DOES CONTINUITY OF COMMUNITY PHARMACY CARE INFLUENCE ADHERENCE TO STATINS?

by

Russell Christie

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Abstract

Background: Improving adherence to medication is a persistent challenge within the health system. Adherence is influenced by many factors at the patient, provider, treatment and health system levels. Adherence may also be affected by continuity of care; defined as the consistent professional relationship between a health provider or source of care and a patient.

Objective: To estimate the strength of association between continuity of community pharmacy care and adherence to statin medication among persons initiating statin therapy in Nova Scotia between 1998 and 2008.

Methods: This was a retrospective cohort study using administrative data from the Nova Scotia Seniors' Pharmacare program. Subjects were included if they were dispensed at least one prescription for a statin medication between 1998 and 2008. Continuity of care was calculated via two methods: the Usual Provider of Care (UPC) index and the Continuity of Care Index (COCI), which measure the density and dispersion of relational continuity of care, respectively. Adherence was calculated using the medication possession ratio. The strength of association between continuity of care and adherence was analyzed using hierarchical regression.

Results: During the study period, 31 592 individual subjects received a first statin dispensation. Adjusted hierarchical regression showed that for each 0.10 increase in continuity of care, the odds of adherence increase by 3% (95% CI: 1.01-1.05). Continuity of care measured by the UPC is highly correlated with continuity of care measured by the COCI (r=0.98).

Conclusions: Continuity of community pharmacy care is positively associated with adherence to statins among Nova Scotian seniors who initiated statin therapy between 1998 and 2008.

List of Abbreviations Used

ABC	Ascertaining Barriers for Compliance Study Group
ATC	Anatomical Therapeutic Classification
CA	Canadian Enhancement (to ICD, 10th revision)
CCI	Canadian Classification of Health Interventions
CHF	Congestive Heart Failure
CI	Confidence Interval
CIHI	Canadian Institute of Health Information
CIHI-DAD	Canadian Institute of Health Information Discharge Abstract Database
CM	Clinical Modification (to ICD, 9th revision)
CMA	Continuous Medication Adherence
COCI	Continuity of Care Index
CRF	Chronic Renal Failure
DIN	Drug Identification Number
HDL	High Density Lipoprotein
HMG-CoA	3-hydroxy-3- methylglutaryl coenzyme A reductase
HTN	Hypertension
ICD	International Classification of Diseases
IMB	Information-Motivation-Behavioural (Model)
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
LDL	Low Density Lipoprotein
MEMS	Medication Event Monitoring System
MI	Myocardial Infarction
MPR	Medication Possession Ratio
MSI	Medical Services Insurance
NSSPP	Nova Scotia Seniors' Pharmacare Program
ODB	Ontario Drug Benefit (Program)
OR	Odds Ratio
PDC	Proportion of Days Covered
PHRU	Population Health Research Unit; Dalhousie University, Department of Community Health and Epidemiology
RAMQ	Régie de l'Assurance Maladie du Québec
RR	Rate Ratio
SAS	Statistical Analysis Software
SD	Standard Deviation
SES	Socioeconomic Status
TC	Total Cholesterol
UPC	Usual Provider of Care (Index)
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study

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Chapter 1: Introduction

The problem of medication non-adherence is so large that, in 2003, the World Health Organization (WHO) concluded that increasing medication adherence would be more beneficial for population health than developing new treatments.(1) This view is based on multiple reports showing that only about 50% of persons prescribed long-term medication are adherent one year after initiating treatment.(1) This phenomenon is seen in different treatments and also among patients with specific conditions including asthma(1-3), hypercholesterolemia(4,5), hypertension(1,6), and diabetes.(1,7)

Hypercholesterolemia, a condition characterized by high serum blood levels of low-density lipoproteins (LDL) and elevated levels of total cholesterol (TC), is a major risk factor for cardiovascular disease.(8) Hypercholesterolemia is a type of dyslipidemia, which is a broader condition, characterized by elevated TC, LDL or triglyceride levels, or a low high-density lipoprotein (LDL) level.(8) Hypercholesterolemia is most often treated with a class of medications called statins.

Non-adherence to statins contributes to negative health and economic outcomes for both patients and the health system.(9-14) With this in mind, many studies have attempted to identify the factors that promote or inhibit adherence.(1,15)

This thesis investigates the impact of the on-going association of a patient with a pharmacy on medication adherence. This association is defined here as the extent to which a single pharmacy dispenses all medications to a patient. This is based on the definition of continuity of physician care proposed by Breslau and Reeb.(16) In 1975, Breslau and Reeb defined continuity of care as “the extent to which a single physician manages the health needs of a patient: the more the patient’s visits are with a single

physician, the more the care is considered continuous." Breslau and Reeb's definition of continuity of care focused on the longitudinal relationship between a patient and the primary care physician. Since then, the concept has been expanded to encompass information transfer (informational continuity), the consistent implementation of care (management continuity) and the interpersonal relationships between health providers and patients (relational continuity).(17,18) Relational continuity has been further subdivided into four domains: dispersion, density, duration and sequence. While previous studies in the literature have examined aspects of relational continuity, they have focused on the density domain and have referred to this domain as either pharmacy loyalty or fidelity.(19,20). This thesis examines both the density and dispersion domains of relational continuity and thus, the broader terminology; "continuity of community pharmacy care" is used from this point onward.

Continuity of care is thought to influence medication adherence by fostering a strong provider-patient relationship, which then translates to increased information uptake and utilization, and subsequently improved adherence.(17). It is possible that this relationship also helps to modify patient beliefs about medication adherence and helps facilitate the identification of patient specific barriers and facilitators of adherence. Continuity of community pharmacy care is also thought to decrease a patient's risk for medication-related problems, including medication interactions, adverse effects, and subsequent non-adherence.(21)

Previous continuity of care studies have assessed the physician-patient relationship, and have found that continuity of physician care is associated with positive outcomes such as decreased hospital resource utilization, decreased hospital readmission

rates, increased health related quality of life and an increase in the quality of the physician-patient relationship.(22) The association between continuity of physician care and medication adherence is not consistent.(6,7,23-25).

Because community pharmacists dispense the majority of medication outside of the acute care setting in Canada and may see patients more frequently than physicians, it is possible that pharmacists have a greater impact on medication adherence than do physicians.(26). However, the longitudinal association between continuity of community pharmacy care and adherence to medications has been infrequently studied. After a literature review, only one study was located that directly assessed this association.(27) Five additional studies have determined patient characteristics associated with concepts of relational continuity of community pharmacy care.(19-21,28,29)

Chapter 2: Literature Review

2.1 The Use Of Administrative Data To Measure Adherence

In this thesis, medication adherence is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."(30) This differs from medication persistence, which is defined by International Society of Pharmacoeconomics and Outcomes Research (ISPOR) as "the duration of time from initiation to discontinuation of therapy."(30)

Medication adherence can be measured by either direct or indirect means; however, there is no consensus as to the best way to measure adherence, or as to what defines a good, adequate or poor adherence level.(1,31,32) Direct methods of measurement involve directly observing medication ingestion, or measuring the presence of the medication or a metabolite of the medication in the patients' blood.(31) Indirect methods of measuring adherence involve gathering information from secondary sources such as patients' self-reports, assessing clinical response, counting remaining pills, using data from electric medication monitors and calculating refill rates and ratios from administrative databases.(31) Direct methods provide a more accurate portrayal of exposure because there is certainty that the patient has consumed the medication. However, these methods are more time consuming and costly to use than indirect methods. Indirect measures offer an easier method of data collection; however, because they provide no way of determining if the patient has actually ingested the medication, they are less accurate than direct measures.(31,33-35) Additionally, patient self-reports of medication adherence can be affected by recall bias.(32)

There are at least 11 methods that can be used to calculate adherence to medications using administrative claims data.(36) The two most common are the proportion of days covered (PDC) and medication possession ratio (MPR).(34) The PDC is utilized when assessing adherence to multiple medications, and the MPR is used to evaluate adherence to a single medication or class of medications, over a defined period.(36) These measures are equivalent when assessing adherence to only one type or class of medication. The MPR is the ratio of the days of medication supplied over the study period, to the duration from the first fill date until last day of follow up.(36,37) The MPR is essentially the same as a third measure of medication adherence: the Continuous Medication Acquisition (CMA) measure.(36) As an indirect measure of medication adherence, the CMA is moderately correlated to serum blood concentrations of the drug under study and also to medication effects.(38) The CMA also does not differ significantly from a patient's pill count ($p=0.68$); possibly indicating that the MPR and pill count produce similar estimates of adherence.(36,39) A MPR greater than or equal to 0.80 has historically indicated adherence to long-term medications.(32,37) However, a meaningful cut point may be different for different drug categories depending on the pathophysiology of the condition.(32)

2.2 Limitations To The Use Of Administrative Data

There are limitations to using administrative data to measure medication adherence, notably inaccurate database coding, limited generalizability outside of the studied population, and restricted information availability.

Coding inaccuracies are always a concern when using administrative data, however the data within prescription claim records are generally thought to be of high

quality.(40,41) This is the case because if a claim is submitted containing false information, the pharmacist is acting fraudulently. If a claim is not submitted at all, the pharmacist will not be reimbursed for the dispensed medication.(32)

In Canada, administrative pharmacy claims data only contain information about the prescriptions that patients fill. Unfilled prescriptions are not captured within the databases. In some other jurisdictions, such as the United Kingdom, records of all written prescriptions are kept. Additionally, if a subject retrieves a prescription from the pharmacy, it is uncertain if the patient ingests the medication over the subsequent weeks.(31,42) Administrative pharmacy data also do not contain pharmacy specific information such as pharmacy type, location, or number or prescriptions dispensed per pharmacy; or patient covariates such as comorbid medical conditions or other lifestyle behaviors. Linkages with other administrative databases need to be established in order to capture these characteristics

2.3 The Role Of Medication Adherence In The Treatment Of Dyslipidemia

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in Canada with direct and indirect costs estimated to be $22 billion in 2000.(43-46) Hypercholesterolemia is a major risk factor for cardiovascular and vascular conditions including myocardial infarction (MI), angina, heart failure, ischemic stroke, carotid stenosis and abdominal aortic aneurysm.(8,47,48)

Hypercholesterolemia, can be treated effectively with a class of medication called hydroxymethylgultaryl coenzyme A (HMG-CoA) reductase inhibitors; commonly known as statins.(49) Other medication classes used to lower cholesterol include fibrates, bile-acid sequestrants, niacin and ezetamibe.(8,49,50) Of these medications, statins are the

most commonly prescribed and confer the greatest cholesterol lowering effect.(51,52) Despite the wide use of statins and their known effectiveness, the prevalence of hypercholesterolemia in Canada remains high and is expected to increase.(44,49,53) Even among patients treated with statins, the prevalence of dyslipidemia is still between 37% and 49%.(54,55) One reason that statin-treated patients continue to experience dyslipidemia is poor medication adherence.(54,55)

Non-adherence to medication is a problem, for if a medication is not taken at the correct dosage or for the correct duration; control of hypercholesterolemia is unlikely to be achieved.(31) Adherence to statins is associated with lower mortality, lower risk of cardiovascular events, lower risk of non-fatal ischemic heart disease, decreased venous thromboembolism, decreased risk of hospitalization, decreased healthcare costs and decreased work absenteeism.(9-14) The association between adherence and decreased risk of hospitalization shows a dose response with patients in the lowest quintile of adherence experiencing the highest number of hospitalizations and vice versa.(13) In an analysis of data from the West of Scotland Coronary Prevention Study (WOSCOPS) patients with less than 75% adherence had a similar risk of all cause death compared to placebo ($p=0.98$).(56) The WOSCOPS was a double blind randomized controlled trial of 6,595 subjects with moderately elevated cholesterol levels who were assigned to treatment with either pravastatin or placebo. No difference was again observed for the composite measure of definite coronary heart disease, death or non-fatal myocardial infarction, indicating that the some benefits of taking statins disappeared at adherence levels below 75%.(56) In comparison, subjects with adherence rates greater than 75% experienced a decreased risk of definite coronary heart disease death or non-fatal

myocardial infarction compared to placebo. Subjects with 100% adherence also experienced statistically significant decreases in coronary artery bypass grafting or percutaneous coronary intervention procedures, as well as a decrease in the composite of definite or suspected coronary heart disease death or non-fatal myocardial infarction. In the WOSCOPS the percentage adherence was based on the frequency of visits with study staff in which new medication was issued to the patient, not on refill data or pill count. Even though the researchers used a non-standard method of measuring adherence, the researchers indicated that once a patient was established on their medication, adherence based on pill count was 93%.

Patients prescribed long-term cardiovascular medications who take at least 80% of their prescribed dose over a given period of time are typically classified as adherent to their medication.(34) At the population level, it has been found that adherence follows a negative curve over time. Between 18% and 28% of patients stop taking their long-term medications as directed after only one dispensation, and many more stop within one year of the first fill.(4,57,58) In a meta-analysis that included 68,592 patients taking statin medications 76% of patients using the statin for secondary prevention and 57% of patients using the statin for primary prevention were adherent over a median 24 month period.(57) Benner and colleagues also demonstrated this negative trend in a single cohort of elderly patients followed for up to ten years.(59) During the first three months of therapy, 79% of patients were adherent to treatment. After six months, this percentage decreased to 56%. After one year, 50% of the cohort were adherent. Extending the follow-up to five and ten years showed adherence levels of 35% and 42%, respectively.(59)

2.3 Theoretical Adherence Framework

Numerous attempts have been made to determine the causes of non-adherence. These investigations have generally focused on patient, provider, treatment or health-system related factors.(1,15)

The process of adhering to a medication is a patient behaviour that can be intentional or non-intentional.(34) Intentional non-adherence occurs when a patient makes a conscious decision to deviate from the prescribed medication regimen.(34) A patient may do this because of beliefs related to the need for the medication, to avoid adverse effects or to reduce spending on medications. Non-intentional non-adherence occurs when a patient forgets to take their medication or is prevented from taking their medication by means beyond their control.(34) Both types of adherence behaviour can be characterized using five theoretical perspectives: biomedical, behavioural, communication, cognitive and self-regulatory.(1)

The Information-Motivation-Behavioural skills model (IMB) is a cognitive framework that describes adherence behaviour. This framework is used in this study to describe how continuity of community pharmacy care could influence medication adherence.(60) The IMB is composed of four domains: motivation, information, behavioural skills, and health outcomes.(60) These four domains work together to influence behaviour change. In the framework, social and demographic factors are moderators of the domains.(61) The following paragraphs explain how continuity of community pharmacy could affect each domain, and therefore could influence medication adherence.

Motivation domain

The motivation domain includes the constructs of personal attitudes towards medication adherence, beliefs about the outcomes of medication adherence, perceived social support to medication adherence and subjective norms. Using concepts from this domain, it is apparent that a trusting relationship with a health professional may positively impact adherence. Trust in physicians and the health-system itself is known to be associated with increased medication adherence.(62-64) We hypothesize that using a consistent pharmacy may facilitate the creation of a strong professional relationship and increased trust with pharmacy staff. Patients who have a strong professional relationship with a pharmacist are in an excellent position to receive support for medication adherence, and to have their perception of subjective norms influenced.

Information domain

The information domain encompasses knowledge about the specific disease state such as the progression of the illness, the types and quality of treatment and the consequences of non-treatment. As explained above, patients who regularly receive their medications from a single pharmacy may experience higher quality communication from the pharmacy staff, and subsequently increased information uptake and utilization, which will then facilitate medication adherence.

Behavioural skills domain

The third domain, behavioural skills, encompasses the learned behaviors that the patient requires in order to be adherent to their medication. These skills are diverse; from the use of compliance packaging, to perceived self-efficacy to take medication as directed, the ability to identify and cope with adverse effects, and the ability to

communicate effectively about medication with health providers. For example, high continuity of community pharmacy care ensures a complete medication profile for each patient. With a complete medication profile, the pharmacist can then easily and accurately identify non-adherence by noting the number of days since the last dispensation. This information prompts the pharmacist to recognize potential non-adherence; allowing for discussions with the patient about the behavioural skills necessary to improve medication adherence.

Outcome domain

The outcomes domain represents the effect of the medication, the patient's objective and subjective health, and adverse effects. One way in which continuity of community pharmacy care can influence the outcomes domain is by decreasing the chance of adverse effects, and subsequent medication discontinuation. For example, muscular pain is the adverse effect most attributed to statin use and is the reason behind 30% of statin discontinuations.(65) Ingesting a statin with an interacting medication that increases the concentration of statin in the blood may promote muscle pain and subsequent non-adherence.(65,66) Pharmacists can help patients avoid this type of interaction, but only if the pharmacist has a complete medication profile for each patient, a computerized clinical decision support system to accurately identifies interactions and the skills to apply that information to individual patients.

In summary, continuity of community pharmacy care can influence each of the four domains of the IMB framework and therefore may affect adherence behaviour. There are, however, at least 30 behavioural change theories that could be used to describe medication-taking behaviour.(67) Because each of these theories is composed of a unique

combination of constructs and none of the theories fully contains all aspects of any other, it is possible that additional constructs not included in the IMB theory impact medication adherence.(67)

Independent of the IMB framework, the WHO has identified five groupings of factors that influence medication adherence. These factors may act as modifiers of the domains in the IMB framework. These are: patient, socioeconomic, provider, treatment, and health system factors.(1) In the following review, patient and socioeconomic factors have been combined. Significant factors that may affect medication adherence and continuity of care are reported, along with confidence intervals, when available.

2.3.1 Patient And Socioeconomic Factors Associated With Adherence

Numerous investigations have sought to determine patient factors associated with medication adherence. In an effort to categorize these factors, the Ascertaining Barriers for Compliance (ABC) study group conducted a systematic review of systematic reviews. Reviews were included if they were published in English between the year 2000 and 2009 and assessed determinants of medication adherence in an outpatient setting. The ABC study found 419 individual determinants of adherence. Of these, 162 different variables positively affected adherence, while 155 negatively affected adherence and 102 had no effect on adherence.(15) Quantitative testing was not done. In general, patients with a lower socio-economic status (SES) had worse adherence than patients with a higher SES. SES indicators in the ABC study included family support systems, education level, number of children in the household, social support, social disease stigma, drug costs, prescription coverage, wage and employment status.(15) Additional patient characteristics associated with non-adherence included younger age, male sex and

cognitive impairment. Being single, poor school performance, unstable housing, lack of health education and lack of hope in recovery were additional barriers to adherence. Additionally, high-risk behaviours such as alcohol abuse, substance abuse and smoking are associated with lower adherence.(15) The number of comorbid medical conditions was noted to increase adherence. In contrast to that finding a study by Yeaw and colleagues has shown that for each one point increase in comorbidity, measured by the Charlton Comorbidity Index, patients have 0.96 the odds of adherence compared to lower scores (95% CI: 0.95-.97).(68)

Specific to statins, a recent meta-analysis has shown that few patient characteristics influence statin adherence.(5) After testing 147 variables, only three patient characteristics were associated with non-adherence. Like the findings of the ABC study, patients with lower income status were 26% more likely to be non-adherent than patients with a higher SES (RR: 1.3, 95% CI: 1.2-1.6). Patients having fewer than two lipid tests prior to their statin prescription were 38% (RR: 1.4, 95% CI: 1.0-1.6) more likely to be non-adherent than patients with two or more tests and patients without a hypertension diagnosis were 16% (RR: 1.2, 95% CI: 1.1-1.2) more likely to be non-adherent than patients with hypertension. Age did not predict medication adherence. Benner and colleagues contradicted this finding when they found that patients aged 75 years and older had 1.2 (95% CI: 1.1-1.2) the odds of adherence compared to younger patients.(59) However, Benner's finding was not observed in a retrospective cohort of patients post MI. Multivariate analysis showed that patients aged 75 to 84 years old had 0.79 the odds of adherence compared to patients aged 65 to 74 years old ($p<0.01$). Patients 85 years and older experienced even lower odds of adherence, having 0.48 the

odds of adherence compared to the 65 to 74 year old age group over a follow-up period up to 30 months (P<0.0001).(69) Confidence intervals were not reported for these age groups.

A retrospective cohort study of over 14,000 patients enrolled in an American, private insurance plan was not included in the previously discussed meta-analysis.(70) This study indicated that females have 0.85 (95% CI: 0.79-0.92) the odds of statin adherence compared to males. The odds of adherence also decreased by 14% for each additional emergency department visit in the year prior to the first statin dispensation (OR: 0.86, 95% CI: 0.78-0.96).(70) Like Lemstra's meta-analysis, higher income quartiles were associated with 1.1 (95% CI: 1.1-1.2) the odds of adherence compared to lower income quartiles. Adding physician characteristics including sex, number of years in practice, country of training and medical specialty to the model did not significantly improve its predictive power.(70)

A second study not contained in the meta-analysis was a retrospective study of over 6,000 patients taking statins. Hierarchical regression models revealed that for each additional comorbid condition, adherence increased by 2% (p=0.002).(58) This study also showed that patients with a history of cardiovascular medication use were 14% more adherent than patients without this medication history (P<0.001). This study was not included in the meta-analysis conducted by Lemstra and colleagues because it measured adherence by a non-standard method.(5) Instead of reporting the ratio of the number of days of available medication to the number of days in the follow-up period, the number of 30-day refills obtained within the one-year period after the statin index prescription was summed and compared to the expected number. Patients with 11 or more refills in a

one-year time period were classified as adherent. Had the investigators used a standard calculation for adherence, it is unclear if the same association would have been observed.(58)

2.3.2 Provider Characteristics Associated with Adherence

Healthcare providers involved in the selection and dispensation of medication include physicians, nurse practitioners, dentists and pharmacists. Of these four health professions, the providers predominantly involved in medication delivery are pharmacists.

One of the first published research articles to examine pharmacy variables associated with medication adherence assessed statin use.(58) In that retrospective cohort study of over 6,000 patients, for each additional 100 statin prescriptions dispensed by the pharmacy over a two month period, adherence to statins increased by 2.5% ($p=0.001$). The study also assessed physician variables and found the opposite result. Over a two-month period, for each additional ten patients that a physician prescribed a statin to, adherence fell 6.7%. It was also determined that, of the variance in adherence that could be attributed to pharmacy or physician characteristics, pharmacy characteristics accounted for 62%, while physician characteristics made up the remaining 38%.(58) This study has limited generalizability because only patients with statin prescriptions of 30 days supply, who had not filled a statin in the 6 months prior to the index statin, and who were patrons of two large national pharmacy chains in the United States of America were included. Patients were excluded if they attended more than one pharmacy. The study may suffer from unmeasured confounding because socioeconomic variables were not

included in the analysis. However, the hierarchical regression model used may have minimized unmeasured confounding at the pharmacy level.

