THE USE OF STATIN DRUG THERAPY FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN PRIMARY CARE: A RETROSPECTIVE COHORT STUDY

by

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Abstract

Statin drugs have been widely studied for their efficacy in secondary prevention by preventing the recurrence of cardiovascular disease (CVD), however their use as a primary prevention strategy in individuals without documented CVD, especially at low risk, is highly controversial among the medical community. The current research study used data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN); a database that houses point-of-care data from physician electronic medical records (EMR) from primary care practices all across Canada. It is a valuable resource to conduct outcomes research on diseases and conditions managed in primary care.

This retrospective inception cohort study assessed whether statin drug use over a period of five years (January 1, 2009 to December 31, 2013) reduced outcomes of CVD and all-cause mortality in a group of primary prevention patients (i.e. patients who have never had CVD) from Newfoundland and Labrador (NL). The CPCSSN database was linked to both the Clinical Database Management System and Mortality Registry housed at the Newfoundland and Labrador Center for Health Information (NLCHI).

The results based on univariate analysis suggested that statin drug use was associated with increased rates of CVD, hospitalization and coronary artery disease (CAD). However, these apparent harmful effects of statins in causing CVD were no longer present when other risk factors of CVD (sex, age, BMI, LDL-C, HDL-C, HTN, smoking status, total cholesterol, total triglycerides and blood pressure) were controlled for using logistic regression. Statin drugs were also significantly associated with decreased rates of all-cause mortality, and this beneficial effect persisted after controlling for CVD risk factors. Our results also demonstrated that statins were significantly associated with an increase in diabetes mellitus (DM) over the study period. The results obtained were similar when we considered compliance and used only those in the exposure group who had used statins for ≥ 80% of the five year follow up period.

The use of statin drugs in a primary prevention situation is still controversial, and the results of this study provide real world data from EMR practices in NL on the effects of statins on CVD outcomes and death. This study concludes that at best, statins had no effect on CVD outcomes but decreased all-cause mortality. The results of a “real-life” assessment of the benefits of using statins in a primary prevention situation are not nearly as impressive as what clinical trials suggest.

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Abbreviations:

ACE-I	Angiotensin Converting Enzyme Inhibitor
APBRN	Atlantic Practice Based Research Network
ATP III	Adult Treatment Panel III
BMI	Body Mass Index
CAD	Coronary Artery Disease
CDMS	Clinical Database Management System)
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
CTT	Cholesterol Treatment Trialists'
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
EMR	Electronic Medical Record
FRS	Framingham Risk Score
HbA1C	Hemoglobin A1C
HDL-C	High Density Lipoprotein Cholesterol
HGM-CoA reductase inhibitors (statins)	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors
HsCRP	High Sensitivity C Reactive Protein
HTN	Hypertension
JUPITER Study	Justification for the use of statins in primary prevention: an intervention evaluating Rosuvastatin
LDL-C	Low Density Lipoprotein Cholesterol
MI	Myocardial Infarction
NL	Newfoundland and Labrador
NLCHI	Newfoundland and Labrador Center for Health Information
NNT	Number Needed to Treat
PDC	Proportion of days covered
PVD	Peripheral Vascular Disease
RCT	Randomized Control Trial
TT	Total Triglyceride
TC	Total Cholesterol
WOSCOPS Study	West of Scotland Coronary Prevention Study

Measurements:

mg milligrams

dL deciliter

mmol millimole

L liter

Converting between mg/dl and mmol/L cholesterol measurements

WX mg/dl * 0.0259= YZ mmol/L

Example: 200 mg/dL x 0.0259 = 5.18 mmol/L

Chapter 1

Introduction

HMG-CoA reductase inhibitors (Statins), the class of drugs shown to lower low-density lipoprotein cholesterol (LDL-C), are among the most widely used prescription drugs worldwide[1]. By lowering cholesterol, statins have demonstrated an ability to reduce the risk of cardiovascular disease (CVD), hospitalization, and death[2]. Approximately 23.6 million statin prescriptions are dispensed from Canadian retail drug stores each year[3].

While statins have demonstrated efficacy in secondary prevention by preventing the recurrence of CVD, their use as a primary prevention strategy is highly controversial among the medical community[4]. Currently, there is much debate over whether statin drugs should be prescribed more broadly for primary prevention or provided only to those at a very high risk of developing CVD in order to avoid unnecessary adverse effects and overmedicating the general public[5].

One of the main arguments opposing the use of statins as a primary prevention strategy is that these drugs do not prevent the onset of CVD enough and that statin drugs may not "achieve an acceptable risk-benefit ratio when treating patients who might have a very small absolute event reduction from statin therapy"[6]. A meta-analysis published in the Lancet reported that a 1 mmol/L reduction in LDL-C in low risk individuals resulted in "an absolute reduction in major vascular events of about 11 per 1000 over 5 years"[4]. The number needed to treat (NNT) is also high, and studies have indicated that in order to prevent one cardiovascular event, 71 primary prevention patients would have to be treated with a statin for 3 to 5 years[7]. Patients who are prescribed statins run the risk of damaging their kidneys and muscles as well as developing diabetes mellitus (DM) type 2[1]. When physicians prescribe a statin to otherwise healthy people,

they may potentially be exposing them to avoidable adverse effects of the drug. The question must be asked as to whether statin drugs should be prescribed to all individuals based on their LDL-C levels or whether statin treatment should be individualized on the basis of clinical judgement?[5]

As a counter argument, other researchers and clinicians would argue that primary prevention of CVD using statins can be regarded as an efficient population based strategy[6]. On a clinical level a 1.1% absolute risk reduction in major vascular events may not appear significant, but when applied on a population basis we begin to understand the positive potential economic impact. CVD is a leading cause of morbidity and mortality in the western world, and individuals with CVD are among the highest users of healthcare resources[8]. Prescribing statins to patients for primary prevention is argued to be cost effective in the long run in terms of reductions in diagnostic procedures, hospitalizations, treatment and long-term care.

It is important to emphasize, however, how careful physicians must be in prescribing medication indiscriminately for the sake of potentially saving government money. This is especially true if it means exposing otherwise healthy people to adverse side effects. As it stands, it is a precarious issue and will need strong supportive real world data for it to be considered. The purpose of the current research will be to explore the potential benefits of statin drugs in primary prevention using Newfoundland and Labrador (NL) point of care physician electronic medical record (EMR) data. This study will investigate whether these drugs decrease adverse health outcomes of CVD and all-cause mortality. Our composite CVD outcome includes the following conditions: coronary artery disease (CAD)/ischemic artery disease, cerebrovascular disease, peripheral artery disease, atherosclerosis, hospitalized due to CVD and death due to CVD.

Literature Review

1.1 The Cost of CVD in Canada

CVD is defined as any disease that "affects the heart, the blood vessels of the heart, and the veins and arteries throughout the body and within the brain"[9]. While Canadian rates of overall mortality from CVD have decreased by nearly 40% in the past decade, it remains the leading cause of morbidity and mortality claiming nearly 30% of all Canadian deaths[10,11]. According to the Public Health Agency of Canada more than 1.4 million Canadians are living with heart disease[11]. The toll on the economy is also great; CVD accounts for three out of the four most expensive health conditions. Annually, CVD accounts for over $22 billion in healthcare expenditure and loss of productivity[9,12].

1.2 Risk Factors of CVD

Risk factors are described as influences (e.g. demographic, clinical, genetic, lifestyle) that contribute to one's likelihood of developing CVD or that contribute to worsening of preexisting CVD. Examples of risk factors include hypertension (HTN), DM, obesity, smoking, excessive alcohol consumption, little to no physical activity, and low income[13]. The Heart and Stroke Foundation (2015) reports that 90% of Canadians have at least one risk factor for CVD[9]. It is suggested that attempting to modify risk factors could reduce the incidence and prevalence of CVD.

Elevated levels of LDL-C, or 'bad' cholesterol as it is more commonly known, is an extremely important risk factor and one on which this research will focus. LDL transports cholesterol from the liver throughout the rest of the body and allows it to collect as plaques on the walls of blood vessels; a condition called atherosclerosis[14]. A buildup of plaque can harden and narrow arteries, making it more difficult for oxygen-rich blood to travel to the heart and other peripheral organs. As a result, this can lead to a heart attack, stroke or death[15]. Nearly 60%

of Canadian adults (ages 40-59) are living with high levels of LDL-C[10]. Globally, the prevalence of raised cholesterol among adults is estimated to be approximately 39%[16].

1.3 Global Risk Assessment Score (Framingham Risk Score)

Individuals at risk of CVD can be categorized based on their prospective percent (%) risk of developing CVD within the next 10 years. This risk level in part explains why a forty-five-year-old female who exercises daily and maintains a healthy diet is less likely to develop CVD compared to a hypertensive male in his late sixties who smokes. It also explains why we may initiate preventative treatment in someone with a high risk lifestyle and not initiate treatment in someone else of the same age. A limitation to most of the previous research was a failure to account for a participant's level of risk of developing CVD. For example: if all of the low risk (<10%) patients were randomized to a study's experimental group and all of the high risk patients to the control group, the study could potentially overestimate the beneficial effects of statins.

As previously discussed, a multitude of risk factors often coexist and can contribute to CVD. The Framingham global risk assessment tool is a validated epidemiological global risk algorithm tool used to predict one's risk of developing CVD over the next 10 years[6,19,20]. The Framingham risk score (FRS) takes into account a patient's age, TC, smoking status, HDL-C, and systolic blood pressure (BP)[20]. Based on their score, patients are considered as low risk (<10%), intermediate risk (10-19%), or high risk (≥20%). This tool is clinically useful as a risk estimation system as it is "methodologically robust and easy to use, addresses clinically relevant risk factors, and results in measurable health gain to a population"[21]. Additionally, the Framingham tool has been studied for its external validity and its ability to generalize as the tool is "derived from a study population with sufficient sample size that is representative of the population to which the function is to be applied"[21].

