# Adherence to lipid-lowering medications and cardiovascular disease prevention in type 2 diabetes mellitus

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*To my mother, Carola*

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## ABSTRACT

**Background and aims:** Globally, cardiovascular disease (CVD) is the major cause of death among patients with type 2 diabetes mellitus (T2DM). Improved control of LDL cholesterol with lipid-lowering medications and patients' adherence to such medications have been shown associate with lower risk of CV events and mortality among T2DM patients. The impact of healthcare providers' adherence to guidelines regarding prescription for lipid-lowering medications is unclear. This thesis aimed to assess and compare i) patients' adherence to lipid-lowering medications, ii) healthcare providers' adherence to lipid-lowering prescription guidelines, and iii) risk of CV events and mortality in relation to patients' adherence to lipid-lowering medication and healthcare providers' guideline adherence among patients with T2DM.

**Patients and methods:** This thesis is based on four observational studies where individualized data were linked between Swedish National Registers. All studies included data about patients with T2DM of at least 18 years of age. To assess patients' adherence, our studies used information about new users of lipid-lowering medications from pharmacy claims data in the Swedish Prescribed Drug Register. Using data from the Swedish National Diabetes Register, guideline adherence was assessed for healthcare providers who treated patients with T2DM and LDL cholesterol above the recommended target values. We used information about cause of death and completed admissions of in and out-patients care to analyze risk of CV events and mortality, adjusted for sex, age, socioeconomic status, and concurrent medications as well as health-related and clinical characteristics.

**Results:** On average, patients' adherence to lipid-lowering medications was higher among secondary prevention patients, smokers and those with concurrent cardioprotective medications, compared to lower adherence among patients born outside of Sweden. Healthcare providers' adherence to lipid-lowering prescription guidelines was higher among patients attributed to secondary prevention and the odds of receiving a prescription associated with patients' individual risk of CV events. Adjusted for potential confounders, risk of CV events was higher among patients with less than complete adherence to lipid-lowering medications and that risk gradually increased as patient adherence declined, independent of prevention group. Healthcare providers' adherence to guidelines had little or no impact on patients' risk of CV events and mortality.

**Conclusions:** Patients' adherence to lipid-lowering medications among patients with T2DM had greater impact on risk of CV events and mortality compared to healthcare providers' adherence to prescription guidelines for such medications. This thesis emphasizes the value of individualized diabetes care among T2DM patients.

**Keywords**: medication adherence, refill adherence, medication persistence, pharmacoepidemiology, lipid-lowering medications, type 2 diabetes mellitus, cardiovascular disease, all-cause mortality, cardiovascular mortality, guideline adherence

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# POPULÄRVETENSKAPLIG SAMMANFATTNING

Hjärt-kärlsjukdomar är den främsta dödsorsaken hos patienter med typ 2-diabetes. Förbättrad kontroll av patientens kolesterolvärden med hjälp av kolesterolsänkande läkemedel och patientens följsamhet till denna behandlingen har visats reducera risken för så väl hjärtinfarkt och stroke som död. Huruvida risken för hjärt-kärlhändelser och död påverkas av den behandlade vårdgivarens följsamhet till de nationella riktlinjerna vad gäller förskrivning av kolesterolsänkande läkemedel är oklart.

Det övergripande syftet med denna avhandling var att undersöka om, och hur, risken för hjärt-kärlsjukdom och död påverkas av patientens följsamhet till kolesterolsänkande läkemedel och den behandlande vårdgivarens följsamhet till förskrivning av sådana läkemedel hos patienter med typ 2-diabetes.

Avhandlingen baseras på observationsstudier där data från vuxna patienter med typ 2-diabetes har länkats mellan flera nationella register. Patienter med tidigare hjärt-kärlsjukdom ansågs använda kolesterolsänkande läkemedel för sekundärprevention, resterande patienter ansågs använda primärprevention. Patientens följsamhet beräknades med hjälp av information om uthämtade läkemedel från Läkemedelsregistret. Vårdgivarens följsamhet representerade förskrivningen av kolesterolsterolsänkande läkemedel till patienter med typ 2-diabetes och högt LDL-kolesterol.

Vi fann att patienter med kolesterolsänkande sekundärprevention, rökare och de med uttag av blodtryckssänkande och blodförtunnande läkemedel hade en högre följsamhet till sin kolesterolsänkande behandling. Lägre följsamhet observerades främst bland patienter födda utanför Sverige. Vårdgivarnas följsamhet till kolesterolsänkande riktlinjer var även den högre bland patienter med sekundärprevention och vid samtidig förskrivning av diabetesmediciner samt blodtryckssänkande och blodförtunnande läkemedel. Vi fann även att risken för hjärt-kärlshändelser ökade med avtagande patientföljsamhet i båda preventionsgrupperna. Vårdgivarnas följsamhet påverkade risken för kardiovaskulära händelser och död i låg utsträckning.

Denna avhandling belyser värdet av individualiserad diabetesvård för patienter med typ 2-diabetes.

# LIST OF PAPERS

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

I. Karlsson SA, Hero C, Eliasson B, Franzén S, Svensson AM, Miftaraj M, Gudbjörnsdottir S, Eeg-Olofsson K, Andersson Sundell K. Refill adherence and persistence to lipid-lowering medicines in patients with type 2 diabetes: A nation-wide register-based study. Pharmacoepidemiology and Drug Safety 2017; 26(10): 1220-1232.

II. Karlsson SA, Hero C, Svensson AM, Franzén S, Miftaraj M, Gudbjörnsdottir S, Eeg-Olofsson K, Eliasson B, Andersson Sundell K. Association between refill adherence to lipid-lowering medications and the risk of cardiovascular disease and mortality in Swedish patients with type 2 diabetes mellitus: a nationwide cohort study. BMJ Open 2018; 8(3): e020309

III. Karlsson SA, Franzén S, Svensson AM, Miftaraj M, Eliasson B, Andersson Sundell K. Prescription of lipid-lowering medications for patients with type 2 diabetes mellitus and risk-associated LDL cholesterol: a nationwide study of guideline *adherence from the Swedish National Diabetes Register*. Submitted.

IV. Karlsson SA, Eliasson, B, Franzén S, Miftaraj M, Svensson AM, Andersson Sundell K. Associations between patients' and healthcare providers' adherence to lipid-lowering medications and risk of cardiovascular events and mortality in patients with type 2 diabetes mellitus in Sweden. Manuscript.

# CONTENT

# ABBREVIATIONS

| | |
|---|---|
| **ATC** | Anatomical Therapeutic Chemical Classification System |
| **BMI** | Body Mass Index |
| **CABG** | Coronary Artery Bypass Grafting |
| **CI** | Confidence interval |
| **CMA** | Continuous measure of medication acquisition |
| **CMG** | Continuous measure of medication gaps |
| **CV** | Cardiovascular |
| **CVD** | Cardiovascular disease |
| **DM** | Diabetes mellitus |
| **eGFR** | Estimated glomerular filtration rate |
| **HbA1c** | Glycated hemoglobin |
| **HDL-C** | High-density lipoprotein cholesterol |
| **HR** | Hazard ratio |
| **ICD** | International Classification of Diseases |
| **ICD-O** | International Classification of Diseases for Oncology |
| **IQR** | Inter quartile range |
| **ISCO** | International System for Classification of Occupations |
| **KM** | Kaplan-Meier (survival curves) |
| **LDL-C** | Low-density lipoprotein cholesterol |
| **LISA** | Longitudinal Integration Database for Health Insurance and Labour Market Studies |
| **MEMS** | Medication Event Monitoring Systems |
| **MICE** | Multivariate Imputations of Chained Equations |
| **MPR** | Medication possession ratio |
| **NDR** | Swedish National Diabetes Register |
| **OR** | Odds ratio |
| **PA** | Physical activity |
| **PCI** | Percutaneous Coronary Intervention |
| **PDC** | Proportion of days covered |
| **PIN** | Personal identity number |
| **SD** | Standard deviation |
| **SPDR** | Swedish Prescribed Drug Register |
| **T2DM** | Type 2 diabetes mellitus |
| **WHO** | World Health Organization |

# DEFINITIONS IN SHORT

| | |
|---|---|
| **Adherence** | The extent to which a person acts in accordance to agreed recommendations |
| **Anatomical Therapeutic Chemical Classification System** | System used for classification of active substances according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties |
| **Cardioprotective medications** | Medications used for prevention of CVD (e.g., antihypertensives, anticoagulants, lipid-lowering medications, etc.) |
| **Guideline adherence** | Healthcare providers' adherence to recommended clinical practice guidelines |
| **Multidose dispensed medications** | Sachets in which medications are dispensed according to the intended time of administration |
| **Over-the-counter medications** | Medications sold without prescription |
| **Pill-count medication adherence** | Medication adherence measured by counting number of pills and compare with prescription instructions |
| **Refill adherence** | Measuring patient adherence using data from pharmacy claims |

# 1 INTRODUCTION

## 1.1 Adherence

### *1.1.1 Medication adherence*

The extent to which a patient follows agreed recommendations from a healthcare provider is referred to as medication adherence [1]. Within healthcare, the importance of bilateral communication between healthcare providers and patients is emphasized as they seek the most appropriate treatment. Adherence should be differentiated from compliance, which refer to how well a patient follows recommendations from a healthcare provider, and suggests a one-sided communication, wherein the healthcare provider decides on a treatment and the patients is assumed to comply. In this context, noncompliance may interpreted as a patient's incompetence to follow instructions [2]. Adherence implies that a patient is free to decide whether to adhere to the treatment.

We currently lack uniformity standards to define medication adherence, although several have been proposed [3-5]. In 2009, the European Society for Patient Adherence, Compliance and Persistence suggested that medication adherence includes initiation, implementation, discontinuation, and persistence to treatment [4]. In this thesis, initiation refers to patients' action of taking their first daily dose of a filled prescription. Implementation represent the proportion of time that patients have medications available during the study period. Discontinuation occurs when patients prematurely stop taking their medications, and persistence refers to the time between initiation and discontinuation of treatment. Patients who never fill their initial prescription are considered primary nonadherent to treatment.

### *1.1.2 Assessing medication adherence*

The most accurate measure of medication adherence involves patients' actual behavior (e.g., ingestion of medications). Because studying such ingestion is difficult, several proxies for direct and indirect measures of patient adherence have been proposed [6]. Measuring substance concentrations in bodily fluids is a direct assessment of medication use. However, this time-consuming

method may overestimate medication adherence if nonadherent patients initiate medications immediately before measurement and then revert to nonadherence.

Indirect measures of adherence include self-reporting (e.g., questionnaires, interviews, diaries, etc.); electronic monitoring using medication event monitoring systems (MEMS); and use of register data (e.g., prescription databases, pharmacy claims databases, etc.) [7]. Self-reporting is susceptible to recall bias, especially if previous medication use occurred several years ago. In MEMS, the bottle cap records each time the medication container is opened and closed, but it does not measure whether the patient actually removes pills from the bottle.

Register data from prescription or pharmacy-claims databases measure patient adherence retrospectively, without the influence of recall bias. However, data on issued prescriptions tend to overestimate adherence because patients do not always fill their prescriptions. Measuring patient adherence using pharmacy-claims data (i.e., refill adherence) correlates to other adherence measures in varying degrees; pill count medication adherence showing highest concordance [6, 8-11]. However, refill adherence cannot assure patients' ingestion of the medications.

Several methods can assess the different aspects of medication use, such as days with or without medications available as well as time of continuous use [6, 8]. The medication possession ratio (MPR), proportion of days covered (PDC), and continuous measure of medication acquisition (CMA) share the ability to measure medication availability [8]. MPR represents the ratio between number of days with medication available and the number of observation days. PDC measures the proportion of days with medication available during the observation period and truncates the total supply to 100% to deal with medication oversupplies. CMA measures adherence during a cumulative period of time. These measures provide similar estimates when CMA and MPR do not permit adherence above 100%.

The continuous measure of medication gaps (CMG) identifies total number of treatment gaps during a study period [8]. The maximum gap method identifies smaller gaps between filled prescriptions and provide information about

insufficient medication supplies among patients with less than complete refill adherence [12-14]. Larger gaps are often used to define premature discontinuation of treatment and help to identify patients' persistence to medications [9, 15].