The type of pharmacy used may impact medication adherence. In a study using medical and prescription claims data from a Medicaid program in the USA, it was found that patients with type 2 diabetes who patronized independent pharmacies had higher adherence to antihyperglycemic medications than patients primarily using chain-franchise pharmacies ($p=0.009$).(71) The average adherence rate was 0.90 (SD ± 0.13) in the independent pharmacy group and 0.88 (SD ± 0.13) in the chain-franchise pharmacy group. After controlling for confounding variables, patients using independent pharmacies had 1.7% greater adherence over a 12 month follow up period than those receiving prescriptions at chain-franchise pharmacies ($p=0.03$). Confidence intervals for these associations were not reported. A similar association was seen in an analysis of urban pharmacies in Saskatchewan where patients using independent pharmacies had 1.4 (95% CI: 1.2-1.5) the odds of remaining adherent and patients using chain-franchise pharmacies had 1.4 (95% CI: 1.2-1.6) the odds of remaining adherent compared to patients using department mass-merchant pharmacies.(72)

Investigations have also found that patients are more likely to be adherent if their prescription was written by a specialist(15,73), if their physician assessed a greater number of patients each week(73), if the physician provided information about how to appropriately use the medication and on how the medication worked(15,74), if the doctor-patient relationship was considered to be of good quality(15), if a greater number of follow up and annual visits were planned or if refills were prescribed with the prescription.(15,58,73) A greater number of prescribers, unclear information provided by

the physician about proper medication use, a poor provider-patient relationship, poor patient-physician communication, inadequate discharge planning and inadequate follow-up by providers all had a negative impact on adherence.(15) Trust in the physician modified the relationship between patient household income and adherence. Patients with low physician trust and income between $10,000 and $15,000 per year had 2.6 the odds of non-adherence compared to patients with an income above $25,000 and high physician trust (95% CI: 1.6-4.3). Patients in the high trust group with a similar income did not experience a statistically significant drop in adherence.(64)

2.3.3 Treatment Characteristics Associated With Medication Adherence

The treatment characteristics associated with medication adherence encompass aspects of the medication regimen such as number of doses taken each day, the indication for the prescription, the therapeutic response and the adverse effects of the medication.

Refill consolidation, which is the act of filling multiple medications at the same time, was positively associated with medication adherence in a study assessing the relationship between therapeutic complexity and adherence. Subjects with complete refill consolidation were those who filled all long-term prescriptions at a single pharmacy visit. It was found that patients with complete refill consolidation had 8.4% increased adherence compared to patients with no consolidation ($p<0.001$).(75)

The number of refills prescribed with and the dose prescribed for each prescription also has an effect on adherence. In a retrospective cohort study of the prescription claims data from 6,436 statin users, adherence increased at a rate of 2% for each refill prescribed on the index prescription ($p=0.003$).(58) In the same study, patients taking a high dose statin (defined as a daily dose of more than 10 mg of atorvastatin or

simvastatin, more than 5 mg of rosuvastatin, and more than 20 mg of pravastatin daily) were 8% less adherent ($p<0.001$) to their medication compared to patients taking a low dose.(58) This may be due to an increase in adverse effects associated with higher statin doses.(76) The percent increase or decrease refers to the change in the total number of 30-day refills over the yearlong adherence measurement period.

The number of days supplied with each prescription may also impact medication adherence. In a retrospective cohort study of subjects using olmesartan, a type of antihypertensive medication, subjects who received 90 days supply of medication with each dispensation were 51% more likely to be adherent over the first year of treatment compared to subjects who received a 30 day supply with each dispensation (OR 0.49, $p<0.0001$).(77)

In Lemstra's meta-analysis of patients using statin medication, of 147 variables tested, two treatment variables had a significant effect on adherence.(5) Patients who used a statin to prevent a first cardiovascular event (primary prevention) were 52% more likely to be non-adherent to their medication than patients who used statins to prevent a recurrence of heart disease (RR 1.5, 95% CI: 1.5-1.5). Additionally, patients taking a statin for the first time were 46% more likely to be non-adherent than previous users of statin medication (RR: 1.5, 95% CI: 1.3-1.6).

2.3.4 Health System Characteristics Associated With Medication Adherence

The health system can modify adherence to medication by influencing overall access to care, the type of care provided (acute or chronic), and the duration of the provider-patient relationship.(6,15,78) Additionally, a lack of provider availability during times convenient to the patient, changing medication formularies and copayment for

medications have been found to negatively impact adherence.(5,58,73) In one study, patients making any copayment for statin medication were 28% more likely to be non-adherent than patients who made no copayment (RR: 1.3, 95% CI: 1.1-1.5).(5)

It is expected that rurality would also impact adherence because patients living in a rural environment my have decreased access to the health system. For example, rural patients may have a harder time accessing rural pharmacies than urban patients have accessing urban pharmacies. This could result in differing adherence rates between the two populations. Studies have shown that patients using rural treatment settings experienced either no effect or a decrease in adherence.(15)

2.3.5 The Interaction Of The Domains And Its Impact On Adherence

The four domains interact when patients and providers work together within the constraints of the health system to improve adherence. To date most interventions requiring additional practitioner interaction or patient action have not been successful. A systematic review and meta-analysis of randomized controlled trials of adherence interventions identified 93 novel interventions that attempt to improve adherence.(79) Less than half of the investigated interventions showed a significant improvement in adherence. Additionally, all interventions associated with increased adherence were complex, and involved combinations of increased convenience, additional follow up by providers, and group support. The review concluded that these complex interventions were minimally effective.

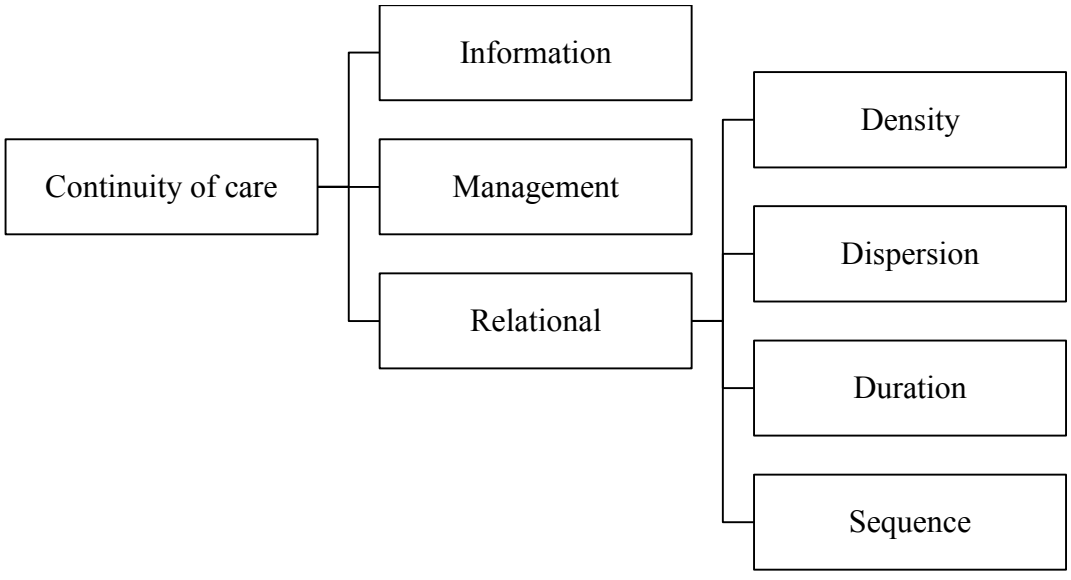
Passive methods to increase medication adherence focus on altering aspects of the medication taking process so that no additional action is required from the health practitioner or patient. For example, there is an inverse relationship between adherence

and daily dosing frequency; adherence increases as daily dosing frequency decreases.(80) As previously noted, refill consolidation may also be an effective passive method of improving adherence, because it is associated with 8.4% higher adherence compared to no consolidation, over a one-year follow-up period ($p<0.001$).(75)

2.4 The Use Of Administrative Data To Measure Continuity Of Care

There are three dimensions to continuity of care (Figure 2.1). Informational continuity links patient information from one provider to the next. Management continuity ensures that health providers administer care in a systematic and consistent manner over multiple diseases or conditions. The third component, relational continuity refers to a continuous therapeutic relationship between a health provider and a patient; linking past and present events.

Figure 2.1: Dimensions and domains of continuity of care



Relational continuity is further divided into four domains: duration, density, dispersion and sequence.(81) Duration is the length of time that a patient has been with a

provider. Density is a measure of the number of contacts a patient has with a specific provider. Dispersion is a measure of the number of distinct providers that a patient visits. Sequence accounts for the order in which providers are seen. A patient who has a high degree of density predominantly uses a single provider or provider group. This is similar to low dispersion, which indicates that the majority of interactions occur with a single provider or provider group.

There is no consensus among published literature on how to best measure continuity of care, nor are there any measurement tools or calculations that captures information of all three dimensions of continuity.(17,81) This has lead the Canadian Foundation for Healthcare Innovation to conclude that multiple measures of continuity of care are required to capture all three dimensions of continuity.(17)

In a systematic review, Jee and colleagues noted that 32 different tools may be used to evaluate continuity of care.(81) Of these, 28 measured one of the four aspects of relational continuity and 15 were calculated using information obtained from medical claims. Density was the most common domain of relational continuity measured, and was most commonly measured using the Usual Provider of Care (UPC) index.(81) Dispersion was the second most frequently measured domain of relational continuity and was most commonly measured using the Continuity of Care Index (COCI).(81)

Both the UPC and COCI produce a continuous variable of continuity between 0.0 and 1.0. Results close to 1.0 indicate high levels of continuity, and results close to 0.0 indicate low levels of continuity. Because the numeric results of each index have no inherent meaning, previous studies that have used continuity of care as an independent

variable have divided continuity into categories based on the distribution of the calculations or arbitrary cut points.(7,82-84)

2.5 Continuity Of Community Pharmacy Care And Adherence

It is thought that having a consistent therapeutic relationship with a healthcare provider or to a source of care such as a health clinic or pharmacy may positively influence adherence to medications.(1,6,85) Despite this, the relationship between continuity of community pharmacy care and medication adherence has been infrequently studied. A search of MedLine and Embase (Appendix A, Lines 11-16) has revealed a single abstract that provides information on the association between continuity of community pharmacy care and medication adherence. That study assessed the association between pharmacy loyalty, which was defined as the proportion of prescriptions redeemed at the most commonly used pharmacy, and medication adherence. This definition is the same as the UPC calculation used to calculate the density of relational continuity of care. Loyal subjects were those who obtained all of their medication from a single pharmacy and non-loyal subjects were those who used more than one pharmacy. The results indicate that in patients with schizophrenia living in Quebec, those who were loyal to their pharmacy over a one year period had 1.3 the odds of being adherent to their antipsychotic medication compared to non-loyal patients (OR: 1.3 95% CI: 1.1-1.5).(27) This study assumed that regular contact with the same pharmacy resulted in a complete medication profile and encouraged a strong provider-patient relationship, which then translated to increased information uptake and utilization, with subsequent improved adherence.

One additional study that attempted to find predictors of medication adherence touched on the concept of continuity of community pharmacy care. Choudhry and colleagues conducted a study designed to assess the relationship between therapeutic complexity and adherence, and found that for each additional pharmacy patronized, statin users experienced a 1.6% decrease in adherence over the subsequent year ($p<0.001$). This trend was also observed when assessing adherence to blood pressure lowering medication.(75)

The relationship between continuity of physician care and medication adherence has been assessed to a greater extent. Of the four studies identified, three show no effect,(6,23,24) and one shows a positive association between continuity of physician care and medication adherence.(7) In the most recent examination of this relationship, Chen and colleagues report that patient-physician pairs with a high continuity relationship had 3.4 the odds of being adherent to their medication than those who had low continuity over a seven-year period (95% CI: 3.2-3.6).(7) A significant increase in adherence was also seen between the medium and low continuity strata (OR: 1.8, 95% CI: 1.7-1.9). The impact of pharmacy or pharmacist variables was not considered.

2.5.1 Protopathic Bias In Previous Continuity Of Care Studies

The majority of studies that have assessed the relationship between continuity of care and any outcome (clinical, resource utilization, treatment plan compliance, or patient satisfaction) assess continuity of care concurrent with the outcome of interest. These studies are at risk of protopathic bias caused when the outcome of interest is assessed during the same time frame as the exposure.(25) For example, studies that assess continuity of care concurrent with medication adherence may incorrectly conclude that

continuity affects adherence, when, in fact, the opposite may be true. In a literature review conducted by van Walraven and colleagues, of the 100 studies identified that assess the association between continuity of care and any healthcare outcome, 82 measured continuity of care during the same time period as the outcome was assessed. This may have obscured the true associations in those studies.

In the one located study that assessed the association between continuity of community pharmacy care and medication adherence, Lauzier and colleagues have avoided this bias by measuring adherence to antipsychotic medication during the year after continuity was assessed.(27) Of the three located physician-patient continuity of care studies that are based on administrative data,(6,7,23) one has avoided this bias.(23) When designing studies to avoid this type of bias, it is assumed that past continuity behaviour is similar to continuity behaviour during the adherence assessment time period.

2.6 Factors Associated With Continuity Of Community Pharmacy Care

Few studies were located that determined the patient characteristics associated with continuity of community pharmacy care. The literature search yielded two studies that determined the sociodemographic characteristics of patients with high levels of continuity of community pharmacy care, as well as three additional studies which include concepts of continuity of community pharmacy care, but do not explicitly calculate it. In the most recent study, Lauzier and colleagues assessed continuity of community pharmacy care by the UPC, and categorized patients with a UPC equal to 1.0 as pharmacy loyal and patients with a UPC less than 1.0 as non-loyal. In Lauzier's study of patients with schizophrenia receiving antipsychotic medication, it was found that males were more likely to be pharmacy loyal (OR: 1.3, 95%CI: 1.2-1.4). Patients aged between

30 and 64 years (OR: 1.7, 95% CI: 1.5 – 2.0) and 65 years or greater (OR: 2.4, 95% CI: 2.0 – 2.9) had increased odds of loyalty when compared to patients between the ages of 20 and 29 years. Patients less likely to be pharmacy loyal had a lower SES (OR: 0.8, 95% CI: 0.7-0.9), a substance use disorder (OR: 0.7, 95% CI: 0.6-0.8), had been dispensed greater than four medication classes in the year prior to antipsychotic initiation (OR: 0.8, 95% CI: 0.7-0.9), and had visited an emergency the department in the year prior to antipsychotic initiation (OR: 0.7, 95% CI: 0.6-0.8).(27)

A second study conducted in Denmark assessed continuity of care using the UPC and found that the average proportion of prescriptions redeemed at a patient's most frequently used pharmacy was 0.93 (SD: 0.14), indicating a high level of relational continuity in the density domain.(19) Older age, male sex, high number of personal prescriptions, and the use of a pharmacy with no additional pharmacies nearby were all associated with a high UPC calculation. This study has limited generalizability because subjects were excluded from the analysis if they had filled less than ten prescriptions during the one-year follow-up period.(19)

Dutch researchers assessed the determinants of continuity of community pharmacy care among patients enrolled in a publically funded health insurance plan. Eighty-nine percent of patients attended only one pharmacy over the one-year study period. Patients more likely to attend multiple pharmacies were 40 years old or younger (OR: 1.7; 95% CI: 1.7-1.8) had three or more medications (OR: 2.9; 95% CI: 2.8-3.0) and had multiple types of prescribers (OR: 2.4; 95% CI: 2.4-2.5).(21)

In another study, the dispersion domain of relational continuity was investigated within a group of urban pharmacies in Saskatchewan.(28) Over a period of almost three

years, between 76% and 82% of patients redeemed at least 75% of their prescriptions from their index pharmacy. Patients using independent pharmacies were more likely to receive at least 75% of their medications from their index pharmacy than patients using chain-franchise or department mass-merchandise pharmacies.

A Canadian Institute for Health Information (CIHI) report of adverse drug reactions experienced by seniors showed that during the 2010-2011 year 69% of seniors used only one pharmacy.(29) This report indicated a much lower level of pharmacy exclusivity among a senior population than the previous investigation in the Netherlands.(21)

Additional data on characteristics associated with continuity of care are found in small survey based reports that examine the physician-patient relationship, not the pharmacy-patient relationship. A questionnaire to general practices in the Netherlands identified that patients who value relational continuity of care are more likely to have children or to have experienced a significant life event in the past five years.(86) What constituted a significant life event was not defined.(86) In a separate study, according to data gathered from children's mothers, disabled children have statistically worse continuity than non-disabled children ($p<0.001$).(87) Marital status, type of illness, education level, level of self perceived health, duration of illness or physician practice type or level were not significantly associated with placing value on continuity of care in survey reports.(86,88)

Both patient sex and the ability to travel to the practice location show conflicting associations with relational continuity of care. Schers and colleagues report that patient age is not associated with continuity, however; Aller and colleagues identified that

patients over the age of 35 years have twice the odds of experiencing relational continuity than patients aged 18-35 years.(86,88) Similarly, the association between the ability to physically travel to the site of care and continuity of care is unclear.(89,90)

Provider characteristics associated with continuity of care have also been discovered through the analysis of survey data. In order to determine the physician characteristics associated with long term patient-physician relationships Gabel and colleagues administered an ethnographic questionnaire to patients who had seen the same family physician for at least 15 years.(89) In that survey, the availability of the physician both during and outside of office hours, physician hospital or university affiliation and certain personal attributes such as caring, personable and dedication were identified by patients as being important to promoting long-term relationships with patients.(89) Patient responses indicated a commute to their physician's office inconvenienced by a far distance or heavy traffic would not prompt them to seek a more convenient physician; possibly indicating that patients prefer to maintain continuity of care if possible.(89) The results of a satisfaction survey of patients from 89 general medical practices in England found that satisfaction with continuity of care was associated with smaller patient rosters and being seen at a clinic that was not a training site.(91) It is important to note that the above variables are associated with satisfaction with continuity of care, and not continuity of care itself.

There is a paucity of research describing health system characteristics associated with continuity of care; however, orienting physician office hours towards the evening and offering telephone counseling and support to patients, as well as establishing professional links to physician clinics is thought to increase continuity of care.(92) The

College of Family Physicians of Canada has suggested that the growth of medical specializations, fragmentation of patient care services and an under-funded health system all negatively influence continuity of care.(93)

2.7 Factors Affecting The Relationship Between Continuity Of Care And Adherence

As both continuity of care and medication adherence may be influenced by factors at the patient, provider, treatment and health system levels, many variables may affect the relationship between continuity of community pharmacy care and adherence to statins.(1,6,92,94,95) These are described in the following section and detailed in Appendix C, Table C1.

Age

Age has been shown to have an inconsistent effect on adherence to medications. In a study by Choudhry and colleagues, patients aged 65 years and older were 5.3% more adherent to statins than younger patients ($P<0.001$).(75) In contrast, the authors of a large meta-analysis concluded that age did not significantly affect adherence to statins.(5) Similarly, the literature is contradictory about the effect of age on continuity of care.(86,88) Lauzier and colleagues report that patients aged 65 years and older have greater odds of continuity of care.(20) However, a patient survey administered at general medical practices in the Netherlands indicated that there is no significant relationship between a patient's age and their expressed need for personal physician continuity.(86) Additionally, a cross-sectional survey study conducted in Spain indicated that patients over age 35 years have twice the odds of using a single primary care physician at least two times for a single condition during the previous year than patients aged 18 to 35 years old.(88)

Gender

Gender has an inconsistent association with both adherence to medications and continuity of care. In some studies, women have shown lower adherence,(58,70) although, meta-analysis has not shown this association.(5) With respect to continuity of community pharmacy care, a retrospective cohort study showed that being male was associated with using only one pharmacy (OR: 1.3, 95% CI: 1.2-1.4) and a cross sectional survey identified that women place a higher value on continuity of physician care than do men (P=0.015).(20,96) In contrast, in a cross sectional survey, Schers and colleagues found no effect of gender on the value placed on continuity of physician care.(86) The relationship between the value on continuity of care and the actual continuity of care is not known.

Socioeconomic status (SES)

Patients with lower SES generally have lower adherence to medications.(15) A meta-analysis of statin users confirmed this finding, noting that patients of lower SES were 26% more likely to be non-adherent than those of higher SES (RR = 1.3, 95% CI: 1.2-1.4).(5) Patients of lower SES, as indicated by the receipt of government income assistance also experience lower continuity of community pharmacy care. These patients have 0.8 the odds of using a single pharmacy compared to patients not receiving assistance (OR: 0.8, 95% CI: 0.7-0.9).(20)

Hypertension Diagnosis

In a meta-analysis of statin users, patients without a diagnosis of hypertension are 16% more likely to be non-adherent than patients with a hypertension diagnosis (RR: 1.2; 95% CI, 1.1-1.2).(5) No quantitative link between the presence of hypertension and

continuity of care could be found in the literature however; having a hypertension diagnosis could result in more frequent visits to a pharmacy due to additional prescription medications. Using a higher number of medications has been linked to lower continuity of community pharmacy care.(20) If multiple hypertension medications are dispensed from multiple pharmacies, this could decrease continuity of care by dispersing treatment over many locations.

Hospitalization

Being hospitalized may influence medication-taking behaviour after hospital discharge. It is possible that the experience of being hospitalized promotes medication adherence if the patient becomes more aware of their poor health. Hospitalization may also influence continuity of community pharmacy care if patients bring new prescriptions to alternate pharmacies. Additionally, family members may fill new prescriptions for the subject at a different pharmacy than the patient usually attends if the patient is not able, upon discharge, to fill their own prescriptions. This could easily happen if new prescriptions are redeemed at community pharmacies that are sometimes located within hospital lobbies.

