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Economic Aspects of Adherence to Hyperlipidemia Treatment in Sweden

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Cardiovascular disease is the leading cause of premature death world-wide and contributes extensively to the escalating costs of healthcare. Given the importance and effectiveness of lipid-lowering therapies for treatment of cardiovascular disease, understanding and quantifying impacts of poor treatment adherence is crucial. The objective of the present study was to estimate persistence and compliance to treatment of hyperlipidemia in Sweden and relate poor treatment adherence to healthcare resource utilization and subsequent costs. The study design was a retrospective register study based on a matched control cohort design using patient-level data from three national registers. The study found that 29 percent of treatment-naïve patients in Sweden were no longer persistent to lipid-lowering therapies one year after initiating treatment and more than half of the patients, 53 percent, were non-persistent after three years. It was more common amongst non-compliant patients to suffer cardiovascular event during the follow-up period of three years. The non-compliant patients were also found to have 8 – 47 percent higher healthcare costs during the second and third year after initiating treatment compared to their compliant counterparts. The results indicate potential for interventions aimed at improving adherence and highlights the need to properly analyze the net cost effect of such interventions.

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1. Introduction

Cardiovascular disease is the leading cause of premature death world-wide and a significant source of disability. Consequently, cardiovascular disease contributes extensively to the escalating cost of healthcare. Elevated levels of blood lipids represent a major risk factor for development of cardiovascular disease. The importance of pharmacological treatment in the prevention of cardiovascular disease has been demonstrated in a large number of clinical trials where the use of lipid-lowering treatment has been found to decrease rates of cardiovascular disease and mortality [1, 2]. However, for obvious reasons "drugs do not work if patients do not take them" [3]. To what extent patients adhere to taking medications as prescribed by their healthcare providers has been gaining increasing interest by researchers in recent times. A previous study based on population data from Swedish clinical practice has demonstrated that, despite a wide use of statin treatments, not all patients reach their treatment goals [4]. It is well established that drug adherence, especially in chronic conditions, is far from optimal and that medication non-adherence is a serious problem in healthcare [3]. Sub-optimal use of treatment can refer both to patients discontinuing treatment (non-persistence) and to patients not following the regimen as prescribed while on treatment (non-compliance).

The adherence to treatment in cardiovascular prevention has been studied in a number of studies internationally. In a large review of published literature on adherence rates, the 12-month compliance rate, measured by medical possession ratio (the number of days of treatment dispensed divided by the number of days between prescription refills) was 67 percent for antihypertensive medication, 76 percent for oral anti-diabetic medication and 74 percent for lipid-lowering therapies. The proportion of patients who were persistent after one year was 62 percent for antihypertensive medication, 62 percent for oral anti-diabetic medication and 66 percent for lipid-lowering therapies [5]. A recent study found that the corresponding compliance rate for statins in Sweden was 59 percent and the number of persistent patients was 73 percent after one year [6]. Several studies have linked treatment non-adherence to increased risk of cardiovascular disease and mortality [7-11].

The impact of poor treatment adherence in cardiovascular disease on total healthcare costs has been investigated in a number of studies over the past decade [12-16]. However, these prior studies have been limited in the sense that they did not control for a spurious relationship between poor adherence and worse health outcomes. A bias of this sort is known in the literature as the "healthy adherer effect" and is defined as the tendency of people who more closely follow their medication regimens to also engage in health-enhancing behavior such as exercising regularly and eating a healthy diet [17]. The few studies that have attempted to establish a causal link between medical adherence and healthcare costs have supported the notion that poor adherence results in higher costs [18, 19]. Since adherence is a multidimensional phenomenon [20] determined by the interplay of several different factors, such as those arising from the healthcare system [3, 21], generalization of results on adherence over different healthcare systems might not be suitable.

The aim of the present study was to estimate persistence and compliance to treatment of hyperlipidemia in Sweden. Furthermore, the objective was to analyze the association between poor adherence to hyperlipidemia treatment and cardiovascular events with associated resource use and costs in Sweden. The persistence and compliance to hyperlipidemia treatment was subsequently assessed. The analyses were performed using patient-level data from three Swedish registers: the National Prescription Register, the National Patient Register, and the Causes of Death Register. With universal coverage these registries provide a unique

opportunity to observe actual adherence in clinical practice. In order to reduce confounders and manage the healthy adherer bias, propensity score matching was employed.

The structure is as follows. Section 2 provides a brief background to cardiovascular disease and the field of health economics. The section furthermore contains significant definitions and concepts. Section 3 states the study objectives. Section 4 contains the method and material while Section 5 holds the results. The analysis of the results and a summary of the study are located in Section 6.

2. Background

2.1 Cardiovascular Disease

Cardiovascular disease (CVD) is defined as disease of the heart and blood vessels and it is the leading cause of death in the world [22-24] and in Sweden, where it attributed to almost 40 percent of the deaths in 2012 [25]. Consequently, CVD contributes extensively to the escalating cost of healthcare [1]. The most common manifestation of CVD is coronary heart disease (CHD), also known as coronary artery disease and ischemic heart disease. CHD has been estimated to be the leading cause of disability in Europe, accounting for 9.7 percent of total disability-adjusted life years [2].

CHD is caused by atherosclerosis, a term for narrowing of the arteries that supply the heart and is due to a gradual build-up of fatty material called atheroma. The narrowing can cause myocardial infarction (MI [heart attack]), angina pectoris (pain or discomfort in the chest or neighboring parts of the body due to insufficient oxygen reaching the heart) and other forms of chronic heart disease. Angina pectoris is usually classified as stable (AP) or unstable (UAP). Other forms of CVD include ischemic stroke (IS), transient ischemic attack (TIA) and peripheral artery disease (PAD).

Hyperlipidemia is quantitatively the most important factor for developing atherosclerosis [26] and is defined as elevated levels of lipids in the blood. Blood lipids are mainly fatty acids and cholesterol and elevated levels of blood lipids really refer to higher concentrations of low-density lipoprotein (LDL-C) particles and lower concentrations of functional high-density lipoprotein (HDL-C) particles. Elevated levels of blood lipids thereby represent a major risk factor for development of CVD. The relationship between cholesterol and the development of CHD has been established through a large number of clinical trials of LDL-C lowering therapies. A meta-analysis of 21 trials of more than 170,000 randomized patients, demonstrated that the incidence of major vascular events was reduced by about 25 percent for each mmol/L of reduction in LDL-C [3]. Hence, clinical trial evidence point strongly at LDL-C being an important risk factor for cardiovascular (CV) events. Other important factors affecting a person's risk of developing CHD are smoking, high blood pressure, type 1 and type 2 diabetes mellitus, physical inactivity, and obesity; these risk factors can be modified, treated or controlled.

Treatment of cardiovascular disease

As hyperlipidemia is one of the major modifiable risk factors for cardiovascular disease, lipid-lowering therapies are an important part of the treatment for CVD. There are five different groups of lipid-lowering therapies: statins, bile acid sequestrates, fibrates, nicotinic acid and cholesterol absorption inhibitor. Statins are used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol [27] and it is the most commonly used lipid-lowering therapy. Five statins currently have a

marketing authorization in Sweden: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

Treatment for CVD can be divided into primary and secondary prevention. Primary prevention includes treatment of patients without clinical history of CVD. Patient groups that are considered for primary prevention includes patients with diabetes, hypertonia, elevated lipid levels and known CVD in the family. In secondary prevention, the aim is to prevent further events in people who already have clinical evidence of CVD.

The current guidelines for treatment with lipid-lowering therapies in Sweden are developed by the Medical Products Agency [28] and The National Board of Health and Welfare [29]. They state that patients with a clinical history of CVD should primarily be offered statins unless the drug is unsuitable due to contraindications or intolerance. In primary prevention a risk calculator designed to estimate a person's ten-year CV event risk is used as an aid to making clinical decisions about how intensively to intervene with lifestyle measures and drug treatments. If the risk is estimated to be above five percent, the patient is primarily advised to lifestyle changes (such as exercise, diet, lowering of stress). If these lifestyles measures are not sufficient, treatment with statins should be considered.

There is strong evidence that secondary prevention for CVD lowers the rates of CVD and mortality [30-35] whilst the results concerning primary prevention are more ambiguous. Primary prevention for patients with diabetes has been found to lower the risk for CVD [36], especially if there is another risk factor, such as smoking or hypertension present [37].

2.2 Health Economics

Health economics can be defined as the application of economic theories, methods, and concepts to the topics of health and healthcare [38]. In this field of economics, researchers deal with topics relating to the allocation of scarce resources in order to improve health. The general importance of effective resource allocation and the growing healthcare costs in all developed countries emphasize the need to assess how to make the best use of the money spent on health and healthcare. Health economists are concerned with these issues and various health economic evaluations are performed to aid decision-makers in maximizing welfare from a limited budget [38].

In Sweden it is the responsibility of the Dental and Pharmaceutical Benefits Agency (TLV) to determine whether or not a pharmaceutical product or dental care procedure should be subsidized by the Swedish state. TLV makes decisions partly on the grounds of health economic assessments which means that all positive effects on human health are analyzed with respect to cost in order to ensure that a medicinal product is cost-effective to use. Therefore, in order to be eligible for subsidization, pharmaceutical companies are required to provide evidence that their products are cost-effective. Low adherence to treatment in real-world setting could result in a sub-optimal effect causing difficulties in estimating the factual utility from treatment. The case can therefore be made that adherence levels should be considered when evaluating the effect of a treatment since factoring in actual adherence is crucial to an accurate assessment of effectiveness and cost-effectiveness of therapy [6, 39].

2.3 Medication Adherence

There is considerable confusion in the literature about the terminology and measurement of the concepts persistence and compliance [40, 41]. The present study will use the following definitions.

Adherence

Adherence is in the present study used as a general term encompassing both the concepts persistence and compliance.

Persistence

Persistence, in a medical context, is defined as "the accumulation of time from treatment initiation to discontinuation of therapy" [41]. This definition can be operationalized in both prospective and retrospective assessments by determining the initiation of treatment to a point in time defined as the end of the observation period. Persistence analyses must include a pre-specified limit on the number of days allowed between refills, known as permissible gap.

Compliance

Medication compliance generally refers to the extent to which a patient acts according to medical or health advice [42]. Compliance is measured over a period of time and reported as a percentage. In retrospective studies, compliance is commonly quantified using medication possession ratio (MPR) [43].

Figure 1 below provides an illustration of the concepts [41].

Figure 1: Definition of compliance and persistence [41]

The World Health Organization has suggested that non-adherence to medication is a common problem that leads to compromised health benefits and serious economic consequences in terms of wasted time, money and uncured disease [44]. Adherence to long-term pharmacological therapy for chronic illnesses in developed countries averages 50 percent and the long-term adherence to lipid-lowering therapies is often found to be poor and declining considerably over time [44]. Several studies indicate that adherence to treatment with statins often is insufficient with between 30 - 50 percent of the patients being non-compliant [5, 45]. Poor adherence has been shown to be an important factor for treatment failure when looking at both high cholesterol levels [46] and morbidity [47-49], and, as a result, non-adherence to treatment is considered to be a CV risk factor [50]. A previous study based on population-based data from Swedish clinical practice has demonstrated that, despite a wide use of statin treatments, not all patients reach their treatment goals [4]. There is limited knowledge on adherence for patients on treatment with lipid-lowering therapies in Sweden [37, 74]. There is however a recent study on treatment patterns and adherence to statins amongst the Swedish population which found that the compliance rate for statins was 59 percent and the number of persistent patients was 73 percent [6].

The level of adherence also appears to have a significant effect on the costs of treatment. High adherence leads to an increase in drug costs [51-54] while low adherence is associated with increased medical events and hence more physician visits and hospital admissions, and longer hospital stays [13, 55]. The increased use of non-drug resources with lower levels of adherence results in higher overall costs for CVD in most studies [13, 56, 57], although some studies are inconclusive [13, 15, 16]. A recent systematic review of literature on poor medication adherence for CHD found that in all of the reviewed studies adherence significantly improved health outcomes, and those studies that analyzed costs found reduced total annual CHD costs (consistently between 294 USD and 868 USD per patient, equating to 10 – 18 percent cost reductions between high and low adherence groups) [58]. The variability in results, both in costs and adherence, can to some extent be attributed different assumptions regarding persistence, different statistical methods employed, and different populations studied which can cause the estimates to not be comparable.

Dependent on what type of adherence study that is being conducted, different aspects of study validly need to be considered. In prospective studies there is a possibility to verify clinically if a patient is still on treatment which is a costly and labor-intensive but the measures becomes accurate. It is therefore possible to argue that prospective studies have high internal validity. The risk with these studies are instead that patients might alter their behavior if they are aware that they are under observation, which will risk the external validity. Retrospective studies of adherence instead employ historical prescription records. These studies are therefore less costly and not concerned by bias due to changing participant behavior, but also less precise because there is no information available as to whether the patient actually has consumed the medication collected from the pharmacy [59]. It is however realistic to assume that patients would not continue to refill a prescription without the intention to adhere [60].

The determinants of low persistence to medical treatment are not very well understood. Adherence is a multidimensional phenomenon [18] determined by the interaction of several different factors, such as those arising from the patient, the physician or from the healthcare system itself [3, 19]. Studies suggest that several factors are important, such as gender [61], demographics [62, 63], sickness- and treatment-related factors [64-67], cost of medication, drug-related side effect, and the patient-physician relationship [68-71]. Numerous interventions with the aim to improve persistence and compliance to treatment have been attempted and investigated [72]. Moreover, there are indications that patients with poor compliance share certain characteristics which supports the theory of the healthy adherer bias. For example, in the prevention of CHD, patients with poor compliance to placebo have been proved to have worse health outcomes compared to their compliant counterparts [73, 74]. A recent systematic review of literature on poor medication adherence for CHD [58] pointed out that a key problem with the literature base is that the overwhelming majority of these studies did not consider the bias arising from different characteristics amongst adherent and non-adherent patients.

3. Objectives

The objective of the study was to estimate persistence and compliance to treatment of hyperlipidemia in Sweden and relate poor treatment adherence to healthcare resource utilization and subsequent costs. The adherence to treatment for hyperlipidemia was to be studied and estimated for all patients in the study population and for different subgroups of patients. The study was based on record-linkage between the Swedish National Patient Register, the Cause of Death Register, and the Swedish Prescribed Drug Register.

4. Design and Method

4.1 Study Design

The study design was a retrospective register study based on a matched control cohort design to evaluate the difference in costs between adherent and non-adherent patients. The study used a longitudinal time period (January 1, 2009, to December 31, 2012) to assess the effect of adherence on cardiovascular outcomes and healthcare costs. One challenge in estimating the effect of adherence on outcomes is that there could be confounding arising from the fact that adherent patients have different characteristics from non-adherent ones, known as the healthy adherer effect. The information on patient characteristics available in the national registries, such as age and disease history, allowed for controlling for some of this confounding and thereby, by using propensity score matching, improving the estimation of a causal link between adherence and outcomes.

Data management and statistical analysis were executed in Stata 12, StataCorp LP, Collage Station, TX, USA. The study design and procedures were approved by the Ethical Vetting Board in Stockholm.

4.2 Study Population

The study was conducted within the Swedish population from January 1, 2009, and December 31, 2012. Patients were identified from data in the Swedish Prescription Registry. Patients were included based on treatment with lipid-lowering medication between January 1, 2009, and December 31, 2009, as this is the most accurate way of identifying hyperlipidemia patients in Sweden. A washout period of twelve months prior to the identification period was used to identify treatment-naïve patients, which refers to patients who newly started their treatment.

Inclusion criteria

The inclusion criteria for the study were as follows:

- Patients on treatment for hyperlipidemia between January 1, 2009, and December 31, 2009 (filling a prescription of one of the following lipid-lowering therapies);
    - Statin treatment (ATC C10AA)
    - Non-statin lipid lowering treatment (ATC C10AB, C10AC02, C10AC04, C10AD, C10AX).
- Females and males aged 18 years and over at the lipid-lowering prescription date

Exclusion criteria

The exclusion criterion for the study was as follows:

- Patients on treatment for hyperlipidemia between January 1, 2008, and December 31, 2008 (filling a prescription of one of the following lipid-lowering therapy);
    - Statin treatment (ATC C10AA)
    - Non-statin lipid lowering treatment (ATC C10AB, C10AC, C10AD, C10AX).

4.2.1 Study cohorts

The identified patients were stratified into three separate cohorts based on CVD risk level from five years prior to their first prescription up until their first prescription according to the following definitions:

Cohort 1: Patients with a history of CV event (prior diagnosis of MI, UAP, IS, CABG, PTCA)

Cohort 2: Patients with a high risk for CV event (prior diagnosis of diabetes, PAD, abdominal aortic aneurysm, TIA, heart failure (HF), AP)

Cohort 3. Patients with a low/unknown risk for CV events (patients not included in the other cohorts)

All primary and secondary diagnoses in the National Patient Register were used when performing the stratification. The ICD-10 and KVÅ-codes used to define these diagnoses are presented in table 25 in the appendix.

