Type 1 diabetes in adults: modern treatment and risk of major coronary events

Viktorija Matuleviciene Anängen

Department of Molecular and Clinical Medicine

Institute of Medicine

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2018

Type 1 diabetes in adults: modern treatment and risk of major coronary events

viktorija.matuleviciene-anangen@sll.se

ISBN 978-91-629-0424-1 (PRINT)
ISBN 978-91-629-0425-8 (PDF)

Printed in Gothenburg, Sweden 2018
Printed by Kompendiet

To my family, for being there for me

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." — Marie Curie

Type 1 diabetes in adults: modern treatment and risk of major coronary events

Viktorija Matuleviciene Anängen

Department of Clinical and Molecular Medicine, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Background: According to the National Diabetes Register (NDR) report (2016), 21.2% of adults with type 1 diabetes (T1D) achieve glycemic targets measured with HbA1c (52 mmol / mol) and 20.1% of patients have very poor glycemic control (HbA1c> 70 mmol / mol). In recent years, a positive trend in improving HbA1c has been observed; despite it, there is a great need to understand how diabetes-care can be improved. Thus, the following questions were formulated: To what extent are international guidelines for visits with HbA1c controls in T1D followed? (Study I) Which of the two most commonly used CGM sensors is most accurate in estimating blood glucose levels and which CGM system is most user-friendly? (Study II) Can some patient subgroups have greater effect on insulin pump treatment than others? (Study III) What is the excess risk of acute coronary events for persons with T1D compared to persons without T1D in Sweden, when modern guidelines have been implemented? How does this risk differ for people with T1D in relation to glycemic control and renal complications? (Study IV)

Material and methods: To calculate the HbA1c yearly measurement rate, we included patients from 10 diabetes clinics in Sweden. Data were collected via the Diab-Base electronic record system (study I). Persons with T1D and insulin pump use for at least 5 years who had HbA1c measurement at the beginning and end of the period and patients with insulin injections were included from Dia-Base in study III. In an economically independent from manufacturers clinical trial on precision and treatment satisfaction with 2 different CGM (Dexcom G4 and Enlite) systems, ambulatory patients with T1D were included (study II). All patients arrived at three scheduled visits for blood sampling and filled in a questionnaire regarding treatment satisfaction. In a study of risk of myocardial infarction in persons with T1D compared to controls (study IV), we included patients registered in NDR (n = 33 886) and 5 randomly selected matched controls (n = 169 223). Through interaction with data from the National Board of Social Services, data were collected on cardiovascular disease, death date and causes of death.

Results and conclusions: Persons with T1D, get fewer than 2 HbA1c controls per year on average in Sweden against recommended 4 controls per year. Patients with insulin injections receive fewer HbA1c controls and need extra focus (study I). We found that DexCom G4 had a higher precision and treatment satisfaction, which is likely to make adequate decisions on treatment (study II). We found no strong predictors for the greater effect of insulin pump on lowering HbA1c. The decrease was 2.5 mmol / mol at very high HbA1c compared with about 2 mmol / mol on average. However, insulin pump treatment has a value since a certain decrease in HbA1c occurs (study III). Persons with T1D still had about 4 times the risk of cardiac

infarction than persons without diabetes in Sweden. The risk is significantly lower for people with good glycemic control and absence of renal complications. Continued focus on better methods for improving HbA1c, as well as primary and secondary prevention of coronary artery disease are essential for reducing the risk of coronary complications in T1D.

Keywords: Diabetes, type 1, HbA1c, CGM, insulin pump, major coronary events

ISBN 978-91-629-0424-1 (PRINT)
ISBN 978-91-629-0425-8 (PDF)

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Enligt rapporten från Nationella Diabetesregistret (NDR) (2016) är det enbart 21,2% av vuxna personer med typ 1 diabetes (T1D) som uppnår glykemiskt mål mätt med HbA1c (52 mmol/mol) och 20,1% av patienterna har mycket dålig glykemisk kontroll (HbA1c>70mmol/mol). Trots att det under de senaste åren observerats en positiv trend, vad gäller förbättring av HbA1c, finns ett stort behov att förstå hur diabetesvården kan förbättras. Mot bakgrund av detta, formulerades följande frågor: I vilken utsträckning följs de internationella riktlinjerna för besök med HbA1c-kontroller vid typ 1 diabetes? (Studie I) Vilken av de två mest använda CGM-sensorerna är mest exakt i att skatta blodsockernivån och vilket CGM-system är mest användarvänligt för patienten? (Studie II) Kan vissa patientsubgrupper ha större effekt av insulinpumpbehandling än andra? (Studie III) Hur skiljer sig risken att drabbas av hjärtinfarkt för personer med typ 1 diabetes och övriga befolkningen i Sverige under 2000-talet när moderna riktlinjer har implementerats? Hur skiljer sig denna risk för personer med typ 1 diabetes beroende på glykemisk kontroll och njurkomplikationer? (Studie IV)

Metoder: För att beräkna HbA1c mätningsfrekvensen inkluderade vi patienter från 10 diabetesmottagningar i Sverige. Data insamlades via det elektroniska journalsystemet Diab-Base (studie I). Patienter med insulinpumpanvändning i minst 5 år och som hade HbA1c mätning i början och slutet av perioden och patienter med insulininjektioner inkluderades från Dia-Base till studie III. I en ekonomiskt oberoende klinisk prövning avseende precision och behandlingstillfredsställelse av 2 olika CGM-system (Dexcom G4 och Enlite) inkluderades ambulatoriska T1D patienter (studie II). Samtliga patienter använde samtidigt de två CGM-systemen och kom på tre planerade återbesök för provtagning. Varje patient fyllde i en enkät avseende behandlingstillfredsställelse. Avseende studie om ökad risk för hjärtinfarkt vid T1D jämfört med kontroller så inkluderade vi patienter som var registrerade i NDR (n=33 886) och 5 slumpmässigt utvalda matchade kontroller (n=169 223). Genom samkörning med data från socialstyrelsens patientregister, inhämtades data om hjärtkärlsjukdom, dödsdatum och dödsorsaker.

Resultat och slutsatser: Hos personer med T1D sker inte ens 2 HbA1c-kontroller per år i genomsnitt i Sverige mot rekommenderade 4 kontroller per år. Patienter med insulininjektioner erhåller färre HbA1c-kontroller och behöver extra fokus (studie I). I en oberoende studie fann vi att DexCom G4 hade en högre precision och behandlingstillfredsställelse, vilket sannolikt är av betydelse för att göra adekvata beslut om behandling (studie II). Vi fann inga starka prediktorer för större effekt av insulinpump på att sänka HbA1c där sänkningen var 2,5 mmol/mol vid mycket höga HbA1c jämfört med ca 2 mmol/mol i genomsnitt. Insulinpumpbehandling har dock ett värde då en viss sänkning i HbA1c sker och effekter finns enligt andra studier på livskvalité och hypoglykemier (studie III). Personer med T1D hade fortsatt ca 4 gånger högre risk för hjärtinfarkt än övriga befolkningen i Sverige. Överrisken är betydligt lägre för personer med god glykemisk kontroll och frånvaro av njursjukdom. Fortsatt fokus på bättre metoder för att förbättra HbA1c, minska rökning, öka fysisk aktivitet och behandla lipidnivåer och blodtrycksnivåer är essentiellt för att minska risken för hjärtinfarkter vid typ 1 diabetes.

LIST OF PAPERS

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

I. Matuleviciene V, Attvall S, Ekelund M, Clements M, Dahlqvist S, Fahlén M, Pivodic A, Haraldsson B, Lind M. A Retrospective Study in 5,989 Patients with Type 1 Diabetes in 10 Outpatient Diabetes Clinics in Sweden of the Frequency of Measuring HbA1c in Clinical Practice. J Diabetes Metab. 2014;5:377

II. Matuleviciene V, Joseph JI, Andelin M, Hirsch IB, Attvall S, Pivodic A, Dahlqvist S, Klonoff D, Haraldsson B, Lind M. A Clinical Trial of the Accuracy and Treatment Experience of the Dexcom G4 Sensor (Dexcom G4 System) and Enlite Sensor (Guardian REAL-Time System) Tested Simultaneously in Ambulatory Patients with Type 1 Diabetes. Diabetes Technol Ther. 2014;16(11):759-67.

III. Clements M, Matuleviciene V, Attvall S, Ekelund M, Pivodic A, Dahlqvist S, Fahlen M, Haraldsson B, Lind M. Predicting the effectiveness of insulin pump therapy on glycemic control in clinical practice: A retrospective study of patients with type 1 diabetes from 10 outpatient diabetic clinics in Sweden over 5 years. Diabetes Technol Ther. 2015;17(1):21-8.

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

CONTENT

ABBREVIATIONS

ADA	American Diabetes Association
AMI	acute myocardial infarction
AN	autonomic neuropathy
ARB	angiotensin II receptor blockers
BG	blood glucose
BMI	body mass index
CACTI	The Coronary Artery Calcification in Type 1 Diabetes study
CDR	Cause of Death Registry
CGM	continuous glucose monitoring
CHD	coronary heart disease
CI	confidence intervals
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRU	clinical research unit
CSII	continuous subcutaneous insulin infusion
CVD	cardiovascular disease
DCCT	The Diabetes Control and Complications Trial
EDC	Epidemiology of Diabetes Complications
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	Food and Drug Administration

FGM	flash glucose monitoring
GEE	Generalized Estimating Equations
HbA1c	Glycosylated Haemoglobin
ICF	informed consent form
IFCC	International Federation of Clinical Chemistry
IPR	Swedish Inpatient Registry
LEA	lower extremity amputation
LISA	Longitudinal Integration database for health insurance and labor market studies
MAD	mean absolute difference
MARD	mean absolute relative difference
MDI	multiple daily injections
MI	myocardial infarction
NDR	National Diabetes Registry
NGSP	National Glycohaemoglobin Standardization Program
OR	odds-ratios
PDR	Prescribed Drug Registry
PKC	protein kinase C
RAAS	renin–angiotensin–aldosterone system
T1D	type 1 diabetes
T2D	type 2 diabetes
UKPDS	UK prospective Diabetes Study Group
WHO	World Health Organization

FOREWORD

Working at the emergency department gave me many opportunities to meet people and families hearing "diabetes" for the first time in that unwanted personal way. Some of them are frightened and wondering what is going to happen to them, others having an infinite number of questions from the first moment or asking if their lifestyle has had an impact on their health in such a bad way. I met patients who believed that medicine is so powerful that nowadays we can cure diabetes like pneumonia. I would love to give that hope, but keep thinking for myself: "Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." — Marie Curie. I met young people who have been ignoring their new life with diabetes and all the rules.

Apparently, a patient and a healthcare provider often have different perspectives on the same topic. I would like to help us to come closer to each other. I believe that science can battle some fears and I hope that this thesis will bring closer to the answer to one of most essential patient questions like: do I have a chance to live MY life?

1 INTRODUCTION

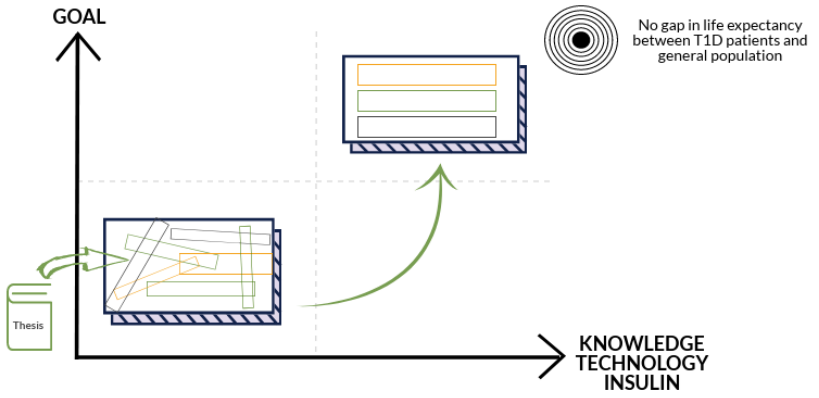
1.1 RATIONALE

According to WHO report, in 2014 approximately 422 million adults aged over 18 years were living with diabetes (1). It is not always easy to differentiate between type 1 and type 2 diabetes (2). Thus, it requires evaluating pancreatic function, for example, to measure C-peptide levels to estimate insulin secretion capability (3). The most significant biomarkers of type 1 diabetes are autoantibodies. The 65kDa form of glutamic acid decarboxylase (GAD65), [pro]insulin, insulinoma antigen 2 (IA-2), zinc transporter 8 (ZnT8), tetraspanin 7 are identified as molecular targets in type 1 diabetes (4). There is no precise global prevalence of type 1 diabetes (1). Type 1 diabetes accounts for 5% to 10% of all diabetes cases (5). Epidemiology in middle and low-income countries is not studied enough (6). However, type 1 diabetes is the major public health problem and affects millions of people globally. We live in the era of fast-developing technologies, knowledge of T1D management grows exponentially, but type 1 diabetes is still challenging health care. The European region currently has the highest prevalence of T1D in children of any area in the world (1); diabetes is not "curable," it continues into adulthood.

The costs associated with diabetes account for approximately 10% of the entire European public health care expenses (7). Severe hypoglycemic events are associated with emergency healthcare resource use and economic costs. Diabetes complications (micro- and macrovascular) account for a significant part of these costs (8). Glycosylated hemoglobin (HbA1c), an estimate of the mean glucose level over the last 2-3 months, is closely associated with the development of diabetes complications (9). A Scottish study showed that of the modifiable risk factors, HbA1c was the most critical cost driver in T1D (10). Well known is that HbA1c levels correlate with the risk of long-term diabetes com-plications (9, 11) - which is the most severe obstacle to mortality reduction in the target population.

Euro Diabetes Index 2014 ranked Sweden as the country with the best diabetes care delivery in Europe (12). However, according to NDR year rapport (2016), just 21.2% of adult persons with type 1 diabetes achieved targets for good glycaemic control (HbA1c<52 mmol/mol) and 20.1% of adult persons with type 1 diabetes in Sweden have inadequate glycaemic control (HbA1c>70 mmol/mol) (13). We know that glycemic control has changed during the last

few years for the better: in 2012, 30% of T1D patients had very poor glycemic control (13).



Despite this apparent improvement of diabetes management, a critical need to understand how to improve glycemic control remains. Therefore, we formulated the following points of interest:

- To support the intensive treatment strategy, diabetes care guidelines recommend monitoring HbA1c at least every third month in patients with glycemic control above the target. To our knowledge, there are few studies evaluating to what extent these guidelines are followed.

- A multicentre observational study over 5 years reported that switching treatment from MDI to CSII was associated with improved HbA1c. This effect decreased however significantly with time, from a relative reduction in HbA1c of 4.6 mmol/mol (≈ 0.42%) at 1 year to 2.2 mmol/mol (≈ 0.2%) at five years of treatment (14). In what subgroup of persons, a greater beneficial effect on HbA1c can possibly be sustained over time has not been evaluated and is another question to answer to optimize diabetes care.

- Continuous glucose monitoring (CGM) is an increasingly common tool to manage glycemia. There are recommendations on when to consider CGM treatment, but in our knowledge, there are no official recommendations for selecting a particular CGM system. Is any CGM device more precise at different glucose levels than others, primarily when hypoglycemia occurs? At the time of designing a study, we could not find any clinical trials comparing patient's subjective experience with different CGM

systems. Both these questions may play a role also for treatment effect and compliance.

The "renaissance" of diabetes care occurred in the last decades of the 20th century and resulted in the perceptible difference to the continuous improvement in life expectancy. Cardiovascular disease (CVD) is the most common cause of death in persons with type 1 diabetes (15, 16). Cardiovascular disease event occurs earlier in persons with T1D than in the general population. Epidemiological studies support the relationship between inadequate glycemic control and cardiovascular events (3). Recent studies suggest that effects of good glycemic control on cardiovascular risk may be more complicated. Optimally managed glycemia solely may not provide the desired cardiovascular risk reduction. Thus, risk might depend on other factors, such as age, gender, diabetes duration and diabetic kidney disease. (3, 17, 18). The excess risk of AMI in persons with T1D since new guidelines of intensive management of diabetes mellitus and improvement regarding the treatment of CVD risk factors such as hyperlipidemia and hypertension were implemented in Sweden has not been estimated. Evaluation of how the excess risk of major coronary events varies as a function of glucose control and presence and severity of renal complications in persons with T1D is another question on target.

Since the prevalence of type 2 diabetes in the global perspective is increasing significantly (1), it is easy to underrate the needs of the 5-10% of patients with type 1 diabetes. I believe this work could lead to better understanding of T1D treatment and guide management for improved outcomes in T1D patients.

Structure of the thesis

The thesis frame is divided into two parts: modern treatment and risk of major coronary events. The light grey box indicates the summary of the chapter.

1.2 TYPE 1 DIABETES, HISTORICAL MOMENTS

The first written records of diabetes come from ancient Egypt around 1500 BC described as "too great emptying of the urine" (19). However, as the defined medical condition diabetes history is counting just a little bit more than 140 year. In the late XIX century, Etienne Lancereaux characterized diabetes as a syndrome and observed that some diabetes patients live many years while others die within 2-3 years (20). This understanding gave a basis for the modern rough breakdown of diabetes to type 1 and type 2.

Type 1 diabetes is caused by the deterioration of insulin-producing pancreatic Beta cells (21). Some years ago, age was one of the most important criteria to diagnose type 1 diabetes.

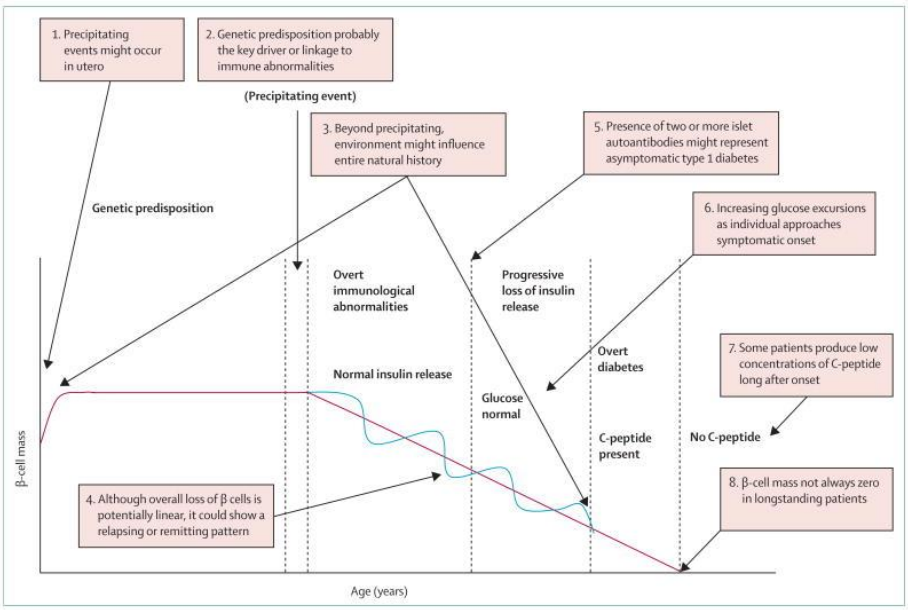


Figure 1. Type 1 diabetes. Natural history. Adapted with the permission after reference 21

Type 1 diabetes generally manifests in children or teenagers. However, it is more evident now that type 1 diabetes can occur at any age, and recent studies show that in certain individuals residual C-peptide can be detected many years after the initial diagnosis was made (21, 22). An even more challenging aspect of diabetes is that children may get type 2 diabetes. The exact cause for type 1 DM is not known. Natural history of type 1 diabetes is presented in figure 1. Genetic factors are identified to contribute to the susceptibility of developing

T1D. Over 20 genes have been found to influence the susceptibility to the T1D (23). Despite it, almost 90% of the newly diagnosed T1D cases have no family history (24, 25). Men and women have the same risk (26).

