Low Statin Persistence Over 36-months is a High-Risk Marker in Adults with Diabetes

by

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Abstract

Statin therapy prevents cardiovascular disease (CVD) in adults with diabetes. There is on-going inconsistency between clinical practice guidelines on whether specific LDL-C levels should be targeted in those on statin therapy. Additionally, real world persistence with statin therapy appears to have plateaued.

To examine the real-world effects of statin use and persistence, and LDL-C levels, on CVD risk, we performed a retrospective cohort study using Alberta administrative health data. We included adults with diabetes and no previous history of CVD, who were 50 years old on April 1, 2012, and followed them until March 31, 2019 for a primary composite outcome of MI, stroke, and revascularization. Statin persistence was defined as the number of 6-month periods in the preceding 3 years during which there were one or more statin dispensations with the first documented window of statin use between April 1, 2009 to September 30, 2009. LDL-C levels (categorized as ≤ or > 2.0 mmol/L) were obtained from linked laboratory results. We conducted a time-varying Cox proportional hazards regression with adjustment for age, sex, income, intensity of diabetes therapy, and other comorbidities.

We included 72,541 individuals (mean age = 65.4 (SD 8.9), 47.6% female). The overall primary outcome rate was 10.4 per 1,000 person-years. Independent of statin use and other variables, LDL-C ≤ 2.0 mmol/L was strongly associated with reduced CVD (adjusted hazard ratio [HR] 0.64 [95% Confidence Interval (CI) 0.59–0.69], p <0.001). A high degree of statin persistence, *i.e.*: statin use in 5 or more of the preceding six-month periods over the previous 3 years was associated with reduced cardiovascular (CV) risk (HR 0.79, [0.71–0.86], p <0.001), compared to those with no statin use in the preceding 3 years. Low statin persistence (statin persistence level (SPL) 1-2 of 6) was associated with higher primary outcome risk compared to

statin non-users (HR 1.34 [1.19–1.51], p <0.001). Moderate statin persistence (SPL 3-4 of 6) showed no association with the primary outcome compared to statin non-users (HR 1.00 [0.88–1.15], p = 0.959)

In adults with diabetes and no previous CVD, statin use in at least 5 of the preceding six-month periods over the previous 3 years appears necessary to yield the proven CVD reducing benefits of statin therapy. Individuals with LDL-C > 2.0 mmol/L and documented statin use in only 1-2 six-month periods in the preceding 3 years are at elevated CVD risk, and may benefit from recall for additional CVD risk reduction.

Preface

This thesis is an original work by Andrew Doma. This research was approved by the Health Research Ethics Board at the University of Alberta (#Pro00109557).

This research represents the combined effort of Andrew Doma, Darren Lau and Dean Eurich. The study is based in part on data provided by Alberta Health and Alberta Health Services, with Alberta Kidney Disease Network housing the data. Data analysis was conducted by Andrew Doma, and interpretation of results was done by Andrew Doma, Darren Lau and Dean Eurich. The manuscript was written and updated by Andrew Doma with feedback from Darren Lau and Dean Eurich.

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This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services

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List of Abbreviations

CABG: Coronary artery bypass grafting

CI: Confidence Interval

CKD: Chronic kidney Disease

CV: Cardiovascular

CVD: Cardiovascular disease

eGFR: Estimated glomerular filtration rate

EMR: Electronic medical record

HbA1c: Hemoglobin A1C

HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A

HR: Hazard Ratio

ICD: International Classification of Diseases

KDIGO: Kidney Disease Improving Global Outcomes

LDL-C: Low-density lipoprotein cholesterol

MI: Myocardial infarction

PCI: Percutaneous coronary intervention

PDC: Proportion of days covered

SD: Standard deviation

SPL: Statin persistence level

Chapter 1: Introduction

1.1 Cardiovascular Disease (CVD) and the Prevalence in Canada

Cardiovascular disease (CVD) remains a major cause of mortality, accounting for 29.8% of all deaths in 2016 throughout Canada.[13] CVD includes myocardial infarction (MI), stroke, and coronary artery disease, often leading to revascularization procedures consisting of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery. Roughly 1 in 12 (2.4 million) Canadians over the age of 20 live with a diagnosed heart disease.[19] CVD tends to affect men earlier and more frequently than women. Men are twice as likely to experience an MI than women. Men experience their first events roughly ~10 years sooner than women, at the ages of 55 to 64 for men, compared to 64 to 74 years of age in women.[19]

1.2 Diabetes Burden in Canada

Diabetes is one of the most common chronic diseases in Canada. Diabetes Canada estimates the prevalence of people diagnosed with diabetes to be 4.1 million in 2023, and projects a climb in prevalence to 5.2 million by 2033.[14] Of those diagnosed with diabetes, 90 to 95% of cases have type 2 diabetes, which is usually associated with metabolic syndrome, adiposopathy, and insulin resistance.[33] Individuals with diabetes have high blood glucose, which can be addressed by a combination of lifestyle modification, non-insulin medications, and insulin therapy.[15] However, the major morbidity and mortality associated with diabetes, for most individuals with type 2 diabetes, is not hyperglycemia *per se.* Diabetes is associated with numerous complications which can lead to substantial impairment in quality of life, mortality, and health care utilization. These complications include CVD, peripheral artery disease, diabetic kidney disease, retinopathy, neuropathy, and diabetic foot disease.[27] Diabetes is the leading

cause of dialysis and non-traumatic amputations in Canada.[23,25] Consequently, the management of diabetes requires multifactorial treatment of risk factors for diabetes-related complications, with a substantial emphasis on general CV and kidney risk reduction, in addition to blood glucose control.[16,24]

1.3 Dyslipidemia Burden in Canada

Dyslipidemia is an overarching term encompassing disorders of metabolism and lipid biochemistry, usually manifesting abnormalities in serum levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol and triglycerides.[4] LDL-C, in particular, is an important constituent of the atherosclerotic plaque responsible for CVD in most patients. Higher LDL-C levels have consistently been associated with increased acute CVD events in epidemiologic studies.[1,2,3] Meta-analyses of trials of statins, a key class of LDL-C lowering medication, have also shown an association between lower achieved LDL-C levels and reduced CVD risk.[5,8,9] Average LDL-C levels cross sectionally in Canada range, irrespective of diabetes status, range from 2.5 mmol/L (aged 18 to 39) to 3.0 mmol/L (aged 40 to 59).[36] An LDL-C level ≥ 5.0 mmol/L is unequivocally high, and usually indicative of familial or genetic condition. For most individuals, whether their LDL-C levels are considered "high" depends on the context provided by an overall CV risk assessment. Most adults with diabetes are considered to be at high CV risk, and in these individuals, Diabetes Canada and Canadian Cardiovascular Society guidelines consider an LDL-C level ≥ 2.0 mmol/L to indicate a need for an adjustment to LDL-C lowering therapy.[29,31]

1.4 Impact of CVD in Adults with Diabetes

Diabetes is considered a leading risk factor for acute CVD events.[28] In adults with diabetes, CVD is the most common cause of death.[29] The increase in MI and MI-related death

associated with diabetes has been long-held to be equal to the increase in risk associated with having previously experienced an MI in adults without diabetes, making diabetes a so-called "cardiovascular disease-equivalent".[20] As a result, LDL-C lowering therapy with a statin is indicated in adults with diabetes age ≥ 40 (or ≥ 30 with a duration of diabetes ≥ 15 years), regardless of other risk factors, including LDL-C level, blood pressure, glycemic control, and smoking status. The use of statins for this purpose, *i.e.*: to reduce the risk of CVD in someone who has not previously experienced CVD or related symptoms, is considered *primary cardiovascular risk reduction,* or, more simply, *primary prevention*.[29,31] Statins are the most commonly prescribed class of medications for the primary prevention of CVD.

1.5 Statins in Adults with Diabetes Prevent CVD

Statins inhibit the production of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, leading to a reduction in the rate of cholesterol biosynthesis in the liver, and an overall reduction in serum LDL-C concentration.[12] Rosuvastatin atorvastatin and simvastatin at doses equal to or above 10mg, 20mg, and 40mg, respectively, are considered high potency, typically associated with LDL-C lowering of 45-60%; other statin-dose combinations have lower potency, typically associated with LDL-C lowering of approximately 35%.[17] In adults without diabetes, statins for primary prevention reduces the risk of acute CVD events consistently across diverse populations and subgroups.[10] The Collaborative Atorvastatin Diabetes Study examined adults with diabetes exclusively, and randomized them to atorvastatin 10mg compared to placebo.[11] Those treated with atorvastatin had follow-up LDL-C levels of approximately 2.0 mmol/L, compared to 3.0 mmol/L in those treated with placebo. Atorvastatin-treated participants had 36% fewer acute coronary heart events and 48% fewer strokes, in relative terms, over 3.9 years of follow-up. There was no increase in adverse events suffered by those given atorvastatin. In

general, statins are considered to have proven efficacy and safety for primary CVD prevention in adults with and without diabetes. However, musculoskeletal side effects, such as myalgias (*i.e.,* muscle pains) are commonly reported when taking statin therapy, and often lead to medication discontinuation.[34]

In addition to the salutary effect of simply being on a statin, meta-analysis of statin trials have shown an association between lower achieved LDL-C levels, and reduced risk of acute CVD. In these trials, each 1 mmol/L decrease in LDL-C was associated with approximately a 20% relative reduction in major vascular events, which appeared similar in the subgroups of those with and without diabetes.[7] More recently, Rana et al.[35] performed a retrospective primary prevention cohort study that showed an independent contribution of reduced LDL-C to lower risk of acute CVD events in adults who were all already on a statin.

