CARDIOVASCULAR RISK REDUCTION,

MEDICATION ADHERENCE AND SOCIO-ECONOMIC STATUS (SES)

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Saskatoon

By

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ABSTRACT

Profound advances in cardiovascular disease (CVD) treatments have been made over the last two decades. However, poor adherence to preventative therapies remains a critical problem in the health of Canadians. Despite decades of research, contemporary knowledge about adherence is often based on theory that has not been confirmed with quantitative research findings. For example, adherence to preventative medications is widely considered to reduce risks for major health outcomes. However, major differences in the estimation of medication adherence benefits exist. Thus, a study was conducted to determine if the association between poor adherence and the risk of death was influenced by the method used to identify optimal adherence. The impact of adherence to statin medications on mortality was assessed among a cohort of 9,051 individuals who received a statin medication following discharge from a hospitalization for acute coronary syndrome (ACS). Using a fixed-summary measure, optimal adherence to statins was not associated with mortality benefits (adjusted HR 0.97, 95%CI 0.86 to 1.09, p=0.60). In contrast, the repeated measures approach resulted in a significant 25% reduction in the risk of death among adherent individuals (adjusted HR 0.75, 95%CI 0.67 to 0.85, p<0.01). However, neither estimate could be regarded as the most robust. Thus, until a gold standard method is established, researchers should report the estimates resulting from both methods.

Among all adherence predictors, socioeconomic status (SES) is widely considered to be prominent because of its associations with many factors theoretically affecting adherence such as economic, social, and education-related features. However, published studies have reported inconsistent results about the impact of SES on adherence. A systematic review of published studies examining predictors of antihypertensive medications adherence was performed. Almost half of studies reviewed neglected to measure SES; and in studies where SES was measured,

income assessment was typically the only measure. Overall, only a minor association between SES and adherence was observed after pooling all available data (pooled adjusted risk estimate for non-adherence according to SES (high versus low) 0.89, 95% CI 0.87 to 0.92; $p<0.001$).

It was hypothesized that the performance of adherence prediction models would improve if SES was represented using more comprehensive measures. A retrospective cohort of individuals who received a statin medication following discharge from a hospitalization for coronary heart disease was identified and followed for one year. Multi-domain measures did not improve the prediction performance of the population adherence model compared to single-domain measures. Overall, all SES measures examined had a very limited impact on prediction adherence.

Supporting patients to adhere to their medications is a vital goal health care providers strive to achieve. Non-adherence to preventative medications is highly prevalent among patients surviving acute coronary syndrome (ACS). However, only few patients receive appropriate care after their ACS through support programs such as cardiac rehabilitation (CR). Because pharmacist's interventions were shown to have beneficial impact on medication adherence in various settings, a streamlined pharmacist's intervention in CR setting was investigated through a randomized clinical trial. The impact of this intervention was assessed through the proportion of patients who achieved optimal adherence. Although this proportion did not improve among the intervention group in comparison to the control group, an unexpected high prevalence of optimal adherence was obtained. A selection bias of highly motivated individuals in this study may explain this extraordinary adherence level.

Results of the four independent research studies included in this dissertation provide novel insight relating to the factors, outcomes, and possible modalities to mitigate non-adherence in Canada. Further research is essential to help in relieving this major population health problem.

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'Whoever does not thank people has not thanked Allah' (Prophet Mohammad)[1]

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[1] (Musnad Ahmad, Sunan At-Tirmidhî)

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DEDICATION

I dedicate this thesis first to the soul of my late father Moffa who passed away due to a heart attack. May his soul be showered with the mercy of Allah. I also dedicate this thesis to my mother Basema, whose dream to graduate could not realized, in spite of the fact of being among the first females to attend pharmacy school at the university of Damascus. I hope that completing my program could partially fulfill your dream.

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CHAPTER -1- INTRODUCTION

"Patient compliance has become the best documented, but least understood, health behaviour"

Becker and Maiman[1]

1.1 Rational

Cardiovascular disease (CVD) is the second leading cause of death in Canada, causing approximately 27 % of all Canadian deaths.[2] In addition, CVD is responsible for a high burden of morbidity across the country. Every year over 55,000 Canadians are treated for a myocardial infarction requiring approximately 500,000 days of hospitalization.[3] As a result, the total cost of CVD exceeds $20 billion dollars annually.[4] Considering that many CVD events recur at a high rate, prevention strategies aimed to patients with established disease is a high priority for the entire nation.[5]

Several pharmacological therapies reduce the risk for recurrent events in patients who survive a heart attack. For example beta-blockers (BB), antiplatelet agents, angiotensin converting enzyme inhibitors (ACEI), and lipid lowering agents such as statins can independently decrease the incidence of new vascular event by almost 25% in addition to improving quality of life.[6,7] Despite these highly successful results in clinical trials, cohort studies have shown that evidence-based pharmacotherapy may be underused in the post-myocardial infarction (post-MI) period. Much of this underutilization can be attributed to poor medication adherence.

1.2 Medication Adherence

Medication adherence is often defined as the act of taking medications according to a prescription given by a health care professional, both in terms of the right dose and the right

interval.[8-10] Various alternative terms for adherence have been proposed to recognize the role of patients in the decision-making process about their medications.[11,12] The term compliance is no longer favoured because it infers a passive obedience to the prescriber's instructions.[10,13] In contrast, the term concordance was proposed to recognize patients as active participants in their own care.[14] Regardless of the term used to describe this phenomenon, it is agreed that medications should be taken in a manner that replicates clinical trials in order to achieve the expected therapeutic benefits. Decades of research have repeatedly shown that adherence to medications is extremely poor among patients with chronic diseases. On average, only half of all patients who are prescribed a long-term (i.e., chronic) medication continue to take it regularly as prescribed.[8] The cost of medication non-adherence has been estimated over $100 billion annually in the United States making it a priority for health care providers and policy makers alike[8]

1.3 Types of non-adherence

By definition, medication non-adherence can be exhibited by individuals who over-use, under-use, or do not take their medications at all. However, the main focus of adherence research relates to the problem of medication under-use, especially among individuals with chronic diseases.[15] Medication non-adherence relating to under-use is commonly stratified into three distinct categories: a) primary non-adherence, b) secondary non-adherence (or poor execution), and C) non-persistence.[9,16] These three types of non-adherence are defined by unique refill patterns and probably differ in terms of their prevalence, causes and potential solutions.[17,18] Accordingly, it is important to identify the specific type of non-adherence reported in published studies to prevent inaccurate interpretations of available data.[19]

Between 5 to 30% of prescriptions ordered for patients are never picked up from a pharmacy. This pattern of non-adherence is defined as "*primary non-adherence*".[20-25] In many prescription databases, it is impossible to distinguish primary non-adherence from cases where prescribers have not issued a prescription at all. In fact, under-prescribing has been the focus of numerous health care system studies looking at the management of patients with chronic diseases.[26-28] However, the emergence of electronic prescriptions and electronic health records has enabled researchers to recognize primary non-adherence that may have been previously misclassified as underprescribing.[29,30] Similarly, the provision of prescriber-issued samples of new medication may also be misclassified as primary non-adherence or underutilization in databases with limited access to prescribing information.[31-33]

Poor execution (or secondary non-adherence) is exhibited when patients skip doses, fail to obtain refills on time, or interrupt therapy for periods of time.[11,34] This pattern of non-adherence is unique because individuals continue to take their medication, albeit in lower-than recommended quantities. As discussed earlier, other terms such as "*non-compliance*" have been used to describe this pattern of medication behaviour, but its use is declining because it implies a paternalistic relationship between patients and prescribers.

Finally, patients often discontinue their medications altogether. This pattern of non-adherence is termed non-persistence.[35] Persistence is often measured by the length of time between filling the first prescription to discontinuation of the medication altogether.[10,11]

1.4 Assessment of adherence using electronic refill claims databases

Electronic prescription refill databases are the most frequently used information sources for adherence studies, and are especially useful for studying large populations.[36] These databases

enable researchers to quantify non-adherence in large cohorts using objective methods and are not subject to the bias associated with self-reporting.

Electronic refill databases can also be linked to other health-administrative databases allowing researchers to examine the association between medication adherence and health outcomes. For example, administrative databases have been used to quantify the level of morbidity and mortality associated with non-adherence by linking prescription records with other health administrative databases.[37-45] For instance, Pladevall *et al* linked prescription records with laboratory data and reported that an increase of 10% in non-adherence to metformin and statins was associated with an increase of 0.14% in HbA_{1c} and an increase of 4.9 mg/dl in LDL cholesterol levels.[46] Similarly, Ho *et al* linked prescription records with vital statistics database and found that adherence to cardio-protective medications including ACE inhibitors or angiotensin receptor blockers, beta-blockers, and statin was associated with a 48% relative reduction in all-cause mortality.[47] However, investigating major health outcomes among adherent and non-adherent patients is difficult due the potential for bias between these non-randomized comparator groups. Little information is available to understand the most robust approach to examine the influence of adherence on major health outcomes.

Adherence estimates generated from electronic dispensation records have been compared with other methods of measurements. Generally, administrative data adherence measures were found to have moderate association with serum or urine medication levels and with physiological effects of the medication.[48] However, some studies showed a strong association with serum drug level and physiological effects. For example, refill measures of adherence to the anticonvulsant medication phenytoin were found to be significantly associated with mean plasma concentration of the medication.[49] Similarly, measures of adherence to blood pressure medications was found

to be strongly associated with controlled blood pressure.[49] In addition, adherence measured through refill databases are highly correlated to pill counts or home inventories.[48,50-52] Grymonpre *et al* examined prescription refill data amongst community-dwelling subjects who were taking 2 or more medications (including ACEIs) during 3 home visits. Compared to pill counts, consistently high concordance was observed for non-ACE inhibitors and ACE inhibitors alike (85% and 95% respectively).[50]

This method, however, has several theoretical limitations. First, filling a prescription constitute a mandatory but not adequate condition for drug consumption. Patients may not consume the medications after they have filled the prescription, or may consume them in erratic times. [53] Accordingly, administrative database measure of adherence may in fact overestimate adherence levels. Second, patients my use free medication samples obtained from their physician, and not fill a prescription through a pharmacy. Third, these databases do not usually include information about medication that can be obtained without a prescription (over the counter medications or OTCs). Lastly, some databases may not include prescriptions filled in pharmacies outside a specific managed care system. Most importantly, administrative databases usually lack important clinical variables required for adherence prediction models. Regardless of its limitations, this method is the most validated practical and low cost method to be used in large population-based studies.

1.5 Specific burden of non-adherence in cardiovascular medications

Adherence to cardiovascular medications is suboptimal. In terms of primary non-adherence, it seems that almost one in five patients do not obtain even a single fill of their prescription for cardiovascular medications. In Massachusetts, for example, a study reported that 20% of new e-prescriptions for anti-hypertensives (AHT) and lipids prescriptions were not filled at all.[29]

Similarly, in Ontario, 26% of patients who survived myocardial infarction (MI) did not fill all cardiovascular medications prescriptions within 120 days after discharge from hospital.[54] Similar findings were reported in other jurisdiction.[55,56]

Poor- execution and non-persistence are also very common with CVD medications. For example, in Saskatchewan, only about 60% of patients surviving an acute MI remained adherent (adherence> 80%) to statins, B-blockers, or ACEI after one year.[57] The remaining 40% either continued their medication with lower frequency, or stopped their medication altogether. Discontinuation rates for statins medications range from 19% at 30 days to 40% after one year of treatment initiation.[58] Likewise, the discontinuation rates of anti-hypertension medications are comparable.[59-61] The highest risk for non-adherence occurs early in the treatment regardless of the type of CVD medication studied. For example, out of all patients classified as non-adherent in their first year of statin therapy, 40% had completely discontinued the medication within 3 months of the first dispensation.[62] In another study, 22% of patients who received a new prescription for statin medication did not have a second fill of their prescription.[63] Among new users of antihypertensive medications, 39% of all non-adherent patients had only received a single refill before quitting.[64] This phenomenon has been shown frequently in the literature among multiple populations.[57,65,66]

Despite the wealth of studies showing very poor adherence to virtually all types of chronic medications. There are signs that rates of adherence have slowly improved in recent years.[67-69] For example, overall adherence to BBs among heart failure patients increased by almost 50% between 1994 and 2003.[70] Similar trends have been observed with statins,[71] and other anti-hypertensive medications[72] but the specific reasons for these positive trends remain unclear.

Nonetheless, a substantial burden of non-adherence remains to virtually all chronic disease medications.

1.6 Importance of medication adherence

Optimal adherence to chronic medications has been associated with positive therapeutic outcomes for many chronic health-conditions.[73-76] For example, individuals exhibiting good adherence to antihypertensives have lower blood pressure than those who do not.[77] Similarly, optimal adherence to cholesterol-lowering medications has been associated with a significant reduction in low density lipoprotein-cholesterol (LDL-cholesterol).[78] More notably, adherence to medications has been associated with significant reductions in morbidity and mortality. For instance, chronic medication adherence was associated with a 44% reduction (95% CI 26% to 57%) in all-cause mortality in a systematic review pooling results from 8 randomized clinical trials and 13 observational cohort studies containing 46,847 subjects with different disease states.[79]

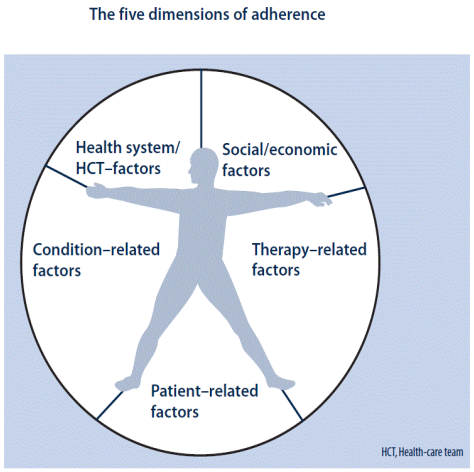
Among these studies, non-adherence to statin medications was found to be associated with increased mortality risk (HR=1.25),[80] and a significant increase in major coronary events following discharge from a myocardial infarction.[81,82] Similarly, stopping statin medications after discharge from a myocardial infarction was found to be associated with an increased risk of a re-infarction (HR= 1.66).[83] However, the estimated effect of optimal adherence to statin medications and mortality has varied significantly between studies. The reduction in mortality associated with optimal statin adherence ranges from 20% in some studies,[80] and up to 80% in others.[84] One of the most important reasons for these variable estimates is the presence of bias between patients who exhibit optimal adherence versus those exhibiting poor adherence. In general, high adherence to a chronic medication may be a marker of other healthy behaviours

that can influence patient outcomes. This 'healthy adherer' effect becomes difficult to identify and account for in analyses of health outcomes associated with various adherence levels.[79] Although many published studies have reported substantial benefits of optimal statin adherence with respect to lower morbidity and mortality, few studies have investigated how different study designs may influence the estimates themselves. More research is needed to understand the most robust approach to obtain valid estimates of the benefits of optimal adherence on health outcomes. These estimates are important for health services planning and policy development as well as understanding the areas where health care services can be improved.

1.7 Determinants of non-adherence

A vast number of potential adherence determinants have been examined previously in the literature.[85-88] The World Health Organization (WHO) divides possible determinants into four broad categories: patient variables, disease variables, treatment variables, and health-system variables.[18,89] Sometimes, social/economic variables are distinguished from patient variables (Figure 1-1).[12] Patient variables include age, gender, race, and patient's beliefs, knowledge and attitudes.[90] Treatment variables include treatment regimen complexity,[91,92] number of doses per day,[93] cost of medications,[8,94,95] the overall burden of prescribed medications,[96] administration route,[97] appearance of the medication,[98,99] side effects[8,16,100] and the duration of the treatment.[101] Disease-related variables include disease severity, symptom severity, and disease duration.[102] Health-system variables include the level of personalized or individual care, the availability of on-site interactions with patients (such as home care), and the quality of the communication between HCP and patients.

Figure 1-1: Categories of the determinants of adherence.*



* Sabate´ E. Adherence to Long-Term Therapies: Evidence for Action. Vol 2011. http://www.who.int/chp/knowledge/publications/adherence_report/en/ ed. Geneva, Switzerland: World Health Orgnization; 2003.

1.7.1 Social-Economic Status (SES)

Socioeconomic status (SES) is an intriguing determinant of non-adherence because of its associations with economic, social, and education-related factors. It is a multifactorial characteristic that represents an individual's position relative to a social hierarchy and is determined by economic, social, and employment-related factors.[103 104] SES cannot be understood without a comparison to others in a given population; individuals with high SES possess more material resources, have greater access to educational opportunities, and receive more social support compared to those in low SES strata.[105]

SES is an important predictor of health status, health care system utilization, as well as health outcomes. Individuals characterized in low SES strata consistently experience poorer health in terms of higher infant mortality as well as higher incidence of both infectious and non-infectious

diseases.[104,106] For example, low SES was found to be associated with a 44% increase in the risk of coronary heart disease after adjusting for all other risk factors.[107]

SES is a complex integration of multiple factors that include both material and social domains.[104] However, the impact of SES on health outcomes cannot be attributed to one factor in isolation of other factors.[106,108] Individuals with low SES may face important barriers to accessing health care services,[109] they may have poor health literacy,[110] they may be unable to prioritize health due to other daily struggles, and/or they may be unable to afford health treatments or lifestyle modification strategies. Although research on SES has primarily focused on the negative impact of these factors on health outcomes, a strong theoretical link can be made for their impact on medication adherence also. Thus, using comprehensive measures of SES could potentially improve the ability of multivariate models to explain the determinants of medication non-adherence. However, objective evidence for the role of SES as a determinant of medication adherence is lacking.

1.8 Interventions to improve adherence

Several randomized controlled trials (RCTs) have been performed to examine interventions focused on improving adherence to chronic medications.[111-115] Interventions may be targeted by the provider at patient-level, or may be applied universally at health-system or policy-levels.[116] Within patient-level interventions, three main categories can be identified: informational, behavioural, and combined strategies.[115] Most adherence interventions provide patient-education or individualized patient-care from allied health care professionals (i.e., pharmacists or nurses).[117]

1.8.1 Pharmacist's interventions

Several studies have examined community pharmacist interventions to increase medication adherence. In a systematic review of studies examining pharmacist interventions to improve care for patients with diabetes, Evans *et al* identified 40 studies overall; 9 of these interventions were targeting medication adherence.[118] In general, interventions involve lengthy multi-steps interactions with patients.[118] For example, in one randomized controlled trial to improve adherence to statin medications, participants were required to return to the pharmacy for five appointments lasting 10-15 minutes each. Visits contained extensive counseling about statin indications, benefits, adverse effects, dosing; importance of adherence, and intended duration of treatment.[119] In addition, a letter were sent to patients to request information about statin medications, any drug-related problems, and barriers to adherence. At the end of the study, adherence did not differ significantly between intervention group and control group (99.5%, and 99.2% respectively).

Altogether, published interventions are expensive and time consuming, making implementing them in real life practice difficult to implement.[117] At the same time, it is recommended that adherence interventions must be multifaceted and persistent in order to impact adherence in a meaningful way. Thus, more work is required to investigate efficient interventions able to support adherence without placing unreasonable demands on health care providers.

1.9 Summary

Poor adherence to medications is a major problem in health care that remains poorly understood. Although estimates about the prevalence of poor adherence have been consistently derived from population based studies, disagreement persists regarding many other facets of this problem. First, despite strong theoretical frameworks for the root causes of poor adherence, the importance

of certain factors such as socioeconomic status remains unproven. Second, widely published estimates of the benefits of optimal adherence on health outcomes have not been scrutinized for the possible role of bias such as the healthy adherer phenomenon. Finally, successful interventions have not been identified; previous attempts have had minimal effects or have been highly demanding on health provider time. Therefore, a PhD. research program was carried out to examine various aspects of medication adherence to cardiovascular medications using various research methodologies.

1.10 Research questions:

1) Does the association between adherence to statin medications and mortality depend on the study design?
2) To what extent can socio-economic status (SES) influence non-adherence to anti-hypertensive (AHT) medications; and what are the approaches used in the literature to account for it?
3) Does the use of multiple-domain measure of SES have a stronger association with non-adherence to statin medications compared to single domain measures?

Can a streamlined, easy to implement pharmacist intervention improve adherence among cardiac rehabilitation patients?

1.11 Research Objectives

The objectives of this program of research were:

1) To perform an observational study examining the association between statin adherence and mortality using a fixed baseline measure (i.e., a summary measure) and a repeated-measures approach to contrast the estimates for benefit and investigate signs of bias in each.

2) To perform a systematic review and meta-analysis of the literature pertaining to SES and non-adherence to AHT medications using population-based electronic prescription data to estimate the proportion of studies that identified SES as a potential risk indicator of non-adherence; to describe the type of SES measurements that were used in each study; and to quantify the association between SES and non-adherence to AHT medications.

3) To perform an observational study examining if the use of the multiple domain measure of SES, the deprivation index, would be a stronger predictor of non-adherence to statin medications compared to single domain measures among a cohort of patients with established CHD in Saskatchewan, Canada.

4) To perform a randomized controlled trial examining if an expanded pharmacist role in a cardiac rehabilitation program can improve the accessibility to patients AND improve health indicators such as adherence and risk factor control.

1.12 Program of Research

This thesis is composed of four separate, but related, studies. Each individual study addresses a specific research question serving the overall research objective related to medication adherence to cardiovascular medications. The first study (chapter 2) is an observational study that compared the association between statin medication adherence and all-cause mortality when adherence was assessed by fixed summary measure and by repeated-measures methods. The second study (chapter 3) is a systematic review and meta-analysis that examined the use of SES as a potential

risk indicator of non-adherence to AHT medications. The third study (chapter 4) is an observational study that compared the association between adherence to statin medications and SES when it was measured by multiple-domain and by single-domain measures. The fourth study (chapter 5) is a randomized clinical trial examining the intervention of clinical pharmacist to improve medications adherence.

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CHAPTER -2- DOES THE ASSOCIATION BETWEEN ADHERENCE TO STATIN MEDICATIONS AND MORTALITY DEPEND ON MEASUREMENT APPROACH? A RETROSPECTIVE COHORT STUDY

2.1 Abstract

Background: Optimal adherence to statin medications has been associated with low mortality rates. However, it is not clear if the estimated benefits of statin adherence are influenced by the measurement strategy. *Objectives:* The aim of this study was to examine the relationship between mortality and statin adherence using two different approaches to adherence measurement (summary versus repeated-measures). *Methods:* A retrospective cohort study was conducted using administrative data from Saskatchewan, Canada between 1994 and 2008. Eligible individuals received statins following discharge from a hospitalization for acute coronary syndrome (ACS). Adherence was measured using proportion of days covered (PDC) expressed either as: 1) a fixed summary measure, or 2) as a repeatedly measured covariate. Cox-proportional hazards models were used to estimate the association between each adherence

measure and mortality after multivariable adjustment. *Results:* Among 9,051 eligible individuals, optimal adherence (≥80%) modeled with a fixed summary measure was not associated with mortality benefits (adjusted HR 0.97, 95%CI 0.86 to 1.09, p=0.60). In contrast, optimal adherence defined by the repeated-measures approach was associated with a significant 25% reduction in the risk of death (adjusted HR 0.75, 95%CI 0.67 to 0.85, p<0.01). *Conclusions:* The relationship between statin adherence and mortality is largely influenced by the measurement approach used. Although surveillance of adherence and health outcomes should continue, estimates must be generated using different measures until the most valid approach can be identified.

2.2 Background

Observational studies using health-administrative databases have reported low mortality rates among individuals exhibiting high adherence to statin medications (HMG Co-A reductase inhibitors).[120] However, these studies have produced highly variable estimates of benefit. Depending on the study, individuals exhibiting high adherence have been associated with 20%,[80] 50%,[121,122] or even 81%[84] lower risks of death. An important source of variability may be due to the different approaches used to measure adherence.

In studies using electronic refill databases, adherence is often measured by the 'medication possession ratio' (MPR) or the 'proportion of days covered' (PDC). This approach estimates the percentage of days during a defined observation period where medication was available for consumption based on the total quantity obtained from pharmacy refills.[25] In descriptive studies, adherence is typically expressed as a single measure summarizing the entire observation period often lasting one year or more.[123-125] Although the summary measure of adherence offers a

simple and straightforward result to represent the entire period of follow-up, it does not account for the possibility that patients may exhibit different levels of adherence over time.

Medication adherence can also be measured repeatedly during a period of follow-up and regarded as a time-dependent variable.[126,127] This measurement method may have advantages over the summary measure because it is more sensitive to changes in adherence over time. For example, a summary adherence measure of 58% calculated over a one-year period could actually reflect an individual with 16% adherence during the first six months and 100% adherence in the last six months of observation. In fact, it has been suggested that a repeated-measures approach is advantageous in revealing a robust association with mortality.[127-129] However, no empiric data can be found to support this claim. Indeed, no previous study has investigated if the association between mortality and medication adherence is influenced by measurement approach. Thus, we contrasted the estimated impact of statin adherence on mortality using two measurement approaches, a fixed summary measure versus repeated-measures, on the same cohort of patients with acute coronary syndrome.

2.3 Methods

2.3.1 Data source

Administrative data maintained by the Saskatchewan Ministry of Health (MOH) were used for this study. Saskatchewan MOH databases contain valid data and have been used to produce high quality pharmacoepidemiological studies.[57,70,130-132] Specifically, we used information from the population registry, prescription drug file (pharmacy dispensations), physician services and hospital services databases. The Saskatchewan MOH covers almost 99% of the province's residents for both physician and hospital services. The only exceptions are federal prisons

inmates and members of the armed forces and the Royal Canadian Mounted Police (RCMP) because they are recipients of the federal government's health benefits. On the other hand, the prescription drug database captures medication dispensations for 90% of the provincial population; it excludes patients who receive federal prescription coverage such as the First Nations population. Information on medications available "over-the-counter" (i.e., OTC) or excluded from the provincial drug formulary were not available in this study.

2.3.2 Cohort

The cohort included individuals at least 30 years of age who received at least one dispensation for a statin medication (i.e., HMG-CoA reductase inhibitor) within 90 days[80,133] of discharge from a hospitalization with a most responsible/primary diagnosis of myocardial infarction (MI) or unstable angina (UA) between January 1st, 1994 and December 31st, 2008. Individuals were required to have continuous beneficiary status for 1825 days (i.e., 5 years) before the index hospitalization and survive for and maintain provincial beneficiary status for at least 102 days after their first statin dispensation. Individuals were excluded if they could not be followed for at least 102 days or received any statin medication within 365 days prior to the index hospitalization. The codes used to identify MI and UA conditions [Appendix 2-1] were shown to have positive predictive, sensitivity, and specificity estimates of 85 to 98%.[134-139] For individuals with several eligible hospitalizations the earliest hospital discharge date for ACS was deemed the index date.