Statin Dose

A retrospective cohort study of an American linked pharmacy and medical claims database identified that patients who were non-adherent to statin therapy had 1.3 the odds of treatment escalation than non-adherent patients (95% CI: 1.3-1.4). Treatment escalation was defined as an increase in the daily statin dose or the addition of ezetamibe, a second lipid lowering medication.(97) This indicates that non-adherence influences the dose of the medication prescribed. In the other direction, a study of the pharmacy

prescription records from two national pharmacy chains in the United States suggested that patients taking a high dose statin have 8.8% worse adherence to statin medications than patients prescribed a low dose statin ($p<0.001$).(58) In that study adherence was based on the number of 30-day statin prescription refills, which is a non-standard secondary measure of adherence. Statin dose could also affect continuity of community pharmacy care. Patients prescribed higher dose statins may have worse cardiovascular disease than patients prescribed lower statin doses, which, in turn, may result in more frequent visits to a pharmacy.

Number of prescribers

Choudhry and colleagues have calculated that among statin users, for each unique prescriber, adherence decreases by 0.25 percentage points over the year after the statin prescription was redeemed ($p<0.001$).(75) Odds ratios and confidence intervals were not reported. Given the small absolute number, the clinical implications of this finding may be mild. It is conceivable that unique prescribers would also affect continuity of pharmacy care. For example, a unique prescriber is likely to be used if a patient receives their prescription in the emergency department, the hospital or from a walk-in clinic as opposed to their usual physician. If a patient receives this prescription at a time when their usual pharmacy is not open, they may be forced to use a different pharmacy, thereby impacting their continuity of care score. If this prescription is for an acute medication, such as an antibiotic, it may be important that the patient fill the prescription as soon as possible, rather than waiting for their usual pharmacy to open.

Number of medications used

The number of medications used may influence both medication adherence and continuity of community pharmacy care. Choudhry and colleagues found that for each additional medication dispensed to a patient, statin adherence increased by 0.89% ($p<0.001$). Similar to that result, Shalansky and colleagues identified that the odds of non-adherence decrease with each additional regularly scheduled medication (OR: 0.85, 95% CI: 0.74-0.96).(98) With respect to continuity of community pharmacy care, Lauzier and colleagues found that patients who used five to eight unique medications had 0.76 (95% CI 0.66-0.87) the odds of using the a single pharmacy for all of their dispensations, and patients who used over 8 medications had 0.59 (95% CI: 0.50-0.69) the odds of using a single pharmacy, compared to patients who used four or less medications.(20)

Number of physician visits

The number of physician visits may also influence both medication adherence and continuity of community pharmacy care. A greater number of physician visits could indicate a greater number of comorbidities or a higher comorbidity burden. Medication adherence decreases as comorbidity burden increases.(6) It has also been found that as the number of visits with a physician increases, adherence decreases. In a study by Shermock and colleagues, patients in the highest tertile of number of visits have 0.7 the odds of adherence compared to the lowest tertile (95% CI: 0.6-0.8).(6) It is also possible that the number of physician visits could impact continuity of community pharmacy care. A greater number of physician visits, could result in a greater number of prescriptions obtained by study subjects. These prescriptions may be redeemed at any pharmacy, thereby impacting the continuity of community care calculations.(16,99)

Place of residence

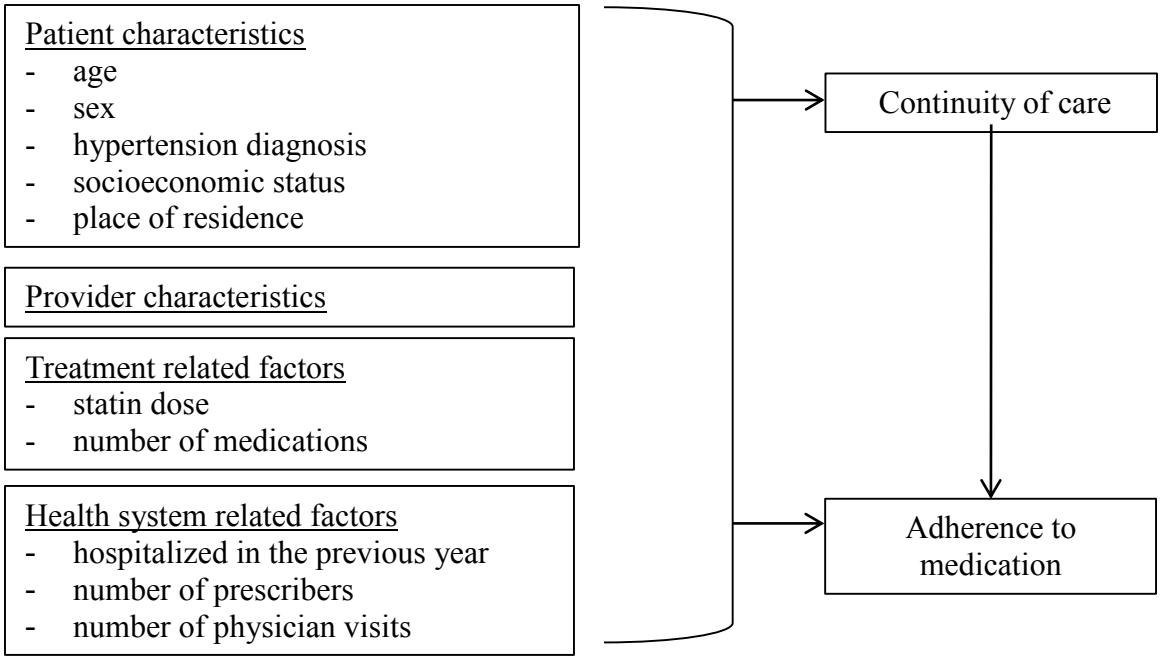
It is possible that living in an urban or rural environment could affect both medication adherence and continuity of community pharmacy care. Patients living in a rural environment may have greater difficulty traveling to their pharmacy to receive their medication, potentially disrupting adherence. Rural living may also impact continuity of care if patients from rural environments are more apt to fill prescriptions at multiple locations out of convenience while they accomplish other daily tasks, such as travel to work, physician appointments or to an urban area for any purpose, rather than make a separate trip to a specific pharmacy. However, patients living in rural areas may be more likely to use a single pharmacy if there is only one pharmacy nearby. Lauzier and colleagues report that patients living in rural areas tend to have greater odds of experiencing continuity of community pharmacy care, but the relationship did not achieve statistical significance (OR: 1.2, 95% CI: 1.0-1.4).(20)

In summary, patient age, sex, and socioeconomic status as well as having a hypertension diagnosis, the dose of statin prescribed, the number of medications used, the number of prescribers, the number of physician visits, whether or not their had been a hospitalization during the year prior to statin index, and place of residence may all affect the relationship between continuity of community pharmacy care and adherence to statins. Figure 2.2 displays factors that may affect the relationship between continuity of community pharmacy care and statin adherence. These factors have been grouped into patient, provider, treatment and health system related factors.

Additional previously discussed factors that may possibly affect the relationship, but are not available to include in the analysis are: the type of pharmacy used and if refills are prescribed with the prescription. Other factors which do not have an evidence base, but

may plausibly affect the relationship between continuity of community pharmacy care and medication adherence include: the location of the pharmacy used, the hours of operation of the pharmacy, the number of pharmacy staff at each pharmacy, the length of training of the pharmacist and other pharmacy staff, the number of years the pharmacist and pharmacy staff have been in practice, the number of patients served at each pharmacy, the indication for the prescription, if the patient has the ability to easily travel to the pharmacy, the patient's level of trust with the pharmacy staff, the health literacy of the subject, the level of social support that the patient had available to facilitate their adherence, the clinical effect and unintended effects that the patient experienced as a result of taking their statin. These additional factors were also unavailable for analysis.

Figure 2.2: Selected factors that may affect the relationship between continuity of community pharmacy care and adherence to statins.



Adapted from: WHO(1), Shermock(6), and Sturmberg(94).

Chapter 3: Objectives

The primary objective of this thesis is to estimate the association between continuity of community pharmacy care and adherence to statin medication among persons initiating statin therapy in Nova Scotia between 1998 and 2008. The hypothesis is that increased continuity of community pharmacy care is associated with greater medication adherence.

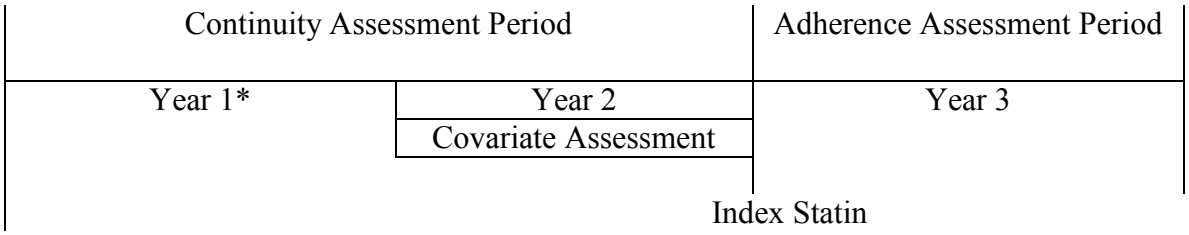
The secondary objective is to test the association between clinical and demographic variables and relational continuity of community pharmacy care in subjects initiating statin medication in Nova Scotia between 1998 and 2008. This will serve as hypothesis generating to guide future research.

Chapter 4: Methods

4.1 Design

This was a retrospective cohort study of subjects enrolled in the Nova Scotia Seniors' Pharmacare Program (NSSPP). Each subject had a maximum of three years of follow-up. Continuity of community pharmacy care was assessed at the time of the first (index) statin prescription, using dispensations that occurred during the two-year period prior to the index statin. Covariates were collected at the time of the index statin prescription, and were gathered from the one-year time period prior to the index prescription. Adherence was assessed during the one-year period immediately after the index statin prescription. All subjects with at least one year of information available in the NSSPP prior to their index statin were included in the analysis. The study timeline is detailed in Figure 4.1.

Figure 4.1: Study Timeline



4.2 Data Source

Data for this study were obtained from the Population Health Research Unit (PHRU) at Dalhousie University. The PHRU houses anonymously coded records from the NSSPP database, the Canadian Institute for Health Information Discharge Abstract

Database (CIHI-DAD), and the Medical Services Insurance (MSI) database. Appendix C, Table C1 shows the data obtained from each database.

The NSSPP database contains patient level information based on medications claimed for coverage. Enrollees in the NSSPP are seniors aged 65 years and older, and are residents of Nova Scotia with a valid Nova Scotia health card. Seniors cannot register in the program if they have any other public or private health insurance that covers most prescriptions.(100) The plan requires enrolled seniors to pay a yearly premium as well as a co-payment for their prescriptions. At the beginning of this study, in the 1998-1999 fiscal year, 88% of seniors in the province were enrolled in the program.(101) Ten years later, in the 2007-2008 year 70% of eligible seniors in NS were enrolled in the program, receiving a total of 3,255,724 prescriptions.(102) Of residents enrolled in the program in the 2007-2008 year, 99% claimed a medication for reimbursement.(102) In Nova Scotia, residents of long-term care facilities continue to have their medications reimbursed by the NSSPP. Typically, long-term care facilities have contracts with community pharmacies to dispense the medication required by the residents of each facility. The number of facilities with these contracts in place is not known. Records of medications dispensed in hospital or hospital outpatient clinics are not contained in the NSSPP. The NSSPP contains the following information used in this study: subject age, subject sex, date of statin dispensations, amount of statin dispensed, drug identification numbers (DIN), prescriber identification number and subject location (urban or rural). Urban or rural location was determined by using the second digit of the forward sortation area of the subjects' postal code. The digit zero signifies a rural area and digits greater than zero signify urban areas.

The CIHI-DAD contains a discharge summary of the demographic, administrative and clinical information from all hospital separations from acute care, same day surgery, rehabilitation or psychiatric facilities in Nova Scotia that have occurred between 1994 and 2012. The information from facilities in Nova-Scotia is sent directly to the CIHI-DAD from acute care facilities or their district health authorities. Until 2004, diagnoses and procedures were reported in the CIHI-DAD using International Classification of Diseases (ICD)-9, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) and ICD-9-CM (Clinical Modification) diagnosis codes. Beginning in 2004-2005 all data was reported using ICD-10-CA (Canadian Enhancement) and Canadian Classification of Health Interventions (CCI) codes. In Nova Scotia in 2007-2008, there were 57 institutions that reported 193,676 abstracts to the database.(103) Information retrieved from this database for the present study includes: being hospitalized in the year prior to the index statin, having a diagnosis of hypertension, diabetes, congestive heart failure or chronic kidney disease.

The MSI database contains dates and records of medically necessary insured physician services that are paid for by the Nova Scotia provincial health system. This database was used to determine the number of times a patient had been seen by a physician in the year prior to the index statin prescription.

The data from the CIHI-DAD and MSI Database had been linked to the NSSPP by PHRU research staff for use in a previous study.(104) Average 2001 household income was included as a measure of socioeconomic status and was estimated based on the average income of the 2001 census enumeration area in which the subject lived. Average 2001 household income was then linked to the dataset by PHRU research staff.

In order to ensure confidentiality, all data analysis was performed at the PHRU on a secure computer terminal.

4.3 Research Ethics Approval

Ethics review was obtained from the Dalhousie University Health Sciences Research Ethics Board on April 30, 2013 (file number 2013-2971).

4.4 Data Quality

The quality of data contained within the NSSPP has not been audited, however drug claims databases are generally thought to contain high quality data because the dispensing pharmacy is required to log claims with the drug plan in order to receive reimbursement for the medication dispensed.(32) The quality of prescription claims has been shown in assessments of two large provincial drug benefit databases. The accuracy of the data contained within the Ontario Drug Benefit (ODB) database is high. In an audit of over 5000 prescriptions obtained at 50 pharmacies in southern Ontario, only 0.7% of dispensations contained an error.(41) An audit of the Régie de l'Assurance Maladie du Québec (RAMQ) prescription claims database indicates that that the patient identification number and quantity dispensed were missing or contained impossible values in 0.4% of records.(40) Only 0.7% of data to indicate if the prescription was new or if the prescription is a refill was missing. The pharmacy identification number, date dispensed, drug class, prescribing physician identification number, drug identification number, and the duration of the prescription contained no missing or impossible values. The overall low percentage of missing or incorrect information indicates that the data quality in the RAMQ is high. While there is no published information on the accuracy of the data contained within the NSSPP, the NSSPP is a prescription claims database that is similar

to both the ODB and RAMQ databases; it is probable that the information contained within the NSSPP is of similar quality.

The CIHI-DAD is used in this study as a source of information on comorbid conditions. This data is subject to frequent audits by CIHI staff. In the audit of the 2007-2008 year, 84% of diagnoses from a selection of patient charts from Nova Scotia institutions were reported in the CIHI-DAD.(103) This indicates underreporting of comorbid conditions. The 2007-2008 audit has a higher sensitivity than the 2005-2006 audit. For the 2005-2006 fiscal year, 70% of diagnoses from a selection of patient charts from institutions in Nova Scotia were contained in the CIHI-DAD. Hypertensive disease was over-reported in 43% of cases, and diabetes was over-reported in 21% of cases.(105)

4.5 Subjects

Subjects were included if they were a member of the NSSPP at any time between January 1, 1996 and April 30, 2008 and had received a first prescription for a statin medication (Table 4.1) after January 1st 1998 and at least one year after enrolment in the program. Patients were identified in the NSSPP by ATC codes C10AA01- C10AA05 and C10AA07. These codes correspond to the statins currently available in Canada. This study is based on data retrieved for a previous study.(104) C10AA06 was not retrieved from the NSSPP for that analysis, and thus was not available for inclusion in this study. C10AA06 is the ATC code for cerivastatin, which was introduced to the Canadian market in 1998 and withdrawn in 2001 due to reports of rhabdomyolysis.(106,107)

Table 4.1 Included statin molecules

Molecule	WHO ATC Code
Simvastatin	C10AA01
Lovastatin	C10AA02
Pravastatin	C10AA03
Fluvastatin	C10AA04
Atorvastatin	C10AA05
Rosuvastatin	C10AA07

Subjects were excluded if they had; a first statin prescription prior to January 1, 1998; not been enrolled on the NSSPP for at least one year prior to the first statin prescription; a prescription code for cerivastatin (C10AA06), a diagnosis or procedure for dialysis or kidney transplant; or a prescription for any other cholesterol lowering medication (Table 4.2) within the 365 days prior to the first statin prescription. Subjects were also excluded if they had only one dispensation date for any medication, hereafter referred to as a pharmacy visit, prior to the index statin. The exclusion of cerivastatin as well as the diagnostic and procedure limitation is in place because the dataset had been previously prepared for another study that had excluded these subjects.(104)

Table 4.2: Exclusions applied to study sample

Exclusion Type	Details	Measurement
Medications	Lipid-modifying agents; WHO ATC: C10AB: Fibrates C10AC: Bile acid sequestrants C10AD: Nicotinic acid and derivatives C10AX: Other lipid modifying agents	Prescription claims
Diagnoses	Chronic Dialysis, kidney transplant	Discharge abstract data, physician fee-for-service claims
Procedures	Chronic Dialysis, kidney transplant	Discharge abstract data, physician fee-for-service claims

4.6 Follow-Up

Subjects were followed for a maximum of three years. The continuity assessment period was defined as at least one year but not more than two years prior to the index statin dispensation This period was chosen because statin medications in Nova Scotia are commonly filled at 30 to 90 day intervals, indicating a minimum of 4 prescriptions fills for chronic medications each year. Shorter continuity assessment periods could inflate the values of continuity for those subjects.(99) Additionally, continuity of care is a time dependent measure, and there was concern that minimizing the continuity assessment period to less than one year would not accurately depict relational continuity. This was a trade-off between adequate length to assess continuity and decreasing the number of eligible subjects in the dataset. Additionally, subjects with only one observation during the continuity assessment period were excluded from the analysis. This was done because at least two visits are required in order for a temporal relationship to be established and assessed.

The adherence assessment period was the one-year after the index statin prescription. Figure 4.1 illustrates the follow-up timeline.

4.7 Study Measures Preparation

The covariates were gathered by from the NSSPP database, the CIHI-DAD and the MSI database by PHRU staff prior to analysis by the investigators. A statistician at the PHRU linked these databases by a unique patient identifier. Upon receipt of the dataset, subject level data were checked for missing variables. Subject missing any information were retained for analysis after the missing values had been coded as "unknown".

4.7.1 Outcome: Adherence Calculation

Adherence was approximated by the MPR, which is an often-used indirect estimation of medication adherence. The MPR is the ratio of the number of days of medication supplied during the adherence period to the number of days in the adherence assessment period.(36) In this study, the MPR was calculated over the 365 days immediately following the first statin prescription. The MPR was calculated for the statin medication class, not for individual statins within the class of medications.

The MPR is a continuous measure between 0.0 and 1.0. Situations of oversupply, which may result due to early refilling or from a dispensation providing medication past the study end-point, will result in an MPR exceeding 1.0, theoretically indicating greater than perfect adherence. For example, a patient has 13 dispensations of 30 days supply of a statin over a 365-day period, the last of which occurred at day 360. Assuming perfect adherence over the 360 days, this patient would have retrieved 390 days of medication over the 365-day period and would have an MPR of 1.07. To account for this type of scenario, final dispensation amounts were truncated to the end of the study period. This is an accepted methods of adjusting an MPR > 1.0.(108,109)

4.7.2 Exposure: Continuity Of Community Pharmacy Care

Continuity of care was assessed in this study by two methods; the Usual Provider of Care (UPC) Index, and the Continuity of Care Index (COCI), which measure the density and dispersion of relational continuity, respectively.

All dispensations successfully submitted to the NSSPP, regardless of medication class, that occurred during the continuity assessment period were used to calculate the UPC and COCI. Subjects who redeemed multiple medications on the same fill date were

considered to have received one dispensation on that date in order to accurately reflect the number of contacts or visits with each pharmacy.

The UPC was calculated as follows(15):

$$UPC = \frac{n_j}{N}$$

Where, n_j is the number of visits to the pharmacy with the most dispensations during the continuity assessment period, and N is the total number of visits to all pharmacies during the continuity assessment period, measured by the number of unique dates for prescription claims during the continuity assessment period. The UPC is a continuous measure between 0.0 (if a subject sees a different pharmacy for every fill), and 1.0 (if a subject uses the same pharmacy for every fill). The UPC is also referred to as "pharmacy loyalty" or the "fidelity coefficient" in previous studies.(19,20)

The COCI was calculated as follows(99):

$$COCI = \frac{\sum_{j=1}^{m} n_j^2 - N}{N(N-1)}$$

Where N is the total number of pharmacy visits in the continuity assessment period, n_j is the number of visits to the same pharmacy, $_j$. The number of pharmacy visits influences this measure, which is consistent with the concept of continuity.(99) When the COCI was developed, the numerator was the sum of un-referred physicians a subject had utilized, that is, the number of physicians seen in addition to their primary physician. We adapted this to be the sum of pharmacies used.

4.7.3 Covariates

Ten potential confounders that may influence the exposure-outcome relationship were determined *a priori*, based on the current literature, biological/social plausibility and the ability to calculate them. Demographic variables measured at the time of the first statin dispensation included: subject age, sex, hypertension diagnosis, average 2001 household income by census enumeration area, and urban or rural place of residence. A binary variable indicated statin dose (low or high), the use of greater than four distinct drugs, hospitalization in the year prior to index, and having greater than four physician visits in the year prior to index. The number of unique statin prescribers was measured during the 365 days after the index statin dispensation.

Age was divided into a categorical variable based on five-year groupings, between ages 65 years and 80 years old. Subjects aged 80 years and older were categorized into a single group. Gender was approximated in this study by the sex variable contained in the NSSPP database. Average 2001 household income was used as an estimate of socioeconomic status and was divided into tertiles. A categorical variable for statin dose was created: subjects were considered to be using a high dose statin if they had been dispensed rosuvastatin ≥10mg, atorvastatin ≥20mg, or simvastatin ≥40mg. Patients were considered to be using a low dose statin if they had been dispensed atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose statins are expected to reduce LDL cholesterol by approximately 40% from baseline. This definition was based on a meta-analysis of the summary estimates from 164 short-term randomized placebo controlled trials.(110)

For analysis of factors associated with continuity of community pharmacy care, a composite variable for cardiovascular disease was created. Subjects were considered to

have cardiovascular disease if they had received a diagnosis of hypertension, congestive heart failure or chronic kidney disease. This covariate is used in the analysis of factors associated with continuity of community pharmacy care, not in determining the strength of the association between continuity of community pharmacy care and medication adherence. All other covariates were dichotomous variables and did not require further manipulation. Appendix C, Table C1 contains a complete description of variables contained in the data set.