### *1.1.3 Guideline adherence*

Guideline adherence refers to the extent to which healthcare providers adhere to recommended clinical practice guidelines (e.g., interventions and prescription of medications). Such guidelines are based on current research and experience with the aim of reducing practice variations, improve patient outcomes, and provide equal care. Despite efforts in implementing treatment guidelines, the impact on clinical practice varies considerably [16, 17]. In Sweden, the National Board of Health and Welfare provides guidelines on a national level [18]. In addition, first and second-line medication treatments are decided by each county council.

Healthcare providers' adherence to guidelines can be measured using data from prescription or pharmacy claims databases as well as using physicians survey data or medical records [15, 19-22]. Although treatment guidelines are intended to support and provide guidance to those who make decisions about treatment, the complexity of guidelines make it difficult to standardize measures of guideline adherence.

### *1.1.4 Factors influencing adherence*

Many factors influence adherence behaviors among healthcare providers and patients. Sometimes the behavior of one party will affect the adherence in the other or vice versa [23, 24]. For example, a patient's attitude toward following the recommended treatment regimen will affect a healthcare provider's prescription for treatment. Furthermore, a healthcare provider's attitude toward the recommended treatment regimen may affect a patient's willingness to adhere to the prescribed treatment [23]. Moreover, healthcare providers who delay the prescription process may affect patients' awareness of recommended treatment or leave patients without available medications and thus involuntarily nonadherent.

Cost-related nonadherence may occur when insurance does not cover the medications and a patient's co-payment negatively affects his or her adherence pattern [25-28]. Patients in Sweden pay a maximum cost during a 12-month period for prescribed medications covered by the Swedish Pharmaceutical Benefits Scheme [29]. The maximum cost has increased from 1800 Swedish krona in 1999 to 2250 Swedish krona in 2018 (1 €≈10 Swedish krona).

### *1.1.5 Consequences of nonadherence*

There is always a reason for nonadherence, whether intended or not. Healthcare providers should always consider that failed therapy may be a consequence of poor adherence. Nonadherence among healthcare providers and patients may lead to negative effects on patients' health. For example, low medication adherence to diabetes medications and cardioprotective medications (e.g., antihypertensives, lipid-lowering medication, anticoagulants) has been found associate with higher risk of hospitalization [30-33]. Furthermore, healthcare provider nonadherence implies that a treatment does not correspond with recommended guidelines or that patients do not receive the appropriate treatment, possibly exposing them to unnecessary risk of morbidities.

On one hand, nonadherence among patients and healthcare providers may result in insufficient treatment. On the other hand, nonadherence may be legitimate in case of premature discontinuation resulting from adverse drug reactions. However, dosage adjustments or changing medications may eliminate any adverse drug reaction, whereas lack of adjustment or changes may result in serious morbidity or death.

## 1.2 Type 2 diabetes mellitus

### *1.2.1 Prevalence and incidence*

The global prevalence of diabetes mellitus (DM) is increasing, almost doubling since the 1980s [34]. In 2017, 8.8% of the world population lived with DM; by 2045, that prevalence will increase with 48% [35]. Type 2 diabetes mellitus (T2DM) accounts for around 90% of all individuals living with DM. Although most individuals with T2DM live in low and middle-income countries, the occurrence of T2DM is more prevalent in high-income countries [35].

In Sweden, the prevalence of DM is estimated at approximately 5%, which is reportedly lower compared to most other countries in Europe or the Americas [36]. This means around 450,000 individuals live with T2DM in Sweden [34]. Between 2007 and 2013, the incidence of DM in Sweden remained stable at 4.4 per 1,000; higher incidence was observed among men compared to women [37].

### *1.2.2 Pathophysiology*

T2DM is a chronic and multifactorial disease that arises from pancreatic beta cell failure and decreasing insulin sensitivity in hepatic, skeletal and adipose tissues [38]. Initially, beta cell production of insulin increases to compensate for the decreased insulin sensitivity and to maintain stable blood glucose levels. The progression of beta cell failure eventually results in hyperglycemia and T2DM.

At the onset of T2DM, more than 80% of beta cell function has been lost. Development of T2DM derives from genetic and environmental factors (e.g., obesity and physical inactivity, especially in individuals with genetic susceptibility). Because T2DM may take years to develop, many individuals have T2DM without knowing it.

### *1.2.3 Complications and risk factors*

Individuals with T2DM have an increased risk of developing microvascular and macrovascular complications [39-41]. Microvascular complications arise from lesions in smaller vessels, especially the eyes, kidneys and nerves. Macrovascular complications result from lesions or erosion in larger vessels and include coronary heart disease, stroke, and peripheral vascular disease.

Atherosclerotic plaque erosion is the major underlying cause of cardiovascular disease (CVD). In T2DM, the atherosclerotic process is enhanced due to factors related to hyperglycemia and insulin resistance, and risk of CVD and mortality is higher already in patients with prediabetes (i.e., impaired fasting glucose or impaired glucose tolerance) [42, 43]. Although mortality rates have declined among Swedish T2DM patients, the risk is still higher compared to individuals without DM, and CVD remains the main cause of death [44].

### *1.2.4 Treatment approach*

In 1996, Sweden established its first guidelines for diabetes care to provide equivalent and knowledge-based healthcare to adult patients with DM [45]. Guidelines are updated when new evidence emerges, and as new treatment regimens have become available.

Management of T2DM includes intensive glycemic control, along with treatment of comorbidities and complications to combat the increased risk of CVD. Improved control of low-density lipoprotein cholesterol (LDL-C) with lipid-lowering medications have been shown associate with reduced risk of CVD and mortality in patients with T2DM [46-49].

During the time period of this thesis, Swedish national treatment guidelines for diabetes care recommended prescription for lipid-lowering medications for all patients with T2DM and LDL-C ≥2.5 mmol/l [50]. For T2DM patients with established CVD, the European Society of Cardiology, International Diabetes Federation and the American Diabetes Association recommended lipid-lowering medications to reduce LDL-C below 1.8 mmol/l [51-53].

## 1.3 Lipid-lowering medications

Lipid-lowering medications help to control elevated lipid levels in patients with dyslipidemia, and includes statins, fibrates, bile acid sequestrants, nicotinic acid and derivatives, and other lipid-modifying agents [54]. Statins are the recommended first-line treatment for CVD prevention in the general population and among T2DM patients worldwide. Although statins accounted for more than 95% of all filled prescriptions for lipid-lowering medications in Sweden during the overall study period of this thesis (2006–2016) [55], we did not study statins exclusively. Hence, the term lipid-lowering medications will be used throughout this thesis.

### *1.3.1 Efficacy and effectiveness*

Efficacy refers to the medications capacity to produce an effect, and effectiveness consider the effect of real-world use. Reduction in risk of ischemic heart disease occurs within the first two years after lowering cholesterol; full reduction is achieved within five years [56]. Lowering LDL-C (and total cholesterol) by 0.6 mmol/l has been shown associate with age-

related risk reduction of ischemic heart disease, from 50% reduction at age 40 years to 20% reduction at age 70 years. Lipid-lowering medication use can reduce serum cholesterol by 1.2 mmol/l, and have been shown to effectively reduce the incidence of major coronary events, coronary revascularization, and stroke in randomized controlled studies [57-61] and in clinical practice among patients with T2DM [46-49].

### *1.3.2 Adherence to lipid-lowering medications and cardiovascular disease – what is already known?*

Previous studies have shown healthcare providers' adherence to lipid-lowering medication guidelines as varying in the general population as well as among patients with DM [21, 22, 62-66]. Moreover, patients with T2DM, concurrent prescription for other cardioprotective medication or attributed to secondary prevention were more likely to receive a prescription for lipid-lowering medications.

Several studies show patients with high refill adherence and long persistence to lipid-lowering medications to associate with lower risk of major coronary events, stroke, and mortality both in primary and secondary prevention in the general population as well as among patients with DM and T2DM [32, 67-77]. However, these studies often dichotomously categorize patients as adherent according to a cut-off, most commonly 80% [12, 67, 70], meaning patients with refill adherence above 80% are considered adherent to treatment; all other patients are defined as nonadherent. Consequently, such studies provide no further information about the risk of CVD and mortality among more than these two levels of refill adherence.

Little is known about the impact of healthcare providers' adherence to lipid-lowering prescription guidelines and patients' refill adherence to lipid-lowering medication in regard to risk of CVD and mortality among patients with T2DM.

# 2 AIM

The overall aim of this thesis was to analyze the risk of CV events and mortality in relation to patients' refill adherence and healthcare provider' guideline adherence to lipid-lowering medications among patients with T2DM. Specifically,

- Study I aimed to assess and compare patients' refill adherence and persistence to lipid-lowering medications in T2DM patients by prevention group.

- Study II aimed to analyze the association between patients' refill adherence and persistence to lipid-lowering medications and risk of CV events and mortality in T2DM patients.

- Study III aimed to assess healthcare providers' adherence to guidelines regarding prescription for lipid-lowering medications in patients with T2DM and LDL-C above recommended target values.

- Study IV aimed to analyze the association between patients' refill adherence, healthcare providers' guideline adherence to lipid-lowering medications, and the subsequent risk of CV events and mortality in T2DM patients.

# 3 METHODS

## 3.1 Study design and setting

This thesis consists of four observational studies that linked individualized data between several Swedish national registers (Table 1). Sweden offers a unique opportunity for register studies because of the comprehensive databases of healthcare-related and socioeconomic data administered and validated by the Swedish National Board of Health and Welfare as well as Statistics Sweden. Linkage between registers is possible through the unique personal identity number (PIN) that since 1947 has been assigned at the time of birth or immigration [78]. PINs are assigned to individuals who intend to stay in Sweden for at least one year. Nonpermanent residents receive coordination numbers, similar to the PIN, which can be used for medical care. However, nonpermanent residents are not registered in national health registers and thus not included in national register studies.

## 3.2 Data sources

Using the unique PINs of individuals, we linked data between the

- Swedish National Diabetes Register (NDR),
- Swedish Prescribed Drug Register (SPDR),
- National Patient Register,
- Cause of Death Register,
- Swedish Cancer Registry, and
- Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA).

Swedish law requires healthcare providers to submit data to the National Board of Health and Welfare [79], which administer and validates the SPDR, the National Patient Register, the Cause of Death Register, and the Swedish Cancer Registry. Statistics Sweden administers the LISA database, which consist of compiled data from different registers.

**Table 1.** Methodological Summary

| | Study | | | |
|---|---|---|---|---|
| | **I** | **II** | **III** | **IV** |
| **Data sources** | | | | |
| Swedish National Diabetes Register | ■ | ■ | ■ | ■ |
| Swedish Prescribed Drug Register | ■ | ■ | | ■ |
| National Patient Register | ■ | ■ | | ■ |
| Cause of Death Register | ■ | ■ | | ■ |
| LISA | ■ | ■ | | ■ |
| Swedish Cancer Registry | | | | ■ |
| **Exposure** | | | | |
| Cardiovascular disease | ■ | ■ | ■ | ■ |
| Refill adherence | | ■ | | ■ |
| Persistence | | ■ | | |
| LDL cholesterol | | | ■ | |
| Guideline adherence | | | | ■ |
| **Outcome** | | | | |
| Refill adherence | ■ | | | |
| Persistence | ■ | | | |
| Guideline adherence | | | ■ | |
| Cardiovascular event | | ■ | | ■ |
| Mortality | | ■ | | ■ |
| **Statistical analyses** | | | | |
| Logistic regression | ■ | | | |
| Multivariate linear regression | ■ | | | |
| Cox proportional hazard regression | ■ | ■ | | ■ |
| Survival analysis | ■ | ■ | | ■ |
| Multiple imputations | | ■ | | ■ |
| Mixed-effect model regression | | | ■ | |

LDL, low-density lipoprotein; LISA, longitudinal integration Database for Health Insurance and Labour Market Studies.

### *3.2.1 Swedish National Diabetes Register*

Launched in 1996 by the Swedish Society for Diabetology, the NDR is a national register that serves as a tool for systemically improving the quality of diabetes care [80]. It contains individualized data on patients' clinical characteristics, the presence of complications, and results from laboratory analyses. Although reporting to the NDR is optional, healthcare providers continuously share patient data with the NDR by electronically transferring medical records or visiting the NDR webpage. Estimates suggest that as of today, 100% of specialized care clinics and 95% of primary care clinics report to the NDR.

All patients included in the register, have been informed about the NDR and understand that they will be registered. If a patient does not consent, data from his or her medical records will not be reported to the NDR. In addition, a patient can request withdrawal from the register at a later date, after which his or her data is removed from the NDR. In 2017, estimates suggest that 96.5% of all Swedish DM patients are registered in the NDR [81]. Comparison between the NDR and the SPDR shows 93% conformity regarding T2DM patients treated with medications for diabetes.