Clinical practice guidelines all recommend the routine use of statin therapy for primary prevention of CVD in adults with diabetes meeting the above age- or duration-based criteria. As a result of the associations between lower LDL-C and lower acute CVD events, the Diabetes Canada and Canadian Cardiovascular Society guidelines additionally recommend that lipid lowering therapy be adjusted – either by changing the type or dose of the statin, or by adding additional non-statin medications – to target LDL-C ≤ 2.0mmol/L. However, not all guidelines are in agreement on this point. Guidelines promulgated by the Alberta PEER group for Canadian family physicians recommend against repeat LDL-C testing and statin titration in individuals already started on statin therapy for reasons of practicality.[26]

1.6 Statins in Women of Childbearing Age

Statin therapy is often considered to be contraindicated in women attempting conception, during pregnancy, and during breastfeeding for potential teratogenesis and the role of LDL-C in

the developing embryo.[32] Over the last 30 years, (1991 to 2021), Canada has seen a shift towards older age of childbearing. Live births among mothers aged 15 to 19 years decreased 428.6%, and among mothers aged 25 to 29 years decreased 11.5%; conversely, live birth rates in women age ≥ 40 years quadrupled in the same time period.[37] Increasing maternal age at pregnancy and births may have a role to play in low statin use observed particularly among younger adult women with diabetes and clear statin indications.[30]

1.7 Medication Adherence and Persistence

Guideline-based recommendations can improve outcomes only to the extent that patients and providers are able to carry out the recommendations, and to the extent that patients continue to take their prescribed medications in the community. Adherence, as an umbrella term, has been defined as the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result.[22] This umbrella term captures two subsidiary concepts. First medication adherence refers to whether patients take their medications as prescribed over a discrete period of time. Second, persistence refers to whether they continue to take their prescribed medications. The distinction between these two concepts has been described as: “Mediation adherence refers to the intensity of drug use during the duration of therapy, whereas persistence refers to the overall duration of drug therapy”.[22] Numerous metrics exist to measure medication adherence, including pill counts, patients diaries, and patient reported adherence instruments.[38,40] With the availability of electronic pharmacy data, the medication possession ratio and the proportion of days covered have emerged as common measures of medication adherence. These measures are calculated from the number of doses or days of medication dispensed relative to the total dispensing period.

In contrast, medication persistence usually refers to duration of time. Five operational definitions of persistence used in anti-hypertensive therapy studies were reviewed by Caetano et al..[6] The simplest measure they identified was the anniversary model, which deems a patient persistent if the patient refills a prescription within a specific interval around the anniversary of starting a medication. The minimum-refills model deems a patient persistent if there is a minimum number of prescriptions per year. The refill-sequence model quantifies persistence as the time between the date of the first prescription and the point at which an unacceptable gap between refills occurs. A variation model utilizing proportion of days covered has been used to determine whether a person is persistent with medication at the end of a certain time – they would be deemed persistent if, during that time, their medication adherence was above a minimum proportion of days covered. Finally, a hybrid measure of persistence estimates the proportion of days covered over multiple time periods to determine the point at which a minimum adherence is no longer demonstrated, as the point at which a patient is no longer persistent. While persistence can combine elements of both medication adherence and longevity of therapy, no measure of persistence has emerged as a research gold standard.

1.8 Statin Use in Adults with Diabetes in Canada

Statin use among adults with diabetes with a specific guideline-based indication for statin therapy in Canada has plateaued at 45-54%,[30] and persistence of statin use may be as low as 50% after 1 year.[39] The reasons for statin non-use are varied, and include loss to medical follow-up, low risk perception, perceptions about the risk of statin-related side effects, actual statin-related side effects, as well as provider / system factors such as lack of clinical recall and routine diabetes case management function in community practices. Statin use in adults with diabetes remained stagnant from 2015 to 2020. Given the known protective benefits of these

medications, addressing statin non-use may provide a substantial long term reduction in CVD from a population-wide perspective. However, several questions remain regarding the duration of statin exposure required to yield a CVD benefit, and the independent contribution of statin use and LDL-C levels to CVD risk reduction. Reducing these uncertainties is a first step to addressing low statin use in adults with diabetes in Canada.

1.9 Objectives, Hypothesis and Methods

1.9.1 Objective and Hypothesis

The objective of this study was to examine the real-world effects of LDL target achievement and statin use and persistence on CVD risk, in adults with diabetes and no previous history of CVD. This research was conducted to identify the clinical outcomes of statin persistence levels and LDL-C target achievement in adults with diabetes. We hypothesized that increasing statin persistence and lower LDL-C would be independent predictors associated with of fewer incident CVD events in adults with diabetes.

1.9.2 Methods

We performed a retrospective cohort study using Alberta administrative health data, accessed via the Alberta Kidney Disease Network / International Chronic Disease Collaboration repository.[21] Covariates were determined through Alberta administrative datasets including Discharge Abstracts Database, National Ambulatory Care Reporting System (emergency department visits and day procedures), Practitioner Claims, Vital Statistics, Provincial Laboratory Data, and Pharmaceutical Information Network datasets, which capture medical services provided to all Alberta residents as part of Alberta's system of universal health care. Notably, medication variables were ascertained using the Pharmaceutical Information Network, which captures prescription drug dispensations data (*e.g.,* agent, days supplied, etc.) for all

Alberta residents at the point-of-sale, regardless of payer, with >98% of pharmacies contributing data. We started with Alberta residents age ≥ 18 with diabetes on or before April 1, 2009. From this closed cohort, a nested study cohort was obtained by taking individuals who were at least 50 years of age and no previous history of CVD on April 1, 2012, and had at least one measurement of LDL-C, hemoglobin A1C (HbA1c), and estimated glomerular filtration rate (eGFR) in the same study year at least once during follow-up. We chose age 50 and higher for inclusion, given the increasing frequency of pregnancy and births among women age > 40.

Statin persistence and LDL-C levels were time varying-covariates updated each year. A bespoke metric for statin persistence was used, defined as the number of 6-month periods in the preceding 3 years during which a statin dispensation was documented. This metric was chosen because it is simple, indicates cumulative statin exposure in the preceding 3 years, and it would be straightforward to implement in EMR-based prescription data for the purposes of quality improvement / case management.

Individuals were followed for CVD, defined as acute MI, acute stroke, or a revascularization procedure, as well as the individual components of this composite outcome, until March 31, 2019. We estimated adjusted hazard ratios as our measure of association for the effects of statin persistence and LDL-C levels, using multivariate Cox proportional hazards regression. We adjusted for comorbidities, sex, age, LDL-C target achievement, HbA1c target achievement, income quintiles, diabetes medications and CKD stage.

1.9.3 LDL-C as a Mediator vs Confounding Variable

While LDL-C has an important etiologic role to play in the pathogenesis of atherosclerosis and acute coronary syndrome. We analyzed LDL-C as an independent predictor from statin use / persistence, recognizing a degree of variability in achieved LDL-C even among

individuals on similar lipid lowering therapy. However, in a time-varying analysis LDL-C may also function as a mediator of the benefit of statin therapy. Simultaneous examination of LDL-C and statin persistence using standard time-varying analyses may lead to a spurious reduction in the apparent effectiveness of statin use / persistence. Recognizing this, we performed sensitivity analyses both including and excluding achieved LDL-C as a time-varying covariate.

1.10 Relevance of Research to Adults Living with Diabetes

A substantial proportion of adults with diabetes are foregoing, whether by choice or by omission, CVD prevention from statin therapy. Our work seeks to generate Alberta data to help inform key questions around the benefit of statins for primary CVD prevention in adults with diabetes: Is there a threshold of cumulative persistence or exposure required to benefit from statin therapy? Should providers should pursue treat-to-(LDL-C) target or prescribe-and-forgot strategies to improve statin use in this higher risk population? Our findings will facilitate future efforts to leverage digital health data for EMRs or patient registries, to identify, recall, and advise high-risk adults and improve CV risk reduction in adults with diabetes.

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Chapter 2: Low Statin Persistence Over 36-months is a High-Risk Marker in Adults with Diabetes

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2.1 Introduction

CVD is the leading cause of morbidity and mortality in adults with diabetes.[12] Among adults living with diabetes, CVD rates are 1-3 times higher in women and 2-5 times higher in men, than among those without diabetes.[12] CV risk reduction in adults with diabetes involves addressing multiple CV risk factors, *e.g.,* hypertension, dyslipidemia, glycemic control, smoking cessation, diet, and physical activity, as well as starting risk-reducing medication.[1,13,20] Statin therapy is a mainstay of CVD prevention, shown to reduce major CV events in adults with diabetes and no previous history of CVD.[3]

In Canada, statin therapy is recommended in all adults with diabetes age > 40 for primary CV risk reduction.[13] While specialist diabetes and cardiology guidelines favour a "treat-to-target" strategy of titrating lipid lowering therapy to achieve a LDL-C concentration ≤ 2.0 mmol/L, or a ≥ 50% reduction from baseline, [12,15] primary care guidelines recommend against repeat lipid testing and cholesterol targets after statin initiation (*i.e.,* a "treat-and-forget" approach).[11] Lipid-lowering therapy trials appear to show increasing CV benefit at lower degrees of achieved LDL-C, but the effects of LDL-C level and the use of the trial agents may be difficult to disentangle, and primary prevention and diabetes populations are under-represented in such trials. Either way, adherence and persistence of statin use appear critical to realizing the trail-derived benefits of statin therapy. However, real-world evidence linking statin persistence

and LDL-C target achievement to CV outcomes in adults with diabetes is limited. In particular, no study has simultaneously examined LDL-C target achievement and variations in cumulative duration of statin persistence in adults with diabetes. Statin persistence is an important quantity, since clinical trials suggest a minimum persistence of 2.5 years to see a meaningful absolute risk reduction from statin therapy.[24]

Statin use among adults with diabetes in Canada has plateaued at 45-54%,[14] and persistence of statin use may be as low as 50% after 1 year.[22] We performed a retrospective cohort study to examine the real-world effects of LDL target achievement and statin use and persistence on CVD risk, in adults with diabetes and no previous history of CVD.

2.2 Methods

2.2.1 Data Sources and Study Design

We performed a retrospective cohort study using Alberta administrative health data, accessed via the Alberta Kidney Disease Network / International Chronic Disease Collaboration repository.[7] Alberta administrative datasets include Discharge Abstracts Database, National Ambulatory Care Reporting System (emergency department visits and day procedures), Practitioner Claims, Vital Statistics, Provincial Laboratory Data, and Pharmaceutical Information Network datasets, capturing medical services provided to all Alberta residents as part of Alberta's system of universal health care. Notably, the Pharmaceutical Information Network captures prescription drug dispensations data (*e.g.,* agent, days supplied, etc.) for all Alberta residents at the point-of-sale, regardless of payer, with >98% of pharmacies contributing data.