The Framingham study has played a large role in the detection and treatment of heart disease by enabling researchers to identify some of the lifestyle and risk factors associated with CVD. This risk information can subsequently be used as a tool when prescribing risk-reducing medications such as statins. In the United States, mortalities associated with CVD have decreased since 1990, a trend largely attributable to using the Global risk assessment as part of a strategy to manage CVD[19].

1.4 Current Guidelines for Managing Cholesterol Levels

Current cholesterol targets published by Statistics Canada (2013) and the Mayo Clinic suggest that normal LDL-C levels for both males and females, ages 20-79, should be below 3.5mmol/L, high-density lipoprotein cholesterol (HDL-C) levels should be above 1.0mmol/L (males) and 1.3mmol/L (females), total cholesterol (TC) for both males and females should be below 5.2mmol/L, and total triglyceride levels (TT) lower than 1.7[10,17].

The most current guidelines at the time of this study* for managing dyslipidemia in Canada were published by the Canadian Cardiovascular Society in 2012[18]. Cholesterol screening is recommended in men >40 and postmenopausal women >50, or at any age in those with the following risk factors: "smoker, DM, arterial HTN, family history of premature CVD, family history of hyperlipidemia, erectile dysfunction, chronic kidney disease (CKD), inflammatory diseases, HIV infection, chronic obstructive pulmonary disease (COPD), clinical evidence of atherosclerosis or abdominal aneurysm, clinical manifestation of hyperlipidemia, or body mass index (BMI) >27"[18].

* While we appreciate that the Canadian College of Family Physicians published more recent guidelines for the management of dyslipidemia in 2015, this study used the guidelines consistent with the timeline of the study. Note that both guidelines are very similar in terms of management principles.

The 2012 guidelines suggest that the FRS be used to estimate a patient's 10-year risk of developing CVD, in addition to a full cholesterol screen and kidney function tests. Table 1 presents the study's recommendations for lipid targets and treatment.

Table 1 Canadian Cardiovascular Society guidelines for the management of lipids by statin therapy (2012). Summary of treatment targets based on Framingham Risk. Source: *http://www.onlinecjc.ca/article/S0828-282X(12)01510-3/pdf*

Risk Level	Initiate therapy if	Primary LCL-C target	Alternative targets
High risk: FRS ≥ 20% Or in patients with: DM, CKD, high risk HTN, atherosclerosis or an aortic aneurysm	Consider treatment in all	≤2 mmol/L or ≥ 50% reduction in LDL-C from baseline	Apo B ≤ 0.8 g/L or non HDL-C ≤ 2.6 mmol/L
Intermediate risk: FRS 10-19%	LDL-C ≥3.5mmol/L For LDL-C <3.5 mmol/L consider if: Apo B ≥1.2g/L or non-HDL-C ≥4.3 mmol/L	≤2 mmol/L or ≥ 50% reduction in LDL-C from baseline	Apo B ≤ 0.8 g/L or non HDL-C ≤ 2.6 mmol/L
Low risk: FRS <10%	LDL-C ≥5mmol/L or familial hypercholesterolemia	≥ 50% reduction in LDL-C	

1.5 Statin Drugs

Several types of statins exist and are sold under a variety of brand names: Lipitor (atorvastatin), Zocor (simvastatin) and Crestor (rosuvastatin) are examples of three commonly used high-potency statins. This research employs the umbrella term 'statin' to refer to the 3 brands of statins previously listed. Statin drugs are among the top three cardiovascular medications dispensed in Canada, along with angiotensin converting enzyme inhibitors (ACE-I) and diuretics[22]. Approximately 23.6 million statins are prescribed each year in Canada[3].

Statins lower LDL-C by inhibiting HMG-CoA reductase, the rate-limiting enzymatic step in cholesterol synthesis, and thus act to decrease the liver's ability to synthesize cholesterol[23]. Statins also have non lipid related effects; they possess "anti-inflammatory properties, inhibit vascular smooth muscle cell proliferation as well as platelet function, and improve vascular endothelial function"[23]. While studies are ambiguous, it has also been suggested that statins slightly increase the levels of HDL-C, or 'good cholesterol'[24].

1.5.1 Side Effects of Statin Drugs

As with most pharmaceuticals, statin drugs have the potential to cause adverse effects. The most commonly reported adverse effects in clinical settings involve the musculature system (e.g. myalgia and myopathy), as well as symptoms of fatigue and weakness[25]. The adverse effects related to muscles range from mild to severe, "and is believed to occur in up to 10-15% of exposed subjects in real world practice"[26]. A number of randomized control trials (RCT) with large sample sizes have "not shown significant differences in the number of subjects reporting muscle symptoms between statin and placebo-allocated groups"[27]. Batteries of trials have assessed the safety of statins and have reported that by and large they are a "safe and tolerable medicine having considerable risk/benefit ratio with the display of only mild and transient adverse effects"[25]. The more severe side effects include rhabdomyolysis – severe muscle damage

leading to elevated levels of creatinine kinase (CK)[28]. This side effect is rare (approximately 5/100000 patient-years)[25,28], and to date neither RCT data nor meta-analyses support a significant increase in rhabdomyolysis following statin use[28]. "Amongst 35 trials including 74,102 subjects over a mean of 17 months follow up reported that statin therapy did not increase the overall risk of rhabdomyolysis compared with placebo[29].

Other very rare side effects commonly linked to statins are: hemorrhagic stroke, cognitive impairments, gastrointestinal tract impairments (e.g. nausea, abdominal pain, diarrhea), cataracts and ocular hemorrhaging, erectile dysfunction, and decreased blood clotting[22]. While research has remained inconclusive, pregnant women are advised not to take statins as they have demonstrated the potential to cause congenital abnormalities[30].

There is currently much debate as to whether statin drugs increase the risk of cancer and to date there is no evidence supporting this[4]. A report published by the Statin Intolerance Panel (2014) suggested that "no effect of statin treatment on cancer incidence or mortality was evident in a meta-analysis of individual data from 175,000 patients in 27 randomized clinical trials of statins"[27]. Additionally, meta-analyses whose follow up period was greater than 6 years found no increase in the incidence of cancer with statin therapy[29].

Another reported side effect of statin use is the incidence of new-onset DM type 2. For this reason the "US Food and Drug Administration in 2012 added a statement to the labels of statin medications indicating that increases in glycated hemoglobin (HbA1C) and fasting glucose levels have been reported with statin use"[31]. This raised concerns among physicians in respect to prescribing statins to patients with pre-existing DM and those with DM risk factors[31]. Statin drugs are thought to cause hyperglycemia by either disrupting the voltage gated calcium

channels in pancreatic beta cells (decreasing insulin production), or by decreasing the number of GLUT4 (glucose transporters) on the intracellular membrane of muscle cells[31].

A report from the Diabetes Subpanel of the National Lipid Association Expert Panel on Statin Safety (2014) reported that despite the modest, but "clinically significant increase in the odds for new-onset DM (~10% compared with placebo or usual care)[31], no changes to clinical practice are recommended other than the measurement of HbA1C or fasting glucose in those deemed to be at elevated DM risk"[31]. Another study published by Shah et al., (2016) reported that "diabetes mellitus was diagnosed in 27% more patients receiving rosuvastatin therapy compared with patients receiving placebo"[32].

These results are replicated in other large studies published after 2014, including reviews by Beckett et al., (2015), Bernardi et al., (2015) and Agouridis et al., (2015). Their studies offer similar conclusions to the Statin Diabetes Task Force report; that statin drugs show a statistically significant increase in the risk of new-onset DM type 2, but this risk is not clinically significant[33]. Bernardi et al., (2015) suggest that risk factors of "age, potency of statin therapy, presence of metabolic syndrome, impaired fasting blood glucose, obesity and previously altered glycated hemoglobin levels" contribute to the likelihood of developing DM from statins[34]. Agouridis et al., (2015) report that "lipophilic statins are more diabetogenic than the hydrophilic ones"[35]. Despite all of this data, it is still believed among the medical community that the well-established benefits of statin therapy in reducing cardiovascular events outweigh the risk of developing DM[35].

1.5.2 Medication Compliance

It is important to be conscious of the fact that the low reporting of side effects in many RCTs is likely attributed to the pretrial run-in phase. This preliminary phase screens participants for their ability to tolerate statins and their side effects in addition to their compliance in taking the

medication. Additionally, these trials often "drop patients who have had a previous history of statin intolerance"[27]. Patients who fail to meet certain thresholds are often excluded from the study, resulting in a potential overestimation of the beneficial effects of statin drugs.

In a real world setting, where medication adherence is not as tightly controlled, many patients do not take their medication as prescribed by their physician due to adverse events even though patients are aware of the medications proven benefits. Bosomworth (2011) suggests, "fewer than 50% of patients take 80% or more of their prescribed statin dosages"[6]. Statin adherence rates after 5 years are estimated to be a low as 25%, with nearly one-third of patients discontinuing therapy within the first year[36]. Shalev et al., (2012) studied the role of statin use for primary prevention using a retrospective cohort study and stratified the cohorts based on statin persistency (proportion of days covered (PDC)). The authors argue in favor of this type of study design by suggesting that the effectiveness of statins when studied using an RCT is often overestimated due to "premature truncation, selective inclusion of high-risk patients, high level of patient care, and titration management which may affect their generalizability to everyday practice"[37]. A retrospective cohort study can "tackle these limitations and quantify the true effect size of statins in "real-world" community practice with higher external validity"[37]. In that study, patients were classified as: <20%, 21% to 39%, 40% to 59%, 60% to 79%, ≥80% compliant with their statin medication. Results indicated a significant decrease in CVD events with each increasing PDC category, and found persistent statin users (≥80%) to have a 22.72% (95% CI: 22.3 to 23.1) lower probably of CVD within the next 10 years compared to non-persistent users (<20%)[37]. For those patients who chose to discontinue statin treatment due to adverse events, there was no randomized, clinical trial evidence that musculature, hepatic, or cognitive effects were irreversible[27,36].