The key sign of type 1 diabetes is the need for insulin treatment due to decreased insulin secretion, which causes hyperglycemia. The typical clinical manifestation of this disease is polyuria, polydipsia and weight loss. Sometimes the first identifiable sign of T1D may be ketoacidosis. Ketoacidosis is an acute life-threatening complication of diabetes caused by reduced insulin levels.

1.2.1 INSULIN DISCOVERY

Insulin was discovered in the early thirties (27). Bunting (unknown surgeon at that time) has formulated an idea and convinced the diabetes coryphaeus prof. J.Macleod (working in Canada), to start the experiment. The central part of the investigation was stopping the flow of nourishment in the pancreatic duct which led to damage in the cells producing digestive enzymes, but not islets of Langerhans, in dogs. Thus, insulin could be extracted. The experiment started in 1921 (27, 28). By the end of the year, the group already worked on purifying of insulin.

The team desired to start experiments in humans. As soon as in 1922 in Toronto, Canada, Leonard Thompson (a 14-year old diabetes patient), received insulin injections (28). Thompson's health improved. Also, already in February insulin was administered to 6 more patients. Leonard Thompson received insulin for 13 years and died of pneumonia at the age of 27 (28, 29).

After just two years, insulin production was extended. There was produced enough insulin to supply the North America continent (29). In 1923 the Nobel Committee decided to award Banting and Macleod the Nobel Prize in Physiology or Medicine (29). Insulin with longer duration of action was introduced in the 1930s; a lot was done to improve the purity of insulin (26). However, not until the 1980s was the first insulin of human amino-acid sequence was introduced to the market.

Table 1. Available insulin formulations (30). Peak and duration of action are dose-dependent and may vary from times listed in the table.

Insulin	Onset of action	Peak of action	Duration of action
Rapid-acting Insulin lispro (Humalog) Insulin glulisine (Apidra) Insulin Aspart (NovoRapid)	10-15 min	0,5-3 h	3-5 h
Insulin Aspart (Fiasp)	5-10 min	1h	3-5 h
Short-acting -Humulin regular	30-60 min	2-4h	5-8 h
Intermediate-acting (NPH)	60-120 min	4-10 h	10-16 h
Long-acting -Insulin detemir (Levemir) -Insulin glargine (Lantus) -Insulin degludec (Tresiba)	60-180 min	minimal peak	17-24 h 24 + h

1.2.2 MAJOR TECHNICAL ACHIEVEMENTS

In 1969 blood glucose meters became available. (31)

In 1976 the first wearable continuous subcutaneous insulin infusion was developed (insulin pump therapy). (31)

In 1999, the Food and Drug Administration approved the first CGM device in the USA. It was called the continuous glucose monitoring system (CGMS) and manufactured by Medtronic MiniMed (Medtronic Diabetes, Northridge, CA). Readings were available to review by physicians only after recording interval of 72 hours, retrospectively. (32)

In 2016, the Food and Drug Administration approved the first hybrid closed-loop system (Medtronic MiniMed 670G) that continuously tracks glucose levels and adapts insulin delivery. (33)

1.2.3 BEYOND THE BASICS

The exact number of patients with type 1 diabetes in the world is not known (1). Only a few countries have established appropriate registries. Approximately 78000 youths are diagnosed with type 1 diabetes every year worldwide (34). The incidence varies a lot among countries. The lowest incidence of T1D is in East Asians and Native Americans, the highest - in Finland, Sardinia, and Sweden (20). A higher than 350-fold difference in the incidence of T1D among the 100 different populations worldwide was reported (34). However, the latest observations show a rapid change in incidence of type 1 diabetes among a genetically stable population (for example, in mainland China incidence in-creased from 0.57:100000 person-years to 3.36:100000 person-years) (35) which may mean that other factors (non-genetical) have an impact on high morbidity. The understanding of these changes in the global and not least historical perspective is crucial for the chances to achieve the successful health-care.

The American Diabetes Association (ADA) has been actively working with creating and spreading of obtained knowledge in diabetes healthcare standards, based on the quality of evidence (34). However, health care for type 1 diabetes patients differs from country to country. The healthcare situation in economically weak countries possibly may be comparable to that in Sweden several decades ago. In the USA more than 98% of persons with type 1 diabetes live longer than six years after the diagnosis, in sub-Saharan Africa - just 1% of patients with newly diagnosed type 1 diabetes can expect to live for the next six years (36). Life expectancy in Mozambique is approximately seven months after type 1 diabetes is diagnosed (36). These vast differences in life expectancy depend on the economic realities of insulin accessibility.

In the USA more than 98% of persons with type 1 diabetes live longer than six years after the diagnosis, in sub-Saharan Africa - just 1% of patients with newly diagnosed type 1 diabetes can expect to live for the next six years (36).

2 DIABETES CARE TODAY: HBA1C, CARDIOVASCULAR COMPLICATIONS AND TECHNICAL DEVICES

2.1 HBA1C TESTS

HbA1c reflects the mean glycemia over the approximately 120 days period (erythrocyte lifetime) and is widely used for the routine monitoring of long-term glycemic status in patients with type 1 diabetes (37, 40, 54). Multiple studies show the strong association between HbA1c levels and micro- and macrovascular complications of diabetes mellitus (10, 15, 38). HbA1c values are also used as the indicator of the quality of diabetes care. In Sweden, approximately 1.2 million HbA1c tests are performed annually (39). More than 100 different commercial tests have been developed to measure HbA1c (40). It raised concerns about the accuracy of measurements which is needed for strict quality management. Insights from the DCCT, and the UK prospective Diabetes Study Group (UKPDS) studies raised the necessity of an accurate, precise HbA1c assay (41). In 1997, a nationwide standardization was introduced. In 2001, IFCC HbA1c reference method approved. The major statement is that all values are to be converted and reported in SI units (mmol/mol) and derived National Glycohaemoglobin Standardization Program (NGSP)/DCCT units (40). In 2007 IFCC and clinical organizations agreed to use these units. In Sweden, the performance of locally measured HbA1c is monitored by Equalis through external quality assessment schemes (42). The National Board of Health and Welfare recommended HbA1c goal for nonpregnant adult with type 1 diabetes is below 52 mmol/mol (43). Distribution of HbA1c levels in adult persons with T1D in Sweden is presented in figure 2.

According to UK type 1 diabetes management guidelines, HbA1c should be checked twice yearly in adult (≥18 y.o.) patients who are meeting treatment goal HbA1c ≤52 mmol/mol and every three months in patients whose therapy is being modified or who are not achieving the goal (44) Similar recommendations are provided by ADA (45). Swedish guidelines have not specified the frequency of HbA1c measurements in adult persons with type 1 diabetes (43). In very elderly or limited lifespan as well as in those T1D patients with a high risk for severe hypoglycemia, the HbA1c goal can be less stringent (46). Results from a British study examining repeat HbA1c tests from three clinical laboratories in 79409 persons with diabetes (both T1D and T2D) showed that in a subgroup of persons with an inadequate glycemic control

(HbA1c ≥53 mmol/mol) testing HbA1c every third month was associated with a 3.8% reduction in HbA1c compared with a 1.5% increase detected with testing HbA1c once per year (47).

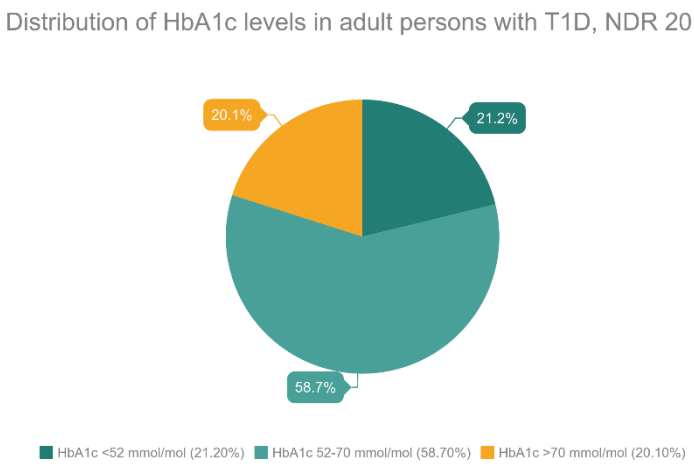


Figure 2. Distribution of HbA1c levels in adult persons with T1D in Sweden (13)

There is no high-quality evidence for the optimum frequency of HbA1c monitoring in the clinical practice (48). Adherence to the HbA1c testing frequency in T1D is not studied enough. Most of the previous research focused on persons withT2D or included patients regardless of the type of diabetes. In brief, J.Lian found that only 12.36% of T2D patients met the ADA recommended HbA1c testing frequency (49). A large retrospective study from Australia reported that about 58.3% of the T2D patients did not have the recommended HbA1c tests (50). In another significant study from the UK, Driskell OJ. reported that just 49% of HbA1c test requests conformed to guidance and highlighted both over-requesting and under-requesting it (51). Suboptimal HbA1c testing in children and youth with diabetes is also reported (52). We could not find studies evaluating the sociodemographic predictors of HbA1c testing among T1D patients.

Many studies prove the association between HbA1c and diabetes complications. According to treatment recommendations, if the therapy has been modified or HbA1c is not meeting the target levels of 52 mmol/mol, the HbA1c check should be done every three months. Evidence supports recommendations. However, most of the studies are performed in patents

with type 2 diabetes. Some studies show non-adherence to the guidelines in terms of HbA1c testing frequency.

2.1.1 CONDITIONS THAT MAY AFFECT HBA1C LEVELS

Conditions that reduce red-blood cells lifespan, or decreases their mean age, falsely lower HbA1c test results (53, 54): bleeding, hemoglobinopathies, hemolysis, renal anemia and vice versa. Conditions that increase the mean age of circulating erythrocytes may affect HbA1c in the opposite direction, in other words elevate HbA1c levels. Most studies investigating the effect of anemia on HbA1c are limited to the small sample groups, but data support that iron deficiency may lead to elevated HbA1c levels (54). The mechanism through which iron deficiency influences HbA1c is not fully understood. Several investigators found that effect of iron deficiency on HbA1c depends on the degree (55, 56) of anemia and some studies suggest that in mild anemia cases effect on HbA1c may lack in clinical relevance (57). Iron deficiency is highly common in the world and affects more than 30% of the population, especially women of childbearing age, approximately 4-12% of women have anemia. Diabetic patients, especially with inadequate glycemic control are at the higher risk to develop chronic kidney disease, which in its turn can cause anemia. The role of glycemic control and the value of HbA1c in these patients are controversial and need further investigation. Few studies investigated the effect of iron supple-mentation or erythropoietin therapy on HbA1c levels in patients with type 1 diabetes. Most of the studies investigated effect in persons without diabetes or in persons with type 2 diabetes showing that iron and erythropoietin-stimulating agents caused the fall in HbA1c values (58-60). Anemia seems to be a factor to consider before making a therapy decision based solely on HbA1c levels.

2.1.2 WHY GLUCOSE LEVEL MATTERS?

Vascular complications of type 1 diabetes (such as retinopathy, nephropathy, and ischemic heart disease) are the unfavorable manifestations of diabetes. Glycemia has been shown to be one of the strongest risk factors of future microvascular and macrovascular complications (10, 11, 15, 64). Unfortunately, the precise mechanism is not fully understood. It has been discussed that some of the tissues are prone to be damaged by chronic hyperglycemia, but others are not (61). It has been suggested that it may

depend on the capability to maintain the constant concentration of the glucose in the cell (61).

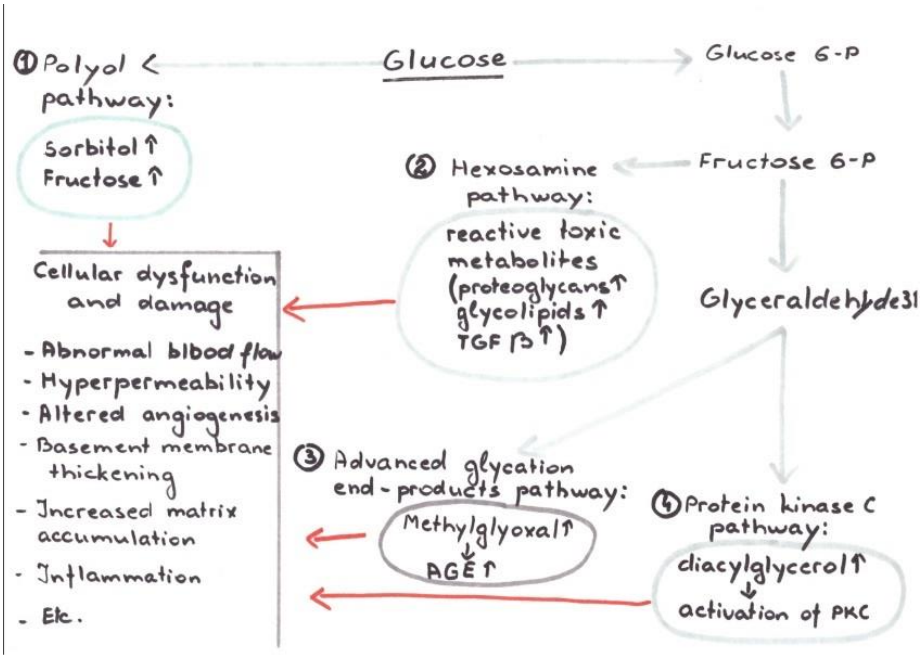


Figure 3. Vascular and interstitial tissue damage causing pathways.

Vascular and interstitial tissue damage is caused by at least four different pathways (61) (shown in figure 3):

1. Polyol pathway
2. Hexosamine pathway
3. Advanced glycation end-products formation
4. Protein kinase C (PKC) pathway

1. Increased polyol pathway (61, 62) leads to oxidative stress due to the ac-cumulation of sorbitol and fructose. Sorbitol is highly hydrophilic and cannot diffuse through the cell membrane unimpeded and causes hyperosmolarity which for its part induces oxidative stress (62).

2. Increased hexosamine pathway flux increases the formation of proteo-glycans, glycolipids and some other toxic metabolites, increases the expression of TGF-beta and causes alterations in the gene expressions. This leads to vascular endothelial dysfunction (62, 63).

3. Increased intracellular formation of advanced glycation end-products arises from intracellular oxidation of glucose to glyoxal and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal. This alters the functional properties of several matrix proteins and promotes the synthesis of growth factors and cytokines (62).

4. Intracellular hyperglycemia increases the amount of DAG, which activates PKC. It is suggested that PKC by depressing nitric oxide production and increasing activity of endothelin-1 causes blood flow abnormalities. Activation of PKC contributes to increased permeability of endothelial cells and micro-vascular matrix protein accumulation (61, 62).

Despite these systemic factors, organ-specific factors are also crucial in the pathogenesis of diabetes-specific complications.

Continuously high blood glucose levels lead to changes on the molecular level in some tissues and manifest the condition of vision impairment, kidney dam-age, and loss of sensation. There are four central pathways of tissue damage.

Clinical effects of hyperglycemia

So far, the previous chapter has focused on pathways triggered on hyperglycemia. The current chapter will discuss clinical effects of chronic hyperglycemia. A considerable amount of literature has been published on T1D complications. The impact of T1D complications on patients' quality of life is significant (3, 157), and a critical need to understand how to reduce risks is still an important issue. Many studies pay particular attention to the effects of glycemic control. Evidence shows that good glycemic control in the early

stage of the disease, reduces the risk of complications (10, 11, 64)). One of the most important studies in the field, the Diabetes Control and Complications Trial (DCCT) was con-ducted between 1983 and 1993 and designed to determine whether intensive treatment would delay or prevent complications in T1D patients. The adjusted mean risk of development of retinopathy in the primary prevention cohort (T1D patients with no previous retinopathy) was reduced by 76% (11). The risk of microalbuminuria decreased by 34%, and neuropathy by 69% (11). DCCT study participants were offered to continue participating in the follow-up study –Epidemiology of Diabetes Interventions and Complications (EDIC). The long-term treatment effects on microvascular and macrovascular complications were evaluated (64). Intensive treatment had the beneficial effect on the incidence of both micro- and macrovascular complications. Several other studies reported evidence on the association between hyperglycemia and diabetes complications (10, 15, 38, 65). DCCT/EDIC studies showed, that higher HbA1c levels at the baseline and during follow up period were associated with hypertension (66, 67). Hypertension contributes to the development of microvascular complications (68) and may mediate the risk of cardiovascular complications (67).

How high levels of blood sugar affect your body? High levels of glucose are unhealthy for your body. If high glucose levels persist, it can cause changes in blood vessels. Blood vessels become hardened and narrowed. This makes difficult for blood to flow through them. Consequences of it: impaired vision (in extreme cases even vision loss), kidney damage, nerve damage, which causes pain, loss of sensation. Larger vessels may be affected as well, and it may lead to a heart attack. Vessels that supply blood to the limbs also may be affected. The worth effect of damage in the large vessels may be an amputation of the limb or even death. Good glycemic control (in clinical studies achieved by using intensive insulin treatment such as multiply daily injections or insulin pump) significantly reduces the risk of vision impairment, kidney damage, and nerve damage.

