STATIN UTILIZATION IN BRITISH COLUMBIA

BY

COLETTE RAYMOND

A thesis
Submitted to the Faculty of Graduate Studies
In Partial Fulfillment of the
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Abstract

Background:
Expenditures on cholesterol lowering medications in Canada are increasing, as prevalent users continue to rise. Few studies explore incident use or indications for use of cholesterol drugs. Although the benefits of statin therapy occur only after at least one year of therapy, few patients persist with statin therapy, and little is known about factors predictive of persistence with statins.
The objectives of this research were to measure prevalent statin use in the population of British Columbia from 1996-2004 and incident statin use from 1999-2004 across specific patient characteristics (sociodemographic and clinical). Additionally, this study sought to describe persistence and predictors of persistence with the first year of statin therapy for incident statin users

Methods:
Statin utilization and demographic data were assessed for the adult population of British Columbia from 1996 to 2004. Information about prescriptions was extracted from PharmaNet, a computer network connecting community pharmacies. Medical and hospital claims for statin users were examined for evidence of ischemic heart disease (IHD), diabetes mellitus (DM), atherosclerosis, cerebrovascular (CVD), peripheral vascular disease (PVD) and hyperlipidemia in the three years prior to the first statin prescription. British Columbia PharmaCare data was used to determine persistence (prescriptions filled within $\leq$ 120 days of one another for 1 year) with statin therapy for new users from 1999 to 2003. Health records were examined for evidence of clinical (medical history, drug, dose, number of medications) and sociodemographic (age, socioeconomic status, year of prescription) characteristics predictive of persistence with statins, as determined from multiple logistic regression methods.

Results
Statin prevalence increased from 1996 to 2004 (13 to 66 per 1000). The greatest use was amongst those aged 65-85. Use of atorvastatin increased with time, while that of simvastatin decreased. Quarterly incident statin use increased with time from 1999 to 2004 (2.9 to 4.9 per 1000). A socioeconomic gradient, where use was greater in those with low socioeconomic status, was observed for incident statin use. Incident atorvastatin and rosuvastatin use increased with time, while new use of other statins decreased. Of incident statin users, 36% had evidence of IHD, 20% DM but no IHD, 5% no DM or IHD, but atherosclerosis, CVD or PVD, 22% hyperlipidemia and 17% no medical conditions that we searched for. Of 168,161 adults that filled a first statin prescription from 1999-2003, 61,177 (36.4%) were persistent for one year. Evidence of the co-morbid conditions of coronary artery disease, diabetes or peripheral vascular disease, a greater number of co-prescribed medications, increasing age, higher socioeconomic status, and use of simvastatin or atorvastatin increased the likelihood of persistence with statins, ($p<0.05$) while statin dose, sex and year of first prescription did not.

Conclusions

Prevalence and incidence of statin use in an entire population has increased dramatically from 1996 to 2004. Although many statin users had evidence for medical conditions that indicate appropriate statin use, many users remain at low risk for cardiovascular disease, and therefore, the benefit of statins in this group remains small. Factors predictive of persistence with statins include: medical history, age, socioeconomic status and drug prescribed. However, persistence with statins remains low, even in patient groups who could benefit from long term therapy.

Acknowledgements

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List of Abbreviations

ACE	Angiotensin converting enzyme
ACG	Adjusted Clinical Group
ACS	Acute coronary syndrome
ATC	Anatomic and Therapeutic Classification
BCLHD	British Columbia Linked Health Database
CHF	Congestive heart failure
CHSPR	Centre for Health Services and Policy Research
CVD	Cerebrovascular disease
CCP	Canadian Classification for Procedures
DDD	Defined daily dose
DE	Days elapsed
DIN	Drug identification number
DM	Diabetes Mellitus
HMO	Health Maintenance Organization
ICD	International Classification of Diseases
IHD	Ischemic heart disease
LDL	Low density lipoprotein
LLD	Lipid lowering drug
MI	Myocardial infarction
OR	Odds ratio
PDC	Percent days covered
PVD	Peripheral vascular disease
RCT	Randomized controlled trial
SES	Socioeconomic status
TID	Thousand inhabitants per day

Chapter 1 Introduction

Expenditures on prescription drugs in Canada have increased dramatically in recent years, and have surpassed spending on physicians at a national level.(1) Certain categories of medications account for large proportions of these expenditures, including medications used to treat and manage cardiovascular disease. Worldwide, the class of cholesterol lowering medications called 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has the largest value of sales of any drug class in recent years. In 2005, for example, total sales of cholesterol lowering drugs were $32.4 billion, an increase of 7% over 2004.(2) Two particular statins, atorvastatin and simvastatin, were the first and fifth top selling prescription drugs worldwide in 2005. Atorvastatin sales totaled $12.9 billion and simvastatin sales totaled $5.3 billion.(3) In Canada, per capita spending on cholesterol lowering agents doubled from 1998 to 2002.(4)

One important factor contributing to the increase in statin use is the increase in the number of landmark randomized controlled trials (RCTs) demonstrating significant benefits of statins to prevent cardiovascular disease.(5-21) The publication of these RCTs has influenced prescribing in Canada; statin prescriptions in Canada increased after publication of several major trials from 1993-99.(22) Statins have been shown in large RCTs to decrease cardiovascular risk for patients using statins for both primary (without established vascular disease) and secondary (with established vascular disease) prevention.(5-21) For patients with established vascular disease, many large RCTs demonstrate that statins prevent recurrence of cardiovascular events and decrease mortality.(12;15;17;19;21) Similarly, for patients with diabetes mellitus but without established vascular disease, RCTs demonstrate that statins decrease cardiovascular

events.(6;11) However, for patients who do not have established vascular disease or diabetes mellitus, the data describing the benefit of statins is somewhat more variable.(11;15;18;20) Those patients who have established vascular disease generally have a greater risk of major cardiovascular events (normally defined as non-fatal myocardial infarction or death from coronary heart disease) than those without, and therefore derive greater risk reduction from pharmacotherapeutic interventions such statins. Pooled results from major statin trials show that in order to prevent major cardiovascular event, 57 patients who have not had an event (primary prevention) need to be treated with a statin for five years, as compared to 27 patients who have already experienced an event (secondary prevention).(23) However, a recommendation for treatment with a statin drug is not only based on the presence or absence of vascular disease, but rather on risk for major cardiovascular events.(24)

Treatment recommendations in the 2003 Canadian Guidelines for dyslipidemia are based on 10-year risk for coronary artery disease.(24) Patients considered to be at high risk for future coronary artery disease include those with established ischemic heart disease (IHD), cerebrovascular disease or peripheral vascular disease, patients with chronic kidney disease, diabetes mellitus and asymptomatic patients in whom the 10 year risk of death from coronary artery disease or nonfatal myocardial infarction is 20% or higher. For these patients, drug therapy, generally with a statin, is recommended in order to obtain a low density lipoprotein cholesterol level less than 2.5 mmol/L.(24) The routine use of statins for primary prevention, however, does remain controversial and numbers needed to treat with statins in order to prevent one cardiovascular event for patients with low cardiovascular risk are high and variable.(25-29)

A treatment-risk paradox has been described, where statins are underused in populations that could benefit greatly from them.(30) Despite known benefits to statins, many utilization studies suggest that lipid lowering drugs, including statins, are underused in populations that could benefit from them, particularly those with existing cardiovascular disease or the elderly (>65 years of age).(31-60) However, it has also been suggested that statins may be overused in patients with low cardiovascular risk,(30;32;38;57;60) with obvious financial implication for public drug plans. The treatment-risk paradox is magnified when persistence with therapy is considered. Patients need to persist with statin therapy for a minimum of one year in order to achieve a clinical benefit from the medications,(61) and it is known that persistence with statins in general, is suboptimal.(62-77)

Researchers have evaluated statin utilization in populations extensively. Analyses of statin utilization in entire populations are few, however, especially those which consider medical history of statin users and persistence with statin therapy. The availability of population based prescription drug databases in Canada has facilitated the linkage of this valuable data with information about other health services utilization amongst statin users. The British Columbia Linked Health Dataset allows for evaluation of prescription drug records for an entire population in the context of the characteristics of the drug users such as reliable and valid sociodemographic measures and health information from hospital admissions and physician visits. Use of the BCLHD databases for health services research has been previously validated.(78;79)

Anderson and Newman's model for health service use(80) will be used as a framework to evaluate the contribution of predisposing, enabling and illness factors on

the three measures of statin utilization. Predisposing factors include age group and gender of statin users, as well as the year of statin prescription. The enabling factor is socioeconomic status, and the illness factors include: medical conditions, co-prescribed medications, drug and statin dose.

1.1 Research Objectives

This research employed British Columbia's population based prescription drug database linked with medical and hospital claims data in order to describe the utilization of statins in the entire population of British Columbia over time. Statin utilization was evaluated by three measures: prevalence, incidence and persistence.

The first objective of this research was to measure prevalent statin use in the population of British Columbia from 1996-2004 across specific patient factors (sociodemographic). The second objective was to measure incident statin use in the population of British Columbia from 1999-2004 across specific patient characteristics (sociodemographic and clinical). Finally, the third objective was to describe persistence and predictors of persistence with the first year of statin therapy for incident statin users.

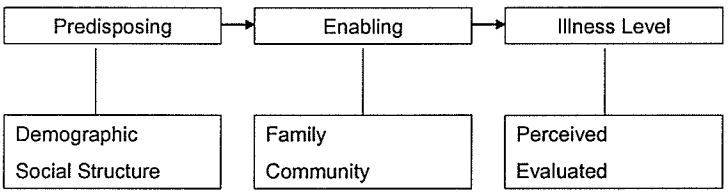
This research will contribute to the epidemiologic literature that describes statin utilization. This research will address use one of the most prescribed drug classes, a key health priority to provincial and federal governments. It will serve as an evidence base for education, intervention and policy making. Finally, this research will serve as background epidemiologic data for further studies of medication utilization including studies of effectiveness and appropriateness.

Chapter 2 Literature Review

2.1 Conceptual Framework

The Anderson Newman model of health services utilization was developed to describe the factors that influence an individual to use health services,(80) and has been applied to many aspects of health services use. The model places individual factors that influence health services use within a context of the health services environment (Figure 1).

Figure 1 Anderson Newman Framework



The three measures of statin utilization can be evaluated in the context of predisposing, enabling and illness factors that may influence access to prescriptions for statins and persistence with statin therapy. Predisposing factors are those that are in place before the onset of the disease (in this research, cardiovascular risk). For this analysis, predisposing factors include age group and gender of statin users, as well as year of statin prescription. Enabling factors are those factors that otherwise enable individuals to access care, in this analysis, the enabling factor is socioeconomic status. Illness or need factors include perceived and evaluated disease and acuity measures. In this analysis the illness factors include: medical conditions, co-prescribed medications, drug and dose of statin.

2.2 Utilization studies of prevalent statin use

Studies that evaluate prevalent statin use in large populations using prescription drug databases describe considerable variability in statin prevalence (Table 1). The representation of different countries, time periods, available drugs, reimbursement policies, populations studied and measure of prevalence all limit a simple comparison of these studies, but studies generally indicate an increase in statin use over time.(37;38;44;46;49;50;53-60;81-85)

Several studies present utilization data for statins at a national or provincial/state level only, with no information about statin use within population subgroups, such as age groups or gender.(54;57;59;81;84) However, comparing statin utilization across these countries is limited by different measures of prevalence including: statin users per population, treatment years, defined daily doses (DDD) per one thousand population per day and prescriptions per 100,000 population. A comparative study of several European countries revealed that statin prevalence varied in 2003 (in DDD per 1000 population per day) from 37.12 in Italy to 99.3 in Ireland. Furthermore, the percentage increase in statin use from 2001-2003 varied from 56% in France to 274% in Ireland.(84)

Canadian studies have shown an increase, but also great variability in statin use. From 1996 to 2001, statin use varied from 10,883 prescriptions (dispensing episodes) per 100,000 in British Columbia to 42,585 prescriptions per 100,000 in Quebec.(54) In Canada, prevalent statin use elderly residents of Nova Scotia quadrupled from 1997 to 2001,(53) and in Ontario from 1994 to 2000.(56) In the general adult population of Manitoba, statin prevalence increased by 1.5 times from 1996 to 1999.(82) Nationally, the number of prescriptions for statins has more than doubled in Canada from 1996-2001.(54)

2.2.1 Statin prevalence by age and sex

Several studies describe statin prevalence using population based prescription drug databases stratified by age and sex, and generally indicate that more males than females use statins, and that statin use increases with age.(38;46;55;56;58;60;82) Martikainen reported greater use of lipid lowering medications for Finnish men than women, with greatest use in middle age groups.(58) Majeed found that in 1996 in the United Kingdom, more men than women were prescribed statins, with greatest use in those age 55-64 and 65-74. Furthermore, there was low prevalent statin use for those with IHD (13% for men and 8% for women), suggesting under prescribing.(46) In 1996 in British Columbia, Canada Savoie found that 2.45% of the total population used statins.(60) Using a population based prescription drug database, this study found that 2.1% of men and 1.63% of women less than 70 years of age were statin users, and 6.98% of men and 9.70% or women over 70 years of age were statin users.(60) In Denmark, Larsen reported that more males than females were prescribed lowering medications (female to male ratio 0.81) from 1993-98, and noted greater use in those greater than 50 then than younger ages. The authors also found that in the year prior to a prescription for a lipid lowering drug, most patients had a prescription to indicate cardiovascular disease or diabetes mellitus (70% in 1995 and 79% in 1998, $p<0.001$), and concluded that statins were under prescribed.(55) In 1999/00 in Manitoba, Canada, Metge reported that elderly patients were more likely to use a statin than non-elderly, and that men were more likely to use a statin than women.(82) Levy reported that over the time period from 1994 to 2000, elderly males in Ontario, Canada were more likely to be prescribed statins than elderly females. Feely reported greater statin use for men than women in Ireland.(38) Taken

together, these results indicate that statin prescribing is greater in males and increases with age, likely reflective of increased cardiovascular risk.(24)

2.2.2 Statin prevalence by socioeconomic status

Many studies have evaluated a socioeconomic gradient in statin prescribing, however, no clear socioeconomic gradient in statin prescribing in both general or specific patient populations has been observed.(30;36;40;47;59;86-98) Most studies that have evaluated a socioeconomic gradient in statin prescribing assess the use of statins in specific high risk patient populations, such as patients with cardiovascular disease, thus limiting generalizability to whole populations.(30;36;47;86;87;89;93;94;98) Several studies have evaluated a socioeconomic gradient in statin use within a general population, but reveal no consistent results across countries.(40;59;88;90;91;95;97) Packham observed significantly less use of lipid lowering medication in United Kingdom general practices with greater deprivation (area level) than those with less deprivation in 1996.(59;91) However, no significant relationship between deprivation and prescribing was observed in 1998, despite the fact that statin prescribing increased to a greater extent in the less deprived areas. The authors speculated that perhaps access to care differed across the different practices, however, the appropriateness of prescribing was not assessed.(59;91) Stocks reported a socioeconomic gradient for statin prescribing in Australia from 2001-2 where men and women with lower socioeconomic status (area deprivation) were prescribed more statins than those with higher socioeconomic status. This observation occurred despite the fact that during the same time period, deaths from coronary heart disease were lowest in those with highest socioeconomic status.(95) Odbuanjo and Usher describe lower statin use for Irish residents with relative deprivation

(neighborhood) than those with relative affluence in 2001-2, although relative disease burden was not measured.(90;97) Thomson observed a socioeconomic gradient in statin prescribing for cardiovascular disease in Denmark, where men with higher socioeconomic status (occupational) were prescribed statins more often than those with lower socioeconomic status, although there was no significant socioeconomic gradient in statin prescribing for men or women without cardiovascular disease.(96) However, Hartz did not observe a socioeconomic gradient in prescriptions for lipid lowering medications in 2001 in Norway.(40) Taken together, these studies that have evaluated statin prescribing in general populations suggest that there may be a socioeconomic gradient in statin prescribing in some countries, but not others.

2.2.3 Statin prevalence by drug or dose

Several studies have evaluated statin prevalence in populations by drug or dose, and have noted similarly changing patterns in statin prescribing over time.(22;48-50;53;56;84;99;100) A study of prescribing trends in a large prescription database in the United States from 1991 – 1997 noted the increased use of simvastatin and pravastatin and decreased use of lovastatin.(49) A study which used survey data to estimate statin use in ambulatory patients in the United States indicated that atorvastatin was the most prescribed statin in 2002. This study also reported the decline in share of patient visits resulting in prescriptions for lovastatin, pravastatin and fluvastatin, with an increase for simvastatin and atorvastatin over a ten year period from 1992-2002.(100) Mamdani(22) and Levy(56) describe the decline of the number of prescriptions for fluvastatin and lovastatin for Ontario seniors from 1993 - 2000, as well as a slow increase in the number of prescriptions for simvastatin and pravastatin and a rapid increase in the number of

prescriptions for atorvastatin over this time period. In another analysis of statin market share from 1999-2000, Bazalo noted an increase in atorvastatin use, accompanied by a decline in use of fluvastatin, lovastatin, pravastatin and simvastatin.(99) Over the same time period, the authors noted dose increases for all statins.(99) In a study that specifically assessed statin use in patients with first myocardial infarctions in Denmark from 1995-2002, doses of simvastatin, pravastatin and atorvastatin increased.(48) In Ireland, Teeling found that for members of a large government prescription drug program, pravastatin was the most commonly prescribed statin from 1997-2003, followed by atorvastatin, simvastatin and fluvastatin, however, atorvastatin demonstrated the greatest increase over time. This study also noted an increase in statin doses with time.(50) Cooke noted an increase in statin dose for seniors in Nova Scotia, Canada and Queensland, Australia from 1997 to 2003.This study also noted an increase in market share of atorvastatin and simvastatin, and a decrease in use of pravastatin, lovastatin and fluvastatin.(53) In a study of statin use in various European countries from 2000-2003, Walley noted that the most common market leaders were simvastatin and atorvastatin(84) These studies indicate that statin doses are increasing, and that overall, simvastatin and atorvastatin are the most commonly prescribed drugs.

2.2.4 Statin prevalence by medical history

Only two studies have evaluated the medical history of statin users, in an attempt to quantify statin use by indication.(37;60) Of statin users in British Columbia in 1996-1997, Savoie found that only 5.5% had evidence through hospital and physician billing claims of a previous myocardial infarction, 19.8% had evidence of other heart disease, and a large majority (74.7%) had no evidence of heart disease.(60) The use of statins for

patients with diabetes mellitus or hyperlipidemia was not evaluated. The authors concluded that statins were under prescribed to populations that could benefit from them and possibly over prescribed to patients with low cardiovascular risk.(60) Dubois evaluated lipid lowering drug use in a large American managed care organization from 1997 to 1999, and found that of patients treated with a lipid lowering drug, approximately one third were using it for coronary artery or atherosclerotic disease (including a previous cardiovascular event, IHD, cerebrovascular disease and peripheral vascular disease).(37) Fourteen percent of lipid lowering drug users had diabetes mellitus (but no coronary artery or atherosclerotic disease). Twenty seven percent had multiple risk factors (hypertension, tobacco, obesity, age), 20% had only one risk factor, and 6% had either documented hypercholesterolemia, or no documented reason for treatment. The authors concluded that there was very little change from 1997 to 1999 in the proportion of patients treated with lipid lowering drugs at each cardiovascular risk category over the study period, and did not note a shift towards increased use in patients with low cardiovascular risk with time.(37)

2.3 Limitations to studies of prevalent statin use

Variation in time of study period, definition of prevalence (both numerator and denominator), measure of exposure (statin users versus defined daily doses), pharmaceutical policies, and study populations, limit cross study comparisons of statin prevalence. Cross country comparisons are limited by differences in health care delivery systems, social structure and pharmaceutical policies. Some studies of prevalent statin use lack findings that can be generalized to an entire population. Several studies present statin utilization as a percentage of prescriptions or users of lipid lowering drugs without

specifically describing statin prevalence, thus limiting the interpretation of these results.(44;57;58;83) Other studies which evaluate statin use in very specific patient populations, such as members of a large managed care organization,(37;45;99) a government program for prescription drugs,(33;38;42;51;56) or a sample of pharmacies,(49) lack generalizability to an entire population. Several studies describe the prevalence of statin use in the Irish General Medical Services Plan, which services approximately one third of the Irish population (and two thirds of prescription drugs filled in Ireland); however, these patients are not representative of Ireland's statin use.(38;50;90;97) Several Canadian studies describe statin prevalence in patient populations older than 65 who receive prescription drugs through provincial drug plans, but lack data to evaluate prevalence in younger age groups.(22;53;56;88) Finally, attempts to address the issue of a socioeconomic gradient in statin prescribing have revealed no clear gradient; however, comparison is limited by variation in country, healthcare systems, available drug coverage, measure of socioeconomic status and year of analysis.(30;36;40;47;59;86-98)

Although several studies describe statin utilization by linking prescription drug data to physician claims,(31;32;37;40;43;46;60;99;101;102) most of these studies assess statin use in a specific population of patients at high risk for cardiovascular disease.(31;32;37;40;43;99;101;102) Most studies that describe statin use in a general population are limited by a lack of medical information to guide decision makers about drug appropriateness.(38;44;49;50;53-59;81-85) Other studies are limited by small sample size,(31;32;40;43;55;85) and still others by their reliance on survey methodology to determine drug exposure.(40;41) Several recent population based studies have assessed

statin utilization by linking large population based prescription drug databases to other medical or hospital claims, however, all studies used data prior to 2000.(37;43;46;60;101) Since the RCT evidence base supporting the use of statins is changing rapidly, as are clinical guidelines, it is appropriate to continue to study trends in prescribing of these drugs.