1.5.3 Primary vs. Secondary Prevention: Previous Literature on Statin Use

The act of preventing or reducing the progression of a disease can be broken into a series of prevention strategies. In primary prevention, the goal is to prevent a disease from occurring, and is accomplished by risk reduction. Primary prevention generally targets specific modifiable risk factors for a given disease[38]. In contrast, secondary prevention is an 'after the fact' measure that attempts to control the progression of a disease. If a disease is discovered in its early stages, secondary prevention can be used to impede more serious symptoms[38].

While the use of statin drugs for secondary prevention has proved efficacious, their use as a primary prevention strategy is highly debated among both the medical and research community, and to date research has been relatively ambiguous. As previously discussed, most research has grouped all primary prevention patients together as a whole without accounting for their level of risk of CVD, and "data has clearly supported the use of statins for high-risk individuals where the benefits have outweighed the risks"[5]. However, due consideration is needed "when extrapolating the potential benefits of statins on mortality to lower-risk primary prevention populations"[39]. Should statins be prescribed for primary prevention, regardless of risk level, or in doing so are physicians running the risk of overmedicating the general public? As it stands, physicians tend to individualize statin prescriptions on the basis of clinical judgement[5].

The WOSCOPS (West of Scotland Coronary Prevention Study) was one of the first RCTs to investigate statin use (pravastatin) for primary prevention. The study investigated whether statins reduced the "combined incidence of nonfatal myocardial infarction (MI) and death from CAD" in men with hypercholesterolemia (LDL >4mmol/L) and no prior CVD[40].

Following a five year follow up, the occurrence of the primary endpoint of nonfatal MI or death from CAD for the statin group compared to the control group was 5.5% vs. 7.9% (RR

0.69; 95% CI 0.57-0.83; P<0.001). The Statin group demonstrated a significant risk reduction in the primary outcome of 31% (95% CI from 17 to 43% P<0.001). The absolute difference in the risk of CVD after 5 years was 2.4%. It is estimated that treating 1000 men (with elevated plasma cholesterol and no previous CVD) for five years with pravastatin would result in "20 fewer nonfatal MI, 7 fewer deaths from CVD, and 2 fewer deaths from other causes than would be expected in the absence of treatment"[40]. Additionally, the WOSCOPS trial did not find any significant differences in adverse effects between the experimental and control group. In the statin group 20 subjects had myalgia and 97 had muscle aches, compared to 19 and 102 in the control group[40].

Brugts and colleagues (2009) performed a meta-analysis and investigated whether statins used in primary prevention reduced all-cause mortality and major coronary and cerebrovascular events in individuals with cardiovascular risk factors but no established CVD. In addition, they wished to examine whether these effects were similar in understudied subgroups such as women, older adults (>65 years), and in people with DM. The meta-analysis of 70,388 participants revealed that statins "significantly reduced the risk of all-cause mortality, major coronary events, and major cerebrovascular events"[24]. Total cholesterol levels were reduced by 17.1%, LDL-C by 25.6%, and TT by 9.3%; results comparable to secondary prevention studies. Compared to controls, patients receiving statin therapy demonstrated a 12% relative risk reduction in all-cause mortality, a 30% relative risk reduction in major coronary events, and a 19% relative risk reduction in major cerebrovascular events[24]. In addition, the studies found no significant association between statin use and risk of cancer (OR 0.97, 95% CI 0.89 to 1.05)[24].

Brugts and colleagues (2009) concluded that statins demonstrated positive outcomes including improved survival "across a broad range of patients at different risk levels, and showed

that there was no significant difference in treatment benefit across a range of clinically defined groups such as men and women, elderly, and those with diabetes"[24].

The JUPITER trial (Justification for the use of statins in primary prevention: an intervention evaluating Rosuvastatin)[41] was one of the most recent and controversial RCTs that assessed statin use for primary prevention in a low risk population. This study randomized approximately 17,000 patients from 1351 sites in 26 countries all of whom had LDL-C levels of <130mg/dL (<3.36 mmol/L) but were at risk of CVD due to elevated levels of high sensitivity C reactive protein (hsCRP) ≥2 mg/L. Relative risk reductions in specific vascular events were reported for the statin group compared to the control group: 54% reduction in MI (P=0.002), a 48% reduction in stroke (P=0.002), a 46% reduction in the need for arterial revascularization (*P*<0.001), and a 20% reduction in all-cause mortality (P=0.02)"[41,42].

For healthy men >50 years and women >60 years the NNT values for 2, 3, 4 and 5 years were 95, 49, 31 and 25 respectively for the primary endpoint of CVD. The authors noted that these NNT values "compare favorably to several other therapies widely considered to be effective in the primary prevention of CVD"[42]. Both the intervention and placebo group were similar in the number of reported serious adverse effects: 1352 and 1377, respectively (P=0.60). In addition, those allocated to receive a statin demonstrated a significant reduction in cancer mortality compared to placebo (35 verses 58, P=0.02).

A study conducted by the Cholesterol Treatment Trialists' (CTT) Collaborators used the global risk assessment tool to categorize a patient's risk of CVD into either low, intermediate or high and assessed whether the side effects of statin drugs outweighed the benefits of CVD reduction. A meta-analysis of 27 studies grouped patients based on their "5-year major vascular event risk on control therapy (<5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30%, ≥30%); in

each, the rate ratio per 1.0 mmol/L of LDL-C reduction was estimated"[4]. The results of this analysis demonstrated that statins significantly reduced the risk of major vascular events and all-cause mortality "irrespective of age, sex, baseline LDL-C or previous vascular disease"[4]. Interestingly, the proportional reduction in vascular events was similar across all risk groups and was "at least as big in the two lowest risk categories as in the higher risk categories"[4].

1.5.4 Summary of Aforementioned Research

The research previously discussed suggests that statin drugs, when used in primary prevention, significantly decreased outcomes of CVD and death in adults (45-79 years) compared to adults who were not taking statins. Among the studies, it was found that the statin groups demonstrated a significant risk reduction in the primary outcome of CVD anywhere between 31 and 54%, and all-cause mortality by 12-20%[24,40-42]. The JUPITER trial reported that the NNT for women > age 60 and men > age 50 for 2,3,4 and 5 years was 95, 49, 31 and 25 respectively[42]. In addition, studies have demonstrated no significant difference in adverse effects between intervention and control group, other than DM type 2.

While it is possible that the results from these RCTs may be an overestimation of the beneficial effects of statins for reasons previously discussed, the results presented by Shalev et al., (2012) from their retrospective cohort study addressed some of the limitation of RCTs[37]. Their study revealed a similar relative risk reduction of CVD of 27.7% for the intervention group, which suggested that the ability of statins to reduce CVD is significant and does apply in a real world setting. Additionally, previous research has suggested that statins have demonstrated a reduction in CVD for different types of participants regardless of their risk factor (e.g. elevated hsCRP levels, hypercholesterolemia, men, women, DM[24]).

1.5.5 Treatment with Statins for Longer than 10 Years

Another aspect to consider when using statins is the duration of treatment required to decrease the occurrence of CVD and the time required for adverse effects to develop. Studies have shown that differences in clinical outcomes have been observed anywhere from 4 to 30 months[36], but despite the many studies that have been published on statins there is "very little randomized, controlled clinical trial evidence of statin therapy beyond 5 years"[36]. In addition, many studies are terminated early due to sufficient number of primary end points that have been documented[36]. Stopping a trial early may exaggerate positive results, produce false positives, and does not allow sufficient time to detect adverse effects of a drug, such as cancer.

A study published by Soverow and Watson (2000) assessed the long-term effects of statin use in both primary and secondary prevention studies. The study concluded that treatment "with a statin for 10 years was superior to treatment for only 5 years"[36]. According to the results of their study, the authors speculated that extending statin therapy beyond 10 years would be expected to "(1) delay atheroma progression, (2) suppress associated vascular risk factors and (3) provide an overall mortality benefit and reduction in cardiovascular events"[36].

The WOSCOPS trial was a primary prevention RCT using pravastatin that demonstrated a 1% absolute risk reduction in all-cause mortality for the exposed group after a median follow up period of 4.9 years. Adding an additional 10 years of post-trial follow up revealed "a significant, sustained 2% (P=0.03) absolute risk reduction in all-cause mortality over the entire follow up period in the pravastatin group compared to the placebo group"[36,43]. This reduction in mortality was evident despite the 50% absolute drop in adherence rate among participants. The fifteen year follow up period also revealed that rates for nonfatal MI and coronary heart disease were 15.5% (placebo group) vs. 11.8% (statin group)[5,43]. Over the long term, "statin use resulted

in the stabilization of plaques, allowing for long term benefit even after users stopped taking the drugs"[5].

1.5.6 Economic Impact of Statin Use for Primary Prevention

Studies by Gotto et al., (2000) have identified the economic benefits of statin use for primary prevention in terms of a reduction in healthcare resource utilization and cost. The study reported that statin treatment reduced the number of cardiovascular hospitalizations by 29%, and the frequency of cardiovascular hospitalizations, therapeutics and diagnostic procedures by 28%, 32% and 23% respectively. The offset in direct cardiovascular medical costs between the statin and placebo group was $524 per patient, a 27% reduction "over the mean study duration of 5.2 years"[8]. In their research, it was estimated that the cost of statin treatment per patient was $4,654[8].

