Heart Failure and Type 1 Diabetes

Excess risk and risk factors

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The function of education is to teach one to think intensively and to think critically. Intelligence plus character - that is the goal of true education.

Martin Luther King, Jr.

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ABSTRACT

Background: Approximately 45,000 individuals live with type 1 diabetes (T1D) in Sweden. Previous studies have shown an increased risk for heart failure in persons with diabetes, but most of the studies have been in the setting of unspecified diabetes or included patients with type 2 diabetes. The aim of this thesis is to study some of the potential risk factors, body weight (expressed as Body Mass Index, BMI, Study I) and renal function (defined by estimated glomerular filtration rate, eGFR (Study II) for heart failure in persons with T1D, and also study a potential excess risk for development of heart failure compared to controls from the general population (Study II). In the fourth study BMI was investigated as a risk factor for myocardial infarction (MI) and mortality. The fifth study is an echocardiography (ultrasound) study evaluating early signs of cardiac dysfunction in persons with T1D.

Material and Methods: For the first four studies data from the National Diabetes Registry (NDR) was linked with entries in the inpatient register (diagnoses from hospital admissions), the cause specific death register (causes of death) and data from statistics Sweden (SCB) including for example level of education. In the second study we studied the excess risk for admission to hospital because of heart failure by comparing 33 402 persons with T1DM and 166 228 matched controls. The screening study with echocardiography is based on 287 persons with T1D.

Results and conclusions: Persons with T1D have four times higher risk for admission to hospital due to heart failure compared to age and sex matched

controls from the general population. The magnitude of the excess risk is dependent on glycemic control and albuminuria. Within the population with T1DM elevated BMI and decreased eGFR are strong risk factors for heart failure. Elevated BMI was not associated with increased risk for MI. Early signs of decreased cardiac function with ultrasound is detectable among 9.9-14.8% of persons with T1DM being 50 years or older, while it is relatively rare below this age (1.7-4.1 %).

Keywords: Diabetes mellitus, type 1, Heart failure, Myocardial infarction

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Diabetes Mellitus typ 1 (T1D) är en sjukdom som cirka 45 000 vuxna i Sverige lever med varje dag. Tidigare studier har visat en ökad risk för hjärtsvikt, men de flesta studier har gjorts på ospecificerad diabetes, främst typ 2-diabetes. Syftet med denna avhandling är att undersöka några av riskfaktorerna; kroppsvikt (uttryckt som kroppsmasseindex, BMI, studie I) och njurfunktion (definierad som beräknad glomerulär filtrationshastighet, eGFR, studie III) och även studera en potentiell överrisk för utveckling av hjärtsvikt vid T1D jämfört med kontroller (studie II). I den fjärde studien undersöks BMI som en möjlig riskfaktor för hjärtinfarkt (MI) och mortalitet vid T1D. Den femte studien är en studie med hjärtultraljud där screening sker av personer med T1D avseende tidiga tecken på hjärtsvikt.

Material och metoder: För de fyra första studierna har data från Nationella Diabetes Registret (NDR) kopplats till slutenvårdsregistret (diagnoser från vård på sjukhus), dödsorsaksregistret och data från Statistiska centralbyrån (SCB) som exempel utbildningsnivå. I den andra studien studerade vi överrisk för inskrivning på sjukhus med anledning av hjärtsvikt genom att jämföra 33 402 personer med T1D och 166 228 matchade kontroller. Den femte studien är baserad på 287 personer med T1D som har genomgått hjärtultraljud.

Resultat och slutsatser: Personer med T1D har i genomsnitt en fyra gånger högre risk för inläggning på sjukhus med anledning av hjärtsvikt. Risken är beroende av glykemisk kontroll och albuminuri. Inom gruppen med T1D är ökat BMI och minskat eGFR starka riskfaktorer för hjärtsvikt. Det finns ingen ökad risk för hjärtinfarkt med ökat BMI. Tidiga tecken på nedsatt hjärtfunktion kan upptäckas med ultraljud hos 9,9–14,8% av personer med T1D över 50 års ålder medan det är relativt ovanligt under denna ålder (1,7–4,1%).

Nyckelord: Diabetes mellitus, typ 1, Hjärtsvikt, Hjärtinfarkt

LIST OF PAPERS

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

I. Vestberg D, Rosengren A, Olsson M, Gudbjörnsdottir S, Svensson AM, Lind M. Relationship Between Overweight and Obesity With Hospitalization for Heart Failure in 20,985 Patients With Type 1 Diabetes: A population-based study from the Swedish National Diabetes Registry. Diabetes Care. 2013;36(9):2857-61.

II. Rosengren A, Vestberg D, Svensson AM, Kosiborod M, Clements M, Rawshani A, Pivodic A, Gudbjörnsdottir S, Lind M. Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study. Lancet Diabetes Endocrinol. 2015;3(11):876-85.

III. Vestberg D, Rosengren A, Olsson M, Gudbjörnsdottir S, Haraldsson B, Svensson AM, Lind M. Decreased eGFR as a Risk Factor for Heart Failure in 13 781 Individuals With Type 1 Diabetes. J Diabetes Sci Technol. 2016;10(1):131-6.

IV. Vestberg D, Rosengren A, Eeg-Olofson K, Miftaraj M, Franzen S, Svensson A-M, Lind M. Body mass index as a risk factor for coronary events and mortality in patients with type 1 diabetes. Open Heart. 2018 Jan 20;5(1):e000727

V. Vestberg D, Johansson M, Letho A, Pivovic A, Hallström S, Ólafsdóttir AF, Rosengren A, Lind M. Investigation of early signs of systolic and diastolic dysfunction among persons with type 1 diabetes. (Manuscript)

CONTENT

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADA	American Diabetes Association
ARB	Angiotensin receptor blocker
BMI	Body mass index
CABG	Coronary artery by-pass grafting
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DPP4	Dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
EF	Ejection fraction
eGFR	estimated Glomerular filtration rate
EPN	Ethical review board
GLP-1	Glucagon like peptide 1
HbA1c	Glycated hemoglobin

HDL	High density lipoprotein
HF	Heart failure
HFmrEF	Heart failure with midrange ejection fraction
HfpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD-10	International Classification of Diseases 10
IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
LAVI	Left atrial volume index
LDL	Low density lipoprotein
MDRD	Modification of diet in renal disease
MODY	Maturity-Onset Diabetes of the Young
NDR	Swedish national diabetes registry
NGSP	National Glycohemoglobin Standardization Program, United states

NICE	National Institute for Health and Care Excellence
NPH	Neutral protamine Hagedorn (insulin)
PCI	Percutaneous coronary intervention
PZI	Protamine zinc insulin
RAAS	Renin-angiotensin-aldosterone system
SGLT2	Sodium/glucose cotransporter 2
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHO	World health organization

1 BACKGROUND

1.1 EVEN THE OLD EGYPTIANS…

Both diabetes and heart failure are diseases known to humankind since millennia. Already in ancient Egyptian papyrus rolls, a disease that appears to be what we today call Type 2 diabetes is described[1]. Heart failure, probably due to ischemic heart disease, is mentioned in the Ebers and Smith Papyrus2 written about 1600 BC[3] and ever since physicians have tried to understand the mechanisms behind the diseases and been trying to treat them.

1.2 DIABETES MELLITUS

1.2.1 A BRIEF HISTORY OF DIABETES

Over the years, it emerged that there are two main types of diabetes, a rapidly progressing one which usually led to early death and mainly affected younger people and another type that was milder and primarily debuted in adulthood[4,5]. The French physican Lancereaux described in 1880 two distinct types of diabetes, fat and thin diabetes: diabète gras and diabète maigre[6] which later evolved into insulin deficient and insulin insensitive diabetes[7]

1.2.2 CLASSIFICATION

A more recent classification defines four main groups; type 1 diabetes, type 2 diabetes, gestational diabetes mellitus and diabetes due to other specific cases[8]

Type 1 diabetes[9] is a primary autoimmune disease where the immune system destroys the insulin-producing beta cells in the pancreas, usually causing an absolute insulin deficiency, where the cells in the body no longer are able to take up glucose from the blood and resulting in hyperglycemia (high blood glucose) along with intracellular starvation. The high concentration of glucose in the blood causes the kidneys to release glucose in the urine, which in turn osmotically draws more water into the urine. The resulting symptoms are strong thirst, polyuria with ensuing risk of dehydration, and, if untreated, finally ketoacidosis.

In type 2 diabetes, in contrast, there is primarily a reduced sensitivity to insulin in the cells of the body and progressively a decreased insulin secretion[10]. Initially the decreased sensitivity can be compensated by increasing insulin production, but this is not sufficient in the long run, leading to the typical

diabetic symptoms with thirst and increased urine production. Since insulin is still produced, intracellular starvation does not occur and therefore you the course of the condition is less dramatic than for type 1 even without treatment. Type 2 diabetes predominantly affects older people, but with increasing rates of overweight and obesity younger individuals are also affected as part of the metabolic syndrome.

Gestational diabetes is diagnosed during the second or third trimester of pregnancy among women without previously known diabetes.

The fourth main group of diabetes comprises “Specific types of diabetes due to other causes” and is a heterogeneous group, for instance including diabetes secondary to diseases of the exocrine pancreas (such as cystic fibrosis or pancreatitis) or drug induced diabetes (secondary to glucocorticoids or HIV medication). The group also includes monogenetic diabetes such as MODY (Maturity-Onset Diabetes of the Young), an inherited autosomal dominant type of diabetes. Persons are typically diagnosed with hyperglycemia before the age of 25 years of age and have an impaired insulin secretion without (or with minimal) defect of insulin action[8,11].

