Pharmacoepidemiologic Studies of Statins in Rheumatoid Arthritis

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES
(Health Care and Epidemiology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

September 2010

ABSTRACT

Introduction: This thesis comprises four studies aimed at improving current understanding of statin use in rheumatoid arthritis (RA), a patient population with established CVD risk. There is need for a better understanding of the cardioprotective role of statins in RA through dual lipid-lowering and anti-inflammatory effects. Since deriving therapeutic effect from medication depends not only on physicians prescribing treatment but also on patients' compliance with therapy, there is also need for better understanding of the impact of statin compliance on relevant outcomes in RA.

Objectives: 1) To evaluate whether statin use has a cardioprotective effect among individuals with RA; 2) To synthesize current evidence on adverse outcomes associated with discontinuation of statin therapy; 3) To evaluate the impact of statin discontinuation on risk of acute myocardial infarction (AMI) among RA patients prescribed with statins; and 4) To evaluate the impact of statin discontinuation on risk of mortality among RA patients prescribed with statins.

Methods: To address Objectives 1, 3, and 4, I conducted three longitudinal studies of a population-based RA cohort in BC. To address Objective 2, I conducted a systematic review.

Results: 1) Statin use is associated with a 31% lower risk of AMI in RA patients; 2) There is a consistent finding of increased risk of adverse outcomes associated with statin discontinuation in different patient populations; highlighting the importance of compliance in patients who are prescribed statins for primary or secondary prevention; 3) Discontinuation of statin therapy is associated with a 67% increased risk of AMI among patients with RA; 4) Discontinuation of statin therapy is associated with 60% and 79% increased risk of cardiovascular disease mortality and all-cause mortality, respectively, in patients with RA.

Conclusion: Altogether as a collective work, this thesis provides supporting evidence for a substantial role of statins in management of CVD, a key comorbidity in RA, and additionally highlights the importance of patient compliance with statin therapy in achieving therapeutic goals of treatment.

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GLOSSARY

RA	Rheumatoid arthritis
CVD	Cardiovascular disease
AMI	Acute myocardial infarction
HMG-CoA	Hydromethyl glutaryl coenzyme A
LDL	Low density lipoprotein
CHD	Coronary heart disease
WOSCOPS	West of Scotland Coronary Prevention Study
4S	Scandinavian Simvastatin Survival Study
RCT	Randomized controlled trial
US	United States
UK	United Kingdom
THIN	The Health Improvement Network
FPP	Farnesyl pyrophospate
GGPP	Geranylgeranyl pyrophosphate
GTP	Guanosine-5'-triphosphate
CRP	C-reactive protein
NOS	Nitric oxide synthase
MMP	Matrix metalloproteinases
SLE	Systemic lupus erythematosus
GPRD	General Research Practice Database

OR	Odds ratio
DAS	Disease Activity Score
ACR	American College of Rheumatology
TARA	Trial of Atorvastatin in Rheumatoid Arthritis
EULAR	European League Against Rheumatism
ACE	Angiotensin converting enzyme
TRACE RA	Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Rheumatoid Arthritis
ESR	Erythroycyte sedimentation rate
ISPOR	International Society of Pharmaecoeconomics and Outcomes Research
DMARD	Disease modifying anti-rheumatic drug
NSAID	Non-steroidal anti-inflammatory drug
MCO	Managed care organization
MSP	Medical Services Plan
ICD	International Classification of Disease
BC	British Columbia
CDIC	Canadian drug identity code
BMI	Body mass index
CVA	Cerebrovascular accident

ACKNOWLEDGEMENTS

My sincerest gratitude to my supervisory committee – Drs. Hyon Choi, Diane Lacaille, Michal Abrahamowicz, and Jacek Kopec – your guidance, support, and expertise has enriched my training. To manuscript co-authors, Drs. Vidula Bhole and Maria Victoria Goycochea-Robles and Lindsay Wall-Burns, thank you for your knowledge, skills, and support. To Angie Kennedy, Dr. Vidula Bhole and Lindsay Wall-Burns for timely and critical reviews, thank you for sharing a piece of this thesis with me.

I thank the Canadian Institutes of Health Research, the Canadian Arthritis Network and the Arthritis Society, and the Michael Smith Foundation for Health for funding support for my PhD training.

The Arthritis Research Centre of Canada (ARC) has seen me through both academic and life successes and challenges, and I thank everyone in this great organization for helping me grow, not just as a scientist, but also as a person. To Dr. John Esdaile for your leadership and support, Shauneen Kellner, Brenda Kapusta, and Lisa Singh for making everything at ARC work so all I have to do is my work, Dr. Antonio Avina for life, career, methodological, and medical advice, and Dr. Eric Sayre and Mushfiqur Rahman for statistical and SAS expertise. I would also like to acknowledge ARC's Consumer Advisory Board, especially Pam Montie, Gordon Whitehead, and Otto Kamansek. Peers have enriched my graduate study experiences: Jennifer Faddegon, Helen McTagggart-Cowan, Mohsen Sadatsafavi, Helen Hsu, Margot Kuo, Chuck Ratzlaff, and Harpreet Chhina.

To my lifelong personal cheerleading squad, AJ, Angeline, Alfred, and Lorenzo De Vera, there is nothing we cannot do because we always have each other. Finally, to my Francis Szabo – if support, encouragement, love, and faith in me were not enough, you have also shown me the beauty of science.

DEDICATION

This thesis represents hard work, dedication, and passion for helping others. All these things I learned from Marilou and Alberto De Vera. Thank you, Mom and Dad.

CO-AUTHORSHIP STATEMENT

Sections of this thesis are multi-authored manuscripts intended for publication in peer-reviewed journals. Details of authors' contributions for Chapters 1 to 6 are as follows.

Chapter 1: Author Contribution: Mary A. De Vera was responsible for design, literature search, collation and summary of papers, retrieval of articles, review of studies, and writing of Chapter 1.

Chapter 2: Author Contributions: Mary A. De Vera was responsible for study concept and design, data management and statistical analyses, interpretation of results, preparation of manuscript, and revisions. Dr. Hyon Choi was responsible for study concept and design, statistical analyses, interpretation of results, and preparation of manuscript and critical review of manuscript. Drs. Diane Lacaille, Michal Abrahamowicz and Jacek Kopec were responsible for interpretation of results, preparation of manuscript and critical review of manuscript.

Chapter 3: Author Contributions: Mary A. De Vera was responsible for study concept and design, conducting literature search, extraction of data, analysis and interpretation of results, preparation of manuscript and revisions. Dr. Diane Lacaille was responsible for study concept, interpretation of results, preparation of manuscript, and critical review of manuscript. Lindsay Wall-Burns and Dr. Vidula Bhole were responsible for conducting literature search, extraction of data, analysis and interpretation of results, preparation of manuscript and critical review of manuscript. Dr. Hyon Choi was responsible for study concept, interpretation of results, and critical review of manuscript.