4.3 Data Sources

The data sources for the present study were individual de-identified patient-data extracted from three selected national compulsory health registers which are governed by the National Board of Health and Welfare. Unique individual patient ID numbers were available for all data sources which allowed for linkage of individual patients between data sets. Merging of data was performed by the Swedish National Board of Health and Welfare where after no identification of patients was possible. Patient consent was not required because of the retrospective nature of the study and the use of de-identified patient data. All diagnoses were coded according to the International Classification of Diseases (ICD-9 until 1997 and ICD-10 from 1997 and onwards).

Swedish Prescription Registry

The National Prescription Register contains information regarding prescriptions filled at pharmacies from year 1999 and is updated on a monthly basis. The Swedish identification number (unique for each citizen) was implemented in the register in July 2005 allowing for studying patients over time and for linkage. Data on dispensed treatments (e.g. statin treatment) were retrieved from the register for all individual patients included in the study cohort. All prescribed medication to the individual patient may be tracked in the national database back until July 2005. Data can be captured on prescribed drug (ATC code), prescription date, dispensing date, dose, pack size, HCP issuing the prescription, and costs associated with the drug prescription.

National Patient Registry

Individual patient data is collected from both in- and outpatient specialist care across all of Sweden in the National Patient Registry. The registry dates back to 1964. From 1987 there is information on all completed inpatient admissions in publicly operated hospitals. The collection of outpatient care data began in 2001. The key variables are diagnosis, surgery, gender, age, region, hospital visits, specialty visits, and hospital admissions and discharges. Detailed data is also available on all medical procedures and surgeries performed in the inpatient and outpatient specialist setting in Sweden. The registry is updated annually in September.

Cause of Death Registry

The Cause of Death Register contains death-dates and cause of death for Swedish citizens. The register contains data from year 1961 and is updated annually.

Data quality

The national and compulsory health registers included in the present study are governed by the Swedish National Board of Health and Welfare. Reporting of information to the registers is compulsory by all healthcare providers. Rigorous validation work is constantly ongoing from the health authority in order to ensure that data are complete, comprehensive and of the highest quality possible. There are a large number of scientific publications based on the data sources that were used in this study [4, 75-77]. All data was examined for completeness.

Concerning missing data, the registers in Sweden are known to have a high degree of completeness due to mandatory reporting of key variables. If information regarding dates, diagnosis codes, or treatment information was completely absent, these records were excluded from the analysis. No imputation was thus performed. In the event that year and month were available but not the day of the month, the 15th of the month was imputed for the date.

4.4 Study Definitions

4.4.1 Definition of time periods

The study period spanned from January 1, 2009, and December 31, 2009. Patients with treated hyperlipidemia were identified based on a filled prescription for lipid-lowering medication between January 1, 2008, and December 31, 2008.

The index date was defined as the date of the first prescription for a lipid-lowering therapy during between January 1, 2008, and December 31, 2008.

The follow-up period for the study was defined as the time from index date to end of study (i.e. December 31, 2012, or patient death, whichever came first). Estimations of the study outcomes of healthcare resource use and costs for the patients were done over this period. The follow-up period was divided into three time periods to allow for estimating short-term and long-term healthcare resource use and costs. The time periods were: 1) 0-365 days after index date, 2) 366 - 730 days after index date, and 3) 731 - 1095 days after index date.

The pre-index period was defined as the 12 months before the index date. The pre-index period was used for the calculation of baseline costs and patient demographics.

4.4.2 Definition of cost variables and resource use

Hospitalizations: A hospital stay was defined from admission to discharge from in-hospital care or discharged as dead. All hospitalizations were collected from the National Patient Registry for the complete observable period for each patient. Hospitalizations with a primary diagnosis of a CV event were also separately accounted for.

Outpatient hospital visits: All outpatient specialist visits were collected from the National Patient Registry for the complete observable period for each patient. Outpatient specialist visits with a primary diagnosis of a CV event were also separately accounted for.

Drug costs: Costs associated with filled prescriptions of one of the drugs listed in Table 37 in the appendix. The prescription registry collects data on the total costs associated with each filled prescription; this information was used to calculate total drug costs. The full cost of a filled prescription was assumed to incur at the dispensing date.

Direct cost of care was estimated based on the number of healthcare visits, hospitalizations, and medical use on an individual patient level. A review of Swedish regional healthcare price lists was undertaken and costs were based on price lists from different healthcare regions in Sweden. Estimation of costs was done by multiplying each resource use with the corresponding average unit cost from the price lists on an individual patient level. Finally, the estimation of average costs per patient was done by summarizing costs for healthcare visits, hospitalizations, surgical procedures, and medications and dividing by the number of patients. Total inpatient costs (hospitalizations, emergency department and surgical procedures), total outpatient hospital costs, and total medication costs were summarized to obtain a measure of total healthcare costs. Hospitalizations and outpatient specialist visits with a primary diagnosis or KVÅ code of a CV event were classified as directly related to a CV event and were also separated accounted for.

All costs in the study are presented in SEK.

4.5 Measurement of Adherence

This section describes the methodology and assumptions used when interpreting the prescription records from the Swedish Prescription Register. This study used refill adherence to estimate adherence. Refill adherence measures the amount of dispensed drugs in relation to time between refills and is in this way an indirect measure of adherence. In countries with universal drug coverage, such as Sweden, refill adherence is considered an accurate measure of overall adherence [3]. Patients receiving inpatient care during the study period were assumed to consume their own filled prescriptions while hospitalized. The estimates of daily dosage (see table 31, Appendix) were created with the help of physicians and patient information leaflets. For most of the lipid-lowering therapies, including all statins, the daily dose was set to one pill daily. When prescriptions overlapped, the overlapping days were added to the subsequent prescription. Both of the assumptions regarding hospitalization drug consumption and estimated daily dose was supported by a recent study which compared two methods for estimating refill adherence to statins in Sweden [78]. The authors found that disregarding hospitalizations did not alter the refill adherence estimates and neither did assumptions that all prescriptions were for one unit per day.

Measurement of persistence

Persistence was operationalized as the number of days on treatment. It was measured from index prescription until the end of the duration of the last prescription. Patients were allowed to have gaps between filled prescriptions, but were defined non-persistent (to have terminated treatment) if they had a gap exceeding the permissible gap. The base permissible gap period in this study was set to 60 days. Sensitivity analysis was made for permissible gap period of 30 and 90 days.

Measurement of compliance

Medication compliance was operationalized as the MPR (medication possession ratio), which measures number of doses dispensed in relation to the dispensing period. It was calculated as the number of days on treatment during the first year after the index prescription divided by 365 and capped at one, thereby generating a percentage. A patient was considered non-compliant if the MPR was lower than 80 percent and compliant of the MPR was 80 percent or higher. The cut-off at 80 percent was chosen because a lower adherence has been associated with an increased risk for adverse outcomes [47, 79].

4.6 Statistical Analysis

This section describes the analyses and the statistical methods used in the study.

4.6.1 Propensity score matching

Propensity-score matching is increasingly being used to reduce the impact of treatment-selection bias when estimating causal treatment effects using observational data. The rationale for choosing the method in the study is based on the structure of the applied data and the nature of the objectives. The data set used in the study is large enough to deal with the complication that the estimation of the propensity score and the matching itself both add variation beyond normal sampling variation [80]. A decent sample size is needed for the balancing property to hold [81]. One limitation of propensity score matching is that it can only estimate mean effects [82], however, the objectives in the study can be fulfilled by providing mean effects. Another limitation with the method is the inability to estimate the local average treatment effect, unlike instrumental variable techniques [82]. One advantage of propensity score matching is that it is non-parametric and thereby does not does not require functional form assumptions. Another aspect of the chosen method is the traditionally strong connection between health economics and the medical literature. Propensity-score matching, one of the methods of using propensity scores, is frequently used in the medical literature [83, 84].

The propensity score is defined as a subject's probability of receiving a specific treatment conditional on the observed covariates [85, 86]. Rosenbaum and Rubin [85] demonstrated that within strata of subjects matched on the propensity score, the distribution of baseline characteristics is similar between treated and untreated subjects.. Propensity score matching entails forming matched sets of treated and untreated subjects who share a similar value of the propensity score [85, 87]. Once a matched sample has been formed, the treatment effect can be estimated by directly comparing outcomes between treated and untreated subjects in the matched sample. If the outcome is continuous (e.g. a scale), the effect of treatment can be estimated as the difference between the mean outcome for treated subjects and the mean outcome for untreated subjects in the matched sample [85].

However, it is essential to note that despite the balancing of observed baseline covariates between treated and untreated subjects, propensity-score matching cannot balance unmeasured characteristics and confounders. This means that propensity-score analyses have the same limitation that all observational studies suffer from, namely remaining unmeasured confounding. In general does not propensity-score approaches overcome initial selection bias, this is however a minor problem in the current study due to the nature of the data.

To compare cardiovascular outcomes and costs between patients with different levels of adherence, propensity score matching was applied to control for confounders and limit bias. The propensity score in this study was defined as a subject's probability of being adherent to hyperlipidemia treatment conditional on observed covariates. The propensity score was estimated using a logistic regression and the caliper approach was used for matching. The caliper method uses a tolerance level of the maximum propensity score distance to avoid the risk of bad matches. However, while the caliper matching approach increases the matching quality, a negative effect might be that the variance of the estimates increases if fewer matches are performed. Another drawback might be that it can be difficult to establish an optimal caliper width. The maximum propensity score distance was therefore set to 0.2 of the standard deviation of the logit of the propensity score in accordance to recommendations by past research on optimal caliper widths [88]. Patients with low adherence within each cardiovascular

disease risk level were matched to patients with high adherence within the same cardiovascular disease risk category based on a 1:1 match.

The quality of the matching was evaluated in line with the guidance provided by previous research [89, 90] which included inspection of common support by graphing and testing covariate imbalance. Standard errors were obtained using bootstrapping methods and an ex-ante limit of ten percent in standardized differences was set for all variables used in the matching. A standard difference that is less than ten percent has been taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups [91]. A statistical transformation was employed on certain variables to allow for possible nonlinearities in the model. Sensitivity analyses based on Rosenbaum's bounding approach [92] were also employed in order to assess how strongly an unmeasured confounder would have to be associated with treatment selection in order for a previously statistically significant treatment effect to become statistically insignificant if the unmeasured confounder had been accounted for. The results from the sensitivity analyses show that for cohort 3 the results were sensitive to a bias that would alter the odds of non-adherence by more than 30 percent. For cohort 2 and cohort 3 the study results were insensitive to a bias that would double the odds of non-adherence but sensitive to a bias that would triple the odds.

The following covariates were included in the matching:

- Age at index date: continuous variable
- Gender: dichotomous variable
- Charlson comorbidity index at index date: continuous variable
- Past CV diagnoses: dichotomous variables
- Past comorbidities diagnoses: dichotomous variables
- Hospital visits during a one-year period prior to index date: continuous variable
- Days of hospitalization during a one-year period prior to index date: continuous variable
- Drug cost during a one-year period prior to index date: continuous variable

The list above includes all accessible variables judged to influence adherence. Other covariates that would have been of interest when estimating the probability of adherence are for instance the income level of the patients and cognitive factors such as concerns about medications [93].

4.6.2 Test of differences in mean total costs

Tests for statistical significance in differences between patients with low adherence and matched patients with high adherence in total mean costs were performed for each time period and each cohort. The appropriate test was arrived at by first graphically examining the data through histograms and box plots. Shapiro-Wilk tests [94] were then performed to test if the differences followed a normal distribution. The data did not look normally distributed, and this was confirmed by the Shapiro-Wilk tests. The cost data were instead roughly γ-distributed, and a generalized linear model with a log-link and robust standard errors to adjust for heteroskedasticity was used, as recommended in previous research [95] for healthcare cost data. A P-value smaller than 0.05 was considered to show statistically significant differences.

4.6.3 Censoring

Patients were censored at end of data availability (i.e. December 31, 2012) or date of death, whichever came first. As patients were followed in parallel to their matched controls, patients were censored when either they themselves or their match died, whichever came first.

4.6.4 Other analyses

To investigate the determinants of adherence, odds ratios was calculated for factors of suspected importance using multiple logistic regression. Cox proportional hazards model was used to calculated hazard ratios to estimate the influence of factors on non-persistence. To compare the survival distributions between groups the log-rank test [96-98] was used.

5. Results

The section contains the results from the study. The first part presents the descriptive statistics and findings concerning adherence for the entire study population, stratified by cohorts. The second part does likewise for the identified matched patients as well presenting their healthcare resource use and corresponding cost.

5.1 Patient Attrition

The patient attrition for the study is illustrated in figure 2 below.

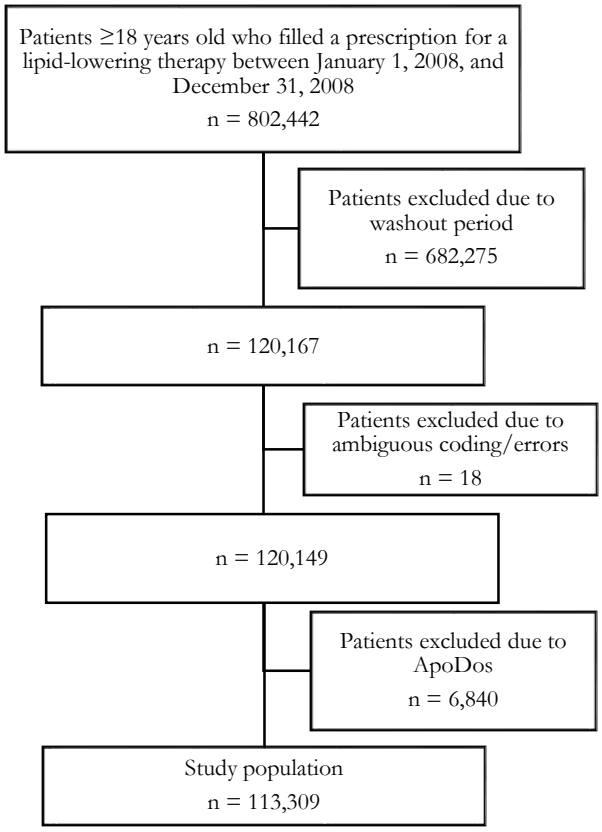


Figure 2: Patient attrition for the study

Between January 1, 2008, and December 31, 2008, a total of 802,442 patients filled at least one prescription for lipid-lowering therapy. The exclusion of patients with filled prescriptions during a 12-months period prior to January 1, 2008, and patients with ambiguous coding resulted in 120,149 treatment-naïve patients. Furthermore, patients with multi-dose dispensed drugs (ApoDos) were excluded. Patients with ApoDos are generally subject to residential care

and obtain their prescribed drugs automatically from the pharmacy every two weeks, which creates an artificially regular drug dispensing pattern. After this last exclusion, the study population consisted of 113,309 patients.

5.2 Study Population: All Patients

The study population was stratified into three cohorts based on the assessed CVD risk. The number of patients per cohort can be seen in figure 3. The division was based on previous diagnoses during a five-year period prior to the index date.

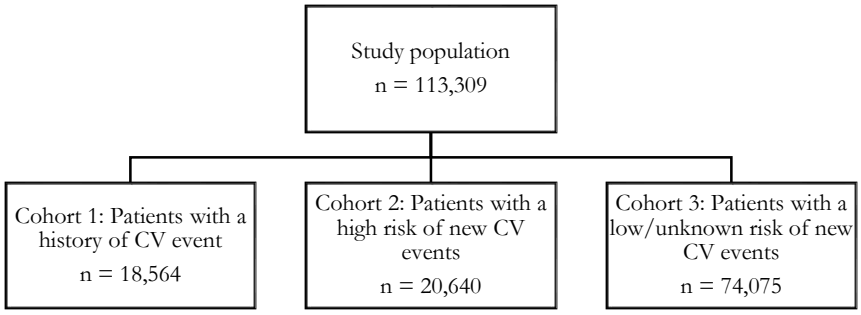


Figure 3: Stratified study population

5.2.1 Descriptive statistics for all patients

Table 1 below describes the characteristics and disease history for the patients with a history of CV event (cohort 1).

Table 1: Descriptive statistics for all patients in cohort 1 (n = 18,564)

Baseline characteristics					
	Female		**Male**		
Gender	6495 (34%)		12099 (65%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	18594	68.19	11.72	68	17
Charlson comorbidity index	18594	1.77	1.49	1	1
History of CV events					
	n	**%**			
Acute myocardial infarction	9569	51%			
Unstable angina pectoris	2562	14%			
Transient ischemic attack	592	3%			
Ischemic stroke	7131	38%			
Heart failure	1841	10%			
Revascularizing procedure	7314	39%			
Other comorbidities					
	n	**%**			
Renal insufficiency	295	2%			
COPD	969	5%			
Depression	608	3%			
Hypercholesterolemia	912	5%			
Diabetes	2393	13%			

Table 2 below describes the characteristics and disease history for the patients with a high risk of CV event (cohort 2).

