Diabetes complications, risk factors, and glycaemic indices in persons with type 1 diabetes

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Gothenburg 2023

Cover illustration: “Runner” by Ingrid Hallström

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ISBN 978-91-8069-475-9 (PRINT)
ISBN 978-91-8069-476-6 (PDF)

Printed in Borås, Sweden 2023
Printed by Stema Specialtryck AB

SVANENMÄRKET
Trycksak
3041 0234

To Ingrid, Arvid, and Agnes

ABSTRACT

Background: Persons with type 1 diabetes are at higher risk of cardiovascular disease and mortality. An important risk factor for diabetes complications is hyperglycaemia. Hyperglycaemia has traditionally been measured using HbA1c, but glycaemic targets are also provided for continuous glucose monitoring. The relation between HbA1c and glycaemic indices from continuous glucose monitoring is complex.

Aims: This thesis aims to evaluate modern diabetes treatment by estimating potential changes in prognosis over time in persons with type 1 diabetes. Another objective is to evaluate if new indices from continuous glucose monitoring can be correlated to HbA1c.

Methods: The populations of persons with type 1 diabetes in papers I, II, and III were retrieved from the Swedish National Diabetes Register and linked to other national registers to collect information on socioeconomic factors, comorbidity, mortality, and diabetes complications. In paper III, each person with type 1 diabetes was matched to 5 controls from the Swedish Total Population Register. In paper IV, data from continuous glucose monitoring from two cohorts of persons with type 1 or type 2 diabetes was analysed. To estimate the contributing risk of each risk factor, statistical Cox regression models have been created and adjusted for other risk factors. Mortality and incidence over time have been standardised by age and sex.

Results: The most important risk factors for atrial fibrillation in persons with type 1 diabetes were age and renal complications. Incidence rates for amputations in persons with type 1 diabetes decreased over time, and the most important risk factors for amputation were renal complications and hyperglycaemia. The cardiovascular prognosis for persons with type 1 diabetes and controls improved over time. For persons with type 1 diabetes without cardiorenal complications, mortality was similar to controls from the general population. At similar levels of HbA1c, time in range was higher in persons with type 2 diabetes than in persons with type 1 diabetes.

Conclusions: Prognosis has improved over time in persons with type 1 diabetes, and risk factor burden, renal complications, and hyperglycaemia must be considered in evaluating the current risk of complications and treatment decisions. The correlation between HbA1c and continuous glucose monitoring indices is strong but varies depending on individual factors and type of diabetes. This should be considered in clinical settings of glycaemic targets and guidelines.

Keywords: Type 1 diabetes, type 2 diabetes, diabetes complication, HbA1c, CGM

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Personer med diabetes har ökad risk för kardiovaskulära komplikationer och dödlighet jämfört med personer från övriga befolkningen. En central riskfaktor för komplikationer och mortalitet är hyperglykemi mätt med HbA1c. Riktlinjer anger målvärden för mått från kontinuerlig glukosmätning men det saknas prospektiva studier med längre tids data från kontinuerlig glukosmätning (CGM) och dess relation till risk för utveckling av sena komplikationer till diabetes.

***Metod*:** Kohorterna med personer med typ 1 diabetes som analyserades i delarbete I, II och III rekryterades från det Svenska Nationella Diabetesregistret. Därefter länkades individerna via personnummer till andra nationella register för att erhålla information om socioekonomiska faktorer, samsjuklighet, mortalitetsdata och diabeteskomplikationer. Personerna i kohorten från delarbete III matchades med 5 kontroller från Registret över Totalbefolkningen. Cox regression och konstruktion av olika Cox modeller genomfördes för att skatta de olika riskfaktorernas effekt på risk för komplikation. Incidenser över tid standardiserades baserat på ålder och kön. Utvärdering av skillnader i CGM-mått baserades på två kohorter med multipel daglig insulinbehandling, en med typ 1 diabetes och en med typ 2 diabetes.

***Resultat*:** De viktigaste riskfaktorerna för förmaksflimmer är högre ålder och njurpåverkan medan riskfaktorer för amputation framförallt är hyperglykemi och njurpåverkan. Total och kardiovaskulär dödlighet sjunker över tid men inte i lika stor utsträckning hos personer med typ 1 diabetes som hos matchade kontroller. För personer med typ 1 diabetes som inte har utvecklat kardiovaskulära eller renala komplikationer är mortaliteten jämförbar med den i den allmänna befolkningen. Mått från kontinuerlig glukosmätning korrelerar med HbA1c men sambandet skiljer sig åt mellan de med typ 1 och typ 2 diabetes.

***Slutsatser*:** Prognosen för personer med typ 1 diabetes förbättras över tid. En sammanvägning av riskfaktorbörda, njurkomplikationer och förekomst av förhöjda blodsockervärden bör göras inför val av utredning och behandling av personer med typ 1 diabetes. Skillnaden i samband mellan HbA1c och CGM-mått hos olika grupper av personer med diabetes bör tas i beaktning vid framtagandet av målvärden för blodsocker både i klinisk vardag och vid utformning av riktlinjer.

LIST OF PAPERS

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

I. Hallström, S., Pivodic, A., Rosengren, A., Ólafsdóttir, A. F., Svensson, A. M., Lind, M. (2019). Risk Factors for Atrial Fibrillation in People With Type 1 Diabetes: An Observational Cohort Study of 36,258 Patients From the Swedish National Diabetes Registry. *Diabetes care*, *42*(8), 1530–1538. https://doi.org/10.2337/dc18-2457

II. Hallström, S., Svensson, A. M., Pivodic, A., Ólafsdóttir, A. F., Löndahl, M., Wedel, H., Lind, M. (2021). Risk factors and incidence over time for lower extremity amputations in people with type 1 diabetes: an observational cohort study of 46,088 patients from the Swedish National Diabetes Registry. *Diabetologia*, *64*(12), 2751–2761. https://doi.org/10.1007/s00125-021-05550-z

III. Hallström, S., Wijkman, M. O., Ludvigsson, J., Ekman, P., Pfeffer, M. A., Wedel, H., Rosengren, A., Lind, M. (2022). Risk factors, mortality trends and cardiovascular diseases in people with Type 1 diabetes and controls: A Swedish observational cohort study. *The Lancet Regional Health. Europe*, *21*, 100469. https://doi.org/10.1016/j.lanepe.2022.100469

IV. Hallström, S., Hirsch, I. B., Ekelund, M., Sofizadeh, S., Albrektsson, H., Dahlqvist, S., Svensson, A. M., Lind, M. (2021). Characteristics of Continuous Glucose Monitoring Metrics in Persons with Type 1 and Type 2 Diabetes Treated with Multiple Daily Insulin Injections. *Diabetes technology & therapeutics*, *23*(6), 425–433. https://doi.org/10.1089/dia.2020.0577

CONTENTS

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
BMI	Body mass index
CGM	Continuous glucose monitoring
CI	Confidence interval
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HF	Heart failure
HR	Hazard Ratio
LDL	Low-density lipoprotein
LEA	Lower extremity amputation
MDI	Multiple daily injections

SD	Standard deviation
SGLT-1i	Sodium-glucose transporter 1 inhibitor
SGLT-2i	Sodium-glucose transporter 2 inhibitor
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAR	Time above range
TBR	Time below range
TIR	Time in range

DEFINITIONS IN SHORT

CGM	Continuous glucose monitoring. A small device is attached to the skin with a sensor inserted in the subcutis. The device automatically measures glucose every 5 to 15 minutes, depending on the model.

1 INTRODUCTION

1.1 HISTORY OF DIABETES

Diabetes was first described as a condition with excessive urine production. Aretaeus of Cappadocia (30 A.D-90 A.D) constructed the word dia-betes with the meaning pass through referring to the "…wasting of flesh and limbs into urine.."[1]. In the following centuries, the development in the field included observations of the sweetness of the urine and different combinations of symptoms. The association between diabetes and acidosis was first described in the nineteenth century. A treatment regimen with periodic starvation and an association between starving and less glucosuria were observed. At the beginning of the twentieth century, three scientists named Zueler, Dohrn, and Marxer treated humans with an extract of pancreatic juice with favourable effects on glucosuria and ketonuria, but due to adverse effects related to the impurity of the drug insulin did not gain therapeutic status until Frederic Banting found a more pure solution and isolated the hormone insulin. The administration of insulin as a therapeutic drug for persons with diabetes was initiated in 1922 and was a life-saving treatment, as seen in Table 1 [2, 3]. The discovery of insulin is often attributed to Frederick Banting, and after some controversies, he and James Macleod were awarded the Nobel Prize in 1923 [4].

Table 1—Mortality Among Diabetic Patients at Specified Ages in Successive Periods, 1897-1961: Experience of Joslin Clinic, Boston, Mass.

	Death Rate per 1,000						
	Naunyn Era	Allen Era	Insulin Era				
Age	1897–1914	1914–1922	1922–1926	1926–1929	1929–1938	1939–1947	1950–1961
10	824.0	386.1	61.4	19.1	8.1	3.3	1.0
20	614.0	410.8	89.4	18.3	12.6	7.9	3.4
30	359.8	236.8	74.8	33.4	13.9	11.3	14.4
40	165.7	115.1	34.7	23.8	16.6	13.6	15.3
50	96.1	77.4	45.3	41.0	30.6	26.7	21.5
60	88.8	112.5	85.2	70.1	66.6	51.6	43.0

Table 1. Mortality in persons with type 1 diabetes before and after the introduction of insulin therapy. Table courtesy of Dr Marks with permission from the American Public Health Association [3].

With insulin treatment, life expectancy in persons with type 1 diabetes was improved radically but was not close to that of the general population [3, 5, 6]. The increased risk of cardiovascular disease in patients with diabetes was first described in the Framingham study published in the 1970s [6, 7]. The Diabetes Control and Complication (DCCT) study, a landmark study in type 1 diabetes, showed a direct correlation between intensive insulin treatment, improved glycaemic balance, and decreasing late complications, including cardiovascular disease, retinopathy, albuminuria, and renal diabetes disease [8, 9]. In the DCCT study, HbA1c was reduced, but this led to an increased risk of hypoglycaemia. Intensive insulin treatment became standard therapy, with the limiting aspect mainly hypoglycaemia. Aiming at maintaining normoglycaemia was difficult since hypoglycaemia then became a predominant problem. In 2015, the "game changer" continuous glucose monitoring (CGM) was introduced on a broad indication to persons with type 1 diabetes, and today, 95% of persons with type 1 diabetes use CGM in Sweden [10]. Globally, however, most persons with type 1 diabetes have no access to CGM and have to rely on capillary blood glucose testing.

Since the first discovery of insulin, the treatment has improved with different insulin solutions with varying action profiles. Treatment and technical systems for measuring and administering insulin have also been developed in recent decades. A person diagnosed with type 1 diabetes 50 years ago had no method of measuring glucose at home or outside the clinic and the insulin doses were often fixed, treatment was focused on survival and preventive measures such as lipid-lowering and renoprotective drugs were still not developed. Modern diabetes care in developed countries, including CGM, automatic insulin delivery pumps, lipid-lowering and renoprotective treatment, multidisciplinary diabetes foot teams, and much more, has increased life expectancy [11, 12]. Still, most people worldwide living with type 1 diabetes do not have access to modern diabetes care, and life expectancy for persons ranges from around 20 years in some African countries to over 75 years in some developed regions [13].