Chapter 4: Author Contributions: Mary A. De Vera was responsible for study concept and design, data management and statistical analyses, interpretation of results, preparation of manuscript, and revisions. Dr. Diane Lacaille was responsible for study concept and design, statistical analyses, interpretation of results,

and preparation of manuscript and critical review of manuscript. Drs. Hyon Choi, Michal Abrahamowicz and Jacek Kopec were responsible for interpretation of results, preparation of manuscript and critical review of manuscript.

Chapter 5: Author Contributions: Mary A. De Vera was responsible for study concept and design, data management and statistical analyses, interpretation of results, preparation of manuscript, and revisions. Dr. Diane Lacaille was responsible for study concept and design, statistical analyses, interpretation of results, and preparation of manuscript and critical review of manuscript. Drs. Hyon Choi, Michal Abrahamowicz and Jacek Kopec were responsible for interpretation of results, preparation of manuscript and critical review of manuscript.

Chapter 6: Author Contributions: Mary A. De Vera was responsible for design, literature search, collation and summary of papers, retrieval of articles, review of studies, and writing of Chapter 6.

CHAPTER 1
INTRODUCTION AND BACKGROUND

1.1 Thesis Overview

1.1.1 Research Statement

The goal of this thesis is to gain a better understanding of statin use in rheumatoid arthritis (RA). In recent years, there has been considerable interest in the role of statins in rheumatologic therapy, given their primary lipid-lowering primary properties and demonstrated anti-inflammatory properties (1-8). An important target for statins is RA, a debilitating chronic inflammatory arthritis where the cardiovascular disease (CVD) risk among patients - underlined by the linking role of inflammation between atherosclerosis and RA (9, 10) - constitutes significant morbidity (11-13) and mediates early mortality (9). However, a limited number of studies call for a better understanding of the potential roles of statins in RA, particularly a cardioprotective role that may arise from dual effects on lipids and inflammation. Subsequently, deriving therapeutic effect from medication depends not only on physicians prescribing treatment but also on patients following the prescribed treatment regimen reasonably closely, or in other words, being compliant with therapy. Thus, an understanding of statin use in RA also calls for an understanding of the impact of statin compliance on adverse CVD and mortality outcomes among patients.

1.1.2 Overview of Thesis Themes and Chapters

This thesis unifies separate research themes and questions on statin use in RA, carved from Canadian Institutes of Health Research programs. Theme 1 is "Statins as Cardioprotective Agents in RA" and addresses a question that is of current interest in the arthritis community: Do statins have a cardioprotective role among RA patients? Theme 2, "Outcomes of Statin Compliance in RA" explores the impact of poor

compliance, namely discontinuation of therapy, specifically in RA patients prescribed with statins. Thus, Theme 2 addresses the question: Among RA patients who are prescribed with statins, what is the impact of statin discontinuation on CVD and mortality outcomes? Figure 1.1 provides an overview of the thesis.

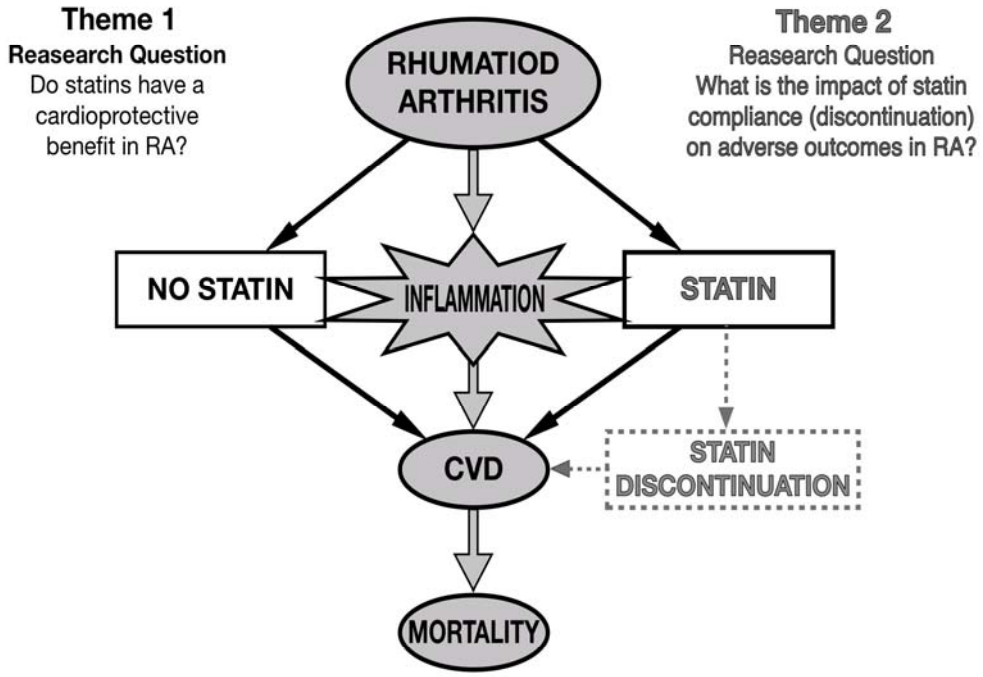


Figure 1.1 Thesis Overview

Addressing research questions under the thesis guiding themes has resulted in a body of work that comprises both original pharmacoepidemiologic studies and a systematic review. Following this introductory chapter, which covers key background material and rationale, are six content chapters of the thesis. Chapter 2 is a population-based pharmacoepidemiologic study evaluating the cardioprotective role

of statins in patients with RA by comparing AMI outcomes between statin-users and non-users. Prior to conducting pharmacoepidemiologic studies evaluating adverse outcomes associated with statin discontinuation in RA patients, a better understanding of current evidence was needed. Chapter 3's systematic review synthesized current literature on statin discontinuation and associated adverse outcomes, and informed subsequent studies in Chapters 4 and 5. Chapter 4 is a population-based cohort study examining the impact of statin discontinuation on risk of acute myocardial infarction (AMI) in patients with RA. An extension of this investigation, Chapter 5 is a population-based cohort study evaluating the association between statin discontinuation and mortality in patients with RA. Chapter 6, the concluding chapter, synthesizes findings from each thesis study and discusses strengths, limitations and potential implications of the collective work.

1.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA), the health problem of interest of this thesis, is a chronic systemic autoimmune disease and one of the most common inflammatory arthritides. Aside from pain, functional disability, patients with RA experience substantial burden of CVD morbidity and mortality. This section reviews the epidemiology of RA and the impacts and potential underlying mechanisms of the significant CVD comorbidity suffered by patients.