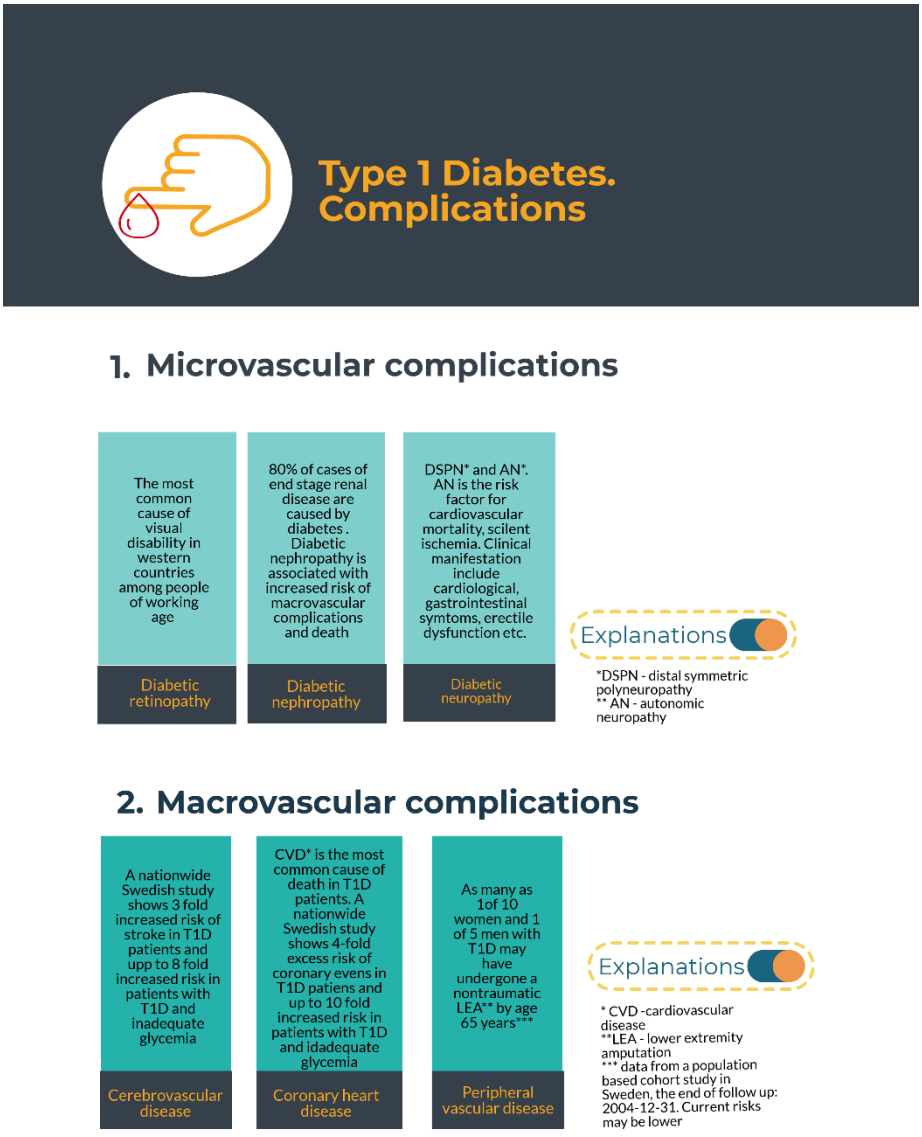


Figure 4. Risk factors associated with microvascular and macrovascular complications in T1D (1, 3, 15, 45, 115-116, 166)

2.2 CARDIOVASCULAR COMPLICATIONS

2.2.1 CARDIOVASCULAR COMPLICATIONS IN T1D

In the World Health Organization (WHO) multinational cohort, cardiovascular disease (CVD) accounted for 44% of T1D deaths (69). A nationwide registry-based Swedish study with 33 915 T1D patients and 169 249 matched controls reported that 2.7% of persons with T1 diabetes and 0.9% of matched controls died from cardiovascular causes (34). The mean follow-up was 8.0 and 8.3 years and the mean age was 35.8 years and 35.7 years in the T1D and matched control groups, respectively. According to a UK study, T1D patients aged over 65 years have a CVD prevalence of 39.5% (70). In a Danish study with 4821 T1D patients, CVD was the main cause of death, 31% and 30% of all death for men and women, respectively (71). Several studies reported no significant difference in incidence of cardiovascular disease in men and women with T1D, the female sex protection seen in the general population was not observed in T1D (3, 72-75). Overall, T1D patients experience CVD more often (3, 15) and earlier than persons without diabetes, when types of CVD are separated, coronary heart disease (CHD) predominates (3, 15, 75).

Children, adolescents, and adults with T1D have increased the thickness of carotid intima-media and elevated plaques compared to healthy age and sex-matched controls (76). The altered endothelial function is observed in T1D even at an early stage of disease and even in patients without detectable atherosclerotic changes (77). Studies prove that risk factors such as diabetes duration, glycemia, dyslipidemia, smoking, albumin excretion rate are associated with intima-media thickness and that the major factor triggering the development of endothelial dysfunction is hyperglycemia (76). It has also been reported that endothelial dysfunction is more severe in patients with presence of microalbuminuria (17). The Pittsburg Epidemiology of Diabetes Complications (EDC) study reported that patients with dysfunctional endothelium have the higher risk to develop coronary heart disease (78). It is known that endothelial dysfunction leads to the development of atherosclerotic changes in the vessels (79). When CHD occurs clinically, the pathophysiological process of atherosclerosis is very advanced.

2.2.2 THE ROLE OF GLYCEMIC CONTROL IN CVD RISK

A Norwegian study, carried out during over 18 years follow-up period prospectively evaluated atherosclerotic changes in coronary vessels with intravascular ultrasound and found strong correlation between atheromatosis and HbA1c, where 1% (≈10 mmol/mol) increase in HbA1c was associated with 6.4% coronary artery stenosis (80). Epidemiological evidence generally

supports the association between hyperglycemia and clinical coronary heart events (3). A registry-based Swedish study reported the strong association between HbA1c and coronary artery disease in a T1D population, showing progressively increasing risks for CHD and CVD with higher HbA1c (81). A Finnish study carried out over an 18 years long follow-up period showed that CVD mortality in middle-aged (at the baseline) patients with type 1 diabetes increases by about 50% with every 1% (≈10 mmol/mol) increase of HbA1c (82). Similar results were shown in a population-based cohort of 879 patients with T1D from Wisconsin: hyperglycaemia was associated with cardiovascular mortality in a dose-dependent manner. Association between hyperglycemia and cardiovascular mortality remained even when glycemia was analyzed as a continuous variable (65).

The importance of strict glycemic control to protect against macrovascular complications in T1D has been established among other things in the DCCT/ EDIC studies. Despite the young age of the participant at the baseline (13 to 40 years at the time of randomization) (11), a long follow up period (mean 17 years) (83) allowed to evaluate cardiovascular risk in the cohorts. The amount of non-fatal and fatal cardiovascular events in the intensive treatment group was lower compared to the conventional treatment group (11, 64, 83). The risk of any cardiovascular disease event in the intensive treatment cohort was reduced by 42 percent. It is important to note that the difference in HbA1c from the end of the DCCT (1993) study (57.4 mmol/mol (7.4%) in the intensive treatment and 76.1 mmol/mol (9.1%) in the conventional treatment group) to year 11 in the EDIC (2004) has attenuated and was 62.8 mmol/mol (7.9%) and 61.7 mmol/mol (7.8%) respectively (11, 84). It is likely that glycemic control in the early years of T1D may play an essential role in the prevention of future complications. The DCCT/EDIC Research Group reported that for 1% (≈ 10 mmol/mol) increase in mean HbA1c, the risk for or major atherosclerotic cardiac event increased by 42% (85).

However, not all previous studies reported the association of inadequate glycemic control with cardiovascular morbidity and mortality, which may indicate that other pathways than effects of glycemic control should also be taken in to account (86, 87). Looking from the other perspective, according to a recent epidemiological registry based (NDR) study, among 18450 type 1 diabetes patients, 1023 had >50 years diabetes duration. A third part of those patients (N=319) had no history of CVD, kidney disease or severe retinopathy. The study reports that these patients were younger and had lower HbA1c compared to those who developed CVD (88).

2.2.3 THE ROLE OF DIABETIC NEPHROPATHY IN CVD RISK

Chronic kidney disease is defined as functional or structural abnormalities of the kidneys, persisting for at least three months (89). Diabetic nephropathy is one of the microvascular complications of DM. Studies show a strong association of it with cardiovascular disease, but this relationship is not fully under-stood (89, 90). Chronic kidney disease is one of the frequent exclusion criteria for participation in major cardiovascular trials. Out of 86 trials, more than 80% excluded patients with end-stage kidney disease and 75% excluded patients with chronic kidney disease (91). This may contribute to a lack of evidence for potential treatment choices. It is known that a person with chronic kidney dis-ease (stage 3) has a higher critical risk of death than progressing to end-stage renal disease (ESRD) (92). Albuminuria is identified as a strong prognostic marker in the T1D population. Microalbuminuria is usually considered as the early manifestation of diabetic nephropathy, but its presence alone does not confirm established kidney disease (18). Approximately 15 years after diabetes diagnosis, 20-30 percent of patients develop microalbuminuria (93, 94).

Microalbuminuria is defined as two of three positive samples with an albumin/creatinine ratio of 3-30 mg/mmol (≈30-300 mg/g) or U-albumin of 20-200µg/min (20-300 mg/l). Macroalbuminuria is defined as two of three positive samples with an albumin/creatinine ratio >30 mg/mmol (≈ >300 mg/g) or U-albumin >200µg/min (>300mg/l). Albuminuria should be confirmed in the absence of urinary tract infections (95).

Several studies observed regression of albuminuria with appropriate treatment and control of risk factors (96, 97). The strongest modifiable factors, associated with improvement of albuminuria were lipid status (low level of cholesterol and/ or triglycerides) and glycemia (HbA1c < 63.9 mmol/mol (<8%). Microalbuminuria of short duration is more likely to regress than microalbuminuria of long duration. However, this improvement cannot guarantee preserved kidney function (98), non-albuminuric diabetic nephropathy is now well recognized (99). Increased HbA1c, systolic blood pressure, early glomerular filtration rate decline, serum uric acid, duration of diabetes, age and the presence of concomitant microvascular complications are associated with progressive diabetic nephropathy (100).

Methods of estimating kidney function:

Estimated glomerular filtration rate (eGFR). May be calculated using exogenous (inulin and iothalamate) and endogenous (urea and creatinine) sub-stances.

CKD-EPI equation - assumed to be more precise than the MDRD study equation and may reduce false-positive results (100).

a) CKD-EPI Creatinine*,

b) CKD-EPI Cystatin C**

c) CKD-EPI Creatinine and Cystatin C***

MDRD study equation

* National kidney foundation recommended method for estimating GFR in adults (102).

** Cystatin C considered to be less affected by patients age and weight than creatinine-based measurements and is the better predictor of micro- and macrovascular complications (103, 104). Cystatin C is not superior to serum creatinine to estimate acute changes in kidney function. Clinical use remains limited.

*** studies show that combining Cystatin C and creatinine as well as age and sex factors, GFR estimation may be most precise (101, 105).

ACE inhibitors and angiotensin II receptor blockers (ARB) are even in the absence of hypertension used to decrease microalbuminuria (106). The renin–angiotensin–aldosterone system (RAAS) blocking agents (ACE inhibitors and ARB) may cause an acute but transient decrease in glomerular filtration rate (GFR)due to the reduction in glomerular hyperfiltration, usually detected by measuring elevated creatinine levels. Both ACE inhibitors and ARB have an important role in the prevention of progression of renal disease (107) and changes in coronary arteries (108). Before angiotensin inhibition along with intensive glycemic control was implemented in daily treatment routines, the incidence of developing overt nephropathy and ESRD was high, up to 35% of study participants developed ESRD (109, 110). Incidence rate has declined

substantially over the years, and recent studies report that the long-term cumulative incidence of overt nephropathy and ESRD has decreased and is lower than 10% (109, 111-112). A Large Finnish study estimating ESRD in a T1D population reported a cumulative incidence risk of ESRD of 2.2% and 7.8% at 20 and 30 years after diagnosis respectively (112). The DCCT/EDIC studies reported that in individuals with over 30 years of diabetes duration less than 2% (10 of 711) of the subjects in the intensive treatment group had developed renal insufficiency and that 6% of the DCCT/EDIC population developed declined renal function (eGFR <60 mL/min/1.73 m2) (113). A recent Italian study, evaluating 2656 patients with type 1 diabetes, reported that 3.7% of patients with diabetes duration 11-20 years and 8% of patients with diabetes duration >30 years developed declined renal function (114).

Several studies have linked diabetic nephropathy with an increased risk of coronary heart disease (115-116), both albuminuria and decreased eGFR have been identified as risk factors for cardiovascular mortality even in the general population (117, 118). It has been reported that patients with chronic kidney disease stage 3 have nearly ten times higher risk of death than the risk of progression to ESRD (119). Traditional risk factors for CVD and hypercoagulable conditions may play a role in it (89). It has been speculated that kidney damage may reflect more general vascular damage in the cardiovascular system which leads to higher cardiovascular disease and mortality risks (120). Other factors as a contribution to insulin resistance, inflammation, hypertension, dyslipidemia play a role in the mechanisms of CVD in patients with diabetes.

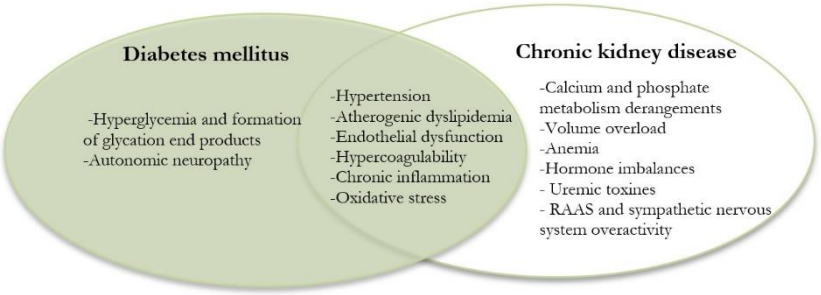


Figure 5. Overview of major established and proposed mechanisms of CVD in patients with DM and CKD. Adapted with permission after reference 89.

In line with previous reports, the association between glycemic control and mortality in patients with kidney transplant has been reported (121). Taking optimal glycemic control perspective in an account, it should be mentioned

that patients with CKD experience hypoglycemia more often than patients without CKD (122). Chronic kidney disease is seen as the dominant contributor to excess mortality in type 1 diabetes and prevention of it is essential to reduce the risk of premature mortality (123). On the other hand, in the past several decades observed decreased incidence rate in kidney disease among T1D patients had not been accompanied by a corresponding decline in CVD (3).

Overall, persons with type 1 diabetes experience cardiovascular disease more often than persons without diabetes. Initial changes in blood vessels may be detected already in children and adolescence. Previously performed studies generally support the association between inadequate glycemic control and clinical coronary heart events (such as myocardial infarction). Persons with type 1 diabetes and renal complications have increased risk of coronary heart disease.

2.3 DIABETES CARE TODAY: TECHNICAL IMPLEMENTATION

2.3.1 ADHERENCE/NON-ADHERENCE TO INSULIN TREATMENT

Currently, in developed countries intensive insulin therapy regimens for T1DM most commonly are delivered by multiple daily injections (MDI) of long-acting basal insulin and short- or rapid-acting prandial insulin formulations. The DARTS Medicines Monitoring Unit reported that HbA1c and diabetes complications are related to inadequate insulin treatment (124).

Figure 6. Some factors affecting adherence to insulin treatment regimen (124-126)

Non-adherence to an insulin treatment regime is common and ranges from 23-77% (125). This makes it difficult to achieve HbA1c targets and has other consequences. The Joslin Behavioural Research group found that 30.5% of T1D patients in their study self-restricted insulin (N=234 women, follow up period 11 years) (126). At baseline, they were younger and had higher HbA1c levels (HbA1c 81 mmol/mol (NGSP 9.6%) in comparison to 67 mmol/mol (NGSP 8.3%) among non-restrictors). By the study results, inadequate insulin treatment increased the relative risk of death by 3.2 times. Some of the previously named factors influencing the adherence to insulin regimen may be

controlled, at least partially, by using continuous subcutaneous insulin infusion therapy.

2.3.2 SUBCUTANEOUS CONTINUOUS INSULIN INFUSION THERAPY (INSULIN PUMP) TREATMENT

In healthy individuals, insulin is produced continuously during the day (basal insulin), in response to meals additional prandial (bolus) secretion of insulin occurs. Modern treatment aims to recreate physiological fluctuation in insulin concentrations during the day (127). Today the most optimal way for patients to deliver insulin is the subcutaneous injection/infusion (other technically possible insulin delivery routes are: intravenous, inhaled, intraperitoneal). The whole conception of insulin pumps is to imitate physiological insulin concentrations by combining basal and bolus insulin delivery. An insulin pump is a portable; battery operated computerized medical device which is attached to a disposable insulin reservoir and infusion set (127). The insulin is carried through an adjustable tube connected to a catheter that is inserted preferably in the abdominal area, upper outer quadrant of the gluteal area. The upper thigh area and the triceps fat pad may also be used (127). Insulin delivery consists of basal insulin (the minimum amount of insulin is needed to maintain glycemia in the target range without inducing hypoglycemia and suppressing ketogenesis and gluconeogenesis) and bolus insulin (to control glycemia during mealtimes), figure 7.

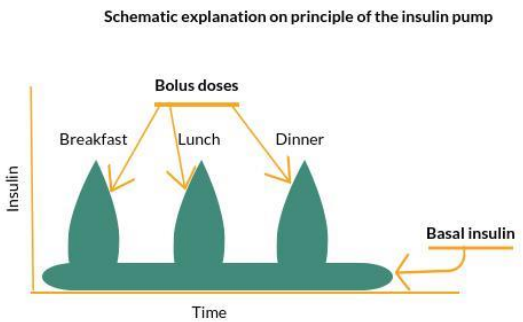


Figure 7. Schematic explanation on principle of insulin pump.

Insulin pumps have been used for more than 35 years (45). According to NDR 2016-year rapport, 22.7% of all adult T1D patients are using insulin pump (13). Insulin pump was one of the chosen methods for intensive treatment arm in the DCCT (11). Devices were large and had technical difficulties. Rapid technological progress meets requirements and have introduced color touch screen, USB-rechargeable batteries, pre-filled insulin cartridges, tubeless pumps and being waterproof.

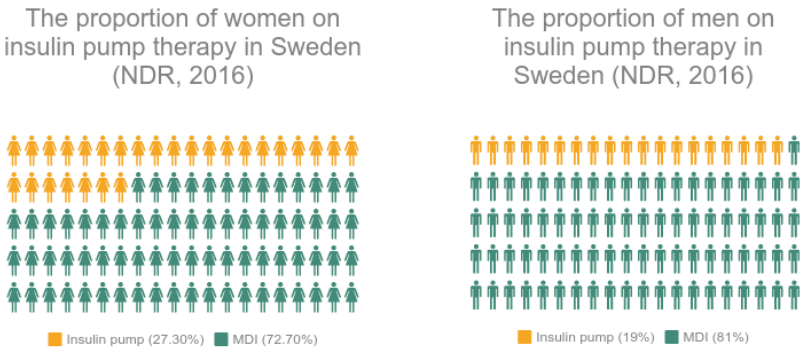


Figure 8. The proportions of men and women on insulin pump therapy in Sweden (13)

In 2013 FDA approved the first device that altered insulin delivery in response to CGM. Sensor-augmented insulin pumps can be programmed to interrupt insulin delivery at the certain glucose level. Medtronic MiniMed 670G approved by FDA as the hybrid closed-loop system that continuously tracks glucose levels and adapts insulin delivery (33). Users still need to adjust mealtime insulin delivery by themselves.

Previous studies on CSII have identified lowered HbA1c when compared with MDI (129), but the effect has been modest (130). Fewer severe hypoglycemic events are associated with CSII, and it is suggested that CSII is associated with quality of life benefits (131, 132). However, treatment with CSII is more expensive than treatment with MDI. Available studies show that CSII is costeffective in comparison to multiple injections in T1D patients with poor

glycemic control and/or hypoglycemia on MDI (133). Selecting patients who would most benefit from insulin pump therapy is still challenging (127).