### *3.2.2 Swedish Prescribed Drug Register*

Established in July 2005 and administered by the National Corporation of Swedish Pharmacies, data from the SPDR is transferred to the National Board of Health and Welfare, which is responsible for the register [82].

The SPDR contains data on all prescriptions filled at Swedish pharmacies and includes variables representing patient characteristics (e.g., sex, age, place of residency), prescriber characteristics (e.g., profession, specialty, type of care), and dispensed item (date of dispensing, formula, package size, dosage instructions, etc.). All medications are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [54]. The SPDR does not include data about over-the-counter medications or medications distributed at hospitals.

### *3.2.3 National Patient Register*

The National Patient Register was established in 1964 and became nationwide in 1987 [83]. Since 2001, the register has covered both public and private healthcare providers. However, the register does not contain data from primary care clinics. The register contains information about all completed admissions from hospital-based care and specialized outpatient care. Diagnoses are classified according to the International Classification of Diseases (ICD) [84], interventions according to the Swedish classification of healthcare interventions (Swedish: Klassifikation av vårdåtgärder) [85], and surgical procedures according to the Swedish classification of surgical procedures (Swedish: Klassifikation av kirurgiska åtgärder) [86]. Since 2015, data is delivered to the National Board of Health and Welfare once per month.

### 3.2.4 Cause of Death Register

Aiming to follow the development of mortality, Sweden has recorded cause of death since 1961 [87]. Deaths are classified according to the ICD [84]. Until 2011, the Cause of Death Register only included individuals registered as residents in Sweden, independent of place of death. Since 2012, the register has included all deaths occurring in Sweden, independent of the deceased's country of residence.

### 3.2.5 Cancer Registry

Established in 1958, the Swedish Cancer Registry contains all primary tumors as defined by the International Classification for Diseases for Oncology (ICD-O) [88]. The register aims to identify the occurrence of cancer over time.

### 3.2.6 Longitudinal integration database for health insurance and labour market studies

Managed by Statistics Sweden, the LISA database, provides individualized data from several different Swedish registers (e.g., the total population register, income and taxation register, etc.) [89]. Data included represent demography, education, employment status, income, and social insurance as well as information about sickness and parental leaves.

## 3.3 Study population and period

Patients aged at least 18 years and registered with T2DM in the NDR were eligible for inclusion in all four studies in this thesis. To identify T2DM patients, Study I, Study II, and Study III used the epidemiological definition of T2DM and Study IV used the clinical diagnosis.

The epidemiological definition of T2DM has been used in several studies from the NDR, and includes patients who receive treatment with diet and/or glucose-lowering medications other than insulin, or who experienced the onset of diabetes at age ≥40 years and received insulin and/or other glucose-lowering medications [90-92]. The clinical diagnosis of T2DM is based on the criteria of the World Health Organization (WHO) (i.e., fasting glucose of ≥7 mmol/l or 2-hour plasma glucose ≥11 mmol/l) [93]. The epidemiological and the clinical definitions of T2DM are highly concordant.

### 3.3.1 Study I

Study I included data about patients who filled at least one prescription for lipid-lowering medications between January 1, 2007 and December 31, 2010. We excluded patients who filled prescriptions for extemporaneous preparations, bile acid sequestrants, or a combination of lipid-lowering substances and/or strengths, as well as those who received noninterpretable dosage instructions during the study period. The methods section of Paper I defines combination therapy. The index date is the dispensing date of the first filled prescription. We followed patients from the date index date until the first filled prescription for multidose dispensed medications, migration, death, or three years after the index date.

### 3.3.2 Study II

Study II included data about patients who filled at least one prescription for lipid-lowering medications between January 1, 2007 and December 31, 2010. We measured refill adherence during an 18-month exposure period, beginning at the index date. We excluded patients who filled a prescription for bile acid sequestrants, extemporaneous preparations, multidose dispensed medications, or a combination of lipid-lowering substances/strengths during the exposure period, as well as those with noninterpretable dosage instructions at index. Exclusion also applied to patients who migrated, experienced a CV event, or died. For outcome measures, patients were followed from the first day after the exposure period until migration, CV event, death, or December 31, 2013.

### 3.3.3 Study III

Between January 1, 2007 and December 31, 2014, all data about T2DM patients were eligible for inclusion. Entries were included if they contained available information about LDL-C, prescription for lipid-lowering medications, and CVD. Our final analysis included entries with LDL-C above recommended target values (≥2.5 mmol/l for primary prevention and ≥1.8 mmol/l for secondary prevention).

### 3.3.4 Study IV

Study IV included data about patients who filled at least one prescription for lipid-lowering medications (bile acid sequestrants not included) between

July 1, 2006 and December 31, 2012. Patients were excluded if they filled prescriptions for lipid-lowering extemporaneous preparations or a combination of lipid-lowering substances/strengths. We also excluded patients who received noninterpretable dosage instructions for the first filled prescription for lipid-lowering medications.

We followed patients from the first day after their first filled prescription ceased (baseline date) until the first filled prescription for multidose dispensed medications, migration, CV event, death, or December 31, 2016. The study period was divided into intervals of 122 days through 2014, followed by intervals of 365 days through 2016.

## 3.4 Exposures

### *3.4.1 Cardiovascular disease*

Because Studies I–IV considered CVD as an exposure, we separated data about patients who had previously experienced CVD into a group for lipid-lowering secondary prevention. We assigned all other data (i.e. patients with no previous history of CVD) to lipid-lowering primary prevention. Although the definition of CVD encompassed diagnosed unstable angina pectoris, myocardial infarction, ischemic heart disease, and stroke as well as surgical procedures for percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), further definition differed in individual studies. A wider definition of CVD in Study I included heart failure, atrial fibrillation, and peripheral artery disease as well as surgical procedures (e.g., amputation). For ICD and surgical procedure codes, see Table 1, Paper I; Table 1, Paper II; and Table S1, Paper IV.

### *3.4.2 LDL cholesterol*

Study III considered LDL-C as an exposure and data was collected from the NDR. We determined healthcare providers' adherence to guidelines regarding lipid-lowering medications among patients with LDL-C values above the recommended target levels (i.e., 2.5 mmol/l in patients without established CVD and 1.8 mmol/l in patients with established CVD) [50, 94].

### 3.4.3 *Refill adherence and persistence*

Study II and Study IV included refill adherence, and Study II included persistence as exposures for CV events and mortality. We determined refill adherence and persistence using dispensing data from the SPDR, and we designated the dispensing date as the start date of each prescription. We assessed the duration of each prescription by dividing the total number of dispensed tablets by the daily dosage. Thus, we determined the end date of each prescription by adding the duration to the start date (Figure 1). We obtained daily dosage from the free-text variable provided by the prescriber. The algorithm we developed and applied to convert the free-text into a numeric value representing the daily dosage was validated in Study I, Study II and Study IV, respectively, and showed more than 98% concordance in all three studies.

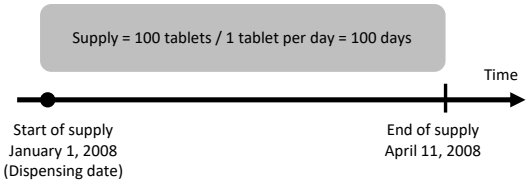



***Figure 1.*** *Assessment of start and end date to each prescription*

We did not assume that patients used overlapping supplies concurrently. In case of overlapping supplies of the same substance and strength, the latter prescription's supply was adjusted forward in time until the preceding supply had ceased (Figure 2A). We deleted any data about remaining supplies that preceded the switch of substance or strength as well as supplies that extended beyond the end of the study period (Figure 2B).

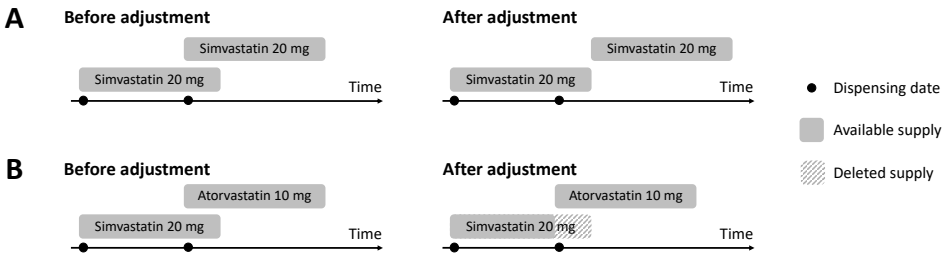



***Figure 2.*** *Example of adjusting for overlapping supplies of A) the same substance and strength, and B) different substances or strengths.*

We assessed refill adherence using the medication possession ratio (MPR), which represented the percentage of days with medications available during the study period. We determined MPR by dividing the number of days with medications available by the total number of observations days. Because we adjusted for overlapping supplies, MPR could not exceed 100%.

Nonadherent patients were identified using the maximum gap method, which identifies smaller gaps between filled prescriptions and provide information about insufficient medication supplies. We considered gaps of at least 45 days, which corresponds to 50% of an average filled supply of lipid-lowering medications in the Swedish setting, between filled supplies as nonadherence to treatment.

Premature discontinuation of treatment was defined as a gap of at least 180 days (corresponds to an average of two filled supplies of lipid-lowering medications in the Swedish setting) between two filled supplies of lipid-lowering medications. Persistence to treatment was measured from the index date until the first occurring discontinuation gap.

Study II assessed MPR and persistence for 18 months (exposure period). MPR was divided into five levels (i.e., 0%–20%, 21%–40%, 41%–60%, 61%–80 and 81%–100%) and patients with a discontinuation gap during the exposure period were classified as nonpersistent. Study IV assessed MPR for each subsequent interval and was categorized as high or low based on an 80% cutoff.

### *3.4.4 Guideline adherence*

Study IV defined exposure to CV events and mortality as healthcare providers' adherence to treatment guidelines (i.e., guideline adherence) regarding prescriptions for lipid-lowering medications in patients with T2DM. Using data from the NDR, we measured guideline adherence as the prevalence of lipid-lowering medication prescription among patients with LDL-C above the recommended targets levels (i.e., ≥2.5 mmol/l for primary prevention and ≥1.8 mmol/l for secondary prevention).

Guideline adherence was assessed for each healthcare provider between 2007 and 2014, and thereafter linked to patients' intervals based on the year in which

the intervals started. For intervals starting in 2006, we used guideline adherence for 2007. If information on guideline adherence was missing, we imputed the adherence of the preceding year. If no preceding guideline adherence was present, we imputed the mean annual guideline adherence from the healthcare provider's county council and type of care. We categorized guideline adherence as high or low based on a cutoff representing the median guideline adherence for primary and secondary prevention (48% and 78%), respectively.

## 3.5 Outcomes

### *3.5.1 Cardiovascular events*

In Study II and Study IV, outcomes of interest encompassed CV events, which included unstable angina pectoris, myocardial infarction (including PCI and CABG), ischemic heart disease, and stroke. Data were collected from the National Patient Register using ICD and surgical procedure codes (Table 1, Paper II and Table S1, Paper IV).

### *3.5.2 Mortality*

We retrieved date and cause of death from the Cause of Death Register and defined all-cause mortality as death due to any cause. CV mortality was defined as death from CVD as the main or contributing cause of death, or registration of a CV event in the National Patient Register within 28 days prior to death.

### *3.5.3 Refill adherence and persistence*

Study I considered refill adherence and persistence as outcomes of interest. Refill adherence was measured using the MPR and the maximum gap method (Section 3.4.3). Persistence represented the time between the index date and the first occurring discontinuation gap (Section 3.4.3).

### *3.5.4 Guideline adherence*

Study III examined prevalence of lipid-lowering medication prescription and defined guideline adherence as the probability of prescribing lipid-lowering medications for patients with T2DM and LDL-C above the recommended

target values. Adjusted for patients' and healthcare providers' characteristics (i.e., risk factors), we presented guideline adherence as crude and adjusted rates. We also presented odds ratios for included risk factors for primary and secondary prevention, respectively.

This measure of guideline adherence differs from that used as an exposure in Study IV (Section 3.4.4). Study IV considered guideline adherence as the prescription prevalence of lipid-lowering medications since the probability of prescription for each healthcare provider and year was not methodological feasible.