1.2.1 Epidemiology of Rheumatoid Arthritis

Prevalence estimates for RA have ranged from 0.5% to 1% in North American and European populations (14). Reported incidence rates range from 0.1 per 1,000 to 0.5 per 1,000 (15) with data in the past decade suggesting that RA incidence appears to be rising after four decades of decline (14). RA is 2 to 3 times

more common in women compared to men (16) and while disease can occur at any age, the highest disease occurrences are seen in the fourth and fifth decades of life (16).

Characterized by progressive and destructive joint inflammation, RA leads to significant morbidity due to pain, and functional disability, as well as early mortality. The mortality risk associated with RA has been evaluated across different populations and settings. Studies have consistently shown that RA is associated with increased mortality, with death rates in RA 1.5 to 3.0 fold higher than in the general population (17). The role of cardiovascular diseases (CVD) as the main cause of excess of mortality in RA has been consistently suggested in previous studies (18, 19). Other causes of premature mortality in RA include infections, cancer, and gastrointestinal, respiratory and hematologic problems (17). Reported predictors of mortality in RA include demographic factors of older age, male sex, and low socioeconomic status and RA specific disease factors including disease activity, disease duration, decreased function, presence of rheumatoid nodules or other extra-articular manifestations and the presence of rheumatoid factor (20).

1.2.2 Cardiovascular Disease Morbidity and Mortality in Rheumatoid Arthritis

Cardiovascular disease (CVD) is a significant co-morbidity as well as the leading cause of excess mortality in RA. In the last decade, epidemiologic studies have demonstrated increased risk of CVD in individuals with RA compared to the general population. Specifically, data from the Nurses' Health Study indicated a two-fold higher risk of AMI among women with RA compared to women without RA, after adjusting for cardiovascular risk factors (adjusted relative risk [RR] 2.00; 95% CI: 1.23-3.29) (12). A similar increased risk for AMI among RA patients was reported based on data on male and female subjects in the Rochester Epidemiology Project (adjusted hazard ratio [HR], 2.13; 95% CI: 1.13-4.03) (13). Previous studies also reported on pooled CVD outcomes. For example, data from the Outcome of Rheumatoid Arthritis

Longitudinal Evaluation cohort showed a three-fold higher risk of pooled CVD outcomes which included AMI, stroke, other arterial occlusive events, arterial revascularization, and CV-death among RA patients as compared to individuals in the general population (adjusted RR, 3.17; 95% CI: 1.33-6.36) (11).

In addition to cardiovascular endpoints, patients with RA were also found to have significantly increased intima-media wall thickness of the carotid artery (21, 22), a well-established intermediate end point of atherosclerosis (23). Moreover, even young RA patients with low disease activity have been demonstrated to have significant endothelial dysfunction (24, 25).

Aside from causing significant morbidity, CVD is also the leading cause of premature mortality in RA (9), with a third to half of excess deaths among RA patients due to increased CVD (26). A recent meta-analysis published by colleagues showed a 50% increase in risk of death from CVD in RA compared to population controls (meta-standardized mortality ratio [SMR] 1.50, 95% CI, 1.39-1.69) (18).

Potential causes for the increased CVD in RA include cytokine-mediated inflammatory pathways causing accentuation of both classic (lipids) and novel (endothelial function or insulin resistance) pathways (27-29), adverse effects of medication, decreased mobility, increased homocysteine level (30), and increased thrombotic factors (fibrinogen, von Willebrand factor, plasminogen activator antigen, and fibrin D-dimer) (31). Furthermore, many similarities have emerged between the inflammation paradigm in the pathogenesis of atherosclerosis and the inflammation mechanism in the pathogenesis of RA (10, 32). These similarities raise the possibility that inflammatory mechanisms responsible for synovial lesions in patients with RA may directly participate in producing atherosclerotic lesions resulting in excess CVD in RA patients (33).

The role of inflammation in mediating CVD risk in RA is subject to recent emphasis in the literature (34). Population data from the Rochester Epidemiology Project of long-term outcomes in RA indicate that traditional cardiovascular risk factors including body mass index (BMI), smoking, hypertension, and diabetes, have weaker associations with heart disease in RA subjects (35, 36). Furthermore, there are observations of "paradoxical" or unexpected effects of these risk factors in RA patients, such as improved survival with declining BMI (37, 38), and notably precipitous decline in total and LDL-cholesterol before RA incidence (36) and lower total and LDL-cholesterol levels in RA patients along with inverse association with inflammation markers (39-41). These findings may suggest the existence of a competing mechanism, that is related to chronic systemic inflammation, which imparts additional CVD risk in RA but not in RA patients, (36). Along with demonstrated association of inflammatory markers and markers of rheumatoid disease with CVD outcomes among RA patients (34, 42), findings altogether suggest the substantial contribution of systemic inflammation and immune dysregulation to CVD risk in RA (36).

1.3 Statins

Statins are a class of lipid-lowering agents and arguably the largest selling drugs in the world. Beyond their well-established cardiovascular efficacy primarily from their lipid lowering effect, they have been demonstrated to have additional effects on inflammation. In this section, a closer look at these drugs includes a brief chronicle of their history and development, and examination of their lipid-lowering and anti-inflammatory properties.

1.3.1 History and Development of Statins

The discovery of statins dates back to the early 1970s with the initial speculation that blood cholesterol levels could be reduced with inhibition of HMG-CoA reductase in the liver (43). In 1971, Dr. Akira Endo and

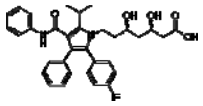
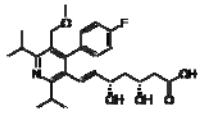
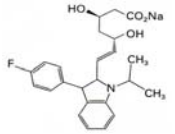
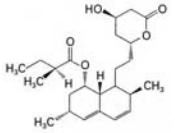
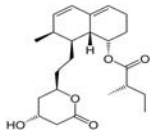
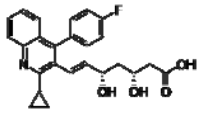
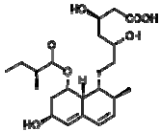
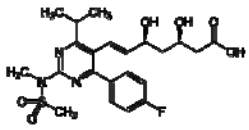
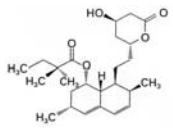
colleagues in Tokyo first isolated mevastatin, the prototype of the statins from *Penicillium citrinum* (43). Early animal studies of mevastatin involving rodents proved it ineffective; however, investigators later showed more promising results in dogs and monkeys. Subsequent clinical studies of mevastatin conducted in the late 1970s and early 1980s among Japanese patients were short-lived, mostly attributed to findings of tumorigenic toxicity, which was also found in earlier canine studies. In the mid 1980s, clinical studies of mevastatin were stopped and development was never resumed (43).