2.4 Utilization studies of incident statin use

Relatively few studies have specifically investigated the incident use of statins in populations (Table 2).(34;55;56;103) Describing these new users allows for a more appropriate comparison across medical histories; researchers can be assured that medical history predates statin use. Three Danish studies describe lower incidence of statin use than the one comparative Canadian study. The Danish studies observed 237 to 323 per 100,000 incident users of lipid lowering drugs in the entire population in 1998, (34;55;103) while the Canadian study observed 2600/100,000 women and 3100/100,000 men over the age of 65 in 2000.(56) The Danish studies take place earlier than the Canadian study (1991-1999 vs. 1994-2000) and contain prescription drug data for the entire population, whereas the Canadian study contains data only for the population older than 65. Another factor that could contribute to the difference in incident prescriptions between countries is the stringent reimbursement policies in Denmark at the time of study. Additionally, the Danish studies presented results for all lipid-lowering drugs, and the Canadian study, for statins only. Despite different time frames, definitions, and findings, all authors concluded that incident prescribing of statins was low.(34;55;56;103)

2.5 Limitations to studies of incident statin use

The few studies that evaluate incident statin use lack any information about the statin users' medical history and therefore about appropriateness of prescribing. Furthermore, although it is known that statin doses are increasing with time,(53;99) no studies have evaluated incident statin use by dose or individual statins.

2.6 Studies of persistence with statins

Several studies have examined rates and predictors of persistence and adherence with statin therapy (Table 3).(62-77;104-112) It is known that statins must be used on a long-term basis in order for benefits on cardiovascular morbidity and mortality to be observed.(24) Despite this widely accepted knowledge, many studies have shown persistence with statins to be poor. Although measures of persistence and adherence, populations and duration of follow-up vary, one year persistence rates with statins as quantified by one commonly employed definition (greater than 80% of days covered with medication) vary from 39-64%.(64;65;74;75;104;106-108)

Factors that predict persistence or adherence with statins include sociodemographic (predisposing and enabling), medical, and drug (illness) factors. Older age predicts persistence with statins in most studies,(66;68-71;74;75;104-106;108) however, other studies show that younger patients are more persistent.(62;65) Although some authors have found no association between socioeconomic status and persistence with statins,(71;72;104) others have found that lower income has shown to predict poor persistence,(65;66) as has non-white race(65;68;75;105) Males are more likely to be persistent with statins than females in most,(75;106;107;107-109) but not all

studies.(65;66;69-72;104) Married statin users have been shown to be more adherent with statin therapy than non-married users.(68) Patients with other risk factors for cardiovascular disease are more persistent or adherent with statins in most(62;64-67;70;71;74;76;77;104;105;107;108), but not all(109) studies. Use of statins for secondary prevention as compared to primary prevention is predictive of persistence or adherence in some(70;71) but not other(67;74;75) studies. Patients with more concurrent cardiovascular medications are more persistent or adherent with statins in some,(62;66;68;76) but not other studies.(107;109) Patients with a greater number of physician visits are more likely to be persistent or adherent than those with fewer physician visits.(74;76;108) Some co-morbid conditions such as depression or diabetes mellitus, and the experience of IHD after initiation with statin therapy have been shown to be predictors of poor persistence with statins.(65) Other predictors of poor persistence or adherence with statins include such varied factors as: patient cost sharing,(75;108) high baseline low density lipoprotein,(106) emergency department visits,(108) and a lower statin dose.(105) Other factors predictive of persistence or adherence with statins include: baseline persistence(104;109), persistence with other therapies,(74) initial response to therapy,(104) an annual lipid examination,(105) full drug coverage,(63) and mail order pharmacy use.(108)

Several studies of persistence with statin therapy have been recently published using Canadian prescription drug databases linked to medical histories through physician billing claims and hospital discharge abstracts.(67;71;74;77) Although definitions of persistence vary in these studies, it is clear that many Canadians do not persist with statin therapy. Catalan found that only 33% of 983 Quebec social assistance patients were

persistent (gap between prescriptions less than one half the duration of the prescription and a minimum of 66% adherence to any single dispensation) with statins at one year. After five years, only 12% were persistent, despite subsidized mediations.(77) The median survival on statin therapy was 172 days (95% CI 155,205). In this analysis, predictors of persistence with statins included: previous nicotinic acid use, increased chronic disease score (based on other prescribed drugs) and cardiovascular disease (based on prescribed drugs and medical history). Patients who were first prescribed lovastatin were more likely to discontinue therapy than those prescribed simvastatin or pravastatin.(77) Jackevicius found that two years after a first statin prescription only 40% of Ontario patients greater than 65 years of age with acute coronary syndromes were adherent (statin dispensed at least every 120 days after first prescription). One third (36%) of statin patients with chronic coronary artery disease and 25% of patients taking statins for primary prevention were persistent with statins. Factors associated with statin discontinuation included: male gender, chronic coronary artery disease, greater number of prescriptions or physicians, and the use of statins for primary prevention. Factors associated with statin adherence included: the presence of diabetes mellitus or hypertension, and an increasing number of physician visits. Adherence was slightly better with simvastatin, pravastatin and atorvastatin relative to lovastatin, while cerivastatin and fluvastatin had slightly worse adherence.(67) Blackburn described persistence with cardiovascular medications following a first cardiovascular event in Saskatchewan using a population based prescription drug database, and found that persistence with statins (greater than 80% of days covered with medications) was 61.8% at 1 year and 48.8% at five years. Persistence with statins was positively associated with: increasing age, number

of physician visits, chronic disease score (overall medication use), increasing beta-blocker and ACE inhibitor adherence.(74) Finally, Perrault described persistence for patients prescribed statins in Quebec, and found that persistence at six months (statin dispensed at least every 60 days after the previous prescription) was 65% and 71% for patients prescribed statins for primary and secondary prevention, respectively. Three years after statin initiation, persistence fell to 35% and 45% for primary and secondary prevention, respectively. Persistence was positively associated with increasing age and the presence of medical conditions such as hypertension and diabetes mellitus.(71)

2.7 Limitations to studies of statin persistence

A major limitation of literature evaluating persistence and adherence with statins is a lack of standard measures or common criteria for non-adherence or non-persistence. Conflicting results in the literature stem from different study designs, populations and measures of persistence, adherence, and discontinuation.(113) Some patient populations studied are very specific, thus limiting the generalizability of the findings from these studies. Examples of specific patient populations where persistence with statins has been assessed include: the elderly(63;64;67) those at high risk for cardiovascular disease,(68;72;74;105;108;110) members of a specific drug plan such as Medicaid,(65;68;104;105;107;108;111;112) or statin users within a specific geographic location.(62;69;106) Other studies have the limitation of a small sample size.(63;64;69;72-75;77;105;106;109;110)

Canadian studies of statin persistence have several limitations. Although large, the Ontario and Quebec cohorts do not represent the entire population; Ontario's prescription drug database only includes patients greater than 65 years of age(67) and Quebec's

prescription drug database only includes 55% of the population.(71;77) Although the study from Saskatchewan is population based, it only addressed persistence with statins for a small group of patients who recently experienced a cardiovascular event, not all patients newly prescribed a statin.(74)

2.8 Literature review: summary and fit of research project

In summary, studies of statin utilization (prevalence and incidence) indicate that use has increased dramatically in the past 20 years. Generally, males use more statins then females and use increases with age, as would be expected due to increased cardiovascular risk. No clear socioeconomic gradient in statin prescribing has been observed, in specific (e.g. post myocardial infarction) or general populations. Trends in use of specific statins have generally indicated that atorvastatin has gradually gained majority market share since it became available. Little data on use of satins by medical history exists.

Studies of persistence with statin therapy consistently show poor persistence; in general 40-60% of users persist with statins at one year. It seems clear that persistence and adherence with statins are greater in older patients, (predisposing factor) and those with higher cardiovascular risk (illness factor), with a greater contribution to persistence from illness factors. However, the contribution of many other factors to persistence with statin therapy remains unclear.

The present study attempts to address limitations of the current literature that evaluates statin utilization by analyzing the prevalence of statin use in an entire population, stratified by important population subgroups, including age, socioeconomic status and drug prescribed, over time. Additionally, analysis of the cohort of incident statin users will allow for description of incident statin users by gender, dose and recent

medical history. The present study attempts to address limitations of the current literature that evaluates statin persistence by analyzing persistence with statins for incident statin users in an entire population, stratified by important population subgroups, including sociodemographic and clinical factors.

Table 1 Studies that assess statin prevalence using prescription drug databases

Study, Location	Source population (N)	Method, study period	Prevalence of statin use
Martikainen (58) Finland 1996	Patients from 89% of Finnish pharmacies (5 million)	Prescription drug database 1993-1994	0.6% men and 0.5% women used LLD in 1994 (69% statin).
Magrini (57) Australia and Europe 1997	Populations of Australia (17 million), Finland (5 million), Norway (4 million), Sweden (9 million). Part of Italy (4 million)	Regulatory authorities data 1990-1994	LLD in 1994: Australia 11.9 DDD/TID (80% statin), Italy 6.7 DDD/TID (67.6% statin), Sweden 5.6 DDD/TID (62.5% statin), Norway 4.9 DDD/TID (91.7% statin), Finland 4.0 DDD/TID (73.3% statin).
Feely (38) Ireland 2000	Members of General Medical Services Eastern Health Board Region (338,025)	Prescription drug database 1994	For patients > 35 years 23.4 per 1000 men taking LLD, and 18.8 per 1000 women (92% statins)
Majeed (46) UK 2000	Patients of 288 general practitioners (l2.1 million)	General Practice Research Database 1996	0.7 % of men and 0.5 % of women used statins. For age 55-64, 2.8% of men and 2.1% women used statins, for age 65-74 2.5% and 2.4% for age 75-84 0.6% and 0.6% and >85 0% used statins.
Packham (59) UK 2000	Patients of 110 general practitioners in Nottingham.	Prescription drug database 1996-1998.	Median statin years of prescribing per 1000 population age 35-69 in 1996 3.8 and in 1998 13.2
Siegel (49) USA 2000	Prescriptions from 35,000 pharmacies in USA (70% of US pharmacies)	Projected prescription sales 1991-1997	Estimated statin prevalence 1,211,000-treatment yrs in 1991 and 4,716,000-treatment yrs in 1997. In 1991 lovastatin 1,210,000 treatment yrs (99.9%), in 1997 simvastatin had highest % 1,520,000 treatment yrs (32%)
Larsen (55) Denmark 2001	Population of Funen county Denmark (470,000)	Prescription drug database 1993-1998.	Statin prevalence 2.0/1000 (1.7 DDD/TID) in 1993 and 9.9/1000 (9.4 DDD/TID) in 1998. For total Denmark, use in 1998 8.4 DDD/TID
Dubois, 2002 (37) USA – 22 states (HMOs	Members of a US HMO 224,880 1997, 300,347 1999	Prescription drug database linked to medical claims 1993-1998.	Increase in overall lipid lowering drug from 1997 – 1999 (5-8% of the total pop). Of pts in highest risk category, treatment not different from 97-99 (39% to 43%) and for the second highest risk category (CAD) treatment rates went from 24% to 28%.
Savoie (60) Canada 2002	Population of British Columbia, Canada (4 million)	Prescription drug database linked to medical claims 1996-1997	Total statin prevalence 2.45 per 100 population. For Women < 70 years of age 1.63 per 100 and > 70 years of age 9.70 per 100. For men < 70 years 2.10 per 100 and >70 years of age 6.98 per 100.
Jacuvicius (54) Canada 2003	Patients from a 4400 pharmacies in Canada (66% of Canadian pharmacies)	Prescription drug database 1996-2002	Statin use in BC 10,883 prescriptions per 100,000 pop ($1,529,174 per 100,000 population). In QC 42,585 prescriptions per 100,000 population (2,766,204 per 100,000 population).
Levy (56) Canada 2003	Population > age 65 in Ontario, Canada (4 million)	Prescription drug database 1994-2000.	5.3% of women in 1994 and 18.5% in 2000 used statins. 4.6% of men in 1994 and 21.2% in 2000.

Study, Location	Source population (N)	Method, study period	Prevalence of statin use
Metge (82) Canada	Population of Manitoba, Canada (1 million)	Prescription drug database 1996-2000	Statin prevalence 2.3% in 96/97, 2.7% in 97/98, 3.1% 98/99 and 3.6% in 99/00. In 99/00 elderly (>65) greater use than non-elderly (123/1000) vs. (22/1000). In 99/00, males more use (37/1000) than females (22/1000)
Walley (81) Europe 2004	Population covered by government drug plans from 16 European countries (33-90% of population)	Sales Data for several European countries 2000	Statin prevalence in DDD/TID varied from 14.74 DDD/TID (Italy) to 59.28 DDD/TID (Norway). Overall European average 11.12 DDD/TID in 1997 and 4180 DDD/TID in 2002
Walley, 2005(84) Europe	Population covered by government drug plans from 16 European countries (33-90% of population)	IMS data – 1997-2003	Statin prevalence in DDD/ 1000 pop/d varied in 2003 from 37.12 (Italy) to 99.3 (Ireland). % increase from 2000-03 varied from 56% (France) to 274 (Ireland) Prescribed daily doses of statins increased.
Silwer, 2005(83) Sweden	Members of the county of Halland, Sweden (277,000 in 02)	Prescription DB 1988-2002	LLD prevalence: in 2002, the number of prescriptions per 100 inhabitants per 3 months was 10. The number of ddd/100 inhabitants per day was 14 (increased from 0 in 1988) (for males 17 and females 12). Estimated prevalence of LLD as 10-14% in 2002.
Jonsson, 2005(85) Sweden	Members of neighbouring Swedish municipalities (n=25,000 each)	Prescription sales in 2000-2002	Statin prevalence in Sweden in DDD/TID: 2000 33.8, 2001 42.7, 2002 52.7. Statin Prevalence for county (age standardized to the population of Sweden as a whole) in 2000 40.4, 2001 48.4, 2002 57. For the municipality B: 61.4, 72.3, 80.9 and municipality A 26.2, 34.4, 41.7 in 2000, 2001 and 2002.
Cooke (53) Canada and Australia 2005	Population > 65 in Nova Scotia Canada (177,000) and in Queensland, Australia (960.000)	Prescription drug database 1997-2001	Statin prevalence from 50 DDD/1000 beneficiaries in 1997 (both populations) to 205 DDD/1000 beneficiaries in 2001
Kucera (44) Czech Republic 2005	Population of 3 heath insurance companies (450,000)	Prescription drug database 1997-2000.	LLD prevalence in 1997 was 11.8 DDD/TID and 143.9 DDD/patient (23% statin) and in 2000 was 24.8 DDD/TID, 201.1 DDD/patient (34% statin). Prevalence in total population 3% 1997 and 4.5% in 2000
Teeling (50) Ireland 2005	Members of General Medical Services Eastern Health Board Region (344,000)	Prescription drug database 1998-2002	7.7% of total population used statins in 2002

DDD= Defined daily dose (see appendix 1) DDD/TID = DDD per thousand inhabitants per day. LLD= lipid lowering drugs

Table 2 Studies that assess statin incidence using prescription drug databases

Study, Location	Source population (N)	Method, study period	Incidence of drug use
Bjerrum (34) Denmark	Patients from Funen county, Denmark (470,000)	Prescription drug database 1994-1999	Incidence of lipid lowering drugs 32.3/100,000/month in 1998 and 46.3/100,000 per month. Incidence rate ratio 1996/95 1.31 (1.23-1.39), 1997/96 1.25 (1.17-1.32), 1998/97 1.27 (1.20-1.35), 1999/98 1.43 (1.35-1.52)
Larsen (55) Denmark	Population of Funen county, Denmark (470,000)	Prescription drug database 1993-1998.	Incidence (no use for 1 year) of lipid lowering drugs (per 1000) for females 0.51, males 0.95, age <65 0.63, age > 65 1.23, total population 0.7 in 1994. In 1998 incidence (per 1000) for females 2.35, males 3.08, age <65 2.06, age > 65 6.17, total population 2.71. Overall, from 1994-1998, 93.6% of patients were treated with statins.
Riahi (103) Denmark	Population of North Jutland, Denmark (492,000)	Prescription drug database 1991-1998.	Incidence (no use since 1991) of lipid lowering drugs in males and females was 89 and 59 per 100,000 person years, respectively (standardized to 1991 population) in 1994. In 1998, the incidence in males and females was 237 and 323 per 100,000 person years, respectively.
Levy (56) Canada	Population > age 65 in Ontario, Canada (4 million)	Prescription drug database 1994-2000.	Incidence (no use for 1 year) of statins (age standardized to the population of Ontario age > 66 in 1996) increased from 840 to 2600/100,000 women and from 810 to 3100/100,000 men from 1994 to 2000.

Table 3 Studies that assess statin persistence using prescription drug databases

Study, Location	Source population (N)	Method, study period	Persistence definition, rates, predictors
Andrade (73) USA 1995	Patients from two HMOs with new prescription for LLD (537 on lovastatin)	Electronic medical record 1988-1990	Discontinuation = > 6 months between last refill and end of study 12.7% for lovastatin
Sung(109) USA 1998	Patients within an HMO taking antihyperlipidemic medications (772)	Prescription drug database linked to medical claims 1993-1995	PDC (>90%) 37%. Medication compliance rate was 74% + 23% Females and those with higher chronic disease score and more medications were less likely to be compliant ($p<0.05$), baseline compliance predicted compliance with antihyperlipidemic
Avorn(64) New Jersey and Quebec Canada 1999	Patients >65 who filled 1 or more prescription for LLD (5611 US and 1676 Canada)	Prescription drug database 1990-1996	PDC (>80%) 64.3% at 1 year for statins. Persistence associated with risk factors for future cardiac events, such as HTN, DM, IHD, and with longer use.
Catalan (77) Canada 2000	Random sample of social assistance patients in Quebec age 45-64 (983) with a new prescription for a statin	Prescription drug database 1987-1994	DE (1/2 duration of dispensation) = discontinuation. At 1 year, 33% persistent, 24% at 2 years, 17% at 3 years, 14% at 4 years, 13% 5 years. Persistence was associated with: co-morbidity, IHD, previous use of nicotinic acid.
Benner (65) USA 2002	Patients on New Jersey Medicaid program (34,501) who filled a new prescription for a statin	Prescription drug database 1990-1999	PDC (>80%) was 60% at 3 months, 43% at 6 months, 39% at one year, and 32% at 120 months. Poor persistence associated with non-white race, lower income, and older age, less IHD morbidity, depression, dementia, and occurrence of IHD after initiating statin.
Jackevicius (67) Canada 2002	Patients >65 in Ontario who filled a new prescription for a statin for ACS (22,379) chronic CAD (36,106) or primary prevention (85,020)	Prescription drug database linked to medical claims 1994-1998	DE (120 days between refills includes 50% of days supplied and 20% grace) = discontinuation. At 2 years persistence 40.1% ACS patients, 36% chronic CAD, and 25.4% primary prevention. Persistence more likely in the chronic CAD and primary prevention than in ACS. Non-adherence associated with CAD, primary prevention, age, male, prescriptions, MD visits
Larsen (69) Denmark 2002	Patients in Funen county who filled a new prescription for a statin (3623)	Prescription drug database 1993-1998	DE (30 days after supply) = discontinuation. Median persistence 41 months. Higher persistence associated with age >65. Continuity (# tablets / # days in persistence period >80%) observed in 95.1%
Wei (72) Scotland 2002	Patients with a first MI and prescribed a statin (427)	Prescription drug database linked to medical claims 1990-1995	PDC >80% in 63.7% mean follow up 2.4 years. Females more adherent than males, but no relationship between deprivation and statin adherence.
White (112) USA 2003	Patients in an HMO newly prescribed a statin (14,825)	Prescription drug database linked to medical claims 1998	PDC at 1 year, persistence = DE (60 days after supply) = discontinuation. PDC at 1 yr 60% + 34% Persistence 221 d.
Abraha (62) Italy 2003	Patients in Umbria, who received a new prescription for statins (39,222)	Prescription drug database linked to medical claims 1998-2002	DE (30 days after supply) = discontinuation and PDC >80%. Median persistence 5.3 months. 12.8% patients persistent. Higher persistence associated with aspirin use and major IHD events; age < 45 years.