1.2 CLASSIFICATION OF DIABETES

Diabetes mellitus is usually classified into four subclasses [14]. Hyperglycaemia in persons with type 1 diabetes is due to deficient insulin production, and in persons with type 2 diabetes, the reason is insulin resistance, often paired with insufficient insulin production. Gestational diabetes is due to impaired insulin secretion when insulin resistance increases in the third trimester of pregnancy. The fourth group of diabetes includes other types of diabetes, for example, diabetes due to pancreatic pathology, monogenetic variations, or other causes [14].

1.3 EPIDEMIOLOGY OF DIABETES

In 2021, more than 500 million people were living with diabetes; among them, around 9 million with type 1 diabetes. The incidence of type 2 diabetes is estimated to increase worldwide, mainly because of increasing rates of obesity and inactive lifestyles [13, 15, 16]. Type 2 diabetes incidence increases in areas with persons with genetic predisposition, changing dietary habits, and inactive lifestyles. In the Middle East, the prevalence of diabetes in the adult population is 16.2 % [15].

The incidence of type 1 diabetes has also increased and is expected to continue to increase. The reasons for this are not fully established, but some theories are that obesity and environmental factors can trigger the immunological process of type 1 diabetes [17, 18]. The majority of persons with type 1 diabetes are diagnosed in childhood, with a peak incidence at age 10-14 years, but many persons develop type 1 diabetes in adulthood [13]. Incidences of type 1 diabetes are high in Nordic countries, including Sweden, Finland, and Norway [19]. With modern diabetes care, life expectancy increases in persons with type 1 diabetes, and prevalence increases. Very low prevalence in low-income countries is probably, at least partly, explained by high mortality rates.

1.4 TYPE 1 DIABETES

Type 1 diabetes is an immunologic disease affecting the pancreatic beta cells, resulting in a lack of insulin [20]. If untreated, insulin deficiency impedes the cells to use glucose, resulting in hyperglycaemia. When the cells cannot use glucose an alternative energy source, fat, is used [21]. The cellular process of using fatty acids as fuel results in excessive production of ketones. Untreated

diabetes type 1 usually results in hyperglycaemia and ketonemia. The hyperglycaemia triggers osmotic diuresis and can develop into ketoacidosis, a condition with dehydration, hyperglycaemia, and acidosis [21].

The insulin in humans is activated through a split between one chain of insulin called C-peptide and insulin. The C-peptide is more easily analysed and interpreted and is used in relation to blood glucose to estimate the remaining production of endogenous insulin [22].

The treatment goals are to keep blood glucose levels close to normoglycaemia and to prevent late complications [11]. Hyperglycaemia accelerates the atherosclerotic process and is an important risk factor for late complications of diabetes [23, 24]. Late complications of diabetes include renal dysfunction, eye complications, hypertension, acute myocardial infarction, heart failure, stroke, neuropathy, and diabetes foot disease [25].

Insulin treatment can be administered with multiple daily injections (MDI) and consists of a combination of long-acting insulin once or twice daily and short-acting insulin to be administered with meals or to correct high glucose levels. Insulin can also be administered with an automatic insulin pump, a device with continuous delivery of short-acting insulin in different doses [26].

Hypoglycaemia is an essential and often restricting adverse effect of exogenously administered insulin [27]. Hypoglycaemia occurs most commonly when the dose of short-acting insulin is too high. A keystone together with insulin treatment is, therefore, self-measurement of glucose levels. Until the late 1970s, there were no means for persons with diabetes to monitor glucose levels on a daily basis, and one could expect that mean glucose levels were higher in that era. The broad introduction of CGM around 2015 in Sweden helped many persons improve their glycaemic control, and patients describe that the usage of CGM also improved their quality of life and decreased fear of hypoglycaemia [28-31].

The CGM is a useful device for persons with insulin-treated diabetes. The different CGM systems measure glucose from a subcutaneous sensor in the interstitial fluid. The CGM systems can activate alerts at different glucose levels to remind the person to act when the glucose is decreasing or increasing [32]. In Sweden, around 95% of all persons with type 1 diabetes use a system of CGM daily [10].

1.5 TYPE 2 DIABETES

Type 2 diabetes is usually described as a lifestyle disease affecting persons at all ages but predominantly middle-aged with sedentary lifestyles and overweight [16]. Hyperglycaemia in type 2 diabetes is mostly due to insulin resistance, and the condition is usually asymptomatic for years. Most persons with type 2 diabetes present with a cluster of clinical findings, including insulin resistance, hypertension, dyslipidemia and central obesity, sometimes called metabolic syndrome [33]. The treatment for persons with type 2 diabetes aims to increase insulin sensitivity with increased physical activity, weight loss, and medications to increase the sensibility to endogenous insulin [33, 34].

Most persons with type 2 diabetes have several risk factors for cardiovascular disease, with onset on average decades later than in persons with type 1 diabetes [13, 16, 35]. The incidence of type 2 diabetes has increased parallel to increased BMI in the population [16].

The treatment of persons with type 2 diabetes has historically been a combination of metformin and insulin or sulfonylureas [36]. In the last decades, new drugs have been introduced to the treatment arsenal [37]. The newer drugs are effective in lowering glucose and also positively affect mortality, nephropathy, and cardiovascular disease in persons with type 2 diabetes [38-44].

Medication implemented in Sweden for type 2 diabetes is except for metformin, an incretin-based therapy called “glucagon-like peptide agonist type 1” (GLP-1) with positive effects on insulin resistance, weight, and glycaemic levels [34]. More incretin-based drugs are under development, and a combined drug of a GLP-I analogue and “Glucose-dependent insulinotropic peptide” (GIP), tirzepatide, has in clinical trials shown beneficial effects on weight reduction and glycaemic balance [45, 46]. Another important treatment for persons with type 2 diabetes is the “Sodium-glucose-co-transporter 2 inhibitor” (SGLT-2i), a drug stimulating the osmotic diuresis and lowering glucose levels. Besides improving glycaemic balance, SGLT-2i also reduces the risk of cardiovascular and renal disease [38, 41, 47, 48]. SGLT-2i had, during some years, an indication for treating persons with type 1 diabetes and overweight but was withdrawn due to commercial interests and the associated increased risk of ketoacidosis [49, 50]. The GLP-1 analogues, the combined GLP-1/GIP, and the SGLT-2i have adverse effects, but none induce hypoglycaemia [37].

If the insulin resistance is advanced, adding insulin to the treatment is possible. Many persons with type 2 diabetes reach glycaemic targets without insulin. However, the glycaemic targets for insulin-treated persons with type 1 diabetes and type 2 diabetes have traditionally been proposed in terms of levels of HbA1c [51]. The glycated hemoglobin concentrations correlate to mean glucose over the preceding 8-12 weeks [52]. In the last consensus report on glycaemic levels of CGM users, persons with type 1 and type 2 diabetes and insulin treatment have the same glycaemic targets [53].

CGM has not been introduced broadly in persons with type 2 diabetes, probably because the first studies on CGM and glycaemic control did not show improvements with clinical significance in HbA1c [54, 55]. CGM metrics in persons with type 2 diabetes and MDI were not well studied in 2021. Since the main restricting adverse event of insulin treatment is hypoglycaemia, it is important to describe CGM metrics in persons with type 2 diabetes with MDI treatment.

1.6 LATE COMPLICATIONS OF DIABETES

Hyperglycaemic-induced micro and macroangiopathy is the leading cause of late complications of diabetes. The atherosclerotic process affects the vascular system and is driven by high blood pressure, hyperlipidemia, hyperglycaemia, and insulin resistance per se [24]. Complications from diabetes include ischemic heart disease, stroke, acute myocardial infarction, heart failure, hypertension, retinopathy, diabetes renal disease, neuropathy, and diabetes foot disease [8, 20, 51]. Late diabetes complications affecting the nerves of the autonomic system can result in autonomic dysregulation of blood pressure, dysfunction of the heart rate, and slower ventricular gastric emptying, resulting in complications like orthostatic hypotension, cardiac autonomic neuropathy, and gastroparesis [56, 57].

Both the pathophysiology and the risk factor burden differ between persons with type 1 diabetes and type 2 diabetes, and some risk factors have a more significant impact on outcomes in persons with type 1 diabetes compared to persons with type 2 diabetes [35, 58-60]. Therefore, it is important to study risk factors for persons with type 1 diabetes separately from persons with type 2 diabetes. Until recently, studies on most complications in persons with diabetes have not distinguished between diabetes type 1 and 2 but have included all persons with diabetes or insulin-treated diabetes [61-65].

1.6.1 PATHOPHYSIOLOGY OF LATE COMPLICATIONS OF DIABETES

Several mechanisms explain the process of hyperglycaemic-induced late complications of diabetes. The cells most vulnerable to hyperglycaemia have deficient downregulation of glucose when exposed to hyperglycaemia, leading to excessive glucose uptake to the cell. Cellular hyperglycaemia activates the production of reactive oxygen species (ROS) and results in cellular oxidative stress. ROS activates several pathophysiological pathways resulting in decreased activity of antiatherosclerotic enzymes and vascular dysfunction due to an imbalance between nitric oxide and ROS [66-68].

One of the activated pathways is the overactivation of aldose reductase. Aldose reductase is an enzyme involved in the cellular uptake of glucose, and overactivation of this enzyme in rats led to increased atherosclerosis. Aldose reductase is expressed in the nerve, retina, glomerulus, and vascular cells [67].

Another mechanism is the increased rate of glycation activated by hyperglycaemia. Different proteins are more prone to be glycated in high glucose concentrations. Excessive amounts of advanced glycation end products (AGEs) are produced and deposited in the endothelial cells in the kidney, retina, and atherosclerotic plaques. HbA1c is an AGE used in clinical practice. Different phenotypes of glycation could be related to variations in the rate of complications of diabetes [69]. In a recently published study of persons with type 1 diabetes, persons with fast-glycation phenotype, categorised as persons with high HbA1c in relation to CGM mean glucose, had higher concentrations of AGEs in the skin and diabetes complication burden compared to persons with slower glycation rate [69].

Other mechanisms activated by hyperglycaemia include the overactivation of protein kinase C, leading to changes in circulation and permeability of the vessels and other metabolic alterations. Taken together, hyperglycaemia induces vascular alterations and proinflammatory processes, resulting in endothelial dysfunction and vessels more vulnerable to atherosclerosis [23, 24, 66, 67, 70].