4.8 Analysis

Statistical analysis was completed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). The statistical significance for all statistical tests was set to $\alpha = 0.05$.

4.8.1 Association Between Continuity Of Community Pharmacy Care And Statin Adherence

To determine the association between continuity of community pharmacy care and statin adherence, the following analysis was conducted separately for both continuity of care measured by the COCI and continuity of care measured by the UPC. The analysis was conducted at the level of the pharmacy that dispensed the index statin prescription. Subjects were considered to be adherent if their MPR was ≥ 0.80, which is the usual cut-point for signifying adherence to cardiovascular medications.(31,32,34)

In the primary analysis the COCI and UPC were analyzed as continuous variables. Hierarchical regression, clustered by index pharmacy was used to estimate the strength of association between continuity of community pharmacy care and adherence to statins. The hierarchical model was used to take into account the variability at both the pharmacy and subject levels, while allowing the pharmacy effect to be

analyzed.(111,112) In addition to the continuity of care indices, the final model was designed to contain the ten selected patient level covariates.

Sensitivity analysis was conducted by dividing the UPC and COCI into different strata (Appendix B, Figure B1a and Figure B1b). First, the continuity measures were divided into two strata: complete continuity (if the UPC or COCI was equal to 1.0) and incomplete continuity (if the UPC or COCI was less than 1.0). In the second sensitivity analysis, the incomplete continuity stratum was further divided into tertiles, leaving four strata (complete, high, moderate and low). A third sensitivity analysis was conducted by defining adherence as an MPR of 0.75, and as an MPR of 0.90. This was done to explore other adherence cut points for long-term cardiovascular medications.(113)

Additional sensitivity analyses were performed by restricting the study population to: 1) subjects living in urban areas, 2) subjects who had been hospitalized in the year prior to their index statin because these populations may have altered adherence or continuity behaviour. A final sensitivity analysis restricting the study population to subjects who had filled 13 or less statin prescriptions during the adherence assessment period was also conducted. Thirteen or less prescriptions are expected to be filled during a one-year period if each prescription is for a 30-day supply.

4.8.2 Predictors Of Continuity Of Community Pharmacy Care

Logistic regression models were used to calculate odds ratios and 95% confidence intervals for factors that may be associated with continuity of community pharmacy care. Subjects with incomplete continuity of community pharmacy care scores were compared to subjects with complete continuity of care scores. Incomplete continuity of care scores are those below 1.0 and complete continuity of community pharmacy care scores are

equal to 1.0. Predictors of continuity of community pharmacy care were measured during the final 365 days of the continuity assessment period. Each predictor was first assessed individually and then together in a multivariate logistic model. All individually tested variables were included in the multivariate logistic model. The dependent variable was continuity of care, as determined by the UPC. Potential predictors of continuity of community pharmacy care were determined *a priori,* based on a literature review. This objective was hypothesis generating. Therefore, a parsimonious model was not constructed because this study did not attempt to determine the best fit for the data. Rather, the objective was to determine the variables that may be important in future modeling.

Sensitivity analysis was completed, limiting the study population to subjects living in urban areas and to subjects who had been hospitalized in the final year of the continuity assessment period.

4.9 Sample Size Calculation

In order to have power ($\beta = 0.2$) to show a significant difference ($\alpha = 0.05$) in adherence between continuity cohorts, 303 subjects were needed in each of the three continuity tertiles.

It was assumed that the proportion of subjects who experienced adherence in the low continuity strata would be between 0.40 and 0.55. This range of probabilities was chosen based on previous adherence studies, which have indicated similar levels during the year after initiating statins or other long-term medications.(1,4,5,7,59)

It was assumed that odds ratios of 1.5 and 3.5 for the difference between the low and medium continuity tertiles and the low and high continuity tertiles, respectively,

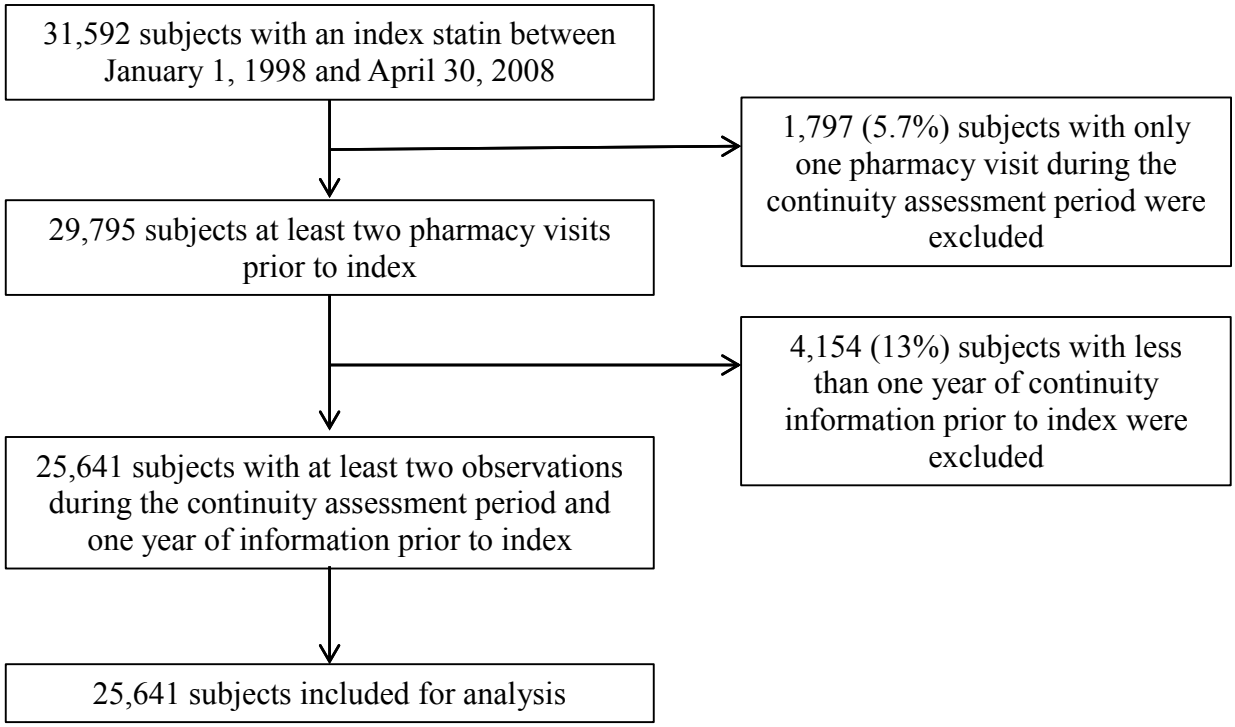
would be observed. These estimates were based on a previous study by Chen and colleagues which estimate an odds ratio of 3.4 for a high continuity tertile compared to the low continuity tertile, and an odds ratio of 1.9 for a medium tertile compared to the low continuity tertile.(7)

Chapter 5: Results

5.1 Description Of The Study Population

There were 31,592 subjects with an index statin prescription between January 1, 1998 and April 30, 2008 who met inclusion criteria. These subjects were dispensed a total of 1,532,464 prescriptions in the two years prior to their index statin. Subjects with a single pharmacy visit during the two years prior to index were excluded, as well as those with less than one year of information available during the continuity assessment period, leaving 25,641 (81%) subjects in the dataset. Figure 5.1 details the process of subject selection.

Figure 5.1: Subject Selection



Demographic characteristics of the study population are found in Table 5.1 at the end of this chapter. Females composed 59% of the population. The majority of subjects were under 75 years old, with 19% were over 80 years old. The mean age was 74 years

(SD: 6.0) and the mean annual household income for the data was $46,500 (SD: $16,000). The majority of subjects had been dispensed greater than four different medications (80%), had greater than four visits to the doctor (91%), had a diagnosis of hypertension (57%), and had not been hospitalized (62%), in the year prior to the index statin prescription. Most subjects received a low dose statin (67%) as their index prescription. During the continuity assessment period subjects used a mean of two pharmacies; made a mean of 30 pharmacy visits to a pharmacy (Appendix B, Figure B2) and received a mean of 51 individual prescriptions. During the adherence assessment period, subjects were dispensed a statin a mean of six times. The average days of medication supplied at each statin dispensation was 49 (Appendix B, Figure B3)

Continuity of community pharmacy care, calculated using the UPC, was skewed towards 1.0. Sixty one percent of subjects had a UPC equal to 1.0. The mean UPC was 0.92 (SD: 0.15). Among the 39% of patients with a UPC less than 1.0, the mean UPC was 0.79 (SD: 0.17). The COCI also indicated that 61% of subjects had a score of 1.0. Like the UPC, the distribution was skewed towards 1.0, with a mean score of 0.87 (SD: 0.21). Of the subjects with a COCI less than 1.0, the mean COCI was 0.68 (SD: 0.21). The complete continuity strata measured by the UPC was identical to the complete continuity strata measured by the COCI. Histograms of the distribution of the UPC and COCI are contained in Appendix B, Figures B4-B7. In each figure, the x-axis is continuity of community pharmacy care and the y-axis is the percent of subjects. The UPC and the COCI were highly correlated, having a correlation coefficient of 0.98. Given that the UPC and COCI are highly correlated, the results of multivariate models are reported for the UPC only. A scatterplot of the relationship between the two

continuity indices is found in Appendix B, Figure B8. Appendix D, Table D1 provides further description of continuity of community pharmacy care in the study population.

The mean MPR for the study population was 0.73 (SD: 0.31), and was skewed towards 1.0 with 59% of subjects having an MPR greater than or equal to 0.80. Appendix B, Figure B9 and Appendix D, Table D2 provide further description of medication adherence in the study population.

5.2 Unadjusted Relationship Between Continuity Of Community Pharmacy Care And Statin Adherence

Table 5.2 shows the unadjusted relationship between continuity of community pharmacy care and statin adherence. The ratio between the Pearson chi-squared and the degrees of freedom was 1.0. Analysis of the UPC as a continuous variable revealed that for each 0.10 increase in continuity of community pharmacy care there was a non-significant 2% increase in the odds of statin adherence over the subsequent year (OR 1.02, 95% CI: 1.00-1.03). Analysis of the UPC as a dichotomous variable or as four strata did not change the relationship. Analysis of the COCI showed a nearly identical result.

5.3 Multivariate Relationship Between Continuity Of Community Pharmacy Care And Statin Adherence

The results of the adjusted relationship between continuity of community pharmacy care, measured by the UPC, and statin adherence are found in Table 5.3. This model included variables listed in Appendix C, Table C1. Four percent of the total variance in the model occurred between pharmacies. (intraclass correlation: 0.04, $p<0.0001$)

After adjustment, for each 0.10 increase in continuity of community pharmacy care, there was a 3% increase in the odds of statin adherence over the subsequent year

(OR: 1.03, 95% CI: 1.00-1.05). In this model, females, subjects using four or less medications, subjects without hypertension and subjects with lower income had decreased odds of adherence. Subjects with more than one statin prescriber had increased odds of adherence compared to subjects with only one statin prescriber. Place of residence had no impact on adherence.

Sensitivity analyses are reported in Appendix D, Tables D3-D9. Altering the adherence cut-point to a MPR of either 0.75 or 0.90 did not markedly change the relationship between continuity of community pharmacy care and statin adherence. Subjects with a MPR $\geq$ 0.75 had 4% increased odds (95% CI: 1.02-1.05) and subjects with a MPR $\geq$ 0.90 had a 2% increased odds of adherence (95% CI: 1.01-1.04). Creating different continuity strata also did not significantly alter the relationship between continuity of community pharmacy care and statin adherence.

Restricting the study population to subjects residing in urban areas at the time of the index statin dispensation showed that for each 0.10 increase in continuity of community pharmacy care, there was a 2% increase in the odds of statin adherence (95% CI: 1.00-1.04), and for rural residents there was a 4% increase in the odds of adherence (95% CI: 1.01-1.07). Among subjects who had been admitted to hospital during the year prior to their index statin dispensation, for each 0.10 increase in continuity of community pharmacy care, there was a non-significant 2% increase in the odds of statin adherence (95% CI: 0.99-1.05). Among subjects with 13 or fewer statin dispensations, for each 0.10 increase in continuity of community pharmacy care, there was a 3% increase in the odds of statin adherence (95% CI: 1.03-1.05).

5.4 Predictors Of Continuity Of Community Pharmacy Care

Appendix D, Table D10 shows the demographic characteristics of subjects with complete continuity of community pharmacy care and those with incomplete continuity of community pharmacy care.

The unadjusted and adjusted relationship between predictor variables and complete continuity of community pharmacy care, defined as a continuity of care score equal to 1.0, are detailed in Table 5.4. The adjusted model contains all variables reported in Appendix C, Table C1. Selected results are reported below.

The adjusted model shows that taking four or less medications was associated with 1.5 the odds of complete continuity of community pharmacy care compared with taking greater than four medications (95% CI: 1.4-1.7). Subjects who saw a physician four or less times had 1.4 the odds of experiencing complete continuity of community pharmacy care compared to subjects who saw a physician more than four times (95% CI: 1.2-1.5). Subjects who were not hospitalized during the final year of continuity assessment had 1.3 the odds of complete continuity of community pharmacy care compared to subjects who were hospitalized (95% CI: 1.2-1.4). Female sex was associated with 0.9 the odds of complete continuity of community pharmacy care (95% CI: 0.8-0.9). After adjustment, place of residence was not associated with a statistically increased odds of experiencing complete continuity of community pharmacy care. Additional results are reported in Appendix D, Table D11

Two sensitivity analyses were conducted which involved restricting the population based on 1) place of residence, and 2) hospitalization status in the year prior to statin index. The results of this sensitivity analysis are presented in Appendix D, Tables

D12 and D13. The results were mostly similar to the primary analysis; however, in both analyses the presence of diabetes became associated with increased odds of experiencing complete continuity of care.

Table 5.1: Demographic characteristics of subjects who met inclusion criteria[e]		
N = 25,641		%
Age (years)	65-69	30
	70-74	29
	75-79	22
	≥ 80	19
Sex	Male	41
	Female	59
Income[a]	High	32
	Moderate	32
	Low	32
	Unknown	4.0
Place of Residence	Urban	59
	Rural	41
Use of greater than four medications[b]	Yes	80
	No	20
Hospitalized[b]	Yes	38
	No	62
Greater than four physician visits[b]	Yes	91
	No	9.0
Statin Dose[c]	High	33
	Low	67
HTN[d]	Yes	57
	No	43
	Mean	SD
Age	74	6
Income	46,500	16,000
Pharmacies used[b]	2	1.0
Pharmacy visits[b]	30	23
Dispensations[b]	51	39

[a]Average 2001 household income in thousands of dollars, by census enumeration area
[b]During continuity assessment period
[c]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[d]Hypertension
[e]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table 5.2: Unadjusted odds ratio of the strength of the association between continuity of care and statin adherence, defined as a Medication Possession Ratio (MPR) ≥ 0.80, among subjects meeting inclusion criteria[d]

		UPC[a]		COCI[b]	
Level of Continuity		OR	95% CI	OR	95% CI
Continuous		1.02	1.00-1.03	1.01	1.00-1.03
1.0		1.0		1.0	
<1.0		0.96	0.91-1.01	0.96	0.91-1.01
1.0		1.0		1.0	
<1.0	High[c]	1.01	0.93-1.09	1.01	0.94-1.10
	Moderate[c]	0.92	0.85-0.99	0.91	0.84-0.99
	Low[c]	0.95	0.98-1.03	0.95	0.88-1.03

[a]Usual Provider of Care Index
[b]Continuity of Care Index
[c]Continuity tertiles created from subject scores <1.0. high = highest tertile, Moderate = second tertile, Low = lowest tertile
[d]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table 5.3: Adjusted relationship between continuous Usual Provider of Care (UPC) index and statin adherence among subjects meeting inclusion criteria[h]

		MPR ≥80[b]	
		OR	95% CI
UPC[a]		1.03	1.01-1.05
Sex	Male	1.00	
	Female	0.94	0.89-0.99
Age (years)	≥ 80	1.00	
	75-79	1.13	1.04-1.22
	70-74	1.17	1.08-1.26
	65-69	1.11	1.02-1.19
Income tertile[c]	High	1.00	
	Mod	0.91	0.85-0.97
	Low	0.86	0.80-0.92
	Unk[g]	0.99	0.86-1.15
Place of Residence	Urban	1.00	
	Rural	0.96	0.90-1.03
Use of greater than four medications[d]	Yes	1.00	
	No	0.91	0.85-0.98
Hospitalized[d]	Yes	1.00	
	No	0.95	0.90-1.01
Greater than four physician visits[d]	Yes	1.00	
	No	0.96	0.87-1.06
Statin Dose[e]	High	1.00	
	Low	1.02	0.97-1.08
Hypertension	Yes	1.00	
	No	0.85	0.81-0.89
Prescribers[f]	1	1.00	
	>1	2.45	2.29-2.61

[a]Usual Provider of Care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table 5.4: Unadjusted and adjusted odds ratios of the relationship between complete continuity of care, measured by the Usual Provider of Care Index (UPC), and sociodemographic and clinical variables in Nova Scotia Seniors Pharmacare beneficiaries meeting inclusion criteria[e]

n=25,641		Unadjusted		Adjusted	
		OR	95% CI	OR	95% CI
Age (years)	≥80	1.00		1.00	
	75-79	1.17	1.28-1.48	1.11	1.03-1.20
	70-74	1.17	1.09-1.26	1.05	0.98-1.13
	65-69	1.38	1.09-1.27	1.19	1.10-1.28
Sex	Male	1.00		1.00	
	Female	0.88	0.83-0.92	0.89	0.84-0.93
Income[a]	≥80	1.00		1.00	
	60<80	1.00	0.84-1.17	1.00	0.85-1.18
	40<60	1.14	0.98-1.32	1.15	0.99-1.34
	20<40	1.16	0.99-1.35	1.18	1.01-1.38
	≤20	1.24	0.86-1.79	1.34	0.92-1.94
	Unk[d]	0.80	0.66-0.98	0.82	0.67-1.00
Place	Urban	1.00		1.00	
	Rural	1.06	1.00-1.11	1.02	0.97-1.08
Use of greater than four	Yes	1.00		1.00	
medications[b]	No	1.80	1.69-1.92	1.54	1.44-1.65
Hospitalized[b]	Yes	1.00		1.00	
	No	1.46	1.39-1.54	1.30	1.23-1.38
Greater than four physician	Yes	1.00		1.00	
visits[b]	No	1.82	1.65-2.00	1.35	1.22-1.50
CVD[c]	Yes	1.00		1.00	
	No	1.08	1.03-1.14	0.97	0.92-1.02
Diabetes	Yes	1.00		1.00	
	No	1.13	1.07-1.20	1.06	1.00-1.12

[a]Average 2001 household income, thousands of dollars, by census enumeration area
[b]During the final year of continuity assessment
[c]Composite of congestive heart failure, chronic kidney disease and hypertension
[d]Unk: income unknown
[e]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Chapter 6: Discussion

6.1 Summary Of Results

Improving medication adherence is a pressing problem for health systems the world over.(1) In Canada, over 40% of the population has hypercholesterolemia, a major risk factor for CVD.(44) Of these persons, between 21% and 63% are not taking drug therapy for the condition.(55,114) Among patients treated for hypercholesterolemia, up to 49% percent do not have the condition well controlled.(55) A lack of adherence to prescribed medications may be one reason for this.

The first objective of this thesis was to determine the association between continuity of community pharmacy care and medication adherence. It was hypothesized that higher levels of continuity of community pharmacy care were associated with increased statin adherence. The results of multivariate hierarchical regression indicate that for each 0.10 increase in continuity of community pharmacy care, there was a 3% increase in the odds of statin adherence over the subsequent year (95% CI: 1.01-1.05). This indicates that patients who obtain medication from a lower number of pharmacies tend to have better adherence to statins. The ratio between the Pearson chi-squared and the DF was 1.0, indicating that the logistic regression model used fit the data well. The between pharmacy variation contributed a significant effect to the model ($P<0.0001$), indicating that there was significant variability between pharmacies; justifying the clustering used.

The secondary objective was to determine the sociodemographic and clinical characteristics of subjects that are associated with continuity of community pharmacy care. We found that the use of four or less medications, not being hospitalized, and

having four or less physician visits was associated with complete continuity of community pharmacy care. We also found that females had decreased odds of experiencing complete continuity of community pharmacy care. Sensitivity analysis did not significantly change these findings.

6.2 Contextualization Of The Results

The level of adherence and continuity of community pharmacy care scores obtained in this thesis are similar to those reported in prior research. In this study, 58% of subjects had a MPR of 0.80 or above and were classified as adherent to their statin over the one-year follow-up period. This is similar to previous studies assessing statin adherence, which report adherence rates close to 50% after one year.(5,70,115)

The average continuity of community pharmacy score calculated using the UPC was 0.92, and 61% of subjects attended a single pharmacy during the continuity assessment period. Lauzier and colleagues observed that 58% of subjects attended a single pharmacy for their prescriptions; a similar result to our study.(20) However, our result is much lower than that of a study in the Netherlands, where 89% of subjects attended a single pharmacy for all of their prescriptions, and lower than a recent CIHI report which found that 69% of seniors in Canada used only one pharmacy during a one year period.(21,29) Table 6.1 summarizes how our result compares to other studies.

Pottegard and colleagues assessed the UPC as a continuous variable and observed an average UPC of 0.93 in a cohort of patients in Denmark, nearly identical to the average UPC observed in our study.(19) The average continuity of community pharmacy care score in our study, calculated using the COCI, was 0.88. This cannot be compared

to other populations because there exists no peer-reviewed studies, indexed by common bibliographic software that use this measure.

Table 6.1: Comparison of complete continuity of community pharmacy care (subjects using only one pharmacy) among studies that report the metric

	Current	Lauzier(20)	CIHI(29)	Buurma(21)
One pharmacy[a]	61%	58%	69%	89%
Country	Canada	Canada	Canada	Holland
Population	Seniors aged 65 and older, enrolled in the NSSPP[b]	Adults 20 years and older, with a diagnosis of schizophrenia, enrolled in the RAMQ[c]	Seniors in Alberta, Manitoba and Prince Edward Island	Beneficiaries of the Social Health Insurance Act[d]
Years	January 1, 1996-April 30, 2008	January 1, 2000-December 31, 2005	2010-2011	January 1, 2001-December 31, 2001

[a]Complete Continuity of Community Pharmacy Care
[b]Nova Scotia Seniors Pharmacare Program
[c]Régie de l'Assurance Maladie du Québec
[d]Employees making less than 33,000 Euro per year, social security recipients and selected elderly groups.

