

Epidemiological Aspects of Cardiovascular Morbidity and Mortality Among Individuals with Diabetes

The Relative Importance of Cardiovascular Risk factors

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Epidemiological aspects of cardiovascular morbidity and mortality among individuals with diabetes: the relative importance of cardiovascular risk factors

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To my family

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ABSTRACT

Background: Long-term trends of cardiovascular complications and death among patients with diabetes have not been studied extensively. In addition, we aimed to examine the effect of multifactorial risk factor control, as well as optimal levels- and relative importance of cardiovascular risk factors, in patients with type 1 diabetes and type 2 diabetes. The analyses for patients with diabetes were compared to the general population.

Method: We used data from the National Diabetes Register along with other Swedish health registries and applied different statistical methods such as survival analysis and different machine learning models to study our research questions. We have focused on the following outcomes: all-cause mortality, acute myocardial infarction, coronary heart disease, cardiovascular disease, stroke and heart failure.

Results: During the period 1998-2014, patients with type 1 diabetes experienced approximately 40% greater relative risk reduction for cardiovascular complications, compared to matched controls, while patients with type 2 diabetes experienced roughly 20% greater risk reduction than their matched controls. A paradoxical finding was the lower relative risk reduction of fatal outcomes in patients with diabetes. Nevertheless, death and complications have decreased substantially during the last two decades.

Multifactorial risk factor control is associated with significant risk reduction for patients with diabetes. Still, patients with type 1 diabetes display 82% and 97% elevated risk for myocardial infarction and heart failure, respectively. For type 2 diabetes, we observed marginally increased risk of death and cardiovascular complications in patients with all risk factor at target level. Moreover, there is a

monotone relationship between number of risk factor at target level and excess risk of outcomes in patients with diabetes. Patients with type 2 diabetes and all risk factors at target level had 16% lower relative risk for myocardial infarction, compared to the general population. The most important risk factors for cardiovascular complications were glycated hemoglobin, physical activity level, systolic blood pressure, low-density lipoprotein cholesterol, albuminuria, as well as risk factors that in some form denote exposure time to the disease (e.g. age, duration of diabetes and age at onset of disease). Lower levels for glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol is associated with reduced risk for cardiovascular complications, compared to matched controls. The relative importance analyses suggest that risk factors contribute differently between outcomes and type of diabetes.

Conclusion: Morbidity and mortality have decreased significantly among individuals with diabetes. Multifactorial risk factor control is associated with significant risk reduction and could perhaps even eliminate the excess risk for cardiovascular disease. Lower levels for selected risk factors than recommended target levels is associated with lower risk for complications. Heart failure is an emerging diabetes-related complication and young individuals with diabetes are at the highest risk of complications.

Keywords: type 1 diabetes mellitus, type 2 diabetes mellitus, cardiovascular epidemiology, cardiovascular medicine, cardiology, epidemiology, all-cause mortality, cardiovascular disease, coronary heart disease, stroke, heart failure, machine learning.

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SAMMANFATTNING PÅ SVENSKA

Vi undersökte långtidstrender i komplikationer och mortalitet bland personer med diabetes, jämfört med matchade kontroller från den allmänna befolkningen. Vi har även studerat möjligheterna att med modern behandling eliminera den förhöjda risken för hjärt-kärlsjukdom och förtida död som medförs av diabetes. Slutligen har vi studerat den relativa betydelsen av kardiovaskulära riskfaktorer samt vilka nivåer som är behäftade med lägst risk för hjärt-kärlsjukdom.

Vi har huvudsakligen fokuserat på komplikationerna akut hjärtinfarkt, stroke, hjärtsvikt, ischemisk hjärtsjukdom, kardiovaskulär sjukdom och död.

Metod

Vi har samkört data från Nationella Diabetes Registret med andra kvalitetsregister för information om komplikationer, socioekonomiska variabler och dödsorsaker. Vi har tillämpat olika statistiska metoder så som överlevnadsanalys och olika maskininlärnings metoder för att studera ovanstående frågeställningar.

Resultat

Under perioden 1998-2014 observerade vi att patienter med typ 1 diabetes upplevde 40 % större riskminskning för icke-fatala kardiovaskulära utfall jämfört med matchade kontroller. Patienter med typ 2 upplevde ungefär 20 % större riskreduktion än kontroller under samma tidsperiod. Ett paradoxalt fynd var att riskminskningen för fatala händelser var likartad hos patienter med typ 1 diabetes och kontroller, medan patienter med typ 2 uppvisade en mindre riskminskning för fatala utfall än deras matchade kontroller. Under de senaste 16 åren har sjukligheten och dödligheten i kardiovaskulära sjukdomar minskat avsevärt hos individer med diabetes.

Patienter med typ 1 diabetes uppvisar en förhöjd risk trots optimal riskfaktorkontroll. Individer med typ 1 diabetes som kontrollerade alla riskfaktorer hade, jämfört med matchade kontroller, 82% ökad risk för akut hjärtinfarkt och 97% ökad risk för hjärtsvikt. Patienter med typ 1 diabetes och flera riskfaktorer uppvisar en förhöjd risk mellan 700-1200% för kardiovaskulär sjuklighet och död, jämfört med kontroller.

För typ 2 diabetes minskade den förhöjda risken för komplikationer stegvis för varje riskfaktor som låg inom terapeutiska målområdet. För patienter med typ 2 med alla riskfaktorer inom målområdet så förelåg ingen nämnvärd ökad risk för död eller stroke men 16% lägre risk för akut hjärtinfarkt. Patienter med diabetes hade högst risk för hjärtsvikt, trots optimal riskfaktor kontroll. De viktigaste riskfaktorerna för kardiovaskulära sjuklighet och död var HbA1c, LDL kolesterol, fysisk inaktivitet och högt blodtryck. Lägre nivåer än dagens rekommenderade riktlinjer för HbA1c och systoliskt blodtryck var associerade med ännu lägre risk för komplikationer bland individer med typ 1 och typ 2 diabetes.

För typ 1 diabetes var HbA1c, följt av diabetesduration och njurfunktion de viktigaste prediktorerna för kardiovaskulära komplikationer.

Slutsats

Morbiditet och mortalitet har minskat avsevärt bland individer med diabetes. Optimal riskfaktorkontroll är associerad med kraftig riskreduktion för kardiovaskulära komplikationer och eliminerar i vissa fall den förhöjda risken. Lägre nivåer än dagens rekommendera riktlinjer för HbA1c och blodtryck är associerat med ännu lägre risk för komplikationer. Unga individer med diabetes har högst risk för komplikationer.

LIST OF PAPERS

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

- I. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, McGuire D.K, Sattar N, Rosengren A, Gudbjörnsdottir S. **Mortality and cardiovascular disease in type 1 and type 2 diabetes.** *The New England Journal of Medicine. N Engl J Med* 2017; 376:1407-1418
- II. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. **Range of risk factor levels: control, mortality, and cardiovascular outcomes in type 1 diabetes mellitus.** *Circulation* 2017 Apr 18;135(16):1522-1531
- III. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A-M, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdottir. **Risk factors, mortality and cardiovascular outcomes in patients with type 2 diabetes.** *The New England Journal of Medicine. N Engl J Med.* 2018 Aug 16;379(7):633-644.
- IV. Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson A-M, Eliasson B, Gudbjörnsdottir S. **Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study.** *Lancet* 2018 Aug 11;392(10146):477-486.
- V. Rawshani A, Rawshani A, Sattar N, Franzén S, McGuire DK, Eliasson B, Svensson A-M, Zethelius B, Miftaraj M, Rosengren A, Gudbjörnsdottir S. **Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes.** *Submitted.*

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ABBREVIATIONS

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
AF	Atrial fibrillation
AMI	Acute myocardial infarction
BMI	Body mass index
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
HF	Heart failure
HR	Hazard ratio
ESRD	End-stage renal disease
IQR	Interquartile range
IPR	Inpatient registry
MI	Myocardial infarction
OPR	Outpatient registry

INTRODUCTION

A brief history of diabetes mellitus

Diabetes mellitus is a complex and heterogeneous metabolic disease that is characterized by persistent hyperglycemia. The disease has a long history stretching back into antiquity. In Ebers papyrus, a preserved medical document dating back to 1,500 B.C, the ancient physicians of Egypt described a condition with excessive thirst and urination that bears resemblance to diabetes.¹

The Indian physicians, Sushruta, and his colleague Charaka (400-500 A.D.), were the first to identify two major categories of diabetes, later to be termed Type 1 and Type 2 diabetes. They recognized diabetes as a syndrome with the hallmark of honey-like urine that affects primarily rich castes with excessive food intake. The Greek physician Aretaeus coined the word diabetes and wrote the first complete description of the disease, first century A.D. He described a disease where affected individuals suffer from polyuria, polydipsia, wasting syndrome and certain death. In 1775, an English physician named Matthew Dobson for the first time identified that glucose was in fact the sweet substance in the urine of patients with diabetes.²

Over the past two centuries, our understanding of the pathogenesis and progression of diabetes has evolved considerably. In 1869, a medical student by the name of Paul Langerhans identified islands of clear cells, which was later named Langerhans islets that differed from the surrounding tissues in the pancreas. Not long afterwards, in 1889, two physicians named Joseph von Mering and Oskar Minkowski experimented on dogs and observed that surgical removal of the pancreas resulted in diabetes. This laid the foundation for Frederick Banting and Charles Best, who in 1921 succeeded in extracting pancreatic gland serum from dogs and administered this extract to diabetic dogs, which resulted in lowering of blood sugar levels. Their success is considered a milestone in the history of medicine. In 1923, the first commercial available insulin product was introduced.

During the 19th century, researchers deciphered gluconeogenesis, glycogenesis and glycogenolysis. Cardiovascular epidemiology began to gain momentum in the 1930s; several studies were set in motion to clarify the cause of cardiovascular disease (CVD). The most famous of these was the Framingham Heart Study, which was initiated in 1948. The Framingham Heart Study was the first to identify several cardiovascular risk factors, including hyperlipidemia, hypertension and diabetes mellitus.

Recent decades have witnessed considerable advances in clinical care paralleled with improved management of risk factors that have transformed diabetes from a fatal illness to a chronic condition. Currently, diabetes is strongly associated with long-term complications such as acute myocardial infarction, stroke, end-stage kidney disease, heart failure and premature death. According to recent research, patients with diabetes have 2 to 5 times greater risk for death and CVD, compared to the general population. This thesis aimed to investigate gaps in knowledge regarding the epidemiological aspects of death and cardiovascular events in patients with diabetes, with a particular focus on the relative importance of cardiovascular risk factors. The following subchapters will briefly describe the current understandings of type 1 diabetes (T1DM) and type 2 diabetes (T2DM).

Type 1 diabetes mellitus

T1DM is a multifactorial disease with both genetic predisposition and environmental factors that triggers an autoimmune response, resulting in T-cell mediated destruction of pancreatic β -cells and immediate need for exogenous insulin therapy. The disease often manifests in children or adolescents, but adults are occasionally also diagnosed with T1DM.

Recent evidence indicates that an inflammatory lesion consisting of immune cells infiltrate the Langerhans islets several years before the onset of T1DM. The progressive loss of β -cells leads to overt T1DM after a latent period. Patients with symptomatic T1DM are believed to have lost approximately 70-90% of their total β -cell mass.^{3,4}

However, not all cases of T1DM are caused by autoimmunity, a minority of the patients with T1DM have no detectable immune response or autoantibodies. A growing body of evidence suggests that these types of T1DM have a strong genetic component. T1DM is the most common form of diabetes in (<15 years of age) and the second most common autoimmune disease in children and adolescents.^{3,5-7}

Epidemiology of T1DM

The epidemiology of T1DM is often described as a conundrum. The incidence and prevalence of the disease varies between countries. Scandinavian countries display the highest incidence in the world in contrast to Asian countries such as China, South Korea and Japan where the incidence is low. The variations in incidence and prevalence of T1DM may be related to genetic predisposition, environmental factors and lifestyle factors such as childhood infections and hygiene.

Genetic studies show that high-risk HLA-DR-DQ genotypes for T1DM, is more common in Scandinavian and European countries compared to Asian countries.⁸ The incidence rates for T1DM tend to be similar between boys and girls, some epidemiological data suggests that the peak in incidence for girls precedes that for boys.^{9,10} Studies from western countries show that incidence increases with age and peaks in pubertal years, according to data from Sweden the incidence peaks between 10-14 years of age.¹¹ The incidence rate drops after pubertal years for girls but remains high in men up to 35 years of age.¹²

Pathophysiology and aetiology of β -cell autoimmunity

T1DM is considered to be an organ-specific autoimmune disease with detectable inflammation surrounding the cells in the Langerhans islets, particularly β -cells. Histological studies reveal a higher concentration of inflammatory cells surrounding the β -cells. T-cell mediated destruction of the pancreatic β -cells results in insulin deficiency. Interaction between T-cells and B-cells lead to formation of autoantibodies, the autoantigens that trigger this molecular process is unknown.

Biomarkers of autoimmunity include autoantibodies that target Langerhans islet cells, molecules such as insulin, glutamic acid decarboxylase (GAD65) or protein tyrosine

phosphatase-like molecules ZNT8, IA-2 and IA-2 β . The first autoantibody that is usually detected in persons with T1DM is GAD65 or insulin specific autoantibodies.¹³

Study of autoantibodies in T1DM will certainly lead to evolved understanding of the aetiology and pathogenesis of this disease. The order of appearance for these autoantibodies is presumably associated with age, genetic differences, environmental- and lifestyle factors.¹⁴ There is a stepwise relationship between increasing numbers of detectable autoantibodies and higher risk of developing symptomatic T1DM. Research indicates that persons who develop T1DM often have autoantibodies many years before the onset of the disease.