2.3.3 Adherence

Adherence was measured from the first statin dispensation date until death, provincial health coverage termination, or end of the study period (December 31, 2008). The PDC method was used to calculate adherence[48,140,141] with an adjustment to prevent overestimation. Specifically,

each statin dispensation was assigned a 'completion date' corresponding to the number of medication doses supplied.[142] If a subsequent dispensation was obtained early, the new supply was not applied until the previous 'completion date' plus one day. Also, any excess supply of medication extending beyond the last follow-up day was removed from the calculation [Figure 2-1].[142] Similar to other studies, 80% level of adherence or higher was considered optimal adherence[143,144] and switching between statins was allowed. Additionally, we removed any days of hospitalization during the observation period from the denominator because medications dispensed to inpatients are not included in the prescription drug database.[145]

The assessment of adherence was applied in two ways. In method "A", a single summary measure of adherence was calculated between the date of the first dispensation and the date of death, provincial health coverage termination, or end of the study period (December 31, 2008). In method "B", the same period of follow-up was divided into three-month intervals (i.e., 102 days) where adherence was measured in each. Unused supplies from a previous interval were applied to the subsequent interval to prevent underestimation.

2.3.4 Analysis Procedure

The association between statin adherence and mortality was graphed using Kaplan-Meier survival probability graph and was assessed using a time-to-event analysis with multivariable Cox proportional-hazard regression models. Each model considered survival starting 102 days post discharge from index hospitalization and contained all available demographic, condition-related, therapy-related, patient-related, and health-system-related variables, as categorical variables [Appendix 2-2], in addition to the adherence category as a dichotomous variable (i.e., high versus low). In method (A), the summary measure of adherence was entered in the model as a fixed baseline covariate, whereas method (B) contained adherence as a time-dependent

repeated-measures covariate assessed every 102 days. We obtained the adjusted hazard ratios (HR) with 95% confidence intervals for adherent patients compared with non-adherent patients. The proportional hazards assumption was assessed visually using the log cumulative hazard (the "log-log") plot and Schoenfeld residuals versus observed event time's plot.[146] Multicollinearity between all non-adherence variables was examined by calculating the variance inflation factor (VIF) where values greater than 10 were interpreted as representing substantial multicollinearity.[147] Baseline variables, except adherence, that had evidence of multicollinearity were removed from the model.

In a sensitivity analysis, adherence was further stratified into three groups (≤20%, 21% - 79%, and ≥80%) versus the binary variable (≥80% vs < 80%) to determine if estimates of benefit were substantially affected. We used SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) to perform the analysis.

2.4 Results

From 43,118 individuals who had a hospitalization with ACS and/or a coronary revascularization procedure in Saskatchewan between January 1st, 1994 and December 31st, 2008, 9,051 individuals (21.0%) met all inclusion criteria [Figure 2-2]. Among all individuals in the cohort, 69.2% (n=6,260) were male and the mean age was 64.8 years (median=66.0, SD=12.3). More than half of patients (58.5%; n=5,292) received a revascularization procedure during their ACS hospitalization. Additionally, roughly one third (36.7%, n=3,325) had a diagnosis of hypertension in the pre-index year, and 13.6% (n=1,232) had a diabetes diagnosis [Table 2-1]. The mean follow-up time was 1,721 days (SD 1,138.4, median 1,525.0) or 4.7 years. The mean PDC calculated over the entire follow-up period was 70.6% (median=84.0%, SD=31.9%), and the percentage of individuals achieving optimal adherence (i.e. ≥80%) was 54.6% (n=4,939).

The percentage of adherent individuals increased substantially over the study period from 40.7% in 1994 to 77.8% in 2008.

Adherence categorization by the fixed baseline summary measure was generally concordant with the repeated measures approach. The adherence category matched on both measures in 76.7% of individuals (median 80.2%, SD=15.4%) However, the concordance between the two measures declined over time [Figure 2-3]. Non-concordance was typically a result of the fixed summary measure classifying non-adherence versus optimal adherence using the repeated-measures approach. In contrast, the percentage of cases of optimal adherence by the fixed summary measure but poor adherence by the repeated-measures was relatively infrequent and remained stable over time [Figure 2-3].

Among the 4,939 individuals exhibiting optimal adherence by the summary measure, 12.3% (n=606) died compared to 14.6% (n=600) of non-adherent individuals. However, optimal adherence (i.e. ≥80%) defined by the fixed summary measure was not associated with a lower risk of death in the time-to-event analysis [Figure 2-4] (crude HR 1.07, 95%CI 0.96 to 1.20, p=0.25; adjusted HR 0.97, 95%CI 0.86 to 1.09, p=0.60). Similar results were obtained when non-adherence was categorized as < 20% (i.e., rather than < 80%) in a sensitivity analysis (crude HR 0.91, 95%CI 0.77 to 1.08; p=0.28; adjusted HR 0.96, 95%CI 0.80 to 1.14). In contrast, optimal adherence measured as a time-dependent variable was clearly associated with a lower risk for death [Figure 2-5] (crude HR 0.80, 95%CI 0.71 to 0.89, p<0.01; adjusted HR 0.75, 95%CI 0.67 to 0.85, p<0.01). Similar results were obtained when non-adherence was categorized as < 20% (i.e., rather than < 80%) in a sensitivity analysis (data not shown). In all cases, the proportionality assumption of the Cox model was met, and no collinearity was observed in included covariates.

2.5 Discussion

We examined the association between statin adherence and the risk of death using two distinct adherence measures that have been used in previous studies.[80] The association was substantially impacted by the measurement approach despite an identical adherence metric (i.e., PDC) and threshold (i.e., ≥80%) for defining optimal adherence. Optimal statin adherence defined by the fixed summary measure was not associated with a beneficial effect on mortality (adjusted HR 0.97, 95%CI 0.86 to 1.09, p=0.60). In contrast, optimal adherence to statins defined by a time-dependent variable was associated with a significantly lower risk of death (adjusted HR 0.75, 95% CI 0.67 to 0.85).

The reasons for such conflicting estimates on the association between statin adherence measurements are not entirely clear. The study was carried out on the same cohort, over the same observation period, and accounted for identical confounders with the exception of adherence measurement. The repeated-measures approach appeared to be more sensitive to situations where patients improved their adherence behavior over time. However, it is impossible to determine if this increased sensitivity to optimal adherence behavior facilitated the detection of a valid relationship with mortality, or if it permitted the influence of survival bias.[128,129] In the latter case, healthy patients with long-standing non-adherence may have had greater opportunity to exhibit optimal adherence in the latter part of the observation period using a repeated-measures approach. To our knowledge, this observation has not been reported previously.

Our study identified a dramatic improvement in statin adherence over the past decade. This trend has been reported previously in other jurisdictions with statins and other medications also.[68,71] Considering these trends, along with steady population decreases in coronary heart

diseases event rates over time,[148] it is possible that the consequences of poor statin adherence may in fact be less dramatic in recent years. Although conflicting results from observational studies could be ideally resolved if randomized trial results were available, the nature of this phenomenon prevents rigorous examination using experimental design.

Some limitations can be noted in this study. First, although PDC is a validated adherence measurement method, our adjustment to prevent overestimation is not validated, and may have affected our estimates. It is possible that this adjustment disadvantaged one of the methods only (i.e., the summary approach or the repeated-measures approach). Second, requiring patients to fill a statin prescription within 90 days of their ACS hospitalization may have excluded patients exhibiting non-adherence at the beginning of follow-up (primary non-adherence). If true, this could have weakened the association through a biased selection of patients. Lastly, the choice of 102 days (3 months) to assess adherence in the repeated-measures method may have influenced the associations observed. However, shorter intervals would result in lower granularity of the measure and longer periods would result in lower sensitivity to periodic changes in adherence.

Estimates for the benefits of statin adherence on mortality are significantly influenced by the measurement methods used and a gold-standard approach cannot be established using conventional techniques. Based on the results of this study, adherence has improved dramatically since the 1990s and is nearing 80% in recent years. Although surveillance of adherence and health outcomes should continue, estimates must be generated using different measures until the most valid approach can be identified.

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Figure 2-1: Adjustment of the adherence measure (proportion of days covered) to prevent overestimation from early refills

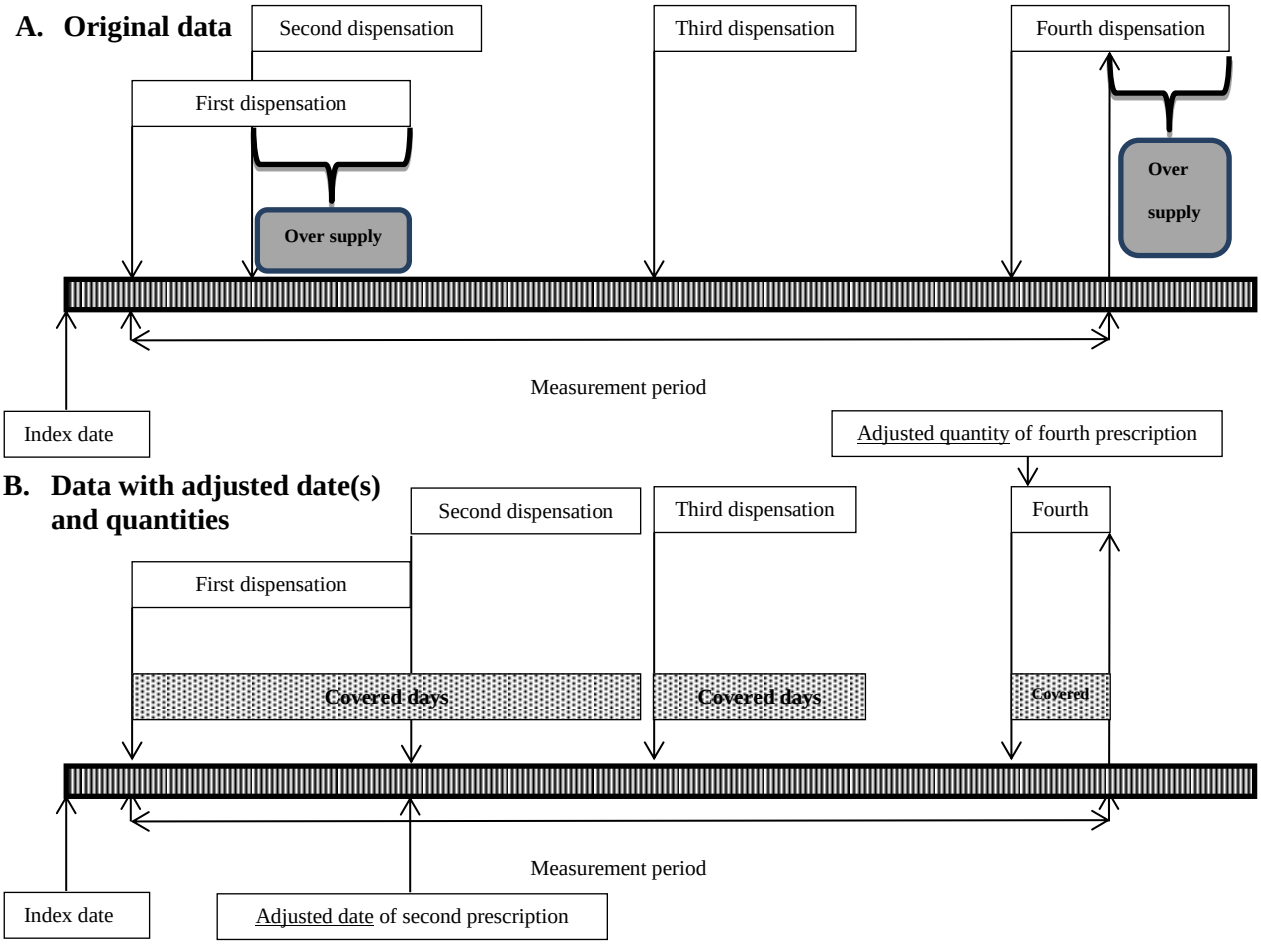


Figure 2-2: Flow chart of individuals in study

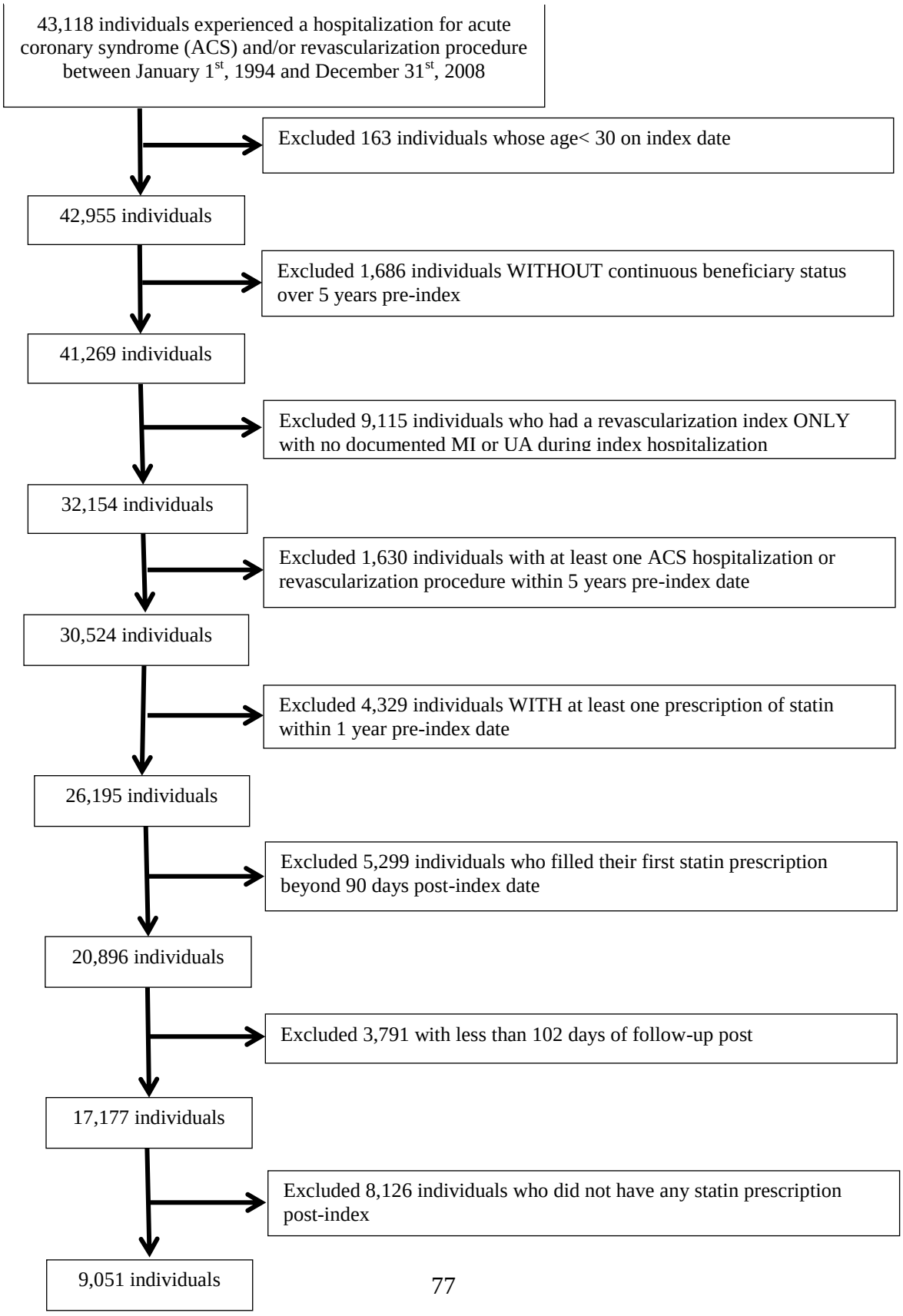
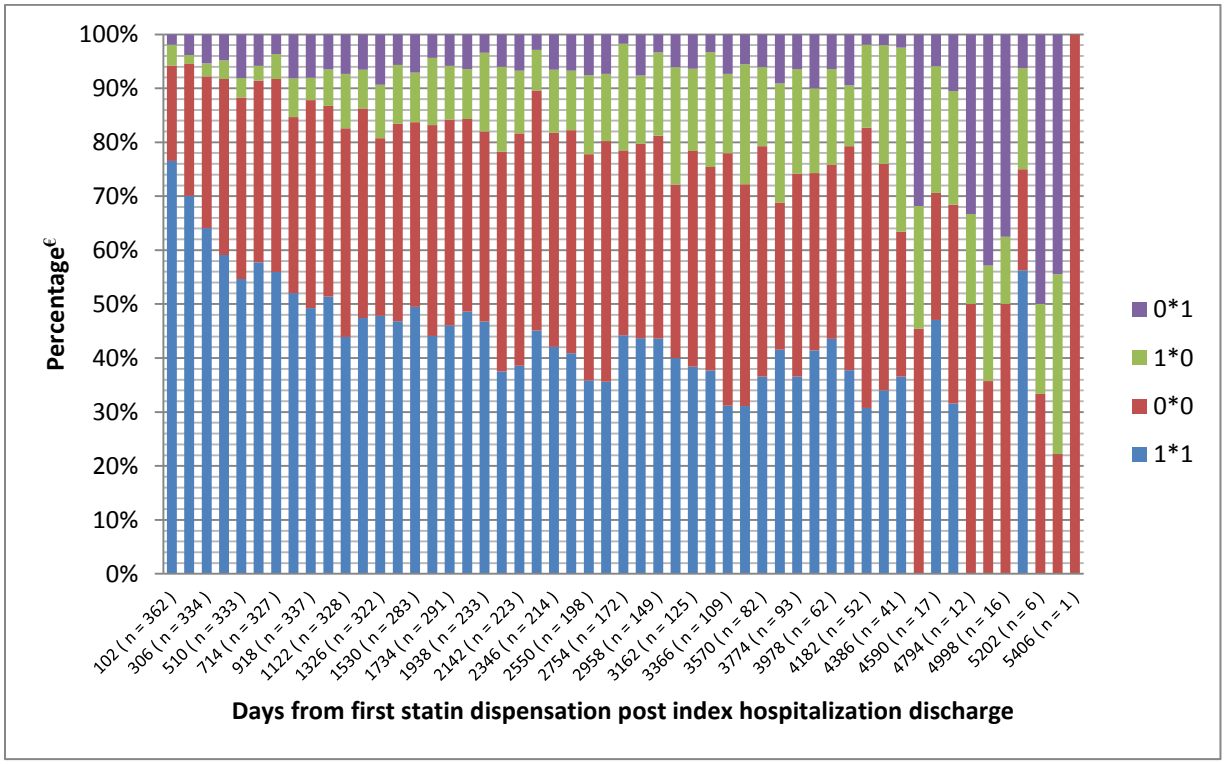


Figure 2-3: Concordance between two measures of statin adherence (summary measure and repeated-measures) among patients with coronary heart disease.[2]



[2] Categories: **concordance**: 1*1: adherent in interval by repeated-measures and by adherent by summary measure or 0*0: non-adherent in interval by repeated-measures and by non-adherent by summary measure; **discordance:** 1*0: adherent in interval by repeated-measures, but non-adherent by summary measure; and 0*1: non-adherent in interval by repeated-measures, but adherent by summary measure.

€ Percentages were calculated among all individuals who survived to this, but not the next, adherence assessment interval.

Figure 2-4: Kaplan-Meier estimates of survival among individuals classified using adherence summary measure (ADH_CONT) as adherent (1) or non-adherent (0).

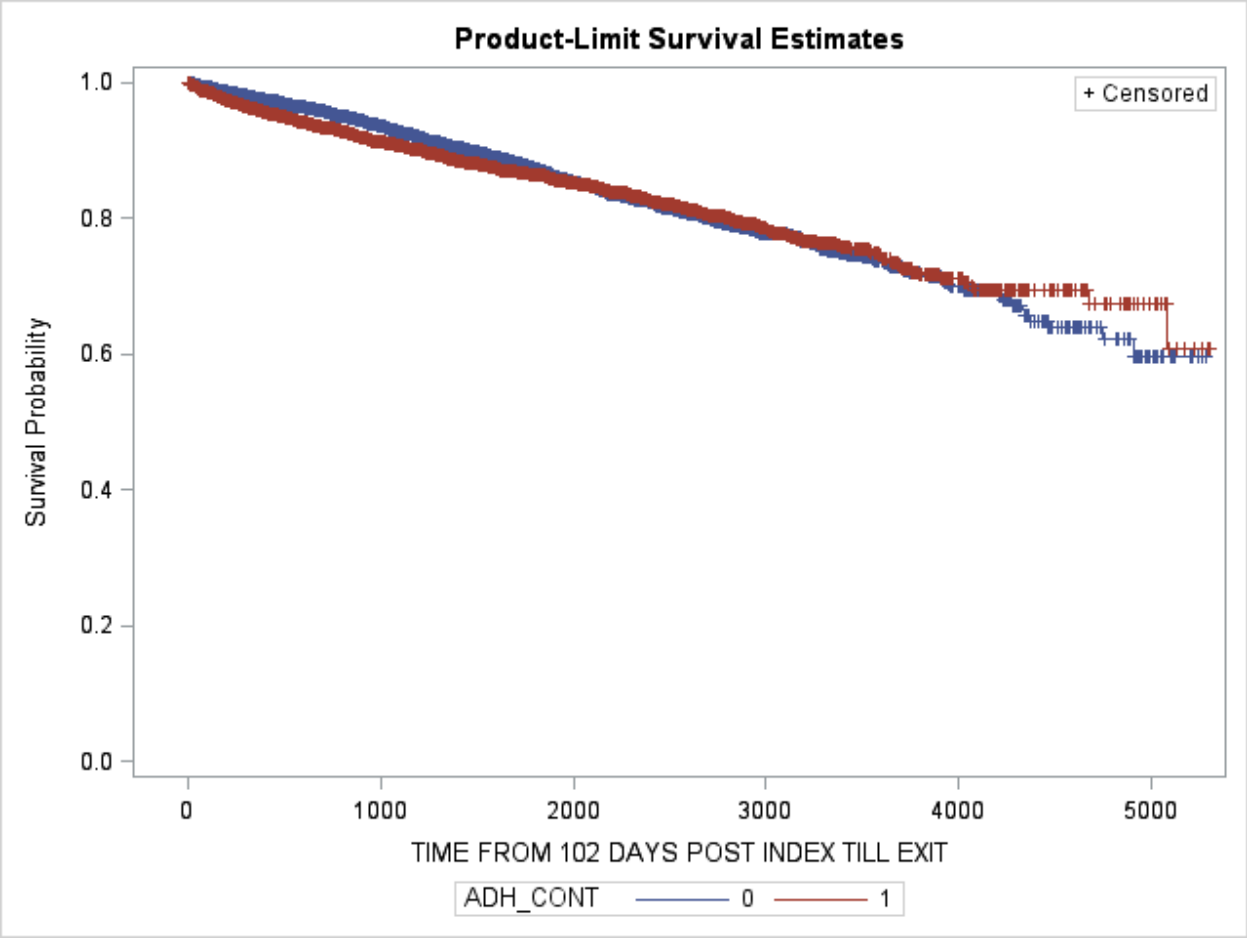


Figure 2-5: Kaplan-Meier estimates of survival among individuals classified using adherence repeated-measures (adh) as adherent (1) or non-adherent (0).