The UPC and COCI were highly correlated, having a correlation coefficient of 0.98. To our knowledge, this finding has not been previously reported.

We found that the odds of adherence increased by 3% with greater continuity of community pharmacy care. This small benefit indicates that continuity of community pharmacy care probably has a smaller effect on adherence than other factors such as age, sex, and pharmacy type; all of which have been associated with odds ratios of greater magnitude.(5,70,72,98)

The finding that continuity of community pharmacy care is associated with increased odds of medication adherence is not the first time this relationship has been observed. Lauzier and colleagues presented research at the 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, which investigated this

relationship.(27) In their analysis of adult subjects with schizophrenia, subjects using a single pharmacy for all of their dispensations had 1.3 the odds of adherence to antipsychotic medications compared to subjects using more than one pharmacy. Our study differed from Lauzier's work because we assessed the relationship among an elderly population who were taking a long-term cardiovascular medication.

Lauzier's study measured continuity of community pharmacy care by the same calculation used in this study, however, rather than analyzing continuity of community pharmacy care as a continuous variable; continuity was dichotomized into complete (UPC = 1.0) and incomplete (UPC < 1.0) continuity.

We conducted a sensitivity analysis by dividing our study population into complete and incomplete continuity, which is directly comparable to Lauzier's work. In our sensitivity analysis we found that subjects with complete continuity of community pharmacy care had 1.1 the odds of statin adherence compared to subjects with incomplete continuity of community pharmacy care (OR: 1.1 95% CI: 1.0-1.2). While Lauzier's result has a greater magnitude of effect than the result seen in the present study, however the direction of the association is the same.

Lauzier's result may have had a greater magnitude because they studied the relationship between continuity of community pharmacy care and adherence in subjects with schizophrenia, not in persons with cardiovascular disease. It is possible that the quality of the provider-patient relationship may be of greater importance to medication adherence in persons with schizophrenia than in persons with cardiovascular disease. There is evidence that for patients with schizophrenia, a strong therapeutic relationship with a physician is associated with a 20% increase in the odds of adherence (OR: 1.2,

95% CI: 1.0-1.4).(116) No studies could be located that assessed the effect of the quality of the physician-patient on adherence relationship in persons taking statins.

The consequences of medication non-adherence in schizophrenia may be more noticeable than in cardiovascular disease. Therefore, medication adherence could also be higher in Lauzier's study because a patient with schizophrenia may be more motivated to be adherent. For the same reason, pharmacists may also be more likely to highlight the importance of medication adherence to patients with schizophrenia. Because complete continuity of community pharmacy care will result in a complete medication profile, the pharmacist can easily identify and take steps with patients to correct non-adherence. If the pharmacist is more likely to stress the importance of medication adherence to patients with schizophrenia than to patients with cardiovascular disease, this could be the reason for the increased magnitude seen in Lauzier's study.

Secondly, Lauzier's research may suffer from unmeasured confounding, which may have inflated the magnitude of the effect. The research is currently published in abstract form only, so a full description of their analysis plan is not available. However, it appears that Lauzier and colleagues did not cluster their subjects at the index pharmacy. In an attempt to minimize confounding at the pharmacy level, we clustered subjects at the index pharmacy.

Our adjusted model showed that subjects who used greater than four medications had increased odds of adherence. This finding was not expected, because taking an increased number of medications is thought to be associated with non-adherence.(1,15,75) This result is not unprecedented though, as Shalansky and colleagues have reported that the odds of adherence are 1.2 (95% CI: 1.0-1.4) for each additional

regularly scheduled daily medication among subjects treated for cardiovascular disease.(98). Additionally, Grant and colleagues, report that adherence levels increase 1.3% for each additional medication that the patient is taking ($p<0.001$).(117) It is possible that subjects using an increased number of medications may be more regimented with their medication taking behaviour, and as a result, have higher adherence rates. It could also be that subjects with more than four medications are more likely to have assistance taking their medications through homecare services or by the help of family or friends. This might have resulted in higher adherence in those subjects. In Nova Scotia, 8.4% of the senior population uses homecare support.(118) Subjects taking more medications may also be in poorer health than subjects taking less, and therefore, they may value and practice medication adherence to a greater extent than their healthier counterparts.

The adjusted model also showed that subjects who had greater than one statin prescriber had an increased odds of medication adherence. This finding was not expected, as previous work has indicated that for each additional prescriber used, statin adherence falls by 0.25 percent ($P<0.01$).(75) However, it is possible that greater than one prescriber could positively impact medication adherence. For example, a subject may have used a second prescriber at a walk-in clinic or at the emergency department if they could not attend their usual physician to get a new prescription. Subjects could have also obtained continuations of their statin prescriptions at outpatient clinics. However, this is unlikely as an outpatient clinic physician will generally not write or renew prescriptions for conditions outside of their specialty. By attending a second physician for a new prescription, subjects will avoid the gap in their therapy that may have resulted if they

had waited until their usual physician was able to see them. In this way, a second prescriber may increase adherence.

A second instance in which it is possible for greater than one prescriber to be associated with increased medication adherence is if the additional prescribers are hospital-based physicians. For example, if a subject has had their statin started by an inpatient physician during a hospitalization, they may have had it continued by their family physician. If an inpatient physician initiates a patient on a statin, it is possible that it is being initiated for secondary cardiovascular prevention. Because adherence rates to statins for secondary prevention are higher than for primary prevention, this could account for the increased odds of adherence observed in subjects with more than one prescriber.(57)

The secondary objective of this thesis was to determine sociodemographic and clinical characteristics associated with continuity of community pharmacy care. Adjusted logistic regression models indicate that the subjects younger than 80 years of age generally have greater odds of having complete continuity of community pharmacy care than those 80 years or older. This is similar to the study by Lauzier and colleagues who found that patients aged 65 years and older experience greater continuity of care than their younger counterparts.(20) The current study demonstrates that the relationship may continue past the age of 65 years old.

Subjects who used greater than four medications, or subjects who were hospitalized during the continuity assessment period also had decreased odds of experiencing complete continuity of community pharmacy care. These findings are consistent with the work by Lauzier et al, who found that the use of greater than four

medication classes and a visit to the emergency department were associated with decreased odds of complete continuity of community pharmacy care.(20) Having a greater number of medications was also associated with decreased continuity of community pharmacy care in a retrospective cohort of subjects in the Netherlands.(21)

The discovery that greater than four physician visits during the continuity assessment period was associated with decreased continuity of care is new. This variable had not been assessed in previous studies of the determinants of continuity of community pharmacy care.(19-21)

This thesis confirms the finding of previous studies that have, after adjustment, all shown that females have decreased odds of experiencing continuity of care or have increased pharmacy-shopping behaviour compared to males.(19-21)

6.3 Strengths

There are several strengths to this study that make it a useful addition to existing adherence literature. Firstly, protopathic bias has been avoided by clearly measuring continuity of community pharmacy care prior to the assessment of statin adherence. Many previous studies assessing the association between continuity of care and subject outcomes assess continuity of care concurrent with adherence.(25) By avoiding this bias we better show the true relationship between continuity of community pharmacy care and statin adherence. However, by assessing continuity of care prior to medication adherence, we were forced to exclude subjects who had less than one year of data available for analysis, and assumed that past continuity behaviour continued during the year after the continuity assessment period. This assumption has been investigated by Gabler and colleagues who found that persons with past purchase behaviour at a specific pharmacy

were significantly more likely to report future purchase intention at the same pharmacy ($p<0.01$).(119)

Through the use of a retrospective dataset the Hawthorne effect has been avoided.(32) In a study assessing medication adherence, the Hawthorn effect occurs when subjects subconsciously alter their adherence behaviour simply because they know that adherence is being observed.(120) As the subjects in this study were gathered from a retrospective database, no such phenomenon was possible. Using a retrospective database also eliminated the possibility of recall bias, which is a concern when assessing adherence using patient questionnaires or other secondary adherence measures.(31,32)

The use of the NSSPP database also offered some advantages. Using the NSSPP database ensured that most eligible prescriptions, regardless of the location or pharmacy from which they were dispensed in the province of Nova Scotia were available for analysis of continuity of community pharmacy care. This also ensured that a large sample size was available.

The breadth of data available in the NSSPP database was a second advantage of using that dataset. Because relational continuity of care is not a prescription specific concept like medication adherence, in order to accurately assess continuity of community pharmacy care, all prescriptions dispensed to a patient over a given time period are required. By using the NSSPP database, all dispensations prior to the index statin could be used to characterize continuity of care. Without a dataset providing wide medication coverage, the continuity calculations would not have been as accurate.

Patients who had a previous prescription for any lipid-modifying agent during the one year prior to the index statin were excluded from the study population. This incident-

user design was used to capture patients when they were initiating statin therapy in order to accurately characterize continuity of community pharmacy care prior to adherence. Additionally, the incident-user design also ensured that subjects who became non-adherent early in their therapy were included in the analysis. Without the incident-user design, the adherence level in the cohort may have been higher which may have biased the result away from the null, if the excluded patients also had low continuity of care scores.

Lastly, by using a hierarchical model, which clustered subjects at their index pharmacy, we attempted to minimize confounding related to unmeasured pharmacy characteristics. In our model, there were 438 pharmacies at which 25,641 subjects were clustered. The hierarchical design may have minimized unmeasured confounding at the pharmacy level, as patients who attend each pharmacy will experience relatively similar services or treatment at that pharmacy. For example, a pharmacy may offer an electronic service to remind patients to refill their medication. It is anticipated that the patients attending this pharmacy may have higher adherence rates than patients attending a pharmacy that does not offer this service. These patients will not have a truly independent outcome (adherence), because they are all influenced by the pharmacy service. By clustering the patients that have experienced this service, we have attempted to minimize the confounding that has occurred due to this unmeasured pharmacy effect.

6.4 Limitations

This study has some limitations that may impact the validity of the results and limit interpretations. These limitations are classified below into three categories: potential for information bias; potential for selection bias; and potential for confounding.

Potential for information bias:

Information bias is present if there was a systemic error in measuring continuity of community pharmacy care or statin adherence. In concordance with many other adherence studies, the assessment of adherence was restricted to the one-year period immediately after initiating treatment. However, adherence to statins may continue to decrease for up to five years after the first dispensation.(59) Limiting the adherence assessment period to the one-year after the index statin has created the potential for bias away from the null, if subjects who would have become non-adherent after the first year of therapy had high continuity of community care scores. If these subjects had low scores, this would bias the result toward the null. Therefore, our study may be most applicable within the first year of therapy.

Secondly, like all adherence studies using prescription claims data, this study is in fact, measuring if the subject has been dispensed their medication by the pharmacy at the designated time interval, not if they have actually ingested the medication.(32) This being said, the MPR is nearly identical to the CMA, which has been moderately correlated with a direct measure of adherence (drug plasma levels) for anti-seizure medication, lending some confidence in the measure of adherence.(38) Like statins, anti-seizure medications are meant to be taken long term, although patients may be more likely to take them because the effects of non-adherence may be more noticeable. Additionally, the MPR

may be similar to a patient's pill count (p=0.68).(36,39) Therefore, while, not a perfect measure of medication adherence, the MPR is a useful secondary adherence measure.

When calculating the continuity of care indices, we were forced to use the pharmacy identification number, rather than the dispensing pharmacist. This may contribute information bias to the study it may be that the actual pharmacy staff are responsible for the potential benefits of continuity of care, not the physical location of the pharmacy staff. The dispensing pharmacist is not a data-point that is received from the NSSPP by the PHRU. Therefore, it could not be analyzed in this thesis and the pharmacy identification number was instead used. However, each pharmacy may have several different pharmacists and some pharmacies may use locum pharmacists. It is not possible to estimate how many individual pharmacy staff members were involved in each statin dispensation, nor is it possible to know if the same pharmacy staff were involved with the patient's continuity of care dispensations were also involved in dispensing a patient's statin. The magnitude of this potential bias is thought to be small because the dispensing pharmacist would have full access to each patient's medication record, which could be used to address non-adherence.

The result may have been biased if subjects obtained medication from sources other than community pharmacies in the province of Nova Scotia; are prevented from using medication obtained from a community pharmacy in Nova Scotia; or begin to pay for their medications privately. Situations such as this may arise if a subject transfers their prescription to another province, enters the hospital system, or enters the penal system. When assessing records of dispensations in the NSSPP database, these patients may appear to be non adherent even thought they might still be obtaining their statin

elsewhere. The number of patients meeting these outcomes is unknown, as the NSSPP database does not contain that information. The average length of hospital stay for a senior in Nova Scotia in 2010-2011 was 9.3 days, so it is not anticipated that hospitalization will cause many subjects to be misclassified as non-adherent.(121) A third instance in which patients may appear to be non-adherent while still taking their medications as directed would occur if their physician verbally orders a dose change that results in a person splitting the dose of their previously dispensed medication.(32) For example, a subject is taking simvastatin 80mg once daily. After a few months of treatment, their physician changes their dose to simvastatin 40mg once daily, so the subject begins splitting their previously dispensed tablets. This subject would appear to have an MPR of 0.50 after the dose change, even though they are taking their medication as directed. It is impossible to determine if this has occurred to any subjects in the study population. All of the above situations result in the possibility of erroneously classifying subjects as non-adherent. The same issue arises in subjects who may have used sample medication or who utilized a friend or family member's medication during the adherence assessment period. There is no reason to suspect that subjects these situations influenced the level of continuity of community pharmacy care that a subject experienced, therefore, the direction of the bias cannot be determined. The magnitude of this bias is likely to be small, because it is not anticipated that these situations frequently arise.

Some subjects may also be directed by their physician or pharmacist to stop taking their statin for a specified period of time to avoid adverse effects or drugs interactions with some types of antibiotics.(122) These subjects would appear to be non-adherent as calculated by the MPR, even though they are using their statin as directed.

We have no method of determining how often this occurred; however, this management is likely to occur only if the antibiotic therapy is short-term (between 5 and 21 days). If a patient were to be on a long-term interacting medication, they would likely be switched to a non-interacting statin.(123) Therefore, the effect on adherence is likely to be small. There is no reason to think that subjects who might have experienced this management would have had differing continuity levels, so the direction of this potential bias cannot be determined.

A further source of information bias may be the definition of adherence used. Patients are generally classified as adherent to long term therapies if they take 80% (MPR = 0.80) of their medication over a defined period of time. This percentage is an arbitrary cut point and was first based on expert opinion.(32) Even so, this definition for adherence has been shown to be associated with many positive outcomes including decreased mortality, cardiovascular events, non-fatal ischemic heart disease, venous thromboembolism, hospitalizations, healthcare costs and work absenteeism.(9-14) However, using an MPR of 0.80 may not be optimal. While the MPR captures general adherence behaviour, it is not able to determine other aspects of medication adherence such as the timing of doses, the days that medication was missed or for how long.(32) For example, an MPR of exactly 0.80 indicates that 73 days of medication were missed over a one-year follow-up period. We do not know if these days were missed sporadically or all at once. In part, due to situations such as this, a higher MPR value of 0.90 has been proposed as a new cut-point for medication adherence.(113) Additionally, the MPR is sensitive to the duration of the adherence interval.(32) For example, if a patient missed four weeks of medication during the second month of a 52-week period, their MPR

would be 0.92, and the subject would be classified as adherent. If an adherence interval of 12 weeks had instead been used, the same subject would have an MPR of 0.67 and would be classified as non-adherent. To combat this problem, it is suggested that the adherence assessment interval take into account the pharmacokinetics and pharmacodynamics of the drug under study.(32) With this in mind, an adherence assessment period of one year after the first statin dispensation was selected for this study. Statins begin to lower LDL cholesterol after the first dose is ingested, however a clinically meaningful change in health outcomes does not occur for one year.(124) Over one year, for each 1.0 mmol/L reduction in LDL cholesterol, there is a significant 10% reduction in major vascular events. Similar results are observed across different statin doses and in patients in different cardiovascular risk categories. In a meta-analysis of intensive LDL lowering compared to less intense LDL lowering with statins, there was a significant 22% reduction in major vascular events per 1.0mmol/L reduction in LDL over one year (RR: 0.78, 95% CI: 0.76-0.80).(125) Subjects at a low risk for any vascular event also had a 38% reduction in the risk of a major coronary event for each 1.0mmol/L reduction in LDL cholesterol over one year (RR: 0.62, 95% CI: 0.47-0.81).(126) Because statins begin to lower cholesterol after the first dose and have a significant effect on major vascular events at one year, a one-year adherence period was selected as the minimum clinically meaningful period over which to measure adherence. We evaluated the effect of this potential bias by determining the effect of continuity of community pharmacy care on two different adherence cut-points (MPR = 0.75 and MPR = 0.90). This did not markedly change the magnitude or direction of the result.

Some subjects may have been directed to take their statin every other day, twice weekly or once weekly in an attempt to decrease the incidence of adverse effects or to decrease medication costs.(127-129) This intermittent dosing will affect the MPR. For example, if a subject is directed to take their statin once weekly and receives a prescription for 12 pills, meant to provide them with a days supply of 84 days. If the quantity dispensed is used they will have a MPR of 0.14 over a 12-week period and will appear to be non-adherent despite taking their statin as directed. Intermittent dosing may lower LDL cholesterol to the same degree as daily dosing but has not been studied to show a decrease in cardiovascular events.(129) The prevalence of intermittent dosing is not known in our study population. We used the days supply variable from the NSSPP database, not the quantities dispensed, to better capture adherence behaviour and therefore, any bias introduced by intermittent dosing is thought to be small. We are unable to estimate the direction of the bias because there is no evidence to suggest that subjects with intermittent dosing schedules have altered continuity behaviour compared to subjects with daily dosing schedules.

Information bias may also be present in this study because the CIHI-DAD was used as a source of information. The covariates collected from the CIHI-DAD are the presence of: a hypertension diagnosis, chronic renal failure, congestive heart failure or diabetes. Because information in the CIHI-DAD is collected from each separation from hospital or day surgery, the only way for a subject to have an accurate covariate set is if they had been used those services in the year prior to their index statin. Diagnoses made at physicians' offices are not contained in the CIHI-DAD until that subject encounters the hospital system. If a subject had not been hospitalized, their covariates were coded as

"no" rather than "missing" in the analytic set. The effect of using the CIHI-DAD as a source of information was investigated by conducting a sensitivity analysis of subjects with a hospitalization during the year prior to their index statin prescription. The result indicated that for each 0.10 increase in continuity of community pharmacy care, the odds of adherence increased by 2% (95% CI: 0.99-1.05). This is similar to the 3% increase in statin adherence observed in the full cohort. While the result was not statistically significant, this was likely due to a loss of power secondary to restricting the cohort size.

Lastly, information bias may be present because we were unable to capture subjects who failed to re-enroll in the NSSPP or who passed away during the adherence assessment period. The magnitude of this bias is thought to be small. In Nova Scotia in 2001, there were 126,965 seniors, of which 6,207 (4.9%) died during 2001.(130) From this, we can estimate that approximately 1,200 subjects in our cohort died before one year of follow-up. If all of these subjects were classified as non-adherent but had higher levels of continuity of community pharmacy care, the result may be biased towards the null, making the observed odds ratio a conservative estimate of the effect of continuity of community pharmacy care on statin adherence. In order to determine the effect of 4.9% of the study population passing away during the adherence assessment period, a random sample of the study population was taken and the MPR values of these subjects was set to 0.0; the worst possible adherence result. The result of this analysis did not markedly differ from the primary result (OR: 1.02, 95% CI: 1.00-1.04).

Potential for selection bias

Selection bias would be present in this study if the manner in which subjects were selected for the study were systematically different from the target population. The target

population is all patients aged 65 years and older taking statin medications. The potential for selection bias exists because the NSSPP is the insurer of last resort and as such, approximately 30% of Nova Scotian seniors are not enrolled in the NSSPP. It is likely that these persons are missing not at random. Seniors who are not enrolled in the NSSPP are likely to have a higher income, have lower medication costs and/or to be in good health compared to program enrollees. Persons with higher income, less healthcare costs and a lower comorbidity burden have been found to have higher medication adherence.(131) Additionally, persons in better health may be taking fewer medications, which has also been associated with increased medication adherence.(6,75) Persons with fewer medications and higher income may experience higher continuity of community pharmacy care levels.(20) Because persons missing from the NSSPP may have higher adherence and continuity of community pharmacy care levels, the result of this study may be biased away from the null. Therefore, these results are only applicable to seniors enrolled in the NSSPP.

Selection bias may be present as subjects were excluded if they had a previous renal dialysis or had a kidney transplant. This exclusion was put in place because a portion of the dataset had been previously prepared for another project that had these exclusions in place.(104) However, less than 0.5% of statin initiators were removed from the study population due to these exclusion criteria. Patients who receive renal dialysis may have similar adherence rates to the general population. Through the use of a Medication Event Monitoring System (MEMS), Curtin and colleagues have shown that that 58% of patients older than 65 years are adherent to their medication (MPR=0.80). Based on this finding, along with the small number of subjects excluded, it is not

anticipated that the result of this study is biased due to excluding patients who have had dialysis. A literature review of kidney transplant patients has found that between 20% and 26% of patients take less than 90% of their anti-rejection medications.(132)These patients may have similar adherence levels to other concomitant medications. These adherence rates are higher than observed in the present study. Because the number of excluded subjects is small, it is expected that the magnitude of this bias is small. No published evidence could be located to suggest that dialysis patients or patients with a prior kidney transplant have different continuity of community pharmacy care levels than the general population; therefore the direction of this bias is unclear.

Potential for confounding

Patients using a statin for secondary prevention are more adherent than patients using statins for primary prevention.(57) Patients using a statin for secondary prevention may also experience altered continuity levels compared to patients using statins for primary prevention if they were in worse health and taking more medications for other conditions prior to their cardiovascular event compared to subjects who initiated statin therapy for primary prevention. The fact that we were unable to determine if a subject was using a statin for primary or secondary prevention is a limitation.

