and NT-proBNP predicts mortality.[76, 77] Mortality varies in patients of the same NYHA class and there is a substantial overlap with regard to biomarkers, measures of quality of life and functional testing.[78] The relationship between symptoms and prognosis is not linear but severe symptoms are associated with poorer prognosis.[77] The mortality is higher in men than women, both in HFrEF and HFpEF.[79, 80]

In UK, the number of comorbidities in patients with HF increased by 60% between 2002 and 2014.[5] Increasing number of comorbidities has been associated with mortality in acute decompensated HFrEF,[81] and the relative importance of non-cardiac comorbidities has increased alongside the decreasing proportions of CV death and cardiac death in HFrEF trials over the last decades.[82] A model based on the Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure trial (PARADIGM-HF),[49] showed that higher age (> 60 years), NYHA class III/IV, diabetes, HF duration > 1 year, male sex, peripheral arterial disease, lower LVEF (< 40%), prior myocardial infarction, lower systolic blood pressure (< 120 mmHg), and lower body mass index (< 30 kg/m2) predict mortality in HFrEF.[77]

Impact of ischaemic heart disease on prognosis in heart failure

After an acute myocardial infarction, patients are at increased risk for recurrent cardiovascular events and the risk is additionally increased for patients with HF.[83-85] The impact of IHD on mortality in patients with HFrEF has, however, been studied in different settings with inconsistent results. Observational studies have shown either similar[86-89] or increased[72, 90, 91] mortality with conflicting results in studies of hospitalized cohorts. Studies from the 1980–1990s, taking the extent of CAD into account, reported similar mortality for patients with non-ischaemic HFrEF compared with patients with limited CAD,[92] but also that increasing severity of CAD associated with increased mortality, emphasizing the adverse impact of IHD in HFrEF.[93] A meta-analysis of randomized controlled trials (RCTs) studying CRT showed that IHD associated with increased all-cause mortality;[56] however, post-hoc analyses of pharmaceutical RCTs in patients treated with ACEI/ARB, beta-blockers and MRA are inconsistent. In The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvap-

tan trial (EVEREST), CAD did not associate with CV mortality after multivariable adjustments.[94] In PARADIGM-HF, investigator reported ischaemic aetiology did not associate with multivariable-adjusted higher hazard of either all-cause mortality, CV mortality or HF hospitalization compared to hypertensive aetiology or I-DCM;[35] however, an analysis of pooled data from PARADIGM-HF and the Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure trial,[95] showed that all-cause mortality rates were higher in ischaemic aetiology than in non-ischaemic aetiology among men, but not among women.[79] In HFpEF there are likewise discrepancies as many observational studies[72, 80, 87-91] report no impact of IHD on mortality, in contrast to RCT.[96]

There are possible reasons for the disparate results. The definition of IHD in studies varies, from clinical IHD as judged by a reporting physician, to the requirement of coronary angiographies. Varying availability and accessibility of coronary revascularization in different regions and periods of time may affect patient selection and complicate comparisons. Cohort composition differences between trials and observational studies are frequent. Elderly patients are more vulnerable than the younger for reasons like age-related decrease in renal function, altered drug pharmacokinetics and pharmacodynamics increasing the risk for toxicity and significant drug interactions.[97, 98] Multimorbidity is common among elderly HF patients. More than 60% of American elderly Medicare beneficiaries with HF have at least five chronic medical conditions and polypharmacy is associated with multiple adverse outcomes.[99, 100] The exclusion of many elderly is evident considering the mean age of patients being approximately 60–65 years in many large HFrEF trials,[31, 32, 34, 44, 45, 49, 50, 101] particularly affecting the generally older cohort with ischaemic aetiology. Women are on average five to ten years older than men at the time of the first myocardial infarction or percutaneous coronary intervention (PCI).[102, 103] Older age and age-related higher comorbidity may in part explain both the under-representation of women in RCTs,[104] and the reported sex-associated variations in prognostic influence of IHD in HF trials.[79] In similarity to many other trials, patients with hypotension and severely reduced renal function were excluded in PARADIGM-HF and patients with previous unacceptable side-effects of ACEI/ARB were excluded. Moreover, all patients were required to complete a pre-trial phase with Enalapril and ARNI treatment before enrolment, from which those with ischaemic aetiology more frequently dropped out, additionally increasing selection bias.[105] The proportion of elderly and women are even higher in HFpEF, most likely explaining the discrepancies between randomized and observational studies.

In the past decades we have also observed a gradual decline of both the incidence and mortality in myocardial infarctions due to a continuous development of effective medical treatment and invasive procedures,[106-108] which may have changed the outcome also for patients with ischaemic HF.

RATIONALITY FOR THIS THESIS

Several circumstances serve as rational for further investigation of the influence of IHD in HF. First, IHD is highly prevalent in HF irrespective of LVEF, and the most common cause of HFrEF. Second, the results from previous studies of the impact of IHD on mortality in patients with HF are conflicting. Third, it is unclear whether the substantial progress made in the treatment of IHD, alongside the continuous changes in demographics, clinical characteristics and comorbidities in the HF population, has improved the prognosis for patients with HF. Fourth, observational studies are frequently presented years after data collection and several frequently cited observational studies include cohorts from the 1990s and early 2000s. Due to the increasing survival seen in the last decades, older age and increasing multi morbidity may have changed the prognostic influence of IHD in a more contemporary real-world cohort.

Previous reports of the influence of baseline variables and comorbidities in I-DCM and DCM are conflicting, possibly due to differences in inclusion- and exclusion criteria, rather small cohorts, or patient inclusion over many decades making comparisons with more contemporary cohorts difficult. The overall increase in comorbidity alongside the increased longevity in DCM may have changed the prognostic impact of comorbidities over time. Data on prognosis and prognostic factors in contemporary Swedish patients with DCM are scarce and the low mortality reported for I-DCM is not transferable to DCM in general.

The pathophysiology differs with HF aetiology. Differences in early treatment response may be of importance for the demonstrated differences in long-time prognosis. The influence of aetiology on early improvement after initiation of GDMT is inadequately studied.

AIMS

- To study the impact of IHD on mortality in a contemporary HF cohort with respect to LVEF, sex, age and HF duration. To study if the mortality for patients with HF and IHD significantly decreased compared to patients with non-ischaemic HF during the years 2000–2012 (*Paper I)*.

- To study the effect of HF duration on comorbid burden and prognosis, and further the prognostic impact of baseline characteristics and comorbidities, in a contemporary DCM cohort (*Paper II)*.

- To investigate changes in baseline characteristics, outcomes and the prognostic impact of baseline characteristics in DCM during the years 2003–2015 (*Paper III)*.

- To investigate if patients with new-onset non-ischaemic HFrEF respond better to initiated GDMT than patients with ischaemic HFrEF, and to assess the degree of investigation for ischaemic aetiology (*Paper IV*).

PATIENTS AND METHODS

Data sources

Data for *Paper I–III* were extracted from the Swedish Heart Failure Registry (SwedeHF; www.swedehf.se), a register of patients with an established diagnosis of HF based on clinical assessment.[109] The register, managed by the Uppsala Clinical Research Center, was formally established in 2003 but includes data from 2000 by retrospective registration. Around 80 variables are recorded at hospital discharge or at outpatient visits and additional patient related information is acquired by linkage to other registers. The Swedish National Patient Register (NPR) provides data of health care episode dates and comorbidities for both in-hospital and outpatient non-primary care. The NPR and the Swedish cause of death register,[110] which provide data on time and cause of death, are maintained by the Swedish National Board of Health and Welfare (www.socialstyrelsen.se).

The Longitudinal integrated database for health insurance and labour market studies, managed by Statistics Sweden (www.scb.se), provides socio-economic data. More than 90% of patients in SwedeHF are registered in specialized care and approximately 60–65% during in-hospital care. The number of reporting health care givers increases, from 45 reporting hospitals in 2007 to 64 out of 75 Swedish hospitals in 2019. Registration in SwedeHF has increased linearly and more than 110,000 individual patients were registered at the end of 2021. The method of reporting the coverage of SwedeHF, i.e. the proportion of patients also registered with HF in the NPR, has varied over the years. The overall coverage is low (approximately 14–15% for incident HF and 20–25% for prevalent HF in 2008–2016), but higher for hospitalized patients (54% for patients with a recorded echocardiographic examination registered by centres reporting ≥ 10 patients in 2014). An updated SwedeHF dataset were analyzed in *Paper II-III* vs *Paper I*.

Data for *Paper IV* were extracted from a research database including all adult patients hospitalized and discharged with a primary International Classification of Diseases (tenth revision) code I42 (cardiomyopathy) or I50 (HF), at the Sahlgrenska University Hospital, Gothenburg, Sweden, between 1 January 2016 and 31 December 2019. All data were originally obtained from medical records and administrative systems.

Paper I

Study population

All 51,060 patients registered in SwedeHF from 11 May 2000 to 31 December 2012 were eligible for inclusion. IHD was defined by reported IHD, angina, previous myocardial infarction, or a previous performed PCI or coronary artery bypass graft surgery (CABG). After exclusion, 17,778 patients were categorized as HF with IHD (IHD) and 13,168 patients as HF without IHD (nonIHD) (*Figure 1*).

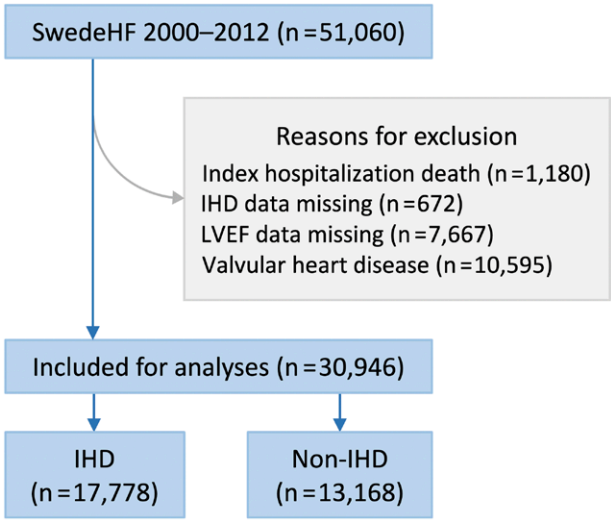

Figure 1. Patient exclusion flow chart.
SwedeHF, Swedish Heart Failure Registry; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; Non-IHD, non-ischaemic heart disease.

Outcomes

The outcome was all-cause mortality, occurring until end of follow-up, 31 December 2012. Comparisons were made for IHD vs non-IHD in the whole cohort, and in subgroups stratified for sex, age group (< 60, 60 to < 70, 70 to < 80, and ≥ 80 years), LVEF group (< 30, 30 to < 40, 40 to < 50, and ≥ 50%), HF duration (< 6 and ≥ 6 months), and index calendar period (2000–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012, with the first 4 years merged because of low numbers).

Statistics

For baseline variable comparisons we used Mann-Whitney U test for continuous variables, Fisher's Exact test for dichotomous variables, Mantel-Haenszel χ^2 trend test for ordered categorical variables and χ^2 test for non-ordered categorical variables. Mortality over calendar periods were standardized for the distribution of age and sex for the first period, 2000–2004. The effect of IHD on mortality between calendar periods was analyzed with Cox regression. The unadjusted cumulative mortality was estimated with survival analysis. Cox regression was used for analysis of time to death. Variables for adjusted analyses were chosen on the basis of presumed importance. Missing categorical variables were treated as a separate unknown category. Missing continuous variables (7.8%) were not imputed. The proportional hazards assumption was assessed by an interaction analysis between the IHD group and log (time).