Robinson (2014) explored the social and economic impact of the Adult Treatment Panel (ATP) III updated guidelines using data from the National Health and Nutrition Examination Survey. Their research indicates "the modest observed reduction in LDL-C of ~0.56mmol/L in statin users likely prevented 40,020 deaths, 61,074 hospitalizations for acute MI ($4.4 billion costs avoided), and 22,272 hospitalizations for stroke ($440 million costs avoided)[44]. A saving of $34,926 per statin user was seen after 10 years of statin use, "or a benefit-to-cost ratio of 4:1"[44]. The paper also estimates potential savings of $2.5 billion for acute MI hospitalizations, and $260 million for stroke hospitalizations, had statins been used by all adults who were eligible according to the ATP III guidelines[44].

It is clear that efforts to prevent CVD are needed in order to limit the growing economic and social burden. "The American Heart Association estimates that by 2030, 40% of the US population is projected to have some form of CVD or HTN, and total medical costs of CVD are

expected to triple from $273 to $818 billion"[14,44]. The widespread availability of statins in addition to the low-cost of generic brands makes it a cost effective prevention strategy for CVD. "These data suggest that statins are more cost effective than aspirin or antihypertensive medication in reducing CVD mortality and morbidity in primary prevention"[5].

1.6 CPCSSN Database and Data Linkage

Nearly 85% of people in Canada have a family physician, and over 70% visit their physician at least once a year[45]. The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) is the first national health database that draws its data from the EMRs of family physicians. During the timeframe of the study (January 1st 2009 to 2013), CPCSSN included 10 research networks across Canada. There were 750 physicians who contributed de-identified data on over one million patients[46]. The network has developed specific algorithms for identifying various chronic diseases: COPD, depression, DM, HTN, osteoarthritis, as well as neurological conditions dementia, epilepsy and Parkinson's disease[46, 47] .

This research will link patient information from the Newfoundland and Labrador CPCSSN (NL-CPCSSN) database with databases held by the NL's Centre for Health Information (NLCHI) in an attempt to explore the relationship between statin use and outcomes of CVD and all-cause mortality in the province of NL. All information is de-identified in order to preserve anonymity of the patients. The NL-CPCSSN database has information from 50 physicians (approximately 10% of all NL family physicians) and over 44,000 patients.

Prior to the development of the CPCSSN database, information available on chronic diseases in Canada was derived from sources such as hospital discharge summaries, billing data and population health surveys[48]. However, these datasets were limited by their "inability to capture data on conditions that did not lead to hospitalizations"[48,49]. Additionally, they were often created for financial management rather than research purposes, and were unreliable when

dealing with self-reporting of subjects[48,49]. The CPCSSN database attempted to mitigate the aforementioned limitations by using a primary care database, which was beneficial in that it "provided a prospective and systematic collection of clinically verified data that could be comprehensive for studying a variety of important outcomes"[48,50]. The use of CPCSSN data for this research allowed us to answer our question with real-world, point of care physician EMR data from NL.

Chapter 2

Research Objective and Questions

2.1 Objective

To investigate whether statin drug therapy decreases the occurrence of CVD[†] and all-cause mortality in primary prevention patients ages 50-70.

2.2 Primary Question

Do patients, ages 50 to 70 who are prescribed statins ("exposed") for primary prevention have reduced outcomes of CVD and all-cause mortality compared to patients who are not prescribed statins ("not exposed")? The primary question stated in PICO format is:

P: People who are between 50 and 70 years of age as of December 31, 2008 and have no history of CVD

I: On a statin drug for primary prevention on December 31, 2008

C: Not on a statin drug on December 31, 2008

O: Develop CVD or die between January 1, 2009 and December 31, 2013

2.3 Secondary Questions

i) Does statin drug use predict secondary outcomes of coronary artery disease/ischemic heart disease, cerebrovascular disease, peripheral vascular disease, hospitalization (any reason), hospitalization due to CVD, or death due to CVD?

ii) To what degree does statin exposure predict the primary outcomes of CVD and all-cause mortality when significant CVD risk factors are controlled for?

[†] The composite outcome of CVD includes: coronary artery disease/ischemic artery disease, cerebrovascular disease, peripheral artery disease, atherosclerosis, hospitalized due to CVD, death due to CVD

iii) To what degree does statin exposure predict the primary outcomes of CVD and all-cause mortality when significant CVD risk factors are controlled for in a population of medication compliant (≥80%) patients?

iv) Is there an increase incidence of diabetes mellitus in people using statins?[‡]

2.4 Hypothesis

2.4.1 Null Hypothesis (H_0)

There will be no statistically significant difference in the incidence of CVD or all-cause mortality between the exposed and non-exposed groups. It will remain a non-significant difference even when risk factors for CVD (e.g. age, sex, diagnosis of HTN, smoker, LDL-C, HDL-C, BMI, sBP and dBP) are controlled for.

There will be no significant difference in the incidence of DM in the exposed group vs. non-exposed group.

2.4.2 Alternative Hypothesis (H_a)

In accordance with previous literature, we anticipate that the data will show a decrease in the rates of CVD and all-cause mortality for patients in the statin exposed group. Using the study conducted by Shalev et al., (2012) as a guideline, we hypothesize that the exposed group would demonstrate a 25-30% relative risk reduction in CVD compared to the non-exposed group. This reduction in the incidence of CVD will persist even when controlling for significant risk factors of CVD.

[‡] The CPCSSN database cannot identify between DM Type 1 and Type 2. In this age group we assume that an overwhelming majority of new onset cases are Type 2.

We do expect a statistically significant increase in the incidence of DM in the exposed group vs. non-exposed group based on studies published by the Diabetes Task Force[31] and Shah et al., (2016).

2.5 Significance of Study and Clinical Implications

While statins have proven efficacious for secondary prevention, their use among primary prevention patients in a real world setting warrants further research. Unlike many RCTs that do an initial pretrial run-in phase and only randomize compliant patients, the current research will provide data from a real-world source on the effects of statins in decreasing adverse health outcomes. In addition to any clinical implications, this research may provide evidence for an economically viable way to reduce healthcare expenditure on CVD and CVD related procedures. As previously discussed, CVD currently accounts for over $22 billion in healthcare expenditure and loss of productivity[12]. Prescribing statins for primary prevention could potentially decrease healthcare resource utilization in terms of emergency room visits, hospitalizations and diagnostic services.

The current study will expand on previous literature in the following ways: (i) the study followed patients retrospectively for a full five year follow up period, eliminating the potential for early termination and (ii) this study is the first ever linkage study using CPCSSN EMR data.

Chapter 3

Methods

3.1 Study Design

This was a retrospective inception cohort study of primary prevention patients aged 50 to 70 years. The purpose was to determine whether the use of statin drugs decreased the development of CVD or all-cause mortality over a five-year period (January 1, 2009 to December 31, 2013) compared to a cohort of patients who were not using statin drugs. There was no recruitment period for this study as the baseline data was collected at the study's start date (zero time): January 1, 2009. There was a clearance period of two years to ensure that outcomes were new cases.

We analyzed secondary data from the NL-CPCSSN database, which was linked to both the NL hospitalization database -- Clinical Database Management System (CDMS) -- and the NLCHI mortality system to establish the cohorts and assess outcomes.

3.2 Participants: Establishing the Study Cohort

The study population consisted of people in the NL-CPCSSN database who on December 31, 2008 were between the ages of 50 and 70 years and had no previous history of CVD during the two-year clearance period. These individuals would be in a primary prevention situation. The exposure cohort consisted of individuals meeting the age criteria who were prescribed a statin as of December 31, 2008. The non-exposed cohort consisted of individuals who were **not prescribed** a statin drug as of December 31, 2008 or 6 months prior. The total number of patient records used in this study was 9,134. Although we have no way of knowing whether patients who were prescribed a statin were actually filling/using their medication, our study is based on the assumption that the exposed group are those who were on a statin drug at baseline because

they had received a prescription prior to the baseline date and there was no indication it had been stopped by the physician.

3.3 Data Sources

3.3.1 Description of Dataset (CPCSSN)

Data from the CPCSSN database was accessible through NLCHI and all data was de-identified. The dataset used for this research project consisted of only NL data. CPCSSN uses a variety of algorithms in order to identify patients with chronic conditions. These diagnostic algorithms use information from billing data, laboratory test results, medications, health conditions/problem list and encounter diagnostics in order to create a disease definition and identify a diagnosis.

Validation studies on CPCSSN data have been conducted at both the Kingston Network (Queen's University, Ontario) and the APBRN network (Memorial University, NL), "in order to assess the validity of EMR-based diagnostic algorithms for the five chronic conditions in the CPCSSN database"[48]. The specificity and sensitivity for all five chronic conditions (DM, HTN, osteoarthritis, COPD and depression) were very high, suggesting that "the diagnostic algorithms yield few false-positive cases…and the majority of true cases are being identified correctly by the CPCSSN algorithms"[48].

Because our study was observational and relied on health data previously recorded by physicians, the only potential risk was identification of an individual. CPCSSN and NLCHI have in place strong de-identification processes to reduce that risk to a minimum. All data that was extracted was de-identified.

The CPCSSN network takes great precautions in order to preserve patient privacy. Each CPCSSN network employee is required to pass a privacy seminar and sign an oath of confidentiality, no identifying information e.g. names, addresses, or telephone numbers were

extracted from the EMRs and all computer files pertaining to the study were password protected. CPCSSN has its own Privacy and Ethics Standing Committee that deals with issues of data collection, patient confidentiality, privacy and ethics approval, and this committee carries out regular privacy assessments and audits at regional networks.