We started with Alberta residents age ≥ 18 with diabetes on or before April 1, 2009. Diabetes was identified using the National Diabetes Surveillance System administrative data case definition,[8] consisting of 1 hospitalization or 2 claims within two years for International

Classifications of Diseases (ICD)-9 code 250 or ICD-10 E10-E14. Patients with codes specifically indicating type 1 diabetes (ICD-9 250.x1 & 250.x3 and ICD-10 E10.xx) were excluded. From this closed cohort, a nested study cohort was obtained by taking individuals who were at least 50 years of age and had no previous history of CVD in the preceding 10 years, on April 1, 2012, and had at least one measurement of LDL-C, hemoglobin A1C (HbA1c), and estimated glomerular filtration rate (eGFR) in the same study year at least once during follow-up.

An age restrictions of at least 50 years was chosen instead of the usual statin indication threshold age of 40 years. The higher age inclusion criteria was intended to avoid selective statin non-use due to fertility concerns and pregnancies among women age 40-49, which have generally increased in Canada over the preceding 30 years.[19] CVD was defined as a previous history of ischemic heart disease, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), stroke, transient attack, or peripheral artery disease (Appendix 1: Table A1 for administrative data definitions).[2,6,23] This led to the creation of a primary prevention cohort of adults (age ≥ 50) with diabetes, followed from April 1, 2012, until a study outcome, or censoring due to death, out migration, or end of follow-up on March 31, 2019. The 3-year period April 1, 2009 – March 30, 2012 was considered a baseline period.

2.2.2 Outcomes

Our primary outcome was a composite MI, stroke, and PCI or CABG, based on hospitalization with a discharge diagnosis (most responsible to secondary diagnoses) or therapeutic intervention with the relevant validated ICD diagnostic codes (Appendix 1: Table A1).[2,6,23] We examined individual components of the composite outcome as secondary outcomes.

2.2.3 Statin Persistence and LDL-C Target Achievement

Statin persistence refers to the duration of time over which medication use is continuously sustained.[4] In operationalizing statin persistence, we took the perspective of a primary care provider, practice manager, or chronic disease case management program, looking backwards over a discrete period of time to identify high risk individuals within a panel of patients. Our aim was to measure statin persistence using a simple metric which may be readily composed by querying a prescription or dispensation database, and also provides a summary of recent cumulative statin exposure. As such, we operationalized statin persistence as the degree of cumulative exposure over the preceding 3 years. Specifically, we divided the 3-year baseline into 6-month periods. Statin persistence was defined as the number of periods in which one or more statin dispensations occurred. There were seven possible levels of statin persistence, ranging from 0, representing no statin use in the preceding 3 years; to 6, *i.e.,* at least one dispensation in each of the 6 preceding six-month periods over the previous 3 years, representing continuous long-term statin exposure. Statin persistence was modelled as a categorical time-varying covariate updated every 6-months based on a moving 3-year assessment window with the first window during the baseline period of April 1, 2009 to March 31, 2012, as illustrated in Appendix 2 (Table A2).

Recognizing that incomplete levels of statin persistence (*i.e.,* 1-5) could indicate either continuous and accumulating use, or discontinuous / lapsed use, we further divided statin users into current / non-current users based on presence of a statin dispensation in the 6-month period immediately preceding the time point of assessing statin persistence (see Appendix 3 [Table A3] for an illustration).

LDL-C target achievement was also configured as a time-varying covariate, assessed every April 1 as a binary variable indicating if the average of all LDL-C measurements in the

preceding years was ≤ 2.0 mmol/L, the Diabetes Canada and Canadian Cardiovascular Society recommended target for LDL-C control in primary prevention.[13,15]

2.2.4 Other Covariates

Other covariates were age, sex, neighbourhood income quintile based on postal code sortation area matching census data, family physician visits, internal medicine visits, emergency department visits, hospitalizations and comorbid medical conditions. Comorbid medical conditions were alcohol misuse, asthma, atrial fibrillation, cancer (lymphoma), cancer (metastatic), cancer (non-metastatic solid organ), CKD, chronic pain, chronic pulmonary disease, chronic viral hepatitis B, cirrhosis, dementia, depression, epilepsy, gout, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, osteoporosis, Parkinson's disease, peptic ulcer disease, peripheral arterial disease, psoriasis, rheumatic disease, schizophrenia, and severe constipation. These conditions were defined until the end of the baseline period (prior to or on March 31, 2012) using validated ICD-9 and ICD-10 case definitions[21] and remained constant throughout the follow-up (April 1, 2012 to March 31, 2019).

Additional time-varying variables were included in the model. HbA1c target achievement (≤ 7.0%, the Diabetes Canada-recommended target for most non-frail individuals)[16] and eGFR were updated every April 1 based on the average of all relevant laboratory measurements in the preceding year. eGFR was ordinally sorted into Kidney Disease Improving Global Outcomes (KDIGO) stages of CKD based on eGFR cut-offs (mL/min/1.73m^2): Stage 1 ≤ 90, 60 ≤ stage 2 < 90, 45 ≤ stage 3a < 60, 30 ≤ stage 3b < 45, 15 ≤ stage 4 < 30 and stage 5 < 15.[10]

2.2.5 Ambiguous Case of LDL-C

With regards to the ambiguity of LDL-C in the study, both causal pathways were considered (Figure 1A & Figure 1B). For all main analyses and statistics LDL-C was treated as a confounding variable and a sensitivity analysis was conducted where the statistics produced are directly related to LDL-C as a mediator.

2.2.6 Statistical Analysis

Characteristics of the cohort, shown by levels of statin use / persistence at baseline, were described using simple means, standard deviations (SD), and proportions. Kaplan Meier survival analysis was used to illustrate the incidence of the primary outcome across levels of statin persistence and LDL-C target achievement. We conducted a multi-variable-adjusted time-varying Cox proportional hazards regressions featuring all of the above covariates. We considered a hazard ratio (HR) statistically significant at $p < 0.05$. Additionally, we tested for interactions between persistence and target LDL-C achievement, and these were included in the model if they were statistically significant.

If a participant did not have any measurements for one or more LDL-C, HbA1c, or eGFR in the preceding year, they were excluded for the person-year in question. They could contribute other person-years of follow-up if they included all of LDL-C, HbA1C, or eGFR measured in the preceding year.

2.2.7 Sensitivity Analyses

While LDL-C achievement (LDL-C level ≤ 2.0 mmol/L or > 2.0 mmol/L) was primarily considered an independent predictor of CVD outcomes in its own right, we recognize that it may simultaneously constitute a mediator of the effect of statin persistence. Accordingly, we performed a sensitivity analysis where LDL-C was removed from the analysis. We performed an

additional analysis featuring data from current statin users only, to ascertain the effect of LDL-C ≤ 2.0 mmol/L among individuals already started on statin therapy.[17]

All analyses were conducted on STATA/MP 18.0 (StataCorp LLC, College Station, Texas). This study was approved by the Health Research Ethics Board at the University of Alberta (#Pro00109557).

2.3 Results

2.3.1 Cohort Characteristics

Among 202,037 Alberta adults with diabetes on April 1, 2009, we included a total of 72,541 adults with diabetes and no history of CVD (Figure 2).

The average age overall was 65.4±8.9 years, with a nearly even balance of men and women, 47.9 and 52.1%, respectively. Each individual contributed an average of 6.9 person-years of follow-up. Most individuals had LDL-C >2.0 mmol/L at baseline (54%) and were treated with oral agents only (64%); an additional 8% and 8% were treated with basal or bolus insulin respectively, and 20% had no record of any anti-hyperglycemic medications at baseline (Table 1).

2.3.2 Statin Persistence and LDL-C Target Achievement at Baseline

At baseline, statin persistence was high (5-6 of the preceding six-month periods over the previous 3 years) (n = 21,337, 47%), moderate (3-4) (n = 5,317, 12%), and low (1-2) (n = 4,568, 10%); a sizeable proportion of individuals (n = 14,136, 31%) had no evidence of statin use during the preceding 3 years (Table 1). LDL-C ≤ 2.0 mmol/L at baseline ranged from 19% to 66% and appeared more frequent with increasing statin persistence (Table 1). Statin non-users were statistically more likely to have HbA1c ≤ 7.0%, and to be on anti-hyperglycemic medications. Among statin-exposed individuals at baseline, those with higher persistence were

more likely to be on an anti-hyperglycemic medication and appeared slightly more likely to be on basal or bolus insulin.

2.3.3 Statin Persistence and LDL ≤ 2.0 mmol/L Throughout Follow-Up

Statin persistence varied during follow-up. It was 0, 1-2, 3-4, and 5-6 in 28%, 8%, 9%, and 55% of person-years, respectively. Examining the statin persistence categories 1-5 (26% of all statin users), the frequency of current statin use based on the immediately preceding 6 months ranged from 42% to 82% (Appendix 4: Table A4), indicating individuals accumulating statin persistence over time. The frequency of statin non-use in the immediately preceding 6 months ranged from 18% to 57%, indicating individuals with discontinuous or lapsed statin use. During the study, in just over half (50.56%) of person-years was LDL-C ≤ 2.0 mmol/L.

2.3.4 Outcomes

During follow-up, 4,331 (6.0%) and 470 (0.65%) individuals were censored for death and out-migration. Nearly three thousand (n = 2,919, 4.0%) individuals experienced a composite CV event (MI, stroke, or PCI/CABG) (1.0 per 100 person-years) (Table 2). In terms of statin persistence, statin users with lower persistence (1-2) had the highest event rate (16.6 per 1,000 person-years); statin users with high persistence (5-6) had the lowest even rate (8.7 per 1,000 person-years); individuals with no recorded statin use in the previous 36 months had intermediate event rates (Table 2). Those with LDL-C ≤ 2.0 mmol/L had a lower primary outcome rate that those with LDL-C > 2.0 mmol/L (Table 2). Kaplan Meier survival log rank tests were $p < 0.05$ for differences by statin use / persistence and LDL achievement (Figure 3A & Figure 3B).

In multi-variable adjusted Cox proportional hazards regression (Table 3), LDL-C ≤ 2.0 mmol/L was most strongly associated with reduced CVD risk (HR = 0.64, [95% CI 0.59-0.69], p

< 0.001), independent of statin use or persistence. High statin persistence (5-6) was also associated with reduced risk of the composite CVD outcome, relative to statin non-users (no use in the preceding 36 months) as a reference group (HR = 0.79 [0.71-0.86], p < 0.001). Moderate statin persistence 3-4 was not associated with CVD risk, and low statin persistence, denoted as 1-2, was associated with increased CVD risk relative to statin non-users (HR= 1.34 [1.19-1.51], p < 0.001) (Figure 4).