Figure 9. Eligibility for insulin pump therapy (127, 134)

2.3.3 CONTINUOUS GLUCOSE MONITORING DEVICES

Many studies have reported that increased frequency of self-blood glucose monitoring improves overall glycemic control (133, 135). However, even frequent self-blood glucose monitoring give information about the glycemia at the certain point of time, without providing information on trend. Continuous glucose monitoring devices solve these difficulties and provide valuable information on direction, duration of glycemic oscillations, frequency continuously around the clock and with no need to pierce the skin multiple times a day. Several technologies and algorithms have been developed and introduced to the market. Currently, available CGM devices have a wire-based enzyme-tipped electrode (sensor) (136). It is placed in the subcutaneous tissue, usually on the abdomen (the forearm or gluteal area are suitable) and transmits the signal wirelessly to a monitor. The CGM device needs to be calibrated according to the manufacturer's recommendations against capillary blood glucose values. Every time the sensor measures glucose levels in the interstitial fluid, the device converts it into the estimate of blood glucose and shows it on a display. CGM provides early alarms for hypoglycemia or hyperglycemia and even information on rapidly changing glycemia (as a symbol on display) (137). Sensors, depending on manufacturer, are recommended to use for 5, 6 or 7 days and need to be changed after worth. Technological as well as physiological (for example, rapidly changing blood glucose values) issues challenge the accuracy of CGM devices.

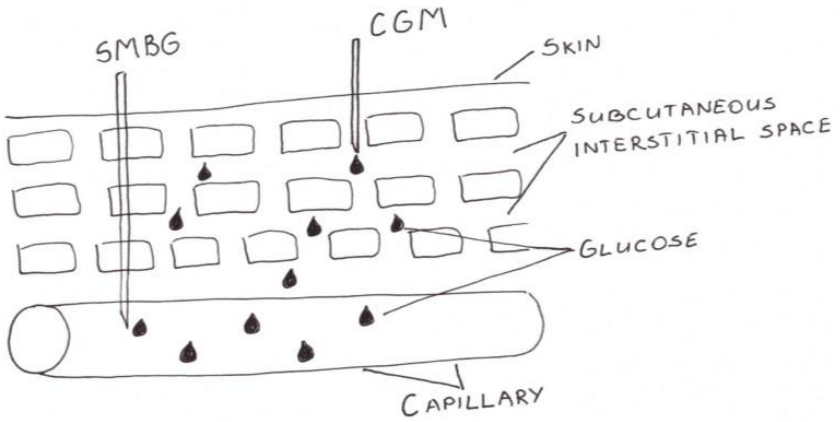


Figure 10. Glucose measurement with CGM and SMBG

The accuracy of CGM devices has improved over time (136). Calibration need has also been reduced to once per day (138). The most precise devices have overall mean absolute relative difference (MARD) of approximately 10% (1387) which is considered sufficient for making a clinical decision without performing a confirmatory capillary blood glucose measurement (140, 141). Sensors of the older generation are still used in the clinical practice. Thus, clinically significant variation in CGM accuracy persists.

Randomized trials have demonstrated the benefit of CGM on glycemic control (142-144) and reduced time spent in hypoglycemia (145) which supports the recommendation to use CGM in patients with unawareness or frequent hypoglycemia with both CSII and MDI (144, 146).

2.3.4 FLASH GLUCOSE MONITORING (FGM)

During recent years Flash Glucose Monitoring (FGM) has also become a treatment option. An FGM system was introduced in 2014 and approved in Europe (144). It consists of a sensor (inserted on the patient's forearm) and

reader de-vice (gets information on the actual glucose value and the 8-hour glucose trend). FGM is factory calibrated and does not need capillary blood glucose to calibrate it on a daily basis. Unlike the CGM, FGM cannot warn the patient of glucose oscillations, hypoglycemia or hyperglycemia. Studies show that overall FGM accuracy is comparable to that in CGM devices (147, 148) and provide evidence that FGM reduces time spent in hypoglycemia by 38% (149).

Studies show that up to 30% of all persons with diabetes are not strictly following treatment recommendations provided by their diabetes-care provider. Persons with type 1 diabetes report different reasons for this. Technical devices, for example, insulin pump, continuous glucose monitoring, flash glucose monitoring or combination of these, may improve adherence to diabetes treatment. Selecting patients who would most benefit from different technical devices is still challenging.

3 AIM

The overall aim of this thesis is to deepen the understanding of type 1 diabetes, particularly effects of different types of modern diabetes treatment and how the basic diabetes treatment is functioning today. It is essential to identify fields that need to be improved to reach better glycaemic control. Another aim is to analyze if the overall major cardiovascular events risk level as well as in the subpopulation of patients with well-managed type 1 diabetes (good glycaemic control and no renal complications) is approaching what we see in the general population.

Aims and objectives of the sub-studies

Study I

To evaluate to what extent the guidelines for the regular Glycosylated Haemoglobin (HbA1c) monitoring of type 1 diabetes are followed in clinical practice in Sweden.

Study II

To evaluate the accuracy, of two commercial continuous glucose monitoring systems (Enlite (Medtronic MiniMed, Inc., Northridge, CA) and Dexcom (San Diego, CA) G4 PLATINUM) in ambulatory patients with type 1 diabetes and their satisfaction with devices.

Study III

To study whether the relative effect of insulin pump therapy on HbA1c differs with respect to baseline characteristics.

Study IV

To study the overall excess risk of major coronary events (acute myocardial infarction (AMI) or death from coronary heart disease (CHD)) among patients with type 1 diabetes and how it is related with respect to glycaemic control and severity of renal complications.

4 PATIENTS AND METHODS

Quantitative designs have been used in this thesis. The summary information of data collection years, design, participants, data collection and analyses in the studies are presented in table 2.

Table 2. Overview of data collection years, design, participants, data collection and analyses in the performed studies.

Study	Data collection (year)	Design	Participants	Data collection	Analyses
I	1 January 2005 to 31 December 2009	Multicenter retrospective observational cohort study based on electronic medical records database	5989 T1D patients	Frequency of HbA1c measurements and other patient characteristics	Mean number of HbA1c checks Generalized Estimating Equations (GEE) models Stepwise logistic regression
II	2013	A non-randomized, non-blinded, 6-day clinical study, simultaneous use of both tested sensors	46 CGM naive T1D patients	CGM, venous and capillary blood glucose, Questionnaire	Wilcoxon signed-rank test Sign test Spearman correlation coefficient

III	2000 to September 2009	Multicenter retrospective observational cohort study based on electronic medical records database	272 T1D patients on CSII and 2437 T1D patients on MDI	HbA1c measurements and other patient characteristics	Fisher's exact test Student's t-test, MIXED procedure
IV	1 January 1998 to 31 December 2011	Nationwide population-based observational cohort study	33170 T1D patients and 164698 matched controls from the general population	Data from NDR and other registries	Rates of events per 1,000 patient years Cox regression

The study cohort for study I and III included patients with type 1 diabetes from 10 hospital-based diabetes clinics for adult outpatients (18 years or older) in Sweden (Figure 11). The study I included all persons with type 1 diabetes, registered in the medical patient record system Diab-Base from 1 January 2005 to 31 December 2009 (n=5989). Study III included persons with type 1 diabetes with diabetes duration of more than one year and CSII treatment for at least 5.5 years. Other inclusion criteria were: available HbA1c values within six months before the start of CSII and at five years ± 6 months (n=272). 82% of all patients on CSII treatment for at least 5.5 years were included. Patients with intermittent use of CSII were excluded. The control group consisted of persons with T1D treated with MDI (n= 2437). The same criteria (diabetes duration and available HbA1c values) were also applied to the persons included in the control group. Controls were matched to each patient from the CSII group with respect to CSII start date. As in the study I data for study III were obtained from the medical patient record system Diab-Base.

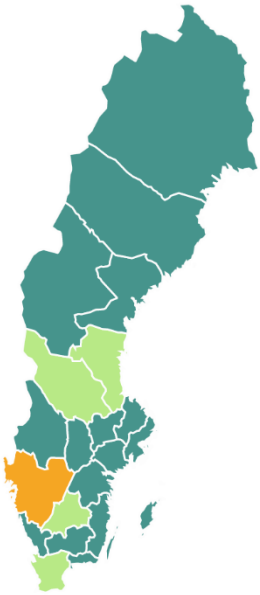


Figure 11. Orange and light green colors indicate counties from where we included persons with T1D to study I and III. Majority of persons with T1D included in study I and III live in the Västra Götaland county (orange).

Study II was performed at the NU-Hospital Group in the western part of Sweden. 46 adult (age 18 or older and <75 years) persons with type 1 diabetes were included. Current pregnancy, cognitive dysfunction and other conditions making CGM use difficult, continuous use of paracetamol, or current use of a CGM sensor were considered as exclusion criteria (for more information, see figure 12). All subjects gave informed consent, an internal review board ethic approved the study.

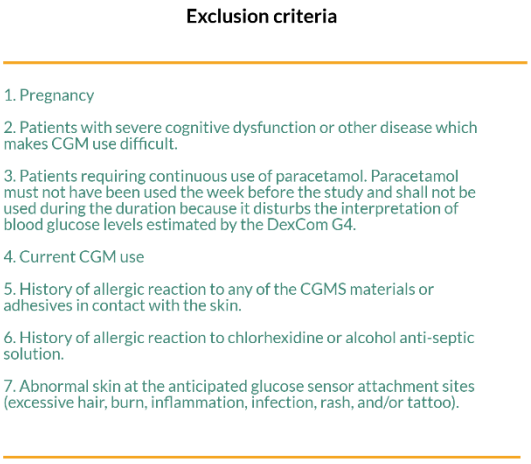


Figure 12. Study II. Exclusion criteria

Study IV was a nationwide population-based observational cohort study. Study subjects (T1D patients without previous myocardial infarction, n=33170) were selected from the National Diabetes Registry (NDR) using the following epidemiologic criteria:

1. Treatment with insulin

2. diagnosis of T1D at ≤30 years of age.

164698 controls matched on age, sex and county were randomly selected from the Swedish Population Register. All T1D patients with previous AMI and their matched controls as well as controls with previous AMI were excluded (figure 13).

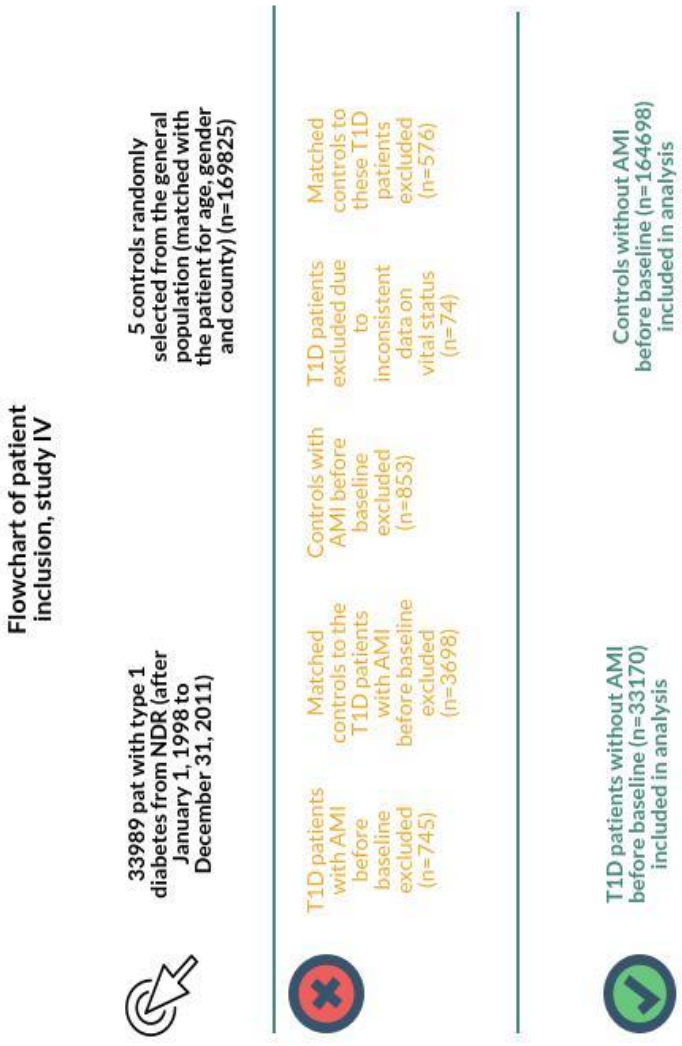


Figure 13. Flowchart of patient inclusion study IV

4.1 DATA SOURCE

Study I, III

Data for the study I and III were obtained from a medical patient record system, Diab-Base (Journalia AB, Östra Ämtervik, Sweden). Diab-Base started in 1994, and since approximately the year 2000 it was used at ten hospital-based diabe-tes clinics for adult outpatients (18 years or older) in Sweden (13). Clinical information (risk factors, treatments, including information on the date of CSII initiation, and complications) was recorded to Diab-base at regular clinic visits. Recorded information, such as HbA1c, blood pressure, blood lipids, body mass index (BMI), type of diabetes, and insulin dose can be retrieved electronically.

Study II

46 adult ambulatory patients with type 1 diabetes at the NU-hospital group were included in the study. Each enrolled study patient had two subcutaneous CGM sensor inserted during a 4-6 days period. Each sensor produced a maximum of 1,440 tissue fluid glucose measurements per 24 hours. Each study patients sampled capillary blood and measured (using HemoCue glucometer) the concentration of glucose 6 to 10 times per day and registered in the written diary. Information on activities, meals, and taken insulin doses was registered by the patients in the written diary. Each patient had three visits to the clinical research unit, during the second and third visits seven venous blood samples and simultaneous capillary blood samples were taken.

Study IV

The study participants (persons with type 1 diabetes) were identified using the epidemiological criteria (type 1 diabetes diagnosed before the age of 30 and that the person was treated with insulin) (15). Clinical data were collected from the NDR. NDR includes information on risk factors, diabetic complications with the year of diabetes onset, and medications in adult patients. Matched controls were randomly selected from the Swedish Population Register which is administered by the Swedish Tax Agency. Information on comorbidities and cause-specific mortality were retrieved by linking personal identifying numbers from persons with T1D and controls to the Swedish Inpatient and

cause of death registries. Information on prescribed drugs was retrieved by linking personal identifying numbers to the Prescribed Drug Registry. Education and country of birth were retrieved from the Longitudinal Integration database for health insurance and labor market studies (LISA by Swedish acronym).

The Swedish Inpatient registry (IPR) includes information on hospitalization and outpatient visits (not visits to the primary care), hospital discharge diagnosis according to International Classification of Disorders (ICD). Currently, more than 99% of all discharges are registered in this register. The positive predictive value (correct diagnosis in IPR, when only primary diagnoses were considered) of the MI has been demonstrated to be 95-98% (148).

The Cause of Death Registry (CDR) contains information on date, the location of death, ICD code and main cause of death. All death cases are registered in CDR. External validation has shown correct diagnosis in 87% for ischemic heart disease.

The Prescribed Drug Registry (PDR) contains information on drug prescriptions dispensed at pharmacies since July 2005. Inpatient prescriptions and over-the-counter medications are not registered in PDR.

The Longitudinal Integration database for health insurance and labor market studies (LISA) started in 1990. The LISA register includes all individuals from 16 years of age that were registered in Sweden as of December 31 for each year and included several demographic, socioeconomic and occupational factors which are updated annually.

4.2 PROCEDURES

Study I

Assessment of the frequency of HbA1c measurements for all patients:

- by the calendar year,
- diabetes outpatient clinic (care unit),
- also, the period when patients achieved

a. good (HbA1c ≤ 52 mmol/mol (7.0%) and

b. inadequate glycemic control (HbA1c> 53 mmol/mol).

Potential predictors for receiving a subsequent HbA1c check within 4 and 7 months after an HbA1c value >53 mmol/mol such as age, sex, type of insulin delivery (MDII or CSII), diabetes duration, HbA1c level, weight, BMI, insulin dose (U/kg), and care unit were examined. According to the guidelines, HbA1c should be tested at least every six months in persons who have good glycaemic control and every three months in persons who have inadequate glycemic control. In real life it may be challenging to retest HbA1c precisely after 3 or 6 months, so we chose to extend the periods to 4 and seven months respectively.

Study II

Adult (age 18 or older and <75 years), CGM naive patients with type 1 diabetes were included in the study. Each study participant was the own control due to simultaneous use of two different sensors. Each patient made three visits to the clinical research unit (CRU). At the first visit informed consent was taken and a complete medical history was obtained. Study personnel inserted two CGM sensors subcutaneously and educated the participant on how to use the CGMs. Subjects were advised to manage their diabetes using the HemoCue SMBG meter (standard glucometer in the Swedish healthcare system) and their usual insulin delivery method. The CGM sensors were calibrated according to each manufacturer's instructions using a capillary blood sample analyzed with the HemoCue analyzer. Subjects were informed not to perform clinical decisions based on the CGM meter and to double check the glucose level with HemoCue SMBG if CGM meter was alarming for low glucose.

The following variables were recorded at the first visit:

age, sex, diabetes diagnosis, data on diabetes complications and comorbidities, insulin delivery and dose, other medications. Persons´ height, weight, waist circumference, abdominal sagittal diameter height, systolic and diastolic blood pressure were measured during the visit to the study centre. Every participant was asked about an average number of subjective hypoglycaemias per month during the last year, smoking habits and duration, alcohol intake.

At visits 2 and 3, each patient was admitted to the CRU to obtain seven venous blood samples on Days 1–3 and 4–6, with an interval of at least 15min. An intravenous catheter was inserted to facilitate blood sample acquisition. Capillary blood was sampled from the fingertip using a lancet at the first and last venous sample and an intermediate sample.

The sensor insertion sites were observed to detect bleeding, inflammation, and infection of the skin or subcutaneous tissue.

Predefined endpoints were:

Primary endpoint

The difference in mean absolute relative difference (MARD) between Enlite (Medtronic MiniMed, Inc., Northridge, CA) and Dexcom (San Diego, CA) G4 PLATINUM.

Secondary endpoints

The accuracy of Enlite (Medtronic MiniMed, Inc., Northridge, CA) and Dexcom (San Diego, CA) G4 PLATINUM sensors at:

- day 1-3
- day 4-6
- hypoglycemia (<4 mmol/L)
- euglycemia (4-10 mmol/L)
- hyperglycemia (>14 mmol/L)

Endpoints were analyzed using capillary glucose values as the reference and investigating MARD and MAD (mean absolute difference), absolute correlation coefficient, median absolute relative difference, median absolute

difference. All statistical analyses were described in the statistical analysis plan (SAP).

During the last visit to the CRU, all patients filled the questionnaire with 13 identically formulated evaluative statements for Enlite and Dexcom G4. Participants could agree or disagree according to visual analog scale (VAS). The patient could also provide free-form text comments on their experience.

Study III

Evaluation of the relative effect of CSII compared with MDI on the HbA1c lev-el at 1, 2, and 5 years with respect to baseline characteristics. Age, sex, diabetes duration, BMI, insulin dose (U/kg/day), baseline HbA1c level, and care unit were examined as possible predictors for greater or lower effect of CSII com-pared with MDI on HbA1c*.