Type 2 diabetes mellitus

T2DM is a multifactorial disease that includes some of the following pathophysiological changes: dysregulation of protein, carbohydrate and lipid metabolism, as well as β -cell dysfunction, insulin resistance or a combination of both.¹⁵ It is now believed that impaired insulin secretion from pancreatic β -cells is the main cause of T2DM development, although, peripheral insulin resistance in skeletal muscle, liver and adipose tissue, often accompanies β -cell dysfunction. Eventually, the metabolism and uptake of glucose deteriorates, resulting in elevated blood sugar levels leading to micro- and macrovascular complications. T2DM is far more common than any other type of diabetes and accounts for approximately 90% of all cases with diabetes.

T2DM should be regarded as a heterogeneous disease with varying clinical features that express themselves as different pathophysiological abnormalities, susceptibility of complications and response to therapeutic options.

Epidemiology of type 2 diabetes mellitus

T2DM has become a major public health concern and the International Diabetes Federation estimates that roughly 400 million individuals (9% of the adult population) worldwide suffer from T2DM, the number is expected to rise above 700 million by 2035.¹⁶

Asia has emerged as the area with a rapidly developing T2DM epidemic, India and China are the epicenters of this epidemic. In these countries, the onset of T2DM is characterized by lower BMI and younger age, compared to Western populations.¹⁷ Regional differences in diabetes are thought to be due to genetic susceptibility that might vary between population, socioeconomic factors and poor living conditions.^{18,19} The largest increases in T2DM have been observed in low- and middle-income countries, whereas western countries now experience a plateau in the incidence of T2DM.

Recent evidence suggests that a new phenotype of T2DM is emerging, the prevalence of childhood and adolescent T2DM has increased dramatically in the past two decades.²⁰ Studies suggest that younger individuals with T2DM have increased risk for cardiovascular disease and death, compared to elderly persons with T2DM. The disease is more prevalent in men than women.

Evidence from twin and family studies suggest that there is a genetical basis of T2DM and genome-wide association studies have identified > 100 robust genetical

associations in large population studies, revealing the complex polygenic nature of T2DM.²¹ Genetics most likely play an important role in the development of T2DM, however the recent increase in prevalence and incidence of the disease cannot be explained by novel genetic mutations but rather lifestyle factors such as sedentary lifestyle and poor nutrition.²²

Pathogenesis of type 2 diabetes

Effective insulin action and insulin secretion is fundamental to maintaining normal glucose levels, this feedback loop system does not function properly in patients with T2DM. The consequence of impaired insulin action in insulin-sensitive tissue and dysfunctional insulin secretion is increasing blood glucose levels. The cause of T2DM includes a combination of genetic-, epigenetic- and lifestyle factors that interacts with another.²³

With respect to hyperglycemia, there are other core defects implicated in the pathogenesis of T2DM. In general, patients with T2DM suffer from insulin resistance in the skeletal muscle, liver and adipose tissue, along with impaired insulin secretion by the pancreatic β -cells. Insulin resistance in adipose tissue leads to accelerated lipolysis and elevated free fatty acid levels (FFA), research indicates that increased FFA levels worsens insulin resistance in muscle, liver and β -cells. It is hypothesized that elevated FFA levels contributes greatly to central β -cell dysfunction.

Research shows that β -cells develop a resistance to glucagon-like peptide 1 (GLP-1) in T2DM, this is believed to accelerate β -cell dysfunction even further. The reabsorption of glucose in the kidneys by the sodium/glucose co-transporter 2 (SGLT-2) leads to increased blood glucose levels and exacerbates the underlying insulin resistance. Moreover, individuals with type 2 diabetes often develop resistance to appetite-regulating neurohormones such as insulin, GLP-1, amylin and peptide YY, leading to weight gain and progression of the disease.

In 1990, researchers reported that a cytokine called tumor necrosis factor- α , which is created by adipocytes and overproduced in obesity, could attenuate metabolism locally and systemically.^{24,25} Consequently, other scientists started examining the relationship between inflammation and metabolic diseases such as T2DM, metabolic syndrome and obesity. Dramatic understanding of the link between inflammation and T2DM followed and numerous cytokines and adipokines were discovered in the following years.

T2DM is associated with obesity and insulin resistance, two conditions that are linked to systemic inflammation. Histological examination of adipose tissue reveals macrophage infiltration around adipocytes and increased secretion of pro-inflammatory cytokines that contribute to chronic systemic inflammation in T2DM. Still, the exact physiological event that resulted in activation of the immune system in obesity remains incompletely understood.

Blood glucose and organ damage

Dysglycemia, the hallmark of diabetes mellitus is presumably the most important factor in this disease and causes organ damage through several proposed

pathways.^{26,27} This leads to micro- and macrovascular complications through the activation of several known pathways, although the exact molecular mechanisms are not fully understood. Vascular and interstitial organ damage is presumably caused from increased formation of advanced glycation end products (AGEs), increased expression of AGE receptors, the polyol pathway, activation of PKC isoforms, increased hexosamine fluctuations and higher intracellular levels of reactive oxygen species (ROS).^{28,29}

Diabetes-related complications

Diabetes-related complications are divided into acute and chronic conditions. Acute complications include the following; diabetes ketoacidosis, hyperglycemic hyperosmolar state, hypoglycemia and diabetes coma. Chronic complications are divided into micro- and macrovascular complications that represent a wide spectrum of different disorder. The macrovascular complications include acute myocardial infarction (AMI), coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease (PAD), whereas microvascular complications include nephropathy, retinopathy, neuropathy and autonomic neuropathic disease.

Patients with T1DM predominantly suffer from CHD, which reflects the accelerated atherosclerotic process in the coronary vasculature of these patients.^{30,31} Epidemiological studies suggest that all cardiovascular complications are declining in patients with diabetes, perhaps with the exception of heart failure. Recent randomized trials and epidemiological observation studies suggest that heart failure is an emerging and probably forgotten diabetes-related complication.³²

In order to decrease the risk for micro- and macrovascular complications, a multifaceted management strategy is necessary. This includes intensive insulin therapy, nutritional awareness, healthy diet, and regular physical exercise. Lifestyle changes and management of cardiovascular risk factors such as hypertension, dyslipidemia, hyperglycemia and overweight is fundamental to diabetes care. A favorable risk factor profile reduces the risk for morbidity and mortality among individuals with diabetes.

The link between diabetes and cardiovascular disease

Cardiovascular disease was uncommon during the beginning of the 19th century, however as some parts of the world underwent industrialization and subsequent lifestyle changes, the prevalence of these diseases increased. During the 1970's the prevalence of cardiovascular disease culminated in the industrialized parts of the world and the 20th century witnessed a rapid increase particularly of fatal CHD. Today, cardiovascular disease is the leading cause of death among individuals with diabetes.

In 1948, Ernest Millard and Howard Root observed that persons with diabetes and poor glucose control have more severe retinopathy than other patients. Molecular research and epidemiological studies in diabetes had implicated hyperglycemia in the pathogenesis of long-term complications, but previous clinical trials had not demonstrated a consistent or convincing beneficial effect of intensive insulin therapy. In 1993, the DCCT was the first study to demonstrate that normalization of glycemic

control by means of intensive insulin therapy reduced the risk of neuropathy, nephropathy and retinopathy by 35% to 70% in patients with insulin-dependent diabetes mellitus (IDDM).

In 1974, the Framingham heart study established diabetes mellitus as a risk factor for cardiovascular complications, their study demonstrated that men and women with diabetes had two and five times elevated risk of heart failure, as compared with non-diabetic individuals. In 1979, the Framingham study demonstrated that patients with diabetes had a twofold to threefold increased risk of intermittent claudication, congestive heart failure and coronary heart disease.³³ Since the publication of these findings, numerous studies were initiated in order to study the epidemiology of diabetes and CVD. Currently, there is an abundance of epidemiological studies that demonstrate an elevated relative risk for CVD among patients with diabetes.³⁴⁻³⁷ The highest relative risk has been shown for CHD and heart failure,³⁸ while some epidemiological reports suggest that diabetes may be protective for some vascular conditions such as hemorrhagic stroke or aortic dissection.³⁹

Coronary mortality has declined substantially in patients with diabetes, both in absolute and relative risks. Between 1990 and 2010, incidence rate of acute myocardial infarction in the US declined from 141 to 46 per 10,000 (68%), while for stroke it declined from 112 to 53 (53%).³⁶

Heart failure has often been neglected as a cardiovascular complication of diabetes, but is now increasingly being recognized. Diabetes mellitus contributes to the development of heart failure through several proposed pathways, beyond the obvious risk of developing ischemic heart disease and hypertension, which both cause heart failure. It is believed that hyperglycemia directly affects the myocardium in a negative way. Elevated blood sugar levels could contribute to non-ischemic fibrotic remodeling of the myocardium, which leads to heart failure. The EMPA-REG study reported that empagliflozin, a sodium-glucose co-transporter-2 inhibitor (SGLT-2) – *that increases the excretion of glucose and sodium in the kidneys* – brought about a 34% reduction in the risk of heart failure in patients with T2DM.³²

Multifactorial risk factor intervention

Patients with diabetes have an increased risk for death and cardiovascular complications, as compared with diabetes free individuals. There are multiple modifiable risk factors for chronic complications in patients with diabetes. For instance hypertension, hyperlipidemia, hyperglycemia, smoking and arguably even albuminuria are modifiable risk factors.⁴⁰⁻⁴² Prospective data on the benefits of multifactorial risk factor intervention in patients with diabetes is sparse. Current guidelines and estimations of treatment effects are based on studies examining one or two risk factors, not the whole range of risk factors.

Randomized clinical trials have extensively evaluated the effect of treating individual risk factors in studies such as The United Kingdom Prospective Diabetes Study (UKPDS), Collaborative Atorvastatin Diabetes Study (CARDS), the Diabetes Control and Complications Trial (DCCT) etc.⁴³⁻⁴⁷

Persons with diabetes are reported to on average have a 2 to 5-fold increased risk of cardiovascular disease (CVD) and death compared to the general population. Even with a glycated hemoglobin level below the target level of 6.9% (52 mmol/mol), the

risk of cardiovascular disease and mortality is still on average twice that of the general population.^{27,48} Based on the results from clinical trials, the American Diabetes Association and other national guideline committees recommend a multifactorial treatment approach.

However, few studies have evaluated the effect of multifactorial risk factor control aimed at several modifiable risk factors in patients with diabetes.^{42,49} Moreover, the preventive strategies for cardiovascular disease in persons with T1DM is sometimes extrapolated from clinical trials based on persons with T2DM. These research questions are therefore even less studied in T1DM.

The Steno-2 study was one of the first clinical trials to evaluate the effect of multifactorial risk factor intervention among patients with T2DM. This unique clinical trial evaluated the cumulative effect of behavior modification and polypharmacological therapy aimed at several modifiable risk factors. The study revealed that multiple risk factor intervention reduced the risk of cardiovascular events among patients with T2DM and microalbuminuria. The Steno-2 study reported a 20% relative risk reduction of cardiovascular events among those with multifactorial risk factor intervention. This magnitude of effect is higher than what is usually observed in studies that apply single-factor interventions.^{40,50,51}

Patients (in Steno-2) receiving intensive multiple risk factor intervention had a significantly greater reduction of systolic and diastolic blood pressure, serum cholesterol, triglyceride levels and urinary albumin excretion. This presumably explains the reduction in risk of cardiovascular events observed among these individuals.⁴⁰ The Steno-2 study also reported a relative risk reduction for CV death by 46% (hazard ratio, 0.54; 95% CI, 0.32 to 0.89).⁴⁰ The Steno-2 studies were not designed to identify which elements of intensive diabetes therapy that contributed most to the reduction in cardiovascular risk.

Nevertheless, the Steno-2 Study only included 160 study participants and the study design precludes the possibility to link observed benefits to achievement of specific treatment targets. Hower et al, observed benefits of tighter cholesterol and blood pressure target on carotid atherosclerosis in the SANDS (stop Atherosclerosis in Native Diabetics study) trial.⁵² The ACCORD trial showed that aggressive treatment of hyperglycemia among patients with T2DM resulted in increased risk for mortality but not cardiovascular events.⁵³ The INVEST study suggested small but significant increases in mortality among patients with diabetes and CHD who achieved systolic blood pressure <130 mm hg compared with less stringent control.⁵⁴

The BARI 2D study was initiated to compensate for shortcomings of the Steno-2 study.⁴⁹ The BARI 2D study included patients with T2DM with angiographically documented stable CHD. This study evaluated the effect of multiple risk factor control during 13 years of follow-up. BARI 2D evaluated 6 risk factors but observed that there is a plateau of benefit at 5 risk factors under control with only a small increase in risk among those who had 6 risk factors under control.

Thus, the evidence base for multifactorial risk factor control is sparse. We therefore aimed to examine the relative risk of multifactorial risk factor control in a nationwide cohort of patients with diabetes, compared to matched controls from the general population.

AIMS

The aim of this thesis was to study the long-term trends of mortality and morbidity among patients with diabetes, and the relative importance of cardiovascular risk factors. The specific aims of the individual studies are listed below.