## 3.6 Covariates

### *3.6.1 Patient characteristics*

Patient characteristics included demographics (age, sex, country of birth), socioeconomic status (marital status, income, education level, employment status, profession), clinical characteristics (diabetes duration, glycated hemoglobin [HbA1c], estimated glomerular filtration rate [eGFR], blood pressure, cholesterol levels, microalbuminuria, macroalbuminuria, body mass index [BMI], kidney disease, cancer), concurrent medications (diabetes medications, antihypertensives anticoagulants or antiplatelets), and health-related characteristics (smoking, physical activity). Figure 3 shows the data source for each covariate.

We did not link sex and country of birth to calendar time. Age was calculated based on birth year and year of data collection. Marital status was categorized as unmarried, married/registered partner, divorced, and widow/widower. Employment status was collected as a binary variable and was categorized as employed, unemployed, or retired. Retirement described patients who were unemployed and at least 65 years of age.

Professions were defined according to the Swedish Standard Classification of Occupations, which is based on the International Standard Classification of Occupations (ISCO) [89]. We categorized professions as upper white collar, lower white collar, blue collar, and other. Our categorization highly corresponds to the ISCO.

Income was collected as individual and family disposable income as well as disposable income per household member. Individual and family incomes represented the annual income for the individual and family, respectively. The disposable income per household member represented the annual family income divided by weighted units of consumption [89].

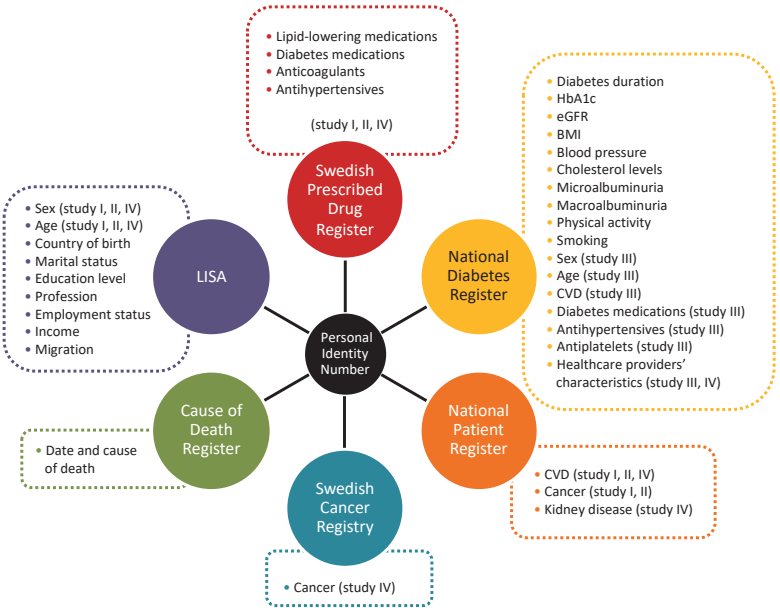



***Figure 3.*** *Variables collected from respective registers*

We calculated diabetes duration based on birth year and year of diabetes diagnosis. eGFR was calculated according to the Modification of Diet in Renal Disease equation, which is based on patient's sex, age, and creatinine level. Microalbuminuria and macroalbuminuria were provided as binary variables. The diagnosis criteria for microalbuminuria was an albumin/creatinine ratio of 3–30 mg/mmol, albumin >200µg/min, or 20-300 mg/l, in two out of three tests within one year. Macroalbuminuria was defined as positive testing for an albumin/creatinine ratio >30 mg/mmol, albumin >200µg/min, or >300 mg/l.

If total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were reported to the NDR concurrently, LDL-C was calculated using the Friedwald equation; otherwise the reported value of LDL-C was used. Smoking was defined as at least one cigarette or pipe per day or stopped smoking within three months. Physical activity was defined as a 30-minute walk (or equivalent) and categorized as less than once a week, 1–2 times per week, 3–5 times per week, or daily.

In Study I and Study II, we collected cancer diagnoses from the National Patient Register and defined cancer as any malignant tumor (ICD codes C00–C97) registered within five years prior to the index date. Study IV collected cancer diagnoses from the Swedish Cancer Registry and defined cancer as any primary tumor (ICD codes C00–C97) registered within five years prior to the baseline date.

Study I, Study II, and Study IV defined concurrent medications as filled prescriptions for diabetes medications (ATC: A10), antihypertensives (ATC: C02, C07, C08, C09) and anticoagulants (ATC: B01), collected from the SPDR. Study III defined concurrent medications as use of diabetes medications (ATC: A10), antihypertensives (ATC: C02, C07, C08, C09) and antiplatelets (ATC: B01AC, N02BA01), as reported in the NDR.

Study IV collected diagnoses of kidney disease from the National Patient Register and defined kidney disease as acute or chronic kidney failure as well as glomerular or renal complications due to T2DM. For ICD codes, see Table S1, Paper IV.

### *3.6.2 Healthcare provider characteristics*

Study III and Study IV used NDR data to determine the characteristics of healthcare providers. We gathered data about healthcare providers at healthcare facility level. Hence, no individual practitioners were identified. Healthcare providers were categorized as primary or specialized care providers, and according to county council.

## 3.7 Statistical methods

### *3.7.1 Statistical methods used in the studies*

Study I analyzed differences in MPR and persistence by prevention group in three models. Model 1 adjusted for age, sex, and socioeconomic status; Model 2 adjusted for age, sex, socioeconomic status, and concurrent medications; and Model 3 adjusted for age, sex, socioeconomic status, concurrent medications, and clinical characteristics. We used multivariable linear regression models to analyze differences in MPR. Risk of discontinuation (i.e., difference in persistence) was analyzed using Cox proportional hazard regression and Kaplan-Meier (KM) survival analysis. Using logistic regression, we analyzed difference in nonadherence by prevention groups according to the maximum gap method.

In Study II, we used Cox proportional hazard regression and KM survival curves to analyze risk of CV event and mortality by five levels of MPR as well as by persistence. We studied data about primary and secondary prevention patients separately, and replaced missing data using multivariate imputations by chained equations (MICE) [94, 95]. Additionally, we compared results from imputed data with results from complete cases.

Study III used mixed-effect model regression to analyze the annual probability of prescribing lipid-lowering medications for T2DM patients with LDL-C exceeding recommended target levels. We also used mixed-effect model regression and odds ratio to assess the odds of prescribing lipid-lowering medications for all patient and healthcare provider characteristics. In the mixed-effect models, prescription for lipid-lowering medications was considered the response, LDL-C and CVD were considered exposures, and the unique person identifier was considered a fixed effect.

Study IV used general linear regression to analyze the association between MPR and guideline adherence. The risk of CV event and mortality was analyzed for each subsequent interval using Cox proportion hazard regression and KM survival curves, adjusted for potential confounders. Covariates and guideline adherence for one interval were considered potential confounders for the subsequent interval of MPR measures. Likewise, MPR for one interval was

considered the exposure for the subsequent interval of outcome measures (Figure S2, Paper IV).

We performed multiple imputations using R version 3.3.2 [96] and the MICE package [94]. All other data management and analyses were performed using SAS software version 9.4 (SAS institute, Cary NC).

### *3.7.2 Logistic and linear regression*

Both logistic and linear regression models measure the association between a dependent variable and one or more categorical and/or continuous independent variables (e.g. sex, physical activity, age, diabetes duration etc.). While the dependent variable in linear regression is continuous (e.g., MPR), logistic regression has a binary dependent variable (e.g., adherent, year or no).

### *3.7.3 Cox Proportional Hazard Regression*

Survival analysis follows individuals to examine time of an event (e.g., disease, death, etc.). Individuals who do not experience the event of interest during the study period are called censored. Reasons for censoring may be due to migration or end of the study. Cox proportional hazard is a regression model that analyzes the association between patients' survival time and several risk factors on survival time. This specific regression model allows us to examine differences in survival between patient groups and for specific risk factors that influence the rate of a particular event happening at a particular point in time.

Hazard function can be interpreted as the risk of an event at a specific time point. Results from the regression model are shown as hazard ratios (HR), which represents the ratio of the hazard for one group compared to another group. HRs above 1 indicates a positive association between a covariate and event probability and thus a negative association with the survival length. The opposite applies to HRs below 1, which indicate a positive association to survival length. HRs equal to 1 indicate no association between covariate and event probability and thus no association with survival length.

### 3.7.4 Kaplan-Meier

The KM survival curves visualize survival of an event over time. Generating KM estimators for different patient categories requires event status (event occurrence or censored), time to event (or time to censoring), and group assignment (e.g., treatment, yes or no). KM estimators can be derived from the Cox proportional hazard regression model and thus provide survival curves adjusted for several risk factors.

### 3.7.5 Mixed-effect models

Mixed-effect models use both fixed and random effects in the same analysis. Thus, such models provide a flexible approach when analyzing data from longitudinal studies with repeated measures per individual as they allow for a variety of correlations patterns.

### 3.7.6 Missing data and multiple imputation

Missing data refers to observations where one or more variables lack information, resulting in incomplete data sets. Multiple imputations involve filling in these missing data according to observed information for the given individual and the relations in data from other individuals in the data set. This technique involves imputing missing values multiple times, analyzing imputed data sets, and pooling of results (Figure 4).

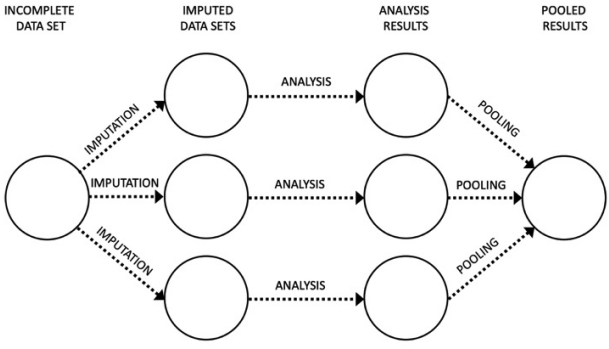



***Figure 4.*** *Multiple imputation process*

MICE is a multiple imputations technique that runs a series of regression models [94, 95]. The variables that is to be imputed is used as a dependent variable; all other covariates are considered independent. Missing values are replaced with predictions (i.e., imputations) from the regression model. When the missing value of one variable has been replaced, that variable is later used as an independent variable in the imputation of another variable. The same procedure is performed for all variables with missing information. When all missing values have been replaced with predictions, one iteration has been performed. Several iterations are performed to allow convergence (i.e. stability) of the distribution of coefficients in the regression models. In this way, the order of imputation is less important. At the end of the iterations, the final predictions are retained, and a complete imputed data set is achieved. The entire imputation process is repeated several times to achieve multiple imputation. The imputed data sets are used in the statistical analysis and results are achieved for each data set. Thereafter, the results are pooled to give a final result.

## 3.8 Ethical considerations

The Regional Ethical Review Board in Gothenburg has approved all studies of this thesis with following reference numbers: 563-12 (Study I), 776-14 (Study II), 1173-16 (Study III), and 312-17 (Study IV).

# 4 RESULTS

## 4.1 Study I

Study I included data about of 97,595 patients, 77% of whom had no established CVD prior to inclusion and thus were assigned to lipid-lowering primary prevention. For patient characteristics, see Table 2, Paper I.

Mean MPR was 71% in the total population, 69% among primary prevention patients and 76% among secondary prevention patients (Table 2, Paper I). The maximum gap method determined that 64% of primary prevention patients and 52% of secondary prevention patients were nonadherent. Around 70% of all patients were persistent for at least one year and around 50% were still filling prescriptions for lipid-lowering medications after three years. Twenty-five per cent of those who discontinued treatment did so within the first year. Thereafter the discontinuation rate decreased to 5% during the third year.

After adjusting for potential confounders, the MPR of secondary prevention patients was 3–6 percentage higher compared to primary prevention patients (Table 3, Paper I). Compared to patients born in Sweden, those who were born if another European country or the Soviet Union, or in Africa or the Americas had between 3 and 12 percentage lower MPR. Compared to patients without diabetes medications, the MPR of those who filled prescription for glucose-lowering medication other than insulin was around 4 percentage higher. Furthermore, MPR was around 4 percentage higher in nonsmoking patients. Although several characteristics showed statistically significant results, we considered differences around 5 percentages as clinically relevant.

In the fully adjusted model, secondary prevention patients showed lower risk of premature discontinuation of treatment (HR=0.91) compared to primary prevention patients (Table 3, Paper I). The pattern of difference in risk of discontinuation was similar to that for difference in MPR. Patients born in another European country or the Soviet Union (HR=1.16–1.25), or Africa (HR=1.64), or the Americas (HR=1.81) all had higher risk of discontinuing treatment. Moreover, patients with glucose-lowering medication other than

insulin (HR=0.84) and nonsmokers (HR=0.82) showed lower risk of discontinuation.