**HbA1c values were converted to the National Glycohaemoglobin Standardization Program and International Federation for Clinical Chemistry standards.*

Study IV

Estimation of the rates of major coronary events for the following age groups 18-34, 35-49, 50-64 and 65 years or greater and by gender in the T1D population and controls was performed. Cox regression analysis adjusted for age and sex and in addition also for comorbidities and level of education was performed to further evaluate the overall excess risk for coronary events in persons with T1D compared to controls. In a next step evaluation of the influence of glycaemic control and renal complications on the risk of AMI and CHD in patients versus controls was performed. Updated mean HbA1c* value, i.e., the mean level of HbA1c until a certain time point, was used to categorize persons with T1D by glycaemic control. Renal complications were categorized into normo-, micro- and macroalbuminuria and stage 5 chronic kidney disease and into stage 1 (eGFR $\geq$ 90 ml/min), stage 2 (eGFR 60-89 ml/min), stage 3 (eGFR 30-59 ml/min), stage 4 (eGFR 15-29 ml/min) and stage 5 chronic kidney disease (renal dialysis, renal transplantation, or eGFR <15 ml/min).

**International Federation of Clinical Chemistry (IFCC) standard measurement units mmol/mol used in the study. Dual reporting according to the National Glycohaemoglobin Standardization Program was also performed.*

4.3 STATISTICAL ANALYSIS

The main statistical methods are described in detail in the respective studies. Statistical methods are summarized in Table 3.

Table 3. The main statistical methods

Study	Point of interest	Used statistical method
All	Demographic characteristics	Continuous variables: mean with SD for normally distributed variables, median (for skewed distributed variables) with min and max values, and within-individual SD as applicable when repeated measures are available Categorical variables: number with percentages.
		Unless otherwise specified, a p-value below 0.05 was considered statistically significant
I	Frequency of HbA1c measurements	-Mean number of HbA1c checks per year for each individual patient -Mean number of HbA1c checks for entire cohort calculated as the mean number of annual means -Mean number of HbA1c checks during the periods of optimal and inadequate glycemic control.
	The probability of HbA1c check within 4 and 7 months after HbA1c measurement >52 mmol/mol	Generalized Estimating Equations (GEE) models. This method was chosen to analyze binary outcome that comes from repeated measures for same individuals.

	Independent predictors of HbA1c check within 4 and 7 months after HbA1c measurement >52 mmol/mol	Stepwise logistic regression: multiple regression performed several times, each time including the strongest and significant correlated variable. GEE models for selected variables performed. OR, CI and p-value were calculated for each variable.
II	Comparison of two CGM systems	Mean absolute relative difference (MARD)- for the primary measure of accuracy, which is the standard method for evaluation of CGM. Mean absolute difference (MAD) Absolute Pearson correlation coefficient Median absolute relative difference (MedARD) Median absolute difference (MedAD) To compare two sets of scores that come from the same participants Wilcoxon signed-rank test was used for continuous variables. To compare categorical differences (differences between pairs of observations) between CGM systems, the Sign test was used.
	Association between capillary and venous blood glucose values	Spearman correlation coefficient and associated p-values.
III	Comparison between CSII and MDI groups	Fisher's exact test for dichotomous variables and Student's t test for continuous variables
	Evaluation of the effect size for interaction variables between each baseline variable (age, sex, diabetes duration, BMI, insulin dose, HbA1c level at the baseline, care unit)	Analysis of covariance Interaction was considered statistically significant for $p<0.10$

IV	Rates of coronary events, compared to the matched controls	Poisson CI, expressed in cases per 1000 patient years
	Expected duration of time until event (major coronary event or death due to CHD) studied for different categories of HbA1c, albuminuria and eGFR	Cox regression, adjusted for following variables: Model 1 – time-updated age and sex Model 2 – model 1 + diabetes duration categories at baseline Model 3 – model 2 + education category, birth in Sweden, comorbidities prior the baseline Overall and stratified by gender. Separate Cox regression models were used to evaluate the risk of major coronary events and death from CHD associated with glycemic control or/and kidney impairment or/and albuminuria during follow-up period. These variables were categorized into blocks (please see paper IV). All Cox models were tested for the proportional hazard assumption and satisfied this assumption.
	Effect per 10 mmol/mol higher updated mean HbA1c	Cox regression within diabetes population.
	Influence of time <2005 vs ≥2005	Cox regression, with baseline comorbidities updated for time period >=2005.
	Effect of HbA1c in the lowest category, ≤ 52 mmol/mol	Sensitivity analysis, by using Cox regression

4.4 ETHICAL CONSIDERATIONS

Study I, III, IV

Ethics approval was obtained for the studies I, III and IV from the ethical committee at the University of Gothenburg, Gothenburg, Sweden. No invasive procedures have been performed in the study I, III and IV.

Study II

The study was approved by the internal review board at the NU-Hospital organization.

Each subject was assigned an anonymous ID number used to identify the subject in all study records. All study subjects were asked to sign an informed consent form (ICF) before initiating any study procedures. The study was conducted in strict accordance with the protocol.

All study participants were informed orally and in written about the purpose of the study, voluntary participation and confidentiality.

5 RESULTS

5.1.1 STUDY I

A Retrospective Study in 5989 Patients with Type 1 Diabetes in 10 Outpatient Diabetes Clinics in Sweden of the Frequency of Measuring HbA1c in Clinical Practice

Main findings:

5989 patients with type 1 diabetes from 10 outpatient diabetes clinics in Sweden were included in the study.

Table 4. Patient characteristics at first visit during years 2005-2009 in Diab-Base in total and in relation to the number of mean number of annual HbA1c measurements performed during the same period. (Reproduced with permission from the publisher)

	Total (n=5989)	**<1 (n=569)**	**1-<2 (n=2894)**	**2-<3 (n=2050)**	**3-<4 (n=371)**	**>=4 (n=105)**
Age (years)	42.9 (16.1) 41.7 (16.0; 89.5) n=5989	42.6 (16.7) 39.7 (17.3; 87.1) n=569	43.2 (16.0) 41.7 (16.2; 85.3) n=2894	44.0 (16.0) 44.1 (16.2; 89.5) n=2050	37.4 (14.9) 35.7 (16.0; 79.4) n=371	37.4 (15.3) 34.9 (16.1; 78.4) n=105
Sex						
Male	3327 (55.6%)	350 (61.5%)	1663 (57.5%)	1082 (52.8%)	179 (48.2%)	53 (50.5%)
Female	2662 (44.4%)	219 (38.5%)	1231 (42.5%)	968 (47.2%)	192 (51.8%)	52 (49.5%)
CSII						
No	4724 (78.9%)	506 (88.9%)	2423 (83.7%)	1506 (73.5%)	223 (60.1%)	66 (62.9%)
Yes	1265 (21.1%)	63 (11.1%)	471 (16.3%)	544 (26.5%)	148 (39.9%)	39 (37.1%)
Diabetes duration (years)	20.9 (14.8) 19.1 (-0.9; 78.4) n=5636	21.9 (14.7) 20.4 (-0.0; 68.7) n=502	21.1 (14.6) 19.1 (-0.9; 78.4) n=2719	21.5 (15.1) 20.2 (-0.9; 69.1) n=1960	15.9 (14.2) 13.6 (-0.2; 59.1) n=358	15.8 (15.0) 14.3 (-0.0; 55.2) n=97

From the chart below, we can see that during the periods with HbA1c >52 mmol/mol, persons with T1D had 1.83 annual HbA1c measurements (the follow-up period from 1 January 2005 to 31 December 2009). See Figure 14.

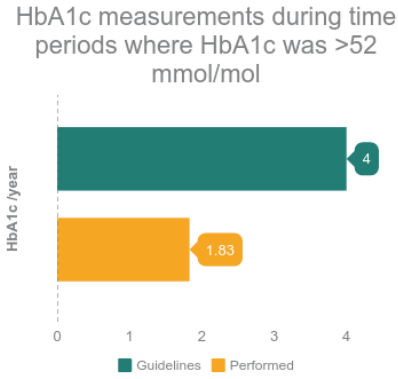


Figure 14. The frequency of HbA1c measurements during the time periods with HbA1c > 52 mmol/mol

As shown in figure 15, only in 35.4% of cases the next HbA1c measurement following an HbA1c >52 mmol/mol was performed within 4 months.

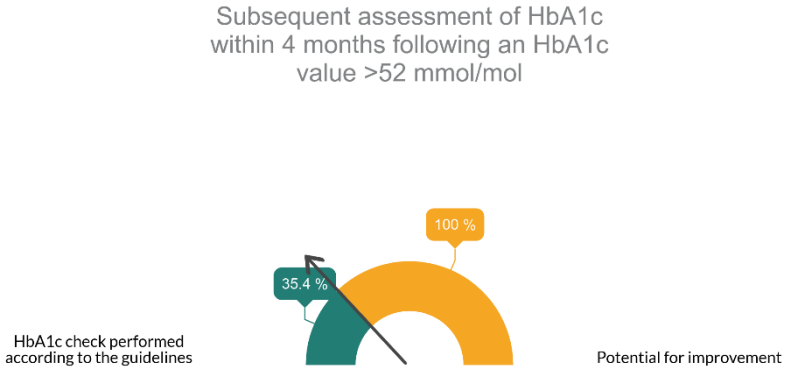


Figure 15. Subsequent assessment of HbA1c within 4 months following an HbA1c value >52 mmol/mol

Patients treated with CSII compared to MDI, younger individuals compared to older, those with shorter diabetes duration, females, patients with higher HbA1c and those who were followed-up in the certain care units had a

significantly higher probability of having the subsequent HbA1c measurement within 4 months (Table 5, article 1).

Table 5. Probability of having a subsequent HbA1c measurement within 4 months after an HbA1c >52 mmol/mol, study I (Reproduced with permission from the publisher)

	Univariable		Multivariable	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (1=male, 2= female)	1.20 (1.12-1.28)	<0.001	1.12 (1.05-1.21)	0.0017
Current age (by 10 years)	0.87 (0.85-0.89)	<0.001	0.94 (0.92-0.96)	<0.001
Diabetes duration (by 10 years)	0.89 (0.87-0.91)	<0.001	0.93 (0.91-0.96)	<0.001
CSII (0=No, 1=Yes)	**1.65 (1.54-1.78)**	<0.001	**1.57 (1.46-1.69)**	<0.001
Current calendar year	1.13 (1.11-1.15)	<0.001	1.14 (1.12-1.17)	<0.001
Current HbA1c	1.38 (1.34-1.41)	<0.001	1.37 (1.34-1.41)	<0.001

As it can be seen from the table above, T1D patients with CSII compared to patients with MDI treatment had approximately 50% higher probability of having a novel HbA1c check within the recommended time interval.

5.1.2 STUDY II

A Clinical Trial of the Accuracy and Treatment Experience of the Dexcom G4 Sensor (Dexcom G4 System) and Enlite Sensor (Guardian REAL-Time System) Tested Simultaneously in Ambulatory Patients with Type 1 Diabetes

Main findings:

46 persons with T1D were enrolled to the clinical study. Those, who had recorded at least 10 capillary glucose values matched at a maximum deviation of 5 minutes from the CGM values, were included in the intention-to-treat analysis (n=38). The table below illustrates some of the main characteristics of the intention-to-treat population (table 6).

Table 6. Demographic characteristics (study II)

Variable	Intention to treat population (n=38)
Age (years)	50.0 (14.3) 50.1 (20.8,73.6)
Sex -male -female	 -25 (65.8%) -13 (34.2%)
Diabetes duration (years)	22.9 (16.0) 18.0 (1.0; 57.0)
Insulin delivery -CSII -MDI	 -10 (26.3%) -28 (73.7%)
HbA1c (IFCC, mmol/mol)	58.9 (10.5) 59.0 (34.0; 77.0)

For continuous variables data are mean (SD)/median (minimum, maximum)/n

The primary endpoint was the difference in MARD between the two systems over the whole study period. As the table 7 shows, there was a significant difference in MARD between the Dexcom G4 and Enlite during the entire study period (primary endpoint), during days 1-3 and days 4-6, as well as during the periods when glucose values were below 4.0 mmol/L and 4.0-10.0

mmol/L (secondary pre-defined endpoints). The Dexcom G4 sensor was hence more accurate during the entire study period and during hypoglycemia and normoglycemia. No significant difference in the accuracy was found at very high glucose levels (>14mmol/L), MARD: 12.1% for Dexcom G4 and 13.9% for Enlite (P=0.24).

By the end of the study period, all study participants completed and returned the questionnaire. The questionnaire required respondents to give information on their satisfaction, easiness and other experiences with CGM systems. We used a visual analog scale with the lowest value of 0, indicating "not true at all" and the highest value of 100, indicating "completely true." As it can be seen from the figure 16, participants felt more positively about the Dexcom G4 system compared to the Enlite system. This was observed in 12 out of 13 questions. Study participants were also asked to give a free-text comment on their experience with Dexcom G4 and Enlite systems. Some of the participants pointed signal disturbances (e.g., low signal) as a very important issue. "Even if sensor accuracy increased, I would not feel safe using this system if a low sensor signal became a frequent problem", - one of the study participants commented.

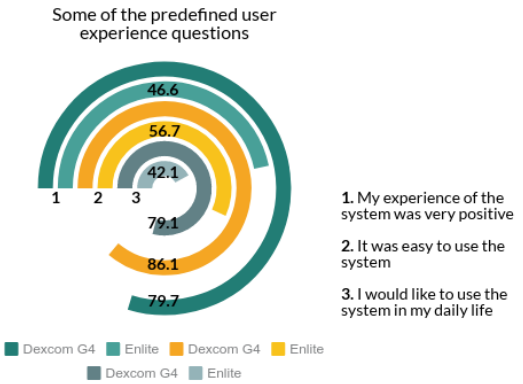


Figure 16. Some of the predefined user experience questions

Table 7. Primary and secondary endpoints of accuracy evaluations, study II. Reproduced with permission from the publisher.

	Dexcom G4	Enlite	Sets of measurements	p-value
MARD (all data)	13.87 (5.24) 12.4 (6.9; 29.1)	17.85 (5.65) 16.8 (9.3; 30.5)	1012	<0.0001
MARD (Capillary glucose levels <4.0 mmol/L)	20.04 (15.13) 17.0 (2.6; 61.7) n=28	34.69 (21.43) 30.4 (2.8;97.1) n=28	80	0.0041
MARD (Capillary glucose levels 4.0-10.0 mmol/L)	14.09 (5.91) 12.9 (5.6; 32.1) n=38	17.33 (6.29) 16.4 (7.8; 36.3) n=38	668	0.0008
MARD (Capillary glucose levels > 14.0 mmol/L)	12.13 (7.96) 11.6 (0.3; 31.5) n=25	13.94 (7.75) 11.8 (2.4; 31.1) n=25	70	0.24
MARD (day 1-3)	15.01 (6.78) 12.9 (5.7; 36.7) n=37	19.41 (7.76) 17.6 (7.0; 38.2) n=37	545	0.0027
MARD (day 4-6)	13.57 (6.70) 12.8 (6.8; 41.1) n=37	15.88 (5.22) 15.8 (6.4; 28.5) n=37	467	0.026

5.1.3 STUDY III

Predicting the Effectiveness of Insulin Pump Therapy on Glycemic Control in Clinical Practice: A Retrospective Study of Patients with Type 1 Diabetes from 10 Outpatient Diabetes Clinics in Sweden over 5 years

Main findings:

In total, 272 CSII patients (82% of all patients having CSII over 5.5 years) and 2437 MDI patients were included in this study to evaluate the 5-year effectiveness of insulin pumps in Sweden.

It can be seen from the data in table 8 that the CSII patient group had significantly higher baseline HbA1c levels compared to the MDI group; the mean HbA1c value was 68.1 mmol/mol (8.39%) vs. 64.7 mmol/mol (8.07%) respectively. Persons with CSII were younger, had shorter diabetes duration. More women than men were treated with CSII than MDI (56% vs. 43%).

Table 8. Baseline characteristics (study III)

Variable	CSII (n=272)	MDI (n=2437)	P-value
Sex -Male -Female	 119 (43.8%) 153 (56.3%)	 1391 (57.1%) 1046 (42.9%)	 <0.001
Age (years)	38.6 (11.3) n=267	45.6 (14.4) n=2437	<0.001
HbA1c (IFCC, mmol/mol)	68.1 (14.2) n=272	64.7 (13.9) n=2437	<0.001
Diabetes duration (months)	15.1 (11.2) n=272	20,1 (13.2) n=2437	<0.001

To determine the effect of CSII treatment compared to MDI from baseline to 5 years, the predictive analysis of change in HbA1c over the time was performed. Our result shows that the higher the baseline HbA1c level, the greater the decrease in HbA1c. As shown in figure 17, changes in HbA1c levels

were observed in both the CSII and MDI groups. The decrease in HbA1c at 5 years for patients, who had HbA1c >75 mmol/mol and BMI of 25 kg/m^2 and were treated with CSII, was 7.5 mmol/mol (≈0.75%) compared to 5 mmol/mol (≈0.5%) for patients treated with MDI. Patients who had HbA1c >75 mmol/mol at baseline, had the most prominent effect at 5 years with an HbA1c decrease of 2.5 mmol/mol (≈0.25%) compared to the MDI group. Significant interactions between CSII treatment and baseline HbA1c and BMI were apparent. The lower baseline BMI, the more significant reduction of HbA1c at the end of the follow-up period (Figure 17). No significant interactions between age, sex, diabetes duration, insulin dose and baseline HbA1c could be detected.

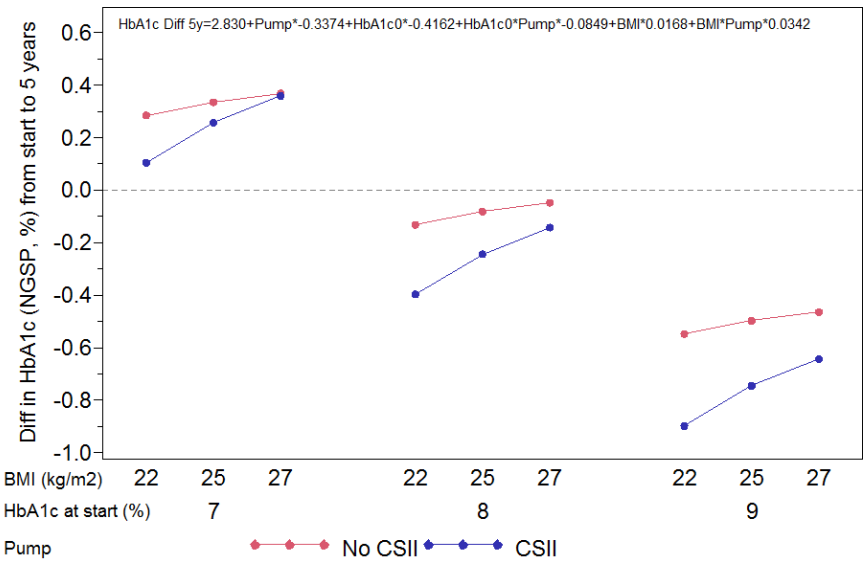


Figure 17. Least square means for change in HbA1c (NGSP, in %) from baseline to 5 years in patents on CSII versus MDI (no CSII), presented for selected baseline HbA1c and BMI values. Reproduced with permission from the publisher

5.1.4 STUDY IV

Glycemic control and Excess Risk of Major Coronary Events in Persons with Type 1 Diabetes

Main findings:

In total, 33 170 persons with T1D and 164 698 controls were included in the analysis. In the study both groups were comparable with respect to mean age (35.3 and 35.1 years) and sex (proportion of women 45.3% and 45.1%). In persons with T1D, mean HbA1c was 65.7 mmol/mol and mean diabetes duration 20.0 years. The median follow-up time for T1D patients and controls were 8.3 years and 8.9 years, respectively. During this period 4.5% of T1D patients and 1.2% of controls suffered AMI or died from CHD.