1.6.2 CARDIOVASCULAR MORBIDITY AND MORTALITY

The main reasons for the shortened life expectancy in persons with diabetes are cardiovascular disease and mortality. The correlation between diabetes and cardiovascular disease was first observed in the Framingham study [7]. Persons with diabetes had a 3-fold higher risk of mortality and cardiovascular death than those without diabetes. In 1993, the landmark study DCCT in persons with type 1 diabetes comparing a mean of 6.5 years of intensive treatment with the conventional treatment was published [8]. The intensive treatment consisted of multiple daily injections of insulin or insulin pump compared to the conventional group with only basal insulin. The DCCT study showed decreased incidences of retinopathy, nephropathy, and neuropathy with intensive treatment compared to conventional therapy [8]. Based on DCCT results, multiple daily insulin injections or insulin pumps became the golden standard of treatment in persons with type 1 diabetes. An extension study of DCCT called the Epidemiology of Diabetes Interventions and Complications (EDIC) study evaluated the effects of the intensive treatment group after the intervention was finalised. The EDIC study showed improved long-term prognosis in the group with intensive therapy on cardiovascular mortality and cardiovascular disease several years after intervention was finished [9, 71].

In the last decades, several studies have shown that the risk for persons with type 1 diabetes is increased for AMI, heart failure, stroke, mortality, and cardiovascular mortality [5, 72-74]. However, recent studies have shown that persons with type 1 diabetes with all risk factors in control have risks comparable to that of the general population [75].

Persons diagnosed with diabetes 50 years ago had less possibilities to maintain glucose levels near normoglycaemia, and neither primary nor secondary prevention existed. Modern diabetes treatment includes lifestyle changes, statins, ACEi/ARB treatment, and a more strict glycaemic balance [76]. The development of complications is usually a process of years to decades, and the delay from improved treatment to incidences of late diabetes complications could, therefore, be expected to be seen after several years. The difference in prognosis for persons with type 1 diabetes compared to the general population could, therefore, be expected to improve in the future.

1.6.3 RENAL COMPLICATIONS

Renal diabetes disease is a complication of diabetes and is also a risk factor for developing other diabetes complications [64, 77, 78]. Diabetes renal disease is categorised into microalbuminuria, macroalbuminuria, renal dysfunction with decreased glomerular filtration, and terminal kidney disease. An international classification of renal disease is the KDIGO CKD, shown below in Table 2, based on the presence of renal disease or systematic disease combined with different levels of glomerular filtration rate (GFR) [79]. GFR is usually estimated by injecting intravenous contrast, measuring the concentration in the blood after a fixed time, and from this, renal clearance can be calculated [79]. In clinical practice, an estimation of GFR, eGFR, is often applied to determine estimated renal filtration. The eGFR is calculated based on information on creatinine levels, age, and sex [80].

Categories of renal dysfunction	**Glomerular filtration rate**
CKD 1	>90 ml/min/1.73 m^2
CKD 2	60-89 ml/min/1.73 m^2
CKD 3	30-59 ml/min/1.73 m^2
CKD 4	15-29 ml/min/1.73 m^2
CKD 5	<15 ml/min/1.73 m^2 or treatment by dialysis

Table 2. Stages of renal dysfunction according to GFR and signs of renal dysfunction or systemic disease according to the KDIGO CKD classification [79].

The first sign of diabetes-related renal dysfunction is often the presence of microalbuminuria. Without treatment, the renal dysfunction usually aggravates into macroalbuminuria and decreased GFR [81]. The presence of albumin in relation to creatinine, the urine albumin creatinine ratio is estimated and classified into micro and macroalbuminuria, as seen in Table 3. In a small proportion of persons, decreased eGFR is observed without precedent albuminuria [82]. The normoalbuminuric chronic kidney disease in persons with type 1 diabetes has been associated with an increased risk of cardiovascular events but without association with renal outcomes [83].

Microalbuminuria	3-30 mg/mmol
Macroalbuminuria	30 mg/mmol

Table 3. Definitions of micro and macroalbuminuria based on the urine-albumin creatinine ratio.

Hyperglycaemia is a prerequisite for developing diabetes renal disease. Hyperglycaemia activates a cascade of other pathophysiological processes, including hypertension, renal hypoxia, and inflammation, resulting in progressive glomerular sclerosis and decreasing renal filtration [84]. The progress of renal dysfunction in persons with type 1 diabetes can be slowed down if maintaining the blood pressure at lower thresholds, normoglycaemia is achieved, and treatment with ACEi/ARB is initiated [77]. In persons with type 2 diabetes, finerenone (a mineralocorticoid antagonist) and SGLT-2i have also shown beneficial effects on renal function [77, 85, 86].

Renal dysfunction is also an important prognostic factor [64]. Persons with type 1 diabetes and renal dysfunction have a higher risk of mortality and cardiovascular diseases [64, 78, 87, 88]. The most advanced stage of renal disease is end-stage renal disease, demanding dialysis or transplantation. In Sweden in 2022, diabetes is the second most common reason for active treatment of terminal kidney disease. Still, the number of persons with type 1 diabetes in treatment for terminal kidney disease has decreased during the last two decades [89].

1.6.4 ATRIAL FIBRILLATION

Atrial fibrillation was first described in an early version of electrocardiogram (ECG) at the beginning of the twentieth century, and the diagnosis is still defined by ECG findings [90]. Atrial fibrillation is a common arrhythmia with clinical significance and is associated with heart failure and decreased physical capacity. Atrial fibrillation is an important risk factor for stroke [91]. Around 10-15% of all persons with atrial fibrillation have no symptoms, and the arrhythmia is often discovered in routine care of persons evaluated for other conditions [91-93].

The long-term Framingham follow-up study showed an increased risk of atrial fibrillation in a mixed group of persons with diabetes, and few studies have been conducted specifically in persons with type 1 diabetes [94]. Risk factors for atrial fibrillation in the general population are hypertension, cardiovascular

disease, and higher age [95]. Atrial fibrillation has generally not been considered a complication of diabetes. Still, in a similar cohort study from the NDR, an excess risk of 13% of atrial fibrillation was observed in persons with type 1 diabetes, increasing further in persons with renal complications and hyperglycaemia [96].

Several possible explanations exist for the excess risk of atrial fibrillation in persons with diabetes, including heart fibrosis, increased risk of arrhythmia with altered electrolytes and hypoglycaemia, and cardiac autonomic neuropathy [97]. Atrial fibrillation is often asymptomatic, but the risk of thromboembolic stroke increases, especially in persons with diabetes [91]. According to recent guidelines, all persons with diabetes and atrial fibrillation should be considered for anticoagulant treatment to reduce their risk of stroke [91].

Since atrial fibrillation in persons with diabetes is such a strong risk factor that anticoagulants should be considered in the primary prevention of stroke, it is of interest to diagnose this even when asymptomatic [91]. Atrial fibrillation is a common arrhythmia, and it may be useful to screen a subgroup of persons at very high risk. Risk factors and their relative impact on the risk of developing atrial fibrillation could be used to evaluate the risk for a person to have atrial fibrillation and could, therefore, be helpful when deciding persons to screen for atrial fibrillation.

1.6.5 DIABETES FOOT DISEASE

The risk for lower extremity amputation is radically increased in persons with diabetes [98, 99]. Diabetes foot disease is a complex combination of pathological changes resulting from long-standing diabetes. Diabetes neuropathy affects the sensibility of the foot, and a small object in the shoe could lead to a wound that is not detected initially due to loss of protective sensation [100]. The degeneration of the functions of the nerves can also affect the configuration of the foot and results in areas that are more exposed to pressure from walking or shoes. Moreover, the atherosclerotic process of the arteries can lead to ischemic zones in the foot, deteriorating the healing process [100, 101]. Amputations of lower extremities are traditionally classified into minor or major amputations. Minor amputation is defined as amputation from the ankle and below, and major amputation is above the ankle [102]. Minor amputation is usually a toe segment, while major amputations usually are above or just below the knee. The grade of disability following an amputation can differ much depending on the level of the amputation.

The reason for amputation is often a problematic ulcer on the foot with slow or no progress in the healing process [100]. Persons with diabetes ulcers are usually cared for by multidisciplinary teams of physicians specialising in diabetes, vascular surgery, infection, and orthopaedic care [103].

Modern care of persons with diabetes foot disease includes information to the patient about diabetes foot disease and self-care, check of sensibility, configuration, and irrigation of the foot [104]. The treatment arsenal for persons with diabetes and problematic ulcers includes regular visits to the podiatry, revascularisation of the arteries, and surgery to improve healing [103].

Diabetes foot disease and lower extremity amputations are among the most feared complications of diabetes and will usually seriously affect the quality of life [105]. Lower extremity amputations increase disability from diabetes and the risk of sick leave from work. Lower extremity amputations are also associated with high healthcare costs [106].

1.7 RISK FACTORS FOR COMPLICATIONS

Many studies, especially of older data, have analysed outcomes in a group with mixed types of diabetes; others have made the distinction between insulin-treated diabetes and non-insulin-treated diabetes. Results from those studies should not be applied to patients with type 1 diabetes since the general risk factor burden in persons with type 1 differs substantially from risk factors for persons with type 2 diabetes [35, 58, 59]. For example, persons with type 1 diabetes usually have a longer duration of diabetes, lower BMI, and lower blood pressure than persons with type 2 diabetes [10, 60]. Therefore, it is essential to estimate how risk factors for complications differ between types of diabetes.

Hyperglycaemia measured in HbA1c is an important risk factor for AMI, heart failure, diabetes renal disease, and mortality [5, 8, 9, 72, 74, 107-109]. With less than a decade of broad use of CGM, late complications have not as established correlations with CGM measures as HbA1c. An important indicator of glycaemic balance from CGM-metrics is the Time In Range % (TIR%), indicating the percentage of time the glucose has been between 3.9-10 mmol/L (70-180 mg/dL) [53]. Most studies on the correlation between HbA1c and CGM metrics, such as TIR%, have been cross-sectional or used short periods of CGM data [110-112].

The problem with cross-sectional studies in this field is the legacy effect, the long-term effects of historical glycaemic levels. A person with historically high levels of HbA1c has a higher risk of complications than a person with historical HbA1c at target, even though the actual glycaemic levels are similar. Another problem with this design is the residual confounding when diabetes complications are undiagnosed and affect glycaemic control. Several complications from diabetes can affect the glucose balance. Many autonomic complications such as gastroparesis, cardiac autonomic neuropathy, and reduced autonomic response to hypoglycaemia are never diagnosed and probably affect glucose fluctuation and TIR [57]. Gastroparesis is a condition when the transit of food from the ventricle is delayed. Gastroparesis can result in unpredictable glucose uptake, frequent postprandial hypoglycaemias, and hyperglycaemias. This imbalance in blood glucose in persons with gastroparesis increases glucose variability and decreases TIR [113-115]. Few prospective studies have been performed with CGM metrics from prolonged periods and the association with diabetes complications [116-118]. In contrast, cross-sectional studies have shown correlations between low TIR or high mean glucose levels and complications, including retinopathy, neuropathy, and cardiovascular disease [110, 117, 119, 120].

Increased BMI, overweight or obesity, is a risk factor for diabetes complications with conflicting results in persons with type 1 diabetes [18, 121-123]. Characteristics indicating clinical diagnosis of type 1 diabetes have traditionally been having average weight, contrasting with type 2 diabetes, which usually comes with overweight. The trend in the general population is also present in the population with type 1 diabetes, with an increasing proportion of persons with overweight or obesity, both in adults and children [18].