Table 2: Descriptive statistics for all patients in cohort 2 (n = 20,640)

Baseline characteristics					
	Female		**Male**		
Gender	8463 (41%)		12177 (59%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	20640	64.31	12.96	65	18
Charlson comorbidity index	20640	1.71	1.48	1	1
History of CV events					
	n	**%**			
Transient ischemic attack	2760	13%			
Heart failure	2334	11%			
Other comorbidities					
	n	**%**			
Renal insufficiency	363	2%			
COPD	950	5%			
Depression	734	4%			
Hypercholesterolemia	843	4%			
Diabetes	10995	53%			

Table 3 below describes the characteristics and disease history for the patients with low/unknown risk of CV event (cohort 3).

Table 3: Descriptive statistics for all patients in cohort 3 (n = 74,075)

Baseline characteristics					
	Female		**Male**		
Gender	37233 (50%)		36842 (50%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	74075	61.55	11.19	62	14
Charlson comorbidity index	74075	0.28	0.83	0	0
Other comorbidities					
	n	**%**			
Renal insufficiency	371	1%			
COPD	1012	1%			
Depression	1999	3%			
Hypercholesterolemia	937	1%			
Diabetes	0	0%			

A comparison between the three cohorts reveals a sharp discrepancy in relation to gender composition, age and disease history. The mean age at index date in the cohort with patients with a history of CV event is higher than for the other cohorts (68 years vs. 64 and 62 years) and constitutes of more males (65 percent vs. 59 and 50 percent). Cohort 3, patients with a low/unknown CV risk, have a notably lower Charlson index score compared to cohort 1 and 2 (0.28 vs. 1.77 and 1.71), indicating healthier patients which also is confirmed by the lower percentage of other comorbidities in the cohort.

Figure 4 below presents what type of lipid-lowering therapy the study population filled at index date, e.g. the index prescription. The most common statin, Simvastin, was filled by more than 93 percent of the patients in the population. All types of statins represented 98.54 percent of the filled prescriptions at index date, while fibrates was filled by 0.41 percent whilst bile acid sequestrates and nicotinic acid compiled of 1.05 percent of the filled prescriptions at index date.

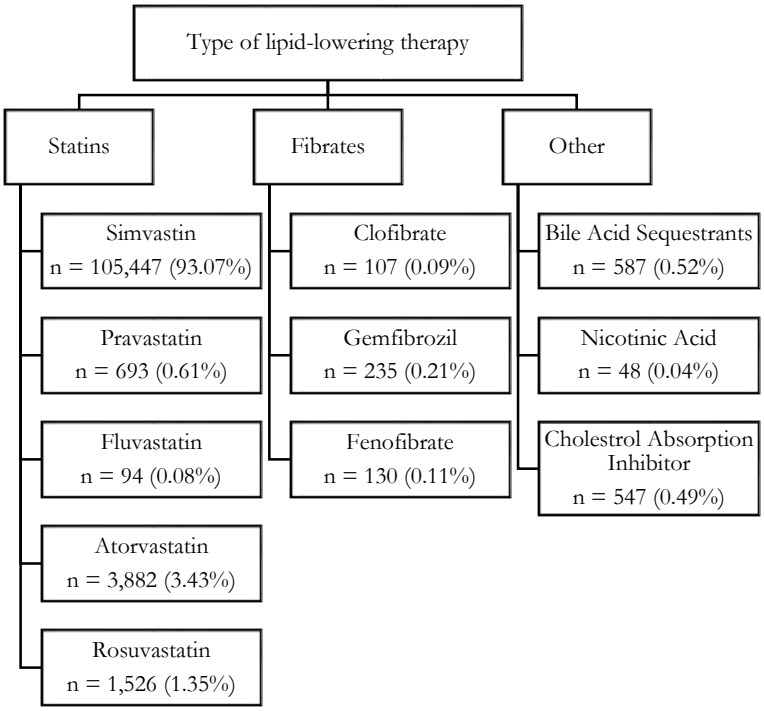


Figure 4: Frequency of lipid-lowering therapies filled at index date

5.2.2 Statistical analysis of adherence

Persistence measure: Kaplan-Meier survival estimates

Nonparametric survival analysis was used to produce estimates of persistence in the form of Kaplan-Meier survival functions. The base permissible gap period was set to two months. The estimated survival function, with treatment termination as failure event, is presented below (figure 5). Patients were right censored for death (date of deaths available up until December 31, 2012) and register limit (December 31, 2012).

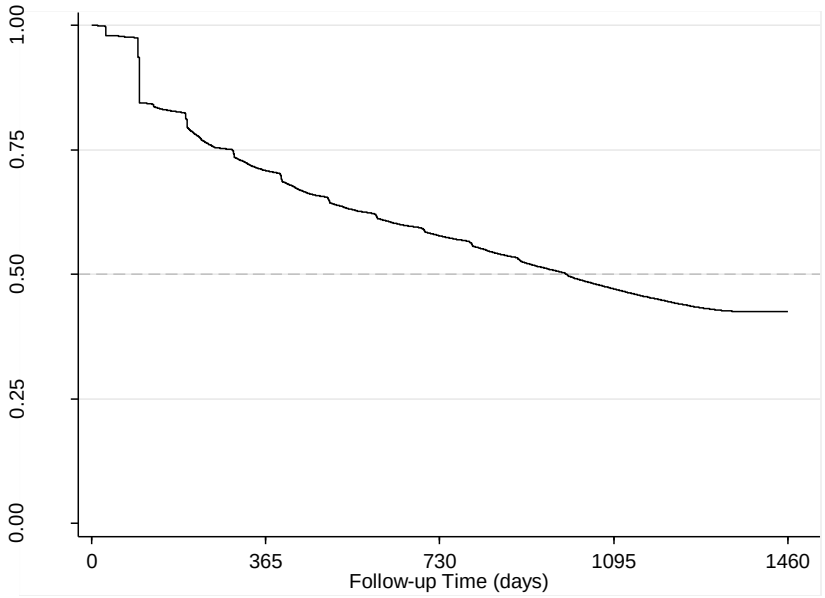


Figure 5: Kaplan-Meier survival function for all patients

The estimated survival function shows that a substantial proportion of all patients terminated treatment after the standard length (100 days) of the index prescription (illustrated as a vertical drop in the beginning of the curve). The proportion of the cohort still on treatment at specific time periods is presented in table 4 below.

Table 4: The estimated proportion on treatment for all patients

Time after index (days)	Survivor Function	Std. Error	95% CI
100	0.8446	0.0011	(0.8425 - 0.8468)
365	0.7082	0.0014	(0.7054 - 0.711)
730	0.577	0.0016	(0.5738 - 0.5801)
1096	0.4705	0.0017	(0.4672 - 0.4738)

As previously noted, a large share of the cohort terminated treatment immediately after the duration of their first filled prescription; more than 15 percent of the patients discontinued treatment after 100 days. A total of 71 percent, 58 percent, and 47 percent were still on treatment after 1 year, 2 years, and 3 years, respectively. The median survival time (i.e. the median number of days on treatment), defined as the earliest time at which half of the study participants have experienced the event [92] (i.e. terminated their treatment), was estimated at 996 days.

Permissible gap period sensitivity analysis

In figure 6 and 7 below two Kaplan-Meier survival functions are presented based on alternative permissible gap lengths.

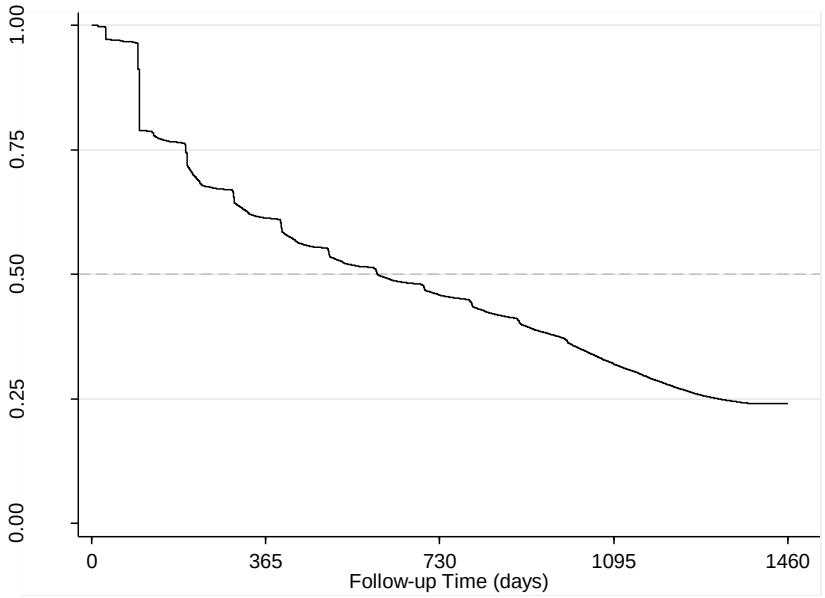


Figure 6: Kaplan-Meier survival function for all patients (Permissible gap = 30 days)

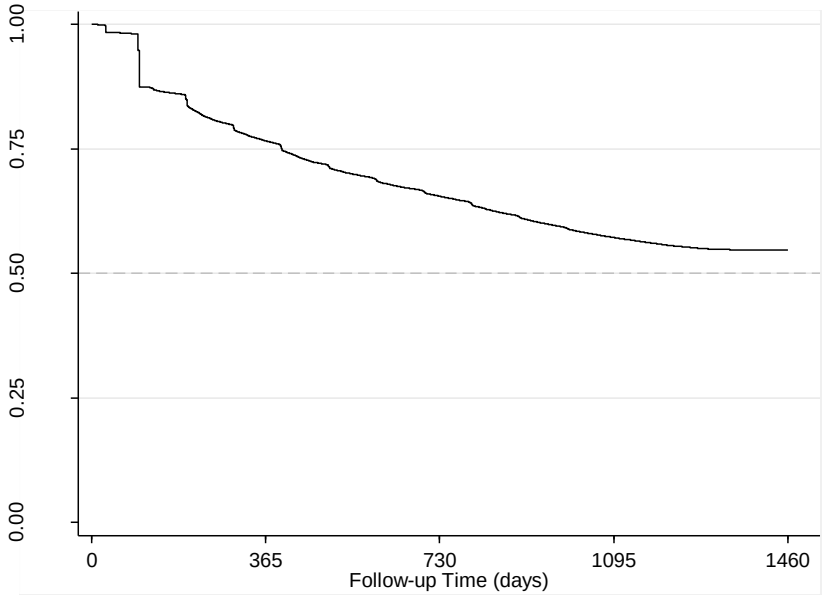


Figure 7: Kaplan-Meier survival function for all patients (Permissible gap = 90 days)

The estimated survival functions show that altering the permissible gap period has a substantial impact on proportion of patients that are classified as persistent. By employing the more conservative gap period of 30 days, almost 10 percentage more patients would be considered non-persistent after one year. The opposite effect can be seen with the more permissible period of 90 days, where additional 6 percentage of the patients would be considered persistent at one year after start of treatment. Table 5 below contains the exact proportion still on treatment by gap lengths at specific time periods.

Table 5: The estimated proportion on treatment by different permissible gap lengths

Time after index (days)	Survivor Function Per. Gap = 30 days	Survivor Function Per. Gap = 60 days	Survivor Function Per. Gap = 90 days
100	0.7893	0.8446	0.8749
365	0.6131	0.7082	0.7659
730	0.4581	0.577	0.6546
1096	0.3196	0.4705	0.5718

Kaplan-Meier survival estimates by cohort, age and drug type

Separate survival curves for the cohorts are shown in Figure 8 below and in the corresponding table 6. The estimated survival functions were significantly different (log-rank test, $p<0.001$).

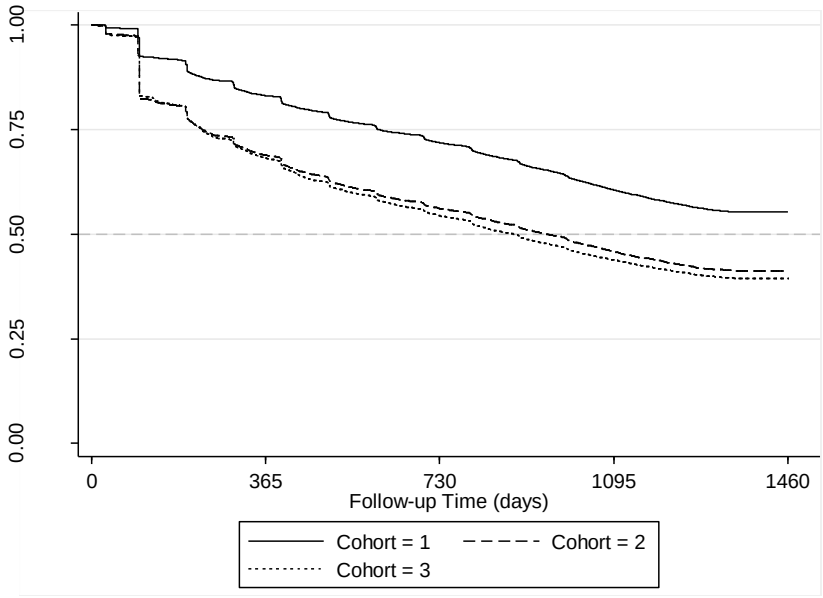


Figure 8: Kaplan-Meier survival function for all patients by cohort

Patients with a history of CV events were clearly the most persistent cohort with over 60 percent of the patients still on treatment three years after initializing treatment. Cohort 2 and 3 were more similar concerning proportion of persistent patients, although patients with high risk for CVD (cohort 2) were more persistent than patients with low/unknown risk (cohort 3) from one year after index date and onwards.

Table 6: The estimated proportion on treatment for all patients by cohort

Time after index (days)	Survivor Function Cohort 1	Survivor Function Cohort 2	Survivor Function Cohort 3
100	0.9249	0.824	0.83
365	0.831	0.6887	0.6814
730	0.7184	0.561	0.5437
1096	0.6049	0.4578	0.4378

Separate survival curves for cohort 2 and cohort 3 by gender are shown in figures 9 and 10 below. The estimated survival functions were significantly different for cohort 2 and cohort 3,

but not for cohort 1 (therefore not shown). (Cohort 2 – log-rank test, p=0. 0.011, Cohort 3 – log-rank test, p<0.001).

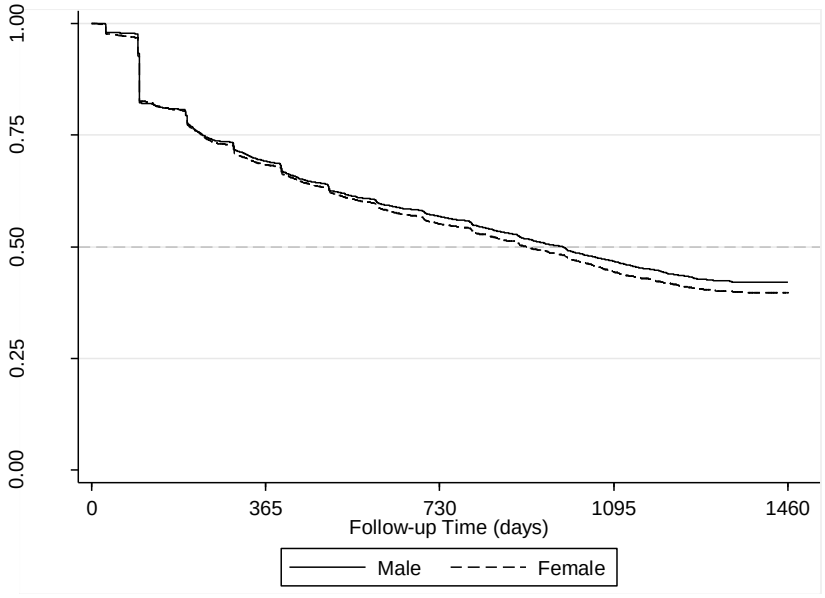


Figure 9: Kaplan-Meier survival function for all patients in cohort 2 by gender

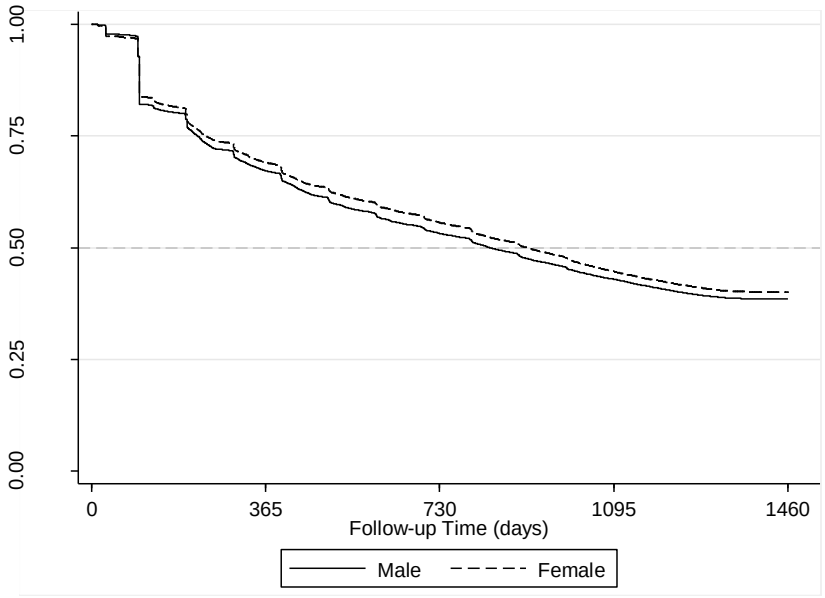


Figure 10: Kaplan-Meier survival function for all patients in cohort 3 by gender

A surprising element is that the most persistent gender differs between the cohorts. In cohort 2 it is the males who are more persistent while in cohort 3 the opposite holds true. In neither cohort is the dissimilarity between the genders sizeable though.