Study, Location	Source population (N)	Method, study period	Persistence definition, rates, predictors
Kopjar (68) USA 2003	Veterans with IHD who were prescribed statins (8,768)	Electronic Medical Records 1999-2000	PDC >80% in 71% at 18 months. Good adherence associated with age>65, white, married, obese, recent prescription of an ACE inhibitor
Valuck(111)USA 2003	Members of a HMO newly prescribed a lipid lowering drug (6,247)	Electronic medical records 1998-2000	PDC continuous (medication possession ratio) 85-92%
Yang (76) UK 2003	Patients who filled >1 prescription for new LLD (15,488 statin users)	General Practice Research Database 1990-1997	DE 3 months after supply = discontinuation. 69.8% persistent at 1 year. Persistence associated with statins, physician visits, more concurrent IHD medications, DM and fewer non-IHD medications.
Abugosh (63) USA 2004	Patients >65 from a New England, HMO organization with a new prescription for a LLD (182 statin users)	Prescription drug database linked to medical claims 1994-1996	DE (6 months between refills) = discontinuation. At 1 year 61% persistent, at 18 months 43% persistent (statin users). Full drug coverage predicted persistence with statins.
Ellis (75) Midwestern USA 2004	Patients from a managed care organization who filled 2 or more statin prescriptions (2258 secondary prevention, 2544 primary prevention)	Prescription drug database linked to medical claims 1998-2001	PDC >90%, >80% >70% = adherent. DE (7 days after supply) = discontinuation. Median discontinuation for primary and secondary prevention 3.4 and 3.7 years. For primary and secondary prevention PDC = 21.5% and 20.4% For PDC>80%, primary and secondary prevention 61.2% and 62.2% adherent. Poor adherence associated with female, <65 and African American, multiple doses and patient cost sharing.
Grant (66) Boston, USA 2004	Patients in a health insurance plan with new prescriptions for statins (5488)	Prescription drug database 1999-2003	17.7% only filled 1 prescription. PDC = 82.1% + 26%. RP = at 1 month 90.5%, at 12 months 67.9%. Predictors of persistence include: older age, higher income, and treatment for HTN and IHD and greater number of concomitant medications.
Mantel-Teeuwise (70) Netherlands 2004	Patients newly prescribed statins (8335)	Prescription drug database linked to medical claims 1998-2002	DE (45 days after supply) = discontinued. At 1 year 61.5% persistent (not discontinued), 46.5% at 2 years. Primary prevention persistence 47.7% at 2 years. If hospitalized for IHD, persistence 57.7% at 2 years. Persistence associated with atorvastatin and higher potency, HTN, hospitalization for IHD. Persistence lower in younger age groups, patients with history of psychotropic drug use.
Blackburn (74) Saskatchewan Canada 2005	Patients prescribed IHD medications following first IHD event (1221)	Prescription drug database linked to medical claims 1994-2001	PDC >80% at 1 year 61.8%, 2 years 53.7%, 53.5% 4 years 49.6%, 5 years 48.8%. Persistence positively associated with increasing age, physician visits, chronic disease score, beta-blocker adherence and ACE inhibitor adherence.
Perreault (71) Quebec, Canada 2005	Patients age 50-64 with a new statin prescription (4316 primary and 13,642 secondary prevention)	Prescription drug database linked to medical claims 1998-2001	DE (60 days after supply) = discontinuation. Persistence for primary and secondary prevention at 6 months: 65% and 71%. At 3 years 35% and 45%. Primary prevention less persistent than secondary. Persistence associated with age, HTN, DM.

Study, Location	Source population (N)	Method, study period	Persistence definition, rates, predictors
Benner(104) South-eastern United States 2005	Patients in a managed care organization with a new prescription for a statin (9,150)	Electronic medical record 1999-2003	PDC> 80% adherent at 3 months 51%, 6 months 40%, 12 months 34%, 18 months 31%, 24 months 28% and 36 months 33%. Predictors of adherence (month 4-36) include: adherence at month 3, age, recent history of revascularization, better decrease in LDL in first 3 months ($p<0.05$)
Campione(105) United States, 2005	Statin users age 50 and older at a Veterans Administration hospital prescribed a statin for > 90 days (4707)	Electronic medical record 2000-2002	PDC (continuous) 83.8% (SD 27%) at 24%. 33.6% <80%. Factors decreasing adherence included: black race, younger age, lower dose ($p<0.05$). Factors increasing adherence included: annual lipid evaluation, HTN, depression, IHD, DM ($p<0.05$).
Caspard(106) Massachusetts 2005	Patients newly started on a statin (4776)	Electronic medical record 1994-1999	Discontinuation = 183 days with no statin prescription. PDC>80% = adherent. 8% filled one prescription only. 20% discontinued in first 6 months. Adherence at 6 months 64%, 55% at one year, 53% at 3 years. Predictors of non-adherence include age <50 years, women, high LDL ($p<0.05$)
Chapman(107) United States 2005	Patients in a managed care plan who initiated statin and antihypertensive therapy (8406)	Electronic medical record 1996-2001	PDC >80% = adherent. 53% 43% and 43% adherent with both therapies at 3,6 and 36 months. 27%, 35% and 39% not adherent to either therapy at 3, 6 and 27 months. Predictors of adherence with both therapies include: fewer number of other medications, age (55-64 vs. older or younger) male sex, starting both therapies together, greater IHD risk, CVD, CHF. ($p<0.05$)
Schultz(108) United States 2005	Patients in a managed care organization newly prescribed a statin and at high risk for CAD (21,239)	Prescription drug database linked to medical claims 1999-2002	PDC >80%=adherent in one year. 9,066 (43%) adherent at 1 year. Predictors of adherence include: older age, men, greater outpatient visits for hyperlipidemia, cardiovascular procedures, hospitalizations, and mail order pharmacy use ($p<0.05$). Statin co-payment and emergency department visits decreased adherence ($p<0.05$)
Valdez(110) United States 2005	Patients in an HMO with hyperlipidemia and statin monotherapy (819)	Prescription drug database and chart review 1998-1999	PDC continuous. PDC >80%=adherent. Mean PDC 96% + 23%. Average days of drug therapy = 294. 76.0% adherent No influence of gender on adherence.

ACS=Acute coronary syndromes, ACE=angiotensin converting enzyme, CAD= coronary artery disease, CHF=congestive heart failure, DE= days elapsed, DM=Diabetes Mellitus, HMO= health maintenance organization, HTN=hypertension, IHD=ischemic heart disease, LDL=low density lipoprotein, MI = myocardial infarction, PDC=proportion days covered

Chapter 3 Research Methods

3.1 Study design

This research was an observational retrospective study. Statin users in the province of British Columbia were characterized through the use of linked administrative databases. The study cohort was created using the databases of the British Columbia Ministry of Health, termed the British Columbia Linked Health Databases (BCLHD). The study outcome measures included: prevalent statin utilization from 1996-2004, incident statin utilization from 1999-2004, and persistence with statins for incident users from 1999-2003.

3.1.1 Data sources

The Centre for Health Services and Policy Research (CHSPR) maintains a repository of longitudinal health services utilization and population health data for the entire population of British Columbia. Known as the BCLHD, this data repository is a population-based, patient-specific collection of databases that contains demographic, medical, hospital and prescription drug utilization records for approximately 4.1 million residents living in British Columbia. Records are linkable across databases and over time in an anonymous way through the use of an encrypted unique identifier. Use of the BCLHD databases for health services research has been previously validated.(78;79) The databases used in this study included: the provincial health plan registry database, PharmaNet prescription drug database, physician claims database and the hospital

discharge abstracts database. A brief description of each of the databases employed in the study follows.

3.1.2 Medical Services Plan Registry

The Ministry of Health of British Columbia provides health insurance for residents. Each time a resident seeks care within the province, data is captured using the person's unique Personal Health Number. Individuals registered with the province to receive health insurance are part of a registry file, which contains age, sex, socioeconomic status, date of birth and date of death or emigration, if appropriate. As individuals can move into or out of the registry file over time, individuals were considered to be registered for any given year if they appeared in the registry files for greater than or equal to 275 days of the year of interest.

3.1.3 Prescription Drug Database (PharmaNet)

Data describing prescription drug utilization were extracted from the British Columbia PharmaNet system. PharmaNet is a computer network linking all pharmacies in the province. The primary use for this computer network is for patient-specific drug use monitoring and insurance claim adjudication. Information from every prescription dispensed in British Columbia is entered into the database, regardless of the reimbursement status of the prescription. All prescriptions filled at retail pharmacies by British Columbia residents living in the community or within long-term care facilities are included in the PharmaNet database. The only prescriptions not captured by PharmaNet are those received by inpatients in acute care and rehabilitative hospitals, residents of penitentiaries, or individuals where the federal government pays for medications, such as

First Nations, veterans, and Royal Canadian Mounted Police. In total, approximately 4% of the population of British Columbia are excluded from the PharmaNet database. Detailed information for each prescription dispensed is captured including: date, drug identification number (DIN) (describes unique drug, dose and dosage form), quantity dispensed, days supplied, physician prescribing number, total amount claimed for the prescription and total amount paid by a specific insurance provider or the individual.

3.1.4 Medical Services Plan Physician Claims Database

The physician claims database contains billing claims generated by physicians for contact with and services provided to patients registered for the provincial health insurance program. This database contains information regarding diagnosis, where each physician visit results in a single diagnosis code. Up to and including the year 2001, these diagnosis codes were classified by the International Classification of Diseases (ICD) version 9 coding system. After 2001 the claims were classified by the ICD 10 system. The British Columbia Ministry of Health converted ICD-10 coding to ICD-9 after 2001. Physician claims in the database are at the 3 digit level ICD-9 and ICD 10 coding system for continuity.

3.1.5 Hospital Separations Abstracts

In British Columbia, as in other provinces in Canada, hospital visits are recorded on the basis of separation (discharge) from the facility. Hospital discharge abstracts contain information on up to 16 ICD-9 (and ICD-10 after 2001) diagnostic codes and procedure codes for diagnoses and procedures that occurred during the hospital stay. The first diagnosis is the primary diagnosis responsible for the hospital stay. Procedures that

occur during the hospitalization are categorized according to the Canadian Classification of Procedures (CCP). Similar to the physician claims database, the British Columbia Ministry of Health converted ICD-10 coding to ICD-9 after 2001.

3.2 Cohort Development

3.2.1 Source Population

The data used for this analysis was extracted from the administrative health databases of the British Columbia Ministry of Health (British Columbia, Canada). These databases contain information for the entire population of British Columbia, approximately 4.1 million residents. The databases accessed were part of the BCLHD, housed at the Centre for Health Services and Policy Research, in Vancouver, British Columbia. In order to evaluate patterns of statin utilization, population prevalence, incidence and persistence with statin therapy were assessed.

3.2.2 Prevalent statin users

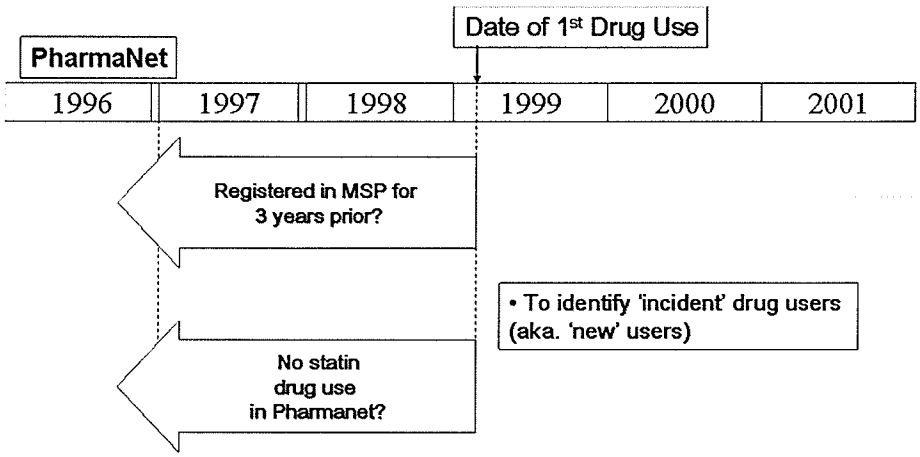
The study cohort for prevalent statin users consisted of every individual who filled at least one prescription for a statin (World Health Organization Anatomical Therapeutic Chemical (ATC) C10AA(114) from 1996-2004 (calendar years). The quarterly prevalence of statin use per 1000 inhabitants was calculated. Unique identifiers were created for each person who filled a prescription for a statin within a quarter. This count of users was the numerator for the calculation of prevalence. The denominator for the prevalence calculation included all individuals registered for the provincially administered, universal public health insurance (British Columbia Medical Services Plan) during the time period of interest. Since, by definition, prevalent statin users only required

receipt of one prescription for a statin to be included in this cohort, no exclusion criteria were applied to this cohort.

3.2.3 Cohort Definition: Incidence Cohort

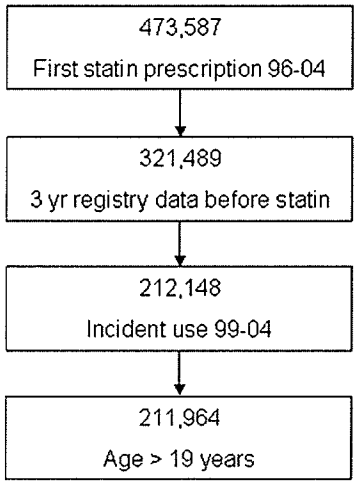
The study cohort for incident statin users included every resident registered for the provincially administered, universal public health insurance (British Columbia Medical Services Plan) and who filled a first prescription for a statin from 1996-2004 (calendar years). In order to ensure a complete medical history, patients who were registered for the British Columbia Medical Services Plan for at least 275 days of the year of the incident statin prescription and each of three years prior to filling a first prescription for a statin (index date) were included. Incident statin users have been defined as those with no prescription for a drug within one year of the index date.(55;56) In order to ensure a more conservative definition of new statin use, however, this analysis employed a three year period with no statin prescription. An incident user was thus defined as an individual who had no claim for a statin prescription in the three year period prior to the index statin prescription. Therefore, any individuals who filled first prescriptions for these drugs from 1996-1998 were excluded from further analysis. Statins have been used in populations less than 19 years of age, but use in this group generally indicates that the statin is being used for a congenital disorder of cholesterol metabolism (e.g. familial hypercholesterolemia).(115) Since these indications are not the typical indications for statins, individuals younger than age 19 were excluded from the analysis. Figure 2 describes the study definition of incidence. The denominator for the incidence calculation included all individuals registered for the British Columbia Medical Services Plan for at least 275 days of each of three years before the year of interest.

Figure 2 Incident statin users



Between 1996 and 2004, 473,587 people filled first prescriptions for statins in British Columbia. Application of the inclusion and exclusion criteria to an initial cohort of incident statin users resulted in a final cohort of 211,964 adult incident statin users with three years of registration in the British Columbia Medical Services Plan for investigation of medical history (Figure 3).

Figure 3 Inclusion and exclusion criteria for incident statin users



3.2.4 Cohort definition: Persistence Cohort

Persistence is defined as the continuous use of a medication over time.(113) In order to characterize patterns of statin use for incident statin users, it was important to evaluate persistence with newly prescribed therapy. Statin persistence was evaluated for the group of incident statin users registered with the British Columbia Medical Services Plan for one complete year after their first statin prescription. The persistence cohort was developed from the incident cohort in order to ensure that the first year of statin use was evaluated. Of the 211, 964 members of the incident statin cohort, 168,161 were registered for the British Columbia Medical Services Plan for 275 days of 365 in the one year period following their first statin prescription. As information about these individuals was available for one full year after the index date, the persistence evaluation was performed for these 168,161 statin users.

3.3 Study Variables

Variables from the British Columbia Medical Services Plan Registry database, the PharmaNet database, the Physician claims database, and the hospital discharge abstract database were used. Other variables were created from variables selected from the existing datasets. Variables from existing datasets are described briefly, and variables that were created for this study are described in more detail in the section that follows. Variables used and created for this study are outlined in Table 4. This table provides a brief description of the variable and the source database.

Table 4 Study variables, data sources and definitions

Variable	Definition / Use	Source
Registry status	Patients are considered registered if they have >275 days of medical service plan coverage for each of the 3 years prior to statin date and for the 1 year after statin date	Registry
Birth Date	Date of Birth	Registry
Death Date	Date of Death	Registry
Client sex	Male, Female, Unknown	Registry
Socioeconomic Deciles	Socioeconomic (neighborhood income per person equivalent) decile related to census. 1= lowest income decile. 10 = highest income decile	Registry
Drug Identification Number (DIN)	Unique number assigned to each dosage form, manufacturer and chemical. Used to determine drug and dose.	PharmaNet
Index date	Date of service for first statin prescription	PharmaNet
Dose	Dose of first statin prescription. Compared with simvastatin equivalents	PharmaNet
Diagnosis code	For 3 years prior to statin date, any diagnosis code (indicating the condition for which the patient is treated by a physician) based on ICD9 codes. To determine a 3 year history of medical conditions of interest: IHD, DM, PVD, CVD atherosclerosis or disorders of lipid metabolism	Medical service plan files. Hospital claims and procedure codes
Diabetes drugs	Any prescription filled for ATCA10 (any DM drug) in 1 year prior to statin date. Adds to definition of DM	PharmaNet
Nitroglycerin	Any prescription filled for ATCC01D (nitrate) in 1 year prior to statin date. Adds to definition of IHD	PharmaNet
Medical Conditions	ANY of the diagnosis codes from PharmaNet files, MSP files, hospital claims files or procedure codes indicating any one of the medical conditions of interest IHD, DM, PVD, CVD atherosclerosis or disorders of lipid metabolism	Medical, Hospital and Procedure codes
Medical Condition Category	IHD only vs. DM no IHD vs. risk equivalent only (atherosclerosis, CVD, PVD) not DM or IHD vs. disorders of lipid metabolism only vs. no evidence of medical conditions searched for	Medical, Hospital and Procedure codes
Cardiovascular risk	Further grouping of medical condition categories by cardiovascular risk. High cardiovascular risk = IHD only,. DM no IHD, risk equivalent only (atherosclerosis, CVD, PVD) not DM or IHD Low cardiovascular risk= disorders of lipid metabolism only vs. no evidence of medical conditions searched for	Medical, Hospital and Procedure codes
Continuous use time	Variable that indicates that the patient registered with Pharmacare for 275 of 365 days after index date and quantifies the time (in months) between the index prescription and the last statin prescription filled within 120 days	PharmaNet
Persistence	Variable that indicates that the patient registered with Pharmacare for 275 of 365 days after index date AND who filled a continuous series of prescriptions for statins within 120 days of one another for one year. (i.e. if continuous use time > 1 yr, patient is persistent)	PharmaNet
Number of unique ATC4> 0	Number of other prescription drugs (different ATC 4 entities) that a patient was prescribed during the year after first statin prescription.	PharmaNet

CVD= cerebrovascular disease, DM= diabetes mellitus, IHD=ischemic heart disease, PVD=peripheral vascular disease

3.3.1 Registry Variables

Variables from the British Columbia Medical Services Plan Registry used in this study included: registry status, age, sex and socioeconomic status. Patients were included in the incidence cohort if they were registered with the British Columbia Medical Services Plan for > 275 of 365 days for each of three years prior to the date of the first statin prescription. This criterion indicated complete registry status for the three years prior to the incident statin prescription. Patients were included in the persistence cohort if they were registered with the British Columbia Medical Services Plan for > 275 of 365 days of the first year after their index date. This criterion indicated complete registry status for the one year after the incident statin prescription was complete.
Statin users were categorized by age in the following groups: 20-44, 45-64, 65-84, >85. Statin users were also categorized by sex according to their registry file: male, female and unknown.

Socioeconomic status (SES) is an important variable to consider when examining patterns of prescription drug utilization, as it may impact access to health care, including prescription drugs.(116) The measure of socioeconomic status used in this study was related to median neighborhood income. The Canadian Census for 1996 and 2001 allows median neighborhood income to be calculated. The population is divided in to deciles by median neighborhood income according to the Census, where the lowest and highest median neighborhood income are the 1st and 10th decile, respectively.(117) This area level measure is an accepted and validated measure of socioeconomic status.(118)

3.3.2 PharmaNet Variables

Variables obtained from the PharmaNet database included drug identification numbers for all prescriptions filled (DIN) and dates of first statin prescriptions (index dates). Variables created from the DINs and index dates included: dose and number of co-prescribed medications.

The PharmaNet database was used to identify statin users. Prescription drug records for the entire population of British Columbia were searched to identify prescriptions for each available statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin). The date of the first prescription for the incidence cohort (index date), drug and dose of the first statin prescription were identified. Since all statins are indicated to be administered once daily, it was assumed that the dose provided was the daily dose. The dose for each index statin prescription was converted to simvastatin equivalents in order to allow for dose comparison across different drugs. Statins were compared according to the amount of drug required to decrease total cholesterol by 25% (atorvastatin 10, simvastatin 20, pravastatin 40, rosuvastatin 2.5, lovastatin 40, fluvastatin 80 mg, cerivastatin 0.4) in a method used by others to compare statin utilization.(119-122) Appendix 1 provides a more detailed description of simvastatin dose equivalents.