Renal diabetes disease develops from historical levels of hyperglycaemia. Renal dysfunction is both a complication of diabetes and a risk factor for other diabetes complications [64, 77, 78, 81]. The first manifestation of renal dysfunction is usually microalbuminuria; if no preventive treatment is initiated, the condition turns into macroalbuminuria and decreased GFR within a few years [81].

Hyperlipidemia, hypertension, diabetes duration, smoking, age and physical inactivity are also established risk factors for mortality and diabetes complications in persons with type 1 diabetes [88, 109, 124].

1.8 GLYCAEMIC INDICES

Management of persons with type 1 diabetes aims at achieving as physiological glycaemic levels as possible to prevent acute and chronic complications of diabetes. HbA1c has been the gold standard for evaluating glycaemic balance, but compared to CGM metrics, HbA1c lacks information on glucose variability and events and time in hypoglycaemia. HbA1c could, except for indicating mean glucose levels, contribute with information on glycation rate. Glycation rate refers to the rate at which glycation occurs, for example the rate of hemoglobulin glycation resulting in HbA1c. There are substantial interindividual variations in glycation rate, and the rate can indicate a risk of late complications beyond hyperglycaemia [69].

The acute complications of diabetes are hypoglycaemia and ketoacidosis. Many persons with insulin-treated diabetes maintain higher glucose levels due to fear and avoidance of hypoglycaemic events. Hypoglycaemia can be a long-term obstacle to attain adequate glucose balance [125]. Therefore, time in hypoglycaemia is an important CGM metric to consider.

Hypoglycaemia is a condition where the glucose concentration is low, and if no treatment is initiated, the hypoglycaemia can affect cerebral function and develop into unconsciousness and convulsions and, in certain instances, death [27]. The risk of hypoglycaemia is reduced when using CGM, and many persons living with type 1 diabetes have reported reduced fear of hypoglycaemia and increased quality of life after initiating CGM [28-31].

The glycaemic metrics from the CGM give valuable information on the daily glycaemic balance and hypoglycaemia events [32, 53]. HbA1c has traditionally been used as an outcome in clinical trials evaluating the effect of different therapies. However, since hypoglycaemia is an essential adverse effect, CGM metrics have been used broadly in clinical trials in recent times. [126].

The most adapted glycaemic metrics from CGM are the percentage of time in range (TIR%) glucose between 3.9-10 mmol/L (70-180 mg/dL), of time below range (TBR%), glucose below 3.9 mmol/L (70 mg/dL), time below 3.0 mmol/L (54 mg/dL), time above range (TAR%) over 10 mmol/L (180 mg/dL) and time above 13.9 mmol/L (250 mg/dL). Fluctuations in glucose are often described in SD of mean glucose and coefficient of variation (CV) of glucose [53]. The formula estimating the CV is: SD of mean glucose/mean glucose.

The CGM metrics are presented in an Ambulatory Glucose Profile (AGP) report, as illustrated in Figure 1. Treatment targets of CGM metrics are individualised based on the patient's preferences, understanding of glycaemic fluctuation, and TBR% in relation to TIR%. A general treatment target for TIR is at least 70%, with TBR up to 4% [53].

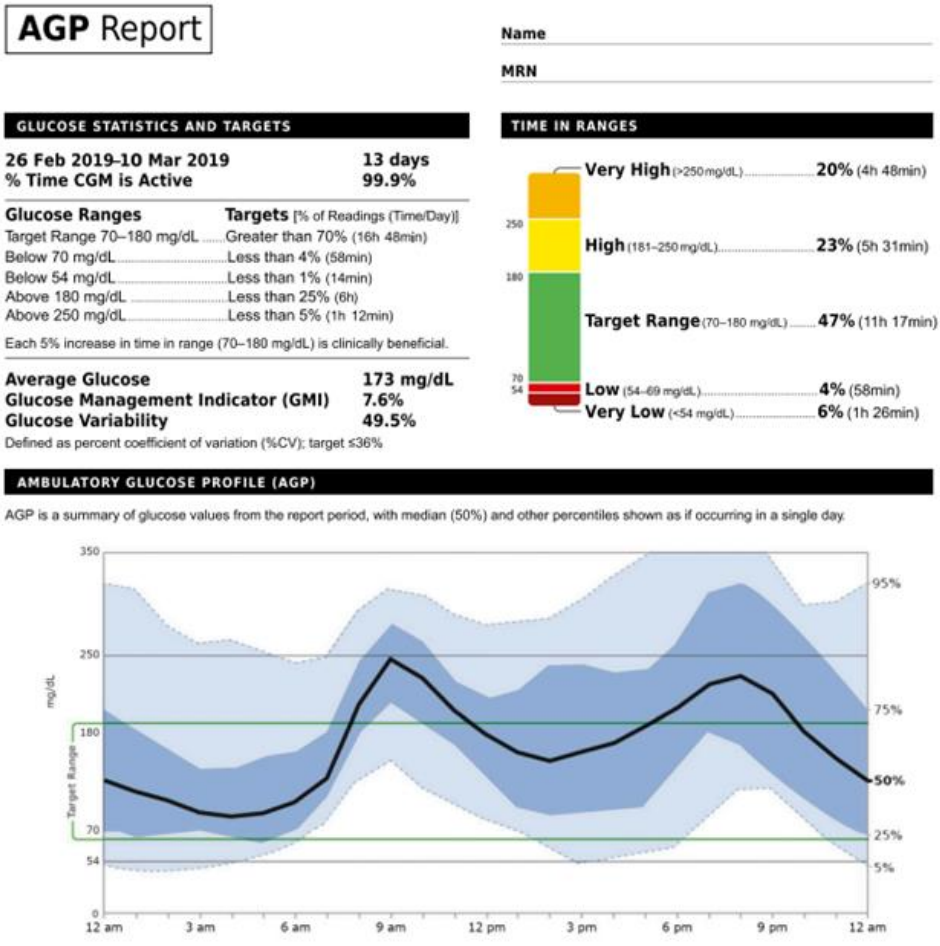

Figure 1. Ambulatory glucose profile of CGM. Ranges 70-180 mg/dL corresponds to 3.9-10 mmol/L, 54 mg/dL to 3.0 mmol/L, 250 mg/dL to 13.9 mmol/L and GMI 7.6% to 60 mmol/mol. Published with permission from the American Diabetes Association [53].

CGM and advanced hybrid closed-loop insulin pumps have shown increased TIR without increasing TBR [28, 31, 127, 128]. Still, there is a great variation in the correlation between TIR and HbA1c between individuals and groups of individuals [129]. We can probably claim that CGM-derived metrics are related to late complications. Still, TIR is not as established as HbA1c in relation to complications, and HbA1c can indicate risk beyond hyperglycaemia [69, 112, 117, 130]. In contrast, the glycaemic measures from CGM are more suitable for adjusting insulin treatment. The use of CGM metrics or HbA1c as the indicator for the risk factor hyperglycaemia is debated, some consider CGM metrics to be the preferable indicator of hyperglycaemia associated with late diabetes complications [112].

1.9 INSULIN TREATMENT

Insulin is a hormone regulating blood glucose. The acute manifestations of under or overdosing on insulin are the potentially severe complications of ketoacidosis and hypoglycaemia in persons with type 1 diabetes [27, 131]. Therefore, insulin treatment is a balancing act of maintaining a low risk of acute complications and aiming to normalise glycaemic levels.

The different insulins have different profiles of duration. Short-acting insulin has a duration of 3-6 hours after injection, and the most long-acting insulin lasts up to 42 hours [132]. About 30 % of adult persons living with type 1 diabetes in Sweden use an insulin pump that delivers short-acting insulin continuously. Around 70 % of adult persons with type 1 diabetes use MDI therapy, a combination of long-acting basal insulin once or twice daily combined with short-acting insulin administered to meals [10].

The patient must determine the required amount of insulin for each meal several times daily. This decision is usually based on many factors affecting the insulin-sensitivity, including actual glycaemic level, planned or performed physical activity, amount of carbohydrates to be ingested, effect of other hormones in the body, and amount of active insulin in the body [132]. As could be understood, the decision is very complex and frequently results in both under and overdosing of insulin followed by hyper or hypoglycaemia.

1.10 RATIONALE FOR THE THESIS

One of the major goals of diabetes therapy is to improve risk factor control and to decrease incidence rates of complications and mortality, closing the gap to incidence rates in the general population.

Updated epidemiological studies of persons with type 1 diabetes are essential to understand the diversity of the manifestations of the disease and to evaluate the effects of modern treatment. Modern diabetes care has improved during the last decades, and with that has followed a decline in risk factor burden. One could expect the current, more advanced care, to affect the prognosis and incidence of late complications in persons with type 1 diabetes. Many studies have shown improved prognosis in persons with good risk factor control. Still, incidence rates of cardiovascular disease and mortality during the recent decade remain increased in persons with type 1 diabetes compared to persons in the general population [13].

The glycaemic control estimated by HbA1c is strongly correlated to all late complications of diabetes [8, 9, 72, 109, 133]. The broad introduction of CGM introduced new methods of evaluating glycaemic control and initiated the debate of whether HbA1c or CGM measures should be used as the treatment target to prevent late complications [112]. Hyperglycaemia in our epidemiological studies was based on HbA1c. Therefore, we wanted to evaluate the new metrics from CGM and their relation to HbA1c to examine the possibilities of deriving HbA1c from CGM metrics or vice versa in coming epidemiological studies. The evaluation of the new metrics from CGM and their relation to HbA1c is of interest to several fields including relating glycaemic metrics to complications in epidemiological studies, understanding glucose patterns for various types of diabetes, and as a base for treatment decisions.

Atrial fibrillation, heart disease, amputation, and many other late complications of diabetes negatively affect physical capacity, socioeconomic factors, quality of life and have a negative prognostic impact on life expectancy. Knowledge of risk factors for amputation and atrial fibrillation in persons with type 1 diabetes could improve prognosis by guiding clinicians in screening and treatment decisions of persons with high risk of atrial fibrillation and amputation.

Modern diabetes care is advanced and requires many resources and activities from the affected individuals and caregivers; therefore, it is necessary to evaluate if modern diabetes care has improved morbidity and prognosis in persons with type 1 diabetes.

2 AIM

The general aim of this thesis is to establish how the prognosis of complications to diabetes has changed over time and determine the risk factors for atrial fibrillation and amputations in persons with type 1 diabetes. The aim was also to explore glycaemic indices and their correlation.

I. To estimate risk factors for atrial fibrillation in persons with type 1 diabetes.

II. To estimate the incidence of lower extremity amputations over time and determine risk factors for amputation in persons with type 1 diabetes.

III. To estimate the incidence of macrovascular complications and mortality over time in persons with type 1 diabetes and to evaluate the importance of renal complications on macrovascular complications.

IV. To estimate the differences in CGM-metrics in insulin-treated persons with type 1 and type 2 diabetes and to investigate if the correlations between HbA1c and CGM-metrics are different in a population with type 1 diabetes compared to persons with type 2 diabetes.