The excess risk of coronary events for persons with T1D compared to controls decreased over time with an adjusted HR of 3.63 (95% CI 3.33-3.95) for calendar years ≥2005 and an HR of 4.80 (95% CI 4.26-5.42) for calendar years <2005.

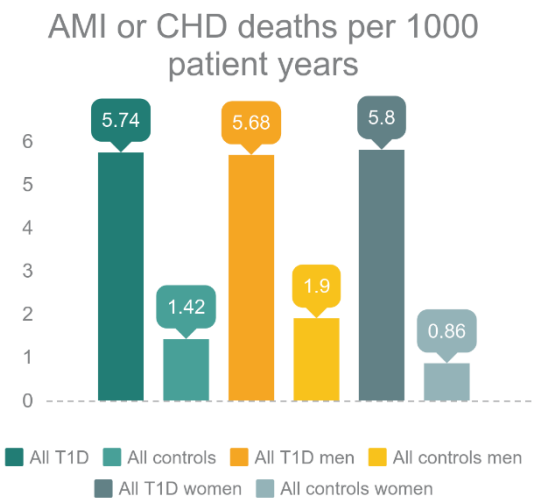


Figure 18. AMI or CHD deaths per 1000 patient years by sex

Interestingly, during the follow-up time, men and women with T1D had similar event rates. In controls, much lower event rates for women were displayed (figure 18), which matches results observed in earlier studies.

The relative risks for AMI or CHD events expressed in HR were higher at younger age (4.65 and 19.15 for 18-49 years of age men and women, respectively vs. 2.73 and 5.21 for 65+ years of age men and women, respectively). The relative risk was also higher for women compared to men, at poor glycemic control and in relation to severity of renal complications. The HRs for men and women with good glycemic control and normoalbuminuria were 1.3 and 3.16, respectively. HRs were persistently higher for women with higher HbA1c levels and higher levels of albuminuria and increased also with lower estimated glomerular filtration rate, calculated using the MDRD equation. Calculations made using the CKD-EPI equation did not change the results.

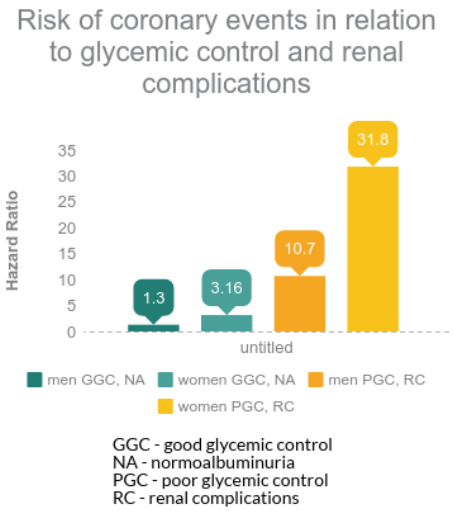


Figure 19. Risk of coronary events among persons with T1D in relation to glycemic control and renal complications compared to matched controls

We also evaluated the relationship between 1% (≈10 mmol/mol) increase in updated mean HbA1c and risk of coronary events within the group of persons with type 1 diabetes. The HR:s for coronary events in relation to 1% (≈10 mmol/mol) higher HbA1c adjusted for age, were 1.33 (95% CI 1.26-1.40) in men and 1.41 (95% CI 1.34-1.49) in women, respectively.

6 DISCUSSION

6.1.1 GENERAL DISCUSSION

Type 1 diabetes is usually diagnosed at childhood or early adulthood (21). Thus, persons with type 1 diabetes are exposed to diabetes related risk factors during a long period of time. Evidence shows that diabetic complications can efficiently be reduced by better glycaemic control (10, 11, 64). Despite this, the gap between the scientific evidence and clinical practice is still big. Currently, just approximately 20% of all adult diabetes patients in Sweden achieve good glycemic control (HbA1c ≤52 mmol/mol) (13.). Unfortunately, at least an equal number of T1D patients have very poor glycemic control (HbA1c > 70 mmol/mol). The present thesis is focused on persons with type 1 diabetes regarding optimising diabetes care including evaluations of HbA1c testing, CGM therapy and insulin pump treatment. Examining cardiovascular outcomes in persons with type 1 diabetes was another issue of high priority.

6.1.2 REGISTRIES AND RECORD-BASED DATABASES

Studies investigating the same group of individuals over a long period of time in clinical practice are of potential great importance in research (83). A medical record based database (Diab-base) was used to study persons with type 1 diabetes from clinical practice regarding frequencies of HbA1c-testing and effect of insulin pump use. Appropriate analyses of databases potentially facilitate an understanding of T1D care and allow to identify factors which might be useful in order to slow or reverse outcomes of interest. The database comprised approximately 7000 persons with type 1 diabetes from 10 different diabetes care units. Results should likely be representative for healthcare of type 1 diabetes patients in Sweden in general.

DCCT and EDIC were of paramount importance. Findings from these and landmark trials of the prevention of cardiovascular disease were implemented clinically (159). NDR, one of the largest databases of its kind, gave us a possibility to study a nationwide T1D population (epidemiological cohort) and evaluate the effects of implemented treatment on the incidence of the outcomes of interest (major coronary events).

A registry is "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a

population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" (154). Sweden has established tradition on national registries, counting more than 100 of those (161, 162). Government-administrated health registries allow to follow the defined group of patients of interest through their life and get valuable information on diagnosis, outcomes, prescribed medications, death year and causes (162). Research data delivered to the research team, as rule is anonymized to as great extent as possible, by e.g. not including the personal identification number. Unfortunately, registers generally only have the possibility to include a limited number of variables and hence information, that may have impact on a certain outcome may not be available. Further it should be noted that the findings from retrospective registry based studies should be interpreted with caution regarding interpretations of causality between risk factors and treatments in relation to outcomes.

6.1.3 HBA1C TESTING

Results from a multicenter study examining repeat HbA1c checks in nearly 80000 persons with diabetes (both T1D and T2D) found that HbA1c testing frequency is associated with HbA1c changes over time (47). HbA1c reduction was associated with testing HbA1c every third month and in contrast HbA1c checks once per year were associated with increasing HbA1c values. In this thesis we show that persons with T1D in Sweden did not even receive two such visits per year on average during the first decade of the 21st century. The care differs between diabetes care units both regarding the mean number of annual HbA1c checks and even in change in HbA1c-levels over time. Little was found in the literature on the question of the adherence to the HbA1c testing frequency in patients with T1D. Earlier studies have not analysed the frequency of HbA1c measurements in T1D, but focused on T2D or included persons with both type 1 and type 2 diabetes. Results of our study agree with the findings of previous studies reporting non-adherence to the guidelines with respect to HbA1c testing frequency (47-52). It seems possible that these results could be explained by a general lack of resources, mainly too few nurses working at diabetes care units. Diabetes nurses are seen as the backbone of diabetes care and patient education. Another possible explanation is that the number of annual HbA1c checks has not been seen as a factor in evaluating the quality of diabetes care. A clinically important finding in our study was that persons with insulin pump treatment got a more extensive care than patients with MDI. Persons with CSII had approximately 50% greater likelihood to get a subsequent HbA1c check within the recommended time range compared to persons on MDI. A possible explanation for this result is

that patients on CSII probably have more contact with healthcare providers due to the need of technical support and possible complications with the CSII therapy. Another possible explanation is that patients treated with CSII may be more interested in their diabetes care than patients treated with MDI and thereby more motivated and eager to receive clinical visits. On the other hand, it seems inappropriate that patients with MDI receive less diabetes care and this group of patients should get more attention from their health care providers.

Previous studies reported the association between increased SMBG and improved overall glycemic control (133, 135). On the other hand, a recent Swedish study shows that less than 50% of T1D patients follow guidelines to check blood glucose levels at least four times per day (151). Non-adherence to health care providers´ recommendations seems to be common and challenges the overall goal to achieve HbA1c targets according to the guidelines.

6.1.4 CONTINUOUS GLUCOSE MONITORING

DCCT study participants in the intensive management group experienced hypoglycaemia 2-3 times more often compared to the conventional treatment arm (163). Risk of hypoglycaemia is still challenging both persons with type 1 diabetes and the health care systems (117, 133, 145). One of the possible technical solutions is continuous glucose monitoring. Several technologies and algorithms have been developed and introduced to the market, not always the same in different countries (137-146). Diabetes centres often base the selection of CGM devices on their local experience and decisions. Clinical trials performed before our study have shown different findings on CGM accuracy. Possible explanation of that may be the use of different generation of sensors, different types of reference methods and small datasets (143). To our knowledge, our study is the first to evaluate patient experiences with different CGM systems. Important to note is that in the previous studies, even though in real life patients perform calibrations with capillary blood glucose values, CGM systems were calibrated using venous blood glucose samples (152). We used the HemoCue system to estimate both capillary and venous glucose values in the clinical trial. The venous samples in our study were 0.78 mmol/L lower than capillary values; the relationship was very strong (correlation coefficient = 0.98). Thus, it may cause the systematically biased results if the reference method and the method used to calibrate the system is not the same, the reference method should be considered. By the two sensors most used during the years in persons with T1D, we showed that the Dexcom sensor was more accurate and patients showed higher treatment satisfaction. This work,

one of the first from the manufacturer economically independent evaluations also forms an essential basis for similar studies of novel sensors.

6.1.5 INSULIN PUMP TREATMENT

Patients with high HbA1c improve their HbA1c somewhat more than those with low to moderately high HbA1c when an insulin pump was introduced in clinical practice. These results are in line with data from previous studies (14, 130). A long follow-up period (>5 years), multicentre design and large control group were the main strengths of our study. Results from some previous studies which were performed without the control group are difficult to interpret because of many other factors that may have impact on HbA1c levels, such as an implementation of new T1D treatment or care strategies (164-165). The length of the follow-up period is of great importance. Effects of any new intervention may give more significant results in the beginning due to increased visit frequency, more attention from the caregiver, higher motivation due to a novel therapy or due to patient education effort. Our study shows that the differences between CSII and MDI in effect on HbA1c changes decreased over time and at the end of the follow-up period were not that great that may be expected (approximately 2.5 mmol/mol in favour of CSII compared to the MDI group in patients with very high HbA1c >75 mmol/mol). Otherwise, previous studies have demonstrated that patient on CSII experience fewer severe hypoglycemic events, reduce variations in blood glucose concentrations and achieve a better quality of life (131-133). We could not identify other clinical variables (except the higher HbA1c levels at the baseline) that would predict greater change in HbA1c over the time. The decision to switch to the CSII treatment likely needs to be taken mainly on other parameters based on individual judgment of the life situation, view and motivation from the patient.

6.1.6 RISK OF MAJOR CORONARY EVENTS

The DCCT/EDIC studies have demonstrated benefits of an intensive diabetes therapy and more evident effect of “metabolic memory” phenomenon lasting years later (64, 83). Reduction of major cardiovascular risk factors in persons with diabetes became a focus point. In the context of improved healthcare guidelines, we evaluated an excess risk of AMI or death from CHD in persons with type 1 diabetes. This nationwide study from 1998 to 2011 shows that the excess risk of AMI or death from coronary events is four-fold higher compared with the general population in Sweden. Another important clinically relevant

finding was that women had greater excess risk of AMI or CHD death at any age compared to men. These results match those observed in earlier studies, such as the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study and Pittsburg Epidemiology of Diabetes Complications (EDC) study in US (3). A systematic review from 26 studies, including 214114 persons with type 1 diabetes shows that women have a roughly twice the excess risk of vascular events, compared with men (156). The exact pathophysiological mechanism of this is not known and needs further investigations. However, some authors have proposed that risk factors may have different impact on men and women, for example HDL (157, 158). Lower levels of HDL are considered to be an important factor contributing to the increased cardiovascular risk (3, 157). Fat distribution patterns, coagulation, insulin resistance have also been proposed as the possible explanations to the lost cardiovascular protection which is usually associated with female sex (3, 157). Other risk factors such as hypertension or hypodinamia differences by gender reported stronger impact of them on women's cardiovascular health (157). It may be believed that women with type 1 diabetes have much higher risk, compared to men. This is however not the case, but these associations are in principle explained by different risks in the general population by sex with respect to MI. In our study we see a very similar incidence rate of major coronary events in men and women with T1D.

Earlier studies have also shown an excess risk of myocardial infarction in persons with type 1 diabetes compared to the general population in various populations (3, 156). However, to our knowledge population-based evaluations of the excess risk in relation to risk factor control have not been extensively performed. Our results show that excess risks of major coronary events are substantially reduced at good glycaemic control and no renal complications. In our study, persons who had good glycemic control and no renal complications had much lower HR compared to the persons with poor glycemic control and albuminuria and/or impaired renal function. HR in persons with good control, especially in men, is narrowing to that in the general population. The relevance of existing guidelines promoting good glycaemic control is clearly supported by the current findings. However, the important question whether targeting general goals for HbA1c is enough to reduce the risk of MI to that in the general population is more difficult to conclude. The adjusted HR in man and women with good glycaemic control and normoalbuminuria was 1.3 and 3.16, respectively. It is possible that persons with current good glycaemic control had worse glycaemic control before the follow-up period. Moreover, the confidence interval for HR in men is wide (0.9 to 1.88), so the substantial excess risk cannot be concluded or excluded in this group. The HR in women was 3.16 with the 95% confidence interval

between 2.14 to 4.65. It indicates that targeting glycemia levels is not enough to effectively reduce the excess risk of coronary events in women. More research in this field is needed. More effective treatment and cardiovascular prevention strategies with the focus on gender differences may be of help.

6.1.7 STRENGTHS OF THE STUDIES

Strengths of study I, III and IV are the large samples, the long length of follow-up and measurement of clinical risk factors. The strength of the studies I and III is the data source, Diab-Base, providing detailed clinical information including all HbA1c values and date for insulin pump start. The study I was the largest study in T1D patients documenting adherence to the treatment guidelines in a real-life population. Study III was able to estimate the effects of CSII on HbA1c from many care units over a long time period whereas most other studies in the field have substantially short follow-ups, are performed at a single centre or lack a control group (164-165). Another strength of study III is that among all patients treated with CSII over five years during the study period, 82% had information on HbA1c before starting CSII and at five years and could be included in the analyses.

A strength of the study II is that the study was performed entirely independently from CGM manufacturers. Other strengths are that all endpoints were predefined and statistical methods were described in a signed statistical analysis plan (SAP) before the database was locked. Every patient was its own control; the same factors influenced both CGM-meters (behaviour, same range of glycemia, same environmental factors). It was the first study evaluating patient's experience of CGM and gave the opportunity to compare two different CGM systems. This kind of experience is not possible to obtain from clinical practice, since in real life patients only use one of the CGM devices.

Strengths of the study IV include the population-based design where nearly all patients with type 1 diabetes in Sweden were included, and presence of matched controls that were randomly selected from the general population. Further, information of comorbidities and level of education existed for both persons with T1D and controls, making it possible to adjust for these variables. Another strength of the study is that the Swedish National Diabetes Registry has a good coverage regarding risk factors.

6.1.8 LIMITATIONS OF THE STUDIES

Some important limitations of the studies need to be considered. Data for study I and III were collected from 10 outpatient diabetic clinics, most of which are in the same geographical region in Sweden. At the same time, more persons with T1D in this region have optimal glycemic control compared to all persons with T1D in Sweden (24.8% vs. 20%), and the quality of diabetes care in this region is therefore likely high (12). It may happen that results could differ in other parts of the country, but it is unlikely that other regions in Sweden perform substantially more HbA1c checks and reach the recommended goal of 4 annual measurements. All psychosocial variables were not available for study I and III. It is possible that various psychosocial variables may be related to the probability of having HbA1c check or usage of an insulin pump and may be related to possibilities to come to clinical visits. Hypoglycemia is difficult to record properly in clinical practice for several reasons. These data were not available for study I, III and IV. Absence of this variable may contribute to the missed aspects of interpretation of results. Information of several important risk factors for coronary events including smoking, blood pressure and lipid levels were not available among controls in Study IV. Further, information of several life-style factors including physical activity and dietary habits were not available in the studies. Data on the use of cardioprotective medications were available only from 2005. (limitation for study IV). Another limitation in study IV is that it cannot be excluded that non-severe AMI may be underdiagnosed to some extent among controls, since persons without diabetes attend their health care provider less frequently compared to the diabetes population. Emigration is one of the possible challenges and it was not possible to get information on whether and when persons who emigrated, died or got AMI.

A limitation to the study II is the short duration used to measure the treatment experience. Another limitation is the selection of participants: every patient needed to come to 3 scheduled visits at the CRU during the limited 6 days period. This influenced the selection of study participants due to social factors and may affect the representability of participants (likely more important for the part of the study regarding treatment satisfaction). Technological progress is very evolutionary, and findings obtained in the study must be interpreted with caution when making recommendations on what CGM device to choose in clinical practice today.

7 CONCLUSION

Study I

In persons with type 1 diabetes with inadequate glycaemic control, HbA1c is measured less than two times per year in clinical practice in Sweden compared to four times per year recommended in guidelines. More frequent visits could likely improve HbA1c levels and reduce the risk of complications. Patients with MDI had lower frequency of HbA1c checks compared with T1D patients on CSII. This patient group needs extra focus.

Study II

In a from the manufacturers economically independent study we found that the Dexcom G4 sensor was associated with both greater accuracy and treatment satisfaction than the Enlite sensor. The high accuracy and treatment satisfaction with the DexCom system is useful information also today since it is still commonly used in clinical practice. We found that independent studies comparing CGM systems had rarely been performed before our study. Hence, there is a need of studies using the same concept as in ours for evaluating novel sensors and CGM systems, especially since long-term comparative randomized trials are difficult to perform before novel sensors or CGM systems are developed and are so far lacking in the field.

Study III

Patients with high HbA1c levels have a greater probability of improved HbA1c after initiating pump therapy, but effects remain relatively moderate even for T1D patients with poor control. Healthcare needs other treatment alternatives in order to improve the glycemic control significantly. Insulin pump treatment is valuable. Thus, a certain reduction of HbA1c occurs, and according to other studies, it has positive impact on the quality of life and time spent in hypoglycemia.

Study IV

T1D patients had approximately four times higher risk of myocardial infarction compared to the general population. However, this level is lower than results from some other historical studies from different part of the world. The absolute risk of coronary events in persons with T1D was similar for men and women, whereas the excess risk compared to the general population was greater for women than for men. A strong relationship exists between

glycaemic control and coronary events in persons with T1D. Excessive risk is much lower for patients with well-controlled diabetes and absence of kidney injury. Intensive cardioprotective strategies are still needed for persons with T1D.