The relationship between statin adherence and continuity of community pharmacy care may also be confounded by the level of rurality that a subject experiences. For example, some patients will be influenced to use only one pharmacy if they live in a rural community and have barriers to accessing additional pharmacies. While there was no method of determining how many pharmacies a patient had easy access to, in Nova Scotia in 2011, 43% of the population is considered to live in a rural area.(133) Twenty-

four percent of all residents in Nova Scotia lived within 800m, and 65% live within 5km of two or more community pharmacies in 2011.(134) However, only 30.6% of rural residents live within 5km of two or more community pharmacies. To assess the impact of this potential confounding, a sensitivity analysis was conducted. Place of residence was measured at the time of the index statin prescription by the second digit of the forward sortation area of the subjects postal code. Among urban residents, the results did not significantly change (OR: 1.02, 95% CI: 1.00-1.05), however the result was no longer statistically significant. This is possibly due to a decrease in the power of the analysis. Among rural residents the odds of adherence was slightly higher than observed in the primary analysis (OR: 1.04, 95% CI: 1.01-1.07). We had no method of determining if a subject had moved from an urban to rural or rural to urban place of residence at any time during the study period. Additionally, by assuming that the home is the origin of all visits to the pharmacy, we were not able to account for the fact that subjects may obtain medication from pharmacies near physician offices, outpatient clinics, employment or shopping locations.

Confounding may also enter the study due to the variation in pharmacy services offered to subjects by individual pharmacies. For example, if a senior is not easily able to attend a pharmacy for refills of their medication, some pharmacists may arrange to deliver the medication to them. This may result in limited to no interaction with the pharmacy staff, which could lead to a lack of opportunity for pharmacy staff to identify prevent and non-adherence. While there was no method of determining if a prescription was delivered or not, by clustering around the index pharmacy it is hoped that some unmeasured influences have been minimized.

Because this study utilizes secondary data, and we have no way to determine if the patient actually attended the pharmacy to pick up their prescription, it is assumed that a dispensation date corresponds with an actual visit by the subject to the pharmacy. However, prescriptions could be dispensed via delivery, care takers could pick up medication for the patient, or patients could have been mailed their prescription. These scenarios would result in minimal to no interaction with pharmacy staff, which may affect the theoretical underpinnings of the continuity of care relationship. Adherence may also be affected if patients have home care assistance, which may facilitate medication taking.

An additional service that may confound the result is the use of electronic reminders to prompt patients to refill prescriptions. This would promote adherence. It is unknown how many community pharmacies in Nova Scotia currently use technology to remind patients to refill their medication on time. According to the theoretical framework used in this study, electronic medication reminders act as a moderator of medication adherence. These technologies could improve adherence, but would not fully solve the problem of non-adherence. Electronic reminders may also promote continuity of care. By providing this service the dispensing pharmacy may create a sense of belonging, and the patient may be more likely to return to that pharmacy for future refills and with future prescriptions. There was no way of knowing if this type of technology was used by the pharmacies in this study.

As stated earlier, in the 2003 landmark report, the WHO indicated that there are five major groupings of factors that effect medication adherence: the patient, provider, socioeconomic, treatment and health-system all exert some influence on medication

adherence.(1) While key subject characteristics that may confound the relationship between continuity of community pharmacy care and adherence to medications have been captured, some important pharmacy characteristics, such as the type of pharmacy, number of prescriptions dispensed at each pharmacy, the location of the pharmacy, the duration of practice of the pharmacists dispensing the statin and the amount of trust a patient has in their pharmacist or pharmacy were not available. By clustering the data at the pharmacy level potential unmeasured confounding has been decreased, but not eliminated. Important patient characteristics, such as the level of independence, (independent versus long term care) as well as treatment characteristics such as the copayment level could also not be taken into account due to the limited data available.

The IMB framework developed by Fisher and colleagues was used to guide this thesis, but many other theories exist that explain medication adherence behaviour.(67) These theories contain many constructs that are not measureable using administrative databases such as the subject's perceived benefits and risks to taking medication, level of self-efficacy, individual therapeutic goals, subjective norms and other social influences.(61,67)

The constructs within each domain of the IMB framework itself also have the ability to modify adherence behaviour. Using administrative data we were not able to measure a subject's knowledge about statins and hypercholesterolemia, motivation to be adherent to statins and the subject's level of various adherence behaviour skills.

6.5 External Validity

This study includes subjects that enrolled in the NSSPP who received a first statin dispensation between January 01, 1998 and April 30, 2008. This population is elderly

and has the costs of most common medications subsidized. Expanding the study population to include younger participants is not possible because there is no publically administered prescription database in Nova Scotia for persons younger than 65 years old that does not restrict enrolment by income category. The younger population may have significantly different adherence behaviour if they do not have a comprehensive drug insurance plan. The younger population may also have significantly different continuity behaviour. This was seen in Lauzier and colleagues' study which showed that subjects younger than 65 years have lower odds of complete continuity of community pharmacy care compared to subjects 65 years and older.(20) Therefore, the results of this thesis may not apply to persons under the age of 65 years.

The average days of statin medication supplied at each dispensation in this study was 49. In Nova Scotia, under the Seniors Pharmacare program, pharmacists are allowed to dispense a maximum of 100 days supply of medication at a single fill.(135) In other jurisdictions, if the days supply is limited to shorter time periods, the result may not be applicable. A shorter days supply may limit the validity of the result to persons in that jurisdiction because adherence is higher if a greater number of days are supplied with each dispensation.(77,136) While a longer days supply appears to be associated with increased medication adherence, it presents decreased opportunity for interaction between patients and pharmacy staff. This may impact relational continuity of community pharmacy care by decreasing the number of interactions between the patient and pharmacy staff, which could impact the quality of the patient-provider relationship. Longer prescription lengths will also decrease the number of chances for pharmacists to monitor patients for adverse events. However, longer prescription lengths may be

preferable to the patient because they will not have to make as many trips to the pharmacy and will pay less pharmacy professional fees, because there will be less dispensations. Shorter prescription lengths could also affect continuity of community pharmacy care because the patient will have increased opportunity to access multiple pharmacies for refills of their medications. Therefore, this result may only be applicable in health-systems that suggest prescription lengths of up to 100 days.

The result may not be applicable to managed care health systems because some of these health systems provide financial incentives for enrolled patients to use preferred community pharmacies.(137) In the current study we have characterized subjects willfully attending pharmacies of their choosing. By providing financial incentive to use specific pharmacies, the continuity behaviour of subjects may be altered, which may weaken or strengthen the result. Additionally, some managed care systems may have contracts with Internet pharmacies. Subjects using an Internet pharmacy may not experience the benefits of continuity of community pharmacy care if the Internet pharmacy does not provide personal counseling with each prescription dispensed. Without this link, patients may not develop a strong therapeutic relationship with their pharmacy and may not experience the benefits of continuity of community pharmacy care that may result from that relationship.

Some health insurance plans also influence adherence by reducing copayments or prescription costs if the patient picks up medication refills on time or who participate in programs aimed at educating them about proper management of their condition.(78) This may alter the result observed in the present study. Therefore, the result may not be

applicable for persons enrolled in medication reimbursement programs that significantly differ from the NSSPP.

6.6 What This Study Adds

To our knowledge, there exist no peer-reviewed studies, indexed by common bibliographic software, that determine the strength of association between two domains of continuity of community pharmacy care and medication adherence. There are also no indexed studies that determine if continuity of community pharmacy care is associated with adherence to a long-term cardiovascular medication, or that evaluate continuity of community pharmacy care in an exclusively senior population. The only previous study of continuity of community pharmacy care and medication adherence focuses on adherence to antipsychotic medication in subjects with schizophrenia over the age of 20 years.(27)

Secondly, this is the third study to determine the strength of association between clinical and demographic variables and relational continuity of community pharmacy care. As such, this study adds to the growing body of literature in that area.

In this study we attempt to standardize terminology used to study of the longitudinal association between a patient and their pharmacy. Previous studies in this field have used the terminology "pharmacy loyalty" or pharmacy "fidelity", but upon inspection, the methods used calculate loyalty or fidelity are consistent with the UPC index calculation in the density domain of relational continuity of care.(19,20,81) Therefore, we have called this concept continuity of community pharmacy care.

This study also determined that the density and dispersion of continuity of community pharmacy care are closely related. These two concepts, calculated using the

UPC and COCI, respectively, have a correlation coefficient of 0.98. This finding has not been reported in peer-reviewed literature that has been indexed by common bibliographic software.

Lastly, this study is the first to quantify continuity of community pharmacy care in the province of Nova Scotia.

6.7 Implications

Implications for research and methods

Although this study indicates that continuity of community pharmacy care is associated with medication adherence, further research into the association is required in order to determine the reasons that the association exists and if the association exists in different study populations, for different classes of medication and over longer time periods. If the association persists, we have provided a good description of which subjects experience higher continuity of care. These results may be used to generate further research hypotheses.

In this study, the positive association between continuity of community pharmacy care and statin adherence became non-significant after restricting the study population to patients who had been hospitalized during the year prior to their index statin. This population of subjects may be in worse health than subjects who were not hospitalized and may be more likely to be using a statin for secondary prevention. The association also became non-significant for those who live in urban areas. It is possible that the non-significance was due to a lack of power secondary to a smaller analytic set; however, it could also be that the association truly does not exist in these patient populations. If this

is the case, greater description of the relationship between continuity of community pharmacy care and medication adherence in these populations is required

Additional research is also needed to determine if the association exists over a longer adherence period and across other medication classes. In this study we assessed adherence over a one-year period, but adherence has been shown to decrease for up to five years after statin initiation.(59) Because statins are taken long-term, it would be beneficial to extend the adherence assessment period.

In order to minimize selection bias, we used an incident user design.(138) This study design was used in order to capture adherence behaviour occurring in the year immediately after statin initiation. The first year of statin therapy is important because adherence rates decrease rapidly in this time period, before beginning to level off.(59) Additionally, the incident user design allows for improved control of confounders by ensuring that all patients are observed at the same point in their therapy, which helps to ensure that the included patients are similar with respect to their decision to retrieve their medication.(138) The study design implicitly assumed that the continuity of care behaviour prior to the index statin continued after the index statin. If adherence is assessed over a longer time period than one year, it needs to be established that the continuity behaviour does not markedly change during that time.

It is unclear why continuity of community pharmacy care positively impacts adherence. Through the use of the IMB framework, we assumed that increased continuity promotes a strong pharmacy-patient relationship, which leads to increased information uptake and utilization, and that the availability of a complete medication profile facilitates the identification of non-adherence, which can then be corrected.

However, other reasons may exist to explain the association. For example, it is possible that patients more likely to be adherent are also regimented in other aspects of their life and are more likely to use a single pharmacy. Further descriptive research may contribute to a more nuanced understanding of the findings in this thesis.

We determined that the UPC and COCI are highly correlated. This indicates that the density and dispersion domains of relational continuity of care are quite similar and have significant overlap. As continuity of community pharmacy care theory develops, it may be possible to combine the density and dispersion into a single domain with a single calculation. Prior to this happening, it must be shown that there is no clear benefit to using one calculation over the other.

Implications for program delivery

After the relationship between continuity of community pharmacy care and medication adherence has been more thoroughly investigated, a second step would be to design programs to assess if requiring subjects to register with a single pharmacy promotes adherence. These programs must be designed judiciously. For patients who use multiple pharmacies, the reason for using multiple pharmacies needs to be determined. It is possible that these patients all preferred to use a single pharmacy but were forced to receive a dispensation elsewhere due to their usual pharmacy being out of stock of the medication required, the pharmacy being closed or due to travel away from their usual pharmacy. This study has characterized adherence behaviour among patients willfully attending multiple pharmacies; it is possible that if patients are required to register with a single pharmacy their adherence may decrease. Before the results of this study are used to guide medication policy, it is important that this question is resolved. Evaluation of

these programs must follow.

The result could also be used to provide a foundation for other adherence interventions. In a systematic literature review the Rand Corporation has identified four key modifiable barriers to medication adherence: cost sharing, regimen complexity, medication beliefs and depression (in patients with diabetes).(139) Of these, medication beliefs are most likely to be influenced by continuity of community pharmacy care, through the development of strong therapeutic relationships between patients and pharmacy staff. Therefore, adherence interventions aimed at increasing medication adherence through modifying patients' medication beliefs should be built upon continuity of community pharmacy care.

Existing provincial programs, such as Cardiovascular Health Nova Scotia, could also use the information in this study to facilitate medication adherence and improve outcomes by educating patients and health-providers in the importance of using a single pharmacy for medications.

In order for these programs to be implemented, patients will need to be educated on the importance of having a consistent pharmacy and how to best choose a pharmacy that suits their needs. If the benefit of continuity of community pharmacy care comes from the relationship that is built between patients and the pharmacy staff, patients and pharmacy staff will need to be informed of this and of how to best build these relationships.

Implications for policy

As it appears that continuity of community pharmacy care has a positive influence on adherence to statins, registration with a single community pharmacy may be beneficial

to both patient outcomes and the health-system. Patients may prefer this model of care. In a study conducted in the United Kingdom, Crook and colleagues determined that pharmacists, patients and the public at large did not seem to be adverse to the idea of registering with a single pharmacy.(140) They found that 62% of patients would be "happy to register with a community pharmacy" and that 52% think that compulsory registration would "improve the quality of service". Fifty three percent of the general public believes that compulsory registration would "improve the quality of service."(140) Pharmacists thought that while compulsory registration would not change how they provided patient care, 98% would feel that they could do more for their patients in a compulsory registration model of care and 76% thought that it would "improve the quality of service."(140) Patients, the public and pharmacists all indicated that the themes that influenced their perception of the benefit of compulsory registration would be the development of professional relationships and improved continuity of care.

In Canada, the views of the patient, provider and public at large on the issue of pharmacy registration are not known, however, registration with a single pharmacy has been investigated as part of capitation reimbursement models. In a capitation reimbursement model, patients' roster to a single pharmacy and pharmacies are reimbursed on a per patient basis, rather than a fee-for service agreement. Capitation models have been studied for their effects on cost containment, but not for patient outcomes, such as medication adherence.(141) In Canada, capitation models of reimbursement are not used, however a capitation model exists in Scotland for extended pharmacy services, but not medication dispensing.(142) Currently, in Nova Scotia, pharmacists are reimbursed in a fee-for-service model.

Pharmacists in Canada are gradually gaining an extended scope of practice. This expanded scope includes tasks such as prescribing refills, prescribing for minor ailments, vaccinating and modifying prescriptions.(143) The expanded scope of practice already directly impacts medication adherence because pharmacists are able to, in certain circumstances, prescribe additional tablets to extend a prescription if the patient cannot see their family physician for a new prescription. This ensures that the patient does not miss days of medication while they are waiting for their family physician appointment. Additionally, pharmacists in Nova Scotia can modify the dose of a prescription; which could help to avoid adverse effects and drug interactions; thereby promoting adherence. As these services become entrenched within the practice of pharmaceutical care, capitation reimbursement models, as opposed to fee-for-service reimbursement models, may start to be explored as a means of remuneration for these services. As the results of this study indicate that medication adherence may be increased if the patient has a single source of pharmacy care, a capitation model may further increase adherence.

Despite the fact that statin adherence is beneficial at the population level, it is also important to consider that there are situations where increasing medication adherence is not optimal. For example, a common antibiotic, clarithromycin, has an interaction with three of the statins (atorvastatin, simvastatin and lovastatin). The interaction increases the levels of statin in the blood and could lead to liver damage or rhabdomyolysis; a potentially serious adverse effect.(123) In order to avoid this interaction and associated adverse effects the dispensing pharmacist may tell the patient to stop taking their statin for the duration of time in which they are taking clarithromycin.(122) Additionally, if a

statin is not prescribed appropriately adherence is not optimal. In this study it was assumed that all statin prescriptions were prescribed in a rational manner.

Similarly, lower continuity of community pharmacy care scores may not accurately reflect poor health behaviour. Patients may utilize multiple pharmacies for entirely valid reasons. For example, if a person receives a prescription for an antibiotic at an after hours walk-in clinic or in the emergency department, their usual pharmacy may have closed for the evening. After receiving a prescription for an antibiotic, it is generally preferable for the patient to begin therapy as soon as possible. Waiting for their usual pharmacy to open will delay therapy and recovery. In a situation like this, attending a different pharmacy to fill the antibiotic prescription is in the subject's best interest.(21)

6.8 Conclusions

The results of this thesis suggest that continuity of community pharmacy care is positively associated with adherence to statins among Nova Scotian seniors who initiated statin therapy between 1998 and 2008. Because medication non-adherence a pervasive problem in the health system, further investigation of this relationship is required, as well as investigations of how to best use this information in policies aimed at increasing adherence to long term medications.

Appendix A: Literature Search

Databases Searched: PubMed, Embase
Original Search Date: December 15, 2012
Years Searched: All available
Limits: English, Humans

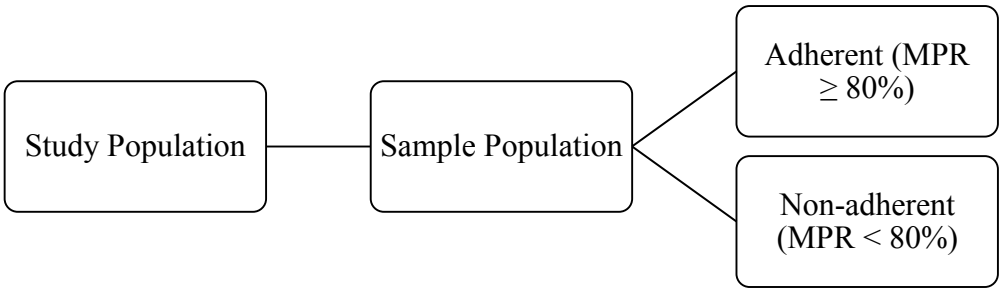
1	Medication[tw] OR Medicine[tw] OR Drug[tw]
2	Adherence[tw] OR Nonadherence[tw] OR Medication adherence[mh] OR Medication persistence[tw] OR Compliance[tw] OR Concordance[tw] OR directly observed therapy[tw] OR treatment refusal[tw] OR patient dropouts[tw] OR concordance[tw] OR medication adherence[tw] OR patient compliance[tw]
4	1 AND 2
5	Cardiovascular disease[mh] OR Statin*[tw] OR Atorvastatin[tw] OR Lipitor[tw] OR Rosuvastatin[tw] OR Crestor[tw] OR Simvastatin[tw] OR Zocor[tw] OR Fluvastatin[tw] OR Lescol[tw] OR Lovastatin[tw] OR Cerivastatin[tw] OR Mevacor[tw] OR Baycol[tw] OR Lipobay[tw]
6	4 AND 5
7	Association[tw] OR associations[tw] OR associat*[tw] OR determinant[tw] OR determinants[tw] OR determin*[tw] OR predictor[tw] OR predictors[tw] OR predict*[tw] OR factor[tw] OR factors[tw] OR variables[tw] OR variable[tw]
8	Retrospective studies[mh] OR Retrospective[tw] OR Administrative[tw]
9	7 OR 8
10	6 AND 9
11	"informational continuity"[tw] OR "management continuity"[tw] OR "relational continuity" [tw] OR "continuity of care"[tw] OR Relational[tw] OR "Continuity of Patient Care"[mh] OR loyal*[tw] OR fidelity[tw]
12	"Pharmacy"[mh] OR "Pharmacies"[mh] OR "Community Pharmacy Services"[mh] OR Pharmac*[tw]
13	11 AND 12
14	13 AND 2
15	medication reconciliat*[tw] OR reconciliation[tw] OR transition[tw]
16	14 NOT 15

[mh] = Medical Subject Heading, or equivalent Emtree term, if available
[tw] = Text Word

Appendix B: Figures

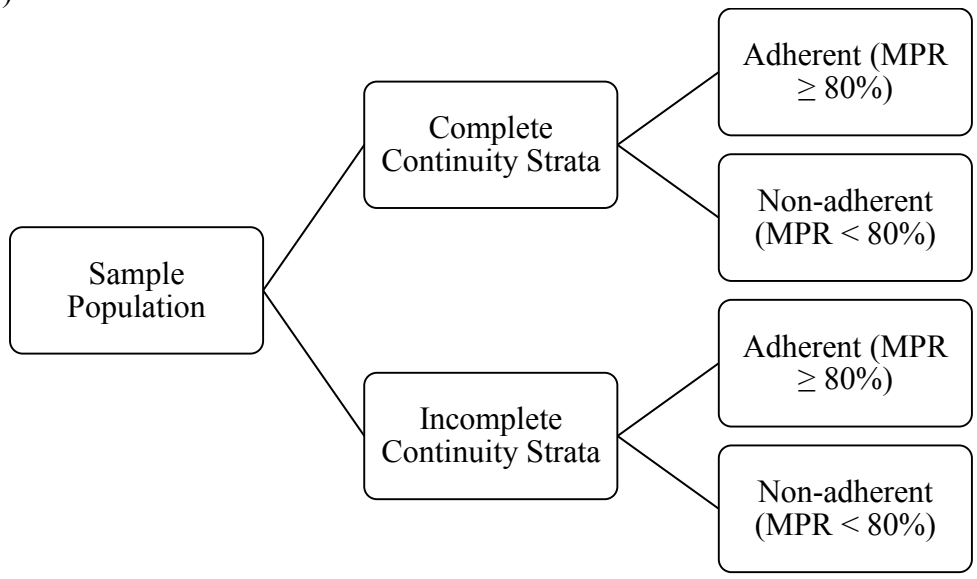
Figure B1: Study Design: a) continuous analysis, b) dichotomous analysis and c) multiple strata analysis.

a)