3.3.2 Description of Dataset: (CDMS)

Hospitalization data was provided by the CDMS and was accessible through NLCHI. All data was de-identified. The CDMS contained information on patient demographics, as well as clinical and administrative hospital data when patients were discharged from inpatient and surgical care services.

3.3.3 Description of Dataset: (NLCHI Mortality System)

Mortality data was provided by the NLCHI Mortality System database and was accessible through NLCHI. All data was de-identified. The database contained demographic, administrative and clinical data from patients who died in the province of NL.

3.3.4 Description of Variables

Table 2 provides a description of each variable as well as the database it was extracted from. Demographic data was collected at baseline (December 31, 2008) and outcome data was collected at the end of follow up (Dec 31, 2013).

Table 2 Source and Description of Study Variables

Type of Variable	Variable	Description of Variable	ICD9[4] or ATC[5] code	Database
Exposure	Statin	Statin prescribed=patients who are listed in the CPCSSN database as being on a statin drug at baseline (Dec 31, 2008) Statin not prescribed=patients who have not used a statin within 6 months of baseline	ATC code starting with C10AA and/or drug name ending in "statin"	CPCSSN
Outcome	CVD	**Coronary artery disease/ischemic heart disease/angina** • Acute myocardial infarction • Other acute and subacute forms of ischemic heart disease • Old myocardial infarction • Angina pectoris • Other forms of chronic ischemic heart disease **Cerebrovascular Disease** • Occlusion of cerebral arteries • Transient cerebral ischemia • Acute but ill-defined cerebrovascular disease • Other and ill-defined cerebrovascular disease • Late effects of cerebrovascular disease **Peripheral Vascular Disease** **Atherosclerosis**	ICD9 code (410) ICD9 code (411) ICD9 code (412) ICD9 code (413) ICD9 code (414) ICD9 code (434) ICD9 code (435) ICD9 code (436) ICD9 code (437) ICD9 code (438) ICD9 code (443) ICD9 code (440)	CPCSSN **Data is extracted from health conditions and billing or encounter CPCSSN EMR tables*

[4] International Classification of Diseases, Version 9
[5] Anatomical Therapeutic Chemical (ATC) Classification System

Outcome	Composite outcome of CVD: created for the study	Coronary artery disease/ischemic artery disease, cerebrovascular disease, peripheral artery disease, atherosclerosis, hospitalized due to CVD, death due to CVD		CPCSSN, CDMS and NLCHI Mortality System
Outcome	Diabetes	**CPCSSN Case Definition** *(National data: 100% sensitivity, 99% specificity, NL only data: 95.6% sensitivity, 97.1 specificity)*[48] **Billing Data**: ICD9 code 250.x, **Medications**: insulin, glyburide, metformin, **Laboratory tests results**: HbA1C >7%, fasting blood sugar >7 mmol/L, **Problem list**: diabetes/NIDDM/DM, **Procedures**: revascularization procedures, coronary artery disease investigation, **Referrals**: ophthalmology, nephrology, neurology, endocrinology, diabetes education, dietician **Note: These were incident cases of diabetes with a clearance period of two years.*	ICD9 Code (250.x)	CPCSSN
Outcome	Hospitalization	Admitted to hospital for any reason Admitted to hospital for CVD		CDMS
Outcome	Death	Did death occur between January 1, 2009 and Dec 31, 2013. Number of months after enrolment patient died Was the cause of death due to CVD?		NLCHI Mortality System
Covariate	Age			CPCSSN
Covariate	Sex			CPCSSN
Covariate	Hypertension	**CPCSSN Case Definition (***National data: 83% sensitivity, 98% specificity, NL only data: 84.9% sensitivity, 93.5% specificity)*[48,49]		

		Billing Data: ICD9 code 401, **Medication**: ACE-I/ACB, diuretics, beta blockers, calcium channel blockers, alpha blockers, **Problem list**: hypertension, **Procedures:** angioplasty, coronary artery stent, **Referrals:** cardiology and nephrology[44]	ICD9 code (401)	CPCSSN
Covariate	Smoking Status	Current Smoker, Past Smoker or Non Smoker at baseline and follow up		CPCSSN
Covariate	Lipid Profile	Total Cholesterol LDL-C HDL-C TC/HDL ratio Total Triglycerides *Most recent measure prior to baseline (Dec 31, 2008) and follow up (Dec 31, 2013)*		CPCSSN
Covariate	Blood Pressure	Systolic Diastolic *Most recent measure prior to baseline (Dec 31, 2008) and follow up (Dec 31, 2013)*		CPCSSN
Covariate	Medication Compliance	Calculated from a patient's prescription start and stop date. Medication compliance is assumed if the exposed group were on a statin at baseline **and** had been prescribed the statin for 80% or more of the time (1460 days) during the five year follow up period. *We are assuming that those prescribed statins are in fact taking their medication as directed.		CPCSSN

3.4 Sample Size Calculation

Sample size was calculated such that if a 15% difference in outcomes was seen between the two cohorts it would be statistically significant. Using an alpha of 0.05 and a power of 90%, a sample size of 244 people was required in each of the two cohorts. This 15% difference was relevant for development of CVD, however detecting a smaller difference in death rates (10%) was important. Using an alpha of 0.5 and a power of 80% a sample size of 411 in each group was required in order to detect a 10% difference in death rates. However, in order to allow for subgroup analysis, we requested from NLCHI all patients who met the study's inclusion criteria.

The sample size calculations were performed using the JavaStat-Binomial Proportion Differences Tool developed by John Pezzullo. The calculator for proportion differences can be found at: http://www.statpages.org/proppowr.html

3.5 Analysis:

All analyses were performed using SPSS software. The initial analysis grouped patients based on their exposure status, however, not all of those in the exposed group remained on a statin for the entire five years of follow up, and we wondered whether the decreased adherence would change the primary outcomes. By including people in the exposed group who had actually stopped taking their statin medication, we were effectively diluting the potential beneficial effect of the statin therapy on our outcomes. We therefore completed a second analysis where the exposed group consisted only of those who were on statins at baseline **and** who had taken the statin for 80% or more of the time (1460 days) during the five year follow up period.

3.5.1 Statistical Analysis

We performed univariate analysis on the demographic data for both the exposed and non-exposed cohorts in order to describe the basic features of the data, and to determine whether the groups were similar or different at baseline.

A chi-square test was used to compare the primary and secondary outcomes (CAD/ischemic heart disease, cerebrovascular disease, PVD, hospitalization for any reason, hospitalization for CVD, death from CVD) by the exposure group. We also used chi-square to compare the incidence of DM between the exposed and non-exposed cohort.

The primary outcomes of CVD and all-cause mortality were then compared to other potential CVD risk factors/predictors at baseline (age, sex, diagnosis of HTN, smoking status, BMI, LDL-C, HDL-C, sBP, dBP, TC, TT). Chi-square with the Pearson continuity correction was used to compare the outcomes of dichotomous data and t-test for equality of means was used to assess the difference between group means of continuous variables.

Logistic regression was used to estimate the relationship between the predictor variable (statin use) and primary outcomes (CVD and all-cause mortality), when only controlling for covariates of age and sex. A second regression was done using the covariates that were significant on univariate analysis. Only those risk factors that were found to be significant predictors of the outcomes on logistic regression are presented in tables 6(b) &7(b). For the logistic regression, all of the missing data was coded as ‘unknown’ allowing us to maintain a large sample size for the analysis.

Chapter 4

Results

Of the 9,134 patient records, we had full data for all patients on age, sex, statin exposure, diagnosis of HTN, individual CVD outcomes, hospitalization and death. We had incomplete data on statin dosage, smoking status (approximately 50% of participants), BMI (approximately 16%), LDL-C (approximately 11%), and BP (approximately 41%). The data was incomplete as it was unavailable for a large proportion of our patients. As such, our analyses were limited by a small sample size of patients who had records for all variables known to increase the risk of CVD.

4.1 Baseline Data

The exposed and non-exposed groups are compared in Table 3. The exposed group has a higher proportion of people with risk factors for CVD: they are more likely to be male, are older, are more likely to have a diagnosis of HTN, have a higher BMI and TT, a lower HDL-C, and have higher sBP. This can be expected given that they were started on a statin drug by their physicians, suggesting that the physicians perceived them as being at higher risk. The exposed group have a better lipid profile with lower total and LDL-C but this is not unexpected given they are taking a statin drug which lowers cholesterol.