Paper II

Study population

All 76,250 patients registered in SwedeHF between 1 January 2003 and 31 December 2016 were eligible for inclusion. After exclusion, 2,019 patients with DCM-duration < 6 months (recent-onset DCM; RODCM) and 1,714 patients with DCM duration ≥ 6 months (long-standing DCM; LDCM) were included for analysis (*Figure 2*).

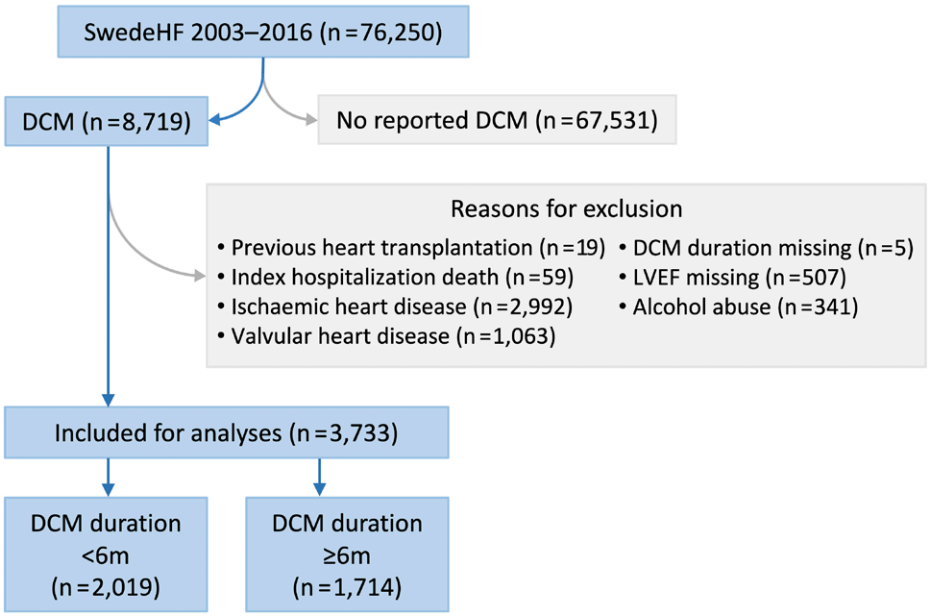

Figure 2. Patient exclusion flow chart.

SwedeHF, Swedish Heart Failure Registry; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; m, months.

Note. Adapted from Silverdal J, Sjöland H, Pivodic A, Dahlström U, Fu M, Bollano E. Prognostic differences in long-standing vs. recent-onset dilated cardiomyopathy. ESC Heart Fail. 2022;9(2):1294-303. Doi.org/10.1002/ehf2.13816. © 2020 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of the European Society of Cardiology.

Outcomes

The outcome measures were; all-cause-, CV-, and non-CV death; heart Tx; all-cause death or heart Tx; all-cause-, CV-, and HF hospitalizations; and a combined outcome of all-cause death, heart Tx and HF hospitalization. Outcomes were analyzed until end of follow-up, 31 December 2016. The influence of DCM duration on comorbidity, and predictors for the combined outcome were analyzed.

Statistics

For baseline variable comparisons we used Mann-Whitney U test for continuous variables, Fisher's Exact test for dichotomous variables, Mantel-Haenszel χ^2 trend test

for ordered categorical variables and χ^2 test for non-ordered categorical variables. For analyses of trends of age and number of comorbidities for different categories of DCM duration, we used the Jonckheere-Terpstra test and multivariable linear regression for the age-adjusted analysis. Multivariable-adjusted Cox regression was used for of time-to-event analyses and a propensity score-matched analysis was performed as sensitivity analysis for all-cause death and the combined outcome. Cox regression was used for predictor analyses.

Paper III

Study population

All patients registered in SwedeHF between 1 January 2003 and 31 December 2015 (n = 69,537) were eligible for inclusion. The SwedeHF database was the same as in Paper II, but the inclusion was restricted to the end of 2015 in order to enable one-year outcomes in all patients. After exclusion, 7,873 patients were included for analysis (*Figure 3*). Patients were divided in three calendar periods; 2003–2007, 2008–2011 and 2012–2015. To compensate the lower registration in SwedeHF during the first years, the first study period was longer.

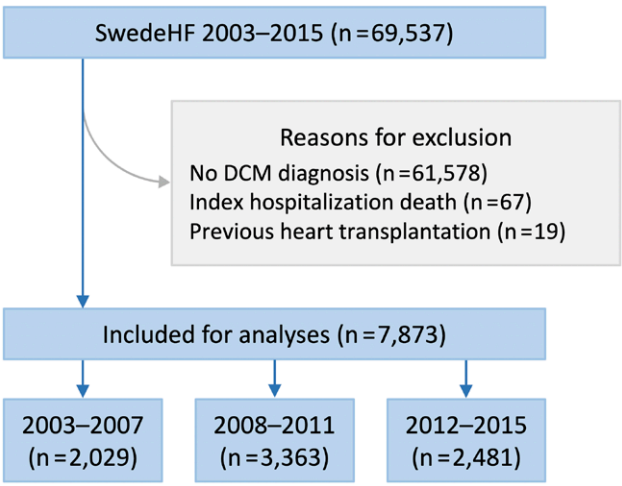

Figure 3. Patient exclusion flow chart.
SwedeHF, Swedish Heart Failure Registry; DCM, dilated cardiomyopathy

Outcomes

The outcome measures were: death, heart Tx, CV hospitalization, HF hospitalization and all-cause hospitalization, all within one year of registration in SwedeHF, and a composite outcome including all these endpoints. Predictors for the combined outcome were analyzed, presented by calendar period.

Statistics

For baseline variable comparisons we used; the Jonckheere-Terpstra test for continuous variables, taking the time period order into account; Mantel-Haenszel χ^2 trend test for dichotomous variables, testing linearity between time periods, and for ordered categorical variables; and χ^2 test for non-ordered categorical variables. Poisson regression were used for event rates analyses. Cox regression were used for predictor analyses, including interaction between predictors and calendar period. Categorical variables with > 1% missing data (NYHA 17.6%, LVEF 5.8%, device treatment 1.4%) were handled as unknown category.

Paper IV

Study population

Data were extracted from the above described register of patients hospitalized at the Sahlgrenska University Hospital. For analyses, we included all 364 patients with recent-onset non-valvular HFrEF who subsequently received follow-up at hospital-based out-patient HF units at Sahlgrenska University Hospital or Angered Hospital for GDMT titration. Recent-onset was defined by no previous medical record of HF or systolic dysfunction at any previous imaging. HFrEF was defined by LVEF < 40% at first evaluation.

Patients first hospitalized without LVEF evaluation were included if a subsequent investigation within 6 months established HFrEF. Patients diagnosed in an out-patient setting were included if they were hospitalized for HF within 6 months of established HFrEF and if no GDMT was initiated before hospitalization. Patients lacking evidence-based benefit of GDMT were not included, i.e. patients with haemodialysis, amyloidosis, and transient systolic dysfunction.

Ischaemic aetiology (IHF) was defined by CAD sufficiently explaining systolic dysfunction. When lacking angiography data, patients with a history of previous myocardial infarction, PCI or CABG were classified as IHF. Patients were also classified as IHF if a later investigation during the full study period revealed signs of a previous myocardial infarction or CAD of explanatory extent. Non-ischaemic aetiology (non-IHF) was defined by non-fulfilled IHF-criteria, after coronary investigation. In cases with neither previous history of IHD, nor performed investigation, the aetiology was classified as unknown.

Outcomes

The primary outcome measure was a hierarchical clinical composite score classifying patients as worsened, improved or unchanged, based on the occurrence of hard (death, heart Tx or HF hospitalization) and/or soft outcomes (changes in LVEF, NYHA and NT-proBNP). Patients were first evaluated for deterioration, then for improvement. Patients neither worsened, nor improved, were classified as unchanged, as long as soft outcome variables were recorded during the 28-week follow-up (*Table 1*). Predictors for composite worsening and improvement, and the frequency of decisions for coronary investigation at the time of established HFrEF were analyzed.

Table 1. Classification of response to treatment

	Clinical composite outcome		
	Worsened	Improved	Unchanged
Hard outcome Death, heart Tx or HF hospitalization	Any	None	None
LVEF change	≥10-unit decrease	≥10-unit increase	Minor change
NYHA change	≥1-point increase	≥1-point decrease	Minor change
NT-proBNP change	≥30% increase	≥30% decrease	Minor change

Heart Tx, heart transplantation; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro B-type natriuretic peptides; NYHA, New York Heart Association functional class.

Statistics

For continuous variables we used Student t-test for two-group comparisons. For dichotomous variables we used Fisher's Exact test for tests between two groups and χ^2 test for tests of all groups. For the overall outcome analyses for three-group comparisons, we used χ^2 test. For two groups comparisons, we used the Mantel-Haenszel χ^2 trend test for overall analyses and Fisher's exact test for dichotomous outcomes. Kruskal-Wallis test was used for analyses of time to soft outcomes. Logistic regression was used for predictor analyses.

Software

In *Paper I–III*, the statistical analyses were performed, and artworks created, using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). In *Paper IV*, the statistical analyses were performed using SPSS Statistics for Macintosh, version 28.0 (IBM Corp., Armonk, NY, USA).

Ethical considerations

All studies were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments,[111] and approved by ethics committees. All studies are observational and no patient was exposed to any activity outside ordinary medical care.

Paper I–III: ethical approval was granted by a multi-site ethics committee, diary numbers: 2012/285-31, 2013/392-32, 2017/510–32. Written informed consent is not required for registration in SwedeHF, but patients are informed of registration and are allowed to opt out. To avoid risk for identification, all analyses were carried out on pseudonymized data reducing the risk for individual patient data exposure.

Paper IV: ethical approval was granted by the regional ethics committee in Gothenburg, diary numbers: 2013/709-13, 2017/T539-17 with additional amendment 2021-01644.

RESULTS

Paper I

Baseline characteristics

Patients with IHD were older (74.6 vs 69.8years, $P < 0.0001$), more often male (67.6% vs 61.2%, $P < 0.0001$) and were more often registered as HF duration ≥ 6 months (53.8% vs 37.5%, $P < 0.0001$). The distribution of LVEF was similar between groups ($P = 0.096$). The prevalence of alcohol abuse and atrial fibrillation was higher in non-IHD, whereas almost all other comorbidities were more frequent in IHD. Patients with IHD were more often treated with beta-blockers and nitrates but less often with MRA.

Mortality with respect to ischaemic heart disease

Over similar median follow-up times, IHD 2.4 years (Interquartile range [IQR] 1.0–4.2) vs non-IHD 2.6 years (IQR 1.1–4.3), the crude mortality event rate per 100 person-years (95% confidence interval [CI]) was higher in IHD for the whole cohort 14.8 (14.4–15.1) vs 9.7 (9.4–10.0), and in all subgroups. The hazard of all-cause death was significantly higher in IHD than in nonHD for almost all subgroups, also after multivariable adjustments. The increased risk associated with IHD decreased with higher age and higher LVEF and was not significantly increased for patients with preserved LVEF (*Table 2*). Stratifying for age and LVEF showed that the risk entailed by IHD diminished with increasing age, and with increasing LVEF within each age category. IHD did not infer increased hazard of death for patients with LVEF ≥ 40% in any age group. The greatest impact of IHD was seen in the youngest with markedly reduced ejection fraction. For patients 80 years of age or older, IHD was prognostically adverse only in patients with LVEF < 30%.