1.2.3 EPIDEMIOLOGY OF TYPE 1 DIABETES

Currently, there are approximately 45,000 persons living in Sweden with type 1 diabetes[12] (Figure 1). Sweden, together with Finland and Sardinia[13], has the highest incidence rate of type 1 diabetes in the world with an incidence of >20/100,000 per year. The reason for this is unknown. Most are diagnosed before puberty[14] but approximately one fourth of those with type 1 diabetes are diagnosed in adulthood[15]. The gender balance differs between different populations, in high prevalence areas (Europe) there is a male excess while low prevalence populations have a female excess. Even if most new cases of T1DM occur in individuals without a family history type 1 diabetes, there seems to be a 1 in 20 lifetime risk to develop type 1 diabetes for individuals with a first degree relative compared to a 1 in 300 lifetime risk in the general population[16]

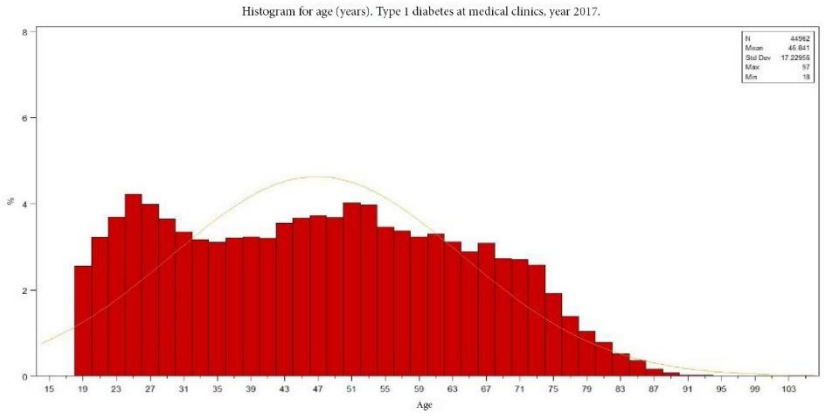

Figure 1 Age of persons with type 1 diabetes in Sweden 2017. Source: NDR, Yearly rapport 2017 (preprint)

1.2.4 TREATMENT OF DIABETES MELLITUS

Ever since the discovery of insulin in the early 1920s treatment of elevated glucose levels in type 1 diabetes is based on supplying insulin to compensate for the body's insulin deficiency[9,17]. Initially the insulin was extracted from animal pancreas (mainly bovine and porcine) and needed to be frequently administrated the duration of the glucose lowering effect was only 6-8 hours[17]. During the 1930s the first long acting insulin, protamine zinc insulin (PZI) was developed leading to a single dose daily regimen of treatment[18]. This was followed by development of other extended insulin formulations in the 1950s such as neutral protamine Hagedorn (NPH) and insulin zinc (Lente)[18]. Subsequently both rapid acting insulin (such as insulin lispro and insulin aspartate) and long acting insulin (ultralente insulin and insulin glargine) were developed[19]. This led to a multiple-dose regimen with a combination of long acting insulin (basal insulin) once or several times a day with short acting insulin (meal or bolus insulin) in connection with food intake, also called a basal bolus insulin regimen[19].

Another way to provide insulin is by a continuous infusion from a pump[20]. This device has been in use for almost 40 years[21] but has become more common in Sweden[12] in recent years. An insulin pump delivers a continuous infusion of short acting insulin via a subcutaneous needle combined with bolus doses of the same insulin in conjunction with meals[20].

Availability and affordability of insulin is not ubiquitous. In parts of the world, there is still a lack of treatment for type 1 diabetes. In 2005 Beran et al[21] published data on life expectancy for persons with diabetes in Mozambique and Zambia. The life expectancy for a newly diagnosed child with type 1 diabetes in rural Mozambique at that period was 7 months[21].

Type 2 diabetes is primarily treated with drugs that modify glucose metabolism, insulin release or insulin sensitivity[23]. The initial recommended drug is metformin (a drug that lowers hepatic glucose production) together with lifestyle modifications. The second drug if needed has traditionally been either a 2nd generation sulfonylurea (a drug group that increases insulin secretion) or a glitazon (e.g thiazolidinedione, a drug that increases insulin sensitivity).

During the last 10 years several new medications for type 2 diabetes[24,25] have been introduced. Among those are the SGLT2 inhibitors, GLP-1 receptor agonists and DPP4 inhibitors.

The GLP-1 receptor agonists give a glucose dependent increase in insulin secretion together with a decreased secretion of glucagon and also leads to slower gastric emptying [23].

DPP-4 inhibitors increase the levels of postprandial (after meal intake) incretin levels (GLP-1 is one of those) by inhibiting the breakdown of incretins[23]

The SGLT2-inhibitors inhibit sodium-glucose co-transporter 2 in the kidneys, leading to reduced renal glucose reabsorption and reduced rate of hyperglycaemia[26,27]. Those are the first class of drugs that showed reduced risk for death of cardiovascular causes, hospitalization for heart failure and death from any cause[27]. Recent studies have also shown promising results with the GLP-1 analogue liraglutide in reducing the rate of MI and CVD death in type 2 diabetes[28]. Some of the compounds used for treating individuals with type 2 diabetes are also considered for use in type 1 diabetes[23].

1.2.5 COMPLICATIONS OF DIABETES

The complications are primarily vascular related, with effects on both large and small blood vessels in the body[29]. For example, diabetes retinopathy (effect on eye vessels that can lead to visual impairment and blindness), diabetic neuropathy (an effect on the small vessels that nourish nerves in, for example, the feet that lead to decreased sensation and ultimately loss of feeling). Diabetes neuropathy increases the risk of developing foot ulcers on the feet (because the patient is not aware of injury), this is exacerbated by microangiopathy (affecting the capillaries of the body) which leads to impaired healing. Diabetes also leads to an increased risk of cardiovascular disease such as myocardial infarction on group level when a population with type 1 diabetes is compared to age matched controls[30,31,32,33]. Persons with type 1 diabetes without renal complications (eGFR >60ml/min and normoalbuminuria) and good glycemic control (HbA1c <52 mmol/mol <6,9%) have nearly the same mortality risk as the general population with HR1.22 (95% CI 0.98-1.52) for all cause mortality and 1.03 (95% CI 0.66-1.60) for CVD mortality[34].

1.3 HEART FAILURE

1.3.1 A BRIEF HISTORY OF HEART FAILURE AND TREATMENT

There are descriptions of what seems to be heart failure from ancient Egypt, Greece and India[2,35]. In the previously mentioned Ebers papyrus there are several mentions of failing heart that leads to "tiredness and overflooding"[2]. Romans were known to use foxglove (digitalis) as a treatment for the failing heart[35] but it is unknown if there was any idea of the mechanism causing heart failure before William Harvey´s description of the circulation in 1628 [35]. The treatment has traditionally been based on removing fluid, initially by bloodletting and leeches, but also with direct drainage of edema[35]. The scientific reintroduction of digitalis into medicine by William Withering in 1785 added another method of treatment. The next step was the introduction of diuretics, where thiazide diuretics were introduced in 1958[35]. But the prognosis was still dismal, and data from the Framingham study shows an age adjusted 5-year mortality of 70% during 1950-1969[36]. In the beginning of the 1980s still only diuretics and digoxin were available to treat heart failure with[37]. A real change to the positive was the results of the CONSENSUS study in 1987 where treatment with the ACE-inhibitor enalapril reduced the mortality for persons with severe heart failure (class IV) by 31%[38]. A larger study (SOLVD) followed with patients with less severe heart failure, but still with mortality benefit[39].

The next step was the angiotensin receptor blockers (ARBs) and the introduction of beta-blockers[37]. Beta blockers had traditionally been seen as contraindicated in heart failure as they had a negative inotropic effect on the heart[40] but based on multiple studies om patients with congestive heart failure this was proved to be wrong[40]. In 1999 the RALES (Randomized Aldactone Evaluation Study) was published in New England Journal of Medicine. The study was halted early as an interim analysis proved a relative risk reduction of 30% for persons treated with spironolactone compared to placebo[41]. Current guidelines developed after a multitude of randomized controlled trials offer many more pharmacological and non-pharmacological treatment modalities in heart failure.

1.3.2 EPIDEMIOLOGY AND CURRENT DEFINITIONS

Even with the progress made in the last 30 years heart failure is still a disease that causes major costs for the society, both for hospital care and for lost life-years[42,43]. The age adjusted prevalence of hospitalizations in Sweden in 2007 was 1.99%[43] with a lightly higher prevalence of 2.03% for men versus 1.93 for women[43]. Five-year mortality after been diagnosed with heart failure in Sweden in 2010 was 52%, with an increased mortality in women (55%) compared to men (49%)[44]. Previous Swedish studies has shown a better prognosis for heart failure of non-ischemic origin compared to ischemic heart failure[45]. Studies from USA still show a 50% five-year mortality[42]. The most common cause of heart failure is ischemic heart disease where parts of the heart muscle have been damaged by oxygen deficiency. European Society of Cardiology (ESC) defines heart failure in their 2016 guidelines[46] as: "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress"[46.]Usually the fluid pools in the legs which are swollen, but in an acute impairment there also leaks fluid in to the lungs.

In the current guidelines[46] heart failure is divided into three groups according to left ventricular ejection fraction (LVEF). Patients with an LVEF <40% are classified with heart failure with reduced ejection fraction (HFrEF), those with LVEF 40-49% and signs and symptoms of heart failure are classified with heart failure with mid-range ejection fraction (HRmrEF). Patients with EF >50% with symptoms of heart failure, elevated natriuretic peptides and either a relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) or diastolic dysfunction (an impaired relaxation of the left ventricle) is classified with heart failure with preserved ejection fraction (HFpEF).

1.3.3 DIAGNOSIS OF HEART FAILURE AND ECHOCARDIOGRAPHY

The diagnosis of heart failure is based on clinical history, Physical examination and ECG together with natriuretic peptides (a biochemical marker that is elevated in heart failure) [46]. The next step is usually a transthoracic echocardiography where the function of the heart is measured with ultrasound. The main measurement is the ejection fraction of the left ventricle calculated by the Simpson method. In the group with midrange or preserved EF additional key measurements are LAVI (left atrial volume index) where the volume of the left atria is indexed to the body surface area (BSA). LAVI >34ml/m2 is a strong indicator of heart failure.

Other functional variables used are E and e`, where E is the blood flow through the mitral valve and e´ is the basal tissue speed in the heart rapid filling phase of the heart. An E/e´ ratio of >12 indicates an increased filling pressure in the left ventricle of the heart.

1.3.4 DIABETES AND HEART FAILURE

In 1974 The Framingham Study[47] firmly established the epidemiologic link between diabetes and HF. The risk of HF was increased 2.4-fold in men and fivefold in women with unspecified diabetes. Regardless of coexisting hypertension or coronary disease the risk increase remained. When patients with prior coronary or rheumatic heart disease were excluded, the relative risk of HF remained elevated at 3.8 in men with diabetes and 5.5 in women. Since then several studies have shown a high incidence of heart failure among persons with diabetes[48]. Essential risk factors seem to be a poor glycemic control and renal dysfunction[48,49] together with age. Until 2011 when Lind et al[49] published their article most large studies were made on type 2 diabetes or mixed diabetes populations. During the last five years there has been a resurge in the interest in heart failure in type 1 diabetes[50,51] where it's called "fatal, forgotten and frequent".

1.4 RISK FACTORS FOR CARDIOVASCULAR DISEASE

1.4.1 WEIGHT AND BODY MASS INDEX

The idea to index a person's weight to their squared length was first published in 1832 by Adolphe Quetelet[52] and called the "Quetelet Index". It was renamed in 1972 to Body Mass Index (BMI) by Ancel Keys[52]. BMI was adapted as a measurement by the world health organization (WHO) as a practical definition of obesity as body fat mass is problematic to measure easily[53]. The current classification of obesity for adults over 20 years of age according to BMI is shown in table 1.