Male sex and increasing CKD stage were also associated with higher CVD risk. There was no evidence of interaction between statin persistence and LDL-C target achievement on CV outcomes (p > 0.05). Outcomes were similar for MI and stroke separately (Appendix 5: Table A5).

2.3.5 Sensitivity Analysis Excluding LDL-C Target Achievement Variable

LDL-C was excluded in this sensitivity analysis, as a potential mediator of the statin persistence association with CVD events (Appendix 6: Table A6). Statin persistence 1-2 continued to be associated with increased risk (HR = 1.41, [1.27-1.56], p <0.001), compared to statin non-users. Statin persistence 3-4 was not associated with the primary outcome and statin persistence 5-6 was associated with a decreased risk (HR = 0.64, [0.59-0.69], p <0.001) – results were essentially unchanged by whether LDL-C target achievement was included.

2.3.6 Sensitivity Analysis Including Only Current Statin Users (Immediately Preceding 6 Months)

When considering only individuals with a recent (immediately preceding 6 months) statin dispensations, we used statin persistence 1-2 as the reference group. Both statin persistence 3-4 (HR = 0.58, [0.48-0.71], p <0.001) and 5-6 (HR = 0.42, [0.36-0.48], p <0.001) were associated with reduced risk, compared to statin persistence 1-2 current users (Appendix 7: Table A7).

2.4 Discussion

In this population-based cohort study of adults with diabetes and no previous history of CVD, both LDL ≤ 2.0 mmol/L and statin use and persistence were independently associated with reduced CV outcomes. Using a persistence metric denoting the number of 6-month periods in the previous 3 years during which statin use was documented, we found that a minimum of 5 to be associated with a lower risk of experiencing a composite outcome consisting of MI, stroke, or revascularization. However, those with persistence of 1 or 2 of 6 actually appeared to have an increased risk of CV events, compared to those not on a statin at all.

Our statin persistence metric represents recent cumulative statin exposure and can be readily implemented for a defined patient panel at a given point in time, using data available in most electronic medical records (EMR). The improvement of CV outcomes with statin use in ≥ 5 six-month periods in the preceding 3 years is similar to the previously characterized 2.5 year minimum persistence to achieve a minimally meaningful absolute risk reduction in randomized trials of statin use for primary prevention.[24] We measured persistence, and not adherence. While persistence refers to the duration of use of a medication, adherence refers to the use of a medication as intended and is usually represented by the proportion of days covered (PDC). Still, the two concepts are related, and 5 out of 6 six-month periods (83%) is also similar, numerically, to the minimum adherence threshold (PDC > 80%) previously identified as being associated with a risk reduction for major adverse CVD events by Simpson et al..[18]

The threshold cumulative exposure of 5/6 may reflect a biologic period required for statin therapy to change atherosclerotic plaque structure and function sufficiently to manifest clinical benefit. Alternatively, individuals with this degree of statin persistence may represent a qualitatively different group on factors that are not captured in our data, which may affect their

subsequent CV risk. We cannot exclude the possibility that 5/6 persistence is an indicator for a healthier user in this observational study. In fact, the 34% relative increase in primary outcome risk associated with having a statin persistence of 1-2 group relative to statin non-users is unlikely to indicate harm from statin use, given concordant evidence from multiple randomized trials showing the benefits of statin therapy for primary prevention. Rather, statin persistence of 1-2 may indicate individuals who were considered at high enough risk by their providers to be started on a statin, but either have not yet accumulated enough statin exposure to see a risk-reduction, or who exhibit inconsistent or lapsed statin use. Whether the association between statin persistence and our primary outcome is biologic or indicative of healthier / un-healthier users, statin persistence is still an important metric, insofar as it provides a clinically actionable *risk indicator.*

In our study, LDL ≤ 2.0 mmol/L was strongly associated with reduced future CV events, apart from statin use / persistence and other confounders. Rana et al.[17] has similarly identified an independent contribution of reduced LDL-C to improved CV risk in a primary prevention cohort of adults with diabetes, all of whom were on a statin. These findings favour a treat-to-target approach to lipid lowering therapy in adults with diabetes, in line with randomized trials of LDL-C lowering medications, where CV benefit appears to accrue at ever-lower levels of achieved LDL-C, without lower limit at which CV benefit plateaus.[9] It is admittedly difficult to determine whether the observed association is causal, or whether lower LDL-C may also indicate a healthier user. However, those with LDL-C > 2.0 mmol/L can still be considered a higher-risk group for whom CV risk reduction could be optimized, including adjusting or titrating lipid lowering therapy, in addition to other multifactorial considerations.

2.4.1 Limitations and Strengths

Our study has several additional limitations. First, we considered all statin therapy similar regardless of the identity, potency, or dose of specific agents prescribed. The potency of lipid lowering therapy is in part subsumed by the LDL-C level, which was included as an independent predictor in our analysis. Second, as in all observational studies involving secondary use of administrative data, there are additional potential confounders that are unmeasured, *e.g.,* smoking status, physical activity, body weight, and family history.[5] Third, statin persistence was estimated from pharmacy dispensations, and may not reflect whether patients consumed their medications as prescribed. Fourth, at any level of statin persistence, there may be heterogeneity in terms of patients accumulating statin exposure by continuous use, versus those who may exhibit discontinuous or lapsed use. We have explored this heterogeneity by including a sensitivity analysis with current statin users only, demonstrating increasing CV risk reduction with increasing statin persistence, and similar associations between LDL-C ≤ 2.0 mmol/L and reduced acute CVD outcomes as in the main analysis. Having said that, individuals can still achieve similar persistence levels through differing trajectories of statin use / non-use, and further analysis of statin use trajectories or histories was beyond the scope of this study.

Limitations notwithstanding, ours is a large population-based study using statin persistence metric that can be readily operationalized, using EMR data, for clinical interactions, practice quality improvement, or chronic disease management. In contrast to previous studies, this study is the first in adults with diabetes to consider simultaneously the effects of cumulative statin exposure and LDL level.

2.4.2 Conclusions

In adults with diabetes and no previous history of CVD, statin use in 5-6 of the six-month periods in the preceding 3 years may represent a minimum degree of statin use / exposure

required to yield trial-based benefits of statin therapy for primary prevention. Conversely, LDL-C > 2.0 mmol/L and documented statin use in only 1-2 six-month periods in the preceding 3 years indicate elevated CV risk. Lower LDL-C was associated with reduced CV risk independent of statin use or persistence. In contrast to simply starting individuals on statin therapy ("treat-and-forget"), our results suggest that on-going follow-up and monitoring is required. Those with low statin persistence (1-2) and/or LDL-C > 2.0 mmol/L should be recalled and followed for additional CVD risk reduction, whether by intensification of lipid-lowering therapy, efforts to improve / sustain medication adherence and persistence, or by addressing additional CV risk factors. The metrics we have used can be implemented in an EMR and are suited for identifying high-risk individuals for recall in the context of practice-based quality improvement or chronic disease management. Given the plateau in statin use in Canada,[14] and limited real-world statin persistence,[15] such efforts may be critical to realizing and maximizing the long-known benefits of statin therapy for primary prevention in adults with diabetes, in the real world.

2.5 Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1: Characteristics of Patients at Baseline

Characteristics of Patients at Baseline*	SPL				Total n = 45,358
	0 of 6 n = 14,136	1-2 of 6 n = 4,568	3-4 of 6 n = 5,317	5-6 of 6 n = 21,337	
Female – no. (%)	6,941 (49.1)	2,207 (48.3)	2,485 (46.7)	10,014 (46.9)	21,647 (47.7)
Index Age – yr (SD)	65.4 (9.3)	64.1 (8.5)	64.5 (8.7)	65.7 (8.9)	65.4 (8.9)
At LDL Target – no. (%)	2,693 (19.1)	1,116 (25.5)	2,823 (53.1)	14,037 (65.8)	20,719 (45.9)
At HbA1c Target – no. (%)	7,695 (54.4)	2,011 (44.0)	2,412 (45.4)	10,399 (48.7)	22,517 (49.6)
KDIGO Categories – no. (%)					
CKD Stage 1	4,685 (33.1)	1,659 (36.3)	1,794 (33.7)	6,034 (28.3)	14,172 (31.2)
CKD Stage 2	7,240 (51.2)	2,272 (49.7)	2,639 (49.6)	11,242 (52.7)	23,393 (51.6)
CKD Stage 3a	1,523 (10.8)	414 (9.1)	567 (10.7)	2,540 (11.9)	5,044 (11.1)
CKD Stage 3b	526 (3.7)	165 (3.6)	227 (4.3)	1,130 (5.3)	2,048 (4.5)
CKD Stage 4	123 (0.87)	46 (1.0)	65 (1.2)	309 (1.5)	543 (1.2)
CKD Stage 5	39 (0.28)	**	**	82 (0.38)	158 (0.35)
Diabetes Mellitus Medication – no. (%)					
No Medication	4,556 (32.2)	901 (19.7)	897 (16.9)	2,673 (12.5)	9,027 (19.9)
Non-Insulin Medication* **	7,977 (56.4)	2,950 (64.6)	3,496 (65.8)	14,583 (68.4)	29,006 (64.0)
Basal Insulin	803 (5.7)	343 (7.51)	442 (8.3)	1,966 (9.2)	3,554 (7.8)
Bolus Insulin	800 (5.7)	374 (8.2)	482 (9.1)	2,115 (9.9)	3,771 (8.3)
Income Quintiles – no. (%)					
First Quintile	3,066 (21.7)	1,064 (23.3)	1,146 (21.6)	4,142 (19.4)	9,418 (20.8)
Second Quintile	3,160 (22.4)	1,000 (21.9)	1,216 (22.9)	4,688 (22.0)	10,064 (22.2)
Third Quintile	2,826 (20.0)	897 (19.6)	1,061 (20.0)	4,257 (20.0)	9,041 (19.9)