Separate survival curves for age groups are shown in figure 11 below. The estimated survival functions were significantly different (log-rank test, p<0.001).

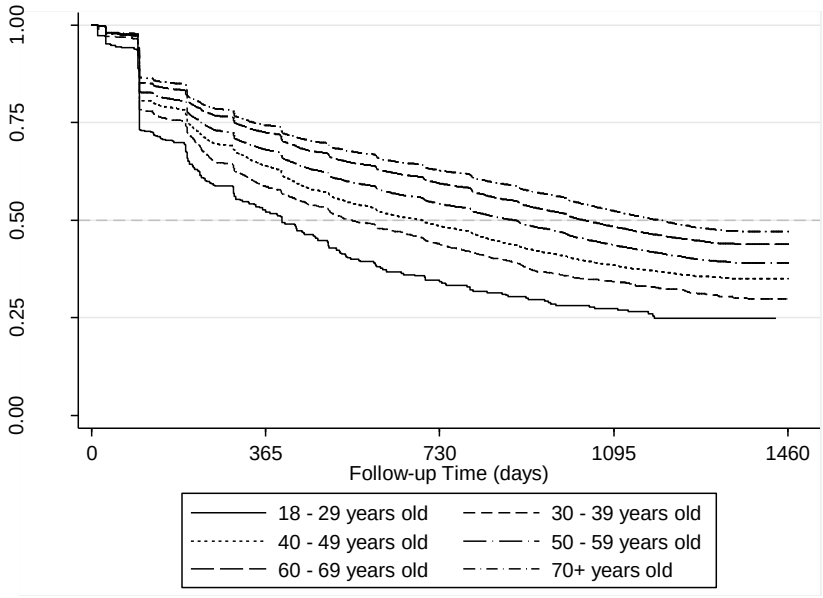


Figure 11: Kaplan-Meier survival function for all patients by age

Age is positively correlated to persistency when considering all patients. The oldest age group, 70 years and older, had more than 50 percent of the patients persistent three years after index date while the youngest age group, 18 to 29 years old, barely had 50 percent persistent patients after the first year.

Separate survival curves for different types of lipid-lowering therapies are shown in Figure 12 below. The estimated survival functions were significantly different (log-rank test, $p<0.001$).

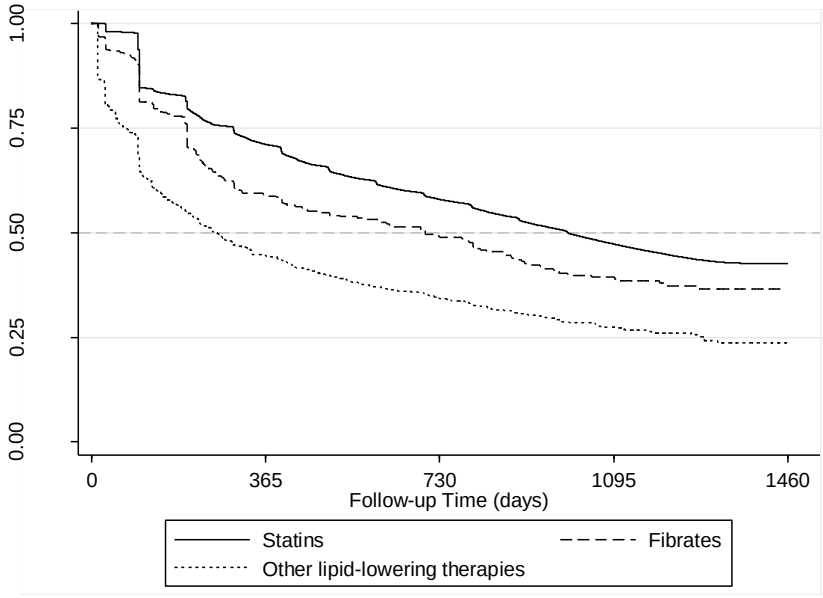


Figure 12: Kaplan-Meier survival function for all patients by index drug type

The group of patients who were given statins as their initial index prescription had a higher proportion of persistent patients throughout the study period. More than half of the patients whose index prescription was of other lipid-lowering therapies had terminated treatment before the end of the first year.

Factors of non-persistence

Table 7 below contains hazard ratios calculated with Cox multiple regression analysis for cohort 1. The hazard ratios reveal the relative risk for non-persistence.

Table 7: Influence on non-persistence by different factors – Cohort 1

Hazard Ratio calculated with Cox multiple regression analysis					
Age in years					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
18 - 29	1.56	0.521	1.32	0.187	(0.81 - 3)
30 - 39	1.12	0.146	0.86	0.387	(0.87 - 1.44)
40 - 49	1.01	0.057	0.22	0.825	(0.91 - 1.13)
50 - 59	1.00	*(reference)*	-	**-**	**-**
60 - 69	0.88	0.031	-3.59	0.000	(0.82 - 0.94)
70 -	0.81	0.028	-6.15	0.000	(0.75 - 0.86)
Gender					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Female	1.00	*(reference)*	-	**-**	**-**
Male	0.96	0.025	-1.51	0.131	(0.91 - 1.01)
Drug type					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Statins	1.00	*(reference)*	-	**-**	**-**
Fibrates	1.42	0.502	0.99	0.323	(0.71 - 2.84)
Other	1.50	0.247	2.44	0.015	(1.08 - 2.07)
History of CV events					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Acute myocardial infarction	0.75	0.027	-8.04	0.000	(0.7 - 0.81)
Unstable angina pectoris	1.00	*(reference)*	-	**-**	**-**
Transient ischemic attack	1.14	0.08	1.83	0.068	(0.99 - 1.31)
Ischemic stroke	0.80	0.03	-5.25	0.000	((0.74 - 0.87)
Heart failure	0.92	0.04	-1.74	0.081	(0.84 - 1.01)
Revasc. procedure	0.89	0.03	-3.50	0.000	(0.84 - 0.95)
Other comorbidities					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
None of the diagnosis below	1.00	*(reference)*	-	**-**	**-**
Renal insufficiency	0.85	0.102	-1.38	0.166	(0.67 - 1.07)
COPD	1.14	0.065	2.23	0.026	(1.02 - 1.27)
Depression	1.31	0.084	4.26	0.000	(1.16 - 1.49)
Hypercholesterolemia	1.21	0.064	3.63	0.000	(1.09 - 1.34)
Diabetes	1.18	0.042	4.60	0.000	(1.1 - 1.26)

The correlation between high age and persistency can also be seen for cohort 1 when regarding the hazard ratios for non-persistence. Patients aged 60 years and older had a 12 - 19 percent lower risk of terminating treatment than patients aged between 50 and 59 years ($p<0.000$ for both). For patients younger than 50 years old there was no statistically significant difference. Factors for non-persistence that were statistically significant for cohort 1 includes CV history; patients with a MI had a 25 percent lower risk of terminating treatment compared to patients who suffered from UAP ($p<0.000$) while IS and a previous revascularizing procedure meant 20 percent and 11 percent lower risk respectively ($p<0.000$ for both). The alteration of risk for a previous diagnosis of TIA or HF was not significant at the five percent significance level, but at the ten percent level (TIA meant a higher risk by 14 percent [$p=0.068$[; HF a lower risk of 8 percent [0.081]). Concerning other comorbidities, patients in cohort 1 who had a

diagnosis of depression, hypercholesterolemia, and diabetes had a higher risk of 18 – 31 percent for terminating treatment.

Table 8 below contains hazard ratios calculated with Cox multiple regression analysis for cohort 2.

Table 8: Influence on non-persistence by different factors – Cohort 2

Hazard Ratio calculated with Cox multiple regression analysis					
Age in years					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
18 - 29	1.47	0.134	4.24	0.000	(1.23 - 1.76)
30 - 39	1.37	0.075	5.73	0.000	(1.23 - 1.53)
40 - 49	1.13	0.043	3.30	0.001	(1.05 - 1.22)
50 - 59	1.00	*(reference)*	-	-	-
60 - 69	0.83	0.024	-6.23	0.000	(0.79 - 0.88)
70 -	0.81	0.023	-7.41	0.000	(0.76 - 0.85)
Gender					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Female	1.00	*(reference)*	-	-	-
Male	0.94	0.019	-2.99	0.003	(0.9 - 0.98)
Drug type					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Statins	1.00	*(reference)*	-	-	-
Fibrates	1.23	0.196	1.33	0.184	(0.9 - 1.68)
Other	2.23	0.256	6.99	0.000	(1.78 - 2.79)
History of CV events					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
None of the diagnosis below	1.00	*(reference)*	-	-	-
Transient ischemic attack	0.77	0.028	-7.20	0.000	(0.72 - 0.83)
Heart failure	0.78	0.029	-6.73	0.000	(0.73 - 0.84)
Other comorbidities					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
None of the diagnosis below	1.00	*(reference)*	-	-	-
Renal insufficiency	0.80	0.069	-2.58	0.010	(0.68 - 0.95)
COPD	1.08	0.055	1.51	0.130	(0.98 - 1.19)
Depression	1.03	0.055	0.51	0.612	(0.92 - 1.14)
Hypercholesterolemia	1.14	0.055	2.62	0.009	(1.03 - 1.25)
Diabetes	1.09	0.026	3.82	0.000	(1.05 - 1.15)

The positive correlation between age and persistency is clearly seen as all the younger age groups (compared to the reference group of 50 – 59 years old) had higher risk of terminating treatment, with ages 18 – 29 having almost twice the risk. Similar to cohort 1, from 60 years and above the risk of non-persistent decreased by 17 – 19 percent. Being male lowered the risk by 6 percent while having any of the CV diagnoses TIA or HF also meant a decrease in the risk by 22 – 23 percent, as did the diagnosis of renal insufficiency (20 percent lower risk). Similar to cohort 1, having a diagnosis of hypercholesterolemia or diabetes increased the risk of non-persistency (9 – 14 percent higher risk).

The correlation between age and non-persistency in cohort 3 is similar to the one for cohort 2; patients above 60 years old have lower risk of terminating their treatment by 11 – 13 percent compared to those aged 50 – 59, while patients younger than 50 years have an increased risk by 13 – 36 percent. The opposite risk by gender compared to cohort 2 which could be seen in

the Kaplan-Meier survival functions (figures 9 – 10) means that males have a 3 percent higher risk to terminate treatment. The only statistically significant diagnosis was renal insufficiency, which meant a 22 percent lower risk of non-persistency.

Table 9 below contains hazard ratios calculated with Cox multiple regression analysis for cohort 3.

Table 9: Influence on non-persistence by different factors – Cohort 3

Hazard Ratio calculated with Cox multiple regression analysis					
Age in years					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
18 - 29	1.36	0.106	3.93	0.000	(1.17 - 1.58)
30 - 39	1.18	0.040	4.83	0.000	(1.1 - 1.26)
40 - 49	1.13	0.021	6.46	0.000	(1.09 - 1.17)
50 - 59	1.00	*(reference)*	-	-	-
60 - 69	0.89	0.012	-8.55	0.000	(0.87 - 0.91)
70 -	0.87	0.013	-9.17	0.000	(0.84 - 0.89)
Gender					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Female	1.00	*(reference)*	-	-	-
Male	1.03	0.011	2.51	0.012	(1.01 - 1.05)
Drug type					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
Statins	1.00	*(reference)*	-	-	-
Fibrates	1.12	0.086	1.48	0.138	(0.96 - 1.3)
Other	2.49	0.117	19.42	0.000	(2.27 - 2.73)
Other comorbidities					
	Haz. Ratio	**Std. Err.**	**z**	**P>z**	**95% CI**
None of the diagnosis below	1.00	*(reference)*	-	-	-
Renal insufficiency	0.78	0.062	-3.15	0.002	(0.67 - 0.91)
COPD	1.03	0.048	0.56	0.573	(0.94 - 1.12)
Depression	1.00	0.033	0.04	0.967	(0.94 - 1.07)
Hypercholesterolemia	1.03	0.048	0.62	0.536	(0.94 - 1.13)

Compliance measure: Medical possession ratio

Compliance was quantified with MPR and calculated from the patient's index prescription up until one year later. The results, shown in table 10 below, demonstrate average MPR per cohort.

Table 10: Medical possession ratio by cohort

Average MPR per cohort					
	n	**mean**	**sd**	**median**	**IQR**
Cohort 1	18594	0.86	0.23	0.99	0.18
Cohort 2	20640	0.74	0.29	0.87	0.46
Cohort 3	74075	0.73	0.29	0.83	0.45

The average MPR for cohort 1 was 0.86, meaning that during the first year after the index prescription the patients with a history of CV events on average complied with their treatment 86 percent of the days. For cohort 2 and 3 the corresponding figures were 74 percent and 73 percent respectively.

Figures 13, 14 and 15 below show the spread of the MPR by cohorts.

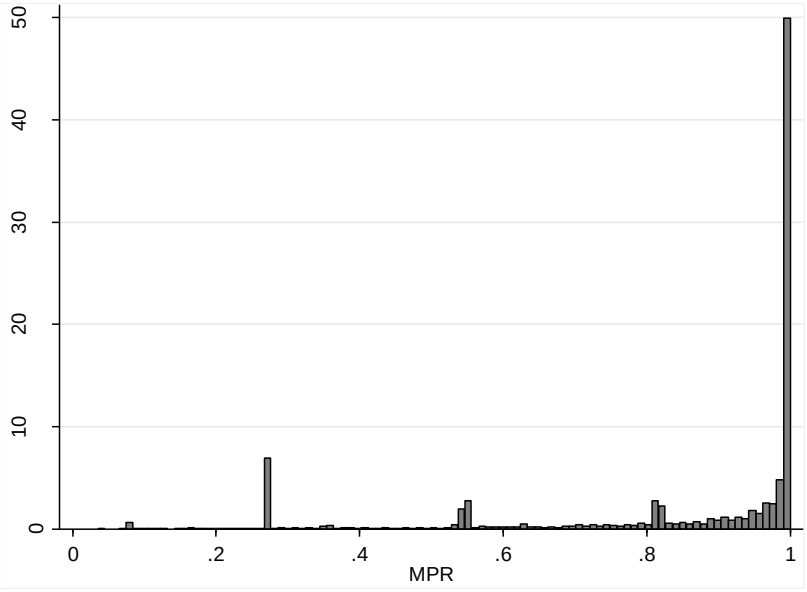


Figure 13: Medical possession ratio for cohort 1

Half of the patients in cohort 1 had perfect compliance during the first year in the follow-up period, illustrated by the highest bar in the figure where MPR equals one. The fact that a significant proportion of the patients only fill their initial index prescription can be seen by the bar located between MPR 0.2 and MPR 0.4 representing around 7 percent of the patients in the cohort. The most common length of the prescriptions are 100 days, yielding a MPR of 0.27 if treatment is terminated thereafter. 78 percent of the patients have a MPR ≥ 0.8.