BMI	**Nutritional status**
<18.5 kg/m^2	Underweight
18.5-24.9 kg/m^2	Normal weight
25.0-29.9 kg/m^2	Pre-obesity (Overweight)
30.0-34.9 kg/m^2	Obesity class I (Obesity)
35.0-39.9 kg/m^2	Obesity class II (Severe obesity)
>40 kg/m^2	Obesity class III (Morbid obesity)

Table 1 Classification of obesity according to BMI Source: WHO.org

Increased BMI is a known risk factor for cardiovascular disease in the general population[42,54] and obesity is associated with shorter life expectancy and increased cardiovascular mortality and morbidity[54]. Globally there is an increasing incidence of both obesity and severe obesity with an age-standardized prevalence of obesity (BMI 30-34.9 kg/m^2) in 2014 of 10.8% for men and 14.9% in women[55]. Severe obesity (35.0-39.9 kg/m^2) was found in 2.3% of men and 5.0% of women worldwide[55]. The distribution of body mass index for persons with type I diabetes in Sweden is visualized in figure 2.

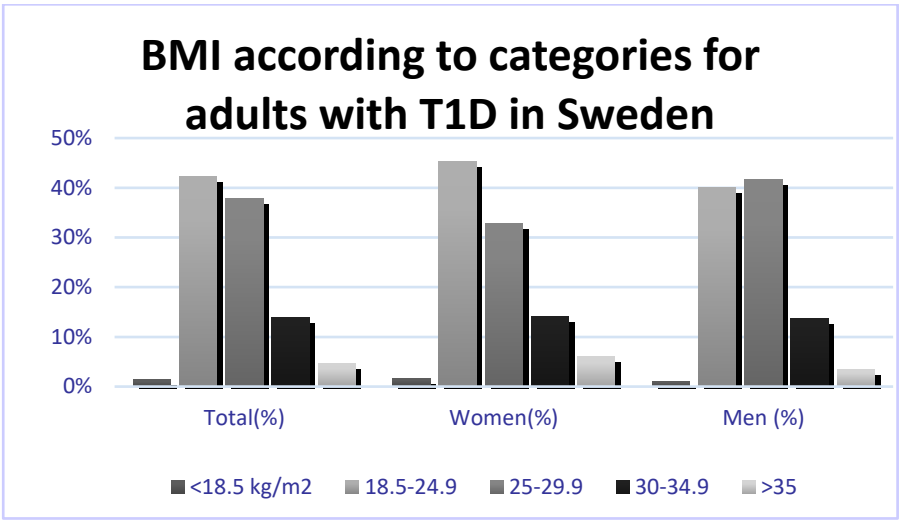

Figure 2 BMI for persons with type 1 diabetes in Sweden. Source: NDR "Knappen". www.ndr.nu

1.4.2 RENAL FUNCTION, ESTIMATED GLOMERULAR FILTRATION RATE (EGFR) AND ALBUMINURIA

Decreased renal function is a known risk factor for heart failure, stroke, coronary heart disease and atrial fibrillation[56,57,58]. There have been several different methods used to estimate glomerular filtration[59], the current recommendation from the American Diabetes Association (ADA) is the use of CKD-EPI[60]. This is a change from when we published Study III where the recommendation was MDRD or CKD-EPI[61]. The first equation to calculate eGFR from creatinine was Cockcroft-Gault[62], followed by MDRD[63] and CKD-EPI[64]. A comparison of the different equations based on our cohort from study III is shown in figure 3. For albuminuria screening it is recommended to use urine albumin to creatinine ratio (A/C) in a random urine sample[60]. The reason for indexing albumin excretion in urine to creatinine is to decrease the rate of false positive and false negative samples due to hydration[60]

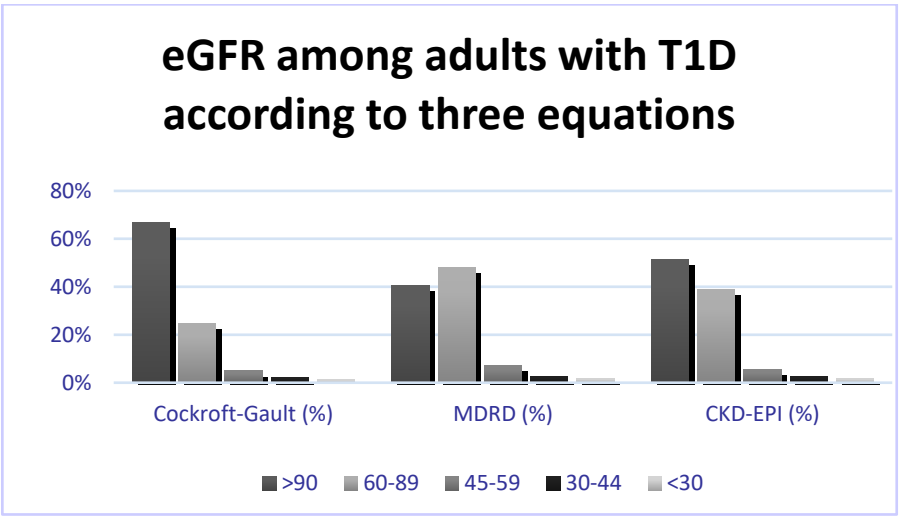

Figure 3 Persons with type 1 diabetes (%) with different degree of renal function according to the different equations for calculating eGFR. Source: Study III

1.4.3 GLYCEMIC CONTROL AND HBA1C

One of the major risk factors for cardiovascular disease (myocardial infarction, angina pectoris, stroke) in type 1 diabetes is problems with the glycemic control, often defined as elevated HbA1c[65]. Glycated hemoglobin (HbA1c) is the weighted average of the blood glucose concentration over the past two to three months[66]. There have historically been different ways to measure HbA1c[67] but after the publication of the Diabetes Control and Complications Trial (DCCT)[68] in 1993 perspectives changed. The DCCT study firmly established HbA1c as an important risk factor for diabetes complications and that intensive glycemic control reduces the risk for complications among persons with type 1 diabetes. Even if the American Diabetes Association soon established a goal for HbA1c it was problematic to use it as the different methods for measuring of HbA1c did not have a common reference[67]. In 2002 the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) published a new reference method for HbA1c[69], but it was not until 2007 the major stakeholders (American Diabetes Association, European Association for the Study of Diabetes, IFCC and the International Diabetes Federation) published a consensus document on the standardization of HbA1c measurement[70]. The document defines the IFCC method as the anchor but also says that HbA1c results should be reported both in IFCC units (mmol/mol) and derived NGSP (United states National Glycohemoglobin Standardization Program) units (%). The current HbA1c goal in adult persons with type 1 diabetes according to ADA is <7.0% (53 mmol/mol) with an opening for a far

more stringent goal of <6.5% (48 mmol/mol) in selected cases[71]. In the United Kingdom, the National Institute for Health and Care Excellence (NICE), has a general glycemic target of 48 mmol/mol (6.5%) for persons with type 1 diabetes to minimize the risk of long-time vascular complications[72]. In Sweden the general target is 52 mmol/mol (6.9%) in adult persons with T1D[12] but also a focus on individual targets and to minimize the number of persons with HbA1c >70mmol/mol (8.6%). The current distribution according to HbA1c levels is shown in figure 4.

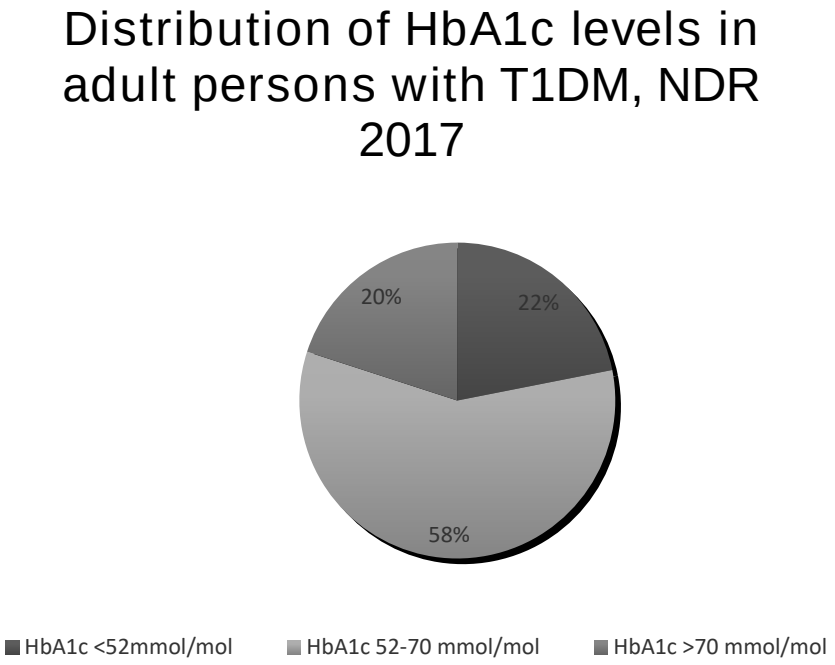

Figure 4 Distribution of HbA1c 2017. Source: NDR yearly report 2017 (preprint)

1.5 The Swedish National Diabetes Registry (NDR)

- Diabetes debut year
- Type of diabetes
- Treatment
- HbA1c
- Weight
- Length
- Blood pressure
- Blood pressure medication
- Serum lipids (Cholesterol, triglycerides, HDL, LDL)
- Lipid lowering medication.
- Albuminuria
- Ischemic heart disease
- Cardiovascular disease
- Diabetes retinopathy
- Smoking and tobacco use
- Physical activity
- Severe hypoglycemia

Figure 5 List of some variables registered in NDR. Source: NDR.nu

The NDR was started in 1996 a quality assurance database for the treatment of diabetes in Sweden[73]. Both hospital and primary care clinics register risk factors and treatment of persons with diabetes managed at their clinic. Among variables registered is type of diabetes (for other see figure 5), since there are individuals in which initially it is uncertain what type of diabetes they have. An epidemiological definition is sometimes used, where an individual diagnosed with diabetes before the age of 30 years and only treated with insulin counts as having type 1 diabetes. This definition has been validated and is correct in 97% of cases[74] and is used in all our registry studies. The NDR is now an integrated part of diabetes care in Sweden and a major source of data for epidemiological research on both type 1 and type 2 diabetes. Approximately 90% of those with diabetes registered in the NDR have Type 2 Diabetes. The inclusion rate is validated with the prescription registry and 91.5% of persons prescribed antidiabetic medication are also found in the NDR[12]. The inclusion rate is probably higher for persons with type 1 diabetes as they are generally treated in specialist clinics and the participation rate for specialist clinics is 100%[12].

