

Epidemiological Aspects on Assessing and Treating Dyslipidemia in Type 1 Diabetes

**Studies from the Swedish National Diabetes
Register**

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UNIVERSITY OF GOTHENBURG

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Epidemiological Aspects on Assessing and Treating Dyslipidemia
in Patients with Type 1 Diabetes – Studies from the Swedish
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Potius seroquam numquam
– Titus Livius 59 BC – 17 AD

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ABSTRACT

Background: Cardiovascular disease (CVD) is a major cause of shortened longevity in individuals with type 1 diabetes. Dyslipidemia is one of the important modifiable risk factors.

Aims: To investigate different aspects of dyslipidemia in type 1 diabetes. Assessing available blood lipid variables as markers of CVD risk in type 1 diabetes and the associations between lipid-lowering therapy (LLT) and CVD in primary prevention. Investigating the adherence to LLT, the association between non-adherence and CVD risk, and the factors associated with non-adherence from a demographic and socioeconomic perspective.

Methods: The studies comprise individuals with type 1 diabetes registered in the Swedish National Diabetes Register (NDR). Clinical characteristics and laboratory measures were collected from the NDR together with data from other nationwide Swedish registries on health and socioeconomic. In study I, Cox regression analyses were performed to assess low-density lipoprotein (LDL)-cholesterol and total cholesterol to high-density lipoprotein (HDL)-cholesterol ratio as predictors of CVD in individuals with type 1 diabetes. In study II, the association between primary prevention with LLT and the risk of CVD was analyzed in 24,330 individuals with type 1 diabetes applying propensity scores to balance the groups. In studies III and IV, we utilized the Swedish Prescribed Drug Register to investigate

adherence and non-adherence in 6192 individuals with type 1 diabetes and novel users of LLT in the context of CVD and socioeconomic.

Results: Total cholesterol to HDL-cholesterol ratio was a better predictor for cardiovascular risk in primary prevention than LDL-cholesterol, with a 12% elevated risk of CVD per 1 unit increase in the ratio. Individuals with type 1 diabetes and no history of CVD had a 22-44% lower risk of CVD and cardiovascular death when on LLT compared to the untreated individuals. High adherence to LLT was associated with a 22% lower risk of non-fatal CVD compared to a lower degree of adherence. Individuals discontinuing LLT within 18 months had a 43% higher risk of non-fatal CVD. Lower adherence was associated with male gender, younger age, marital status, and country of birth.

Conclusion: These observational studies emphasize the importance of regularly assessing and treating dyslipidemia in individuals with type 1 diabetes in order to achieve full cardioprotective treatment and lessen the cardiovascular burden in the type 1 diabetes population.

Keywords: Type 1 diabetes, LDL-cholesterol, dyslipidemia, lipid-lowering treatment, cardiovascular disease, adherence, discontinuation, socioeconomic status

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SAMMANFATTNING PÅ SVENSKA

Hjärtkärlsjukdom är den vanligaste orsaken till förkortad livslängd hos individer med typ 1 diabetes. Blodfettssänkning är en viktig modifierbar riskfaktor för hjärtkärlsjuklighet, men det mesta vi känner till om blodfettssänkning vid diabetes, härstammar från forskning kring individer med typ 2 diabetes. Även om båda formerna av diabetes har hyperglykemi som gemensam nämnare, så finns det också viktiga skillnader

Målsättningen med denna avhandling var att undersöka olika aspekter på blodfettssänkning vid typ 1 diabetes genom att 1). Undersöka de blodfetter vi mäter i daglig klinisk praxis och försöka hitta den blodfettsmarkör som bäst indikerar risk att utveckla hjärtkärlsjukdom. 2). Analysera association mellan förebyggande blodfettssänkande behandling och hjärtkärlsjuklighet vid typ 1 diabetes. 3). Analysera följsamheten till behandling med blodfettssänkande läkemedel och kopplingen mellan hög respektive låg följsamhet och risken att drabbas av hjärtkärlsjukdom. 4). Undersöka orsaker till låg följsamhet ur ett demografiskt och socioekonomiskt perspektiv.

Studierna som presenteras i den här avhandlingen omfattar individer med typ 1 diabetes som är registrerade i det Nationella Diabetesregistret (NDR). Information om kliniska karaktäristika och laboratorieprover inhämtades från NDR och samkördes med andra svenska register med information om läkemedelsanvändning, sjukdomstillstånd, dödsorsaker och socioekonomi. Statistiska metoder användes för att utvärdera sambanden mellan olika blodfettsmarkörer och blodfettssänkande behandling mot risken att drabbas av hjärtkärlsjuklighet.

Hos individer med typ 1 diabetes visade sig kvoten total-kolesterol genom HDL-kolesterol vara bättre på att förutsäga risk för hjärtkärlsjukdom än LDL-kolesterol, framförallt hos de individer som inte redan stod på blodfettssänkande behandling. Hjärtkärlfriska individer med typ 1 diabetes som behandlades med blodfettssänkande behandling hade en 22-44% lägre risk att drabbas av hjärtkärlsjukdom inklusive död av hjärtkärlsjukdom, jämfört med obehandlade individer. Individer med hög följsamhet till blodfettssänkande behandling hade en 22 % lägre risk för icke-dödlig hjärtinfarkt jämfört dem med lägre följsamhet. Individer som avslutade behandlingen inom 18 månader efter behandlingsstart hade 43 % högre risk för icke-dödlig hjärtinfarkt. Lägre följsamhet kunde ses hos de yngre, hos

ensamstående och frånskilda samt om individen hade ett annat födelse-land än Sverige. Kvinnor hade högre följsamhet än män 18 månader efter behandlingsstart, men inte efter 3 år. Efter 3 år hade 42 % av individerna slutat med blodfettssänkande läkemedel. De med högre disponibel inkomst slutade mindre ofta än de med lägre inkomst.

Slutsats: Dessa observationsstudier understryker vikten av att behandla och också regelbundet utvärdera behandlingen av blodfettssubstanser hos individer med typ 1 diabetes och på så sätt minska risken för framtida hjärtkärlsjukdom.

LIST OF PAPERS

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

- I. Hero C, Svensson A-M, Gidlund P, Gudbjörnsdóttir S, Eliasson B, Eeg-Olofsson K. LDL-cholesterol is not a good marker of cardiovascular disease in Type 1 diabetes. *Diabet Med.* 2016, 33(3):316-323
- II. Hero C, Rawshani A, Svensson A-M, Franzén S, Eliasson B, Eeg-Olofsson K, Gudbjörnsdóttir S. Association between use of lipid-lowering therapy and cardiovascular diseases and death in individuals with type 1 diabetes. *Diabetes Care.* 2016;39(6):996-1003
- III. Hero C, Karlsson S, Franzén S, Svensson A-M, Miftaraj M, Gudbjörnsdóttir S, Andersson Sundell K, Eliasson B, Eeg-Olofsson K. Adherence to lipid-lowering therapy and risk for cardiovascular disease and death in type 1 diabetes mellitus. *Accepted for publication BMJ Open Diabetes Research and Care*
- IV. Hero C, Karlsson S, Franzén S, Svensson A-M, Miftaraj M, Gudbjörnsdóttir S, Andersson Sundell K, Eliasson B, Eeg-Olofsson K. Impact of socioeconomic factors and gender on refill adherence and persistence to lipid-lowering therapy in type 1 diabetes. *Manuscript*

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ABBREVIATIONS

4S	Scandinavian Simvastatin Survival Study
ACC	American College of Cardiology
AHA	American Heart Association
apoB	Apolipoprotein B
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HDL-c	High-density lipoprotein-cholesterol
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
HPS	Heart Protection Study
HR	Hazard ratio
ICD	International Classification of Diseases
K-M	Kaplan-Meier
LDL	Low-density lipoprotein
LDL-c	Low-density lipoprotein-cholesterol
LISA	Longitudinal Integration Database for Health Insurance and Labor Market Studies
LLT	Lipid-lowering therapy
LPL	Lipoprotein lipase
MICE	Multiple imputations by chained equations
MPR	Medication possession ratio
NA	Not applicable
NDR	National Diabetes Register

non-HDL-c	Total cholesterol – HDL-cholesterol
NPR	Swedish National Patient Register
OR	Odds ratio
PIN	Personal identity number
PCSK-9	Proprotein convertase subtilisin/kexin type 9
SD	Standard deviation
sdLDL	Small dense LDL
SES	Socioeconomic status
SPDR	Swedish Prescribed Drug Registry
SRB1	Scavenger receptor B1
T1DM	Type 1 diabetes mellitus
TC	Total cholesterol
VLDL	Very-low-density lipoprotein

1 INTRODUCTION

1.1 Type 1 diabetes mellitus

Etiology and pathophysiology in type 1 diabetes

Type 1 diabetes mellitus is commonly referred to as an autoimmune disease, which is preceded by T-cell mediated autoimmune destruction of insulin-producing beta cells in the Langerhans cells of the pancreas.¹ Genetic susceptibility and different environmental and/or nutritional mechanisms are involved in the pathway of disease development. As a marker of the autoimmune process, one or more auto-antibodies can be detected in more than 90% of individuals on presentation.² The currently known auto-antibodies include islet cell, insulin, glutamic acid decarboxylase 65 (GAD65), zinc transporter 8, and tyrosine phosphatase IA-2 and IA-2 β antibodies.³ These auto-antibodies can be detected in susceptible individuals many years before the onset of the disease, but also exist in individuals that will never develop diabetes. There are also individuals with type 1 diabetes without detectable auto-antibodies. Questions on the etiology and pathophysiology behind type 1 diabetes are therefore far from fully answered.^{4,5}

Type 1 diabetes can be diagnosed at any age, but at least 30% of cases are diagnosed at <15 years of age, making it one of the most common chronic diseases among children.⁶ Type 1 diabetes is also defined as a metabolic disease and, besides the insulin deficiency leading to hyperglycemia, the lack of insulin also affects lipid and protein metabolism. Compared to the situation in type 2 diabetes where the insulin deficiency is relative, there is usually an immediate need for exogenous insulin replacement therapy at diagnosis with type 1 diabetes.

History of diabetes

Looking at diabetes from a broad and historical angle, the symptoms of the disease were possibly first described in an ancient Egyptian papyrus, the Ebers papyrus, dated around 1500 BC.⁷ Due to its characteristics in those affected, the condition was given the name diabetes in the 2nd century AD (from the Greek word “diabaino” – to pass through) by Aretaeus of Cappadocia, a

famous physician in ancient Greece. In 1674, Dr Tomas Willis from England added mellitus (honey in Latin) to diabetes due to the sweet taste of the urine from affected individuals; however, the pathophysiology behind diabetes mellitus remained a mystery for more than the subsequent 200 years. Then, in the 19th century, various pieces of evidence started to come together. Firstly, the French physiologist Claude Bernard discovered the glycogenic actions of the liver in the mid-19th century. Secondly, Paul Langerhan, a German medical student at that time, identified islands of cells in the pancreas that differed from the surrounding tissue, which were later named the islets of Langerhans. The discovery was presented in an 1869 thesis entitled “Contributions to the Microscopic Anatomy of the Pancreas”. However, the function of these islets was still unknown. Thirdly, 20 years later, two physicians by the names of Joseph von Mering and Oskar Minkowski discovered, more or less by serendipity, that surgical removal of the pancreas resulted in the symptoms described for the disease known as diabetes mellitus.⁸ These three discoveries were subsequently interlaced with the work of other scientists and eventually led to the discovery of insulin.

Brief story of insulin

On December 2, 1921, a 14-year old boy, Leonard Thompson, arrived at the emergency department at Toronto General Hospital.⁹ He had been diagnosed with diabetes at 12 years of age. On presentation, he was gravely malnourished and in a constant state of acidosis. At that time, the only known way to treat diabetes was through a diet low in carbohydrates, and high in fat and protein, a diet that could postpone an inevitable death for a year or two. The boy was put on a strict diet in hospital, but with no success. The doctors gave him only weeks to live.

At the same time in Toronto, two researchers, Dr Frederick Banting and medical student Charles Best, were searching for a solution to treat diabetes. In the summer of 1921, they had successfully managed to isolate insulin from the pancreas of dogs and then gave this insulin to cure other dogs who had diabetic symptoms induced by pancreas removal. However, the results were highly variable due to the poor purification of the substance and a biochemist, Bert Collip, was engaged to help with purification. On January 11, 1922, Leonard Thompson was given the first injection. On the next day, his blood glucose level had fallen, but only marginally. Collip kept on working on

purification and a second injection given 12 days later was a success! Thompson's blood glucose dropped to 6.7 mmol/L. Thompson now received daily injections and started to recover. A lifesaving discovery had seen its light. A month later, six other persons with diabetes had been treated with the extract, initially called isletin. In April 1922, the substance was given its name: insulin.

In 1923, Dr Banting and Dr MacLeod, who was head of the laboratory, were rewarded with the Noble prize for the discovery of insulin. Dr Banting decided to share his part of the prize money with Dr Best, while Dr MacLeod shared his with Dr Collip. However, the comprehensive history of the discovery and development of insulin is a far more intriguing story.¹⁰

Epidemiology of type 1 diabetes

When insulin was introduced in 1922, type 1 diabetes was a rare disease and the incidence remained low between 1925 and 1955. Since the middle of the 1950s, the incidence and prevalence have risen steadily worldwide, but the incidence varies markedly between different parts of the world and even within different regions within countries.^{11,12} In Europe, there has been an average 3.5% incremental year-on-year rise since the 1950s.^{13, 14}

The latest estimates from the International Federation of Diabetes in 2017 on type 1 diabetes incidence in children and adolescents <20 years of age show that Scandinavian countries have some of the highest incidence rates of type 1 diabetes in the world, with Finland being at the top end with almost 60 cases per 100,000 persons annually^{15,16}. Further, Kuwait and Saudi Arabia stand out as countries with a rapidly increasing incidence of type 1 diabetes at around 44.5 and 33.5 per 100,000 annually, respectively. Kuwait has now taken the second place in the list of countries with the highest incidence of type 1 diabetes among individuals <20 years of age, while Sweden qualifies for third place with an incidence of 39.5 per 100,000 annually. The incidence has been historically low and remains so in, for example, many Asian countries. For example, in Thailand, the incidence of type 1 diabetes was estimated to be around 0.7 per 100,000 annually in 2017.¹⁵ The incidence in China has also been low historically at 2.0 per 100,000 annually, but there have been reports of a rapidly increasing incidence in recent decades in several provinces with average annual increases of 12-14%.^{17,18} The fast-changing incidence trends

since the mid-20th century cannot be explained merely by genetic changes; consequently, a multitude of environmental and nutritional factors are under scrutiny in order to find an answer to this conundrum.¹⁹

1.2 Cardiovascular disease in type 1 diabetes

Epidemiological aspects

After the discovery of insulin in 1922 and with that the prevention of fatalities due to diabetes itself, premature atherosclerosis and cardiovascular complications have emerged as major problems in the longer term.²⁰ Finding early data on the epidemiology of cardiovascular disease (CVD) in type 1 diabetes is difficult and hampered by the previous somewhat arbitrary definitions of diabetes into insulin- and non-insulin-dependent diabetes until 1998 when the classification changed into type 1 and type 2 diabetes, respectively.²¹ However, in a study published in 1987 by Krolewski and colleagues,²² 292 patients from three different cohorts (born 1939, 1949, and 1959) diagnosed with insulin-dependent diabetes with onset before 21 years of age were followed for 20-40 years: by 55 years of age, 35% had died from coronary artery disease. A more recent study by Soedamah-Muthu et al.²³ investigated first-time CVD events in a type 1 diabetes population of almost 7500 individuals (mean age 33 years) between 1992 and 1999, which concluded that men with type 1 diabetes ages 45-55 years had an absolute CVD risk similar to that of men in the general population who were 10-15 years older. The difference was even greater in women, with an overall relative risk for CVD being 7.7-times higher for women and 3.6-times higher for men. The absolute risk of CVD is now similar in men and women with type 1 diabetes, as opposed in the general population, where women have a lower incidence than men.²⁴

Since these data were published, considerable improvements have been accomplished with respect to the incidence of and survival rates from CVD; however, CVD, and particularly coronary heart disease (CHD), is still the most common cause of death among adults with type 1 diabetes.^{25,26} The excess overall risk for a coronary event has recently been estimated to be 4-times higher in Swedish subjects with type 1 diabetes compared to matched controls in the general population, which is consistent with data from other developed countries.^{27,28} Hence, the risk of CVD highly affects life expectancy in type 1 diabetes. In a recent Swedish study,²⁹ it was estimated that a diagnosis of type

1 diabetes could result in a loss of up to 17.7 years of life in women and 14.2 years in men, depending on time of disease onset, compared to individuals without diabetes. The globally increasing incidence of type 1 diabetes in combination with the increased risk of premature atherosclerosis and CVD in individuals with type 1 diabetes is a cause of concern.