In 1976, a few years after the discovery of mevastatin, scientists at Merck & Co. began their own pursuit of isolating a similar molecule and in 1979, isolated the second natural statin, lovastatin (43). In animal studies, lovastatin was slightly more effective than mevastatin in inhibiting HMG-CoA reductase and lowering plasma cholesterol. In 1980, the first clinical study of lovastatin was conducted in the USA but was later suspended due to concern about the negative effects of mevastatin in Japanese canine studies (43). By 1982, clinical studies of lovastatin had resumed and collective data on over 1200 patients with severe hypercholesterolemia consistently demonstrated effectiveness and safety of the drug (44, 45). In 1987, lovastatin was approved by the US Food and Drug Administration and marketed in the USA by Merck & Co.

The next period in the history of statins was marked by the development of semi-synthetic statins, which were chemically modified variants of their parent natural statins. The rationale for synthesizing these molecules was that alterations of the chemical composition of the natural statins would result in drugs that are more potent. In 1986, scientists at Merck & Co. derived simvastatin from lovastatin and showed that the derivative was approximately two times more potent than the parent molecule in inhibition of HMG-CoA reductase. Also in the same year, Japanese scientists synthesized the semi-synthetic statin, pravastatin, from mevastatin (43).

The development of synthetic statins, which began in the 1990s and continues today, marks the most recent activities in the history of statin development. Fluvastatin, an early synthetic statin, was developed by the generic drug company Sandoz and later marketed in 1993. Other synthetic statins currently in the market are atorvastatin (Pfizer), rosuvastatin (AstraZeneca), and simvastatin (Merck & Co; patent expiry 2006). Cerivastatin, a synthetic statin marketed by Bayer, was withdrawn in 2001 due to 52 fatal cases of rhabdomyolysis leading to kidney failure that were linked to use of the drug (46). Pitavastatin is a synthetic statin that is currently marketed in Asian countries and not available in North America. Table 1.1 provides an overview of characteristics of statins including generic and brand names and molecular structures.

Table 1.1 Summary of Statins

Generic Name	Brand Names	Type of Statin	Molecular Structure
Atorvastatin	Lipitor	Synthetic	
Cerivastatin*	Lipobay Baycol	Synthetic	
Fluvastatin	Lescol	Synthetic	
Lovastatin	Mevacor Altocor Altoprev	Natural	
Mevastatin**		Natural	
Pitavastatin	Livalo Pitava	Synthetic	
Pravastatin	Pravachol Selektine Lipostat	Semi-synthetic	
Rosuvastatin	Crestor	Synthetic	
Simvastatin	Zocor Lipex	Semi-synthetic	

***Statin prototype, never marketed; *Withdrawn in 2001*

1.3.2 Lipid Lowering Properties of Statins

Some basic background on lipids, particularly cholesterol and its role as a risk factor for coronary heart disease (CHD), is important for understanding the mechanism of action of statins. The term lipid applies to any naturally occurring substance that is fat-soluble and water-insoluble; and includes fats, oils, waxes, and cholesterol. Functions of lipids within the body include storing energy, acting as building blocks for cellular components, and acting as signalling molecules in biochemical reactions.

Cholesterol is a lipid and as an essential component of cell membranes has important functions in intracellular transport and cell signalling. It is transported in aqueous plasma by lipoproteins, most prominently, low-density lipoprotein (LDL), body which accounts for 60-70% of blood cholesterol. Elevated blood cholesterol is well-established prominent risk factor for CHD (43).

The liver is the organ targeted by statins. It is in the liver cells where statins inhibit HMG-CoA reductase in the rate-limiting step of cholesterol synthesis (Figure 1.1) through competitive binding to the enzyme's active site (43). The result of this inhibition is reduction in cholesterol biosynthesis and decrease in cholesterol concentration within hepatic cells. Compensatory mechanisms involving increased synthesis of LDL receptors, in turn results in reduction in LDL levels in the bloodstream as LDL are drawn out of circulation into the liver where the cholesterol is reprocessed into bile salts.

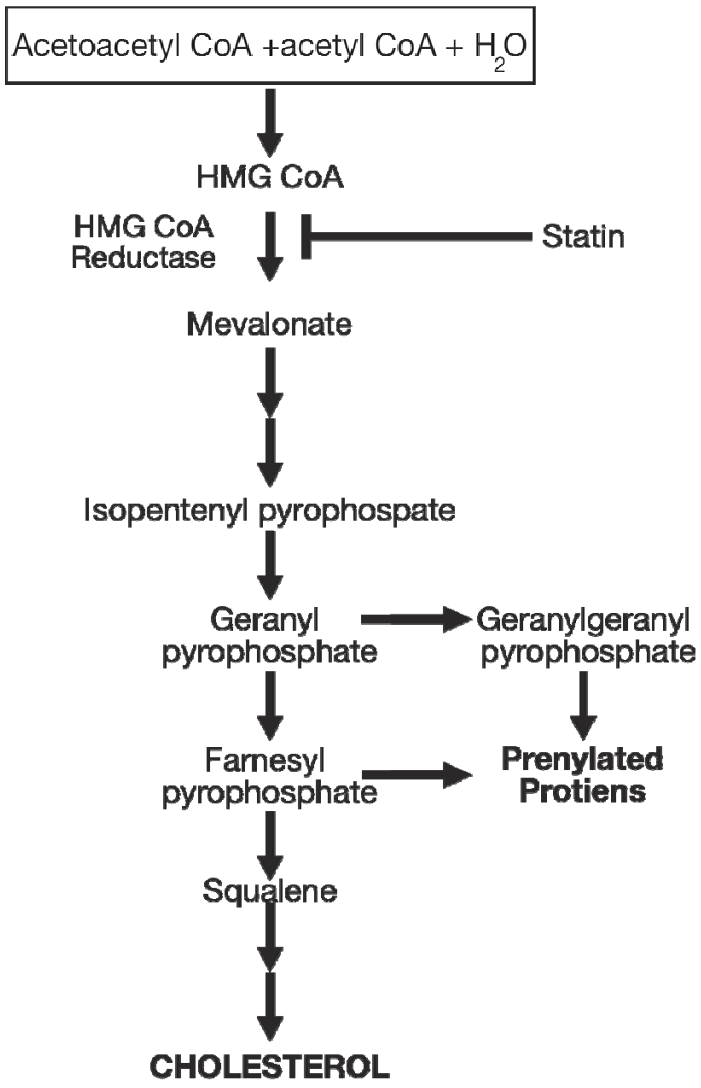


Figure 1.1 Statin Mechanism of Action by the HMG-CoA Reductase Pathway

The efficacy of statins in primary and secondary prevention of vascular events has become well established. Landmark randomized controlled trials (RCT) include the West of Scotland Coronary Prevention Study (WOSCOPS) (N=6,595) which provided evidence for a primary preventive role by showing reduction of cardiovascular events in middle-aged male patients with moderate hyperlipidemia but no history of CVD (relative reduction in risk, 31%; 95% CI, 17-44%) (47). The Scandinavian Simvastatin