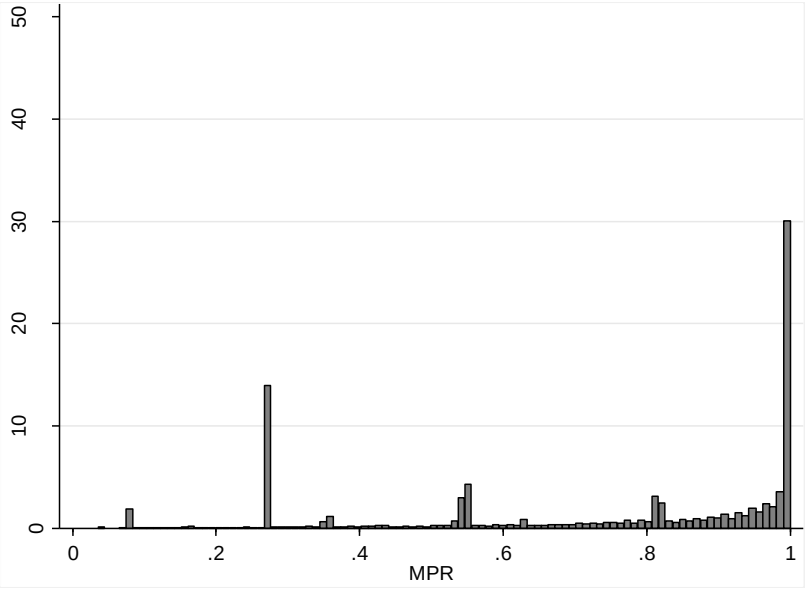


Figure 14: Medical possession ratio for cohort 2

In cohort 2 there were fewer patients who showed perfect compliance, slightly less than a third of the patients entirely complied with their treatment. The share of patients who terminated their treatment after the index prescription was higher than for cohort 1, around 14 percent. 59 percent of the patients have a MPR ≥ 0.8.

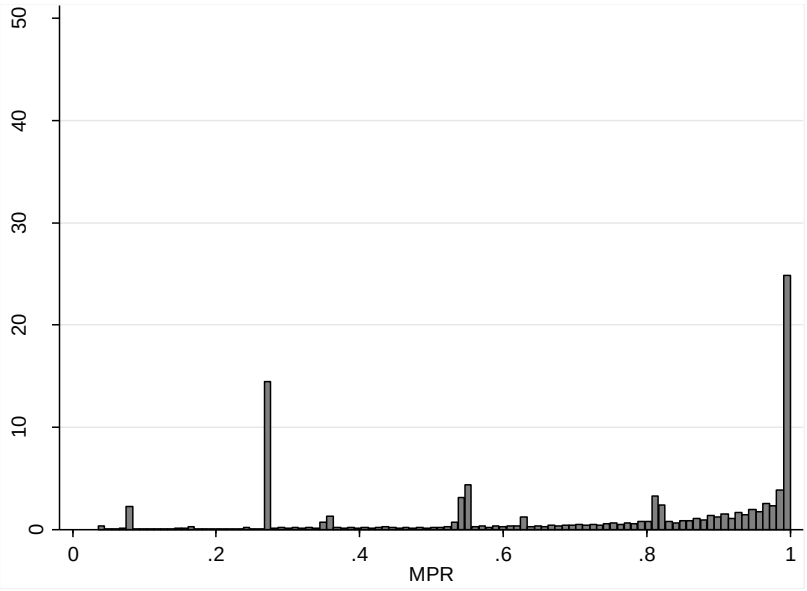


Figure 15: Medical possession ratio for cohort 2

Cohort 3 is similar to cohort 2 in terms of spread of the MPR, but have even less fully compliant patients – around a quarter of the patients have a MPR of 1. Almost 15 percent have a MPR corresponding to treatment termination after the index prescription. 57 percent of the patients have a MPR ≥ 0.8.

5.3 Study Population: Matched Patients

Within the different cohorts, patients with low compliance (non-compliant patients; defined as MPR<80%) were matched to patients with high compliance (compliant patients; defined as MPR≥80%). This is illustrated in figure 16 below.

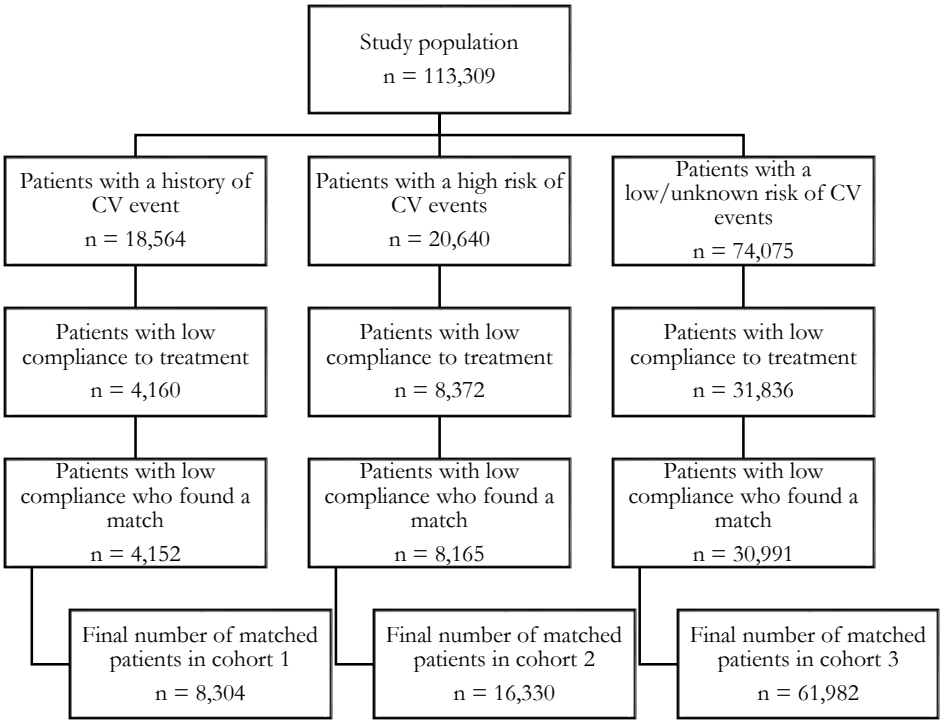


Figure 16: Patient attrition for matched patients

Eight patients with a history of CV event could not find a suitable match resulting in a final number of 8,304 matched patients (4,152 pairs) in cohort 1. For cohort 2, 207 patients with low adherence could not be matched which lead to the final number of 16,330 matched patients (8,165 pairs). 845 patients could not be matched in cohort 3, hence the final number of 61,982 matched patients (30,991 pairs).

5.3.1 Descriptive statistics over matched patients

Table 11 below describes the characteristics and disease history for the matched patients with a history of CV event.

Table 11: Descriptive statistics over matched patients in cohort 1

Demographic & background characteristics					
Patients with high compliance	**Female**		**Male**		
Gender	1778 (43%)		2374 (57%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	4152	69.05	12.28	70	17
Charlson index	4152	1.92	1.68	1	2
Patients with low compliance	**Female**		**Male**		
Gender	1678 (40%)		2474 (60%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	4152	68.81	12.27	70	17
Charlson index	4152	1.89	1.63	1	2

History of CV events	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
Acute myocardial infarction	1654	40%	1796	43%
Unstable angina pectoris	604	15%	629	15%
Transient ischemic attack	196	5%	181	4%
Ischemic stroke	2026	49%	1848	45%
Heart failure	435	10%	462	11%
PTCA	1214	29%	1210	29%

Other comorbidities	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
Renal insufficiency	83	2%	88	2%
COPD	281	7%	260	6%
Depression	139	3%	202	5%
Hypercholesterolemia	265	6%	243	6%
Diabetes	599	14%	579	14%

The group of matched patients with low compliance in cohort 1 consisted of a larger share of males than the matched patients with high compliance; they were also marginally younger and with a lower Charlson comorbidity index score. The share of past diagnoses between the groups were similar with a somewhat higher proportion of MI and depression amongst the low compliance patients. There were more patients with a diagnosis of IS in the group of patients with high compliance.

Table 12 below describes the characteristics and disease history for the matched patients with high risk of CV event.

Table 12: Descriptive statistics over matched patients in cohort 2

Demographic & background characteristics					
Patients with high compliance	**Female**		**Male**		
Gender	3661 (45%)		4504 (55%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	8165	63.79	13.22	65	19
Charlson index	8165	1.70	1.50	1	1
Patients with low compliance	**Female**		**Male**		
Gender	3543 (43%)		4622 (57%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	8165	63.78	13.16	65	19
Charlson index	8165	1.70	1.46	1	1

History of CV events	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
Transient ischemic attack	912	11%	945	12%
Heart failure	785	10%	813	10%

Other comorbidities	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
Renal insufficiency	148	2%	117	1%
COPD	340	4%	391	5%
Depression	300	4%	313	4%
Hypercholesterolemia	378	5%	342	4%
Diabetes	4579	56%	4502	55%

The two groups of matched patients within cohort 2 were almost identical with respect to age and Charlson comorbidity index score. The proportion of females and males within the groups were also similar as wells as past diagnoses.

Table 13 below describes the characteristics and disease history for the matched patients with low/unknown risk of CV event.

Table 13: Descriptive statistics over matched patients in cohort 3

Demographic & background characteristics					
Patients with high compliance	**Female**		**Male**		
Gender	15607 (50%)		15384 (50%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	30991	61.21	11.21	62	15
Charlson index	30991	0.27	0.83	0	0
Patients with low compliance	**Female**		**Male**		
Gender	15655 (51%)		15336 (49%)		
	n	**mean**	**sd**	**median**	**IQR**
Age at index date	30991	61.33	11.17	62	15
Charlson index	30991	0.27	0.82	0	0

Other comorbidities	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
Renal insufficiency	148	2%	145	2%
COPD	392	5%	415	5%
Depression	821	10%	876	11%
Hypercholesterolemia	400	5%	394	5%
Diabetes	0	0%	0	0%

The two groups of matched patients within cohort 3 were almost identical with respect to all variables.

Figure 17 below presents what type of lipid-lowering therapy the matched patients filled at index date (not stratified by cohort). The most common statin, Simvastin, was filled by almost 93 percent of the patients in the population. All types of statins represented 97.39 percent of the filled prescriptions at index date, fibrates was filled by 0.47 percent whilst other lipid-lowering therapies compiled of 1.15 percent of the filled prescriptions at index date.

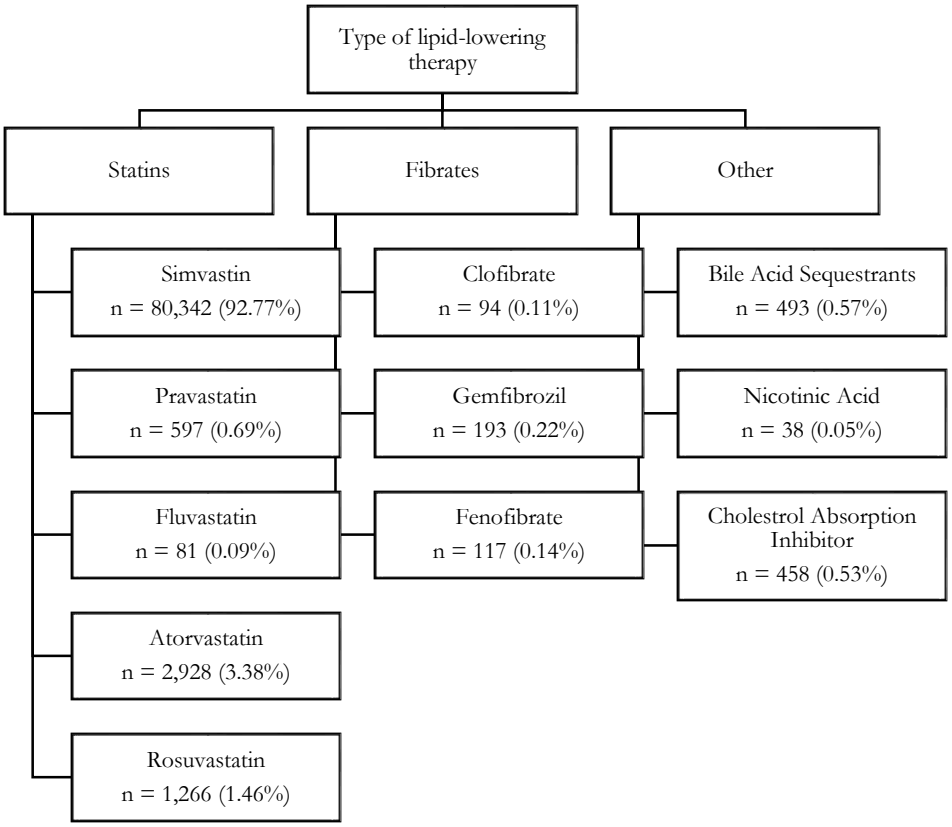


Figure 17: Frequency of lipid-lowering therapies filled at index date by matched patients

5.3.2 Cardiovascular events during follow up

In table 14 below the proportion of compliant and non-compliant patients who had CV events during follow-up period by cohort is presented.

Table 14: Proportion of patients with cardiovascular events by cohort

Number of new CV events during study time				
Cohort 1	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
No new CV events	3399	82%	3196	77%
One new CV event	545	13%	663	16%
Two new CV events	139	3%	185	4%
Three or more new CV events	69	2%	108	3%
Cohort 2	**Patients with high compliance**		**Patients with low compliance**	
	n	**%**	**n**	**%**
No new CV events	7314	90%	7184	88%
One new CV event	635	8%	689	8%
Two new CV events	150	2%	199	2%
Three or more new CV events	66	1%	93	1%

Cohort 3	Patients with high compliance		Patients with low compliance	
	n	%	n	%
No new CV events	29677	96%	29529	95%
One new CV event	1107	4%	1211	4%
Two new CV events	160	1%	187	1%
Three or more new CV events	47	0%	64	0%

In cohort 1, 18 percent of the patients with high compliance to treatment suffered at least one CV event during the follow-up period. For patients with low compliance, the corresponding figure was 23 percent. This difference was statistically significant (Wilcox signed-rank test, $p<0.0001$).

Fewer patients in cohort 2 suffered from CV events, where 10 percent of the compliant patients and 12 percent of the patients with low compliance had at least one CV event during the follow-up period. This difference was statistically significant (Wilcox signed-rank test, $p=0.0012$).

Cohort 3 was the cohort with the least amount of CV events; 5 percent of the patients with high compliance and 5 percent of the patients with low compliance had at least one CV event during the follow-up period. This difference was statistically significant (Wilcox signed-rank test, $p=0.0039$).

Time to first event

In table 15 below the average time to first event by adherence and cohort is presented.

Table 15: Average time to first cardiovascular event during follow-up by cohort

Cohort 1	**n**	**mean**	**sd**	**median**	**IQR**
Patients with high compliance	753	438.37	401.52	315	682
Patients with low compliance	956	503.11	392.79	435	690
Cohort 2	**n**	**mean**	**sd**	**median**	**IQR**
Patients with high compliance	851	459.97	390.82	364	684
Patients with low compliance	981	608.02	392.18	581	649
Cohort 3	**n**	**mean**	**sd**	**median**	**IQR**
Patients with high compliance	1314	531.10	414.78	455	768
Patients with low compliance	1462	684.85	375.58	682.5	620

Amongst all the cohorts there is a tendency for patients with high compliance to have CV events earlier. The difference in average days to first event by compliance for cohort 1, 2, and 3 are 67 days, 48 days, and 154 days respectively.

Figures 18 below shows the time to first event by compliance for cohort 1.

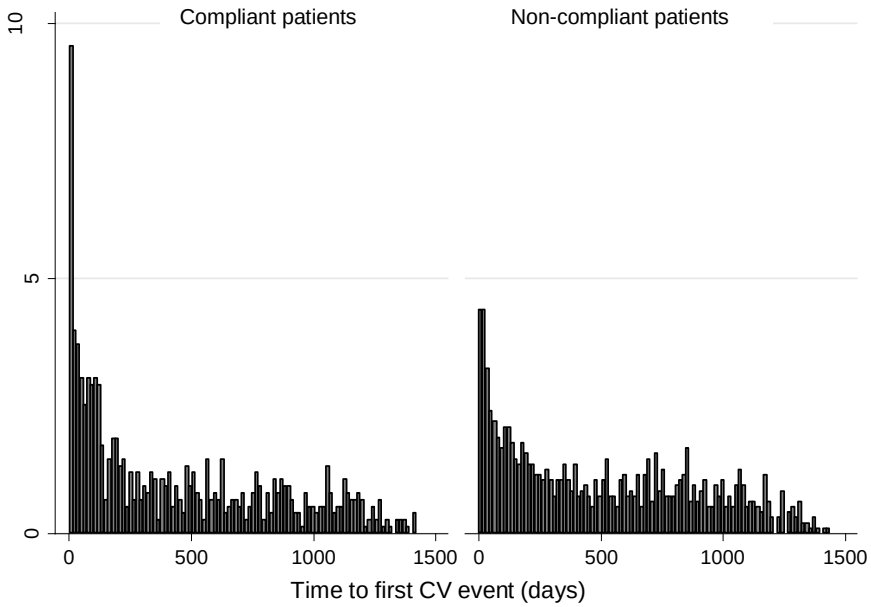


Figure 18: Time to first event for cohort 1 by compliance

There is a tendency in cohort 1 for patients with high compliance to have their first event earlier than patients with low compliance. Amongst patients with a history of CV events who had a new CV event during the follow-up period, 14 percent of the compliant patient suffered their new event within 0 – 30 days after the index prescription whilst 9 percent of the non-compliant had their event in that same period.