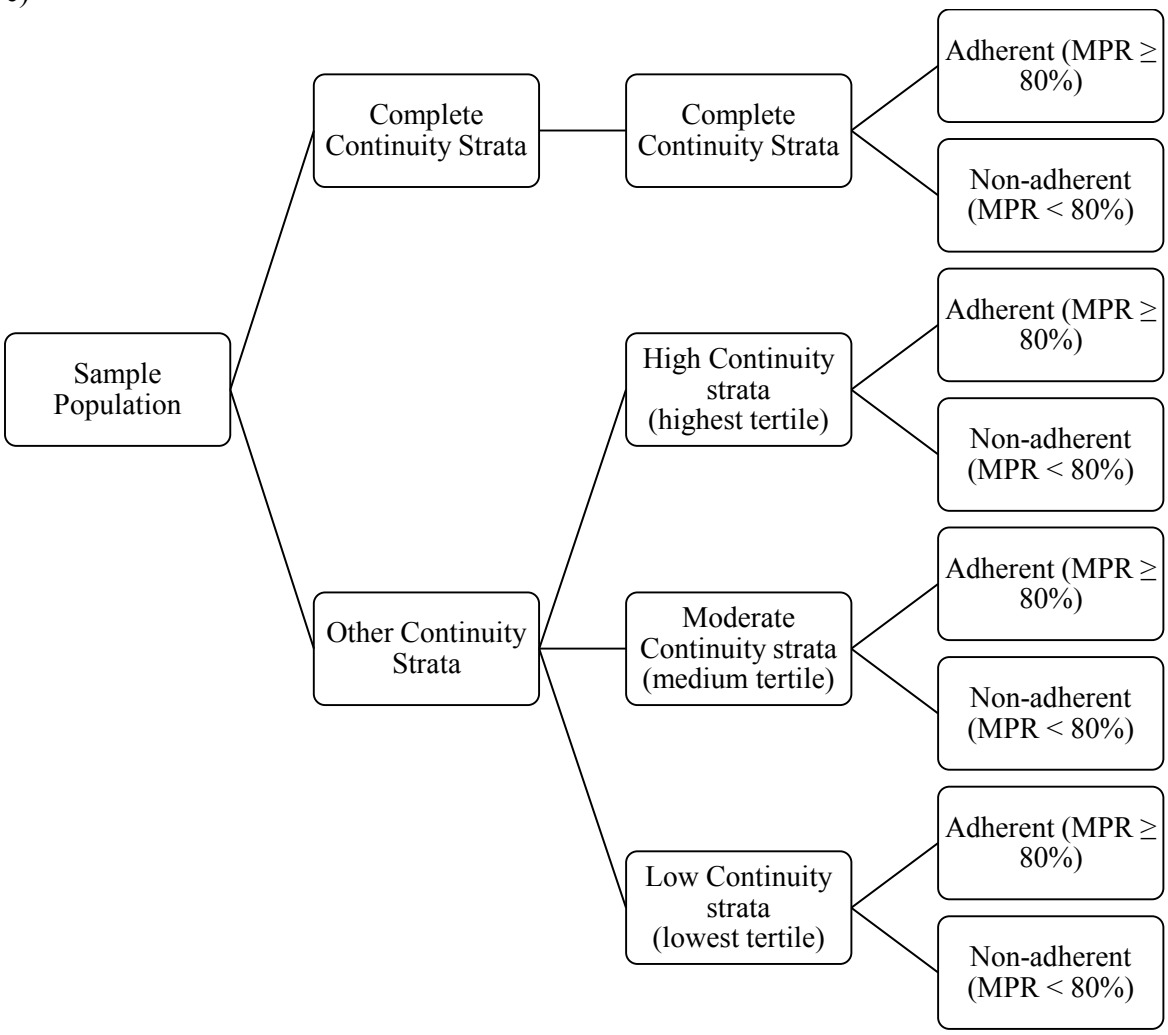
MPR: Medication Possession Ratio

b)



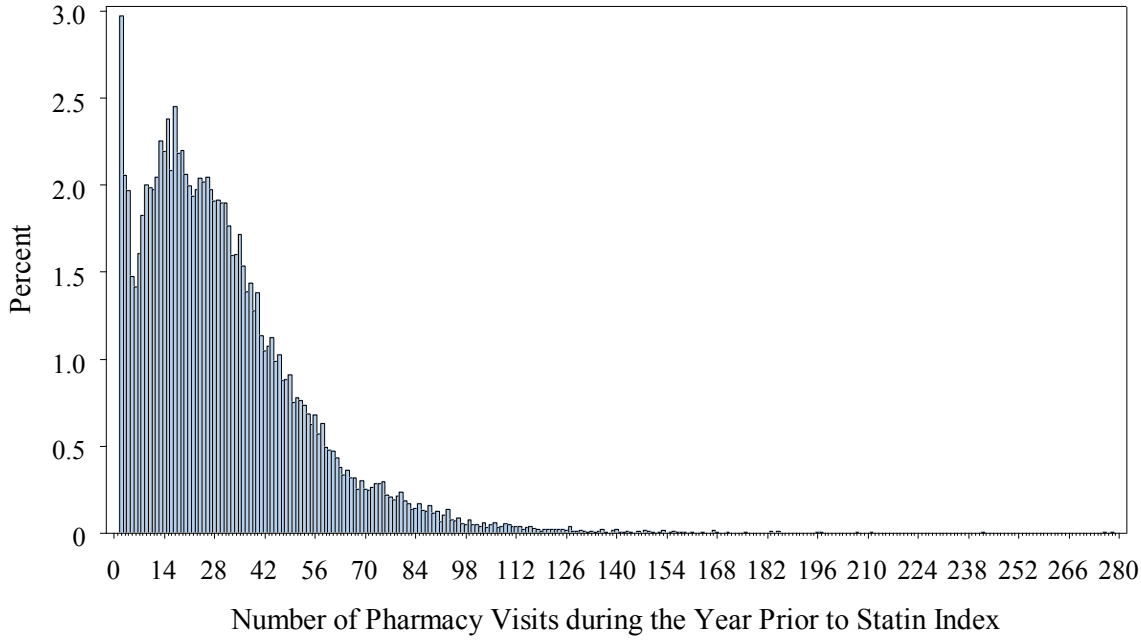
Complete Continuity Strata:	Subjects with continuity of community pharmacy care scores equal to 1.0
Incomplete Continuity Strata:	Subjects with continuity of community pharmacy care scores less than 1.0
MPR	Medication Possession Ratio

c)



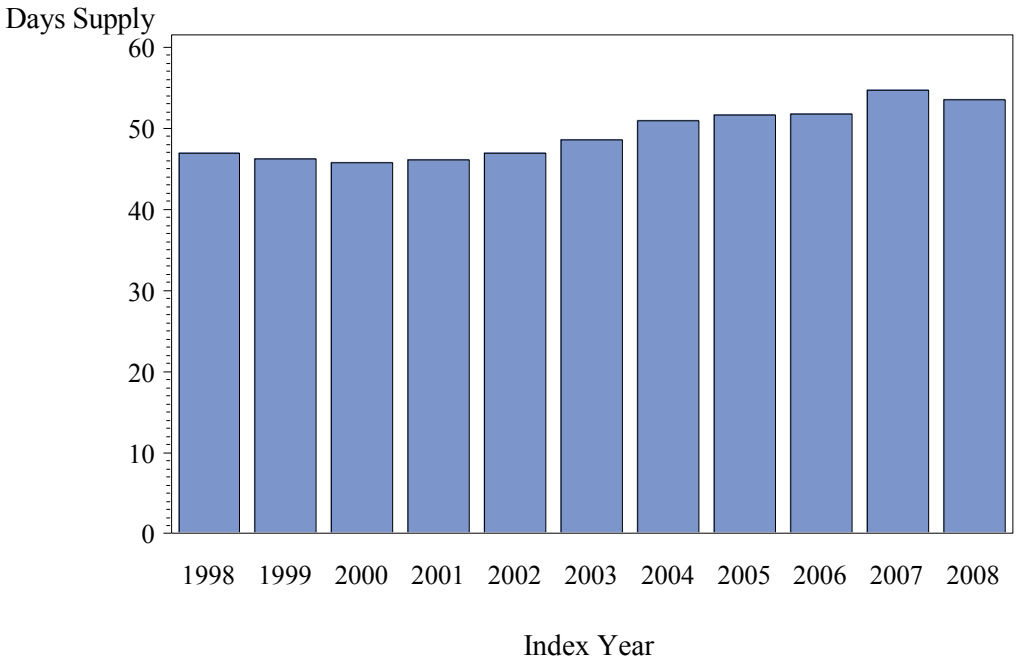
Complete Continuity Strata:	Subjects with continuity of community pharmacy care scores equal to 1.0
Incomplete Continuity Strata:	Subjects with continuity of community pharmacy care scores less than 1.0
MPR	Medication Possession Ratio

Figure B2: Distribution of the number of pharmacy visits[a] for prescription dispensations to eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[b] during the final year of the continuity assessment period. Number of subjects: 25,641.



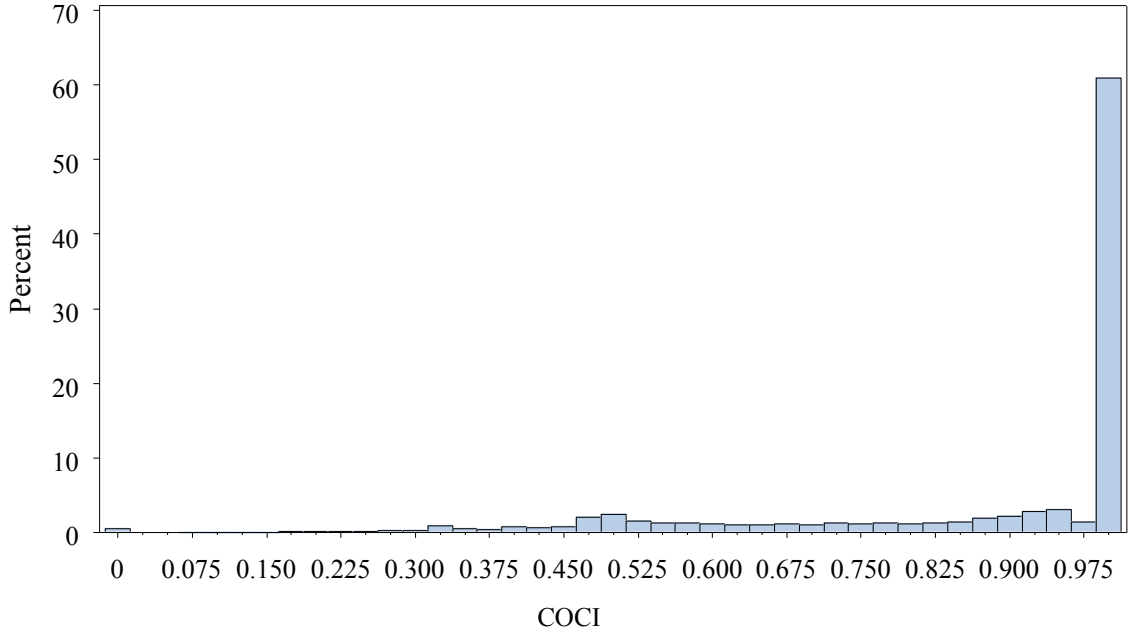
[a]Pharmacy visit: an individual dispensation date. Multiple prescriptions dispensed on a single date are counted as a single pharmacy visit.
[b] Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B3: Distribution of the average amount of statin medication supplied at each dispensation to eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a], by year.



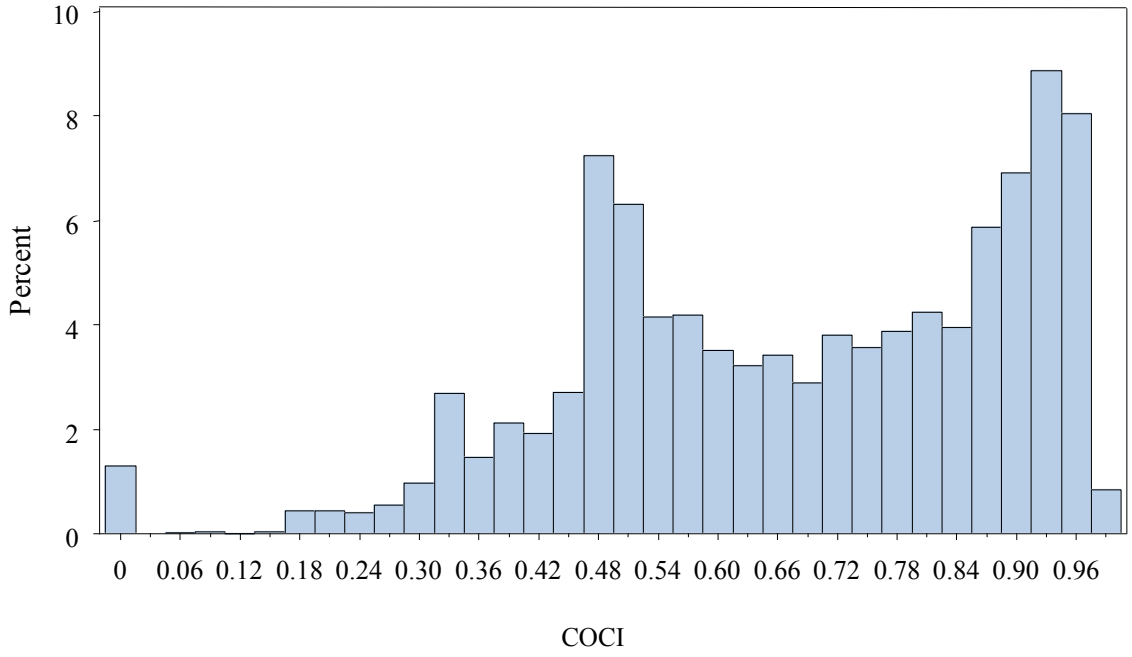
[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B4: Distribution of the Continuity of Care Index (COCI) among eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a], where 1.0 indicates all dispensations from a single pharmacy and lower scores indicate multiple pharmacies providing dispensations. Number of subjects: 25,641.



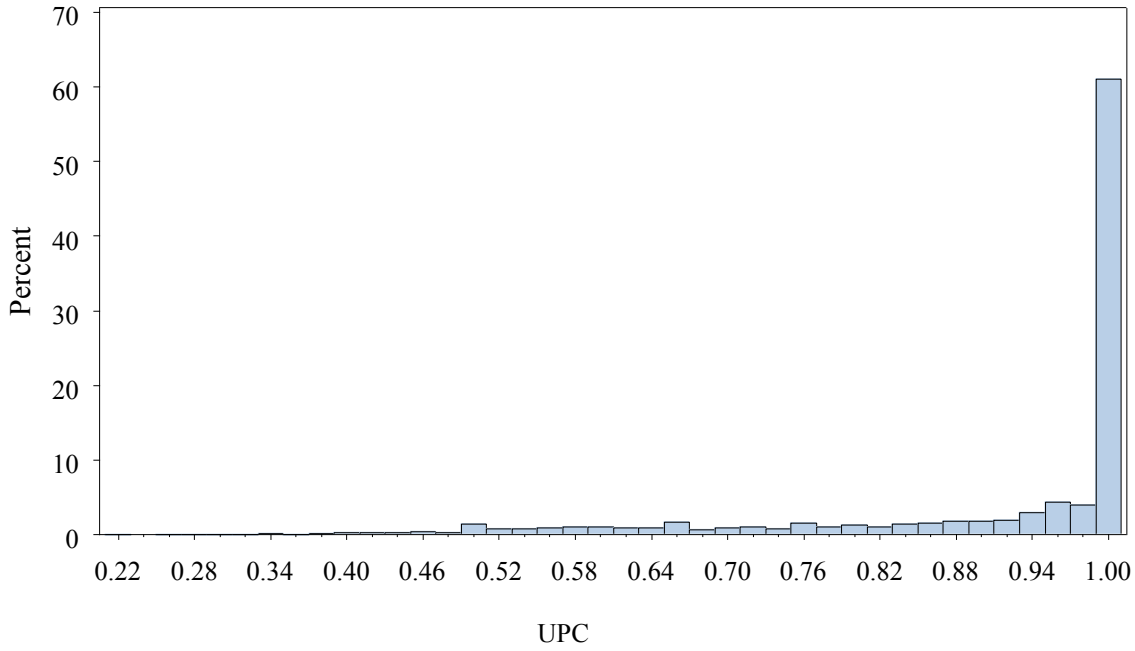
[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B5: Distribution of the Continuity of Care Index (COCI) among eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a], with Continuity of Care Index scores less than 1.0. Number of subjects: 10,031.



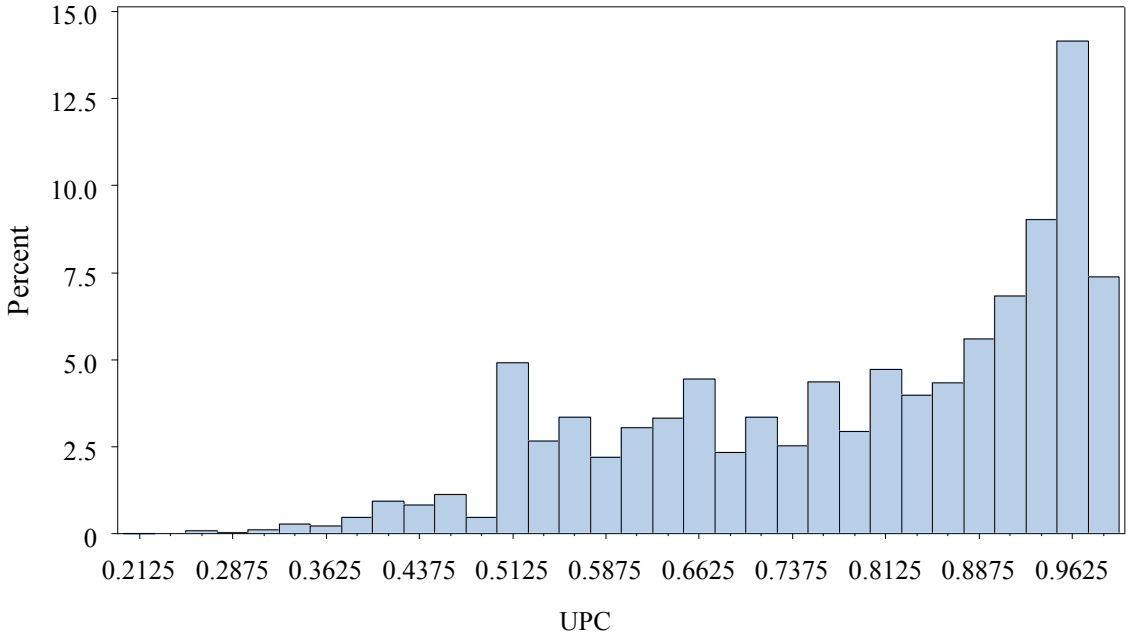
[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B6: Distribution of Usual Provider of Care (UPC) Index, eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a], where 1.0 indicates all dispensations from a single pharmacy and lower scores indicate multiple pharmacies providing dispensations. Number of subjects: 25,641.



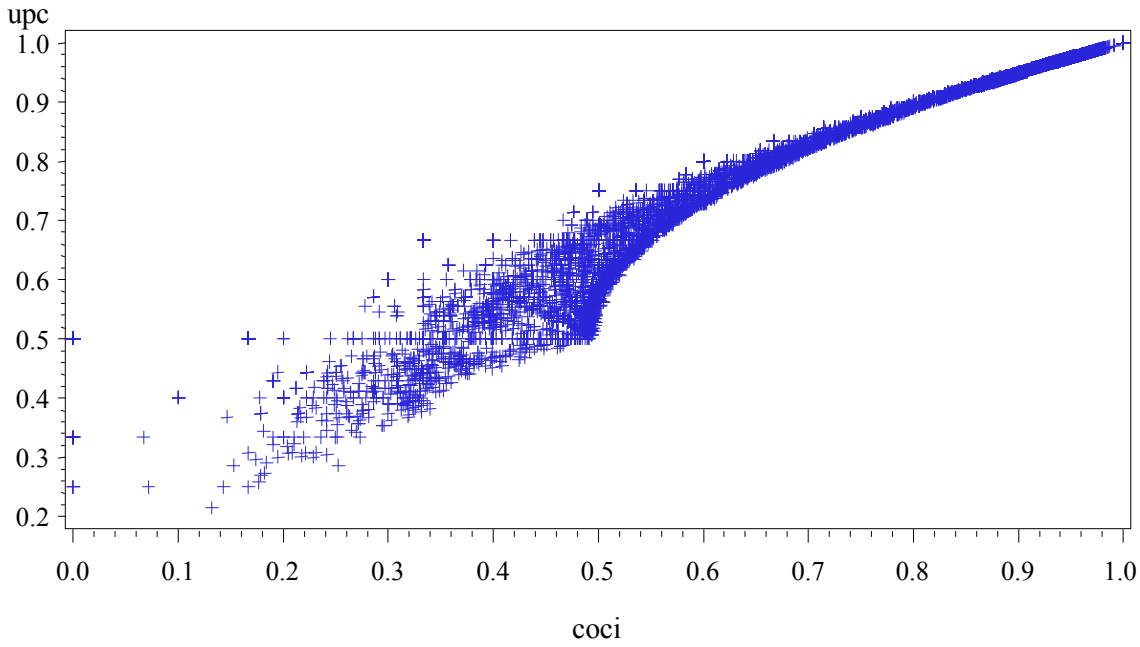
[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B7: Distribution of the Usual Provider of Care (UPC) Index among eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a] and had a UPC index scores less than 1.0. Number of subjects: 10,031.



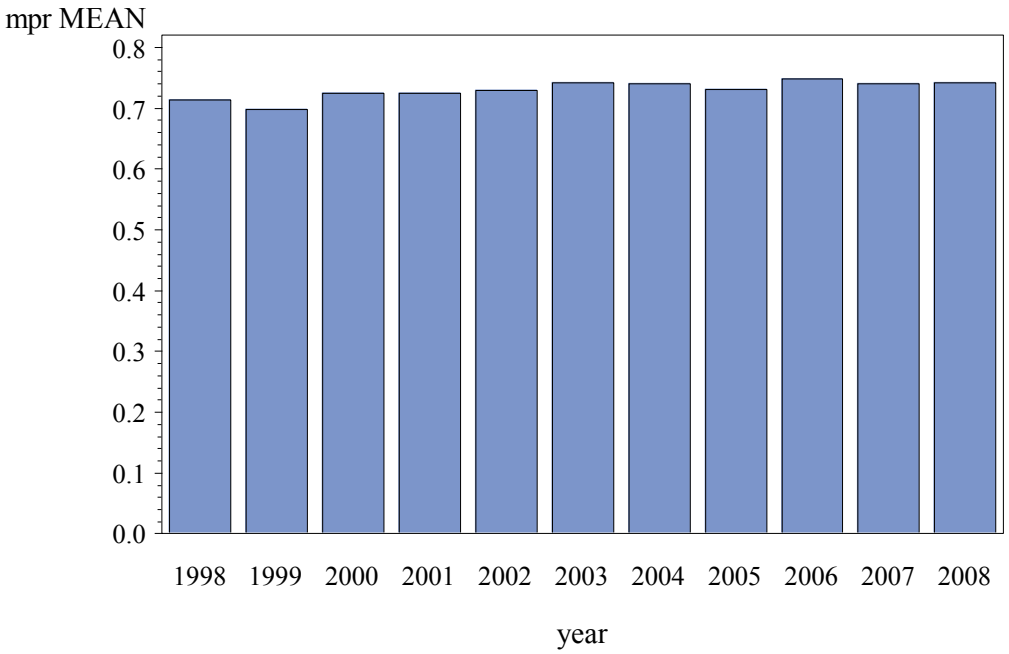
[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B8: Correlation between the Usual Provider of Care (UPC) Index and the Continuity of Care Index (COCI) in eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a]. Correlation Coefficient: 0.98



[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Figure B9: Distribution of the Medication Possession Ratio (MPR) among eligible beneficiaries of the Nova Scotia Seniors' Pharmacare Program who met inclusion criteria[a], by year index statin received. Number of subjects: 25,641.



