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Diabetes Mellitus and Heart Failure

Registry Based Studies on Risk Factors, Prognosis and Impact of Treatment

by

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Stockholm 2017

To the ones I love

A sense of curiosity is nature's
original school of education

Smiley Blanton (1882-1966)

CONTENTS

Abstract

Heart failure and diabetes is a common combination. In the presence of diabetes heart failure prognosis becomes very serious, but the exact reasons are not understood. A limitation while interpreting existing data is that they usually derive from heart failure populations in whom patients with diabetes are selected, in small proportions and their characteristics are less well explored. This explains why it still is uncertain which factors are prognostically most important. Moreover, whether diabetes impacts prognosis differently in heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced (HFrEF) ejection fraction has not been fully investigated. In these respects analyses of nationwide registry based heart failure populations may provide valuable information.

Aims
To study the combination of diabetes and heart failure in a contemporary, unselected heart failure population by analysing

1. Demographic characteristics and long-term prognosis
2. Whether there are differences between women and men in this respect
3. The impact of diabetes in ischaemic versus non-ischaemic heart failure and the role of revascularization
4. The influence of diabetes in different types of heart failure

Diabetes and heart failure
Of 36 274 patients with clinician judged heart failure registered in the Swedish Heart Failure Registry (SwedeHF) from specialist care between 2003-2011, 24% had reported diabetes. The patients were followed for mortality until September 2011. Diabetes was an independent predictor of mortality particularly in the age group ≤65 years (OR 1.61; 95% CI 1.36-1.92) compared to patients >80 years (OR 1.46; 95% CI 1.31-1.62). This pattern was apparent despite a more extensive pharmacological treatment in patients with diabetes and although a similar left ventricular and renal function in patients with and without diabetes.

Influence of diabetes in women and men with heart failure
Women represented 39% of the SwedeHF population irrespective of diabetes state. In the presence of diabetes the mortality risk increased by 70% in women (OR 1.72; 95% CI 1.53-1.94) and by 40% in men (OR 1.47; 95% CI 1.34-1.61), but age-adjusted survival did not differ between women and men with diabetes (log-rank p=0.18). In contrast women without diabetes had a better prognosis than their male counterparts (log-rank p<0.0001). Women with diabetes and heart failure, in particular those ≤65 years, had a risk factor profile resembling that of men with a high prevalence of ischaemic heart disease and hypertension.

Ischaemic versus non-ischaemic heart failure and the role of previous revascularization in diabetes
The impact of diabetes in ischaemic versus non-ischaemic heart failure was studied in 35 163 patients in SwedeHF. A particularly high proportion of diabetes was reported in patients with ischaemic compared with non-ischaemic heart failure (31% versus 18%). As many as 90% of patients with diabetes had at least one preventable comorbidity of which ischaemic heart disease and hypertension were most frequent. Diabetes had a negative impact on survival irrespective of whether the aetiology was ischaemic or non-ischaemic. The highest mortality was, however, seen in those with ischaemic aetiology (adjusted HR 1.41; 95% CI 1.33-1.50 versus 1.30; 1.20-1.41). A history of coronary revascularization was associated with better survival after propensity score adjustment. Still revascularisation had only been performed in half the diabetes patients.

Impact of diabetes in heart failure with different left ventricular function
Among 30 696 patients in SwedeHF followed until December 2014, 22% had HFpEF, 21% HFmrEF and 57% HFrEF. The prevalence of diabetes was similar across the groups (24-25%). In the presence of diabetes the clinical characteristics of patients with HFmrEF resembled those in the HFrEF group. Diabetes had a negative impact on mortality with the highest risk increase in patients with HFmrEF (HR 1.51; 95% CI 1.39-1.65) and HFrEF (HR 1.46; 95% CI 1.39-1.54). A similar impact although slightly less apparent was seen in patients with HFpEF (HR 1.32; 95% CI 1.22-1.43).

Conclusion
From these analyses in a nationwide, contemporary heart failure population it can be concluded that diabetes is present in 24% to 31% of the patients. The combination of heart failure and diabetes compromises survival irrespective of sex, heart failure aetiology or heart failure entity. The increased mortality risk varies between 30-70% depending on age, sex and aetiology. Systolic dysfunction and ischaemic heart disease are associated with the worst prognosis. Although associated with an improved longevity coronary revascularization seems to be underused. The worse prognosis associated with diabetes may partly be explained by a heavier comorbidity burden but the existence of a diabetes cardiomyopathy cannot be ruled out. In the future improved attention of these patients are needed and studies searching for a better understanding of underlying mechanisms opening for novel treatment modalities.

SAMMANFATTNING

Hjärtsvikt och diabetes är en vanlig kombination. I närvaro av diabetes är hjärtsviktsprognosen mycket allvarlig men bakomliggande orsaker är inte helt klarlagda. Tolkningen av tillgängliga data försvåras av att de vanligtvis härrör från hjärtsviktspopulationer där patienter med diabetes är selekterade, fåtaliga och bristfälligt karaktäriserade. Detta förklarar varför det fortfarande är oklart vilka faktorer som är prognostiskt viktigast. Vidare, är det ofullständigt utrett hur diabetes påverkar prognosen vid hjärtsvikt med bevarad (HFpEF), lätt sänkt (HFmrEF) och sänkt (HFrEF) ejektionsfraktion. Nationella registerbaserade hjärtsviktspopulationer kan i dessa avseenden tillföra värdefull information.

Syfte
Att studera kombinationen diabetes och hjärtsvikt i en nutida, stor oselekterad hjärtsviktspopulation genom att analysera

1. Demografiska karakteristika och långtidsprognos
2. Huruvida det finns olikheter mellan kvinnor och män i detta hänseende
3. Betydelsen av diabetes vid ischemisk och icke-ischemisk hjärtsvikt och betydelsen av revaskularisering
4. Betydelsen av diabetes vid olika typer av hjärtsvikt

Diabetes och hjärtsvikt
Av 36 274 patienter med kliniskt diagnosticerad hjärtsvikt registrerade i det Svenska hjärtsviktregistret (SwedeHF; RiksSvikt) från specialistsjukvården mellan 2003-2011, hade 24% rapporterad diabetes. Patienterna följdes avseende dödlighet till och med september 2011. Diabetes var en oberoende prediktor för mortalitet, särskilt i åldersgruppen ≤65 år (OR 1.61; 95% CI 1.36-1.92) jämfört med patienter >80 år (OR 1.46; 95% CI 1.31-1.62). Detta mönster sågs trots mer extensiv läkemedelsbehandling hos patienter med diabetes och liknande vänsterkammar- och njurfunktion hos patienter med och utan diabetes.

Betydelsen av diabetes hos kvinnor och män med hjärtsvikt
Kvinnor utgjorde 39% av RiksSvikt-populationen oavsett diabetesstatus. I närvaro av diabetes ökade risken för död med 70% hos kvinnorna (OR 1.72; 95% CI 1.53-1.94) och med 40% hos männen (OR 1.47; 95% CI 1.34-1.61), men den åldersjusterade överlevnaden skiljde sig inte åt mellan kvinnor och män med diabetes (log-rank p=0.18). I motsats hade kvinnor utan diabetes en bättre prognos än deras manliga motsvarigheter (log-rank p<0.0001). Kvinnor med diabetes och hjärtsvikt hade en riskfaktorprofil som liknade den hos männen med högre förekomst av ischemisk hjärtsjukdom och hypertoni, särskilt tydlig hos de under 66 år.

Ischemisk jämfört med icke-ischemisk hjärtsvikt och betydelsen av revaskularisering vid diabetes
Betydelsen av ischemisk och icke-ischemisk hjärtsvikt studerades hos 35 163 patienter i RiksSvikt. En särskilt stor andel diabetes förekom hos patienter med ischemisk jämfört med icke-ischemisk hjärtsvikt (31% vs. 18%). Hela 90% av patienterna med diabetes hade minst en förebyggbar komorbiditet bland vilka ischemisk hjärtsjukdom och hypertoni var de vanligaste. Diabetes hade en negativ inverkan på överlevnad oavsett om hjärtsviktsorsaken var ischemisk eller icke-ischemisk. Den högsta dödligheten sågs dock hos de med ischemisk etiologi (justerad HR 1.41; 95% CI 1.33-1.50 jfrt.1.30; 1.20-1.41). Tidigare genomförd revaskularisering var kopplat till en förbättrad överlevnad efter justering med propensity score men revaskularisering hade bara utförts hos hälften av patienterna med diabetes.

Betydelsen av diabetes vid hjärtsvikt med olika vänsterkammarfunktion
Av 30 696 patienter i RiksSvikt följda till december 2014 hade 22% HFpEF, 21% HFmrEF och 57% HFrEF. Förekomsten av diabetes var densamma i de tre grupperna (24-25%). I närvaro av diabetes liknade kliniska karakteristika hos HFmrEF dem hos HFrEF gruppen. Diabetes hade en negativ inverkan på dödlighet med den högsta risken hos patienter med HFmrEF (HR 1.51; 95% CI 1.39-1.65) och HFrEF (HR 1.46; 95% CI 1.39-1.54). En liknande inverkan, om än något mindre uttalad, sågs hos patienter med HFpEF (HR 1.32; 95% CI 1.22-1.43).

Konklusion
Baserat på analyser av en nationell samtida hjärtsviktspopulation kan man konkludera att diabetes förekommer hos 24% till 31% av patienterna. Kombinationen hjärtsvikt och diabetes påverkar överlevnaden negativt oavsett kön, hjärtsviktsorsak eller hjärtsviktstyp. Den ökade risken för död varierar i storleksordningen 30-70% beroende på ålder, kön och etiologi. Systolisk dysfunktion och ischemisk hjärtsjukdom är associerat med en sämre prognos. Koronar revaskularisering är kopplat till en förbättrad överlevnad men ter sig underanvänd. Den av diabetes försämrade prognosen kan delvis förklaras av en större samsjuklighetsbörda men förekomsten av en specifik diabeteskardiomyopati kan inte uteslutas. I framtiden behövs en ökad uppmärksamhet kring diabetes och hjärtsvikt samt studier som ger en bättre förståelse för bakomliggande mekanismer och som kan öppna nya behandlingsmodaliteter.

List of Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
AGEs	Advanced Glycated End-products
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
BMI	Body mass index
CHARM	Candesartan Heart failure-Assessment of Reduction in Mortality and morbidity trial
CG	Cockroft-Gault
CI	Confidence Interval
CIBIS-II	Cardiac Insufficiency Bisoprolol Study II
CKD	Chronic Kidney Disease
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
DCCT	Diabetes Control and Complications Trial
DM	Type 2 diabetes
DPP-4	Dipeptidylpeptisase-4
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in heart Failure
ESC	European Society of Cardiology
eGRF	estimated Glomerular Filtration Rate
FFA	Free Fatty Acids
GLP-1	Glucagon-like peptide-1
HF	Heart Failure
Hb	Haemoglobin
HFmrEF	Heart Failure mid-range Ejection Fraction
HFpEF	Heart Failure preserved Ejection Fraction
HFrEF	Heart Failure reduced Ejection Fraction
HR	Hazard ratio
iDCM	Idiopathic Dialated Cardiomyopathy
IHD	Ischaemic Heart Disease
LVEF	Left Ventricular Ejection Fraction
LEADER	Liraglutide Effect of Cardiovascular Outcome Results
MERIT-HF	Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure
MDRD	Modification of Diet in Renal Disease
MRA	Mineralocorticoid receptor antagonist
NT pro-BNP	N-Terminal Pro-Natriuretic Peptide
NYHA	New York Heart Association
OR	Odds ratio
PARADIGM-HF	Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality in Heart Failure
RAAS	Renin angiotensin aldosterone system
RALES	Randomized Aldactone Evaluation Study
SD	Standard deviation
SGLT-2	Sodium-glucose cotransporter-2
SOLVD	Studies of Left Ventricular Dysfunction trial
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
SwedeHF	The Swedish Heart Failure Registry (RiksSvikt)

List of Original Papers

The thesis is based on the following studies, which will be referred to by their Roman numerals.

I. Johansson I, Edner M, Dahlström U, Näsman P, Rydén L, Norhammar A.
Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? - An observational study from the Swedish Heart Failure Registry
Eur J Heart Fail 2014; 16: 409-18. Doi. 10.1002/ejhf.44

II. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A.
Risk factors, treatment and prognosis in men and women with heart failure with and without diabetes
Heart 2015;101:1139-1148. Doi.10.1136/heartjnl-2014-307131

III. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A.
Prognostic Implications of Type 2 Diabetes in Ischemic and Nonischemic Heart Failure
J Am Coll Cardiol. 2016;68:1404-1416. Doi. 10.1016/j.jacc.2016.06.061

IV. Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, Norhammar A.
Type 2 diabetes and heart failure, characteristics and prognosis in preserved, mid-range and reduced left ventricular function
Submitted manuscript

INTRODUCTION

Diabetes Mellitus

History

The earliest known notes of diabetes are more than 3500 years old, written on the Egyptian Ebers Papyrus dated at 1552 B.C. where the physician Hesy-Ra mentions the symptom of excess urination (Figure 1). Around the same time, the Indian physician Charaka identified a disease called 'madhumea' or 'honey urine' that attracted flies and ants. The Greek Apollonius of Memphis is usually credited the term 'Diabetes' (Greek 'diabainen') meaning 'to pass through' used for the first time 230 B.C. referring to a disease that provokes incessant thirst and immoderate loss of urine. Ancient Greek, Chinese, Egyptian, Indian and Persian physicians had noticed the sweet taste of urine and in 1675 Willis added the Latin word mellitus (melli'tus) meaning 'sweetened like honey' referring to the urinary taste. In 1776 Dobson managed to measure urinary glucose in such patients and found it increased.[1] The earliest detailed reference to diabetes dates back to the 2nd century when the Greek Aretaeus of Cappadocia described symptoms and the course of the disease but it was not until 1552 the text was published in Venice as a first Latin edition. The understanding of the involvement of the pancreas came around 1889 when Von Mering and Minkowski noted that dogs deprived their pancreas, developed symptoms typical for diabetes.[2,3] In 1869 Langerhans discovered "islands of richly innervated, clear cells that stained differently than the rest of the pancreas". Laguesse confirmed his findings in 1893 suggesting there were secretory glands within the pancreas and designated them the name 'islets of Langerhans'. De Meyer in 1910 termed the pancreatic secretion lacking in diabetes 'insulin' to denote its origin from the insulae of Langerhans.[4] Still it was not until 1921 that Banting, Best and Macleod showed that the administration of extract from pancreatic island cells to pancreatectomised dogs, counteracted the hyperglycaemia that characterises diabetes. The first patient, who was treated with the purified insulin, was the 13-year old Leonard Thompson in Canada.[5]

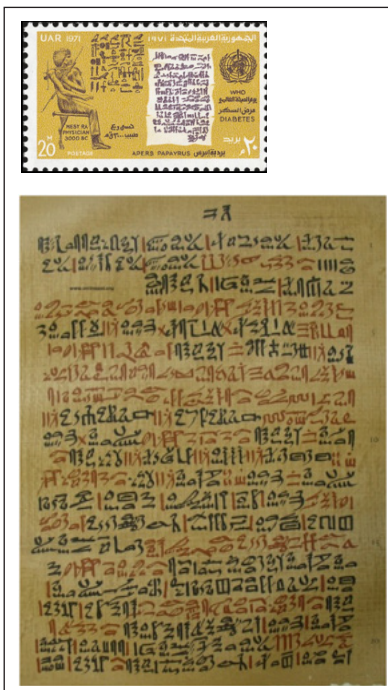

Figure 1. Ebers Papyrus.

That there may be different forms of diabetes was hypothesised during the 1920s. In 1926, MacLean suggested the distinction between 'hepatic glycosuria' and 'true diabetes' and in the 1930s Himsworth, trying to understand why hyperglycaemia occurred, postulated that it relates either to insulin deficiency or insulin insensitivity.[6] Oral glucose lowering agents were introduced in the 1950s with sulfonylureas and biguanides and 50 years thereafter other classes of glucose lowering drugs entered the market most recently incretins (Glucagon-like peptide-1 (GLP-1) receptor antagonists and Dipeptidylpeptidase (DPP-4) inhibitors) and Sodium glucose transport receptor inhibitors (SGLT-2). Until the discovery of insulin patients, especially those with type 1 diabetes, died shortly after the onset of the disease.

Definition and classification of diabetes mellitus

Diabetes is a metabolic disorder characterized by hyperglycaemia with disturbances in carbohydrate, fat and protein metabolism due to defects in insulin secretion, insulin action or both.[7] Diabetes causes microvascular complications potentially leading to dysfunction or failure of important organs including retinopathy (causing blindness), nephropathy (causing renal failure) and neuropathy (causing autonomic dysfunction and paraesthesia).[7] In parallel, the metabolic perturbations increase the risk of macrovascular complications leading to coronary artery, peripheral artery and cerebrovascular disease.[7] The World Health Organization (WHO) has issued guidelines for the diagnosis of diabetes mellitus since 1965 but the first widely accepted classification of diabetes including its pre-states, was introduced in 1979 by the National Diabetes Data Group followed by the WHO in 1980. The classification has since been slightly modified by the WHO and the American Diabetes Association (ADA) with the most recent recommendations issued in 2006 plus 2011,[7,8] and 2017 respectively.[9] Plasma glucose estimation in fasting and post-prandial state, or haemoglobin A1c (HbA1c; reflecting the average glycaemia during the last 2-3 months, the normal life span of a red blood cell) constitutes the basis of diagnostic criteria as outlined in Table 1.[7-9] The threshold for the diagnosis, regardless of method, is primarily determined by the level above which diabetes retinopathy start to develop.[8,9] Of note, impaired glucose tolerance is usually present several years before diagnosis, during which the risk of macrovascular complications is already present.[10]

Table 1. Diagnostic criteria of diabetes and other dysglycaemic categories according to the WHO 2006[7], 2011[8] and the ADA 2014[11] definitions. Glucose levels refer to venous plasma measurement.