8 FUTURE PERSPECTIVES

The present thesis shows that health care strategies for persons with type 1 diabetes were not optimal during the period our studies were conducted (1998-2014). Impaired glycaemic control was strongly associated with the risk of coronary events in persons with T1D and highlights the importance to focus on better methods to improve the glycemic control. Systematic and continuous efforts should be made to ensure that essential parts of diabetes care, such as follow up visits at the diabetes care clinics, especially for those patients who are on MDI treatment, are improved. It is essential that independent comparative studies of sensors and CGM systems are performed since we show here that both accuracy and treatment satisfaction can greatly differ between sensors and CGM systems. Such information is of use for clinicians and decision makers in treating persons with T1D. Improved tools for guiding the choice of modern therapies including CGM and insulin pump therapy would be beneficial. Since the effect on HbA1c of insulin pump in clinical practice is modest also in persons with poor glycaemic control clinicians need to be aware that other treatment strategies are crucial for improving the overall glycaemic control in persons with T1D.

More research is needed to estimate to what extent modifiable risk factors affect the progression of cardiovascular complications and how coronary events can be reduced in persons with T1D. Cardioprotective strategies, including primary and secondary prevention, need to be improved. Specific smoking cessation programs for persons with type 1 diabetes could be implemented. Continued aggressive treatment with lipid-lowering (statin) medication is essential, but further investigations particularly for type 1 diabetes patients are needed. It is most likely that a similar preventive effect exists for this patient group since it has been shown in many other populations. The difficult question is to know at what age such an intervention is beneficial, i.e. whether early treatment at a young age has an effect later on in life.

ACKNOWLEDGEMENT

I would like to express my special appreciations to:

Marcus Lind, my main supervisor. Thank you for sharing your knowledge and experience with me and your patience with me over the years.

Stig Attvall and **Börje Haraldsson**, my co-supervisors, for all developing knowledge and assistance.

Aldina Pivodic for your valuable help and all statistical advice.

Sofia, Mervi, Agneta for your time and help conducting the study.

Anna Jansson, head of the Department of Emergency Medicine for making all this possible. Without your support my PhD could have never happened.

Karin Moks, my friend, and colleague. Thank you so much for being the one person I could talk to. Thank you for all care and support.

My love **Daniel**, thank you for endless support, listening and understanding and, of course, all cups of tea and coffee you made during this time. My achievements would never have been possible without you.

Our dearest treasures **Eneja, Elija, Bella**, and **Olivia**. I am so happy to have you in my life.

The very special thanks to my mother **Ana**, father **Aloyzas** who taught me not to give up (***ačiū mama ir tėti, kad išmokėte niekada nepasiduoti***) and my parents in law **Gunilla** and **Sören**, who believed in me. Without you I would not be where I am now.

Also, my sincere gratitude to **all my colleagues and personnel** at the **Department of Emergency medicine at Karolinska University Hospital** and **NÄL** (Trollhättan and Uddevalla) where my research journey started.

Many thanks to all participating nurses, physicians and other staff members who have contributed to Diab-base and NDR.

I also want to thank Novonordisk Foundation, the Region of Västra Götaland, the Swedish State (supporting ALF grants) and the Swedish Society of Physicians being main funders for the included studies in this thesis.

I can no other answer make but thanks, and thanks, and ever thanks…-**William Shakespeare**

REFERENCES

1. Global report on diabetes. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf (Last accessed: October 8, 2017).

2. Largay, J. (2012). Case study: New-onset diabetes: How to tell the dif-ference between type 1 and type 2 diabetes. Clinical Diabetes, 30(1), 25-26.

3. De Ferranti, S. D., De Boer, I. H., Fonseca, V., Fox, C. S., Golden, S. H., Lavie, C. J., ... & Zinman, B. (2014). Type 1 diabetes mellitus and cardiovascular disease. Circulation, 130(13), 1110-1130.

4. Wenzlau, J. M., & Hutton, J. C. (2013). Novel diabetes autoantibodies and prediction of type 1 diabetes. Current diabetes reports, 13(5), 608-615.

5. Classification and Diagnosis of Diabetes. American Diabetes Associa-tion Diabetes Care 2015 Jan; 38(Supplement 1): S8-S16. http://care.diabetesjournals.org/content/38/Supplement_1/S8.full-text.pdf. (Last accessed: October 8, 2017)

6. Ekoé, J. M., Zimmet, P., & Williams, R. (Eds.). (2001). The epidemi-ology of diabetes mellitus: an international perspective. John Wiley & Sons.

7. Estimates of cost of diabetes per year in the European Union and in other European countries. https://ec.europa.eu/health//sites/health/files/major_chronic_diseases/docs/idf_cost_2011.pdf. (Last accessed: October 8, 2017).

8. Franciosi, M., Lucisano, G., Amoretti, R., Capani, F., Bruttomesso, D., Di Bartolo, P., ... & Nicolucci, A. (2013). Costs of treatment and com-plications of adult type 1 diabetes. Nutrition, Metabolism and Cardiovascular Diseases, 23(7), 606-611.

9. Nordwall, M., Arnqvist, H. J., Bojestig, M., & Ludvigsson, J. (2009). Good glycemic control remains crucial in prevention of late diabetic complications–the Linköping Diabetes Complications Study. Pediatric diabetes, 10(3), 168-176.

10. Govan, L., Wu, O., Briggs, A., Colhoun, H. M., McKnight, J. A., Mor-ris, A. D., ... & Lindsay, R. S. (2011). Inpatient costs for people with type 1 and type 2 diabetes in Scotland: a study from the Scottish Dia-betes Research Network Epidemiology Group. Diabetologia, 54(8), 2000-2008.

11. Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl j Med, 1993(329), 977-986.

12. Health Consumer Powerhouse. Euro Diabetes Index 2014. Report. https://healthpowerhouse.com/files/EDI-2014/EDI-2014-report.pdf (Last accessed: October 13, 2017).

13. NDR annual report 2016. https://www.ndr.nu/ (Last accessed: October 13, 2017)

14. Carlsson, B. M., Attvall, S., Clements, M., Gumpeny, S. R., Pivodic, A., Sternemalm, L., & Lind, M. (2013). Insulin Pump—Long-Term Effects on Glycemic Control: An Observational Study at 10 Diabetes Clinics in Sweden. Diabetes technology & therapeutics, 15(4), 302-307.

15. Lind, M., Svensson, A. M., Kosiborod, M., Gudbjörnsdottir, S., Pivodic, A., Wedel, H., ... & Rosengren, A. (2014). Glycemic control and excess mortality in type 1 diabetes. New England Journal of Med-icine, 371(21), 1972-1982.

16. Livingstone, S. J., Levin, D., Looker, H. C., Lindsay, R. S., Wild, S. H., Joss, N., ... & McKnight, J. A. (2015). Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. Jama, 313(1), 37-44.

17. Dogra, G., Rich, L., Stanton, K., & Watts, G. F. (2001). Endothelium-dependent and independent vasodilation studied at normoglycaemia in type I diabetes mellitus with and without microalbuminuria. Diabeto-logia, 44(5), 593-601.

18. Bakris, G. L., & Molitch, M. (2014). Microalbuminuria as a risk pre-dictor in diabetes: the continuing saga. Diabetes Care, 37(3), 867-875.

19. Karamanou, M., Protogerou, A., Tsoucalas, G., Androutsos, G., & Poulakou-Rebelakou, E. (2016). Milestones in the history of diabetes mellitus: The main contributors. World journal of diabetes, 7(1), 1.

20. Introduction to diabetes mellitus. https://www.diapedia.org/introduction-to-diabetes-mellitus/1104337136/etienne-lancereaux-1829-1910 (Last accessed: October 13, 2017)

21. Atkinson, M. A., Eisenbarth, G. S., & Michels, A. W. (2014). Type 1 diabetes. The Lancet, 383(9911), 69-82.

22. Winter, W. E., Harris, N., & Schatz, D. (2002). Immunological mark-ers in the diagnosis and prediction of autoimmune type 1a diabetes. Clinical Diabetes, 20(4), 183-191.

23. Chiang, J. L., Kirkman, M. S., Laffel, L. M., & Peters, A. L. (2014). Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes care, 37(7), 2034-2054.

24. Parkkola, A., Härkönen, T., Ryhänen, S. J., Ilonen, J., Knip, M., & Fin-nish Pediatric Diabetes Register. (2013). Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed chil-dren. Diabetes Care, 36(2), 348-354.

25. Soltesz, G., Patterson, C. C., & Dahlquist, G. (2007). Worldwide childhood type 1 diabetes incidence–what can we learn from epidemi-ology? Pediatric diabetes, 8(s6), 6-14.

26. Rosenfeld, L. (2002). Insulin: discovery and controversy. Clinical chemistry, 48(12), 2270-2288.

27. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancre-atic extracts in the treatment of diabetes mellitus. Preliminary report. Can Med Assoc J 1922;12:141-146.

28. Living with Diabetes. Leonard Thompson. http://www.diabetes.co.uk/pioneers/leonard-thompson.html (Last accessed: October 13, 2017).

29. The discovery of insulin. https://www.nobelprize.org/educational/medicine/insulin/discovery-insulin.html (Last accessed: October 13, 2017).

30. Donner, T. (2015). Insulin–pharmacology, therapeutic regimens and principles of intensive insulin therapy.

31. The history of Diabetes https://www.diabeteshealth.com/the-history-of-diabetes/ (Last accessed: December 17, 2017).

32. Summary of safety and effectivenes data. CGMS https://www.accessdata.fda.gov/cdrh_docs/pdf/P980022b.pdf (Last accessed: December 17, 2017).

33. Medical Devices. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm522764.htm (Last accessed: October 14, 2017).

34. Schatz, D. A., Haller, M., & Atkinson, M. (2010). Type 1 Diabetes, An Issue of Endocrinology and Metabolism Clinics of North America, E-Book (Vol. 39, No. 3). Elsevier Health Sciences.

35. Wang, B., Yuan, J., Yao, Q., Li, L., Yan, N., Song, R., ... & Zhang, J. A. (2016). Incidence and temporal trends of type 1 diabetes in China: a systematic review and meta-analysis. The Lancet Diabetes & Endocri-nology, 4, S13.

36. International Insulin Foundation. Diabetes Foundation Report on insu-lin-requiring diabetes in sub-Saharan Africa. London, International Insulin Foundation, 2005. http://www.access2insulin.org/diabetes-foundation-report-on-insulin-requiring-diabetes-in-sub-saharan-africa.html (Last accessed: October 13, 2017)

37. Reynolds, T. M., Smellie, W. S. A., & Twomey, P. J. (2006). Cases in primary care laboratory medicine: Glycated haemoglobin (HbA1c) monitoring. BMJ: British Medical Journal, 333(7568), 586.

38. Nordwall, M., Abrahamsson, M., Dhir, M., Fredrikson, M., Ludvigs-son, J., & Arnqvist, H. J. (2015). Impact of HbA1c, followed from on-set

of type 1 diabetes, on the development of severe retinopathy and nephropathy: the VISS Study (Vascular Diabetic Complications in Southeast Sweden). Diabetes care, 38(2), 308-315.

39. HbA1c diagnostic. https://www.equalis.se/media/93807/gunnar-nordin_hba1c-diagnostik.pdf (Last accessed: December 17, 2017)

40. Weykamp, C. (2013). HbA1c: a review of analytical and clinical as-pects. Annals of laboratory medicine, 33(6), 393-400.

41. Goodall, I. (2005). HbA1c Standardisation Destination–Global IFCC Standardisation How, Why, Where and When: A Tortuous Pathway From Kit Manufacturers, via Inter-laboratory Lyophilized and Whole Blood Comparisons to Designated National Comparison Schemes. Clinical Biochemist Reviews, 26(1), 5.

42. Equalis. https://www.equalis.se/en/start/ (Last accessed: October 13, 2017).

43. Nationella riktlinjer för diabetesvård. https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20633/2017-5-31.pdf (Last accessed: December 17, 2017).

44. Type 1 diabetes in adults: diagnosis and management https://www.nice.org.uk/guidance/ng17/chapter/1-recommendations (Last accessed: Januari3, 2018).

45. Standards of Medical Care in Diabetes—2017. http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf (Last accessed: December 17, 2017).

46. Dhaliwal, R., & Weinstock, R. S. (2014). Management of Type 1 Diabetes in Older Adults. Diabetes Spectrum: A Publication of the American Diabetes Association, 27(1), 9–20.

47. Owen J. Driskell, David Holland, Jenna L. Waldron, Clare Ford, Jonathan J. Scargill, Adrian Heald, Martin Tran, Fahmy W. Hanna, Peter W. Jones, R. John Pemberton, Anthony A. Fryer. Reduced Testing Frequency for Glycated Hemoglobin, HbA1c, Is Associated With Deteriorating Diabetes Control Diabetes Care Oct 2014, 37 (10) 2731-2737.

48. National Institute for Clinical Excellence. (2004). Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. http://www. nice. org. uk/pdf/CG015NICEguideline.pdf. (Last accessed: December 17, 2017).

49. Lian, J., & Liang, Y. (2014). Diabetes management in the real world and the impact of adherence to guideline recommendations. Current medical research and opinion, 30(11), 2233-2240.

50. Paul, C. L., Piterman, L., Shaw, J. E., Kirby, C., Barker, D., Robinson, J., ... & Sanson-Fisher, R. W. (2016). Patterns of type 2 diabetes monitoring in rural towns: How does frequency of HbA1c and lipid testing compare with existing guidelines? Australian Journal of Rural Health, 24(6), 371-377.

51. Driskell, O. J., Holland, D., Hanna, F. W., Jones, P. W., Pemberton, R. J., Tran, M., & Fryer, A. A. (2012). Inappropriate requesting of gly-cated hemoglobin (Hb A1c) is widespread: assessment of prevalence, impact of national guidance, and practice-to-practice variability. Clin-ical chemistry, 58(5), 906-915.

52. Waitzfelder, B., Pihoker, C., Klingensmith, G., Case, D., Anderson, A., Bell, R. A., ... & Rodriguez, B. L. (2011). Adherence to guidelines for youths with diabetes mellitus. Pediatrics, peds-2010.

53. Cohen, R. M., Franco, R. S., Khera, P. K., Smith, E. P., Lindsell, C. J., Ciraolo, P. J., ... & Joiner, C. H. (2008). Red cell life span heterogenei-ty in hematologically normal people is sufficient to alter HbA1c. Blood, 112(10), 4284-4291.

54. English, E., Idris, I., Smith, G., Dhatariya, K., Kilpatrick, E. S., & John, W. G. (2015). The effect of anaemia and abnormalities of eryth-rocyte indices on HbA1c analysis: a systematic review. Diabetologia, 58(7), 1409-1421.

55. Rajagopal, L., Ganapathy, S., Sundaram Arunachalam, V. R., & Ramraj, B. (2017). Does Iron Deficiency Anaemia and its Severity In-fluence HbA1C Level in Non Diabetics? An Analysis of 150 Cases. Journal of clinical and diagnostic research: JCDR, 11(2), EC13.

56. Coban, E., Ozdogan, M., & Timuragaoglu, A. (2004). Effect of iron deficiency anemia on the levels of hemoglobin A1c in nondiabetic pa-tients. Acta haematologica, 112(3), 126-128.

57. Silva, J. F., Pimentel, A. L., & Camargo, J. L. (2016). Effect of iron deficiency anaemia on HbA1c levels is dependent on the degree of anaemia. Clinical biochemistry, 49(1), 117-120.

58. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. Diabetes Care. 2010 Nov; 33(11):2310-3.

59. Rafat D, Rabbani TK, Ahmad J, Ansari MA. Influence of iron metabo-lism indices on HbA1c in non-diabetic pregnant women with and without iron-deficiency anemia: effect of iron supplementa-tion.Diabetes Metab Syndr. 2012 Apr-Jun; 6(2):102-5.

60. Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I 1999 Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediatr Int 41:357–362

61. Kitada, M., Zhang, Z., Mima, A. and King, G. L. (2010), Molecular mechanisms of diabetic vascular complications. Journal of Diabetes Investigation, 1: 77–89.

62. Brownlee, M. (2001). Biochemistry and molecular cell biology of dia-betic complications. Nature, 414(6865), 813-820.

63. Schleicher, E. D., & Weigert, C. (2000). Role of the hexosamine bio-synthetic pathway in diabetic nephropathy. Kidney international, 58, S13-S18.

64. Nathan, D. M. (2005). Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med, 353, 2643-2653.

65. Shankar A, Klein R, Klein BE, Moss SE: Association between glyco-sylated hemoglobin level and cardiovascular and all-cause mortality in type 1 diabetes. Am J Epidemiol. 2007, 166: 393-402.

66. de Boer IH, Kestenbaum B, Rue TC, et al.; Diabetes Control and Com-plications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Insulin therapy, hyper-glycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med 2008;168: 1867–1873

67. Bower, J. K., Appel, L. J., Matsushita, K., Young, J. H., Alonso, A., Brancati, F. L., & Selvin, E. (2012). Glycated hemoglobin and risk of hypertension in the atherosclerosis risk in communities study. Diabe-tes care, 35(5), 1031-1037.

68. Donnelly, R., & Horton, E. (Eds.). (2008). Vascular complications of diabetes: current issues in pathogenesis and treatment. John Wiley & Sons.

69. Morrish, N. J., Wang, S. L., Stevens, L. K., Fuller, J. H., Keen, H., & WHO Multinational Study Group. (2001). Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia, 44(2), S14.

70. Chapman M., Crockett S., Purvis T., Anderson M., Whittaker P., Bhattacharjee R., et al. (2013) Macrovascular disease in the elderly with type 1 diabetes. J Diabetes Metab 4: 299

71. Jørgensen ME, Almdal TP, Carstensen B Time trends in mortality rates in type 1 diabetes from 2002 to 2011. Diabetologia. 2013 Nov; 56(11):2401-4.

72. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia. 2003 Jun; 46(6):760-5.

73. Dabelea D, Kinney G, Snell-Bergeon JK, Hokanson JE, Eckel RH, Ehr-lich J, Garg S, Hamman RF, Rewers M, Coronary Artery Calcification in Type 1 Diabetes Study. Effect of type 1 diabetes on the gender dif-ference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study.Diabetes. 2003 Nov; 52(11):2833-9

74. Kalyani RR, Lazo M, Ouyang P, Turkbey E, Chevalier K, Brancati F, Becker D, Vaidya D Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults.Diabetes Care. 2014; 37(3):830-8.

75. Schnell, O., Cappuccio, F., Genovese, S., Standl, E., Valensi, P., & Ceriello, A. (2013). Type 1 diabetes and cardiovascular disease. Cardiovascular diabetology, 12(1), 156.

76. Dalla Pozza, R., Bechtold, S., Bonfig, W., Putzker, S., Kozlik-Feldmann, R., Netz, H., & Schwarz, H. P. (2007). Age of onset of type 1 diabetes in children and carotid intima medial thickness. The Journal of Clinical Endocrinology & Metabolism, 92(6), 2053-2057.