Table 3 Cohorts at Baseline (December 31, 2008). Comparison of Exposed vs. Non-Exposed Groups

		Total N=9134	Exposed N=720	Non-Exposed N=8414	P value exposed vs non-exposed
Sex (n/%)	**Female**	5421 (59.3%)	374 (51.9%)	5047 (60.0%)	0.001Χ
	Male	3713 (40.7%)	346 (48.1%)	3367 (40.0%)	
Age Mean (SD)		58.3 (5.7)	60.2 (5.6)	58.1 (5.7)	0.001Τ
Existing HTN Diagnosis		1171 (12.8%)	298 (41.4%)	873 (10.4%)	0.001 Χ
Smoking Status	**Current/Ever**	1906 (20.9%)	180 (3.9%)	1726 (37.4%)	0.309 Χ
	Never	2705 (29.6%)	232 (5.0%)	2473 (53.6%)	
BMI† Mean (SD)		28.3 (5.5) N=1486	29.2 (4.4) n =158	28.2 (5.6) n=1328	0.035 Τ
TC†† Mean (SD)		5.6 (1.06) N=1019	5.2 (1.08) n=204	5.7 (1.04) n=815	0.001 Τ
LDL cholesterol Mean (SD)		3.5 (0.90) N=964	3.1 (0.97) n=199	3.6 (0.86) n=765	0.001 Τ
HDL Cholesterol Mean (SD)		1.3 (0.39) N=958	1.2 (0.35) n=197	1.4 (0.39) n=761	0.001 Τ
HDL/Total Ratio Mean (SD)		4.5 (1.3) N=951	4.5 (1.2) n=196	4.5 (1.3) n=756	0.70 Τ
TT Mean (SD)		41.6 (0.97) N=869	1.8 (0.96) n=187	1.5 (0.97) n=682	0.003 Τ
Systolic BP††† Mean (SD)		128.9 (14.6) N=3140	131.4.7 (13.7) n=558	128.4 (14.8) n=2582	0.001 Τ
Diastolic BP Mean (SD)		78.4 (8.5) N=3141	78.8 (8.2) n=558	78.2 (8.6) n=2583	0.12 Τ

Χ P value for Chi Square

Τ P value for T test

† BMI data was only available on 16.3% of patients

†† Lipid data was only available on 10.6% of patients

††† BP data was only available on 34.4% of patients

4.2 Univariate Analysis of the Effect of Statins on Primary and Secondary Outcomes

The results of the univariate analysis are detailed in tables 4a and 4b. The exposed group, being on a statin at baseline was 1.36 times more likely to develop the composite outcome of CVD during the five year follow up period. There was no significant difference in all-cause mortality between the two groups. The results for the secondary outcomes, which consisted mainly of the individual components of the composite outcome, are detailed in table 4b. Those in the exposed group were either at increased risk of the outcome (CAD and hospitalization for any reason) or there was no difference between the groups.

4.3 Baseline Risk Factors and the Primary Outcomes

Given the unexpected outcomes for the main predictor variable of exposed vs. unexposed, we assessed how the known CVD risk factors in our data were associated with our primary outcomes. If there was also a reversal of expected results, we would have been concerned that our data was coded incorrectly. For example, if known risk factors for CVD (e.g. high sBP, smoking, increased age, HTN) were negatively associated with CVD, we would be concerned that there was an error with the data. However, as shown in tables 5a and 5b, the risk factors were associated in the expected direction: males, older people, those with higher BMIs, smokers, those with lower HDL-C, and those with higher sBP were all more likely to have the composite outcome of CVD. Similarly, males, older people, and smokers were more likely to experience all-cause mortality. These results provide validity for the data and suggest our findings related to statin exposure are not systematically biased in some way.

Table 4 Table of Primary and Secondary Outcomes vs. Statin Exposure

Table 4(a): Primary Outcomes

	Exposure to Statin at Baseline		OR; 95% CI; P value	Interpretation
	Yes	No		
Composite Outcome: All CVD	89 (12.4%)	791 (9.4%)	1.36 (1.08-1.72) 0.012 (Pearson Chi Square Continuity Correction)	People in the exposed group (on a statin at baseline) were significantly more likely (1.36 times) to experience the composite outcome than those in the non-exposed group.
All-Cause Mortality	15 (2.1%)	264 (3.1%)	0.66 (0.39-1.11) 0.143	The outcome of all-cause mortality was not significantly different between the exposed and non-exposed groups

Table 4(b): Secondary Outcomes

	Exposure to Statin at Baseline		OR; 95% CI; P value	Interpretation
	Yes	No		
Coronary Artery Disease/Ischemic Heart Disease	53 (7.4%)	467 (5.6%)	1.35 (1.01-1.81) 0.054 (Pearson Chi Square Continuity Correction)	People in the exposed group were significantly more likely (1.35 times) to develop CAD compared to the non-exposed group.
Cerebrovascular Disease	13 (1.8%)	118 (1.4%)	1.29 (0.73-2.30) 0.478 (Pearson Chi Square Continuity Correction)	The outcome of cerebrovascular disease was not statistically significantly different between the exposed and non-exposed groups
Peripheral Vascular Disease	15 (2.1%)	113 (1.3%)	1.56 (0.91-2.69) 0.145 (Pearson Chi Square Continuity Correction)	The outcome of PVD was not statistically significantly different between the exposed and non-exposed groups
Hospitalization Any Reason	416 (57.8%)	4424(52.8%)	1.23 (1.06-1.44) 0.008 (Pearson Chi Square Continuity Correction)	People in the exposed group were significantly more likely (1.23 times) to be hospitalized for any reason compared to those in the non-exposed group
Hospitalization for CVD Reason	30 (4.2%)	297 (3.5%)	1.19 (0.81-1.74) 0.436	The outcome of hospitalization for CVD was not statistically significantly different between the exposed and non-exposed groups

			(Pearson Chi Square Continuity Correction)	
CVD Mortality	4 (0.6%)	34 (0.4%)	1.38 (0.49-3.89) 0.539 (Fisher's Exact test)	The outcome of CVD mortality was not significantly different between the exposed and non-exposed groups

Table 5 Effect of Baseline Risk Factors on Primary Outcomes

Table 5(a): CVD (composite outcome)

		Composite Outcome (Any CVD)		OR; 95% CI; P value (Mean Diff (SD) for continuous variables	Interpretation
		Yes	No	1.93 (1.68-2.22) 0.001 (Pearson Chi Square Continuity Correction)	Males were significantly more likely (1.93 times) to have an outcome of CVD compared to females
Sex	**Male**	487 (13.1%)	3226		
	Female	393 (7.2%)	5028		
Mean Age (SD)		60.32 (5.9)	58.04 (5.6)	Mean Diff 2.32 (1.93-2.93) 0.001 (t-test for equality of means)	Older people were significantly more likely to have an outcome of CVD compared to younger people
HTN diagnosis at baseline	**Yes**	117 (10.0%)	1054	1.05 (0.85-1.29) 0.696 (Pearson Chi Square Continuity Correction)	People with a diagnosis of HTN at baseline were no more likely to have an outcome of CVD compared to those without HTN at baseline
	No	763 (9.6%)	7200		
Currently or Ever Smoked	**Yes**	272 (14.3%)	1634	2.03 (1.68-2.46) 0.001 (Pearson Chi Square Continuity Correction)	Current or ever smokers were significantly more likely (2.03 times) to have an outcome of CVD compared to those who had never smoked
	No	205 (7.6%)	2500		
LDL-C Mean (SD)		3.48 (0.98) N=96	3.53 (0.90) N=868	Mean Diff: -0.05 (-0.24-0.14) 0.624 (t-test for equality of means)	People with higher LDL-C were no more likely to have an outcome of CVD compared to those with lower LDL-C
HDL-C Mean (SD)		1.24 (0.33) N=95	1.33 (0.40) N=863	Mean Diff: -0.095 (-0.18- (-0.01)) 0.025 (t-test for equality of means)	People with a low HDL-C were significantly more likely to have an outcome of CVD compared to those with a higher HDL-C
BMI Mean (SD)		29.7 (6.6) N=129	28.2 (5.4) N=1357	Mean Diff: 1.55 (0.56-2.54) 0.010 (t-test for equality of means)	People with a higher BMI were significantly more likely to have an outcome of CVD compared to those with a lower BMI
sBP Mean (SD)		131.5 (15.1) N=262	128.7 (14.6) N=2878	Mean Diff: 2.85 (1.00-4.71) 0.003 (t-test for equality of means)	People with a higher sBP were significantly more likely to have an outcome of CVD compared to those with a lower sBP

dBP Mean (SD)	78.5 (8.3) N=263	78.4 (8.5) N=2878	Mean Diff: 0.10 (-0.97-1.18) 0.854 (t-test for equality of means)	People with a higher dBP were no more likely to have an outcome of CVD compared to those with a lower dBP
TC (Mean)	5.41 (1.06) N=99	5.58 (1.07) N=920	Mean Diff: -0.17 (-0.39-0.05) 0.136 (t-test for equality of means)	People with a higher TC were no more likely to have an outcome of CVD compared to those with lower TC
TT (Mean)	1.59 (0.79) N=85	1.58 (0.99) N=784	Mean Diff: 0.00 (-0.21-0.22) 0.959 (t-test for equality of means)	People with a higher TT were no more likely to have an outcome of CVD compared to those with lower TT

Table 5(b): All –cause mortality

		All-cause mortality		**OR; 95% CI; P value (Mean Diff (SD) for continuous variables**	**Interpretation**
		Yes	No	1.53 (1.21-1.94) 0.001 (Pearson Chi Square Continuity Correction)	Males were significantly more likely (1.53 times) to die compared to females
Sex	**Male**	142 (3.8%)	3571		
	Female	137 (2.3%)	5284		
Mean Age (SD)		61.02 (5.9)	58.18 (5.7)	Mean Diff: 2.84 (2.14-3.55) 0.001 (t-test for equality of means)	Older people were significantly more likely to die compared to younger people
HTN diagnosis at baseline	**Yes**	37(3.2%)	1134	1.04 (0.73-1.48) 0.984 (Pearson Chi Square Continuity Correction)	People with a diagnosis of HTN at baseline were no more likely to die compared to people without HTN
	No	242(3%)	7721		
Currently or Ever Smoked	**Yes**	72 (3.8%	1834	2.49 (1.69-3.66) 0.001 (Pearson Chi Square Continuity Correction)	People who currently or previously smoked were significantly more likely (2.49 times) to die compared to those who had never smoked
	No	42 (2.2%)	2663		
LDL-C Mean (SD)		3.56 (1.1) N=17	3.52 (0.90) N=947	Mean Diff: 0.04 (-0.50-0.58) 0.882 (t-test for equality of means)	People with higher LDL-C were no more likely to die compared to those with lower LDL-C
HDL-C Mean (SD)		1.24 (0.33) N=17	1.33 (0.39) N=941	Mean Diff: -0.085 (-0.26-0.09) 0.308 (t-test for equality of means)	People with lower HDL-C were no more likely to die compared to those with lower HDL-C