Fourth Quintile	2,668 (18.9)	895 (19.6)	1,002 (18.8)	4,285 (20.1)	8,850 (19.5)
Fifth Quintile	2,416 (17.1)	712 (15.6)	892 (16.8)	3,965 (18.6)	7,985 (17.6)
Select Comorbidities – no. (%)*ϒ					
Asthma	453 (3.2)	137 (3.0)	151 (2.8)	609 (2.9)	1,350 (3.0)
Atrial Fibrillation	391 (2.8)	113 (2.5)	173 (3.3)	663 (3.1)	1,340 (3.0)
Cancer	734 (5.2)	218 (4.8)	253 (4.8)	1,072 (5.0)	2,277 (5.0)
Chronic Pain	3,967 (28.1)	1,297 (28.4)	1,423 (26.8)	5,837 (27.4)	12,524 (27.6)
Chronic Pulmonary Disease	1,985 (14.0)	643 (14.1)	729 (13.7)	2,907 (13.6)	6,264 (13.8)
Depression	1,695 (12.0)	568 (12.4)	651 (12.2)	2,499 (11.7)	5,413 (11.9)
Gout	1,682 (11.9)	566 (12.4)	694 (13.1)	2,987 (14.0)	5,929 (13.1)
Hypertension	9,828 (69.5)	3,246 (71.1)	4,060 (76.4)	17,578 (82.4)	34,712 (76.5)
Hypothyroidism	1,927 (13.6)	536 (11.7)	690 (13.0)	2,665 (12.5)	5,818 (12.8)
Osteoporosis	1,413 (10.0)	416 (9.1)	463 (8.7)	2,088 (9.8)	4,380 (9.7)
Peripheral Arterial Disease	46 (0.33)	**	48 (0.90)	90 (0.42)	202 (0.45)

**At baseline, the total number of unique patients and observations was 45,358*

***Blank cells are supressed data due to small sample sizes per privacy regulations in Alberta*

****Non-Insulin Medications were: metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinedione, glucagon-like peptide-1 agonists, dipeptidyl peptidase 4, and sodium-glucose transport protein 2 inhibitors*

**ϒSelect comorbidities shown here are all CV comorbidities and comorbidities with a prevalence > 5%*

Table 2: Primary and Subcomponents of Composite CV Outcomes

	SPL	LDL-C Target Achievement*$^{\tau}$	Outcomes			
			Primary Composite Outcome**	Stroke	MI	PCI/CABG
# of Events at Each SPL – no. (Event Rate per 1000PY	0 of 6	Overall *n = 79,171 PY	932 (11.8)	398 (5.0)	439 (5.5)	101 (1.3)
		At Target *n = 15,871 PY	139 (8.8)	72 (4.5)	57 (3.6)	12 (0.76)
		Not At Target *n = 63,301 PY	793 (12.5)	326 (5.2)	382 (6.0)	89 (1.4)
	1-2 of 6	Overall *n = 22,889 PY	380 (16.6)	137 (6.0)	156 (6.8)	87 (3.8)
		At Target *n = 4,789 PY	57 (11.9)	26 (5.4)	19 (4.0)	12 (2.5)
		Not At Target *n = 18,100 PY	323 (17.8)	111 (6.1)	137 (7.6)	75 (4.1)
	3-4 of 6	Overall *n = 24,816 PY	283 (11.4)	110 (4.4)	127 (5.1)	46 (1.9)
		At Target *n = 11,846 PY	109 (9.2)	36 (3.0)	52 (4.4)	21 (1.8)
		Not At Target *n = 12,969 PY	174 (13.4)	74 (5.7)	75 (5.8)	25 (1.9)
	5-6 of 6	Overall *n = 153,012 PY	1324 (8.7)	496 (3.2)	538 (3.5)	295 (1.9)
		At Target *n = 109,010 PY	880 (8.1)	339 (3.1)	346 (3.2)	198 (1.8)
		Not At Target *n = 44,002 PY	444 (10.1)	157 (3.6)	192 (4.4)	97 (2.2)
	Total	Overall *n = 279,888 PY	2919 (10.4)	1141 (4.1)	1260 (4.5)	529 (1.9)
		At Target *n = 141,517 PY	1185 (8.4)	473 (3.3)	474 (3.3)	243 (1.7)
		Not At Target *n = 138,372 PY	1734 (12.5)	668 (4.8)	786 (5.7)	286 (2.1)

**n = total person-years (PY) of time at risk throughout follow-up (April 1, 2012 to March 31, 2019)*

***Primary Composite Outcome = First subcomponent event*

**$^{\tau}$LDL-C Target Achievement = Overall is all individuals regardless of LDL-C Target Achievement, At LDL-C Target is ≤ 2.0 mmol/L and Not At LDL-C Target is > 2.0 mmol/L*

Table 3: Multivariate Cox Regression Analysis in 72,541 Patients (With 279,888 Person-Years)

Variables*		HR (95% CI)	P-Value
Sex**		1.87 (1.72, 2.03)	<0.001
Age Per Decade Increase		1.52 (1.45, 1.59)	<0.001
Persistence Levels**	**1-2 of 6**	1.34 (1.19, 1.51)	<0.001
	3-4 of 6	1.00 (0.88, 1.15)	0.959
	5-6 of 6	0.79 (0.71, 0.86)	<0.001
KDIGO Categories**	**CKD Stage 2**	1.14 (1.02, 1.27)	0.023
	CKD Stage 3a	1.42 (1.24, 1.63)	<0.001
	CKD Stage 3b	1.68 (1.43, 1.98)	<0.001
	CKD Stage 4	1.82 (1.45, 2.29)	<0.001
	CKD Stage 5	3.09 (2.11, 4.53)	<0.001
At LDL-C Target**		0.64 (0.59, 0.69)	<0.001
At HbA1c Target**		0.78 (0.72, 0.85)	<0.001

**Select variables are shown, above. This multivariate Cox Regression model has been adjusted for all characteristics described in the Methods section / Appendix 8: Table A8*

***Reference groups: Sex = Female, Persistence Level = 0 of 6, KDIGO Category = CKD Stage 1, Not at LDL-C Target (>2.0mmol/L) & Not at HbA1c Target (>7.0%)*