- I. Investigate long-term trends in incidence and risk of all-cause mortality and cardiovascular outcomes among patients with diabetes, compared to age-, sex- and county matched controls from the general population.
- II. To analyze if the excess risk of death and cardiovascular outcomes in persons with T1DM can be eliminated by means of optimal risk factor control. To investigate the benefit of maintaining risk factors within therapeutic guideline target levels.
- III. To analyze which risk factors that appears to be the most important in primary prevention of persons with T2DM. Also, we investigated the benefit of multiple risk factor control as well as optimal levels for three selected risk factor in persons with T2DM. Similar to the second paper, we explored the possibilities to eliminate excess risk by means of optimal risk factor control in T2DM.
- IV. To examine if age of onset of T1DM is an important risk stratifier and how this factor relates to excess risk for mortality and cardiovascular events. To assess differences in risk between women and men with T1DM, according to age at onset of disease.
- V. To examine which risk factors that appears to be most important for predicting death and cardiovascular events among persons with T1DM. Similar to the third paper, we examined the optimal level for three selected risk factors.

PATIENTS AND METHODS

Study registries

This thesis includes information from several national health registries. The main data source is the National Diabetes Register (NDR). Due to the unique Swedish personal identification number we have the possibility to link data from the following national health registries: the Swedish Inpatient and Outpatient Registry (IPR and OPR), Cause of Death Registry and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA).

The NDR was initiated in 1996 and includes information on clinical characteristics, risk factors, laboratory analyses, complications of diabetes, and medications for patients 18 years of age or older. The registry includes more than 500,000 individuals with diabetes. Each patient provides informed consent for inclusion in the register, and virtually all patients in Sweden with diabetes are included. More than 95% of all individuals with T1DM and 90% of individuals with T2DM in Sweden are included in the NDR.

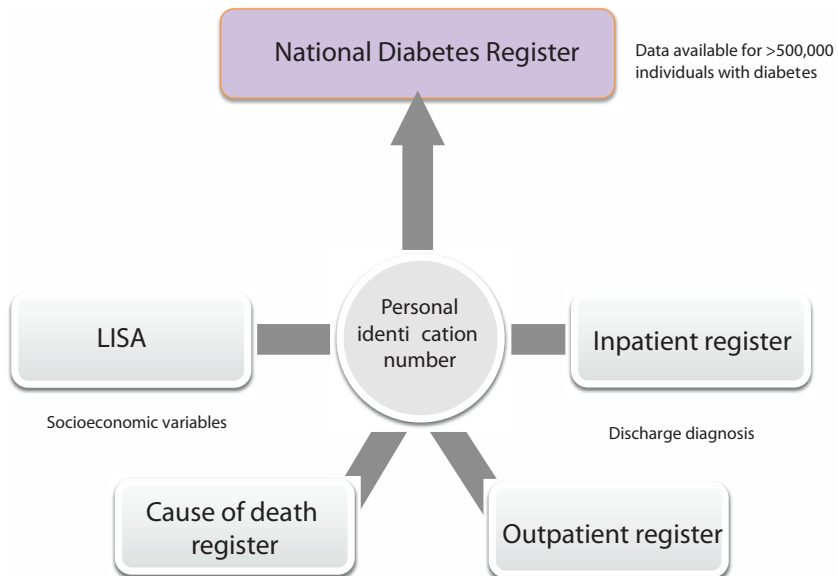


Figure 1. Schematic figure of all health registries that were included

The Cause of Death Register provides information for date and cause of death, the registry had complete coverage since 1961. The IPR and OPR include all inpatient- and outpatient diagnoses with complete coverage since 1987. The LISA database provides information about socioeconomic status (education, income, occupation and ethnicity) with complete coverage since 1990.

We included patients with diabetes that were ≥ 18 years or older and registered in the NDR between January 1, 1998 – December 31, 2012. Approximately 430,000 patients with T2DM and 37,000 patients with T1DM were included in the analyses of this thesis. All studies were approved by the Regional Ethics Review Board of Gothenburg, Sweden (**diary numbers: epn 563-12**).

Outcomes

Information on cardiovascular events and deaths were retrieved by linking data to the Swedish Inpatient Register and the Cause of Death register, using the 9th and 10th revision for International classification of disease (ICD). We assess the following ICD-codes: coronary heart disease (410-414 [ICD-9], I20-I25 [ICD-10], of which 410 and I21 coded acute myocardial infarction); stroke (431-434, 436 [ICD-9], I61-I64 [ICD-10]) and hospitalization for heart failure (428 [ICD-9], I50 [ICD-10]).

In addition to the abovementioned outcomes, we include other outcomes for mainly two reasons, the outcome is either specified as an exclusion criteria or adjusted for as a comorbidity, we included the following outcomes: atrial fibrillation (427D [ICD-9], I48 [ICD-10]), end-stage kidney disease (V42A, V45B, V56A, V56W [ICD-9], Z940, Z491, Z492, Z992 [ICD-10]) and amputation (NHQ09, NHQ11, NHQ12, NHQ13, NHQ14, NHQ16, NHQ17, NHQ99, NGQ09, NGQ19, NGQ99, Nfq19, Nfq99 [ICD-10]).

We analyzed both fatal and non-fatal outcomes in each study, for fatal outcomes we included up to 5 contributory causes for fatal outcomes and up to 7 contributory causes for non-fatal outcomes. The sensitivity and specificity for these diagnoses have been validated previously.⁵⁵

Definition of type 1 diabetes and type 2 diabetes

The studies in this thesis are based on the main two forms of diabetes mellitus, namely T1DM and T2DM. T1DM was defined using the epidemiologic definition: treatment with insulin and diagnosis at ≤ 30 years of age. T2DM was also defined using the epidemiologic definition: treatment with diet with or without the use of oral antihyperglycemic agents or treatment with insulin with or without the use of oral antihyperglycemic agents; the latter category only applied to patients who were 40 years of age or older at the time of diabetes diagnosis.

The concordance between the epidemiological definitions and clinicians classification have been scrutinized previously, the concordance among patients diagnosed with diabetes before 2004 and 2009 was 96% and 95%, respectively.

Statistical methods

This thesis includes several statistical approaches that address different research questions. A brief discussion of the statistical methods follows.

In Study I, we used a Cox regression model that includes the following covariates: age, gender, a discrete variable termed type (i.e. either patient with diabetes or matched control) and a continuous variable termed *time-period*. Also, we included two interaction terms in these Cox models. The first interaction variable was between type and time-period (*type*time-period*), which allows us to evaluate the changes in relative risk between patients with diabetes and matched controls. The second interaction includes type with age and gender, since we believe that these variables should exert separate effects on the Cox model for patients with diabetes and matched

controls. In addition, we assessed age and sex standardized incidence rates for patients with diabetes and matched controls.

The variable *time-period* consisted of two consecutive calendar years. Therefore we exponentiated the interaction variable *type*time-period* by 5 to estimate a ten-year relative rate reduction, we applied the same method for confidence intervals.

In Study II, we constructed 6 groups according to number of risk factors that were within therapeutic guideline target levels (0 to 5 risk factors). These risk factors included glycated hemoglobin, systolic and diastolic blood pressure, hyperlipidemia, smoking status and renal function. Thereafter, we calculate crude incidence rates as number of events per 10,000 persons-years of observation for death and cardiovascular events according to number of risk factors within target levels in patients with T1DM. Also, we used Cox regression to estimate the risk of each outcome among persons with T1DM, compared to matched controls. These regression models were adjusted for income, education, marital status, immigrant status, age, duration of diabetes and status at baseline with regard to a history of conditions. The models were stratified on sex to allow for different underlying baseline hazards for men and women.

In Study III, we investigated three separate research questions. We constructed a Cox model to estimate the excess risk in people with T2DM in relation to the number of risk factors within target range. As for T1DM, number of factors within target ranged from 0 to 5. These models were stratified on sex and we used age as the time-scale. Socioeconomic variables such as income, education, marital status and country of origin were also included in these models. These regression models did not include physical activity, body mass index and the use of statins or antihypertensive medications since the data are not available for matched controls.

In the first ancillary analysis, we evaluated the relative importance of multiple risk factors. There are different statistical approaches to estimate the relative importance for covariates in a regression model. We used statistical methods that were available for Cox regression (explained relative risk [R^2] and the Chi-square method), A strong risk factor will contribute more to the predictive ability, compared with a less strong predictor.

In these Cox models, the variable age was used as the time-scale. When age was included as a covariate in the Cox model it outperformed all other predictors by far (displaying the largest R^2). The second application available to assess relative importance of risk factors in the cox model is the explained log-likelihood of each predictor. This statistical model estimates the partial effect of each risk factor by quantifying the proportion of explainable log-likelihood explained by each risk factor.

In the third ancillary analyses, we used a Cox model with restricted cubic splines for continuous variables to assess the hazard function for different values for risk factor. We set the guideline target levels as reference values for each risk factor. The risk factors that were studied were the following: glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol. For glycated hemoglobin we used 53 mmol/mol (7.0%), for systolic blood pressure 140 mmHg and for low-density lipoprotein cholesterol 2.5 mmol/L.

In Study IV, we used Cox regression to analyze the association between age at diagnosis of T1DM and risk of outcomes. The regression models included age as the time-scale, gender, socioeconomic variables, duration of diabetes and previous histories of cardiovascular events. Persons with T1DM were categorized into five groups according to age at diagnosis.

In Study V, we used Cox regression and machine-learning models to assess the relative importance of risk factors among persons with T1DM. In addition, we set out to investigate the association of different levels for the selected risk factors glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol. The cox regression models that we used in this study are virtually identical to the cox models in **Study III**.

Machine learning models are robust statistical tools to assess relative importance of risk factors, particularly when the number of features (predictors) is large. We constructed machine learning models referred to as random survival forest and gradient boosting, which are supervised ensemble techniques that deploy decision trees to predict the response variable. The algorithm includes evaluations of variable importance at each split (node) in the tree. The predictive value of each risk factor is averaged from all trees to estimate the relative importance of each predictor. A significant advantage of machine learning is the inherent capability to detect and handle higher-order interactions and non-linearity in the data.

Imputation of missing data

Epidemiological studies often involves handling of missing data, researchers can chose to study complete cases only or use imputation techniques to maximize power and avoid selection bias. We used an imputation method called multivariate imputation by chained equations (MICE) to impute datasets with complete data. First, MICE impute each missing variable with mean values. The model creates linear and logistic regression for all variables to predict coefficients for missing values, using the complete dataset. We compared the result from imputation with different imputation methods and mean values for risk factors, before and after imputations.

RESULTS

Study I: Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Reports show that incidence rates of death and cardiovascular events have declined among persons with and without diabetes. Our primary objective was to compare the change in relative risk of outcomes over time, between patients

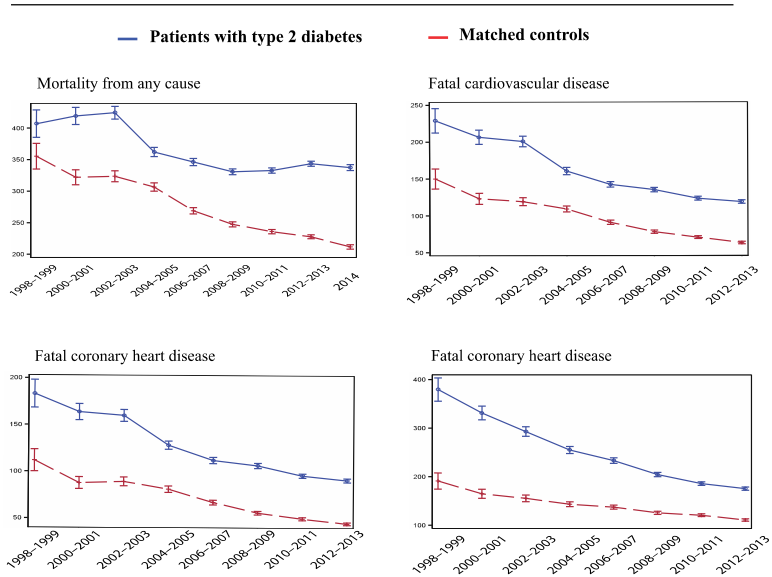


Figure 2. Cardiovascular outcomes and death among patients with type 2 diabetes and matched controls. Standardized incidence rates per 10,000 person-years.

with diabetes and matched controls. The analysis revealed substantial decreases in relative risk for persons with and without diabetes. Patients with diabetes had a significantly greater relative risk reduction for non-fatal cardiovascular events. We did not observe this for fatal outcomes, patients with T1DM had comparable relative risk reduction as matched controls.

Patients with T2DM had more than 20% greater relative risk reduction for non-fatal cardiovascular outcomes, compared to matched controls. For patients with T2DM, we report that the general population experienced almost 10% greater risk reduction than patients with diabetes. This paradoxical finding is to our knowledge a previously unknown feature in cardiovascular epidemiology for patients with T2DM.