Temporal trend of mortality with respect to ischaemic heart disease

Throughout the entire study period, mortality standardized for age and sex was higher in IHD. After adjustments for time-updated age, sex, LVEF group and HF duration, the increased risk associated with IHD did not decrease significantly over time, P for interaction = 0.28 (*Figure 4*).

Paper II

Baseline characteristics

Patients with RODCM were significantly younger (58.9 years vs 62.5 years) with a slightly lower male predominance (70.7% vs 73.7, $P = 0.041$). The distribution of LVEF and NYHA categories suggested worse ventricular function, but better functional capacity in RODCM. Except for smoking, all analyzed comorbidities were more frequent in LDCM with significant differences in 11 of 13 comorbidities. In RODCM, treatment with ACEI/ARB and beta-blockers were more frequent, whereas MRA and devices were less often used.

Comparing RODCM with LDCM further divided by the median duration of DCM (3.5 years [IQR 0.7–7.4]), the age-adjusted number of comorbidities (95% CI) increased

Table 2. Adjusted hazards of all-cause death, IHD vs non IHD

	Adjusted for age and sex		Multivariable-adjusted†	
	HR (95% CI)	*P* value[1] or *P* value for interaction[2]	HR (95% CI)	*P* value[1] or *P* value for interaction[2]
All individuals	1.23 (1.18–1.28)	<0.0001[1]	1.16 (1.11–1.22)	<0.0001[1]
Sex				
Male	1.25 (1.18–1.31)	0.40[2]	1.16 (1.10–1.23)	0.83[2]
Female	1.20 (1.13–1.28)		1.15 (1.08–1.24)	
Age				
<60 years	1.58 (1.34–1.88)	<0.0001[2]	1.56 (1.30–1.87)	<0.0001[2]
60–<70 years	1.48 (1.33–1.65)		1.42 (1.27–1.59)	
70–<80 years	1.29 (1.20–1.39)		1.18 (1.09–1.28)	
≥80 years	1.16 (1.10–1.23)		1.10 (1.04–1.17)	
LVEF				
<30%	1.55 (1.44–1.67)	<0.0001[2]	1.39 (1.28–1.51)	<0.0001[2]
30–39%	1.30 (1.20–1.41)		1.20 (1.10–1.31)	
40–49%	1.09 (1.00–1.19)		1.12 (1.02–1.23)	
≥50%	1.03 (0.96–1.12)		0.96 (0.88–1.04)	
Heart failure duration				
<6 months	1.16 (1.09–1.23)	0.71[2]	1.18 (1.11–1.26)	0.37[2]
≥6 months	1.18 (1.11–1.24)		1.14 (1.07–1.21)	

† Adjusted for age, sex, LVEF (group) and heart failure duration (unless subgroup variables), index period, smoking, hypertension, atrial fibrillation, diabetes, lung disease, haemoglobin, creatinine clearance, systolic blood pressure, New York Heart Association class, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, mineralocorticoid receptor antagonists, beta blockers, diuretics, digoxin, statins, oral anticoagulants, peripheral artery disease, stroke/transient ischaemic attack, cancer, follow-up specialty and device therapy.
CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

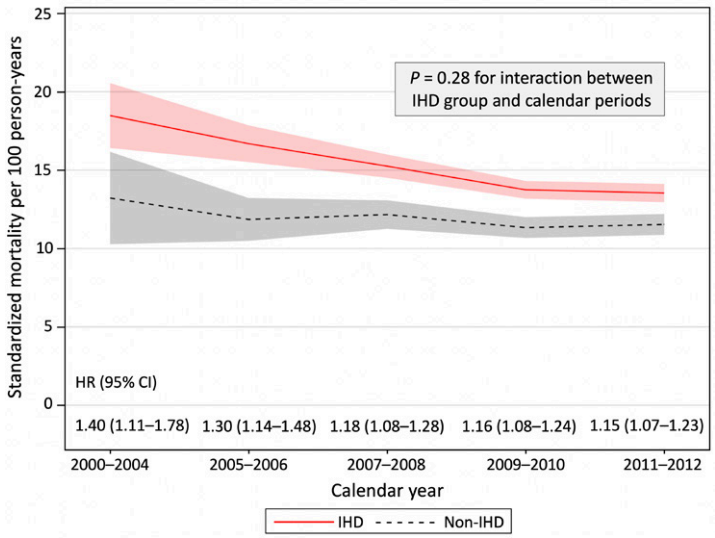

Figure 4. Mortality rates over calendar periods, standardized for age and sex. Hazard ratios for mortality, IHD vs non-IHD, adjusted for time-updated age, sex, LVEF group, and HF duration.

CI confidence interval; HF; heart failure; HR, hazard ratio; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; non-IHD, non-ischaemic heart disease.

Note. Table and Figure adapted from Silverdal J, Sjöland H, Bollano E, Pivodic A, Dahlström U, Fu M. Prognostic impact over time of ischaemic heart disease vs. non-ischaemic heart disease in heart failure. ESC Heart Fail. 2020;7(1):264-273. Doi.org/10.1002/ehf2.12568.

with increasing duration of DCM: RODCM 1.19 (1.15–1.24) vs LDCM duration ≤3.5 years 1.52 (1.49–1.56) vs LDCM duration > 3.5 years 1.85 (1.78–1.92), $P < 0.0001$.

Impact of heart failure duration on prognosis and comorbid burden

The unadjusted cumulative incidence of the composite outcome (all-cause death, heart Tx, and HF hospitalization was higher in LDCM. All studied outcomes were significantly more frequent in LDCM than in RODCM (*Table 3*). The age- and sex-adjusted all-cause mortality (95% CI) was 5.5% (5.0–6.0) for LDCM vs 2.9% (2.6–3.2) for RODCM (multivariable-adjusted HR 1.56; 95% CI 1.34–1.82; $P < 0.0001$). The propensity score-matched analyses yielded similar results for all-cause death (HR 1.57; 95% CI 1.31–1.87; $P < 0.0001$) and for the combined endpoint (HR 1.33; 95% CI 1.18–1.51; $P < 0.0001$).

Table 3. Outcomes by DCM duration

Endpoint	RODCM		LDCM		LDCM vs RODCM Hazard ratio (95% CI)‡
	Events n (%)	Event rate† Age- and sex-adjusted	Events n (%)	Event rate† Age- and sex-adjusted	
All-cause death	327 (16.2)	2.9 (2.6–3.2)	577 (33.7)	5.5 (5.0–6.0)	1.56**** (1.34–1.82)
CV death	173 (8.6)	1.5 (1.2–1.7)	356 (20.8)	3.2 (2.8–3.6)	1.67**** (1.36–2.05)
Non-CV death	154 (7.6)	1.4 (1.2–1.7)	221 (12.9)	2.3 (2.0–2.6)	1.42** (1.13–1.79)
Heart Tx	22 (1.1)	0.1 (0.1–0.2)	43 (2.5)	0.3 (0.2–0.5)	2.12**** (1.14–3.91)
All-cause death or heart Tx	348 (17.2)	3.3 (2.9–3.6)	616 (35.9)	6.5 (6.0–7.1)	1.63**** (1.41–1.90)
All-cause hospitalization	1158 (57.4)	21.8 (20.6–23.1)	1101 (64.2)	26.7 (25.2–28.3)	1.17*** (1.06–1.28)
CV hospitalization	940 (46.6)	15.2 (14.3–16.2)	923 (53.9)	19.3 (18.1–20.6)	1.19*** (1.07–1.32)
HF hospitalization	727 (36.0)	10.2 (9.5–10.9)	776 (45.3)	14.4 (13.4–15.4)	1.36**** (1.21–1.53)
All-cause death, heart Tx or HF hospitalization	893 (44.2)	12.5 (11.7–13.3)	989 (57.7)	18.0 (16.9–19.1)	1.37**** (1.24–1.52)

†Event rate per 100 person-years, 95% confidence intervals computed by using exact Poisson limits. ‡ Hazard ratios by Cox regression analyses adjusting for index age, sex, location for registration, systolic blood pressure, heart rate, New York Heart Association functional class, left ventricular ejection fraction, left bundle branch block, haemoglobin, estimated glomerular filtration rate, acetylsalicylic acid, statins, diuretics, implantable cardioverter defibrillator/cardiac resynchronization therapy, hypertension, diabetes, atrial fibrillation, lung disease, stroke/transient ischemic attack, liver disease, renal disease, dialysis, non-coronary vascular disease, sleep apnoea, cancer within the last 3 years, musculoskeletal or connective tissue disorder within the last 3 years. CI, confidence interval; CV, cardiovascular; Heart Tx, heart transplantation; HF, heart failure; IQR, interquartile range; LDCM, dilated cardiomyopathy with long-standing HF; RODCM, dilated cardiomyopathy with recent-onset HF.
** = p<0.01 *** = p<0.001 **** = p<0.0001.

Note. Adapted from Silverdal J, Sjöland H, Pivodic A, Dahlström U, Fu M, Bollano E. Prognostic differences in long-standing vs. recent-onset dilated cardiomyopathy. ESC Heart Fail. 2022;9(2):1294-303. Doi.org/10.1002/ehf2.13816.

A number or baseline characteristics were independently associated with higher hazard of the combined outcome in both RODCM and LDCM (*Figure 5*). In RODCM only did male sex, lower haemoglobin and treatment with acetylsalicylic acid associate with increased risk, whereas statins associated with lower. In LDCM only did heart rate ≥ 75 beats per minute, AF, impaired renal function, musculoskeletal or connective tissue disease within 3 years, and treatment with diuretics associate with increased hazard of the combined outcome.