2 AIM

The overall aim for this thesis is to investigate the risk of heart failure among persons with type 1 diabetes and identify major risk factors for the development of heart failure in this population. Identification of major risk factors gives clinicians and persons with type 1 diabetes areas to focus on and may also lead to guidelines to identify those who should have closer follow-up or additional examinations such as echocardiography

2.1 AIMS AND OBJECTIVES OF THE SUB-STUDIES

2.1.1 STUDY I

The aim of the first study in the thesis was to investigate the effect of obesity and overweight on the risk for development of heart failure in persons with type 1 diabetes

2.1.2 STUDY II

The aim of the second study was to determine the overall excess risk for heart failure in individuals with type 1 diabetes compared to the general population and estimate the excess risk according to level of glycemic control and albuminuria

2.1.3 STUDY III

The aim of the third study was to quantify the increase in risk for the development of heart failure with decreasing renal function in individuals with type 1 diabetes and to compare three different formulas (Cockcroft-Gault, MDRD and CKD-EPI) for calculating eGFR and quantifying the risk for development of heart failure.

2.1.4 STUDY IV

The aim of the fourth study was to investigate the potential relationship between body mass index (BMI) and the risk for myocardial infarction, coronary events, total mortality and coronary death in persons with type 1 diabetes.

2.1.5 STUDY V

The aim of the fifth study was to investigate to which extent there are early signs of systolic and diastolic dysfunction among persons with type 1 diabetes and how this is correlated to previously identified risk factors for hospitalization for heart failure.

3 COHORTS AND METHODS

All studies in the thesis use a quantitative approach. The first four studies (study I-V) are nationwide observational cohort studies based on register data. The fifth study (Study V) is a cross-sectional study with participants recruited from two centers in the Region Västra Götaland, Sweden

3.1 THE COHORTS

For the first four articles we used data from NDR as the basis for the analyses. The cohorts from NDR have then been linked with other registries, both to add additional background variables and to obtain data on outcomes. The registries that have been used for additional background variables are the Swedish inpatient registry, and the Longitudinal integration database for health insurance and labor market studies (LISA, from Statistics Sweden) and for study II controls identified from the Swedish Total Population Register[75,76]. Endpoints have been retrieved from the Swedish inpatient registry and cause specific death registries. The diagnoses in the inpatient register have been validated for major cardiovascular disorders[78,79]. For the diagnosis of heart failure 82% has been confirmed as definitive, 16% as questionable (usually due to lack of echocardiography) and 2% miscoded[77]. Diagnosis of acute MI has been shown to be valid in 91% of the cases in the hospital discharge register[79], however there is less validity in the cause specific death register with an agreement of 83% between cause of death and last main diagnosis for death in hospitals[80].

3.1.1 STUDY I

For the first study ”The relationship between overweight and obesity with hospitalization for heart failure in 20,985 patients with type 1 diabetes: A population-based study from the Swedish National Diabetes Registry (NDR)” we identified a cohort of all patients included within the NDR during 1998-2003 age 18 or older who had type 1 diabetes and no known HF. Patients were followed until hospitalization for HF (ICD-10 code I50), death or until 31 December 2009.

3.1.2 STUDY II

In the second study "Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study" we included patients with at least one registration in the NDR from Jan 1, 1998, to Dec 31, 2011. For each patient with type 1 diabetes at first registration, five age-matched, sex-matched, and county-matched controls without a registration for type 1 diabetes in the NDR were randomly selected from the general population in Sweden. A total of 33 402 patients and 166 228 matched controls were identified. Participants were followed until first hospital admission for heart failure defined as International Classification of Diseases 10 (ICD-10) code of I50 as either a primary or a contributory diagnosis, until death or until the end of 2011.

3.1.3 STUDY III

The third study "Decreased eGFR as a risk factor for heart failure in 13,781 individuals with type 1 diabetes" was planned to use the same cohort as in study I but there was only creatinine data available for less than 1% of the individuals registered from 1998 to 2001. Among those registered in 2002 65% of individuals and 81% in 2003 had at least one creatinine value registered in the NDR. Study III is based on those in the original cohort from article I with at least one reliable creatinine measurement, as well as data on Hba1c, blood pressure and BMI. The final study cohort consists of 13,718 individuals who were followed from the first creatinine measurement until hospitalization for HF, defined as a principal or contributory discharge diagnosis of heart failure (ICD-10 I50), death from any cause, or the end of 2009.

3.1.4 STUDY IV

The fourth study "Body mass index (BMI) as a risk factor for coronary events and mortality in 17447 persons with type 1 diabetes" is based on an updated cohort from NDR consisting of all patients registered between January 2002 and December 2004 with type 1 diabetes and with at least one measurement of BMI. Patients were followed from their first inclusion in the NDR in 2002–2004 until hospital admission with a primary or secondary discharge diagnosis for HF (ICD-10 I50), death or until Dec 31, 2011. Besides HF, we retrieved diagnoses of atrial fibrillation (I48), valve disease (I05-I09 and I34-I36) and myocardial infarction (I21) from the hospital discharge register.

3.1.5 STUDY V

For the fifth study “Prevalence and risk factors for decreased cardiac function among 287 persons with type 1 diabetes” we invited persons with type 1 diabetes treated either at the diabetes clinic in Uddevalla, Trollhättan or at Östra Sjukhuset to participate in the study, 287 persons with type 1 diabetes accepted and were included in the study. We also recruited persons without diabetes to serve as possible controls and to blind the examiners when conducting the study to prevent bias. All participants received an appointment at one of the involved sites where an echocardiographic examination was made, where they also filled in a questionnaire with background data. Blood tests were drawn both for immediate analysis and for inclusion in a biobank for later investigation of markers for cardiac function and possible risk factors.

Table 2. Comparison of cohorts in the different studies					
Study	**I**	**II**	**III**	**IV**	**V**
Numbers of participants	20 985	33 402 /166 288	13 781	17 499	287
% Women	45%	45%	45%	45%	44%
Mean Age	38.6 years	35.0 years	41.1 years	39.5 years	53.8 years
Inclusion criteria	Type 1 diabetes and no HF	Type 1 diabetes and no HF or matched control without HF	Type 1 diabetes, no HF and registered creatinine value	Type 1 diabetes and no MI	Type 1 diabetes and age >40 or age >30 with additional risk factor
Start date	1998-2003	1998-2011	1998-2003	2002-2004	2013
Followed until	2009	2011	2009	2011	Not relevant
Endpoints	HF or death	HF or death	HF or death	MI, CABG, PCI or death	Cardiac dysfunction

3.2 STATISTICAL METHODS

3.2.1 CUMULATIVE INCIDENCE, INCIDENCE RATES AND ADJUSTED INCIDENCE RATES IN PERSPECTIVE

The cumulative incidence is the number of events that happen during a study[81] and is described as a proportion between events and number of participants. The problem with cumulative incidence is that it may change with follow-up time. Another metric is incidence rate where we calculate ratio between the number of events and the participant´s contributed follow-up time[82]. This is usually described as events/ 1000 patient years. When comparing incidence rates between different groups it is sometimes adjusted with Poisson regression to compensate for different distribution of common risk factors in the studied groups[83]. One example is in figure 6 where we show incidence rates from Study I adjusted for age, sex and diabetes duration

3.2.2 ESTIMATION OF RISK AND COX REGRESSION

The main statistical method used in the studies is cox regression[84] which is a type of survival model used in mainly medical research[85]. A survival model tries to describe the relationship between the time that passes before a certain event happens in respect to one or more covariates (factors) than may be associated with the event. In a proportional hazard model an increase in a covariate is multiplicative in respect to the Hazard ratio. Hazard ratio (HR) is a number that indicates the risk increase (or decrease) for an individual with a certain covariate(Pocock). For example, in Study I the HR for hospitalization for persons with a BMI of 30-35 kg/m^2 was 1.55 (95% CI, 1.20–1.99) when compared to BMI 20–25 kg/m^2. An HR of 1.55 is interpreted as a 55% risk increase compared to the other group. Even a high HR may be of no interest if baseline risk for the event is low (if a disease has a prevalence of incidence of 1 in 100,000 an HR of 4 makes it to 4 in 100,000). The numbers within brackets are the 95% confidence interval, it indicates how accurate the risk estimate is. The "true" risk in the studied population is with 95% certainty within the 95% CI.[85].

3.3 ETHICAL CONSIDERATIONS AND ETHICAL APPROVAL

All studies in the thesis have been approved by the regional Ethics Review Board at the University of Gothenburg (Gothenburg, Sweden). For the first four studies data from NDR is used and all participants have provided verbal informed consent for inclusion in the register (NDR). For study V all participants have provided written informed consent at the time of inclusion in the study.

Ethical approval for study I, III and IV is registered as EPN 612-08 (with addendum T220-11 for study IV). Approval for study II is EPN 540-11 and T391-12. The fifth study, Study V, has ethical approval EPN 240-12.

4 RESULTS

4.1 STUDY I

In the first study "Relationship between Overweight and Obesity with Hospitalization for Heart Failure in 20,985 Patients With Type 1 Diabetes: A population-based study from the Swedish National Diabetes Registry" we investigated the risk for hospitalization for heart failure related to BMI. This study showed that obesity and overweight is a strong risk factor for admission to hospital for heart failure among persons with type 1 diabetes after adjustment for other known risk factors such as myocardial infarction.

In our cohort of 20,985 persons 635 (3%) were admitted to hospital with a primary or secondary diagnosis of heart failure during a mean follow-up of 9 years. HF incidence increased with rising BMI (se figure 6) when adjusted for age, sex and diabetes duration. We showed in a multivariable Cox regression adjusted for age, sex, diabetes duration, smoking HbA1c, systolic and diastolic blood pressure, baseline cardiovascular co-morbidities and blood pressure medications that persons with BMI 30-35 kg/m2 had a HR for heart failure of 1.55 (95% CI, 1.20–1.99) with BMI 20-25kg/m2 as a reference. For persons in the group with BMI >35 kg/m2 the HR was 2.90 (95% CI, 1.92–4.37).

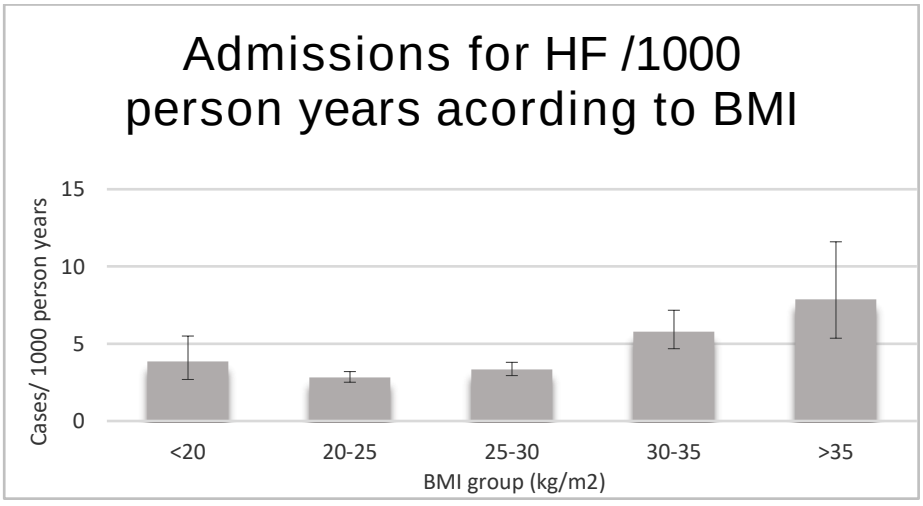

Figure 6 Admissions for heart failure/1000 patient years adjusted for age, sex and diabetes duration. Source: Study I

4.2 STUDY II

The second study "Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study" investigated the risk for development of heart failure for persons with type 1 diabetes compared to persons in the general population. The numbers of admissions for heart failure / 1000-person years are shown in figure 7.