Pathophysiological aspects

The reasons behind the premature development of atherosclerosis and enhanced risk of CVD in type 1 diabetes is multifactorial and far from totally explained.³⁰⁻³¹ Traditional risk factors for CVD such as hypertension, dyslipidemia, smoking, and obesity also play important roles in the development of atherosclerosis and CVD in diabetes, but are more prominent in type 2 than in type 1 diabetes. The diabetes-specific risk of hyperglycemia has, on the other hand, been observed to have a more fundamental effect on the CVD risk in type 1 diabetes than in type 2 diabetes.³²⁻³³ In the landmark Diabetes Control and Complication Trial,³⁴ intensive treatment of hyperglycemia eventually led to a subsequent 42% decrease in CVD.

The presence of microalbuminuria in diabetes patients has, for a long time, been recognized as an independent risk factor for atherosclerotic CVD development and mortality.^{35,36} Diabetic kidney disease is, in itself, linked to several cardiovascular risk factors, i.e. hypertension, dyslipidemia, hypercoagulability, and chronic inflammation.^{37,38} Low-density lipoprotein (LDL)-cholesterol has also been found to be an independent risk factor associated with progression of nephropathy.^{35,39} In a recent observational study,³³ stage 5 kidney disease was connected to a 39-fold risk elevation for cardiovascular mortality compared to matched controls. Earlier research suggested that the excess risk for CVD in diabetes alone was linked to the development of nephropathy.³⁵ This has been refuted by subsequent studies where the increased risk of CVD remains, even in patients with normoalbuminuria.^{28,33}

Achieving better glycemic control in combination with treatment of hypertension and/or albuminuria has led to a successively declining incidence of diabetic nephropathy.⁴⁰ However, despite improved glucose control and no renal complications, there is still an excess risk of CVD and death, and a shorter life expectancy, in individuals with type 1 diabetes compared to the background

population, especially in women where the usual cardiovascular protection of the female gender seems erased for unclear reasons. So, more action needs to be undertaken to prevent type 1 diabetes individuals from developing CVD.^{24,29,41}

Dyslipidemia plays a crucial role in the process of atherosclerosis and CVD development.⁴² Dyslipidemia is an important modifiable risk factor and studies have shown a substantial reduction of CVD risk by treating dyslipidemia and lowering LDL-cholesterol.^{43,44} Even in young patients with diabetes, arterial stiffness is accelerated by poor glycemic control and higher levels of traditional cardiovascular risk factors including lipid abnormalities.⁴⁵

1.3 Hypercholesterolemia and atherosclerosis

Cholesterol

François Poulletier, a French physician-chemist, is said to be the first person to obtain pure cholesterol from gallstones in 1784. Thirty years later, the substance was named as cholesterine by a French chemist, Michael E Chevreul (solid bile in Greek, “chole” for bile, “steros” for solid).⁴⁶ The formula of the molecule was established in 1888 by the Austrian botanist Friedrich Reintzner,⁴⁶ but the complete structure of cholesterol was first completely elucidated in 1932 following pioneering research by Adolf Windaus and Dr Henry Wieland, both of whom were earlier Noble prize winners in 1926 and 1928, respectively.⁴⁷

Cholesterol is a so-called lipid, a fatty substance. It is an important structural building block in the outer cell membrane of every cell and is also present in organelles within the cell. Chemically, cholesterol is both a steroid and an alcohol. It is a basic molecule for the building of steroid hormones and vitamin D, and is an important component of bile⁴⁸.

Lipid metabolism in brief

Cholesterol in the body is derived from two pathways. The first is the exogenous pathway, i.e. from the food we digest. The second is by endogenous production in the liver, where it is packed into particles known as lipoproteins and delivered to plasma as very-low-density lipoprotein (VLDL). VLDL

particles contain triglycerides, cholesterol, and cholesteryl esters surrounded by proteins and phospholipids, which render the particles transportable in plasma. The proteins surrounding the lipoproteins are called apolipoproteins and extend through the surface of the lipoprotein, giving it stability and facilitating transport. Apolipoprotein B (apoB), which is produced in the liver, is the primary apolipoprotein attached to atherogenic lipoproteins, i.e. VLDL and LDL.⁴⁸

Lipid metabolism is somewhat complex. To simplify matters, the VLDL particle is released into the blood stream and delivers triglycerides to various cells in the tissues with the help of an enzyme called lipoprotein lipase (LPL).⁴⁸ LPL is bound to cells in the tissues and breaks down VLDL in plasma. The end product is the LDL particle, which is the main carrier of cholesterol in the body. Hepatic and non-hepatic tissues internalize LDL particles through the LDL receptor or the LDL receptor-like protein.⁴⁸ In the liver, LDL-cholesterol is converted into bile acids and secreted into the intestine via the biliary system. In non-hepatic tissues, LDL-cholesterol is used for hormone production or cell membrane synthesis, or stored.⁴⁸ In arterial walls that expose a dysfunctional endothelium, excess LDL particles can enter into the intima layer of the artery and there be internalized by macrophages, leading to the formation of foam cells, and ultimately plaque formation and atherosclerosis.^{48,165} High-density lipoprotein (HDL) particles, on the other hand, transport cholesterol from the peripheral cells back to the liver, facilitating the efflux of cholesterol from macrophages, thus enabling reverse cholesterol transport.^{48,49} Apolipoprotein AI (apoAI) that is attached to the HDL particle is produced in the liver and the intestine. It is secreted as a lipid-poor particle into the plasma, developing into nascent HDL and later on maturing into HDL₃ and HDL₂ by interacting with ATP-binding cassette transporters (ABCA1 and ABCG1 receptors) and the scavenger receptor B1 (SRB1) on the cell surface. These receptors are responsible for cholesterol efflux from macrophages to the HDL particle.^{49,50} The mature HDL particle can deliver cholesterol back to the liver directly or indirectly: directly, through the SRB1 receptor on the liver cells⁵⁰ and, indirectly, by exchanging its cholesterol content for triglycerides with the VLDL and LDL particles through the cholesteryl ester transporter protein enzyme.⁵¹

History of hypercholesterolemia and atherosclerosis

There is strong scientific support that hypercholesterolemia is harmful to the vessels in the body. At the start of the 20th century, atherosclerosis was well described in the scientific literature, but was considered an inevitable process connected to aging. One of the leading hypotheses at that time was that atherosclerosis might be the result of excessive intake of animal protein. Dr Anitschkow, a Russian physician at the Institut der Kaiserlichen Militärmedizinischen Akademie in St Petersburg, searched for proof to support this hypothesis. Together with colleagues, he undertook several experiments, where they fed rabbits a diet of milk, egg, and meat, after which the rabbits started to display vascular lesions in the aorta which was described as a rich infiltration of fatty substances in the intima. In subsequent experiments, several scientists tried to determine whether a specific protein was involved in this process. By successively excluding foodstuffs, they discovered that the villain was actually the egg, and not even egg white as egg yolk alone was sufficient.

Eventually, Dr Anitschkow with a colleague, Dr Chalатов, showed that it was cholesterol, extracted from egg yolk, which in itself could duplicate the former results on the aorta without the addition of any protein.^{52,53} This confirmed what Windaus, the foremost steroid chemist of the 1920s and 1930s, had already found in 1910, when he reported that human aortic plaques contained more than 20-fold higher concentrations of cholesterol. It has been proposed that the cause of the findings of Anitschkow and colleagues was due to the very high blood cholesterol that was induced in the rabbits; however, Dr Anitschkow showed that even lower amounts could cause fatty streaks in the arteries, although this required a longer duration of exposure.

Of course, an animal study in rabbits cannot prove causality in human atherosclerosis; however, by the experimental research described above and following groundbreaking epidemiological, clinical and genetic studies, the connection between high cholesterol, development of atherosclerosis, and increased CVD risk as a consequence is well established.^{54,55,69,177} One of the landmark studies is the Seven Countries Study by Ancel Keys, physiologist at the University of Minnesota, who showed that the incidence of heart attacks among more than 12,000 middle-aged men from 16 different cohorts in seven countries, was strongly related to the blood level of cholesterol.⁵⁴ The Framingham Heart Study, launched in 1948 and still ongoing, was an equally

important study of that time, which also found a linear association between CVD and blood cholesterol levels, as well as the enhancing effects from the addition of diabetes, hypertension, and smoking to the risk scenario.^{55,56} Excess dietary cholesterol as a causal pathway for atherosclerosis has been challenged and rechallenged many times since then.⁵⁷⁻⁵⁹ Quite recently a meta-analysis was published, again putting the egg, and dietary cholesterol, into the spotlight.⁶⁰

Lipoproteins and the LDL receptor

The experiments of Dr Anitschkow and colleagues were not paid any attention for many years, but the role of cholesterol in human atherosclerosis received renewed interest in the 1940s when the genetic connection between high cholesterol levels and heart attacks was found in several Norwegian families by the Norwegian physician, Carl Müller.⁶¹ This was the first description of familial hypercholesterolemia, an inherited disorder of lipid metabolism characterized by premature CVD. John Gofman, an American molecular biologist, brought the next piece to the lipid puzzle. Using an ultracentrifuge, he separated and discovered the various lipoproteins and gave them names, such as LDL and HDL. Even in the 1950s, he and his team indicated that high LDL-cholesterol was strongly connected to the risk of myocardial infarction.⁶²

Finally, in 1974, the discovery of the LDL receptor by the Noble Prize laureates, Dr Mike Brown and Dr John Goldstein, tied the knots together between cholesterol and lipoprotein metabolism.⁶³ This discovery contributed to the explanation of the regulation of lipoproteins in serum and helped to establish a link between high LDL-cholesterol levels and cardiovascular heart disease.⁶⁴

History of HMG-CoA reductase inhibitors (statins)

After the evidence became obvious that high blood cholesterol levels and CVD were linked, scientists started searching for efficient cholesterol-lowering drugs. Treatment for hypercholesterolemia had consisted mainly of dietary recommendations and often poorly tolerated medications with modest effects on LDL-cholesterol, until Akira Endo, a biochemist from Japan, discovered in the 1970s that metabolites produced by a mold could affect the synthesis of cholesterol in parasites. From this knowledge, the first 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor was

developed and named compactin.⁴⁶ This compound was later developed into lovastatin, which was marketed in 1987 as the first of the statin drug class.

Initially, many physiologists and even cardiologists were not convinced of the utility of statin treatment. The definite proof of its protective benefits came in 1994 when the results of the Scandinavian Simvastatin Survival Study (4S) on secondary prevention with statins in patients with CHD were announced and showed a 42% reduction in death by myocardial infarction with statin treatment compared to placebo.⁶⁵ A 1997 *post-hoc* analysis investigating the 202 patients with diabetes in the 4S trial, 12% were treated with insulin, confirmed that patients with diabetes also benefitted from statin treatment, maybe even more so due to a higher absolute risk.⁶⁶

Mechanism of HMG-CoA reductase inhibitors (statins)

HMG-CoA reductase inhibitors, i.e. statins, block the pathway for synthesizing cholesterol in hepatocytes by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway.⁴⁶ This leads to reduced production of mevalonate, which is one of the molecules involved in the cascade that produces cholesterol. When the hepatocytes can no longer produce cholesterol, the reduced levels of liver cholesterol are compensated by the synthesis of more LDL receptors that draw cholesterol out of circulation and reduce the amount of LDL-cholesterol in plasma^{46,64} Besides the reduction of LDL-cholesterol in plasma, statins have also shown other beneficial pleiotropic effects on atherosclerosis such as plaque stabilization, and reduction of platelet activation and plaque inflammation.⁶⁷

1.4 Dyslipidemia in type 1 diabetes

Dyslipidemia has historically been defined by US population studies where a serum total cholesterol of about 3.8 mmol/L was deemed as optimal from a CHD perspective, corresponding to an LDL-cholesterol of around 2.6 mmol/L.^{68,69} Furthermore, there is epidemiological evidence which indicates that an LDL-cholesterol level >2.6 mmol/L is associated with an increased CVD risk in patients with type 1 diabetes.⁷⁰ However, lipid disorders in individuals with type 1 diabetes can be characterized by both quantitative and/or qualitative abnormalities depending on circumstances such as glycemic

control, the presence of obesity and/or insulin resistance, and also by the fact that insulin is administered subcutaneously as opposed to released directly from the pancreas.^{71,72}

Insulin is an important regulator of lipid metabolism. Insulin has antilipolytic effects and, by inhibition of hormone-sensitive lipase, insulin promotes storage of triglycerides in adipose tissue and reduces the release of free fatty acids to the circulation. Insulin decreases VLDL production from the liver both by reducing the influx of free fatty acids and also directly in the hepatocyte. Insulin activates LPL and also directly stimulates LPL synthesis. Activated LPL reduces triglyceride levels in plasma through catabolism of triglyceride-rich lipoproteins. Insulin increases the expression of LDL receptors and removes LDL-cholesterol from circulation and also affects HDL-cholesterol metabolism by activating lecithin-cholesterol acyl transferase and hepatic lipase, enabling maturation and liver uptake of the HDL particle.⁷²

In general, lipid levels in individuals with type 1 diabetes are similar to those of patients without diabetes, provided glucose control is good.⁷² Hence, the quantitative lipid pattern in type 1 diabetes often differs from lipid patterns in those with type 2 diabetes, who frequently present with hypertriglyceridemia and low HDL-cholesterol.^{73,74} With bad glycemic control, overweight, and insulin resistance, a more atherogenic lipid distribution is often also seen in subjects with type 1 diabetes, with higher triglycerides, higher LDL-cholesterol, and lower HDL-cholesterol in plasma. This is partly due to the insulin deficiency, leading to reduced LPL activity and to defective removal of triglyceride-rich lipoproteins from the circulation, which in turn renders HDL-cholesterol to be loaded with triglycerides and removed from the circulation by the scavenger receptor.^{75,76} At higher glycated hemoglobin A1c (HbA1c) levels, LDL particles are shifted from buoyant to small dense LDL (sdLDL) particles. sdLDL particles have a reduced affinity for the LDL receptor and are more likely to be taken up by macrophages in the endothelium, forming foam cells.^{77,78}

Even when glycemic control is optimized, qualitative lipid disorders are still observed in patients with type 1 diabetes. These are thought to have atherogenic properties. The underlying pathophysiology is not fully understood but peripheral hyperinsulinemia due to subcutaneously administered insulin and,

from this, LPL activation could be part of the explanation.⁷² Also, the hyperglycemic environment in type I diabetes promotes glycation of apoB in the LDL particle, which reduces binding capacity to the LDL receptor and, instead, glycated LDL particles are taken up by macrophages in the arterial walls, eventually forming foam cells.⁷⁹