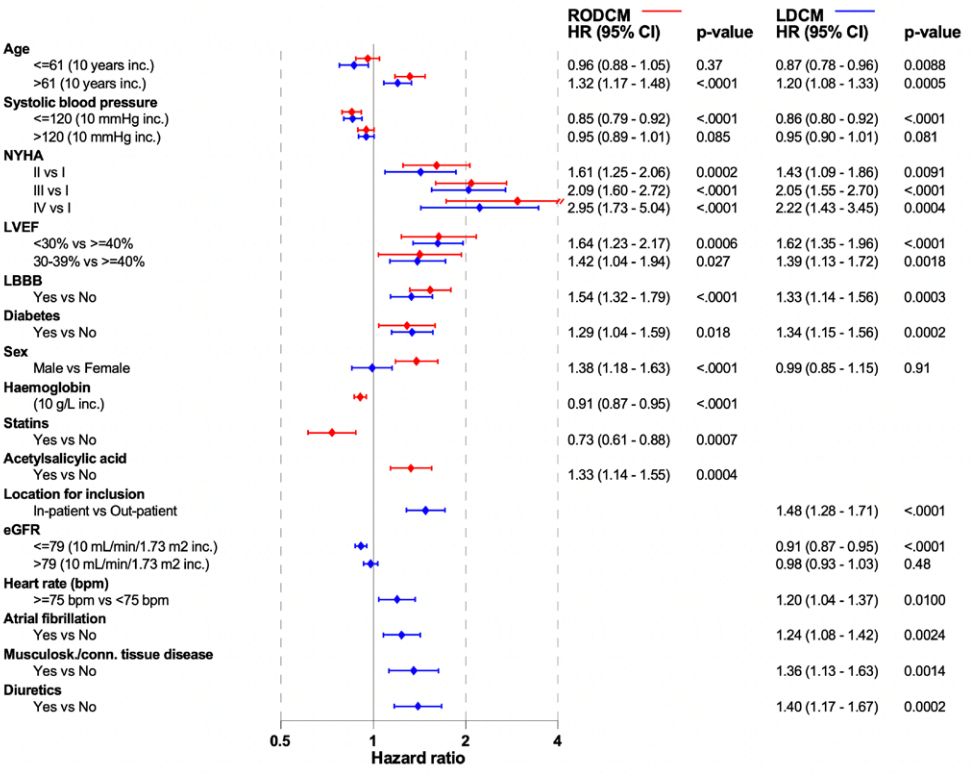

Figure 5. Multivariable-adjusted Cox regression analysis of predictors for the combined outcome of all-cause death, heart transplantation, or heart failure hospitalization, by dilated cardiomyopathy duration.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LBBB, left bundle branch block; LDCM, long-standing dilated cardiomyopathy; LVEF, left ventricular ejection fraction; Musculosk./conn. tissue disease, musculoskeletal or connective tissue disorder within last 3 years; NYHA, New York Heart Association functional class; RODCM, recent-onset dilated cardiomyopathy

Note. Reprinted from Silverdal J, Sjöland H, Pivodic A, Dahlström U, Fu M, Bollano E. Prognostic differences in long-standing vs. recent-onset dilated cardiomyopathy. ESC Heart Fail. 2022;9(2):1294-303. Doi.org/10.1002/ehf2.13816.

Paper III

Baseline characteristics

Comparing the baseline variable composition between the three calendar periods, several statistically significant small changes were seen. The mean age increased (63.9 to 64.9 years) and the proportion of women increased gradually (22.5% to 27.6%). The proportional distribution of categorized LVEF and NYHA showed somewhat better function. The prevalence of diabetes and AF were similar, whereas HT increased (38.6% to 52.5%). Renal function improved (mean estimated glomerular filtration rate 69.1 to 72.7 ml/min/ 1.73m2). Some differences in treatment were noted. Beta-blocker use increased gradually (89.5% to 93.4%), whereas Digoxin use was halved (24.1% to 11.7%). Treatment with ICD/CRT increased, mainly due to increased use of ICD. Treatment with ACEI/ARB and MRA was stable.

Temporal trend of prognostic impact of baseline characteristics

During the whole study period, the overall age- and sex-adjusted one-year event rates per 100 person years (95% CI) for outcomes were: death 8.9 (8.1–9.7), heart Tx 0.4 (0.3–0.6), HF hospitalization 40.8 (39.2–42.4) and composite endpoint 72.9 (70.6–75.3). With the exception of heart Tx, both the crude and the age- and sex-adjusted one-year incidence of all specified outcomes was progressively lower over the study periods (*Table 4*).

Table 4. One-year event rates, by calendar period and total study period

Endpoint	Period 1 2003–2007	Period 2 2008–2011	Period 3 2012–2015	Total study period 2003–2015
	Age- and sex-adjusted one-year event rates per 100 person years (95% CI)			
All-cause mortality	10.7 (9.3–12.2)	8.3 (7.4–9.3)	8.1 (7.1–9.3)	8.9 (8.1–9.7)
Transplantation	0.3 (0.1–0.5)	0.5 (0.3–0.8)	0.4 (0.2–0.6)	0.4 (0.3–0.6)
Heart failure hospitalization	45.0 (41.7–48.6)	41.6 (39.2–44.2)	36.4 (33.8–39.2)	40.8 (39.2–42.4)
Cardiovascular hospitalization	61.8 (57.7–66.2)	59.2 (56.1–62.4)	49.1 (45.9–52.4)	56.5 (54.5–58.5)
All-cause hospitalization	74.6 (70.0–79.5)	72.0 (68.5–75.6)	58.2 (54.7–61.9)	68.0 (65.8–70.3)
Composite endpoint	80.6 (75.8–85.7)	76.2 (72.6–80.0)	63.1 (59.5–66.9)	72.9 (70.6–75.3)

Composite endpoint: One-year mortality, heart transplantation or all-cause hospitalization.
CI, confidence interval.

Note. Adapted from Sjöland H, Silverdal J, Bollano E, Pivodic A, Dahlström U, Fu M. Temporal trends in outcome and patient characteristics in dilated cardiomyopathy, data from the Swedish Heart Failure Registry 2003-2015. BMC Cardiovasc Disord 2021;21(1):307.

Over the entire period, the risk for all-cause mortality decreased yearly by 4% (risk ratio [RR] 0.96; 95% CI 0.94–0.98; $P = 0.0002$) For the composite endpoint, and for HF-, CV- and all-cause hospitalization, the risk decreased yearly by 3% (RR 0.97; 95% CI 0.96–0.98; $P < 0.0001$).

Diabetes, AF, higher age, lower LVEF, higher NYHA class and loop diuretic use were associated with increased hazard of the age- and sex-adjusted composite outcome in all three study periods, whereas ACEI/ARB use was associated with lower risk. Only NYHA, MRA use and treatment with device (ICD/CRT) showed significant interaction with time; the risk for the symptomatic vs the asymptomatic patients increased, and the risk increase associated with MRA use and device treatment was lost for the third period (*Figure 6*). After additional adjustments for NYHA class, LVEF, any device treatment and hypertension, analyses showed significant interaction with time for: female sex, with lower risk than men in the last period, P for interaction = 0.029; loop diuretics, with increasing risk over time, P for interaction = 0.028; and lower LVEF, with increasing risk over time, P for interaction = 0.043.

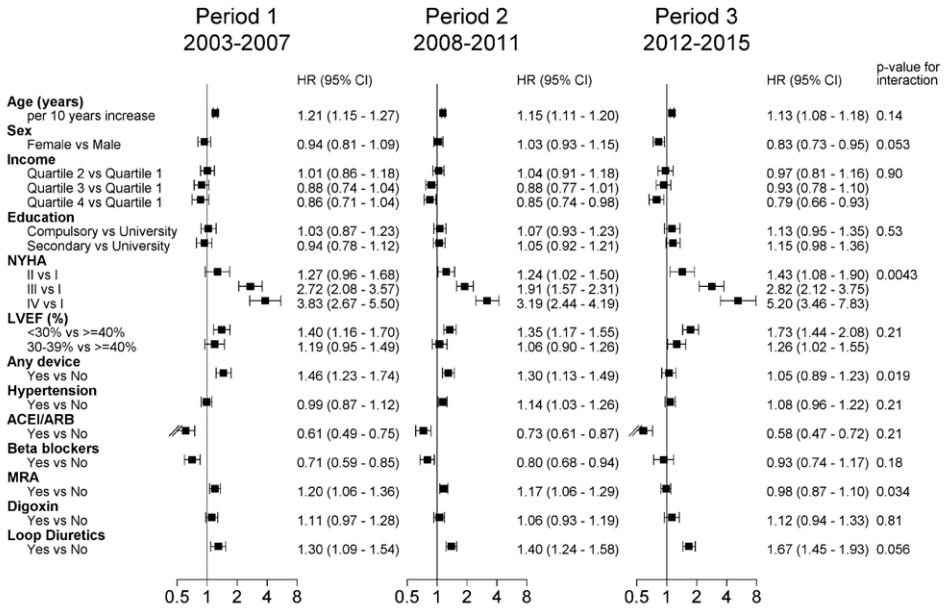

Figure 6. Age- and sex-adjusted hazard of one-year composite endpoint (death, heart transplantation, and all-cause hospitalization) over calendar periods, and interaction with time.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association functional class.

Note. Adapted from Sjöland H, Silverdal J, Bollano E, Pivodic A, Dahlström U, Fu M. Temporal trends in outcome and patient characteristics in dilated cardiomyopathy, data from the Swedish Heart Failure Registry 2003-2015. BMC Cardiovasc Disord 2021;21(1):307. © The Author(s) 2021. Published by BMC.

Paper IV

Baseline characteristic

Among the 364 patients analyzed, HFrEF aetiology was classified as nonIHF in 203, as IHF in 114 and as unknown in 47. Comparing nonIHF vs IHF, the male predominance was similar but nonIHF patients were younger (61.0 vs 69.4 years, $P < 0.001$). The mean LVEF was lower (26% vs 31%, $P < 0.001$) and the prevalence of hypertension, diabetes and cerebrovascular disease was significantly lower in non-IHF. The prevalence of previous and new-onset AF was similar.

At 6 months, almost all patients were treated with RAS blockade and beta-blockers, and the MRA use was similar between groups; however, the mean doses of RAS blockade and MRA were significantly higher in non-IHF than in IHF. The use of ARNI was low but significantly higher in non-IHF, 19% vs 8%.

Response to GDMT in new-onset non-ischaemic- vs ischaemic HFrEF

Patients with non-IHF showed better overall composite changes. In non-IHF, improvement was almost four times more frequent than worsening, whereas improvement was as frequent as worsening in IHF. The dominating reason for composite worsening in both groups were HF hospitalization, although less than half as frequent in non-IHF as in IHF. LVEF improvement was twice as frequent in non-IHF as in IHF, and the overall changes in NT-proBNP were more favourable for non-IHF, whereas no difference in overall changes in NYHA class was noted (*Table 5*). Median times to last evaluation of LVEF, NT-proBNP and NYHA were similar between groups. Multivariable-adjusted predictor analyses showed significant association between IHF and composite worsening (odds ratio [OR] 2.94; 95% CI 1.51–5.74; $P = 0.002$) and composite improvement (OR 0.35; 95% CI 0.18–0.65; $P < 0.001$). Lower SBP and higher LVEF both associated with unfavourable changes, with small OR and borderline significance.

Among patients not previously investigated for IHD (n = 261), a decision for coronary investigation was made in 69.0%, compared to 71.8% for patients with previous IHD without acute myocardial infarctions at the index hospitalization (n = 39).

Table 5. Outcomes, by heart failure aetiology

Outcome	Non-IHF *n* = 203 %	IHF *n* = 114 %	*P* value†
Composite clinical outcome	*n* = 194	*n* = 107	< 0.001
Worsened	19.1	43.9	< 0.001
Improved	74.2	43.9	< 0.001
Any hard outcome	17.7	39.5	< 0.001
Death within 28 weeks	2.0	5.3	0.228
Heart Tx within 28 weeks	0	0.9	0.442
HF hospitalization within 6 months	16.3	36.8	< 0.001
LVEF	*n* = 150	*n* = 73	< 0.001
Worsened ≥ 10 units	0	6.8	
Improved ≥ 10 units	70.0	35.6	
NYHA	*n* = 162	*n* = 66	*0.302*
Worsened ≥ 1point	0.6	0	
Improved ≥ 1point	69.8	56.1	
NT-proBNP	*n* = 161	*n* = 63	0.001
Worsened ≥ 30%	7.5	19.0	
Improved ≥ 30%	80.1	58.7	

†Overall *P* values from analyses including patients not investigated for IHD presented in italics.
Heart Tx, heart transplantation; HF, heart failure; IHF, ischaemic aetiology; LVEF, left ventricular ejection fraction; Non-IHF, non-ischaemic aetiology; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association functional class.