Figure 19 below shows the time to first event by compliance for cohort 2.

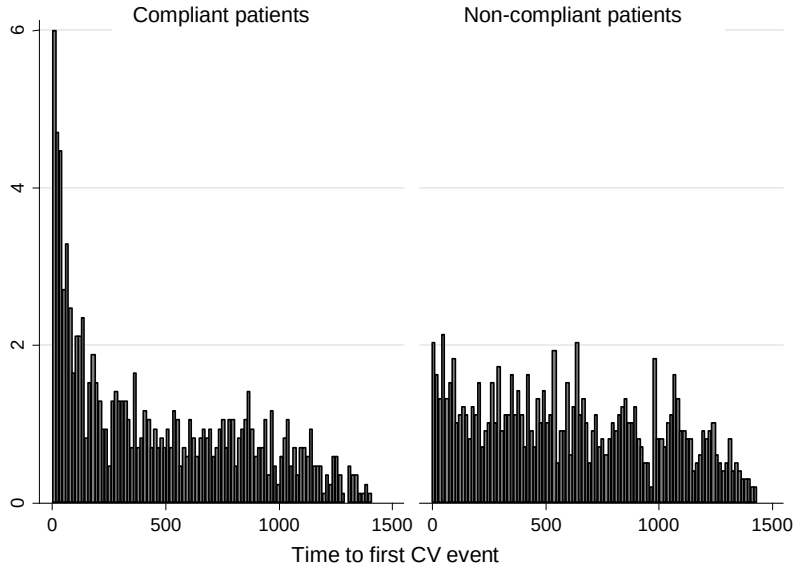


Figure 19: Time to first event for cohort 2 by compliance

There is also a tendency in cohort 2 for patients with high compliance to have their first event earlier than patients with low compliance. The dissimilarity is even more enhanced in cohort 2 where the difference between compliant and non-compliant patients who have a CV event during the first 30 days after index is 7 percentage points (compliant patients; 11 percent and non-compliant; 4 percent).

Figure 20 below shows the time to first event by compliance for cohort 3.

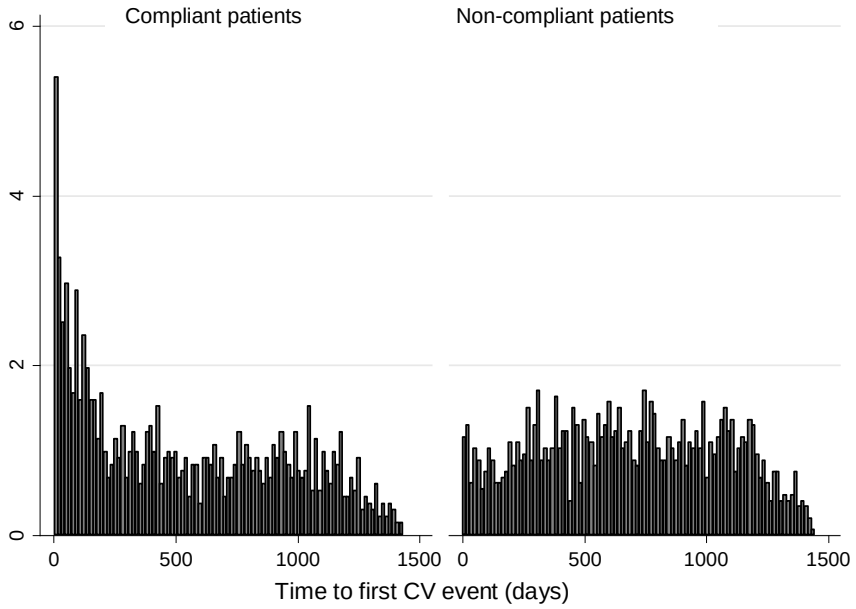


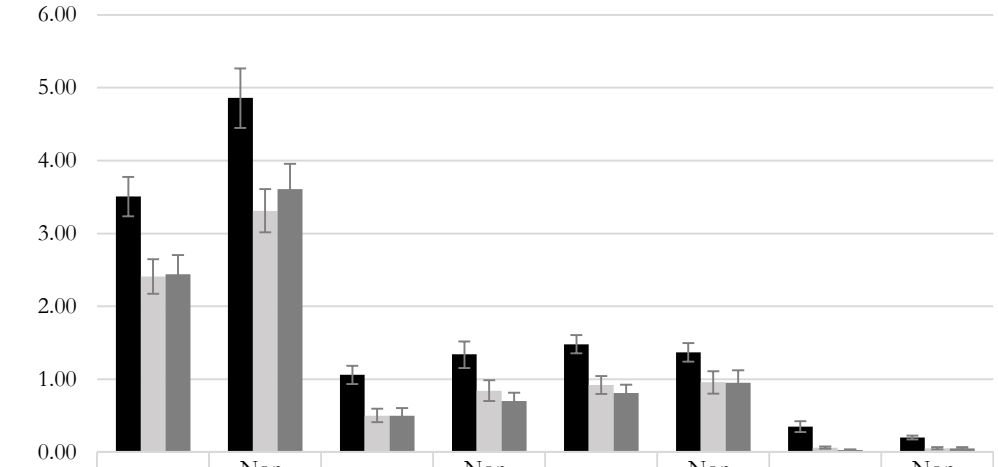
Figure 20: Time to first event for cohort 3 by compliance

Amongst patients with a low/unknown risk of CV events who had a CV event during the follow-up period, 9 percent of the compliant patient suffered their new event within 0 – 30 days after the index prescription whilst 3 percent of the non-compliant had their event in the same period.

5.3.3 Healthcare resource utilization

This section presents the healthcare resource utilization for the matched patients by cohort. The resource use is divided into three time periods; 0 – 365 after the index prescription (Year 1), 366 – 730 days after the index prescription (Year 2), and 731 – 1095 days after the index prescription (Year 3). The resource use will be presented as total resource use – implying all the resource use for the time period – and CV resource use – which only accounts for resource use that had a primary diagnosis corresponding to a CV event (see table 27 in the appendix for specific codes). The resource use is presented separately for patients with low compliance and patients with high compliance and the figures include a 95 percent confidence interval.

Figure 21 and table 16 below present resource use and accompanying regression analysis for cohort 1.



	Total hospitalization (days)		CV hospitalization (days)		Total outpatient visits		CV outpatient visits	
	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
Year 1	3.51	4.86	1.06	1.34	1.48	1.37	0.35	0.20
Year 2	2.41	3.31	0.50	0.84	0.92	0.96	0.06	0.05
Year 3	2.44	3.61	0.50	0.70	0.81	0.95	0.03	0.05

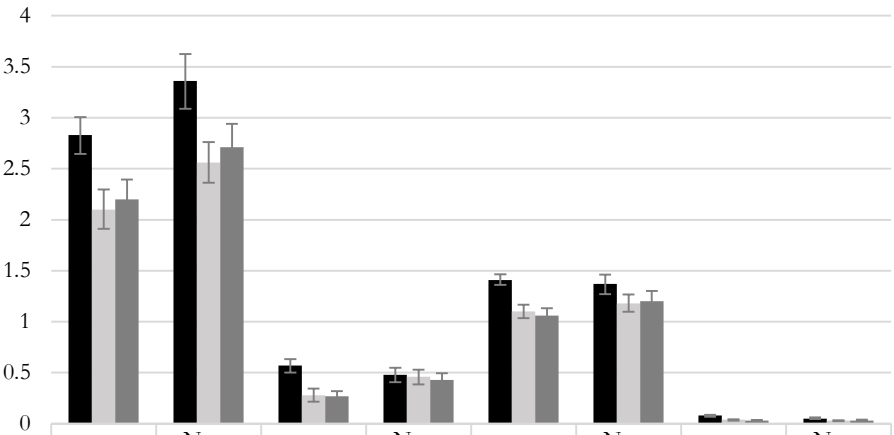
Figure 21: Healthcare resource use for cohort 1 with 95% CI

Table 16: Regression analysis of healthcare resource use on non-compliance for cohort 1

Total hospitalization (days)					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.3852	0.0806	5.60	0.0000	(1.24 - 1.55)
366 – 730 days after index	1.3758	0.0931	4.71	0.0000	(1.2 - 1.57)
731 – 1095 days after index	1.4787	0.1095	5.28	0.0000	(1.28 - 1.71)
Total CV hospitalization (days)					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.2603	0.1163	2.51	0.0120	(1.05 - 1.51)
366 – 730 days after index	1.6703	0.2120	4.04	0.0000	(1.3 - 2.14)
731 – 1095 days after index	1.3917	0.1790	2.57	0.0100	(1.08 - 1.79)

The non-compliant patients in cohort 1 had on average more hospitalized days during all three years, both in regards to all hospitalization and to those with CV events as main diagnosis. The compliant patients had more physician visits with CV events as main diagnosis to specialists (CV outpatient visits) than the non-compliant patients. Both the compliant and the non-compliant patients had a downwards trend in CV resource use over the three years. The first year during the follow-up period was the most resource use heavy for both patients groups, both in regards to total and CV resource use. The regression analysis found that there was a statistically significant difference for non-compliance for hospitalization resource use in all periods.

Figure 22 and table 17 below present resource use and accompanying regression analysis for cohort 2.



	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
	Total hospitalization (days)		CV hospitalization (days)		Total outpatient visits		CV outpatient visits	
First year	2.83	3.36	0.57	0.48	1.41	1.37	0.08	0.05
Second year	2.1	2.56	0.28	0.46	1.1	1.18	0.04	0.03
Third year	2.2	2.71	0.27	0.43	1.06	1.2	0.03	0.03

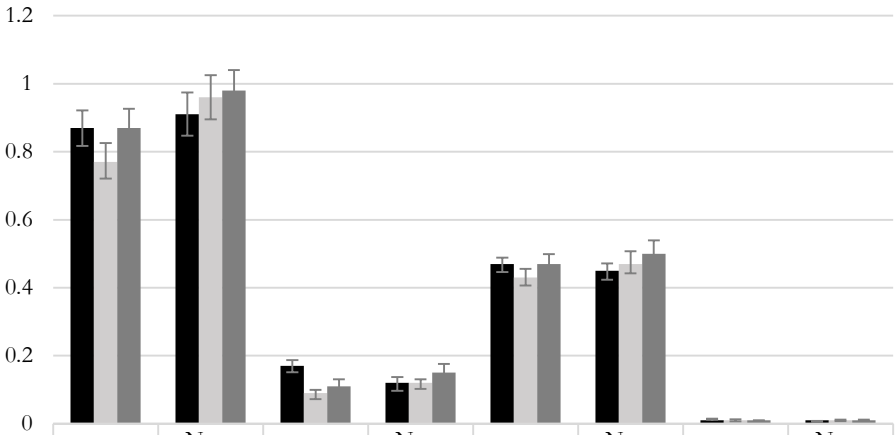
Figure 22: Healthcare resource use for cohort 2 with 95% CI

Table 17: Regression analysis of healthcare resource use on non-compliance for cohort 2

Total hospitalization (days)					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.1874	0.0621	3.29	0.0010	(1.07 - 1.32)
366 – 730 days after index	1.2178	0.0744	3.22	0.0010	(1.08 - 1.37)
731 – 1095 days after index	1.2316	0.0766	3.35	0.0010	(1.09 - 1.39)
Total CV hospitalization (days)					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	0.8428	0.0808	-1.78	0.0750	(0.7 - 1.02)
366 – 730 days after index	1.6272	0.2295	3.45	0.0010	(1.23 - 2.15)
731 – 1095 days after index	1.5844	0.1973	3.70	0.0000	(1.24 - 2.02)

During the first year after the index prescription, the compliant patients had slightly more CV resource use than the non-compliant patients but by the second year the resource use had decreased by roughly half. For the non-compliant patients the CV hospitalization instead remained as on the average half a day's hospitalization throughout the three years. The regression analysis found that there was a statistically significant difference for non-compliance for hospitalization resource use in all periods, apart from hospitalizations for CV events during the first year.

Figure 23 and table 18 below present resource use and accompanying regression analysis for cohort 3.



	Total hospitalization (days)		CV hospitalization (days)		Total outpatient visits		CV outpatient visits	
	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
First year	0.87	0.91	0.17	0.12	0.47	0.45	0.01	0.01
Second year	0.77	0.96	0.09	0.12	0.43	0.47	0.01	0.01
Third year	0.87	0.98	0.11	0.15	0.47	0.5	0.01	0.01

Figure 23: Healthcare resource use for cohort 3 with 95% CI

Table 18: Regression analysis of healthcare resource use on non-compliance for cohort 3

Total hospitalization (days)					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.0476	0.0490	0.99	0.3210	(0.96 - 1.15)
366 – 730 days after index	1.2412	0.0606	4.43	0.0000	(1.13 - 1.37)
731 – 1095 days after index	1.1338	0.0532	2.67	0.0070	(1.03 - 1.24)
Total CV hospitalization (days)					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	0.6908	0.0713	-3.58	0.0000	(0.56 - 0.85)
366 – 730 days after index	1.3601	0.1380	3.03	0.0020	(1.11 - 1.66)
731 – 1095 days after index	1.3708	0.1593	2.71	0.0070	(1.09 - 1.72)

The matched patients in cohort 3 have the least resource use compared to the other two cohorts. The compliant and non-compliant patients also have a similar average resource use over the years with the biggest discrepancy being for hospitalization days during the third year. The compliant patients had higher average days hospitalized for CV events during the first year. The regression analysis found that there was a statistically significant difference for non-compliance for hospitalization resource use in all periods, apart from total hospitalizations during the first year.

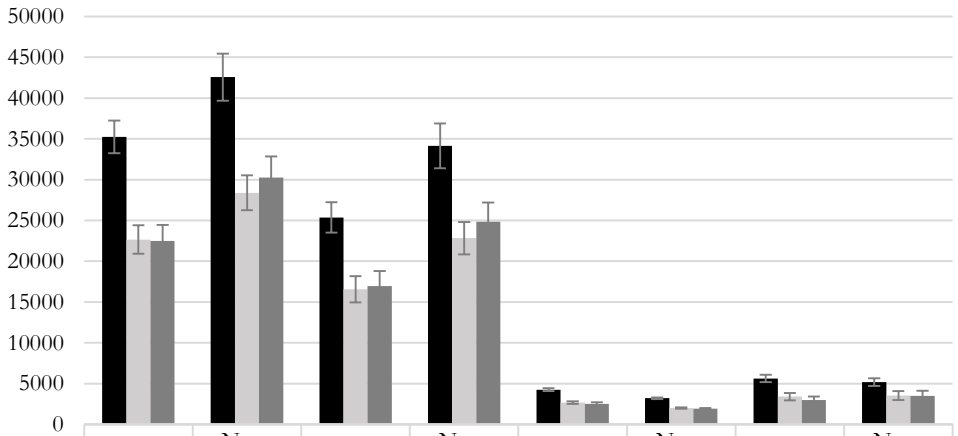
5.3.4 Cost for healthcare resource utilization

This section presents the costs for the healthcare resource utilization for the matched patients. The costs are divided into three time periods; 0 – 365 days after the index prescription (Year 1), 366 – 730 days after the index prescription (Year 2), and 731 – 1095 days after the index prescription (Year 3). The total cost (cost for all healthcare resource use) and the total CV cost (cost for all resource use related to CV events) are presented in different figures. These

numbers are also broken down into three categories; the inpatient cost (hospitalization and surgery), the outpatient cost (specialist visits), and prescription cost (the cost for drugs). The figures include a 95 percent confidence interval. Tables are also presented with the difference in costs between the compliant and non-compliant patients (calculated by subtracting the compliant patient's cost from the non-compliant patient's costs within the matched pair). Accompanying tables over regression analysis of annual cost on non-compliance (where compliance is a binary variable which equals zero if the patient is compliant and one if the patient is non-compliant) are also found in the section. All figures and tables are separated by cohort.

Cohort 1

Figure 24 below presents the total costs for resource use by compliance for cohort 1.