Patients with type I diabetes often have an increased amount of sdLDL.⁸⁰ This is due to an increased exchange of cholesteryl esters for triglycerides through an activated cholesteryl ester transporter protein enzyme rendering triglyceride-rich LDL particles.⁸¹ Triglyceride-rich LDL is then transformed to sdLDL by hepatic lipase in the liver and returned to circulation. As mentioned previously, sdLDL is more atherogenic than its buoyant relative. The sdLDL particle has a lower affinity for the LDL receptor but higher affinity for intimal proteoglycans, which favor the penetration of the LDL particle into the endothelium in the arterial wall.⁸² The sdLDL particle also has an increased susceptibility to oxidation and oxidized LDL stimulates the macrophage to form cytokines, which amplify the inflammatory atherosclerotic process.⁸³

An association between oxidized LDL and increased intima media thickness has been shown in type I diabetes.⁸⁴ LDL modified by advanced glycation end-products is also associated with increased intima media thickness.⁸⁴

HDL-cholesterol is claimed to be atheroprotective with anti-inflammatory and anti-oxidative properties.⁸⁵ HDL-cholesterol levels in type I diabetes have been reported to be high, although there are other reports about low levels.⁸⁶⁻⁸⁸ Several studies indicate that HDL in individuals with type I diabetes has lost some of its protective mechanisms due to glycation and oxidative modification of the HDL protein and that its ability to suppress inflammatory signals is reduced.^{89,90} For example, paraoxonase, an anti-oxidative enzyme associated with HDL-cholesterol, is reduced in patients with type I diabetes leading to less protection against oxidative damage.⁹¹ Glycation of apoA1 in the HDL-cholesterol particle also impairs the HDL-mediated reverse cholesterol pathway since glycated HDL is less effective in promoting cholesterol efflux from the endothelial cells.⁹²

Treatment of dyslipidemia in general

Statins are the mainstay of hyperlipidemia treatment today. There is a significant body of research showing a reduced risk of CVD, particularly CHD, as well as stroke and cardiovascular mortality in not only secondary prevention for those with known CVD but also in primary prevention for those at high risk.^{93,94} The LDL-cholesterol reduction obtained by statin treatment depends on dose and choice of compound. With a high-intensity statin, LDL-cholesterol can be reduced by >50% from baseline. The CVD risk reduction achieved depends on baseline risk as well as the extent of LDL reduction.⁹⁵

Statins are generally well tolerated. In randomized controlled trials, side effects are unusual and usually dose-related, the most serious being rhabdomyolysis, which occurs very rarely.⁹⁶ In observational studies,^{97,98} 10-15% of treated persons complain, mostly about unspecific muscular side effects. However, in studies where side effects experienced with statins have been tested against placebo, there was no difference between the active substance and placebo.⁹⁹ Many patients who discontinue statin therapy due to perceived side effects can also tolerate a statin when later rechallenged with the same or another statin.⁹⁸

Ezetimibe inhibits the uptake of cholesterol and plant sterols in the small intestine. As monotherapy in patients, its effect is modest with a lowering of LDL-cholesterol of around 15%. Ezetimibe is usually used as a complement to statin therapy when goals of lipid control are not achieved or as monotherapy when statins are not tolerated. Studies have shown an additive effect on the reduction of CVD outcomes from ezetimibe in combination with a statin in patients with prior acute coronary syndrome, but there are no outcome data with ezetimibe monotherapy.^{100,101}

PCSK9 inhibitors are human monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK-9). By binding to PCSK-9, the number of LDL receptors increase and LDL-cholesterol is cleared from plasma. Added to statin therapy at maximum tolerated doses, they will lower LDL-cholesterol by an additional 40-60%. Studies have shown an additional effect when added to statins with a relative risk reduction of around 15-20% on cardiovascular outcomes but not on overall survival.^{102,103} These agents are injected subcutaneously every 2 to 4 weeks. Side effects have mostly been injection site reactions. PCSK-9 inhibitors are presently very expensive compared to other

lipid-lowering agents and are, to date, reserved for those with a very high residual risk despite use of a statin at a maximum tolerated dose or due to statin intolerance.

Fibric acid derivatives (fibrates) lower triglycerides and raise HDL-cholesterol by activating the nuclear receptor peroxisome proliferator-activated receptor- α .¹⁰⁴ In a large study,¹⁰⁵ one of the fibrates, gemfibrozil, showed a reduced risk of myocardial infarction, but it did not affect overall survival. The indication for fibrates is mainly severe hypertriglyceridemia or pronounced combined hyperlipidemia, possibly in combination with a statin. However, the combination of gemfibrozil with a statin is not recommended due to the enhanced risk of serious muscle side effects.¹⁰⁶

Bile acid sequestrants bind bile acids in the intestine and inhibit reabsorption, which leads to increased bile production in the liver with an increased uptake of LDL-cholesterol and clearance of LDL-cholesterol from plasma.¹⁰⁷ A modest effect has been shown on coronary artery disease for cholestyramine, but no effect on mortality.¹⁰⁷

Statin treatment of dyslipidemia in type 1 diabetes

Since the 4S trial on simvastatin was published in 1994, there has been an overwhelming number of randomized controlled trials as well as observational studies of statin treatment both in primary and secondary prevention of CVD, showing that treatment of dyslipidemia reduces the risk of CVD morbidity and mortality substantially in the general population at risk as well as in patients with diabetes.¹⁰⁸⁻¹¹¹ Some of these studies exclusively included individuals with diabetes, but most of them focused on populations with type 2 diabetes. There is a lack of randomized controlled trials involving patients with type 1 diabetes and guidelines for treating dyslipidemia in patients with type 1 diabetes have largely been extrapolated from studies in other patient groups.^{66,110,112,117}

In current guidelines for treating dyslipidemia,¹¹³⁻¹¹⁵ two major statin studies are often referred to as the foundation of the treatment recommendations in type 1 diabetes. The first was the Heart Protection Study (HPS) which included 20,000 patients, almost 6000 of whom had diabetes and 615 were diagnosed with type 1 diabetes. In the HPS, simvastatin treatment was associated with a 24% cardiovascular event reduction in individuals with type 1 diabetes, which was,

however, not statistically significant.¹¹⁶ The second study was a meta-analysis from the Cholesterol Treatment Trialists' Collaborators investigating 14 randomized trials, looking specifically at 18,686 patients with diabetes, of whom only 1466 were diagnosed with type 1 diabetes, and with the largest contribution of patients coming from the HPS. There was a significant 21% proportional reduction in major vascular events per 1 mmol/L reduction in LDL-cholesterol in patients with diabetes, but the evidence of benefit for the patients with type 1 diabetes was limited, probably due to low power (hazard ratio (HR) 0.79, 99% confidence interval [CI] 0.62-1.01).⁴³

Due to the low numbers of type 1 diabetes patients involved in the statin trials, questions have remained on when, how, and to what extent individuals with type 1 diabetes with dyslipidemia should be treated with lipid-lowering medication, preferably statins.¹¹⁷

1.5 Adherence to medication

Adherence is commonly defined as to what extent a patient follows agreed recommendations from a health care provider, for example in taking medication, following a diet, or executing lifestyle changes. Adherence has in this respect replaced the earlier often used term of compliance, where compliance more generally refers to patients who are acquiescent or obedient when they follow health care providers' recommendations. According to WHO,¹¹⁸ the concept of adherence encompasses five different dimensions, (social and economic factors, organization of the health care system, the condition treated, therapy-related factors, and patient-related factors), which influence adherence in different ways.

Assessing medication adherence

The most reliable way to measure medication adherence is to actually watch patients ingest their medications, but this is rarely either feasible or ethical. Several proxies have therefore been developed. Usually, medication adherence is assessed by division into two different measurement methods, direct or indirect.¹¹⁹

An example of direct measurement, except for watching the patient actually ingesting the medication, is to measure the substance in a blood or urine sample

from the patient. This is not only time consuming, but also has flaws, for example if ingestion of the medication is intensified just days before measurement. Indirect measures of adherence include electronic monitoring with the help of medication event monitoring systems or patient-completed questionnaires or diaries of their medication intake. Medication event monitoring systems can be manipulated in several ways as can questionnaires. With questionnaires, there is also a risk of recall bias. Another indirect way of measuring adherence is to use registry data, as we have in our studies on adherence. By retrieving data about pharmacy claims, we can measure adherence in a retrospective way and estimate prescription refill adherence by calculating the medication possession ratio (MPR). This method has been evaluated as a reliable way for measuring adherence to medication in chronic conditions.¹²⁰

Medication adherence can be divided into four different entities: initiation, implementation, discontinuation, and persistence with medication.¹²¹ In our studies on refill adherence, initiation equals the first ingested dose of a filled prescription and implementation is the proportion of time that the patient has medication available, i.e. MPR, during the study period. We also assessed discontinuation, i.e. prematurely stopping the medication. Persistence is defined as the period between initiation and discontinuation of treatment.

Adherence and persistence to lipid-lowering therapy in diabetes

Adherence to medication has been recognized as an important area for improvement.¹¹⁸ It has been estimated that poor adherence to cardiovascular medication alone could be responsible for approximately 9% of CVD events in Europe.¹²² In the overall population, research indicates that adherence can be as low as 50%, sometimes even lower, when it comes to treating chronic conditions. Adherence to lipid-lowering therapy (LLT) is not an exception, rather the contrary.^{123,124}

Several observational studies on adherence to LLT in individuals with diabetes, mainly type 2 diabetes, show that the adherence and persistence to treatment is of major concern.¹²³ The consequence of low adherence to LLT is a reduced protection against CVD and, as statin therapy is efficient in lowering LDL-cholesterol and in reducing CVD morbidity and mortality, adherence to statin therapy remains a challenge in clinical practice that needs to be

addressed.^{125,126} However, the level of adherence in patients with type 1 diabetes and the effects of non-adherence on the risk of cardiovascular outcomes are less researched.

1.6 Socioeconomics and type 1 diabetes

Socioeconomic status (SES) is a composite measure of an individual's economic and sociological position in society. There are a variety of ways to measure SES but, usually, variables of income, education, and occupation are included. SES measured by income, education, and social position in relation to others is a powerful predictor of health.^{127,128} The Whitehall study published in 1984 by Marmot et al.¹²⁷ was one of the first studies to establish the strong inverse relationship, beyond what could be explained by smoking and other cardiovascular risks, between employment grade and the risk of dying from CHD. That study followed 17,530 men employed in the British civil service and showed 3-times higher mortality rates for men in the lowest civil service classification than for those in the highest grade. Traditional coronary risk factors were accountable for only one-third of the differences between the grades.

There is a significant impact of SES on a multitude of diseases, including CVD, even in countries with fairly equal access to health care for their residents.¹²⁸ In individuals with type 1 diabetes, there are studies showing associations between low SES and increased risk of long-term micro-and macrovascular complications as well as mortality.¹²⁹⁻¹³¹

Socioeconomic and demographic factors as predictor of adherence

Individuals with low SES have a higher prevalence of cardiovascular risk factors and higher mortality than their more fortunate peers.¹²⁸ Poor adherence to cardiovascular medication, as a result of low SES, could be part of the explanation for the residual cardiovascular risk despite preventive interventions in individuals with type 1 diabetes.¹³²⁻¹³⁵

Several patient characteristics that have been valued as important concerning long-term persistence to medication and characteristics associated with poor adherence could also be related to features in the socioeconomic spectra with

the presence of psychological problems, cognitive impairment, and lack of insight and knowledge about the disease as well as lack of belief in the treatment.¹¹⁹

Predictors of low adherence and persistence have been investigated in several studies before, but with conflicting results on, for example, the influence of education, gender, and age.¹³⁵⁻¹³⁹ Comparison of study results on adherence and persistence to medication relative to socioeconomic and demographic influences have to be performed with careful consideration with respect to the context in which the study is conducted, since there are important differences depending on not only where and when, but also how, the research is conducted. Such circumstances could, for instance, be the charge for a visit to the doctor and the cost for the medication prescribed. In Sweden, social benefits provide health care and medications at a heavily subsidized cost with fixed co-pays up to a ceiling, whereas in other countries, for example in the USA, residents are dependent on health insurance for reimbursement.^{140,142} In most European countries though, more than 50% of outpatient prescriptions are reimbursed from public funds and, despite social benefits covering most of the cost, income has still qualified as an important predictor for medication adherence.^{132,141}

2 AIM

The overall aim of this thesis is to expand the knowledge on several different aspects of dyslipidemia and its treatment in type 1 diabetes, i.e. the best way to use lipid variables in risk assessment, to find support for the importance of LLT in primary prevention, and, finally, to investigate and understand adherence patterns and why adherence matters.

Specific aims of the included studies

1. To assess clinically available lipid parameters in relation to risk of CVD in type 1 diabetes.
2. To investigate the association between LLT and CVD in individuals with type 1 diabetes and no history of CVD, i.e. primary prevention.
3. To assess the adherence to LLT in type 1 diabetes and the effects of non-adherence on the risk of developing CVD.
4. To investigate the factors associated with non-adherence to LLT from a demographic and socioeconomic perspective in individuals with type 1 diabetes.

3 PATIENTS AND METHODS

Patients

This thesis is based on four observational studies. All the included participants were diagnosed with type 1 diabetes and enrolled from the Swedish National Diabetes Register. In each study, the inclusion and exclusion criteria were defined depending on the research question and the cohorts differ accordingly. An overview is presented in Table 1.

Diabetes diagnosis and definition

Sweden follows the current WHO diagnostic criteria for diabetes, i.e. fasting plasma glucose ≥ 7.0 mmol/L or 2-hr plasma glucose ≥ 11.1 mmol/L. In 2014 HbA1c was also accepted as a diagnostic criterion in type 2 diabetes. In **study I**, we used the clinician's classification of diabetes type (henceforth referred to as *clinical definition*). In **studies II-IV**, we used an *epidemiological definition* of type 1 diabetes as a proxy: treatment with insulin alone and diagnosis at ≤ 30 years of age.

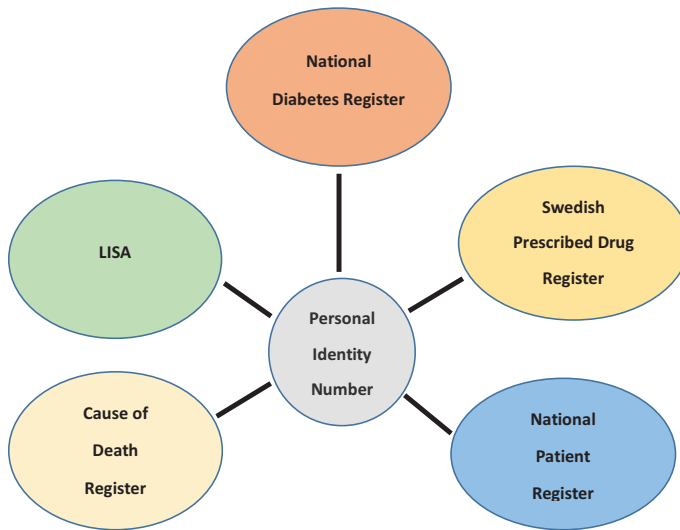
Data sources

The four studies covered in this thesis obtained information by linking data from several nationwide registries in Sweden (Fig. 1). Linkage of the registries is made possible due to the unique 12-digit personal identity number (PIN) that, since 1947, is assigned to each Swedish citizen at the time of birth or immigration.¹⁴³ Following approval by the Swedish Ethical Review Authority, a file with data from the Swedish National Diabetes Register (NDR) was sent to the Swedish National Board of Health and Welfare for linkage with the Swedish National Patient Register (NPR), the Cause of Death Register, and the Swedish Prescribed Drug Register (SPDR) (**studies II and IV**), and also with the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) database administered by Statistics Sweden (**studies II-IV**). The linked data were then returned in an anonymized manner by replacing PINs with serial numbers.