Dysglycaemic category	WHO 2006[7], 2011[8]	ADA 2014[11]
Diabetes Mellitus		
Fasting plasma glucose	≥7.0 mmol/L (126mg/dL)	≥7.0 mmol/L (126mg/dL)
2h post load glucose	≥11.1mmol/L (200mg/dL)	≥11.1mmol/L (200mg/dL)
HbA1c (Mono S)/(IFCC)	≥6.5% / ≥48 mmol/mol	≥6.5% / ≥48 mmol/mol
Random plasma glucose	symptoms + ≥11.1mmol/L (200mg/dL)	symptoms + ≥11.1mmol/L (200mg/dL)
Impaired glucose tolerance (IGT)		
Fasting plasma glucose	<7.0 mmol/L (126mg/dL)	<7.0 mmol/L (126mg/dL)
2h post load glucose	≥7.8 and <11.1 mmol/L (≥140mg/dL and <200mg/dL)	≥7.8 and <11.1 mmol/L (≥140mg/dL and <200mg/dL)
Impaired fasting glucose (IFG)		
Fasting plasma glucose	6.1-6.9 mmol/L (110-125 mg/dL)	5.6-6.9 mmol/L (110-125 mg/dL)
2h post load glucose	<7.8 mmol/L (<140 mg/dL)	<7.8 mmol/L (<140 mg/dL)
High risk HbA1c	-	5.7-6.4% /(39-47 mmol/mol)

Based on the aetiological background WHO has, as outlined in Table 2, sub-divided diabetes into four main groups: type 1, type 2, other specific types and gestational diabetes.[7] Although each type is important this thesis focuses on type 2 diabetes, which will be referred to as *diabetes* throughout the rest of the thesis.

Table 2. Four main groups of diabetes classification according to the WHO.[7]	
Type 1 diabetes	Accounts for 5-10% of all diabetes and is usually aquired during childhood with abrupt onset caused by a cellular-mediated autoimmune destruction of the pancreatic β-cells leading to an absolute insulin deficiency and the need of lifelong insulin treatment. Latent autoimmune diabetes in adults (LADA) is a similar form although with a slower onset occurring in the adult. The aetiology is not fully understood but is considered to be a combination of genetic predisposition and environmental factors.
Type 2 diabetes (previously non-insulin dependent ot adult-onset diabetes)	Comprises 90-95% hence the vast majority of all diabetes patients and develops gradually often at middle age. Characterised by insulin resistance together with a relative deficiency in insulin secretion and do not require insulin to survive. Factors of importance are co-existent abdominal obesity, hypertension, hyperlipidaemia, physical inactivity, smoking and genetic predisposition.
Other specific types	Include diabetes resulting from several genetic mutations e.g. maturity onset diabetes (MODY), diabetes following pancreatic diseases, infections or drug use.
Gestational diabetes	Hyperglycaemia first recognised during pregnancy and that resolves after delivery. Gestational diabetes is present in approximately 2% of all pregnant women in Sweden. There is an increased risk for both the foetus and the mother during and the immediate time around pregnancy and these women are at increased risk of developing type 2 diabetes later in life.

Epidemiology

Prevalence - According to the International Diabetes Federation (IDF) the global prevalence of diabetes in the adult population approached 9% in 2015 and is, due to ageing populations and changes in life style habits, rapidly increasing towards an expected prevalence of 10.4% in 2040.[10] The corresponding proportion in Sweden is somewhat lower, 6.3%.[10] The prevalence is highly dependent on age, type of investigated population and screening methods. In the western societies diabetes is presumed to be undiagnosed in about 40% of all those afflicted.[10]

Incidence - The age-standardized, annual incidence of diabetes, reported to be 2.2 and 2.3/1000 person-years in Dutch men and women respectively, is rather uniform in several European countries.[12] According to a report from a community in northern Sweden the incidence of diabetes is 3-4/1000 inhabitants. It has been stable or slightly decreasing during the past 40 years.[13,14]

Risk factors – Besides increasing age the most important risk factors for diabetes are excess body weight especially abdominal obesity, low physical activity and poor dietary habits. In addition ethnicity, family history and a history of gestational diabetes are important.[7,9] Diabetes is often clustering with other risk factors including hypertension, dyslipidaemia, insulin resistance and abdominal obesity, usually referred to as the 'metabolic syndrome', all multiplying the risk of cardiovascular disease.[7]

Prognosis

Apart from microvascular complications, diabetes increases the risk of macrovascular complications including various cardiovascular disease manifestations and heart failure by two to four times.[15] Both micro- and macrovascular complications have decreased as a result of an improved, multifactorial risk factor management.[16-18] Furthermore, life expectancy in patients with diabetes is approaching that of those without, although there is still a gap between people with and without this disease.[19,20]

Pathophysiology

Diabetes is a complex metabolic disorder caused by a combination of impaired insulin signalling and insulin resistance in the liver and the skeletal muscles resulting in decreased glucose uptake in peripheral tissues, mainly the liver and the muscles, and increased hepatic glucose production (schematically summarised in Figure 2). The combined effect of these factors deranges the glycaemic control inducing a chronic state of hyperglycaemia. In compensation, the pancreatic β-cells initially increase their insulin production thus giving rise to a hyperinsulinaemic state in order to maintain normoglycaemia, this 'pancreatic reserve' is progressively exhausted leading to manifest diabetes as a result of insufficient insulin production.[6,21] During the gradual deterioration of glucose regulation, patients may have Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) as outlined in Table 1. It is believed that patients with impaired glucose tolerance already have an up to 80% loss of their β-cell function.[22]

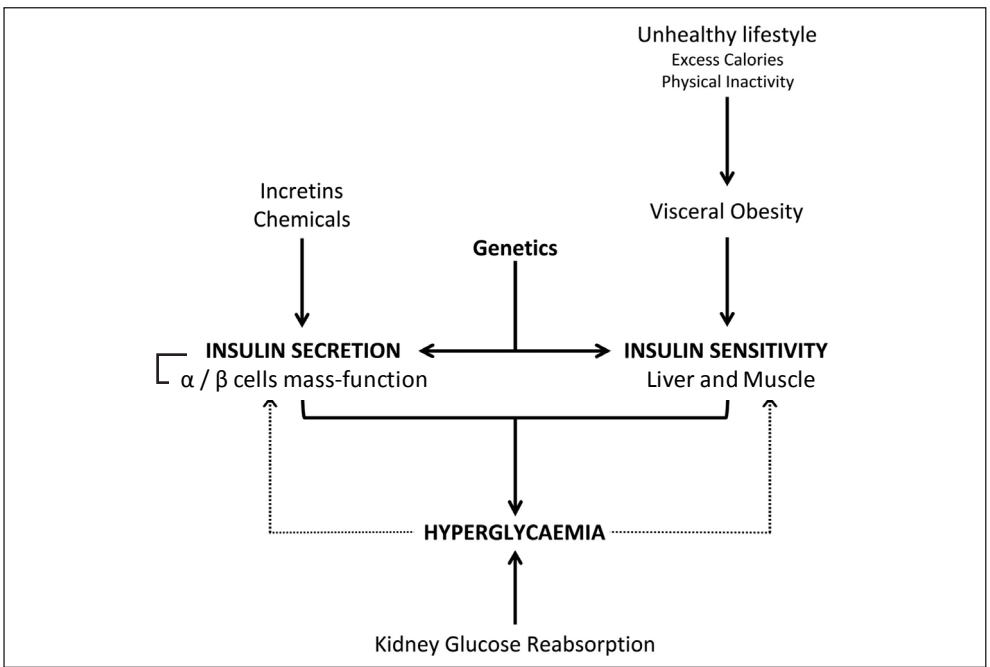

Figure 2. Schematic diagram of diabetes pathophysiology. Reproduced from Zaccardi et al.[6] with permisssion from BMJ Publishing Group Ltd.

Treatment

Insulin is the mandatory and life-saving therapy for patients with type 1 diabetes. For patients with diabetes (type 2), lifestyle advice, focusing on no smoking, weight loss or at least stabilisation and, probably even more important, increased physical activity, is the base upon which glucose lowering oral agents or insulin may be added.[7,9] Modern glucose lowering therapy does mainly belong to one of the following three groups i) insulin providers (insulin, sulphonylureas, metglinides, GLP-1 receptor agonists, DPP-4 inhibitors), ii) insulin sensitizers (metformin, peroxisome proliferator-activator receptor (PPAR) agonists) and iii) glucose

reabsorption inhibitors (SGLT-2 inhibitors).[23] There is still a debate on the optimal target for glucose control. Presently a HbA1c <53 mmol/mol (<7.0% DCCT) is recommended but individualisation is advocated in relation to age, potential comorbidities and vulnerability.[8,9,23] Importantly, diabetes requires a multifactorial management taking concomitantly occurring cardiovascular risk factors among them hyperlipidaemia and hypertension into account. The treatment should be target driven and lipid- and blood pressure targets are, according to international guidelines, more stringent for patients with than those without diabetes.[23]

Heart Failure

History

The platform for the future understanding of the role of the heart was established in 1628 when Harvey in his *Excercatio anatomica de motu cordis et sanguinis in animalibus* published the first modern view of the circulatory system. He demonstrated that the heart pumped blood via arteries, to the tissues and back through veins. This contrasted the ancient view of Galen and revolutionized the scientific field (Figure 3).[24]

Interest in abnormal heart structure in the form of ventricular dilatation and concentric

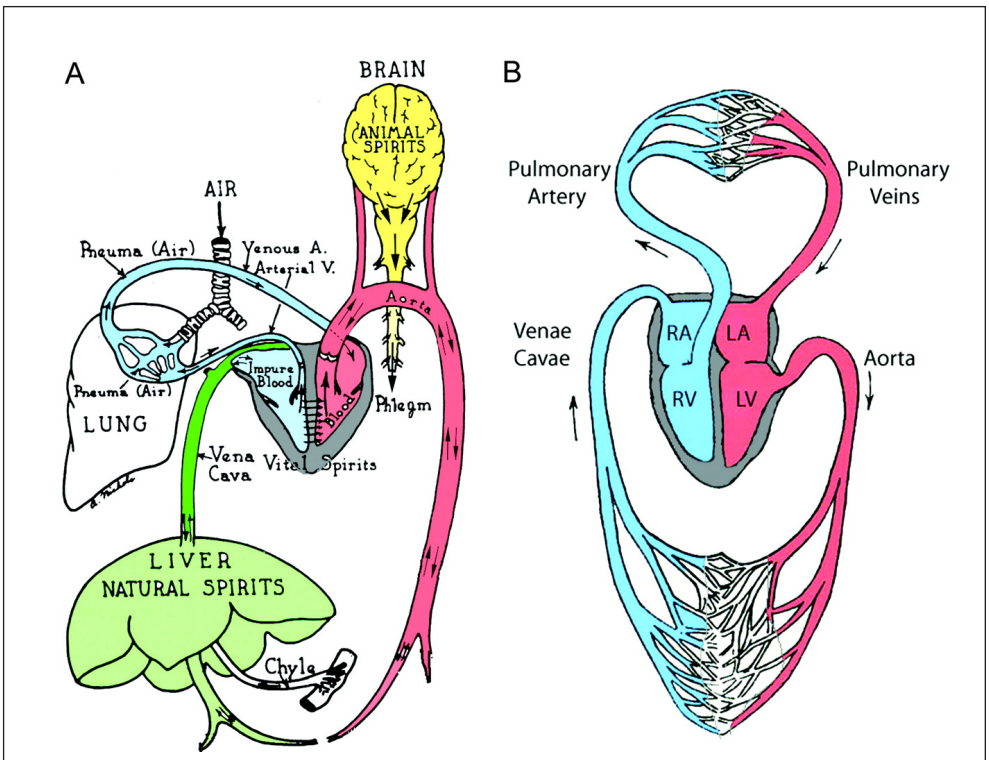

Figure 3. Two views of the circulation A) Galen's view and B) Harvey's view. (By permission from Katz et al.[24] as adopted from Major RH, *A History of Medicine.* Springfield; III: CC Thomas; 1954: and from Starling EH, *Principles of Human Physiology*, Philadelphia, Pa: Lea & Febiger; 1926.)

hypertrophy was much in focus during the 18th century. Dilatation was considered to weaken the contractile power as stated by Bertin in 1833. About 60 years later Osler postulated that while initially adaptive, concentric hypertrophy by time may become maladaptive and compromise the prognosis.[24] The discovery that X-rays could visualize the interior of the body by Röntgen in 1895 enhanced the understanding of cardiac enlargement and pulmonary fluid accumulation associated with heart failure. Starling's demonstration in 1918 that the contracting power of the myocardium is enhanced by an increased end-diastolic volume, as described in his '*Law of the heart'*,[25] paved the way for understanding normal circulatory physiology. Cardiac catheterization, described by Forssman and further developed by Cournand and Richards, provided insights in the disturbed haemodynamic caused by myocardial contractile deficiency causing a reduction in cardiac output and increased filling pressures.[24] Non-invasive studies of myocardial performance became possible when Edler and Hertz in 1954 introduced echocardiography.[26] Myocardial biology started to attract interest in the 50:s when for example, Olson stated that 'the problem underlying heart failure is impaired energy consumption by the contractile machinery' suggesting that failing hearts are energy starved.[27] Theories of reduced myocardial contractility as a contributor to heart failure developed in the 1960s.[24] A major advance in the understanding of the pathophysiology behind heart failure came in 1983 when Harris provided clear evidence that, as a response to a too low cardiac output neurohormonal activation caused vasoconstriction, salt and water retention and adrenergic stimulation as an initially physiologic but subsequently deleterious adaptation.[28]

The treatment for heart failure was for centuries restricted to drugs that increased the power of the failing heart. Ancient Romans, Egyptians, Syrians and Greeks used cardiac glycosides including sea onion (*Scilla maritima).* The beneficial effects of *Digitalis* were first described by Withering in 1785. Attempts to tackle the fluid retention that characterised heart failure was originally performed by means of bloodletting and leaches and later on by Southey's tubes that, when inserted into the oedematous legs, drained the excessive fluid accumulation.[29] Even in the 1920s, physicians witnessed that 'little could be done for most cardiac patients except to try to determine what was wrong, after which the treating physicians would wait until the patient died to see who was correct'.[24] In the 20th century, diuretics were introduced and offered symptom relief. A major breakthrough came in the 1980- and 1990s with the understanding that targeting the untoward neurohormonal activation by means of angiotensin converting enzyme inhibitors (ACEi) and beta-blockers offered not only symptomatic relief but also prolonged life.

Definition and classification of heart failure

The 2016 European management guidelines defines heart failure as a clinical syndrome characterized by a combination of symptoms and typical signs of myocardial dysfunction caused by structural and/or functional abnormalities impairing the ability of the heart to receive and/or eject appropriate amounts of blood at rest or during stress (Table 3).[30] Cardinal symptoms are breathlessness, fatigue and peripheral oedema. They form the basis of the diagnosis if combined with objective signs of myocardial engagement, most commonly investigated by means of echocardiography supplemented by increased concentrations of natriuretic peptides and their precursors (NT-proBNP; BNP) that are secreted in increased amounts due to myocardial extension.[30]

In clinical practice, heart failure has been labeled as due to systolic or diastolic malfunction. The former relates to an impaired capacity to eject blood from the left ventricle and the

latter to compromised left ventricular filling due to impaired myocardial relaxation. This terminology was subsequently abandoned since they were not mutually exclusive.[30] The current classification is instead based on left ventricular ejection fraction (LVEF). Patients with heart failure despite a normal LVEF are considered to have *heart failure with preserved ejection fraction* (*HFpEF*; LVEF ≥50%). Those with heart failure and a LVEF of 40-49% represent a borderline group, which in the most recent European management guidelines has been defined as *"mid-range" heart failure* (*HFmrEF)* while patients with heart failure and a LVEF <40% are labeled as *heart failure with reduced ejection fraction* (*HFrEF*). HFrEF is the most well defined entity, and the current evidence-based pharmacological therapy, with an impact on morbidity and mortality, is restricted to this group.[30]

The main clinical classification of the severity of heart failure was presented by the New York

Table 3. Definition of heart failure according to the 2016 European Society of Cardiology (ESC). Adapted with permission from ESC guidelines 2016.[30]

HFpEF	HFmrEF	HFrEF
1. Symptoms ± signs	1. Symptoms ± signs	1. Symptoms ± signs
2. LVEF ≥50%	2. LVEF 40-49%	2. LVEF <40%
3. Elevated levels of natriuretic peptides	3. Elevated levels of natriuretic peptides	
4. Relevant structural heart disease* or diastolic dysfunction	4. Relevant structural heart disease* or diastolic dysfunction	

Symptoms = Dyspnoea at rest or excercise, fatigue, tiredness, ankle swelling
Signs = Tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly
* Left ventricular hypertrophy/left atrium enlargement

Heart Association (NYHA) positioning the patients in one of four classes (Table 4).[31] A NYHA class can be applied in all heart failure patients irrespective of aetiology and level of care.