For incident statin users, persistence with therapy over the first year was evaluated. Persistence was defined as a continuous series of prescriptions filled within 120 days of one another over a one year period.(67;123;124) This definition of persistence provides a dichotomous variable – patients were persistent with therapy if they filled prescriptions within 120 days of one another for one year. This definition of persistence is generous;

users were only required to fill a prescription (for any duration) within 120 days of the previous prescription. As the British Columbia provincial drug plan (PharmaCare) has a maximum allowable days supply of 100 days, this definition of persistence allows for a 20% variation in the number of days between prescriptions.

For the persistence cohort, a count the number of different Anatomic and Therapeutic Category (ATC) level 4 drugs (number of chemical subgroups) in the individual's prescription drug records over the one year period after the incident statin prescription was conducted. This variable served as a proxy for co-morbidity (chronic disease score) based on number of different medications used over that year.(125) The number of ATC4 medications prescribed in the one year after the incident statin prescription was an independent (predictor) variable in the analysis of predictors of persistence with statins.

3.3.3 Physician Claims and Hospital Discharge Abstract Database Variables

Medical and hospital records were searched for three years prior to the index date, and prescription drug records were searched for one year prior to the index date in order to evaluate medical history. For each incident statin user, the Medical Services Plan physician claims database was searched for each of the three years prior to study cohort entry in order to locate any medical conditions that would indicate a reason for the statin prescription. Medical conditions were grouped according to the Johns Hopkins Adjusted Clinical Group (ACG) Case mix system.(126) Physician claims were evaluated for the presence of: ischemic heart disease (IHD), diabetes mellitus (DM), cerebrovascular disease (CVD), peripheral vascular disease (PVD) atherosclerosis, and disorders of lipid metabolism in the physician claims database. A complete list of the diagnostic codes used

to define these medical conditions is outlined in Appendix 2. Similarly, hospital separations abstracts were searched for the same medical conditions. Hospital discharge abstracts were also searched for Canadian Classification of Procedures (CCP) indicative of IHD, CVD and PVD, such as cardiac revascularization and carotid endarterectomy. In order to expand the definitions of DM and IHD, the PharmaNet records were searched for the presence of any prescription for a blood glucose lowering agent (ATC A10)(114) or for a nitrate (ATC C01D)(114) in the one-year period prior to the index statin date. The presence of a prescription for a blood glucose lowering agent or a nitrate indicated DM and IHD, respectively. The definition of one year prior to the incident statin prescription for this search of other prescription drugs was chosen for convenience.

Based on the medical history obtained from seeking the presence of these medical conditions in the physician claims, hospital discharge abstracts and prescription drug records, incident statin users were divided into five mutually exclusive medical condition categories (Table 5). The medical condition categories were chosen based on the availability of RCT data supporting the use of statins.(24) Incident statin users were further divided according to cardiovascular risk based on medical condition categories, also according to RCT data supporting the use of statins.(24) Incident statin users with high cardiovascular risk included those with IHD, DM, CVD, PVD, or atherosclerosis in medical and prescription drug records.(24) Incident statin users with low cardiovascular risk were those with disorders of lipid metabolism only and those with no discernable reason for therapy in medical and prescription drug records. Due to the administrative nature of the data, there was no information about many cardiovascular risks, including: family history, obesity, renal dysfunction, hypertension, cholesterol levels or smoking

status. A more detailed description of the variables relating to medical history used in this study can be found in Appendix 2.

Table 5 Medical condition category and cardiovascular risk for incident statin users

Medical Condition Category	Cardiovascular Risk
IHD	High
DM, but no IHD	
No claims for DM or IHD, but PVD, CVD or atherosclerosis (also called risk equivalent, as these patients are at equivalent risk for an ischemic event as patients who have already experienced such an event)(24)	
No IHD, DM, PVD, CVD or atherosclerosis but evidence of disorders of lipid metabolism	Low
No claims for IHD, DM, PVD, CVD or disorders of lipid metabolism (no discernable reason for therapy)	

3.3.4 Variables for persistence analysis

For the analysis of persistence with statin therapy in the one year after incident prescription, persistence was the outcome (dependent) variable. Patients were classified as persistent or non-persistent, and then a variety of predictor (independent) variables were evaluated to determine their contribution to explaining persistence with statin therapy. Independent variables included in the multivariate analysis of persistence include: age group, sex, year of prescription (predisposing factors) socioeconomic status (enabling factor), medical condition category (DM, IHD, CVD, PVD, atherosclerosis, disorders of lipid metabolism), statin prescribed, and number of other drugs prescribed in the one year after the statin prescription (illness factors).

3.4 Analysis

3.4.1 Prevalence calculation

The prevalence of statin use was expressed in terms of the number of users per quarter by: age group, socioeconomic status, and drug (specific statin). The count of unique statin users at each quarter of the study period was the numerator for the calculation of prevalence. The denominator for the prevalence calculation included all individuals registered for the provincially administered, universal public health insurance (British Columbia Medical Services Plan). For each category of analysis (age group and socioeconomic status) only those individuals registered with the British Columbia Medical Services Plan for the year of interest were included in the denominator for the prevalence calculation. Since the numerator (count of statin users) was determined quarterly, but the denominators determined annually, the denominators were corrected for quarterly analysis using exponential population estimates.

3.4.2 Incidence calculation

Incident statin use was expressed in terms of incident users per quarter by age group, sex, socioeconomic status, drug, dose, and medical condition category. For each strata of statin users, for example age 20-44, a numerator was calculated by counting the number of individuals who met the criteria for incident users with that identified variable (age 20-44 at first statin prescription) at each quarter of the study period. Incidence was calculated with several denominators. Overall, the denominators for the incidence calculation included all individuals registered for the British Columbia Medical Services Plan for at least 275 days of each of three years before the year of interest, and the year of

interest. For each age group, a separate denominator, which included all individuals who met the registry requirement within a specific age group at that particular quarter, was used. Similarly, for the incidence calculation by socioeconomic status, a separate denominator, including all individuals who met the registry requirements within each socioeconomic strata for that particular quarter, was used. For the incidence calculation by sex, a separated denominator for all individuals who met the registry requirement and who had male or female sex indicated on their registry file for the British Columbia Medical Insurance Plan was used. For the analysis of incidence by drug, the denominator was the total population who met the registry criteria. In a similar manner to the prevalence calculation, since each numerator (count of incident statin users) was determined quarterly, but the denominators annually, the denominators were corrected for quarterly analysis using exponential population estimates.

3.4.3 Trends in data over time

Linear regression was employed to determine if the series of values for quarterly prevalence and incidence demonstrated a linear trend. For statin prevalence, regression equations were developed for each age group, socioeconomic strata, and drug. For statin incidence, regression equations were developed for each age group, socioeconomic strata, sex, drug, dose and medical condition category. The dependent variable for each regression equation was the incidence or prevalence of statin use. The independent variable in each regression equation was time, expressed as quarters. Regression lines which were statistically significant ($p<0.05$) were those where the slope of the entire line was significantly different from zero.

3.4.5 Persistence

The distribution of persistence (persistent with statin therapy at one year vs. not) was examined in a logistic regression model. As the outcome variable was dichotomous, logistic regression is an appropriate analytic technique. Logistic regression was used to determine the contribution of each patient-level independent variable on persistence with statin therapy (outcome variable). The logistic regression model predicts the log odds of persistence vs. non-persistence with statin therapy; the equation was manipulated to calculate a probability value for persistence with statin therapy. Selection for inclusion into the model for persistence was based upon literature suggesting that variables would influence persistence with statins. Variables included in the multivariate analysis of persistence were: age group, sex, socioeconomic status, medical condition category, year of prescription, statin prescribed, and number of other drugs prescribed in the one year after the statin prescription. Odds ratios (OR) were presented for each significant independent (predictor) variable and goodness-of-fit tests were performed in order to determine the most appropriate model to select. Analyses were conducted at the alpha=0.05 significance level. All analysis for this research was conducted using Statistical Analysis Software (SAS) version 9.0 (SAS Institute, Cary, North Carolina, United States).

3.5 Ethical Considerations

Approval for the study protocol from the University of Manitoba Research Ethics Board, the University of British Columbia Research Ethics Board, and the British Columbia Ministry of Health was obtained. All data was kept in the secure computing environment at the Centre for Health Services and Policy Research.

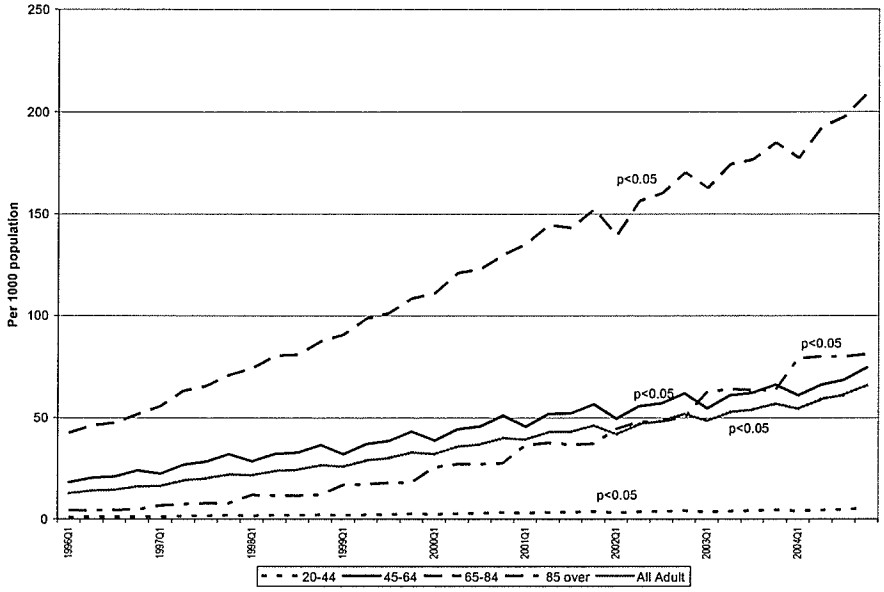
Chapter 4 Results

4.1 Prevalence

4.1.1 Prevalent statin use by age

Between 1996 and 2004, the number of adults using statins in British Columbia increased from 13 to 66 per 1000, an increase of over 400%. Statin use in all age groups increased over time where the slope of the regression line was greater than zero ($p<0.05$), although there was not a clear age gradient in statin use (Figure 4). The greatest prevalent statin use was in the 65-84 age group; statin use in this group increased 386% from 43 to 209 per 1000. The age group with the next greatest statin use at most time points was age 45-64. The prevalent use in this age group increased from 18 to 75 per 1000. However, in late 2002, the over 85 age group became the group with the second most prevalent statin use. Prevalent statin use in this elderly population increased from 4 to 81 per 1000, an increase of nearly 20 times. The age group with the lowest prevalence of statin use at all time points was the 20-44 age group. Prevalent statin use in this age group increased from 1 to 6 per 1000.

Figure 4 Prevalence of statin use in British Columbia 1996-2004 by age group

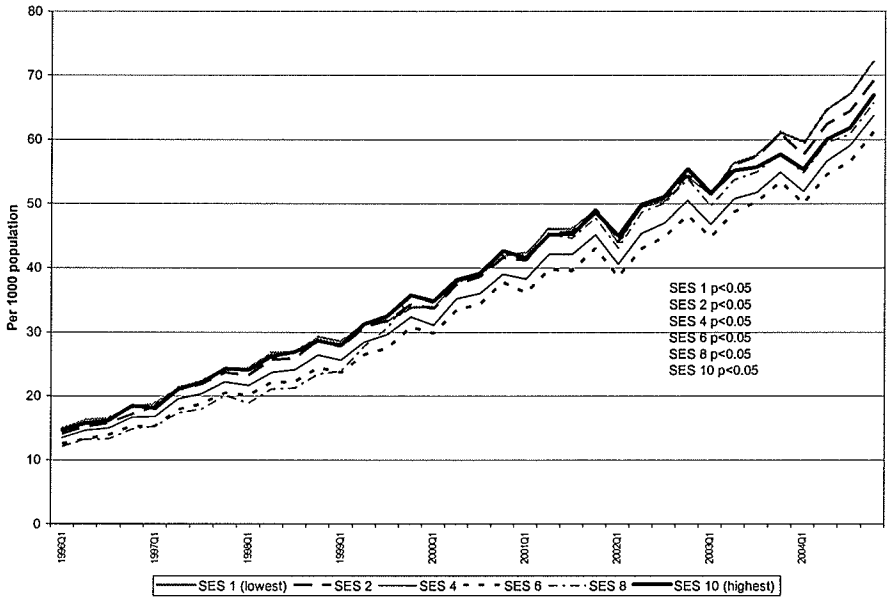


4.1.2 Prevalent statin use by socioeconomic status

Prevalent statin use increased in all socioeconomic strata over time, where the slope of the regression line was greater than zero ($p<0.05$). Figure 5 presents the prevalence of statin use by socioeconomic status as measured by median neighborhood income. For the sake of clarity, the lowest (SES 1), highest (SES 10), and every second income decile are presented graphically. There was no clear socioeconomic gradient in prevalent statin use. The prevalence of statin use in the group with the lowest socioeconomic status increased from 14.9 to 72.0 per 1000 over the study period. If statin represents the burden of cardiovascular disease, it would be expected that there would be the lowest statin use in groups with highest socioeconomic status. However, SES 4 and 6 demonstrated the lowest prevalence of statin use. Prevalent statin use increased from 13.4 to 63.6 per 1000 throughout the study period for SES 4 and from 12.5 to 61.1 per 1000 for SES 6. The groups with highest socioeconomic status, such as SES 8 and 10

demonstrated the highest prevalent statin use. Statin use in SES 8 increased from 12.0 to 65.7 per 1000 over the study period, while the prevalence of statin use in SES 10 increased from 14.6 to 66.9 per 1000. This suggests the absence of a socioeconomic gradient in prevalent statin use in British Columbia.

Figure 5 Prevalence of statin use in British Columbia 1996-2004 by socioeconomic status

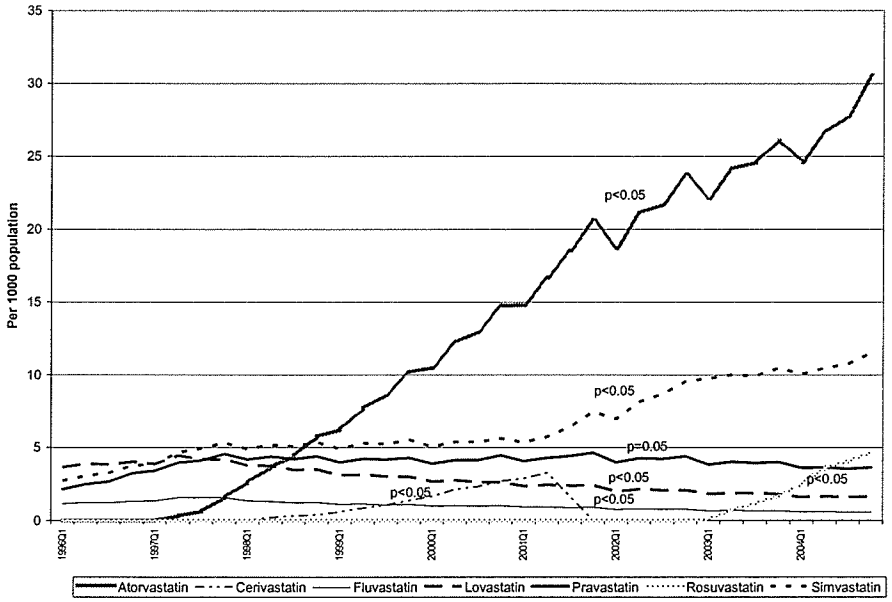


4.1.3 Prevalent statin use by drug

Analysis of prevalent statin use by drug over time reveals a changing practice pattern (Figure 6). There was a significant change in use of all drugs over time, where the slope of the regression line was different from zero ($p<0.05$) for each drug. However prevalent use of some drugs increased (positive slope), while the use of others decreased (negative slope). Atorvastatin demonstrated the greatest increase in prevalent use over time and was the most prescribed statin from the last quarter of 1998 through the end of the study period. Prevalent use of atorvastatin increased from 0.008 per 1000 at the

beginning of 1997 when the product was launched, to 30.5 per 1000 at the end of 2004. The prevalent use of simvastatin also increased throughout the study period, although not as dramatically as atorvastatin. Prevalent use of simvastatin increased from 2.7 to 11.5 per 1000 over the study period. The use of pravastatin increased slightly; from 2.1 to 2.3 per 1000. The use of fluvastatin and lovastatin generally decreased with time. The use of fluvastatin decreased from 1.1 to 0.6 per 1000 and the use of lovastatin decreased from 3.6 to 1.6 per 1000. The quick uptake of new agents into routine use is exemplified by cerivastatin and rosuvastatin. Cerivastatin use increased from 0.002 per 1000 in the first quarter of 1998 when it was marketed, increased rapidly to 3.3 per 1000 in the second quarter of 2001, and then rapidly declined at the end of 2001 after market withdrawal due to hepatotoxicity. Similarly, after the launch of rosuvastatin at the beginning of 2003, its prevalent use increased from 0.1 per 1000 to 4.6 per 1000 by the end of the study period, indicating rapid adoption of rosuvastatin.

Figure 6 Prevalence of statin use in British Columbia 1996-2004 by drug

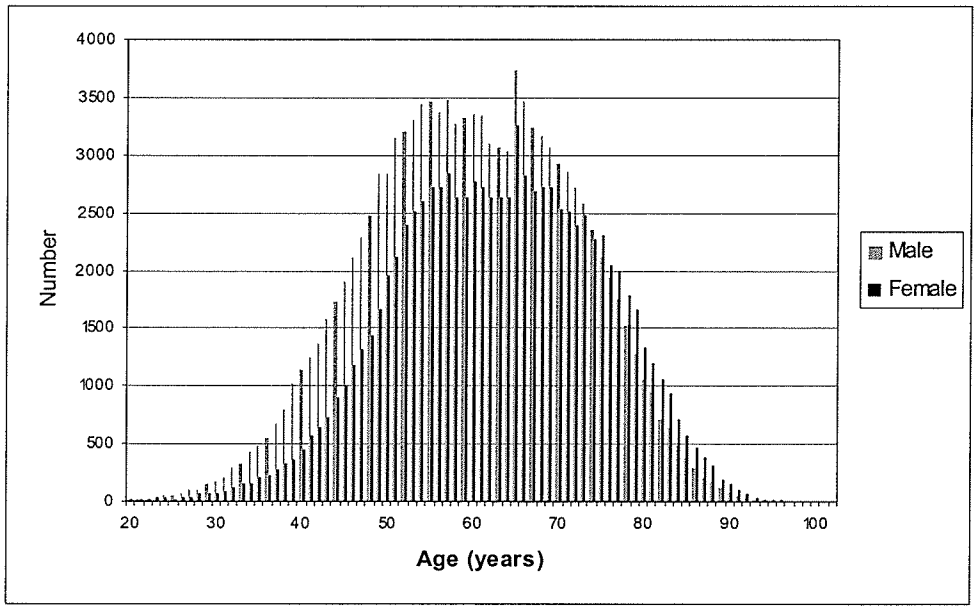


4.2 Incidence

4.2.1 Cohort characteristics: incident statin users

Between 1999 and 2004, 211,964 adults who had been living in the province of British Columbia for at least three years, (and had not filled a prescription for a statin during that time) filled a first statin prescription. The age and sex distribution of incident statin users is presented in Figure 7. The mean age of incident statin users was 61.2, and the cohort was 55.2% male. Most statin users were in the 45-64 year age group (49.8%) and in the 65-84 year age group (39.8%), followed by 20-44 (8.6%) and finally over 85 (1.8%). A more detailed description of all of the variables analyzed for incident statin users over the study period is presented in Appendix 3.