Table 1. Study design and overview of the characteristics of studies I-IV.

	Study I	Study II	Study III	Study IV
Study design	Cohort study	Cohort study	Cohort study	Cohort study Cross-sectional design
Inclusion, end-of-study	2003-2006, Dec 2011	2006-2008, Dec 2012	2006-2010, Dec 2013 (2015)	2006-2010, 36 months after inclusion
Mean follow-up (years)	6.8	6.0	3.6 (CVD), 3.9 (total mortality)	NA (assessment time 18 and 36 months)
Inclusion criteria	Type 1 diabetes 18-79 years with and without LLT	Type 1 diabetes ≥ 18 years of age without history of CVD	Type 1 diabetes ≥ 18 years of age, novel users of LLT	Type 1 diabetes ≥ 18 years of age, novel users of LLT
Number of patients	30,778	24,230	6,192	6,192 at 12 months and 6,122 at 36 months
Exposure	LDL-c, TC/HDL-c, non-HDL-c	LLT	Refill adherence and non-persistence of LLT	Socioeconomic characteristics, age and gender
Outcomes	Fatal/non-fatal CVD	Fatal/non-fatal CVD, total mortality	Fatal/non-fatal CVD, total mortality	Refill adherence, non-persistence to LLT at 18 and 36 months
Main statistical methods	Cox regression analyses Complete case analyses	Propensity scores with logistic regression, MICE, Cox regression analyses, K-M analysis	Cox regression analyses, MICE, smoothing splines	Multivariate logistic regression, Complete case analyses
<i>Abbreviations:</i> CVD, cardiovascular disease; HDL-c, high-density lipoprotein-cholesterol; K-M, Kaplan-Meier; LDL-c, low-density lipoprotein-cholesterol; LLT, lipid-lowering therapy; MICE, multiple imputations by chained equations; NA, not applicable; non-HDL-cholesterol (TC minus HDL-c); TC, total cholesterol.				

Fig. 1. Schematic of the health registries included in the studies. Abbreviations: LISA, Longitudinal Integration Database for Health Insurance and Labor Market Studies



The Swedish National Diabetes Register

The Swedish NDR has been an important tool for quality control and improvement in diabetes care in Sweden for more than two decades.¹⁴⁴ It was started in 1996 and, in 2018, contained registrations for 438,519 individuals ≥ 18 years of age with diabetes, of whom 46,230 had a clinical diagnosis of type 1 diabetes. Given that the prevalence of diabetes in Sweden is estimated at 5.5%, 94% of individuals with diabetes in Sweden are covered in the NDR. It is estimated that 100% of specialized care clinics and 95% of primary care clinics report to the NDR. Hence, the ascertainment of individuals with type 1 diabetes in Sweden exceeds 97%.

The NDR includes information on clinical characteristics, laboratory parameters, risk factors, and medications for the patients. All patients included in the registry have been informed about the NDR, about their enrollment, and provided verbal consent. Patients can deny enrollment in the registry or withdraw their consent at any time after enrollment. The validity of data in the

registry has been assessed, which demonstrated that 94% of data entries in the NDR were correct (NDR Annual Report 2005).¹⁴⁵

Registries kept by the Swedish Board of Health and Welfare

The NPR, Cause of Death Register, and the SPDR are all administered and validated by the National Board of Health and Welfare. It is mandatory for health care providers to submit patient data to the registries.

The NPR was initiated 1964 and has nationwide coverage regarding inpatient visits since 1987 and more recently specialized outpatient care. The inpatient registry has been validated and contains information on all hospitalizations, including mandatory information on all principal and secondary hospital discharge diagnoses, classified according to the International Classification Disease (ICD) system.^{146,147} The registry also includes data on surgical and non-surgical procedures and information on date of contact. Since 2001, the NPR has covered both public and private health care providers.

The Cause of Death Registry has existed since 1961 and includes information on causes of mortality, also classified according to the ICD, as well as dates of death.¹⁴⁸

The SPDR has, since 1 July 2005, data on all prescriptions filled in Sweden. The registry contains data on patient characteristics (age, sex, and place of residency) and dispensed item (type of medicine or formula, package size, date of dispensing, and free text dosage instructions from the prescriber) as well as prescriber characteristics (i.e. profession, specialty, and type of care).

Longitudinal Integration Database for Health Insurance and Labor Market Studies

The LISA database managed by Statistics Sweden integrates data from several sources from the labor market, and educational and social sectors. LISA holds annual registrations on socioeconomic variables since 1990, including all individuals ≥ 16 years of age (≥ 15 years of age since 2015) that are registered in Sweden as of December 31 for each year. LISA was used to retrieve information on the participants disposable income, educational level, marital status, and country of birth.^{149,150}

Measurements of adherence and persistence

In **studies III and IV**, we assessed refill adherence to lipid-lowering medications by calculating the MPR, i.e. according to dispensing data on refilled prescriptions from the SPDR. We also assessed non-persistence to medication, which is referred to as discontinuation in our studies. MPR is the ratio between the number of days with the medicine available divided by the number of observation days. Discontinuation was defined as a gap of ≥ 180 days between two filled supplies of lipid-lowering medications. In **study III**, we calculated measures of MPR and discontinuation at 18 months and in **study IV** also at 36 months.

To obtain daily dosage by converting free-text on the prescriptions to numeric values, an algorithm was developed and has been previously used in studies on adherence to LLT in type 2 diabetes.^{151,152} Validation of the algorithm in these studies showed 98% concordance. When calculating MPR, the dispensing date was designated as the start of each prescription of lipid-lowering medication. The duration for each prescription was then assessed by dividing the total number of dispensed tablets by the daily dosage. Overlapping supplies were adjusted forward in time until the preceding supply had ceased. In case of a switch in dose or substance, the surplus of medication was deleted, as were supplies that remained after the end of the study period.

MPR was calculated both as a continuous measure and as dichotomized data with a cut-off value $>80\%$ defined as high adherence and $\leq 80\%$ as low adherence, a common cut-off in studies on refill adherence, which enables comparison with earlier research on adherence.¹⁵³

Statistical methods

Baseline characteristics in the studies are described by mean values \pm the standard deviation (SD) for continuous variables, as frequencies (%) for categorical values, and also medians and interquartile range for the measures of MPR. In **study I**, Satterthwaite's unpooled t-test was used to analyze the significance levels between the compared groups. Two-tailed p-values <0.05

were considered statistically significant in all of the four studies. The CI was set at 95%.

Mean standardized differences, i.e. the difference between the means for the groups divided by the mutual SD, was used in **study II** to assess the ability of the propensity score to balance baseline characteristics. A standardized difference of <10 % was considered non-significant.¹⁵⁴

A **variance ratio** was calculated in **study II** for the matched analysis and is the mean ratio of variance of a variable between two groups that are compared. A variance ratio of 1.0 equals perfect balance.¹⁵⁴

Regression analyses

Regression analyses are statistical methods for testing the relation and the significance of the relation between a dependent and an independent (explaining) variable.¹⁵⁵ If there are many independent variables (covariates), a multiple regression analysis is used. Several regression models have been used in the four presented studies.

Cox proportional hazards model (Cox regression) is a semi-parametric multiple regression analysis that describes the time to an event based on a number of covariates. It estimates the relative risk of an event occurring at time t , provided that the event (our outcome measure) has not yet occurred.¹⁵⁶ Cox regression is a survival analysis and, as the name indicates, the analysis assumes that the risk is proportional over time. By adding confounding variables to the model, the estimated effect of the exposure on the outcome will be beyond what can be explained by a covariation between exposure and the confounding factors. The result is described as a proportion that is the incidence of the exposed versus the incidence of the unexposed, which results in a ratio called the HR. An HR that equals 1 indicates no difference between exposed and unexposed on the outcome. An HR above 1 indicates an increased risk (or probability) for the outcome from the exposure and a value below 1 indicates reduced risk (or probability). Cox regression analyses were used in **studies I-III**.

The key assumption of proportional hazard was evaluated by graphics in all studies. In **study I**, we also utilized Schoenfeldt residuals to test the assumption. In **study I**, violations were indicated in some of the models, but this was solved by stratifying the Cox models for the variables violating the assumption.

Kaplan-Meier curves can be used to study survival, but this estimator is univariate and describes survival in relation to one exposure variable. Hence, the model is not adjusted for other covariates.¹⁵⁶ It is a non-parametric method and describes the relation between survival probability and time of follow-up. The probability of survival is the proportion of individuals that are alive (i.e. has not yet experienced the outcome studied) at a certain point in time (patients at risk). Kaplan-Meier curves have been used in the matched cohort in **study II**.

Logistic regression analysis is used when the dependent variable is binary (or dichotomous).¹⁵⁶ It models the likelihood that an event will occur, e.g. the probability of being treated or untreated with LLT. Logistic regression was used in **study II** to calculate propensity scores and, in **study IV**, when estimating the effect on adherence and non-persistence from sociodemographic factors.

Propensity score analyses were used in **study II**. A propensity score is the conditional probability of being exposed to, for example, a particular treatment, given the individual's covariates. Propensity scores is one of several ways to adjust for confounding.^{157,156} Propensity score were used to create matched groups (treated *vs.* untreated) and to perform stratified analyses. Cox regressions were performed in the overall cohort by stratifying for the propensity score using eight strata and, in the matched analysis, by adjusting for propensity score in the two groups. The matched analysis gives us the average treatment effect in the treated, whereas the stratified analysis demonstrates the average treatment effect in the whole cohort. Matching was performed using a caliper width of 0.01 and without replacement, rendering perfectly aligned distributions of propensity scores.

Spline functions are used to relax the assumption of linearity and thus better capture non-linear associations between predictors and dependent variables.¹⁵⁸

In **study II**, restricted cubic splines were used to model the association between continuous variables and the exposure of main interest (being treated with lipid lowering drugs). In **study III**, a smoothing spline with seven degrees of freedom modelled the effect of MPR as a continuous measure by fitting a Cox regression model to one of the imputed data sets adjusted for age, sex, and previous CVD.

Missing data

In **studies I and IV**, the regression models included complete case data sets, i.e. only patients with complete data regarding the predictors included in the models. In **studies I, III, and IV**, baseline characteristics were collected before the index date up to 2 years prior to inclusion with last observation carried forward.

In **studies II and III**, missing data were handled by multiple imputation. We used the MICE (multivariate imputation by chained equations) algorithm to impute datasets with complete data.¹⁵⁹ This is done by generating multiple regression models where each missing variable is modelled by conditioning on the other variables in the data, which creates multiple datasets with plausible values for missing data. Separate analyses were run on each imputed data set and the results were then pooled using Rubin's rules. In **study II**, the propensity score was also based on imputation of missing data by repeatedly creating datasets (in total 10) for the missing variable and then calculate an average estimate for the propensity score.^{160,161}

Statistical analyses in **studies I and II** were performed with SAS statistical software versions 9.2 and 9.3, respectively, and R 3.0.2. In **studies III and IV**, the analyses were performed with SAS version 9.4 and, in **study III**, also with R 3.4.3.

Ethical considerations

The present thesis is based on studies with searches in, and merging of several national registries with the NDR as a starting point. The NDR continuously collects nationwide observational data regarding almost all individuals with a diagnosis of type 1 diabetes in Sweden. This collection is regulated by the

Patient Data Act and the General Data Protection Regulation.^{162,163} All data from the registries are presented in an aggregated form and anonymized so that no information can be traced to the individual.

Patients may, at any time and without giving reasons, request that their data in the NDR should be erased. The collected data are utilized for quality control and improvement in diabetes care, but the data can also be used for research under strictly regulated conditions. The individuals involved in the studies are not asked in person if they wish to participate, but all who are included have previously consented to inclusion in the NDR. To ask every single person for consent before inclusion would not have been feasible considering the large number of included individuals in each study and could also introduce an inclusion bias to the study.

No patients were involved in setting the research question nor in the design, conduct, or interpretation of the data. There is, of course, a risk that individuals may experience a violation of their integrity when personally stated and collected data are used for research purposes and they do not themselves have the opportunity to choose the type of research they may participate in. Therefore, it is very important that the studies we carry out are relevant and drive the research area forward so that the benefit of participating in research exceeds the risk of injury to the individual.

For each study in this thesis, we have received ethical approval from the Regional Ethics Review Board at the University of Gothenburg (EPN Diary Numbers: 563-12 and 776-14).

Methods overview

This section will give a brief summary of the background, aims, participants, and methods of the four studies. An overview of the characteristics of the studies can be found in Table 1 and details on each of the studies are available in the appendix. Pros and cons of the methodology, including statistical considerations, can be found in the discussion section.

Study I

The aim of **study I** was to investigate the association of different blood lipids levels by the risk of CVD in type 1 diabetes by assessing LDL-cholesterol, non-HDL-cholesterol, and total cholesterol/HDL-cholesterol ratio. The study included 30,778 individuals with type 1 diabetes, 18-79 years of age, included between 2003 and 2006. The mean-follow-up time was 6.8 years and end of study was 31 December 2011.

Exposure was baseline LDL-cholesterol, non-HDL-cholesterol per mmol/L and the total cholesterol/HDL-cholesterol ratio per unit, and, further, LDL-cholesterol and total cholesterol/HDL-cholesterol ratio divided into octiles. Outcome was a composite of fatal and non-fatal CVD. Baseline characteristics were collected from the NDR, and outcome events from the NPR and the Cause of Death Register.

The patients were divided into two groups, those treated and not treated with LLT. From the group with LLT, we extracted a subgroup of patients that also had a history of CVD. Based on one of the prevailing guidelines for statin treatment,¹⁶⁴ a fourth group consisted of individuals ≥ 40 years of age without a history of CVD but with one or more risk factors that we could identify in the NDR (i.e. hypertension and/or albuminuria and/or smoking).

Cox regression analyses were then performed for cardiovascular events in relation to baseline lipid levels as previously described. The models were adjusted for traditional cardiovascular risk factors, treatments, and also for a history of CVD when applicable.

Study II

The aim of **study II** was to investigate the association between LLT and CVD and death in primary prevention in individuals with type 1 diabetes. In total, 24,230 individuals with type 1 diabetes ≥ 18 years of age and with no history of CVD were included between 2006 and 2008, with the study ending on 31 December 2012. The mean follow-up was 6 years and 78% were not treated with LLT at the start of the study. Exposure was treatment or no treatment with LLT. Outcomes were fatal/non-fatal CHD, CVD and all-cause death. CVD was a composite of cardiovascular heart disease, myocardial infarction and stroke.

Non-fatal CHD was defined as myocardial infarction, unstable angina, percutaneous coronary intervention and coronary artery bypass grafting. Acute myocardial infarction, stroke and cardiovascular death were also analyzed separately (for details on outcomes see attached article).

Baseline characteristics were collected from the NDR, and outcome events from the NPR and the Cause of Death Register. Data on socioeconomic variables were retrieved from LISA.

Two different analyses were performed (Fig. 2). A propensity score for the probability of being treated with LLT, based on 32 different clinical and socioeconomic variables, was calculated for each of the included individuals. The two groups, those with and without treatment, were balanced by stratification for the propensity score, and the propensity score was then used to estimate the effect of LLT on the cardiovascular outcomes and all-cause death by Cox regression analyses adjusted for all of the variables.