Survival Study (4S) (N=4,444) patients with angina pectoris or previous AMI) demonstrated a secondary prevention role by showing that compared to the placebo-treated group, simvastatin-treated subjects had fewer CHD deaths (relative risk [RR], 0.58; 95% CI, 0.46-0.73), CVD deaths (RR, 0.65; 95% CI, 0.52-0.80), and deaths from all causes (RR, 0.70; 95% CI, 0.58-0.85) (48). The largest RCT to date, Heart Protection Study (N= 20,536) showed significant reduction in all cause mortality (RR, 0.87; 95% CI, 0.81-0.94) among subjects on simvastatin compared to those on placebo (49).

Pharmacoepidemiologic studies based on data from a US managed care organization (50) and the UK Health Improvement Network (THIN) database (51) have also demonstrated cardioprotective benefits of statins, in real world, general population settings. Specifically, using automated data from the Fallon Community Health Plan in Massachusetts, US, Seeger et al. demonstrated that after applying propensity score methods to control for confounding by indication (for statin use), individuals who initiated statin therapy had a 31% lower risk of AMI compared to non-initiators (hazard ratio [HR], 0.69; 95% CI, 0.52-0.93) (50). Smeeth et al. utilized propensity score methods on THIN data and also reported reduction of AMI (HR, 0.87; 95% CI, 0.77-0.98) in statin users as compared to non-users (51).

Generally, statins as a class are well tolerated and have a favourable safety profile (52). In both the WOSCOPS and 4S clinical trials, there were no differences between treated and placebo groups with respect to discontinuation due to adverse events (43). The most commonly reported non-serious adverse events during statin treatment include gastrointestinal symptoms, headache, and rash (52). Rare and serious adverse events that have been reported include hepatoxicity (1-2%) (52). For example, in the WOSCOPS trial, 32 subjects in the placebo arm had liver enzymes greater than three times the upper limit of normal (>3x ULN) compared to 42 subjects in the pravastatin arm. Perhaps the most recognized serious

adverse events reported with statin use are muscle adverse effects which include myalgia and myopathy (<1% incidence) (52).

1.3.3 Anti-Inflammatory and Immunomodulatory Properties of Statins

Beyond their primary lipid-lowering properties, molecular, animal, and clinical data indicate that statins have broader cholesterol-independent effects. In particular, statins have a wide range of effects on cells and tissues involved in inflammation and/or autoimmunity processes (1, 53). Anti-inflammatory and immunomodulatory properties of statins are thought to arise because inhibition of mevalonate synthesis also has limiting effects on synthesis of other important lipid intermediates, particularly isoprenoids (Figure 1.1). Isoprenoids act as molecular switches that affect a number of cellular pathways. They include the 15-carbon molecule isoprenoid farnesyl pyrophosphate (FPP) and the 20-carbon isoprenoid geranylgeranyl pyrophosphate (GGPP) which are small lipid functional groups that attach to guanosine-5'-triphosphate (GTP) binding proteins (54). This lipid attachment, referred to as isoprenylation (hence proteins are isoprenylated), allows anchoring of these proteins in the cell membrane (54). Statin-induced decreases in the isoprenylation of these proteins leads to modulation of signalling pathways that involve a number of inflammatory mechanisms such as: 1) endothelial nitric oxide synthase; 2) tissue plasminogen activator; 3) endothelin 1; 4) plasminogen activator inhibitor 1; and 5) C-reactive protein (CRP).

Numerous molecular studies have demonstrated anti-inflammatory and/or immunomodulatory effects of statins. To highlight, these include: 1) inhibition of interactions between leukocytes and endothelial cells that precede leukocyte egress from the vasculature; 2) effects on reactive oxygen and nitrogen intermediate production (i.e. up-regulation of endothelial cell nitric oxide synthase [eNOS] expression, inhibition of inducible NOS, induction and formation of oxygen radicals by endothelial cells); 3) suppression

of inflammatory cytokine release including interleukin-6 (IL-6) and IL-1β; 4) inhibition of matrix metalloproteinases (MMPs) in human macrophage and vascular smooth muscle cells; 5) inhibition of NF-κB activation in monocytes and endothelial cells; 6) activation of anti-inflammatory transcription factors (i.e. peroxisome proliferator-activated receptors); and 7) inhibition of T-cell activation and co-stimulatory molecules (1, 53).

Correspondingly, animal studies spanning simple models of inflammation to complex models of non-rheumatic inflammatory diseases and rheumatic diseases have also shown statin anti-inflammatory effects. Table 1.2 provides a summary of these models, the specific statin studied, and main findings. Simple models of inflammation include the classic carrageenan-induced footpad edema model (55) and air-pouch model (56), both in mice. In the former model, simvastatin was shown to reduce to extent of the edema and in the latter model, lovastatin, pravastatin, and simvastatin significantly reduced leukocyte recruitment into air pouches. Studies involving more complex models of non-rheumatic autoimmune and inflammatory diseases included allergic asthma (57), experimental colitis (animal model of irritable bowel syndrome) (58), myocarditis (59), uveitis (60), experimental autoimmune encephalomyelitis (an animal model of multiple sclerosis) (61, 62), and sepsis (63) (Table 1.2). Finally, statin anti-inflammatory effects have also been shown in complex animal models of rheumatic diseases including antiphospholipid syndrome (64), lupus (65), and collagen-induced arthritis (CIA), an animal model of RA (66). Notably, in the later model, immuno-suppressive effects of simvastatin were demonstrated in the treatment of CIA as well as prevention of new cases by up to 50% (66).

Furthermore, human studies of statins in inflammatory and autoimmune diseases, including both non-rheumatic and rheumatic diseases have also demonstrated statins' anti-inflammatory properties (Table

1.2)[1]. Studies of statins in kidney transplant patients similar showed reduction in kidney transplant graft rejection rate (67, 68). Findings in other non-rheumatic diseases include 44% reduction in the number of MRI-enhancing lesions in multiple sclerosis patients (69), 30% risk reduction in diabetes mellitus (70), 47% reduced risk of colon cancer (71), and a 71% reduced risk of dementia (including Alzheimer's disease) (72).