3 PATIENTS AND METHODS

3.1 POPULATIONS

Papers I, II, and III

The Swedish national registries are a valuable source of information to evaluate incidences, risk factor control, complications, and mortality over time. The first three papers are epidemiological studies based on the Swedish National Diabetes Register [134-136]. Linking to other national registers (described in more detail below) using a personal identification number enabled retrieving information on socioeconomic factors, comorbidity, complications, and cause of death.

Registries

The NDR is a quality register initiated in 1996 to evaluate the quality of care in persons with diabetes. The register collects information related to diabetes including information on the onset of diabetes, treatment regimen, complications like retinopathy and foot disease, and levels of risk factors such as blood pressure, lipids, renal complications, and HbA1c (Figure 2). The register includes most persons with type 1 diabetes and has nationwide coverage.

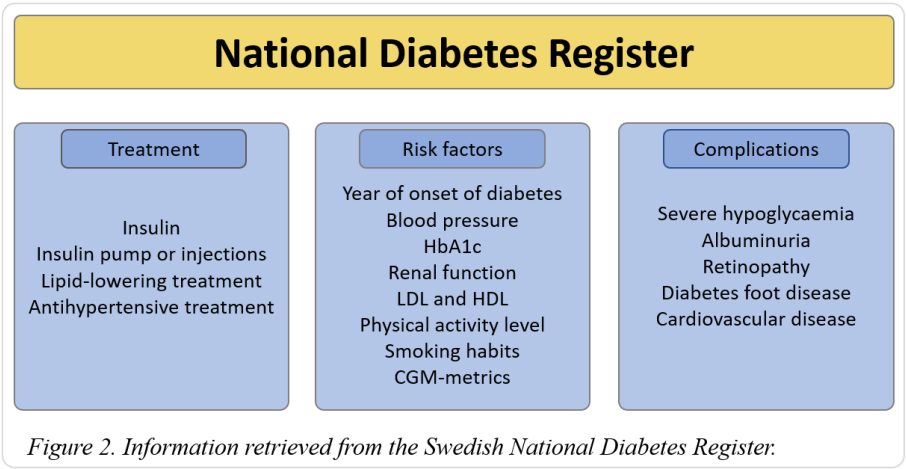

Figure 2. Information retrieved from the Swedish National Diabetes Register.

The cohorts used in the current studies of persons with type 1 diabetes are collected from the NDR using an epidemiologic definition of persons with type

1 diabetes as “persons with initial treatment of insulin and below the age of 30 at the onset of diabetes”. This definition has been estimated to be correct in about 97% of the persons defined as persons with type 1 diabetes [137].

Sources of information from other registers included in the database are shown in Figure 3. Information on the county of residence, country of birth, and education of each person in the cohort in papers I, II, and III and the matched controls in paper III were retrieved by linking to the Longitudinal Integration Database for Health and Insurance (LISA) [138].

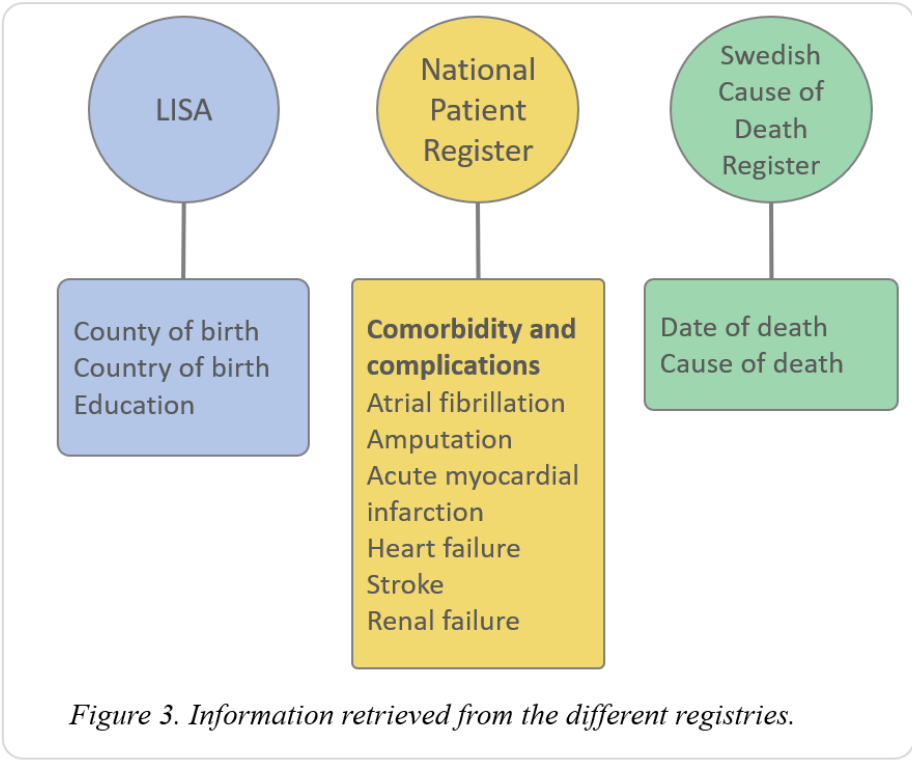

Figure 3. Information retrieved from the different registries.

The Swedish Cause of Death Register has been used to retrieve date and cause of death information. The register was introduced in 1961 and is held by the Swedish National Board of Health and Welfare. It is mandatory to report to this register and the coverage is nationwide, including virtually all deceased Swedish persons [139].

Information on comorbidity, complications, and cardiovascular outcomes was retrieved from The National Patient Register (NPR). The NPR contains

information on all diagnoses from in-hospital care from 1987 and onwards and includes diagnoses from outpatient care since 2001. The NPR contains diagnoses coded according to the International Classification of Diseases (ICD) version 9 (until 1996) and 10. The specific ICD codes applied to retrieve information on comorbidities and cardiovascular complications of the analysis can be found in the supplementary appendix of papers I, II, and III.

It is mandatory to report diagnoses to the NPR and the coverage is virtually total [140]. The validity of the diagnoses in the NPR varies, however, the validity of major diagnoses such as myocardial infarction, heart failure, and atrial fibrillation diagnosis is considered to be high [141-143]. The diagnosis of amputation has not been validated, but the code for the surgical procedure of amputation had high validity [140].

Paper IV

Two cohorts from two randomised controlled studies were selected to analyse differences in CGM measures in persons with type 1 and type 2 diabetes [28, 144, 145].

The cohort of persons with type 1 diabetes was retrieved from the GOLD study [28]. The GOLD study was a multicenter randomised controlled trial with a cross-over design over 16 months with two treatment periods of 6 months and an in-between wash-out period of 4 months. The GOLD study included 161 persons with type 1 diabetes and insulin MDI treatment. The primary aim was to evaluate the effect on HbA1c of adding CGM compared to capillary blood glucose testing to standard diabetes therapy in persons with type 1 diabetes. The procedure included screening participants with run-in masked CGM data and randomisation to the first treatment with or without CGM. After a wash-out period, treatments were switched between the randomised groups. Baseline data was retrieved, including anthropometrics, insulin doses, and c-peptide levels. The study is explained more in detail elsewhere [28]

The second cohort was retrieved from the MDI-Liraglutide study. The MDI-liraglutide study was a double-blind, multicenter, randomised controlled trial evaluating the effect on HbA1c of adding liraglutide to overweight persons with type 2 diabetes and MDI treatment [145]. 124 persons were included, and the procedure included screening with run-in data, information on baseline characteristics, and levels of C-peptide and HbA1c. After screening, each participant was randomised to treatment or placebo [145].

The GOLD and the MDI-liraglutide both included persons from different parts of Sweden with impaired glucose control, at least 58 mmol/mol (7.5%), with MDI insulin treatment, and CGM data in both studies was retrieved using the same model of CGM (Dexcom G4) [28, 145].

3.2 PROCEDURES

Papers I, II, and III

The cohort of persons with type 1 diabetes was retrieved from the NDR based on the epidemiologic definition of type 1 diabetes. The cohort of NDR was then linked to the NPR, the Swedish Cause of Death Register, and the LISA register. The cohort in paper III was also linked to the Total Population Register. Baseline characteristic was collected from NDR, the LISA register, and, for comorbidities, the NPR register. The patients were followed from first registration in the NDR from the defined study start to the end of the study period or death. Information on atrial fibrillation, amputation, cardiovascular disease, and mortality during the study period was retrieved from the NPR and the Swedish Cause of Death Register. The information on risk factors from the NDR was treated as updated values. A time-updated value for the risk factors HbA1c, SBP, DBP, LDL-cholesterol, and HDL-cholesterol was estimated as the mean of all values until the outcome or end of the study. Time-updated values (the last of the preceding values) were used for age, eGFR, albuminuria categories, smoking, and comorbidities. This method was selected to estimate the long-term exposure of each risk factor.

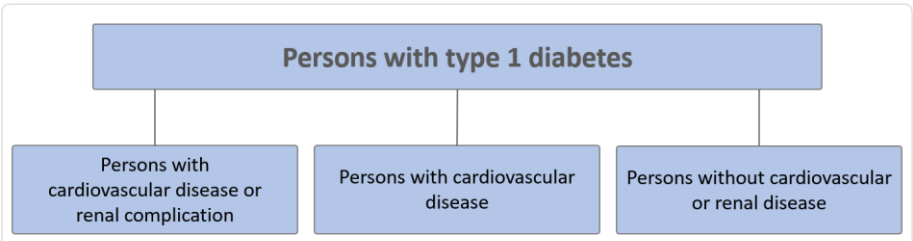

Figure 4. Stratification of persons 45 years or older with type 1 diabetes in paper III.

In paper III, the cohort of persons with type 1 diabetes was matched by age, sex, and county to 5 controls from the Total Population Register. The analysis for mortality and cardiovascular diseases was estimated in persons ≥45 years with diabetes type 1 and controls and for persons with and without cardiovascular or renal complications, as seen in Figure 4. A person with

established cardiovascular disease was considered to have cardiovascular complications, and a person with micro- or macroalbuminuria or decreased eGFR <60 ml/min/1.73 m^2 was considered to have renal complications.

Paper IV

The baseline data of all participants from the GOLD and the MDI liraglutide study was retrieved. CGM data from blinded CGM used in the run-in period of both studies was collected to analyse glycaemic balance without changes in treatment.

3.3 STATISTICAL METHODS

Continuous variables are presented as means SD or median and IQR in all papers. Categorical values are presented as numbers (n) and %. All tests for variation between groups were two-tailed and conducted at a 0.05 significance level.

Paper I

The estimation of the impact each risk factor had on the risk of atrial fibrillation was mainly based on Cox regression. Cox regression is a survival regression model including time-aspect in the analysis estimating time to event.

In diabetes, there is usually an intrinsic relationship between risk factors and complications. Renal failure is a complication of diabetes but is usually a result of long-standing hyperglycaemia and is also a risk factor for complications of diabetes. Risk factors for AMI are, amongst others, hyperglycaemia and renal dysfunction. Hyperglycaemia, therefore, contributes to the risk of AMI as a risk factor and as a risk factor for kidney disease. To evaluate the risk of each risk factor, statistical Cox regression models adjusted for other risk factors were created. In paper I, 3 statistical Cox models were created, and risk factors were analysed with the baseline value and as an updated value. Model A was adjusted for age and gender, and model B was further adjusted for education, birth in Sweden, diabetes duration, and baseline comorbidities. Model C was further adjusted for smoking, HbA1c, BMI, SBP, and DBP. Due to the strong collinearity between DBP and SBP, the models were not adjusted for SBP when DBP was analysed as a risk factor and vice versa.