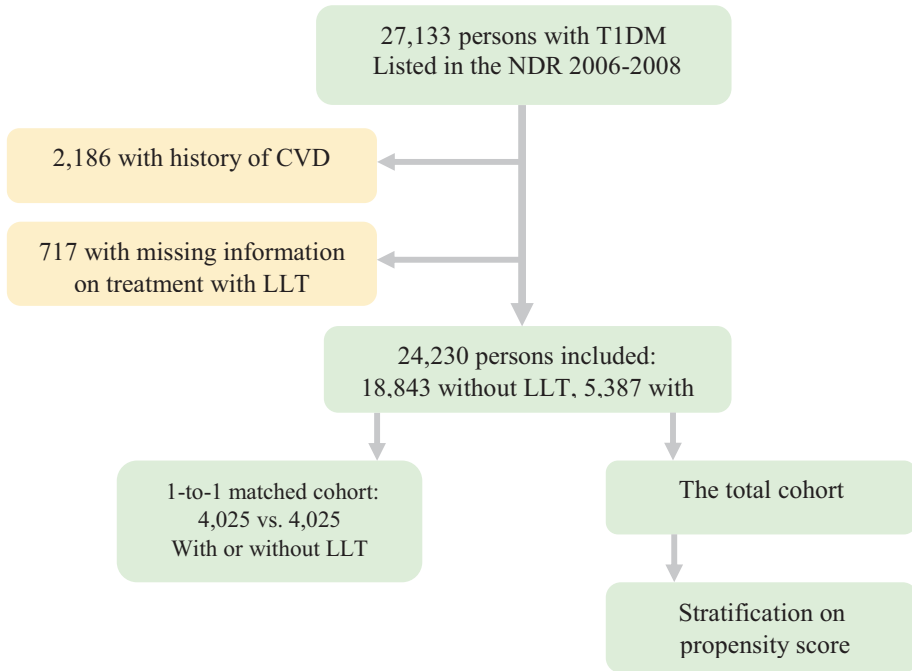
The propensity score was further used in a 1:1 matched cohort comparing individuals with LLT to individuals without LLT, also evaluating the effect of LLT on the risk of the outcomes with the help of Cox regression analyses.

The latter analyses provided us with the average treatment effect in those actually treated whereas the first analyses gave us the average treatment effect in the whole cohort if all were to be treated.

Study III

The aim of **study III** was to assess level of adherence to and discontinuation of LLT, mainly statins, and the associations with the risk of CVD in individuals with type 1 diabetes. In total, 6192 individuals with type 1 diabetes ≥ 18 years were included when initiating novel LLT between 2006 and 2010, with the study ending on 31 December 2013 and in April 2015 for all-cause death. Mean-follow-up time was 3.6 and 3.9 years, respectively.

Fig. 2. Flowchart for study II. Abbreviations: CVD, cardiovascular disease; LLT, lipid-lowering therapy; NDR, National Diabetes Register; T1DM, type 1 diabetes mellitus.

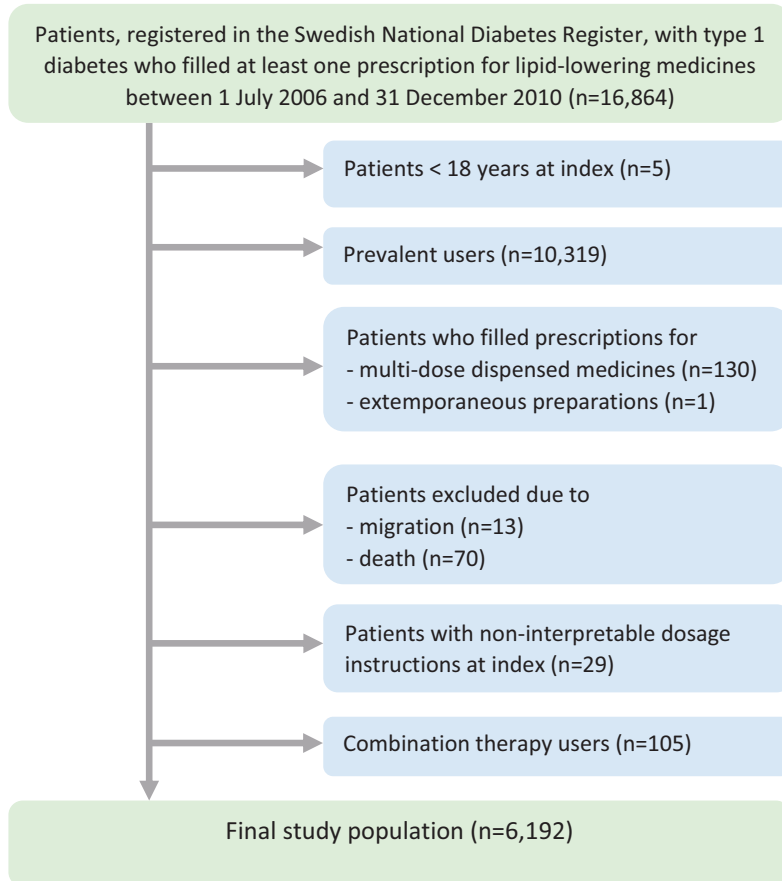


Exposures were refill adherence and discontinuation. Outcomes were non-fatal CVD, fatal CVD, non-fatal and fatal CVD, and all-cause death. A CVD event was a composite of myocardial infarction, unstable angina, percutaneous coronary intervention and/or coronary artery bypass grafting, stroke, peripheral vascular disease, endovascular interventions, and/or peripheral artery bypass grafting. Stroke was defined as fatal or non-fatal cerebral infarction, intracerebral hemorrhage, or unspecified stroke.

Information on baseline characteristics, comorbidities (history of CVD, atrial fibrillation, heart failure, and cancer), other medications (antihypertensive medications and anticoagulants including aspirin) and outcome events were collected from the NDR, the SPDR, the NPR, the Cause of Death Register, and LISA.

Novel users were identified by excluding those who had filled a prescription for LLT within 365 days prior to inclusion. We also excluded participants with prescription of substances, dosages, or preparations that were difficult to interpret for the algorithm used (see Fig. 3).

Fig. 3. Flowchart for study III.



After 18 months, refill adherence of LLT was measured by calculating the MPR both as a continuous measure and dichotomized with a cut-off value $>80\%$ defined as high adherence and $\leq 80\%$ as low adherence. Non-persistence to LLT (i.e. discontinuation) was defined as being without LLT on hand for ≥ 180 days. Individuals were thereafter followed until a cardiovascular event,

death, or end of follow-up on 31 December 2013. Cox regression analyses adjusted for traditional cardiovascular risk factors and socioeconomic status were then performed to assess levels of adherence and discontinuation of LLT as predictors of non-fatal, fatal, non-fatal/fatal CVD, and all-cause death.

Study IV

The aim of **study IV** was to assess the impact of socioeconomic factors, age and gender on the adherence to and discontinuation of LLT after 18 and 36 months on therapy. The participants in **study IV** were the same as in **study III** and, after application of exclusion criteria, 6122 individuals remained for analysis at 36 months. Socioeconomic status, gender, and age were exposures in **study IV**, and level of adherence and discontinuation the outcomes.

Information on baseline characteristics, comorbidities (history of CVD and cancer), other medications (antihypertensive medications and anticoagulants including aspirin), and outcome events were collected from the NDR, SPDR, NPR, Cause of Death Register, and LISA.

The socioeconomic variables retrieved from the LISA database were disposable income, level of education, marital status, and country of birth. Disposable income was stratified into quartiles. Education was stratified into three levels, i.e. compulsory school or lower (≤ 9 years), upper secondary school (10-12 years), and post-secondary (>12 years, college/university). Marital categories were single, married, divorced, or widowed. Immigrant status was defined as Swedish native or immigrant depending on country of birth.

Refill adherence and discontinuation were calculated as in **study III** but in **study IV** also at 36 months. A multivariate logistic regression analysis was then performed to assess the impact of socioeconomic status on refill adherence to and discontinuation of LLT at 18 and 36 months after initiation of LLT. The models were adjusted for age, gender, previous CVD, and socioeconomic status. In a second analysis, we also adjusted for smoking and physical activity (see Methodological consideration in the Discussion section).

4 RESULTS

The following section will describe the main findings of each of the included studies.

Study I. Blood lipid levels associated with cardiovascular disease

Baseline characteristics for the four subgroups and the number of events during follow-up are summarized in Table 2 (for a full detailed description see attached published article in the appendix). The mean age of the whole cohort was 46 years with a mean diabetes duration of 21 years and 44% were women. In total, 10% of the cohort had a history of CVD and 27% were on LLT. It should be pointed out that 41% of patients ≥ 40 years of age with one or more CVD risk factor were treated with lipid-lowering medication. Baseline lipid variables did not differ substantially between the patients without and with lipid-lowering medication. Mean LDL-cholesterol was 2.7 mmol/L in both treated and untreated patients, and the total cholesterol/HDL-cholesterol ratio was 3.2 and 3.3, respectively. There were a total of 4733 events of fatal/non-fatal CVD events over a mean-follow up of 6.8 years.

Adjusted HRs with 95% CIs with CVD as the outcome are presented in Table 3 for LDL-cholesterol and non-HDL-cholesterol per 1 mmol/L increase, and for the total cholesterol/HDL ratio per unit increase. Cox regression analyses showed that, in subjects without LLT, there was a 9% higher risk of CVD per 1 mmol/L increase in LDL-cholesterol. In the other three subgroups, there was no statistically significant association between LDL-cholesterol and the risk of CVD. The total cholesterol/HDL-cholesterol ratio was significantly associated with risk of CVD in all groups except in the subgroup with a history of CVD and LLT.

Table 2. Baseline characteristics in 30,778 patients with type 1 diabetes ages 18-79 years, outcomes, and mean follow-up duration in all and in subgroups of patients either not treated or treated with lipid-lowering medication.

Baseline variable	All patients (N=30,778)	All patients without LLT (N=22,606)	Patients age ≥ 40 years + CVD risk factor (N=9324)	All patients with LLT (N=8172)	Patients with CVD + LLT (N=1973)
Age (years)	46 \pm 15	43 \pm 14	57 \pm 10	56 \pm 12	60 \pm 10
Female, %	44	45	44	42	38
Diabetes duration (years)	21 \pm 14	19 \pm 13	26 \pm 15	26 \pm 15	31 \pm 16
HbA1c (mmol/mol)	64 \pm 14	63 \pm 14	64 \pm 14	66 \pm 14	67 \pm 14
BMI (kg/m ²)	26 \pm 4	25 \pm 4	26 \pm 4	27 \pm 4	27 \pm 5
Lipid-lowering medication, %	26.6	0	41.3	100	100
eGFR (mL/min)	84 \pm 24	87 \pm 23	77 \pm 23	75 \pm 24	68 \pm 24
CVD history, %	9.6	4.4	0	24.1	100
Fatal/non-fatal CVD events, n (%)	4733 (15.4)	2196 (9.7)	1978 (21.2)	2537 (31.0)	1339 (67.9)
Fatal/non-fatal CVD per 1000 person-years	22.8	13.8	32.4	51.7	169.1
Mean follow-up (years)	6.8	7.0	6.6	6.0	4.0
Data are given as means \pm SD or frequencies (%). Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; LLT, lipid-lowering therapy; SD, standard deviation.					

Adjusted HRs for the octiles of LDL-cholesterol and the total cholesterol/HDL-cholesterol ratio are shown in Fig. 4 for the patients with no LLT and for the subgroup age ≥ 40 years with one or more CVD risk factors. There was no significant association for LDL-cholesterol in any of the patient groups, while the total cholesterol/HDL-cholesterol ratio showed an incremental pattern of higher risk for CVD per higher octile in the patients without LLT and in the patients ≥ 40 years with one or more CVD risk factors.

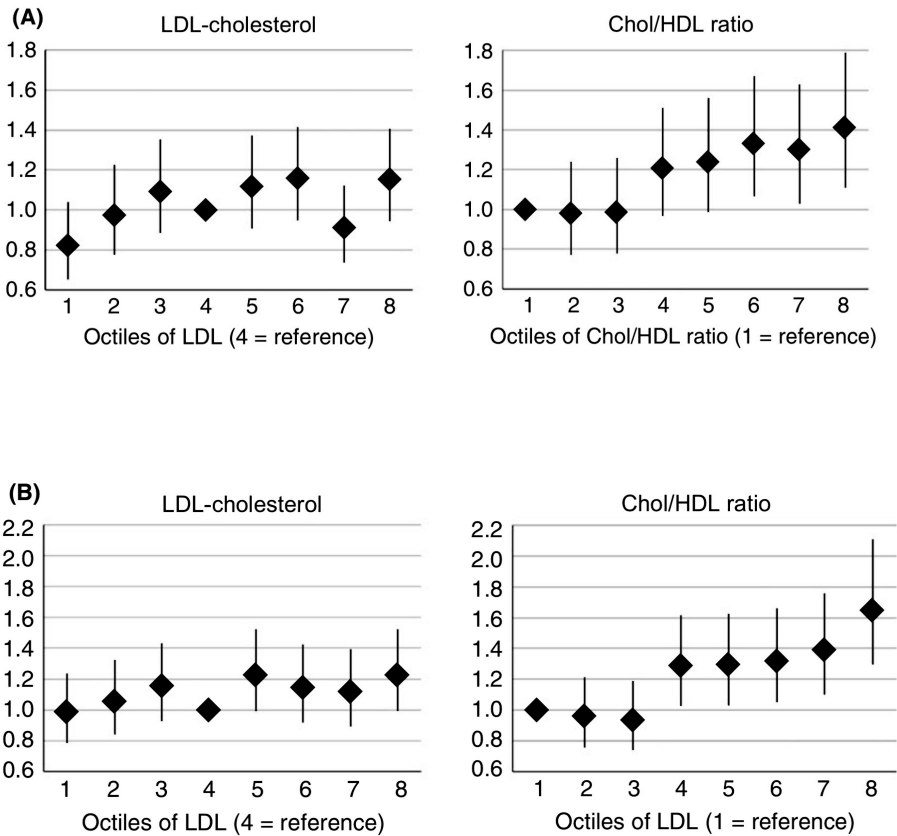
Table 3. Adjusted HR (95% CI) for fatal/non-fatal CVD with LDL-cholesterol, total cholesterol/HDL-cholesterol ratio and non-HDL-cholesterol as predictors in 30,778 patients with type 1 diabetes.

Patient group	LDL-cholesterol		TC/HDL-cholesterol ratio		Non-HDL-cholesterol	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All patients without LLT	1.09 (1.01-1.18)	0.02	1.12 (1.05-1.20)	<0.001	1.10 (1.02-1.19)	0.01
Patients age ≥ 40 years + 1 CVD risk factor	1.07 (0.99-1.16)	0.07	1.16 (1.09-1.24)	<0.001	1.09 (1.02-1.18)	0.02
All patients with LLT	1.02 (0.95-1.09)	0.65	1.08 (1.02-1.15)	0.01	1.02 (0.96-1.09)	0.52
Patients with CVD and LLT	1.02 (0.92-1.13)	0.67	1.04 (0.95-1.14)	0.43	1.02 (0.92-1.13)	0.66

Adjusted for diabetes duration, BMI, systolic blood pressure, HbA1c, albuminuria, eGFR, smoking, antihypertensive medication, CVD history, heart failure, atrial fibrillation, and insulin administration method. Also adjusted for HDL-cholesterol in the LDL models and LLT in patients age ≥ 40 + 1 CVD factor. Non-HDL-cholesterol is TC minus HDL-cholesterol.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD: cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; TC, total cholesterol.

Fig. 4. Adjusted hazard ratios for CVD in patients without LLT (panel A) and in patients ≥ 40 years + CVD risk factor (panel B) by octiles of LDL-cholesterol and the total cholesterol/HDL-cholesterol ratio, respectively. Abbreviations: CVD, cardiovascular disease; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Chol, total cholesterol.