BMI Mean (SD)	27.4 (6.3) N=30	28.4 (5.5) N=1456	Mean Diff: -0.94 (-3.30-1.42) 0.423 (t-test for equality of means)	People with higher BMI were no more likely to die compared to those with lower BMI
sBP Mean (SD)	129.5 (17.2) N=81	128.9 (14.6) N=3059	Mean Diff: 0.63 (-3.20-4.45) 0.746 (t-test for equality of means)	People with a higher sBP were no more likely to die compared to those with a lower sBP
dBP Mean (SD)	77.8 (8.6) N=81	78.4 (8.5) N=3060	Mean Diff: -0.60 (-2.52-1.33) 0.539 (t-test for equality of means)	People with a higher dBP were no more likely to die compared to those with a lower dBP
TC (Mean)	5.5 (1.4) N=19	5.7 (1.1) N=1000	Mean Diff: -0.02 (-0.69-0.66) 0.950 (t-test for equality of means)	People with a higher TC were no more likely to die compared to those with lower TC
TT (Mean)	1.7 (0.86) N=17	1.6 (0.98) N=852	Mean Diff: 0.13 (-0.32-0.57) 0.553 (t-test for equality of means)	People with a higher TT were no more likely to die compared to those with lower TT

4.4 Logistic Regression with the Primary Outcome of CVD as the Dependent Variable

We first used logistic regression to assess the relationship between statin exposure at baseline and the primary outcomes of CVD and all-cause mortality when controlling for covariates of age and sex (Table 6a). Because the exposed group was older and had a greater proportion of males, both of which increase the risk of CVD, we postulated that the increased likelihood of CVD in the group taking statins might be due to the bias associated with these higher risk people. This was in fact the case and as shown in table 6a the increased risk of CVD in those people taking statins was no longer statistically significant when age and sex were controlled for: (OR 1.13; 95% CI 0.89-1.43; P=0.304). Age and sex remained significant predictors of CVD.

We also used logistic regression and included as covariates age and sex plus the other predictors of CVD (Table 6b) that were significant under univariate analysis (HDL-C, BMI, sBP, and smoking status). Only the risk factors that were significant after doing the logistic regression were presented in table 6b (age, sex, BMI, smoker). Being on a statin at baseline still did not significantly predict our CVD composite outcome in either direction.

4.5 Logistic Regression with the Primary Outcome of All-cause Mortality as the Dependent Variable

We used a similar process for logistic regression using all-cause mortality as the dependent variable. When controlling for just age and sex (Table 7a) we see that statin use significantly predicts all-cause mortality in the negative direction, i.e. being on a statin was associated with decreased rates of all-cause mortality. When we added smoking status to the covariate list, the results remained the same.

Table 6(a) Logistic Regression Estimating the Relationship Between Statin Exposure at Baseline and the Primary Outcome of CVD when Controlling for Covariates of Age and Sex (N=9134).

Variables	Beta	Standard Error	P value	Odds Ratio	95%CI	
					Lower	Upper
Statin Exposure at Baseline	.125	.121	.304	1.133	.893	1.437
Sex	.668	.072	.000	1.951	1.694	2.247
Age	.070	.006	.000	1.073	1.060	1.086
Constant	-6.726	.379	.000	.001		

Table 6(b) Logistic Regression Estimating the Relationship Between Statin Exposure at Baseline and the Primary Outcome of CVD when Controlling for Covariates that were Significant on Univariate Analyses (age, sex, HDL, BMI, sBP, smoking status) (N=9134).

Variables	Beta	Standard Error	P value	OR	95% CI	
					Lower	Upper
Statin Exposure at Baseline	0.107	0.122	0.382	1.113	0.876	1.414
Sex	0.643	0.072	0.001	1.903	1.651	2.193
Age	0.072	0.006	0.001	1.075	1.062	1.088
BMI ≥30	-0.431	0.194	0.026	0.650	0.444	0.951
Current, Ever smoker	-0.691	0.099	0.001	0.501	0.413	0.609
Constant	-6.789	0.381	0.001	0.001		

Table 7(a) Logistic Regression Estimating the Relationship Between Statin Exposure at Baseline and the Primary Outcome of All-Cause Mortality when Controlling for Covariates of Age and Sex (N= 9134).

Variables	Beta	Standard Error	P value	OR	95% CI	
					Lower	Upper
Statin Exposure at Baseline	-.626	.270	.020	.535	.315	.908
Sex	.446	.122	.000	1.561	1.229	1.984
Age	.087	.011	.000	1.091	1.069	1.114
Constant	-8.829	.652	.000	.000		

Table 7(b) Logistic Regression Estimating the Relationship Between Statin Exposure at Baseline and the Primary Outcome of All-Cause Mortality when Controlling for Baseline Covariates that were Significant on Univariate Analyses (age, sex, and smoking status) (N=9134).

Variables	Beta	Standard Error	P value	OR	95% CI	
					Lower	Upper
Statin Exposure at Baseline	-0.609	0.270	0.026	0.547	0.322	0.930
Sex	0.424	0.123	0.001	1.528	1.201	1.943
Age	0.087	0.011	0.001	1.091	1.069	1.114
Current, Ever smoker	-0.910	0.198	0.001	0.403	0.273	0.593
Constant	-8.892	0.651	0.001	0.001		

4.6 Logistic Regression Using Only Medication Compliant Individuals in the Exposed Group

We next assessed whether medication compliance (i.e. how compliant patients were in taking their medication) had an effect on our outcomes. When only using those exposed individuals who had taken statins for ≥80% of the time during the follow up period, the number of patients in the exposed group decreased from 720 to 633. Thus, 87.9% of our exposed population took their medication for at least 1460 days of the five year follow up period. Results demonstrate that statin exposure is still not a significant predictor of CVD (Table 8a), however, it remains a significant predictor of all-cause mortality (Table 8b).

4.7 Incidence of Diabetes in the Exposed vs. Non-exposed Cohort

The percentage of new cases of DM in the exposed population was 10.3% compared to 7.4% in the non-exposed. People in the exposed cohort were 1.42 times more likely to develop DM at follow up compared to those in the non-exposed. After accounting for medication compliance, (Table 9b) people in the exposed group were still significantly more likely (1.49 times) to develop DM at follow up.

Table 8(a) Logistic Regression Estimating the Relationship Between Statin Exposure (based on ≥80% compliance) and the Primary Outcome of CVD when Controlling for Covariates that were Significant on Univariate Analyses (N=9047).

Variables	Beta	Standard Error	P value	OR	95% CI	
					Lower	Upper
Statin Exposure at Baseline	0.141	0.128	0.271	1.151	0.896	1.479
Sex	0.644	0.073	0.001	1.904	1.651	2.196
Age	0.072	0.006	0.001	1.075	1.061	1.088
BMI ≥30	-0.443	0.195	0.023	0.642	0.438	0.941
Current, Ever smoker	-0.688	0.100	0.001	0.503	0.413	0.611
Constant	-6.778	0.383	0.001	0.001		

Table 8(b) Logistic Regression Estimating the Relationship Between Statin Exposure (based on ≥80% compliance) and the Primary Outcome of All-Cause Mortality when Controlling for Covariates that were Significant on Univariate Analyses (N=9047).

Variables	Beta	Standard Error	P value	OR	95% CI	
					Lower	Upper
Statin Exposure at Baseline	-1.814	0.507	0.001	0.163	0.060	0.440
Sex	0.410	0.125	0.001	1.507	1.179	1.926
Age	0.086	0.011	0.001	1.090	1.067	1.113
Current, Ever smoker	-0.945	0.204	0.001	0.389	0.261	0.579
Constant	-8.841	0.662	0.001	0.001		

Table 9(a) Statin Exposure vs. Diagnosis of Diabetes at Follow up (N=9134).

	Statin Exposure at Baseline		OR; 95% CI; P value	Interpretation
	Yes	**No**		
Diabetes Dx at follow up	139 (10.3%)	1210	1.42; (1.17-1.73) 0.001	People in the exposed group were significantly more likely (1.42 times) to develop diabetes at follow up compared to the non-exposed group
No Diabetes Dx at follow up	581 (7.4%)	7204		

Table 9(b) Statin Exposure vs. Diagnosis of Diabetes at Follow up in the Medication Compliant Population (N=9047).

	Statin Exposure at Baseline		OR; 95% CI; P value	Interpretation
	Yes	**No**		
Diabetes Dx at follow up	127 (9.5%)	1210	1.49; (1.22-1.83) 0.001	People in the exposed group were significantly more likely (1.49 times) to develop DM at follow up compared to the non-exposed group
No Diabetes Dx at follow up	506 (6.6%)	7204		

Chapter 5

Discussion

5.1 Summary of Study

The current research study investigated the use of statin drug therapy among primary prevention patients using EMR data provided by family physicians in NL. The research questions asked whether statin drug therapy decreased the occurrence of CVD and all-cause mortality and whether this effect changed when we accounted for known CVD risk factors of age, sex, BMI, LDL-C, HDL-C, HTN, TC, TT, smoking, and BP. Additionally, we wished to investigate the effects of medication compliance on our primary outcomes, and whether statin use increased the adverse effect of DM in our study population.

In accordance with previous research, our alternative hypothesis (H_a) stated that the statin exposure group would experience fewer outcomes of CVD and all-cause mortality compared to the control group. Using the study conducted by Shalev et al., (2012) as a guideline, we hypothesized that the exposed group would demonstrate a 25-30% relative risk reduction in CVD compared to the non-exposed group. Lastly, we expected a significant increase in the incidence of DM type 2 in our statin group.