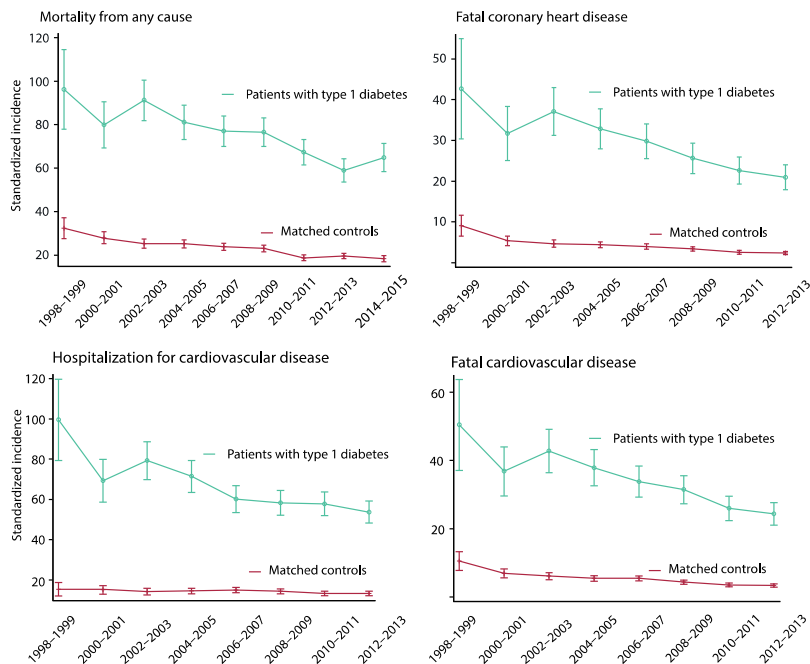


Figure 3. Cardiovascular outcomes in patients with type 1 diabetes and matched controls were matched for age, sex and county. Standardized incidence rates per 10,000 person-years.

Mortality among patients with T2DM changes by -69.6 deaths (95% CI, -95.9 to -43.2) per 10,000 person-years. In matched controls, mortality was -134.7 deaths (95% CI, -145.2 to -124.1) per 10,000 person-years. Patients with T2DM, continue to display an excess risk for CVD and death, compared to matched controls. Hospitalization for cardiovascular disease experienced the greatest relative risk reduction out of all outcomes in patients with T2DM.

Death among patients with T1DM was -31.4 deaths (95% CI, -56.1 to -6.7) per 10,000 person-years. Hospitalization for CHD experienced the greatest absolute decline out of all outcomes in patients with T1DM, -69.6 (95% CI, -97.7 to -41.5) per 10,000 person-years.

A combination of standardized incidence rates and cox models offers a unique opportunity to assess this research question accurately. It is sometimes challenging to determine the absolute change in incidence rates for cardiovascular events and death in patients with diabetes and matched controls. We used cox models to estimate the relative risk reduction in all study participants. Moreover, the cox model allows us to compare the change in relative risk over time, between patients with diabetes and matched controls.

Table 1. Adjusted Hazard Ratios and 95% Confidence Intervals for Outcomes in Patients with Type 2 and Type 1 diabetes. First time-period versus Last time-period and Ratio of Hazard Ratios Comparing Patients with Diabetes versus Matched Controls.*

Outcomes	Patients with type 1 diabetes, Matched Controls		Patients with type 1 diabetes versus Matched Controls		Patients with type 2 diabetes, Matched Controls		Patients with type 2 diabetes versus Matched Controls	
	Hazard ratio during a 10-year period		Hazard Ratio	<i>p-value for interaction</i>	Hazard ratio during a 10-year period		Hazard Ratio	<i>p-value for interaction</i>
Death								
All-cause mortality	0.71 (0.66, 0.78)	0.77 (0.72, 0.83)	1.08 (0.99, 1.18)	0.086	0.79 (0.78, 0.80)	0.69 (0.68, 0.70)	0.87 (0.85, 0.89)	<0.0001
Cardiovascular disease	0.58 (0.50, 0.68)	0.62 (0.53, 0.72)	1.06 (0.89, 1.26)	0.53	0.54 (0.52, 0.55)	0.50 (0.49, 0.52)	0.94 (0.90, 0.98)	0.0036
Coronary heart disease	0.56 (0.48, 0.67)	0.55 (0.46, 0.65)	0.97 (0.80, 1.18)	0.74	0.52 (0.50, 0.53)	0.48 (0.46, 0.50)	0.94 (0.89, 0.98)	0.0093
Hospitalization								
Cardiovascular disease	0.64 (0.56, 0.72)	0.91 (0.82, 1.01)	1.43 (1.25, 1.62)	<0.0001	0.56 (0.54, 0.57)	0.71 (0.68, 0.73)	1.27 (1.22, 1.32)	<0.0001
Myocardial infarction	0.63 (0.55, 0.73)	0.87 (0.75, 1.00)	1.37 (1.16, 1.62)	0.0002	0.50 (0.48, 0.52)	0.62 (0.59, 0.65)	1.24 (1.18, 1.31)	<0.0001
Coronary heart disease	0.56 (0.50, 0.64)	0.78 (0.70, 0.87)	1.39 (1.22, 1.58)	<0.0001	0.55 (0.53, 0.57)	0.67 (0.65, 0.69)	1.22 (1.17, 1.27)	<0.0001
Stroke	0.65 (0.55, 0.77)	0.95 (0.82, 1.10)	1.47 (1.22, 1.76)	<0.0001	0.61 (0.59, 0.63)	0.76 (0.73, 0.79)	1.24 (1.18, 1.31)	<0.0001
Heart failure	0.87 (0.74, 1.01)	1.01 (0.86, 1.18)	1.16 (0.97, 1.40)	0.10	0.71 (0.69, 0.73)	0.84 (0.81, 0.87)	1.18 (1.12, 1.23)	<0.0001

* The analysis was based on a Cox regression model that was adjusted for time-updated age, time-updated time period, sex and interaction terms.
^ These values are ratios of hazard ratios for patients with diabetes, compared to matched controls during a 10-year time period. A value above 1 means greater event rate reduction in patients with diabetes than in matched controls.

This table shows the relative risk reduction for outcomes among patients with diabetes and matched controls. Each hazard ratio represents the change in relative risk for a ten-year period. We compare the change in relative risk over time between patients and matched controls by incorporating an interaction term (*type*time-period*). As an example, the risk reduction for fatal CHD among patients with T1DM was not

significantly greater than matched controls (HR, 0.97; 95% CI, 0.80 to 1.18). In contrast, non-fatal CHD declined by 39% more in patients with T1DM than matched controls (HR 1.39; 95%, 1.22 to 1.76). Patients with T2DM experienced a 27% greater relative risk reduction for non-fatal CVD, compared to matched controls (hazard ratio 1.27; 95%, 1.22 to 1.32).

Study II: Range of risk factor levels/controls, mortality and cardiovascular outcomes in type 1 diabetes

Observational studies have recently established that persons with T1DM with glycated hemoglobin levels below therapeutic target levels of 6.9% (52 mmol/mol), still have increased risk for cardiovascular events and death, compared to matched controls.

We therefore decided to study the possibilities of reducing or eliminating excess risk for CVD and mortality in patients with T1DM, by means of multifactorial risk factor control.

This cohort comprised of 33,333 persons with T1DM and 166,529 matched controls. Patients were categorized into 6 groups, based on number of risk factors at target level, ranging from 0–5 risk factors. We investigated the following risk factors: glycated hemoglobin, systolic- and diastolic blood pressure, low-density lipoprotein cholesterol, smoking and renal function (i.e. micro- and macroalbuminuria).

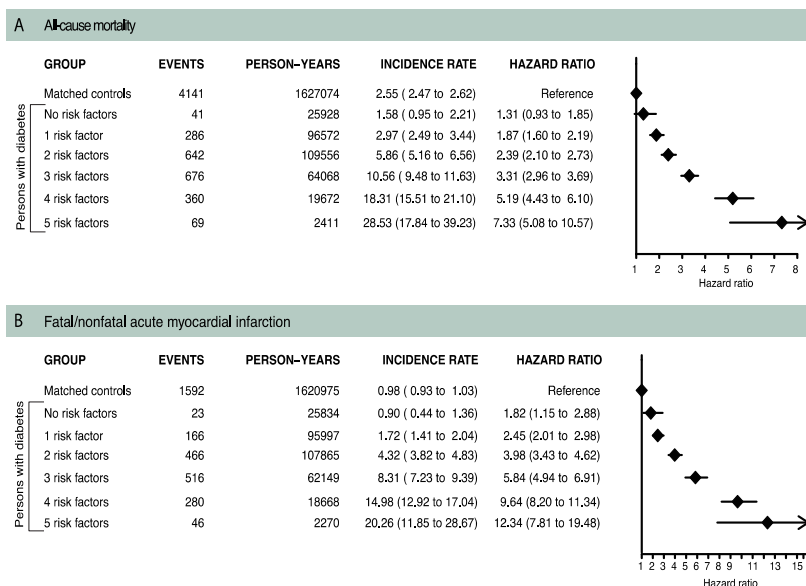


Figure 4. Adjusted hazard ratio for death and myocardial infarction according to number of risk factors at target in patients with type 1 diabetes, compared to matched controls.

Incidence rate for all-cause mortality in persons with T1DM with all risk factors within therapeutic target level was 1.58 (95% CI, 0.95 to 2.21) death per 1000 person-years, the adjusted hazard ratio for mortality in this patient group was 1.31 (95% CI, 0.93 to 1.85). The hazard ratio for patients with diabetes and none of the 5 risk factors at target level was 7.33 (95% CI, 5.08 to 10.57).

Persons with T1DM, with all risk factors within therapeutic target levels continued to display an elevated risk for acute myocardial infarction and hospitalization for heart failure, 1.82 HR (95% CI, 1.15 to 2.88) and 1.97 HR (95% CI, 1.04 to 3.73) respectively. Patients with T1DM appear to have greatest risk for hospitalization for heart failure, irrespective of the number of risk factors at target. We performed a subanalysis and studied the risk of mortality in patients with T1DM, for men and

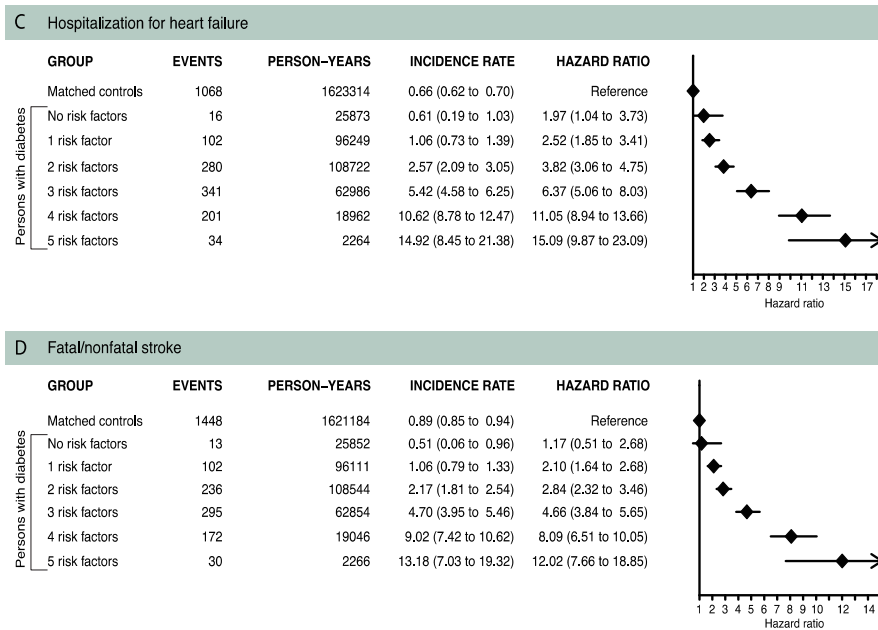


Figure 5. Adjusted hazard ratios for hospitalization for heart failure and stroke according to number of risk factors at target in patients with type 1 diabetes, compared to matched controls

women. The adjusted hazard ratios were very similar between both genders. Our analysis of multifactorial risk factor control in patients with T1DM revealed a monotone relationship between increasing number of risk factors and increasing risk for outcomes.

Study III: Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes

The importance of multifactorial risk factor intervention in patients with T2DM has been studied sparsely. The Steno-2 research group analyzed cumulative risk reduction from multifactorial risk factor intervention, compared to standard care for selected cardiovascular risk factors. Their findings suggest that multifactorial risk factor

intervention leads to risk reduction for all-cause mortality, micro- and macrovascular complications and amelioration of several cardiovascular risk factors.^{40,42,50,51}

A drawback of these studies was the small study cohort that included less than 400 study participants. The Steno-2 studies investigated the effect of multifactorial risk factor intervention against all risk factors concurrently, compared to standard care for all risk factors. Our study used a nationwide cohort of patients with T2DM to study the risk of death and cardiovascular outcomes for each risk factor within therapeutic target level. We studied the following risk factors: glycated hemoglobin, blood pressure, low-density lipoprotein cholesterol, smoking status and renal function (i.e. micro- and macroalbuminuria).

After applying exclusion criteria, the analyses included 271,174 patients with T2DM and 1,355,870 matched controls.

Numbers of risk factors at target

Our findings show that persons with T2DM and all risk factors at target had marginally increased risk for death and stroke, while risk for acute myocardial infarction was lower than matched controls. In patients with T2DM and all risk factors at target, the risk for mortality was HR 1.06 (95% CI, 1.00 to 1.12) and for acute myocardial infarction HR 0.84 (95% CI, 0.75 to 0.93). Patient with T2DM seems to have highest risk for hospitalization of heart failure, even with all risk factors at target, patients with diabetes have 45% (HR 1.45 (95% CI, 1.34 to 1.57) excess risk for heart failure compared to matched controls.