77. Nascimento, A. M. M. D. A., Sequeira, I. J., Vasconcelos, D. F., Gan-dolfi, L., Pratesi, R., & Nóbrega, Y. K. D. M. (2017). Endothelial dysfunction in children with type 1 diabetes mellitus. Archives of Endocrinology and Metabolism, (AHEAD), 0-0.

78. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ: Coro-nary calcium in adults with type 1 diabetes. Diabetes 49:1571–1578, 2000

79. Anderson, T. J., Gerhard, M. D., Meredith, I. T., Charbonneau, F., Delagrange, D., Creager, M. A., ... & Ganz, P. (1995). Systemic nature of endothelial dysfunction in atherosclerosis. The American journal of cardiology, 75(6), 71B-74B.

80. Larsen J, Brekke M, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. Diabetes. 2002 Aug; 51(8):2637-41.

81. Eeg-Olofsson, K., Cederholm, J., Nilsson, P. M., Zethelius, B., Svens-son, A. M., Gudbjörnsdóttir, S., & Eliasson, B. (2010). Glycemic con-trol and cardiovascular disease in 7,454 patients with type 1 diabetes. Diabetes Care, 33(7), 1640-1646.

82. Juutilainen, A., Lehto, S., Rönnemaa, T., Pyörälä, K., & Laakso, M. (2008). Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care, 31(4), 714-719.

83. Nathan, D. M., & DCCT/Edic Research Group. (2014). The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes care, 37(1), 9-16.

84. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treat-ment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643.

85. Nathan, D. M., Bebu, I., Braffett, B. H., Orchard, T. J., Cowie, C. C., Lopes-Virella, M., ... & Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. (2016). Risk factors for cardi-ovascular disease in type 1 diabetes. Diabetes, db151517.

86. Orchard TJ, Olson JC, Erbey JR, et al. Insulin resistance-related fac-tors, but not glycemia, predict coronary artery disease in type 1 diabe-tes: 10-year follow-up data from the Pittsburgh Epidemiology of Dia-betes Complications Study, Diabetes Care , 2003, vol. 26 (pg. 1374-9)

87. Forrest KY, Becker DJ, Kuller LH, et al. Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study, Atherosclerosis , 2000, vol. 148 (pg. 159-69)

88. Adamsson Eryd, S., Svensson, A. M., Franzén, S., Eliasson, B., Nils-son, P. M., & Gudbjörnsdottir, S. (2017). Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up. Diabetic Medi-cine, 34(3), 411-418.

89. Pálsson, R., & Patel, U. D. (2014). Cardiovascular complications of diabetic kidney disease. Advances in chronic kidney disease, 21(3), 273-280.

90. Torffvit O, Lövestam-Adrian M, Agardh E, Agardh CD Nephropathy, but not retinopathy, is associated with the development of heart dis-ease in Type 1 diabetes: a 12-year observation study of 462 pa-tients. Diabet Med. 2005 Jun; 22(6):723-9.

91. Charytan, D., & Kuntz, R. E. (2006). The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. Kidney international, 70(11), 2021-2030.

92. Eriksen BO, Ingebretsen OC The progression of chronic kidney dis-ease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006 Jan; 69(2):375-82.

93. Orchard, T. J., Dorman, J. S., Maser, R. E., Becker, D. J., Drash, A. L., Ellis, D., ... & Kuller, L. H. (1990). Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes, 39(9), 1116-1124.

94. Newman, D. J., Mattock, M. B., Dawnay, A. B. S., Kerry, S., McGuire, A., Yaqoob, M., ... & Hawke, C. (2005). Systematic review on urine albumin testing for early detection of diabetic complications.

95. KDOQI Clinical Practice Guidelines and Clinical Practice Recommen-dations for Diabetes and Chronic Kidney Disease. KDOQI. Am J Kid-ney Dis. 2007 Feb; 49(2 Suppl 2):S12-154.

96. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003 Jun 5; 348(23):2285-93.

97. Group, T. M. C. S. (1999). Predictors of the development of microal-buminuria in patients with Type 1 diabetes mellitus: a seven-year pro-spective study. Diabetic Medicine, 16(11), 918-925.

98. Bruce A Perkins, MD, MPH, Linda H Ficociello, PhD, Bijan Roshan, MD, James H Warram, MD, ScD, and Andrzej S Krolewski, MD, PhD In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require pro-gression to proteinuria.

99. Radcliffe, N. J., Seah, J. M., Clarke, M., MacIsaac, R. J., Jerums, G., & Ekinci, E. I. (2017). Clinical predictive factors in diabetic kidney dis-ease progression. Journal of diabetes investigation, 8(1), 6-18.

100. Amin R, Widmer B, Prevost AT: Risk of microalbuminuria and pro-gression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. BMJ. 2008, 336: 697-701.

101. A. Levey, L. A. Stevens, C. H. Schmid et al., "A new equation to esti-mate glomerular filtration rate," Annals of Internal Medicine, vol. 150, no. 9, pp. 604–612, 2009.

102. CKD-EPI equation. https://www.kidney.org/content/ckd-epi-creatinine-equation-2009. (Last accessed: October 10, 2017).

103. Maahs DM, Ogden LG, Kretowski A, Snell-Bergeon JK, Kinney GL, Berl T, Rewers M Serum cystatin C predicts progression of subclinical coronary atherosclerosis in individuals with type 1 diabetes. Diabetes. 2007 Nov; 56(11):2774-9.

104. Premaratne E, MacIsaac RJ, Finch S, Panagiotopoulos S, Ekinci E, Je-rums G Serial measurements of cystatin C are more accurate than cre-atinine-based methods in detecting declining renal function in type 1 diabetes. Diabetes Care. 2008 May; 31(5):971-3.

105. Bashier, A. M., Fadlallah, A. A. S., Alhashemi, N., Thadani, P. M., Abdelgadir, E., & Rashid, F. (2015). Cystatin C and its role in patients with type 1 and type 2 diabetes mellitus. Advances in Endocrinology, 2015.

106. Tarnow, L., Rossing, P., Jensen, C., Hansen, B. V., & Parving, H. H. (2000). Long-term renoprotective effect of nisoldipine and lisinopril in type 1 diabetic patients with diabetic nephropathy. Diabetes Care, 23(12), 1725-1730.

107. Shahbazian, H., & Rezaii, I. (2013). Diabetic kidney disease; review of the current knowledge. Journal of Renal Injury Prevention, 2(2), 73.

108. Maahs DM, Snell-Bergeon JK, Kinney GL, Wadwa RP, Garg S, Ogden LG, Rewers M : ACE-I/ARB treatment in type 1 diabetes patients with albuminuria is associated with lower odds of progression of coronary artery calcification. J Diabetes Complications 2007; 21: 273– 279

109. Bojestig, M., Arnqvist, H. J., Hermansson, G., Karlberg, B. E., & Ludvigsson, J. (1994). Declining incidence of nephropathy in insulin-dependent diabetes mellitus. New England Journal of Medicine, 330(1), 15-18.

110. Krolewski AS, Warram JH, Christlieb AR, Busick EJ, Kahn CR. The changing natural history of nephropathy in type I diabetes. The Ameri-can journal of medicine. May 1985;78(5):785-794.

111. Martínez-Castelao, A., Navarro-González, J. F., Górriz, J. L., & de Al-varo, F. (2015). The concept and the epidemiology of diabetic nephropathy have changed in recent years. Journal of clinical medi-cine, 4(6), 1207-1216.

112. Finne, P., Reunanen, A., Stenman, S., Groop, P. H., & Grönhagen-Riska, C. (2005). Incidence of end-stage renal disease in patients with type 1 diabetes. Jama, 294(14), 1782-1787.

113. DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Inter-ventions and Complications study. Lancet Diabetes Endocrinol. 2014 Oct; 2(10):793-800.

114. Piscitelli, P., Viazzi, F., Fioretto, P., Giorda, C., Ceriello, A., Geno-vese, S., ... & De De Cosmo, S. (2017). Predictors of chronic kidney disease in type 1 diabetes: a longitudinal study from the AMD Annals initiative. Scientific Reports, 7.

115. Tuomilehto, J., Borch-Johnsen, K., Molarius, A., Forsen, T., Rastenyte, D., Sarti, C., & Reunanen, A. (1998). Incidence of cardiovascular dis-ease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. Diabetologia, 41(7), 784-790.

116. Keith, D. S., Nichols, G. A., Gullion, C. M., Brown, J. B., & Smith, D. H. (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Ar-chives of internal medicine, 164(6), 659-663.

117. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M, Alberta Kidney Disease Network. Re-lation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010 Feb 3; 303(5):423-9

118. Bello AK, Hemmelgarn B, Lloyd A, et al. Associations among esti-mated glomerular filtration rate, proteinuria, and adverse cardiovascu-lar outcomes. Clin. J. Am. Soc. Nephrol. 2011;6(6):1418–26.

119. Eriksen BO, Ingebretsen OC The progression of chronic kidney dis-ease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006 Jan; 69(2):375-82.

120. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A : Albuminuria reflects widespread vascular damage: the Steno hypothesis. Diabetologia 1989; 32: 219– 226

121. Stadler M, Auinger M, Anderwald C, Kastenbauer T, Kramar R, Fein-bock C, Irsigler K, Kronenberg F, Prager R : Long-term mortality and incidence of renal dialysis and transplantation in type 1 diabetes melli-tus. J Clin Endocrinol Metab 2006; 91: 3814– 3820

122. Moen, M. F., Zhan, M., Walker, L. D., Einhorn, L. M., Seliger, S. L., & Fink, J. C. (2009). Frequency of hypoglycemia and its significance in chronic kidney disease. Clinical Journal of the American Society of Nephrology, 4(6), 1121-1127.

123. Groop, P. H., Thomas, M. C., Moran, J. L., Wadèn, J., Thorn, L. M., Mäkinen, V. P., ... & Forsblom, C. (2009). The presence and severity of

chronic kidney disease predicts all-cause mortality in type 1 diabe-tes. Diabetes, 58(7), 1651-1658.

124. Morris, A. D., Boyle, D. I., McMahon, A. D., Greene, S. A., MacDon-ald, T. M., Newton, R. W., & DARTS/MEMO Collaboration. (1997). Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The Lancet, 350(9090), 1505-1510.

125. Riaz, M., Basit, A., Fawwad, A., Ahmedani, M. Y., & Rizvi, Z. A. (2014). Factors associated with non-adherence to insulin in patients with type 1 diabetes. Pakistan journal of medical sciences, 30(2), 233.

126. Aronson, R. (2012). The role of comfort and discomfort in insulin therapy. Diabetes technology & therapeutics, 14(8), 741-747.

127. Pickup, J. C. (2012). Insulin-pump therapy for type 1 diabetes melli-tus. New England Journal of Medicine, 366(17), 1616-1624.

128. Doggrell, S. A., & Chan, V. (2015). Adherence to insulin treatment in diabetes: can it be improved? Journal of diabetes, 7(3), 315-321.

129. Hoogma, R. P. L. M., Hammond, P. J., Gomis, R., Kerr, D., Brut-tomesso, D., Bouter, K. P., ... & Torlone, E. (2006). Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. Diabetic Medicine, 23(2), 141-147.

130. Misso, M. L., Egberts, K. J., Page, M., O'connor, D., & Shaw, J. (2010). Cochrane review: Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Evidence-Based Child Health: A Cochrane Review Journal, 5(4), 1726-1867.

131. Nicolucci, A., Maione, A., Franciosi, M., Amoretti, R., Busetto, E., Capani, F., ... & Morviducci, L. (2008). Quality of life and treatment satisfaction in adults with Type 1 diabetes: a comparison between con-tinuous subcutaneous insulin infusion and multiple daily injections. Diabetic Medicine, 25(2), 213-220.

132. Roze, S., Smith-Palmer, J., Valentine, W., Portu, S., Nørgaard, K., & Pickup, J. C. (2015). Cost-effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections of insulin in Type 1 diabetes: a systematic review. Diabetic Medicine, 32(11), 1415-1424.

133. Pfützner, A., Weissmann, J., Mougiakakou, S., Daskalaki, E., Weis, N., & Ziegler, R. (2015). Glycemic variability is associated with frequency of blood glucose testing and bolus: post hoc analysis results from the ProAct Study. Diabetes technology & therapeutics, 17(6), 392-397.

134. Insulinpump (CSII) treatment in adult persons with type 1 diabetes. http://www.internetmedicin.se/page.aspx?id=2293 (Last accessed January 8, 2018).

135. Jin, S. M., Baek, J. H., Suh, S., Jung, C. H., Lee, W. J., Park, C. Y., ... & Kim, J. H. (2017). Factors Associated with Greater Benefit of a National Reimbursement Policy for Blood Glucose Test Strips in Adult Patients

with Type 1 Diabetes: A Prospective Cohort Study. Journal of Diabetes Investigation.

136. American Asociation of Clinical Endocrinologists and American Col-lege of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement https://www.aace.com/files/position-statements/outpatient-glucose-monitoring-consensus-statement.pdf (Last accessed October 14, 2017).

137. Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastrototaro J Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous moni-toring system. Diabetes Technol Ther. 2004 Apr; 6(2):105-13.

138. From Two to One Per Day Calibration of Dexcom G4 Platinum by a Time-Varying Day-Specific Bayesian Prior. Acciaroli G, Vettoretti M, Facchinetti A, Sparacino G, Cobelli C Diabetes Technol Ther. 2016 Aug; 18(8):472-9.

139. Bailey, T. S., Chang, A., & Christiansen, M. (2014). Clinical accuracy of a continuous glucose monitoring system with an advanced algo-rithm. Journal of diabetes science and technology, 9(2), 209-214.

140. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Kovatchev BP, Patek SD, Ortiz EA, Breton MD Diabetes Technol Ther. 2015 Mar; 17(3):177-86.

141. FDA News Release 12-20-2016: FDA expands indication for continu-ous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decision. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534056.htm (Last accessed: October 14, 2017).

142. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Re-search Foundation Continuous Glucose Monitoring Study Group. Con-tinuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476

143. Langendam, M., Luijf, Y. M., Hooft, L., DeVries, J. H., Mudde, A. H., & Scholten, R. J. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. The Cochrane Library.

144. Rodbard, D. (2017). Continuous glucose monitoring: a review of re-cent studies demonstrating improved glycemic outcomes. Diabetes Technology & Therapeutics, 19(S3), S-25.

145. van Beers CA, DeVries JH, Kleijer SJ, Smits MM, Geelhoed-Duijvestijn PH, Kramer MH, Diamant M, Snoek FJ, Serné EH Contin-uous glucose monitoring for patients with type 1 diabetes and im-paired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol. 2016 Nov; 4(11):893-902.

146. Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW, T1D Exchange Clinic Network. Continuous Glucose Monitoring in Pa-tients

With Type 1 Diabetes Using Insulin Injections. Diabetes Care. 2016 Jun; 39(6):e81-2

147. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S The Perfor-mance and Usability of a Factory-Calibrated Flash Glucose Monitor-ing System. Diabetes Technol Ther. 2015 Nov; 17(11):787-94.

148. Ólafsdóttir, A. F., Attvall, S., Sandgren, U., Dahlqvist, S., Pivodic, A., Skrtic, S., ... & Lind, M. (2017). A clinical trial of the accuracy and treatment experience of the flash glucose monitor FreeStyle Libre in adults with type 1 diabetes. Diabetes Technology & Therapeutics, 19(3), 164-172.

149. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R Novel glucose-sensing technology and hypoglycaemia in type 1 diabe-tes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016 Nov 5; 388(10057):2254-2263.

150. Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J. L., Reuterwall, C., ... & Olausson, P. O. (2011). External review and vali-dation of the Swedish national inpatient register. BMC public health, 11(1), 450.

151. Moström, P., Ahlén, E., Imberg, H., Hansson, P. O., & Lind, M. (2017). Adherence of self-monitoring of blood glucose in persons with type 1 diabetes in Sweden. BMJ Open Diabetes Research and Care, 5(1), e000342.

152. Luijf, Y. M., Mader, J. K., Doll, W., Pieber, T., Farret, A., Place, J., ... & Arnolds, S. (2013). Accuracy and reliability of continuous glucose monitoring systems: a head-to-head comparison. Diabetes technology & therapeutics, 15(8), 721-726.

153. Petrie, D., Lung, T. W., Rawshani, A., Palmer, A. J., Svensson, A. M., Eliasson, B., & Clarke, P. (2016). Recent trends in life expectancy for people with type 1 diabetes in Sweden. Diabetologia, 59(6), 1167-1176.

154. Gliklich, R. E., Dreyer, N. A., & Leavy, M. B. (Eds.). (2014). Regis-tries for evaluating patient outcomes: a user's guide (No. 13). Gov-ernment Printing Office.

155. Summary of safety and effectivenes data. CGM https://www.accessdata.fda.gov/cdrh_docs/pdf/P980022b.pdf (Last ac-cessed December 8, 2017).

156. Huxley, Rachel R., et al. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. The Lancet Diabetes & Endocrinology, 2015, 3.3: 198-206.

157. Roeters van Lennep, J. E., Westerveld, H. T., Erkelens, D. W., & van der Wall, E. E. (2002). Risk factors for coronary heart disease: impli-cations of gender. Cardiovascular research, 53(3), 538-549.

158. Ganjali, S., Dallinga-Thie, G. M., Simental-Mendía, L. E., Banach, M., Pirro, M., & Sahebkar, A. (2017). HDL functionality in type 1 diabe-tes. Atherosclerosis, 267, 99-109.

159. Bott, U. W. E., Mühlhauser, I., Overmann, H., & Berger, M. (1998). Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes care, 21(5), 757-769.

160. Skyler, J. S. (2004). DCCT: the study that forever changed the nature of treatment of type 1 diabetes: Diabetes Control and Complications Trial—a glycaemic control study in type 1 diabetes. The British Jour-nal of Diabetes & Vascular Disease, 4(1), 29-32.

161. A list of the Swedish National Quality Registries http://kvalitetsregister.se/englishpages/findaregistry/allswedishqualityregistries. 2028.html (Last accessed: December 29, 2017).

162. Emilsson, L., Lindahl, B., Köster, M., Lambe, M., & Ludvigsson, J. F. (2015). Review of 103 Swedish healthcare quality registries. Journal of internal medicine, 277(1), 94-136.

163. Diabetes Control and Complications Trial Research Group. (1997). Hypoglycemia in the diabetes control and complications trial. Diabe-tes, 46(2), 271-286.

164. Bruttomesso, D., Pianta, A., Crazzolara, D., Scaldaferri, E., Lora, L., Guarneri, G., ... & Confortin, L. (2002). Continuous subcutaneous in-sulin infusion (CSII) in the Veneto region: efficacy, acceptability and quality of life. Diabetic medicine, 19(8), 628-634.

165. Garmo, A., Garmo, H., Ärnlöv, J., & Leksell, J. (2011). Long-term treatment effects of insulin pump therapy. Practical Diabetes, 28(7), 295.

166. Jonasson, J. M., Ye, W., Sparén, P., Apelqvist, J., Nyrén, O., & Brismar, K. (2008). Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes. Diabetes Care, 31(8), 1536-1540.