Epidemiology

Table 4. New York Heart Association (NYHA) classification of heart failure.

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

Prevalence - The prevalence of heart failure in western adult populations varies between 1-2%. It increases with advancing age to a prevalence of 10% above 65 years.[30,32-34] The prevalence is increasing due to an aging population but importantly also due to improved survival not the least in ischaemic heart disease.[30,35,36]
The proportion of patients with HFpEF varies between 22-73% depending on the LVEF

cut off and the study population.[30,37,38] It is likely that the distribution on HFpEF, HFrEF and HFmrEF will change over time with improved treatment and an aging population with more comorbidity. As an example data from the Olmstead County show that the proportion of HFpEF among patients hospitalized for heart failure increased from 38 to 54% between 1987 and 2001.[39]

Incidence - The annual incidence of heart failure is 5-10/1000 individuals, rapidly increasing with age and in general higher in men than women.[30,40] In Rotterdam the lifetime risk to develop heart failure (after 55 years) was 33% in men and 29% in women and US data are similar.[41,42] Time trends vary, but it seems as if the increase during the 1980s,[43,44] has been reverted or at least stabilised during the past decades as illustrated in Figure 4.[33,45-48]

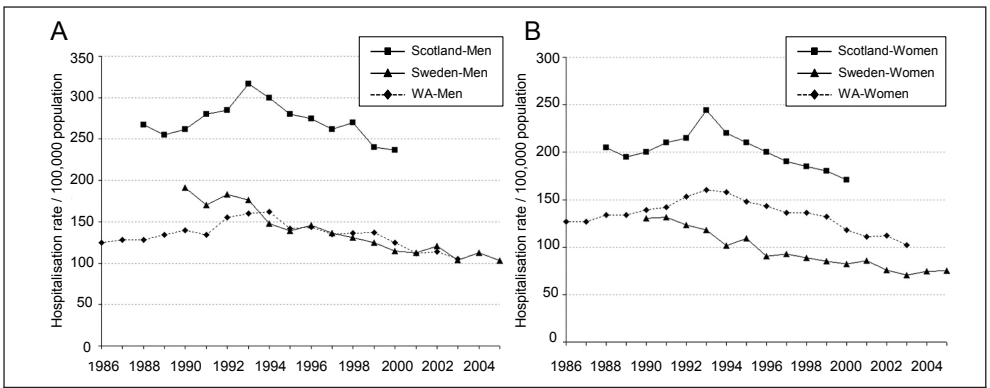

Figure 4. Time trends of age-standardised rates of first hospitalization of heart failure as principal diagnosis in (A) men and (B) women in Scotland (Jhund et al.[46]), Sweden (Barasa et al.[45]) and West Australia (WA; Teng et al.[47]). The age-standardised rates were based on the standard populations in 2001 for Scotland and WA and in 2000 for Sweden. Reproduced from Teng et al.[47] with permission from Wolters Kluwe Heath, Inc.).

Risk factors - The most common etiological entities, accounting for approximately 40% of all cases, are hypertension and ischaemic heart disease (IHD). Other contributors are atrial fibrillation, valvular heart disease, pulmonary disease and alcohol abuse. Less common are myocardial infiltrative, inflammatory and toxic engagements.[30] Diabetes, obesity and traditional risk factors for IHD are important even for heart failure.[15,49]

The different heart failure entities HFpEF, HFmrEF and HFrEF are considered to have a somewhat different risk factor profile with increasing age, long-standing hypertension, diabetes, atrial fibrillation and female sex commonly seen in HFpEF while IHD, smoking and male sex are more prevalent in HFrEF.[30] Whether there are specific risk factors that cause HFmrEF remains to be elucidated.

Prognosis

Mortality among patients with heart failure is high despite the improvement seen with the introduction of modern evidence-based treatment as detailed below.[45-47,50] Since then age adjusted mortality has remained relatively stable with a better survival in women than men,[33,42,48] and with a similarly compromised long-term prognosis in patients with HFpEF and HFrEF.[37,38,51]

Pathophysiology

Heart failure develops when the heart is unable to deliver sufficient amounts of blood to meet the bodily requirements or has to increase its filling pressures to keep an adequate cardiac output. The reasons may be myocyte death and/or dysfunction, myocardial remodelling or a combination. To maintain a sufficient cardiac output three adaptive mechanisms will be activated, which explains why patients, at least during some time can be relatively asymptomatic despite a compromised cardiac function;[52]

1) *The Starling mechanism* by means of which an increased preload, reflected by an elevated end-diastolic volume, increases ventricular performance.[25]
2) *Neurohormonal activation* increasing myocardial performance by means of an enhanced sympathetic tone and stimulation of the renin-angiotensin-aldosterone system (RAAS) in order to maintain arterial pressure and perfusion to vital organs.[28]
3) *Myocardial remodelling* including dilatation of the cardiac chambers and myocardial hypertrophy to meet the increased demands induced by the augmented filling pressures.

The former two represent a more or less immediate response, which during some time may be advantageous but, if persistent, will contribute to myocardial remodelling and in the long run to a successively deteriorating myocardial function. Thus, as illustrated in Figure 5, neurohormonal activation, although initially a physiological response, leads to a negative, vicious cycle,[52] which in addition leads to myocyte loss, collagen deposit and myocardial fibrosis.[53]

Modern treatment

Symptoms related to congestion have since long been possible to counteract by diuretic agents. These should be used on demand i.e. intermittently and with caution since they have several adverse effects and may further increase the already enhanced neurohormonal activation. It was not until the introduction of neurohormonal deactivation by means of ACE inhibitors after the publication of the CONSENSUS and SOLVD trials in 1987 and 1991 respectively,[54,55] that

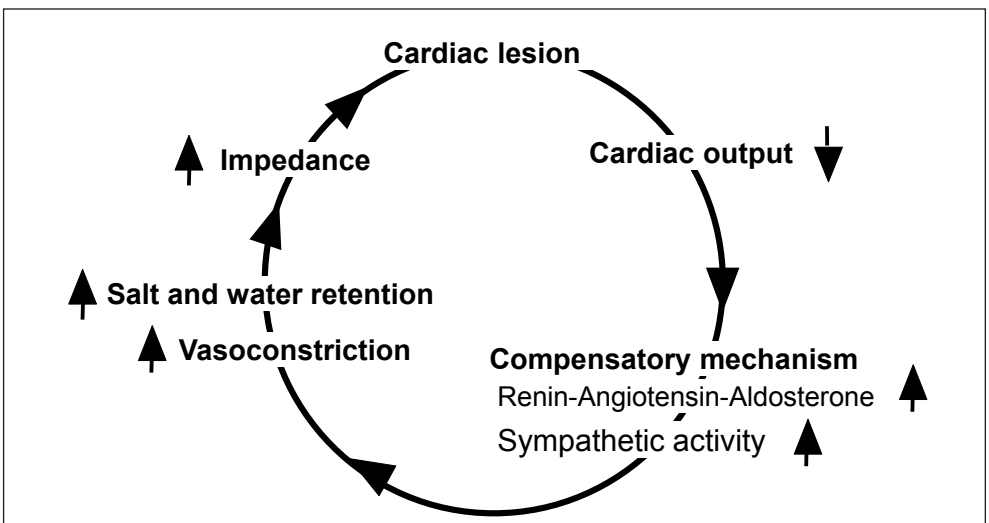

Figure 5. Neurohormonal activation caused by depressed myocardial function leads to a vicious circle further compromising the already reduced myocardial function.

both symptoms and longevity could be improved (table 5). Outcome was further enhanced by beta-blockers introduced in 1999 after reduction in mortality was demonstrated in the CIBIS-II, MERIT-HF and COPERNICUS trials.[56-58] In 2003, Angiotensin II Receptor Blockers (ARB) given to patients intolerant to ACEi was shown to improve outcomes in the CHARM-Alternative trial,[59] and Mineralocorticoid receptor antagonists (MRA) were subsequently added in refractory cases following the RALES,[60] and EMPHASIS-HF trials.[61] Most recently the Angiotensin II Receptor blocker Neprilysin Inhibitor (ARNI) was shown superior to the ACEi in reducing mortality as demonstrated in PARADIGM-HF trial in 2014.[30,62] Besides pharmacological treatment, implantable devices may offer symptomatic relief and survival benefits in selected cases e.g. Cardiac Resynchronization Therapy (CRT) in patients with intra-ventricular conduction defects and Intra Cardiac Defibrillators (ICD) in patients prone to develop ventricular tachycardia or fibrillation. For end-stage heart failure, left ventricular devices and heart transplantation offer good symptom relief and reduced mortality.[30] Last but not least physical exercise have beneficial effects in the form of improved physical ability and quality of life. The favourable impact of revascularisation in patients with heart failure of ischaemic origin is still uncertain.[30,64]

Table 5. Landmark randomized trials with improved outcome in heart failure with reduced LVEF.

Acronym	Drug class	Publication year	Study name
CONSENSUS	ACEi	1987	Cooperative North Scandinavian Enalapril Survival Study[54]
SOLVD	ACEi	1991	Studies of Left Ventricular Dysfunction[55]
CIBIS-II	Beta blocker	1999	Cardiac Insufficiency Bisoprolol Study II[56]
MERIT-HF	Beta blocker	1999	Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure[57]
COPERNICUS	Beta blocker	2001	Carvedilol Prospective Randomized Cumulative Survival[58]
CHARM	ARB	2003	Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity[59]
RALES	MRA	1999	Randomized Aldactone Evaluation Study[60]
EMPHASIS-HF	MRA	2011	Eplerenone in Mild Patients Hospitalization and Survival Study in heart Failure[61]
PARADIGM-HF	ARNI	2014	Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality in Heart Failure[62]

Diabetes Mellitus and Heart Failure

Epidemiology

Prevalence - The prevalence of diabetes is considerably higher in patients with cardiovascular disease than in the general population. Several studies reported on previously undetected diabetes in more than 25% of patients with myocardial infarction and another 40-45% with IGT when screened with an oral glucose tolerance test.[65,66] Similar proportions were detected in patient populations with cerebral and peripheral vascular disease.[67] The prevalence of diabetes in heart failure populations varies ranging between 13-47%.[68] The combination of diabetes and heart failure from a general population was investigated in the Reykjavik study revealing a diabetes prevalence of 12% in people with compared to 3% in those without heart failure. The combination increased by age and is slightly more common among men than

women.[32] In an elderly Italian population diabetes was found in 30% of the 10% with heart failure.[34] Moreover, insulin resistance and undiagnosed glucose abnormalities are common in heart failure patients.[69,70] Clinical trials in stable heart failure patients usually report a prevalence of known diabetes between 20-35%,[71-73] approaching 40-45% in decompensated heart failure.[74] Information on the prevalence of diabetes according to the type of heart failure is sparse.[75]
Conversely, in diabetes populations, several epidemiological studies report on a high prevalence, 12-22%, of heart failure.[76-78] Moreover there was a high prevalence of unknown heart failure (28%), mostly HFpEF, in a recent study of Dutch people above the age of 60 years.[79]

Incidence - In the Framingham cohort the incidence of heart failure was twice that among men and five times higher in women with than without diabetes during 18 years of follow-up.[80] In 2004, the Kaiser Permanente Northwest study comparing patients with and without diabetes identified an incidence of heart failure of 30.9 and 12.4/1000 person years respectively. The incidence increased with poor glycaemic control.[81] A Swedish study from 2012 on >80 000 patients with diabetes observed an increased incidence of heart failure with deteriorating glucose control ranging from 13.8 to 25.8/1000/person years during seven years.[82]

Risk factors – Diabetes and heart failure share many risk factors among them family history, age, overweight and a sedentary life-style,[30,83,84] and in addition people with diabetes are at risk for IHD and hypertension, two of the most important risk factors for heart failure.[30]

The concept that there may be a direct relation between diabetes and heart failure dates back to 1954 when the Danish Professor Lundbæk published an article on clinically important complications in patients with diabetes underlining that heart disease was common and suggested the presence of a *diabetes specific cardiomyopathy*.[85] Twenty years later Rubler et al.[86] published supporting data, although only based on four post-mortem cases. They concluded that myocardial disease seemed to be a complication to diabetes in itself and not merely caused by coronary artery disease. Shortly thereafter the Framingham study presented epidemiological evidence for a strong relation between heart failure and diabetes indicating that this association could not solely be explained by traditional risk factors for coronary artery disease.[80]

Diabetes cardiomyopathy is presently defined as the presence of myocardial dysfunction in a patient with diabetes without other obvious causes for cardiomyopathy, such as coronary artery disease, hypertension or valvular heart disease.[87] Seferovic et al. recently extended this by postulating that diabetes cardiomyopathy may give rise to both HFpEF and HFrEF.[88]

Prognostic implications of the combination of diabetes and heart failure

There is growing evidence that diabetes and heart failure aggravates the prognosis of each other. This has been shown in observational investigations of selected populations [74,89-91] and in several randomized heart failure trials,[73,92,93] especially in ischaemic heart failure[71,91,92,94]. For example, annual mortality in patients with diabetes has been reported to be as high as 36% in patients with heart failure compared with 3% in patients without.[95] Another observational study of diabetes patients above 65 years found a mortality of 32.7 compared with 3.7 per 1000 person years during five years of follow-up in patients with and without heart failure respectively.[78]

The majority of the studies are restricted to HFrEF populations. Corresponding data investigating prognostic implications in HFpEF are infrequent but indicate that diabetes predicts mortality even in this entity.[71,96] There is a need for prognostic information from unselected patient populations subjected to a contemporary management.

Pathophysiology in relation to diabetes and heart failure

There are several pathophysiological characteristics considered involved in diabetes cardiomyopathy as summarised in Figure 6.

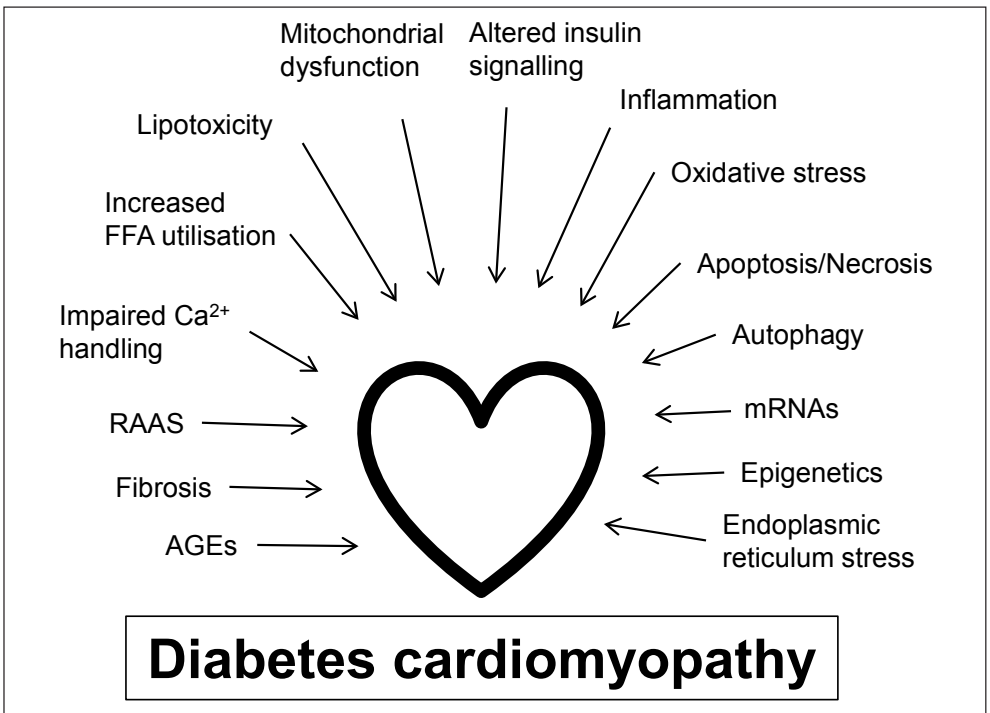

Figure 6. Possible mechanism involved in diabetes cardiomyopathy. Adapted from Bugger et al.[87] with permission of Springer.