The most important risk factors were also analysed with the change of risk related to one SD of each risk factor. The advantage of standardized HR is the indication of the effect size independent of the scales of the variables [146]. The scale of each risk factor differs much, for example, between one eGFR unit and one BMI unit. The clinical effect of a change in one unit of eGFR is clinically much different than a change of one unit in BMI. The SD of each risk factor estimates the variation in each risk factor's value. Standardised HR of a risk factor is the attributable risk change related to a change of one SD of the analysed variable.

In addition, the most important risk factors were analysed as categorical variables to estimate at what value a risk factor increases the risk of an event. We also evaluated the relative impact of various risk factors for atrial fibrillation by estimating the pseudo-R^2.

Paper II

Similar statistical methods as in paper I were applied. Cox regression models were created, and HR for each time-updated risk factor value was considered both as a continuous and categorised variable. In paper II, the incidence of amputations divided into 3-year intervals was estimated and presented in event per 1000 person-years as crude incidence and incidence adjusted for age and sex. Incidence was presented with 95% confidence intervals calculated with Poisson regression.

Paper III

Similar methods for analysing incidences, as in paper II, were applied to estimate mortality and cardiovascular incidence. Incidence rates were furthermore estimated for 3-year intervals per 1000-person-years. Analyses of subgroups of patients with and without cardiovascular and cardiorenal diseases were performed (Figure 4).

Paper IV

Means, medians, and IQR were estimated for continuous variables. Independent t-test was applied when comparing groups normally distributed and Fisher's non-parametric permutation test for groups not normally distributed.

To estimate the glycaemic variation between the persons with type 1 and type

2 diabetes, the SD of mean CGM glucose was related to the specific levels of HbA1c. Direct comparison with two-sample t-test was performed at two specific cut-offs of HbA1c at which mean SD was estimated for the persons with type 1 diabetes and type 2 diabetes. A multivariable analysis examined whether other variables affected the relationship between TIR% and HbA1c.

3.4 ETHICAL CONSIDERATIONS

Papers I, II, and III were based on information from the NDR and other registers. The statistical analyses have been performed on data coded with study ID.

Paper I

Paper I evaluated risk factors for atrial fibrillation and the study was performed within the ethical approvement DNR 776-14.

Paper II

Paper II evaluated incidence over time and risk factors for amputation and was performed within the ethical approvement DNR 604-17.

Paper III

Paper III evaluated mortality and complications in diabetes compared to controls on data until 2019 and was performed within the ethical approval DNR 2019-01229

Paper IV

All persons included in the GOLD and the MDI-Liraglutide were informed verbally and in writing about the study procedure and voluntary participation. All patients in both studies gave verbal and written consent to participate and were assigned a study ID to enable linkage between the anonymous person and the data.

The ethical approval supporting study IV is based on the ethical approvals of two randomised controlled trials evaluating the effects of liraglutide or CGM to standard treatment on glycaemic control in patients with multiple daily injections, dnr 857-13, dnr 596-12. The Swedish Medical Product Agency approved the MDI-liraglutide trial, dnr 151:2012/53796.

4 RESULTS

4.1 PAPER I

This study aimed to evaluate risk factors for atrial fibrillation in persons with type 1 diabetes.

36 258 persons with type 1 diabetes registered in the NDR from 1 January 2001 until 31 December 2012 were included in the cohort and followed up until 31 December 2013 [134]. The mean age was 35,6 (SD 14.6) years, and the median follow-up was 9,7 years. During this period, 749 persons were registered in NPR for atrial fibrillation. Risk factors for atrial fibrillation were older age, male gender, cardiovascular diseases, renal complications, increased BMI, and HbA1c. Analyses of categorised risk factors determined that the risk attributable to HbA1c was seen at a high level of HbA1c of more than 82 mmol/mol (9.7%) [134].

The risk attributable to the most important risk factors of atrial fibrillation estimated in standardised HR are shown in Table 4. The standardised HR is highest for older age, macroalbuminuria, decreasing eGFR, coronary heart disease, and HbA1c.

Time-updated variable	**SD of the variable**	**Standardised HR per 1 SD change (95% CI)**
Age (years)	14.43	3.91 (3.34-4.59)
Macroalbuminuria (yes/no)	0.60	1.61 (1.43-1.82)
eGFR (mmol/min/1.73 m^2)	24.90	1.58 (1.46-1.72)
Coronary heart disease (yes/no)	0.26	1.29 (1.23-1.35)
HbA1c (mmol/mol)	12.90	1.19 (1.09-1.30)

Table 4. Standardised HR for the most important risk factors of atrial fibrillation [134].

4.2 PAPER II

The aim of this study was to estimate incidence over time and risk factors for lower extremity amputations in persons with type 1 diabetes.

46 088 persons with type 1 diabetes registered in the NDR between 1 January 1998 and 2 October 2019 were included in this observational study [135]. The mean age was 32.5 (SD 14.5) years, and the median follow-up was 12.4 years. During the studied period, 1519 persons underwent lower extremity amputation. The mean age for first amputation in persons with type 1 diabetes was 50.1 years. The group of persons with amputation had at baseline generally higher cardiovascular risk profiles, including older age, male gender, higher HbA1c, and a higher proportion of persons with albuminuria than those without amputation. As seen in Figure 5, incidence rates decreased over the last decade.

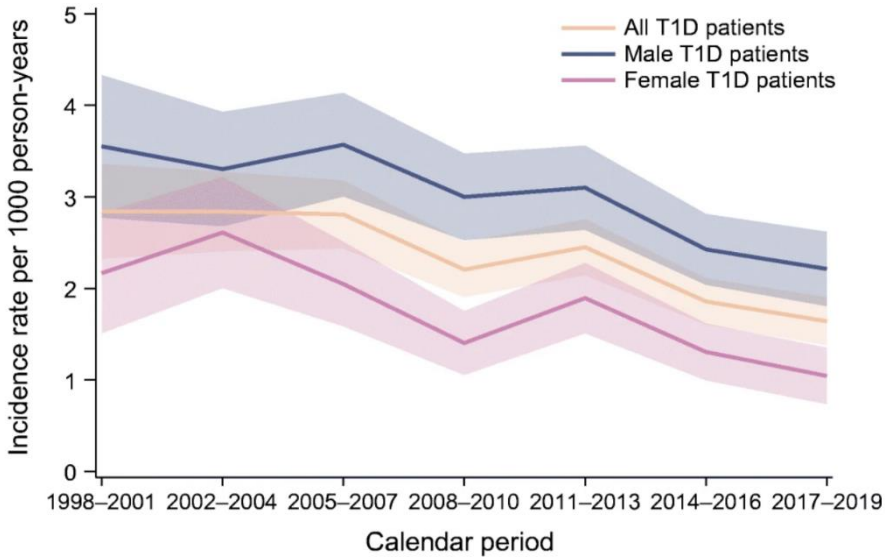

Figure 5. Standardised incidence rates with 95% CIs for any amputation in people with type 1 diabetes over time. Reproduced from paper II with permission from Springer Link [135].

The standardised HR indicated that renal complications, macroalbuminuria, and decreasing eGFR were important risk factors. HbA1c, age, and coronary heart disease were also important risk factors for amputation, as seen in Table 5. When risk factors were considered categorical variables, the attributable risk of hyperglycaemia increased from levels of 52 mmol/mol (6.9%) HbA1C and the risk of BMI was only seen at underweight. Decreased renal function increased the risk of amputation from filtration ≥90 mmol/min/1.73 m^2.

Renal complications were an important risk factor for amputation, and the decreasing incidence of amputations was parallel to the increase in eGFR over time.

Time-updated variable	**SD of the variable**	**Standardised HR per 1 SD increase (95% CI)**
Macroalbuminuria (yes/no)	0.56	2.05 (1.90-2.21)
HbA1c (mmol/mol)	12.86	1.97 (1.88-2.06)
Age (years)	15.24	1.72 (1.54-1.92)
eGFR (mmol/min/1.73 m^2)	24.70	1.69 (1.61-1.77)
Coronary heart disease (yes/no)	0.27	1.25 (1.21-1.29)

Table 5. Standardised HR for the most important risk factors for lower extremity amputations [135].

4.3 PAPER III

This study included 45 575 persons with type 1 diabetes and 220 141 persons from the general population [136]. The mean age at baseline in persons with type 1 diabetes was 32.4 (SD 14.7) years and 31.6 (SD 14.0) years in controls. The mean duration of diabetes in the group with diabetes was 18.2 (SD 14.8) years. Standardised mortality rates decreased for persons with type 1 diabetes but not to the same extent as for the controls. Mortality rates in 2017-2019 were 7.62 and 2.23 per 1000 person-years in persons with type 1 diabetes and controls, respectively. In persons with type 1 diabetes, mortality rates in the first period (2002-2004) compared to the last period (2017-2019) were 9.59 (95% CI 8.73-10.44) and 7.62 (95% CI 7.16-8.08), respectively. A similar trend with decreasing incidence but excess risk compared to controls was seen in the incidence of cardiovascular mortality, AMI, heart failure, and stroke, as seen in Table 6. The risk of all outcomes in the last period was 3.4-5.0 times higher for persons with type 1 diabetes than controls.

	Incidence rates 2002-2004 (per 1000 person-years)		**Incidence rates 2017-2019 (per 1000 person-years)**	
	Controls	**T1D persons**	**Controls**	**T1D persons**
Mortality	4.11 (3.85-4.36)	9.59 (8.73-10.44)	2.23 (2.13-2.33)	7.62 (7.16-8.08)
Cardiovascular mortality	0.80 (0.69-0.91)	3.16 (2.67-3.65)	0.27 (0.23-0.30)	1.56 (1.36-1.77)
AMI	0.98 (0.86-1.11)	5.82 (5.14-6.50)	0.66 (0,60-0,72)	3.30 (2.98-3.61)
Heart failure	1.04 (0,91-1.17)	4.86 (4.24-5.47)	0.87 (0.81-0.94)	3.75 (3.42-4.08)
Stroke	1.16 (1.02-1.30)	4.24 (3.66-4.81)	0.72 (0.66-0.79)	2.46 (2.18-2.73)

Table 6. Incidence rates in controls and persons with type 1 diabetes in the first and the last period. Numbers are presented as incidence rates per 1000 per person-years with 95% confidence intervals [136].

When persons with type 1 diabetes ≥45 years were stratified according to having or not having cardiorenal complications, persons with T1D without cardiorenal complications had the same or even lower mortality rates than the overall rate among all controls from the general population (Figure 6).