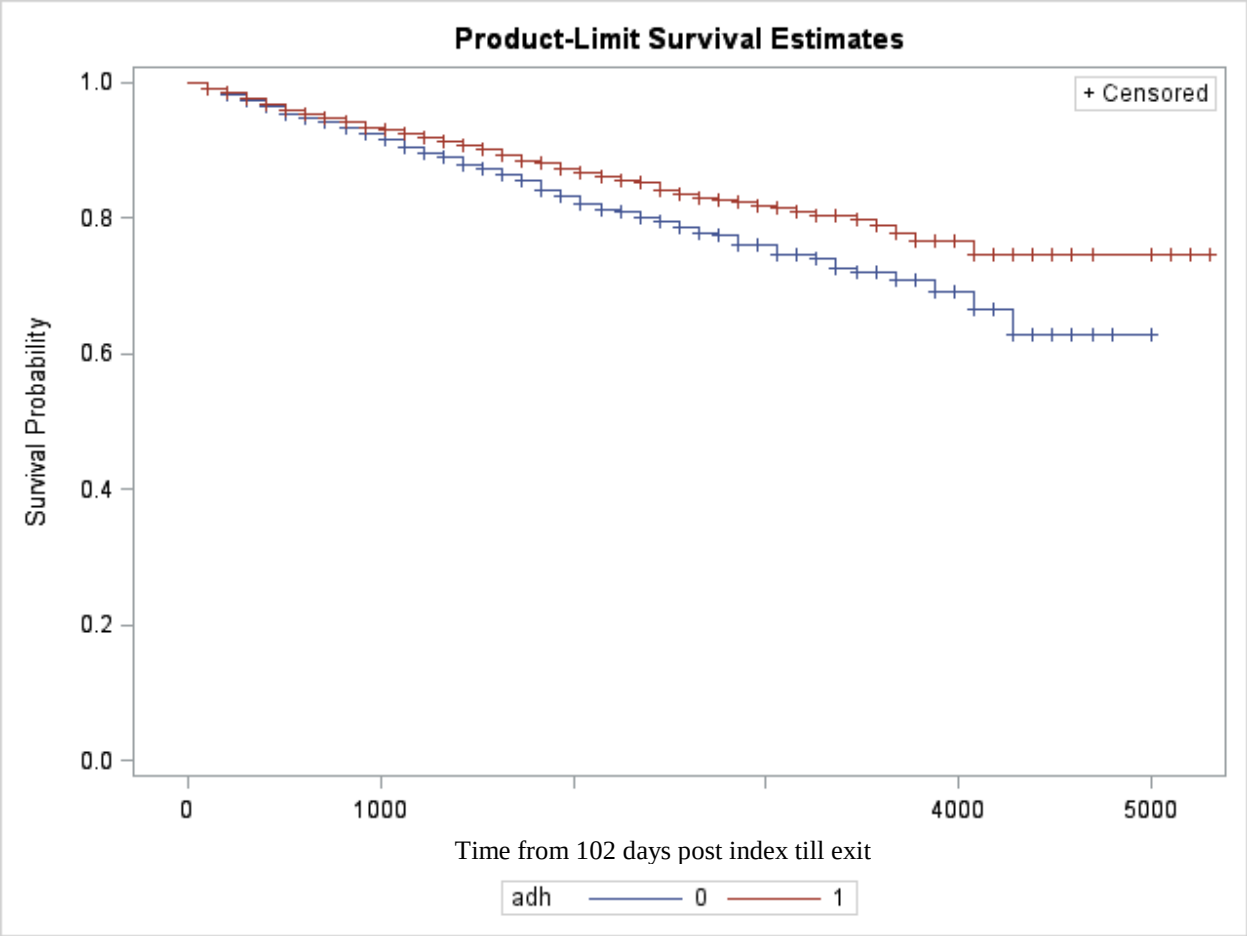


Figure 2-6: Kaplan-Meier estimates of survival among individuals classified using the first and last adherence periods (adh) as (1) continuously adherent, (2) declined adherence, (3) improved adherence, and 4) continuously non-adherent

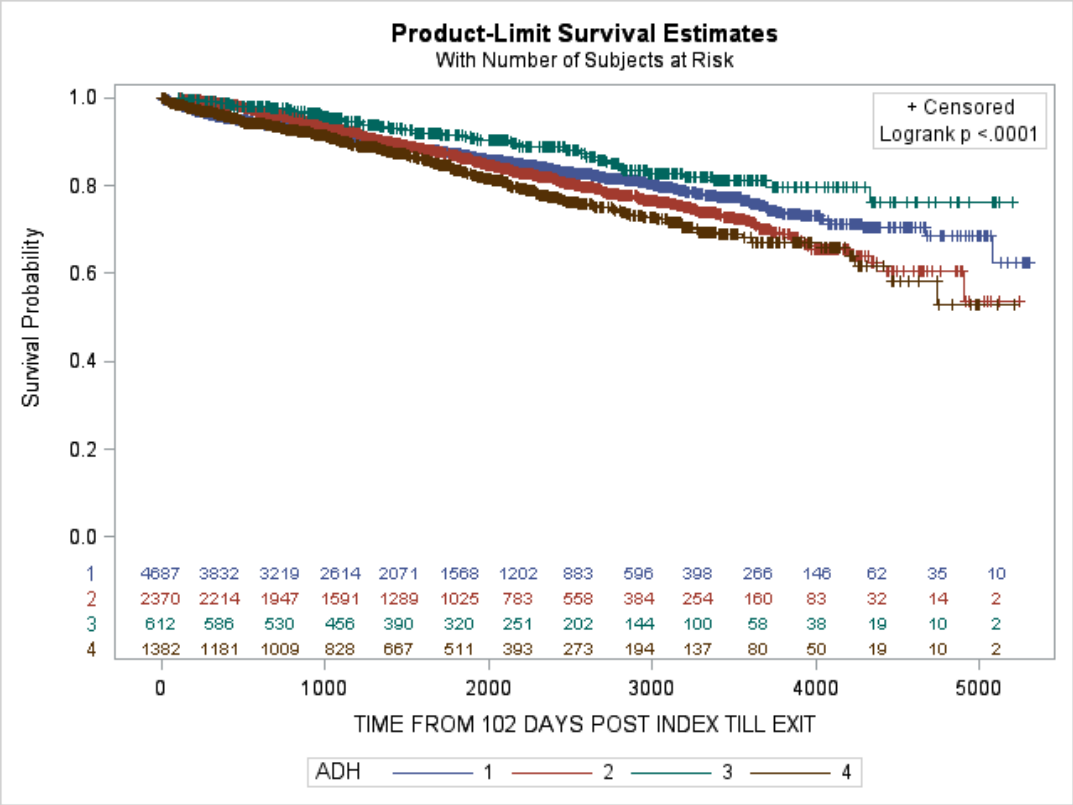


Figure 2-7: Kaplan-Meier estimates of survival among individuals classified using only the last adherence period (adh) as (1) adherent, and (0) non-adherent

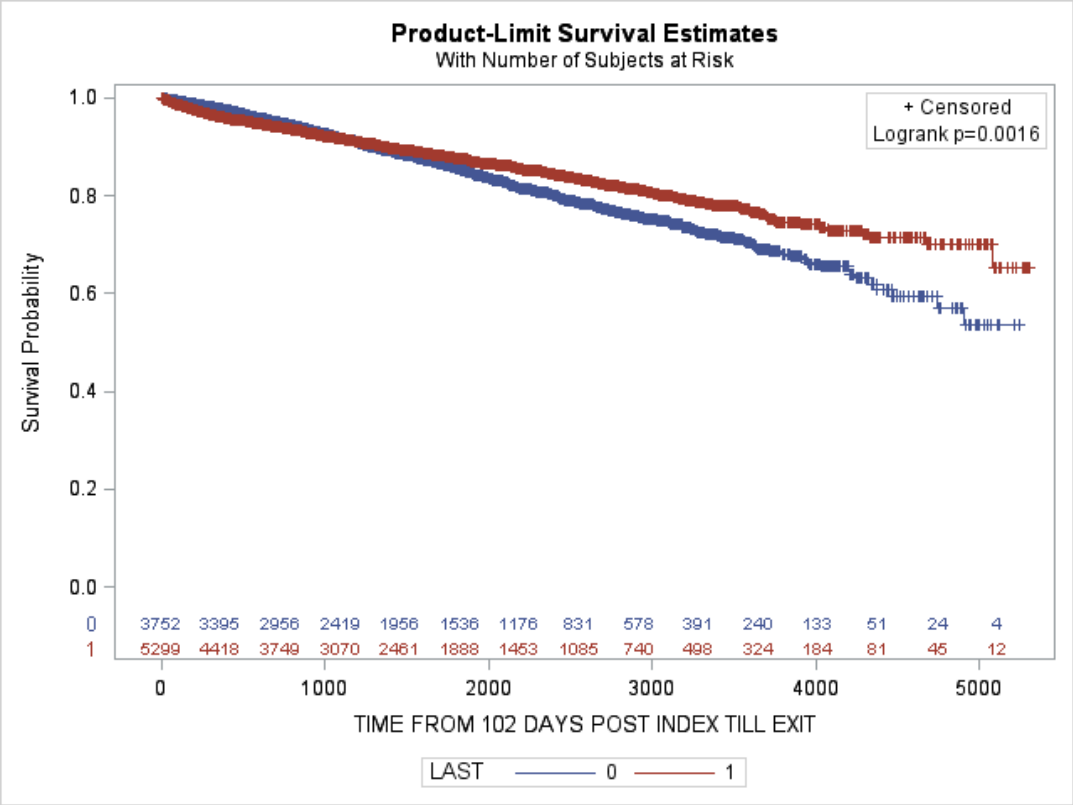


Table 2-1: Characteristic of individuals included in cohort

Characteristics		*Adherence <80% as defined by a summary measure (n*=4,112; 45.4%)		*Adherence ≥ 80% as defined by a summary measure (n*=4,939; 54,6%)		*Overall N*=9,051		*P-value from Chi-Square or t-test*
		n	%	n	%	N	%	
PDC, mean (SD)		0.41	(0.25)	0.95	(0.07)	0.71	(0.32)	<0.01
Death		600	14.6	606	12.3	1206	13.3	<0.01
Age (years)	mean (SD)	64.16	(12.57)	65.35	(12.04)	64.81	(12.30)	<0.01
	<55	1036	25.2	1311	26.5	2347	25.9	<0.01
	55-65	849	20.6	1062	21.5	1911	21.1	
	66-73	1177	28.6	1495	30.3	2672	29.5	
Male, (n, %)		2854	69.4	3406	69.0	6260	69.2	0.65
Index year	1994-1997	329	8.0	218	4.4	547	6.0	<0.01
	1998-2001	1141	27.7	922	18.7	2063	22.8	
	2002-2005	1777	43.2	2018	40.9	3795	41.9	
	2006-2008	865	21.0	1781	36.1	2646	29.2	
Follow-up (in days) from first prescription, mean (SD)		1931.43	(1134.79)	1546.42	(1111.51)	1721.34	(1138.35)	0.16
Time from index to statin prescription,	mean (SD)	8.46	(19.43)	6.22	(16.82)	7.24	(18.09)	<0.01
	>1 day	1011	24.6	894	18.1	1905	21.0	<0.01
Type of index diagnosis	ACS+ revascularization procedure	2098	51.0	3194	64.7	5292	58.5	<0.01
	ACS only	2014	49.0	1745	35.3	3759	41.5	
Any hospitalization in pre-index year, (n, %)		1011	24.6	1109	22.5	2120	23.4	0.02
Charlson comorbidity score (Deyo adaptation) >1, (n, %)		325	7.9	404	8.2	729	8.1	0.63
Diagnosis in hospital or physician records in pre-index year	Diabetes	532	12.9	700	14.2	1232	13.6	0.09
	Hypertension	1406	34.2	1919	38.9	3325	36.7	<0.01
High statin dose* on first prescription post index, (n, %)		2141	52.1	3166	64.1	5307	58.6	<0.01
Duration (in days) of index hospitalization,	mean (SD)	8.40	(7.73)	9.24	(8.12)	8.86	(7.95)	<0.01
	≤10 days, (n, %)	935	22.7	1378	27.9	2313	25.6	<0.01
Atorvastatin on first prescription post index, (n, %)		2388	58.1	2933	59.4	5321	58.8	0.21
≥5 physician's visits in the first 3 months following the first statin prescription		3030	73.7	3849	77.9	6879	76.0	<0.01
Deprivation index quintile	Missing	168	4.1	161	3.3	329	3.6	0.06
	1 (most deprived)	871	21.2	947	19.2	1818	20.1	
	2	680	16.5	789	16.0	1469	16.2	

	3	881	21.4	1109	22.5	1990	22.0	
	4	779	18.9	1006	20.4	1785	19.7	
	5 (least deprived)	733	17.8	927	18.8	1660	18.3	
At least one prescription in post-index year	ACEI/ARB	3199	77.8	4282	86.7	7481	82.7	<0.01
	anticoagulants	586	14.3	870	17.6	1456	16.1	<0.01
	Antiplatelet	2228	54.2	3180	64.4	5408	59.8	<0.01
	BB	3449	83.9	4262	86.3	7711	85.2	<0.01
	CCB	890	21.6	1078	21.8	1968	21.7	0.83
	Diuretics	1389	33.8	1865	37.8	3254	36.0	<0.01
	HF BB	46	1.1	92	1.9	138	1.5	<0.01
	Nitrates	2916	70.9	3529	71.5	6445	71.2	0.57
	Other lipid drugs	213	5.2	187	3.8	400	4.4	<0.01
>4 distinct (non-statin) medications received in post-index year		2397	58.3	3302	66.9	5699	63.0	<0.01
Specialty of prescribing physician of the first statin prescription	GP	633	15.4	579	11.7	1212	13.4	<0.01
	cardiologist	1937	47.1	2673	54.1	4610	50.9	
	internist	984	23.9	998	20.2	1982	21.9	
	cardiac surgeon	239	5.8	384	7.8	623	6.9	
	other	319	7.8	305	6.2	624	6.9	

Abbreviations: ACS: Acute Coronary Syndrome; ACEI/ARB: Angiotensin Converting Enzyme-Inhibitor /Angiotensin Receptor-Blockers; BB: Beta-blockers; CCBs: Calcium Channel Blockers; DM: Diabetes Mellitus; GP: General Practitioner; HTN: Hypertension; PROC: Procedure of revascularization.

*High dose statin was defined[149-152] as having rosuvastatin >5mg, atorvastatin ≥20mg, or simvastatin ≥40mg

Appendix 2-1: Subjects' selection of eligible individuals depending on the existence of coronary heart diseases

Subject Selection Diagnoses from Hospital Services Database		
ICD-9*	**ICD-10-CA**	**Description**
410	I21 - I22.xxx	myocardial infarction (MI)
411	I20.0xx and I24.xxx	unstable angina (UA)
*ICD-9 was used until March 31, 2001, when ICD-10-CA reporting started		
ICD-9: Manual of the international statistical classification of diseases, injuries, and causes of death, 9th revision. Geneva: The Organization; 1977. ICD-10-CA: International statistical classification of diseases and related health problems, tenth revision, Canada. Canadian Institute for Health Information; 2003.		

Appendix 2-2: Variables considered for the baseline adjustment

Variable category	Included variables
Demographic variables	• age at index date • gender • year of discharge
Condition-related variables	• type of index diagnosis (ACS only, ACS plus revascularization) • duration of index hospitalization • number of days between index date and first dispensation of statin
Therapy-related factors	• filling at least one prescription for specific cardiovascular medication(s) during the first year post-index including (beta-blockers; angiotensin converting enzyme-inhibitor (ACEI) or angiotensin receptor-blockers (ARB); calcium channel blockers (CCBs); diuretics; anticoagulants; antiplatelet; nitrates; or other lipid drugs - yes/no for each) [Appendix 2-3] • filling at least one prescription with a quantity of 28 tablets[153] as an evidence of unit-of-use packaging[154,155] • receiving a high (versus low) statin dose on first prescription post index[149-152] • the individual statin used on first prescription post index (atorvastatin versus others)[156] • burden of medications defined as the total number of distinct medications' therapeutic groups dispensed to subject
Patient-related factors	• socio-economic status (SES) assessed by the deprivation index (DI) developed by *Pampalon et al.*[157] This was identified by mapping individuals' residential postal codes to geographic-level statistics for the Statistics Canada census.[158] • comorbidities calculated by Deyo-adapted Charlson score method using hospitalizations data[159-162] • specific comorbid conditions of diabetes,[163] and hypertension[58] reported in any physician or hospitalization visit in the year prior to the index date [Appendix 2-4]
Health system-related factors	• specialty of prescribing physician for the first statin dispensation **(**general practitioner (GP), cardiologist, general internist, cardiac surgeon, other) • number of physicians visits in the first 3 months following the first statin dispensation • any prior hospitalization in the pre-index year.

Appendix 2-3: Medications assessed in the multivariable model

Medication category	Medications included	
Statin mediation (i.e., HMG-CoA reductase inhibitors)	Atorvastatin, atorvastatin / amlodipine combination, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin	
Angiotensin Converting Enzyme-Inhibitors (ACE-Inhibitors)	Benazepril, captopril, cilazapril, cilazapril / HCTZ combination, enalapril, enalapril/HCTZ combination, fosinopril, lisinopril lisinopril/HCTZ combination, perindopril ,perindopril/indapamide combination, quinapril quinapril/HCTZ combination, ramipril, and trandolapril	
Angiotensin Receptor-Blockers (ARBs)	Candesartan, candesartan/HCTZ combination, eprosartan, eprosartan / HCTZ combination, irbesartan, irbesartan/HCTZ combination, losartan, losartan/HCTZ combination, olmesartan, Olemsartan/HCTZ combination, telmisartan, telmisartan/HCTZ combination, valsartan, and valsartan/HCTZ combination	
Beta Blockers	Acebutolol, atenolol, atenolol / chlorthalidone combination, labetolol, metoprolol, metoprolol / HCTZ combination, nadolol, oxprenolol, pindolol, pindolol/HCTZ combination, propranolol, propranolol / HCTZ combination, timolol, and timolol / HCTZ combination	
Calcium Channel Blockers (CCBs)	Dihydropyridine (DH-CCB)	Amlodipine, felodipine, nicardipine, and nifedipine long acting,
	Non-dihydropyridine (NDH-CCB)	diltiazem, and verapamil
Diuretics	Amiloride, amiloride/HCTZ, bumetanide, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide (HCTZ), indapamide, metolazone, spironolactone, spironolactone/HCTZ, triamterene, triamterene/HCTZ	
Anticoagulants	Acenocoumarol, dalteparin, enoxaparin, heparin, nadroparin, tinzaparin, warfarin	
Antiplatelet	ASA, clopidogrel, dipyridamole /ASA, pentoxifylline, sulfinpyrazone, ticlopidine	
Nitrates	Erythrityl tetranitrate, isosorbide dinitrate, isosorbide-5-mononitrate, nitroglycerin	
Other lipid drugs	Bezafibrate, cholestyramine, clofibrate, colestipol, ezetimibe, fenofibrate, gemfibrozil, niacin, probucol	

Appendix 2-4: Comorbid conditions

Comorbid conditions used in the multivariable model from hospital and physician administrative health databases		
ICD-9*	**ICD-10-CA**	**Description**
250.x	E10 - E14.xxx	Diabetes & diabetes with complications
401 - 404.x	I10 to I15.xxx except when I11 is reported with I50 where's case is considered heart failure	hypertension
*ICD-9 was used until March 31, 2001, when ICD-10-CA reporting started		
ICD-9: Manual of the International Statistical Classification of Diseases, Injuries, and Causes Of Death, 9th revision. Geneva: The Organization; 1977. ICD-10-CA: International Statistical Classification of Diseases and Related Health Problems, tenth revision, Canada. Canadian Institute for Health Information; 2003.		

CHAPTER -3- SOCIO-ECONOMIC STATUS AND NON-ADHERENCE TO ANTI-HYPERTENSIVE DRUGS. A SYSTEMATIC REVIEW AND META-ANALYSIS*

3.1 Abstract

Background: Although conventional wisdom suggests that low socio-economic status (SES) is a robust predictor of medication non-adherence, the strength of this association remains unclear. *Objectives*: i) to estimate the proportion of studies that identified SES as a potential risk indicator of non-adherence; ii) to describe the type of SES measurements; iii) to quantify the association between SES and non-adherence. *Research Design*: Systematic review and meta-analysis. *Data Sources*: We searched multiple electronic databases for studies examining non-adherence to anti-hypertensives measured by electronic prescription databases where explanatory factors were considered. A random-effects model meta-analysis was performed and heterogeneity was examined using the I^2 statistic. *Results*: Fifty-six studies with 4,780,293 subjects were included. Twenty-four (43%) did not report any SES measures. When it was reported (n=32), only 7 (13%) examined more than one component but none performed a multi-dimensional assessment. The majority of studies relied upon income or income-related measures (such as prescription-drug benefits or co-payments) (27/32, 84%). Meta-analysis could be quantified in 40 cohorts reported in 30 studies. Overall, the pooled adjusted risk estimate for non-adherence according to SES (high versus low) was 0.89, 95% CI 0.87 to 0.92; I^2=95%, p<0.001. Similar patterns were observed in all subgroups examined. *Conclusion*: published studies have not found a strong

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association between low SES and non-adherence to anti-hypertensive medications. However, important limitations in the assessment of SES can be identified in virtually all studies. Future studies are required to ascertain if a stronger association is observed when SES if determined by comprehensive measures.

3.2 Introduction

Socio-Economic Status (SES) is a multi-dimensional construct that represents an individual's position relative to other people in the community. It is commonly considered a product of the interaction between material and social factors. Material factors include income, education and employment, whereas social factors are usually represented by living arrangements and family structure.[1] In health-care research, low SES has proven to be a strong predictor of health-care utilization, morbidity, and premature death.[2-5] Low SES may also be an important determinant of non-adherence to chronic medications such as antihypertensives (AHTs).[6,7]

SES is an intriguing factor in the search for determinants of population-level non-adherence to AHTs because of its associations with economic, social, and education-related factors. Indeed, all of these factors may influence regular medication use.[8] Although the relationship between SES and non-adherence has been inconsistent,[9] we hypothesized that methodological approaches may have attenuated an important relationship. Electronic prescription databases are the most frequently used methods for non-adherence assessment,[10,11] however, they often lack important patient-level information required to describe SES in detail. As a result, indirect measures of income such as receipt of prescription-drug benefits through government co-payments are often used as the sole indicators of SES in many studies,[12-15] while direct measures of income from taxation records are rarely utilized.[6] In addition, studies generally do not account for non-income related SES factors and even fewer incorporate multiple SES measurements representing different dimensions.[16,17] Finally, several population-based studies can be identified where SES factors are absent altogether.[18-20]

In order to understand the extent to which SES may influence non-adherence to AHT medications, as well as the approaches used to account for it, we conducted a systematic review and meta-analysis of the literature pertaining to SES and non-adherence to AHT medications using population-based electronic prescription data. Our study had three objectives: i) to estimate the proportion of studies that identified SES as a potential risk indicator of non-adherence; ii) to describe the type of SES measurements that were used in each study; iii) to quantify the association between SES and non-adherence to AHT medications.

3.3 Methods

3.3.1 Search Strategy

We used a comprehensive search strategy of electronic databases including: Medline (OVID,1964 to February 24, 2012), Embase (OVID,1947 to February 24, 2012), International Pharmaceutical Abstracts (OVID, 1970 to January 31, 2012), the Cochrane Library (Wiley, 1800 to February 28, 2012), Scopus (Elsevier, from 1823 to February 28, 2012), CINAHL (EBSCO, 1937 to February 28, 2012), PsycINFO (OVID, 1806 to February Week 3 2012), Sociological Abstracts (ProQuest, 1952 to February 28, 2012), ProQuest Dissertations & Theses (PQDT) (1639 to February 28, 2012), Web of Science (Thomson Reuters, 1899 to February 28, 2012), and OAIster (1975 to Dec 31, 2011). Reference lists of identified articles were manually searched for additional studies not captured in the electronic database reviews.

3.3.2 Study Selection

Studies were included if they satisfied the following criteria: a) examined non-adherence to AHT medications, b) used electronic prescription databases as the source of non-adherence information, and c) conducted multivariable modelling to determine the independent effect of

explanatory covariates on the outcome of non-adherence; and d) were published in English or French. Eligible AHT medications included angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs), beta-blockers (BBs), calcium channel blockers (CCBs) or thiazide diuretics for any indication. Studies were not restricted by design or publication date. In some cases, we contacted authors of studies to clarify or obtain data.

3.3.3 Review Procedure and Assessment of Methodological Quality

The identification of studies was carried out in two steps. First, after removal of duplicates, two of the authors (WA and ML) examined the titles and abstracts identified in the initial search. Secondly, the same two reviewers (WA and ML) examined full-text articles for each study identified in the first step for both eligibility and methodological quality. Disagreement between the two reviewers was resolved by additional review and discussion and then, if required, with tie-breaking by a third reviewer (DB). Quality of included studies was assessed by the reviewers (WA and ML) with a checklist developed by the International Society for Pharmacoeconomics and Outcome Research (ISPOR) for retrospective database studies.[21,22] This checklist has been used in systematic reviews previously,[23] and it consists of 27 quality review questions related to data source, research design, study population, variable definitions, statistics and discussion.

From each study, we determined whether a SES measure was assessed by identifying any material factor (e.g., income, education or employment) or social factor (e.g., living alone, or family structure) that was included in the non-adherence model. In cases were these traditional SES measures were not used, we identified ethnicity as a possible indirect measure in a sensitivity analysis. Ethnicity was defined as any categorization according to race or any cultural factor.[24,25] We also recorded estimates of the ratio effects measures of non-adherence to AHT medications along with 95% confidence intervals (95% CI) corresponding to the measure of

SES. Additionally, we abstracted information on region of origin, publication year target medication(s), adherence measurement (MPR-related versus discontinuation-related[11]) number of subjects (total/ low SES/ higher SES), follow-up (observation) days, and the number of SES domains captured in each study. We categorized SES covariates as income-related and non-income-related and sub-categorized income-related SES covariates as follows: income-level, health-plan coverage or medication copayment amount, and receipt of social assistance or income security benefits. Income-level factors were identified as direct (e.g., by linking taxation data to dispensation records) or indirect (e.g., from census neighbourhood or coverage type).

3.3.4 Statistical Analysis

We assessed the agreement in study inclusion/exclusion between reviewers in each step by Cohen's kappa statistic (κ).[26] We adopted the following interpretations for κ: $0.60 < \kappa$ was considered low agreement, $0.60 \leq \kappa \leq 0.79$ was considered good agreement and $\kappa \geq 0.80$ was considered very good agreement.[27] We assessed heterogeneity using the I^2 statistic and corresponding τ^2 (Tau-squared) test. This statistic represents the proportion of variability that can be attributed to between-studies variability.[28] We adopted the following interpretations for the I^2 statistic: 0% to 40%-low heterogeneity; 41% to 74% - moderate heterogeneity, and 75% to 100% - considerable heterogeneity. All estimates were pooled where possible irrespective of the level of heterogeneity observed and subgroup analyses completed to explore potential sources of study heterogeneity.[29] We then conducted a random-effects model meta-analysis using the inverse-variance (IV) method to estimate the effect of SES on medication non-adherence from the pooled data.[28-30] A random-effects model accounts for potential heterogeneity between the populations and unmeasured confounding.[28] For studies reporting more than one non-adherence measure, we prioritized Medication Possession Ratio-related (MPR-related) outcomes over other measures.

MPR is calculated usually by summing all days' supply during a certain period of observation of the medication and divide it by the total days of that period.[10] For studies reporting more than one SES variable, we used the measure with the largest effect size regardless of the direction of the association. When categorical SES measures had more than two levels, we reported the risk estimate of the highest SES level relative to the lowest.

Subgroup analyses were conducted for type of non-adherence measurement, type of medication, type of SES measurement, and the region of origin of the data. We used the Z-test for overall effects and $\chi 2$ statistic to test for differences in the between-groups effects.[31] Finally, because ethnicity may be considered an indirect SES measurement,[24,25] we performed a sensitivity analyses by including ethnicity as a measure of SES to assess the proportion of studies that identified SES as a potential risk indicator of non-adherence. Additionally, we performed a sensitivity analysis by using the estimate with the lowest effect size instead of the highest for studies reporting more than one SES variable. We evaluated publication bias visually using the funnel plot.[32] We adopted the protocol developed by The Cochrane Collaboration and used Review Manager (Version 5.1.7 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) to perform the meta-analysis.[29]

3.4 Results

3.4.1 Included studies

Our search identified 11,351 titles/abstracts with 56 studies meeting our inclusion criteria. (Figure 3-1; eTable 3-1). Overall agreement for inclusion/exclusion of studies between the reviewers was found to be good (κ=0.79, and κ=0.69 for first and second steps respectively) (Figure 3-1). Of these 56 included studies, eight studies[33-39] scored less than 50% on the

methodological quality review. The median methodological quality score was 68% and inter-quartile range was 19%.

Table 3-1 summarizes the characteristics of included studies. The total number of subjects included in our review was 4,708,293 (range 236 to 1,075,285 per study). The majority of studies were conducted in Europe (11/56, 20%) and North America (34/56, 61%). Studies ranged from assessing one AHT medication (6/56, 11%), to assessing combinations of two medications or more. Non-adherence was measured by discontinuation/non-persistence (25/56, 45%), Medication Possession Ratio (MPR) related measurements (26/56, 47%) or both (5/56, 8%). The follow up duration was 180 days or less in 13 studies, 181 days to 365 days in 31 studies, and more than 365 days in 8 studies.