Compared to primary prevention patients, the KM survival curves showed higher persistence rates among secondary prevention patients in all three models (Figure 2, Paper I).

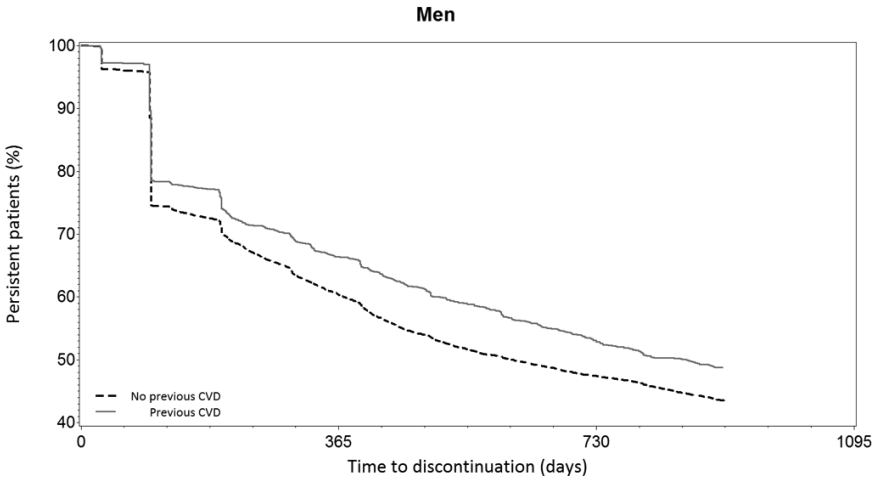
### *4.1.1 Differences between men and women*

Among primary prevention patients, mean MPR was 70% for men and 69% for women (Table 2). The corresponding numbers for secondary prevention patients were 77% for men and 74% for women. The proportion of patients with treatment gaps of at least 45 days was similar within the prevention groups. Among secondary prevention patients, men showed higher persistence to treatment compared to women. Persistence was similar in the primary prevention group. KM survival curves from the fully adjusted model showed higher persistence among male secondary prevention patients, compared to no difference in women's persistence between the prevention groups (Figure 5).

**Table 2**. Refill adherence and persistent by gender in study I

| | **Primary prevention n=75,464** | | **Secondary prevention n=22,131** | |
|---|---|---|---|---|
| | **Men (n=41,931)** | **Women (n=33,533)** | **Men (n=14,465)** | **Women (n=7,666)** |
| **MPR (%)** | *n* (%) | *n* (%) | *n* (%) | *n* (%) |
| ≤20 | 5,114 (12.2) | 4,679 (14.0) | 1,149 (7.9) | 868 (11.3) |
| 21-40 | 4,406 (10.5) | 3,566 (10.6) | 1,118 (7.7) | 685 (8.9) |
| 41-60 | 4,203 (10.0) | 3,167 (9.4) | 1,152 (8.0) | 589 (7.7) |
| 61-80 | 6,176 (14.7) | 4,383 (13.1) | 1,670 (11.6) | 825 (10.8) |
| >80 | 22,032 (52.5) | 17,738 (52.9) | 9,376 (64.8) | 4,699 (61.2) |
| Mean (SD) | 69.6 (30.7) | 68.8 (32.1) | 77.4 (28.4) | 74.3 (31.2) |
| Median (IQR) | 81.9 (---) | 82.2 (---) | 91.4 (---) | 91.1 (---) |
| **Treatment gaps ≥45 days** | | | | |
| Nonadherent | 26,993 (64.4) | 21,244 (63.4) | 7,404 (52.2) | 4,015 (52.3) |
| **Persistence** | | | | |
| One year | 30,424 (72.6) | 24,008 (71.6) | 10,975 (75.9) | 5,335 (69.5) |
| Two years | 25,845 (61.6) | 20,231 (60.6) | 9,180 (63.5) | 4,318 (56.3) |
| Three years | 24,041 (57.3) | 18,790 (56.0) | 8,309 (57.4) | 3,814 (49.8) |
| Mean days (SD) | 761.7 (420.7) | 751.1 (424.1) | 784.5 (403.7) | 717.8 (423.4) |
| Median days | 1,095 (---) | 1,095 (---) | 1,095 (---) | 1,063 (---) |

MPR, medication possession ratio



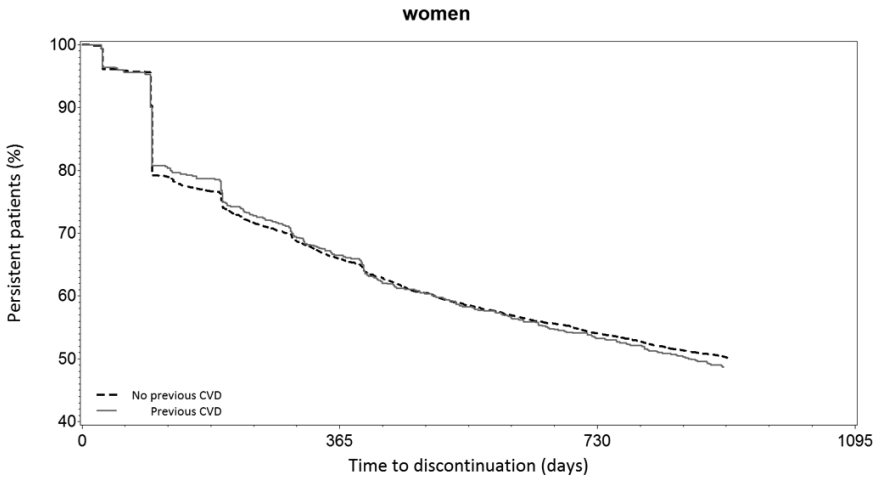




***Figure 5.*** *Kaplan-Meier survival curves for persistence to lipid-lowering medications in T2DM patients by sex and prevention group*

## 4.2 Study II

Study II followed 86,568 patients, of whom 86.5% had initiated lipid-lowering primary prevention at inclusion. For patient characteristics, see Table 2, Paper II. Mean MPR was 77% among primary preventions; 78% were persistent during the 18-month exposure period. Among secondary prevention patients, mean MPR was 83%; 83% were persistent for 18 months.

Compared with patients with MPR >80%, the risk of any CV event gradually increased with lower MPR level, independent of prevention group (Table 3, Paper II). Greatest risk was observed for myocardial infarction. Compared to patients with MPR >80%, the risk of myocardial infarction ranged from 39% to three-folded increased risk among primary prevention patients and between 40% to two-folded increased risk among secondary prevention patients. The risk of all-cause and CV mortality was higher among patients with MPR ≤80%, compared to those with MPR >80%. However, we observed no clear trend between the MPR levels.

Furthermore, risk of CV events and CV mortality was 64% and 15% higher in nonpersistent primary prevention patients compared to persistence patients, respectively (Table 4, Paper II). The corresponding numbers for nonpersistent secondary prevention patients was 33% and 29% higher, respectively.

Adjusted for potential confounders, KM survival curves shows higher survival of any CV event with higher MPR levels in both prevention groups (Figure 2, Paper II). For all-cause mortality, the survival curves were similar between the MPR levels.

### *4.2.1 Differences between men and women*

Both prevention groups showed little difference in mean MPR between the sexes (Table 3). Among primary prevention patients, 6% of men and 4% of women experienced a CV event during the study period, and around 2% of both men and women died. CV mortality accounted for 58% of deaths among men compared to 48% among women. In secondary prevention patients, 40% of men and 49% of women experienced a CV event, 29% of men and 42% of

women died, and CV mortality constituted 33% and 29% of all deaths in men and women, respectively.

**Table 3.** MPR divided by prevention group and sex

| | **Primary prevention n=74,909** | | **Secondary prevention n=11,659** | |
|---|---|---|---|---|
| | **Men n=41 470** | **Women n=33 439** | **Men n=7 676** | **Women n=3 983** |
| **MPR** | n (%) | n (%) | n (%) | n (%) |
| ≤20% | 2,652 (6.4) | 2,232 (6.7) | 378 (4.9) | 220 (5.5) |
| 21–40% | 3,508 (8.5) | 2,660 (8.0) | 417 (5.4) | 249 (6.3) |
| 41–60% | 4,132 (10.2) | 3,259 (9.8) | 539 (7.0) | 331 (8.3) |
| 61–80% | 6,110 (14.7) | 4,469 (13.4) | 884 (11.5) | 459 (11.5) |
| >80% | 24,969 (60.2) | 20,819 (62.3) | 5,458 (71.1) | 2,724 (68.4) |
| Mean (SD) | 77.1 (26.4) | 77.9 (26.8) | 83.2 (24.2) | 81.7 (25.6) |
| Median (IQR) | 89.9 (38.8) | 90.9 (38.0) | 95.8 (27.1) | 95.4 (27.8) |

MPR, medication possession ratio

After adjusting for potential confounders, we noticed a trend of gradually higher risk of any CV event with lower MPR level in both sexes and prevention groups (Tables 4 and 5). However, we observed no statistically significant difference among primary prevention women with MPR 61%–80%. In both prevention groups, the risk of all-cause and CV mortality was higher in patients with MPR ≤80%. However, no clear trend was observed among MPR levels.

**Table 4.** Hazard ratios for men and women among primary prevention patients

| | | Men n=41,470 | | | | | Women n=33,439 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Crude | | Adjusted | | | Crude | | Adjusted | |
| | MPR (%) | N of events | Hazard ratio (95% CI) | p–value | Hazard ratio (95% CI) | p–value | N of events | Hazard ratio 95% CI | p–value | Hazard ratio 95% CI | p–value |
| Any CV event | 0–20 | 172 | 1.65 (1.57–1.73) | <0.0001 | 1.62 (1.54–1.71) | <0.0001 | 101 | 1.71 (1.60–1.82) | <0.0001 | 1.53 (1.43–1.64) | <0.0001 |
| | 21–40 | 165 | 1.40 (1.33–1.48) | <0.0001 | 1.40 (1.33–1.47) | <0.0001 | 94 | 1.30 (1.22–1.39) | <0.0001 | 1.28 (1.19–1.37) | <0.0001 |
| | 41–60 | 209 | 1.33 (1.27–1.39) | <0.0001 | 1.26 (1.20–1.32) | <0.0001 | 128 | 1.34 (1.26–1.42) | <0.0001 | 1.28 (1.20–1.36) | <0.0001 |
| | 61–80 | 335 | 1.33 (1.28–1.38) | <0.0001 | 1.27 (1.23–1.32) | <0.0001 | 144 | 1.05 (0.99–1.11) | 0.1134 | 1.03 (0.97–1.09) | 0.3197 |
| | 81–100 | 1634 | ref | ref | ref | ref | 801 | ref | ref | ref | ref |
| All–cause mortality | 0–20 | 64 | 1.33 (1.22–1.44) | <0.0001 | 1.24 (1.15–1.35) | <0.0001 | 39 | 1.41 (1.27–1.56) | <0.0001 | 1.20 (1.08–1.34) | 0.0008 |
| | 21–40 | 62 | 1.17 (1.08–1.27) | 0.0002 | 1.18 (1.09–1.29) | <0.0001 | 42 | 1.34 (1.21–1.49) | <0.0001 | 1.36 (1.23–1.51) | <0.0001 |
| | 41–60 | 83 | 1.22 (1.13–1.31) | <0.0001 | 1.14 (1.06–1.23) | 0.0004 | 42 | 1.00 (0.90–1.11) | 0.9813 | 0.92 (0.83–1.02) | 0.1145 |
| | 61–80 | 136 | 1.24 (1.17–1.31) | <0.0001 | 1.16 (1.10–1.23) | <0.0001 | 63 | 1.08 (1.00–1.18) | 0.0656 | 1.11 (1.02–1.21) | 0.0171 |
| | 81–100 | 663 | ref | ref | ref | ref | 327 | ref | ref | ref | ref |
| CV mortality | 0–20 | 41 | 1.53 (1.38–1.69) | <0.0001 | 1.45 (1.30–1.60) | <0.0001 | 23 | 1.83 (1.60–2.11) | <0.0001 | 1.53 (1.33–1.77) | <0.0001 |
| | 21–40 | 39 | 1.32 (1.19–1.47) | <0.0001 | 1.33 (1.19–1.48) | <0.0001 | 20 | 1.41 (1.22–1.64) | <0.0001 | 1.40 (1.20–1.62) | <0.0001 |
| | 41–60 | 51 | 1.34 (1.22–1.47) | <0.0001 | 1.25 (1.14–1.37) | <0.0001 | 24 | 1.27 (1.10–1.45) | 0.0007 | 1.15 (1.00–1.33) | 0.0439 |
| | 61–80 | 79 | 1.29 (1.19–1.39) | <0.0001 | 1.21 (1.12–1.31) | <0.0001 | 29 | 1.10 (0.97–1.25) | 0.1308 | 1.17 (1.03–1.33) | 0.0169 |
| | 81–100 | 370 | ref | ref | ref | ref | 148 | ref | ref | ref | ref |