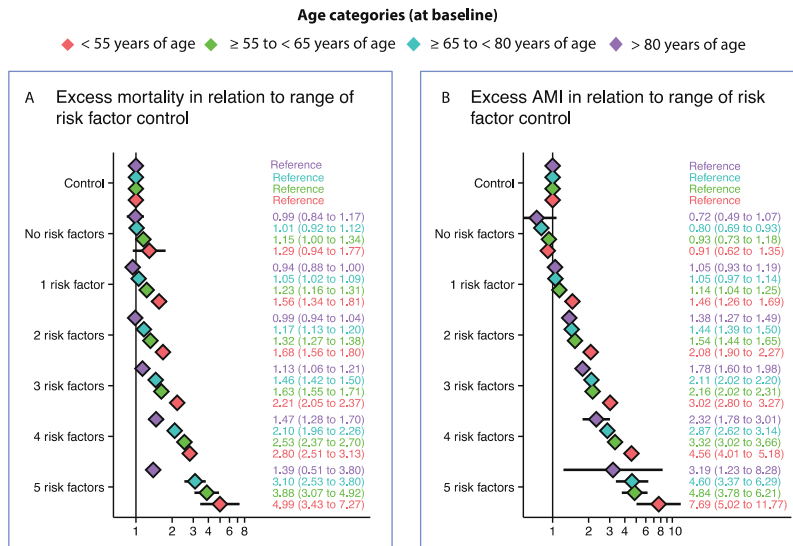


Figure 6. Adjusted hazard ratios for death and myocardial infarction according to age at baseline and number of risk factors within target level in patients with type 2 diabetes, compared to matched controls

Our analyses demonstrate a monotone relationship between increasing number of risk factors within therapeutic target level and lower risk for death and cardiovascular outcomes. Patients with T2DM with none of the 5 risk factors within target level have about 500–1800% excess risk for death and cardiovascular events. In addition, we noticed a monotone relationship between younger age at baseline in patients with T2DM and increased risk for outcomes.

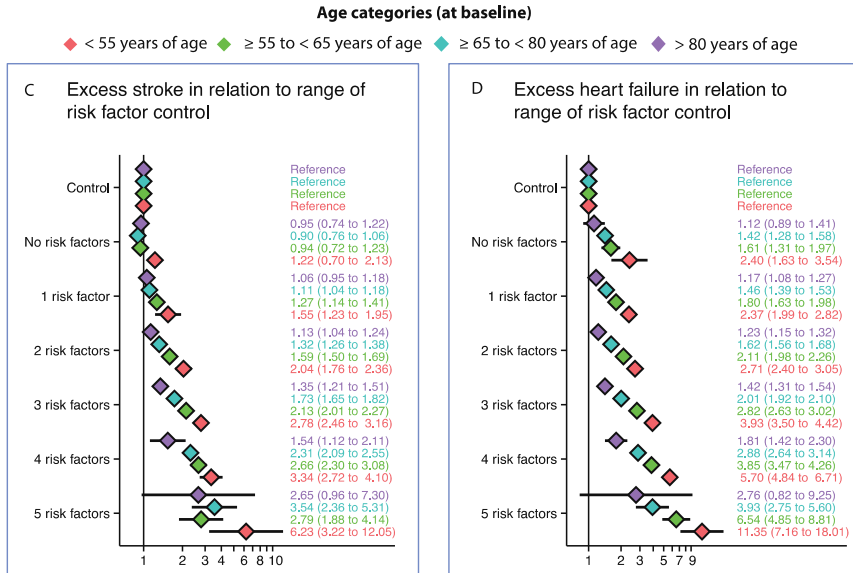


Figure 7. Adjusted hazard ratios for stroke and heart failure according to age at baseline and number of risk factors within target level in patients with type 2 diabetes, compared to matched controls

Adolescents with T2DM (<55 years of age) had highest risk for death and cardiovascular, out of all age groups, irrespective of the number of risk factors at target. We did not observe excess risk for outcomes in elderly individuals with T2DM (≥80 years of age or older), hazard ratios for this patient group was at most, marginally increased.

Strength of association for risk factors

In an ancillary analysis, we studied the strength of association of every risk factor to identify the strongest predictor for cardiovascular disease and death. We used two specific applications for the Cox model to estimate the relative importance of each risk factor. Our analyses reveals that low physical activity, glycated hemoglobin, systolic blood pressure, low-density lipoprotein cholesterol and smoking are the most important predictors for cardiovascular disease and death in patients with T2DM.

We performed these analyses in two different cohorts for patients with T2DM, one cohort with and without previous CVD at baseline. For premature death, smoking, low physical activity and marital status were the strongest predictors, these results were evident in both cohorts.

For acute myocardial infarction, glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol were the strongest predictors. The strength of association analysis showed virtually similar results for myocardial infarction and stroke, with the exception of duration of diabetes and low physical activity that were more important predictors for stroke than myocardial infarction.

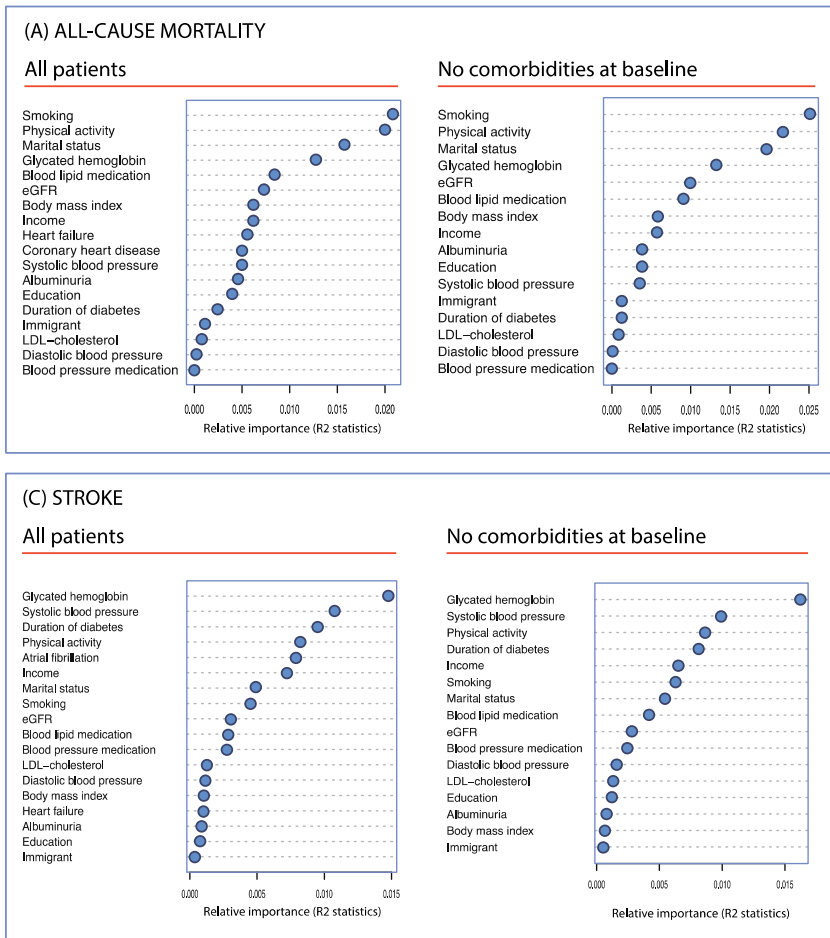


Figure 8. Strength of association of risk factors for death and stroke among patients with type 2 diabetes

For heart failure, there was a clear difference between the cohorts with and without comorbidities at baseline. In persons with T2DM and history of conditions at baseline, the strongest predictor for hospitalization of heart failure was atrial fibrillation. In a cohort without comorbidities at baseline, the strongest risk factors proved to be body mass index, glycated hemoglobin and low physical activity.

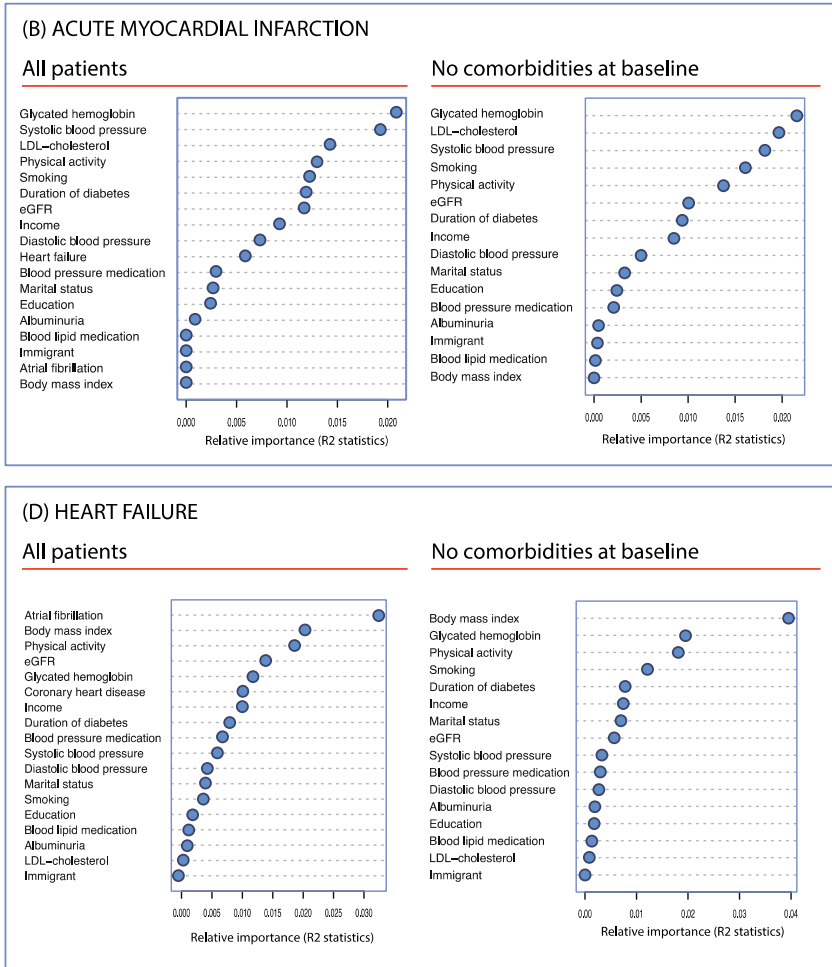


Figure 9. Strength of association of risk factors for myocardial infarction and heart failure among patients with type 2 diabetes

Optimal levels for selected risk factors

In the second ancillary analysis, we constructed cox models with restricted cubic splines for continuous covariates. Our primary objective was to analyze risk for death and cardiovascular events according to various levels of three selected risk factors.

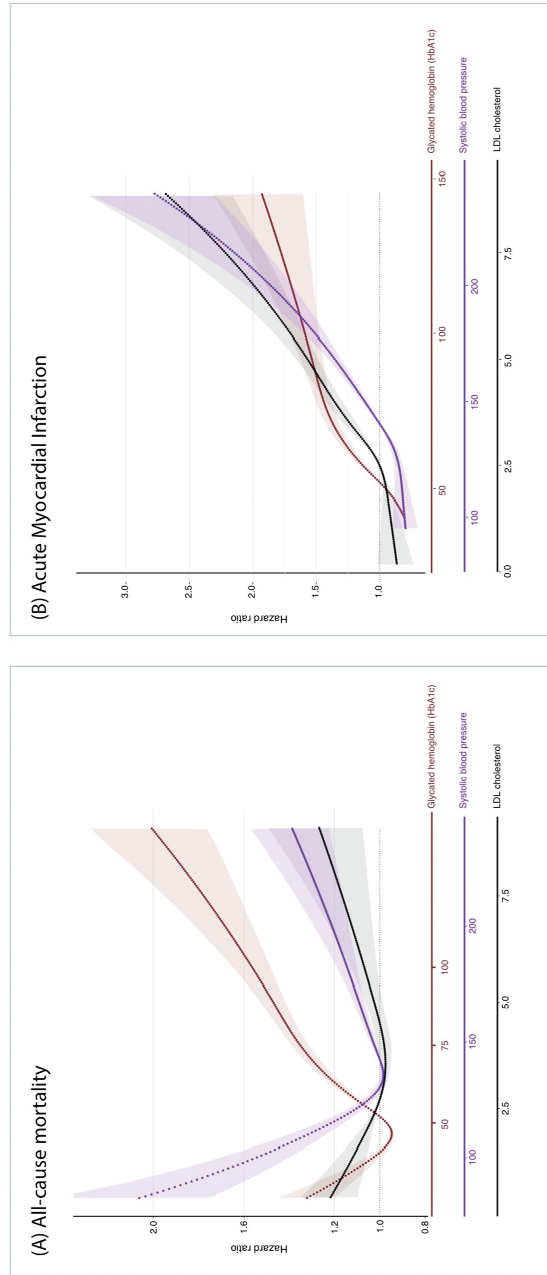


Figure 10. Risk associated with varying levels of glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol for all-cause mortality and acute myocardial infarction in patients with type 2 diabetes

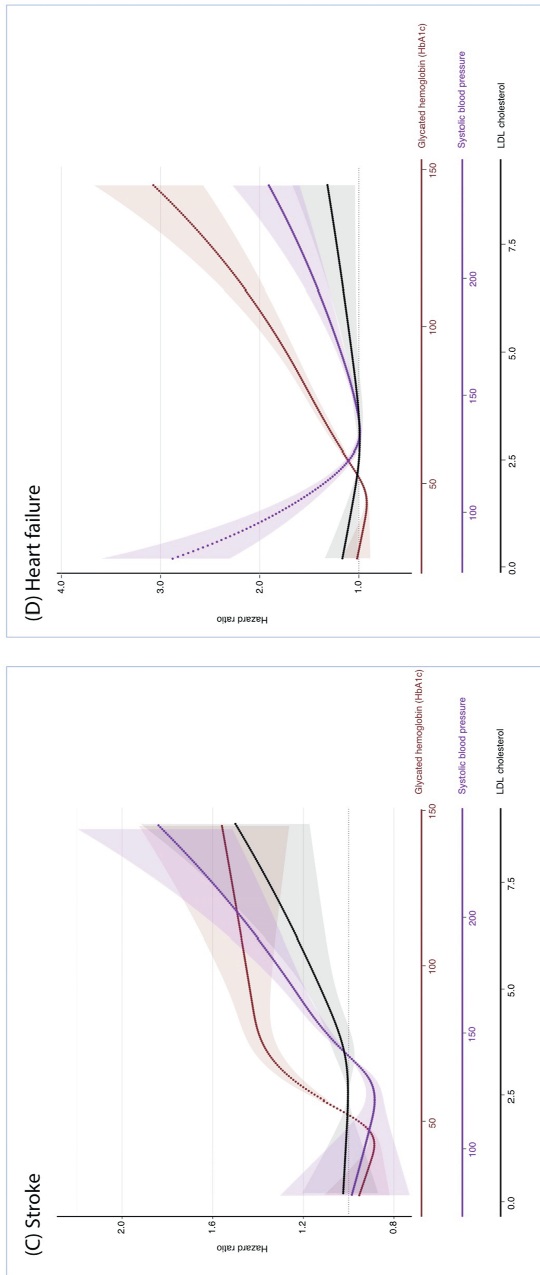


Figure 11. Risk associated with varying levels of glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol for stroke and heart failure in patients with type 2 diabetes

We investigated the following risk factors: glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol. According to our models, these three risk factors display non-linear association with mortality and heart failure, whereas the risk of myocardial infarction and stroke displays a fairly linear relationship with these risk factors. Increasing levels of glycated hemoglobin seemed to be associated with most prominent increase in risk for mortality, stroke and heart failure.