In a multivariable analysis for the risk for admission to hospital for HF for persons with type 1 diabetes compared to controls and adjusted for time-updated age, sex, time updated diabetes duration, birth in Sweden, educational level and baseline co-morbidities the HR for persons with type 1 diabetes was 4.69 (95%CI 3.64-6.04) when compared to controls.

The risk increased with poor glycemic control (increasing Hba1c), impaired renal function (decreasing eGFR according to MDRD) and degree of albuminuria. Persons with type 1 diabetes, good glycemic control and absence of microalbuminuria had no significant excess risk with HR 1.59 (95% CI 0.70-3.58)

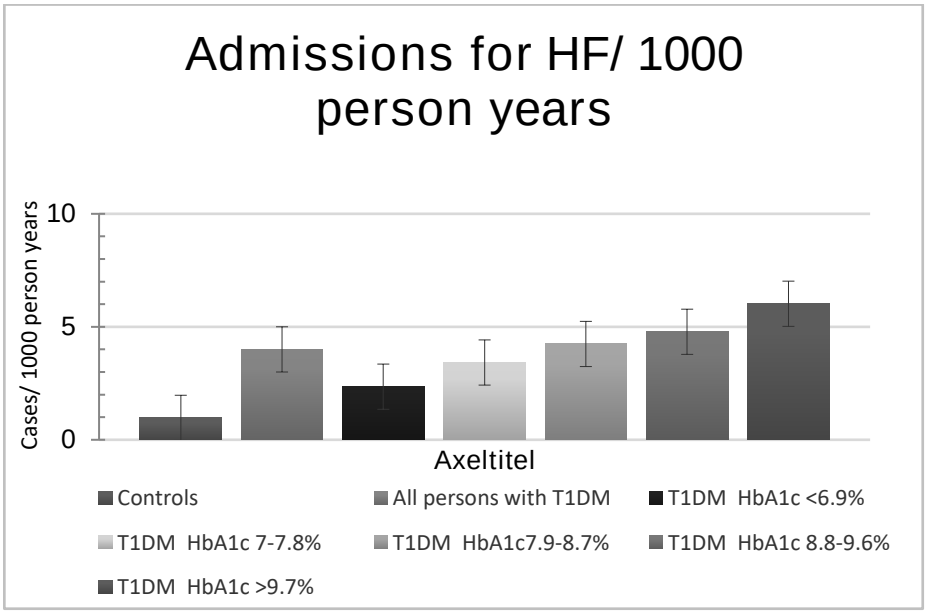

Figure 7 Admissions for HF/ 1000-person years according to HbA1c categories at baseline. Source: Study II

4.3 STUDY III

In the third study where we investigated the relationship between decreased renal function (in this article defined as decreased eGFR, estimated or calculated glomerular filtration rate) in 13 718 individuals with T1D, among those 330 were admitted to hospital with main or contributory diagnosis of HF. When we compared three different equations for calculating eGFR (Cockcroft-Gault, MDRD and CKD-Epi) we saw that regardless of which equation that was used there was a significantly increased risk for development of heart failure with decreased eGFR.

For eGFR 45-60 ml/min/1.73 m^2, hazard ratios (HRs) for hospitalization (reference >90 mL/min/1.73 m_2) were 3.18 (95% CI 2.17, 4.65), 2.12 (1.16, 3.08), and 2.44 (1.69, 3.55) respectively when using the Cockcroft-Gault, MDRD, and CKD-EPI formulas respectively. With eGFR <30 ml/min/1.73 m_2 there was a HR of 3.78 (2.15, 5.91), 3.44 (2.14, 5.51), and 3.51 (2.21, 5.51) compared to normal renal function (>90 mL/min/1.73 m_2) respectively.

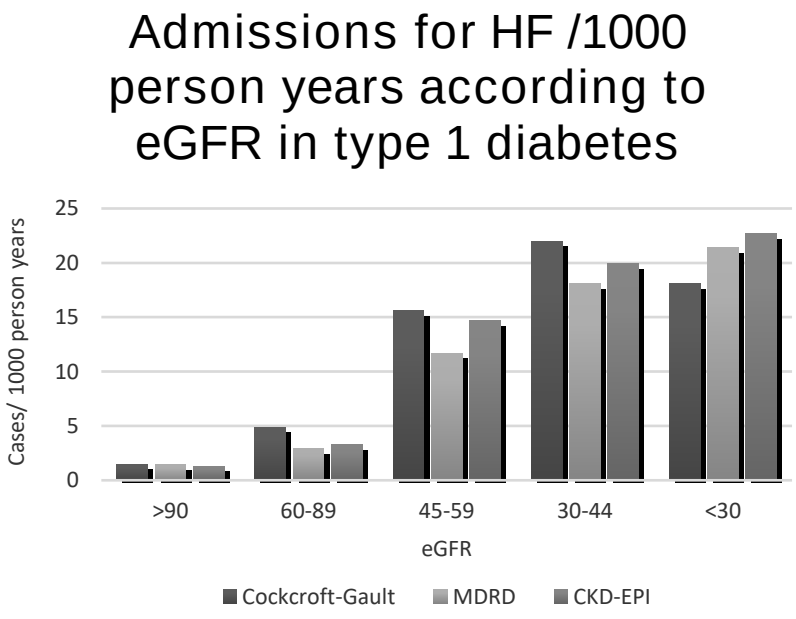

Figure 8 Admissions for HF/ 1000-person years according to eGFR. Source: Study III

4.4 STUDY IV

In the fourth study we investigated BMI as a risk factor for myocardial infarction and cardiac mortality. During a mean follow up time of 8.5 years 819 persons were diagnosed with myocardial infarction as primary or secondary diagnosis (ICD-10 I21), 901 had a major coronary event (ICD-10 I21 or I20-I25 together with operation code for PCI (Percutaneous coronary intervention) or CABG (Coronary artery by-pass grafting). There were 276 persons who died from ischemic heart disease (ICD-10 I20-I25 according to the cause specific death register) and a total mortality of 1261 (any registration in the cause specific death register). The proportion of persons in each BMI category for each endpoint is presented in figure 9. In multivariate survival analysis (Cox regression) adjusted for sex, age, diabetes duration, HbA1c, smoking, lipid-lowering agents, blood pressure medications and level of education (Model 4 in Study III) there was no significant relationship between BMI and risk for myocardial infarction (all 95% CI included 1). The same results applied to major coronary events for model 4. There was an increased risk for overall mortality and coronary mortality in the underweight group (BMI <18.5kg/m2) when compared to BMI 18.5-24.9 kg/m^2 with a HR of 3.99 (95% CI 1.41-11.29) for mortality in Ischemic heart disease and HR 5.41 (95% CI 3.32-8.92) for total mortality.

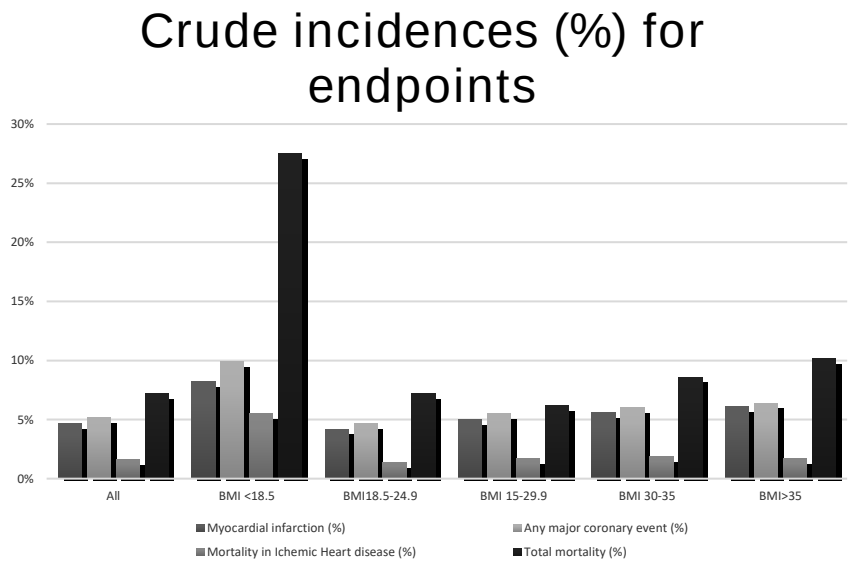

Figure 9 Crude incidence (%) for adults with T1DM according to BMI group and endpoint. Source: Study IV

4.5 STUDY V

In the fifth study we investigated the prevalence of systolic and diastolic cardiac dysfunction in a population of 287 persons with type 1 diabetes (160 men (55.7%) and 127 women (44.3%)). Systolic dysfunction was defined as EF <50% or evidence of regional wall motion abnormalities. Diastolic dysfunction was defined as LAVI >34ml/m2 and e´(sept) less than 8 cm/s. For a group of investigated persons that were investigated first (n=18) there were not stored images of sufficient quality for a reliable calculation of left atrial volume. Instead an experienced cardiologist made a balanced visual assessment of diastolic dysfunction, the prevalence in this group was 2 out of 18 (11%). According to the definitions used for systolic and diastolic dysfunction 23 had systolic dysfunction (8.2%) and 24 diastolic dysfunction (9%). Both in the group with systolic and diastolic dysfunction there were non-significantly more women compared to the whole cohort (56.5% women vs 43.5% for systolic dysfunction and 54.2% vs 45.8% for diastolic dysfunction). Among those with systolic dysfunction, 6 (26.1%) had a previous myocardial infarction compared to 6 (2.3%) in the group without systolic dysfunction. The prevalence of systolic and diastolic dysfunction in the group without previous myocardial infarction was 6.3% with, systolic dysfunction, and 8.7% with diastolic dysfunction. Most persons with systolic dysfunction had an EF of 45-50% and only 3 persons had EF <45%.