Figure 1A: LDL-C as a Confounder on the Causal Pathway

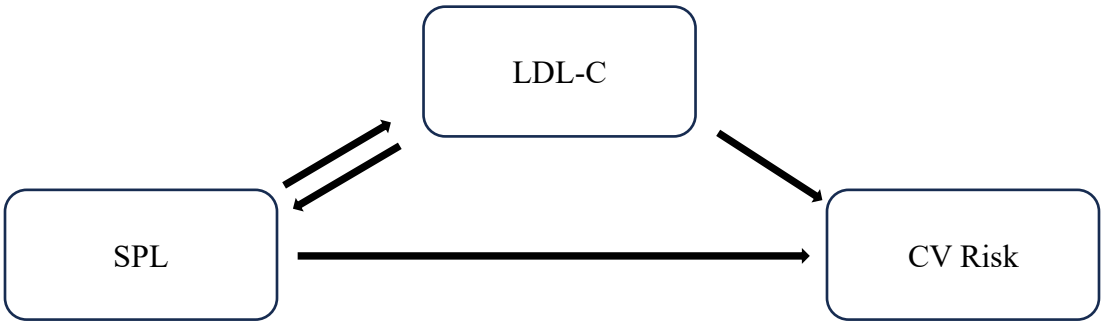


Figure 1B: LDL-C as a Mediator on the Causal Pathway

Figure 2: Flow Diagram of Sample Selection

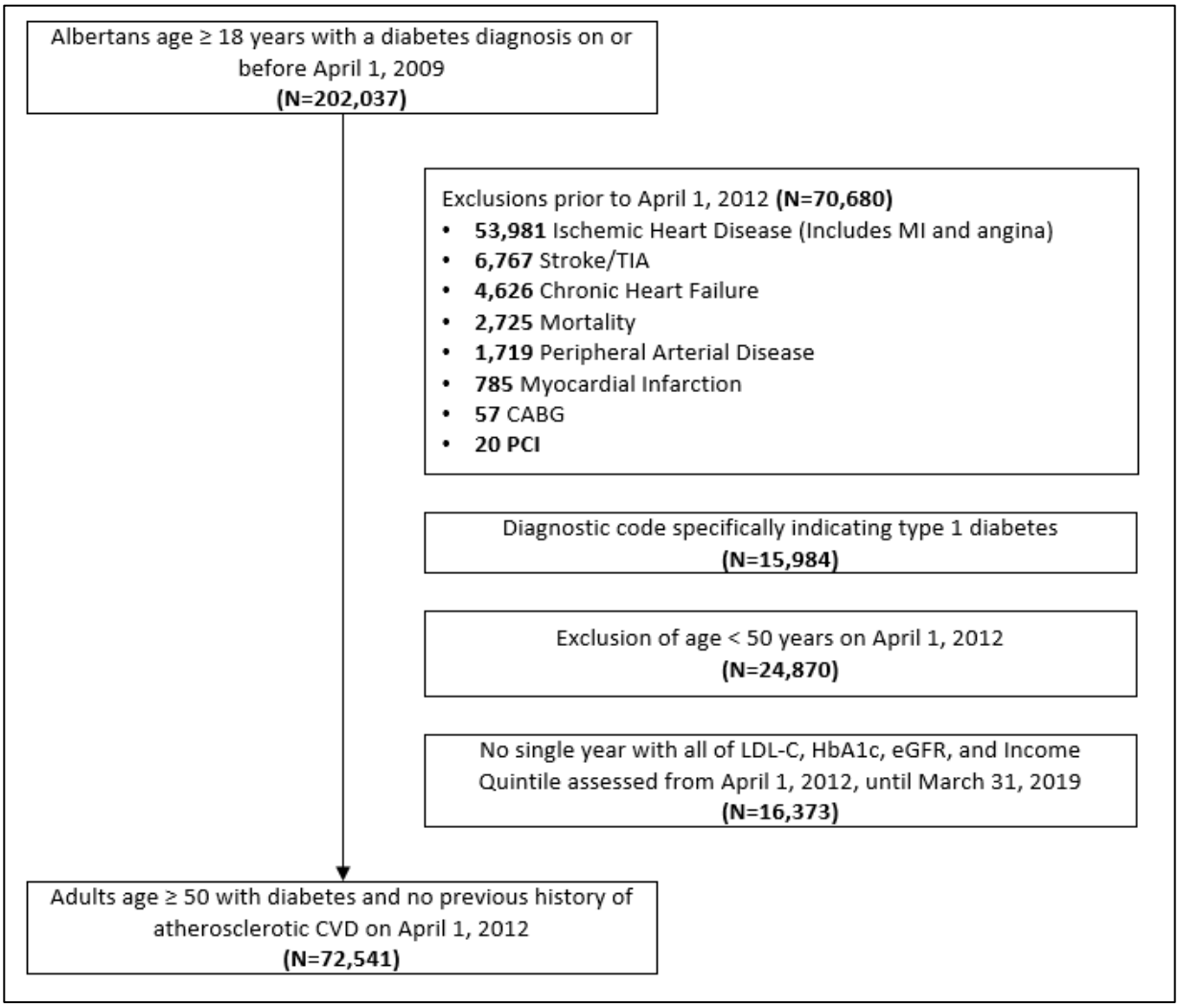


Figure 3A: Kaplan-Meier Survival Probability Estimates by SPL

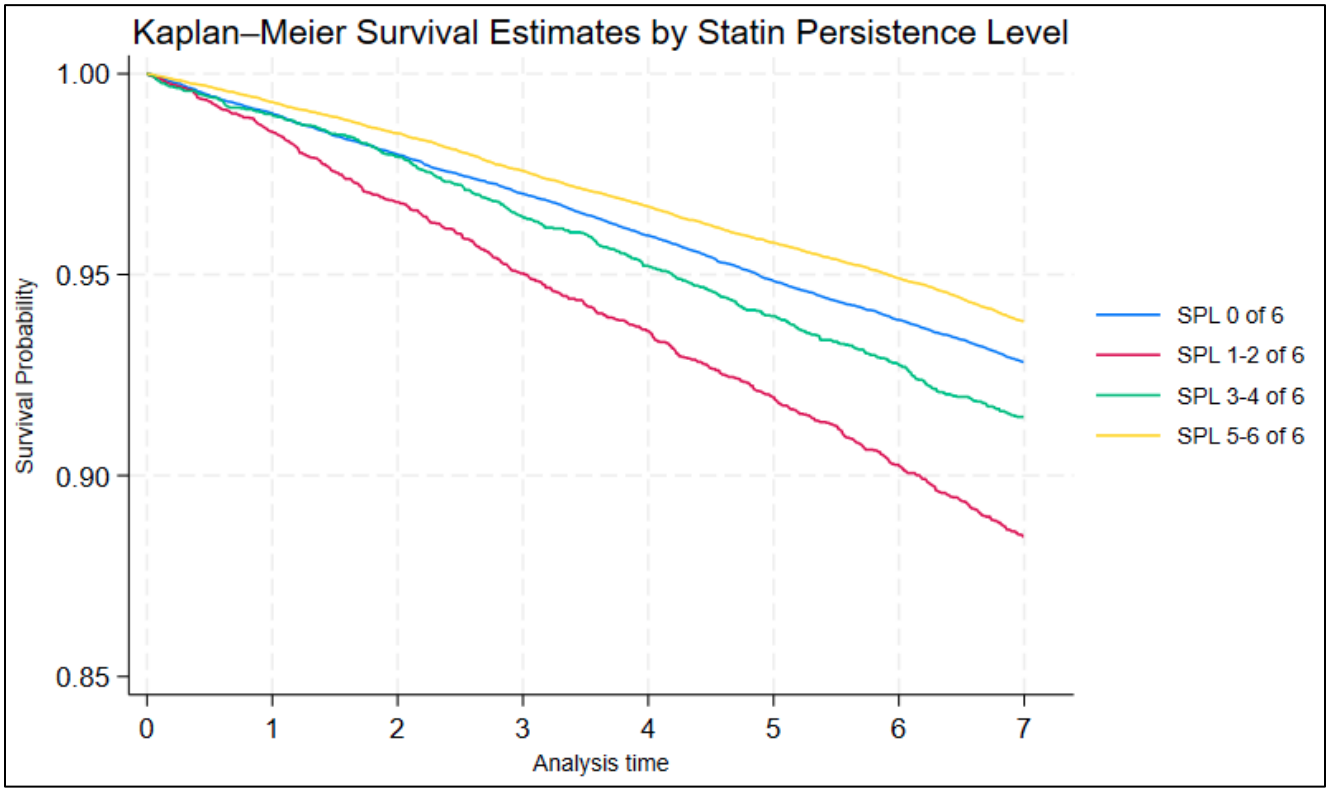
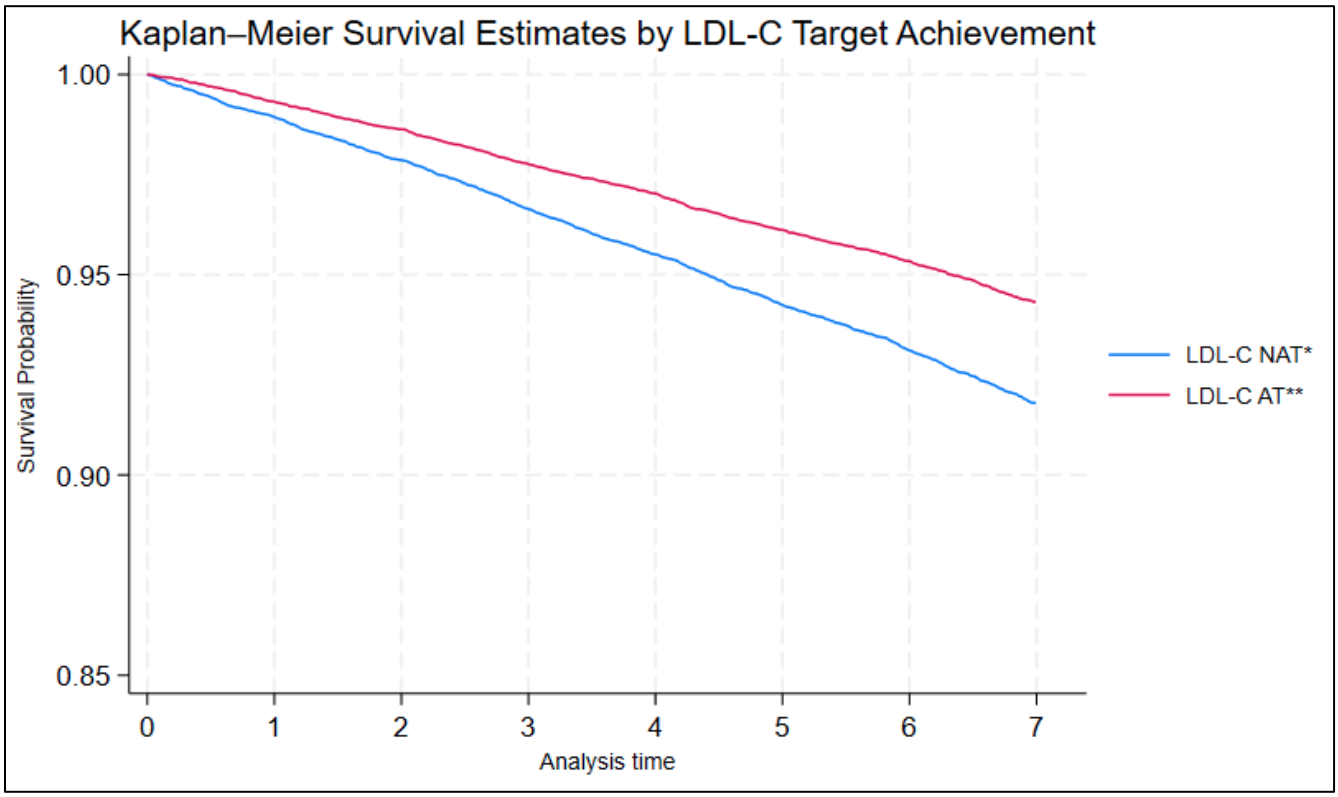


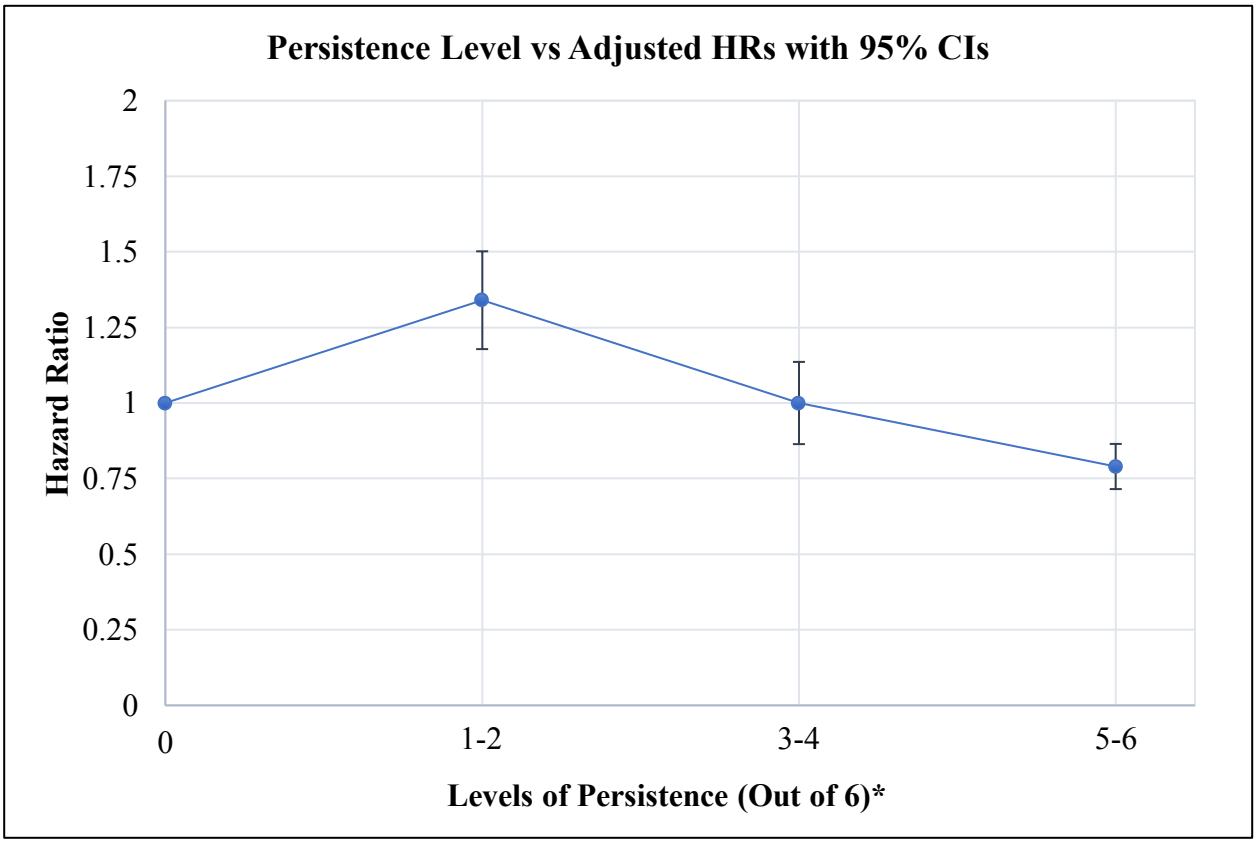
Figure 3B: Kaplan-Meier Survival Probability Estimates by LDL-C Target Achievement