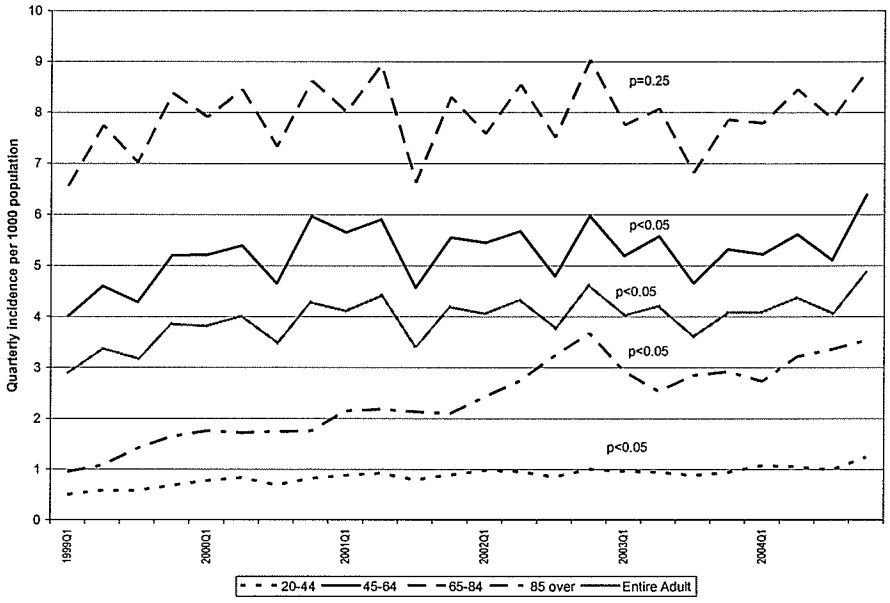
Figure 7 Age and sex distribution of incident statin users



4.2.2 Incident statin use by age

The quarterly incidence of statin use in all British Columbia adults increased from 2.9 per 1000 at the beginning of 1999 to at 4.9 per 1000 by the end of 2004. Figure 8 describes incident statin use by age groups from 1999-2004. All age groups demonstrated cyclical and seasonal patterns of incident statin use, with generally lowest use in the third quarter and highest use in the fourth quarter of each year. When various age groups were compared, all groups except 65-84 demonstrated significantly increased incident statin use over time, where the slope of the regression line was greater than zero ($p<0.05$). As with the prevalence analysis, there was not a clear age gradient observed with incident statin use. The greatest incident statin use throughout the study period occurred in the 65-84 age group. Quarterly incidence in this group increased from 6.6 to 8.8 per 1000 from 1999 to 2004, although there was not a statistically significant upward trend over time ($p=0.25$). The age group with the second greatest incident statin use was age 45-64. Quarterly incidence of statin prescribing in this age group increased from 4.0 to 6.4 per 1000 ($p<0.05$). Incident statin use in the elderly population (over 85) increased from 0.9 1000 to 3.5 per 1000 over the study period, an increase of nearly 4 times ($p<0.05$). The age group with the lowest incident statin use at all time points was the age 20-44 group. The quarterly incidence of statin prescribing in this age group increased from 0.5 per 1000 to 1.2 per 1000 over the study period ($p<0.05$).

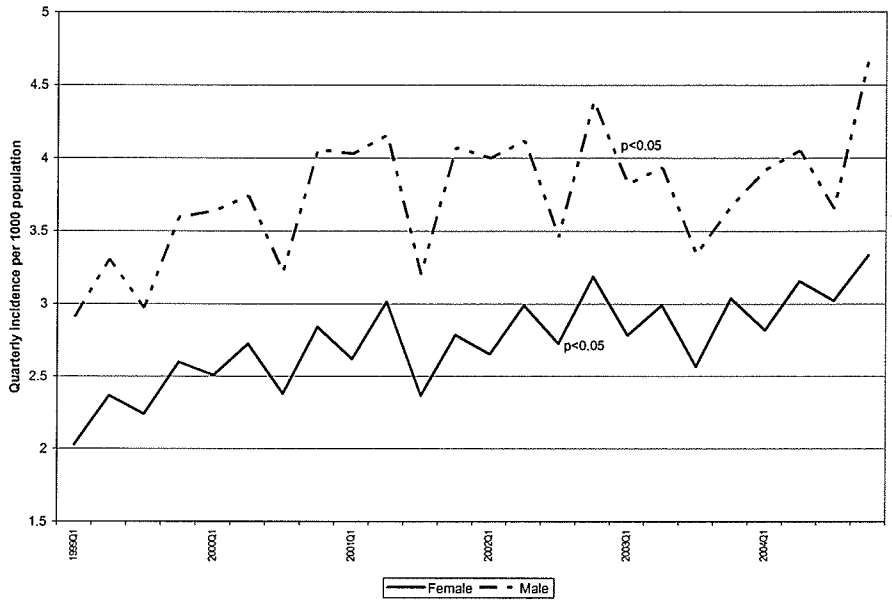
Figure 8 Incident statin use in British Columbia 1999-2004 by age group



4.2.3 Incident statin use by sex

Of the 211, 964 incident statin users included in the study cohort, 211, 405 (99.74%) had male or female sex indicated on their registration with the British Columbia Medical Insurance Plan, and were therefore included in the numerator calculation of incident statin use by sex. Males had a higher incidence of statin use than females at all time points, although the cyclical patterns of use over time were similar in both groups. Figure 9 describes incident statin use by sex from 1999-2004. For males, the quarterly incidence of statin prescribing increased from 2.9 to 4.7 per 1000 from 1999 to 2004, and the slope of the regression line was greater than zero ($p<0.05$). Over this same time period, quarterly incidence increased from 2.0 to 3.3 per 1000 for females ($p<0.05$).

Figure 9 Incident statin use in British Columbia 1999-2004 by sex

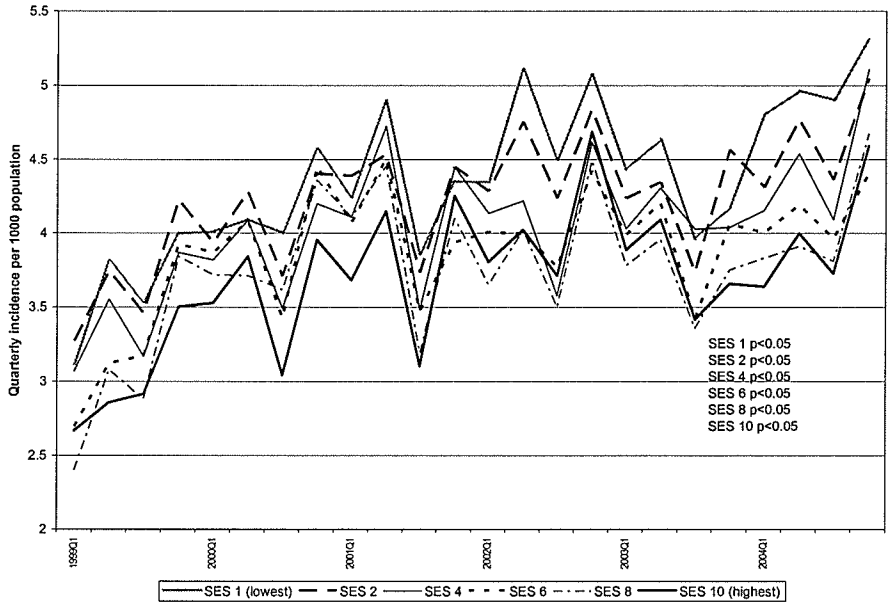


4.2.4 Incident statin use by socioeconomic status

Of the 211, 964 incident statin users, 202, 807 (95.68%) had a value for socioeconomic status (income decile) indicated on their registration with the British Columbia Medical Insurance Plan, and were included in the numerator calculation of incident statin use by socioeconomic status. All groups demonstrated an increase in incident statin use over time, where the slope of the regression line was greater than zero ($p<0.05$). Figure 10 presents the quarterly incidence of statin use by socioeconomic status for the lowest (SES 1), highest (SES 10), and every second income decile. A clear socioeconomic gradient in incident statin use was observed. Those in lower socioeconomic status groups (SES 1 and 2) had greater incident statin prescribing than higher socioeconomic status groups (SES 8 and 10). The quarterly incidence in SES 1 increased from 3.1 to 5.3 per 1000 ($p<0.05$); similarly for SES 2, quarterly incidence increased from 3.3 to 5.0 per 1000 ($p<0.05$). Incident use in SES 4 and 6 demonstrated

moderate incident statin prescribing. Quarterly incidence increased from 3.1 to 5.1 per 1000 throughout the study period for SES 4 ($p<0.05$) and from 2.7 to 4.4 per 1000 for SES 6 ($p<0.05$). The groups with higher socioeconomic status had the lowest incident use. Quarterly statin incidence in SES 8 increased from 2.4 to 4.7 per 1000 ($p<0.05$), while the quarterly incidence in SES 10 increased from 2.7 to 4.6 per 1000 ($p<0.05$). This suggests that a socioeconomic gradient exists for incident statin prescriptions in British Columbia, where those with lower socioeconomic status have a greater incidence of statin prescriptions than those with higher socioeconomic status.

Figure 10 Incident statin use in British Columbia 1999-2004 by socioeconomic status



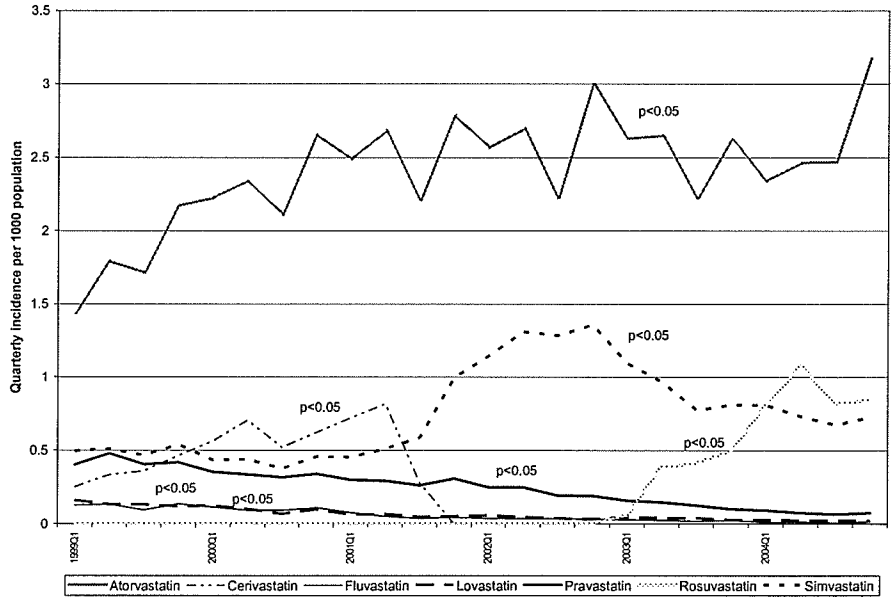
4.2.5 Incident statin use by drug

All 211, 964 incident statin users were included in the numerator calculation of incident statin use by drug. The most commonly prescribed incident statin was atorvastatin (60.6%), followed by simvastatin (18.9%), pravastatin (6.2%), cerivastatin

(5.8%), rosuvastatin (5.4%), lovastatin (1.7%) and fluvastatin (1.5%). Overwhelmingly, atorvastatin was the most commonly prescribed incident statin at all points in time. Simvastatin was the second most commonly prescribed incident statin. However, simvastatin use accounted for at maximum, 34% of new statin prescriptions in 2002, and declined after that. Rosuvastatin use rose quickly to gain a proportion of the incident statin market after it was launched at the beginning of 2003; its use peaked at 24% of new statin prescriptions in the second quarter of 2004. Cerivastatin use approached 20% of incident statin prescriptions throughout 2001, however, incident use rapidly declined to zero after market withdrawal. Figure 11 depicts the quarterly incidence of statin use by the specific drugs from 1999-2004. There was a significant change in use of all drugs with time, where the slope of the regression line was different from zero ($p<0.05$), however incident use of some drugs increased (positive slope), while the use of others decreased (negative slope). Atorvastatin demonstrated the greatest increase in incident use over time; quarterly incidence of atorvastatin use increased from 1.4 to 3.4 per 1000 at the end of 2004. The quarterly incidence of simvastatin prescribing increased from 0.5 to 1.4 per 1000 at the end of 2002, but then incident simvastatin use declined through the end of the study period to 0.7 per 1000 at the end of 2004. The incident use of pravastatin, lovastatin and fluvastatin decreased over the study period. The quarterly incidence of pravastatin decreased from 0.4 to 0.07 per 1000 over the study period. The quarterly incidence of lovastatin decreased from 0.16 to 0.02 per 1000 and the quarterly incidence of fluvastatin decreased from 0.12 to 0.02 per 1000 over the study period. Quarterly incidence of cerivastatin use increased from 0.25 per 1000 at the beginning of 1999, to peak 0.81 per 1000 at the beginning of 2002, but then declined to zero after being

withdrawn from the market. The rapid adoption of rosuvastatin after marked launch at the beginning of 2003 was demonstrated by a rapid increase in incident use. Quarterly incidence of rosuvastatin increased from 0.06 to 0.84 per 1000 by the end of the study period, indicating rapid adoption of rosuvastatin for patients first prescribed a statin.

Figure 11 Incident statin use in British Columbia 1999-2004 by drug

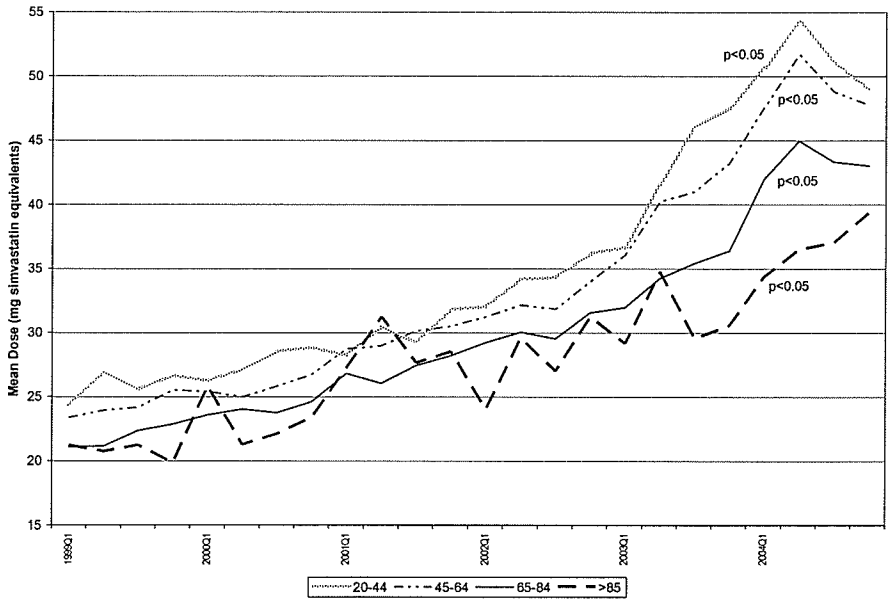


4.2.6 Incident statin use by dose

All 211, 964 incident statin users were included in the numerator calculation of incident statin use by dose. For each incident statin prescription, the dose was converted to simvastatin equivalents as outlined in Appendix 2. The mean dose for incident statin users was 32.9 mg (simvastatin equivalents). The most commonly prescribed dose for new users was 20 mg (57.0%), followed by 80 mg (19.4%), 10 mg (14.5%), 40 mg (4.3%), 5 mg (2.1%), 120 mg (1.63%) 15 mg (0.82%) 160 mg (0.41%) and 360 mg(0.01%).

Overall, the dose (simvastatin equivalents) of incident statin prescriptions increased for all age groups (Figure 12). There was a significant increase in statin dose with time for all age groups, where the slope of the regression line was greater than zero ($p<0.05$). A clear age gradient in dose was observed, with the highest doses (simvastatin equivalents) for incident prescriptions in the younger age groups. The highest doses were in the 20-44 age group, where the mean dose increased from 24.3 mg to 48.9 mg ($p<0.05$). This was followed by the middle age groups, where over the study period, the mean dose increased from 23.4 to 47.8 and from 21.1 mg to 43.0 mg for the 40-64 year and 65-84 age groups, respectively ($p<0.05$). The lowest doses for incident statin prescriptions were used in the elderly (>85) year age group, where the mean dose increased from 21.2 to 39.3 mg over the five year period of analysis ($p<0.05$).

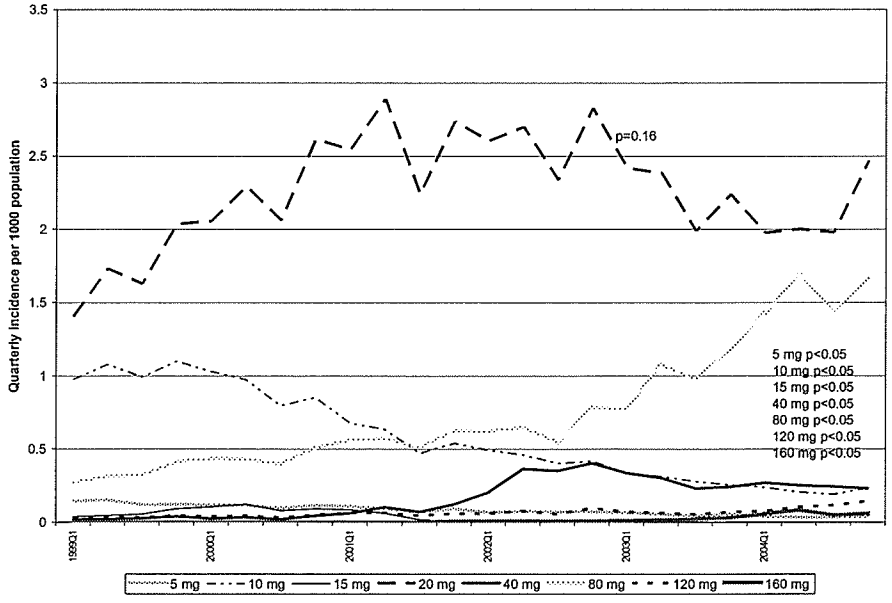
Figure 12 Mean dose of incident statin prescriptions by age groups 1999-2004



When incident prescribing is analyzed by different doses (simvastatin equivalents), the quarterly incidence of lower doses of statins decreased with time as the incidence of

higher doses of statins increased (Figure 13). All doses demonstrated a significant change in use with time, where the slope of the regression line was different from zero ($p<0.05$), except 20 mg (simvastatin equivalents). The incident use of some doses increased (positive slope), while the use of others decreased (negative slope). The quarterly incidence of the 20 mg (simvastatin equivalents) increased from 1.4 to 2.9 per 1000 in 2001, and then gradually declined over the remainder of the study period to 2.5 per 1000 at the end of 2004. The quarterly incidence of 10 mg (simvastatin equivalents) decreased from 1 to 0.2 per 1000 ($p<0.05$). The decrease in incident use of 10 and 20 mg doses (simvastatin equivalents) was mirrored by an increase in the quarterly incidence of higher doses, namely the use of 80 mg, which increased from 0.3 to 1.7 per 1000 ($p<0.05$). The use of 40 mg also increased through the end of 2002 (from 0.02 to 0.4 per 1000), then decreased to 0.2 per 1000 by the end of the study period ($p<0.05$).

Figure 13 Incident statin use in British Columbia 1999-2004 by dose



4.2.7 Incident statin use by medical history

The medical history from medical and prescription drug records revealed that many incident statin users had medical conditions to indicate that their statin was to manage high cardiovascular risk. The distribution of medical conditions in the 211, 964 incident statin users over the entire study period is described in Table 6.

Table 6 Medical conditions for incident statin users 1999-2004

Medical Condition	**Number of incident statin users with condition (%)**
Ischemic heart disease	74,542 (35.2)
Diabetes Mellitus	63,644 (30.0)
Peripheral vascular disease	7,427 (3.5)
Cerebrovascular disease	15,608 (7.4)
Atherosclerosis	8,285 (3.9)
Disorders of lipid metabolism	88,286 (41.7)
Diabetes drugs*	41,424 (19.5)
Nitroglycerin*	32,551 (15.4)
Risk equivalent (peripheral vascular disease, cerebrovascular disease or atherosclerosis)	26,616 (12.6)

*any prescription in year before incident statin prescription

Based on the medical conditions identified through examination of administrative claims data, incident statin users were divided into five mutually exclusive medical condition categories (Table 7).

Table 7 Medical condition categories for incident statin users 1999-2004

Medical Condition Category	**Number of incident statin users (%)**
Ischemic heart disease	74,542 (35.2)
Diabetes Mellitus with no ischemic heart disease	43,257 (20.4)
Risk equivalent* but no ischemic heart disease or diabetes mellitus	9,781 (4.6)
Disorders of lipid metabolism but no ischemic heart disease or diabetes mellitus, or risk equivalent	47,634 (22.5)
No claims for of IHD, DM, PVD, CVD or disorders of lipid metabolism (no discernable reason for therapy)	36,750 (17.3)

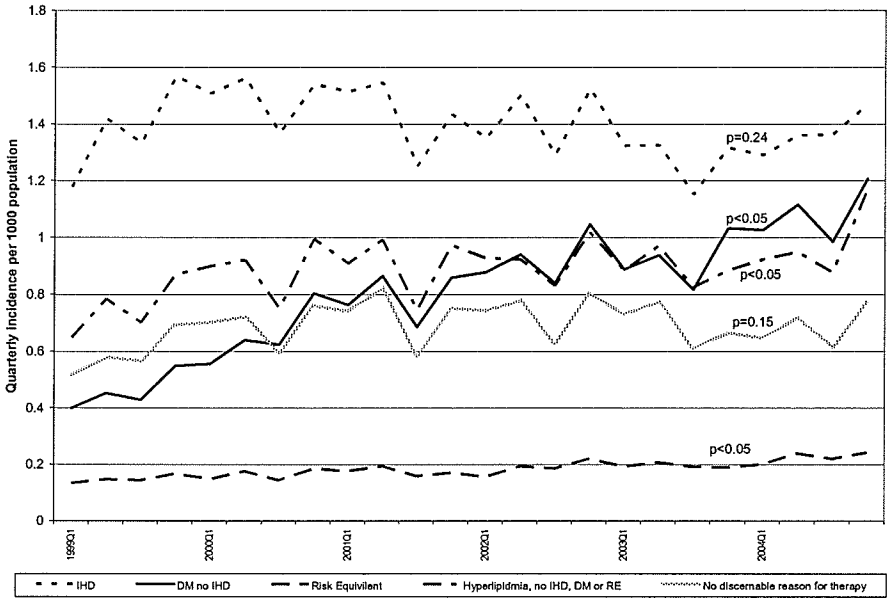
*Risk equivalent (peripheral vascular disease, cerebrovascular disease or atherosclerosis)

The largest group of incident statin users was those with IHD (35%). The proportion of incident statin users with this diagnosis decreased from 41% to 30% from 1999-2004. This was mirrored by an increase in the proportion of new statin users with a diagnosis of DM, but no IHD; the proportion of new statin users in this group increased from 14% to 25%. Incident statin users with medical conditions indicative of high cardiovascular risk (IHD, DM, PVD, CVD or atherosclerosis) in medical and prescription drug records account for 60% of all incident statin users over the study period.