3.4.2 SES Measures

Overall, 24/56 studies (43%) did not assess SES with any material or social measure. However, when ethnicity was considered as an eligible SES measure, the proportion of studies with no SES measure decreased to 19/56 studies (34%). An SES measure was lacking in all studies published prior to 2004 (9 studies), compared to 15 of 47 studies (32%) published between 2004 and 2012. Of the 32 studies which assessed SES, two studies did not report estimates of the effect of SES on non-adherence and could not be obtained from authors.[40,41]

No study organized SES variables into multidimensional scales or indices such as a deprivation index.[42,43] From all studies that assessed SES, 25 studies (78%, 25/32) identified only one SES measure among their study subjects. Of these, prescription-drug coverage or medication copayment amount based on income was most commonly used (17/25 studies). [9,15,38,44-57] Four studies captured income level,[41,58-60] three studies used social assistance benefits or income security benefits,[61-63] and education level was identified in one study only.[64]

Seven studies (22%, 7/32) identified more than one SES measure in their study population. All of the studies contained at least one income-related variable and three identified income-related measures only.[36,39,65] Non-income variables in the remaining studies included education and employment,[66] education,[67] living alone[40] or household composition.[6]

In total, seven studies captured income level either alone or in addition to other SES measures. Of these, classification into income groups was obtained directly by linking taxation data to dispensation records in three studies,[6,59,67] indirectly from census neighbourhood income in two studies[40,58] and indirectly from low-income drug coverage in two studies.[60,65]

3.4.3 Non-adherence with higher SES

Excluding the two studies where an estimate could not be obtained,[40,41] we extracted data for 40 cohorts in 30 studies reporting an SES variable. Higher SES was associated with lower risk of non-adherence in 31/40 cohorts (77.5%), with no difference in one cohort, and with higher risk of non-adherence in 8 cohorts (Figure 3-2). Overall, the pooled adjusted risk estimate indicated a lower risk of non-adherence among individuals with higher SES: 0.89 (95% CI 0.87-0.92; $p<0.001$); however, high heterogeneity was observed (Tau=0.01; I^2 = 95%). Inspection of the funnel plot did not suggest potential publication bias (Figure 3-3).

To explore heterogeneity in the results, we performed several sub-group analyses. However, similar results were observed in studies scoring above 50% on the quality checklist (pooled adjusted risk estimate 0.90, 95% CI 0.87-0.92, I^2=95%) and scoring below 50% (pooled adjusted risk estimate 0.86, 95% CI 0.66-1.12, I^2=84%). A sub-group analysis was not performed on non-income related measures because they were only identified in one study. Studies that used discontinuation as the endpoint (pooled adjusted risk estimate 0.91, 95% CI 0.87-0.96, I^2=92%) showed consistent results with those that used MPR-related measures (0.88, 95% CI 0.85-0.92,

I^2=93%), and studies from North America and Europe (0.90, 95% CI 0.87-0.94, I^2=95%) produced similar results to those from other countries (0.86, 95% CI 0.81-0.92, I^2=87%). In the sensitivity analysis, using the measure with the lowest effect size (for studies reporting more than one SES variable) did not change the pooled adjusted risk estimate (0.90, 95%CI 0.88-0.92, I^2=95%). Smaller heterogeneity was observed in certain cohorts restricted by specific type of medication used. Pooled adjusted risk estimate representing the influence of higher SES were different for cohorts receiving ACEIs (0.83, 95%CI 0.79-0.88, I^2=0%), BBs (0.77, 95%CI 0.66-0.9, I^2=95%), CCBs (0.98, 95%CI 0.85-1.14, I^2=70%), HCTZ (0.81, 95%CI 0.74-0.90, I^2=0%), or for ARBs (1.0 95%CI 1.0-1.0, I^2=84%), where the test for subgroup difference was significant $p<0.001$) (Figure 3-4). However, the pooled estimate remained relatively consistent with the overall findings.

3.5 Discussion

Among published studies of non-adherence to AHT medications using electronic prescription databases, 43% did not account for any SES measure despite their theorized importance as a determinant of non-adherence.[8] When SES was assessed, the vast majority of studies identified single factors relating to income and none examined SES using a comprehensive measure. Pooled analyses indicated that higher SES is associated with an 11% decrease in the adjusted-risk of non-adherence; however, heterogeneity between included studies was very high. Although the quantitative impact of SES on medication non-adherence cannot be confirmed from this meta-analysis due to high levels of heterogeneity, incomplete (or absent) SES measures, and inconsistent approaches in the literature, these results clearly demonstrate major deficiencies in previous attempts to understand this complex issue. As a result, SES cannot be considered a strong predictor of medication non-adherence because the evidence supporting this view remains

theoretical at best, at least with respect to antihypertensive medications. In reality, it must be recognized that current knowledge about SES and non-adherence is extremely poor.

To our knowledge, this is the first systematic review specifically evaluating the effects of SES on non-adherence to AHT medications and the results suggest that more research is needed to ensure consistent and comprehensive approach to the assessment of SES as a possible risk indicator. We chose hypertension as disease state because of its prevalence, chronicity, lack of symptoms and treatability.[68] It has been clearly shown that the prevalence of non-adherence to AHT medications is high and adverse health outcomes are commonly observed compared to those demonstrating optimal adherence.[69-71] As a result, even small improvements in non-adherence are likely considered clinically meaningful.[72-75]

The most probable explanation for these findings is that administrative databases including electronic prescription databases do not have ready access to SES information. However, the importance of the SES factors as potential risk indicators of non-adherence may also be under-recognized. Accordingly, our understanding of the complex relationship between SES and medication non-adherence is likely incomplete because it is based on studies using a very limited set of SES measures, at least in studies focused on AHT medications.

SES could be an important determinant of non-adherence not only through its impact on affordability and access to medications, but through its effect on health literacy and medication knowledge.[76] Indeed, higher SES reduced the risk estimate of non-adherence in 31/40 of cohorts examined; however the opposite effect of SES was observed in 8/40 cohorts examined. Thus, our systematic review confirms and characterizes the inconsistent findings relating to SES and non-adherence reported in previous narrative reviews.[11,77,78]

Our review had several limitations. First, our study examined AHT studies only, so the results may not generalize to other chronic disease medications. Second, we only included studies that used electronic prescription databases as the source of non-adherence information. However, electronic prescription databases are the most frequently used source of non-adherence information among large populations.[10] Third, it is highly likely that the pooled risk estimates was influenced by the lack of detailed SES information and the inconsistent approaches to SES measurement in the published literature. Indeed, the vast majority of SES measures were restricted to income-related measures. Even more, all included studies are observational cohort studies; thus, their estimates may be highly influenced by residual confounding. However, subgroup analyses did not reveal systematic differences between studies stratified by quality, country of origin, SES measure, or adherence measure. Fourth, we used the checklist developed by ISPOR for retrospective database studies to assess publications' quality. However, a new questionnaire developed by AMCP/NPC/ISPOR Comparative Effectiveness Research Collaborative Initiative, could have improved our quality assessment.[79] Lastly, although we did not observe any publication bias, it is possible that negative studies assessing SES and non-adherence could not be published.

SES is frequently overlooked in studies of non-adherence to AHT medications using electronic prescription databases and it has never been examined in a comprehensive way. Based on the available literature, higher SES appears to be associated with a small reduction in the occurrence of non-adherence to AHT medications. However, this estimate is based on studies that contained many limitations. Thus, more research is clearly needed to help clarify this relationship. Considering the public health importance of this outcome and the relative lack of knowledge

about its determinants, failure in taking SES into account could prevent targeting of interventions for those who need them.

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Appendix 3-1: eTable : Studies identified in the systematic review

Reference (Year)/ Country	Medication(s) studied	Adherence measure	No of subjects (total/low SES/ high SES)	Follow-up (days)	SES covariates studied	OR/HR of non-adherence (95%CI) p-value	SES measure used	Number of domain(s) in SES measure (one/Multiple)	Quality score
Wong[114] (2011)/Hong Kong	HCTZ	Discontinuation	(9398/ 2536/6862)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1.00 (reference) 0.85 (0.74–0.98) 0.027	Payment status	one	13/25 (>50%)
Rasmussen[80] (2007)/ON, Canada	BBs, CCBs	PDC	BBs cohort: (24319/7232/17087), CCBs (9168/3212/5956)	365	**BBs cohort** Low income (no/yes) **CCBs cohort** Low income (no/yes)	**OR for PDC <40% vs.≥80%** 1.05(0.91-1.11) **OR for PDC<40% vs. ≥80%** 1.07(0.94-1.23)	Income	one	18/25 (>50%)
Setoguchi[68](2010) /New Jersey, USA	ABs, BBs	PDC	46,278	365			None	NA	15/25 (>50%)
Monane[115] (1997) / New Jersey, USA	ACEIs, BBs, CBs, HCTZ	Days covered	8643	365			None	NA	14/25 (>50%)
Bloom[59] (1998)/ USA	ACEIs, ARBs, BBs, CCBs, HCTZ	Discontinuation	21723	365			None	NA	15/25 (>50%)
Degli Esposti[60] (2002)/Italy	ACEIs, BBs, CCBs, HCTZ	Discontinuation	16783	365			None	NA	17/25 (>50%)
Yang[116] (2009)/USA	ACEIs, ARBs	PDC	1075285	180			None	NA	14/26 (>50%)
Shaya[117] (2009)/Maryland, USA	Combination of ACEIs, CCBs, or HCTZ	MPR	568	365 (at least)			None	NA	15/25 (>50%)
Elliott[61] (2007)/USA	amlodipine, HCTZ, lisinopril, valsartan	Discontinuation	60685	365			None	NA	15/24 (>50%)
Perreault[118] (2005)/Québec, Canada	ACEIs, BBs, CCBS, diuretics alone or in combination	Discontinuation	(21011/4412/16599)	365	Social assistance (no/yes)	**OR for Discontinuation** 0.75(0.70-0.79)	Social assistance status	one	15/24 (>50%)
signorovitch[119] (2012) / USA	BBs	Discontinuation	173200	365			None	NA	14/25 (>50%)
Taira[120] (2007) / Hawaii, USA[120]	ACEIs, ARBs, BBs, CCBs, HCTZ	MPR	(28395/19499/8896)	365-1095	**Education** <High school High school College Post-graduate	**OR for MPR<80%** 1(reference) 0.91(1.00-0.83) 0.84(0.91-0.77) 0.87(1.00-0.77)	Education	one	17/25 (>50%)
Van Wijk[121] (2008)/ Pennsylvania USA, BC Canada and the Netherland	ACEIs, ARBs, BBs, CCBs, HCTZ	Discontinuation	USA: (9664/3651/6013) Canada: (25377/7180/14647), The Netherland: (24603/13763/10840)	365 (at least)	**USA cohort** Income Low High **Canada cohort** Income Low Medium High **The Netherlands cohort** Income Low High	**HR for Discontinuation** 1 (reference) 1.06 (0.98–1.14) 0.130 **HR for Discontinuation** 1 (reference) 0.86(0.79–0.93)<0.001 0.81(0.77–0.85)<0.001 **HR for Discontinuation** 1 (reference) 0.95(0.90–0.99)0.016	Income	one	16/24 (>50%)

Wong[122] (2010)/Hong Kong	ACEIs	MPR	(6408/1622/4786)	-	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00_(reference) 0.85(0.72-1.02)0.08	Payment status	one	19/24 (>50%)
Yeaw[123] (2009)/USA	ARBs	Discontinuation and PDC	7722	360	Copay of index medication Copay of index medication	**OR for Discontinuation** 1.00(1.00-1.00)<0.001 **OR for PDC<80%** 1.00(1.00-1.00)<0.001	Copay	one	19/25 (>50%)
Lamb[70] (2009)/Saskatchewan, Canada	ACEIs, ARBs, BBs	Fill frequency	8805	365			None	NA	19/25 (>50%)
Gogovor[124] (2007)/Quebec, Canada	ACEIs	Discontinuation	Secondary prevention: (1620/521/1099), primary prevention: (4596/933/3663)	216 (mean)	**Secondary prevention** Social assistance (no/yes) **Primary prevention** Social assistance (no/yes)	**OR for discontinuation** 0.98(0.79–1.20) **OR for discontinuation** 0.79(0.70–0.90)	Social assistance status	one	
Vegter[125] (2011)/The Netherland	ACEIs, ARBs	Discontinuation	51181	365			None	NA	17/24 (>50%)
Siegel[126] (2007)/USA	ACEIs, ARBs, CCBS, HCTZ, and alpha blockers	MPR	40492	180 (At least)			None	NA	17/25 (>50%)
Friedman[127] (2010)/Ontario, Canada	ACEIs, ARBs, CCBS, HCTZ	Discontinuation and MPR	(207473/40778/40258) total/lowest quintile/highest quintile	730	Income (per quintile) Income (per quintile) Income (per quintile)	**OR for discontinuation (same medication)** 0.96(0.96-0.97)<.0001 **OR Class discontinuation (any AHT medication)** 0.97(0.98-0.97)<.0001 **OR for MPR<80%** 0.91(0.89-0.93)<.0001	Income	one	18/25 (>50%)
Wong[128] (2011)/Hong Kong	ACEIs	Discontinuation	(7153/1839/5314)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1(reference) 0.86(0.73-1.00)0.055	Payment status	one	19/25 (>50%)
Corrao[129] (2009)/Italy	ACEIs, BBs, CCBs, diuretics	Discontinuation	(71469/14293/14293) (total/lowest quintile/highest quintile)	365	Income >2333 € Income 1500–2333 € Income 1083–1500 € Income 625–1083 € Income ≤625 € Living together Living alone	**HR for discontinuing** 0.98(0.95-1.02) 1.01(1.00-1.02) 1.01(1.00-1.02) 1.02(1.01-1.04) 1.00(reference) 1.00(reference) 1.00(0.98-1.02)	Income/Household composition	one/one	14/25 (>50%)
Eagle[130] (2004)/USA + 13 countries	ACEIs, BBs	Discontinuation	BBs: (7738), ACEIs: (2379)	180			None	NA	17/25 (>50%)
Wong[131] (2010)/Hong Kong	Combination therapy including triamterine/HCTZ, amiloride/HCTZ, irebesartan/HCTZ, and losartan/HCTZ	Discontinuation	(29253/7299/21954)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1.00(reference) 0.90(0.81–1.00)0.059	Payment status	one	17/25 (>50%)
Wogen[132] (2003)/USA	Amlodipine, valsartan, lisinopril	Discontinuation	(142945)	365			None	NA	19/25 (>50%)
Yang[133] (2010)/USA	ACEIs, ARBs	PDC	(599141)	270 (minimum)			None	NA	19/25 (>50%)

Kramer[134] (2006)/USA *	BBs	PDC	(17035/3419/13616)	360	**Health plan type** Commercial v Medicare / Males age 35-64 Commercial v Medicare / Females age 35-64 Commercial v Medicare / Males age 65+ Commercial v Medicare / Females age 65+	**OR for PDC<75%** 0.33(0.26-0.42) 0.42(0.23-0.77) 0.67(0.57-0.78) 0.57(0.48-0.69)	Health plan type	one	15/25 (>50%)
Degli Esposti[135] (2002)/Italy	ACEIs, ARBs, BBs, CCBs, diuretics	Discontinuation	(7312)	1005			None	NA	18/25 (>50%)
Shah[136] (2009)/Minnesota, USA	ACEIs, ARBs, BBs	Discontinuation	BBs: 248, ACEI:180	1530 (Mean)			None	NA	20/25 (>50%)
Wong[137] (2010)/Hong Kong	BBs	Discontinuation	(19177/5088/14089)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1.00 (reference) 0.78 (0.71–0.85) <0.001	Payment status	one	22/25 (>50%)
Ude[138] (2008)/Germany	ACEIs	MPR	221881	365-547			None	NA	19/25 (>50%)
Sung[139] (2009)/Korea	ACEIs, ARBs, BBs, CCBs, HCTZ, combination	CMA	(725220/670678/52265)	365 (Minimum)	**Health security program** NHIP MAP	**OR for CMA<80%** 0.99(0.97-1.02) 1.00(reference)	Health plan type	one	19/25 (>50%)
Evans[64] (2009)/Saskatchewan, Canada	ACEIs, ARBs, BBS, CCBs	Discontinuation	(52039/10865/41174) (total/SAP+Family+Senior/none)	365	**Income security benefit** None SAP Family-based Senior-based	**OR for discontinuation** 0.88(0.76-1.00)0.05 1(reference) 0.63(0.51-0.76) <0.0001 0.95(0.89-1.03) 0.23	Income security benefit	one	21/25 (>50%)
Wong[140] (2009)/Hong Kong	CCBs	MPR and discontinuation	(20156/5280/14876)	180	**Pay status** Fee waivers Fee payers **Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.92(0.83-1.00)0.05 **OR for discontinuation** 1.0 (reference) 0.87 (0.73–1.04) 0.128	Payment status	one	20/25 (>50%)
Wong[141] (2010)/Hong Kong	HCTZ	MPR	(8551/2279/6272)	180	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.78(0.68-0.89) <0.001	Payment status	one	20/25 (>50%)
Wong[142] (2009)/Hong Kong	ACEI, BBs, CCBs, HCTZ	Discontinuation	(93286/24814/68472)	180	**Pay status** Fee waivers Fee payers	**OR for Discontinuation** 1.00 (ref.) 0.83 (0.79–0.87) <0.001	Payment status	one	18/25 (>50%)
Wong[143] (2010)/Hong Kong	ACEIs, ARBs, BBs, CCBs, HCTZ, others (including a-blockers, potassium-sparing and other diuretics, vasodilators and combos)	MPR	(83884/21860/62024)	189 (max)	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.88(0.84-0.92) <0.001	Payment status	one	19/25 (>50%)
Wong[144] (2009)/Hong Kong	BBs	MPR	(15918/4057/11861)	Two consecutive visits	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.86(0.78-0.94)0.001	Payment status	one	13/25 (>50%)
Frech-Tamas[145] (2010)/USA	ACEIs, ARBs, BBs, CCBs, HCTZ, combination	MPR	(68538)	365	Average copay	**OR MPR<80%** 0.977< 0.0001	Copay	one	17/23 (>50%)

Pataky[146] (2007)/BC, Canada	ACEIs, BBs	PDC	ACEIs: (11494/4117/3220), BBs: (12949/4587/3674) (Total /Top30% /low30%)	365	**ACEIs group:** Private Payer Income Group Low 30% middle 40% top 30% Social Assistance (no/yes) **BBs group:** Private Payer Income Group Low 30% middle 40% top 30% Social Assistance (no/yes)	**OR for PDC<80%** 0.81(0.74-0.89)<0.001 1.00(reference) 1.10(1.00-1.22)0.062 0.83(0.74-0.93)0.002 1.15(0.93-1.40)0.191 0.88(0.80-0.96)0.007 1(reference) 1.03(0.93-1.14)0.612 0.88(0.79-0.99)0.034 1.08(0.88-1.31)0.460	Health plan type/Income group/Social assistance	one/one/one	17/25 (>50%)
Rasmussen[147] (2007)/Denmark	BBs	First gap	Income (29160/9709/9738), Education (29160/15078/3430)	180	**Age 30-64 year** Income High Medium Low Education High Medium Low **Age 65-74** Income High Medium Low Education High Medium Low	**OR for first gap>90days** 1.02(0.96–1.10) 0.79 1.01(0.95–1.08) 0.79 1(reference) 1.08(0.99–1.17) 0.03 0.97(0.92–1.03) 0.03 1(reference) 1.11(1.01–1.22)0.05 1.01(0.93–1.11)0.05 1(reference) 1.05(0.93–1.18)0.68 1.03(0.95–1.12)0.68 1(reference)	Income /Education	one/one	18/25 (>50%)
Roe[148] (2000)/USA	ACEIs	Discontinuation	236	180			None	NA	16/25 (>50%)
Khan[149] (2010)/Ontario, Canada**	ACEIs, ARBs, BBs, CCBs, HCTZ, ACEIs+ HCTZ	MPR	Income:(3571/1453/2118), living alone(3571/704/2867)	365	No OR reported for SES covariates		Income/Living alone	one/one	17/26 (>50%)
Corrao [150] (2010)/Italy	ACEIs, ARBs, BBs, CCBs, alpha-blockers	Discontinuation	CDL cohort (433680), CSD (12491)	270			None	NA	14/25 (>50%)
Van Dijk 2007 [151] /The Netherland	ACEIS, ARBs, BBs, and diuretics	Early drop-out and Refill adherence	14219	365	**Education** Precollege College/university **Type of insurance** Public Private **Employment status** Not employed/school Employed/school **Education** Precollege College/university **Type of insurance** Public Private **Employment status** Not employed/school Employed/school	**OR for early drop-out** 1(reference) 1.34(1.06-1.69) 1(reference) 1.12(0.93-1.35) 1(reference) 1.08(0.88-1.32) **OR for refill adherence<80%** 1(reference) 1.04(0.85-1.27) 1(reference) 1.09(0.95-1.25) 1(reference) 1.07(0.89-1.27)	Education/ type of health insurance/ employment status	one/one/one	16/24 (>50%)
Van Wijk 2007[152] /The Netherland	ACEIs, ARBs, BBs, CCBs and HCTZ	Reinitiating after discontinuation	(18357/11027/ 7330)	Max 2190	**Type of insurance** Public Private	**OR for NOT reinitiating** 1(reference) 0.99(0.95–1.04)	Type of insurance	one	16/24 (>50%)
Van Wijk 2005[153] /The Netherland	ACEIs, alpha-blockers, BBs, CCBs and HCTZ	Discontinuation	(2325/840/1485)	-	**Type of insurance** Public Private	**OR for discontinuation** 1(reference) 1.16(0.93-1.47)	Type of insurance	one	16/24 (>50%)
Lai[154] /(2011) / Canada**	ACEIs, BBs, CCBs, and diuretics	PDC	(9926/2377/1649)	365	**Income**	**OR for PDC<80%**	Income	one	19/25 (>50%)

Charles [155] (2003)/ USA	ACEIs, BBs and CCBs	Adherence ratio	ACEI cohort (2377), BBs cohort (1659), CCB (2148)	540			None	NA	**11/24 (<50%)**
Baily [156] (1996)/USA	ACEIS, adrenergic agents, alpha-blockers, BBs, CCBs, direct vasodilators, and thiazide diuretics	Refill failure	1366	-			None	NA	**11/25 (<50%)**
Glader [157] (2010) /Sweden	ACEIs/ARBs, BBs, CCBs, diuretics	Persistence	12152	720			None (Living alone vs institutionalized and the support of next of kin were not considered as SES)	NA	**11/25 (<50%)**
Zeng [158] (2010) /USA	ARBs and CCBs	PDC	4525	365	**Type of insurance** Medicaid Commercial HMOs **Copay category** 0-5$ 6-15$ 16-25$ 26-50$ >50$	**OR for PDC<80%** 1(reference) 0.60(0.44-0.81)0.01 1(reference) 1.08(0.94-1.25) 0.95(0.82-1.11) 1.09(0.94-1.23) 1.49(1.28-1.75)	Type of insurance/ copayment category	1/1	**11/24 (<50%)**
Brixner [159] (2008) / USA	Valsartan and HCTZ combination`	MPR	8711	365			None	NA	**12/25 (<50%)**
Patel [160] (2008) / USA	HCTZ alone or with combined with either ACEI, ARBs or BBs	MPR and discontinuation	48212	365	**Type of insurance** Medicaid Commercial HMOs	**HR for discontinuation** 1(reference) 0.75 <0.0001	Type of insurance/ average copay	1/1	**12/25 (<50%)**
Roe [161] (1999) / USA	ACEIs	MPR	869	210			None	NA	**12/24 (<50%)**
Liberman (39) / (2011) / USA	ACEIs, ARBs	MPR	ACEIs: 7400 ARBs:3274	365	**ACEIs:** **Income (by zip code)** Highest quintile Lowest quintile **Copayment** Highest quintile Lowest quintile **ARBs:** **Income (by zip code)** Highest quintile Lowest quintile **Copayment** Highest quintile Lowest quintile	**OR for MPR<80%** 0.84(0.73-0.98) 1(reference) 1.09(0.55-2.17) 1(reference) 0.65(0.52-0.81) 1(reference) 1.53(1.09-2.13) 1(reference)	Income / Copayment ($ per day of supply)	1/1	**8/24 (<50%)**

Abbreviations: ACEIs: Angiotensin Converting Enzyme Inhibitors; AHT: Antihypertensive; ARBs: Angiotensin Receptor Blockers; BBs: Beta Blockers; CCBs: Calcium Channel Blockers; CI: Confidence Interval; HCTZ: Hydrochlorothiazide; HMO: Health Maintenance Organization; HR Hazards Ratio; M+C: Medicare + Choice; MAP: Medical Aid Program; MPR: Medication Possession Ratio; NA: Not Applicable; NHIP: National Health Insurance Program; OR Odds Ratio; PDC: Proportion of Days Covered; POS: Point Of Service, PPO: Preferred Provider Organization; SAP Saskatchewan Assistance Plan

* Risk estimates were obtained through contact with author(s).