[a]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin

Appendix C: Background Table

Table C1: Description of data used in creating the Medication Possession Ratio (MPR), Continuity of Care Index (COCI), Usual Provider of Care (UPC) index and those used to adjust the association between continuity of community pharmacy care and medication adherence; as well as those used to predict characteristics associated with continuity of community pharmacy care

Use	Variable	Source Table	Source Variable	Unit of Measurement	Categories
Adherence calculation (MPR)	Index Date (first statin dispensation)	NSSPP	Date	Ordinal	None
	Date of statin dispensations during one-year term after index date	NSSPP	Date	Continuous	None
	Quantity dispensed for each statin dispensation	NSSPP	Quantity Dispensed	Count	None
Continuity calculation (UPC, COCI)	Dispensing pharmacy of index prescription	NSSPP	Pharmacy ID	Categorical	None
	Dispensing pharmacy for all dispensations in two year period before index	NSSPP	Pharmacy ID	Categorical	None
Covariates used in104the analysis of the association between continuity of care and statin adherence	Gender	NSSPP	Sex	Dichotomous	0 = Female 1 = Male
	Age	NSSPP	Age	Ordinal	0 = 65-69 1 = 70-74 2 = 75-79 3 = 80 and older
	Income	2001 Canadian Census Data	Average 2001 household income	Continuous	0 = 1st tertile 1 = 2nd tertile 2 = 3rd tertile

Use	Variable	Source Table	Source Variable	Unit of Measurement	Categories
Covariates used in the analysis of the association between continuity of care and statin adherence	Place of residence	NSSPP	Forward sortation area of postal code	Dichotomous	0 = rural 1 = urban
	Statin Dose	NSSPP	Drug identification number (DIN)	Dichotomous	0 = low 1 = high
	Greater than four distinct drugs	NSSPP	ATC codes	Dichotomous	0 = no 1 = yes
	Hospitalized in previous year	CIHI-DAD	Hospital admission	Dichotomous	0 = no 1 = yes
	Greater than four physician visits in the previous year	MSI	Sum of physician visits per patient	Dichotomous	0 = no 1 = yes
	Number of unique prescribers	NSSPP	Provider ID	Dichotomous	0 = 1 prescriber 1 = 2 or more prescribers
	Hypertension diagnosis	CIHI-DAD, MSI database	ICD-9 codes: 401.x-405.x ICD-10 codes: I10.x-I15.x	Dichotomous	0 = no 1 = yes
Predictors of continuity of community pharmacy care	Sex	NSSPP	Sex	Dichotomous	0 = Female 1 = Male
	Age	NSSPP	Age	Ordinal	0 = 65-69 1 = 70-74 2 = 75-79 3 = 80 or older
	Income	2001 Canadian Census Data	Average 2001 household income	Continuous	0 = ≤ $20,000 1 = $20,000≤$40,000 2 = $40,000≤$60,000 3 = $60,000≤$80,000 4 = ≥$80,000

Use	Variable	Source Table	Source Variable	Unit of Measurement	Categories
Predictors of continuity of community pharmacy care (continued from previous page)	Place of residence	NSSPP	Forward sortation are of postal code	Dichotomous	0 = rural 1 = urban
	Greater than four distinct drugs	NSSPP	ATC codes	Dichotomous	0 = no 1 = yes
	Hospitalized in previous year	CIHI-DAD	Hospital admission	Dichotomous	0 = no 1 = yes
	Greater than four physician visits in the previous year	MSI database	Sum of physician visits per patient	Dichotomous	0 = no 1 = yes
	Chronic cardiovascular condition	CIHI-DAD, MSI database	ICD-9 codes: CHF : 428.x CKD : 585.x HTN : 401.x-405.x ICD-10 codes: CHF: I50.x CKD: N18.x HTN: I10.x-I15.x	Dichotomous	0 = no 1 = yes
	Diabetes	CIHI-DAD, MSI database	ICD 9 codes: 250.x ICD-10 codes: E10.x-E14.x	Dichotomous	0 = no 1 = yes

ATC: Anatomical Therapeutic Classification
CHF: congestive heart failure;
CIHI-DAD: Canadian Institute for Health Information Hospital Discharge Abstract Database;
COCI: Continuity of Care Index
CRF: chronic renal failure;
HTN: hypertension;
ICD-9: International Classification of Diseases, 9th Revision
MPR: Medication Possession Ratio
MSI: Medical Services Insurance

NSSPP: Nova Scotia Seniors' Pharmacare Program;
Physician Billings: Nova Scotia Medical Services Insurance Physician Billings database;
UPC: Usual Provider of Care Index

Appendix D: Results Tables

Table D1: Baseline continuity of community pharmacy care of Nova Scotia Seniors Pharmacare beneficiaries meeting inclusion criteria[f]

			Mean	SD[e]
UPC[a]			0.92	0.15
COCI[b]			0.87	0.21
UPC[a]	<1.0[c]		0.79	0.17
COCI[b]	<1.0[c]		0.68	0.22
			n	%
UPC[a]	1.0		15,610	61
	< 1.0		10,031	39
	1.0		15,610	61
	< 1.0[d]	High	3,349	13
		Moderate	3,337	13
		Low	3,345	13
COCI[b]	1.0		15,610	61
	<1.0		10,031	39
	1.0		15,610	61
	< 1.0[d]	High	3,346	13
		Moderate	3,371	13
		Low	3,314	13

[a]Usual Provider of Care Index
[b]Continuity of Care Index
[c]Continuity of care scores less than 1.0 indicate that the subject has been dispensed medication from more than one pharmacy.
[d]Continuity tertiles created from subject scores <1.0. high = highest tertile, Moderate = second tertile, Low = lowest tertile
[e]Standard deviation
[f]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D2: Summary of medication adherence to statins among Nova Scotia Seniors Pharmacare beneficiaries, among subjects meeting inclusion criteria[c], calculated by the Medication Possession Ratio (MPR) during the year after the index statin prescription

		n	%
MPR[a] category	MPR ≥ 0.80	15,096	59
	MPR < 0.80	10,545	41
		Mean	SD
MPR[a]		0.73	0.31
Number of statin prescriptions[b]		6.0	3.8

[a]Medication Possession Ratio

[b]During the year after the index statin prescription

[c]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D3: Adjusted relationship between continuous Usual Provider of Care (UPC) index and statin adherence for two adherence definitions: Medication Possession Ratio (MPR) ≥ 0.75 and MPR ≥ 0.90, among subjects who met inclusion criteria[h].

		MPR ≥75[b]		MPR ≥90[b]	
		OR	95% CI	OR	95% CI
UPC[a]		1.04	1.02-1.05	1.02	1.01-1.04
Sex	Male	1.00		1.00	
	Female	0.95	0.90-1.01	0.94	0.90-0.99
Age (years)	≥ 80	1.00		1.00	
	75-79	1.12	1.04-1.22	1.11	1.02-1.20
	70-74	1.19	1.10-1.29	1.11	1.03-1.20
	65-69	1.13	1.05-1.22	1.05	0.98-1.14
Income tertile[c]	High	1.00		1.00	
	Mod	0.92	0.86-0.98	0.90	0.84-0.96
	Low	0.88	0.82-0.94	0.84	0.78-0.90
	Unk[g]	0.99	0.85-1.15	1.02	0.88-1.17
Place of Residence	Urban	1.00		1.00	
	Rural	0.94	0.89-1.01	0.94	0.88-1.00
Use of greater than four	Yes	1.00		1.00	
medications[d]	No	0.92	0.86-0.98	0.86	0.81-0.92
Hospitalized[d]	Yes	1.00		1.00	
	No	0.97	0.93-1.05	0.93	0.88-0.99
Greater than four physician	Yes	1.00		1.00	
visits[d]	No	0.97	0.88-1.07	0.95	0.86-1.05
Statin Dose[e]	High	1.00		1.00	
	Low	1.03	0.98-1.09	0.90	0.94-1.04
Hypertension	Yes	1.00		1.00	
	No	0.85	0.81-0.90	0.86	0.82-0.91
Number of prescribers[f]	1	1.00		1.00	
	>1	2.66	2.49-2.84	2.09	1.96-2.21

[a]Usual provider of care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D4: Adjusted relationship between complete continuity of community pharmacy care (continuity of care score equal to 1.0) and statin adherence among subjects who met inclusion criteria[h]

		MPR ≥0.80[b]	
		OR	95% CI
UPC[a]	1.0	1.00	
	<1.0	0.90	0.86-0.96
Sex	Male	1.00	
	Female	0.94	0.89-0.99
Age (years)	≥ 80	1.00	
	75-79	1.13	1.04-1.22
	70-74	1.17	1.08-1.25
	65-69	1.10	1.02-1.19
Income tertile[c]	High	1.00	
	Mod	0.91	0.85-0.97
	Low	0.86	0.80-0.92
	Unk[g]	0.99	0.86-1.15
Place of Residence	Urban	1.00	
	Rural	0.97	0.91-1.03
Use of greater than four	Yes	1.00	
medications[d]	No	0.91	0.85-0.97
Hospitalized[d]	Yes	1.00	
	No	0.95	0.90-1.00
Greater than four	Yes	1.00	
physician visits[d]	No	0.96	0.87-1.05
Statin Dose[e]	High	1.00	
	Low	1.02	0.97-1.08
Hypertension	Yes	1.00	
	No	0.85	0.81-0.89
Number of prescribers[f]	1	1.00	
	>1	2.45	2.29-2.61

[a]Usual provider of care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first

statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D5: Adjusted relationship between four Usual Provider of Care (UPC) index strata and statin adherence among included subjects[h]

		MPR ≥80[b]	
		OR	95% CI
UPC[a]	1.0	1.00	
	High	0.95	0.87-1.03
	Mod	0.87	0.80-0.94
	Low	0.90	0.83-0.98
Sex	Male	1.00	
	Female	0.94	0.89-0.99
Age (years)	≥ 80	1.00	
	75-79	1.13	1.04-1.22
	70-74	1.17	1.08-1.26
	65-69	1.10	1.02-1.19
Income tertile[c]	High	1.00	
	Mod	0.91	0.85-0.97
	Low	0.86	0.80-0.92
	Unk[g]	1.00	0.86-1.15
Place of Residence	Urban	1.00	
	Rural	0.96	0.91-1.02
Use of greater than four	Yes	1.00	
medications[d]	No	0.91	0.85-0.97
Hospitalized[d]	Yes	1.00	
	No	0.95	0.90-1.01
Greater than four physician	Yes	1.00	
visits[d]	No	0.96	0.87-1.05
Statin Dose[e]	High	1.00	
	Low	1.02	0.97-1.08
HTN	Yes	1.00	
	No	0.85	0.81-0.89
Number of prescribers[f]	1	1.00	
	>1	2.45	2.29-2.61

[a]Usual provider of care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown

[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D6: Adjusted relationship between continuity of community pharmacy care and statin adherence among included subjects[h] who live in urban areas of Nova Scotia

		MPR ≥80[b]	
		OR	95% CI
UPC[a]		1.02	1.00-1.04
Sex	Male	1.00	
	Female	0.95	0.89-1.02
Age (years)	≥ 80	1.00	
	75-79	1.09	0.98-1.21
	70-74	1.14	1.03-1.26
	65-69	1.10	1.00-1.22
Income tertile[c]	High	1.00	
	Mod	0.86	0.79-0.94
	Low	0.81	0.74-0.88
	Unk[g]	0.99	0.82-1.19
Use of greater than four	Yes	1.00	
medications[d]	No	0.92	0.84-1.00
Hospitalized[d]	Yes	1.00	
	No	0.93	0.87-1.01
Greater than four	Yes	1.00	
physician visits[d]	No	0.94	0.82-1.07
Statin Dose[e]	High	1.00	
	Low	1.04	0.97-1.12
Hypertension	Yes	1.00	
	No	0.86	0.80-0.92
Number of prescribers[f]	1	1.00	
	>1	2.42	2.22-2.63

[a]Usual provider of care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D7: Adjusted relationship between continuity of community pharmacy care and statin adherence among included subjects[h] who live in rural areas of Nova Scotia

		MPR ≥80[b]	
		OR	95% CI
UPC[a]		1.04	1.01-1.07
Sex	Male	1.00	
	Female	0.93	0.86-1.01
Age (years)	≥ 80	1.00	
	75-79	1.18	1.04-1.34
	70-74	1.21	1.07-1.36
	65-69	1.11	0.98-1.25
Income tertile[c]	High	1.00	
	Mod	0.96	0.89-1.11
	Low	0.95	0.85-1.07
	Unk[g]	1.02	0.80-1.30
Use of greater than four	Yes	1.00	
medications[d]	No	0.92	0.83-1.02
Hospitalized[d]	Yes	1.00	
	No	0.98	0.90-1.07
Greater than four	Yes	1.00	
physician visits[d]	No	0.98	0.85-1.13
Statin Dose[e]	High	1.00	
	Low	0.99	0.91-1.08
Hypertension	Yes	1.00	
	No	0.84	0.77-0.91
Number of rescribers[f]	1	1.00	
	>1	2.49	2.25-2.75

[a]Usual provider of care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D8: Adjusted relationship between continuity of community pharmacy care and statin adherence among included subjects[h] hospitalized during the year prior to the index statin.

		MPR ≥80[b]	
		OR	95% CI
UPC[a]		1.02	0.99-1.05
Sex	Male	1.00	
	Female	0.95	0.87-1.04
Age (years)	≥ 80	1.00	
	75-79	1.11	0.98-1.26
	70-74	1.11	0.99-1.25
	65-69	0.92	0.81-1.04
Income tertile[c]	High	1.00	
	Mod	0.92	0.82-1.02
	Low	0.90	0.81-1.01
	Unk[g]	0.90	0.71-1.15
Place of Residence	Urban	1.00	
	Rural	0.95	0.87-1.05
Use of greater than 4	Yes	1.00	
Drugs[d]	No	0.93	0.79-1.08
Greater than 4 doctor visits[d]	Yes	1.00	
	No	1.06	0.55-2.06
Statin Dose[e]	High	1.00	
	Low	1.05	0.96-1.14
Hypertension	Yes	1.00	
	No	0.83	0.76-0.90
Number of prescribers[f]	1	1.00	
	>1	2.83	2.58-3.10

[a]Usual provider of care index
[b]Medication possession ratio
[c]Average 2001 household income, by census enumeration area
[d]During the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the adherence assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D9: Adjusted relationships between continuity of community pharmacy care and statin adherence among included subjects[h] who received 13 or fewer statin dispensations during the adherence assessment period.

		MPR ≥80[b]	
		OR	95% CI
UPC[a]		1.03	1.02-1.05
Sex	Male	1.00	
	Female	0.93	0.88-0.98
Age (years)	≥ 80	1.00	
	75-79	1.15	1.06-1.25
	70-74	1.21	1.12-1.31
	65-69	1.15	1.06-1.24
Income tertile[c]	High	1.00	
	Mod	0.91	0.85-0.97
	Low	0.86	0.80-0.92
	Unk[g]	0.93	0.80-1.08
Place of Residence	Urban	1.00	
	Rural	0.97	0.91-1.03
Use of greater than 4	Yes	1.00	
Drugs[d]	No	0.93	0.87-1.00
Hospitalized[d]	Yes	1.00	
	No	0.97	0.91-1.03
Greater than 4 doctor visits[d]	Yes	1.00	
	No	0.95	0.86-1.05
Statin Dose[e]	High	1.00	
	Low	1.03	0.98-1.09
Hypertension	Yes	1.00	
	No	0.84	0.80-0.89
Number Prescribers[f]	1	1.00	
	>1	2.39	2.24-2.55

[a]Usual Provider of Care Index
[b]Medication Posession Ratio
[c]Average 2001 household income, by census enumeration area
[d]During the final year of the continuity assessment period
[e]Low dose: atorvastatin < 20mg, simvastatin < 40mg, rosuvastatin < 10mg or any dose of pravastatin, lovastatin or fluvastatin. High dose: all other molecules and strengths
[f]During the continuity assessment period
[g]Unk: income unknown
[h]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first

statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D10: Demographic characteristics of included subjects[f], stratified by complete or incomplete continuity of community pharmacy care

		Complete[a]		Incomplete[b]	
		n	%	n	%
Age (years)	65-69	4,884	31	2,716	27
	70-74	4,570	29	2,985	30
	75-79	3,375	22	2,201	22
	≥ 80	2,781	18	2,129	21
Sex	Male	6,655	57	3,959	39
	Female	8,955	43	6,072	61
Income[c]	≤20	92	1.0	53	1.0
	20<40	5,461	36	3,376	35
	40<60	7,670	52	4,808	50
	60<80	1,471	10	1,056	11
	≥80	434	3.0	310	3.0
	Unk[e]	482	3.0	428	4.0
Place of residence	Urban	9,065	58	5,959	59
	Rural	6,541	41	4,070	41
Use of greater than four medications[b]	Yes	11,866	76	8,535	85
	No	3,744	24	1,496	15
Hospitalized	Yes	5,388	35	4,368	44
	No	10,222	65	5,663	56
Greater than four physician visits[b]	Yes	14,007	90	9,437	94
	No	1,603	10	594	6.0
CVD[d]	Yes	9,239	59	6,119	61
	No	6,371	41	3,912	39
Diabetes	Yes	4,112	26	2,895	29
	No	11,498	74	7,136	71

[a]Subjects with continuity of care scores equal to 1.0
[b]Subjects with continuity of care scores less than to 1.0
[c]Average 2001 household income, thousands of dollars, by census enumeration area
[d]Composite of congestive heart failure, chronic kidney disease and hypertension
[e]Unk: income unknown
[f]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D11: Predictors of continuity of community pharmacy care among included subjects[e] living in urban areas at the end of the continuity assessment period

n=15,024		Unadjusted		Adjusted	
		OR	95% CI	OR	95% CI
Age (years)	≥80	1.00		1.00	
	75-79	1.14	1.03-1.26	1.07	0.97-1.18
	70-74	1.15	1.05-1.26	1.03	0.93-1.13
	65-69	1.41	1.28-1.55	1.20	1.09-1.32
Sex	Male	1.0		1.0	
	Female	0.83	0.77-0.88	0.83	0.77-0.89
Income[a]	≥80	1.0		1.0	
	60<80	1.02	0.86-1.21	1.03	0.87-1.23
	40<60	1.19	1.02-1.40	1.23	1.05-1.44
	20<40	1.21	1.03-1.42	1.27	1.08-1.50
	≤20	1.30	0.90-1.89	1.43	0.98-2.07
	Unk[d]	0.79	0.63-0.98	0.84	0.67-1.06
Use of greater than four medications	Yes	1.0		1.0	
	No	1.78	1.63-1.94	1.48	1.35-1.63
Hospitalized[b]	Yes	1.0		1.0	
	No	1.45	1.36-1.56	1.29	1.20-1.38
Greater than four physician visits[b]	Yes	1.0		1.0	
	No	2.05	1.79-2.35	1.56	1.35-1.80
CVD[c]	Yes	1.0		1.0	
	No	1.06	0.99-1.13	0.95	0.88-1.01
Diabetes	Yes	1.0		1.0	
	No	1.17	1.09-1.26	1.10	1.02-1.19

[a]Average 2001 household income, by census enumeration area
[b]During the final year of continuity assessment
[c]Composite of congestive heart failure, chronic kidney disease and hypertension
[d]Unk: income unknown
[e]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

Table D12: Predictors of continuity of community pharmacy care among included subjects[e] who were hospitalized during the final year of continuity assessment

N=9,756		Unadjusted		Adjusted	
		OR	95% CI	OR	95% CI
Age (years)	≥ 80	1.00		1.00	
	75-79	1.21	1.08-1.36	1.18	1.05-1.33
	70-74	1.13	1.01-1.26	1.06	0.95-1.19
	65-69	1.37	1.22-1.54	1.27	1.13-1.24
Sex	Male	1.00		1.00	
	Female	0.83	0.77-0.90	0.87	0.80-0.94
Income[a]	≥80	1.00		1.00	
	60<80	1.08	0.83-1.40	1.10	0.85-1.44
	40<60	1.09	0.87-1.38	1.13	0.89-1.43
	20<40	1.07	0.85-1.36	1.13	0.88-1.44
	≤20	0.97	0.57-1.66	1.05	0.61-1.80
	Unk[d]	0.70	0.52-0.96	0.74	0.54-1.01
Place	Urban	1.00		1.00	
	Rural	0.96	0.88-1.04	1.02	0.94-1.11
Use of greater than four medications[b]	Yes	1.00		1.00	
	No	2.08	1.79-2.43	1.95	1.66-2.28
Greater than four physician visits[b]	Yes	1.00		1.00	
	No	1.88	0.98-3.60	1.27	0.65-2.48
CVD[c]	Yes	1.00		1.00	
	No	1.09	1.01-1.19	1.02	0.93-1.11
Diabetes	Yes	1.00		1.00	
	No	1.18	1.08-1.27	1.13	1.04-1.24

[a]Average 2001 household income, by census enumeration area
[b]During the final year of continuity assessment
[c]Composite of congestive heart failure, chronic kidney disease and hypertension
[d]Unk: income unknown
[e]Dispensed first statin at least one year after enrolling in the Nova Scotia Seniors' Pharmacare program; at least two dispensation dates for any medication prior to the first statin. No dispensation for cerivastatin; or any other cholesterol lowering medication; no diagnosis of renal dialysis or renal transplant in the year prior to the first statin.

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