Incident statin use by medical condition category was generally consistent, as seen in Figure 14. The greatest use occurred in the group with IHD. Quarterly incidence increased from 1.18 to 1.47 per 1000 for individuals with IHD, however the slope of the regression line was not different from zero ($p=0.24$). The quarterly incidence for those with DM but no IHD showed the greatest change over the study period; incidence in this group increased from 0.4 to 1.2 per 1000, and the slope of the regression line was different from zero ($p<0.05$). Over the study period, incident use in those with PVD, CVD or atherosclerosis (risk equivalent) increased from 0.13 to 0.24 per 1000 ($p<0.05$). For patients with disorders of lipid metabolism only, quarterly incidence increased from 0.65 to 1.17 per 1000 over the study period ($p<0.05$). For patients with no discernable reason for therapy in the examination of medical history by administrative claims data, the quarterly statin incidence increased from 0.52 to 0.77 per 1000. The slope of this regression line was not different from zero ($p=0.15$). When the three medical condition groups that indicate the incident statin prescription was for high cardiovascular risk (IHD, DM or risk equivalent conditions in medical and prescription drug records) are combined, quarterly incidence increased from 1.7 to 2.9 per 1000. In the groups with low

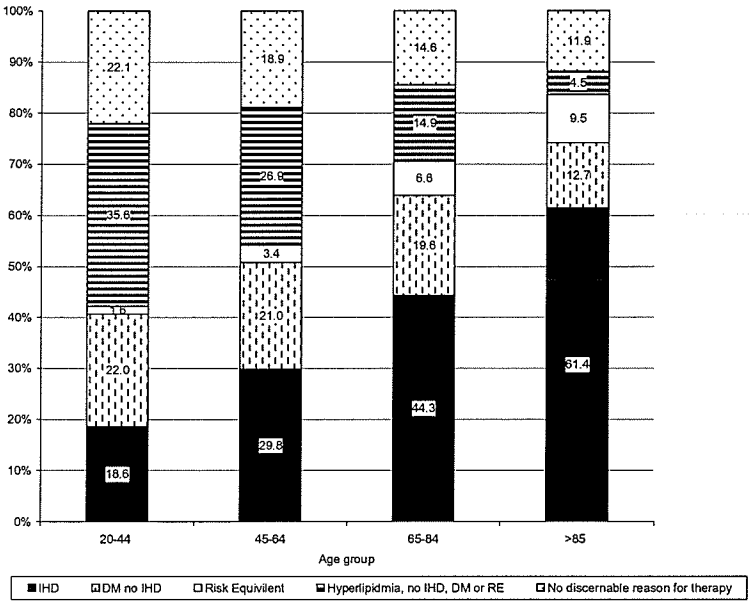
cardiovascular risk (disorders of lipid metabolism only or no discernable reason for therapy in medical and prescription drug records), the incidence of statin prescribing increased from 1.2 to 1.9 per 1000 per quarter.

Figure 14 Incident statin users by medical condition category



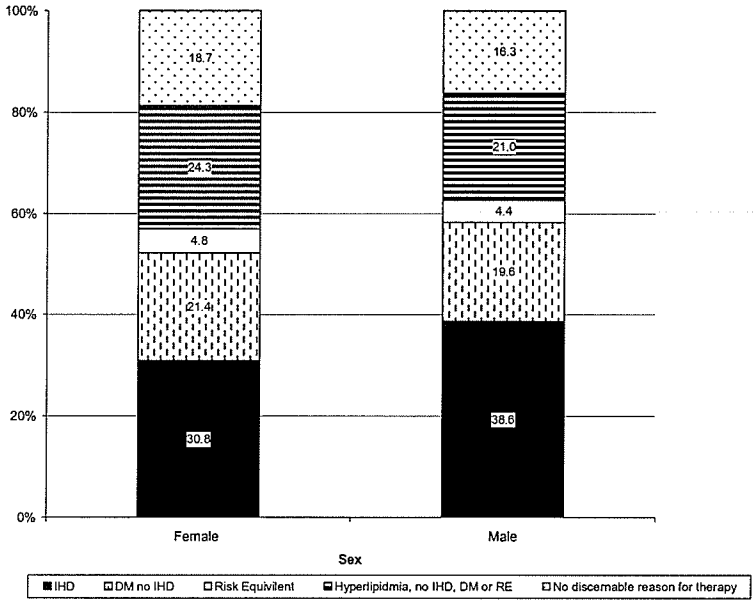
Incident statin users described by medical condition category and according to age group are described in Figure 15. A greater proportion of younger incident statin users had low cardiovascular risk than older incident statin users. The proportion of 20-44 year old incident statin users with no IHD, DM, PVD, CVD or atherosclerosis was 58%. This proportion decreased to 46%, 29% and 16% in the 45-64, 65-84 and >85 age groups, respectively. Only 0.25% of total incident statin users were age 85 and older with low cardiovascular risk (disorders of lipid metabolism only or no discernable reason for therapy). However, 12% of all total incident statin users were age 65-84 with low cardiovascular risk.

Figure 15 Incident statin use by age group and medical condition category



Incident statin users by medical condition category and sex is described in Figure 16. A greater proportion of female incident users compared to male users had low cardiovascular risk. Forty three percent of female and 37% of male incident statin users had no IHD, DM, PVD, CVD or atherosclerosis in medical and prescription drug records. When further analyzed by the total study population, women and men with low cardiovascular risk were 19% and 21% of the total group of incident statin users, respectively.

Figure 16 Incident statin use by sex and medical condition category



Incident statin users by medical condition category and socioeconomic status is described in Figure 17. More incident statin users in the lowest socioeconomic status group (SES 1) were prescribed a statin for documented IHD, DM, PVD, CVD or atherosclerosis as compared to the highest socioeconomic status group (SES 10). The proportion of incident statin users with high cardiovascular risk was 65% in SES 1 and 56% in SES 10, respectively, consistent with an expected higher burden of disease in patients with lower socioeconomic status.

Figure 17 Incident statin use by socioeconomic status and medical condition category

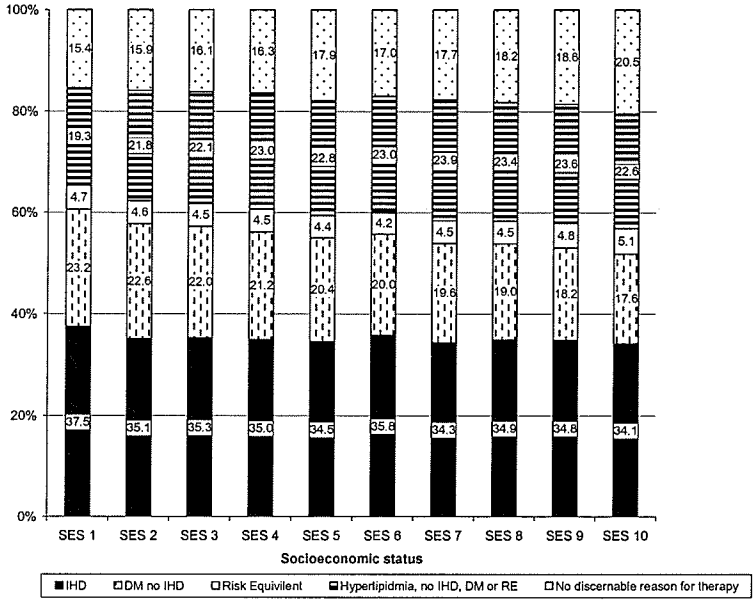
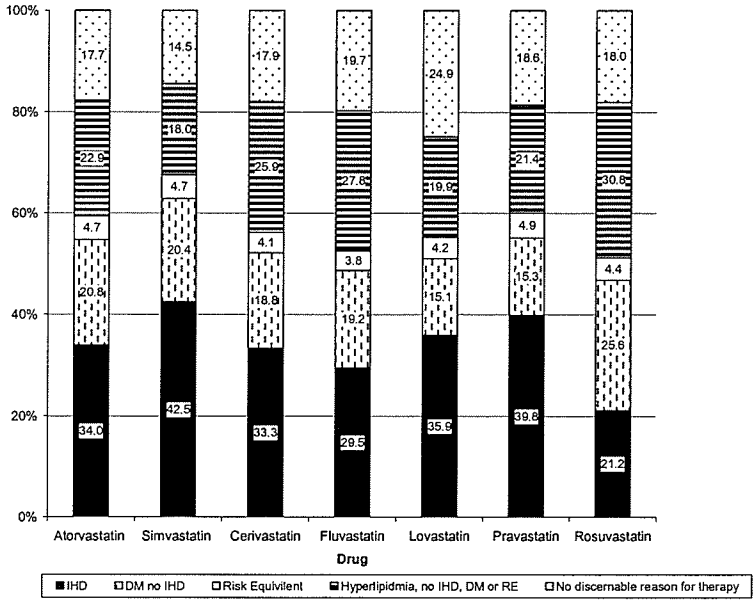


Figure 18 describes incident statin users by medical condition category and drug. The proportion of incident statin users prescribed a statin for high cardiovascular risk varied from 51% for rosuvastatin to 68% for simvastatin.

Figure 18 Incident statin use by drug and medical condition category

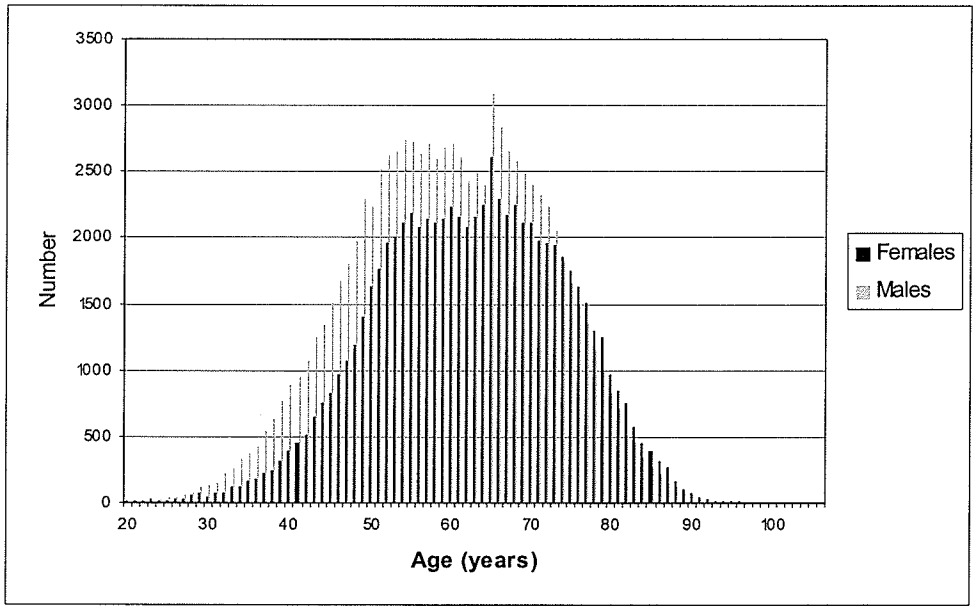


4.3 Persistence with statin therapy

4.3.1 Cohort characteristics: Persistence Cohort

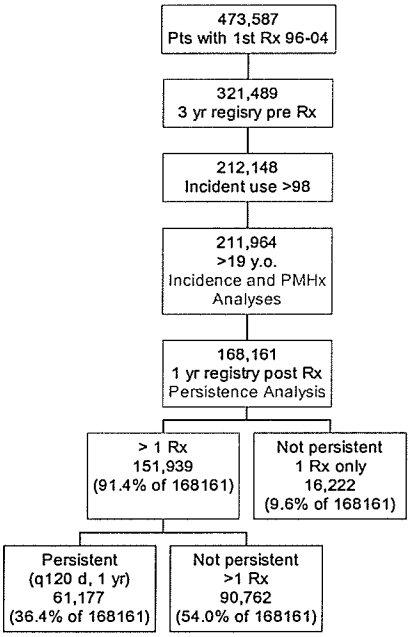
Of the 211, 964 members of the incident statin cohort, 168,161 were registered for British Columbia Medical Services Plan for 275 days of 365 in the one year period following their first statin prescription. The age and sex distribution of this population, the persistence cohort, is presented in Figure 19. The mean age was 61.2 years, and the cohort was 55.2% male. Most statin users were in the 45-64 year age group (49.9%) and in the 65-84 year age group (40.0%), with fewer statin users in the 20-44 and >85 year age groups (8.4 and 1.6%, respectively). A more detailed description of all of the variables analyzed for the persistence cohort is presented in Appendix 4.

Figure 19 Age and sex distribution of persistence cohort



Of 168,161 incident statin users, 61,177 (36.4%) were persistent with therapy over the first year of therapy, 16,222 (9.6%) users filled only one statin prescription in the one year observation period, and 90,762 (54.0%) filled more than one statin prescription but were not persistent with therapy. The 16,222 and 90,762 were combined to form a non-persistent group of 106,984 (63.6% of the persistence cohort). A diagram of patients included in the persistence cohort and those deemed persistent and non-persistent is depicted in Figure 20.

Figure 20 Construction of persistence cohort, determination of statin persistence

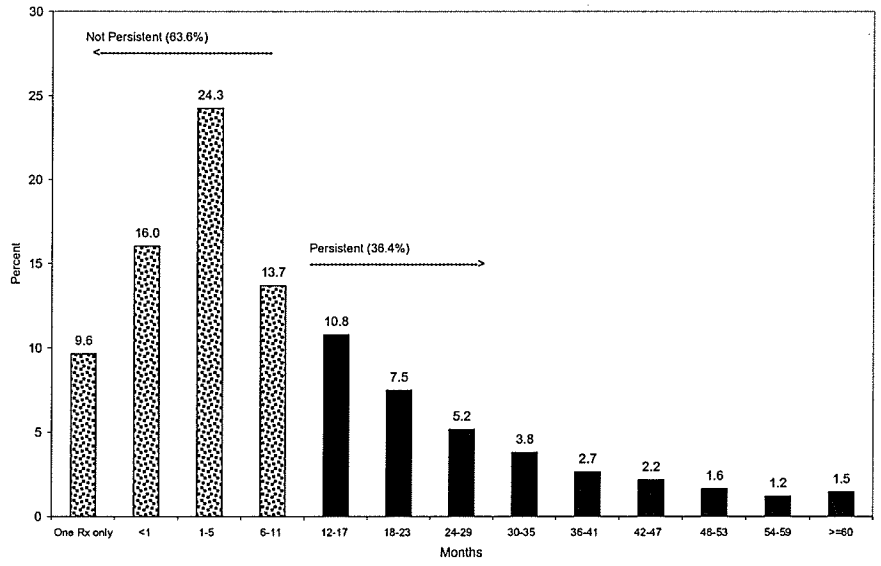


4.3.2 Continuous months of statin therapy

A graphic depiction of the number of continuous months of statin therapy is presented in Figure 21. Twenty four percent of incident statin users filled a series of prescriptions for one to five months. In other words, these statin users filled more than

one statin prescription, but their last prescription before an interruption in therapy (>120 days) occurred between one and five months of the first prescription. Similarly, 16% of incident statin users filled more than one statin prescription, but their last prescription before an interruption in therapy (>120 days) occurred within one month of the first prescription. Fourteen percent of incident statin users filled a continuous series of statin prescriptions for between six and 11 months. When combined with the 9.6% of incident users who filled only one prescription in the one year study period, these groups form a large group (63.6%) of non-persistent incident statin users.

Figure 21 Continuous statin use



4.3.3 Factors predictive of statin persistence: univariate logistic regression

Persistence with statin therapy according to patient characteristics and the unadjusted odds ratio of persistence with statin therapy is presented in Table 8. Explanatory variables included in the analysis include age group, sex, medical condition

category, socioeconomic status, drug prescribed, number of co-prescribed medications, statin dose and year of incident prescription. From univariate analysis, age, socioeconomic status, drug, dose, medical condition category, and co-prescribed medications were significant predictors of persistence with statin therapy over the first year of therapy. Persistent incident statin users are: more often greater than 65 years of age, from neighborhoods with higher socioeconomic status, prescribed atorvastatin or simvastatin at a higher dose than non-persistent statin users. Furthermore, persistent incident statin users were more likely to have high cardiovascular risk and a greater number of co-prescribed medications. Sex, and some years of incident prescription did not influence the likelihood of persistence with statin therapy. The most significant differences between persistent and non-persistent incident statin users in unadjusted analysis were related to age (predisposing factor), and medical condition category (illness factor). Incident statin users who were older than 65 were 2.0 times more likely to persist with statin therapy than incident statin users between the ages of 20-44. Similarly, incident statin users with IHD, DM or a risk equivalent medical condition (PVD, CVD or atherosclerosis) were: 1.57, 1.27 and 1.44 times as likely to be persistent with statin therapy as patients with low cardiovascular risk. Grouped together, 39.8% of incident statin users at high cardiovascular risk were persistent with statin therapy as compared to 31.3% of incident statin users with low cardiovascular risk.

Table 8 Prevalence and unadjusted odds ratios in predicting persistence or non-persistence with incident statin use in first year of use

Variable	Persistent (n=61,177)	Not persistent (n=106,984)	Unadjusted odds ratio (95% Confidence Interval)
Age group			
20-44	3,555 (5.8%)	10,600 (9.9%)	Reference
45-64	29,434 (48.1%)	54,478 (50.9%)	1.61 (1.55 - 1.68)
65-84	27,109 (44.3%)	40,343 (37.7%)	2.00 (1.92 - 2.09)
>85	1,079 (1.8%)	1,563 (1.5%)	2.06 (1.89 - 2.24)
Sex			
Male	33,693 (55.1%)	59,155 (55.3%)	Reference
Female	27, 312 (44.6%)	47,546 (44.4%)	1.01 (0.99 - 1.03)
Medical Condition Category			
IHD	25,006 (40.9%)	35,092 (32.8%)	1.57 (1.53 -1.60)
DM, but no IHD	11,935 (19.5%)	20,677 (19.3%)	1.27 (1.23 - 1.30)
RE, but no DM or IHD	2,977 (4.8%)	4,536 (4.2%)	1.44 (1.37 - 1.51)
Disorders of lipid metabolism only or no discernable reason for therapy	21,259 (34.8%)	46,679 (43.7%)	Reference
Socioeconomic Status			
High (SES 3-10)	48,851 (79.9%)	84,599 (79.1%)	1.05 (1.02 - 1.08)
Low (SES 1-2)	12,326 (20.1)	22,385 (20.9%)	Reference
Drug			
Atorvastatin	37,744 (61.7%)	64,476 (60.3%)	1.13 (1.11 - 1.16)
Simvastatin	12,056 (19.7%)	20,460 (19.1%)	1.14 (1.11 - 1.18)
Others	11,377 (18.6%)	22,048 (20.6%)	Reference
Number of co-prescribed medications			
Low (<4)	15,142 (24.8%)	33,867 (31.7%)	Reference
Medium (4-6)	22,232 (36.3%)	38,284 (35.8%)	1.30 (1.27 - 1.33)
High (>6)	23, 803 (38.9%)	34,833 (32.6%)	1.53 (1.49 - 1.57)
Dose			
< 20 mg	11,978 (19.6%)	21,943 (20.5%)	Reference
20 mg	36,355 (59.4%)	62,579 (58.5%)	1.06 (1.04 - 1.09)
> 20mg	12,844 (21.0%)	22,462 (21.0%)	1.05 (1.02 - 1.08)
Year			
1999	10,839 (17.7%)	17,863 (16.7%)	Reference
2000	12,607 (20.6%)	20,695 (19.3%)	1.00 (0.97 - 1.037)
2001	12,117 (19.8%)	22,191 (20.7%)	0.90 (0.87 - 0.93)
2002	13,474 (22.0%)	22,721 (21.2%)	0.98 (0.95 - 1.01)
2003	12,140 (19.8%)	23,514 (22.0%)	0.85 (0.82 - 0.88)

IHD=ischemic heart disease, DM= diabetes mellitus, RE=Risk equivalent (peripheral vascular disease, cerebrovascular disease or atherosclerosis)

4.3.4 Factors predictive of statin persistence: multivariate logistic regression

In order to evaluate the unique contribution that each of these factors provided to the likelihood of persistence with statin therapy, and to determine which factors were significant in predicting persistence, multiple logistic regression was conducted. A stepwise regression was selected (over forward and backward elimination) as the

multivariate model according to goodness of fit tests. Using stepwise logistic regression in SAS, the following logistic regression model was constructed:

$$Y = -1.4157 + 0.2741\,x1 + 0.1774x2 - 0.0256x3 - 0.0747x4 + 0.4252\,x5 + 0.5585x6 + 0.5220x7 + 0.3054x8 + 0.1702x9 + 0.2547x10 + 0.00636x11 - 0.1088x12 - 0.0384x13 - 0.1711x14 + 0.0742x15 + 0.1386x16 + 0.1120x17$$

Where:

x1= high number of co-prescribed medications
x2= medium number of co-prescribed medications
x3 = female sex
x4 = unknown sex
x5 = age group 45-64
x6 = age group 65-85
x7 = age group >85
x8 = ischemic heart disease
x9 = diabetes mellitus with no ischemic heart disease
x10 = risk equivalent (peripheral vascular disease, cerebrovascular disease or atherosclerosis) but no ischemic heart disease or diabetes mellitus
x11 = year 2000
x12 = year 2001
x13 = year 2002
x14 = year 2003
x15 = high socioeconomic status (SES 3-10)
x16 = low socioeconomic status (SES 1-2)
x17 = atorvastatin
x18 = simvastatin

The minus 2 log likelihood of the model (intercept and covariates) was 217454.12 and for the intercept alone, 220483.75. All tests for model significance were significant ($p<0.0001$). The c statistic (measure of the discriminative power of the logistic equation) was 0.579. The adjusted odds ratios from this logistic regression are presented in Table 9. These odds ratios describe the odds of being an incident statin user that persists with therapy after adjusting for the other regression variables in the model.