** Risk estimates could not be obtained through contact with author(s).

Figure 3-1: Flow chart for titles/abstracts and articles included in the review

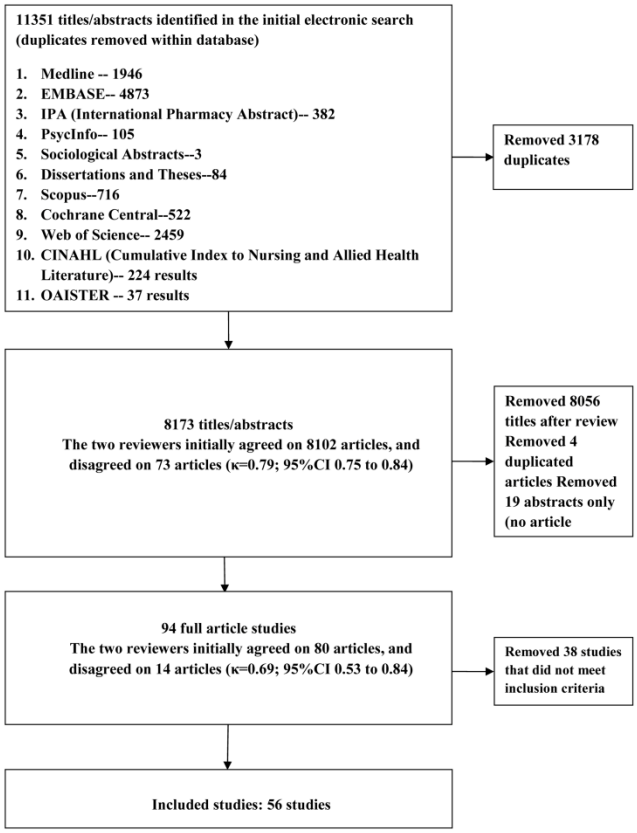
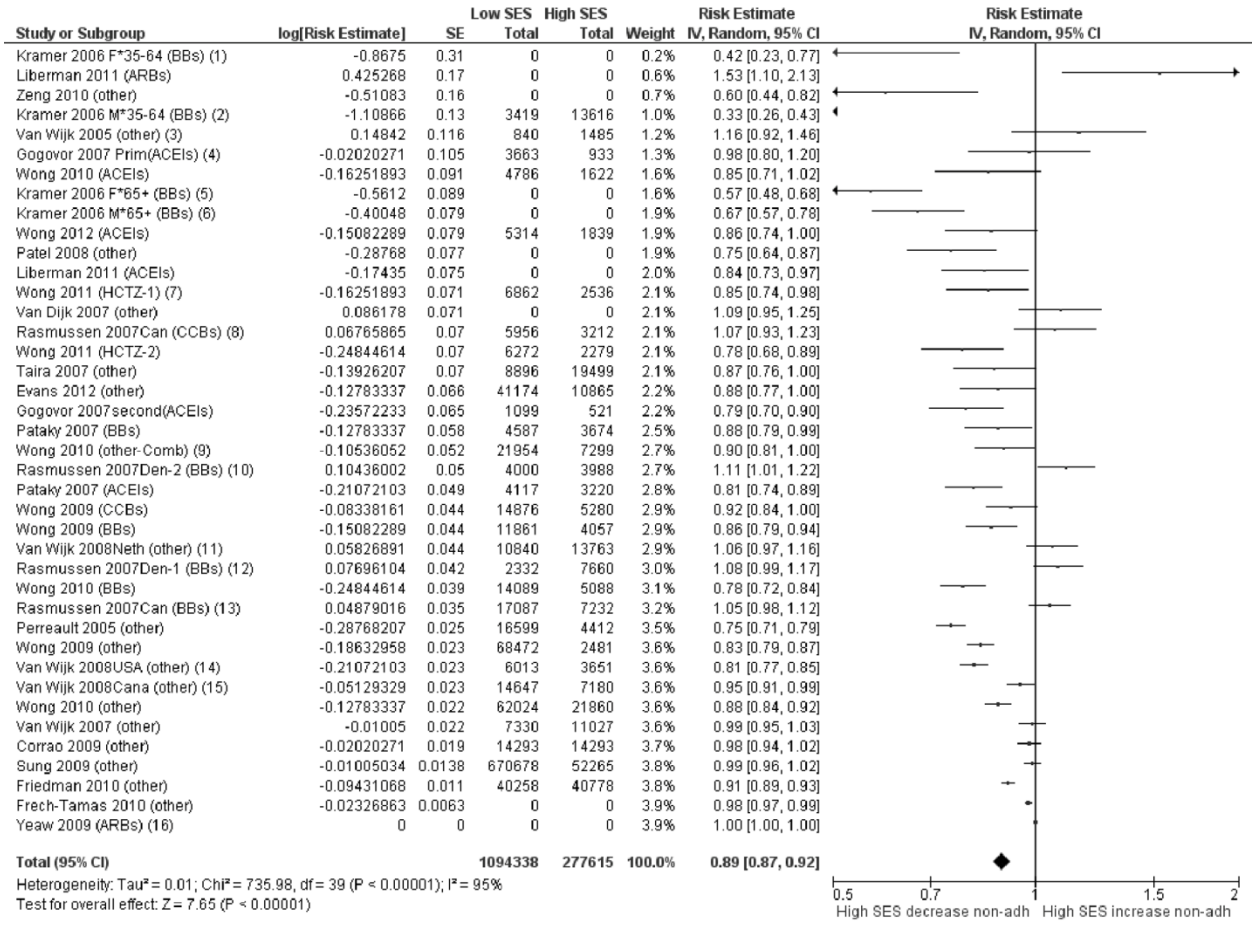


Figure 3-2: Pool risk estimates of non-adherence with high SES



Study or Subgroup	log[Risk Estimate]	SE	Low SES Total	High SES Total	Weight	Risk Estimate IV, Random, 95% CI
Kramer 2006 F*35-64 (BBs) (1)	-0.8675	0.31	0	0	0.2%	0.42 [0.23, 0.77]
Liberman 2011 (ARBs)	0.425268	0.17	0	0	0.6%	1.53 [1.10, 2.13]
Zeng 2010 (other)	-0.51083	0.16	0	0	0.7%	0.60 [0.44, 0.82]
Kramer 2006 M*35-64 (BBs) (2)	-1.10866	0.13	3419	13616	1.0%	0.33 [0.26, 0.43]
Van Wijk 2005 (other) (3)	0.14842	0.116	840	1485	1.2%	1.16 [0.92, 1.46]
Gogovor 2007 Prim(ACEIs) (4)	-0.02020271	0.105	3663	933	1.3%	0.98 [0.80, 1.20]
Wong 2010 (ACEIs)	-0.16251893	0.091	4786	1622	1.6%	0.85 [0.71, 1.02]
Kramer 2006 F*65+ (BBs) (5)	-0.5612	0.089	0	0	1.6%	0.57 [0.48, 0.68]
Kramer 2006 M*65+ (BBs) (6)	-0.40048	0.079	0	0	1.9%	0.67 [0.57, 0.78]
Wong 2012 (ACEIs)	-0.15082289	0.079	5314	1839	1.9%	0.86 [0.74, 1.00]
Patel 2008 (other)	-0.28768	0.077	0	0	1.9%	0.75 [0.64, 0.87]
Liberman 2011 (ACEIs)	-0.17435	0.075	0	0	2.0%	0.84 [0.73, 0.97]
Wong 2011 (HCTZ-1) (7)	-0.16251893	0.071	6862	2536	2.1%	0.85 [0.74, 0.98]
Van Dijk 2007 (other)	0.086178	0.071	0	0	2.1%	1.09 [0.95, 1.25]
Rasmussen 2007Can (CCBs) (8)	0.06765865	0.07	5956	3212	2.1%	1.07 [0.93, 1.23]
Wong 2011 (HCTZ-2)	-0.24844614	0.07	6272	2279	2.1%	0.78 [0.68, 0.89]
Taira 2007 (other)	-0.13926207	0.07	8896	19499	2.1%	0.87 [0.76, 1.00]
Evans 2012 (other)	-0.12783337	0.066	41174	10865	2.2%	0.88 [0.77, 1.00]
Gogovor 2007second(ACEIs)	-0.23572233	0.065	1099	521	2.2%	0.79 [0.70, 0.90]
Pataky 2007 (BBs)	-0.12783337	0.058	4587	3674	2.5%	0.88 [0.79, 0.99]
Wong 2010 (other-Comb) (9)	-0.10536052	0.052	21954	7299	2.7%	0.90 [0.81, 1.00]
Rasmussen 2007Den-2 (BBs) (10)	0.10436002	0.05	4000	3988	2.7%	1.11 [1.01, 1.22]
Pataky 2007 (ACEIs)	-0.21072103	0.049	4117	3220	2.8%	0.81 [0.74, 0.89]
Wong 2009 (CCBs)	-0.08338161	0.044	14876	5280	2.9%	0.92 [0.84, 1.00]
Wong 2009 (BBs)	-0.15082289	0.044	11861	4057	2.9%	0.86 [0.79, 0.94]
Van Wijk 2008Neth (other) (11)	0.05826891	0.044	10840	13763	2.9%	1.06 [0.97, 1.16]
Rasmussen 2007Den-1 (BBs) (12)	0.07696104	0.042	2332	7660	3.0%	1.08 [0.99, 1.17]
Wong 2010 (BBs)	-0.24844614	0.039	14089	5088	3.1%	0.78 [0.72, 0.84]
Rasmussen 2007Can (BBs) (13)	0.04879016	0.035	17087	7232	3.2%	1.05 [0.98, 1.12]
Perreault 2005 (other)	-0.28768207	0.025	16599	4412	3.5%	0.75 [0.71, 0.79]
Wong 2009 (other)	-0.18632958	0.023	68472	2481	3.6%	0.83 [0.79, 0.87]
Van Wijk 2008USA (other) (14)	-0.21072103	0.023	6013	3651	3.6%	0.81 [0.77, 0.85]
Van Wijk 2008Cana (other) (15)	-0.05129329	0.023	14647	7180	3.6%	0.95 [0.91, 0.99]
Wong 2010 (other)	-0.12783337	0.022	62024	21860	3.6%	0.88 [0.84, 0.92]
Van Wijk 2007 (other)	-0.01005	0.022	7330	11027	3.6%	0.99 [0.95, 1.03]
Corrao 2009 (other)	-0.02020271	0.019	14293	14293	3.7%	0.98 [0.94, 1.02]
Sung 2009 (other)	-0.01005034	0.0138	670678	52265	3.8%	0.99 [0.96, 1.02]
Friedman 2010 (other)	-0.09431068	0.011	40258	40778	3.8%	0.91 [0.89, 0.93]
Frech-Tamas 2010 (other)	-0.02326863	0.0063	0	0	3.9%	0.98 [0.97, 0.99]
Yeaw 2009 (ARBs) (16)	0	0	0	0	3.9%	1.00 [1.00, 1.00]
Total (95% CI)			**1094338**	**277615**	**100.0%**	**0.89 [0.87, 0.92]**

Heterogeneity: Tau² = 0.01; Chi² = 735.98, df = 39 (P < 0.00001); I² = 95%
Test for overall effect: Z = 7.65 (P < 0.00001)

(1) Female aged 35-64; BBs: Beta blockers
(2) Male aged 35-64
(3) Other: more than one antihypertensive medication were used
(4) Primary prevention cohort; ACEIs: Angiotensin Converting Enzyme Inhibitors
(5) Female aged 65 years and more
(6) Female aged 65 years and more
(7) HCTZ: Hydrochlorothiazide
(8) Canada cohort; CCBs: Calcium Channel Blockers
(9) Combination medications
(10) Denmark-Age 65-74 years cohort
(11) The Netherland cohort
(12) Denmark-Age 30-64 years cohort
(13) Canada cohort
(14) USA cohort
(15) Canada cohort
(16) ARBs: Angiotensin Receptor Blockers

Figure 3-3: Funnel plot of studies identified in the systematic review

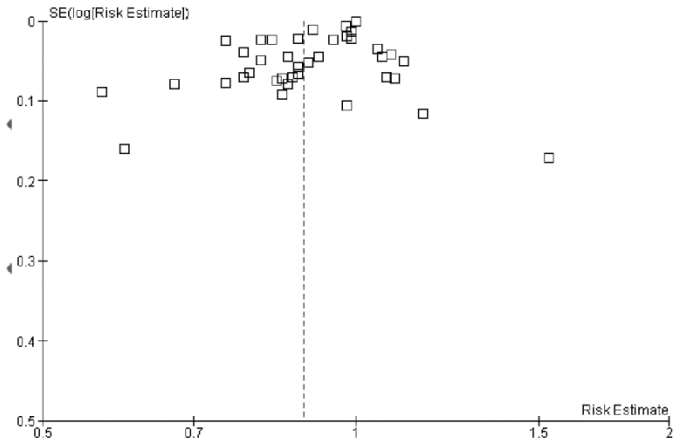


Figure 3-4: Pool risk estimates of non-adherence with high SES, stratified by medication studied

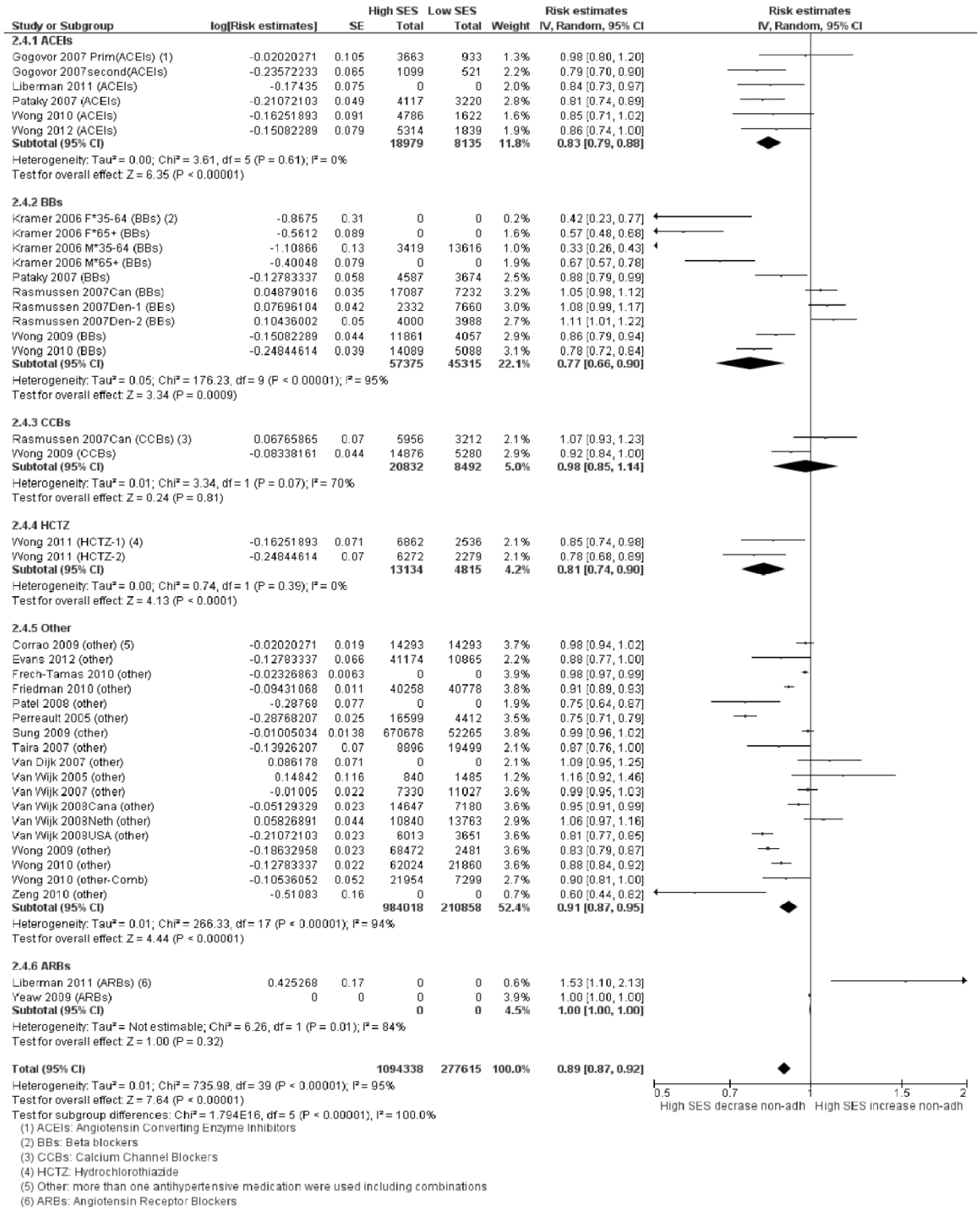


Table 3-1: Characteristics of included studies

Characteristic		Number of subjects	% of total sample (n=4708293)	Number of studies (%) (*N* = 56)
Region of data origin	North American	2666720	56.6%	35 (62.5%)
	Europe	880224	18.7%	10 (17.9%)
	Other countries	1161349	24.7%	11 (19.6%)
Date of publication	Before 2004	206025	4.4%	9 (16.1%)
	2004 and after	4502268	95.6%	47 (83.9%)
AHT Medication(s) studied	ACEIs	27114	0.6%	6 (10.7%)
	ARBs	18396	0.4%	2 (3.6%)
	BBs	102690	2.2%	6 (10.7%)
	CCBs	29324	0.6%	2 (3.6%)
	HCTZ	17949	0.4%	2 (3.6%)
	Other (if more than one medication was studied)	4512820	95.8%	38 (67.8)
Adherence measure type	MPR-related	3058762	65%	26 (46.4%)
	Discontinuation	1351749	28%	25 (44.6%)
	Both	297782	6.3%	5 (9.0%)
Number of SES measurements	None	2961112	62.9%	24 (42.9%)
	One	1546235	32.8%	25 (44.6%)
	> One	200946	4.3%	7 (12.5%)
If SES was not assessed (*N*=24), did study assess ethnicity?	Yes	1761764	37.4%	5 (8.9%)
	No	1199348	25.5%	19 (33.9%)
SES measure	One SES measure -Non-Income related			
	Education	28395	0.6%	1 (1.8%)
	One SES measure -Income related			
	Prescription drug coverage or medication copayment amount	1171195	24.9%	17 (30.4%)
	Income level	267379	5.7%	4 (7.1%)

	social assistance benefits or income security benefits	79266	1.7%	3 (5.4%)
	More than one SES measure			
	Two income related measures	4525	0.1%	2 (3.6%)
	Three income related measures	24443	0.5%	1 (1.8%)
	Income related + one non-income related measure	104200	2.2%	3 (5.4%)
	Income related + two non-income related measures	14219	0.3%	1 (1.8%)
Method to measure income	Direct			
	Link with taxation records	150609	3.2%	3 (5.4%)
	Indirect			
	Health plan	53603	1.1%	2 (3.6%)
	Neighbourhood	200370	4.3%	2 (3.6%)
Follow-up days category	Up to 180	1426148	30.3%	13 (23.2)
	181-365	2753990	58.5%	31 (55.4%)
	>365	502138	10.7%	8 (14.3%)
	-	26107	0.6%	4 (7.1%)

Abbreviations: ACEIs: Angiotensin Converting Enzyme Inhibitors; AHT: Antihypertensive; ARBs: Angiotensin Receptor Blockers; BBs: Beta Blockers; CCBs: Calcium Channel Blockers; HCTZ: Hydrochlorothiazide; Medication Possession Ratio

eTable 3-1: Studies identified in the systematic review

Reference (Year)/ Country	Medication(s) studied	Adherence measure	No of subjects (total/low SES/ high SES)	Follow -up (days)	SES covariates studied	OR/HR of non-adherence (95%CI) p-value	SES measure used	Number of domain(s) in SES measure (one/Multiple)	Quality score
Wong[164] (2011)/Hong Kong	HCTZ	Discontinuation	(9398/ 2536/6862)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1.00 (reference) 0.85 (0.74–0.98) 0.027	Payment status	one	13/25 (>50%)
Rasmussen[80] (2007)/ON, Canada	BBs, CCBs	PDC	BBs cohort: (24319/7232 /17087), CCBs (9168/3212/ 5956)	365	**BBs cohort** Low income (no/yes) **CCBs cohort** Low income (no/yes)	**OR for PDC <40% vs.≥80%** 1.05(0.91-1.11) **OR for PDC<40% vs. ≥80%** 1.07(0.94-1.23)	Income	one	18/25 (>50%)
Setoguchi[68](2010) /New Jersey, USA	ABs, BBs	PDC	46,278	365			None	NA	15/25 (>50%)
Monane[165] (1997) / New Jersey, USA	ACEIs, BBs, CBs, HCTZ	Days covered	8643	365			None	NA	14/25 (>50%)
Bloom[59] (1998)/ USA	ACEIs, ARBs, BBs, CCBs, HCTZ	Discontinuation	21723	365			None	NA	15/25 (>50%)
Degli Esposti[60] (2002)/Italy	ACEIs, BBs, CCBs, HCTZ	Discontinuation	16783	365			None	NA	17/25 (>50%)
Yang[166] (2009)/USA	ACEIs, ARBs	PDC	1075285	180			None	NA	14/26 (>50%)
Shaya[167] (2009)/Maryland, USA	Combination of ACEIs, CCBs, or HCTZ	MPR	568	365 (at least)			None	NA	15/25 (>50%)
Elliott[61] (2007)/USA	amlodipine, HCTZ, lisinopril, valsartan	Discontinuation	60685	365			None	NA	15/24 (>50%)
Perreault[168] (2005)/Québec, Canada	ACEIs, BBs, CCBS, diuretics alone or in combination	Discontinuation	(21011/4412 /16599)	365	Social assistance (no/yes)	**OR for Discontinuation** 0.75(0.70-0.79)	Social assistance status	one	15/24 (>50%)
signorovitch[169] (2012) / USA	BBs	Discontinuation	173200	365			None	NA	14/25 (>50%)

Taira[170] (2007) / Hawaii, USA[170]	ACEIs, ARBs, BBs, CCBs, HCTZ	MPR	(28395/19499/8896)	365-1095	**Education** <High school High school College Post-graduate	**OR for MPR<80%** 1(reference) 0.91(1.00-0.83) 0.84(0.91-0.77) 0.87(1.00-0.77)	Education	one	17/25 (>50%)
Van Wijk[171] (2008)/ Pennsylvania USA, BC Canada and the Netherland	ACEIs, ARBs, BBs, CCBs, HCTZ	Discontinuation	USA: (9664/3651/6013) Canada: (25377/7180/14647), The Netherland: (24603/13763/10840)	365 (at least)	**USA cohort** Income Low High **Canada cohort** Income Low Medium High **The Netherlands cohort** Income Low High	**HR for Discontinuation** 1 (reference) 1.06 (0.98–1.14) 0.130 **HR for Discontinuation** 1 (reference) 0.86(0.79–0.93)<0.001 0.81(0.77–0.85)<0.001 **HR for Discontinuation** 1 (reference) 0.95(0.90–0.99)0.016	Income	one	16/24 (>50%)
Wong[172] (2010)/Hong Kong	ACEIs	MPR	(6408/1622/4786)	-	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00_(reference) 0.85(0.72-1.02)0.08	Payment status	one	19/24 (>50%)
Yeaw[173] (2009)/USA	ARBs	Discontinuation and PDC	7722	360	Copay of index medication Copay of index medication	**OR for Discontinuation** 1.00(1.00-1.00)<0.001 **OR for PDC<80%** 1.00(1.00-1.00)<0.001	Copay	one	19/25 (>50%)
Lamb[70] (2009)/Saskatchewan, Canada	ACEIs, ARBs, BBs	Fill frequency	8805	365			None	NA	19/25 (>50%)
Gogovor[174] (2007)/Quebec, Canada	ACEIs	Discontinuation	Secondary prevention: (1620/521/1099), primary prevention: (4596/933 / 3663)	216 (mean)	**Secondary prevention** Social assistance (no/yes) **Primary prevention** Social assistance (no/yes)	**OR for discontinuation** 0.98(0.79–1.20) **OR for discontinuation** 0.79(0.70–0.90)	Social assistance status	one	
Vegter[175] (2011)/The Netherland	ACEIs, ARBs	Discontinuation	51181	365			None	NA	17/24 (>50%)
Siegel[176] (2007)/USA	ACEIs, ARBs, CCBS, HCTZ, and alpha blockers	MPR	40492	180 (At least)			None	NA	17/25 (>50%)
Friedman[177] (2010)/Ontario, Canada	ACEIs, ARBs, CCBS, HCTZ	Discontinuation and MPR	(207473/40778/40258) total/lowest quintile/highest quintile	730	Income (per quintile) Income (per quintile) Income (per quintile)	**OR for discontinuation (same medication)** 0.96(0.96-0.97)<.0001 **OR Class discontinuation (any AHT medication)** 0.97(0.98-0.97)<.0001 **OR for MPR<80%** 0.91(0.89-0.93)<.0001	Income	one	18/25 (>50%)
Wong[178] (2011)/Hong Kong	ACEIs	Discontinuation	(7153/1839/5314)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1(reference) 0.86(0.73-1.00)0.055	Payment status	one	19/25 (>50%)
Corrao[179] (2009)/Italy	ACEIs, BBs, CCBs, diuretics	Discontinuation	(71469/14293/14293) (total/lowest quintile/highest quintile)	365	Income >2333 € Income 1500–2333 € Income 1083–1500 € Income 625–1083 € Income ≤625 € Living together Living alone	**HR for discontinuing** 0.98(0.95-1.02) 1.01(1.00-1.02) 1.01(1.00-1.02) 1.02(1.01-1.04) 1.00(reference) 1.00(reference) 1.00(0.98-1.02)	Income/Household composition	one/one	14/25 (>50%)

Eagle[180] (2004)/USA+ 13 countries	ACEIs, BBs	Discontinuation	BBs: (7738), ACEIs: (2379)	180			None	NA	17/25 (>50%)
Wong[181] (2010)/Hong Kong	Combination therapy including triamterine /HCTZ, amiloride /HCTZ, irebesartan /HCTZ, and losartan/ HCTZ	Discontinuation	(29253/7299 /21954)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1.00(reference) 0.90(0.81–1.00)0.059	Payment status	one	17/25 (>50%)
Wogen[182] (2003)/USA	Amlodipine, valsartan, lisinopril	Discontinuation	(142945)	365			None	NA	19/25 (>50%)
Yang[183] (2010)/USA	ACEIs, ARBs	PDC	(599141)	270 (minimum)			None	NA	19/25 (>50%)
Kramer[184] (2006)/USA*	BBs	PDC	(17035/3419 /13616)	360	**Health plan type** Commercial v Medicare / Males age 35-64 Commercial v Medicare / Females age 35-64 Commercial v Medicare / Males age 65+ Commercial v Medicare / Females age 65+	**OR for PDC<75%** 0.33(0.26-0.42) 0.42(0.23-0.77) 0.67(0.57-0.78) 0.57(0.48-0.69)	Health plan type	one	15/25 (>50%)
Degli Esposti[185] (2002)/Italy	ACEIs, ARBs, BBs, CCBs, diuretics	Discontinuation	(7312)	1005			None	NA	18/25 (>50%)
Shah[186] (2009)/Minnesota, USA	ACEIs, ARBs, BBs	Discontinuation	BBs: 248, ACEI:180	1530 (Mean)			None	NA	20/25 (>50%)
Wong[187] (2010)/Hong Kong	BBs	Discontinuation	(19177/5088 /14089)	180	**Pay status** Fee waivers Fee payers	**OR for discontinuation** 1.00 (reference) 0.78 (0.71–0.85) <0.001	Payment status	one	22/25 (>50%)
Ude[188] (2008)/Germany	ACEIs	MPR	221881	365-547			None	NA	19/25 (>50%)
Sung[189] (2009)/Korea	ACEIs, ARBs, BBs, CCBs, HCTZ, combination	CMA	(725220/670 678/52265)	365 (Minimum)	**Health security program** NHIP MAP	**OR for CMA<80%** 0.99(0.97-1.02) 1.00(reference)	Health plan type	one	19/25 (>50%)
Evans[64] (2009)/Saskatchewan, Canada	ACEIs, ARBs, BBS, CCBs	Discontinuation	(52039/1086 5/41174) (total/SAP+ Family+Senior/none)	365	**Income security benefit** None SAP Family-based Senior-based	**OR for discontinuation** 0.88(0.76-1.00)0.05 1(reference) 0.63(0.51-0.76) <0.0001 0.95(0.89-1.03) 0.23	Income security benefit	one	21/25 (>50%)
Wong[190] (2009)/Hong Kong	CCBs	MPR and discontinuation	(20156/5280 /14876)	180	**Pay status** Fee waivers Fee payers **Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.92(0.83-1.00)0.05 **OR for discontinuation** 1.0 (reference) 0.87 (0.73–1.04) 0.128	Payment status	one	20/25 (>50%)