**LDL-C NAT = Not At LDL-C Target (LDL-C > 2.0 mmol/L)*

***LDL-C AT = At LDL-C Target (LDL-C ≤ 2.0 mmol/L)*

Figure 4: Overall Adjusted HR Persistence Level Trend with 95% CIs



**Reference Group = 0 of 6 Statin Persistence*

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Appendices

Appendix 1: Table A1: Administrative ICD-9 and ICD-10 Definitions

Inclusion/Exclusion		ICD-9 / CCP	ICD-10 / CCI	Source/Reference/PPV
Inclusion				
Diabetes Algorithm: 1 hospitalization or 2 claims in 2 years or less		250 **Type I:** 250.x1, 250.x3	E10-E14 **Type I:** E10.xx	**Source**: Hospitalizations, claims **Reference**: Hux et al, Diabetes Care 2002;25:62-69 Codes to identify Type I diabetes are based on discharge abstracts prepared by CIHI. **PPV:** 0.80
Exclusion				
Atherosclerotic CVD				
CAD				**Reference:** Tu K, et al. Can J Cardiol. 2010;26(7):e225-8. PPV: 0.82
	Ischemic Heart Disease Algorithm: 1 hospitalization (most responsible or any secondary diagnosis) or 2 claims in 1 year	410-414	I20-I25	**Source**: Hospitalizations, claims
	CABG Algorithm: 1 CCP or 1 procedure/CCI	**ICD-9-CM (procedure):** 361, 362 **CCP**: 48.1	**CCI**: 1IJ76	**Source**: Hospitalizations, claims, ACCS
	PCI Algorithm: 1 CCP or 1 procedure/CCI	**ICD-9-CM (procedure):** 0066, 3601, 3602, 3603, 3605, 3606	**CCI**: 1IJ50, 1IJ54GQ-AZ, 1IJ57GQ	**Source**: Hospitalizations, claims, ACCS

		CCP: 51.59C, 51.59D, 51.59E, 51.59F		
Stroke/TIA Algorithm: 1 hospitalization (most responsible or any secondary diagnosis) or 2 claims in 1 year				
	Ischemic or unspecified stroke	362.3 (excl. 362.34 [transient arterial occlusion]), 434.0 434.1, 434.9, 436	I63 (excl. I63.6), I64, H34.1 (central retinal artery occlusion)	**Source**: Hospitalizations, claims **Reference**: Tu K, et al. Can J Cardiol. 2013;29:1388-1394. **PPV:** 0.86
	Hemorrhagic stroke	430, 431, 432	I60, I61	
	TIA	362.34, 435	G45 (excl. G45.5), H34.0 (transient retinal artery occlusion)	
	Peripheral arterial disease Algorithm: 1 hospitalization or 1 claim or 1 ACCS	440.2	I70.2	**Source:** Hospitalizations, claims, ACCS **Reference:** Fan et al, J Am Med Inform Assoc 2013 20(e2):e349–54. **PPV:** 0.94
Outcome		**ICD-9 / CCP**	**ICD-10 / CCI**	**Source/Reference**
Hospital admission for CV event				
	MI Algorithm: 1 "most responsible" or "secondary diagnosis" hospitalization	410	I21, I22	**Source**: Hospitalization **Reference**: Chu A, et al. CMAJ. 2019;191(47):E1291-8. Tu JV, et al. JAMA. 2009;302(21):2330-7. **PPV:** 0.80
	Angina (unstable and stable) Algorithm: 1 "most responsible" or "secondary diagnosis" hospitalization	411, 413	I20	
Hospital admission for Stroke or TIA				

	Ischemic or unspecified stroke Algorithm: 1 "most responsible" or "secondary diagnosis" hospitalization			**Source**: Hospitalization **Reference**: Tu K, et al. Can J Cardiol. 2013;29:1388-1394. **PPV:** 0.82
	Hemorrhagic stroke Algorithm: 1 "most responsible" or "secondary diagnosis" hospitalization	430, 431, 432	I60, I61	
	TIA Algorithm: 1 "most responsible" or "secondary diagnosis" hospitalization	362.34, 435	G45 (excl. G45.5), H34.0 (transient retinal artery occlusion)	
CV death				
	In-hospital death with a "most-responsible" or "secondary diagnosis" of MI, Angina, or Stroke/TIA	See above	See above	**Source**: Hospitalization
Vital statistics registered death with any of the following:				
	Ischemic heart disease	410-414	I20-25	
	Other forms of heart disease	420-429	I30-I52	
	Cerebrovascular disease	430-438	I60-I69	
	Intraoperative and post-procedural complications and disorders of circulatory system NEC	429.4	I97.0, I97.110, I97.120, I97.130, I97.190, I97.410, I97.411, I97.61	
	Unknown cause of death	798	R99	
Heart failure				
	Algorithm: 1 "most responsible" or "secondary diagnosis" hospitalization	398.91, 402.01, 402.11, 402.91,	I09.9, I25.5, I42.0, I42.5–I42.9, I43, I50	**Source**: Hospitalizations

		404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428		**Reference**: Quan et al, Health Serv Res. 2008;43(4):1424–41 **PPV:** 0.99 Quan et al, Med Care. 2005;43(11):1130–9. **PPV:** 0.87
All-cause mortality				
	In-hospital or vital statistics-registered death from any cause			
Cardiac revascularization				
CABG	Algorithm: 1 CCP or 1 CCI	**CCP**: 48.1	**CCI**: 1IJ76	**Source**: Hospitalizations, claims, ACCS **Reference**: Chu A, et al. CMAJ. 2019;191(47):E1291-8. **PPV:** 0.80
PCI	Algorithm: 1 CCP or 1 CCI	**CCP**: 51.59C, 51.59D, 51.59E, 51.59F	**CCI**: 1IJ50, 1IJ54GQ-AZ, 1IJ57GQ	

Appendix 2: Table A2: A Single Patient Statin Persistence Calculation for Time Period 7

Time Period (6-Months)	Statin Dispense (Binary)	SPL*
Period 1	**1**	-
Period 2	**1**	-
Period 3	**0**	-
Period 4	**1**	-
Period 5	**1**	-
Period 6	**1**	-
Period 7	**-**	5 of 6

***One SPL calculation utilizes a binary statin dispense variable over six 6-month periods. For this patient the SPL level in time period 7 used time periods 1 to 6 where a dispensation of statins occurred 5 times. Thus, an SPL 5 of 6 is identified for time period 7 for this patient as a possible of six 6-month time periods where a dispensation of statins could have occurred, only 5 were fulfilled.*

Appendix 3: Table A3: A Single Patient Medication Calculation of Current Use vs Non-Current Use Calculation

Time Period (6-Months)	Statin Dispense (Binary)	Current vs Non-Current Statin Use (Binary)*
Period 1	**1**	-
Period 2	**1**	Current Statin Use
Period 3	**0**	Current Statin Use
Period 4	**1**	No Current Statin Use
Period 5	**1**	Current Statin Use
Period 6	**1**	Current Statin Use
Period 7	**-**	Current Statin Use

***Current vs non-current statin use was updated every 6-months based on the binary statin dispense variable*

Appendix 4: Table A4: Frequency and Percentage of Current Statin Use by SPL

SPL	Most Recent Statin Usage	Total PY*	Current Use of (no. – PY)	Current Use of (% of PY)
1 of 6	**Current Use*$^{\varphi}$**	12,091	5,115	42.3
2 of 6	**Current Use*$^{\varphi}$**	10,978	6,387	58.2
3 of 6	**Current Use*$^{\varphi}$**	11,131	7,379	66.3
4 of 6	**Current Use*$^{\varphi}$**	13,685	9,878	72.2
5 of 6	**Current Use*$^{\varphi}$**	24,755	20,328	82.1

***Total person-years (PY) of time at risk throughout follow-up (April 1, 2012 to March 31, 2019) by SPL*

**$^{\varphi}$Current Use was defined as having at least one dispensation in the most recent 6-month period*

Appendix 5: Table A5: Multivariate Cox Regression Analyses for Individual Subcomponent Outcomes

Outcome: MI			
Variables*		**HR (95% CI)**	**P-Value**
Sex**		1.83 (1.62, 2.07)	<0.001
Age Per Decade Increase		1.41 (1.31, 1.52)	<0.001
Persistence Levels**	**1-2 of 6**	1.12 (0.93, 1.34)	0.224
	3-4 of 6	0.98 (0.80, 1.19)	0.817
	5-6 of 6	0.72 (0.63, 0.83)	<0.001
KDIGO Categories**	**CKD Stage 2**	1.09 (0.93, 1.27)	0.306
	CKD Stage 3a	1.30 (1.05, 1.59)	0.014
	CKD Stage 3b	1.81 (1.43, 2.29)	<0.001
	CKD Stage 4	2.35 (1.71, 3.23)	<0.001
	CKD Stage 5	4.73 (2.87, 7.80)	<0.001
At LDL-C Target**		0.59 (0.52, 0.66)	<0.001
At HbA1c Target**		0.77 (0.68, 0.88)	<0.001
Outcome: Stroke			
Variables*		**HR (95% CI)**	**P-Value**
Sex**		1.38 (1.21, 1.56)	<0.001
Age Per Decade Increase		1.77 (1.64, 1.90)	<0.001
Persistence Levels**	**1-2 of 6**	1.19 (0.98, 1.44)	0.075
	3-4 of 6	0.98 (0.80, 1.21)	0.880
	5-6 of 6	0.70 (0.61, 0.80)	<0.001
KDIGO Categories**	**CKD Stage 2**	1.29 (1.07, 1.56)	0.009
	CKD Stage 3a	1.71 (1.36, 2.13)	<0.001
	CKD Stage 3b	1.76 (1.36, 2.27)	<0.001
	CKD Stage 4	1.94 (1.36, 2.75)	<0.001
	CKD Stage 5	2.95 (1.60, 5.45)	0.001
At LDL-C Target**		0.70 (0.62, 0.81)	<0.001
At HbA1c Target**		0.76 (0.67, 0.87)	<0.001