Table 9 Adjusted odds ratios for factors predicting persistence with incident statin therapy based on multivariate analysis

Variable	Adjusted odds ratio (95% Confidence Interval)
Age group	
20-44	1.0
45-64	1.53 (1.47 - 1.59)
65-84	1.75 (1.68 - 1.82)
>85	1.69 (1.54 - 1.84)
Medical Condition Category	
IHD	1.36 (1.32 - 1.39)
DM, but no IHD	1.19 (1.15 - 1.22)
RE, but no DM or IHD	1.29 (1.23 - 1.36)
Disorders of lipid metabolism only or no discernable reason for therapy	1.0
Socioeconomic Status	
High (SES 3-10)	1.08 (1.05 - 1.10)
Low (SES 1-2)	1.0
Drug	
Atorvastatin	1.15 (1.12 - 1.18)
Simvastatin	1.12 (1.08 - 1.16)
Others	1.0
Number of co-prescribed medications	
Low (<4)	1.0
Medium (4-6)	1.19 (1.16 - 1.23)
High (>6)	1.31 (1.28 - 1.35)
Year	
1999	1.0
2000	NS
2001	0.90 (0.87 - 0.93)
2002	NS
2003	0.84 (0.82 - 0.87)

IHD=ischemic heart disease, DM= diabetes mellitus, RE=Risk equivalent (peripheral vascular disease, cerebrovascular disease or atherosclerosis)

The results from the multiple logistic regression model indicate that significant predictors of persistence with statin therapy include: older age (predisposing factor), high socioeconomic status (enabling factor), drug prescribed, high cardiovascular risk, and high number of co-prescribed medications (illness factors). Incident statin users who were in all age categories greater than 20-44 had increased odds of persisting with therapy; however there was not a clear age-related gradient in likelihood of persistence. The group with the greatest odds of persistence was those in age 65-84. This group was 1.75 times as likely to persist with statin therapy as those in the 20-44 year age group. Incident statin

users with higher socioeconomic status were slightly more likely to be persistent with statin therapy than patients in lower socioeconomic status groups. Incident statin users who had medical conditions indicative of high cardiovascular risk had significantly greater odds of persisting with statin therapy. This finding was most significant for those statin users with IHD; these patients were 1.36 times as likely to persist with statin therapy as patients who had no documented medical conditions indicative of high cardiovascular risk. Similarly, patients prescribed more than four different medications were more likely to persist with statin therapy; patients with four to six and more than seven medications were 1.2 and 1.3 times as likely to persist with statin therapy as those taking less than four medications. Being prescribed atorvastatin or simvastatin as compared to other statins increased the likelihood of persistence with therapy; patients prescribed atorvastatin and simvastatin were 1.15 and 1.12 times as likely to persist as patients prescribed other statins. Some years of the incident prescription were predictive of non-persistence with therapy; patients who received incident statin prescriptions in 2001 and 2003 were less likely to persist with statin therapy than with incident statin prescriptions in 1999. However, there was no clear trend in the strength or significance of the relationship between incident prescription year and persistence with statin therapy. Neither patient sex nor dose of statin prescribed contributed to persistence with statin therapy.

4.4 Results summary

In summary, prevalent and incident statin utilization increased in British Columbia adults from 1996-2004. Prevalent statin use increased from 13 to 66 per 1000, with greatest use amongst those aged 65-85. There was no socioeconomic gradient in prevalent

statin use. The prevalent use of atorvastatin increased with time, while that of simvastatin decreased. Quarterly incident statin use increased from 1999 to 2004 (2.9 to 4.9 per 1000). Males had greater incident statin use than females, and incident use was greatest amongst those aged 65-84. Unlike with prevalent statin use, there was a socioeconomic gradient observed in incident statin use, where those with lowest socioeconomic status had the greatest incident use. Incident atorvastatin and rosuvastatin use increased with time, while that of other statins decreased. Of incident statin users, 36% had evidence of IHD, 20% DM but no IHD, 5% atherosclerosis, CVD or PVD, 22% hyperlipidemia only and 17% had no discernable indication for therapy on examination of medical and prescription drug records. Quarterly incidence for those with high cardiovascular risk (IHD, DM, atherosclerosis, CVD or PVD), increased from 1.7 to 2.9 per 1000, (overall, 60% of incident statin prescriptions) and incident statin use also increased for those with low cardiovascular risk from 1.2 to 1.9 per 1000.

Of 168,161 adults that filled a first statin prescription from 1999-2003, 61,177 (36.4%) were persistent for one year. Factors which increased the likelihood of persistence with statins included: increasing age (predisposing factor), higher socioeconomic status (enabling factor), the co-morbid conditions indicative of high cardiovascular risk, a greater number of co-prescribed medications and use of simvastatin or atorvastatin (illness factors).

Chapter 5 Discussion

This population based analysis of statin utilization demonstrated a five fold increase in prevalent use from 1996-2004 and 1.7 fold increase in incident use from 1999-2004. Statin use was greater in males than in females, and in older age groups. A socioeconomic gradient, with greater use in lower socioeconomic strata was observed for incident statin use. However, statin use in the population remains suboptimal. Although the majority (60%) of incident statin users were at a high cardiovascular risk (as defined by medical and prescription drug records), there were still many statin users without high cardiovascular risk. Furthermore, most patients who initiate statin therapy, including those at high cardiovascular risk, do not persist with statin therapy. Only 36% of incident statin users were persistent with statin therapy over the first year. Predisposing factors (age) and illness factors (cardiovascular risk) had the greatest impact on persistence with statins.

5.1 Prevalence and incidence

An increase in both incident and prevalent statin use was observed over the study period. These findings are consistent with other studies that have evaluated statin utilization over time.(44;49;53-57;59;82-85) Despite the increase in statin utilization observed in this study, national level data indicates that British Columbia had the lowest statin use (number of prescriptions and dollars spent) of all Canadian provinces from 1996 to 2001.(54) In the only other comparative study in an entire population, Metge observed higher prevalent use from 1996-2000 in Manitobans.(82) In 1998/99, 3.1% of Manitobans filled prescriptions for statins,(82) and during that same period, 2.4-2.7% of

British Columbians were prevalent statin users. Perhaps the differences can be explained by a greater prevalence of cardiovascular disease in Manitoba during that time period, an older population, or greater cardiovascular risk amongst Manitobans.(127)

5.1.1 Age and Gender

Like other studies that have evaluated statin utilization across several age groups,(38;46;55;56;58;60;82) this study observed increased statin use with age, up to age 65-84, and then relatively low use in those older than 85. As cardiovascular risk increases with age,(24) it is generally appropriate that statin use increased with age. As limited RCT data for statin efficacy in those older than 85 exists,(128;129) no large statin trials have included patients greater than age 82,(12;15) and no statin trial has shown a mortality benefit of statin therapy in patients older than 70,(15) it is likely appropriate that incident statin use in the oldest age group was low. However, an increase in incident and prevalent statin use in this age group was observed over time, suggesting that some prescribing is not based on the results of RCTs.

This study observed greater incident statin use in males as compared to females, consistent with other studies that have evaluated statin utilization by gender.(38;46;55;56;58;60;82) Since cardiovascular disease occurs more frequently in males than females, and since the benefits of statin therapy have been demonstrated in RCTs more clearly in men than in women,(130) it is likely appropriate that there was greater use of statins in males, overall. An age and sex interaction also exists, where older males have greater risk for cardiovascular disease than females.(24) However, the use of statins in women is not without controversy; to date, no RCT has demonstrated a benefit to statins in reducing overall mortality in women.(130-132)

5.1.2 Socioeconomic Status

There was no obvious socioeconomic gradient in prevalent statin users observed in this study, consistent with existing studies which have shown no clear socioeconomic gradient in statin use for general or specific (for example, post myocardial infarction) patient populations.(30;36;40;47;59;86-98) However, this study did observe a socioeconomic gradient in incident statin use, where those with higher socioeconomic status had lower use. This finding is appropriate, considering the higher burden of cardiovascular risk factors in those with low socioeconomic status.(116;133) Two other Canadian studies have evaluated the impact of socioeconomic status on statin utilization, and yielded conflicting results.(30;47) A Quebec study of elderly patients with a recent myocardial infarction did not observe differences in the number of prescriptions for cardiovascular drugs by socioeconomic status (median family income, average monthly rent and percentage of high school graduates).(47) However, a study from Ontario found a socioeconomic gradient in statin prescribing in elderly patients with high cardiovascular risk, where patients not prescribed statins were more likely to have low socioeconomic status (household income less than $22,000) than those who were prescribed statins.(30) The variable nature of provincial drug formularies in Canada(134) makes it difficult to determine if a clear socioeconomic gradient in statin prescribing exists in Canada. Since both published Canadian studies and the current study assessed only prescriptions filled (as opposed to prescriptions written), it is possible that this socioeconomic gradient in statin prescribing does exist, but was not captured by this analysis. Furthermore, as both comparator studies evaluated prevalent statin prescribing in elderly populations at high cardiovascular risk only, comparison to the current research of incident and prevalent user

in a general population with all levels of cardiovascular risk, is limited. While there may(30) or may not(47) be a socioeconomic gradient in statin prescribing in high risk elderly patients in Canada, it appears that a socioeconomic gradient in incident statin exists in this study. However, it appears to be in the appropriate direction, with greater use in lower socioeconomic strata. Perhaps the difference in the socioeconomic gradient in incident and prevalent users can be explained by differences in persistence with therapy over long periods of time (more than one year) or the relative cost of therapy to patients.

5.1.3 Drug

As in other studies, this analysis observed a general increase in prescriptions for atorvastatin, rosuvastatin and simvastatin over time, with a corresponding decrease in the use of other statins.(22;48-50;53;56;84;99;100) Prevalent and incident use was most influenced by the use of atorvastatin, which gradually took over statin market share since release in 1997. Atorvastatin has many large RCTs describing the ability of this medication to prevent major cardiac events.(28;135) However, the statin prescribing trends described in this study reveal many prescriptions for statins that were written without rigorous RCTs to support their use. Atorvastatin enjoyed significant media attention in Canada,(136) and indeed gained market share before there was published RCT evidence describing the impact of atorvastatin on mortality, only first published in 2003.(11) Similarly, despite an absence of data demonstrating any influence of rosuvastatin on mortality or even cardiovascular morbidity at the time of this study,(137) this drug enjoyed rapid uptake for incident statin users, also suggesting a proportion of statin prescriptions that were not based on RCT evidence.

5.1.4 Dose

Over the study period, the doses for incident statin users increased in all age groups. It is known that statin doses have increased over time,(50;53;99) however, this is the first study that addresses incident statin users in order to evaluate drug dose over time. An increase in RCTs that demonstrate benefit for higher doses of statins, including simvastatin 40 mg(7;12) and atorvastatin 80 mg(5;8) is likely the most important contributing factor to this increase in statin dose with time.

5.1.5 Cardiovascular risk

The majority of incident statin users (60%) had medical conditions indicative of high cardiovascular risk, including IHD, DM, PVD, CVD and atherosclerosis and therefore appropriate use of statins. Although the proportion of incident statin users with high cardiovascular risk did not change greatly over the study period, there were still many statin users without high cardiovascular risk based on medical and prescription drug records. Likely, several of these seemingly low risk individuals had multiple cardiovascular risk factors that would put them at high cardiovascular risk and that were unaccounted for by this analysis using medical and prescription drug claims, such as obesity, smoking, family history or hypertension. Despite this possible misclassification, there are likely still a proportion of statin users with single or minimal cardiovascular risk factors being treated with statins. For these individuals, minimal RCT evidence supports the use of statins.

Despite a paucity of RCT evidence to demonstrate that statins prevent major cardiac events in women and or elderly (>65) with low cardiovascular risk, these populations accounted for many incident statin users in the study cohort. For example,

19% of incident statin users over the study period were women with no medical conditions indicative of high cardiovascular risk in medical and prescription drug records. It is known the incidence of major cardiac events in women is lower and lags approximately 10 years behind men.(138) However, no RCT has demonstrated any impact of statins on major cardiac events for women or elderly patients taking statins for primary prevention.(135;139-141) Major statin trials for primary prevention included fewer than 20% women, and primary outcomes for these trials were not significant for women.(11;18;20) Furthermore, a meta-analysis analysis of primary prevention trials of statins in women has revealed no statistically significant effect of statins for any endpoints.(130) Similarly, the PROSPER study which evaluated pravastatin in elderly patients (age 70-82 years), showed no benefit to statin therapy in the primary prevention cohort (n=3,239), and no mortality benefit to statins for primary or secondary prevention patients.(15) Despite lack of RCT evidence for efficacy, use of statins in these populations in British Columbia was considerable.

The results of this study can be placed into context through comparison with two similar studies who evaluated medical history of statin users.(37;60) Savoie observed that only a minority (14%) of prevalent statin users in British Columbia had high cardiovascular risk (as indicated by physician claims) in 1995,(60) Dubois observed that 33% of statin users in a large managed care organization had coronary artery or atherosclerotic disease in 1997-1999.(37) Dubois observed that another 14% had diabetes.(37) Similarly, the current study observed that 35% of incident statin users from 1999-2004 had claims indicative of IHD in the medical, hospital and prescription drug records up to an including three years prior to their incident prescription, and that another

20% had diabetes. Differences in methodologies, (Savoie searched for claims indicative of previous myocardial infarction or other heart disease in prevalent users while Dubois searched for a previous cardiovascular event, IHD, cerebrovascular disease and peripheral vascular disease) and year of analysis likely account for the differences observed between these studies of British Columbia statin users. The results of the current study reflect both an increase in RCT evidence for the use of statins and uptake of this information into practice with time.

It is important to consider the findings from this study in terms of what proportion of the population of British Columbia *should* be taking statins. Many studies have suggested that statins are under prescribed to segments of the population, who have a clear indication for these drugs,(30;60;100;142) with possible implications on cardiovascular mortality.(143) Estimates of cardiovascular risk in Canada suggest that 13 to 17% of Canadians have a high risk (history of cardiovascular disease, or $\geq$15% chance of developing cardiovascular disease in 10 years).(144;145) The results of the current study indicate that by the end of 2004, 6.6% of British Columbian adults were taking statins (prevalent users), suggesting under use of statins in high risk populations. Although this study did not seek to evaluate if enough patients at high cardiovascular risk were being treated with a statin, it is certainly likely many British Columbians with high cardiovascular risk were not treated with statins. The results of this study also reveal that many patients with low cardiovascular risk (and no RCT evidence for any benefits to statins), such as women or those older than 85 without previous cardiovascular disease, may be over treated with statins.

An important factor to consider when evaluating the possible overuse of statins in British Columbia, are the Canadian Lipid Guidelines.(24) These guidelines, have been criticized for recommending statin therapy for patients who are at low cardiovascular risk, and who are part of a patient population that lacks RCT data for a benefit to statins.(25;145) In the context of population-based effectiveness and cost-effectiveness of statins, some have suggested that statins be reserved for high risk individuals in order to gain maximal benefit from these drugs.(25;27;144;145) Other guidelines have been criticized for recommending statin therapy for low risk individuals.(145;146)

The population effectiveness of statins has not been overwhelming; it has been argued that despite a massive increase in statin use worldwide, there has been a minimal effect on public health due to cardiovascular disease.(147;148) For example, statin use has accounted for less than 3% of the total fall in death rates from IHD in the United Kingdom from 1981-2000.(147;148) Furthermore, the increased use of lipid lowering drugs has only accounted for a modest decline in standardized admission rates for acute myocardial infarction in England.(149) This is despite a significant benefit from statins that would be expected from clinical trials; a recent meta-analysis of RCTs suggested that statins (combined results for all populations studied) reduce major cardiac events by 23%.(135) In addition to the selection of uncomplicated, motivated and closely followed patients in the setting of a RCT,(150) factors contributing to differences between reality and RCTs could include the overuse of statins in low risk populations,(50;60) and lack of persistence with therapies.(151)

5.2 Persistence

As with previously published studies that evaluate persistence with statins in specific populations, this study demonstrated poor persistence; only 36% of first statin users were persistent at one year. Additionally, the proportion of patients persistent with statin therapy did not change over the study period. Poor persistence and adherence with statins has been linked to cardiovascular morbidity,(151) and has been proposed as an explanation for a smaller impact on cardiovascular morbidity and mortality outside the setting of a RCT than would be anticipated.(20;73;152;153)

5.2.1 Sociodemographic characteristics

Of the predisposing and enabling factors evaluated, age and socioeconomic status influenced persistence with statin therapy. Consistent with the findings of previous studies, this study found better persistence with older age groups, but without a clear age gradient. Several previous studies noted greater persistence with those in the middle to older ages compared to the very elderly.(104;107) Our analysis of persistence by several small age categories may account for this difference. For example, several studies have evaluated statin persistence by large age groups such as seniors vs. non-seniors.(63;65;67;69;75) It is clear from the results of this study that all age groups were more persistent with statins than those in the 20-44 age group. This study did not find an influence of gender on persistence, consistent with several previously published studies.(65;66;69-71;104) However, a socioeconomic difference in persistence was observed, where those with higher socioeconomic status were slightly more likely to be persistent with statins.

There did not appear to be a significant contribution of the year of first prescription for statin therapy to the likelihood of persistence with statin therapy, as with other studies that have evaluated this variable.(65;76;77)

5.2.2 Clinical Characteristics

Several illness factors such as cardiovascular risk and co-prescribed medications influenced persistence with statin therapy. As with several other studies,(62;66;68;76) an increased likelihood of persistence with a greater number of co-prescribed medications was observed. As with other studies, (62;64-67;70;71;74;76;77;104;105;107;108) this study observed that patients at highest risk for cardiovascular disease were more likely to be persistent with statin therapy than those at lower risk. However, there was no significant predictive effect of statin dose on persistence. Although one study found lower statin dose to be predictive of poor persistence in a small sample of Veterans,(105) another Canadian study found no influence of statin dose on persistence.(77) The current study reports that those prescribed atorvastatin and simvastatin were more likely to be persistent with statin therapy. This result is similar to that of two Canadian studies, which found greater persistence with atorvastatin, pravastatin and simvastatin than lovastatin.(67;77) Perhaps this effect was due to accumulating large RCTs supporting the use of atorvastatin or simvastatin as compared to other statins, which has influenced prescribing,(22) and may have influenced persistence.

5.3 Limitations

This analysis has several limitations that must be considered when interpreting the results. Administrative data is collected for purposes other than research, and as such, is

subject to several limitations. By nature of prescription drug databases being administrative databases, a potential exists for miscoding or missing data fields. Extensive validation of the datasets used in this research should serve to minimize this potential limitation. Several other limitations related to the use of administrative databases to define and describe populations, demographics and health service utilization must be accounted for in developing conclusions from this research.

One important limitation to this analysis was that it only assessed the population that filled prescriptions and not the population who should have filled prescriptions for statins. A truly comprehensive analysis of statin use and cardiovascular risk reduction in a population would have evaluated the burden of cardiovascular disease within the population in order to determine how many British Columbians should have been taking statins.