Wong[191] (2010)/Hong Kong	HCTZ	MPR	(8551/2279/6272)	180	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.78(0.68-0.89) <0.001	Payment status	one	20/25 (>50%)
Wong[192] (2009)/Hong Kong	ACEI, BBs, CCBs, HCTZ	Discontinuation	(93286/24814/68472)	180	**Pay status** Fee waivers Fee payers	**OR for Discontinuation** 1.00 (ref.) 0.83 (0.79–0.87) <0.001	Payment status	one	18/25 (>50%)
Wong[193] (2010)/Hong Kong	ACEIs, ARBs, BBs, CCBs, HCTZ, others (including a-blockers, potassium-sparing and other diuretics, vasodilators and combos)	MPR	(83884/21860/62024)	189 (max)	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.88(0.84-0.92) <0.001	Payment status	one	19/25 (>50%)
Wong[194] (2009)/Hong Kong	BBs	MPR	(15918/4057/11861)	Two consecutive visits	**Pay status** Fee waivers Fee payers	**OR for MPR<80%** 1.00(reference) 0.86(0.78-0.94)0.001	Payment status	one	13/25 (>50%)
Frech-Tamas[195] (2010)/USA	ACEIs, ARBs, BBs, CCBs, HCTZ, combination	MPR	(68538)	365	Average copay	**OR MPR<80%** 0.977< 0.0001	Copay	one	17/23 (>50%)
Pataky[196] (2007)/BC, Canada	ACEIs, BBs	PDC	ACEIs: (11494/4117/3220), BBs: (12949/4587/3674) (Total /Top30% /low30%)	365	**ACEIs group:** Private Payer Income Group Low 30% middle 40% top 30% Social Assistance (no/yes) **BBs group:** Private Payer Income Group Low 30% middle 40% top 30% Social Assistance (no/yes)	**OR for PDC<80%** 0.81(0.74-0.89)<0.001 1.00(reference) 1.10(1.00-1.22)0.062 0.83(0.74-0.93)0.002 1.15(0.93-1.40)0.191 0.88(0.80-0.96)0.007 1(reference) 1.03(0.93-1.14)0.612 0.88(0.79-0.99)0.034 1.08(0.88-1.31)0.460	Health plan type/Income group/Social assistance	one/one/one	17/25 (>50%)
Rasmussen[197] (2007)/Denmark	BBs	First gap	Income (29160/9709/9738), Education (29160/15078/3430)	180	**Age 30-64 year** Income High Medium Low Education High Medium Low **Age 65-74** Income High Medium Low Education High Medium Low	**OR for first gap>90days** 1.02(0.96–1.10) 0.79 1.01(0.95–1.08) 0.79 1(reference) 1.08(0.99–1.17) 0.03 0.97(0.92–1.03) 0.03 1(reference) 1.11(1.01–1.22)0.05 1.01(0.93–1.11)0.05 1(reference) 1.05(0.93–1.18)0.68 1.03(0.95–1.12)0.68 1(reference)	Income /Education	one/one	18/25 (>50%)
Roe[198] (2000)/USA	ACEIs	Discontinuation	236	180			None	NA	16/25 (>50%)
Khan[199] (2010)/Ontario, Canada**	ACEIs, ARBs, BBs, CCBs, HCTZ, ACEIs+ HCTZ	MPR	Income:(3571/1453/2118), living alone(3571/704/2867)	365	No OR reported for SES covariates		Income/Living alone	one/one	17/26 (>50%)
Corrao [200] (2010)/Italy	ACEIs, ARBs, BBs, CCBs, alpha-blockers	Discontinuation	CDL cohort (433680), CSD (12491)	270			None	NA	14/25 (>50%)

Van Dijk 2007 [201] /The Netherland	ACEIS, ARBs, BBs, and diuretics	Early drop-out and Refill adherence	14219	365	**Education** Precollege College/university **Type of insurance** Public Private **Employment status** Not employed/school Employed/school **Education** Precollege College/university **Type of insurance** Public Private **Employment status** Not employed/school Employed/school	**OR for early drop-out** 1(reference) 1.34(1.06-1.69) 1(reference) 1.12(0.93-1.35) 1(reference) 1.08(0.88-1.32) **OR for refill adherence<80%** 1(reference) 1.04(0.85-1.27) 1(reference) 1.09(0.95-1.25) 1(reference) 1.07(0.89-1.27)	Education/type of health insurance/employment status	one/one/one	16/24 (>50%)
Van Wijk 2007[202] /The Netherland	ACEIs, ARBs, BBs, CCBs and HCTZ	Reinitiating after discontinuation	(18357/11027/ 7330)	Max 2190	**Type of insurance** Public Private	**OR for NOT reinitiating** 1(reference) 0.99(0.95–1.04)	Type of insurance	one	16/24 (>50%)
Van Wijk 2005[203] /The Netherland	ACEIs, alpha-blockers, BBs, CCBs and HCTZ	Discontinuation	(2325/840/ 1485)	-	**Type of insurance** Public Private	**OR for discontinuation** 1(reference) 1.16(0.93-1.47)	Type of insurance	one	16/24 (>50%)
Lai[204] /(2011) / Canada**	ACEIs, BBs, CCBs, and diuretics	PDC	(9926/2377/ 1649)	365	**Income**	**OR for PDC<80%**	Income	one	19/25 (>50%)
Charles [205] (2003)/ USA	ACEIs, BBs and CCBs	Adherence ratio	ACEI cohort (2377), BBs cohort (1659), CCB (2148)	540			None	NA	**11/24 (<50%)**
Baily [206] (1996)/USA	ACEIS, adrenergic agents, alpha-blockers, BBs, CCBs, direct vasodilators, and thiazide diuretics	Refill failure	1366	-			None	NA	**11/25 (<50%)**
Glader [207] (2010) /Sweden	ACEIs/ARBs, BBs, CCBs, diuretics	Persistence	12152	720			None (Living alone vs institutionalized and the support of next of kin were not considered as SES)	NA	**11/25 (<50%)**
Zeng [208] (2010) /USA	ARBs and CCBs	PDC	4525	365	**Type of insurance** Medicaid Commercial HMOs **Copay category** 0-5$ 6-15$ 16-25$ 26-50$ >50$	**OR for PDC<80%** 1(reference) 0.60(0.44-0.81)0.01 1(reference) 1.08(0.94-1.25) 0.95(0.82-1.11) 1.09(0.94-1.23) 1.49(1.28-1.75)	Type of insurance/copayment category	1/1	**11/24 (<50%)**
Brixner [209] (2008) / USA	Valsartan and HCTZ combination`	MPR	8711	365			None	NA	**12/25 (<50%)**
Patel [210] (2008) / USA	HCTZ alone or with combined with either ACEI, ARBs or BBs	MPR and discontinuation	48212	365	**Type of insurance** Medicaid Commercial HMOs	**HR for discontinuation** 1(reference) 0.75 <0.0001	Type of insurance/average copay	1/1	**12/25 (<50%)**
Roe [211] (1999) / USA	ACEIs	MPR	869	210			None	NA	**12/24 (<50%)**

Liberman (39) / (2011) / USA	ACEIs, ARBs	MPR	ACEIs: 7400 ARBs:3274	365	**ACEIs:** **Income (by zip code)** Highest quintile Lowest quintile **Copayment** Highest quintile Lowest quintile **ARBs:** **Income (by zip code)** Highest quintile Lowest quintile **Copayment** Highest quintile Lowest quintile	**OR for MPR<80%** 0.84(0.73-0.98) 1(reference) 1.09(0.55-2.17) 1(reference) 0.65(0.52-0.81) 1(reference) 1.53(1.09-2.13) 1(reference)	Income / Copayment ($ per day of supply)	1/1	**8/24 (<50%)**

Abbreviations: ACEIs: Angiotensin Converting Enzyme Inhibitors; AHT: Antihypertensive; ARBs: Angiotensin Receptor Blockers; BBs: Beta Blockers; CCBs: Calcium Channel Blockers; CI: Confidence Interval; HCTZ: Hydrochlorothiazide; HMO: Health Maintenance Organization; HR Hazards Ratio; M+C: Medicare + Choice; MAP: Medical Aid Program; MPR: Medication Possession Ratio; NA: Not Applicable; NHIP: National Health Insurance Program; OR Odds Ratio; PDC: Proportion of Days Covered; POS: Point Of Service, PPO: Preferred Provider Organization; SAP Saskatchewan Assistance Plan

* Risk estimates were obtained through contact with author(s).

** Risk estimates could not be obtained through contact with author(s).

CHAPTER -4- MULTIPLE VERSUS SINGLE-DOMAIN MEASUREMENTS OF SOCIO-ECONOMIC STATUS (SES) FOR PREDICTING NON-ADHERENCE TO STATIN MEDICATIONS: AN OBSERVATIONAL POPULATION-BASED COHORT STUDY

4.1 Abstract

Background: Socioeconomic status (SES) is strongly linked to several theoretical determinants of medication non-adherence and may therefore be an important predictor at the population level. However, it is a complex characteristic that cannot be easily represented in population-based models. We compared the performance of multiple versus single domain measures of SES as predictors of statin adherence. *Methods:* This study was a retrospective cohort using population-based administrative data mapped to area-level census information from Saskatchewan, Canada between 1994 and 2008. Eligible individuals received a statin medication following discharge from a hospitalization for coronary heart disease and were followed for one year. Logistic regression models were constructed to assess the predictors of optimal adherence using different types of SES measures. The relative impact of each SES measure was assessed by its adjusted odds ratio and improvement over the predictive accuracy of the base model. *Results:* More than two thirds (i.e., 68.8%; 6,517/9,478) of eligible individuals exhibited optimal adherence (i.e. $\geq$ 80%) at one year. The estimated impact of SES on optimal adherence differed depending on the SES measure tested. The highest performing single-domain measure, household income (OR 0.75; 95% CI 0.72 to 0.92; model c-statistic improvement 0.4%, p=0.04) generated a similar result to the multiple-domain measure (adjusted OR 0.74; 95% CI 0.62 to 0.88; model c-statistic improvement 0.7%, p=0.01). *Conclusion:* Multi-domain measurements of SES using

administrative databases mapped to census data are not associated with better performance in predicting medication adherence compared to single-domain measures such as household income.

4.2 Background

Non-adherence to statin medications (i.e., HMG CoA reductase inhibitors) is a well-known and highly prevalent barrier to the prevention of cardiovascular events in patients who have coronary heart disease (CHD).[54,57,71,80,84,212] However, even with extensive research into its potential causes, robust predictors of non-adherence have never been found.[58] Strong theoretical reasoning points to socioeconomic status (SES) as an important predictor of non-adherence.[16] However, a recent systematic review found high SES to be associated with an 11% decrease in the odds of non-adherence to antihypertensive medications.[213] In relative terms, this impact was quite small and was obtained from studies demonstrating an excessive degree of heterogeneity.

Substantial variation exists with respect to the approaches used to account for SES. Out of 56 eligible antihypertensive adherence studies identified in the systematic review above, 24 studies (43%) had no measure of SES. When SES was identified, it was typically represented by a single measure relating to income or medication co-payment. Although economic factors are likely important,[104] SES may influence medication non-adherence through several other means such as health care access, availability of support, and/or health literacy.[86]

Multiple-domain measures such as poverty or deprivation indices[177,214-219] account for the various elements of SES, effectively predict health outcomes, and can be estimated from census data in population-based studies.[157] For example, the deprivation index (DI) developed by Pampalon *et al*[157] provides an overall SES ranking based on three material (i.e., income,

education and employment) and three social determinants (i.e., living arrangements, family structure, and living condition). This measure was developed in Canada, and has been strongly associated with mortality in previous studies.[220-222] Despite the apparent relevance to medication adherence research, multiple-domain SES measures have rarely been used.[218,219] We hypothesized that the use of this multiple domain measure of SES would be a stronger predictor of non-adherence to statin medications compared to single domain measures among a cohort of patients with established CHD in Saskatchewan, Canada.

4.3 Methods

4.3.1 Data source

A retrospective, observational study was conducted using administrative data maintained by the Saskatchewan Ministry of Health (MOH) and area-level census information. The government of Saskatchewan maintains several databases including the population registry, prescription drug file (pharmacy dispensations), physician services and hospital services databases. Nearly 99% of all residents in Saskatchewan are covered by the Saskatchewan Ministry of Health for physician and hospital services. Inmates of federal prisons, the armed forces and the Royal Canadian Mounted Police (RCMP) are not included because they receive health benefits from the Canadian federal government. The prescription drug data captures dispensations for approximately 90% of Saskatchewan's residents. This database does not capture dispensations for patients who are eligible for federal prescription coverage (such as First Nations population) and does not capture medications excluded from the provincial formulary or over-the-counter (OTC) medications. Each dispensation record captures several fields including: patient study ID, dispensing date, medication name, drug identification number (DIN) and quantity dispensed.

The only SES variables captured with the MOH are receipt of income security benefits and the level of cost sharing by the Drug Plan. Other SES indicators were obtained by mapping subjects' residential postal codes to national census statistics summarized for specific geographic areas (i.e., dissemination areas DA) in Saskatchewan defined and collected by Statistics Canada.[223] A DA is the smallest standard geographic area with a population of 400 to 700 persons, and all census data are disseminated at this level.[223] Saskatchewan databases have previously been used to perform high quality studies of drug utilization and outcomes.[57,70,130-132]

This approval for this study was obtained from the Biomedical Research Ethics Board (Bio-REB #10-162) at the University of Saskatchewan.

4.3.2 Cohort

Eligible study individuals were at least 30 years of age and received at least one dispensation for a statin medication within 90 days[80,133] of discharge from a hospitalization for CHD between January 1st, 1994 and December 31st, 2008. Similar to previous studies,[57] existence of CHD was verified by a hospital discharge with a primary/most responsible diagnosis of an acute coronary syndrome (ACS) and/or a hospital or physician-claim procedure code for coronary revascularization. ACS was identified using the International Classification of Diseases (ICD) diagnostic codes for myocardial infarction (MI) or unstable angina (UA) captured through the hospital discharge file [Appendix 4-1]. Coronary revascularization procedures (i.e., coronary artery bypass surgery (CABG) or percutaneous coronary interventions (PCI)) were captured through the physician services database (i.e., fee-for-service claims) and/or the hospital discharge file [Appendix 4-1]. The positive predictive value, sensitivity, and specificity of ACS identification using administrative databases have been estimated between 85-98%.[134-139] For

individuals with multiple eligible hospitalizations, the earliest hospital discharge for CHD within the study period was considered the index date.

Individuals were excluded if they were enrolled as a provincial beneficiary for less than five years preceding the CHD hospitalization, experienced a ACS/revascularization within the previous five years, received a statin medication within the previous one year, or if they died or their coverage was terminated < 365 days following their first statin dispensation.[57,65]

4.3.3 Measures

4.3.3.1 Adherence

We measured one-year adherence using the "tablets-per-day" method that assumes all statin medications are prescribed for use once per day.[224] "Tablets-per-day" was calculated by dividing the sum of all tablets dispensed by the total number of days in the observation period (i.e., 365 days). Consistent with previous studies, optimal adherence was defined using a threshold of 80% or higher.[143,144] Switching between statin medications was allowed and number of days spent in the hospital during follow-up period was subtracted from the denominator because hospitalized patients in Saskatchewan receive medications from institutional supplies that are not captured through the prescription drug database.[145] Previous studies have shown the tablets per day measure to be highly correlated with other measures of adherence using Saskatchewan data.[57,70]

4.3.3.2 Socio-Economic Status (SES)

For each eligible individual, both single-domain and multi-domain measurements of SES were estimated. Single domain SES indicators included provincial medication benefit (any level of cost sharing by the Drug Plan for the first statin prescription), cost of prescription not paid by the government (<29$, 29$ to 59$, 60$ to 79$, and ≥80$ in Canadian dollars), receipt of income

security benefits, and area of residence (rural/urban). Also, the Statistics Canada 2001 community profile was used to estimate household income quintile.[225] For this ecological variable, individuals were assigned the mean income level corresponding to the 'dissemination area' identified by their residential postal code [Appendix 4-2].

The multi-domain measure of SES was the deprivation index (DI) outlined by Pampalon *et al.*[157] This variable is also an ecological measure derived from aggregate-level SES variables reported in the 2006 census at the level of 'dissemination-areas'. The DI was expressed as a quintile relative to all Saskatchewan residents [Appendix 4-2]. In addition to testing the overall DI score, the individual material and social domain scores were tested separately to ensure their influence on adherence was consistent.

4.3.4 Analysis Procedure

Crude and adjusted odds ratios (ORs) for the effect of each SES indicator were obtained from logistic regression models using optimal adherence (Tablets-per-day $\geq$ 80%) as the dependent variable. To obtain the adjusted ORs, a multiple logistic regression model was initially built using non-SES factors only. Subsequently, each SES indicator was added to this "base" model separately to obtain its adjusted OR. The resulting models containing each SES indicator were assessed for the size of the OR corresponding to SES. In addition, the overall predictive accuracy of each model containing an SES indicator was compared to the base-model using the c-statistic,[226] and Brier score.[226] The change in c-statistic was tested using the DeLong test.[227] Several categories of non-SES factors were considered for the adjusted "base" model including demographic, condition-related, therapy-related, patient-related, and health-system-related factors [Appendix 4-3]. Variable selection was carried-out using the process described by Hosmer and Lemeshow.[228] Briefly, a multivariable model was created with all variables that

were significantly associated with the outcome on univariate analysis. Then, variables were retained in the final model were either significantly associated with the outcome or improved model fit.[228] Variables that were deemed clinically important and included in the adjusted model regardless of their statistical significance include age, sex, and index year. Multicollinearity was examined by calculating the variance inflation factor (VIF) where values more than 10 were interpreted as important multicollinearity.[147] The primary analysis was executed using cases where all SES information were available, and then verified using the entire population after imputing missing SES information using a multiple imputation approach.[229-231] In the multiple imputations method we first formed a predictive model for the missing quintiles based on all other available subjects' variables including age, sex, year of index, and comorbidity score. A multiple imputation approach was then employed to designate income quintile, using a Monotone logistic regression method. This method is favored to achieve the best prediction as it accounts for both the natural variability of data as well as the uncertainty of the imputation process.[229-231] We used SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) to perform the analysis.

4.4 Results

A total of 43,118 individuals were discharged from hospital in Saskatchewan between January 1st, 1994 and December 31st, 2008 with a primary/most responsible diagnosis of an acute coronary syndrome (ACS) and/or a procedure for coronary revascularization. From them, 9,478 individuals (22.0%) received a dispensation for a statin mediation within 90 days of the index date and met all other inclusion criteria [Figure 4-1]. The mean age of individuals on their index date was 64.6 years (SD=11.9; median=66.0; IQR=55.0 to 74.0) and 70.6% (n=6,688) were male. Almost one half of all individuals (49.8%; n=4,719) received a revascularization procedure

during the course of their ACS hospitalization. The remaining individuals either had an ACS hospitalization only (36.0%; n=3,414), or revascularization procedure only (14.2%; n=1,345). More than one half of individuals received atorvastatin as their first statin prescription post-index (55.5%; n=5,260). The average number of days between hospital discharge and the first statin dispensation was 8.5 (SD=19.6) [Table 4-1]. A DI quintile was not available for 3.5% of the cohort, while income quintile was missing for 33.4%. Thus, all SES information were available for 6110 (64.5%) of our cohort.

More than two thirds (68.8%; n=6,517) of all statin users in our cohort achieved optimal adherence (i.e. $\geq$ 80%) at one year. The percentage of adherent individuals increased substantially over the study period from 54.1% in 1994 to 75.8% in 2007 [Figure 4-2]. A similar trend was noticed among individuals classified with low SES using all six single-domain and three multiple-domains SES measures (data not shown).

The estimated association of SES with statin adherence varied depending on the SES measure tested (Table 4-2). The OR associated with the multiple-domain DI indicated a 26% decrease in the odds of achieving optimal adherence for individuals classified in the lowest SES quintile compared to the highest (adjusted OR 0.74; 95% CI 0.62 to 0.88). Similarly, two single-domain measures, rural versus urban residence (adjusted OR 0.77; 95% CI 0.68 to 0.87), and lowest versus highest household income quintile (adjusted OR 0.75; 95% CI 0.63 to 0.90) produced similar estimates (Figure 4-3). In contrast, no significant association between SES and adherence was observed using the four remaining single-domain measures: provincial medication benefit, prescription cost not covered by the government, and receipt of income security benefits.

Minimal improvements in predictive accuracy (<1%) was observed over the baseline model when any of the SES measures were included and none of the models were highly predictive when estimated using the c-statistic (Table 4-2). Further, Brier scores were similar in models containing single-domain or multiple-domains measures and were not improved over the base model. Similar results were obtained when the individual components of the DI were tested individually and when the three most significant SES measures were added simultaneously to the model. Also, results were similar when we imputed missing values using multiple imputations (data not shown). The independent effects of all non-SES variables in addition to DI quintiles on the odds of being adherent to statin medications are reported in [Table 4-3].

The consistent performance between the multiple domain DI and single-domain household income appeared to be a result of a correlation between the two measures (Spearman's correlation coefficient 0.65; 95%CI 0.63 to 0.66). restricting the cohort to individuals classified in the highest and lowest quintiles based on the DI or household income, the correlation between measures was highly significant (Spearman's correlation coefficient 0.94; 95%CI 0.94 to 0.95).In contrast, rural/urban status was not strongly correlated with either the DI or household income (data not shown).

4.5 Discussion

We compared the association between various SES measures defined from health-administrative databases and aggregated census data as predictors of statin adherence among individuals with CHD between 1994 and 2008. Overall, first-year adherence to statin medications improved dramatically over the period of study, from 54.1% in 1994 to 75.8% in 2007. Prediction accuracy of multivariable models were only slightly improved with the addition of SES measures, regardless of the type. Further, the multiple-domain DI did not perform remarkably

better than all single-domain measures despite its theoretical advantages of representing factors including low income, low education/literacy, and poor access to care. Low SES estimated by the multiple-domain DI was associated with a 26% reduction in the odds of being adherent (OR=0.74, 95%CI 0.62 to 0.88, p=<0.01). On the other hand, low SES estimated by household income resulted in very similar findings (OR 0.75; 95% CI 0.63 to 0.90) with similar prediction accuracy.

Theoretically, SES assessment should reflect its multifaceted nature by considering several factors from material and social domains.[104] Previous studies on the determinants of medication adherence have largely focused on economic measures of SES, possibly missing the influence of other SES domains through health behavior,[232] health literacy,[233] and communication.[234] However, the theoretical advantages of using a multiple-domain measure of SES to predict medication adherence were not realized in this retrospective cohort study. One possible explanation is that medication non-adherence is a ubiquitous problem among all patient groups regardless of demographic or socio-economic factors. The evidence for the latter hypothesis is mounting as predictive accuracy of adherence models derived in this study and others has been far from optimal when studied at the population level.[235] In addition, the multiple-domain measure of SES used in this study was highly concordant with the single-domain measure of household income suggesting the multiple-domain measure may have been limited in its ability to discriminate individuals beyond income.

The trend towards increasing levels of adherence observed in this study is positive and consistent with previous research.[67-69] However, a sizeable number of individuals (n=8,971) were excluded for not receiving any statin prescriptions after hospital discharge. This number of individuals represents 48.6% of all individuals who would be otherwise eligible for inclusion in our cohort.

It is assumed these individuals either did not receive a prescription from a physician, or failed to get it filled at the pharmacy (i.e., primary non-adherence).[20-25] SES may have influenced both of these situations but the databases used in this study provided no information to allow discrimination between them. Adding this number to the number of non-adherent individuals in our cohort would raise the estimate of the proportion of patients who are potentially divested from the benefits of statin medications from 31.2% to 64.7%.

Our study has several strengths: different measures of SES derived from administrative databases and census data were examined; the cohort was relatively homogeneous because subjects have a single condition (CHD) and are prescribed a medication for which there is no alternative class; and the covered population was virtually universal with no restrictions on age or socioeconomic status. However, there are also several limitations. First, SES variables were estimated from national census data reported by geographic DAs and not reported at the individual level. Also, due to restrictions in the availability of data, the census information used for income assessment was from the 2001 census, whereas the multiple domains DI was derived from the 2006 census. However, the geographic distribution of the Saskatchewan population remained relatively stable during this period. Second, our data do not have clinical information on patients such as disease severity or laboratory values which may influence adherence. Third, our model was not cross-validated in an external sample. Thus, its generalizability to other patient cohorts is not known. Even more, our study was performed on statin medications, which may limit the generalizability to other chronic disease medications. Fifth, no information was available from private insurers; thus, prescription costs not paid by the government may not have resulted in out-of-pocket payments for all individuals. Lastly, we excluded patients who died or whose coverage terminated during the first year post index date. Although patients who survive for one year post

index date may be systematically different from those who die, the consequences of statin non-adherence are most likely evident among early survivors. Finally, we were unable to identify a gold-standard SES measure, so the aim was to determine which measure accounted for the largest proportion of adherence. However, we cannot be sure that measures with the strongest association with SES were necessarily the best performing measures.

To our knowledge, this is the first study that systematically examined the association between different measures of SES derived from administrative databases and census data and medication adherence. Considering that the vast majority of previous studies on medication adherence have used single-domain SES indicators, our study indicated that available multi-domain measures are not better in accounting the overall burden of non-adherence. More research is needed to find the best methodology to account for this confounding.