DISCUSSION

In this thesis, we have shown that IHD entails a worse prognosis in a broad spectrum of patients with HF and that the risk of death remains higher for patients with IHD despite significant improvements in the treatment of IHD.

In DCM, one of the most important causes of non-ischaemic HFrEF, we have shown the adverse effect of longer HF duration and the relationship between longer HF duration and higher comorbid burden. Moreover, we have analyzed outcomes and prognostic factors and described the changes in comorbidities and their prognostic importance over time.

We have also analyzed the clinical response to GDMT in recent-onset HFrEF and shown a better response in patients with non-ischaemic causes than in patients with ischaemic aetiology.

Ischaemic heart disease in heart failure

Impact of ischaemic heart disease on mortality in heart failure

In *Paper I,* we showed that the crude mortality increased markedly with older age to yearly mortality of over 20% in patients ≥ 80 years of age regardless of the presence of IHD. IHD was associated with higher mortality in all age groups, also after multivariable adjustments, but the impact diminished with increasing age likely due to increasing numbers of competing adverse non-cardiac comorbidities. The crude mortality was highest in patients with IHD and LVEF < 30%. It seems likely that patients in the lowest LVEF group represent those with larger myocardial infarctions or more disseminated CAD, factors previously associated with worse prognosis. With respect to LVEF, the greatest impact of IHD on mortality was also found in the groups of reduced LVEF, in part explained by the low absolute mortality in non-ischaemic HFrEF. Notably, the lowest mortality of all groups was found in non-ischaemic HFrEF. The results are in line with several real-world studies as previously described. With increasing LVEF, the adverse effect of IHD diminished, mainly due to increased mortality in non-IHD. IHD had no impact on mortality in HFpEF, in support of previous studies, both including and excluding patients with valvular heart disease.[72, 80, 90, 91]

In HFpEF, patients are generally characterized by older age and a greater comorbid burden, and the adverse effect of these factors most likely levelled the effect of IHD. Stratification by age showed that the diminishing adverse influence of IHD with increasing LVEF was similar for all age groups and that IHD was not associated with mortality for patients with EF ≥ 40% in any age subgroup. IHD was associated with increased mortality comparably for both sexes, and a recent analysis of SwedeHF showed a similar adverse impact of IHD in men and women regardless of the LVEF category.[112] Differences in age and comorbidity may explain the adverse impact of IHD also in women, as compared with HFrEF trials.[79] The mortality was lower for patients with recent-onset HF than for those with long-standing disease, but the adverse influence of IHD on mortality was similar for both groups.

Initial response to treatment in heart failure with reduced ejection fraction

The use of a clinical composite outcome was initially proposed for treatment evaluation in HF trials.[113] The consideration of both deterioration and improvement in functional and subjective measures of effect, also in patients not experiencing hard endpoints, increases the number of patients contributing to the assessment of treatment effect. The statistical power increases, which may enable conclusive results in studies with shorter follow-up, and retrospective analyses have shown increased treatment evaluation sensitivity compared to trials focusing on hard endpoints only.[114]

In our short-term study of recent-onset non-valvular HFrEF (*Paper IV*), patients with non-IHF more often improved after treatment initiation, displaying both less frequent composite worsening and more frequent composite improvement compared with IHF patients. The 28-week mortality of 3.2%, similar between groups, compares well to the one-year mortality of 9% reported in a recent study of 3,900 patients hospitalized for new-onset HFrEF and investigated for IHD.[115] CAD is associated with increased re-hospitalization in chronic HFrEF, and in our study, the almost three times greater odds for composite worsening in IHF compared with non-IHF was mostly explained by a doubled incidence of HF hospitalization.[94] The NT-proBNP changes were more favourable in non-IHF. In-hospital reduction of NT-proBNP (most often by ≥ 30%) in decompensated HF is associated with a better prognosis,[116] and initiation of treatment with ARNI in acute decompensated HFrEF reduces NT-proBNP and HF re-hospitalization within 8 weeks as compared with ACEI, further supporting the prognostic value of NT-proBNP reduction also in the first months after discharge.[117] GDMT induces reverse remodelling, i.e. the reversal of the structural changes of a failing heart, such as LV dilatation, LVEF reduction and atrial enlargement.[118-121] Reverse remodelling measured by LVEF improvement is favourable,[17-19, 119, 122] and was twice as frequent in non-IHF as in IHF in our study. Previous studies reporting superior treatment response in non-IHF most often evaluated changes ≥ 1 year after baseline;[17, 18, 123] however, our findings suggest that LVEF recovery occurs during the first months in a substantial proportion of patients.

Plausible reasons for the adverse impact of ischaemia

There are plausible explanations for the inferior reverse remodelling, the worse clinical response and the increased risk of death in IHF. Although HF may be transient, e.g. in septicaemia, the underlying causes of HF most often remain after the development of overt HF. Myocardial infarctions result in secondary scarring and permanent loss of contractile tissue, which may explain inferior LV recovery. Myocardial scars/fibrosis are also substrates for malignant ventricular tachyarrhythmias. Although the yearly incidence of SCD reported in HFrEF trials has diminished in the last two decades to approximately 3%, SCD still constitutes 30–40% of all deaths in HFrEF.[124] Myocardial scarring is, however, not restricted to patients with myocardial infarctions. Magnetic resonance imaging studies from the last ten years report evidence of scarring in 27–56% of patients with DCM.[125-128] Both the presence and the extent of scarring are associated with ventricular arrhythmias in IHF and non-IHF, but irrespective of scarring, the yearly event rate of ventricular tachyarrhythmia is greater in IHF

than in non-IHF.[129] While meta-analyses of implantable converter-defibrillator (ICD) trials have shown a reduction of all-cause death both in IHF and non-IHF,[130, 131] the role of ICDs in primary prevention of SCD in non-IHF has changed in recent years. In the largest and most recent RCT, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH),[132] ICD failed to reduce all-cause death compared with usual care, findings that resulted in downgraded recommendations for the use of ICD in non-IHF in the most recent European guidelines.[1] The patients were, in comparison to previous older trials, very well treated with ACEI/ARB, beta-blockers, MRA and CRT, which likely explains the low yearly event rate of SCD (< 2%) and the overall non-significant effect.

Subgroup analyses and a recent long-term follow-up analysis have shown significantly lower all-cause mortality for patients ≤ 70 years of age,[133, 134] to some extent modifying the initial interpretation; however, as patients were not treated with ARNI which reduces SCD,[135] or SGLT2-inhibitors which may reduce the risk for lethal arrhythmias and thus the beneficial effects of ICDs even further, the overall efficacy of ICDs for primary prevention of SCD in non-IHF is still debatable.

Even if patients with previous myocardial infarctions are at increased risk for recurrent CV events, the prognosis after myocardial infarctions has improved significantly. In Sweden, the mortality after ST-elevation myocardial infarctions decreased progressively from 22% in 1995–1996 to 14% in 2007–2008, and similarly in non-ST-elevation myocardial infarctions from 26% in 1995–1996 to 15% in 2011–2012, presumably due to the demonstrated improvement in medication and the steep increase in in-hospital coronary investigations and percutaneous interventions.[106, 107] The success in the treatment of acute myocardial infarctions, however, had no major impact on mortality in patients with HF. Although the mortality for patients with IHD appeared to diminish over the years 2000–2012, the mortality was higher in IHD during the entire study period, with no statistically significant change over time (*Paper I*).

Impact of coronary investigation and intervention

While studies report the prevalence of ischaemic aetiology or significant CAD to be 25–50% in new-onset HF,[87, 136, 137] American studies report that only a minority of HFrEF patients without myocardial infarction are investigated for IHD.[115, 138] In our study, decisions for investigating ischaemia were made in approximately 70% of patients hospitalized for new-onset HFrEF without myocardial infarction (*Paper IV*). Besides the possible influence of differences in health care systems and study set-ups, a likely reason for the higher proportion of investigations is the selection of patients planned for follow-up at dedicated outpatient HF clinics, thus limiting the number of very old and multimorbid. Interestingly there was no difference in coronary investigations between patients with or without previously known IHD.

The reasons for investigating IHD are several. As we have shown, IHD entails a worse prognosis and precise diagnostics are required for optimal treatment, be it invasive or medical. According to current guidelines, invasive coronary investigations are recommended in patients with refractory angina or symptomatic ventricular arrhythmias, and may be considered in patients with HFrEF with an intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests.[1] RCTs

evaluating revascularization in HFrEF patients without acute coronary syndromes or angina are scarce. A meta-analysis reported better long-term survival after revascularization and superior effect of CABG vs PCI; however, most studies were observational and only one of the RCTs evaluating CABG vs medical treatment was completed.[139] The Coronary-artery bypass surgery in patients with left ventricular dysfunction trial (STICH)[140] showed lower CV death and lower hospitalization after CABG but no difference in all-cause mortality over 56 months, partly due to procedure-related fatalities; however, a significant reduction of all-cause mortality was shown in a ten-year follow-up, thus providing evidence of possible long-term benefit for select patients.[141]

The recently published Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2)[142] evaluating PCI on top of GDMT in patients with ischaemic HFrEF, extensive CAD and demonstrable viability did not meet the expectations. Compared with GDMT, PCI did not reduce all-cause death or HF hospitalization over a median follow-up of 3.4 years. Moreover, revascularization did not increase LVEF at six or twelve months, questioning ischemia-induced myocardial stunning as the cause for persistent LVEF reduction.

Invasive treatment possibilities aside, patients undergoing coronary investigation are more likely to receive medical treatment recommended for the prevention of future cardiovascular events.[143, 144] Although the adverse influence of single-vessel disease has been disputed,[92] updated data have recently been presented. In a study of 22,000 patients undergoing coronary angiography during HF diagnostic work-up, single-vessel disease was associated with all-cause death in comparison to no CAD/non-obstructive CAD,[145] emphasizing the importance of coronary investigation for optimal risk reduction.

A definitive diagnosis of non-ischaemic HFrEF, possible only after a coronary investigation, should also lead to a proper assessment of the underlying cause, including an evaluation of hereditary disease, and the risk for SCD. Further, increased knowledge of the natural history of any condition will aid the caregivers in helping the individual patient, also when no additional treatment is available.

Dilated cardiomyopathy

In *Paper II and III*, we focused on the prognosis in DCM with attention to comorbidities. Most studies evaluating the effect of comorbidities in HFrEF do not stratify by aetiology. Less data are available for non-ischaemic HFrEF or DCM and predictive models based on mixed populations may not adequately reflect the impact of comorbidities on outcome in DCM.

Impact of heart failure duration on prognosis

During 2003–2016, the overall age- and sex-adjusted yearly all-cause mortality and HF hospitalization rates were 4.0% and 12%, respectively (*Paper II*). The yearly all-cause mortality for patients with RODCM was 2.9%, which can be compared with 5.4% reported in non-valvular non-ischaemic HFrEF (1998–2006),[146] 5% in recent-onset I-DCM and myocarditis (2002–2008),[147] and 1.1% in recent-onset I-DCM in the Heart Muscle Disease Registry of Trieste (2005–2015).[70] In patients with LDCM, the

yearly mortality of 5.5% (crude 7.0%) may be compared with the crude mortality of 7.7% in patients with I-DCM in PARADIGM-HF (2010–2012),[35] 5.0% in the control arm of DANISH (2008–2014),[132] and approximately 3% in patients with I-DCM referred for cardiovascular magnetic resonance imaging (2000–2011).[148] Comparing studies is complicated by the varying inclusion/exclusion criteria, but the survival of the SwedeHF DCM cohort seems similar to several contemporary studies and trials. Comparing RODCM with LDCM, all outcomes were more frequent in LDCM with HR 1.56 for all-cause death and HR 1.37 for the combined outcome of all-cause death, heart transplantation or HF hospitalization. A propensity score-matched analysis yielded similar results.