Study II. Association between lipid-lowering therapy and CVD risk in primary prevention in type 1 diabetes

As expected, there were several differences between those with or without LLT at inclusion (for details, see Table 1 in the appendix). The patients who were on LLT were older (mean age 50 *vs.* 36 years) and had a longer diabetes duration (mean 34 *vs.* 21 years), and other parameters such as kidney function, coexisting conditions, and other medical treatments also differed. In both groups, 12% were smokers. A total of 6% had a birth country other than Sweden and this did not differ between the groups. Despite the crude differences between the groups, the propensity score allowed balancing the 32 covariates included in the analysis. In the matched cohort, there were virtually no differences between those with and without LLT, but at the expense of excluding a large proportion of individuals. The majority of those excluded had high propensity scores with LLT (see Fig. 7 in the Discussion section).

In the overall cohort, the crude event rate was about 4-times higher in the those treated with LLT compared to those untreated; however, in the matched cohort, the event rates were similar in the two groups, except for all-cause death showing 13.2 and 9.9 deaths per 1000 person-years in the persons without LLT compared to those on treatment (see table 2 in the appendix and Fig. 5).

The stratified analysis for the mean treatment effect in the overall cohort showed a significant association between treatment with LLT and all types of cardiovascular morbidity and mortality, with the most pronounced effect being on all-cause death and stroke which showed a risk reduction of 44% for those on LLT compared to those without LLT (Fig. 6). In the matched analysis, which thus describes the mean effect of LLT in those already treated with LLT (or the average treatment effect in the treated), we could see a significant association in favor for LLT only for all-cause death, with an almost 30% risk reduction for those on LLT compared to those without LLT, and with borderline significance for cardiovascular death (Fig. 6).

Fig. 5. Kaplan-Meier curves for all-cause death in the matched cohort.

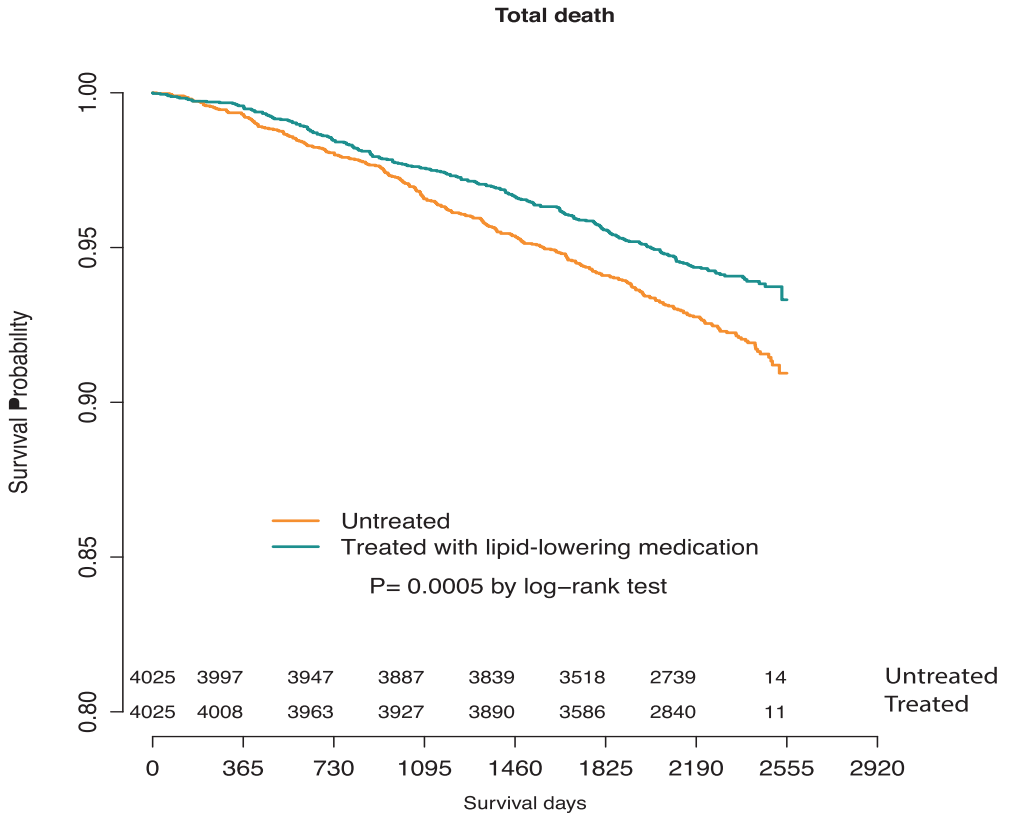
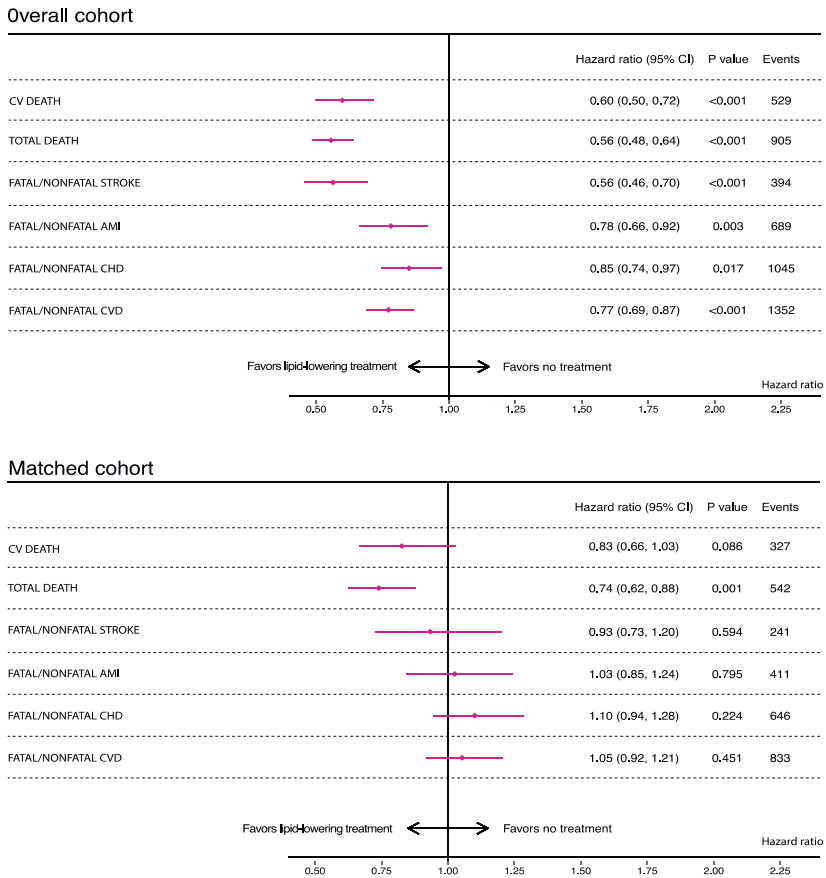


Fig. 6. Hazard ratios and 95% confidence intervals by means of Cox regression for patients treated versus not treated with lipid-lowering medication in the overall cohort and in the matched cohort. Abbreviations: CV, cardiovascular; AMI, acute myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease.



Study III. Adherence to lipid-lowering therapy is associated with the risk of CVD in type 1 diabetes patients

In the overall cohort of novel users of LLT, 6192 patients were included, of whom 9% had CVD prior to inclusion (for detailed description of baseline characteristics and MPR measurements see Table 1, attached manuscript). Mean age was 45 years, mean diabetes duration was 29 years, and 58% were male. The vast majority of the patients, 99%, were treated with statins, most commonly simvastatin (see supplementary Table 1 in manuscript). Analysis of the mean MPR showed that the participants had access to LLT covering 73% of the days over 18 months. When MPR was dichotomized into $\text{MPR} \leq 80\%$ representing low adherence and $\text{MPR} > 80\%$ representing high adherence, 52% of the participants had a high adherence. Those with an $\text{MPR} \leq 80\%$ had a mean MPR of 48% and those with $\text{MPR} > 80\%$ had a mean MPR of 95%. Within 18 months, 27% of the participants had discontinued LLT.

Those with high adherence more often had concurrent medication (for antihypertensive medication: 51% vs. 33%) and a history of CVD (11% vs. 7%), while low adherence (15% vs. 11%) and discontinuation (17% vs. 12%) of LLT were more common amongst smokers. Individuals with prior CVD discontinued LLT to a lesser extent than those with no history of CVD (8% vs. 10%). The number of events was collected for 18 months after initiation of LLT and showed a total of 637 non-fatal CVD events, 58 fatal CVD events, and 302 all-cause deaths, with a mean follow-up of 3.6 years for non-fatal events and 3.9 years for fatal events.

In the adjusted models, high adherence to LLT, i.e. $\text{MPR} > 80\%$, was associated with a risk reduction for non-fatal CVD as well as for the composite of non-fatal and fatal CVD of 22% and 21%, respectively, compared to low adherence (see Table 2, attached manuscript). Discontinuation of LLT was associated with a 43% higher risk of non-fatal CVD. An $\text{MPR} > 80\%$, was associated with a higher risk of fatal CVD, although not statistically significant (HR 1.96, 95% CI 0.96-4.01). For all-cause death, we could not identify any association with low adherence or discontinuation of LLT.

Since those with an MPR $\leq 80\%$ involve a wider span of level of adherence than those with MPR $>80\%$, we also analyzed the impact of MPR as a continuous measure on the relative rate of non-fatal CVD by fitting a Cox regression model to MPR with the effect modelled by a smoothing spline. This shows that the highest risk for CVD can be seen in those with an MPR $<40\%$, while the lowest risk was in those with an MPR $>80\%$ (see Fig. 2 in the manuscript).

Study IV: The influence of sociodemographic factors on adherence and persistence in type 1 diabetes

For baseline characteristics of the overall cohort and measures of adherence and discontinuation at 18 months, see the results section of **study III** in the attached manuscript. Of all patients, 45% were married, 12% divorced, and 7% had a birth country other than Sweden. A third of the participants had >12 years of education, while 17% had ≤ 9 years of education. After 36 months, 48% had an MPR $>80\%$ compared to 52% at 18 months. The mean MPR at 36 months for those with low and high adherence was 53% and 94%, respectively. At 36 months, the proportion of those discontinuing had increased from 27% to 42%.

The odds ratios with 95% CIs for gender, age, and socioeconomic parameters on MPR are presented as forest plots in Fig. 1 and in supplementary Table 3 in the appendix. Women were more likely to be adherent than men in the shorter term, but there was no longer a significant difference at 36 months. Age had a large impact on MPR, where the oldest age group was the most adherent at 18 and 36 months and had an MPR $>80\%$, which was 2.5- to 3-times more often than the youngest age group. Adherence also increased incrementally with age. Marital status influenced adherence significantly where divorced individuals were less adherent than married individuals consistently over time. Single persons had the same adherence as married persons for the first 18 months, but were less adherent at 36 months. Those having a country of origin other than Sweden were less adherent than Swedish natives at 36 months. Income did not affect MPR except at 36 months where those in quartile 3 had an MPR $>80\%$ more often than those in quartile 1.

Discontinuation followed the same pattern as low adherence (see Fig. 2 and supplementary Table 4 in the appendix). That is, people with low adherence also discontinued medication to a higher extent. For the first 18 months, women were less prone to discontinue LLT compared to men, but there was no longer a difference between genders at 36 months. Age had a large and incremental impact on discontinuation of medication where those >52 years of age were the most persistent with LLT compared to those <36 years. Divorced individuals discontinued LLT more frequently than married persons, a pattern that was strengthened over time. More single than married persons discontinued LLT after 36 months. As for the influence of income on discontinuation rate, those being in the two highest income quartiles discontinued LLT to a lesser degree compared to the lowest quartile. This pattern was strengthened over time. People born in a country other than Sweden were about 1.5-times more prone to discontinue LLT compared to native Swedes. Level of education had no impact on LLT discontinuation.

5 DISCUSSION

The aim of this thesis was to extend the knowledge on dyslipidemia in patients with type 1 diabetes from a clinical perspective by approaching the subject from different angles concerning the assessment and treatment of dyslipidemia. This thesis shows that LDL-cholesterol is not the best blood lipid marker for CVD risk in type 1 diabetes and that LLT in primary prevention is associated with a lower risk of CVD. This thesis also supports that adherence to LLT is important for optimized prevention of CVD and that socioeconomic factors affect adherence over time. These findings are important since individuals with type 1 diabetes are often diagnosed with diabetes at a young age and have an increased lifetime risk of CVD due to their long diabetes duration and exposure to cardiovascular risk factors.^{29,31}

Importance of blood lipid markers

Entrapment of LDL particles in the arterial intima layer is the main cause of development of atherosclerotic lesions and hyperglycemia is one of several enhancing factors.^{165,167} Treatment of high LDL-cholesterol levels has therefore been the main target for limiting the consequences of atherosclerosis. Many guidelines for primary prevention of dyslipidemia in diabetes have focused on specific levels of LDL-cholesterol to initiate statin therapy.^{115,164} They also set treatment targets for LDL-cholesterol depending on baseline risk of CVD despite the fact that most trials of statins and CVD outcomes actually tested specific doses of statins rather than targeting a certain LDL-cholesterol goal.¹⁶⁶ In accordance with **study I**, several studies in patient categories other than type 1 diabetes patients have shown that LDL-cholesterol is not the best predictor of cardiovascular risk among measured lipid variables.¹⁶⁸⁻¹⁷⁰

In **study I**, the total cholesterol/HDL-cholesterol ratio had a better predictive value than LDL-cholesterol in all patients, except for those with a history of CVD who were already on treatment. The ratio also displayed an incrementally higher risk of CVD per higher octile compared to LDL-cholesterol. The low predictive value of lipid parameters in people already on LLT could be due to lower LDL-attributable risk for events in the treated; however, on the other hand, both LDL-cholesterol and non-HDL-cholesterol have been predictive of

residual CVD risk in other studies of patients without diabetes.^{171,172} In our study, we did not have access to apolipoprotein levels, which could also have been of interest for assessing other aspects of lipoprotein metabolism in this particular subgroup with a considerable number of events and residual CVD risk despite treatment.¹⁷³

There are other studies from both the UK and Finland that have shown the limited predictive value of LDL-cholesterol in individuals with type 1 diabetes. In those studies, non-HDL-cholesterol and apoB, or apoB/apoA1 ratio were all better for the prediction of CVD.^{174,175} Furthermore, when developing a risk model for predicting 5-year risk of CVD in Swedish patients with type 1 diabetes, total cholesterol and HDL-cholesterol were included as important risk predictors whereas LDL-cholesterol was not.¹⁷⁶

Epidemiologic, genetic, and experimental research has shown that the process of atherosclerosis is driven by the concentration of LDL in plasma and by the duration of exposure to LDL-cholesterol.^{69,177} The clear correlation between the lowering of LDL-cholesterol with statin treatment to the reduction of cardiovascular events further supports the causal link between LDL-cholesterol and CVD.¹¹² However, in **study I**, we did not find support for LDL-cholesterol as a marker of increased risk for CVD. One reason could be the way we measure LDL-cholesterol in clinical practice. When this study was performed, the most commonly used method to measure LDL-cholesterol was indirectly by using the Friedewald's equation. Studies show that LDL-cholesterol is underestimated in young individuals when using this equation, especially at low LDL-concentrations and if triglycerides are >1.7 mmol/L.^{178,179} Another reason might be that we measure LDL-cholesterol and not LDL particles. Depending on the amount of cholesterol in the particles and if there is a dominance of buoyant or sdLDL particles, the LDL-cholesterol could over- or underestimate CVD risk since sdLDL particles have been found to be more atherogenic than more buoyant particles.^{82,180}

Several other atherogenic lipoproteins are also not assessed by measuring LDL-cholesterol in plasma. Non-HDL-cholesterol, which is the combined measure of LDL-cholesterol and VLDL-cholesterol, is considered more atherogenic than LDL-cholesterol or VLDL-cholesterol alone. Non-HDL-cholesterol is simply calculated by subtracting HDL-cholesterol from total

cholesterol and has a high correlation with apoB.¹⁸¹ ApoB is the main protein embedded in LDL and VLDL particles and, hence, also represents a more comprehensive picture of atherogenicity than LDL-cholesterol alone, but is less used in clinical practice. Glycogenated apoB also has atherogenic properties in itself and is an enabler for LDL to be deposited in the intima of the arterial wall.¹⁸² Another lipoprotein with atherogenic properties is lipoprotein(a). Lipoprotein(a) is a modified form of the LDL particle, with an additional specific apolipoprotein(a) that is attached to apoB of LDL. Lipoprotein(a) is a genetically determined causal risk factor for CVD, but is not yet a target for treatment.¹⁸³ In our study, non-HDL-cholesterol was significantly associated with a higher risk for CVD in the untreated patients.