4.6 Disclaimer

This Study is based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

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Table 4-1: Characteristic of individuals included in cohort

Characteristic		Non-Adherent (n=2,961; 31.2%) n(%)	Adherent (n=6,517; 68.8%) n(%)	Total (n=9,478) n(%)	Chi-square or T-test p-value
Age	mean (SD)	64.3(12.2)	64.7(11.8)	64.6(11.9)	0.01
	<55	717(24.2%)	1465(22.5%)	2201(23.0%)	0.30
	55-65	777(26.2%)	1772(27.2%)	2579(26.9%)	
	66-73	653(22.1%)	1447(22.2%)	2132(22.2%)	
	≥74	814(27.5%)	1833(28.1%)	2685(27.9%)	
Male gender		2087(70.5%)	4601(70.6%)	6688(70.6%)	0.91
Index year	1994-1997	269(9.1%)	406(6.2%)	675(7.0%)	<0.01
	1998-2001	829(28.0%)	1637(25.1%)	2466	
	2002-2005	1298(43.8%)	2904(44.6%)	4202	
	2006-2007	565(19.1%)	1570(24.1%)	2135	
Type of index diagnosis	ACS+PROC	1219(41.2%)	3500(53.7%)	4719(49.8%)	<0.01
	ACS only	1316(44.4%)	2098(32.2%)	3414(36.0%)	
	PROC only	426(14.4%)	919(14.1%)	1345(14.2%)	
Duration (in days) of index hospitalization	mean (SD)	9.2(8.5)	8.2(9.9)	8.9 (9.0)	<0.01
	≥10 days	669(22.6%)	1820(27.9%)	2489(26.3%)	<0.01
Time from index to statin prescription	mean (SD)	10.3(21.4)	7.7(18.7)	8.5(19.6)	<0.01
	more than 1 day	842(28.4%)	1421(21.8%)	2263(23.9%)	<0.01
At least one prescription in post-index year	BB	2411(81.4%)	5538(85.0%)	7949(83.9%)	<0.01
	ACEI/ARB	2213(74.7%)	5403(82.9%)	7616(80.4%)	<0.01
	CCB	672(22.7%)	1476(22.7%)	2148(22.7%)	0.96
	diuretic	977(33.0%)	2426(37.2%)	3403(35.9%)	<0.01
	anticoagulants	426(14.4%)	1099(16.9%)	1525(16.1%)	<0.01
	antiplatelet	1461(49.3%)	3928(60.3%)	5389(56.9%)	<0.01
	nitrates	1942(65.6%)	4281(65.7%)	6223(65.7%)	0.92
	other lipid drugs	192(6.5%)	229(3.5%)	421(4.4%)	<0.01
At least one statin prescription with 28 days' supply in post-index year		102(3.4%)	505(7.8%)	607(6.4%)	<0.01
High statin dose on first prescription post index[€]		1497(50.6%)	3563(54.7%)	5060(53.4%)	<0.01
Atorvastatin on first prescription post index		1674(56.5%)	3586(55.0%)	5260(55.5%)	0.17
>4 distinct (non-statin) medications received in post-index year		1649(55.7%)	4083(62.7%)	5732(60.5%)	<0.01
Chronic disease score ≥4		1389(46.9%)	2968 (45.5%)	4357 (46.0%)	0.22
Diagnosis in hospital or physician records in pre-index year	DM	400 (13.5%)	905(13.9%)	1305 (13.8%)	0.62
	HTN	1045(35.3%)	2474(38.0%)	3519(37.1%)	0.01
Specialty of prescribing physician of the first statin prescription	GP	439 (14.8%)	697(10.7%)	1136(12.0%)	<0.01
	cardiologist	1341(45.3%)	3364(51.6%)	4705(49.6%)	
	internist	643(21.7%)	1236(19.0%)	1879(19.8%)	
	cardiac surgeon	323(10.9%)	787(12.1%)	1110(11.7%)	
	other	215(7.3%)	433(6.6%)	648(6.8%)	
≥5 physician's visits in the first 3 months following the first statin dispensation		2150(72.6%)	5027(77.1%)	7177(75.7%)	<0.01
Any hospitalization in pre-index year		861(29.1%)	2100(32.2%)	2569(27.1%)	<0.01
Rural residence	yes	1663(56.2%)	2608(48.5%)	4825(50.9%)	<0.01
Household income quintile	missing	1077(36.4%)	2091(32.1%)	3168(33.4%)	-
	1 (lowest)	395(13.3%)	777(11.9%)	1172(12.4%)	<0.01
	2	370(12.5%)	892(13.7%)	1262(13.3%)	
	3	362(12.2%)	931(14.3%)	1293(13.6%)	
	4	393(13.3%)	857(13.2%)	1250(13.2%)	
	5 (highest)	364(12.3%)	969(14.9%)	1333(14.1%)	
Provincial prescription benefit[Ω]		987(33.3%)	2483(38.1%)	3470(36.6%)	<0.01
level of Rx cost not covered by the Drug Plan	<29$	667(22.5%)	1668(25.6%)	2335(24.6%)	<0.01
	29$ to 59$	753(25.4%)	1650(25.3%)	2403(25.4%)	
	50$ to 79$	821(27.7%)	1570(24.1%)	2391(25.2%)	
	≥80$	720(24.3%)	1629(25%)	2349(24.8%)	
Receipt of income security benefits		679(22.9%)	1431(22.0%)	2110(22.3%)	0.29
Deprivation index quintile	missing	117(4.0%)	220(3.4%)	337(3.6%)	-

	1 (most deprived)	603(20.4%)	1220(18.7%)	1823(19.2%)	
	2	510(17.2%)	1012(15.5%)	1522(16.1%)	
	3	609(20.6%)	1467(22.5%)	2076(21.9%)	0.01
	4	590(19.9%)	1322(20.3%)	1912(20.1%)	
	5 (least deprived)	532(18.0%)	1276(19.6%)	1808(19.1%)	
Material component of deprivation index (quintile)	**missing**	117(4.0%)	220(3.4%)	337(3.6%)	-
	1 (most deprived)	588(19.9%)	1161(17.8%)	1749(18.5%)	
	2	598(20.2%)	1329(20.4%)	1927(20.3%)	
	3	687(23.2%)	1429(21.9%)	2116(22.3%)	0.01
	4	568(19.2%)	1369(21.0%)	1937(20.4%)	
	5 (least deprived)	403(13.6%)	1009(15.5%)	1412(14.9%)	
Social component of deprivation index (quintile)	**missing**	117(4.0%)	220(3.4%)	337(3.6%)	-
	1 (most deprived)	588(19.9%)	1221(18.7%)	1809(19.1%)	
	2	483(16.3%)	1141(17.5%)	1624(17.1%)	
	3	502(17.0%)	1172(18.0%)	1674(17.7%)	0.15
	4	580(19.6%)	1190(18.3%)	1770(18.7%)	
	5 (least deprived)	691(23.3%)	1573(24.1%)	2264(23.9%)	

Abbreviations: ACS: Acute Coronary Syndrome; ACEI/ARB: Angiotensin Converting Enzyme-Inhibitor /Angiotensin Receptor-Blockers; BB: Beta-blockers; CCBs: Calcium Channel Blockers; DM: Diabetes Mellitus; GP: General Practitioner; HTN: Hypertension; PROC: Procedure of revascularization.

€: High dose statin was defined[150,151] as having rosuvastatin >5mg, atorvastatin ≥20mg, or simvastatin ≥40mg

Ω: Provincial prescription benefit was defined as any cost-sharing by government health insurance on first statin dispensation after index date

Table 4-2: The adjusted independent effects of each SES variables on the probability of being adherent to statin medication

Variable		Odds Ratio Estimate	95% Wald Confidence Limits		p-value from Wald Chi-Square test	Brier Score	C-statics (95% Confidence Limits)	Change in C-statistics from base model (0.651)		p-value from DeLong test for C-statistics change
								absolute	%	
Residence	**Rural**	0.814	0.72	0.92	**<0.01***	0.196	0.653 (0.638 to 0.668)	0.0037	0.57%	**0.04***
Household income quintile	**1 (lowest)**	0.75	0.63	0.90	**<0.01***	0.196	0.653 (0.638 to 0.668)	0.0031	0.48%	**0.04***
	2	0.92	0.77	1.11	0.77					
	3	1.01	0.84	1.21	0.08					
	4	0.88	0.74	1.05	0.60					
	5 (highest)	reference			-					
Provincial prescription benefit		1.13	0.99	1.29	0.08	0.208	0.650 (0.635 to 0.665)	0.0005	0.08%	0.54
level of prescription cost not covered by the Drug Plan ($)	**<29**	1.03	0.86	1.24	0.49	0.208	0.650 (0.635 to 0.665)	0.0002	0.03%	0.75
	29$ to 59	0.92	0.78	1.10	0.19					
	50$ to 79	1.02	0.85	1.21	0.67					
	≥80	reference			-					
Receipt of income security benefits		0.86	0.74	1.00	0.05	0.196	0.650 (0.635 to 0.665)	0.0009	0.14%	0.27
Deprivation index quintile	**1 (most deprived)**	0.76	0.64	0.91	**<0.01***	0.196	0.654 (0.639 to 0.669)	0.0046	0.71%	**0.01***
	2	0.91	0.76	1.10	0.21					
	3	0.92	0.76	1.11	0.49					
	4	0.82	0.68	1.01	0.29					
	5 (least deprived)	reference			-					
Quintile of material component of deprivation index	**1 (most deprived)**	0.78	0.64	0.94	**<0.01***	0.196	0.653 (0.638 to 0.668)	0.0031	0.48%	**0.03***
	2	0.97	0.80	1.17	0.56					
	3	0.92	0.77	1.10	0.74					
	4	1.04	0.88	1.24	0.05					
	5 (least deprived)	reference			-					
Quintile of social component of deprivation index	**1 (most deprived)**	0.76	0.64	0.91	**0.01***	0.196	0.651 (0.636 to 0.666)	0.0016	0.25%	0.28
	2	0.91	0.76	1.10	0.54					
	3	0.92	0.76	1.11	0.49					
	4	0.82	0.68	1.00	0.29					
	5 (least deprived)	reference			-					

Table 4-3: The independent effects of all non-SES variables and DI on the odds of being adherent to statin medication from multivariate logistic regression model

Characteristic		Odds Ratio Estimate	95% Wald Confidence Limits		p-value from Wald Chi-Square test
Deprivation index quintile	**1 (most deprived)**	0.74	0.62	0.88	**<0.01**
	2	0.83	0.69	1.00	0.21
	3	1.02	0.85	1.22	**0.03**
	4	0.93	0.78	1.12	0.51
	5 (least deprived)	reference			-
Age	**<55**	reference			
	55-65	1.11	0.95	1.31	0.06
	66-73	0.98	0.83	1.17	0.55
	≥74	0.97	0.81	1.15	0.37
Male gender		0.98	0.86	1.11	0.72
Index year	**1994**	reference			
	1995	0.93	0.41	2.11	**0.04**
	1996	1.43	0.68	3.03	0.69
	1997	1.51	0.74	3.07	0.87
	1998	1.64	0.81	3.31	0.66
	1999	1.75	0.88	3.48	0.29
	2000	1.46	0.73	2.90	0.60
	2001	1.69	0.85	3.35	0.40
	2002	1.34	0.68	2.66	0.14
	2003	1.58	0.80	3.14	0.80
	2004	1.57	0.79	3.13	0.87
	2005	1.95	0.98	3.91	**0.02**
	2006	1.89	0.95	3.80	**0.05**
	2007	2.54	1.26	5.13	**<0.01**
Type of index diagnosis	**ACS+PROC**	reference			
	ACS only	0.68	0.58	0.79	**<0.01**
	PROC only	0.94	0.77	1.14	0.16
Duration of index hospitalization ≥10 days		1.24	1.08	1.44	**<0.01**
Time from index to statin prescription more than 1 day		0.84	0.73	0.97	**0.02**
At least one prescription in post-index year	**BB**	1.21	1.04	1.41	**0.01**
	ACEI/ARB	1.44	1.24	1.68	**<0.01**
	anticoagulants	1.12	0.95	1.33	0.19
	antiplatelet	1.45	1.29	1.64	**<0.01**
	other lipid drugs	0.43	0.33	0.56	**<0.01**
At least one statin prescription with 28 days' supply in post-index year		2.09	1.57	2.78	**<0.01**
High statin dose on first prescription post index		0.92	0.79	1.06	0.25
Atorvastatin on first prescription post index		0.75	0.66	0.86	**<0.01**
Choric disease score ≥4		1.08	0.95	1.23	0.26
Specialty of prescribing physician of the first statin prescription	**GP**	reference			-
	cardiologist	1.20	0.97	1.49	0.48
	internist	1.12	0.90	1.40	0.63
	cardiac surgeon	1.24	0.93	1.65	0.44
	other	1.24	0.94	1.64	0.44
≥5 physician visits in the first 3 months following the first statin dispensation		1.21	1.06	1.39	**0.01**
Any hospitalization in pre-index year		0.86	0.75	0.98	**0.02**

Abbreviations: ACS: Acute Coronary Syndrome; ACEI/ARB: Angiotensin Converting Enzyme-Inhibitor /Angiotensin Receptor-Blockers; BB: Beta-blockers; CCBs: Calcium Channel Blockers; DM: Diabetes Mellitus; GP: General Practitioner; HTN: Hypertension; PROC: Procedure of revascularization.

Figure 4-1: Flow chart of individuals in study

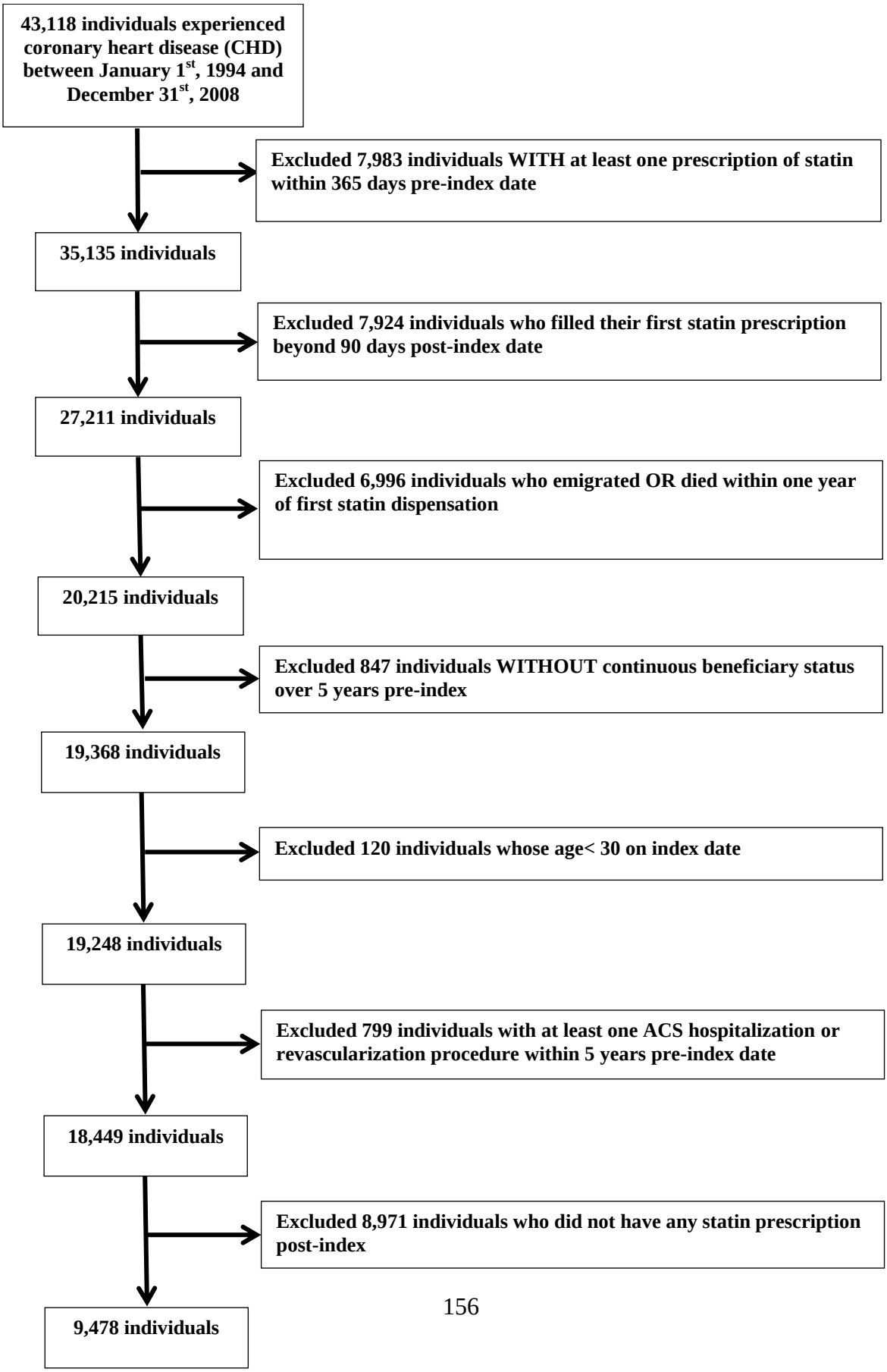
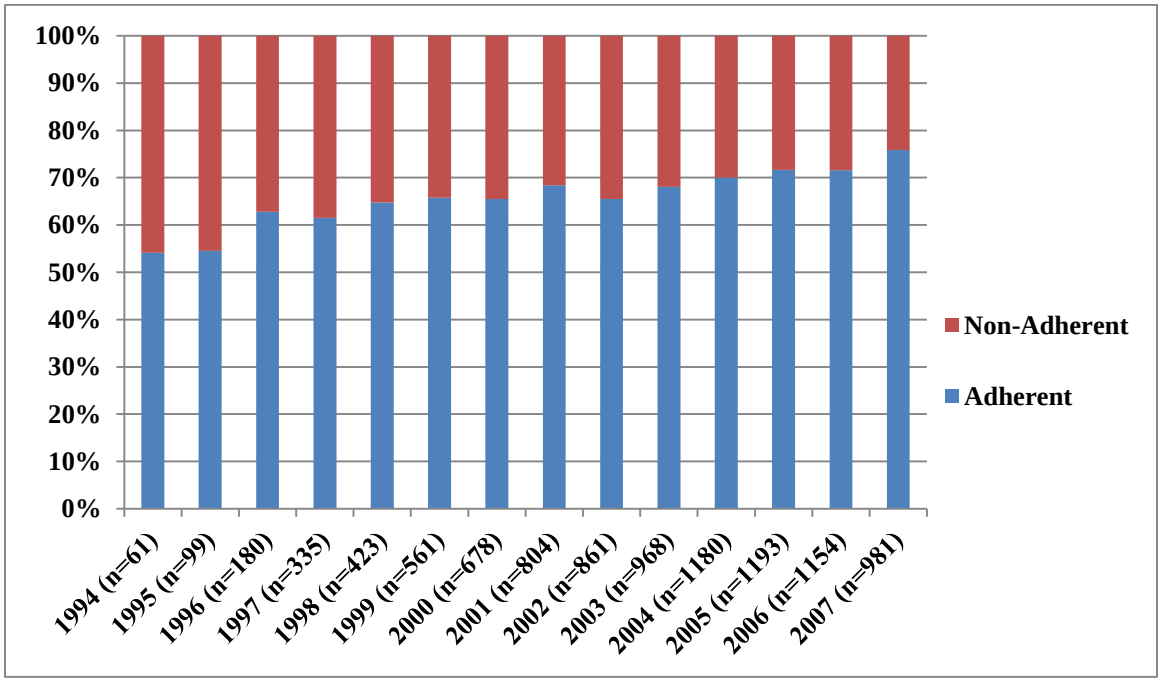
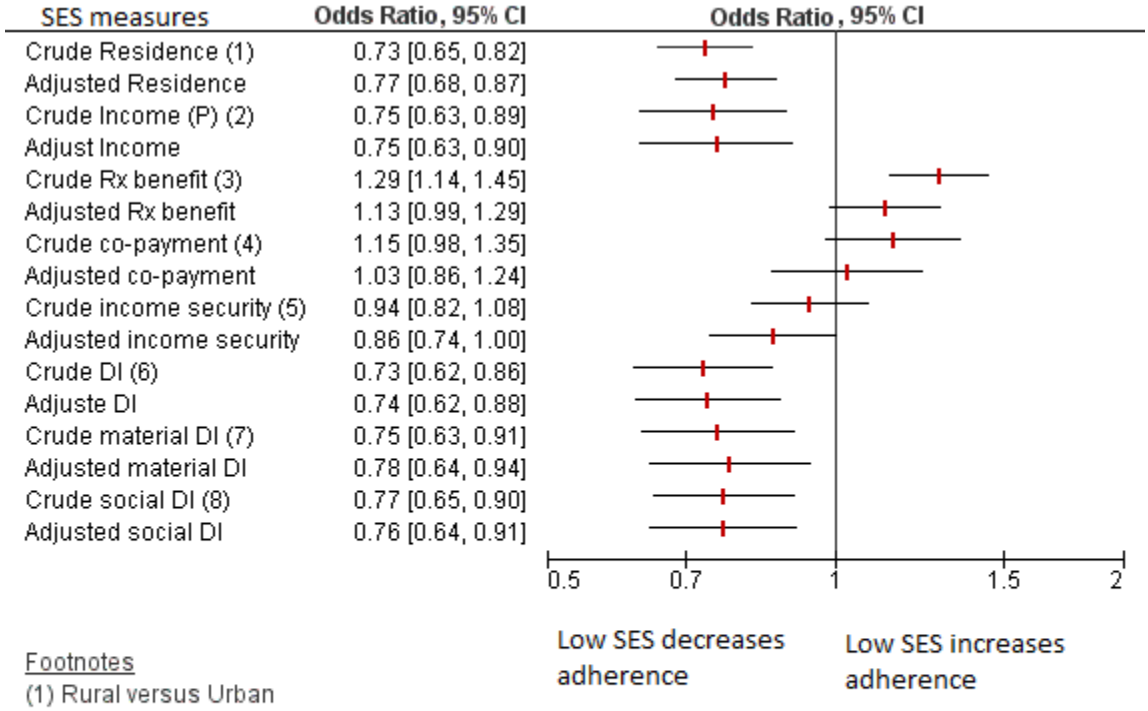


Figure 4-2: Percentage of individuals exhibiting adherence ≥80% to statin medications during the first year post ACS hospitalization, stratified by index year



*Adherence was defined by a "tablets per day" of 80% or higher

Figure 4-3: The crude and adjusted independent effects of each SES variables on the probability of being adherent to statin medication



Footnotes
(1) Rural versus Urban
(2) Lowest household income quintile versus highest
(3) Having provincial prescription benefit versus none
(4) Amount in Canadian dollars of prescription cost not covered by the Drug Plan (<29$ versus ≥80$)
(5) Receipt of income security benefits versus none
(6) Lowest deprivation index quintile versus highest
(7) Lowest material deprivation index quintile versus highest
(8) Lowest social deprivation index quintile versus highest

Appendix 4-1: Subjects' selection of eligible individuals depending on the existence of CHD

Subject Selection Diagnoses from primary/most responsible diagnosis Hospital Services Database		
ICD-9*	**ICD-10-CA**	**Description**
410	I21 - I22.xxx	myocardial infarction (MI)
411	I20.0xx and I24.xxx	unstable angina (UA)
*ICD-9 was used until March 31, 2001, when ICD-10-CA reporting started		
ICD-9: Manual of the international statistical classification of diseases, injuries, and causes of death, 9th revision. Geneva: The Organization; 1977. ICD-10-CA: International statistical classification of diseases and related health problems, tenth revision, Canada. Canadian Institute for Health Information; 2003.		

Subject Selection Revascularization Procedures from Physician's Services Database and Hospital Services Database			
Physician database	Hospital services database		Description
FSC	CCP*	CCI	
328A		1.IJ.50.GQ-BD-x	PTCA/PCI^
329A		1.IJ.50.GQ-BF-x	
331A	48.02	1.IJ.50.GQ-OA-x	
335A	48.03	1.IJ.57.GQ-xx-x	
548A	48.09	1.IJ.57.GS-xx-x	
138L	48.1x	1.IJ.76.xx-xx-x	CABG†
153L			
154L			
155L			
161L			
654L			
655L			
* CCP was used for procedures until April 1st 2001, when CCI reporting started ^ The term PCI (percutaneous coronary intervention) now replaces PTCA (percutaneous transluminal angioplasty) because it includes the use of balloons, stents and atherectomy devices while PTCA is a nonsurgical procedure to relieve narrowing and obstruction of vessels. †CABG: Coronary Artery Bypass Surgery			
FSC: Physician fee-for-service codes (FSCs) are listed in the Payment schedule for insured services provided by a physician in Saskatchewan http://www.health.gov.sk.ca/adx/aspx/adxGetMedia.aspx?DocID=2453,94,88,Documents&MediaID=1658&Filename=physician-payment-schedule-april-2008.pdf **CCP:** Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures, Statistics Canada 1986. **CCI:** Canadian Classification of Health Interventions , Canadian Institute for Health Information 2003			

Appendix 4-2: Socio-Economic Status (SES) measures

SES measure	Database source	Domain
Income security benefit (yes/no)	Individual was a recipient of provincial or federal income security benefits on index date.	Single
Provincial prescription benefit (yes/no)	Provincial Drug Plan shared cost of first statin dispensation after index date.	Single
Prescription copayment cost in CDN dollars not covered by the drug plan (<29$, 29$ to 59$, 60$ to 79$, and ≥80$)	Level of prescription cost not covered by the provincial drug plan on first statin dispensation after index date.	Single
Household income quintile	The mean household income in the dissemination area (DA) of individual's postal code on index date (categorized in quintiles relative to provincial population), based on Statistics Canada 2001 community profile.	Single
Rural residence (yes/no)	Individual's area of residence's postal code on index date was mapped to rural agglomeration area as defined by Statistics Canada.	Single
Deprivation Index (DI)	Individual's postal code on index date mapped to dissemination area (DA): three material and three social SES domains (categorized as quintiles relative to all residents of Saskatchewan), based on 2006 census data.	Multiple
Quintile of material component of deprivation index	Individual's postal code on index date mapped to dissemination area (DA): three material SES domains (categorized as quintiles relative to all residents of Saskatchewan), based on 2006 census data.	Multiple
Quintile of social component of deprivation index	Individual's postal code on index date mapped to dissemination area (DA): three social SES domains (categorized as quintiles relative to all residents of Saskatchewan), based on 2006 census data.	Multiple

Appendix 4-3: Non-SES variables considered for the adjusted "base" model

Variable category	Included variables
Demographic variables	• age at index date • gender • year of discharge
Condition-related variables	• type of index diagnosis (ACS only, ACS plus revascularization, or revascularization only) • duration of index hospitalization • number of days between index date and first dispensation of statin
Therapy-related factors	• filling at least one prescription for specific cardiovascular medication(s) during the first year post-index including (beta-blockers; angiotensin converting enzyme-inhibitor (ACEI) or angiotensin receptor-blockers (ARB); calcium channel blockers (CCBs); diuretics; anticoagulants; antiplatelets; nitrates; or other lipid drugs - yes/no for each) [Appendix4-4], • filling at least one prescription with a quantity of 28 tablets[153] as an evidence of unit-of-use packaging.[154,155] • receiving a high (versus low) statin dose on first prescription post index,[149-152] • the individual statin used on first prescription post index (atorvastatin versus others)[156] • burden of medications defined as the total number of distinct medications' therapeutic groups dispensed to subject
Patient-related factors	• Chronic Disease Score (CDS),[236] • specific comorbid conditions of diabetes,[163] and hypertension[58] reported in any physician or hospitalization visit in the year prior to the index date [Appendix 4-5]
Health system-related factors	• specialty of prescribing physician for the first statin dispensation **(**general practitioner (GP), cardiologist, general internist, cardiac surgeon, other) • number of physicians follow-up visits in the first 3 months following the first statin dispensation • any prior hospitalization in the pre-index year.