Impact of comorbidity on prognosis

Patients with RODCM were approximately four years younger than those with LDCM, and almost all studied comorbidities were more frequent in LDCM. The lower LVEF in RODCM is reasonable due to the shorter time with treatment, but the functional capacity was nevertheless better than in LDCM, probably due to younger age and less comorbidity. The lower use of ACEI/ARB and beta-blockers in LDCM may be explained by lower tolerability due to slightly older age and lower renal function. The number of comorbidities was increased with HF duration, also after adjustment for age, possibly due to a general physical vulnerability in the HF population.

Previous studies of factors associated with outcomes are not consistent. In our study, increasing NYHA score, lower LVEF, low blood pressure (< 120 mmHg), older age (above the median age of 61 years) and diabetes, all known predictors of CV- and all-cause death in contemporary chronic HFrEF,[77] were associated with the composite outcome regardless of HF-duration. In LDCM, older age was, however, favourable for patients younger than 61 years. Varying DCM aetiologies may matter as genetic aetiology is associated with earlier onset and worse prognosis.[149] Male sex was associated with outcome in RODCM, in keeping with other studies of recent onset I-DCM.[147, 150] In previous studies of DCM without specified disease duration, male sex has been either neutral or adverse,[148, 151] and in LDCM, male sex was not adverse, in contrast to chronic HFrEF.[77] LBBB has been shown to predict CV death and CV death/HF hospitalization in chronic HFrEF.[77] In I-DCM, new-onset LBBB in patients with long-standing disease is associated with all-cause mortality, unlike LBBB at first diagnosis.[152] In our study, LBBB was associated with a > 30% risk increase for the composite outcome for both RODCM and LDCM. Low haemoglobin was adverse in RODCM but not in LDCM, again in contrast to chronic HFrEF.[77] Reduced renal function and atrial fibrillation were unfavourable in LDCM, as previously shown for DCM[69, 151, 153] and chronic HFrEF.[154, 155] In HFrEF, the prognosis for patients with atrial fibrillation secondary to HF is worse than when the arrhythmia triggers HF.[156] Atrial fibrillation was adverse only in LDCM, and the higher prevalence in LDCM suggests a higher proportion of atrial fibrillation provoked by HF, compared with RODCM.

In RODCM only, treatment with acetylsalicylic acid was associated with increased risk, whereas statin use was associated with lower. Associations with these agents might have been expected in IHD, which in our case as far as possible was excluded. As the SwedeHF variable does not require coronary angiography, unrecognized IHD cannot be excluded; however, statins did not influence outcome in LDCM, in keeping

with previous analyses of SwedeHF and randomized HFrEF trials.[157, 158] It seems reasonable that continuous fluid retention despite optimized treatment would serve as a marker of more advanced disease, and treatment with diuretics was adverse in LDCM, as previously shown in a meta-analysis in HFrEF.[159]

Temporal trends of prognosis, demographics, clinical features and therapy

Previous studies of I-DCM cohorts over time have reported higher LVEF and lower NYHA class at the time of diagnosis, and declining one-year mortality.[69, 70, 160] In addition, a Swedish NPR-based study of patients hospitalized for non-ischemic HF during 1987–2003 showed a decreasing mean yearly mortality of approximately 5% in patients 35–65 years old.[161] Data on changes of comorbidity in DCM cohorts over time are scarce.

In the SwedeHF DCM cohort, one-year all-cause mortality and hospitalizations decreased yearly by 4% and 3%, respectively, during 2003–2015 (*Paper III*). Changes in demographics and patient clinical characteristics were observed. The proportion of women increased. Investigation with coronary angiography in HF diagnostic work-up increased three-fold in Sweden during the study period.[145] Women were less often investigated than men but presented more often with non-significant CAD, increasing the relative number of women diagnosed with non-IHF compared with men. Renal function improved, and the overall changes in categorized LVEF and NYHA functional class were favourable. Higher NYHA class was associated with an increasingly higher risk for the composite endpoint of one-year all-cause death, heart Tx and all-cause hospitalization compared with the asymptomatic, the proportion of which was stable. Older age was constantly associated with higher risk but the overall adverse effect of the slightly increased mean age over time was neutralized. The prevalence of hypertension increased very similarly to the increase noted in the entire SwedeHF cohort[162] and a Danish nationwide HF study,[163] contrasting to the decreasing prevalence in Sweden over the last 30 years.[164] Even though increasingly frequent, a diagnosis of hypertension was not associated with the composite outcome in any calendar period. The prevalence of diabetes and atrial fibrillation were stable, as were the associated increased risk in all study periods.

The use of ACE/ARB was unchanged over the study period. There was no linear trend in the use of MRA. The usage was reduced from the first to the second period and then increased for the last period, possibly explained by the publication of the EMPHASIS-HF trial (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms),[48] and the subsequently updated 2012 treatment guidelines. The use of devices, mainly ICD, increased slightly but is still underused, in line with the results from a previous analysis of SwedeHF patients with HFrEF, regardless of HF aetiology.[165]

Strengths and limitations

All studies are observational; hence, we do not claim causality when evaluating the relationships between baseline characteristics and outcomes.

SwedeHF, used for *Paper I–III*, comprises data from a real-world cohort without exclusion criteria and is thus more representative than trial populations. The large

sample size reduces the significance of random errors. Registration at secondary- and tertiary-level hospitals from all parts of Sweden, save the northern region, increases the generalizability. However, some limitations must be considered. The incomplete coverage of SwedeHF introduces a risk of selection bias, which may reduce validity. Registration of IHD does not require coronary investigation, which increases the risk of misclassification of patients with subclinical CAD. Classifications similar to ours, however, are frequent in observational studies and trials, maintaining comparability. In the SwedeHF database analyzed for *Paper I*, we classified patients with angina as IHD. Although frequent in IHD, angina also occurs in non-ischaemic HF. Angina without CAD, however, has not been associated with mortality in either HFrEF[166] or HFpEF,[96] and the possible misclassification of non-ischaemic patients with angina as IHD should not contribute to the noted higher mortality in IHD. The SwedeHF variable "valvular disease" is registered if deemed clinically significant, with no further definition. Lacking data on both the grade and the mechanism of valvular dysfunction, patients with "valvular disease" were excluded from analyses in *Paper I–II*, as were patients with alcohol abuse. Although reducing validity, exclusion of patients with severe valvular heart disease and substance abuse are common in RCTs and observational studies, again not reducing comparability.

Paper II–III are the first studies analyzing outcomes, prognostic factors and temporal trends for patients with DCM registered in SwedeHF.

In *Paper II*, we excluded patients with IHD to minimize the risk of inaccurate inclusion of patients with ischaemic HFrEF, thus possibly excluding patients with concomitant CAD not primarily causing the systolic dysfunction.

In *Paper III*, we applied less strict exclusion criteria, assuming the implicit exclusion of significant IHD and valvular disease when registering DCM, increasing the generalizability. Comparisons over time may be influenced by differences in non-measured or unknown circumstances. In the early years, the number of units reporting to SwedeHF was lower, increasing the selection bias and reducing the validity of the comparison by the period of inclusion in *Paper III*. Although the cohort composition may differ between hospitals, there have been no considerable changes in the proportion of patients with DCM in SwedeHF, ranging from 12–13% in the early years to 11–12% in the later years. It seems unlikely that the slight changes in the definition of DCM during the studied period would have significantly influenced the results.

The register used for *Paper IV*, comprises all patients hospitalized with a primary diagnosis of cardiomyopathy or HF at all three hospitals constituting the Sahlgrenska University Hospital, hence representing secondary- and tertiary level in-patient care of all hospitals in Gothenburg. Registration based on the primary diagnosis in electronic records ensured coverage. Availability of medical records enabled verification of data collection and classification of aetiology and functional status by an experienced cardiologist.

We included only patients with follow-up at HF outpatient clinics, and while this results in selection bias, the cohort represents the population of the current clinical

practice. Including only post-myocardial infarction patients with systolic dysfunction who were subsequently re-admitted for HF introduces selection bias. The readmission was not automatically considered an outcome; however, these patients may constitute a fraction with greater myocardial damage or less positive response to treatment compared with post-myocardial infarction patients not re-admitted at all. The total number of patients experiencing acute myocardial infarction with systolic dysfunction, transient or permanent, during the study period is unknown.

CONCLUSIONS

In non-valvular HF, IHD was associated with a significantly higher risk of mortality in both men and women, in all age groups, in all groups of systolic dysfunction and both in recent-onset and chronic HF. The increased risk entailed by IHD diminished gradually with older age and higher LVEF. Despite improvements in the treatment of acute and chronic IHD over the last decades, the mortality for patients with IHD and HF was significantly higher than for patients with non-ischaemic HF during 2000–2012.

In DCM, one of the most important causes of non-ischaemic HFrEF, we found that the comorbid burden increased with increasing HF duration, also after adjustments for age. HF duration ≥ 6 months is associated with a worse prognosis. AF was prognostically adverse in long-standing HF only, whereas increasing NYHA score, lower LVEF, older age (> 61 years), LBBB, lower blood pressure (< 120 mmHg) and diabetes were associated with the composite endpoint all-cause death, heart Tx or HF hospitalization irrespective of HF duration. During 2003–2015, the one-year mortality and hospitalizations decreased by 4% and 3%, respectively. The patients appeared less severely affected over time, with less severe symptoms and better systolic function. The adverse impact of male sex and markers of disease severity increased slightly, whereas no changes in the impact of comorbidities were observed.

Patients hospitalized with recent-onset non-ischaemic HFrEF responded better to initialized GDMT than patients with ischaemic HFrEF. The NT-proBNP reduction and symptom relief were better, and LVEF recovery was twice as frequent. In almost one-third of patients selected for follow-up at outpatient HF clinics, no investigation for IHD was initiated at the time of HF diagnosis.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Our analyses of real-world HF patients support the previous studies reporting poorer prognosis in ischaemic HFrEF compared with other aetiologies, despite the considerable treatment improvements of acute and chronic CAD. Continuous efforts to investigate, address and prevent the conditions increasing the risk of IHD are crucial for a significant impact on the summarized burden of HFrEF.

DCM is one of the most important causes of non-ischaemic HFrEF. Increased understanding of the aetiological differences in prognosis and treatment response is helpful to optimize disease management for further risk reduction. The pathophysiological differences between HFrEF aetiologies, ischaemic vs non-ischaemic and also within DCM, are important fields for future research. Cardio-genetics may increase our understanding of the varying negative response to toxic agents, persistent tachyarrhythmia etc. and enable the identification of genetically susceptible individuals for possible future development of drugs for prevention and treatment.

Contemporary HFrEF therapy is primarily aimed at restoring physiological balance, rather than targeting the primary cause of systolic failure. While this treatment strategy in many cases is effective in reducing symptoms and adverse outcomes, the morbidity and mortality are still considerable. Besides the continuous investigation of reversible adverse pathways common for HFrEF, aetiology-targeting treatment strategies are warranted. The need for an increased understanding of the pathophysiological differences in various aetiologies, and of the interplay with precipitating and contributing factors and comorbidities is thus essential.