The majority of those with either systolic or diastolic dysfunction were over 50 years of age (n=18, 78% systolic and n=22, 92% diastolic). Among those over 50 the prevalence was 11.2% for systolic dysfunction and 14.8% for diastolic dysfunction. In the group who were less than 50 years old there were 5 cases of systolic and 2 cases of diastolic dysfunction, the prevalence of systolic dysfunction was 4.1% and 1.7% for diastolic dysfunction

In a univariate analysis for systolic dysfunction, age, diabetes duration, decreased renal function (eGFR) and previous myocardial infarction were significant ($p<0.05$), after adjustment for age only age and previous myocardial infarction remained significant ($p<0.05$). The univariate analysis for diastolic dysfunction was significant for age, diabetes duration and decreased renal function (eGFR) ($p<0.05$), after adjustment for age no other factor except age remained significant ($p<0.05$).

According to the questionnaire only 1 person in the cohort had a previous diagnosis of heart failure. There were 38 persons who stated that they were more easily tired when doing physical activities than their peers of the same age. In this group there was 3 with systolic- and 3 with diastolic dysfunction according to our previous definition.

5 DISCUSSION

In the five studies included in this thesis different aspects of cardiovascular disease among persons with type 1 diabetes were investigated. The focus for the dissertation is heart failure, but since myocardial infarction is one of the main risk factors for development of heart failure in the general population, we also investigated coronary disease. As we found BMI to be a strong risk factor for hospitalization for heart failure BMI was also investigated as a risk factor for coronary disease.

5.1 SUMMARY OF RESULTS

In the first study (Study I) we have shown that obesity (BMI >30 kg/m2) is a strong risk factor for hospitalization for heart failure among persons with type 1 diabetes even after adjustment for classical risk factors for cardiovascular disease. As there was a lack of studies investigating the excess risk for heart failure we compared persons with type 1 diabetes and controls from the general population. We found in study II that there is a four times increased risk for hospitalization for heart failure for persons with type 1 diabetes compared to age, sex and county matched controls from the general population. The risk increase was lower among those who had good glycemic control and no albuminuria. In the group with both well controlled diabetes and normoalbuminuria there was no significant excess risk for heart failure when compared to controls. Decreased renal function measured by different equations for calculating eGFR as a risk factor for heart failure was the focus of study III. We found that regardless of equation used, the risk of admission to hospital for heart failure, was increased with lower eGFR. We also compared the information gain between equations and both MDRD and CKD-EPI added predictive information regarding hospitalization for heart failure on top on Cockcroft-Gault. As we had found BMI to be a strong risk factor for HF we decided to study BMI as a risk factor for myocardial infarction and mortality. In study IV we found that there was no increased risk for myocardial infarction related to BMI in our cohort of persons with type 1 diabetes. This may indicate that there are different mechanisms behind heart failure and myocardial infarctions. One specific weakness with the methods used in the first four studies is the reliance on hospital admissions as an endpoint and it is possible that we might have missed persons at an early stage of heart failure. One way to handle this is to do a cross-sectional study such as study V, where we searched for early signs of cardiac dysfunction in a group of persons with type 1 diabetes. Such a study could also gain knowledge whether it could be beneficial to screen certain patient groups with T1D with echocardiography to prevent future HF. We found 24 (out of 287, 8.4%) persons with both systolic

and diastolic cardiac dysfunction and interestingly the previously published risk factors for hospitalization for heart failure were not applicable here.

5.2 CURRENT RESULTS IN PERSPECTIVE

Recently a similar investigation as our studies I and IV was published evaluating BMI as a risk factor for cardiovascular disease in the general population[54]. Their population with middle aged men and women (age of 40-50 years, 21 390 men and 51 100 women, 5.5% unspecified diabetes for men and 4.2% for women) was slightly older than the one in our studies (mean age in study I 38.6 years SD 13.7 years and in study IV 39.5 SD 13.2 years) but is the closest for comparison. In their population the HR for heart failure in the overweight group (BMI 25-29.9 kg/m2) was 1.22 (95% CI 1.07-1.40) for men and 1.37 (95% CI 1.21-1.55) for women compared to 0.95 (95% CI 0.73-1.24) in our diabetes cohort in study I. A similar comparison for HR for myocardial infarction showed an HR of 1.18 (95% CI 1.09-1.28) for men and 1.42 (95% Ci 1.29-1.57) for women with overweight in the general population and an HR of 1.02 (95% CI 0.82-1.27) in our diabetes cohort from study IV. In both cases overweight was seemingly a stronger risk factor for both heart failure and myocardial infarction for persons in the general population than for persons with type 1 diabetes.

However, some caution must be exercised in comparing HR for CVD directly between different populations as what they show is the risk increase for overweight compared to normal weight within the population with and without type 1 diabetes.

An important perspective is the risk estimate for both heart failure and myocardial infarction when investigating persons with and without type 1 diabetes. As we showed in study II, persons with type 1 diabetes have a four-fold increased risk for heart failure due to their diabetes (or closely related risk factors, HbA1c and albuminuria). A similar level of risk increase also exists for myocardial infarction[33]. One reason for the lower impact of BMI on the risk of MI among persons with type 1 diabetes may be that type 1 diabetes is an important risk factor itself. The additional risk from overweight and obesity seen in the general population may then be attenuated by type 1 diabetes.

5.3 BMI A RISK FACTOR FOR HEART FAILURE BUT NOT MYOCARDIAL INFARCTION, MAY IT BE DIABETIC CARDIOMYOPATHY?

One interesting result from the studies in the thesis is the different importance of BMI as a risk factor when we compare heart failure and myocardial infarction (Study I and IV) in very similar cohorts. Myocardial infarction is mainly a result of coronary artery disease[86] while the etiology for HF is more multifactorial (Johnson) but includes ischemia secondary to coronary artery disease. Several studies in the general population have shown a dose response-effect of BMI on the risk for heart failure[87] and the effect of BMI persists after adjustment for classic cardiovascular risk factors (hypertension, unspecified diabetes, age and smoking) and after adjustment for myocardial infarction[89]. Proposed mechanisms are through increased levels of pro-inflammatory cytokines and other mediators such as adipokines[90,91,92] that have been proposed to have a role in increased cardiac fibrosis. There may also be a degree of lipotoxicity[91]. Studies on heart remodeling after bariatric surgery have shown a decreased left ventricular muscle mass after weight loss[93] possibly due to decreased demand on the heart. For persons with diabetes, there is an ongoing discussion where there is a special type of cardiomyopathy, "diabetic cardiomyopathy" in diabetes. This seems to be the case in type 2 diabetes but is more uncertain in type 1 diabetes[94]. In 2007 Konduracka et al[95] published a study in the European Heart Journal where they compared 185 persons with T1DM and 105 persons without diabetes and found no support for the theory that T1DM leads to diabetic cardiomyopathy. Early changes in diastolic function have been shown among children and adolescents with type 1 diabetes[96]. More recently there have been several evaluations published from a Danish group (one thousand and one study) investigating echocardiographic changes in patients with T1DM. Their results[97] support our findings of a higher prevalence of heart failure among persons with type 1 diabetes and decreased renal function as a risk factor. The current theories of diabetic cardiomyopathy[98] describe a chain of events with hyperglycemia leading to oxidative stress and autonomic dysfunction. There are also theories of autoimmune effects causing heart failure in type 1 diabetes[99].

5.4 TYPE 1 DIABETES AND SCREENING WITH ECHOCARDIOGRAPHY

Study V was initiated to study the prevalence of cardiac dysfunction among persons with T1D. We decided to not exclude persons with previous MI as we wanted the cohort to represent the patients that a clinician sees in everyday practice. As we found that 1 in 9 among persons over the age of 50 with T1D had a systolic dysfunction and 1 in 7 had diastolic dysfunction clinicians should consider referring persons in this group to echocardiography. The majority of those with systolic dysfunction had only regional wall dysfunction or slightly reduced EF (45-50%), implying that we hopefully can prevent or slow down the progression to decompensated heart failure (but a prospective study is needed to prove it). A liberal use of beta blockers and RAAS (Renin-angiotensin-aldosterone system) -blockers, both for hypertension and prevention of renal complications but also as a treatment for early cardiac dysfunction may be in order.

The value of liberal screening among persons with T1D in the age group 30-50 years is more questionable as there were only 1 in 25 who had systolic dysfunction and 1 in 60 with diastolic dysfunction.

When we compare our results with other similar studies, Wai et al[100] found echocardiographic changes in 30% of their population of 185 persons, most of those diastolic dysfunction (27 cases, 14.6% of their cohort) and a low rate of systolic dysfunction (4 cases 2.1%) they saw most of their cases of diastolic dysfunction in the group >40 years, supporting screening in the older group.

5.5 THE DIFFERENCES BETWEEN RISK IN THE EPIDEMIOLOGICAL STUDIES AND THE CROSS-SECTIONAL STUDY

It would be reasonable to believe that the two risk factors for hospitalization for heart failure studied (Obesity in Study I and decreased eGFR in study III) would have shown significance in the screening study with echocardiography (Study V). In study I, 635 (3%) were admitted to hospital during 9 years of follow-up, if we should follow our participants from study V (n=287) for 9 years (as in study I) we could postulate that approximately 9 persons (based on a follow up of 2583-person years and an incidence of 3,3/1000 person years in the group with BMI 25- <30) would have been admitted to hospital for heart failure. That is one every year and it possible that certain risk factors with the design of our echocardiography screening study may have been detected in a larger patient cohort. One should also bear in mind that hospitalization for heart failure is often due to severe uncompensated heart failure, a later stage of the disease). The same theory may explain the lack of significance for decreased eGFR in study V. Other possible explanations include that we only used one measurement of the risk factor whereas in the epidemiologic studies repeated measurements over many years were generally used to estimate the mean exposure. In future projects it will be possible to link the current database to the NDR for obtaining information of risk factors over time.

5.6 STRENGTHS OF THE STUDIES

When studying the time dependent effect of risk factors one of the more time efficient methods is a retrospective cohort study[101] as used in Study I-IV. The main strengths of our studies are related to the ability to follow individuals between different registers in Sweden (through their personal identification number) and the ability to follow our cohorts for a long time. In all the four first studies we had a large sample size (number of participants) and were able to follow them for a long time. The cohorts should also be representative for persons with type 1 diabetes in Sweden. Most persons with type 1 diabetes meeting the inclusion criteria for the studies were included. In study II a specific strength is the long follow-up time for both persons with T1D and matched controls. A strength of the fifth study (Study V) is the data on cardiac function that is unobtainable from registers and may form the basis for future decisions on screening in selected groups with T1D

5.7 LIMITATIONS OF THE STUDIES

There are some important limitations that need to be considered, in all the first four studies (Study I-IV) we rely on data registered in other registers both for study variables, co-morbidities and endpoint variables. Our results rely heavily on the accuracy of the registration both in NDR, the inpatient register and the cause specific death register. Validation of data in those registers[74,77,78] are paramount for the results of our studies.