The normal myocardial energy production is generated via β-oxidation of free fatty acids (FFA) to about 70% while oxidation of glucose, lactate and other products e.g. ketones contributes with about 30%.[97] Diabetes already at rest causes a deviation of the energy production away from glucose towards β-oxidation of FFA, which in this situation may contribute with 90% of the production of energy rich adenosine phosphate (ATP). This pathway is an efficient energy provider in states of a sufficient oxygen supply. Glucose oxidation provides more energy per mole oxygen, which is an advantage when oxygen supply is limited.[98] Multiple factors underlie the shift seen in diabetes. Decreased insulin production and sensitivity compromise glucose transportation (via GLUT 4) into the myocytes. Insulin deficiency further enhances lipolysis inducing an increase of circulating FFA thereby further stimulating myocardial utilization of FFA as the predominating energy substrate, a process largely driven by the

translation factor peroxisome proliferator-activator receptor-α (PPAR-α).[99] Unfortunately increased β-oxidation of FFA inhibits glucose oxidation via Randle´s cycle,[100] contributing to diminished cardiac efficiency. The myocardial ability to shift the energy source from FFA to glucose is further restricted in stressful situations.[97,101] The myocardial lipid overload is believed to have toxic effects in itself. This has been referred to as lipotoxicity and is characterized by non-oxidative pathways generating toxic lipid intermediates that may contribute to mitochondrial dysfunction, oxidative stress, perturbed cellular signalling, increased inflammatory activity, necrosis and apoptosis ultimately accelerating the process of myocardial fibrosis.[87,99] Oxidative stress is also thought to rise as a consequence of hyperglycaemia by activated reactive oxygen species (ROS)-driven pathways and of processes triggered by protein kinase C (PKC). Increased levels of inflammatory cytokines will further enhance insulin resistance.[21]

Myocardial contractility is also impaired in diabetes by disturbed Ca^{2+} handling via decreased Ca^{2+} influx through L-type Ca^{2+} channels, and by reverse mode Na^{2+}/Ca^{2+} exchange. Furthermore chronic hyperinsulinaemia is involved in impairment of the phosphatidylinositol 3-kinases (PI3K)/Akt pathway, among others thought to play part in vascular constriction and increased apoptosis thereby further promoting left ventricular remodelling.[87,99]

Another assumption is that Advanced Glycation End products (AGEs) that are more common in diabetes, by cross-linking with collagen disturbs the normal degradation of collagen inducing accelerated myocardial fibrosis that increases myocardial stiffness and compromises relaxation.[87]

In summary the major metabolic derangements thus far postulated as explanations for diabetes cardiomyopathy are deranged metabolism, reduced myocardial substrate production, toxic effects from metabolites, increased oxidative stress, disturbed Ca^{2+} handling, increased myocardial stiffness/fibrosis and reduced coronary flow reserve.

Treatment

Heart failure treatment in diabetes

For the most part, evidence-based heart failure therapy has a proportionately similar efficacy in patients with and without diabetes.[23,26] Beta-blockers were initially questioned because of their propensity to worsen insulin sensitivity and blunt hypoglycaemic symptoms. There is, however, clear evidence that this therapy benefits patients with diabetes and heart failure.[103,104] Likewise RAAS-inhibition has similar effects in patients with and without diabetes. MRAs and Renin inhibitors should be used with caution in patients with diabetes due to commonly concomitant renal impairment.[104] Diuretic agents including thiazides and loop diuretics are efficient and usually unavoidable for the relief of symptoms of congestion.[23] Whether these recommendations are followed in the everyday clinical care is incompletely explored.

Diabetes treatment in heart failure

Glucose lowering in heart failure patients is complicated by the potential side effects of the pharmaceutical agents. Whether such phenomena is even part of the explanation for the serious prognosis of heart failure when diabetes is present is not known. Insulin sensitizers have the propensity to worsen heart failure by inducing fluid retention and some agents were because of this withdrawn from the market.[105-107] Metformin was for long considered

contraindicated due to the assumption that the risk for lactic acidosis became increased, especially in the presence of impaired renal function. More recent data did not verify this and metformin is recommended as first-hand choice in the current European management guidelines.[23] The benefit of insulin treatment in patients with diabetes and heart failure is debated. The main effect of insulin is to decrease blood glucose but it may also increase myocardial blood flow, decrease heart rate, increase sodium retention i.e. fluid retention and cause a modest increase in cardiac output.[108,109] Beneficial effects on myocardial function have been reported, but also that insulin may be associated with increased morbidity[110] and mortality.[111,112] Concerns have been raised regarding a potentially increased risk of heart failure hospitalization seen with the DPP-4 inhibitor saxagliptin[113] and additionally a tendency even with alogliptin,[114] however, not confirmed for sitagliptin.[115,116] Promising are the findings with the SGLT-2 inhibitor empagliflozin that decreased the need for heart failure hospitalisations by 35% in the EMPA-REG OUTCOME study in patients with diabetes and established cardiovascular disease,[117] which probably was a driving force behind the 13% mortality reduction seen with this SGLT-2 inhibitor.[118] Two studies with the GLP-1 receptor agonists liraglutide and semaglutide (LEADER and SUSTAIN-6) recruiting patients with diabetes with established cardiovascular disease or at high cardiovascular risk revealed mortality (LEADER) and morbidity benefits (SUSTAIN 6), however, without impact on heart failure hospitalization.[119,120]

Drugs targeting metabolic modulation e.g. trimetazidine, etoxomir and dichloroacteate that shifts myocardial metabolism from β-oxidation of FFA towards glucose utilisation have so far not provided great promise even if further exploration is mandated.[121-123] A potential myocardial metabolic modulating effect by GLP-1 receptor agonists are still under extensive investigation. So far the results are conflicting.[124,125] Promising emerging modulators are ketones and glucagon.[101,126]

In summary, major efforts in the management of hyperglycaemia and myocardial metabolism have been the subject of research for a long time, although it is only just recently that the impact of heart failure development has been successfully intervened with.

Revascularization

Regardless of the presence of diabetes revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is a cornerstone when managing patients with myocardial ischemia.[127] According to the FREEDOM trial CABG is to be preferred over PCI in patients with diabetes and multivessel or complex vessel disease,[128] and when PCI is preferred patients with diabetes should be given drug eluting stents.[128] The STICH trial, including both patients with and without diabetes, addressed the prognostic importance of CABG in a randomized trial of patients with LVEF <35% and with two- and three-vessel disease. In the intention to treat analyses the STICH investigators reported on lower cardiovascular and total mortality in the CABG group.[129] However, in the viability sub-study of STICH, there was no correlation between myocardial viability and benefits with the use of CABG. Although these studies have provided information, there is still a lack of studies on the prognostic impact of revascularization in unselected, well-defined populations of heart failure patients with diabetes.

Sex and gender aspects of diabetes and heart failure

More women than men live with heart failure partly due to their longer life expectancy. In addition survival in heart failure is mostly reported as better in women, who tend to develop heart failure at older ages, more often with HFpEF and less frequently due to IHD than men.[130] The protective effect against IHD seen in women seems to be attenuated in the presence of diabetes.[15,131] That women with diabetes have a poor prognosis after myocardial infarction and high heart failure prevalence was first described in 1961 by Björck and colleagues.[132] Their findings were confirmed by Kannel et al. in 1974 in the Framingham cohort.[80] The reason for the increased cardiovascular risk in women with diabetes is not completely understood, but there are indications that women with compared with those without diabetes are more likely to have multivessel coronary artery disease,[133] and it has been suggested that they do not get a fully established evidence-based management although previous reports regarding this are contradictory.[134-139]

Prognosis related to sex and gender differences (the former relating to biological and the latter to sociocultural aspects), in heart failure patients with diabetes are sparse and somewhat contradictory. The Danish Investigators and Arrythmia ON Dofetilide (DIAMOND) reported that diabetes negatively impacted survival particularly in women who got less of evidence-based treatment,[140] while a large meta-analysis including 42 000 patients demonstrated that women with diabetes had a slightly better survival than men after adjustments for important confounders but much higher mortality compared with women without diabetes.[51] Mechanisms behind these findings remain to be elucidated.

Rational for registry based analyses

Patient registries have the advantage over randomised clinical trials to offer comprehensive patient materials without any inclusion or exclusion restrictions. This is particularly true for nationwide, multicentre registries with high quality and validated variables. Such registries offer better information on the true prevalence of the actual patient category and their everyday management and prognosis than clinical trials with all their restrictions. However, to derive appropriate information and draw adequate conclusions from registry-based analyses, it is mandatory to be aware of the quality and validity of reported variables and knowledge on limitations related to non-randomised treatment data. Thus, registry based analyses on treatment effects cannot serve as a substitute to randomised trials. They do, however, generate hypotheses for future research.

Swedish National Quality Registries

Swedish National Quality Registries were originally instituted to enable quality follow-up to improve health care. Since the initiation of the first registry in 1975, another 96 have been added across all health care production with continuous financial support provided from the Swedish state (http://kvalitetsregister.se/englishpages). Swedish registries are unique due to the ten-digit personal number of each Swedish citizen, which apart from enabling the initiation of well-functioning registries also allows cross-linking the registries with each other, leading to increased knowledge about treatment patterns and prognosis. The registries have thereby evolved into not only being a provider of information for quality follow-up but also bringing valuable source of information for researchers. The validity and quality of the registries are determined according to four certification levels (level 1-3 and candidate level,

where level 1 equals top certification) issued by the Swedish National Board of Health and Welfare.[141] Quality is ensured by the requirements to follow specific pre-set goal criteria for each certification level. Every quality registry is obliged to have a registry holder and a steering group. Whether financial support is provided is annually judged upon the relevance, design, competency and follow-up ensuring high quality and appropriate use of common financial resources.

Gaps in knowledge

According to available data the combination of heart failure and diabetes is common and ominous. Still there is a lack of knowledge on how this combination is best managed. Moreover, further elucidation is needed when it comes to the reasons for the impact of diabetes and what risk factors are most important for the compromised survival. Among them are the influence of sex, heart failure aetiology and heart failure type. Large, registry based analyses comparing heart failure patients with and without diabetes may provide valuable information, in particular if derived from unselected contemporary populations. In this context, the Swedish Registry on Heart Failure (SwedeHF) offers a unique opportunity to analyse the nature of heart failure in patients with diabetes in a population collected from all day practices across Swedish hospitals and outpatient clinics. The real proportion of such patients, and insight into the actual long-term prognoses and management can be analysed. With such expanded knowledge, it should be possible to give useful advice for improving the outlook for this patient category.

Aims

The overall aim is to study patients with diabetes and heart failure in order to provide a deeper understanding of underlying reasons for their poor prognosis and to identify possible roads to improvement.

Specific aims are to analyse

I. the risk factor panorama and treatment pattern in heart failure patients comparing patients with and without diabetes and to investigate the association between diabetes and long-term prognosis. **(Study I)**

II. whether risk factor pattern, use of evidence-based heart failure therapy and long-term survival differs between women and men in heart failure patients with and without diabetes. **(Study II)**

III. the proportions and prognostic impact of ischaemic and non-ischaemic heart failure and to investigate the role of previous revascularization in patients with and without diabetes. **(Study III)**

IV. the prevalence, demographic characteristics and prognostic implications of diabetes in patients with preserved (HFpEF), mid-range (HFmrEF) and reduced (HFrEF) heart failure. **(Study IV)**

PATIENTS AND METHODS

Patients

The four studies behind this thesis are based on a study population extracted from the Swedish Heart Failure Registry, SwedeHF, slightly adapted for the individual study purposes as detailed in Table 6.

Table 6. Summary of the four studies behind this thesis.

	Study I	Study II	Study III	Study IV
Aim	DM vs. No DM, characteristics and prognosis	DM, differences in women and men	DM and ischaemic vs. non-ischaemic HF. Role of revascularization	DM in different types of HF; HFpEF, HFmrEF and HFrEF
Data source	SwedeHF			
Study design	Prospective observational registry study			
Source population	Specialist HF care			
Inclusion criteria	Clinician judged HF, known DM status	Clinician judged HF, known DM status and sex	Clinician judged HF, known DM and IHD status	Clinician judged HF, known DM and LVEF status
Inclusion years	2003-2011			
End of follow-up	30th Sept 2011	30th Sept 2011	30th Sept 2011	31st Dec 2014
Outcome	All-cause mortality			
Number of patients	36 274	36 274	35 163	30 696
Sub group distribution	-	39% W / 61% M	51% IHD / 49% no IHD	22% HFpEF / 21% HFmrEF / 57% HFrEF
Proportion with diabetes	24%	Women: 23% Men: 25%	IHD: 30% No IHD: 19%	HFpEF: 25% HFmrEF: 24% HFrEF: 24%
Adjustments	Baseline characteristcs, risk factors and treatment			
Staistical analysis	Descriptive statistics and hypothesis testing, survival by Kaplan Meier and Logistic regression.	Descriptive statistics and hypothesis testing, survival by Kaplan Meier and logistic regression. Age-matched analyses.	Descriptive statistics and hypothesis testing, survival by Kaplan Meier and Cox proportional hazard regression. Propensity score analysis.	Descriptive statistics and hypothesis testing, survival by Kaplan Meier and Cox proportional hazard regression.

Abbreviations: DM, Type 2 diabetes; HF: Heart Failure; HFmrEF, Heart failure mid range Ejection Fraction; HFpEF, Heart failure preserved Ejection Fraction; HFrEF, Heart failure reduced Ejection Fraction; Specialist HF care, Hospital ward (internal medicine or cardiology) or specialist out patient clinic; M, Men; SwedeHF, The Swedish Heart Failure Registry; W, Women

Definitions

Most variables were defined as outlined in SwedeHF and the most pertinent of them are listed below. For a full description see Appendix 1.

Heart failure - Diagnosed by the attending physician based on guideline recommendations at the time of inclusion (current definition, Table 3).

Type 1 and 2 diabetes – The physician in charge reported history of diabetes stratified according to type 1, or type 2 reported by glucose lowering regime (life-style advice only, oral glucose lowering drugs and/or insulin). For the studies comprised in this thesis type 2 diabetes was reclassified *yes or no.* All patients with type 1 diabetes were excluded from the thesis.

IHD defined as *present,* whether verified or not by coronary angiography, or *absent* based on the case history from patient records. An adapted definition was used for IHD in **Studies III-IV** where patients reported as *without IHD* but with a confirmed coronary revascularization procedure or history of *previous myocardial infarction* were reclassified as having IHD.

Revascularization – Reported by the physician in charge as a history of coronary artery bypass surgery (CABG) and/or percutaneous coronary intervention (PCI).

LVEF - The most recently estimated EF reported stratified into four different classes: LVEF ≥50%, 40-49%, 30-39% and <30%. An estimated EF was not obligatory for inclusion in the SwedeHF and it was not possible to report by which method the LVEF had been estimated.

NYHA class – Defined according to the New York Heart Association classification of symptom severity (Table 4).[31]

Renal function - Based on serum creatinine, the *Estimated Glomerular Filtration Rate (eGFR)* was estimated according to the Cockroft-Gault formula **(Studies I-II)**[142] or by the MDRD formula **(Studies III-IV)**[143]. It was expressed as a continuous variable as well as categorized into four groups: >90, 60-89, 30-59 and <30 ml/min or ml/min/1.73m^2

Chronic Kidney Disease (CKD) – Based on the evaluated eGFR, CKD was considered present at clearance <60 mL/min in **Studies I-II** and <60 mL/min/1.73m^2 in **Study III-IV.**

Laboratory measurements

Measurements of NT-proBNP, Hb, creatinine, blood lipids, random plasma glucose and glycosylated haemoglobin A1c (HbA1c) were accepted as analysed by the local hospital laboratories.

Source of data

The Swedish Heart Failure Registry (SwedeHF)

The Swedish Heart Failure Registry (abbreviated *SwedeHF* throughout the thesis but until March 2015 referred to as *S-HFR*) is a National Quality Registry holding patients with clinician-judged heart failure. The registry was initiated in 2003 by Professor Ulf Dahlström, Linköping and Associate Professor Magnus Edner, Stockholm. The registry was created to provide quality follow-up of heart failure diagnosis and treatment in Sweden and to identify areas in need of further efforts to reach an optimal and equal heart failure evidence-based

management according to actual guidelines all over Sweden.[144] An additional objective was to provide comprehensive information for epidemiologic research on heart failure patients as reflected by contemporary all day practice. The registry is supported by the Swedish National Board of Health and Welfare and is independent of commercial interests. A detailed description is available,[145] and the protocol, registration forms and annual reports can be found at http://www.swedehf.se.

Data collection and follow-up

SwedeHF is an online-based registry comprising >70 pre-selected variables related to risk factors, treatment and indicators of myocardial function. During the time period covered by the present thesis (2003-2011) variables were reported at the time for hospital discharge or after an out patient visit via an internet-based case report form to a central database at Uppsala Clinical Research Center (UCR). The database is run monthly against the Swedish population registry by use of the unique ten-digit personal number of each Swedish citizen, thereby providing information necessary for analyses of all-cause mortality. This information is therefore complete without any loss of follow-up.

Quality indicators

Coverage - SwedeHF has since the start steadily increased in coverage from 14 including centres reporting 861 patients in 2003 to 65 centres and 47 000 unique patients in 2011, when 83% of all hospitals in Sweden and 10% of the primary care centres were connected. The time period covered in **Studies I-IV** starts in January 2003 and lasts until the end of September 2011. In the annual SwedeHF report from that year it is reported that the registry had an estimated coverage of 82%,[146] and had reached the certification level 3 issued by the Swedish National Board of Health and Welfare.[140]

Coverage estimates may, however, be uncertain and complicated mainly by two reasons: 1) heart failure is a clinical syndrome without a distinct starting point; 2) there is some uncertainty on how to report the International Classification of Diseases *(ICD)* codes for heart failure since there may be varying position as a 1st or 2nd diagnosis during a hospital stay. For 2011 two different methods were applied to evaluate the coverage. The results differed significantly from 82% coverage based on hospitalisation data from the Swedish *Epidemiological Centre* to 37% in a more recent estimate when using data on hospitalization provided by the Swedish Board of Health and Welfare and that in contrast to the former also required echocardiographically verified heart failure.[147]

Reported and missing variables - Examples of variables reported in 100% are age, sex, creatinine, and haemoglobin. The majority of other, clinically important variables on baseline characteristics and treatment have a reported frequency >95%. Echocardiography was registered in 87% of the patients, NYHA class was available in 69%. NT-proBNP was not mandatory before 2011 and is only available in about 26%. HbA1c was reported in 6% and random plasma glucose in about 28%.