The study definition of a prevalent statin user counted all patients who filled any prescription for a statin in British Columbia during the study period as statin users, which may have overestimated prevalent statin users by accounting for patients who filled prescriptions, but did not take tablets. Of all written prescriptions, it has be estimated that 14% are never filled and another 13% are never taken.(154) Similarly, patients who received physician samples for statins, and then did not go on to fill a prescription for statins would not have been included in the analysis of prevalent statin users. Others not included in the prevalent users include those not included in the Pharma Net database, such as those residing in hospitals. It is most likely, however, that the number of patients taking statins but not included as prevalent statin users would be minimal.

The study definition of an incident statin user may have misclassified patients who had previously tried a statin, and then discontinued three years prior to their index statin prescription. Similarly, medications not accounted for by prescription claims databases such as physician samples would not be included in the analysis. This practice was likely common with newly marketed brand name drugs such as statins. However the continued use of physician samples is unlikely and the date of eventual first statin prescription would have captured these individuals. Those not included in the prevalence analysis, such as First Nations, were not included in the incidence analysis. However, as with the prevalence analysis, it is likely that this population would be minimal.

The analysis of medical history of incident statin user could not be exhaustive as the analysis was based upon administrative data, and not a verbal history, physical examination of a patient, or a chart review. Although the analysis searched for a three year history of cardiovascular disease or risk, a reliance on ICD coding may have underestimated cardiovascular risk. There are many cardiovascular risks not accounted for in this analysis, including: family history, obesity, renal dysfunction, hypertension, cholesterol levels and smoking status. In order to account for the potential to misclassify patients, the ICD codes included in the analysis to determine any type of atherosclerotic process were more sensitive than specific, to bias the results towards including the most patients with any type of cardiovascular risk.

Despite these precautions, it is possible that the study underestimated the proportion of incident statin users with high cardiovascular risk. It is possible that an incident statin user could have a 10 year risk of death from coronary artery disease or nonfatal myocardial infarction is 20% or higher due to cardiovascular risk factors that

would not be discovered though administrative data. For example, a patient could have chronic kidney disease, with a 10 year risk of death from coronary artery disease or nonfatal myocardial infarction of 20% or higher, and a clear indication for a statin. Since many patients with chronic kidney disease have diabetes mellitus as the primary cause of chronic kidney disease, and a further significant proportion of patients with chronic kidney disease have some evidence of cardiovascular disease,(155) the proportion of statin users with chronic kidney disease and no other reason to be at high cardiovascular risk would be minimal. However, an incident statin user could be a 75-79 year old male smoker elevated blood pressure, cholesterol and a positive family history for heart disease, but not have seen a physician for the three years prior to his incident statin prescription. This incident statin user would be misclassified by this analysis as having low cardiovascular risk. The similarity of the results of this study to one with similar methods that evaluated the medical history of statin users in an American managed care organization, but that had access to clinical conditions such as obesity and smoking status,(37) (this study revealed that approximately 50% of statin users did not have DM, IHD, CVD or PVD) suggest that misclassification in the current study is minimized.

Limitations to the persistence analysis include limitations of the measure of persistence and limitations of the variables included in the multivariate analysis. The study measure of persistence may have overestimated persistence; in order to meet the study definition of persistence, statin users only had to fill a prescription (for any days supply) once every 120 days for one year. This definition allows for considerable pill free days. Similarly, the persistence measure may have underestimated persistence with statins, patients could have filled prescriptions for longer durations (patients can fill prescriptions

for as many days as they would like, they would only have to pay for quantities greater than 100 days), and in order to avoid fees (such as dispensing fees, or Pharmacare deductible fees), patients may have filled for greater quantities, therefore falling into the study definition of non-persistence, despite regularly taking statin tablets. Additionally, as the study measure of persistence was based on drug dispensing by nature of administrative data, patients who filled prescriptions regularly, but did not actually take the medications would be considered to be persistent. Given the general consistency of the results of previously published studies, using similar persistence measures,(67;124) it is likely that the study measure of persistence was reasonably accurate.

Although the multivariate model evaluating factors predictive of statin persistence included many important sociodemographic and clinical factors, administrative data cannot capture other predisposing, enabling, or illness factors that may contribute to medication persistence for patients with chronic diseases. Such factors include: depression, stress, anxiety, loss of control, health beliefs, motivation to change, reasoned action and self-efficiency.(113) While it is known that these factors likely contribute to persistence with medication, the ability to capture these factors using administrative data is extremely limited. The impact of other interventions, which may improve statin compliance, was not captured. Such interventions include: being well informed about statin therapy(156) interacting with a pharmacist,(157) or being shown coronary artery calcium as evidence of cardiovascular risk.(158)

5.4 Policy implications

The results of this study indicate that statin use in the population remains suboptimal. There is underutilization of statins in populations at high cardiovascular risk,

and possible overuse of statins in populations at low cardiovascular risk. All statin users are less than optimally persistent. It has been proposed that an efficient strategy for reducing deaths from cardiovascular disease would be to target patients at with high cardiovascular risk for statin therapy,(144) however, others have argued that the incidence of coronary heart disease could be reduced by 80% if all men and women over the age of 55 took some sort of polypill containing a statin, aspirin, and an antihypertensive.(159) Given the financial implications of the drug cost alone for such a radical intervention, and large numbers needed to treat in order to prevent one event in low risk patients, the latter is likely an unwise policy decision. However, policymakers need to take notice of the increasing body of evidence that suggests a care gap for those at high cardiovascular risk not treated with statin therapy. Possible policy implications of this study include a call for better use statins, including an emphasis on prescribing for populations at high risk of cardiovascular disease. An educational policy targeted at prescribers would be feasible to encourage more appropriate prescribing for high risk patients.

An important policy consideration is that of relative expenditure on statins. Canada currently spends approximately 1% of total healthcare expenditures on statins (1.7 billion Canadian dollars) annually,(54) as compared to only 2% of healthcare resources allocated to the entire public health sector.(144) As Canadian prescribers generally choose only one of at most, three different statins for incident prescriptions,(160) pharmaceutical policy, rather than prescriber or patient education would likely be a more effective strategy to maintain population benefit from these drugs while managing drug expenditures. From a strictly practical perspective, the practice of tablet splitting,

proposed to offset considerable out of pocket expenses for patients, could save patients up to nearly $40 per month.(23)

At a population and at an individual level, policies that encourage persistence with therapies that reduce cardiovascular risk are important to consider. Interventions that contribute to persistence and adherence with statins include personalized, patient focused interventions that involve close contact with health professionals, such as pharmacists.(161)

5.5 Knowledge Translation

The results of this research will be shared directly with key pharmaceutical policy decision-makers in the province of British Columbia, as the Ministry of Health will review all manuscripts prior to publication. The results of this research have been shared at the Centre for Health Services and Policy Research's Annual Conference: Towards a National Pharmaceutical Strategy, the Canadian Association of Population Therapeutics Conference and will be presented at the International Society of Pharmacoepidemiology Conference in 2006. The Centre for Health Services and Policy Research disseminates research findings through summaries, reports, public seminars, discussion papers and web and print media. The author will work with a Communications Manager in order to ensure that the results of this study are communicated through the Centre for Health Services and Policy Research website.

5.6 Conclusions and future studies

The BCLHD is a complete population health services database and as such provides a unique opportunity to analyze longitudinal health and medication histories.

The use of the BCLHD allowed for statin utilization within a population to be characterized in meaningful ways over time. This study revealed that both prevalent and incident statin use in the population has increased. Greatest use occurred in the age group 65-84, and in males. Although most new statin prescriptions are for people with high cardiovascular risk, many statin prescriptions are for those where RCT evidence does not show significant benefit to statin therapy. Statin utilization is complicated by the fact that most new users do not persist with therapy for a period long enough to gain a benefit from these medications that could reduce cardiovascular risk.

Future studies of statin utilization in the population of British Columbia could focus on care gaps, and seek to answer the research questions: who should be receiving prescriptions statins and how does this compare to who is receiving prescriptions for statins? Further work could also include an economic analysis of drug expenditures on statins by medical condition category in order to reveal areas where drug spending is not based on RCTs. Finally, the research question could be broadened and some of the limitations of administrative data research could be addressed with mixed methods studies. For example, qualitative methods could further address factors contributing to filling or not filling a first statin prescription or factors associated with persistence with statins. These findings could be combined with a quantitative analysis of long term persistence with therapy.

Chapter 6 References

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Appendix 1

Dose conversion to simvastatin(119-122)

Drug	Simvastatin Equivalents
Atorvastatin	5 mg = Simvastatin 10 mg 10 mg = Simvastatin 20 mg 20 mg = Simvastatin 80 mg 40 mg = Simvastatin 120 mg 80 mg = Simvastatin 160 mg
Cerivastatin	0.2 mg = Simvastatin 10 mg 0.3 mg = Simvastatin 15 mg 0.4 mg = Simvastatin 20 mg 0.8 mg = Simvastatin 40 mg
Fluvastatin	20 mg = Simvastatin 5 mg 40 mg = Simvastatin 10 mg
Lovastatin	20 mg = Simvastatin 10 mg 40 mg = Simvastatin 20 mg
Pravastatin	10 mg = Simvastatin 5 mg 20 mg = Simvastatin 10 mg 40 mg = Simvastatin 20 mg
Rosuvastatin	5 mg = Simvastatin 40 mg 10 mg = Simvastatin 80 mg 20 mg = Simvastatin 160 mg 40 mg = Simvastatin 320 mg

Appendix 2

Variables, data sources and definitions pertaining to medical history.

Variable Name, Data file	Definition	Explanation of use
Medical Service Plan (MSP) files		
Diagnosis code	For 3 years prior to statin date, any diagnosis code (indicating the condition for which the patient is treated by a physician) based on ICD9 codes	To determine a 3 year history of diabetes, ischemic heart disease, peripheral vascular disease, cerebrovascular disease atherosclerosis or hyperlipidemia
Diagnosis code for diabetes	John's Hopkins ACG Case mix system (END01) over a period of three years. (ICD9 250)	(126)
Diagnosis code for Ischemic heart disease	Johns Hopkins ACG Case mix system CAR03 (ICD9 410-414) over a period of three years.	(126)
Diagnosis code for Cerebrovascular Disease	Johns Hopkins ACG Case mix system NUR05 (ICD9 430-438) over a period of three years.	(126)
Diagnosis code for Peripheral vascular disease	Johns Hopkins ACG Case mix system GSU11 (ICD 440.2, 440.3) over a period of three years.	(126)
Diagnosis code for atherosclerosis	Johns Hopkins ACG Case mix system CAR10 (ICD 429.2, 440.0-1, 440.8,9) over a period of three years.	
Diagnosis code for hyperlipidemia	Johns Hopkins ACG Case mix system CAR11 (ICD 272) over a period of three years (includes familiar hypercholesterolemia).	
Hospital Claims files		
Diagnosis code	For 3 years prior to statin date, any diagnosis code (up to 16 <2001 and up to 25 > 2001 diagnoses that a patient may experience while in hospital) based on ICD9 codes and ICD 10 codes converted by Canadian Institute for Health Information to ICD 9 codes.	To determine a 3 year history of diabetes, Ischemic heart disease, peripheral vascular disease, cerebrovascular disease atherosclerosis or hyperlipidemia
Diagnosis code for diabetes	John's Hopkins ACG Case mix system (END01) over a period of three years. (ICD9 250)	
Diagnosis code for Ischemic heart disease	Johns Hopkins ACG Case mix system CAR03 (ICD9 410-414) over a period of three years.	(126)
Diagnosis code for Cerebrovascular Disease	Johns Hopkins ACG Case mix system NUR05 (ICD9 430-438) over a period of three years.	(126)
Diagnosis code for Peripheral vascular disease	Johns Hopkins ACG Case mix system GSU11 (ICD 440.2, 440.3) over a period of three years.	(126)

Diagnosis code for atherosclerosis	Johns Hopkins ACG Case mix system CAR10 (ICD 429.2, 440.0-1, 440.8,9) over a period of three years.	
Diagnosis code for hyperlipidemia	Johns Hopkins ACG Case mix system CAR11 (ICD 272) over a period of three years.	
Procedure codes	Canadian Classification of Procedures (CCP). For 3 years prior to statin date, any procedure code (based on CCP codes and Canadian Classification of Health Intervention codes converted by Canadian Institute for Health Information to CCP codes).	To determine a 3 year history of diabetes, Ischemic heart disease, peripheral vascular disease, cerebrovascular disease, atherosclerosis or hyperlipidemia
Procedure codes for Ischemic Heart Disease	4802, 4803, 4804, 4805, 4809, 481,4811,4812,4813,4814,4815,4816 4817,4819,482,483	
Procedure codes for peripheral vascular disease	501, 5013, 5014, 5015, 5016, 5017, 5018, 5019, 5024, 5026, 5027, 5028, 5034, 5036, 5037, 5038, 5129, 5122, 5123, 5124, 5125, 5126	
Procedure codes for cerebrovascular disease	5011, 5012	

Appendix 3

Variables for utilization analysis – incident prescriptions

Age

N	Average	Median	SD	Min	Max
211,964	61.26	61	12.1	20	106

Age Group

Age Group	Frequency	Percent
20-44	18,224	8.6
45-64	105,565	49.8
64-84	84,369	39.8
≥ 85	3,806	1.8
Total	211,964	100

Sex

Sex	Frequency	Percent
Female	94,415	44.54
Male	116,990	55.19
Total (M/F)	211,405	99.74
Unknown	559	0.26
Total	211,964	100

Socioeconomic status (SES)

SES	Frequency	Percent
1	21,691	10.23
2	22,383	10.56
3	21,068	9.95
4	20,516	9.68
5	19,395	9.15
6	20,040	9.45
7	20,174	9.52
8	18,322	8.64
9	20,065	9.47
10	19,135	9.03

Total (1-10)	202,807	95.68
Unknown	9,157	4.32
Total	211,964	100

Drug

Drug	Frequency	Percent
Atorvastatin	128,538	60.64
Cerivastatin	12,312	5.81
Fluvastatin	3,074	1.45
Lovastatin	3,500	1.65
Pravastatin	13,091	6.18
Rosuvastatin	11,422	5.39
Simvastatin	40,027	18.88
Total	211,964	100

Dose

N	Average	Median	SD	Min	Max
211,964	32.93	20	28.7	5	320

Dose	Frequency	Percent
5	4,438	2.09
10	30,793	14.53
15	1,734	0.82
20	120,434	56.82
40	9,054	4.27
80	41,175	19.43
120	3,447	1.63
160	864	0.41
320	24	0.01

One Prescription

Value	Frequency	Percent
One prescription only	30,337	14.31
More than one	181,627	85.67
Total	211,964	100

Ischemic Heart Disease (IHD)

Value	Frequency	Percent
Not Present	137,422	64.83
Present	74,542	35.17
Total	211,964	100

Diabetes (DM)

Value	Frequency	Percent
Not Present	148,320	69.97
Present	63,644	30.03
Total	211,964	100

Peripheral Vascular Disease (PVD)

Value	Frequency	Percent
Not Present	204,537	96.5
Present	7,427	3.5
Total	211,964	100

Cerebrovascular Disease (CVD)

Value	Frequency	Percent
Not Present	196,356	92.64
Present	15,608	7.36
Total	211,964	100

Atherosclerosis (ATH)

Value	Frequency	Percent
Not Present	203,679	96.09
Present	8,285	3.91
Total	211,964	100

Hyperlipidemia (LIP)

Value	Frequency	Percent
Not Present	123,678	58.35
Present	88,286	41.65
Total	211,964	100

Diabetes Drugs

Value	Frequency	Percent
Not Present	170,540	80.46
Present	41,424	19.54
Total	211,964	100

Nitroglycerin (NTG)

Value	Frequency	Percent
Not Present	179,413	84.64
Present	32,551	15.36
Total	211,964	100

Risk Equivalent (RE = PVD or CVD or ATH)

Value	Frequency	Percent
Not Present	185,348	87.44
Present	26,616	12.56
Total	211,964	100

Medical Condition Category

Value	Frequency	Percent
IHD	74,542	35.17
DM, no IHD	43,257	20.41
RE, no IHD or DM	9,781	4.61
Hyperlipidemia no IHD, DM, or RE	47,634	22.47
No medical conditions that were sought	36,750	17.34
Total	211,964	100

Appendix 4

Variables for persistence analysis

Reg1 (continued registry for >275 days of the one year after incident statin prescription)

Value	Frequency	Percent
0	43,803	20.67
1	168,161	79.33
Total	211,964	100

Outcome Variable: Persistence

Value	Frequency	Percent
Persistent	61,177	36.38
Not persistent	106,894	63.38
Total	168,161	100

Outcome Variable: One Prescription

Value	Frequency	Percent
One prescription only	16,222	9.65
More than one	151,939	90.35
Total	168,161	100

Explanatory Variable: Age Group

Age Group	Frequency	Percent
20-44	14,155	8.42
45-64	83,912	49.90
64-84	67,452	40.11
$\geq$ 85	2,642	1.57
Total	168,161	100

Explanatory Variable: Sex

Sex	Frequency	Percent
Female	74,858	44.52
Male	92,848	55.21
Unknown	455	0.27
Total	168,161	100

Explanatory Variable: Socioeconomic status (SES)

SES	Frequency	Percent
1	16,973	10.09
2	17,738	10.55
SES LOW (1-2)	34,711	20.64
3	16,674	9.92
4	16,195	9.63
5	19,395	9.08
6	20,040	9.49
7	20,174	9.58
8	18,322	8.65
9	20,065	9.48
10	19,135	9.08
Unknown	9,157	4.32
SES High (3-10 and unknown)	133,450	79.36

Explanatory Variable: Drug

Drug	Frequency	Percent
Atorvastatin	102,220	60.79
Simvastatin	32,516	19.34
Other	33,425	19.88
Total	168,161	100

Explanatory Variable: Dose

Dose	Frequency	Percent
< 20	33,921	20.17
20	98,934	58.83
> 20	35,306	21.00
Total	168,161	100

Explanatory Variable: Year

Year	Frequency	Percent
1999	28,702	17.07
2000	33,302	19.80
2001	34,308	20.40
2002	36,195	21.52
2003	35,654	21.20
Total	168,161	100

Explanatory Variable: ATC4 (number of co-prescribed medications at the time of incident statin prescription)

N	Average	Median	SD	Min	Max
168,161	5.81	5.0	3.58	1	37

Value	Frequency	Percent
High > 6	58,636	34.87
Medium 4-6	60,516	35.99
Low < 4	49,009	29.14
Total	168,161	100

Explanatory Variable: Medical Condition Category

Value	Frequency	Percent
IHD	60,098	35.74
DM, no IHD	32,612	19.39
RE, no IHD or DM	7,513	4.47
Hyperlipidemia no IHD, DM, or RE	38,042	22.62
No medical conditions that were searched for	29,896	17.78
Total	168,161	100

Distribution of persistence by explanatory variables

Variable	Persistent (n=61,177)	Not persistent (n=106,984)
Age group		
20-44	3,555 (25.1%)	10,600 (74.9%)
45-64	29,434 (35.1%)	54,478 (64.9%)
65-84	27,109 (40.2%)	40,343 (59.8%)
>85	1,079 (40.8%)	1,563 (59.2%)
Sex		
Male	33,693 (36.3.1%)	59,155 (63.7%)
Female	27, 312 (36.5%)	47,546 (63.5%)
Medical Condition Category		
IHD	25,006 (41.6%)	35,092 (58.4%)
DM, but no IHD	11,935 (36.6%)	20,677 (63.4%)
RE, but no DM or IHD	2,977 (39.6%)	4,536 (60.4%)
Hyperlipidemia alone or no medical conditions sought	21,259 (31.0%)	46,679 (69.0%)
Socioeconomic Status		
High (SES 3-10)	48,851 (36.6%)	84,599 (63.4)
Low (SES 1-2)	12,326 (35.5%)	22,385 (64.5)
Drug		
Atorvastatin	37,744 (36.9%)	64,476 (63.1%)
Simvastatin	12,056 (37.1%)	20,460 (62.9%)
Others	11,377 (34.0%)	22,048 (66.0%)
Number of co-prescribed medications		
Low (<4)	15,142 (30.9%)	33,867 (69.1%)
Medium (4-6)	22,232 (36.7%)	38,284 (63.3%)
High (>6)	23, 803 (40.6%)	34,833 (59.4%)
Dose		
< 20 mg	11,978 (36.8%)	21,943 (63.3%)
20 mg	36,355 (59.4%)	62,579 (58.5%)
> 20mg	12,844 (36.4%)	22,462 (63.6%)
Year		
1999	10,839 (37.8%)	17,863 (62.2%)
2000	12,607 (37.9%)	20,695 (62.1%)
2001	12,117 (35.3%)	22,191 (64.7%)
2002	13,474 (37.2%)	22,721 (62.7%)
2003	12,140 (34.0%)	23,514 (66.0%)