Increasing values for these three risk factors displayed almost a linear relationship with AMI. Moreover, lower levels than recommended target levels were associated with reduced risk for myocardial infarction. For stroke and AMI we notice a plateau after a certain level for glycated hemoglobin, whereas systolic blood pressure and low-density lipoprotein cholesterol displays a clear linear relationship for increasing levels.

For stroke, we observed that lower levels of glycated hemoglobin and systolic blood pressure were associated with significant risk reduction in patients with T2DM. For heart failure, increasing levels of glycated hemoglobin displayed a clear association with increasing risk. A clear non-linear association is only seen for systolic blood pressure in all-cause mortality and heart failure.

Study IV: Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide register-based cohort study

Age at onset of diabetes is presumably an important factor for death and CVD in T1DM, but this variable is not considered in current risk mitigation strategies. Therefore, we set out to determine to contribution of age at onset as a risk factor for cardiovascular events and death in individuals with T1DM.

We performed all analyses for patients with T1DM and compared them with matched controls. Our analyses shows that persons with T1DM with disease onset before 10

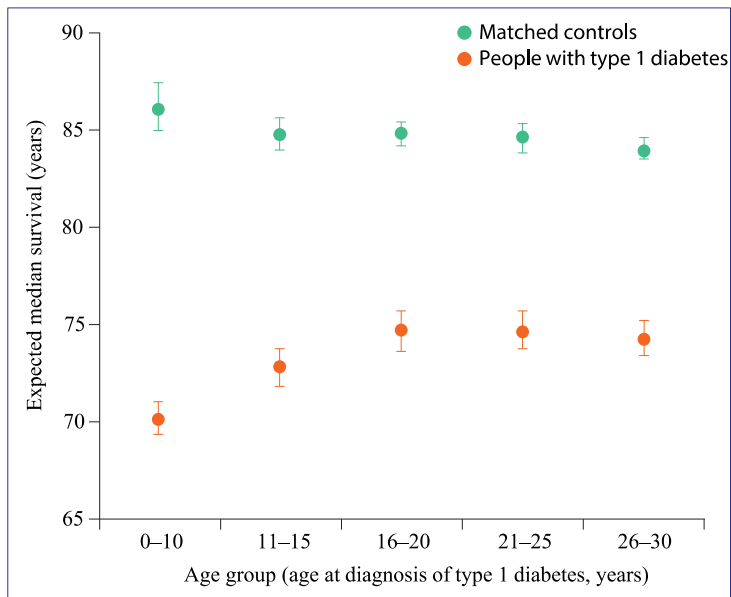


Figure 12. Expected median survival for age at onset of type 1 diabetes compared to matched controls

years of age had 30-times increased risk of AMI, women with T1DM had 60-times increased risk for CHD and 90-times higher risk for myocardial infarction. Onset of T1DM at 25–30 years of age was associated in approximately 5-times lower risk of death and CVD, compared to the age group 0-10 years.

Moreover, we constructed cox models to assess conditional mean survival, which showed that patients with T1DM lost several life-years from their disease. Patients with T1DM that were diagnosed before 10 years of age had 16.0 life-years lost due to their disease, life-expectancy seems to be shorter in women with T1DM. The conditional mean survival increases in patients with higher age at onset of diabetes.

The adjusted hazard ratio for mortality was highest in the youngest age group and the risk decreased in a stepwise fashion with increasing age. Comparable results were seen for cardiovascular mortality. Patients with onset of disease before 10 years of age have 30-times higher risk for CHD (HR 30.50 (95% CI, 19.98 to 46.57)), corresponding hazard ratios for heart failure is HR 12.90 (95% CI, 7.39 to 22.51).

We observed significant differences in risk for cardiovascular outcomes and death between women and men. Being a woman with T1DM seems to be associated with higher risk for cardiovascular events and death, compared with men.

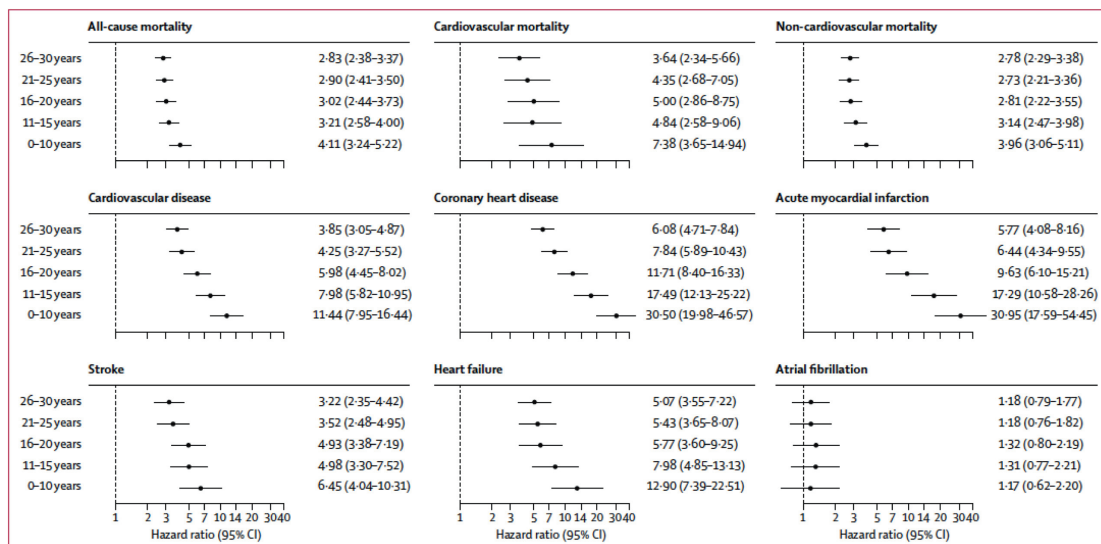


Figure 13. Adjusted hazard ratios for age at onset of type 1 diabetes for mortality and other cardiovascular outcomes

Women with T1DM had particularly high risk for CHD and AMI, hazard ratio 58.73 (95% CI, 28.86 to 119.55) and hazard ratio 92.07 (95% CI, 32.72 to 253.47), respectively.

Men with T1DM had greater risk for developing heart failure, compared to women. Also, we studied the causes of death and noticed that circulatory- and endocrine causes of death are the most common causes of death among persons with T1DM, and the prevalence of these outcomes increases in younger age groups.

Study V: Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes

We investigated the strength of association for risk factors and varying levels of glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol for cardiovascular events and death, in patients with T1DM.

We used two developed applications for the cox proportional hazards model with two separate machine learning models, to accurately assess the relative importance of risk factors among patients with T1DM. The cohort that we studied included 32,611 patients with T1DM.

The results show that age was the strongest predictor for death and CV outcomes. Risk factors that capture some element of time (e.g. age, age at onset of diabetes or duration of diabetes) all demonstrated elevated strength of association. Glycated hemoglobin and albuminuria were the two risk factors that had highest relative importance measure, second to age. Income and systolic blood pressure were also strong predictors for mortality. The strongest predictors for myocardial infarction were duration of diabetes, LDL-C and glycated hemoglobin.

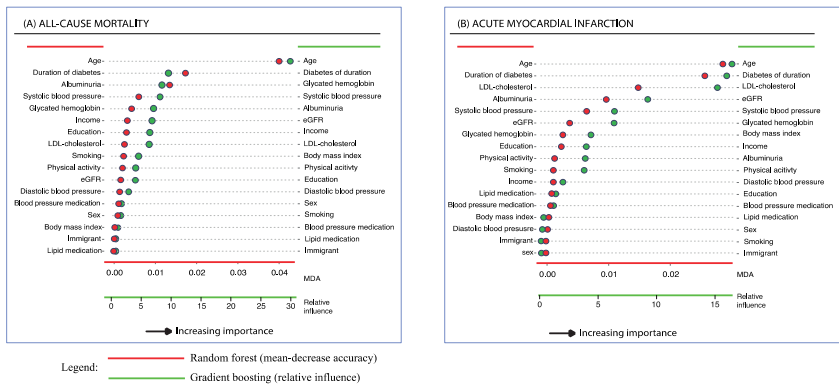


Figure 14. Strength of association of risk factors for mortality and myocardial infarction in patients with type 1 diabetes according to machine learning models random forest and gradient boosting

Our machine learning models suggest that duration of diabetes, albuminuria and systolic blood pressure interact with glycated hemoglobin. For each mmol/l higher LDL-C, the risk for myocardial infarction increased with 47% (HR 1.47; 95% CI, 1.39 to 1.55). We observed rather similar findings for stroke and myocardial infarction, with the exception of systolic blood pressure and low physical activity level that were more associated with stroke. Each unit increase in systolic blood pressure was associated with 1.5% increase in hazard ratio (HR 1.015; 95% CI, 1.011 to 1.02), equating to 16% (12–20%) risk difference for each 10-mmHg increase.

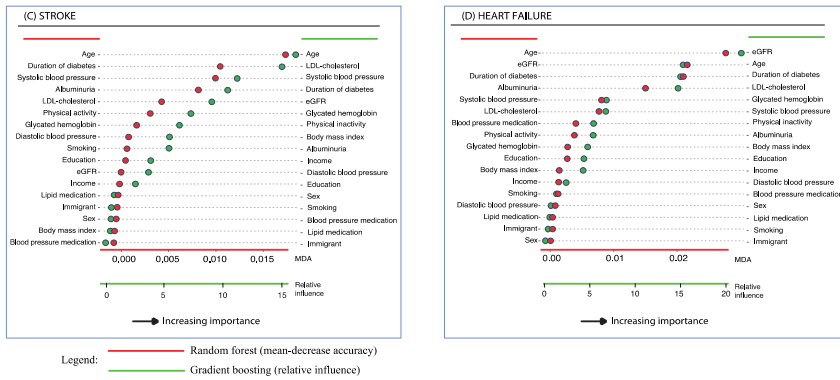


Figure 15. Strength of association of risk factors for stroke and heart failure in patients with type 1 diabetes according to machine learning models random forest and gradient boosting.

The strength of association for risk factors is quite similar between the cox models and machine learning analyses. Bear in mind, that the machine learning analyses takes higher-dimensional interactions into account, meaning that other risk factors could interact and modify the strength of association for other risk factors.

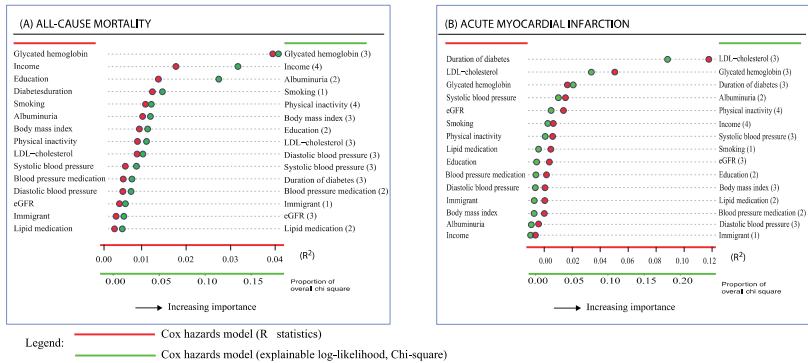


Figure 16. Strength of association of risk factors for mortality and acute myocardial infarction in patients with type 1 diabetes according to the explained relative risk model (R²) and the explained log-likelihood model

According to our models, risk factors that denote some kind of exposure time, e.g. age, age at onset of diabetes and duration of diabetes, all interact and modify the strength of association for risk factors.