[1] Human studies of statins in RA will be discussed in ensuing section (1.4 THEME 1: STATINS AS CARDIOPROTECTIVE AGENTS IN RHEUMATOID ARTHRITIS)

Table 1.2 Animal and Human Studies Demonstrating Anti-Inflammatory / Immunomodulatory Effects of Statins

Study	Statin	Results
Animal Studies		
Simple Models		
Carrageenan-induced footpad edema (mouse)	Simvastatin	↓ extent of edema (54)
Air-pouch model of inflammation (mouse)	Simvastatin, Lovastatin, Pravastatin	↓ leukocyte recruitment (55)
Complex Models: Non-Rheumatic Inflammatory Disease		
Experimental allergic asthma (mouse)	Simvastatin	↓ interferon-γ and interleukin-6; improved pathology (56)
Experimental colitis (irritable bowel syndrome) (mouse)	Pravastatin	↓ colon inflammation (57)
Experimental autoimmune myocarditis (rat)	Fluvastatin	↓ pathophysiological severity (58)
Experimental autoimmune uveitis (mouse)	Lovastatin, Atorvastatin	↓ retinal pathology (59)
Experimental autoimmune encephalomyelitis (MS) (mouse)	Atorvastatin	↓ inflammatory infiltration in central nervous system (60)
Experimental autoimmune encephalomyelitis (MS) (mouse)	Atorvastatin	Prevented or reversed chronic and relapsing paralysis (61)
Experimental sepsis (mouse)	Simvastatin	↓ mortality (62)
Complex Models: Rheumatic Disease		
Antiphospholipid syndrome (mouse)	Fluvastatin	↓ thrombus formation (63)
Experimental lupus model (mouse)	Atorvastatin	↓ disease activity (64)
Collagen-induced arthritis (RA) (mouse)	Simvastatin	↓ incidence of arthritis and histologic score (65)
Human Studies		
Non-Rheumatic Diseases		
Kidney transplantation (non-blinded, randomized study; N=48)	Pravastatin	↓ rates of both acute and multiple rejection episodes (66)
Kidney transplantation (non-blinded, randomized study; N=57)	Simvastatin; Pravastatin	↓ rejection rate (67)
Multiple sclerosis (open-label study; N=30)	Simvastatin	↓ number of MRI enhancing lesions by 44% (68)
Diabetes (randomized trial, post-hoc analysis; N=5,974)	Pravastatin	↓ risk of diabetes by 30% (69)
Colon Cancer (case-control study; N=1,953 cases; 2,015 controls)	All statins	↓ risk of colon cancer by 47% (70)
Dementia (nested case-control study; N=284 cases; 1,080 controls)	All statins	↓ risk of dementia by 71% (71)
Rheumatic Diseases*		
Lupus Nephritis (open-label case-series; N=3)	Simvastatin	↓ proteinuria levels (72)
Systemic lupus erythematosus (RCT; N=72)	Rosuvastatin	↓ high-sensitivity CRP (73)

1.4 Theme 1: Statins as Cardioprotective Agents in Rheumatoid Arthritis

Theme 1 of the thesis represents the first step taken towards addressing the overarching goal of gaining a better understanding of statin use in RA, by evaluating the cardioprotective role of statins in RA using a hard CVD outcome. The significant CVD morbidity in RA combined with the demonstrated benefits of statins spanning both lipid-lowering and anti-inflammatory effects, as highlighted in aforementioned sections, has conceivably sparked the recent "great deal of excitement" about the potential roles of statins in RA. This section introduces the potential roles of statins in RA and provides a synthesis of current evidence for these roles. While it may perhaps be the most tenable role, the cardioprotective role, postulated to arise from dual effects of statins on lipids and inflammation, is also the least studied with lack of studies evaluating hard CVD outcomes. Whether such studies are needed or whether extrapolation of results from studies in RA evaluating intermediate CVD markers or studies non-RA populations evaluating CVD outcomes is sufficient evidence-base has been subject to debate. In examining current evidence, this supports the rationale for the ensuing thesis pharmacoepidemiologic study comparing AMI outcomes in statin users and non-users in a cohort of patients with RA.

1.4.1 Overview of Potential Roles of Statins in Rheumatoid Arthritis

In the last 5 years, numerous review articles on statin therapy in rheumatic diseases have been published including 6 reviews discussing potential statin roles in inflammatory arthritides such as RA and SLE (1, 2, 6, 7, 75, 76), 8 reviews specific to RA (4, 5, 77-82), and 1 review specific to SLE (83). An abundance of editorials and/or commentaries further echo this interest on potential roles of statins in rheumatic diseases (3, 8, 84-87). Based on their properties described in previous sections, potential statin roles in RA are two-

fold: 1) a role in prevention of RA as suggested by studies demonstrating protective effect of statins against the risk of new cases of non-rheumatic inflammatory/autoimmune diseases including multiple sclerosis (69), diabetes mellitus (70), colon cancer (71), and dementia (72); and 2) a role in management of RA which may encompass both an anti-inflammatory/antirheumatic role given their demonstrated anti-inflammatory/immunomodulatory effects and a cardioprotective role driven by their lipid lowering effects and anti-inflammatory effects.

Yet along with great interest, is recognition that these potential roles of statins in RA have been evaluated in limited studies. Indeed, at the conceptualization stages of this thesis (2006), potential statin effects in RA were reported in several studies - comprising two abstracts (88, 89), two letters (24, 90), and three manuscripts (25, 73, 91) – with most focusing on statin anti-inflammatory/antirheumatic effects and one study evaluating a cardioprotective effect using an intermediate CVD marker outcome (25). An update of this literature synthesis in 2010 shows recent additional studies of statin anti-inflammatory/antirheumatic effects (92-97) and preventive effects (98-100). Table 1.3 provides a summary of studies of statins in RA according to the two potential roles discussed.

Table 1.3 Human Studies Evaluation Potential Roles of Statins in Rheumatoid Arthritis