**Select variables are shown, above. This multivariate Cox Regression model has been adjusted for all characteristics described in the Methods section / Appendix 8: Table A8*

***Reference groups: Sex = Female, Persistence Level = 0 of 6, KDIGO Category = CKD Stage 1, Not at LDL-C Target (>2.0mmol/L) & Not at HbA1c Target (>7.0%)*

Appendix 6: Table A6: Multivariate Cox Regression Analysis Without the Inclusion of LDL-C Target Achievement Variable

Variables*		HR (95% CI)	P-Value
Sex**		1.72 (1.61, 1.85)	<0.001
Age Per Decade Increase		1.46 (1.40, 1.52)	<0.001
Persistence Levels**	**1-2 of 6**	1.41 (1.27, 1.56)	<0.001
	3-4 of 6	0.95 (0.85, 1.07)	0.388
	5-6 of 6	0.64 (0.59, 0.69)	<0.001
KDIGO Categories**	**CKD Stage 2**	1.17 (1.06, 1.29)	0.002
	CKD Stage 3a	1.42 (1.26, 1.60)	<0.001
	CKD Stage 3b	1.60 (1.40, 1.84)	<0.001
	CKD Stage 4	1.80 (1.49, 2.16)	<0.001
	CKD Stage 5	3.19 (2.41, 4.22)	<0.001
At HbA1c Target**		0.77 (0.71, 0.82)	<0.001

**Select variables are shown, above. This multivariate Cox Regression model has been adjusted for all characteristics described in the Methods section / Appendix 8: Table A8*

***Reference groups: Sex = Female, Persistence Level = 0 of 6, KDIGO Category = CKD Stage 1 & Not at HbA1c Target (>7.0%)*

Appendix 7: Table A7: Current User Multivariate Cox Regression Analysis*

SPL**	Most Recent Statin Usage	HR (95% CI)	P-Value
3-4 of 6	**Current Use*$^{\varphi}$**	0.58 (0.48, 0.71)	<0.001
5-6 of 6	**Current Use*$^{\varphi}$**	0.42 (0.36, 0.48)	<0.001

**This sub-analysis multivariate Cox Regression model has been adjusted for all characteristics described in the Methods section / Appendix 8: Table A8*

***Reference Group = 1 of 6 SPL & Current Statin User*

**$^{\varphi}$Current Use was defined as having at least one dispensation in the most recent 6-month period*

Appendix 8: Table A8: Characteristics of Patients throughout Follow-up

Characteristics of Patients*	SPL				Total n = 279,888
	0 of 6 n = 79,171	1-2 of 6 n = 22,888	3-4 of 6 n = 24,815	5-6 of 6 n = 153,012	
Female – PY (%)	39,839 (50.3)	11,167 (48.8)	11,742.5 (47.3)	71,284 (46.6)	134,032.5 (47.9)
Index Age – yr (SD)	65.35 (9.3)	64.04 (8.5)	64.50 (8.7)	65.68 (8.7)	65.35 (8.9)
At LDL Target – PY (%)	16,017.5 (20.2)	4,832 (21.1)	11,942.5 (48.1)	109,669.5 (71.7)	142,461.5 (50.9)
At HbA1c Target – PY (%)	46,118.5 (58.3)	10,545 (46.1)	11,428.5 (46.1)	76,260 (49.8)	144,352.5 (51.6)
KDIGO Categories – PY (%)					
CKD Stage 1	22,989.5 (29.0)	7,227 (31.6)	7,807 (31.5)	39,188 (25.6)	77,211.5 (27.6)
CKD Stage 2	42,363.5 (53.8)	11,688 (51.1)	12,559.5 (50.61)	80,960 (52.9)	147,571 (52.7)
CKD Stage 3a	9,508 (12.0)	2,672.5 (11.7)	2,898 (11.7)	20,967.5 (13.7)	36,046 (12.9)
CKD Stage 3b	3,703 (4.7)	1,056.5 (4.6)	1,226 (4.9)	9,489 (6.2)	15,474.5 (5.5)
CKD Stage 4	950.5 (1.2)	354.5 (1.6)	393 (1.6)	2,671 (1.8)	4,369 (1.6)
CKD Stage 5	261.5 (0.33)	97 (0.42)	129.5 (0.52)	645.5 (0.42)	1,133.5 (0.40)
Diabetes Mellitus Medication – PY (%)					
No Medication	25,245 (31.9)	4,563.5 (19.9)	4,063 (16.4)	17,129.5 (11.2)	51,001 (18.2)
Non-Insulin Medication**	42,662 (53.9)	13,814 (60.4)	15,489.5 (62.4)	98,923 (64.7)	170,888.5 (61.1)
Basal Insulin	6,471 (8.2)	2,437.5 (10.7)	2,807.5 (11.3)	19,270 (12.9)	31,436 (11.2)
Bolus Insulin	5,398 (6.8)	2,280.5 (10.0)	2,653 (10.7)	18,148.5 (11.9)	28,480 (10.2)
Income Quintile – PY (%)					
First Quintile	16,979 (21.5)	5,230.5 (22.9)	5,533.5 (22.3)	30,595 (20.0)	58,338 (20.8)
Second Quintile	17,426.5 (21.5)	5,241 (22.9)	5,492.5 (22.1)	33,173 (21.7)	61,333 (21.9)
Third Quintile	16,112.5 (20.4)	4,610.5 (20.1)	4,991 (20.1)	30,996.5 (20.3)	56,710.5 (20.3)

Fourth Quintile	15,588 (19.7)	4,385.5 (19.2)	4,847.5 (19.5)	30,993.5 (20.3)	55,814.5 (19.9)
Fifth Quintile	13,670 (17.3)	3,628 (15.9)	4,148.5 (16.7)	28,163 (18.4)	49,609.5 (17.7)
Comorbidities – PY (%)					
Alcohol Misuse	1,833 (2.3)	500 (2.2)	533.5 (2.2)	2,508 (1.6)	5,374.5 (1.9)
Asthma	2,667 (3.4)	748 (3.3)	715.5 (2.9)	4,375 (2.9)	8,505.5 (3.0)
Atrial Fibrillation	1,923.5 (2.4)	467.5 (2.0)	561.5 (2.3)	4,126 (2.7)	7,078.5 (2.5)
Cancer (Lymphoma)	380.5 (0.48)	105.5 (0.46)	122.5 (0.49)	584.5 (0.38)	1,193 (0.43)
Cancer (Metastatic)	714 (0.90)	164.5 (0.72)	172.5 (0.70)	1,138 (0.74)	2,189 (0.78)
Cancer	3,884 (4.9)	970 (4.2)	1,048.5 (4.2)	6,979 (4.6)	12,881.5 (4.6)
CKD	315 (0.40)	84.5 (0.37)	143 (0.58)	860.5 (0.56)	1,403 (0.50)
Chronic Pain	22,612.5 (28.6)	6,771 (29.6)	6,922.5 (27.9)	41,116.5 (26.9)	77,422.5 (27.7)
Chronic Pulmonary Disease	10,913 (13.8)	3,227.5 (14.1)	3,296 (13.3)	19,613.5 (12.8)	37,050 (13.2)
Chronic Viral Hepatitis B	230 (0.29)	48 (0.21)	51.5 (0.21)	200.5 (0.13)	530 (0.19)
Cirrhosis	510.5 (0.64)	64 (0.28)	66 (0.27)	202.5 (0.13)	843 (0.30)
Dementia	809.5 (1.0)	174 (0.76)	236.5 (0.95)	1,449 (0.95)	2,669 (0.95)
Depression	9,470.5 (12.0)	2,813 (12.3)	3,093.5 (12.5)	17,656 (11.5)	33,033 (11.8)
Epilepsy	861.5 (1.09)	218 (0.95)	228 (0.92)	1,515.5 (0.99)	2,823 (1.0)
Gout	9,217 (11.6)	2,765 (12.1)	3,089.5 (12.5)	20,543.5 (13.4)	35,615 (12.7)
Hypertension	53,433 (67.5)	15,834.5 (69.2)	17.991 (72.5)	122,450.5 (80.0)	209,709 (74.9)
Hypothyroidism	10,921 (13.8)	2,785 (12.2)	2,919 (11.8)	18,738.5 (12.3)	35,363.5 (12.6)
Inflammatory Bowel Disease	1,027 (1.3)	222 (0.97)	229.5 (0.92)	1,198 (0.78)	2,676.5 (0.96)
Irritable Bowel Syndrome	1,675.5 (2.1)	516 (2.3)	475.5 (1.9)	2,724.5 (1.8)	5,391.5 (1.9)
Multiple Sclerosis	427.5	104.5	104.5	715.5	1,352

	(0.54)	(0.46)	(0.42)	(0.47)	(0.48)
Osteoporosis	7,876.5 (10.0)	2,006 (8.8)	2,154.5 (8.7)	13,879 (9.1)	25,916 (9.3)
Parkinson's Disease	508 (0.64)	98 (0.43)	127.5 (0.51)	826 (0.54)	1,559.5 (0.56)
Peptic Ulcer Disease	215.5 (0.27)	69 (0.30)	62.5 (0.25)	322 (0.21)	669 (0.24)
Peripheral Arterial Disease	179.5 (0.23)	93.5 (0.41)	117.5 (0.47)	594.5 (0.39)	985 (0.35)
Psoriasis	823.5 (1.0)	220.5 (0.96)	257.5 (1.0)	1,698.5 (1.1)	3,000 (1.1)
Rheumatic Disease	2,154 (2.7)	529 (2.3)	506 (2.0)	3,010 (2.0)	6,199 (2.2)
Schizophrenia	1,225.5 (1.6)	291 (1.3)	342.5 (1.4)	2,225 (1.5)	4,084 (1.5)
Severe Constipation	1,430.5 (1.8)	361.5 (1.6)	367 (1.5)	2,079.5 (1.4)	4,238.5 (1.5)

**Throughout follow-up, the total number of unique patients was 72,541 with 279,888* person-years *(PY) of time at risk*

***Non-Insulin Medications are any one of: metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinedione, glucagon-like peptide-1 agonists, dipeptidyl peptidase 4, and sodium-glucose transport protein 2 inhibitors*