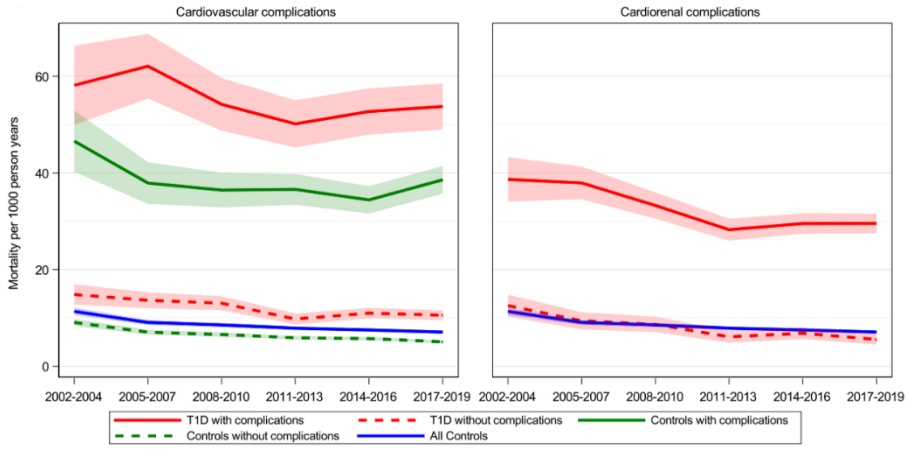

Figure 6. Standardised incidence rates for mortality with 95% CI (shadowed area) in controls ≥45 years, in controls ≥45 years with and without cardiovascular complications (left panel), and in T1D persons ≥45 years with and without cardiovascular or cardiorenal complications (right panel). Reproduced from paper III with permission from Elsevier [136]

Incidence rates for AMI in persons with type 1 diabetes without cardiovascular complications were higher compared to the risk in persons from the general population and were similar to controls from the population with established cardiovascular complications. In the group of persons with type 1 diabetes patients with glycaemic levels below 59 mmol/mol (7.6%) and without cardiorenal complications, the incidence rates for AMI decreased over time and were similar to those of controls in the general population.

Risk factor burden in persons with type 1 diabetes decreased over time, including mean blood pressure levels, LDL-cholesterol, and percentage of smokers. BMI was the only modifiable risk factor that increased over time.

4.4 PAPER IV

In this paper, we evaluated differences in CGM metrics in persons with MDI-treatment and diabetes [144]. We found differences in CGM metrics between persons with type 1 and type 2 diabetes even though HbA1c and CGM mean glucose were similar. The population included in the cohort of persons with type 2 diabetes had a mean duration of diabetes of 17.1 (SD 7.8) years and a mean C-peptide level of 0.67 (SD 0.46) nmol/L compared to persons with type 1 diabetes with mean duration of diabetes 22.5 (SD 12.1) years and mean C-peptide levels of 0.05 (SD 0.041) nmol/L.

Persons with type 1 diabetes spent more time in hypoglycaemia than those with type 2 diabetes, and persons with type 2 diabetes had higher time in range than those with type 1 diabetes at similar levels of HbA1c. Glucose variability was higher in persons with type 1 diabetes than those with type 2 diabetes. SD of mean glucose in persons with type 1 diabetes was higher than in persons with type 2 diabetes with SD 4.4 (SD 0.7) versus 3.0 (SD 0.75) mmol/L, respectively. This trend was maintained at all levels of HbA1c.

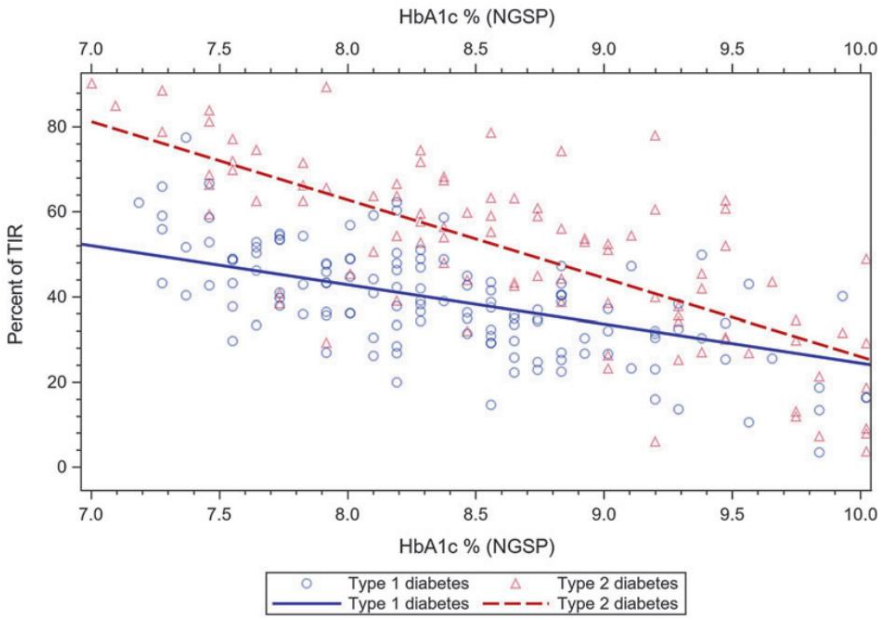

Figure 7. Relationship between TIR% and HbA1c in persons with type 1 and type 2 diabetes. Reproduced from paper IV with permission from Mary Ann Liebert, inc [144].

The relationship between TIR% and HbA1c was also different in persons with type 1 diabetes compared to in persons with type 2 diabetes, as can be seen in Figure 7. For persons with an HbA1c between 60 and 71 mmol/L (7.6 and 8.6%), 1 mmol/mol (0.1%) increase in HbA1 corresponded to around 0.68% decrease in TIR in persons with type 1 diabetes, but in a reduction of TIR of 1.37% in persons with type 2 diabetes. These differences in the relationship between HbA1c and TIR were maintained up to levels of HbA1c 78 mmol/mol (9.3%).

Multiple testing of the correlation between TIR% and HbA1c showed that the association between HbA1c and TIR% depended on the type of diabetes.

5. DISCUSSION

In large cohorts of persons with type 1 diabetes, we found hyperglycaemia and renal complications to be important risk factors for amputation, mortality, cardiovascular mortality, AMI, stroke, and heart failure [135, 136]. Renal complications and older age were strong risk factors for atrial fibrillation. We also found a decreasing risk of diabetes complications over time for amputations, mortality, cardiovascular mortality, and macrovascular complications [135, 136]. Persons with type 1 diabetes still have an excess risk for mortality compared to controls from the general population. However, mortality for persons with type 1 diabetes without cardiorenal complications was similar to mortality for controls from the overall population [136]. Correlations between HbA1c and CGM metrics are complex and depend on individual characteristics. HbA1c remains important as an indicator of precedent hyperglycaemia and the risk of development of late diabetes complications. CGM metrics provide valuable information on daily glucose fluctuation and continuously updated information on glucose control.

In persons with diabetes, the thromboembolic risk for a person with atrial fibrillation is increased to the extent that all persons with diabetes and atrial fibrillation should be evaluated for anti-coagulants to prevent stroke [91]. Clinical stroke is a severe condition that could be prevented in many persons with atrial fibrillation if correct treatment is initiated. A considerable proportion of persons with atrial fibrillation have no symptoms of arrhythmia and are unaware of their condition; this unawareness could be increased in persons with diabetes and cardiac autonomic neuropathy [93]. As we found renal complications and age to have the greatest relative importance for the risk of developing atrial fibrillation, persons with high risk can in many cases easily be identified. Screening of high-risk individuals in this population and early prevention could decrease the incidence of stroke in persons with type 1 diabetes.

Amputation is one of the most feared complications of diabetes and is usually the last option in persons with prolonged healing of a diabetes foot ulcer [100]. A multidisciplinary approach to decrease the risk of diabetes foot disease and amputations was introduced broadly around year 2000 [65, 103]. Despite this, incidence rates have remained unchanged, as recently shown, on data until 2013 [98]. We used a longer observation period until 2019 and found a

decreasing incidence in the last years. The lag time between risk factor exposure and the outcome of diabetes complications is long [133].

Complications could result from decades of high-risk factor burden, especially for complex disorders such as diabetes foot disease and amputation [9]. Still, we found decreasing levels of amputations along with decreasing mean HbA1c. This could be explained by the positive effect of lower glycaemic levels in the healing process [147]. Many persons with diabetes ulcers have developed other diabetes complications, such as cardiovascular disease. In persons with cardiovascular disease, glycaemic control has special recommendations with higher target HbA1c and lower TIR% to avoid hypoglycaemia [53, 148]. In observational studies of the relationship between healing diabetes foot ulcers and improved glycaemic control, results have been conflicting or inconclusive [149]. Our results could indicate that persons with diabetes ulcers could benefit from a more intense insulin treatment during the healing process to reduce the risk of amputation.

Cardiovascular diseases explain much of the shortened life expectancies in persons with diabetes, and risk factor control decreases the risk for macrovascular complications [150]. Several publications show renal complication as a negative prognostic indicator related to mortality and macrovascular complications [78, 87, 88]. In the DCCT/EDIC study, higher mortality rates could be seen in the conventionally treated group 20 years after the trial was terminated, even though HbA1c levels were similar in both groups after the finalised intervention. This shows the possible lag time between hyperglycaemia and complications [133].

The prognosis of younger persons and persons affected by type 1 diabetes today is probably not reflected in epidemiological studies including persons diagnosed with type 1 diabetes 50-60 years ago. These persons have lived without modern diabetes treatment for around 40 years. In an attempt to avoid the differences in legacy effect, we stratified the cohort to persons ≥45 years old and without renal complications. Microalbuminuria is a relatively early sign of diabetes complications and indicates precedent hyperglycaemia, which is why this cohort without renal complication could be supposed to have a historically good glycaemic balance. In this low-risk stratified population of persons with type 1 diabetes, we found that mortality decreased to similar levels as in the overall controls from the general population over time. This could indicate a future trend with a much more favourable prognosis in persons with good glycaemic control than seen in previous epidemiological studies.

Persons with diabetes without previous AMI used to have similar incidence rates of AMI as controls from the general population with established cardiovascular disease. Type 1 diabetes was considered a risk factor equivalent to cardiovascular disease [151, 152]. In low-risk individuals without renal complications and HbA1c below 58 mmol/mol (7.5%), this equivalent seems no longer to be true. This indicates that for AMI, diabetes is currently not an equivalent to cardiovascular disease in young persons diagnosed with diabetes and good glycaemic control.

Glycaemic indices, HbA1c, and CGM metrics provide information that is complementary. Similar studies on TIR metrics, such as the DCCT/EDIC on HbA1c and the correlation to complications over time, will not be performed. The main reason is that a study with a similar design would be unethical since hyperglycaemia is an established risk factor for complications.

Consensus documents highlight the importance of TIR%, and increased time in TIR% seems to be protective with respect to developing late complications of diabetes. Several publications have examined the possibility of correlating CGM metrics to HbA1c since landmark diabetes studies are based on glycaemic levels measured in HbA1c [129, 153, 154]. However, the relationship between HbA1c and TIR% is complex and differs markedly between individuals and groups of individuals. We found that persons with different types of diabetes and MDI treatment differed in CGM metrics. Time in hypoglycaemia is an important physiologic and psychological adverse effect of insulin treatment. Persons with type 1 diabetes had an increased risk of hypoglycaemia, and the TIR% at a given HbA1c was lower than in those with type 2 diabetes. Therefore, persons with type 2 diabetes should probably strive for higher TIR% to reach the same target HbA1c as persons with type 1 diabetes, maintaining less risk of hypoglycaemia. A possible explanation for the differences in CGM metrics is the remaining C-peptide levels in this population of persons with type 2 diabetes [155].