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REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.

2. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, 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. *J Card Fail*. 2021.

3. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats A. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2022.

4. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175(6):996-1004.

5. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;391(10120):572-580.

6. Khera R, Kondamudi N, Zhong L, Vaduganathan M, Parker J, Das SR, et al. Temporal Trends in Heart Failure Incidence Among Medicare Beneficiaries Across Risk Factor Strata, 2011 to 2016. *JAMA Netw Open*. 2020;3(10):e2022190.

7. Wideqvist M, Rosengren A, Schaufelberger M, Pivodic A, Fu M. Ten year age- and sex-specific temporal trends in incidence and prevalence of heart failure in Västra Götaland, Sweden. *ESC Heart Fail*. 2022.

8. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail*. 2013;15(9):995-1002.

9. Lindmark K, Boman K, Olofsson M, Tornblom M, Levine A, Castelo-Branco A, et al. Epidemiology of heart failure and trends in diagnostic work-up: a retrospective, population-based cohort study in Sweden. *Clin Epidemiol*. 2019;11:231-244.

10. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22(8):1342-1356.

11. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25(18):1614-1619.

12. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6(3):606-619.

13. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106(24):3068-3072.

14. Cohn JN, Johnson G. Heart failure with normal ejection fraction. The V-HeFT Study. Veterans Administration Cooperative Study Group. *Circulation*. 1990;81(2 Suppl):III48-53.

15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270.

16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.

17. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation*. 2014;129(23):2380-2387.

18. Lupon J, Diez-Lopez C, de Antonio M, Domingo M, Zamora E, Moliner P, et al. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail*. 2017;19(12):1615-1623.

19. Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study. *Eur Heart J*. 2019;40(26):2110-2117.

20. 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(18):e895-e1032.

21. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail*. 2019;21(6):715-731.

22. White PD, Myers MM. The Classification of Cardiac Diagnosis. *JAMA*. 1921.

23. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858.

24. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, et al. Navigating the crossroads of coronary artery disease and heart failure. *Circulation*. 2006;114(11):1202-1213.

25. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310(9):959-968.

26. Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011;123(3):327-334.

27. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2008;29(2):270-276.

28. Elliott P. Cardiomyopathy. Diagnosis and management of dilated cardiomyopathy. *Heart*. 2000;84(1):106-112.

29. Codd MB, Sugrue DD, Gersh BJ, Melton LJ, 3rd. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. *Circulation*. 1989;80(3):564-572.

30. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10(9):531-547.

31. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293-302.

32. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353(9146):9-13.

33. Cohn JN, Tognoni G, Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.

34. 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. *Lancet*. 2003;362(9386):772-776.

35. Balmforth C, Simpson J, Shen L, Jhund PS, Lefkowitz M, Rizkala AR, et al. Outcomes and Effect of Treatment According to Etiology in HFrEF: An Analysis of PARADIGM-HF. *JACC Heart Fail*. 2019;7(6):457-465.

36. McKenna CJ, Codd MB, McCann HA, Sugrue DD. Alcohol consumption and idiopathic dilated cardiomyopathy: a case control study. *Am Heart J*. 1998;135(5 Pt 1):833-837.

37. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, et al. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. *N Engl J Med*. 2016;374(3):233-241.

38. Ware JS, Amor-Salamanca A, Tayal U, Govind R, Serrano I, Salazar-Mendiguchia J, et al. Genetic Etiology for Alcohol-Induced Cardiac Toxicity. *J Am Coll Cardiol*. 2018;71(20):2293-2302.

39. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, et al. Genetic Variants Associated With Cancer Therapy-Induced Cardiomyopathy. *Circulation*. 2019;140(1):31-41.

40. Petretta M, Pirozzi F, Sasso L, Paglia A, Bonaduce D. Review and metaanalysis of the frequency of familial dilated cardiomyopathy. *Am J Cardiol*. 2011;108(8):1171-1176.

41. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The Diagnosis and Evaluation of Dilated Cardiomyopathy. *J Am Coll Cardiol*. 2016;67(25):2996-3010.

42. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes D, Jr., Kucheryavaya AY, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report-2018; Focus Theme: Multiorgan Transplantation. *J Heart Lung Transplant*. 2018;37(10):1155-1168.

43. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273(18):1450-1456.

44. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651-1658.

45. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.

46. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39(1):26-35.

47. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709-717.

48. Zannad F, McMurray JJ, 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;364(1):11-21.

49. McMurray JJ, 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;371(11):993-1004.

50. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008.

51. 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;383(15):1413-1424.

52. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875-885.

53. Bohm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol*. 2013;102(1):11-22.

54. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2020;382(20):1883-1893.

55. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N Engl J Med*. 2021;384(2):105-116.

56. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J*. 2013;34(46):3547-3556.

57. Remme WJ, Swedberg K, Task Force for the D, Treatment of Chronic Heart Failure ESoC. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22(17):1527-1560.

58. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26(11):1115-1140.

59. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10(10):933-989.

60. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail*. 2019;21(11):1306-1325.

61. Taylor CJ, Ordonez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *Bmj*. 2019;364:l223.

62. Stewart S, Ekman I, Ekman T, Oden A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). *Circ Cardiovasc Qual Outcomes*. 2010;3(6):573-580.

63. Pfuntner A, Wier LM, Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

64. Wideqvist M, Cui X, Magnusson C, Schaufelberger M, Fu M. Hospital readmissions of patients with heart failure from real world: timing and associated risk factors. *ESC Heart Fail*. 2021;8(2):1388-1397.

65. Al-Omary MS, Khan AA, Davies AJ, Fletcher PJ, McIvor D, Bastian B, et al. Outcomes following heart failure hospitalization in a regional Australian setting between 2005 and 2014. *ESC Heart Fail*. 2018;5(2):271-278.

66. Nichols GA, Reynolds K, Kimes TM, Rosales AG, Chan WW. Comparison of Risk of Re-hospitalization, All-Cause Mortality, and Medical Care Resource Utilization in Patients With Heart Failure and Preserved Versus Reduced Ejection Fraction. *Am J Cardiol*. 2015;116(7):1088-1092.

67. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1981;47(3):525-531.

68. Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1983;51(5):831-836.

69. Ushigome R, Sakata Y, Nochioka K, Miyata S, Miura M, Tadaki S, et al. Improved Long-Term Prognosis of Dilated Cardiomyopathy With Implementation of Evidenced-Based Medication - Report From the CHART Studies. *Circ J*. 2015;79(6):1332-1341.

70. Merlo M, Cannata A, Pio Loco C, Stolfo D, Barbati G, Artico J, et al. Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail*. 2020;22(7):1111-1121.

71. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J*. 2018;39(20):1770-1780.

72. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation*. 2009;119(24):3070-3077.

73. 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). *Eur J Heart Fail*. 2017;19(12):1586-1596.

74. Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. *Eur J Heart Fail*. 2009;11(9):855-862.

75. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*. 2012;33(14):1750-1757.

76. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation*. 1997;96(2):509-516.

77. Simpson J, Jhund PS, Lund LH, Padmanabhan S, Claggett BL, Shen L, et al. Prognostic Models Derived in PARADIGM-HF and Validated in ATMOSPHERE and the

Swedish Heart Failure Registry to Predict Mortality and Morbidity in Chronic Heart Failure. *JAMA Cardiol*. 2020;5(4):432-441.

78. Caraballo C, Desai NR, Mulder H, Alhanti B, Wilson FP, Fiuzat M, et al. Clinical Implications of the New York Heart Association Classification. *J Am Heart Assoc*. 2019;8(23):e014240.

79. Dewan P, Rorth R, Jhund PS, Shen L, Raparelli V, Petrie MC, et al. Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women. *J Am Coll Cardiol*. 2019;73(1):29-40.

80. Sharma K, Mok Y, Kwak L, Agarwal SK, Chang PP, Deswal A, et al. Predictors of Mortality by Sex and Race in Heart Failure With Preserved Ejection Fraction: ARIC Community Surveillance Study. *J Am Heart Assoc*. 2020;9(19):e014669.

81. Pandey A, Vaduganathan M, Arora S, Qamar A, Mentz RJ, Shah SJ, et al. Temporal Trends in Prevalence and Prognostic Implications of Comorbidities Among Patients With Acute Decompensated Heart Failure: The ARIC Study Community Surveillance. *Circulation*. 2020;142(3):230-243.

82. Rush CJ, Campbell RT, Jhund PS, Connolly EC, Preiss D, Gardner RS, et al. Falling Cardiovascular Mortality in Heart Failure With Reduced Ejection Fraction and Implications for Clinical Trials. *JACC Heart Fail*. 2015;3(8):603-614.

83. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. 2015;36(19):1163-1170.

84. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J*. 2010;31(22):2755-2764.

85. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304(12):1350-1357.

86. Ng AC, Sindone AP, Wong HS, Freedman SB. Differences in management and outcome of ischemic and non-ischemic cardiomyopathy. *Int J Cardiol*. 2008;129(2):198-204.

87. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2013;15(7):808-817.

88. Coles AH, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Darling CE, et al. Magnitude of and Prognostic Factors Associated With 1-Year Mortality After Hospital Discharge for Acute Decompensated Heart Failure Based on Ejection Fraction Findings. *J Am Heart Assoc*. 2015;4(12).

89. 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. *Eur J Heart Fail*. 2017;19(12):1574-1585.

90. Rusinaru D, Houpe D, Szymanski C, Levy F, Marechaux S, Tribouilloy C. Coronary artery disease and 10-year outcome after hospital admission for heart failure with preserved and with reduced ejection fraction. *Eur J Heart Fail*. 2014;16(9):967-976.

91. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. *Circ Heart Fail*. 2017;10(6).

92. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. *J Am Coll Cardiol*. 2002;39(2):210-218.

93. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR, Jr., Chaitman BR, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation*. 1994;90(6):2645-2657.

94. Mentz RJ, Allen BD, Kwasny MJ, Konstam MA, Udelson JE, Ambrosy AP, et al. Influence of documented history of coronary artery disease on outcomes in patients admitted for worsening heart failure with reduced ejection fraction in the EVEREST trial. *Eur J Heart Fail*. 2013;15(1):61-68.

95. McMurray JJ, Krum H, Abraham WT, Dickstein K, Kober LV, Desai AS, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *N Engl J Med*. 2016;374(16):1521-1532.

96. Badar AA, Perez-Moreno AC, Hawkins NM, Jhund PS, Brunton AP, Anand IS, et al. Clinical Characteristics and Outcomes of Patients With Coronary Artery Disease and Angina: Analysis of the Irbesartan in Patients With Heart Failure and Preserved Systolic Function Trial. *Circ Heart Fail*. 2015;8(4):717-724.

97. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1):6-14.

98. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. *Br J Clin Pharmacol*. 2015;80(4):796-807.

99. Unlu O, Levitan EB, Reshetnyak E, Kneifati-Hayek J, Diaz I, Archambault A, et al. Polypharmacy in Older Adults Hospitalized for Heart Failure. *Circ Heart Fail*. 2020;13(11):e006977.

100. Centers for Medicare & Medicaid Services. Chronic Conditions among Medicare Beneficiaries. 2018. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Chartbook_Charts.html.

101. Konstam MA, Gheorghiade M, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297(12):1319-1331.

102. Potts J, Sirker A, Martinez SC, Gulati M, Alasnag M, Rashid M, et al. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: Insights from 6.6 million PCI procedures in the United States. *PLoS One*. 2018;13(9):e0203325.

103. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-952.

104. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes*. 2010;3(2):135-142.

105. Desai AS, Solomon S, Claggett B, McMurray JJ, Rouleau J, Swedberg K, et al. Factors Associated With Noncompletion During the Run-In Period Before Randomization and Influence on the Estimated Benefit of LCZ696 in the PARADIGM-HF Trial. *Circ Heart Fail*. 2016;9(6):e002735.

106. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. *Eur Heart J*. 2018;39(42):3766-3776.

107. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J*. 2017;38(41):3056-3065.

108. The National Board of Health and Welfare (Socialstyrelsen). Myocardial infarctions in Sweden 1990-2013. http://www.socialstyrelsen.se/publikationer2014/2014-11-13. 2014.

109. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail*. 2010;12(1):25-31.

110. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765-773.

111. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.

112. Stolfo D, Uijl A, Vedin O, Stromberg A, Faxen UL, Rosano GMC, et al. Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum: Phenotyping, and Prognostic and Therapeutic Implications. *JACC Heart Fail*. 2019;7(6):505-515.

113. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail*. 2001;7(2):176-182.

114. Packer M. Development and Evolution of a Hierarchical Clinical Composite End Point for the Evaluation of Drugs and Devices for Acute and Chronic Heart Failure: A 20-Year Perspective. *Circulation*. 2016;134(21):1664-1678.

115. McGuinn E, Warsavage T, Plomondon ME, Valle JA, Ho PM, Waldo SW. Association of Ischemic Evaluation and Clinical Outcomes Among Patients Admitted With New-Onset Heart Failure. *J Am Heart Assoc*. 2021;10(5):e019452.

116. McQuade CN, Mizus M, Wald JW, Goldberg L, Jessup M, Umscheid CA. Brain-Type Natriuretic Peptide and Amino-Terminal Pro-Brain-Type Natriuretic Peptide Discharge Thresholds for Acute Decompensated Heart Failure: A Systematic Review. *Ann Intern Med*. 2017;166(3):180-190.

117. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med*. 2019;380(6):539-548.

118. Tardif JC, O'Meara E, Komajda M, Bohm M, Borer JS, Ford I, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. *Eur Heart J*. 2011;32(20):2507-2515.

119. Martens P, Nijst P, Verbrugge FH, Dupont M, Tang WHW, Mullens W. Profound differences in prognostic impact of left ventricular reverse remodeling after cardiac resynchronization therapy relate to heart failure etiology. *Heart Rhythm*. 2018;15(1):130-136.

120. Bao J, Kan R, Chen J, Xuan H, Wang C, Li D, et al. Combination pharmacotherapies for cardiac reverse remodeling in heart failure patients with reduced ejection fraction: A systematic review and network meta-analysis of randomized clinical trials. *Pharmacol Res*. 2021;169:105573.

121. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, et al. Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). *Circulation*. 2021;143(6):516-525.

122. Merlo M, Stolfo D, Anzini M, Negri F, Pinamonti B, Barbati G, et al. Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: does real healing exist? *J Am Heart Assoc*. 2015;4(1):e001504.

123. Wilcox JE, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Heywood JT, et al. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J*. 2012;163(1):49-56 e42.

124. 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;377(1):41-51.

125. Lehrke S, Lossnitzer D, Schob M, Steen H, Merten C, Kemmling H, et al. Use of cardiovascular magnetic resonance for risk stratification in chronic heart failure: prognostic value of late gadolinium enhancement in patients with non-ischaemic dilated cardiomyopathy. *Heart*. 2011;97(9):727-732.

126. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, et al. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. *Heart Rhythm*. 2014;11(5):856-863.

127. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S, et al. T1-Mapping and Outcome in Nonischemic Cardiomyopathy: All-Cause Mortality and Heart Failure. *JACC Cardiovasc Imaging*. 2016;9(1):40-50.

128. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, et al. Outcome in Dilated Cardiomyopathy Related to the Extent, Location, and Pattern of Late Gadolinium Enhancement. *JACC Cardiovasc Imaging*. 2019;12(8 Pt 2):1645-1655.

129. Disertori M, Rigoni M, Pace N, Casolo G, Mase M, Gonzini L, et al. Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction: A Meta-Analysis. *JACC Cardiovasc Imaging*. 2016;9(9):1046-1055.

130. Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace*. 2010;12(11):1564-1570.

131. Beggs SAS, Jhund PS, Jackson CE, McMurray JJV, Gardner RS. Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators: a review and meta-analysis. *Heart*. 2018;104(2):144-150.

132. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med*. 2016;375(13):1221-1230.

133. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, et al. Age and Outcomes of Primary Prevention Implantable Cardioverter-Defibrillators in Patients With Nonischemic Systolic Heart Failure. *Circulation*. 2017;136(19):1772-1780.

134. Yafasova A, Butt JH, Elming MB, Nielsen JC, Haarbo J, Videbaek L, et al. Long-Term Follow-Up of DANISH (The Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality). *Circulation*. 2022;145(6):427-436.

135. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J*. 2015;36(30):1990-1997.

136. Hasselbalch RB, Pries-Heje M, Engstrom T, Sando A, Heitmann M, Pedersen F, et al. Coronary risk stratification of patients with newly diagnosed heart failure. *Open Heart*. 2019;6(2):e001074.

137. Peiro OM, Ferrero M, Romeu A, Carrasquer A, Bonet G, Mohandes M, et al. Performance of Coronary Angiography in the Detection of Coronary Artery Disease in Patients with Systolic Left Ventricular Dysfunction and No Prior Ischemic Heart Disease. *J Clin Med*. 2022;11(4).

138. Doshi D, Ben-Yehuda O, Bonafede M, Josephy N, Karmpaliotis D, Parikh MA, et al. Underutilization of Coronary Artery Disease Testing Among Patients Hospitalized With New-Onset Heart Failure. *J Am Coll Cardiol*. 2016;68(5):450-458.

139. Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, et al. Survival Benefits of Invasive Versus Conservative Strategies in Heart Failure in Patients With Reduced Ejection Fraction and Coronary Artery Disease: A Meta-Analysis. *Circ Heart Fail*. 2017;10(1):e003255.

140. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364(17):1607-1616.

141. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N Engl J Med*. 2016;374(16):1511-1520.

142. Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R, Ryan M, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. *N Engl J Med*. 2022.

143. Flaherty JD, Rossi JS, Fonarow GC, Nunez E, Stough WG, Abraham WT, et al. Influence of coronary angiography on the utilization of therapies in patients with acute heart failure syndromes: findings from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2009;157(6):1018-1025.

144. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.

145. Bollano E, Redfors B, Rawshani A, Venetsanos D, Volz S, Angeras O, et al. Temporal trends in characteristics and outcome of heart failure patients with and without significant coronary artery disease. *ESC Heart Fail*. 2022;9(3):1812-1822.

146. Teeter WA, Thibodeau JT, Rao K, Brickner ME, Toto KH, Nelson LL, et al. The natural history of new-onset heart failure with a severely depressed left ventricular ejection fraction: implications for timing of implantable cardioverter-defibrillator implantation. *Am Heart J*. 2012;164(3):358-364.

147. McNamara DM, Starling RC, Cooper LT, Boehmer JP, Mather PJ, Janosko KM, et al. Clinical and demographic predictors of outcomes in recent onset dilated cardiomyopathy: results of the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 study. *J Am Coll Cardiol*. 2011;58(11):1112-1118.

148. Halliday BP, Gulati A, Ali A, Newsome S, Lota A, Tayal U, et al. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. *Eur J Heart Fail*. 2018;20(10):1392-1400.

149. Escobar-Lopez L, Ochoa JP, Mirelis JG, Espinosa MA, Navarro M, Gallego-Delgado M, et al. Association of Genetic Variants With Outcomes in Patients With Nonischemic Dilated Cardiomyopathy. *J Am Coll Cardiol*. 2021;78(17):1682-1699.

150. Cannata A, Fabris E, Merlo M, Artico J, Gentile P, Pio Loco C, et al. Sex Differences in the Long-term Prognosis of Dilated Cardiomyopathy. *Can J Cardiol*. 2020;36(1):37-44.

151. Karatolios K, Holzendorf V, Richter A, Schieffer B, Pankuweit S, Competence Network Heart Failure G. Long-term outcome and predictors of outcome in patients with non-ischemic dilated cardiomyopathy. *Int J Cardiol*. 2016;220:608-612.

152. Aleksova A, Carriere C, Zecchin M, Barbati G, Vitrella G, Di Lenarda A, et al. New-onset left bundle branch block independently predicts long-term mortality in patients with idiopathic dilated cardiomyopathy: data from the Trieste Heart Muscle Disease Registry. *Europace*. 2014;16(10):1450-1459.

153. Nuzzi V, Cannata A, Manca P, Castrichini M, Barbati G, Aleksova A, et al. Atrial fibrillation in dilated cardiomyopathy: Outcome prediction from an observational registry. *Int J Cardiol*. 2021;323:140-147.

154. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*. 2009;11(7):676-683.

155. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol*. 2006;47(10):1987-1996.

156. Smit MD, Moes ML, Maass AH, Achekar ID, Van Geel PP, Hillege HL, et al. The importance of whether atrial fibrillation or heart failure develops first. *Eur J Heart Fail*. 2012;14(9):1030-1040.

157. Alehagen U, Benson L, Edner M, Dahlstrom U, Lund LH. Association between use of statins and outcomes in heart failure with reduced ejection fraction: prospective propensity score matched cohort study of 21 864 patients in the Swedish Heart Failure Registry. *Circ Heart Fail*. 2015;8(2):252-260.

158. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9645):1231-1239.

159. Kapelios CJ, Bonou M, Malliaras K, Athanasiadi E, Vakrou S, Skouloudi M, et al. Association of loop diuretics use and dose with outcomes in outpatients with heart failure: a systematic review and meta-analysis of observational studies involving 96,959 patients. *Heart Fail Rev*. 2022;27(1):147-161.

160. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, et al. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail*. 2014;16(3):317-324.

161. Shafazand M, Schaufelberger M, Lappas G, Swedberg K, Rosengren A. Survival trends in men and women with heart failure of ischaemic and non-ischaemic origin: data for the period 1987-2003 from the Swedish Hospital Discharge Registry. *Eur Heart J*. 2009;30(6):671-678.

162. SwedeHF annual reports. Available from: https://www.ucr.uu.se/rikssvikt/om-rikssvikt/arsrapporter.

163. Christiansen MN, Kober L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, et al. Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. *Circulation*. 2017;135(13):1214-1223.

164. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *The Lancet*. 2021;398(10304):957-980.

165. Schrage B, Uijl A, Benson L, Westermann D, Stahlberg M, Stolfo D, et al. Association Between Use of Primary-Prevention Implantable Cardioverter-Defibrillators and Mortality in Patients With Heart Failure: A Prospective Propensity Score-Matched Analysis From the Swedish Heart Failure Registry. *Circulation*. 2019;140(19):1530-1539.

166. Parikh KS, Coles A, Schulte PJ, Kraus WE, Fleg JL, Keteyian SJ, et al. Relation of Angina Pectoris to Outcomes, Quality of Life, and Response to Exercise Training in Patients With Chronic Heart Failure (from HF-ACTION). *Am J Cardiol*. 2016;118(8):1211-1216.