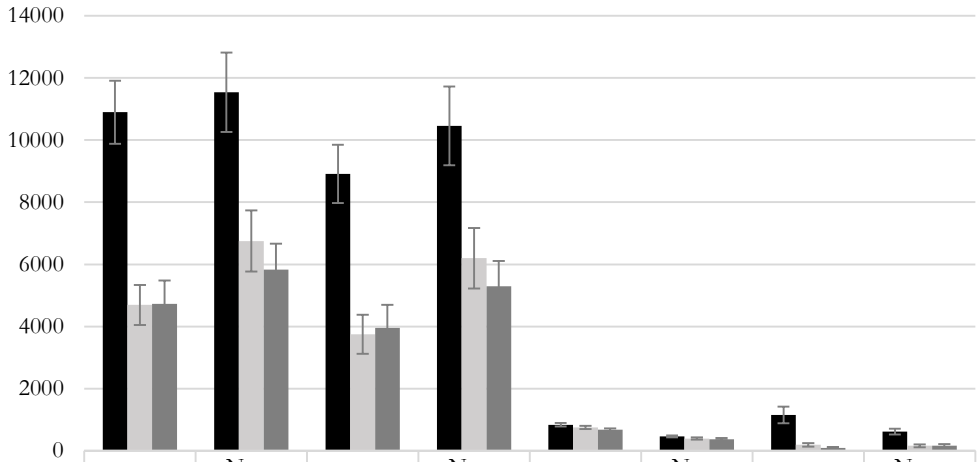


	Total cost		Total inpatient cost		Total prescription cost		Total outpatient cost	
	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
First year	35258	42559	25366	34146	4260	3217	5632	5196
Second year	22658	28389	16566	22834	2681	2022	3411	3533
Third year	22484	30276	16977	24841	2504	1930	3002	3505

Figure 24: Total costs for resource use by compliance for cohort 1 with 95% CI

The non-compliant patients in cohort 1 had a higher total cost of resource use during all the three years after the index prescription. The compliant patients had higher total prescription costs which besides lipid-lowering therapies includes antihypertensive and anti-diabetic medication. Both the compliant and the non-compliant patients had the highest annual total cost during the first year after the index prescription.

Figure 25 below presents the total costs for CV resource use by compliance for cohort 1.



	Total CV cost		CV inpatient cost		CV prescription cost		CV outpatient cost	
	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
First year	10897	11538	8908	10457	838	463	1151	619
Second year	4694	6751	3749	6199	754	393	191	160
Third year	4728	5833	3958	5295	676	371	94	167

Figure 25: Total costs for cardiovascular resource use by compliance for cohort 1 with 95% CI

The non-compliant patients had on average higher total CV cost during each of the three years following the index prescription. An interesting aspect is that the total CV costs during the second and third year are almost half of what they were during the first year for both the non-compliant and compliant patients.

Table 16 below presents the difference in costs between compliant and non-compliant patients in cohort 1.

Table 19: Difference in annual cost between compliance for cohort 1

	n	mean	sd	median	IQR
Total cost					
0 – 365 days after index	4152	7301	117027	-728.25	35426
366 – 730 days after index	3823	5730	87939	-293	18097
731 – 1095 days after index	3527	7792	98670	-232.5	17880
Total CV cost					
	n	**mean**	**sd**	**median**	**IQR**
0 – 365 days after index	4152	641	53725	-157.5	3569.5
366 – 730 days after index	3823	2057	37066	-169	285
731 – 1095 days after index	3527	1105	33568	-142.5	253

Non-compliant patients had on average higher costs, both for all healthcare resource use and for CV-related resource use.

Table 17 below presents the results from a regression on annual costs by non-compliance for cohort 1.

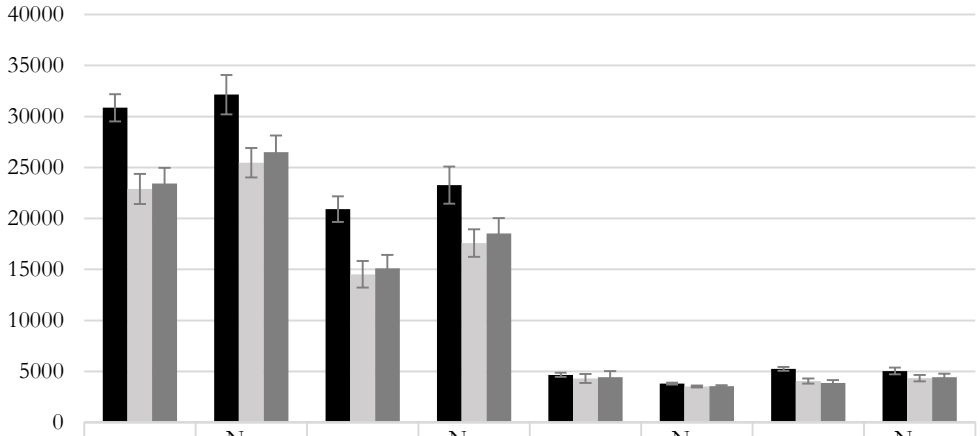
Table 20: Regression analysis of annual cost on non-compliance for cohort 1

Total cost					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.2071	0.0546	4.16	0.0000	(1.1 - 1.32)
366 – 730 days after index	1.2529	0.0690	4.10	0.0000	(1.12 - 1.4)
731 – 1095 days after index	1.3466	0.0838	4.78	0.0000	(1.19 - 1.52)
Total CV cost					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.0588	0.0781	0.77	0.4390	0.9163
366 – 730 days after index	1.4383	0.1466	3.57	0.0000	1.1778
731 – 1095 days after index	1.2337	0.1344	1.93	0.0540	0.9965

The regression analysis of annual cost of total resource use showed that non-compliant patients incurred markedly higher costs than compliant patients and that the differences were statistically significant ($p<0.0000$ of all years). Non-compliant patients had 21 – 35 percent higher costs during the three years that followed the index prescription. The difference for CV-related costs during the first year was not statistically significant. During the second year, non-compliant patients incurred 43 percent higher CV-related costs ($p<0.0000$) and 23 percent higher costs during the third year (however not statistically significant at the five percent significance level, $p=0.0540$).

Cohort 2

Figure 26 below presents the total costs for resource use by compliance for cohort 2.

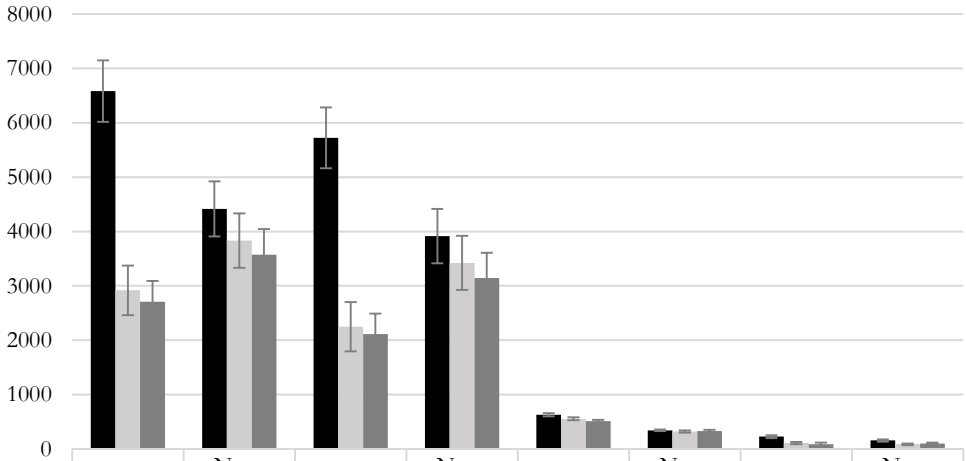


	Total cost		Total inpatient cost		Total prescription cost		Total outpatient cost	
	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
First year	30854	32139	20917	23274	4672	3817	5265	5048
Second year	22892	25462	14519	17589	4310	3523	4063	4350
Third year	23417	26494	15111	18515	4424	3549	3882	4430

Figure 26: Total costs for resource use by compliance for cohort 2 with 95% CI

Non-compliant patients in cohort 2 had on average higher total costs during all of the three years, although compliant patients had the higher total prescription costs during the same periods.

Figure 27 below presents the total costs for CV resource use by compliance for cohort 2.



	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
	Total CV cost		CV inpatient cost		CV prescription cost		CV outpatient cost	
First year	6580	4414	5721	3914	630	343	229	157
Second year	2918	3832	2251	3423	556	323	111	87
Third year	2708	3574	2111	3145	510	330	87	99

Figure 27: Total costs for cardiovascular resource use by compliance for cohort 2 with 95% CI

The compliant patients in cohort 2 had on average higher total costs for CV-related resource use during the first year after the index prescription. For the second and third year the non-compliant patients instead had on average higher costs.

Table 18 below presents the difference in costs between compliant and non-compliant patients in cohort 2.

Table 21: Difference in annual cost between compliance for cohort 2

Total cost	**n**	**mean**	**sd**	**median**	**IQR**
0 – 365 days after index	8165	1284	108499	-1357	25597
366 – 730 days after index	7834	2570	93042	-276	19454
731 – 1095 days after index	7490	3077	99597	-129	19606.5
Total CV cost	**n**	**mean**	**sd**	**median**	**IQR**
0 – 365 days after index	8165	-2166	35122	-149.5	251
366 – 730 days after index	7834	915	30686	-147	231.5
731 – 1095 days after index	7490	867	26776	-115	219

Non-compliant patients in cohort 2 had on average higher costs, both in total and for CV-related only with the exception of CV-related costs during the first year.

Table 19 below presents the results from a regression on annual costs by non-compliance for cohort 2.

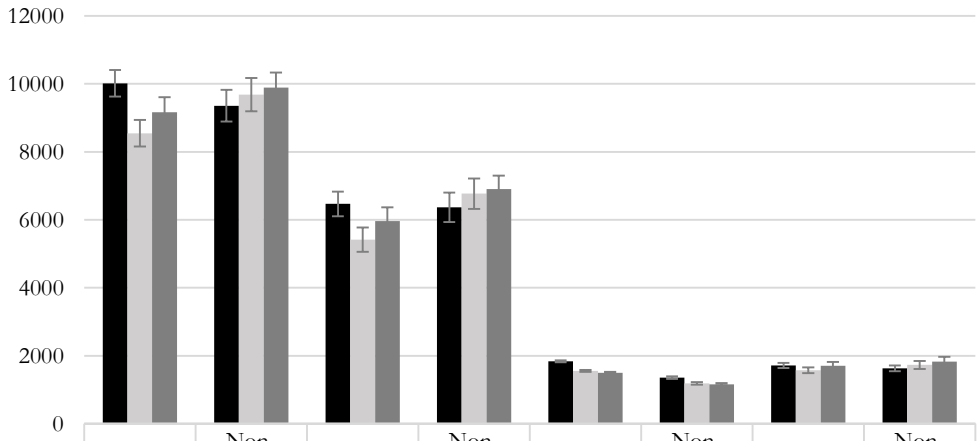
Table 22: Regression analysis of annual cost on non-compliance for cohort 2

Total cost					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	1.0416	0.0393	1.08	0.2800	(0.97 - 1.12)
366 – 730 days after index	1.1123	0.0484	2.45	0.0140	(1.02 - 1.21)
731 – 1095 days after index	1.1314	0.0520	2.69	0.0070	(1.03 - 1.24)
Total CV cost					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	0.6708	0.0490	-5.47	0.0000	(0.58 - 0.77)
366 – 730 days after index	1.3135	0.1371	2.61	0.0090	(1.07 - 1.61)
731 – 1095 days after index	1.3202	0.1303	2.81	0.0050	(1.09 - 1.6)

The regression analysis of annual cost of total resource use showed that compliant patients in cohort 2 incurred 37 percent higher CV-related costs than non-compliant patients during the first year and that this difference was statistically significant (p<0.0000). Non-compliant patients had 31 – 32 percent higher CV-related costs during the second and third year that followed the index prescription (p=0.0090 and p=0.0050). The difference for total costs during the first year was not statistically significant. During the second year, non-compliant patients incurred 11 percent higher total costs (p=0.0140) and 13 percent higher costs during the third year (p=0.0070).

Cohort 3

Figure 28 below presents the total costs for resource use by compliance for cohort 3.

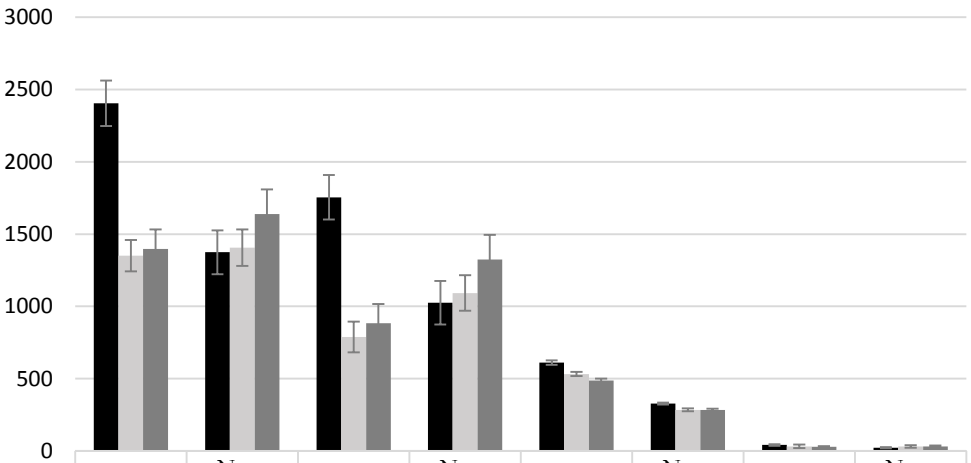


	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
	Total cost		Total inpatient cost		Total prescription cost		Total outpatient cost	
First year	10015	9354	6467	6368	1835	1356	1713	1629
Second year	8544	9683	5415	6767	1555	1185	1574	1731
Third year	9163	9887	5958	6900	1497	1162	1708	1824

Figure 28: Total costs for resource use by compliance for cohort 3 with 95% CI

Compliant patients in cohort 3 had on average higher total costs for resource use than non-compliant patients while the opposite relation was true for the second and third year. The matched patients in cohort 3 had the lowest cost for resource use of the three cohorts.

Figure 29 below presents the total costs for CV resource use by compliance for cohort 3.



	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant	Compliant	Non-compliant
	Total CV cost		CV inpatient cost		CV prescription cost		CV outpatient cost	
First year	2406	1375	1754	1025	610	327	41	22
Second year	1351	1406	788	1092	532	284	31	30
Third year	1398	1638	884	1325	487	283	28	30

Figure 29: Total costs for cardiovascular resource use by compliance for cohort 3 with 95% CI

The compliant patients in cohort 3 had on average higher total costs for CV-related resource use during the first year after the index prescription. For the second and third year it was instead the non-compliant patients who on average had higher costs.

Table 23 below presents the difference in costs between compliant and non-compliant patients in cohort 3.

Table 23: Difference in annual cost between compliance for cohort 3

Total cost					
	n	**mean**	**sd**	**median**	**IQR**
0 – 365 days after index	30991	-661	54339	-198.5	4290
366 – 730 days after index	30646	1138	55204	-206.5	3785.5
731 – 1095 days after index	30171	724	55774	-174.5	3947.5
Total CV cost					
	n	**mean**	**sd**	**median**	**IQR**
0 – 365 days after index	30991	-1031	19567	-137.5	182.5
366 – 730 days after index	30646	55	14892	-152	226.5
731 – 1095 days after index	30171	239	19338	-111	209.5

The compliant patients in cohort 3 had on average higher costs than non-compliant patients, both for total healthcare resource use and CV-related resource use, during the first year. During the second and the third years the non-compliant patients instead had on average higher costs.

Table 24 below presents the results from a regression on annual costs by non-compliance for cohort 3.

Table 24: Regression analysis of annual cost on non-compliance for cohort 3

Total cost					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	0.9340	0.0302	-2.12	0.0340	(0.88 - 0.99)
366 – 730 days after index	1.1332	0.0393	3.60	0.0000	(1.06 - 1.21)
731 – 1095 days after index	1.0790	0.0365	2.25	0.0250	(1.01 - 1.15)
Total CV cost					
	Exp. Coef.	**Robust SE**	**z**	**P>z**	**95% CI**
0 – 365 days after index	0.5715	0.0374	-8.56	0.0000	(0.5 - 0.65)
366 – 730 days after index	1.0411	0.0641	0.65	0.5130	(0.92 - 1.17)
731 – 1095 days after index	1.1712	0.0849	2.18	0.0290	(1.02 - 1.35)

The regression analysis of annual cost of total resource use showed that compliant patients in cohort 3 incurred 63 percent higher CV-related costs than non-compliant patients during the first year and that this difference was statistically significant ($p<0.0000$). Non-compliant patients had 17 percent higher CV-related costs during the third year that followed the index prescription ($p=0.0290$). The difference for CV-related costs during the second year was not statistically significant. During the first year, compliant patients incurred 7 percent higher total costs ($p=0.0340$). Non-compliant patient had 7 – 13 percent higher total costs during the following two years ($p<0.0000$ and $p=0.0250$).

6. Discussion and Conclusion

This concluding section will begin with an analysis where the results and their implications are discussed. Thereafter the validity of the study and its limitations will be reflected upon before the study is summarized.