In many guidelines for the treatment of lipid disorders, LDL treatment targets are still present. In the recently published guidelines on management of dyslipidemia in diabetes from the American Diabetes Association, an LDL-cholesterol >2.5 mmol/L is regarded as a risk factor together with hypertension, albuminuria, chronic kidney disease, and a family history of premature atherosclerotic CVD, and hence a basis for decision on initiation of statin treatment for those <40 years of age.¹¹⁴

In the 2018 guideline from American College of Cardiology and American Heart Association (ACC/AHA) on management of blood cholesterol treatment, supplemented with a guideline for primary prevention in 2019,^{95,184} the recommendation for patients with diabetes without a history of CVD is a statin of moderate intensity in all patients between 40-75 years of age having an LDL-cholesterol of ≥ 1.8 mmol/L, without calculating the risk of a future CVD event since the risk is deemed to be high and risk prediction unnecessary. In the presence of multiple risk factors or if the patients are 50-75 years of age or have an LDL-cholesterol >4.8 mmol/L, they suggest high-intensity statin treatment. The ACC/AHA guidelines do not differentiate the recommendations depending on whether the patient has type 1 or type 2 diabetes, except when evaluating risk enhancers where they suggest a diabetes duration >20 years could be a reason to treat lipids earlier and more intensively in type 1 diabetes.

The National Institute for Health and Care Excellence (UK) guidelines on treatment of dyslipidemia go further than the ACC/AHA guidelines and suggest that all adult patients with type 1 diabetes should be considered for

statin treatment, regardless of lipid levels, and certainly offered statin treatment from 40 years of age and/or with a diabetes duration >10 years.¹⁸⁵

Benefits of lipid-lowering therapy in type 1 diabetes

The scientific evidence in guidelines for treating dyslipidemia in type 1 diabetes are largely extrapolated from lipid-lowering trials in populations other than those with type 1 diabetes. Individuals with type 1 diabetes that are included in randomized trials are few; they are also often older and have more concurrent diseases than the individuals that would be considered for primary prevention according to guidelines.^{43,116}

The largest dyslipidemia treatment trial involving patients with type 1 diabetes is still the HPS published in 2002-2003 with 20,056 patients, of whom 3% had type 1 diabetes.¹¹⁶ The mean age in this type 1 diabetes population was 62 years and about half of the diabetes cohort had no CVD prior to inclusion but were deemed as being at high risk for CVD events. When simvastatin 40 mg was compared to placebo, there was a 24% reduction in major vascular events, albeit not significant. The HPS is still the main source of evidence for the effect of statin treatment on CVD in type 1 diabetes together with the meta-analysis of 14 trials including 1466 type 1 diabetes patients out of 18,686 diabetes patients, which showed a 21% proportional reduction of major vascular events per 1 mmol/L reduction in LDL-cholesterol in type 1 diabetes patients, but with limited direct evidence of benefit.⁴³

Study II is an observational study including individuals with type 1 diabetes and no history of CVD, comparing outcomes for CVD in those with and without LLT (99% statins). A propensity score for LLT was calculated based on patient characteristics and two different analyses were then performed. The first was an analysis where patients were stratified on propensity score, showing that, if we were to treat all of the participants with LLT, this would be associated with a 22-44% lower risk of CVD and death after a mean follow-up of 6 years. The second was an analysis where patients were matched depending on propensity score, which showed the average effect in who were treated. In the matched analysis, there was a significant risk reduction only for all-cause death (30%). Our interpretation is that the effect of LLT is

underestimated in the matched cohort and that the limited effect of LLT on the cardiovascular outcomes could be explained by a selection bias in the matching process (see methodological considerations). Altogether, **study II** adds support to previous randomized controlled trials showing cardioprotection with LLT in primary prevention and underscores the importance and benefits of LLT for primary prevention in type 1 diabetes.

Importance of adherence to lipid-lowering therapy in type 1 diabetes

Adherence and persistence to medication in chronic conditions is known to be poor and this has a significant impact on health outcomes.¹¹⁸ Outside the clinical trial environment, many patients have suboptimal adherence. This affects clinical outcome in the general population as well as in patients with diabetes.^{126,186-190} It has been calculated that 9% of CVD events in Europe could be caused by low adherence to cardiovascular medication alone.¹²² Several observational studies in the general population and in patients with type 2 diabetes have shown that persistence to LLT could be as low or even lower than 50%.^{123,151,191,192}

Less is known about adherence to LLT in type 1 diabetes. In **study III**, we investigated adherence and non-persistence (i.e. discontinuation) to therapy in patients with novel use of LLT and risk of CVD. Adherence was assessed over 18 months after initiation of LLT, of which 99% were statins. During the assessment period, 27% of the patients discontinued their medication and 52% had an MPR >80%, which corresponds to filled prescriptions and medicines at hand for more than 8 out of 10 days. Those with a high adherence, i.e. with MPR >80% had a lower risk (21-22%) of fatal/non-fatal CVD and non-fatal CVD compared to those with a lower adherence. Those who had discontinued their LLT within 18 months after initiation had a 43% higher risk of non-fatal CVD. Discontinuation of LLT had no impact on fatal CVD in this study.

Refill adherence to LLT has been studied in other patient categories. Cramer et al.¹⁵³ published a review in 2007 of 139 studies on adherence conducted between 2000 and 2005: 13% of the studies were on treatment of dyslipidemia. The most reported measure of adherence was 12-month MPR: overall MPR was 72%, while 51% had an MPR >80% for LLT, which was almost identical

to our results in **study III** on 18-month adherence (mean MPR 72%, and 52% in the population with MPR >80%). A majority of the included studies showed a positive association between high adherence and lower risk for CVD.

Another systematic review assessed 84 real-world studies on adherence and persistence with statins published from 2005 to 2016,¹⁹³ of which 21 studies evaluated MPR with a cut-off at $\geq 80\%$. Follow-up ranged from 6 months to 3 years. Results for MPR $\geq 80\%$ ranged from 18% to 92%. The majority of the studies included in this review reported a significant association between high adherence and reduction in CVD events. Data from a Swedish study in type 2 diabetes patients assessing the impact of refill adherence on CVD outcomes showed a graded increase of CVD risk depending on level of adherence with HRs for CVD ranging from 1.33 to 2.36 in primary prevention and from 1.19 to 1.58 in secondary prevention for those with MPR $\leq 80\%$.¹⁵²

Even though other studies on adherence differ with respect to measures of adherence, follow-up time, and patient characteristics, they add support to the finding in our study that adherence is inversely associated with CVD risk. Clearly, suboptimal adherence to and premature discontinuation of LLT is a matter of concern and, if we want to achieve the full benefit of LLT, it needs to be addressed.

Association between sociodemographic factors and adherence

The reasons for low adherence and low persistence to LLT are complex and should preferably be evaluated in all aspects that encompasses the concept of adherence.¹¹⁸ Adherence and persistence to LLT in relation to sociodemographic factors, physician-related factors, and the effects of other medications and comorbidities have been investigated in different patient categories, under different circumstances, and with varying results.^{123,135,137,139} In type 1 diabetes, socioeconomic status has been shown to predict future diabetic complications.¹²⁹⁻¹³¹ In **study IV**, we wanted to investigate the reasons for non-adherence to LLT from a demographic and socioeconomic perspective. We followed the same cohort as in **study III**, but assessed adherence and rate of discontinuation of LLT also at 36 months.

Those with high adherence (MPR >80%) had decreased from 52% at 18 months to 48% at 36 months. According to other studies,^{123,186} adherence to statins tends to deteriorate in the first few years after starting therapy and then remains at the same level for those continuing with the therapy. It was notable in our study of individuals with type 1 diabetes that those who discontinued LLT had increased from 27% at 18 months to 42% at 36 months; hence, persistent patients constituted only 58% of the cohort 3 years after starting LLT. This is of concern since Law et al.¹⁹⁴ had already shown in the 1990s that long-term high adherence and persistent use of LLT were associated with increased protection from cardiovascular events.

In line with the results from **study IV** where divorced individuals, and later on also unmarried individuals, had lower adherence and more often discontinued LLT than married persons, marital status has been previously recognized as a predictor for adherence to medication in a study with self-reporting of cardiovascular medication 1 year after coronary intervention. In that study,¹³⁶ unmarried individuals presented with lower adherence than married individuals. A cross-sectional study on Lebanese patients with dyslipidemia has also reported lower adherence to statins in divorced individuals.¹⁹⁵

Contrary to our study, several studies have shown that women are less likely to be adherent and, in one, women were less persistent but more adherent to LLT.^{137,139,196} In **study IV**, we found that lower adherence and premature discontinuation of LLT were associated with male gender and younger age. However, there was no longer a difference between genders at 36 months, but the association between adherence and age had strengthened. Co-payment and low income have been reasons for low adherence in several studies.^{137,134} Many of these studies were conducted in the US and are not really comparable to our study since Swedish social benefits provide almost complete economic coverage for health care and medications with fixed co-pays up to a ceiling.¹⁴⁰ Nonetheless, we could still see an association between disposable income and persistence to LLT in our study, where those in the highest income quartiles discontinued LLT to a lower extent.

According to earlier research on adherence patterns, major predictors of poor adherence are depression, cognitive impairment, treatment of asymptomatic disease, inadequate follow-up, side effects, lack of belief, lack of insight into

the illness, poor provider-patient relationship, barriers to care or medication, missed appointments, complexity of treatment, and cost.¹¹⁹ Many of these predictors could also be interlaced with socioeconomic status, such as low health literacy, even though education did not have an impact on adherence in our study. The association between young age and low adherence of treatment as seen in **study IV** could also be explained by some of the factors mentioned above and maybe indicate that young people have a sense of being invulnerable as long as there are no symptoms of deteriorated health. In a systematic review and meta-analysis,¹³⁵ Mann and colleagues showed an age-inverted U-shaped relationship between age and adherence, with highest adherence at 50-65 years of age. This age range includes the patients in the highest age quartile in our study, who also had the highest level of adherence.

Areas for improvement in lipid-lowering therapy

Today, there is strong scientific support that we can prevent or delay cardiovascular complications in type 1 diabetes by adequately addressing and treating risk factors that affect the small and large vessels in the body.^{34,44,197} Contemporary data show that onset of type 1 diabetes at a young age is an important predictor for future risk of CVD²⁹. Hence, greater focus on primary prevention for atherosclerotic CVD might be warranted for those with early onset of the disease.

Dyslipidemia is an important contributor to the enhanced risk of premature atherosclerosis and CVD that individuals with type 1 diabetes encounter.^{30,74,198-200} Even when lipid profile measurements show values within the normal range, lipid particles can still be abnormal in several ways in the diabetes setting.⁷²

According to international as well as Swedish national guidelines on primary prevention of CVD, lipid-lowering medications can still be underused in patients with type 1 diabetes.^{145,201} The Swedish Board of Health and Welfare recommends that treatment decisions in individuals with type 1 diabetes are based on risk estimation.²⁰² It is then important to take into account that patients with type 1 diabetes are usually young with a low 10-year risk compared to other patients evaluated for preventive treatment, but still have a high lifetime risk for CVD due to a long diabetes duration.

Also, if we want to improve adherence and persistence to LLT, as well as adherence to other recommendations that we want to infer for improved health, we have a responsibility as prescribers and caregivers to address the barriers of adherence. According to guidelines, it is important to identify low or no adherence by monitoring lipid variables regularly at clinical visits, discuss reasons for this, and find solutions together with the patient.^{95,114} It has been recognized that health care professionals are important co-actors in the low adherence estimates that are achieved for LLT. In one study,²⁰³ it was found that over 80% of statin discontinuations by health care practitioners were due to adverse reactions classified as not serious.

Methodological considerations: benefits and disadvantages

The studies included in this thesis are all observational cohort studies. In an observational study, the exposure we want to assess has already been assigned to the individuals included in the study and the researcher cannot, for example, control who receives or does not receive treatment with a certain drug. This demands considerations in the statistical analysis because the groups that are being compared may differ in several ways in addition to exposure, which may affect the results.

In a randomized controlled trial, the exposure is assigned randomly between participants, which gives the opportunity to compare exposed and unexposed populations that are alike in all other aspects. If a randomized clinical trial is performed correctly and in a large enough sample (strength), it renders a high *internal validity* to the study, i.e. the study results in that particular group of participants have high credibility. This is why a randomized clinical trial ranks higher than an observational study when it comes to drawing causal conclusions.²⁰⁴

An observational study can, on the other hand, if properly managed, reflect the clinical reality outside of the research protocol and thus contribute to a high *external validity*, that is the results can be applied to a larger proportion of the population about which you wish to draw a conclusion.²⁰⁵ However, to be able to draw such a conclusion, it is important to address the challenges that come

with an observational study, i.e. random and systematic errors. The STROBE (Strengthening the Reporting in Observational studies in Epidemiology) statement initiative provides recommendations and a checklist on how to report observational research and make it easier to assess the strengths and weaknesses of the studies reported in the medical literature.²⁰⁶

Random errors

In all measurements, there is random variability and this could lead to findings that are merely due to chance. There are two main statistical analyses to assess the role of chance in the results obtained:

- 1) To calculate the probability (p) value, which is the probability of achieving a test result at least as extreme as the observed result, assuming that the null hypothesis is correct. The null hypothesis is the hypothesis that there is no difference, for example when comparing treated and untreated. A p-value of <0.05 is often used as a threshold for rejection of the null hypothesis. This means that the probability of finding a difference, even when there is none, is 5%;
- 2) To estimate CI where the width of the interval reflects the statistical variability around a point estimate.¹⁵⁵ The most commonly used CI is 95% which means that we can be 95% confident that the CI includes the true mean.

One of the strengths of the studies included in this thesis is the large number of individuals participating and the quantity of events. This reduces the risk of random errors. However, in observational studies, a large number of statistical hypothesis tests are often performed, all with a nominal significance level of 5%. The large number of tests means that the probability of rejecting at least one true null hypothesis is far greater than 5% and the interpretation of the results should therefore be based on the overall results rather than the outcome for individual tests.

Systematic errors

Systematic errors, also referred to as bias, are not affected by the size of the study and can distort the results unless taken care of. Systematic errors are usually divided into three categories; selection bias, information bias, and confounding, but they are often interlaced with each other.¹⁵⁵

Selection bias. There are several types of selection bias but they all refer to the selection of the participants in a study. Selection bias can, to some extent, be controlled by the selection criteria for those included. If there are many criteria excluding participants in a study, the sample size will shrink and the sample will become less representative of the population about which you want to draw conclusions, i.e. the external validity will decrease. One of the strengths with the studies in this thesis is that the NDR has high coverage where >95% of adults with type 1 diabetes in Sweden and 100% of outpatient diabetes clinics are represented in the register. This reduces the risk of selection bias when drawing conclusions about this specific population, but it does not eliminate the risk.