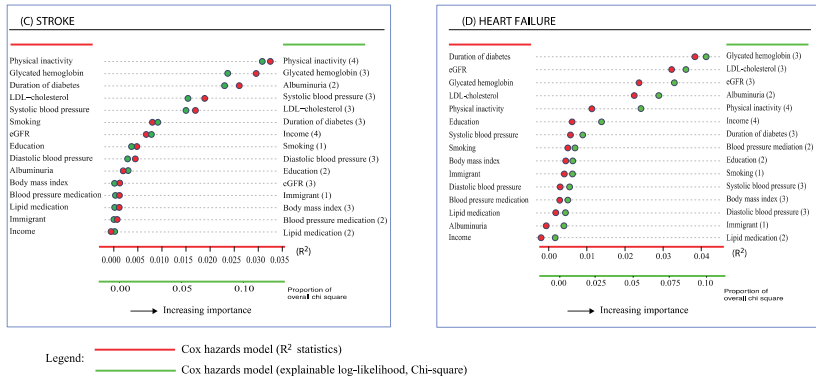


Figure 17. Strength of association of risk factors for stroke and heart failure in patients with type 1 diabetes according to the explained relative risk model (R^2) and explained log-likelihood model.

In a complementary analysis, we excluded age and duration of diabetes as predictors from the machine learning models. This gives us the opportunity to compare strength of association for risk factors in a model with and without these strong interacting predictors.

The complementary analysis showed that systolic blood pressure and eGFR increased significantly in strength of association when age and duration of diabetes are omitted from the machine learning analyses.

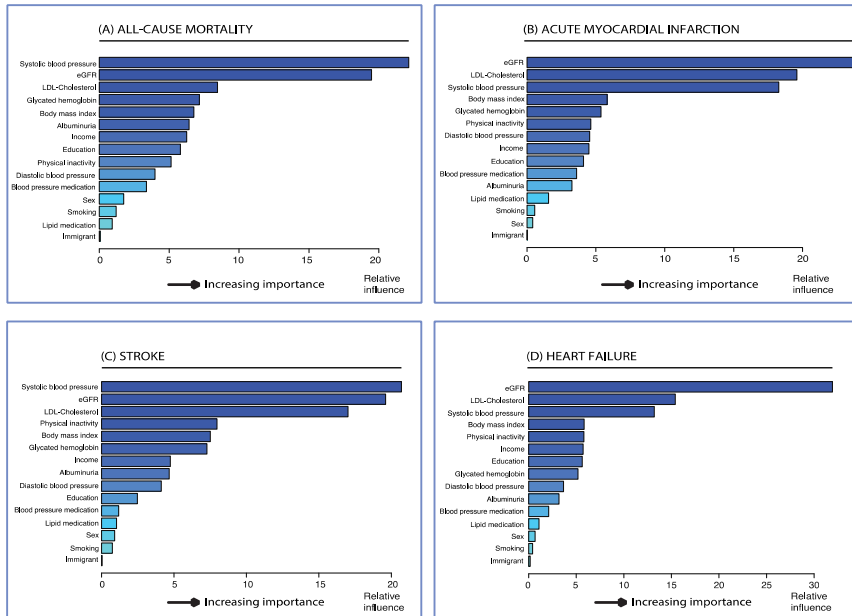


Figure 18. Strength of association of risk factors, according to gradient boosting without age and duration of diabetes for outcomes in patients with type 1 diabetes

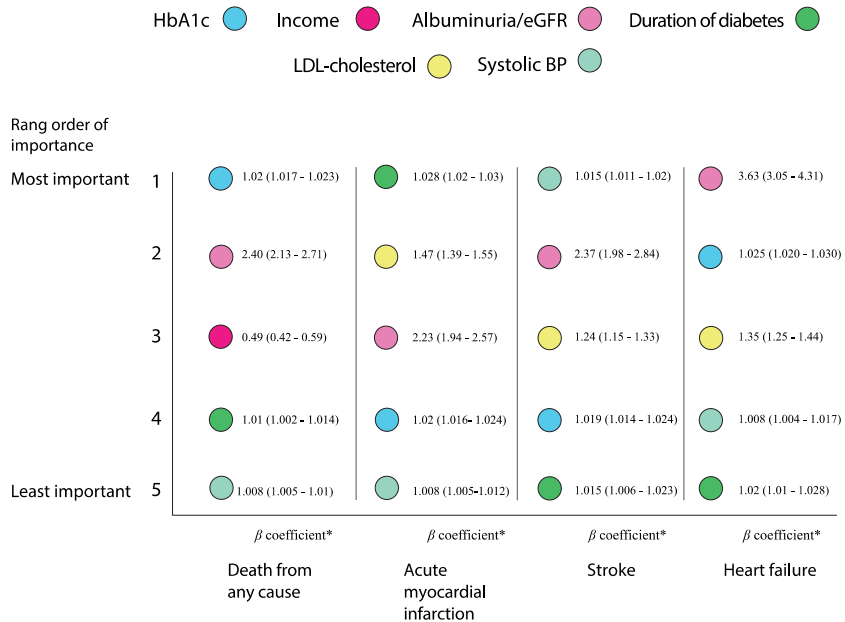
The importance of glycated hemoglobin decreases for all outcomes, in machine learning models that does not include age and duration of diabetes, see Figure 21 for more details. The effect of glycated hemoglobin is maybe partly mediated through the predictor's duration of diabetes and age.

In a final analysis on strength of association for risk factors, we averaged the relative contribution of each risk factor to their respective model, and calculated an average from all four statistical models and for each outcome. The averaged relative contribution of each risk factor for each outcome was termed *relative importance*, see figure 18 for more details. It is difficult to compare results between the cox models and machine learning analyses.

Predictors for mortality & cardiovascular complications

RISK FACTOR	RANG
Albuminuria/eGFR	1
HbA1c	2
Duration of diabetes	3
Systolic BP	4
LDL-cholesterol	5

Different model building for the relative importance analyses showed that all these risk factors interacted significantly with age and duration of diabetes



Legend: The strength of association for predictors was ranked according to highest relative contribution of each risk factor in every model and outcome. In addition to the relative importance of risk factors, we estimated unstandardized regression coefficient* with the Cox model, standardized coefficients would enable direct comparison between relative importance of predictors, but this was not possible since albuminuria is a categorical variable.

Figure 19. The relative importance of risk factors for cardiovascular outcomes and death among patients with type 1 diabetes. This figure is based on the relative contribution from all statistical models.

Analysis of optimal levels for risk factors in patients with T1DM

Similar to **study III**, we analyzed the associated risk for varying levels of the selected risk factors, glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol. Lower levels for systolic blood pressure and low-density lipoprotein cholesterol below current guideline levels were associated with lower risk for cardiovascular events and death.

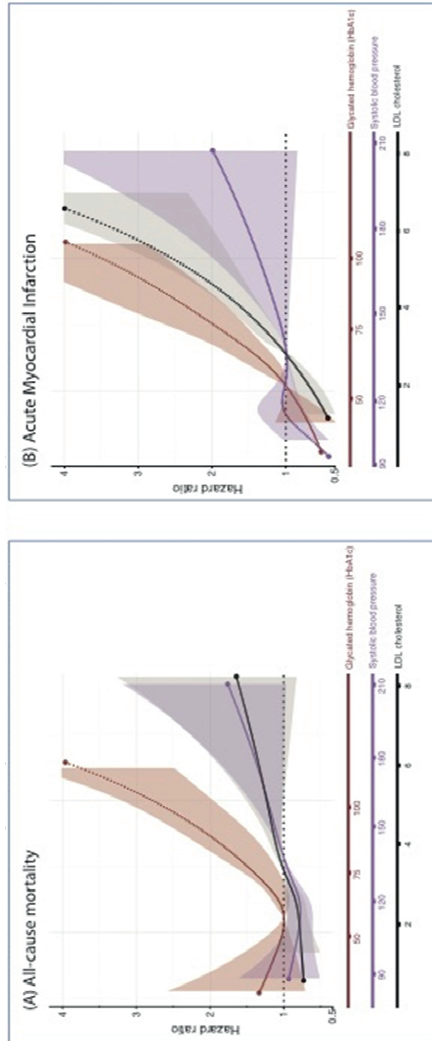


Figure 20. Association between varying levels of glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol and risk for all-cause mortality and myocardial infarction in patients with type 1 diabetes

Lower levels of glycated hemoglobin than current target levels is associated with lower risk for myocardial infarction, stroke and heart failure, however, glycated hemoglobin displayed a U-shaped relationship for mortality. We observed a linear relationship between these risk factors and myocardial infarction.

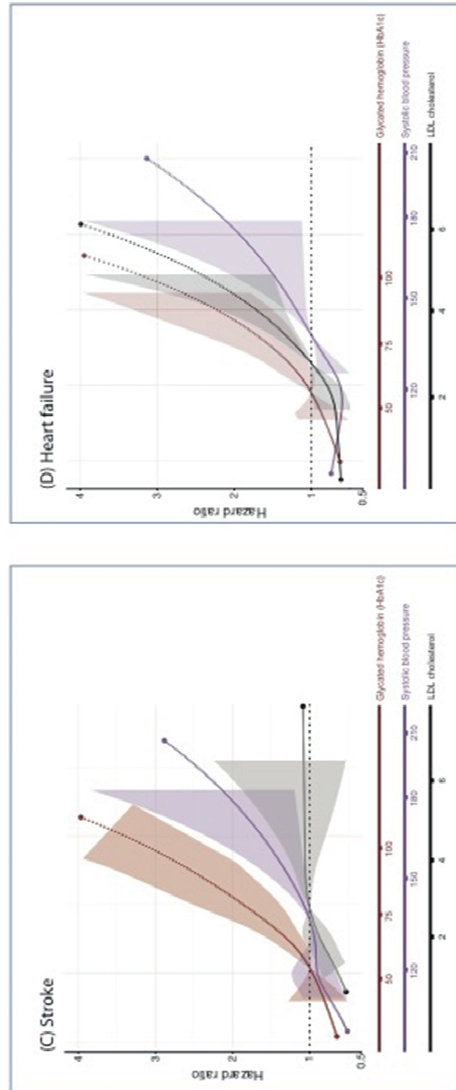


Figure 21. Association between varying levels of glycated hemoglobin, systolic blood pressure and low-density lipoprotein for stroke and heart failure among patients with type 1 diabetes

DISCUSSION

Two decades of continual decline in cardiovascular events and death

We report significant reductions in incidence and risk of cardiovascular outcomes and mortality in patients with diabetes and the general population. Our analysis shows that the reduction in relative risk of fatal outcomes was not significantly different between patients with T1DM and matched controls, whereas patients with T2DM experienced a significantly lower relative risk reduction of fatal outcomes, compared to their matched controls. For non-fatal outcomes, the relative risk declined by roughly 20-40% more in patients with diabetes, compared to matched controls. Patients with diabetes continue to display 2 to 4 times elevated risk for all cardiovascular outcomes and death, compared to the general population.

Our findings are consistent with long-term trends in death and cardiovascular disease associated with diabetes in North America and Western Europe.^{36,38,56,57} The incidence and risk for heart failure did not decline significantly among patients with T1DM or their matched controls, while patients with T2DM experienced a greater risk reduction compared to matched controls. These findings are noteworthy since major risk factors for heart failure such as coronary heart disease, blood pressure levels and macroalbuminuria has decreased to a greater extent in patients with T1DM compared to patients with T2DM. There are several hypotheses for the increased risk for heart failure in patients with diabetes, our observations suggest that there are biological processes that we lack sufficient understanding of and treat less well.

The reduction in cardiovascular outcomes and death reflects a combination of advances in clinical care and patient management of diabetes. Two research studies showed that the most attributable factors for the decline in CHD is improvement in cardiovascular risk factors, approximately 50% of the decline in this outcome was explained by risk factors.^{58,59} According to our data, rates of cardiovascular risk factors are gradually decreasing in patients with diabetes. Mean baseline glycated hemoglobin levels changed from 66.2 to 68.4 mmol/mol for type 1 diabetes, and from 60.2 to 56.7 mmol/mol in patients with type 2 diabetes.

Previous studies from the NDR has showed a significant decrease in glycated hemoglobin levels from 1998 to 2006, afterwards mean glycated hemoglobin levels began to increase in the type 1 diabetes population. The increase from 2006 and onwards is presumably a result of three influential randomized clinical trials, namely ACCORD, ADVANCE and VADT, whose result were likely extrapolated to patients with T1DM.^{53,60,61} Significant changes were also observed for low-density lipoprotein cholesterol, prevalence of macroalbuminuria, systolic blood pressure and increased usage of antihypertensive and statin medications.

In summary, the study demonstrates that patients with diabetes, including the general population, have experienced a substantial reduction for cardiovascular disease and mortality during the last two decades. Interestingly, we observed a paradoxical finding between fatal and non-fatal events for patients with type 1 diabetes and type 2 diabetes, compared to controls. Explaining the decrease of cardiovascular disease and mortality is imperative in order to understand success factors and plan for future risk mitigation strategies.

Multifactorial risk factor control in type 1 diabetes

Our research group recently demonstrated the effect of having glycated hemoglobin levels below recommended guidelines levels <6.9% (<52mmol/mol) in type 1 diabetes, and reported that these patients continued to display on average 2 times greater risk for cardiovascular events and death.²⁷ Therefore, we selected 5 modifiable and traditional risk factors to assess whether maintaining these predictors within therapeutic target range would be associated with reduced or eliminated excess risk for cardiovascular events and death. We compared these results with matched controls from the general population.

This study indicates that patients with T1DM with all risk factors at target level, still display 97% and 82% excess risk for heart failure and acute myocardial infarction, respectively. We observed a non-significant excess risk for all-cause mortality and stroke, the lack of statistical significance is most likely due to low statistical power. We identified a monotone association between the number of risk factor not at target levels and increased risk for outcomes. Poor risk factor control in patients with T1DM is associated with 7 to 15 times greater risk for outcomes, compared to matched controls.