6.1 Analysis of the Results

The results from this study show that of the 113,309 treatment-naïve patients who filled a prescription of a lipid-lowering therapy between January 1, 2009, and December 31, 2009, 71 percent were persistent one year after the initial index prescription and 47 percent were still persistent after three years. This is similar to the findings of a recent study on statin adherence in Sweden where 73 percent of the studied population were persistent after one year and after three years 54 percent remained on treatment [6]. The similarity is despite the difference in how persistency was defined – the referred study used a permissible gap of 90 days unlike the present study which only allowed 60 days to pass between prescriptions. The lack of well-defined measures for adherence causes a discrepancy amongst research which makes comparisons over studies problematic. The sensitivity analysis on length of permissible gap in the present study demonstrated the importance of the problem; from the most conservative length of 30 days to the more generous length of 90 days the percent of persistent patients at one year after index varied from 61 percent to 77 percent.

Another similarity between the results is that the patient disease history noticeably affects the tendency for adherence – patients with a history of CVD, or diagnosed with a risk factor for CVD, tend to continue with their treatment for a longer period of time than patients lacking these diagnoses [6]. This could be seen in the present study by the stratification of the study population into cohorts and the divergent persistency rates for these cohorts. The share of persistent patients was constantly around 15 percent higher for patients with a history of CV events compared to patients with a high risk of CV events from one year after initializing treatment up to four years afterwards. There was also a difference between patients with high risk of CV events and patients with low/unknown risk but much smaller – after one year the share of persistent patients was less than one percent higher in the high risk cohort which only grew to two percent after three years.

Within the cohorts, certain diagnoses were factors of persistence (notably in cohort 1; MI and IS, in cohort 2; TIA and HF, and in cohort 3; renal insufficiency) as well as factors of non-persistence; diabetes was estimated to lead to 18 percent higher risk of non-persistence in cohort 1 and 9 percent higher risk in cohort 2. These results are in line with research that has found that primary-prevention patients (e.g. patients without history of CVD) are less adherent to treatment compared to those opted for secondary prevention [99]. Another comorbidity that was studied, depression, was only found to be associated with non-adherence for patient with a history of CV events but was for those patients predicted to increase the risk of non-persistency by as much as 31 percent. Depression has in a previous study been found to by its own not to be associated with medication adherence, but during stressful periods that followed major life events depression was found to be strongly associated with non-adherence [100].

Other determinants of non-persistence were found to be age and drug type. There was a tendency for increased adherence with increasing age. This tendency is in agreement with previous studies on statins as well as other drug groups [99, 101-104]. Unlike other research on predictors of cardiovascular medication adherence [105], gender was not a clear-cut predictor of adherence (gender was a non-significant factor of persistency for cohort 1, and had conflicting effect on adherence in cohort 2 and 3).

The study used MPR as a measure of compliance and the results showed that 78 percent of the patients with a history of CV events had a MPR ≥ 0.8. Corresponding figures for cohort 2 and 3 were 59 percent and 57 percent respectively. This was in accordance with the previous study in Swedish setting where 59 percent of the patients had a compliance measure over 0.8 [6]. Based on the level of the MPR were patients classified as compliant or non-compliant to treatment. The non-compliant patients were then matched to compliant patients based on a propensity score. The descriptive statistics reveal that compared to all patients within the cohort, the matched patients were proportionally more often female and older in cohort 1 and 2. The matched patients in cohort 1 also had proportionally fewer MI and IS diagnoses, but a slightly higher Charlson comorbidity index score. The descriptive statistics for the matched patients in cohort 3 were similar to those for all patients, except for a noticeably higher proportion of patients with a diagnosis of depression.

The results from the present study reveal that patients with high compliance had statistically significantly fewer CV events during the follow-up period within all the three cohorts. The largest divergence was found for patients with a history of CVD where 23 percent of the non-compliant patients had a new CV event, five percentage points more than for the compliant patients (18 percent). For the other patient groups, the difference was two percentages points and one percent for cohort 2 and 3 respectively. The indication that higher compliance to treatment leads to fewer CV events has been found in previous research, both in terms of

primary prevention [106-108] and secondary prevention [19, 109, 110]. It is furthermore interesting to note the time to first event separated by compliance-level. There is a greater proportion of compliant patients compared to non-compliant patients who suffer their new event within a relatively short time from the index date. Amongst patients with a history of CV events who had a new CV event during the follow-up period, there was 14 percent of the compliant patient who suffered their new event within 0 – 30 days after the index prescription whilst nine percent of the non-compliant had their event in that same period. The dissimilarity is even further enhanced in cohort 2 where the difference in proportions between compliant and non-compliant patients who have a CV event during the first 30 days after index is seven percentage points (compliant patients; 11 percent and non-compliant; four percent). The difference in cohort 3 is six percentage points (compliant patients; nine percent and non-compliant; three percent). The finding that patients who experience events early during the follow-up period were more often (later) classified as compliant is in accordance with other studies which found that patients are more likely to be compliant after suffering complications due to CVD [111, 112].

In order to analyze the association between poor adherence to hyperlipidemia treatment and cardiovascular events, healthcare resource use was assessed for all of the matched patients. The healthcare resource use was assed annually from the first to the third year after the index prescription and included days of hospitalization, outpatient medical visits, revascularizing procedures, and prescriptions. Non-compliant patients with a history of CVD (cohort 1) were found to have been hospitalized on average more than compliant patients with a history of CVD for all three years, both in regards to all hospitalization and to hospitalization directly associated with CV events. This difference was reflected in costs as the non-compliant patients had 20 – 34 percent higher total healthcare costs during the three years. For costs directly related to CV events, the difference between the compliance levels was only statistically significant during the second year where it was estimated that non-compliant patients had 43 percent higher CV costs. (The third year displayed 23 percent higher costs but only at the ten percent significance level.)

Also within cohort 2, patients with high CVD risk, had the non-compliant patients on average more hospitalization days for both total and CV event resource use, except for the first year's CV hospitalization. This exception was also reflected in the costs directly related to CV events where the compliant patients were found to have 33 percent higher inpatient costs (due to hospitalization and surgery) than the non-compliant patients. It is interesting to view this finding in the light of the time to first event which was described earlier in this section. If patients who have events are more likely to become compliant, then the divergence on costs during the first year might not reflect the influence compliance has on cost but rather the effect an event might have on succeeding compliance. Such a possible effect could also be seen in cohort 3 where compliant patients were estimated to have 63 percent higher CV event-related costs during the first year. The difference in average CV costs between compliant and non-compliant patient was in the subsequent years reversed; both in cohort 1 – where non-compliant patients had on average 17 percent higher cost in the third year – and in cohort 2 – where non-compliant patients had 31 percent and 32 percent higher cost in the first and second year respectively. An explanation for why cohort 1 does not demonstrate a similar pattern could be the high variance on number of CV events during the follow-up period.

As for the costs for total healthcare resource utilization for cohort 2 and 3, the results show that the non-compliant patients had on average higher costs than the compliant patients (11 – 13 percent for cohort 2; 8 – 13 percent for cohort 3). Seen over the cohorts, the largest driver

of costs was inpatient resource use which includes hospitalization and surgeries. As expected, the prescription costs, both in total and for lipid-lowering therapies only, for the compliant patients were higher than for the non-compliant patients for all time period and cohorts. The first year after the index prescription was the costliest year for all the patients in cohort 1 and 2 and for the compliant patients in cohort 3. It is worth noting however that patients were not required to stay alive throughout the follow-up period, leading to 15 percent fewer patients amongst the matched patients in the third year than in the first year for cohort 1. For cohort 2 and 3, there were eight percent and three percent fewer patients respectively. If the most severely ill patients who demanded most resources deceased in the start of the follow-up period, the average cost over the years could differ due to this. However, this would not impact the estimates of difference amongst the compliance levels.

6.2 Validity and Limitations of the Study

The present study is based on retrospective data from three national registers and does therefore not suffer from sampling bias or run the risk of bias due to changing participant behavior. It can as such be deemed a high degree of external validity, particularly in relevance to the studied healthcare system. All retrospective studies on adherence must however be wary of the so-called healthy adherer bias; the possibility of confounders between high adherence to treatment and otherwise health-enhancing behavior. A potential healthy adherer bias would impair the internal validity of the study.

By employing the statistical technique of propensity score matching in the present study, the common problem of healthy adherer bias in adherence studies was addressed. By matching non-adherent patients with adherent patients based on observed baseline characteristics that predict the probability of adherence, the aim was to reduce or eliminate the effects of confounding that arises from using observational data. An important component of assessing whether the propensity score model has been adequately specified involves comparing the matched subjects within the propensity score matched sample. By comparing means, distributions, and standard differences the matching was assess to have adequately eliminated the observed confounding. There is however constantly the risk of unobserved covariates. To estimate the robustness of the estimates, sensitivity analysis of the matching was conducted. The idea behind the analysis is to see how strongly an unmeasured confounder would have to be associated with treatment selection in order for a previously statistically significant treatment effect to become statistically non-significant if the unmeasured confounder had been accounted for. The results from the sensitivity test indicated that the estimates for patients with high and low/unknown risk of CV events were considerably robust, while the estimates for patients with a history of CV event could suffer if an unobserved confounder would affect the probability of non-adherence by more than 30 percent. However, this does not mean that unobserved heterogeneity exists but instead states that the confidence interval for the effect would include zero if an unobserved variable caused the odds ratio of treatment assignment to differ between the non-adherent and adherent patients by more than 1.30.

Another potential study limitation concerns patients who receive a prescription for a lipid-lowering therapy but never filled the prescription. This feature of non-adherence could not be included in the present study since the analysis was based on pharmacy records of prescriptions that get filled, not all prescriptions issued by healthcare personnel. Persistence measures for all patient groups could therefore have been overestimated, but the degree of the bias cannot be measured.

A limitation with respect to resource use was that certain healthcare resources could not be included in the study such as primary care. The main shortcoming in terms of costs was perhaps the omission of indirect costs, i.e. loss of production in the economy due to non-adherence. Data on disability and sick leave for the study population were not acquired and could therefore not be accounted for.

6.3 Summary

This was a retrospective register study of actual treatment adherence behavior for patient with hyperlipidemia in Sweden and an assessment of its clinical and economic implications from a healthcare perspective. The analyses were performed using patient-level data from three Swedish registers: the National Prescription Register, the National Patient Register, and the Causes of Death Register. The objective of the study was to estimate persistence and compliance to treatment of hyperlipidemia in Sweden and relate the non-adherence to healthcare resource utilization and subsequent costs. The analysis was performed on a study population of 113,309 treatment-naïve patients who filled a prescription for a lipid-lowering therapy between January 1, 2009, and December 31, 2009.

In summary, the present study found that 29 percent of treatment-naïve patients in Sweden were non-persistent to lipid-lowering therapies one year after initiating treatment and more than half of the patients, 53 percent, were no longer persistent after three years. Patients with a history of CV events had the highest compliance to treatment as 78 percent of the patients could be classified as compliant, with a MPR over 80 percent. Patients with high and low/unknown risk of CV events had a lower share of compliant patients, 59 percent and 57 percent had a MPR over 80 percent respectively. It was more common amongst non-compliant patients to experience a CV event during the follow-up period of three years; especially for patients with a history of CV events where five additional percentage points of the non-compliant patients had an event compared to the compliant patients. Dependent on CV event risk level, the effect that low compliance had on healthcare resource utilization and consequent costs differed. Non-compliant patients with a history of CV events had 20 – 34 percent higher costs for healthcare resource use than the compliant counterparts during the years in the follow-up period. For patients with high risk of CV events, non-compliance was estimated to cause 11 – 13 percent higher costs during the second and third year after treatment initiation. Non-compliant patients with a low/unknown risk of CV events had 8 – 13 percent higher cost during the last two years of follow-up.

Even though the results validate that there is statistically significant difference in costs between compliance rates for patients on lipid-lowering treatment, it is imperative to also consider the economic significance of increasing adherence. The findings from the present study highlights the different effects an improved adherence will have amongst different populations of patients. When additionally taking into account that an enhanced adherence will lead to higher prescription costs, it might not be cost-efficient to spend resources on increased adherence for all groups of patients. With this in mind, interventions for improving adherence should target accurate patient groups where the reduction of healthcare resource use by higher adherence is shown to be cost-effective. The findings from the present study suggest that disease history and age should be used as determinants for identifying these groups of patients.

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8. Appendix

8.1 Codes for Diagnoses and Medication

Table 25: Diagnoses for risk stratification

Disease/Procedure	ICD-10 code/KVÅ code	Cohort
Myocardial Infarction	I21; I22; I23	1
Unstable angina pectoris	I20.0	1
Ischemic stroke	I63; I65; I66; I67.2; I167.8	1
Diabetes	E10; E11; E12; E13; E14	2
Peripheral artery disease	I70; I71; I74	2
Abdominal aortic aneurysm	I71.3; I71.4	2
Heart failure	I50	2
Transient ischemic attack	G45.9	2
Angina pectoris	I20.1-9; I25.1	2
Revascularization procedures	FND10-20; FNG02; FNG05; PCQ10; PCQ20; PCQ30; PCQ40; PCQ99	1

Table 26: Diagnoses for comorbidities

Disease	ICD-10 code
Diabetes	E10; E11; E12; E13; E14
Renal insufficiency	N18
COPD	J40; J41; J42; J43; J44
Depression	F30 – F39
Familial hypercholesterolemia	E78.0

Table 27: Diagnoses for cardiovascular events

Disease/Procedure	ICD-10 code/KVÅ code
Myocardial Infarction	I21; I22; I23
Unstable angina pectoris	I20.0
Ischemic stroke	I63; I65; I66; I67.2; I167.8
Heart failure	I50
Transient ischemic attack	G45.9
Revascularization procedures	FND10-20; FNG02; FNG05; PCQ10; PCQ20; PCQ30; PCQ40; PCQ99

Table 28: Charlson comorbidity index

Disease	ICD-10 code	Score
Myocardial Infarction	I21; I22; I23	1
Congestive Heart Failure	I50; I11.0; I13.0; I13.2	1
Peripheral Vascular Disease	I70; I71; I72; I73; I74; I77	1
Cerebrovascular Disease	I60-I69; G45; G46	1
Dementia	F00-F03; F05.1; G30	1
Chronic Pulmonary Disease	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
Connective Tissue Disease	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86	1
Ulcer Disease	K22.1; K25-K28	1
Mild Liver Disease	B18; K70.0; K70.3; K70.9; K71; K73; K74; K76.0	1
Diabetes Mellitus Insulin dependent Non-Insulin dependent	 E10.0; E10.1; E10.9 E11.0; E11.1; E11.9	1
Hemiplegia or paraplegia	G81; G82	2
Moderate-Severe Renal Disease	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2

Diabetes Mellitus with End Organ Damage Insulin dependent Non-Insulin dependent	 E10.2-E10.8 E11.2-E11.8	2
Any Tumor	C00-C75	2
Leukemia	C91-C95	2
Lymphoma	C81-C85; C88; C90; C96	2
Moderate-Severe Liver Disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
Metastatic Solid Tumor	C76-C80	6
AIDS	B21-B24	6

Table 29: Possible index drug medications

Drug Type	Drug Name	ATC code
Statin treatment	Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin, Simvastatin	C10AA05, C10AA04, C10AA03, C10AA07, C10AA01
Fibrates	Fenofibrate, Clofibrate, Gemfibrozil	C10AB05, C10AB01, C10AB04
Cholesterol Absorption Inhibitors	Ezetimibe	C10AX09
Nicotinic acid	Niacin	C10AD02
Bile Acid Sequestrants	Colestipol	C10AC02

Table 30: Drugs included in calculations of drug costs

Type of medication	ATC code
Statin treatment	C10AA
Non-statin lipid-lowering treatment Fibrates Bile acid sequestrants Nicotinic acid and derivatives Other lipid modifying agents	 C10AB C10AC C10AD C10AX
Antithrombotics	B01AC
Anti-diabetic medications	A10
Nitrates	C01D
Antihypertensives	C02, C03, C07-09

Table 31: Estimated daily drug dose

Drug Type	Drug Name	ATC code	Estimated daily dose
Statin treatment	Atorvastatin	C10AA05	1 unit per day
	Fluvastatin	C10AA04	1 unit per day
	Pravastatin	C10AA03	1 unit per day
	Rosuvastatin	C10AA07	1 unit per day
	Simvastatin	C10AA01	1 unit per day
Fibrates	Fenofibrate	C10AB05	1 unit per day
	Clofibrate	C10AB02	3/1 unit per day if strength is 200/400 mg
	Gemfibrozil	C10AB04	1 unit per day
Cholesterol Absorption Inhibitors	Ezetimibe	C10AX09	1 unit per day
Nicotinic acid	Niacin	C10AD02	1 unit per day
Bile Acid Sequestrants	Colestipol	C10AC02	9/4 units per day if strength is 1/5 g