MPR, medication possession ratio; CV, cardiovascular

**Table 5.** Hazard ratios for men and women among secondary prevention patients

| | | Men n=7,676 | | | | | Women n=3,983 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Crude | | Adjusted | | | Crude | | Adjusted | |
| | MPR (%) | N of events | Hazard ratio (95% CI) | p–value | Hazard ratio (95% CI) | p–value | N of events | Hazard ratio 95% CI | p–value | Hazard ratio 95% CI | p–value |
| Any CV event | 0–20 | 342 | 2.08 (2.00–2.16) | <0.0001 | 2.31 (2.23–2.40) | <0.0001 | 235 | 2.23 (2.13–2.34) | <0.0001 | 2.40 (2.29–2.51) | <0.0001 |
| | 21–40 | 345 | 1.59 (1.53–1.64) | <0.0001 | 1.78 (1.71–1.85) | <0.0001 | 221 | 1.80 (1.72–1.88) | <0.0001 | 1.93 (1.84–2.02) | <0.0001 |
| | 41–60 | 343 | 1.30 (1.26–1.35) | <0.0001 | 1.45 (1.39–1.50) | <0.0001 | 240 | 1.58 (1.51–1.65) | <0.0001 | 1.62 (1.55–1.70) | <0.0001 |
| | 61–80 | 487 | 1.27 (1.23–1.31) | <0.0001 | 1.36 (1.31–1.40) | <0.0001 | 254 | 1.21 (1.16–1.26) | <0.0001 | 1.27 (1.22–1.33) | <0.0001 |
| | 81–100 | 1558 | ref | ref | ref | ref | 984 | ref | ref | ref | ref |
| All–cause mortality | 0–20 | 128 | 0.83 (0.78–0.88) | <0.0001 | 0.98 (0.92–1.03) | 0.4052 | 103 | 0.93 (0.87–0.99) | 0.0315 | 0.99 (0.93–1.06) | 0.8410 |
| | 21–40 | 178 | 0.89 (0.84–0.93) | <0.0001 | 1.10 (1.04–1.15) | 0.0003 | 142 | 1.12 (1.06–1.18) | 0.0001 | 1.26 (1.19–1.33) | <0.0001 |
| | 41–60 | 227 | 0.95 (0.91–0.99) | 0.0143 | 1.14 (1.09–1.19) | <0.0001 | 154 | 0.98 (0.93–1.04) | 0.5604 | 1.05 (0.99–1.11) | 0.0930 |
| | 61–80 | 319 | 0.91 (0.88–0.95) | <0.0001 | 1.03 (1.00–1.08) | 0.0881 | 258 | 1.21 (1.15–1.26) | <0.0001 | 1.30 (1.24–1.36) | <0.0001 |
| | 81–100 | 1395 | ref | ref | ref | ref | 996 | ref | ref | ref | ref |
| CV mortality | 0–20 | 52 | 1.06 (0.96–1.16) | 0.2522 | 1.22 (1.12–1.34) | <0.0001 | 32 | 1.04 (0.93–1.17) | 0.5253 | 1.14 (1.01–1.28) | 0.0286 |
| | 21–40 | 59 | 0.92 (0.84–1.00) | 0.0547 | 1.12 (1.03–1.23) | 0.0084 | 46 | 1.30 (1.17–1.43) | <0.0001 | 1.48 (1.34–1.63) | <0.0001 |
| | 41–60 | 68 | 0.89 (0.82–0.96) | 0.0040 | 1.06 (0.98–1.15) | 0.1598 | 41 | 0.94 (0.85–1.04) | 0.2354 | 0.99 (0.89–1.10) | 0.8295 |
| | 61–80 | 106 | 0.95 (0.89–1.02) | 0.1316 | 1.05 (0.98–1.13) | 0.1458 | 77 | 1.29 (1.19–1.40) | <0.0001 | 1.41 (1.30–1.52) | <0.0001 |
| | 81–100 | 445 | ref | ref | ref | ref | 278 | ref | ref | ref | ref |

MPR, medication possession ratio; CV, cardiovascular

## 4.3 Study III

Study III included 1,204,376 observations from 322,046 T2DM patients reported by 1,325 healthcare providers (Figure 1, Paper III). Sixty-three per cent of all observations were attributed to lipid-lowering primary prevention. For patient characteristics see, Table 1, Paper III.

Between 2007 and 2014, prevalence of lipid-lowering medication prescription for patients with LDL-C above recommended target levels ranged 40%–49% in the primary prevention group and 72%–78% in the secondary prevention groups, respectively (Figure 2, Paper III). Adjusted guideline adherence increased from 36% in 2007 to 46% in 2014 for primary prevention and from 59% to 66% for secondary prevention.

Independent of prevention group, the odds of receiving a prescription for lipid-lowering medications was generally higher in patients who were treated by specialized healthcare providers (Figures 3 and 4, Paper III). Furthermore, we observed higher odds in patients who were physically active more than once a week, smokers, and those with concurrent prescriptions for other cardioprotective medications. In primary prevention patients, the odds of receiving lipid-lowering medications were lower for men and patients aged 80 years or older and higher with increasing diabetes duration. Among secondary prevention patients, odds were higher for men and lower with increasing diabetes duration.

### *4.3.1 Differences between men and women*

Forty-one percent of all observations among men were attributed to secondary prevention compared to 32% among women. Between 2007 and 2014, the prevalence of receiving a prescription for lipid-lowering medications was 52%–60% and 55%–62% for primary prevention men and women, respectively (Table 6). For secondary prevention patients, the corresponding ranges were 77%–82% and 73%–78% for men and women, respectively. Among primary prevention patients, healthcare providers' guideline adherence to lipid-lowering medication prescription was initially higher among female primary prevention patients. After leveling off, the guideline adherence remained similar between the sexes (Tables 7). Adjusted for potential

confounders, guideline adherence among secondary prevention patients showed similar rates between the sexes over time (Table 8).

**Table 6.** Prevalence of lipid-lowering medication prescription by year, categorized by prevention group and sex

| Year | Primary Prevention | | Secondary Prevention | |
|---|---|---|---|---|
| | Men *n* (%) | Women *n* (%) | Men *n* (%) | Women *n* (%) |
| 2007 | 21,057 (51.5) | 19,095 (54.6) | 15,051 (76.9) | 8293 (73.2) |
| 2008 | 27,319 (54.7) | 24,833 (57.4) | 19,632 (79.2) | 10,924 (75.0) |
| 2009 | 35,661 (57.5) | 31,484 (59.8) | 25,902 (81.1) | 14,420 (77.2) |
| 2010 | 57,101 (59.3) | 51,737 (61.5) | 41,068 (81.5) | 23,511 (77.7) |
| 2011 | 72,578 (59.9) | 64,964 (61.5) | 52,124 (82.3) | 29,206 (77.9) |
| 2012 | 72,723 (59.5) | 62,825 (60.5) | 51,366 (81.4) | 28,243 (76.7) |
| 2013 | 64,399 (58.6) | 53,893 (58.9) | 45,704 (79.7) | 23,986 (73.7) |
| 2014 | 65,559 (57.5) | 53,041 (56.8) | 50,066 (79.1) | 25,784 (73.6) |

**Table 7.** Probability of prescribing lipid-lowering medication in primary prevention patients

| Year | Men | | Women | |
|---|---|---|---|---|
| | Crude probability (95% CI) | Adjusted probability (95% CI) | Crude probability (95% CI) | Adjusted probability (95% CI) |
| 2007 | 33.5 (32.8–34.1) | 33.7 (31.9–35.5) | 37.3 (36.6–38.0) | 38.7 (36.6–40.9) |
| 2008 | 38.2 (37.6–38.7) | 38.1 (36.3–39.8) | 41.3 (40.7–41.9) | 42.6 (40.5–44.7) |
| 2009 | 42.3 (41.7–42.8) | 42.1 (40.3–43.9) | 44.7 (44.1–45.3) | 45.6 (43.5–47.79 |
| 2010 | 44.4 (43.9–44.9) | 45.1 (43.3–46.9) | 46.6 (46.0–47.1) | 47.6 (45.5–49.7) |
| 2011 | 47.0 (46.5–47.5) | 46.3 (44.4–48.1) | 48.0 (47.5–48.6) | 46.9 (44.8–49.0) |
| 2012 | 48.2 (47.7–48.7) | 46.6 (44.7–48.4) | 48.1 (47.6–48.6) | 46.6 (44.5–48.8) |
| 2013 | 48.9 (48.4–49.4) | 46.9 (45.0–48.8) | 47.8 (47.2–48.3) | 46.3 (44.1–48.4) |
| 2014 | 49.9 (49.4–50.5) | 46.2 (44.3–48.1) | 48.2 (47.6–48.7) | 46.0 (43.8–48.1) |

**Table 8.** Probability of prescribing lipid-lowering medication in secondary prevention patients

| Year | Men | | Women | |
|---|---|---|---|---|
| | Crude probability (95% CI) | Adjusted probability (95% CI) | Crude probability (95% CI) | Adjusted probability (95% CI) |
| 2007 | 72.2 (71.67–2.8) | 58.0 (55.7–60.4) | 68.2 (67.4–69.1) | 59.9 (56.8–62.8) |
| 2008 | 74.6 (74.0–75.1) | 62.8 (60.6–65.0) | 70.1 (69.3–70.8) | 63.5 (60.7–66.3) |
| 2009 | 76.3 (75.8–76.8) | 66.0 (63.8–68.0) | 72.1 (71.5–72.7) | 66.8 (64.2–69.4) |
| 2010 | 76.6 (76.2–77.0) | 68.5 (66.4–70.5) | 71.7 (71.1–72.3) | 67.4 (64.7–70.0) |
| 2011 | 77.3 (76.9–77.7) | 69.3 (67.3–71.3) | 71.5 (71.0–72.1) | 69.4 (66.8–71.9) |
| 2012 | 75.9 (75.5–76.3) | 68.1 (66.0–70.1) | 69.6 (69.1–70.2) | 67.9 (65.2–70.4) |
| 2013 | 74.5 (74.1–75.0) | 66.7 (64.6–68.8) | 67.3 (66.7–67.9) | 66.8 (63.9–69.5) |
| 2014 | 73.7 (73.3–74.2) | 66.5 (64.3–68.5) | 66.2 (65.6–66.9) | 65.3 (62.5–68.0) |

With some exceptions, the odds of receiving a prescription for lipid-lowering medications were similar between the sexes within the prevention groups. In the primary prevention group, odds were higher among men receiving diabetes medications and/or antiplatelets and also for those treated within specialized care. Additionally, women smokers and those aged 46–60 years showed higher odds (Table 9). In secondary prevention, higher odds were observed among men with antiplatelets as well as smoking women.