Variables registered in SwedeHF had not been validated at the time of the present data extraction. Continuous quality monitoring started in 2012 and has so far reported a varying quality of the registered data between the different reporting centres. Low consistency between reported information to SwedeHF and the original patient record is mainly seen for NYHA-classes, alcohol consumption and smoking.[146] It can be assumed that these observations may be relevant even before 2012.

Study populations and design

The original study population comprise all patients from hospital-based (68%) and specialised outpatient heart failure clinics (32%) registered in SwedeHF January 1, 2003 to September 30, 2011. The patient selection in **Studies I-IV** is presented in Figure 7.

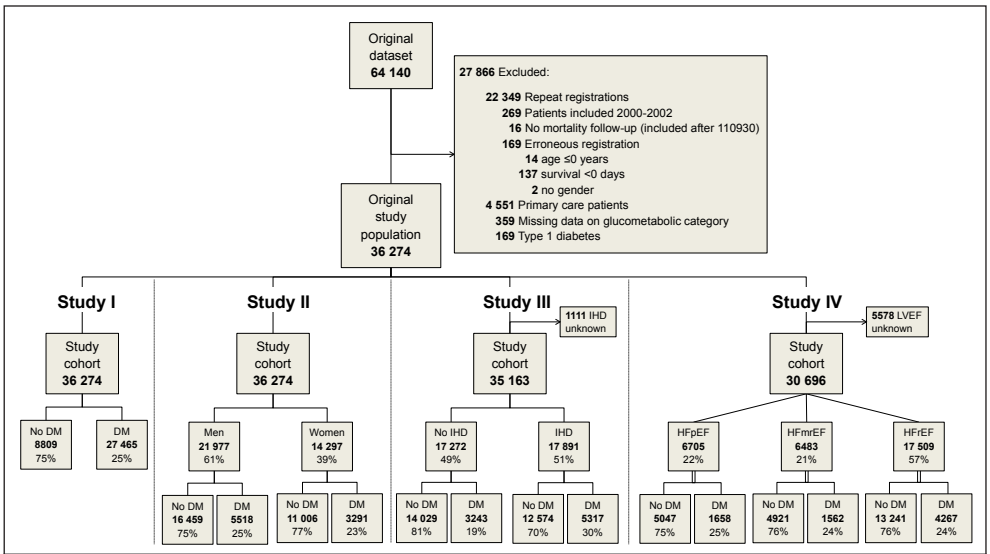

Figure 7. Schematic patient selection in **Studies I-IV**.

Specific study aims, population and design

Study I

To test the hypothesis that risk factor pattern, treatment and prognosis differ between patients with and without diabetes in a contemporary heart failure population collected from an everyday health care setting.

The original study population was analysed comparing patients with and without diabetes. The impact of diabetes was further studied in sub-groups of different age groups: ≤65 years, 66-80 and >80 years. Follow-up for all-cause mortality lasted until September 30, 2011.

Study II

To test the hypothesis that sex and gender influences risk factor pattern, prescribed treatment and the vital prognosis in heart failure patients in the presence of diabetes to the disadvantage of women with diabetes.

The original study population was used and analysed stratified by sex, diabetes and age groups; ≤65 years, 66-80 and >80 years. To further circumvent age bias, three sub-cohorts of age-matched populations were constructed (±1 year) and compared: (1) men and women with diabetes; 2) women by diabetes status; 3) men by diabetes status. Follow-up for all-cause mortality lasted until September 30, 2011.

Study III

To test the hypothesis that ischaemic heart failure is common in patients with diabetes and negatively impacts prognosis. Further to investigate previous revascularization pattern and analyse whether the role of previous revascularization differs in patients with and without diabetes.

All patients with available information on the presence or absence of IHD were selected. Baseline and prospective survival analyses were performed stratified by diabetes and IHD and further in patients with IHD according to diabetes status and history of revascularization. Follow-up for all-cause mortality lasted until September 30, 2011.

Study IV

To test the hypothesis that diabetes is more common in HFpEF than in the other two entities and that the prognostic implication is similar in all types of heart failure.

All patients from the original study population with reported information on LVEF were selected and analysed according to heart failure entity; HFpEF, HFmrEF and HFrEF and further stratified by diabetes. Follow-up for all-cause mortality lasted until December 31, 2014.

Statistical analyses

All analyses in the PhD-project were undertaken by use of SAS statistical software, version 9.3 (**Studies I-II**) and version 9.4 (**Studies III-IV**). A 5% level of significance with a two sided p-value of <0.05 was considered statistically significant.

Descriptive statistics and hypothesis testing

Studies I-IV - Differences in continuous variables between independent groups were tested for statistical significance by use of Student's t-test or when more than two independent groups by ANOVA-test and Kruskal-Wallis significance test**.** Natriuretic peptides were logarithmically transformed prior to t-test. Quantitative, normally distributed variables are presented as the mean (SD) and 95% confidence intervals (CI) or, when appropriate median and range. Categorical variables were compared testing the hypotheses of variables in contingency tables through chi-square test and are presented as counts and proportions (%). In analysing laboratory variables, impossible values were excluded from analysis.

Survival analyses

Four per cent survived less than 30 days after inclusion in SwedeHF and in order to avoid bias on its effect between patients with and without diabetes, analyses were also performed excluding those. This did not change overall baseline characteristic and prognostic differences in the comparison of patients with and without diabetes, therefore all the all patients were kept in the analysis. As a general rule, variables included in the multivariate adjustment models were those with less than 5% reported missing values and a univariate p-value <0.05 and include baseline characteristics, patient history and on-going treatment or else, when covariates where considered clinically important with the potential of altering the outcome, such were included as detailed in Table 7.

Differences in all-cause mortality between the groups were analysed by log-rank test and illustrated through Kaplan-Meier curves in **Studies I-III** and further by age-adjusted survival curves in **Studies III-IV** by use of Cox regression analysis. Uni-, and multivariate logistic regression models were used to detect predictors of mortality in **Studies I-II** while Cox proportional hazard regression was applied in **Studies III-IV.** A formal test of interaction between mortality, sex and diabetes was performed in **Study II** by use of logistic regression. In **Study IV,** interaction was tested between mortality, LVEF and diabetes by use of Cox proportional hazard regression. A sensitivity analysis was performed in **Study IV** excluding those with pervious valvular heart disease.

Table 7. Summary of multiple covariate adjustments in **Studies I-IV**.	
Study I	**Main model:** Diabetes, age, gender, HF duration, blood pressure, IHD, hypertension, atrial fibrillation, pulmonary disease, revascularization, valvular surgery, eGFR class, Hb class, weight, ACEi, ARBs, beta-blockers, MRAs, diuretics, digitalis, nitrates, antithrombotic agents. **Additional model:** LVEF added
Study II	**Total cohort:** Diabetes, age, gender, level of care, blood pressure, HF duration, LVEF, blood pressure, IHD, hypertension, atrial fibrillation, pulmonary disease, revascularisation, valvular surgery, eGFR class, haemoglobin class, weight, ACEi, ARBs, beta-blockers, MRAs, diuretics, digitalis, nitrates, statins and antithrombotic agents **Matched groups:** Above model minus diabetes or gender in their specific groups
Study III	**Model 1:** Diabetes, age, gender, level of care, HF duration, weight, blood pressure, LVEF-class, eGFR-class, Hb-class, hypertension, atrial fibrillation, pulmonary disease, ACEi, ARB, beta-blockers, MRAs, diuretics, digitalis, nitrates, statins, antithrombotic agents **Model 2:** NYHA class and heart rate added to Model 1
Study IV	**Model 1:** Diabetes, age, gender, level of care, HF duration, weight, blood pressure, Hb class, eGFR class, IHD, hypertension, atrial fibrillation, pulmonary disease, valvular heart disease, revascularization, ACEi, ARB, MRA, beta-blockers, diuretics, statins, nitrates, Aspirin, anticoagulants

Matched analyses (age and sex)

Study II: Three age-matched (±1 year) sub-cohorts were constructed (detailed in Figure 1, **Study II**): 1) men and women with diabetes (n=6452; mean age 76.2 vs. 77.1 years); 2) women by diabetes status (n=6582; mean age 77.5 vs. 76.5 in those with and without diabetes respectively); 3) men by diabetes status (n=11036; 72.6 vs. 71.6 in those with and without diabetes).

Evaluation of coronary intervention by propensity score analysis

Study III: Due to the observational character of the investigation, a propensity score model was applied to avoid potential bias regarding the impact of previous revascularization on all-cause mortality. The propensity score, expressing the probability of an assigned treatment, in this case revascularization, given a set of known baseline characteristics was used to balance the study population in regard to a chosen dependent variable.[148] Logistic regression was used to estimate individual propensity scores for the history of revascularization in patients with IHD and diabetes (n=5182) with a good fit (Hosmer and Lemeshow-test; p=0.27 [p>0.05 is considered a good fit] and c-statistic of 0.7) based on 26 baseline variables (including demographics, medical history and reported pharmacological treatment).[148] The selected variables were those that affected all-cause mortality in univariate logistic regression given they had a reasonably low amount of missing data. An individual propensity score was estimated for 3467 patients with complete information of all variables. The impact of previous revascularization on all-cause mortality was thereafter determined by means of Cox regression adjusted for the propensity score.

Ethical considerations

Establishment of the SwedeHF and registration and analysis of data were approved by the Swedish National Review Board of Health and Welfare, the Swedish Data Protection Authority and the Ethical Review Board at Linköping University. SwedeHF in itself and **Studies I-IV** agree with the Declaration of Helsinki. Individual patient consent is not required or obtained, but patients are informed of being entered into the registry and are allowed to opt out (Dnr 2011/1922-31/3 and M196-09).

RESULTS

Selected patient characteristics for **Studies I-IV** are presented in the Table 8.

Table 8. Selected patient characteristics in **Studies I-IV**. P-value <0.0001 unless otherwise stated.

	STUDY I		STUDY II			
			No DM		DM	
	No DM	DM	Men	Women	Men	Women
Number of patients	27 465	8809	16 459	11 006	5518	3291
Proportions	75%	25%	60%	40%	63%	37%
VARIABLES						
Demographics						
Age, mean ± SD, years	75±13	74±11	73±13	79±12	73±11	78±10
Age-group (%)						
≤65	21	20	26	14	25	12
66-80	38	49	41	33	51	45
>80	41	31	33	53	24	43
Male sex (%)	60	63	100	.	100	.
Level of care (%), Hospital/O.P.	66/34	73/27	62/38	74/27	69/31	81/19
Weight, mean ± SD, kg	76±18	84±19	81±16	67±16	89±18	76±18
Duration of HF (%; ≥6 months)	47	56	47†	46†	57†	56†
NYHA (%), III & IV	42	51	40	22	50	51
CKD-MDRD (%)	50	59	44	58	54	68
CKD-CG (%)	56	53	47	69	46	66
Disease history (%)						
Ischemic heart disease	45	59	49	40	62	54
Hypertension	43	60	40	48	58	63
Atrial fibrillation	49	45	49†	50†	45†	45†
Pulmonary disease	17	19	17	18	17	18
Valvular heart disease	22	18	20	24	17	20
iDCM	12	9	15	8	11	6
Previous intervention (%)						
Revascularisation	22	32	28	13	38	23
Valvular surgery	5†	5†	6	5	6	4
Biochemical						
Hb-class (% anaemia)	34	45	36	31	46	42
NT-proBNP (pg/ml; median)‡	2860†	2870†	2673	3112	2736	3208
Left ventricular function (%)						
LVEF ≥50%	22†	22†	15	32	16	33
LVEF 40-49%	21†	21†	20	23	20	23
LVEF 30-39	27†	27†	20	24	29	23
LVEF <30%	30†	30†	35	21	35	21

†Not significant, ‡ Logarithimically transformed prior to t-test.

Table 8. Selected patient characteristics in **Studies I-IV**, continued.

	STUDY III				STUDY IV					
	No IHD		IHD		HFpEF		HFmrEF		HFrEF	
	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM
Number of patients	14 029	3243	12 574	5317	5047	1658	4921	1562	13 241	4267
Proportions	81%	19%	70%	30%	75%	25%	76%	24%	76%	24%
VARIABLES										
Demographics										
Age, mean ± SD, years	73±14†	74±11†	77±11	75±10	78±11	76±9	75±12†	74±10†	72±13†	72±11†
Age-group (%)										
≤65	27	23	15	17	13	15	22	20	29	25
66-80	35	45	41	52	36	50	41	52	42	51
>80	38	31	44	31	50	35	37	28	29	24
Male sex (%)	56†	57†	65†	66†	44	47	60	61	71	73
Level of care (%), Hospital/O.P.	65/32	73/27	68/32	74/26	75/25	83/17	60/40	70/30	59/41	67/33
Weight, mean ± SD, kg	76±19	86±21	75±16	83±18	74±18	86±20	77±18	85±20	77±17	84±18
Duration of HF (%; ≥6 months)	41	49	54	61	48	53	46	55	45	58
NYHA (%), III & IV	38	47	46	54	39	44	31	40	45	57
CKD-MDRD (%)	45	55	56	62	55	63	48	58	46	57
CKD-CG (%)	50	48	62	57	63	55	51†	50†	49†	50†
Disease history (%)										
Ischemic heart disease	.	.	.	.	38	49	51	66	50	68
Hypertension	41	60	45	59	52	68	45	63	38	55
Atrial fibrillation	55	51	43	40	57	50	51	48	44	40
Pulmonary disease	17	20	18	18	21	25	17	20	16†	17†
Valvular heart disease	22	18	21	18	30	21	22	18	22	19
iDCM	16	12	7†	7†	3	2	6	4	20	15
Previous intervention (%)										
Revascularisation	.	.	48	53	16	24	27	36	25	38
Valvular surgery	5	14	6†	6†	7	6	6†	7†	5†	4†
Biochemical										
Hb-class (% anaemia)	30	41	40	47	41	49	33	46	30	41
NT-pro-BNP (pg/ml; median)‡	2625†	2610†	3203†	3121†	2275†	1835†	2227	2658	3147	3628
Left ventricular function (%)										
LVEF ≥50%	26	31	18†	17†	100	100	.	.	.	.
LVEF 40-49%	20	19	23†	22†	.	.	100	100	.	.
LVEF 30-39	24	21	31†	31†	.	.	.	.	48	48
LVEF <30%	30	29	29†	31†	.	.	.	.	52	52

†Not significant, ‡ Logarithimically transformed prior to t-test.

Study I

Characteristics of diabetes vs. no diabetes in the total cohort

Of 36 274 patients, 8 809 (25%) had diabetes. The patients with diabetes were somewhat younger (mean age 74 vs. 75 years), more often of male sex, had longer heart failure duration and were more often in NYHA class III-IV while LVEF was similar in the two groups. As detailed in Table 8, patients with diabetes had more comorbidities, particularly hypertension (60 vs. 43%) and IHD (59 vs. 45%). Of the latter, 32% of patients with and 22% of those without diabetes respectively had been revascularized. Renal function did not differ substantially between patients with and without diabetes. When evaluated by the Cockroft-Gault formula the proportion with CKD was 53 and 56% and according to the MDRD estimation 59 and 50% respectively. Pharmacological treatment was more extensive in those with diabetes and, in general ACEi/ARBs and RAAS- and beta-blockade was frequently used and MRAs were less commonly prescribed. Use of device treatment was limited (<3% of the total population received cardiac resynchronisation).

Mortality

The median follow-up time was 1.9 years (range 0 to 8.7). Survival was significantly lower in those with compared with those without diabetes (log-rank p<0.0001). One-year mortality was 23% in patients with and 19% in those without diabetes and the corresponding proportions after five years were 59% and 52% respectively. The mortality difference was most apparent in patients below the age of 65 years (Figure 8 a-c) and in that group diabetes was associated with a 60% higher adjusted mortality risk (OR 1.61; 95% CI 1.31-1.92, p<0001). The increased mortality among patients with diabetes was evident across all age groups. Important independent predictors of mortality among patients with diabetes were an eGFR <30 ml (OR 4.43; 95% CI 3.41-5.75, p<0.0001), the presence of IHD (OR 1.68; 95% CI 1.47-1.94), a LVEF <30% (OR 1.73; 95% CI 1.46-2.07, p<0.0001) and the presence of pulmonary disease (OR 1.45; 95% CI 1.25-1.68, p<0.0001).