A possible explanation for the excess risk of myocardial infarction is hyperglycemia. For instance, patients with T1DM that have all risk factors within target range, still have on average higher glycated hemoglobin levels than matched controls without diabetes. Moreover, recommended target levels for glycated hemoglobin in patients with T1DM is still higher than the average glycated hemoglobin level in an individual without diabetes. Hyperglycemia accelerates the atherosclerotic process in coronary arteries and the average duration of diabetes in this study is 17 years at baseline, meaning that all study participants with diabetes have been exposed to, at least, slightly elevated glycated hemoglobin levels for many years.

The abovementioned hypothesis is also applicable to our results for heart failure. Recent evidence suggests that hyperglycemia leads to heart failure through numerous mechanisms. Elevated blood glucose levels leads to the development of coronary heart disease, acute myocardial infarction, hypertension and macroalbuminuria that all contribute to the development to heart failure. In addition to these pathophysiological processes, hyperglycemia could also be a causal risk factor for heart failure. Molecular research indicates that hyperglycemia leads to interstitial fibrotic remodeling of the myocardium, a condition that is associated with diastolic dysfunction and eventually heart failure.

Another possible explanation for the increased risk of myocardial infarction and heart failure could be the residual risk observed in diabetics with hypertension and hyperlipidemia that were treated to target levels with statins and antihypertensive medications. Research suggests that inflammation and perhaps other processes could explain the residual risk in patients with risk factor control as a result of pharmacological treatment. Our study suggests that multifactorial risk factor control and perhaps intensive risk factor therapy is necessary to further reduce or eliminate excess risk for myocardial infarction and heart failure in patients with T1DM. The increased use of lipid lowering treatments, antihypertensive medication and insulin pumps will likely reduce the excess risk of all cardiovascular outcomes, including heart failure.

A holistic approach to risk factors in type 2 diabetes

In this comprehensive epidemiological study we report that multifactorial risk factor control in patients with T2DM is associated with, at most, marginally increased risk for cardiovascular events and death, compared to the general population. Our analysis even indicates that attaining all 5 selected risk factors at target level can eliminate excess risk for myocardial infarction.

Interestingly, we observe a stepwise association between younger age, increasing numbers of risk factors at baseline, and greater risk for events. This emphasizes the importance of multifactorial risk factor control and intensive risk factor therapy in younger individuals (<55 years of age) with T2DM. There is still an elevated risk for heart failure in patients with T2DM, even with all 5 risk factors at target level. Our analysis of multifactorial risk factor control does not specify which risk factor that is most important to control for preventing future cardiovascular disease and death among patients with T2DM. Therefore, we sought to investigate the strength of association for risk factors to determine which predictor that contributes most to the outcomes.

The results show that physical activity, smoking, glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol contributes most to cardiovascular events and death. This analysis reveals several interesting pathophysiological differences between these outcomes. For instance, glycated hemoglobin is the strongest predictor for myocardial infarction and stroke, followed by systolic blood pressure and low-density lipoprotein cholesterol. Moreover, smoking, physical activity, marital status followed by glycated hemoglobin, seems to be the most important risk factor for death, whereas body mass index, glycated hemoglobin and physical activity are the strongest risk factors for heart failure. Clinical studies that have investigated the effect of increased physical activity have yet failed to demonstrate a beneficial effect from increased physical activity level. Nevertheless, epidemiological studies repeatedly demonstrate the importance of physical activity level.⁶²⁻⁶⁴

The most important risk factors for heart failure are atrial fibrillation, body mass index, glycated hemoglobin and renal function. In our complementary analysis we studied a population without atrial fibrillation at baseline, which showed that body mass index is the strongest predictor, followed by glycated hemoglobin and physical activity, suggesting that a cardio-renal mechanism contributes to heart failure in patients with T2DM. Overweight and obesity, along with elevated glycated hemoglobin levels, leads to increasing hemodynamic stress through greater hemodynamic load, fluid retention, weight gain and electrolyte disorders.

In our final research question regarding risk factors in patients with T2DM, we investigated the possibilities to reduce risk with lower levels than recommended target levels for the selected risk factors, glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol. Our results show that lower levels for systolic blood pressure is associated with lower levels for cardiovascular outcomes and death. The SPRING study and observational studies have showed that systolic blood pressure levels below target levels results in reduced risk for outcomes. The ACCORD blood pressure trial examined systolic blood pressure levels <120 mmHg vs. <140 mmHg, without a significant effect on intensive blood pressure control.^{53,65-}

In this article, we attempted to answer fundamental questions regarding risk factors for patients with T2DM. In summary, our findings suggest that multifactorial risk factor control is imperative for reducing excess risk for cardiovascular events and death, moreover, intensive multifactorial risk factor control seems even more important for young individuals with T2DM. The strongest risk factors for outcomes were physical activity, smoking, glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol. Our real-world data analysis shows that lower levels for glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol, than recommended target levels are associated with reduced risk for outcomes.

Age at onset of type 1 diabetes

Age of onset is a presumably an important variable for cardiovascular disease and death that carries information about important factors such as total glycemic load, varying autoimmune activity, genetic differences and differences in clinical care due to age.

Therefore, we investigated the association of age at onset of disease in patients with T1DM. We noticed substantial differences in risk between different groups of age at onset. Patients with T1DM with disease onset before 10 years of age had 30 times greater risk of AMI, whereas women with T1DM had 60 times increased risk for CHD and 90 times increased risk for AMI.

Harjutsalo et al, has studied the effect of early-onset (0-14 years) and late onset (15-29 years) type 1 diabetes and observed that early-onset T1DM is associated with roughly 3 times increased risk for CHD than those with late-onset T1DM.⁶⁸ Our study reveals an interesting finding, T1DM seems to be particularly associated with accelerated atherosclerosis of the coronary arteries and women seem to have highest risk for this outcome.

Research shows that early-onset T1DM is associated with more aggressive insulinitis and fewer insulin-producing beta-cells at disease onset.⁶⁹ The strong relationship between cardiovascular disease, particularly coronary heart disease suggests that patients with T1DM that reach 30-40 years of age should be considered for lipid lowering treatment. Treatment of risk factors glycated hemoglobin, blood pressure and dyslipidemia should perhaps be viewed differently in patients with early-onset T1DM. Our results indicate that age at onset of T1DM is an essential factor that should be considered in all future risk mitigation strategies for patients with type 1 diabetes.

Importance of risk factors in type 1 diabetes

In this study, we combined traditional cox regression with modern machine learning analyses to assess the relative importance of risk factors in patients with T1DM.⁷⁰⁻⁷² We incorporated the machine learning models for several reasons such as increased robustness, precision but more importantly the advantage of including higher-

dimension interactions between multiple predictors, which has to be specified in the cox regression.

Our results show that glycosylated hemoglobin, renal function, duration of diabetes, LDL-C and systolic blood pressure are the most important predictors for cardiovascular events and death in patients with T1DM. Our results suggest different pathophysiological processes for the development of these outcomes considering the variability in the strength of association of risk factors. Glycosylated hemoglobin and albuminuria were the strongest predictors for mortality and heart failure, in contrast to myocardial infarction and stroke, where conventional cardiovascular risk factors such as LDL-C, glycosylated hemoglobin and systolic blood pressure proved to be the most important predictors.

Our analyses suggest that albuminuria and duration of diabetes is in part explained by the integration of several inter-related pathophysiological mediators, for instance, age, HbA1c and blood pressure. Albuminuria was associated with 2- to 4-times greater risk for death and cardiovascular outcomes. Each mmol/mol higher HbA1c was associated with 2% increased relative risk for death, or 23% relative risk per 1% higher HbA1c.

According to our analyses of optimal levels, glycosylated hemoglobin, systolic blood pressure and LDL-C display almost a linear relationship for risk of stroke and AMI. The present analysis shows that LDL-C is a strong predictor for AMI, stroke and HF, demonstrating approximately 35-50% higher relative risk for each mmol/l increase in LDL-C. This is an important finding since it further substantiates the importance of lipid lowering treatment in patients with T1DM.

Strengths and limitations of the studies

All studies in this thesis are based on observational studies from the national diabetes register. In these studies, virtually all patients with type 1 diabetes and type 2 diabetes in Sweden are included, with information available on comorbidities, medications and risk factors.

We use imputation techniques to fill missing data for patients in order to avoid selection bias and increase statistical power. All studies are based on the epidemiological definition of type 1 diabetes and type 2 diabetes. These definitions are well validated and there is a strong concordance between the epidemiological definition and a clinician's classification. We use both novel and conventional statistical methods. All studies are based on baseline characteristics to model long-term outcomes, it is likely that time-updated models would have yielded more accurate risk associations, but our statistical approach decreases the risk of reverse causation biasing the results.

These studies included several risk factors in most models, however we are aware that it is impossible to completely overcome the limitation of residual confounding. In our studies on multifactorial risk factor control we know that we could not distinguish between patients that attained risk factors within target level by means of medical treatment or patients that were within target range without any specific intervention. It is conceivable that our models are somewhat affected by reverse causation, we apply different modeling strategies to limit the influence of this.

CONCLUSIONS

The incidence and risk of cardiovascular disease and death has decreased substantially in patients with diabetes and the general population. The risk for non-fatal outcomes has decreased more among patients with diabetes, compared to controls. Interestingly, fatal outcomes declined more in matched controls than patients with T2DM, whereas patients with T1DM experienced a risk reduction for fatal outcomes similar to matched controls. Still, patients with diabetes continue to display 2 to 4 times greater risk of cardiovascular outcomes and mortality, compared to the general population. The relative risk of heart failure decreased less compared to the other outcomes over the study period, both in patients with diabetes and matched controls.

Multifactorial risk factor control is associated with significant risk reduction for cardiovascular events and death among patients with T1DM. Attaining all 5 selected risk factors within target range still results in 97% and 82% excess risk for heart failure and acute myocardial infarction, respectively. Patients with T1DM and poor risk factor control have several hundred percent-elevated risk compared to matched controls.

Multifactorial risk factor control in patients with T2DM is associated with significantly lower risk for cardiovascular disease and outcomes. Patients with T2DM and all risk factors within therapeutic target range had, at most, 10% elevated risk for outcomes, compared to controls. Patients with optimal risk factor control had 16% lower risk for myocardial infarction, compared to the general population. We observed a monotone relationship between increasing number of risk factors not within target range, and increased risk for outcomes. Moreover, we noticed a stepwise association between age at baseline and risk for outcomes, younger at baseline is associated with increasing risk for outcomes.

The strongest predictors for cardiovascular events and death in type 2 diabetes were the following: age, physical activity level, glycated hemoglobin, systolic blood pressure, smoking and low-density lipoprotein cholesterol. Our analyses suggests that these outcomes have different pathophysiological processes since the strength of association analysis shows differing results for each outcome, however, the strongest risk factors for myocardial infarction and stroke were fairly similar. Lower levels for glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol, than current guideline levels is associated with lower risk for outcomes.

Age at onset of type 1 diabetes is an important predictor that should be incorporated in future risk mitigation strategies since the variable is highly associated with future cardiovascular disease, particularly acute myocardial infarction. Women with T1DM have particularly high risk for cardiovascular disease.

The strongest risk factors for type 1 diabetes are the following: age, glycated hemoglobin, albuminuria, duration of diabetes, low-density lipoprotein cholesterol and systolic blood pressure. Glycated hemoglobin is a strong predictor, and its association is most likely integrated with age, albuminuria or duration of diabetes. LDL-C is a stronger predictor than previously appreciated with approximately 35-50% elevated risk for each mmol/l increase in LDL-C. For the three selected risk factors, we noticed almost a linear relationship between higher levels than recommended guideline levels and higher risk for outcomes. Our machine learning analyses reveals that age and duration of increasing are presumably strong predictors

since the effect of glycated hemoglobin, systolic blood pressure and low-density lipoprotein cholesterol is likely integrated in those risk factors.

FUTURE PERSPECTIVES

The present thesis shows large reductions in cardiovascular disease and mortality among patients with diabetes and for the general population. Multifactorial risk factor control was associated with substantial reduction in excess risk for complications among patients with type 1 diabetes and type 2 diabetes, compared to the general population.

Future research, preferably clinical trials, is warranted to determine the effect of multifactorial risk factor intervention, compared to standard care. This thesis attempts to further the understanding of relative risk for heart failure in patients with diabetes and the general population. Still, there is great demand for further research on the relationship between heart failure and diabetes.

Moreover, our analyses reveal large variations in risk of outcomes between different age groups. The health care system and research community should investigate the effect of different risk mitigation strategies in order to reduce the large excess risk in younger individuals with diabetes.

The relative importance analyses indicate that risk factors contribute to cardiovascular outcomes and death in different ways. The strength of association for risk factors differ not only for outcomes but also between type 1 diabetes and type 2 diabetes. Cardiometabolic risk factors contribute the most to acute myocardial infarction and stroke, whereas risk factors for heart failure and death differ from other outcomes. As such, the analysis suggests different pathophysiological pathways for the development of cardiovascular disease, heart failure and death. Forthcoming research should combine clinical data, bioimaging and genetics to increase our understanding of diabetes-related complications.

Finally, recent clinical trials along with our research indicate that optimal levels for risk factors are perhaps lower levels than current therapeutic guideline levels. Also, optimal levels for risk factors presumably vary between different age groups.

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Our ultimate aim is to give something valuable in return and hopefully this thesis can. If you, who is holding this book is someone living with diabetes I hope that our work will benefit you someday.

If you who are holding this book are a nurse, physician or anyone working with individuals with diabetes, I know that your work is extremely important and I'm privileged to be apart of the community striving to improve the wellbeing of these individuals.

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