**Table 9.** Odds ratios for primary prevention men and women

| | Primary prevention | | Secondary prevention | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| **Factors** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** |
| Specialized vs. primary care | 1.24 (1.15–1.33) | 1.05 (0.96–1.14) | 1.44 (1.29–1.60) | 1.39 (1.22–1.59) |
| Age, 46–60 years vs. <45 years | 0.98 (0.95–1.02) | 1.12 (1.08–1.16) | 0.90 (0.85–0.96) | 0.91 (0.83–1.00) |
| Age, 61–80 years vs. <45 years | 0.51 (0.47–0.55) | 0.57 (0.54–0.61) | 0.49 (0.46–0.54) | 0.48 (0.44–0.54) |
| Diabetes duration, 5–10 years vs. <5 years | 1.18 (1.14–1.21) | 1.14 (1.11–1.18) | 0.90 (0.86–0.95) | 0.93 (0.88–0.98) |
| Diabetes duration, >10 years vs. <5 years | 1.20 (1.16–1.25) | 1.17 (1.12–1.21) | 0.81 (0.77–0.86) | 0.88 (0.82–0.94) |
| HbA1c, high vs. low | 1.03 (1.01–1.06) | 1.05 (1.02–1.07) | 1.09 (1.06–1.13) | 1.01 (0.97–1.06) |
| Diabetes medication, yes vs. no | 1.58 (1.53–1.64) | 1.50 (1.45–1.56) | 1.43 (1.36–1.50) | 1.43 (1.35–1.52) |
| Antihypertensives, yes vs. no | 1.87 (1.81–1.94) | 1.88 (1.81–1.95) | 3.11 (2.90–3.34) | 2.95 (2.71–3.21) |
| Antiplatelets, yes vs. no | 1.93 (1.86–2.01) | 1.79 (1.72–1.87) | 2.50 (2.38–2.63) | 2.12 (2.01–2.25) |
| Systolic blood pressure, high vs. low | 0.96 (0.94–0.99) | 0.99 (0.96–1.01) | 0.96 (0.93–0.99) | 0.98 (0.94–1.01) |
| Diastolic blood pressure, high vs. low | 0.95 (0.93–0.98) | 0.98 (0.95–1.00) | 0.95 (0.92–0.98) | 0.94 (0.91–0.97) |
| Total cholesterol, high vs. low | 0.94 (0.91–0.97) | 0.92 0.87–0.97) | 0.80 (0.77–0.83) | 0.79 (0.75–0.83) |
| HDL cholesterol, high vs. low | 1.19 (1.15–1.23) | 1.15 (1.12–1.18) | 1.17 (1.12–1.22) | 1.06 (1.01–1.11) |
| Triglycerides, high vs. low | 1.18 (1.15–1.22) | 1.16 (1.13–1.20) | 1.12 (1.08–1.17) | 1.19 (1.14–1.25) |
| eGFR, high vs. low | 1.04 (0.99–1.09) | 1.02 (0.98–1.05) | 1.03 (0.98–1.07) | 0.96 (0.92–1.01) |
| Microalbuminuria, yes vs. no | 1.04 (1.01–1.08) | 1.03 (0.99–1.07) | 1.03 (0.99–1.08) | 0.99 (0.94–1.05) |
| Macroalbuminuria, yes vs. no | 1.05 (0.97–1.15) | 1.11 (0.99–1.23) | 0.88 (0.81–0.95) | 0.90 (0.80–1.01) |
| BMI, high vs. low | 1.02 (0.99–1.05) | 0.96 (0.93–0.99) | 1.11 (1.06–1.16) | 1.04 (0.99–1.09) |
| PA, 1–2 times/week vs. less than once/week | 1.05 (1.02–1.08) | 1.05 (1.02–1.09) | 1.09 (1.05–1.14) | 1.13 (1.08–1.19) |
| PA, 3–5 times/week vs. less than once/week | 1.03 (0.99–1.06) | 1.07 (1.04–1.11) | 1.13 (1.08–1.18) | 1.21 (1.15–1.28) |
| PA, daily vs. less than once/week | 1.01 (0.98–1.05) | 1.06 (1.03–1.10) | 1.10 (1.05–1.15) | 1.23 (1.16–1.29) |
| Smoking, yes vs. no | 1.08 (1.04–1.13) | 1.20 (1.15–1.25) | 1.05 (0.98–1.11) | 1.32 (1.22–1.43) |

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; PA, physical activity.

## 4.4 Study IV

Study IV included 123,460 patients, 88% of whom had initiated lipid-lowering medications for primary prevention. For patient characteristics, see Table 1, Paper IV.

Compared to high-adherent patients (MPR above 80%), primary prevention patients with low refill adherence (MPR 80% or less) showed 41%–49% higher risk of experiencing a CV event, 35% higher risk of all-cause mortality, and 37%–39% higher risk of CV mortality (Table 2, Paper IV). Compared to those treated by high-adherent healthcare providers, low-adherent patients showed an 8% increased risk of CV events and an 11% increased risk of CV mortality. Additionally, high-adherent patients showed an 13% increased risk of CV mortality. Otherwise, we observed no statistically significant difference between guideline adherence levels.

Compared to high-adherent patients, secondary prevention patients with low refill adherence had 16%–19% higher risk of CV event, 33–34%% higher risk of all-cause and CV mortality (Table 2, Paper IV). We observed no statistically difference in risk of outcome dependent on guideline adherence level among secondary prevention patients.

With some exceptions, generally the risk of experiencing a CV event or mortality was higher with increasing age and diabetes duration, among smokers and with lower income per household member as well as lower kidney function (Table 3, Paper IV). Lower risk was observed among those who were born outside of Sweden, who filled prescriptions for anticoagulants or antihypertensives, or with higher HDL-C or BMI.

### *4.4.1 Differences between men and women*

Compared to women, male primary prevention patients showed 57% higher risk of experience a CV event, 38% higher risk of all-cause mortality, and 54% higher risk of CV mortality (Table 3, Paper IV). Corresponding risk for male secondary prevention patients were 34% higher for CV events, 46% higher for all-cause mortality, and 48% higher for CV mortality. Aside from the differences in risk of outcomes between the sexes, the general pattern of higher

risk among low-adherent patients regardless of guidelines adherence level was observed among men and women, in both prevention groups.

# 5 DISCUSSION

## 5.1 Main findings

### *5.1.1 Refill adherence and persistence*

In Study I, overall mean MPR was 71%, and 55% of patients had an MPR greater than 80%. More than 70% of all patients were persistent for at least one year and more than 50% were still filling prescription for lipid-lowering medication after three year. Similar results have been observed in previous studies among patients with DM or established CVD [97-100]. However, most studies report 12-month MPR, meaning adherence was higher among our study population during a 3-year period. Furthermore, the discontinuation rate was higher during the first year after initiation and decreased during the second and third year. The same findings have been observed in studies from Finland [98] and the Netherlands [99].

On average, patients with previous CVD who received treatment with lipid-lowering secondary prevention showed higher refill adherence compared to primary prevention patients, even after adjusting for potential confounders. Moreover, the maximum gap method showed that primary prevention patients were more likely to be nonadherent. However, our results showed little difference in persistence, suggesting that most T2DM patients were persistent to their lipid-lowering medications for up to 3 years, independent of prevention group. However, primary prevention patients tended to have longer periods of insufficient medication supplies without prematurely discontinuing treatment.

The greatest difference in refill adherence and risk of discontinuation of treatment occurred in patients who were born in Africa or the Americas. Although these patients represented only 2% of the total study population, it is important to identify patient groups at risk of nonadherence to achieve optimal use of medications.

### *5.1.2 Guideline adherence*

In Study III and Study IV (2007–2014), prevalence of lipid-lowering medication prescription among patients with T2DM and risk-associated LDL-C values was higher in the secondary prevention group compared to primary

prevention. This was expected because the LDL-C target level for secondary prevention is lower (1.8 mmol/l vs. 2.5 mmol/l) and guidelines highly recommend lipid-lowering medications in the treatment regimen following myocardial infarction or stroke [50, 51]. Similar results have been observed in previous studies, which report higher adherence to guidelines among patients attributed to secondary prevention or in primary prevention patients with risk factors associated with higher risk of CVD [21, 22, 63, 65, 66].

The adjusted probability of prescribing lipid-lowering medications (i.e., guideline adherence in Study III), increased between 2007 and 2011, and then levelled off in both prevention groups. This suggest a fairly consistent prescription pattern among Swedish healthcare providers with only small year-to-year fluctuations. Furthermore, the odds of receiving a prescription for lipid-lowering medications was higher among patients whose characteristics usually associate with increased CVD risk (e.g., men, concurrent prescription of other cardioprotective medications, smoking, etc.). Our findings are in line with previous research that reports varying guideline adherence to lipid-lowering medication prescription between primary and secondary prevention among T2DM patients, as well as the association between prescription and CVD risk factors [21, 22, 63-66]. Thus, healthcare providers treating T2DM in Sweden seem to have based the prescription for lipid-lowering medication on more than the LDL-C value alone, as suggested by the guidelines.

In Study IV, healthcare providers' level of guideline adherence showed little or no impact on patients' risk of CV events or death, regardless of prevention group. However, in our assessment of guideline adherence lipid-lowering medication prescription was used as a binary variable. Hence, we did not consider prescribed medication class or strength and thus not treatment intensity. Furthermore, we did not consider conditions that may have been contraindicated for lipid-lowering medications use, or patients' experience of adverse drug reactions due to such medications. Therefore, we may have underestimated healthcare providers' adherence to lipid-lowering prescription guidelines.

Healthcare providers' adherence to guidelines showed little or no impact on patients' refill adherence. However, we did not consider other healthcare

professions patients may encounter in their diabetes care (e.g., nurses, dieticians, physical therapists, pharmacists, etc.). In fact, healthcare providers' attitudes and beliefs concerning management of diabetes have shown to influence T2DM patients self-management behaviors, and those with access to a diabetes team, group training programs, or specialized diabetes nurses had better HbA1c control [23, 101].

Importantly, level of guideline adherence does not equal quality of care. Examples of extremes include healthcare providers with low guidelines adherence who mostly treat patients with severe diseases that may be contraindicated for lipid-lowering medications. In this context, the healthcare provider is acting according to guidelines, but our study identified this a nonadherence. Another extreme is a healthcare provider who prescribes lipid-lowering medications to every patient who fits guideline recommendations because the provider feels obligated to do so. In this context, the healthcare provider adheres to guidelines, but we know nothing about the communication between provider and patients. Hence, we do not know if the provider informed patients about the medications or the reasons for the prescription.

### *5.1.3 Risk of CV events and mortality*

Study II showed increased risk of CV events among patients with low levels of refill adherence (MPR 80% or less), compared to those with high level of refill adherence (MPR above 80%). This concur with previous studies [32, 67-77]. However, we also found the risk of CV events to increase gradually in relation to level of refill adherence in both prevention groups, suggesting that risk of CV events changes when refill adherence levels are below 80%. Although previous studies frequently categorized patients as adherent or not based on the 80% cutoff our data suggests that dividing MPR by more than these two levels better portrays the difference in risk between patients with less than complete adherence.

Importantly, the level of refill adherence tells little about patients' actual pattern of medication use, especially in a lengthy study period. Each level of MPR below 80% includes patients who occasionally forget to take their medications or actively choose to prematurely discontinue treatment. In Study II, an MPR of 41%–60% included patients who took their medications every

other day as well as those who discontinued treatment halfway through the study period.

In Study IV, level of refill adherence seemed more important than level of guideline adherence regarding risk of CV events and mortality. Independent of providers' level of guideline adherence, patients with high refill adherence showed lower risk of CV event and mortality compared to patients with low refill adherence. However, we observed no statistically significant difference in risk among low- or high-adherent patients based on the guideline adherence level except in primary prevention patients who were treated by low-adherent healthcare providers. This should not be interpreted as healthcare providers' adherence to treatment guidelines are unimportant as prescribing is a prerequisite for medication use among patients. Thus, healthcare providers should not refrain from prescribing lipid-lowering medications according to guidelines.

### *5.1.4 Differences between men and women*

Adjusted for potential confounders, men showed higher odds of receiving a prescription for lipid-lowering medications in both prevention groups. However, little difference was observed in prescription prevalence and guideline adherence between the men and women within the prevention groups. Furthermore, except for minor differences, patient characteristics associated with higher or lower odds or receiving a prescription for lipid-lowering mediation were similar between the sexes.

In general, men have higher risk of developing CVD compared to women, which may explain the higher odds of receiving a prescription for lipid-lowering medications. Otherwise, our results suggest that the prescription process among Swedish healthcare providers is similar among T2DM patients, intendent of sex. However, in our assessment of guideline adherence, no information about prescribed medication class or strength was considered. Hence, do not know if there are differences in choice of treatment between men and women with T2DM.

Overall, we observed little difference in refill adherence among men and women within the prevention groups. After adjusting for potential

confounders, the KM survival curves showed higher persistence among men with secondary prevention compared to those with primary prevention. However, among women no difference in persistence was observed between the prevention groups. Women and patients with primary prevention have previously been shown associate with higher risk of nonpersistence to lipid-lowering medications among T2DM patients [99].

Risk of CV events and mortality was similar between men and women within the prevention groups even at multiple levels of refill adherence. This indicates a beneficial effect of higher levels of refill adherence to lipid-lowering medications among men and women with T2DM.