Author	Year	Type*	Study	Statin	Results
			STATINS IN PREVENTION OF RA		
Jick	2008	M	Nested case-control (N=313 RA, 1,252 controls)	All statins	↓odds ratio for RA (99)
Holmqvist	2009	A	Case-control (N=1,973 RA, 2,230 controls)	All statins	No association with RA or activity at RA onset (100)
Amittal	2009	A	Retrospective cohort (N=211,627 statin users)	All statins	↓hazard ratio for RA (101)
Hippisley-Cox	2010	M	Prospective cohort (N=225,922 statin users)	All statins	No association with RA (102)
			STATINS IN MANAGEMENT OF RA		
			ANTIRHEUMATIC ROLE in RA		
Kanda	2002	L	Open-label case-series (N=8)	Simvastatin	↓tender joints; ↓ESR; ↓CRP (89)
Abud-Mendoza	2003	M	Open-label case-series (N=5)	Atorvastatin	Clinical improvement on ACR20 clinical response (72)
Abud-Mendoza	2003	M	Short-time open clinical trial (N=15)	Simvastatin	ACR50 or better response; ↓CRP (72)
Hochman	2004	A	Cross-sectional (N=6,265; 968 statin users)	All statins	↑ function on Health Assessment Questionnaire (88)
McCarey	2004	M	Double-blind, randomised placebo-controlled (N=116)	Atorvastatin	↓ RA disease activity; ↓ESR; ↓CRP (91)
Okamoto	2007	M	Cross-sectional (N=7,512; 4,152 statin users)	All statins	↓ swollen joint counts, ↓CRP (93)
Maki-Petaja	2007	M	Double-blind randomised crossover with etezimibe (N=20)	Simvastatin	↓ disease activity; ↓CRP (94)
Charles-Shoeman	2007	M	Double-blind, randomised placebo-controlled (N=20)	Atorvastatin	↓ high-sensitivity CRP (96)
Kanda	2007	M	Open-label case-series (N=24)	Simvastatin	↓CRP; clinical improvement (87, 97)
Shirinsky	2009	M	Open-label case-series (N=33)	Simvastatin	Clinical improvement on EULAR response (98)
			CARDIOPROTECTIVE ROLE in RA		
VanDoornum	2004	M	Open-label case-series (N=29)	Atorvastatin	↓ arterial stiffness (92)
Hermann	2005	L	Double-blind, randomised placebo-controlled (N=20)	Simvastatin	↑ endothelial function (90)
Tikiz	2007	M	Randomised, placebo-controlled (N=45)	Simvastatin	↑ endothelial function; ↓CRP (95)

**Type of publication: M-published manuscript; A-abstract in conference proceedings; L-letter to editor reporting study results*

1.4.2 Potential Role of Statins in Prevention of Rheumatoid Arthritis

Few recent studies have evaluated the potential protective effect of statins in RA (Table 1.3). Rationale for this potential effect has been built on demonstrated anti-inflammatory/immunomodulatory effects overall and particularly in animal models of RA as well as human studies. Specifically, when Leung et al examined the effects of simvastatin in CIA, they not only demonstrated immuno-suppressive effects in the treatment of this animal model of RA, but also showed prevention of new cases by up to 50% (66). Studies of statin use in other diseases with an inflammatory component in their pathogenesis may also suggest that statins could also potentially reduce the risk of developing RA.

A recent case-control study (N=313 RA cases; N=1,252 controls) using the UK General Research Practice Database (GPRD) explored this potential link and observed an inverse association between statin use and RA (98). Specifically, when the authors compared individuals with hyperlipidemia who received statins to individuals with hyperlipidemia who did not use statins, the adjusted odds ratio (OR) for RA was 0.59 (95% C: 0.37-0.96) (98). At the most recent meeting of the American College of Rheumatology in 2009, two abstracts were presented that further explored this potential role. However, results were conflicting. Using data from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study, Holmqvist et al. conducted a case-control study 1,973 RA patients and 2,230 controls and evaluated the associations between i) statin use and risk of RA and ii) statin use and RA disease activity at diagnosis (99). They reported that statin use was neither associated with risk of RA (adjusted OR 1.0; 95% CI 0.7-1.5) nor with disease activity at diagnosis (99). Also presenting on a similar topic were Amittal et al. who used population-based data in Israel to conduct a retrospective cohort study on the association between statin use and RA development (100). However in contrast to Jick's and Holmqvist's studies, Amittal et al. evaluated all statin users and looked at statin compliance as their exposure of interest. Authors reported

that statin users in the highest quintile of compliance had a 40% significant decrease in the incidence of RA (confidence limits not reported in the abstract) (100). Whether statins have a protective effect remains inconclusive as a recent report published online by the British Medical Journal based on the QResearch general practice research database in England and Wales did not demonstrate a protective effect of statin use on incidence of RA (101).

1.4.3 Potential Roles of Statins in Management of Rheumatoid Arthritis

1.4.3.1 Statins as Anti-Inflammatory/Anti-Rheumatic Agents in Rheumatoid Arthritis

Synthesis of current literature shows a greater number of studies evaluating potential anti-inflammatory/anti-rheumatic roles of statins in RA (Table 1.3). The earliest clinical studies evaluating anti-inflammatory/antirheumatic roles of statins have been based on open-label designs, very small sample sizes, but with consistently promising results. For example, Kanda et al.'s 2002 report on 8 RA patients receiving simvastatin and followed for 12 weeks, showed improved patient outcomes (compared to baseline measures before start of therapy) as measured by number of tender joints and patient self-assessment of disease activity on visual analog scale (90). Subsequently, in a short-term clinical trial of 15 patients, Abud-Mendoza et al. reported that compared to RA patients receiving methotrexate and choloroquine, those receiving methotrexate and simvastatin showed ACR50 or better response after 8 weeks (73).

The most promising study is the Trial of Atorvastatin in Rheumatoid Arthritis (TARA), a double-blinded, randomized placebo-controlled trial of investigating the efficacy of atorvastatin among 116 patients with RA (91). Patients were followed over 6 months and co-primary outcomes were change in DAS28 and proportion meeting European League Against Rheumatism (EULAR) response criteria. Authors reported

that RA disease activity improved significantly on atorvastatin compared with placebo (difference in DAS28 change, 0.5; p=0.004). Response was achieved in 31% of patients on atorvastatin compared with 10% on placebo (p=0.006) (91).

1.4.3.2 Statins as Cardioprotective Agents in Rheumatoid Arthritis

Based on their well-established CVD efficacy, statins are expected to have at least a similar degree of efficacy on CVD outcomes among RA patients. Effects may be further ameliorated through statin effects on systemic inflammation in RA. Yet, despite the considerable interest in the potential for statins to target CVD risk in RA via effects on lipids and inflammation, no study has evaluated a cardioprotective effect directly using a hard CVD outcome (Table 1.3). To date, supporting evidence for beneficial effects of statins on CVD in RA have been drawn from: 1) studies evaluating intermediate correlates of CVD in RA (24, 25, 94), 2) secondary findings from studies evaluating RA disease outcomes such as the TARA trial (91); or 3) studies evaluating statin effects in other patient populations including previous and more recent RCTs such as the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (102).