In **study I**, only those with measured lipid values during the inclusion period were eligible for the study and, in **studies I and IV**, the regression models included only complete case data sets. Hence, only those with complete records of variables were included in the analysis. If the missing variables were not entirely random, and related to the unobserved variable and the available data, this could introduce a selection bias. If not, it will only affect the power of the study. Other ways of handling missing variables will be further discussed below.

In **studies III and IV**, patients were excluded if they died during the first 18-month exposure assessment period, as it would not have been feasible to investigate risk of CVD and death in people who were not alive in **study III**. However, people who had a cardiovascular event during this assessment period remained in the study, without counting the events, since excluding them would have been to exclude those with the highest baseline risk and with the largest benefit from treatment; this would instead infer a selection bias in the cohort that was being assessed. However, a sensitivity analysis including only

those with no event during the exposure assessment period showed only marginal effects on the estimates.

Indication bias is a subgroup of selection bias. This happens when factors that influence the treatment a patient is prescribed also influence outcome. This can lead to *confounding by indication* if the predictors for the outcome are unevenly distributed between the compared groups¹⁵⁶. The concept of confounding and how to handle it is discussed below.

One type of indication bias is the *reverse causality*, i.e. when the treatment seems to have caused the outcome that we evaluate.¹⁵⁶ This can arise when early manifestations of the outcome influence the selection of medication. In **study III**, we had a lag time between the introduction of LLT and the start of follow-up for outcome events to minimize this, but reverse causality cannot be ruled out as one of the possible reasons for the finding of a non-significant association between LLT and cardiovascular death.

Information bias happens when information is measured, collected, or interpreted improperly and the errors are distributed unevenly between compared groups. Information bias can be broken down into two types, *differential* and *non-differential misclassification*.¹⁵⁶ Non-differential misclassification happens when the information is incorrect, but it is incorrect in all of the groups that are being compared and, hence, does not lead to a bias. Differential misclassification happens when the information errors differ between compared groups and can then lead to under- or overestimating an effect when comparing them.

The data utilized in the studies in this thesis stem from registries and there is a risk that some variables could be incorrectly reported. However, they are mostly characterized as non-differential misclassification, i.e. there are likely to be about the same amount of misclassifications in all of the groups we compare, which is facilitated by the large number of participants in each study. The data reported to the NDR from outpatient clinics are transferred electronically directly from records in about 60% of cases. The validation of transferred data already starts when the data are transferred to the registry. Examples of validation rules include controlling of PIN against the population registry and controlling whether the data transferred are reasonable.

Missing data can be categorized as a sort of information bias and can also introduce a selection bias depending on how the missing data are handled.²⁰⁸ Missing data can reduce power and affect the precision of CIs estimated in the analysis and also lead to a biased estimate of the result of the analysis. How to handle missing data depends on the degree of missing data, and the mechanisms and patterns behind this. Missing data can be divided into three different categories depending on the reason.²⁰⁷ *Missing completely at random* is when there are no systematic differences between the missing values and the observed values, i.e. non-differential. *Missing at random* is when a systematic difference between the missing variables and the observed variables can be explained by a difference in the observed data. *Missing not at random* is when the systematic difference remains after taking the observed data into account.

In **studies I and IV**, we used complete case data sets for the regression analyses, excluding those with missing data, leading to reduced power with fewer participants in the analyses. In **study I**, this is reflected as relatively wide CIs, especially when analyzing the octiles of lipid variables in each subgroup, but still with enough power to draw conclusions. In **study I**, we have no reason to believe that the missing data would affect the inference of the data. In **study IV**, we also only analyzed complete data sets in the logistic regression models where the models were adjusted for age, gender, all socioeconomic variables, and previous CVD since these variables were appreciated as the most important available confounders considering the research question. We had almost complete data for these variables. However, we did not adjust for smoking and physical activity, two variables with a considerable degree of missing data in the registry (about 20% and 33% missing data, respectively). These are variables that could count as important proxies for healthy behavior. This might affect both the predictor and the outcome. However, when adding those two variables to the analysis, the point estimates were only marginally affected, but the variability became wider due to the smaller sample.

In **studies II and III**, the missing data were handled by means of multiple imputations, described under Statistical methods.¹⁵⁹ Multiple imputation has emerged as the preferred way to handle missing data in biostatistics and is said to perform better than analyzing complete case data sets. However, it is still a form of qualified guessing of what a variable would be when modelling against

the other variables in the dataset. Moreover, it does not, and cannot, take unmeasured variables into account in the estimation.

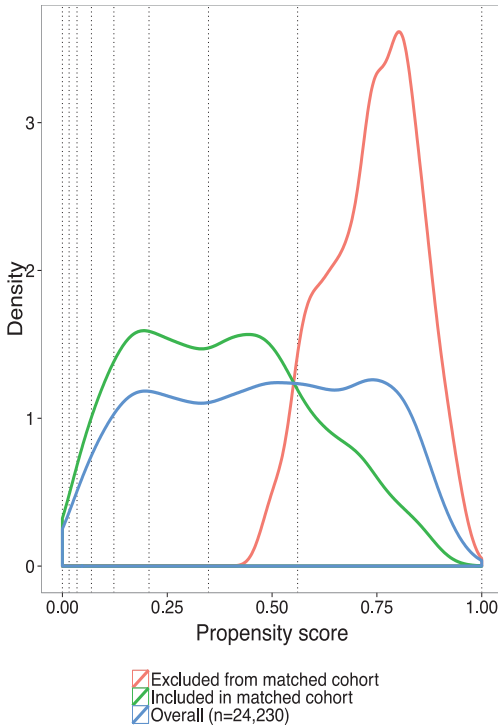
Reporting to the LISA database is mandatory; hence, there are very few missing data for socioeconomic variables among those used in **studies II-IV**. The data reported in LISA have been rated correct with a high degree of accuracy.¹⁵⁰ Also, reporting to the NPR and Cause of Death Register is mandatory and the accuracy of CVDs in these registries have been validated as reasonably good, around 95% for myocardial infarction and stroke.^{147,148} For heart failure, 80% of the diagnoses have been validated as correct.¹⁴⁶

Confounding can be defined as the confusion of effects. A confounder is a variable that influences both the independent and the dependent variable and, as such, can cause associations that are not true.¹⁵⁵ Confounding happens when independent variables (or predictors) are unevenly distributed between the groups that are being compared. The impact of confounding variables (known or perceived) can be limited by randomization, matching, restriction, or stratification of the participants. Another way is to adjust for the confounding variables in the statistical analyses. Often, several of the methods are used. However, sometimes, there can be unknown or unmeasured factors leading to residual confounding effects. This can only be solved by randomization.

In **study II**, propensity scores were used as a way of dealing with confounding by balancing the baseline variables between the groups and make them comparable. The two different methods of handling propensity score in **study II** gives us answers to different questions. By matching those who are treated with LLT to those untreated but with the same propensity scores, we investigate the treatment effect in those already treated (average treatment effect in the treated). By stratifying on the propensity score instead, we examine how the effect on the outcome would be if we shifted the whole cohort from being untreated to being treated (average treatment effect). Emphasis has been placed on the stratified analysis because it explores our main research question, i.e. the benefit of prescribing LLT to those who are not already treated. In the matched analysis, we only had a statistically significant association between LLT and all-cause death, with a 30% risk reduction. We believe that the reason for this is a selection bias where the majority of the patients who were excluded belonged to the proportion of patients with very

high propensity scores, i.e. those with a high baseline risk that would certainly benefit from LLT. This is illustrated in Fig.7.

Fig.7. Distributions of propensity score in the overall cohort (blue), the matched cohort (green) and among persons on lipid-lowering treatment that were excluded from the matched cohort (red). Note that excluded and included only includes persons on lipid-lowering treatment.



In all the studies in this thesis (**studies I-IV**), we had access to extensive information about patient characteristics, with information on important cardiovascular risk factors, laboratory parameters, socioeconomic factors, comorbidities, concurrent medication, and complications. This is a major strength. However, there are also things we do not know about the participants included, for example family history of premature CVD, the occurrence of traits such as depression or cognitive dysfunction, alcohol consumption, or other unhealthy or healthy behaviors. Information about these potential confounders could have influenced the assessments of adherence behavior in **studies III-IV** as well as the outcomes in **studies I-III**, but we believe that

inclusion of these confounders would have changed the results only marginally.

Other considerations

The time period of 18 months for assessment of MPR and discontinuation rate in **study III** (36 months in **study IV**) and six possible prescription refills during this period within the Swedish reimbursement system is a strength since it has been recommended to have at least three prescription refills for the expected medication supply to allow for a meaningful estimation.²⁰⁸

In **studies III and IV**, we investigated adherence and persistence to a defined treatment (LLT). An important strength of these studies is that we measured prescription refill adherence which gives a reasonable assessment of adherence behavior in real life as it is not altered by the patient knowing that adherence is measured, as opposed to studies of self-reports, pill counts, or being included in a clinical trial.¹¹⁹ On the other hand, there are also important potential confounders for which we have not been able to adjust. One is the fact that we do not have clinical information in our data on whether treatment was terminated by the prescribing physician for completely adequate reasons. We do not have information on adverse reactions or unwarranted side effects perceived by the patient or documented by the physician. Unwarranted side effects are one of the most common reasons for non-persistence. Side effects accounted for 60% of discontinuation in one large survey.¹³⁸

Finally, all our studies include adult participants with a wide age range from 18 years up to 79 years in **study I** and with no upper age limit in **studies II-IV**. Hence, we cover a broad spectrum of individuals with type 1 diabetes, which is a strength, but also a challenge. For example, the baseline risk of the participants differ depending on age when interpreting results on cardiovascular outcomes. Another example is in **study IV** where we assessed adherence and persistence as an outcome of several sociodemographic parameters in adult participants of all ages. Investigating socioeconomic characteristics in such a broad group is a challenge since many are in a transitional phase in life, e.g. changes in educational, work, or marital status. On the other hand, if we had only analyzed participants between 35 and 60 years of age, there are other considerations, such as the emergence of long-

term diabetic complications making it more difficult to analyze the influence of merely socioeconomic parameters.

6 CONCLUSION

The present thesis covers different research angles with respect to dyslipidemia in individuals with type 1 diabetes, one of the major modifiable risk factors for CVD.

Observational studies have been recognized as an important complement to randomized controlled trials when evaluating interventions and treatments in life outside of study protocols. The Swedish NDR is a nationwide registry with an almost complete coverage of the Swedish population with type 1 diabetes. The NDR not only serves as a feedback tool improving daily clinical work, but also, when linking to other nationwide registries, renders the opportunity to follow the effects of treatments and implementation of clinical guidelines in real life.

When drawing conclusions regarding the results obtained from the studies included in this thesis, several improvements have emerged regarding assessment and treatment of dyslipidemia in type 1 diabetes in clinical practice.

LDL-cholesterol was not the best marker for CVD in type 1 diabetes and, since our study was performed, many guidelines have excluded a defined level of LDL-cholesterol as the primary reason for initiating treatment of dyslipidemia, unless it is very high at baseline.

In patients with type 1 diabetes, mean age 39 years, and no history of CVD, LLT was associated with a 22-44% reduction in the risk of CVD and cardiovascular death, confirming the effects of LLT seen in randomized controlled trials. Hence, primary prevention with LLT is important if we aim to reduce the risk of CVD and lessen the difference in life expectancy between individuals with type 1 diabetes and the background population.

On the other hand, we were able to show a high discontinuation rate from LLT and, that those discontinuing their LLT within 18 months of starting treatment, had a 43% higher risk for a non-fatal cardiovascular event in the following mean 3.6 years. This reflects the importance of adherence to LLT once initiated. The individuals with high adherence to LLT, taking their tablets more

than 8 out of 10 days, also showed a 21% lower risk for non-fatal CVD compared to those with lower adherence. The reasons for low adherence and premature discontinuation of LLT is, of course, multifaceted. However, we could show that adherence and discontinuation might be negatively influenced by lower age, lower income, marital status (being divorced or single), and being born in a country other than Sweden, although educational level did not have an impact on adherence measures. These factors can be important to keep in mind when evaluating adherence in clinical practice.

In the Swedish national guidelines for treating dyslipidemia in diabetes, it is recommended that patients with high or very high risk for a cardiovascular event should be offered statin treatment, with a dose intensity depending on level of risk. LDL-cholesterol measurement is recommended to be used primarily as a basis for discussion on adherence. These observational studies emphasize the importance of regularly assessing and treating dyslipidemia in individuals with type 1 diabetes in order to achieve optimal cardioprotective treatment and lessen the cardiovascular burden in the population with type 1 diabetes.

7 FUTURE PERSPECTIVES

Almost 100 years have passed since the first insulin injection was given to the first patient with type 1 diabetes. Since 1922 we can treat the trait, but there is still no cure for the disease. In anticipation of a definite cure, the risk of long-term complications as a consequence of living with the disease, must be addressed.

More than 100 years have also passed since Dr Anitschkow did his groundbreaking trials elucidating the role of cholesterol in the pathogenesis of atherosclerosis. Atherosclerosis is no longer considered an inevitable effect of aging and research has given us insights in how to prevent and treat the consequences of the trait. Even so, we have not been able to prevent the development of atherosclerosis in itself and cardiovascular disease remain the leading cause of premature morbidity and mortality in individuals with type 1 diabetes.

The causal link between LDL cholesterol and the initiation of the atherosclerosis process is now well established by epidemiological, experimental and genetic research. Mendelian randomization studies have shown the impact of long-term cumulative exposure of arteries to LDL cholesterol. The benefits of earlier intervention was also recently presented in a comprehensive review showing that initiating treatment of dyslipidemia at a younger age may further reduce the risk of myocardial infarctions and stroke later in life.²⁰⁹ In the future earlier interventions might prove more effective than initiating treatment when the cardiovascular manifestations are already present. This is even more essential to individuals with type 1 diabetes mellitus, due to their increased risk of premature development of atherosclerosis.

When individuals were included in **study I** (2003-2006), only 40% of those >40 years of age and with at least one more risk factor received treatment for dyslipidemia. In the annual NDR report from 2018, >60% of the type 1 diabetes population >40 years of age were documented as receiving LLT. This is a step in the right direction. However, receiving a prescription of lipid-lowering treatment does not necessarily mean that the prescribed medication will be ingested. From a future perspective, and in order to increase adherence,

it is important to convey our knowledge on the best available evidence of the treatments that we recommend, and to deal with concerns and expectations from the patients.

Other risk factors contributing to the progress of atherosclerosis must of course also be addressed in order to stifle the development of vascular disease. Besides optimizing glycemic control, the importance of adopting a healthy lifestyle early in life must be conveyed, i.e. to stick to a healthy diet, stay physically active and avoid the use of tobacco. These are all important modifiable risk factors for atherosclerosis and cardiovascular disease, but harder to implement than saying.

As for treating dyslipidemia, statins are by far the most investigated and documented treatment, and are also believed to positively affect vessels beyond their LDL-cholesterol-lowering effects.⁶⁷ Having said that, new treatments need to be explored and will probably play an important role in the near future for the prevention of atherosclerotic disease development and treatment of CVD risk.²¹⁰ Apart from non-statin LDL-lowering agents that are already on the market, such as PCSK-9 inhibitors and ezetimibe, there are several compounds at different developmental stages in trials for treatment of different aspects of dyslipidemia,²¹¹⁻²¹³

Hopefully this thesis will contribute to a greater attention towards the need for taking action against cardiovascular risk factors in general, and dyslipidemia in particular, and that our efforts in the near future will close the gap of reduced longevity between individuals with type 1 diabetes and the general population.

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APPENDIX