## 5.2 Methodological considerations

Internal validity is the ability to draw a causal link between the exposure and outcome in a study, whereas external validity is the ability to generalize the study findings. In randomized controlled studies, close monitoring of follow-up and strict inclusion criteria result in patient groups that are as equal as possible, thus increasing the internal validity of the study. However, a highly selective study population results in limited external validity. Observational studies do not randomize patients, contributing to possible bias and low validity. However, observational studies reflect the routine of clinical practice, which results in high external validity. Thus, randomized controlled studies followed by observational studies give a more accurate picture of the causal link of a treatment as well as its applicability to clinical practice.

Random and systematic errors may affect the validity of a study. Random errors (i.e., statistical fluctuations in data resulting from precision limitations of measurements) can be reduced by increasing sample size. Systematic errors (i.e., reproducible inaccuracies that point in the same direction due to imperfect calibration of measurement devices) may be difficult to detect. Systematic errors are not dependent on sample size and include selection bias, information bias, and confounding. Selection bias, which occurs when a selected population does not represent the targeted population, may result in an inaccurate conclusion from the statistical analysis. Information bias arises from inaccurate measurement, collection, or interpretation of key information. Nondifferential misclassification happens when the information is incorrect

across the study population, whereas differential misclassification occurs when information errors differ between groups, such as between exposed and unexposed (e.g., missing information, incorrect disease codes, etc.). Confounding refers to variables that influence both exposure and outcome and may provide alternative explanations for an observed association.

### *5.2.1 Study design and settings*

Because we linked data between registers using patients' PIN, our data collection was considered complete in relation to the information available at the time of collection. Data may be reported to the registers at different times or intervals, possibly delaying availability. Thus, time of data collection may influence the extraction of data from the registers. The SPDR compiles data on a monthly basis. In comparison, reporting cause of death to the Cause of Death Register may take longer because the National Board of Health and Welfare, which validates the register, may request additional information. However, lag time in the registers was not considered an issue due to the large study populations in our studies.

The populations of Study I, Study II, and Study IV were collected from the same sources and according to similar inclusion and exclusion criteria. Differences in study period and time of data collection resulted in varying population sizes. Study II and Study IV excluded patients who experienced outcomes during the exposure period or first filled prescription, respectively. Thus, we may have excluded the most fragile patients and introduced selection bias. However, baseline characteristics remained similar between Study I, Study II, and Study IV, suggesting stability in the composition of study population.

In all studies, patients with T2DM were identified through the NDR. Patient coverage in the NDR is almost complete as of today. In relation to the overall inclusion period of this thesis, national coverage of patients with DM increased from 43% in 2006 to 87% in 2012 [102, 103]. Thus, the study populations in this thesis do not represent the true T2DM population of Sweden. However, we believe that our large nationwide study populations of T2DM patients allowed a realistic assessment of clinical practice for diabetes care in Sweden.

### 5.2.2 Exposures and outcomes

Study I, Study II and Study IV used SPDR data to assess patients' behavior regarding lipid-lowering medication use. Estimates suggest that the SPDR maintains complete coverage of all filled prescriptions from Swedish pharmacies [104]. Its data collection process is automated and based on administrative systems. Sometimes, in agreement with patients, the dispensing process is made in advance to make it easier for patients to collect their medications. However, the process needs to be reversed if patients do not collect their medications, in order to return the medications to the pharmacy storage. In the SPDR, this reverse transaction generates records with negative values. In Study I, Study II, and Study IV we excluded negative transactions and their corresponding positive transactions from the data set before estimating filled medication supplies. Thus, our assessment of refill adherence and persistence was considered reliable. However, the SPDR does not include medications distributed at hospitals; hence, we may have underestimated refill adherence and persistence in patients who were hospitalized during the study period.

In Study I, Study II, and Study IV, we collected diagnosis codes for CVD from the National Patient Register. The National Patient Register is validated by the National Board of Health and Welfare and is estimated to have full coverage [105]. Patients' PIN was estimated to be either missing or incorrect in 1.6% of all admissions between 1988 and 2016. Furthermore, an evaluation of patients' diagnosis of acute myocardial infarction between 1987 and 1995 showed that diagnosis at discharge matched established diagnosis criteria in 86% of the cases [106]. Thus, the collection of CVD diagnosis from the National Patient Register is reliable.

Coverage in the Cause of Death Register is considered complete because deaths are registered there regardless of whether any cause of death is reported [107]. However, there is some uncertainty regarding coverage of reported cause of death, which is missing in 1%–2% of the cases. Poorly specified information may require additional information, delaying data about cause of death. In Study I, Study II and Study IV, we collected date and cause of death from the Cause of Death Register. To ensure proper identification of CV

mortality, we considered both CVD as main or contributing cause of death, and diagnosis of CVD in the National Patient Register prior to death.

### *5.2.3 Missing data*

This thesis is based on data from different registers with different degrees of missing information. Depending on the extent of missing data, the nature of missingness and the way one chooses to handle missing information often plays a major role in the outcome of statistical analyses.

Missing completely at random refers to when there is no relationship between the missing information about a covariate and any values in the data set, missing or observed. In that case, running a statistical analysis based on observations with complete information about the covariates of interest (i.e., complete case analysis) may reduce the study population but will not introduce selection bias. If the missing information is not random (i.e., the missing value is related to the reason it is missing), complete case analysis may result in a small highly selective study population that does not represent the population of interest, thus introducing selection bias. However, excluding variables with missing information from the analysis could result in inaccurate conclusions due to unadjusted confounding. In this case, imputation of data may be suitable.

Data collected from the SPDR, the National Patient Register, the Cause of Death Register, the Swedish Cancer Registry, and the LISA database contained little or no missing information. Because patients with T2DM usually visit their healthcare provider once a year and healthcare providers may not measure all characteristics each medical visit, variables in the NDR contains varying degrees of missing data. Although we cannot exclude the risk that data was missing not at random, we have no reason to believe that the healthcare providers would selectively exclude data. Because such data is most likely missing at random, we performed multiple imputation to replace missing data in Study II and Study IV.

In Study I, we chose not to replace missing information. Instead, we analyzed the difference in refill adherence and persistence between primary and secondary prevention patients in three successive models. Moving from crude

to fully adjusted model (complete cases), we excluded 80% of the study population due to missing information. However, the difference in refill adherence and risk of discontinued treatment remained similar between the models, and the fully adjusted model included nearly 20,000 patients. Thus, the results of Study I are considered reliable.

In Study II and Study IV, we replaced missing information by performing multiple imputations. We used sensitivity analyses to evaluate the impact of multiple imputations and obtained similar results for imputed data and complete case analyses. Thus, the risk of bias due to handling missing data was of little concern.

In Study III, more than 50% of data had missing information about either LDL-C, CVD, or lipid-lowering medication use. Since we considered these variables as exposures or outcomes, replacing missing information was not methodologically appropriate. However, the distribution of key variables defining the study population was similar between included and excluded data. Thus, exclusion of observations with missing information did not distort the composition of the study population. Nonetheless, we cannot exclude the possibility that data was missing not at random.

### *5.2.4 Strengths and limitations*

The greatest strength of this thesis is the linkage of data between several national registers using the unique PIN, which allowed us to collect data from a large number of T2DM patients and extensively adjust for individualized risk factors. The NDR, which is one of the leading diabetes registers worldwide, collects data from both primary and specialized care clinics. This is a great strength because most T2DM patients receive treatment within primary care, which is not covered by the National Patient Register. Therefore, this thesis highly reflects clinical practice in Sweden.

Another strength is our access to SPDR data about filled prescriptions, which allowed us to assess patients' adherence based on the active behavior of patients rather than the prescriber. Using information on prescribed medications may overestimate patient adherence because not all patients fill their prescriptions. Although filled prescriptions do not equal ingestion of

medications, it takes us one step closer to the patients and their medication use. However, the SPDR does not include information about prescribed medications that were never filled. Hence, we could not estimate the extent of primary nonadherence (i.e., patients who never filled their initial prescription).

The SPDR uniquely provided us with information about prescribed daily dosage, meaning we did not need to use a proxy. The algorithm we developed to convert the free-text variable that represented the daily dosage was validated in Study I, Study II, and Study IV, respectively. Hence, our assessment of filled supplies and measures of refill adherence is considered to highly reflect the intended medication use as prescribed.

A major limitation of this thesis involves factors associated with prescription or use of lipid-lowering medications that were not considered in our studies. Because guidelines are intended for patients without contraindications, patients having any of these conditions should have been excluded or censored. Furthermore, we had no information about experienced adverse drug reactions, which would have been a legitimate cause for not prescribing lipid-lowering medications. Thus, we may have underestimated healthcare providers' adherence to lipid-lowering prescription guidelines.

In Study II and Study IV, we did not consider the substance or strength of medications when we analyzed risk of CV events and mortality. Although statins are by far the most widely used class of lipid-lowering medications in Sweden and worldwide, statins with greater potency to lower LDL-C can reduce the risk of a CV event, possibly explaining the difference in risk of a CV event.

# 6 CONCLUSIONS

Our investigation of the association between risk of CV events and mortality in relation to patients' refill adherence to lipid-lowering medications and healthcare providers' adherence to lipid-lowering prescription guidelines among T2DM patients resulted in the following conclusions:

Healthcare providers' adherence to guidelines was higher among patients assigned to secondary prevention of CVD. Furthermore, the odds of receiving a prescription for lipid-lowering medications was higher among patients with risk factors of developing CVD (e.g., men, concurrent prescriptions for other cardioprotective medications, and smoking).

Secondary prevention patients, those with concurrent use of other cardioprotective medications, and smokers showed higher refill adherence and longer persistence to lipid-lowering medications. Additionally, we observed lower refill adherence and higher risk of premature discontinuation among patients born outside of Sweden.

Compared to high-adherent patients (i.e., refill adherence above 80%), the risk of a CV event was higher among low-adherent patients (i.e., refill adherence of 80% or less) and that risk gradually increased as refill adherence declined, independent of prevention type. Furthermore, risk of mortality was higher among low-adherent patients. However, we were unable to identify a clear trend among levels of refill adherence.

With some exceptions, healthcare providers' adherence to guidelines had little or no impact on T2DM patients' adherence to refilling prescriptions for lipid-lowering medications or patients' risk of CV events and mortality.

Out findings emphasize the value of individualized diabetes care among T2DM, and will be valuable to guideline and policy makers as well as healthcare providers and patients as they evaluate and improve the use of lipid-lowering medications to ensure optimal, standardized and equal care among patients with T2DM.

# 7 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVE

T2DM is a complex disease that requires an extensive treatment regimen in order to reduce the increased risk of morbidity and mortality. Our findings suggest that the extent to which patients take their lipid-lowering medications as prescribed had a greater impact on risk of CV events and mortality compared to the healthcare providers' adherence to lipid-lowering prescription guidelines. Additionally, we found differences in patients' adherence and persistence to lipid-lowering medications associated with several patients' characteristics (e.g., established CVD, country of birth, marital status, concurrent medications, smoking, etc.) To prevent therapy failure and risk of morbidity, healthcare providers should be aware and observant of differences in adherence and persistence.

Although dyslipidemia is a strong risk factor for developing CVD, other risk factors also play a role. Hence, lipid-lowering medications are only part of the recommended treatment regimen in patients with T2DM. Patient who receive lipid-lowering medications often receive prescriptions for other cardioprotective medications as well. In fact, high adherence to lipid-lowering medications, glucose-lowering, and antihypertensives has separately been shown to associate with lower risk of CV events and mortality among T2DM patients [75]. Therefore, healthcare providers should consider patients' adherence to all cardioprotective medications when analyzing the association between adherence and risk of CV events and mortality. From this, the question arises of whether any particular adherence pattern is more efficient in T2DM patients. For example, is high adherence to lipid-lowering medications more efficient in preventing CVD and mortality compared to the combined effect of low adherence to diabetes medications, lipid-lowering medications, antihypertensives, and anticoagulants?

Dividing patients according to level of refill adherence tells little about the actual pattern of medication use. For example, patients with 50% refill adherence may take their medications less often than prescribed or they may be completely adherent during one half of a study period and then prematurely discontinue treatment. For those reasons, dividing patients according to their refill pattern over time (i.e., trajectories of medication adherence) may provide

a more accurate picture of medication use as an exposure. Previous studies have shown patient characteristics and the first filled prescriptions of lipid-lowering medications to associate with predictions of future adherence trajectories [108]. Considering the comprehensive databases of filled prescriptions, healthcare-related data and socioeconomic variables, Sweden offers excellent opportunities for analyzing medication trajectories. These trajectories can be used by healthcare providers to estimate patients' probability of developing patterns associated with increased risk of CV events and mortality, and thus identifying patients most likely to benefit from adherence interventions.

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