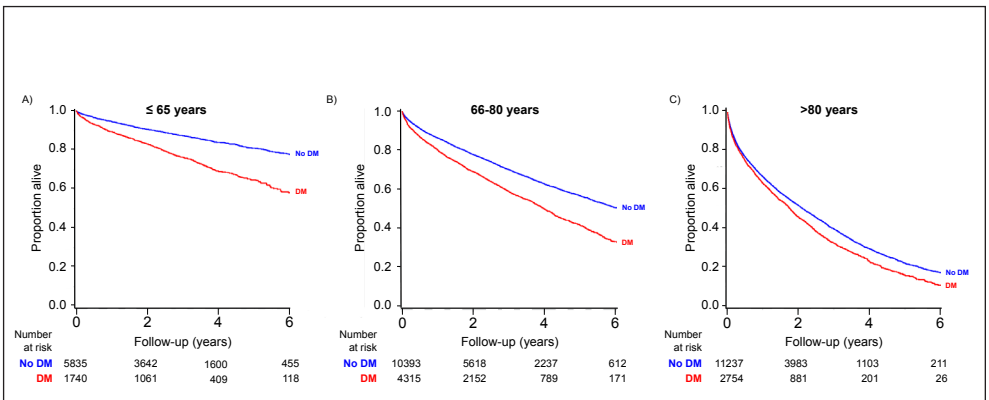

Figure 8. Kaplan Meier curves of survival by diabetes (DM) status and age group, in panel A) patients ≤65 years, panel B) patients 66-80 years and panel C) patients >80 years of age. Log-rank p<0.0001 in all comparisons.

Study II

Comparison of sex differences in the total cohort

Thirty-nine per cent of the 36 274 patients were women and they were in general older than men (Table 8). The prevalence of diabetes was similar among women and men (23 vs. 25%). Figure 9 presents the comorbidity pattern. Women were, regardless of their diabetes status, less likely to receive evidence-based heart failure treatment such as RAAS-inhibition and beta-blockers while they were more frequently prescribed diuretics (Figure 10) and in case of IHD, women less often had a history of revascularization compared with men.

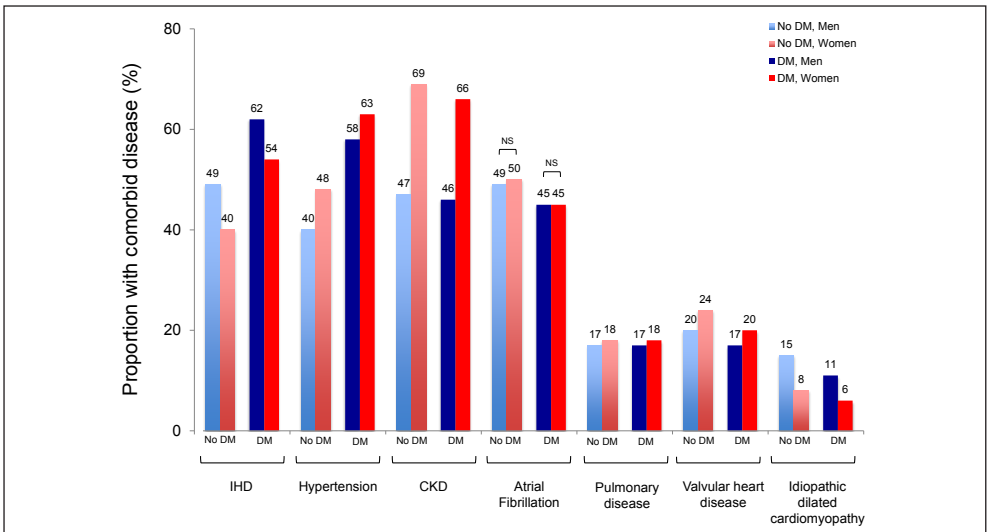

Figure 9. Comorbidities stratified by diabetes (DM) and sex. P-value <0.0001 unless otherwise stated. NS=Not Significant.

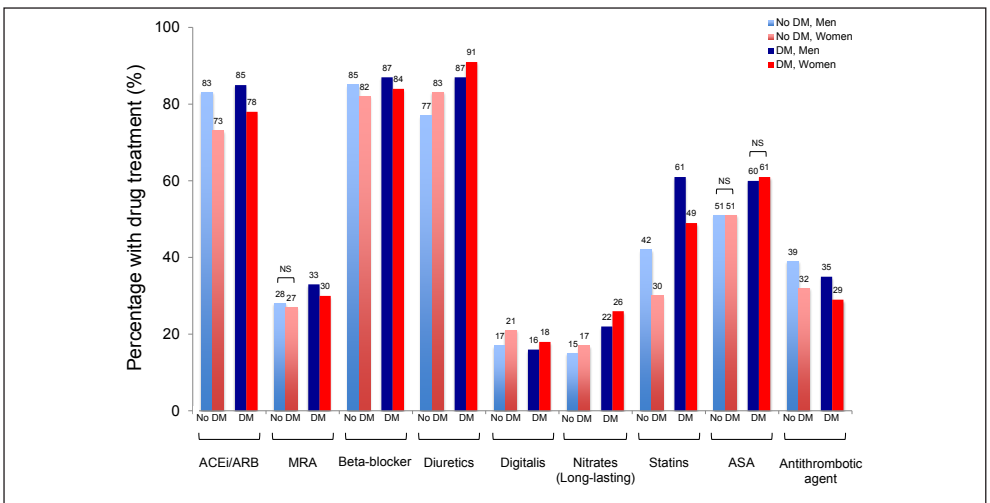

Figure 10. Pharmacological treatment stratified by diabetes (DM) and sex. P-value <0.0001 unless otherwise stated. NS=Not Significant.

Comparison of men and women with diabetes

Women with diabetes were older than their male counterparts (78 vs. 73 years). They did more frequently have hypertension, CKD (66% vs. 46%) and HFpEF (LVEF ≥50%; 33 vs. 16%) while IHD was more common in men apart from in the age-group ≤65 years where the proportions with IHD and hypertension were similar (49 vs. 52% and 58 vs. 57% respectively) as was the severity of heart failure symptoms expressed as NYHA class (class III-IV 50% vs. 51%).

Comparison of women with and without diabetes

Women with and without diabetes were of similar age (79 vs. 78 years). Patients with diabetes were heavier, had a longer duration of heart failure, were more frequently in NYHA classes III-IV (51 vs. 43%) and had a slightly higher median NT-pro-BNP (3208 vs. 3112 pg/ml) while renal function was similar. Further, IHD and hypertension were more frequent among women with diabetes particularly in the age-group ≤65 years where these comorbid diseases were twice as common in the presence of diabetes.

Comparison of men with and without diabetes

The mean age in men with and without diabetes was similar (73 years). Men with diabetes were heavier, had a longer duration of heart failure and were more often in NYHA classes III-IV (50 vs. 40%). Irrespective of age IHD and hypertension were more frequent in patients with diabetes while LVEF, eGFR and NT-pro-BNP was uninfluenced of the diabetes state.

Mortality

The median follow-up time was 1.9 years (range 0-8.7). Survival was significantly lower in patients with diabetes regardless of sex (Figure 11 a-c). The age-matched cohorts reveal that, within the diabetes group, there was no survival difference between men and women (log-rank p=0.18; Figure 11a). In contrast women without diabetes had a better prognosis than their male counterparts (log-rank p<0.0001). Women with diabetes had reduced longevity compared with those without (Figure 11b) and a similar pattern, albeit somewhat less apparent, was seen in men (Figure 11c). The Forest plot in Figure 12 presents unadjusted and adjusted associations of sex, diabetes and mortality. In the diabetes population, female sex did not remain as an independent predictor of mortality after extensive covariate adjustment, not among all patients with diabetes and heart failure (OR 0.90; 95% CI 0.79-1.03; p=0.14) nor in the age-matched diabetes group (OR 0.92; 95% CI 0.79-1.06; p=0.25).

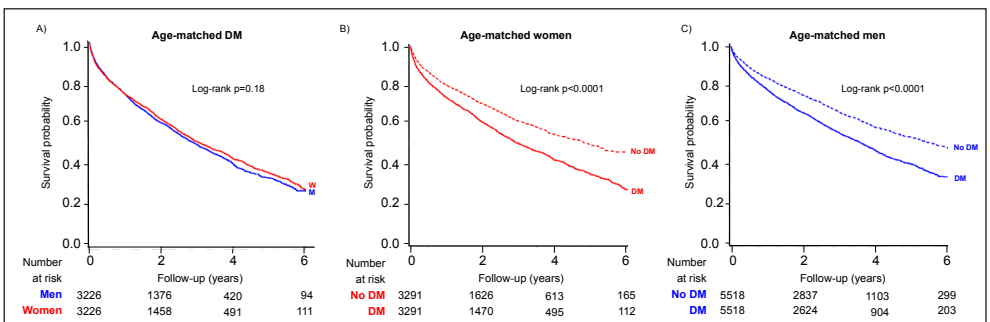

Figure 11. Survival by sex in A) the age-matched diabetes (DM) cohort, B) survival in women (W) by DM in the matched female sub-cohort and C) survival in men (M) by DM in in the age-matched male sub-cohort.

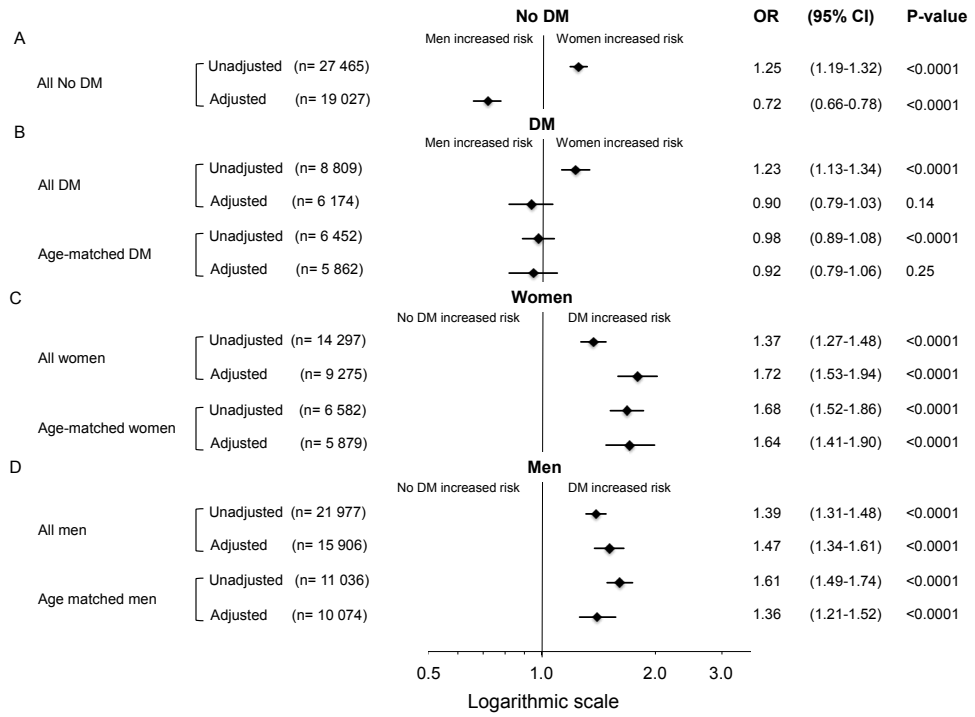

Figure 12. Unadjusted and adjusted association between sex and mortality in A) the entire population without diabetes (DM); B) in the entire population with DM and in an age-matched sub-cohort. Unadjusted and adjusted association between DM and mortality in sex-specific overall, and age-matched sub-cohorts in C) women and; D) men.

Among the women, diabetes was an independent predictor of mortality (adjusted OR 1.72; 95% CI 1.53-1.94; p<0.0001 in the total and OR 1.64; 95% CI 1.41-1.90; p<0.0001 in the age matched female cohort). The same pattern was observed in men (adjusted ORs in the total and age matched cohort OR 1.47; 95% CI 1.34-1.61; p<0.0001 and OR 1.36; 95% CI 1.21-1.52; p<0.0001).

Study III

Important clinical characteristics are presented in Table 8. IHD was reported in 51% of the 35 163 patients. The proportion of IHD among patients with diabetes was higher, 62%, than in those without, 47%. Previous revascularisation had been performed in 53% and 48% of patients with and without diabetes respectively.

Patients with diabetes with and without IHD

Diabetes patients with IHD were slightly older (75 vs. 74 years), more often men (66 vs. 57%) with a history of smoking. They, more frequently had reduced LVEF and CKD while

associated comorbidities such as atrial fibrillation and idiopathic dilated cardiomyopathy, hypertension and pulmonary disease were less common (Table 8). Eighty eight per cent of the patients with diabetes without IHD had at least one co-morbidity, increasing to 90% if idiopathic dilated cardiomyopathy was added (Table 9). Pharmacological heart failure treatment was similar in the diabetes patients with and without IHD.

Table 9. Comorbidity pattern stratified by ischemic vs. non-ischemic aetiology and by diabetes (DM).

	No Ischaemic Heart Disease			**Ischaemic heart disease**		
	No DM n=14 029	**DM** n=3 243		**No DM** n=12 574	**DM** n=5 317	
	81%	19%		70%	30%	
Variables	**n (%)**	**n (%)**	**p-value**	**n (%)**	**n (%)**	**p-value**
Combinations						
HT/AF	9958 (73)	2563 (80)	<0.0001	8164 (68)	3852 (76)	<0.0001
HT/AF/COPD	10 442 (78)	2639 (85)	<0.0001	8675 (73)	3952 (80)	<0.0001
HT/AF/COPD/VHD	10 763 (83)	2617 (88)	<0.0001	8790 (78)	3903 (83)	<0.0001
HT/AF/COPD/VHD/iDCM	11 349 (88)	2674 (90)	0.0004	8836 (79)	3897 (84)	<0.0001
HT/AF/COPD/VHD/iDCM/CKD	11 911 (93)	2817 (93)	<0.0001	9825 (88)	4294 (92)	<0.0001

Abbreviations: AF, Atrial Fibrillation; CKD, Chronic kidney disease; COPD, Chronic Obstructive Pulmonary Disease; HT, Hypertension; iDCM, Idiopathic Dilated Cardiomyopathy; DM, Diabetes; VHD, Valvular Heart Disease
n (frequency) % (percentage).

Patients with IHD in relation to revascularization

Patients with diabetes without a history of revascularization were older (mean age 77 vs. 73 years) and considerably more often women (43 vs. 26%) with less comorbidities and less reported evidence-based pharmacological heart failure treatment. A similar pattern was seen in patients without diabetes.

Mortality

The most serious prognosis was seen in patients with IHD and diabetes, especially in those without previous revascularization as illustrated in the age adjusted survival curves in Figures 13 and 14. Diabetes remained as an independent mortality predictor in all adjustment models regardless of the presence of IHD or not. The extensively adjusted HR for mortality imposed by diabetes was 1.41 (95% CI 1.33-1.50, p<0.0001) in patients with and 1.30 (95% CI 1.20-1.41, p<0.0001) in those without IHD. Diabetes remained an independent mortality predictor among revascularized IHD patients (adjusted HR 1.36; 95% CI 1.24-1.48, p<0.0001) as well as in IHD patients without previous revascularization (HR 1.45; 95% CI 1.33-1.56, p<0.0001).

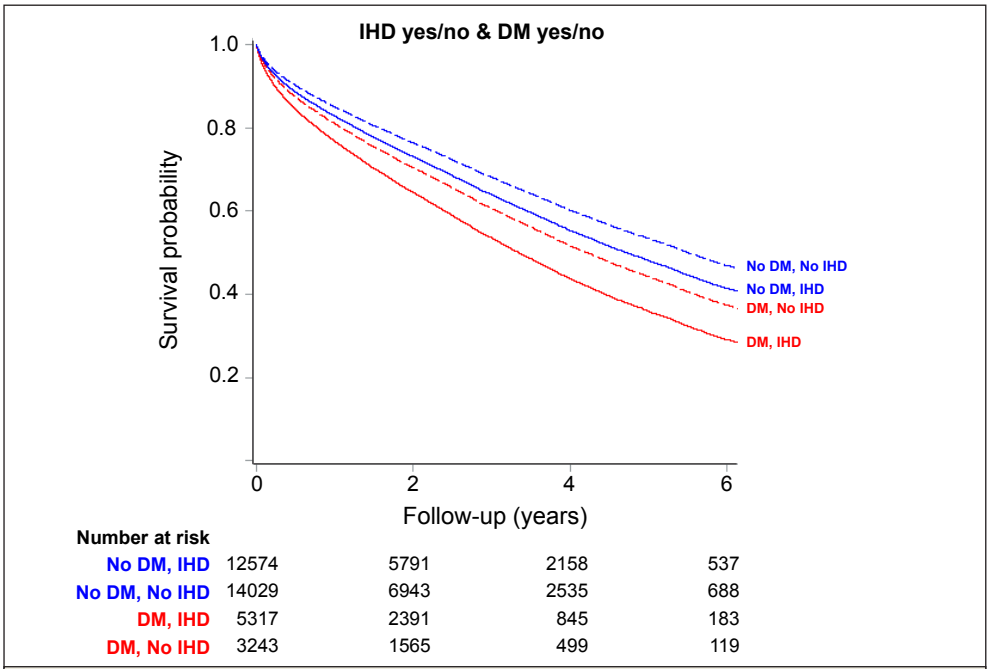

Figure 13. Age-adjusted survival curve stratified by diabetes (DM) and ischemic heart disease (IHD).