The fifth study, as a cross-sectional study, has one limitation in the lack of previous data on exposure for studied risk factors. Another limitation is the change in evaluation method for diastolic dysfunction during the study from a balanced visual assessment to a definition based on LAVI and e´sept. This led to a need for reassessment of previous stored ultrasound images and in minor group there was no stored data for assessment of left atrial volume for calculation of LAVI. In most of those cases a visual assessment was used instead.

6 CONCLUSION

In this thesis we have shown that persons with type 1 diabetes have a higher risk for hospitalization for heart failure, but this risk is attenuated with good glycemic control and prevention of renal complications such as albuminuria. Excess weight (increased BMI) and decreased eGFR seem to be important risk factors for heart failure while BMI does not seem to influence the risk for myocardial infarction among persons with type 1 diabetes. Clinicians should be aware of the possible benefit of screening in persons with T1D 50 years or older with echocardiography since the prevalence of systolic dysfunction was 11.2% and 14.8% for diastolic dysfunction in this patient group. This may be of special concern if reduced physical function level exists. Although obesity, hyperglycemia and reduced renal function were not associated with cardiac dysfunction in our echocardiography study, clinicians should likely be aware of these risk factors for future hospitalization of heart failure and include these in among the considerations when deciding whether to screen an individual patient with echocardiography. Whether general screening of persons with T1D 50 years or older should be performed cannot yet be determined from the current and previously performed studies. Preferentially a large randomized trial with echocardiography in persons with T1D should be performed showing whether beneficial effects exist in preventing cardiac dysfunction and heart failure. However, such a study will require large resources and take long time and is unclear whether it will be performed in the near future.

7 FURTHER PERSPECTIVES

This thesis highlights that there is still a lot to do in the area of type 1 diabetes and heart failure, as most of the included studies are retrospective cohort studies we cannot prove causative effects and to further investigate the effect of risk factor treatment a prospective study is in order. A follow-up of persons screened with echocardiography (for example a cohort as our study V) could provide more information on how heart failure develops over time among persons with type 1 diabetes. Also, this could lead to additional information on the relative importance of risk factors. Further work to reach the set goals for glycemic control will hopefully reduce the risk for heart failure. New classes of drugs developed for type 2 diabetes, especially SLGT 2-inhibitors, that have already showed a decreased rate of hospitalization for heart failure in type 2 diabetes[102,103], may lead to decreased morbidity if the safety and effects are similar in type 1 diabetes. Identification of high risk patients and screening those with echocardiography may be a step forward both for early treatment of heart failure but also as a basis for future research on the mechanisms causing decreased heart function in type 1 diabetes.

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9 REFERENCES

1. *Nwaneri C. Diabetes mellitus: a complete ancient and modern historical perspective. Webmed Central Diabetes 2015;6(2):WMC004831*
2. *Saba MM, Ventura HO, Saleh M, Mehra MR. Ancient Egyptian medicine and the concept of heart failure. J Card Fail. 2006 Aug;12(6):416-21.*
3. *Ebbell B The papyrus Ebers. Copenhagen and Oxford: Oxford university Press. 1937*
4. *Harley G: Diabetes: IT'S Various Forms and Different Treatments. London, Walton and Mabberley, 1866*
5. *Tattersall RB 2010 The history of Diabetes Mellitus. In R. Holt, C. Cockram, A. Flyvbjerg & R. Goldstein (Ed.), Textbook of Diabetes (4th ed.). Blackwell Publishing*
6. *Lancereaux E . Nouveaux faits de diabète sucré avec alterations du pancrèas. Bull Acad Méd 8 May 1888*
7. *Gale EA.The discovery of type 1 diabetes. Diabetes. 2001 Feb;50(2):217-26.*
8. *American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes 2018. Diabetes Care 2018;41(Suppl. 1):S13–S27*
9. *Atkinson MA, Eisenbarth GS, Michels AW.Type 1 diabetes. Lancet. 2014 Jan 4;383(9911):69-82.*
10. *Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. Postgrad Med J. 2016 Feb;92(1084):63-9.*
11. *Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spégel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark Å, Lahti K, Forsén T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables.Lancet Diabetes Endocrinol. 2018 Mar 1. pii: S2213-8587(18)30051-2*
12. *NDR Yearly report 2016, 2017 ISSN 2001-2632*

13. *Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G, EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. Lancet. 2009; 373:2027–33.*

14. *Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes.Endocrinol Metab Clin North Am. 2010 Sep;39(3):481-97.*

15. *Haller MJ, Atkinson MA, Schatz D Type 1 diabetes mellitus: etiology, presentation, and management. Pediatr Clin North Am. 2005 Dec; 52(6):1553-78.*

16. *Redondo MJ, Fain PR, Eisenbarth GS Genetics of type 1A diabetes.Recent Prog Horm Res. 2001; 56():69-89.,*

17. *McCall AL1, Farhy LS. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. Minerva Endocrinol. 2013 Jun;38(2):145-63.*

18. *Hirsch IB. INSULIN ANALOGUES. N Engl J Med. 2005 Jan 13;352(2):174-83.*

19. *DeWitt DE1, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003 May 7;289(17):2254-64.*

20. *Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. N Engl J Med. 2012 Apr 26;366(17):1616-24*

21. *Beran D, Yudkin J, de Courten M. Access to care for patients with insulin-requiring diabetes in developing countries: case studies of Mozambique and Zambia. Diabet Care 2005;28: 2136-40*

22. *Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycemia. Br Med J. 1978 Jan 28;1(6107):204-7.*

23. *American Diabetes Association 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2018 Diabetes Care 2018 Jan; 41(Supplement 1): S73-S85.*

24. *Kaiser D, Oetjen E. Something old, something new and something very old: drugs for treating type 2 diabetes. Br J Pharmacol. 2014 Jun;171(12):2940-50.*

25. *Tamez-Perez HE, Delgadillo-Esteban E, Soni-Duque D, Hernández-Coria MI, Tamez-Peña AL. SGLT2 inhibitors as add on therapy in type 2 diabetes: a real world study. J Diabetes Metab Disord. 2017 Jun 30;16:27*

26. *Nair S1, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus.J Clin Endocrinol Metab. 2010 Jan;95(1):34-42.*

27. *Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.*

28. *Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators.Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22.*

29. *Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med. 1993 Jun 10;328(23):1676-85.*

30. *Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care 2006;29:2528–2538*

31. *Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish Registry Linkage Study. PLoS Med 2012;9:e1001321*

32. *Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care 2006;29:798–804*

33. *Matuleviciene-Anängen V, Rosengren A, Svensson AM, Pivodic A, Gudbjörnsdottir S, Wedel H, Kosiborod M, Haraldsson B, Lind M .Glycaemic control and excess risk of major coronary events in persons with type 1 diabetes. Heart. 2017 Nov;103(21):1687-1695.*

34. *Ahlén E, Pivodic A, Wedel H, Dahlqvist S, Kosiborod M, Lind M. Glycemic Control, Renal Complications, and Current Smoking in Relation to Excess Risk of Mortality in Persons With Type 1 Diabetes.J Diabetes Sci Technol. 2016 Aug 22;10(5):1006-14.*

35. *Davis RC, Hobbs FD, Lip GY. ABC of heart failure. History and epidemiology. BMJ. 2000 Jan 1;320(7226):39-42.*

36. *Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002 Oct 31;347(18):1397-402.*

37. *McMurray JJ. Improving outcomes in heart failure: a personal perspective. Eur Heart J. 2015 Dec 21;36(48):3467-70.*

38. *The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study. N Engl J Med. 1987;316:1429-1435.*

39. *The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293-302.*

40. *Doughty RN, MacMahon S, Sharpe N. Beta-blockers in heart failure: promising or proved? J Am Coll Cardiol. 1994 Mar 1;23(3):814-21.*

41. *Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J.The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.N Engl J Med. 1999 Sep 2;341(10):709-17.*

42. *Benjamin E, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018 Jan 31.*

43. *Parén P, Schaufelberger M, Björck L, Lappas G, Fu M, Rosengren A. Trends in prevalence from 1990 to 2007 of patients hospitalized with heart failure in Sweden.Eur J Heart Fail. 2014 Jul;16(7):737-42.*

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

45. *Shafazand M, Schaufelberger M, Lappas G, Swedberg K, Rosengren A. Survival trends in men and women with heart failure of ischaemic and non-ischaemic origin: data for the period 1987-2003 from the Swedish Hospital Discharge Registry .Eur Heart J. 2009 Mar;30(6):671-8.*

46. *Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975.*

47. *Kannel WB, Hjortland M, Castelli WP (1974) Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 34:29–34 8.*

48. *Erqou S, Lee CT, Suffoletto M, Echouffo-Tcheugui JB, de Boer RA, van Melle JP, Adler AI. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. Eur J Heart Fail. 2013 Feb;15(2):185-93*

49. *Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, Svensson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study.Lancet. 2011 Jul 9;378(9786):140-6.*

50. *Gilbert RE. Heart failure: fatal, forgotten, and frequent in type 1 diabetes too. Lancet Diabetes Endocrinol. 2015 Nov;3(11):832-4*

51. *McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol. 2014 Oct;2(10):843-51.*

52. *Eknoyan G. Adolphe Quetelet (1796-1874)--the average man and indices of obesity.Nephrol Dial Transplant. 2008 Jan;23(1):47-51.*

53. *WHO. Physical STATUS: the use of and interpretation of ANTHROPOMETRY, report of a WHO expert committee 1995*

54. *Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM1. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. JAMA Cardiol. 2018 Feb 28.*

55. *NCD Risk Factor Collaboration (NCD-RisC) Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet. 2016 Apr 2;387(10026):1377-1396.*

56. *GANSEVOORT RT, CORREA-ROTTER R, HEMMELGARN BR, JAFAR TH, HEERSPINK HJ, MANN JF, MATSUSHITA K, WEN CP.CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR RISK: EPIDEMIOLOGY, MECHANISMS, AND PREVENTION.LANCET. 2013 JUL 27;382(9889):339-52.*

57. *GO AS, CHERTOW GM, FAN D, MCCULLOCH CE, HSU CY: CHRONIC KIDNEY DISEASE AND THE RISKS OF DEATH, CARDIOVASCULAR EVENTS, AND HOSPITALIZATION. N ENGL J MED 2004;351:1296–1305.*

58. *CHANG A, KRAMER H. SHOULD EGFR AND ALBUMINURIA BE ADDED TO THE FRAMINGHAM RISK SCORE? CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE RISK PREDICTION.NEPHRON CLIN PRACT. 2011;119(2):C171-7; DISCUSSION C177-8.*

59. *STEVENS LA, CORESH J, GREENE T, LEVEY AS. ASSESSING KIDNEY FUNCTION—MEASURED AND ESTIMATED GLOMERULAR FILTRATION RATE. N ENGL J MED. 2006;354(23): 2473-2483.*