Hyperglycaemia estimated by HbA1c is a strong risk factor for complications of diabetes, as shown in papers I, II, and III. The differences in the type of diabetes and perhaps remaining insulin production are important to consider when establishing glycaemic targets in CGM metrics in clinical practice and guidelines.

Strengths and limitations

One of the strengths of papers I, II, and III is that almost all persons with type 1 diabetes in Sweden are included in these studies with nationwide coverage. Another strength is the information on risk factor burden from persons with type 1 diabetes from the NDR. Furthermore, data from NDR reflects real-world diabetes care. In paper IV, a strength was that both populations were included from the same background population, had similar mean HbA1c, treatment with MDI, and had the same model of CGM-system. Finally, the fact that both groups had similar glycaemic control and CGM mean glucose levels enabled a valid comparison of the CGM metrics in the groups.

Limitations of the studies are mainly related to the study design based on data from registers, which means that some data is missing. In paper III, a limitation was that we had no information on risk factor burden in the controls from the general population and, therefore, no information on renal function. Moreover, our results are based on risk factor burden from 2002 onward. Historical high-risk factor burden affects the prognosis as seen in the DCCT study, and we do not have information on historical risk factor burden before 2002. This can probably affect our results. However, we had information on risk factor burden over an essential period.

In observational studies such as ours, residual confounding can affect the results by overestimating or underestimating the attributable risk of each risk factor. This is probably why being underweight and not overweight increases the risk of amputation in our study. Underweight in a person with long-standing type 1 diabetes can be due to weight loss caused by gastroparesis. Gastroparesis results from neuropathy and neuropathy is one of the most important complications leading to diabetes foot ulcers. Therefore, underweight per se is probably not a risk factor for amputation but a surrogate variable indicating neuropathy or other important comorbidity.

In paper IV, one limitation was that persons with HbA1c ≥58 mmol/mol (7.5%) were excluded, and the results of this study could be different in persons with better glycaemic control. Moreover, CGM measurements in persons with type 2 diabetes of today probably differ from the results in our study since modern treatment with GLP-1 analogue or SGLT-2i is associated with less glycaemic variability and time in hypoglycaemia. Another limitation is that our results are probably not valid for the heterogeneous group of persons with type 2 diabetes. The MDI-Liraglutide group had a mean BMI of 33.6 kg/m^2 and

considerable remaining insulin production after 17 years of diabetes duration. Our results can probably not be extrapolated to CGM metrics in lean persons with type 2 diabetes and low remaining insulin production since their metrics are probably more similar to those with type 1 diabetes.

6 CONCLUSION

The risk of atrial fibrillation is increased in persons with type 1 diabetes, and the mechanisms are unclear. We found that the most important risk factors for atrial fibrillation in persons with type 1 diabetes are renal complications and older age. Screening for atrial fibrillation in high-risk persons could lead to earlier initiation of stroke-prevention treatment.

The incidence of lower extremity amputations in persons with type 1 diabetes decreased over two decades, and the most important risk factors were renal dysfunction and hyperglycaemia. We saw a decreasing incidence of amputations along with decreasing levels of HbA1c. This could indicate a positive effect on ulcers healing from lower HbA1c. Persons with diabetes ulcers could benefit from more intense glycaemic control even though this group usually has less strict glycaemic targets due to multimorbidity.

Mortality and cardiovascular complications over two decades have decreased in persons with type 1 diabetes and in controls. However, the excess risk associated with type 1 diabetes persisted, except among persons without cardiorenal complications who had rates similar to or even slightly lower than in controls. Epidemiological studies on the prognosis of late complications of diabetes could overestimate the current risk associated with type 1 diabetes in young persons, especially if glycaemic balance is good. Therefore, we might expect further improvement in prognosis in persons with type 1 diabetes in the coming decades.

HbA1c and CGM metrics provide information that is complementary. CGM metrics are valuable in clinical practice to evaluate actual insulin regimens, but the correlation between glycaemic indices and HbA1c varies depending on individual factors and type of diabetes. There is rising evidence for the importance of CGM metrics and their relation to late complications of diabetes. Still, one should not assume that CGM metrics have a stronger association with diabetes complications than HbA1c, nor are CGM CGM-metrics easily translated on a population level to values of HbA1c.

7 FUTURE PERSPECTIVES

The prognosis for persons with type 1 diabetes is improving, and with the modern care of today, we could expect more persons with type 1 diabetes to have more risk factors under control. However, some risk factors should be taken into special consideration, such as renal dysfunction and increasing weight.

Among persons with diabetes, the proportion of people with type 1 diabetes is small, around 2 %. The commercial interest in developing treatment for persons with type 1 diabetes is, therefore, lower than drug development for persons with type 2 diabetes. Several new drugs have been registered for persons with type 2 diabetes, including SGLT-2i, GLP-1 analogues, and other incretin-based therapies.

The SGLT-2i dapagliflozin was approved for treatment in persons with type 1 diabetes but withdrawn from the market due to "a conflict of commercial interests" [156]. SGLT-2/1i inhibitors have shown positive results on glycaemic control and weight loss without increasing hypoglycaemia in persons with type 1 diabetes [157-159]. On the negative side, the risk of ketoacidosis increased in persons with dapagliflozin and type 1 diabetes, but not to the extent that it was withdrawn from the market [159]. SGLT-2i has also shown an effect in decreasing the progress of renal disease and improving cardiovascular prognosis in persons with type 2 diabetes, outcomes that probably could be extrapolated to the population with type 1 diabetes [38, 39, 41, 49]. For commercial reasons, this drug, which is likely to have positive effects on risk factor burden and prognosis, is unavailable for persons with type 1 diabetes. In the future, it is essential to evaluate the effect of SGLT-2i in persons with type 1 diabetes and overweight and in other high-risk individuals since it could be expected to have beneficial effects on weight, renal disease, and glycaemic balance.

We found only one modifiable risk factor, BMI, increasing over time in persons with type 1 diabetes. Traditionally, type 1 diabetes persons have been described as lean, but lifestyle factors, intensive insulin treatment, and energy-dense diets have affected weight in persons with type 1 diabetes. The proportion of overweight and obese persons with type 1 diabetes is similar to that of the general population, with a prevalence of around 40%. Weight reduction in overweight or obese persons with type 1 diabetes is not well

studied but is probably beneficial for health. A possible tool for weight reduction in persons with type 1 diabetes could be incretin-based drugs.

New drugs are usually tested in randomised controlled trials in high-risk groups. For example, several studies on drugs evaluating cardiovascular effects included only high-risk individuals with type 2 diabetes. Empagliflozin, Dapagliflozin, and Liraglutide included persons with type 2 diabetes with high risk factor burden or established cardiovascular disease [38, 39, 43]. Similar methods have been applied in evaluations of renoprotective treatment [44, 85]. We found cardiovascular risks very different in high-risk and low-risk persons with type 1 diabetes. Evaluating treatment in groups with potentially greater benefits has not been performed in persons with type 1 diabetes. Still, it is essential to evaluate the effects of drugs such as SGLT-2i, finerenone, GLP-1 analogues, and other incretin-based therapies in high-risk persons with type 1 diabetes.

Finally, diabetes care has improved much in the last decade with the development of new technology such as CGM, advanced insulin pumps, and digital insulin pens. It is important to evaluate existing drugs that probably would positively affect prognosis even more in subgroups of persons with type 1 diabetes. Risks of acute complications have to be balanced with the long-term risk of progression of renal disease and increasing weight in persons with high BMI and type 1 diabetes.

ACKNOWLEDGEMENT

I want to express my sincere gratitude and appreciation to family, friends, colleagues and co-authors involved in the work with this thesis. I would especially like to thank:

Marcus Lind, principal supervisor, for sharing your profound research knowledge, inspiration, patience and sense of humour in supporting the work with this thesis. I could not have chosen a better supervisor. Thank you for your good friendship during these years.

Annika Rosengren, co-supervisor, for sharing your immense experience in research with me and for your advice and invaluable input.

Magnus Löndahl, co-supervisor, for your helpful advice and comments.

Aldina Pivodic, **Henrik Imberg** and **Nils-Gunnar Persson** for statistical advice throughout the years.

All co-authors of the manuscripts, thank you for sharing your invaluable knowledge with me.

Katarina Glise-Sandblad, my fellow companion during my PhD. Thank you for your support, encouragement, friendship, talks, walks, and sad and fun moments.

Shilan Ahmadi and **Ramanjit Singh,** thank you for good collaboration and your diabetes research enthusiasm.

To the most supportive research nurses and dietician **Marie Ekström, Anna Folino**, **Magdalena Stosic**, **Christina Larsson**, **Sheyda Sofizadeh**, **Arndís Finna Ólafsdottír** and **Sofia Sterner Isaksson,** who have created a friendly research environment in the "paviljongerna" and helped me along with the work with the clinical trials at the research department at Östra Hospital and Dalabergs vårdcentral.

Ulrika Forslund-Grenheden for help with administration related to the work with this thesis.

To the current head of the Internal Medicine, Emergency and Geriatric Department at Östra Hospital, **Sofia Ekdahl**, for your efforts to enable diabetes research and for supporting the work with this thesis.

Annika Dotevall, my former clinical supervisor and current colleague. I appreciate your support during those years, for sharing your clinical experience with me, and for guiding me into research.

All former and present fellow PhD students and researchers at the Internal Medicine, Emergency and Geriatric Department at Östra Hospital for creating a research-friendly atmosphere. And to all colleagues at the department of MGA Östra for friendliness and good clinical support.

My dear colleagues and friends **Beatrice Aldenborg** and **Jacob Philipsson,** for all the laughter and pleasant breaks from research.

To my parents, **Kerstin** and **Per,** for all your support and your firm conviction, and therefore a self-fulfilling prophecy, that red-haired persons are stubborn.

My brothers, **Petrus**, **Simon** and **David**. Thank you for always being there and your lifelong support when I need you. I am grateful for growing up with you. And also thanks to **Katrin**, **Mette,** and all the children for making our family reunions hilarious, engaging, loud and messy.

My parents-in-law, **Christina** and **Erling**, for all the help with our children, lunch packs and supportive spirit.

Magnus, for everything: your love, patience, encouragement, well-developed axolotl care, lousy cooking and outstanding talent in making me laugh.

Ingrid, **Arvid** and **Agnes,** for unconditional love and all the inspiration, energy, activity, conflicts and laughter you share with me and everyone around you. I am most fortunate to have you in my life.

Many thanks to all persons participating in studies and clinical trials. Thanks to everyone participating in the NDR register, including patients, nurses and other staff members.

The work with this thesis was supported by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement, regionala FoU medel Västra Götalands regionen, the Swedish Heart-Lung Foundation, Fonden för Rehabilitering och medicinsk forskning and Gothenburg society of medicine.

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