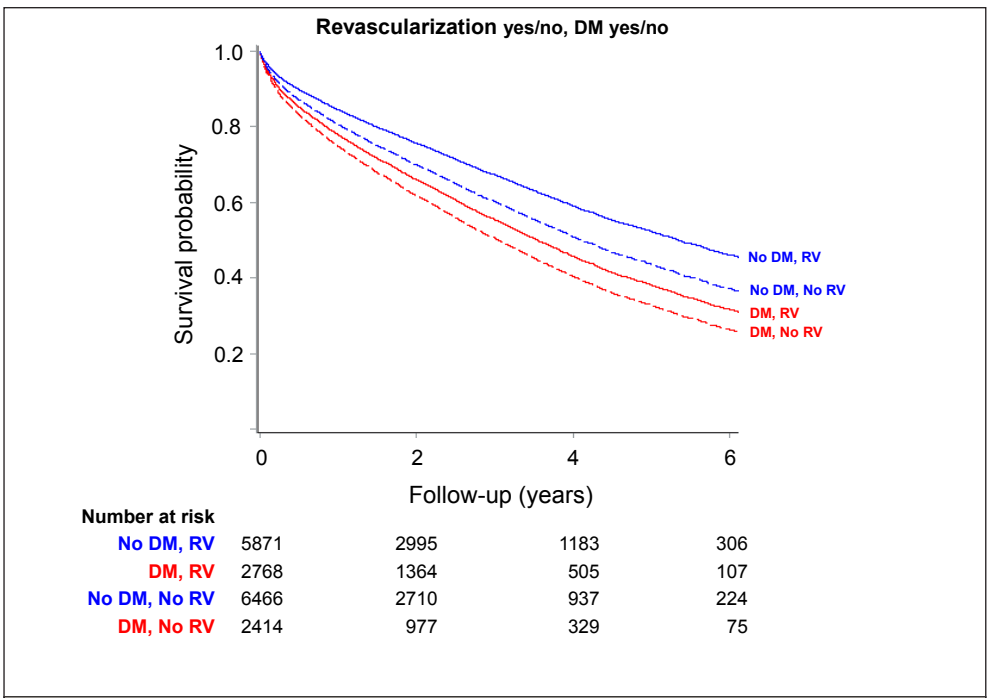

Figure 14. Age-adjusted survival in patients with ischemic heart failure stratified by history of revascularization (RV) and diabetes (DM).

Previous revascularization and prognosis

Among patients with diabetes and IHD previous revascularization was associated with decreased mortality (adjusted HR 0.82; 95% CI 0.75-0.91, p<0.0001) and this association remained after adjusting for the propensity score of previous revascularization (HR 0.87; 95% CI 0.78-0.96, p<0.0001). Revascularization was associated with an improved prognosis even in patients without diabetes (adjusted HR 0.89; 95% CI 0.83-0.96, p<0.0001).

Study IV

Twenty two percent of the 30 696 patients had HFpEF (n=6705), 21% had HFmrEF (n=6483) and 57% HFrEF (n=17 509). The prevalence of diabetes was similar in these three groups (HFpEF=25%; HFmrEF and HFrEF=24%). Patients with HFpEF were older and more often female with hypertension and renal impairment. IHD was more frequent in patients with HFmrEF and HFrEF. In diabetes, clinical characteristics differed above all between those belonging to HFpEF, compared with the groups with HFmrEF and HFrEF. Pulmonary disease was more often seen in HFpEF patients while IHD and a history of revascularization was more frequent in patients with HFmrEF and HFrEF. There were no major differences between diabetes patients with HFmrEF and HFrEF apart from previous hypertension that was more common in HFmrEF than HFrEF and male sex as well as idiopathic dilated cardiomyopathy that was more prevalent in HFrEF.

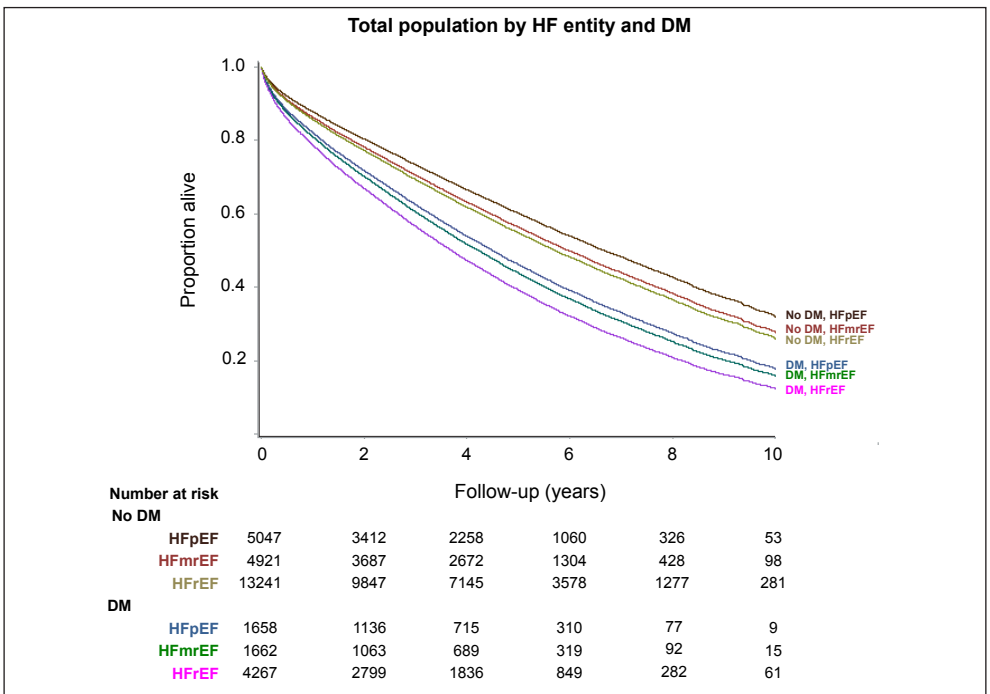

Figure 15. Age-adjusted long-term survival in the total population by heart failure entity and diabetes. Abbreviations used: HF; Heart Failure, HFpEF; Heart Failure preserved Ejection Fraction, HFmrEF; Heart Failure mid-range Ejection Fraction, HFrEF; Heart Failure reduced Ejection Fraction, diabetes; DM.

Impact of diabetes on mortality in the three HF entities

The median follow-up time was four years (range 0-12 years). Total mortality was higher and age-adjusted median survival time shorter in the presence of diabetes regardless of heart failure entity but with the worst outcome in patients with HFrEF (Figure 15). Adjusted HRs associated with diabetes were in HFpEF (1.32; 95% CI 1.22-1.43, p<0.0001), HFmrEF (HR 1.51; 95% CI 1.39-1.65, p<0.0001) and HFrEF (HR 1.46; 95% CI 1.39-1.54, p<0.0001; p for interaction =0.0049). These associations remained after excluding patients with a history of valvular disease as well in sub groups with and without IHD. When HFpEF and HFmrEF were analysed as one group, i.e. with LVEF ≥40% as a cut point, the proportion with diabetes was 24% and the adjusted HR increased to 1.37; 95% CI 1.22-1.55, p<0.0001 while if assembling HFmrEF and HFrEF as a group (LVEF <50%), the proportion of diabetes was 24% and the adjusted HR of mortality associated with diabetes was 1.49; 95% CI 1.36-1.64, p<0.0001. When an LVEF ≥50% was used as the reference, the adjusted HR for mortality imposed by diabetes increased by deteriorating LVEF.

A summary of results in **Studies I-IV** showing HR of mortality imposed by diabetes in different sub-groups is outlined in Figure 16.

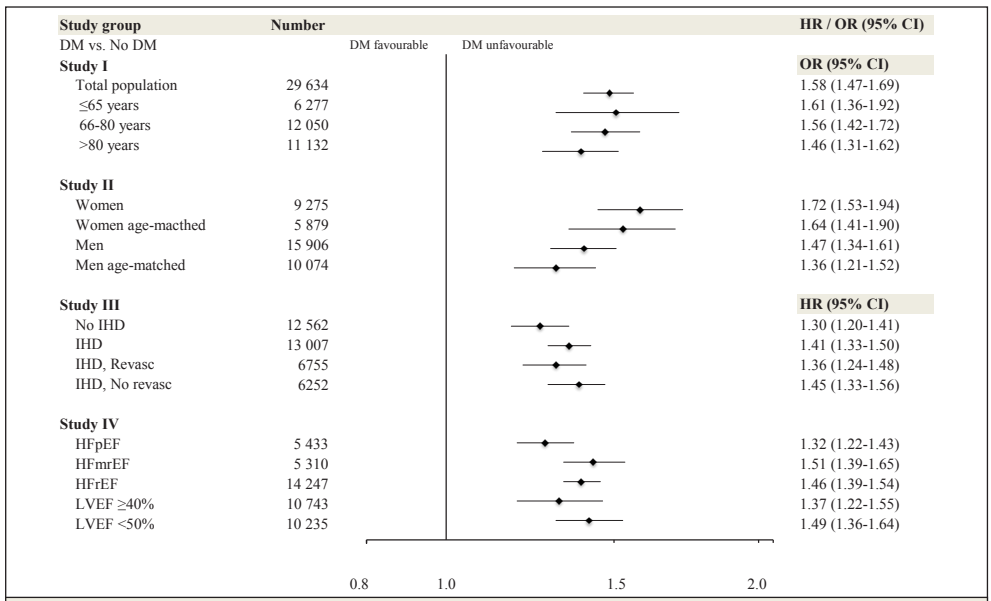

Figure 16. Independent associations of diabetes (DM) and mortality reported as adjusted Odds Ratios (OR) or Hazard Ratios (HR). P<0.0001 accross all four studies. ORs and HRs presented are values generated by multiple covariate adjustements as detailed under each study.
HFpEF=LVEF≥50%, HFmrEF=LVEF 40-49%, HFrEF=LVEF<40%.

General Discussion

This thesis demonstrates that the combination of heart failure and diabetes is common and serious confirming observations in elderly reports and extending them to a contemporary everyday life perspective.

The objective with this thesis was to bring more light into some prevailing gaps in knowledge by analysing a nationwide heart failure population provided by the SwedeHF registry from different angles. Focus points were to describe i) the contemporary phenotype and prognosis in relation to diabetes (**Study I**); ii) the impact of female sex (**Study II**); iii) the importance of ischaemic-, and non-ischaemic heart failure aetiology (**Study III**); and iv) the role of heart failure with reduced and preserved LVEF (**Study IV**).

Diabetes and heart failure – a common combination

Diabetes was reported as present in 24-25% of the total heart failure population (**Study I**), as well as in sub-groups of men and women (**Study II**), and in HFpEF, HFmrEF and HFrEF respectively (**Study IV**). A particularly high proportion of diabetes, 31%, was seen in patients with ischaemic heart failure (**Study III**). The prevalence of diabetes in heart failure populations varies greatly, ranging from 13-47%, depending on the studied population and how diabetes was defined.[68] Our findings correspond with reports from other chronic, stable heart failure populations.[71,149,150] as does the proportions of diabetes in ischaemic versus non-ischaemic heart failure in **Study III**.[71,151] This proportion was lower than the approximately 40% reported in studies on patients hospitalized for acute, decompensated heart failure.[74,152,153] The higher prevalence of diabetes in these populations may relate to a more serious condition comprising a higher risk for deterioration in patients with diabetes.[154] Another reason could be that the present population emanates from a nationwide registry thereby including the whole spectrum of heart failure patients. The latter assumption gets support from the high proportion, 58%, of diabetes patients in NYHA class I and II i.e. patient with less severe heart failure state. The present broad recruitment base from contemporary, everyday clinical praxis makes it reasonable to believe that the present proportion of 24% is representative. This does not contradict that more sophisticated screening methods, not the least an oral glucose tolerance test, would have disclosed that a higher proportion, maybe as many as two thirds of the heart failure patients, would have been diagnosed with dysglycaemia i.e. IGT or previously undetected diabetes.[10,32,65,66,70,73] It may indeed be considered a drawback not to identify such patients since others report that their prognosis is particularly serious.[70,73] Other reasons that the combination of diabetes and heart failure will further increase is the predicted rise in the overall prevalence of diabetes in combination with improved longevity[155,19,20], improved survival following acute coronary artery syndromes,[156] and by means of a better multifactorial management.[16,157,158] Accordingly, especially patients with diabetes will live and develop heart failure to a larger extent than some decades ago.

Prognostic impact of diabetes in heart failure

As described in the introduction, the combination of diabetes and heart failure carries a serious prognosis.[71,74,78,80,91,96,159] A caveat is that most reports originate from sub-group analyses of

trial populations or single hospital registries with a frequently poorly defined definition and treatment of diabetes. Thus, it is very likely that these patients represented a selected, not too sick and by this reason not representative group. **Studies I-IV** fills this knowledge gap by presenting data from an everyday heart failure population receiving modern care. It was observed that diabetes had an independent impact on the prognosis across all studied sub-groups, increasing the mortality risk with 30-70%. **Study I** demonstrates that diabetes is associated with a compromised survival regardless of age, indeed most pronounced among the youngest patients. This pattern was apparent despite a more extensive pharmacological treatment in heart failure patients with diabetes and although the distributions of LVEF and renal function were similar compared with patients without diabetes. Still the higher NYHA classes and NT-proBNP levels in patients with diabetes indicate a more advanced disease state. Based on these observations two important pieces of information should be highlighted. First that it is important to consider whether diabetes is present or not, at the least in younger heart failure patients, since it indicates a need for intensified care and follow-up. Secondly that further research and improved therapies are eagerly needed to improve outcome in diabetes patients with heart failure.

Diabetes in relation to heart failure with different left ventricular function

HFpEF and HFrEF have been considered equally common in heart failure and with a comparable prognostic impact.[37,38,160] As observed in **Studies I** and **IV** the proportions with HFpEF, HFmrEF and HFrEF in SwedeHF was uninfluenced by the presence of diabetes or not, 22% had HFpEF, increasing to 43% if LVEF cut-off was set at ≥40% instead of ≥50%. These findings are in line with other contemporary heart failure populations.[37,74] Since none of the present patients came from primary care there may have been an underestimation of patients with HFpEF, a patient category probably so far less frequently handled in specialist care.[161] The characteristics of the diabetes patients by heart failure type corresponded with reports from the general heart failure population, i.e. patients with HFpEF were more often older, women, with a history of hypertension and atrial fibrillation compared with patients with HFrEF that to a larger extent were men with a higher prevalence of IHD.[30]

It seems as if diabetes worsens the prognosis both in HFpEF and HFrEF even if data are somewhat sparse and mostly based on retrospective sub-group analyses of selected populations.[73,162-167] Analyses of HFmrEF with a focus on diabetes are so far lacking. Whether diabetes impacts prognosis differently in HFrEF and HFpEF has not been fully explored since few studies, if any, compared HFrEF and HFpEF with diabetes as a primary objective.[71,96,149] The present data enabled such comparisons as reported in **Study IV**. It was noted that diabetes had a severe impact on survival irrespective of the type of heart failure. Following extensive adjustments this impact was most apparent in HFmrEF, of similar magnitude in HFrEF while less pronounced in HFpEF. The present observation contradicts the results from CHARM trial in which the relative risk of cardiovascular death or heart failure hospitalization conferred by diabetes was more pronounced in HFpEF than HFrEF.[71] One reason might be a different outcome measure (cardiovascular death and worsening heart failure in CHARM vs. total mortality in the present study). Another reason could be differences in the studied populations. CHARM recruited younger patients with a less advanced heart failure and comorbidity pattern compared with the unselected patients in the present analysis (e.g. mean age 67 vs. 76 years in the HFpEF-groups). Moreover, it is possible that the cut-off for HFpEF

in CHARM, a LVEF ≥40% vs. ≥50% in the current analysis, resulted in a HFpEF group with more severe prognosis in CHARM.[71]
The impact of diabetes was somewhat increased when the HFmrEF and HFpEF groups were combined in **Study IV** but still lower than the risk conferred by diabetes in HFrEF. In line with our observations the Valsartan in Acute Myocardial Infarction trial (VALIANT), including patients with ischaemic heart failure also reported that diabetes was associated with a higher risk of major cardiovascular events across the range of LVEF with an increasing risk with lower LVEF.[96] Recent observations from the PARADIGM-HF trial, including LVEF <40%, point to a higher hazard of events related to diabetes with deteriorating LVEF.[73] The present findings do also get support by a Spanish report from the Registro Nacional de Insuficiencia Cardiaca (RICA) registry, in which diabetes independently predicted outcome after one year with a trend towards higher mortality in HFrEF.[149]
Study IV provided a diabetes specific description of the newly instituted HFmrEF phenotype. It could be concluded that such patients, in the presence of diabetes, resemble patients with HFrEF in their clinical characteristics and prognosis. Accordingly, the relevant question arises whether the introduction of the entity HFmrEF has any clinical value or if it is a matter of academic interest only. Future studies will provide further insights on this topic. The observations in **Study IV** strengthen the evidence that diabetes increases the mortality risk across all sub-groups of heart failure. Moreover, it underscores the need of enhanced therapy in diabetes patients with heart failure regardless of heart failure entity.

Underlying mechanisms for the dismal prognosis imposed by diabetes in heart failure

Two major theories behind the dismal prognosis related to diabetes after heart failure deserves attention: 1) the heavier burden of associated risk factors and comorbidities in patients with diabetes and 2) the existence of a diabetes cardiomyopathy.