60. *AMERICAN DIABETES ASSOCIATION. 10. MICROVASCULAR COMPLICATIONS AND FOOT CARE: STANDARDS OF MEDICAL CARE IN DIABETES-2018. DIABETES CARE. 2018 JAN;41(SUPPL 1):S105-S118..*

61. *AMERICAN DIABETES ASSOCIATION. STANDARDS OF MEDICAL CARE IN DIABETES—2014. DIABETES CARE. 2014;37(SUPPL 1):S14-S80*

62. *COCKCROFT DW, GAULR MH. PREDICTION OF CREATININE CLEARANCE FROM SERUM CREATININE. NEPHRON. 1976;16(1):31-41.*

63. *LEVEY AS, BOSCH JP, LEWIS JB, GREENE T, ROGERS N, ROTH D. A MORE ACCURATE METHOD TO ESTIMATE GLOMERULAR FILTRATION RATE FROM SERUM CREATININE: A NEW PREDICTION EQUATION:MODIFICATION OF DIET IN RENAL DISEASE STUDY GROUP. ANN INTERN MED. 1999;130:461-470.*

64. *LEVEY AS, STEVENS LA, SCHMID CH, ET AL. CKD-EPI (CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION). A NEW EQUATION TO ESTIMATE GLOMERULAR FILTRATION RATE. ANN INTERN MED. 2009;150(9):604-612.*

65. *DIABETES CONTROL AND COMPLICATIONS TRIAL/EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (DCCT/EDIC) RESEARCH GROUP. RISK FACTORS FOR CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES. DIABETES. 2016 MAY;65(5):1370-9.*

66. *REYNOLDS TM, SMELLIE WS, TWOMEY PJ. GLYCATED HAEMOGLOBIN (HBA1C) MONITORING. BMJ. 2006 SEP 16;333(7568):586-8.*

67. *LITTLE RR, ROHLFING CL. THE LONG AND WINDING ROAD TO OPTIMAL HBA1C MEASUREMENT CLIN CHIM ACTA. 2013 MAR 15;418:63-71.*

68. *DCCT RESEARCH GROUP. THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG TERM COMPLICATIONS IN INSULIN DEPENDENT DIABETES MELLITUS. NEW ENGL J MED. 1993; 329:977–986.*

69. *JEPPSSON JO, KOBOLD U, BARR J, FINKE A, HOELZEL W, HOSHINO T, MIEDEMA K, MOSCA A, MAURI P, PARONI R, THIENPONT L, UMEMOTO M, WEYKAMP C; INTERNATIONAL FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE (IFCC).APPROVED IFCC REFERENCE METHOD FOR THE MEASUREMENT OF HBA1C IN HUMAN BLOOD.CLIN CHEM LAB MED. 2002 JAN;40(1):78-89.*

70. *Consensus Committee. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation.Diabetes Care. 2007 Sep;30(9):2399-400.*

71. *American Diabetes Association.6. Glycemic Targets:Standards of Medical Care in Diabetes 2018 Diabetes Care 2018;41(Suppl. 1):S55–S64*

72. *Type 1 diabetes in adults: diagnosis and management NICE guideline 26 August 2015 nice.org.uk/guidance/ng17 accessed 180303*

73. *Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B; Steering Committee of the Swedish National Diabetes Register.The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care.Diabetes Care. 2003 Apr;26(4):1270-6.*

74. *Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Glycemic control and cardiovascular disease in 7.454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33(7):1640-1646.*

75. *Rosengren A, Vestberg D, Svensson AM, Kosiborod M, Clements M, Rawshani A, Pivodic A, Gudbjörnsdottir S, Lind M. Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study. Lancet Diabetes Endocrinol. 2015;3(11):876-85.*

76. *Vestberg D, Rosengren A, Eeg-Olofson K , Miftaraj M, Franzen S, Svensson A-M, Lind M. Body mass index as a risk factor for coronary events and mortality in patients with type 1 diabetes. Open Heart. 2018 Jan 20;5(1):e000727*

77. *Ingelsson E, Arnlov J, Sundstrom J, Lind L. The validity of a diagnosis of heart failure in a hospital discharge register. Eur J Heart Fail 2005; 7: 787–91.*

78. *Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11: 450.*

79. *Elo SL, Karlberg IH. Validity and utilization of epidemiological data: a study of ischaemic heart disease and coronary risk factors in a local population. Public Health. 2009 Jan;123(1):52-7*

80. *Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. Int J Epidemiol. 2000 Jun;29(3):495-502.*

81. *Setia M S Methodology Series Module 1: Cohort Studies Indian J Dermatol. 2016 Jan-Feb; 61(1): 21–25.*

82. *Koletsi D, Pandis N. Introduction to incidence rates and time-changing variables for cohort studies.Am J Orthod Dentofacial Orthop. 2017 Jul;152(1):131-132.*

83. *Koletsi D, Pandis N. Poisson regression. Am J Orthod Dentofacial Orthop. 2017 Aug;152(2):284-285..*

84. *Cox, DR,"Regression Models and Life-Tables". Journal of the Royal Statistical Society, Series B. 197). 34 (2): 187–220*

85. *Pocock SJ, McMurray JJ, Collier TJ. Making Sense of Statistics in Clinical Trial Reports: Part 1 of a 4-Part Series on Statistics for Clinical Trials.J Am Coll Cardiol. 2015 Dec 8;66(22):2536-49.*

86. *Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet. 2017 Jan 14;389(10065):197-210.*

87. *Johnson FL. Pathophysiology and etiology of heart failure. Cardiol Clin. 2014 Feb;32(1):9-19, vii.*

88. *Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, Vatten LJ. Body Mass Index, Abdominal Fatness, and Heart Failure Incidence and Mortality: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies.Circulation. 2016 Feb 16;133(7):639-49*

89. *Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS Obesity and the risk of heart failure. N Engl J Med. 2002 Aug 1;347(5):305-13.*

90. *Ho JE, McCabe EL, Wang TJ, Larson MG, Levy D, Tsao C, Aragam J, Mitchell GF, Benjamin EJ, Vasan RS, Cheng S. Cardiometabolic Traits and Systolic Mechanics in the Community.Circ Heart Fail. 2017 May;10(5).*

91. *Zhai AB, Haddad H. The impact of obesity on heart failure.Curr Opin Cardiol. 2017 Mar;32(2):196-202.*

92. *Lau WB, Ohashi K, Wang Y, Ogawa H, Murohara T, Ma XL, Ouchi N. Role of Adipokines in Cardiovascular Disease.Circ J. 2017 Jun 23;81(7):920-928.*

93. *Vest AR, Patel AR. The Heavy Heart: Metabolic Mechanisms and Myocardial Mechanics. Circ Heart Fail. 2017 May;10(5).*

94. *Hölscher ME, Bode C, Bugger H. Diabetic Cardiomyopathy: Does the Type of Diabetes Matter? Int J Mol Sci. 2016 Dec 18;17(12). pii: E2136..*

95. *Konduracka E, Gackowski A, Rostoff P, Galicka-Latala D, Frasik W, Piwowarska W. Diabetes-specific cardiomyopathy in type 1*

DIABETES MELLITUS: NO EVIDENCE FOR ITS OCCURRENCE IN THE ERA OF INTENSIVE INSULIN THERAPY.EUR HEART J. 2007 OCT;28(20):2465-71.

96. *BRUNVAND L, FUGELSETH D, STENSAETH KH, DAHL-JØRGENSEN K, MARGEIRSDOTTIR HD. EARLY REDUCED MYOCARDIAL DIASTOLIC FUNCTION IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS A POPULATION-BASED STUDY.BMC CARDIOVASC DISORD. 2016 MAY 25;16:103.*

97. *JENSEN MT, SOGAARD P, ANDERSEN HU, BECH J, HANSEN TF, GALATIUS S, JØRGENSEN PG, BIERING-SØRENSEN T, MØGELVANG R, ROSSING P, JENSEN JS.PREVALENCE OF SYSTOLIC AND DIASTOLIC DYSFUNCTION IN PATIENTS WITH TYPE 1 DIABETES WITHOUT KNOWN HEART DISEASE: THE THOUSAND & 1 STUDY.DIABETOLOGIA. 2014 APR;57(4):672-80.*

98. *MARWICK TH, RITCHIE R, SHAW JE, KAYE D. IMPLICATIONS OF UNDERLYING MECHANISMS FOR THE RECOGNITION AND MANAGEMENT OF DIABETIC CARDIOMYOPATHY.J AM COLL CARDIOL. 2018 JAN 23;71(3):339-351.*

99. *SEFEROVIĆ PM, PAULUS WJ. CLINICAL DIABETIC CARDIOMYOPATHY: A TWO-FACED DISEASE WITH RESTRICTIVE AND DILATED PHENOTYPES. EUR HEART J. 2015 JUL 14;36(27):1718-27, 1727A-1727C.*

100. *WAI B, PATEL SK, ORD M, MACISAAC RJ, JERUMS G, SRIVASTAVA PM, BURRELL LM. PREVALENCE, PREDICTORS AND EVOLUTION OF ECHOCARDIOGRAPHICALLY DEFINED CARDIAC ABNORMALITIES IN ADULTS WITH TYPE 1 DIABETES: AN OBSERVATIONAL COHORT STUDY. J DIABETES COMPLICATIONS. 2014 JAN-FEB;28(1):22-8.*

101. *SONG J W, CHUNG KC OBSERVATIONAL STUDIES: COHORT AND CASE-CONTROL STUDIES PLAST RECONSTR SURG. 2010 DEC; 126(6): 2234–2242.*

102. *ZINMAN B, WANNER C, LACHIN JM, FITCHETT D, BLUHMKI E, HANTEL S, MATTHEUS M, DEVINS T, JOHANSEN OE, WOERLE HJ, BROEDL UC, INZUCCHI SE; EMPA-REG OUTCOME INVESTIGATORS.EMPAGLIFLOZIN, CARDIOVASCULAR OUTCOMES, AND MORTALITY IN TYPE 2 DIABETES N ENGL J MED. 2015 NOV 26;373(22):2117-28.*

103. *KOSIBOROD M, CAVENDER M, FU AZ, WILDING JP, KHUNTI 2, HOLL R, NORHAMMAR A, BIRKELAND KI, JØRGENSEN ME, THURESSON M, ARYA N, BODEGÅRD J, HAMMAR N, FENICI P; CVD-REAL INVESTIGATORS AND STUDY GROUP*. LOWER RISK OF HEART FAILURE AND DEATH IN PATIENTS INITIATED ON SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS VERSUS OTHER GLUCOSE-LOWERING DRUGS: THE CVD-REAL STUDY (COMPARATIVE EFFECTIVENESS OF CARDIOVASCULAR OUTCOMES IN NEW USERS OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS). CIRCULATION. 2017 JUL 18;136(3):249-259.*