The data was analyzed first according to the initial assessment of baseline exposure to statins and subsequently analyzed using only a medication compliant population. The latter allowed us to attribute the outcomes only to those people in the exposed group who remained on a statin for at least 80% of the five year follow up period. In contrast to our hypothesis, the univariate analysis revealed that the statin exposed group had higher rates of CVD (composite outcome), CAD and hospitalization compared to the non-exposed group. All other secondary outcomes were not significant. This positive association between statin exposure and CVD was no longer

significant when we performed a logistic regression and controlled for significant risk factors of age, sex, HDL-C, BMI, sBP and smoking status. In support of our hypothesis, our univariate analysis revealed that statin use was associated with a decrease in all-cause mortality at the end of follow up. This association remained significant even after controlling for CVD risk factors. Additionally, in accordance with our H_a our exposed group was found to have statistically significant higher rates of DM compared to the control group.

5.2 Interpretation of Findings

5.2.1 Primary Outcomes

While the univariate analysis suggested that statin drugs actually increased the likelihood of developing CVD when used for primary prevention, logistic regression revealed that this was due to the difference in CVD risk between the groups. In the end, statin usage had no effect on CVD outcomes.

As a better assessment of baseline risk, it will be important to calculate the FRS for each patient, and stratify patients based on their perceived 10-year CVD risk (≤10%, 10-19%, ≥20%). Due to missing data we were unable to calculate Framingham scores. While risk stratification will be important for future research, it is possible that it would not have made a difference in our study. Results published by the CTT Collaborators (2012) revealed that statins significantly reduced the risk of major vascular events and all-cause mortality "irrespective of age, sex, baseline LDL-C or previous vascular disease"[4]. Interestingly, the proportional reduction in vascular events was similar across all risk groups and was "at least as big in the two lowest risk categories as in the higher risk categories" [4]. It may be the case that even though we failed to stratify our cohorts based on risk, this would not have mattered.

The primary outcome of all-cause mortality, controlling for other risk factors under logistic regression, was found to be significantly decreased in our statin exposed group. Note there was

no significant difference in CVD specific related mortality between the two groups. As previously discussed, statins have been shown to have non lipid related effects. They possess "anti-inflammatory properties, inhibit vascular smooth muscle cell proliferation as well as platelet function, and improve vascular endothelial function"[23]. It has also been suggested that statins slightly increase the levels of HDL-C, or 'good cholesterol'[24]. This could explain the protective factor of statins in terms of all-cause mortality. A second possibility is the fact that due to other comorbidities and risk factors, these patients were more likely to be prescribed other risk reducing medications (e.g. beta blockers, ACE-I, aspirin) in addition to lifestyle changes to reduce their chance of disease.

Table 5 examined whether risk factors of CVD were significantly associated with the primary outcomes of CVD and all-cause mortality. Table 5a suggested that sex (male), increased age, history of smoking, decreased HDL-C, increased BMI and increased sBP were significantly associated with the composite outcomes of CVD. Likewise, sex (male), increased age and history of smoking were significantly associated with all-cause mortality (Table 5b). These findings are in accordance with known risk factors for CVD morbidity and mortality, and as previously discussed provide validity for the data by suggesting that our findings related to statin exposure are not systematically biased in some way.

5.2.2 Medication Compliance

According to previous research, medication adherence rates among statin users can be as low as 25% after five years[36], with "fewer than 50% of patients take 80% or more of their prescribed statin dosages"[6]. Other studies have reported that patients who were more compliant with their medication were less likely to develop CVD[37]. It could therefore be hypothesized that controlling for medication compliance in our study population would result in more profound decreases in the rates of our primary outcomes (CVD and all-cause mortality).

Of the 720 patients initially exposed to statin therapy at baseline, 633 (87.9%) remained on a statin for ≥80% of the study period. The value of 80% was chosen as a target in order to remain consistent with current literature[6,37]. This large proportion of 87.9% compliance was unexpected. When we repeated the logistic regression analysis using only those exposed patients who had been compliant, there was no difference in the results.

Although we do not know the reason why 12.1% of patients were not adherent or discontinued with statin medication by the end of follow up, likely possibilities are related to adverse effects, inability to adhere to daily medication, medication cost, or death.

5.2.3 Incidence of Diabetes

By the end of follow up, 14.8% of patients in the study had developed DM. In concordance with our hypothesis, a significantly higher number of these patients were using a statin. However, the modest increase of 2.9% was not as high as what was reported by the Diabetes safety task force[31] and Shah and colleagues[32]. Recall that the CPCSSN case definition for diabetes was cited as 100% sensitivity, 99% specificity, and for NL only data: 95.6% sensitivity, 97.1 specificity[48]. It is possible however, that the algorithm may not identify DM if the care was provided somewhere else (i.e. not by the primary care physician) or the data was not entered by the provider in the EMR. There is also the possibility of a time delay; a patient may be diagnosed with DM months before the algorithm detects the disease due to the requirement of multiple data points.

5.2.4 Summary of Results

In summary, our analysis suggests that statin drugs, when used for primary prevention, do not reduce the likelihood of developing CVD but do result in a decrease in all-cause mortality when other significant risk factors were controlled for.

5.3 Limitations

This study's data was obtained by linking several databases and as a result there were various limitations with respect to data linkage and secondary data use in general. A limitation to secondary data use is incomplete information and poor documentation resulting in reduced sample size, especially when attempting regression analysis. The validity of the CPCSSN database relies on the accuracy of the physician's EMR, and how exact the physicians were at recording their patients past and current medical history. Family history, weight, height, and other lab and clinical data are often not reported if the patient is healthy. Smoking status is inconsistently recorded in EMRs. For example: if the smoking status column is blank, it could mean that the patient is either a non-smoker or the physician failed to document it. This ambiguous recording might affect the accuracy of our data, and "assuming that the patient does not have the condition overestimates the accuracy of the CPCSSN diagnostic algorithm"[48]. While the use of an 'unknown' categorical variable is a legitimate means of dealing with missing data when performing regression analysis, it is possible that it can lead to an overestimation of the effect of the intervention or exposure as it maintains the power by maintaining the sample size.

As previously discussed, data for risk factors were poorly recorded in our patient population and as a result we were unable to calculate a patient's FRS and stratify them accordingly. Even if this was possible, a lack of family history would have led to a misclassification bias with high risk patient's potentially being classified as low-moderate based on their risk factors. Additionally, we did not assess whether patients were taking other medications in addition to statins (e.g. beta blockers, ACE-I) which could further reduce their risk of CVD. For future studies, matching could be employed when choosing cohorts to ensure that they are statistically similar at baseline. Matching was not used for this study as we had intended to use the FRS to

stratify patients. Lastly, we had no information regarding medication dosage. It is very likely that the intensity of statin treatment increased for patients over the study period. However, if this were the case we should have seen a more significant decrease in outcomes of CVD.

For our study we assessed medication adherence as 80%. We chose to define compliance as evidence that the statin was prescribed for 80% of the follow-up time. It is important to distinguish between EMR prescription data and real world patient compliance. Our study assumed that patients were adherent to their medication if they were being prescribed a statin according to their EMR chart. However, this differs from "real" compliance as we do not know whether patients were actually filling their prescriptions and taking their medication daily. While it is possible to calculate adherence for RCT studies (e.g. subjective measurements by asking patients and family members, objective measurements by counting pills and examining pharmacy refill records, or biological measurements by detecting the presence of the drug in blood or urine[51]) it is difficult to measure adherence during a retrospective cohort study.

Lastly, no discussion on the benefits of statin drugs would be complete without discussing the potential adverse effects in a real world population. Unfortunately, this study could not provide such information as the CPCSSN database rarely records adverse events. For those patients who stopped taking statins during the study period, it is possible that a proportion stopped due to adverse events, poor compliance, cost or death, but as previously mentioned we do not know for certain.

A limitation to the CPCSSN database specifically is that it represented a population of patients who i) saw a primary care physician during the study period, and ii) whose primary care physician uses an EMR. To date, 50 physicians (approximately 10% of all NL primary care providers) and over 44,000 patient records are sent to CPCSSN; 38 physicians (76%) are located

in the urban settings of St. John's and Corner Brook while 12 physicians (24%) are located in more rural communities across the province. The CPCSSN database may not be representative of the provincial and/or national population.

5.4 Recommendations for Future Research

Future research will require a larger data set with more complete data for each patient. This may be achieved by using the entire Canadian CPCSSN dataset, once it is able to perform linkage studies with each province. Currently only NL, Manitoba and Ontario have those capabilities. As of now, the CPCSSN database has 8 years worth of data, and physicians are continually learning how to better and more accurately record their patient data in EMRs.

Using a matched cohort approach would also be useful in future studies. Matching for age and sex, for instance, would result in more similar groups.

Future studies could examine length of time on a statin compared to outcomes of CVD. As previously mentioned, a study that also examines adverse effects of statins (besides DM) will be important for assessing efficacy and risk-benefit ratio in a real world setting.

5.5 Conclusions

The elements of this paper have real-world implications and suggest that the benefits of using statins in a primary prevention situation are not nearly as impressive as what randomized clinical trials suggest. This contradicts current wisdom, and has important implications for practitioners.

After taking into account the various limitations, we still have to take seriously the findings of this study: The results cannot be ignored because several things speak to their validity: i) known risk factors in the data (e.g. age, sex, smoking) predict outcomes in the directions expected; ii) we were not able to calculate Framingham scores but we were able to control for a number of risk factors.

After performing all analyses, we can conclude that at best, statins had no effect on CVD outcomes but do decrease all-cause mortality.

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