Aspects of risk factors and comorbidity

The demographic observations in **Studies I** and **III** depict a pattern largely corresponding to previous reports i.e. that patients with diabetes were slightly younger but burdened with more comorbidities and a higher BMI than those without diabetes. **Study I** identified IHD and hypertension as the most common comorbidities, present in two thirds of the diabetes patients. IHD together with reduced renal function were among the most important predictors of mortality while the presence of hypertension decreased the risk, probably reflecting intense risk factor treatment rather than being protective per se. **Study III** revealed that 88% of diabetes patients without IHD had at least one other comorbidity known to cause heart failure among them hypertension, CKD, atrial fibrillation, pulmonary disease and valvular heart disease. Importantly several of these comorbidities are manageable with well-established therapeutic or preventive strategies underscoring the importance of optimizing preventive measures, in which context IHD require some extra attention.
It is debated if diabetes impacts the prognosis differently in ischaemic and non-ischaemic heart failure and previous data provided conflicting results.[71,92,151,166,168,169] In **Study III** diabetes had an adverse impact on prognosis irrespective of ischaemic or non-ischaemic aetiology. The highest mortality was, however, seen in those with diabetes and ischaemic heart failure, who had a 40% risk increase contra 30% in non-ischaemic heart failure. In some previous studies

diabetes predicted worse outcome only in patients with ischaemic aetiology,[92,166,168] while another study noted an association only in non-ischaemic heart failure.[169] The interpretation of these studies is hampered since the patients were recruited before a wide implementation of modern, evidence-based treatment and furthermore most studies were limited to patients with LVEF <35%. A sensitivity analysis in **Study IV** confirmed that the adverse impact of diabetes in ischaemic and non-ischaemic heart failure persists in subgroups with different LVEF. More contemporary data is provided by the CHARM trial.[71] In line with the present observations it was noted that diabetes predicted mortality irrespective of ischaemic or non-ischaemic aetiology including an extended analysis of HFpEF patients. Further support is gained from a recent community based multicentre, outpatient study from the UK in which diabetes predicted higher mortality irrespective of ischaemic aetiology or not in both HFpEF and HFrEF.[151] A possible interpretation of the diverging results may be that in contemporary heart failure populations subjected to modern evidence-based treatment, as in SwedeHF, CHARM and the UK populations, it may be that competing risk of other serious circumstances outweighed the impact of diabetes in the past, while a presently improved management of concomitant risk factors enhances the impact of diabetes.

Revascularization was addressed in **Study III**, which revealed that the prognosis was less severe in ischaemic heart failure in the presence of a history of coronary interventions. This finding is supported by previous data,[170] underlining the importance of ruling out IHD and the necessity to carefully investigate the possibility to revascularize patients with diabetes. Unfortunately only 50% of eligible patients had been subjected to such interventions, even less among the women with diabetes. There are a couple of reasonable explanations for the low use of revascularization. The risk of an intervention may have been considered high due to the large comorbidity burden and diabetes often causes a more diffuse atherosclerosis lessening the opportunity or even willingness to perform a PCI or CABG. It is unlikely that these conditions can fully explain such large proportion as 50% of eligible patients. Coronary angiography and interventions are freely available in Sweden and convincing evidence, favouring revascularization to improve the prognosis in patients with diabetes and acute coronary syndromes and multivessel disease, have been provided by the Fragmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) and the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optional Management of Multivessel Disease (FREEDOM) trials,[128,171] It should, however, be admitted that none of these trials specifically addressed revascularization in the presence of heart failure. A meta-analysis of 3088 patients with left ventricular dysfunction and signs of preserved myocardial viability reported on a strong association between revascularization and survival.[172] Unfortunately, this analysis did not present data from the diabetes sub-group, but based on present knowledge at least 20-30% of the studied population should have diabetes.[65,66] The concept of revascularization in patients with established heart failure has been challenged by the results of the Surgical Treatment for Ischaemic Heart Failure (STICH) trial, which randomized 1212 patients with IHD and left ventricular dysfunction to optimal medical therapy alone or optimal medical therapy plus CABG. The initial five-year follow-up provided neutral results in an intention-to treat analysis, but it was believed that a large cross-over undermined the statistical power. This assumption was subsequently strengthened by an as-treated analysis.[173,174] Indeed, a recently published ten-year follow-up of STICH (STICH Extension Study; STICHES) reported that CABG was significantly

superior to medical therapy alone even when analysed according to the intention-to-treat principle providing evidence for the benefits of coronary interventions in heart failure.[64] Two retrospective studies, applying propensity score analyses, strengthen the benefit of CABG over medical therapy in patients with IHD and left ventricular dysfunction.[175,176] There is nonetheless a gap in knowledge in demand of prospective clinical trials assessing myocardial viability with cardiac MRI or PET and the actual impact of revascularization in patients with diabetes and ischaemic heart failure.[23,177] The on-going Revascularization for Ischaemic Ventricular Dysfunction (REVIVED) trial studying the efficacy and safety of PCI in systolic heart failure will hopefully provide further insights. Until this and similar trials are available, an interpretation of **Study III** is that there may be a potential benefit of revascularization and that it is reasonable to offer all patients with diabetes a thorough investigation not to miss an opportunity to revascularize if deemed feasible.

Diabetes cardiomyopathy

Studies I-IV showed that the adverse prognosis imposed by the presence of diabetes in heart failure is apparent despite similar treatment and that it persists even after extensive adjustment lending support to the hypothesis that a specific diabetes cardiomyopathy may be part of the dismal outlook. Still out of all diabetes patients in **Study III** only 7-10% were without a reasonable etiological background. Thus, the present observations do not support that a diabetes cardiomyopathy in its *pure* form,[178] is common. This does not contradict that something inherent in diabetes *contributes to* or *aggravates* the dismal outlook in heart failure. As described in the introduction it can be driven by various mechanisms (see page 21). They may, however, also be explained by long-standing, poorly controlled hypertension or merely be a result of ageing. Another assumption behind the increased heart failure prevalence and poor prognosis in patients with diabetes is that the group judged clinically to have non-ischaemic heart failure may have a compromised myocardial function secondary to silent ischemia or atherosclerosis in small vessels, causing hibernation or stunning, as well as scar tissue resulting from silent myocardial infarctions.[179,180]

Sex and gender aspects

In general, women are considered protected from premature cardiovascular disease, an advantage that is attenuated in the presence of diabetes.[15,130,181] It has also been noted that women have a survival advantage over men in heart failure.[182-184] **Study II** addressed this question and found that diabetes attenuated the survival benefit seen in women compared to men with heart failure. This extends the observations in a meta-analysis by Martinez-Selles et al,[51] based on populations derived from clinical trials to patients in everyday practice. In **Study II** diabetes was a strong risk factor for adverse prognosis in both sexes, although we found a slightly higher mortality association in women. Survival within the diabetes group did not differ between men and women after consideration of the higher age and more frequent CKD in women. These data are in line with a previous report based on a myocardial infarction population, indicating no adverse relationship with female sex in itself but rather related to more frequent comorbidities in women with diabetes such as IHD, hypertension and CKD.[185]

Women with heart failure and diabetes more often had HFpEF compared with men with diabetes. This is consistent with contemporary population-based heart failure registries and

reasonably reflects that women develop heart failure at a more advanced age compared with men.[134,137,186] One main difference, revealed by comparing women with and without diabetes, was that women with diabetes more frequently had coexistent IHD, in fact even more apparent at ages ≤65 years, where IHD was twice as common. In this context one may say that women with diabetes and heart failure had a more 'male-like' risk factor profile. **Study II** indicates that the suspected underuse of revascularization in ischaemic heart failure takes place irrespective of sex, reported in 43% of the women and 61% of the men with diabetes. Moreover, women with diabetes and HFrEF were to a lesser extent prescribed ACEi/ARBs but got more diuretics. The most comprehensive evidence-based treatment was seen in men with diabetes regardless of age group. This may partially be explained by reduced renal function and precautions taken due to higher age in women, but a subconscious disparity in management cannot be ruled out as supported by some previous reports[134,135,187] but not all.[137-139]

Strengths and limitations

This thesis is based on data from SwedeHF, a nationwide heart failure registry, to the best of our knowledge one of the largest of its kind. At the time of data extraction it comprised 47000 unique patients from 83% of the Swedish hospitals (university and regional hospitals) and 6% of Swedish primary care clinics, the latter being excluded from the present study. Thus, the studied population represents patients under specialist care. The great number of patients enabled diabetes focused analyses of pre-specified heart failure sub-populations. Another major strength with registry studies is the unselected nature of data i.e. without any restricting inclusion and exclusion criteria. This is of particular importance when addressing a sick population, as people with diabetes that are often excluded from clinical trials.

It should be acknowledged that SwedeHF coverage at the time of data extraction was fairly low in the early years introducing a bias directed towards heart failure interested centres with a probably better than overall managed patient population but possibly also those with the most dismal prognosis. This selection decreased over time with expanding numbers of engaged clinics. Another selection bias relates to the voluntary reporting of patients introducing the risk of missing data. Moreover diagnostic criteria may have varied throughout Sweden since SwedeHF did not validate reported data before 2012. As already underlined the true proportion of patients with diabetes may have been underestimated since it was based on case histories and ongoing treatment only.[65,66] Type 1 diabetes was not evaluated but comprises a small proportion of all patients with this disease. Although the estimation of renal function may vary by different formulas it is not believed that the results in **Studies I-IV** were influenced in any clinically relevant extent. The definition of IHD was expanded in **Studies III-IV** in an attempt to miss as few patients with this diagnosis as possible, but information on patient history at the time of inclusion was sometimes incomplete and IHD might have been undiagnosed in asymptomatic diabetes patients.[179,180] Missing data unfortunately compromised the interpretation of prognostically important heart failure variables in particular NT-proBNP and to a lesser extent NYHA class. Finally, there was no information on diabetes duration and very limited data on glycaemic control, two factors with prognostic implications.[82]

As always with observational studies like the present the findings should be seen as hypothesis generating rather than representing established facts. Still the very large database allowed

for extensive adjustments including a large number of clinically relevant confounders. In addition, when exploring the impact of revascularization in **Study III** the application of a propensity score for treatment in the adjustment model, which to some degree mimics randomization although only considering measured variables, strengthened the assumptions of the benefit of the coronary interventions.
Although all-cause mortality is a robust and reliable outcome, we did not have cause-specific information on mortality or of other cardiovascular events, which would have been interesting to further deepen the understanding behind the high mortality. A median follow-up of 1.9 years in **Studies I-III** may appear short, but is mainly an effect of the larger proportion of patients included during the most recent part of the study-period. The follow-up period ranged between 0 and 8.7 years in study **I-III** and was in general rather long. Moreover, mortality follow-up was extended in **Study IV** to a median of four years (range 0-12 years). If anything this strengthened the association between diabetes and a dismal outcome.

Future perspectives

Although major advances have been made in improving morbidity and mortality in heart failure patients, diabetes continues to portend an adverse prognosis more or less without exception and without important disparities in the heart failure treatment. Future studies should focus on finding ways to improve prognosis for these patients. Such studies should for instance include advanced imaging methods of well-defined diabetes populations in order to further understand the mechanisms behind diabetes specific myocardial and extra-myocardial changes. A continued search for novel treatment agents and new treatment targets is needed. The beneficial effects with reduced mortality of new glucose-lowering agents such as SGLT-2 inhibitors and GLP-1 receptor agonists are of particular interest. Notably, the mechanistic explanation of the reduction of heart failure events associated with the SGLT-2 inhibitor empagliflozin is needed. It would also be of great interest to study if the prevention of cardiovascular events with SGLT-2 inhibition can be extended to diabetes patients without pre-existing cardiovascular disease as well as to heart failure patients with undiagnosed glucose disturbances. Basic research including epigenetic studies can potentially increase the understanding of the underlying mechanisms of diabetes cardiomyopathy.

In all day practice efforts are needed to increase the awareness among health care personnel of the high prevalence and adverse outcome of the combination of heart failure and diabetes. This relates in particular to younger patients, women and patients with ischaemic heart disease. Accordingly, a comprehensive risk assessment in patients at elevated risk of diabetes and heart failure should be encouraged and the evaluation of intensified treatment and follow-up considered. Patients with diabetes and signs of myocardial dysfunction should be offered a cardiology consultation for the optimization of their treatment and evaluation of the potential need for revascularization.[176] Moreover, the prescription of newer glucose lowering agents should be encouraged according to already adopted recommendations in international management guidelines.[9,30]

CONCLUSIONS

Based on the studies comprised in this thesis it can be concluded that:

1. The combination of heart failure and diabetes is common with a diabetes prevalence of about 25% both in men and women and irrespective of heart failure entity, increasing to one third in patients with ischaemic heart failure.

2. Diabetes is associated with a compromised longterm survival, increasing the mortality risk by 30-70% with the most serious impact in younger patients, in those with ischaemic heart disease and in patients with compromised systolic function.

3. Comorbidites are common in heart failure patients with diabetes. As many as 90% have at least one preventable comorbidity of which ischaemic heart disease and hypertension are most frequent. A history of coronary revascularization is associated with better outcome but seems underused.

4. In heart failure, diabetes increases the mortality risk by 70% in women and by 40% in men. Age-adjusted survival does not differ between men and women with diabetes. Accordingly, the prognostic advantage in women compared with men with heart failure is attenuated in the presence of diabetes. Women with diabetes and heart failure have a risk factor profile resembling that of men with a high prevalence of ischaemic heart disease and hypertension.

5. Diabetes is an independent predictor of mortality in both HFpEF and HFrEF. In diabetes, the HFmrEF entity resembles HFrEF in clinical characteristics, risk factor pattern and prognosis, indicating that the introduction of the mid-range entity, HFmrEF, may be unnecessary.

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Appendix A. Pre-defined definitions in the Swedish Heart Failure Registry (SwedeHF)		
Variables		**Definition**
i)	Heart failure	Diagnosed by the attending physician based on guideline recommendations at the time of the inclusion.
ii)	NYHA class	Classified according to the New York Heart Association classification of heart failure based on symptoms and exercise capacity: NYHA class I: No limitation in physical activities. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea. NYHA class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea. NYHA class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation or dyspnea. NYHA class IV: Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.
iii)	Ischemic heart disease	Based on case history, classified as: Yes, verified by coronary angiography Yes, not verified by coronary angiography No
iv)	Idiopathic dilated cardiomyopathy	According to the definition in the SwedeHF, patients were assumed to have idiopathic dilated cardiomyopathy if signs of dilated cardiomyopathy in the absence of ischemic heart disease or hypertension as underlying reason.
v)	Diabetes	Defined as having a history of this diagnosis, specified as type 1 or type 2 in combination with glucose lowering treatment in the form of life-style advice only or combined with oral glucose-lowering drugs and/or insulin.
vi)	Revascularization	History of coronary artery bypass surgery (CABG) and/or Percutaneous Coronary Intervention (PCI)
vii)	Hypertension	Reported by the attending physician based on case history and/or on-going blood pressure-lowering therapy.
viii)	Ejection Fraction (EF)	The most recently estimated Doppler Echocardiography-based left ventricular ejection fraction was stratified into four different classes: EF ≥ 50, 40-50, 30-39 and <30%. An estimated EF was not obligatory for inclusion in the SwedeHF and it was not possible to report by which method the EF had been estimated.

ix)	Hemoglobin level (Hb in g/L)	Classified as: Normal: Female ≥120, Male ≥130 Mild anemia: Female 100-120, Male 110-130 Anemia: Female ≤100, Male ≤110
x)	HbA1c	Expressed according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Mono S values, used until 2010, were converted by the formula HbA1c (IFCC; mmol/mol) = 10.45 x HbA1c (Mono S; %) - 10.62
xi)	Duration of heart failure	According to the definition in the SwedeHF, the time since diagnosis or initiation of heart failure treatment, stratified as ≥ or < 6 months duration.
xii)	Atrial fibrillation/flutter	According to the definition in the SwedeHF patient history with a diagnosis of either atrial fibrillation or flutter.
xiii)	Pulmonary disease	According to the definition in the SwedeHF diagnosis of, or on-going/previous treatment for pulmonary disease of importance e.g. COPD, asthma, pulmonary tumors, fibrosis, TBC, Sarcoidosis etc. Stratified as Yes/No
xiv)	Valvular heart disease	Case history of present or previous valvular disease of clinical importance.
xv)	Myocardial infarction	According to the definition in SwedeHF, patient history of diagnosis of myocardial infarction or specific, objective signs of changes secondary to myocardial infarction such that can be seen on e.g. ECG or echocardiography.
FURTHER DEFINITIONS AND CLASSIFICASTIONS IN THE THESIS:		
i)	eGFR **(Study I-II)**	Estimated by use of the Cockroft-Gault formula[142], calculated based on serum creatinine taking age, weight and gender into consideration according to the following formula: [(140-age) x weight x 1.23 x (0.85 if female)] / Creatinine (µmol/L). Classified as (ml/min/1.73m^2): <30, 30-59, 60-89 and >90
ii)	eGFR **(Study I-II)**	Estimated by use of the MDRD formula[143], calculated based on serum creatinine, taking age and gender into consideration according to the following formula: 186 x [Creatinine (µmol/L)/88.4]$^{-1.154}$ x age$^{-0.203}$ (x 0.742 if female)(x1.212 if black). Classified as (ml/min): <30, 30-59, 60-89 and >90
iii)	Mean arterial pressure	Mean arterial pressure = 2/3 Diastolic blood pressure + 1/3 Systolic blood pressure
iv)	Pulse pressure	Pulse pressure = Systolic blood pressure – Diastolic blood pressure