Appendix 4-4: Medications assessed in the multi-variate model

Medication category	Medications included
Statin mediation (i.e., HMG-CoA reductase inhibitors)	Atorvastatin, atorvastatin / amlodipine combination, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin
Angiotensin Converting Enzyme-Inhibitors (ACE-Inhibitors)	Benazepril, captopril, cilazapril, cilazapril / HCTZ combination, enalapril, enalapril/HCTZ combination, fosinopril, lisinopril lisinopril/HCTZ combination, perindopril ,perindopril/indapamide combination, quinapril quinapril/HCTZ combination, ramipril, and trandolapril
Angiotensin Receptor-Blockers (ARBs)	Candesartan, candesartan/HCTZ combination, eprosartan, eprosartan / HCTZ combination, irbesartan, irbesartan/HCTZ combination, losartan, losartan/HCTZ combination, olmesartan, Olemsartan/HCTZ combination, telmisartan, telmisartan/HCTZ combination, valsartan, and valsartan/HCTZ combination
Beta Blockers	Acebutolol, atenolol, atenolol / chlorthalidone combination, labetolol, metoprolol, metoprolol / HCTZ combination, nadolol, oxprenolol, pindolol, pindolol/HCTZ combination, propranolol, propranolol / HCTZ combination, timolol, and timolol / HCTZ combination
Calcium Channel Blockers (CCBs)	Amlodipine, felodipine, nicardipine, nifedipine long acting, diltiazem, and verapamil
Diuretics	Amiloride, amiloride/HCTZ, bumetanide, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide (HCTZ), indapamide, metolazone, spironolactone, spironolactone/HCTZ, triamterene, triamterene/HCTZ
Anticoagulants	Acenocoumarol, dalteparin, enoxaparin, heparin, nadroparin, tinzaparin, warfarin
Antiplatelet	ASA, clopidogrel, dipyridamole /ASA, pentoxifylline, sulfinpyrazone, ticlopidine
Nitrates	Erythrityl tetranitrate, isosorbide dinitrate, isosorbide-5-mononitrate, nitroglycerin
Other lipid drugs	Bezafibrate, cholestyramine, clofibrate, colestipol, ezetimibe, fenofibrate, gemfibrozil, niacin, probucol

Appendix 4-5 Comorbid conditions

Comorbid conditions used in multivariable model from Hospital Services and physician services Database		
ICD-9	**ICD-10-CA**	**Description**
250.x	E10 - E14.xxx	Diabetes & diabetes with complications
401 - 404.x	I10 to I15.xxx except when I11 is reported with I50 where's case was considered heart failure	hypertension
*ICD-9 was used until March 31, 2001, when ICD-10-CA reporting started		
ICD-9: Manual of the international statistical classification of diseases, injuries, and causes of death, 9th revision. Geneva: The Organization; 1977. ICD-10-CA: International statistical classification of diseases and related health problems, tenth revision, Canada. Canadian Institute for Health Information; 2003.		

CHAPTER -5- PHARMACIST INTERVENTION IN CARDIAC REHABILITATION: A RANDOMIZED CONTROLLED TRIAL*

5.1 Abstract

Purpose: We aimed to determine the extent to which a telephone-based pharmacist intervention would: a) be utilized by individuals not attending a traditional Cardiac Rehabilitation (CR) program; b) facilitate adherence to cardiovascular medications. *Methods:* We conducted a randomized, controlled open-label trial among patients eligible for CR in Saskatoon, Canada. Patients were invited to participate in a telephone-based CR regardless of participation in the formal program. Subjects in the intervention group were assessed by the CR pharmacist and received education and counseling on medication adherence. The primary endpoint was adherence to cardiovascular medication assessed by electronic filling records over a minimum of six months. Mean adherence was expected to reach 70% during the follow up period. *Results:* Patient recruitment was halted early due to low enrolment. Of the 95 patients randomized, 90% had also registered in the traditional CR program. During the follow-up period, 129 telephone interactions were performed (median 2 calls) with every subject receiving at least one interaction. Over the study period, the mean adherence to all recently initiated cardiovascular medications combined was 88.8% in the intervention group and 89.9% in the usual care group (p=0.73). *Conclusions:* Participation in traditional CR programs does not appear to be influenced by the availability of telephone-based education and support. Further, the high rate of adherence among the control group may suggest that CR programs are attracting 'healthy adherers' who

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volunteer for such programs while missing those with the greatest need for health system resources.

5.2 Introduction

Enrollment in cardiac rehabilitation (CR) programs is known to be poor, ranging from 15-50% of the targeted population.[1] Ironically, patients who do not participate in CR programs have more cardiovascular risk factors such as smoking, sedentary lifestyle, poor diet and higher LDL-Cholesterol, while having less knowledge about how to manage these factors.[2] Several barriers to CR participation have been identified, but convenience (i.e., proximity) appears to be an important factor.[3]

For patients who do participate in CR programs, individual and long-term follow-up to support optimal medication use is not typically provided despite a high prevalence of medication non-adherence in the post-Acute Coronary Syndrome (post-ACS) setting.[4] For example, it has been reported that approximately 60% of patients surviving their first cardiovascular event remained adherent to statins, Beta-blockers or Angiotensin Converting Enzyme-Inhibitors (ACE-Inhibitors)/ Angiotensin Receptor-Blockers (ARBs) one year post-ACS.[5] As non-adherence is an important predictor of mortality in high risk cardiovascular patients, interventions to improve adherence are likely to improve patient outcomes.[6] Consequently, the Canadian Guidelines for Cardiac Rehabilitation emphasize medication adherence strategies as a core component of CR.[7]

Telephone interventions have been shown to be effective in improving medication adherence;[8] at the same time, providing a CR service over the telephone may improve the accessibility/convenience among patients who cannot attend a traditional program. We conducted a prospective, randomized, controlled open-label trial to determine the effectiveness of adding a telephone-based CR intervention aimed at improving adherence to cardiovascular medications. We hypothesized that the intervention would improve medication adherence and

its convenience would result in significant increase in the utilization of CR services by CR invitees not attending the traditional program.

5.3 Methods

5.3.1 Subjects

Between Oct 1st 2009 and June 30th 2010, all patients who received a mailed invitation to participate in the CR program in Saskatoon, Saskatchewan, Canada were invited to participate in our trial, irrespective of whether they chose to participate in the formal CR program. Patients expressing interest were enrolled if they were over 30 years of age and met the following inclusion criteria: 1. experienced an Acute Coronary Syndrome (ACS) hospitalization [ST elevation Myocardial Infarction (STEMI), Non-STEMI, Percutaneous Transluminal Coronary Intervention (PTCA), or Coronary Artery Bypass Graft (CABG) surgery] or revascularization procedure within the previous 3 months; and 2. Were newly initiated on at least one cardiovascular medication (statin, ACE-Inhibitor/ARB or Beta-blocker) defined as no prior use within the previous one year. The rationale for this criterion is that non-adherence has shown to be higher among patients initiating new medications.[9] Each ACS event was confirmed by a documented diagnosis within the hospital chart. Patients were excluded if they had inaccessible laboratory results or prescription data to confirm eligibility.

5.3.2 Randomization

The principal investigator (W.A.) obtained informed consent from subjects and randomized them in permuted blocks of six to receive either a pharmacist-intervention or usual care. Group allocation codes were prepared before trial initiation using a random number table and were kept

in sealed envelopes and opened sequentially by the principal investigator (W.A.) for every new subject. Neither subjects nor the researcher were blinded to the intervention.

5.3.3 Intervention

Initially, the pharmacist telephoned all subjects in the intervention group and followed a specific set of probes to identify barriers to optimal utilization or adherence with post-ACS medications. These probes consisted of four questions the principle investigator (W.A.) asked subjects during the initial interview. The four questions are: 1) is there any medication you are not sure why it was prescribed to you? 2) Do you have any issues or problems with the medications you are taking? 3) Have you heard or read any negative information or "facts" about your drugs? 4) Do you have any question about your doctor's recommendations? Based on this assessment, the pharmacist established the date of the next call within one to two weeks according to the need to support medication adherence including education on side effects or intolerance, cost concerns and drug interactions. The pharmacist contacted family physicians if warranted to address important issues.

5.3.4 Endpoints

The primary endpoint was the mean adherence to newly initiated cardiovascular medications (ACE-Inhibitors/ARBs, Beta-blockers and/or statins) beginning from the date of enrolment in the trial until the end of follow-up. Adherence for post-ACS medications was determined using the Medication Possession Ratio (MPR) for each therapeutic category using electronic dispensation records. Switching between members of the same medication category was allowed. Optimal adherence was defined as an MPR greater than or equal to 80%, which is consistent with other studies.[5]

5.3.5 Sample size calculation

We anticipated that the control group would exhibit a mean adherence level to newly initiated cardiovascular medications of 70% over six months of follow-up.[10,11] Therefore, 72 patients per arm were required to detect a 15% improvement in the mean adherence level within the intervention group at an alpha of 0.05 and beta of 0.80.

5.3.6 Data Analysis

We used $\chi 2$ test to compare the differences between frequency values and Student's t-test to compare mean values for statistical significance. PASW statistics 18 software (IBM Corporation 2010) was used to perform statistical tests.

The trial was approved by the Biomedical Research Ethics Board (Bio-REB #09-152) at the University of Saskatchewan.

5.4 Results

Over the 9 month recruitment period, 235 individuals were invited to participate in the trial following a cardiac hospitalization together with the letter of invitation for the CR program. Additionally, 82 patients were referred to CR by a health care professional and were invited during the CR. Thus, a total of 317 eligible patients were invited to participate in the trial. Among those 317 patients, 152 (48%) attended the traditional CR program, and 165 (52%) did not. Out of the 152 patients who enrolled in the traditional CR program, 67% (103 /152) also agreed to participate in the pharmacist-intervention trial. Conversely, of 165 invitees who did not enroll in the CR program, only 11% (19/165) agreed to participate in the trial despite two mailed invitations and one phone call attempt. Subject recruitment was halted on June 30th, 2010 due to slow enrolment. Altogether, of the 122 patients who agreed to participate, 27 were excluded due to ineligibility. Ultimately, of the 95 patients who were enrolled, 90% (86 / 95)

had also participated in the CR program. One patient died shortly after randomization, and his data was not included in the analysis.

There were no statistically significant differences between the pharmacist-intervention and usual care groups in any baseline characteristic after randomization. Mean age of trial participants overall was 62.8 yrs, 78.7% were male, and the mean household income based on each subjects' residence area was $68723.60 per annum which is close to the mean household income in the city of Saskatoon of $66507.00 reported in 2006 census. However, only 2% of trial participants lived in low income areas, in spite of the fact that 29% of Saskatoon's population reside in these areas with higher cardiovascular morbidity. The mean time from hospital discharge to randomization was 55.1 days and the mean follow-up time was 320 days. Most patients (71.2%) initiated at least three new cardiovascular medications (including Clopidogrel). The utilization of cardiovascular medications was optimal with 100% for statins, 98% for ACE-Inhibitors and 96% for Beta-blockers [Table 1].

Among subjects in the pharmacist-intervention group, 129 telephone interactions were performed (median 2; range 1-8) with every subject receiving at least one interaction. In contrast, four interactions were made with the usual care group in order to address a clinical question that could not be ethically ignored by the pharmacist.

The mean MPR of all newly initiated cardiovascular medications over the trial period was 88.8% [95% Confidence Interval (CI) 84.2%–93.9%] among subjects in the pharmacist-intervention group compared to 89.9% [95%CI 86.0%–94.2%] in the usual care group despite no ongoing support during the trial period (p=0.73). Adherence was also similar between groups when calculated for each cardiovascular medication category, as well as for all cardiovascular medications (previously and newly initiated combined) [Table 2]. Overall, the proportion of

individuals exhibiting optimal adherence (MPR ≥ 80%) to each newly initiated cardiovascular medication was 82.6% and 79.2% in pharmacist-intervention and usual care groups respectively (p=0.44). Subgroup analyses revealed consistent findings among men, women, type of event, and duration of follow up.

5.5 Discussion

We conducted a randomized controlled open-label trial that examined a pharmacist intervention to improve cardiovascular medication adherence among patients being discharged from hospital after an ACS. In contrast to the high rate of participation among patients who had concurrently enrolled in the traditional CR program, interest among non-CR participants was minimal despite the apparent convenience of our telephone-based trial. As a result, over 90% of our subjects had also volunteered for CR. Although power was lower than anticipated due to slow recruitment, none of the outcomes differed between groups. However, the problem of low power seems irrelevant considering the control group exhibited a mean adherence rate of almost 90% when we were expecting a rate of 70% based on published studies.[12]

The high level of adherence observed in our trial might have been due to the beneficial influence of the CR program itself. CR patients receive education and counseling that covers risk reduction and healthy behavior recommendations, which may have influenced the optimal outcomes among our study sample.[13] Alternatively, selection bias may have resulted from the fact that patients participating in clinical trials are perhaps unique from those who do not.[14] Along similar lines, it is highly probable that patients attending CR programs are unique. Specifically, the voluntary nature of CR programs may result in the selection of low-risk subgroups or "healthy adherers" overall.[15] That is to say, the high rates of adherence, risk factor management, and medication use observed in our study may have been a result of healthy behavior that is over-

represented among patients volunteering for CR programs. Low recruitment is a well-recognized problem in CR; and the voluntary nature of these programs likely results in highly selected participants who would be at very low risk for major cardiac outcomes. The results of our study would appear to support this hypothesis.

Our trial had some limitations. First, randomization, intervention, data collection, and analyses were all performed by the principal investigator (W.A) due to budget constraints. Second, our trial was not blinded and therefore patients knew that adherence would be assessed at the end of the trial. As a result, study results may have been influenced by the Hawthorne effect. Third, our trial had a low power due to slow recruitment. However, we believe it is unlikely that the null findings were the result of a type II error. Subjects in the control group exhibited extremely high adherence (90%) and the p-value calculated for the primary endpoint showed no indication of a trend ($p= 0.73$). Regardless, evidence for an improvement in adherence among patients with optimal adherence would be a moot point and would not likely result in improved health outcomes.

Our data suggest that patients who participate in voluntary CR programs may not require long-term individual support for medication use. Furthermore, our results indicate that many CR programs are catering to 'healthy adherer' individuals while missing those at the greatest need of these health system resources. Further studies would be required to confirm these findings.

5.6 References

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Table 5-1: Patient characteristics in the 2 groups

Characteristic	Pharmacist intervention N=46	Usual care N=48	P-value
Age in years: mean (SD)	62.4(10.5)	63.5(11.9)	0.72
Gender: n (%) female	9 (20%)	11 (23%)	0.65
Attended CR: n (%)	42 (91%)	43 (86%)	0.75
SES by neighborhood average family income: mean (SD)	66844.4 (18055.5)	70524.5 (19046.6)	0.39
SES by income groups: n (%)			0.60
<$30000	2 (4.3%)	0	-
$30000-59999	16 (34%)	13 (27.1%)	-
$60000-80000	13 (27.7%)	10 (20.8%)	-
>$80000	12 (25.5%)	12 (25%)	-
Suppressed*	4 (8.5%)	13 (27.1%)	-
Diagnosis: n (%)			0.15
STEMI	3 (6.5%)	0	-
NSTEMI	4 (8.7%)	0	-
Stent	7 (15.2%)	12 (25%)	-
CABG	10 (21.7%)	10 (20.8%)	-
STEMI +Stent	13 (28.2%)	17 (35.4%)	-
NSTEMI +Stent	6 (13%)	4 (8.3%)	-
STEMI+CABG	1 (2.1%)	2 (4.2%)	-
NSTEMI+CABG	2 (4.3%)	3 (6.3%)	-
Time from hospital discharge to randomization in days: mean (SD)	51.8 (30.6)	58.3 (35)	0.35
Observation time in days: mean (SD) and range in days	322.9 (78.8) 185-433	318 (80) 195-451	0.73
Medication use n (%)			0.88
Statin	46 (100%)	48 (100%)	-
ACE-Inhibitor/ARB	46 (100%)	46 (95.8%)	-
Beta-blocker	44 (95.7%)	46 (95.8%)	-
Clopidogrel	34 (73.9%)	36 (75%)	-
ASA	43 (93.5%)	43 (89.6%)	-
Warfarin	4 (8.7%)	9 (18.8%)	-
Clopidogrel+ASA	32 (69.6%)	34 (70.8%)	-
Clopidogrel+ASA+Warfarin	2 (4.3%)	5 (10.4%)	-
Number of new medications of Statin, ACE-Inhibitor/ARB, BB, and Clopidogrel n (%)			0.93
1	5 (10.9%)	5 (10.4%)	-
2	8 (17.4%)	9 (17.8%)	-
3	11 (23.9%)	14 (29.2%)	-
4	22 (47.8%)	20 (41.7%)	-
Specific new medication (n) %			0.90
Statin	35 (76%)	39 (81.5%)	-
ACE-Inhibitor/ARB	33 (71.7%)	32 (66.7%)	-
BB	40 (87%)	41 (85.4)	-
Clopidogrel	34 (73.9%)	33 (68.8%)	-
Number of concurrent medications (number of therapeutic classes) in the observation period (SD)	8 (3.3%)	7.2 (2.7)	0.20
Baseline LDL-C mean (SD)	3.1 (1.11)	3.2 (1.13)	0.27

*Residents of neighborhoods from small communities outside the city of Saskatoon were excluded because they are suppressed in census data

Abbreviations: SES: Socio-Economic Status; STEMI: ST elevation Myocardial Infarction; NSTEMI: Non- ST elevation Myocardial Infarction; CABG: Coronary Artery Bypass Graft; ACE-Inhibitors: Angiotensin Converting Enzyme-Inhibitor, ARB: Angiotensin Receptor Blocker (ARB), ASA: Acetyl-salicylic Acid (or Aspirin), LDL-C: Low-Density Lipoprotein Cholesterol

Table 5-2: Summary of adherence outcomes

Outcome	Pharmacist intervention N=46	Usual care N=48	P-value
Mean MPR[+] for all newly initiated cardiovascular medications (SD)	88.8% (16.4%)	89.9% (14.2%)	0.73
Mean MPR[+] for newly initiated statins (SD)	87.2% (23.4%)	89.8% (16.4%)	0.58
Mean MPR[+] for newly initiated ACE-Inhibitors/ARBs (SD)	87.6% (19.3%)	92.1% (14.6%)	0.30
Mean MPR[+] for newly initiated Beta-Blockers (SD)	89.1% (16.6%)	89.5% (19.9%)	0.92
Mean MPR[+] for newly initiated Clopidogrel (Plavix) (SD)	95.7% (11.1%)	85.8% (30.9%)	0.83
Mean MPR[+] for all cardiovascular medications (previously and newly initiated combined) (SD)	88.2% (16.7%)	90.6% (11.2%)	0.43
The proportion of subjects exhibiting optimal adherence of MPR more than or equal to 80% to newly initiated Statins, ACE-Inhibitors/ARBs, and Beta-Blockers	82.6% (38/46)	79.2% (38/48)	0.44
Mean persistence* to newly initiated statins (SD)	381.2 days (115.9)	403.0 days (126.0)	0.39
Mean persistence* to newly initiated ACE-Inhibitors/ARBs (SD)	349.3 days (104.7)	374.4 days (105.5)	0.34
Mean persistence* to newly initiated Beta-blockers (SD)	355.7 days (107.2)	381.0days (116.2)	0.31

+MPR was calculated by dividing the sum of all daily medication supplies of the same therapeutic category during the follow-up period by the total days in this interval *Persistence is defined as the time between the first and last fills of medication during the follow-up period.

Abbreviations: MPR: Medication Possession Ratio, ACE-Inhibitors: Angiotensin Converting Enzyme-Inhibitors, ARBs: Angiotensin Receptor Blockers, SD: standard deviation.

CHAPTER -6- SUMMARY

6.1 Summary of research

Four separate, but related, research questions related to cardiovascular medication adherence were addressed in this program of research. The first study (chapter 2) demonstrated that estimated mortality benefits associated with statin adherence are substantially influenced by the measurement approach and no one approach can be regarded as gold standard. Findings of the second study (chapter 3) challenged conventional wisdom by refuting a strong relationship between low SES and poor adherence to anti-hypertensive medications using a systematic review and meta-analysis of the literature. Correspondingly, the third study (chapter 4) showed that using multi-domain measurements of SES from ecological measures does not improve the performance of a predictive model for adherence. The fourth study (chapter 5) indicated that the availability of a pharmacist intervention, consisting of mainly telephone-based education and support, does not affect medication adherence among individuals participating in traditional CR programs.

Numerous studies have reported benefits of optimal adherence on mortality rates and other important clinical outcomes.[1-5] However, methods to estimate the association between medication adherence and major health outcomes have been highly variable. Chapter 2 reports the impact of modifying the approach to measuring adherence to statin medications for estimating the association between adherence and mortality. Among 9,051 individuals who received a statin medication in Saskatchewan, the estimated benefits of high (versus low) adherence were substantially impacted by the measurement strategy used. When statin adherence was examined as a repeated measure, a strong association with mortality was observed suggesting robust benefits of optimal adherence. In contrast, optimal adherence defined by a

single summary measure indicated no relationship with mortality at all. Although it has been suggested that the repeated measures approach for classifying optimal adherence is less vulnerable to survival bias,[6,7] the study reported in Chapter 2 provides strong evidence against this claim. In fact, the repeated measures approach consistently produced more favourable risk estimates for optimal adherence to statins as well as other medications with no known effects on clinical outcomes.[1] This is the first study to challenge the notion that optimal statin adherence (versus low statin adherence) is an independent predictor of death among community dwelling populations. Future research is needed to determine the extent to which each measurement approach is vulnerable to bias. Uncovering the true relationship between statin adherence and major health outcomes is critical to better understand the public health burden of medication non-adherence in today's health care system.

One of the most widely recognized predictors of mortality and/or major health outcomes in Canadian health care is socioeconomic status (SES). Strong theoretical evidence suggests SES is an important cause of poor medication adherence because of its association with an individual's economic, social, and education-related factors. However, the quantitative relationship between SES and medication adherence had not been clearly described.[8] Chapter 3 describes a systematic review of adherence to antihypertensive medications using population-based electronic prescription data. Several important discoveries were generated from this study. First, the comprehensive review of the literature clearly demonstrated that SES has not been carefully measured in medication adherence prediction models. Almost half of studies reviewed lacked any variable relating to SES and the remaining studies relied heavily on income/economic assessments as a surrogate marker of SES. As a result, the validity of the observed association between SES and medication adherence is still in question. To evaluate the validity of these

assessments, a comparison study was warranted. Indeed, meta-analysis of all eligible studies in Chapter 3 revealed a weak association between SES and adherence.

Based on the results in Chapter 3, another study was conducted in Chapter 4 to evaluate if a comprehensive measure of SES might be a more robust predictor of poor medication adherence compared to conventional methods identified in the systematic review. However, despite the theoretical advantages, use of a multiple-domain SES measure did not substantially improve the predictive accuracy of a population-based model. In fact, the addition of any SES measure had a very mild impact on predicting adherence overall. Although SES does appear to be a significant predictor of SES, its influence on the overall burden of poor adherence at the population level is very small.

Finally, Chapter 5 reports on the findings of a randomized trial focused on improving medication adherence among patients surviving an ischemic heart event.[9] Historically, few patients receive interdisciplinary support after hospital discharge through support programs such as cardiac rehabilitation (CR).[10] It was hypothesized that a streamlined intervention carried out by a pharmacist might improve uptake in cardiac rehabilitation-type services and also improve medication adherence through a low-cost efficient intervention. Using a randomized, controlled design, no difference in the percentage of individuals achieving optimal adherence was observed among patients receiving the pharmacist intervention. However, both study groups (intervention and control) exhibited extremely high adherence levels throughout the study period. Clearly, the research subjects recruited for the study were not at-risk for poor adherence. This finding highlights the importance of volunteer bias, not just in research studies, but in health care programs such as cardiac rehabilitation. It is possible that these programs provide service to low-risk or healthy adherer type individuals who may not be at risk for poor outcomes. In a

health care system such as Canada, where resources are stretched, health care services must be aligned to support individuals at the highest risk for poor outcomes. Programs to support medication adherence will be more effective if a deeper understanding of at-risk populations can be achieved through robust research programs.

During the course of this research program, medication adherence was examined from different perspectives. The four independent research studies reported in this dissertation helped clarify the nature of this widespread problem. In brief, it can be concluded that low SES is not responsible for a disproportionate level of poor adherence despite the strong theoretical linkages. In addition, in contrast to previously published studies, the association between poor adherence to statin medications and premature death cannot be verified due to a previously unrecognized effect of measurement approach on the results of such studies. Finally, traditional health services interventions must have better access to risk indicators for poor adherence. Although the problem is widespread, certain populations exhibit high levels of adherence without the need for additional support.

Despite years of research, our understanding about medication adherence continues to evolve. This dissertation has contributed important information to the area of medication adherence by generating quantitative evidence that challenges traditional theoretical paradigms and conventional wisdom. It is essential that research continues in this area to increase the availability of quantitative data to accompany the wealth of theoretical frameworks and behavioural theories. Eventually, high quality research will uncover the true nature of this important public health problem.

6.2 References

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