Recent trials of statins in RA patients evaluating intermediate correlates of CVD have provided indirect evidence for a cardioprotective benefit of statins in individuals with RA. In a case series of 29 RA patients, Van Doornum et al. evaluated the effects of atorvastatin on their primary outcome of arterial stiffness, a marker of vascular dysfunction and independent risk factor for CVD (25). Authors reported a 12% reduction in arterial stiffness among patients after 12 weeks of treatment (25). Two RCTs subsequently evaluated the effect of statins on endothelial dysfunction, a key event in early atherogenesis that has been demonstrated in RA patients with both high and low disease activity. Specifically, Hermann et al. reported

that endothelial function, as measured by flow-mediated dilation, significantly improved after 4 weeks of treatment with simvastatin compared with placebo (5.5 $\pm$ 0.7% vs. 3.8 $\pm$ 0.4%; p-value = 0.02) (24). In the second RCT, Tikiz et al. compared the effects of angiotensin-converting enzyme (ACE) inhibitors, simvastatin and placebo on endothelial function in three randomized groups of RA patients and reported that patients who received statins showed significant improvement in endothelial-dependent vasodilation while no change was seen in patients who received ACE inhibitors or placebo (94).

Evaluation of serum markers of inflammation, such as CRP, as secondary outcomes in studies evaluating anti-inflammatory/anti-rheumatic effects of statins may also provide support for a cardioprotective role of statins in RA. This may be particularly relevant as elevated CRP levels correlate with accelerated atherosclerosis in RA patients (103-105). In the TARA trial, authors also reported a 50% decline in C-reactive protein (CRP) levels in the statin arm compared to placebo ($p<0.0001$) (91). Other clinical studies showing reduction in CRP levels with statin use include an open-label case series in 24 patients (96), a cross-sectional study of 7,512 RA patients with 4,152 statin users (92), and a double blind randomized crossover study of 20 patients (95).

Based on the CVD efficacy of statins established in previous RCTs, statins are expected to have at least a similar degree of efficacy on CVD outcomes among RA patients. However, generalizability of these results should be cautioned given that vascular risk in patients in these prior RCTs may be driven more by lipid effects. Findings from the JUPITER study of individuals with low LDL levels but elevated CRP levels (102) may be more appropriately extrapolated to RA patients as discussed in an editorial by study authors on whether “patients with RA should receive statin therapy” (86).

Whether results from studies evaluating intermediate markers of CVD or those evaluating effects of CVD risk factors and statins in non-RA populations can be directly extrapolated to RA patients remains unclear. Population data from the Rochester Epidemiology Project of long-term outcomes in RA indicate that traditional cardiovascular risk factors including body mass index (BMI), smoking, hypertension, and diabetes, have weaker associations with heart disease in RA subjects (35, 36). Furthermore, there are observations of "paradoxical" or unexpected effects of these risk factors in RA patients, such as improved survival with declining BMI (37, 38), and notably precipitous decline in total and LDL-cholesterol before RA onset (36) and lower total and LDL-cholesterol levels in RA patients along with inverse association with inflammation markers (39-41). Altogether these data suggest that a substantial contribution of systemic inflammation and immune dysregulation to CVD risk in RA may be more targeted by statins via anti-inflammatory effects instead of lipid effects (36). Altogether, these lingering questions could only be sufficiently addressed with evaluation of statin effects on hard CVD outcomes, specifically in RA (106).

Currently, management guidelines for CVD in RA recommend therapy with statins in the context of demonstrated CVD risk factors, and with consideration of excess RA-associated risk (107). Despite promising results of studies of statins in RA, there is still much debate on the potential cardioprotective role of stains in RA and whether patients with RA should receive statins for primary prevention of CVD, regardless of clinical indication for statin initiation (86, 106). Indeed, studies evaluating a hard CVD outcome would be valuable in this regard. Currently, a multicentre trial, the Trial Atorvastatin for the Primary Prevention of Cardiovascular Events in Rheumatoid Arthritis (TRACE RA), is in progress in the UK. With an aim to recruit 4,000 RA patients and randomize them to atorvastatin or placebo, results are not anticipated until 2015. In the meantime, the interest, along with the debates and the need for an understanding of this role, continue to grow.

It is in this setting, that Theme 1 of the thesis was conceived. With an aim to address an important and clinically relevant question in contemporary rheumatology, the objective is to evaluate the potential cardioprotective role of statins in RA using a population-based cohort and methods of pharmacoepidemiology.

1.5 Theme 2: Outcomes of Statin Compliance in Rheumatoid Arthritis

The thesis shifts from an examination of the cardioprotective effect of statins in RA patients when users are compared to non-users, to a closer look at those patients prescribed with statins to evaluate the impact of compliance to statin therapy on adverse CVD and mortality outcomes. In recent years, less than optimal efficacy of statins in real-world settings has been attributed to poor patient compliance with therapy. Simply prescribing statins is insufficient; it is important that patients closely follow prescribed treatment regimens to derive expected drug benefits. In exploring this issue specifically in RA patients, Theme 2 represents a practical approach to gaining a better understanding of statin use in RA. This section introduces terms and concepts encountered in medication compliance research, synthesize current evidence on the problem of statin discontinuation generally and specifically in RA, and identify gaps in knowledge addressed in this thesis.

1.5.1 Introduction to Research on Medication Compliance

Studying medication compliance or what patients actually do with their prescribed drugs and subsequent impacts has become an area of research known as *pharmionics* (108). While the concept of compliance to drug therapy may be superficially simple, it is quite complex in its underlying details. There are two potential distinct problems of medication taking: 1) poor execution of the dosing regimen, such that scheduled doses

are delayed or omitted, which may lead to transient interruptions in drug action; and 2) patient-initiated discontinuation of the medication, which may lead to long term or permanent loss of drug effects (108).

Historically, literature on medication compliance has been hampered by a lack of clarity on which problem of medication taking is described, and inconsistent and interchanged use of the terms "*compliance*", "*adherence*", and "*persistence*." To briefly highlight some of the historical uses of these terms, Haynes and Sackett defined the term *compliance* as "the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (109). While they suggested interchangeable use with the term *adherence*, a New England Journal of Medicine review gave preference for the latter based on the rationale that it acknowledges that the patient has active involvement in his/her care and does not simply participate through passive following of physician recommendations (110). Another term that has also been used is *persistence* (111). The historical inconsistency and interchanged use of these terms has been problematic as it fails to take into account, the actual problem of medication taking studied.

Given that there are two potentially distinct problems with medication taking, clarity on which problem is studied is important, whether the study goal is to describe and quantify the problem or evaluate impacts of the problem. For the purposes of this thesis, terms and definitions for problems of medication taking are first clarified as follows. *Compliance* is the overarching term describing medication taking and encompasses both execution of dosing and discontinuation of therapy. Terms to capture specific problems of medication taking were adopted from proposed definitions by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group (112, 113). Specifically, *adherence* refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking, essentially

speaking to the first problem of medication taking. *Persistence* refers to "the act of conforming to a recommendation of continuing treatment for the prescribed length of time" (113). However, since it implies that period of use is of interest rather than the problem of stopping therapy, the term *discontinuation* is additionally proposed. Table 1.4 summarizes terms.

Table 1.4 Terms and Concepts of Medication Compliance

Term	Thesis Definition	Problem of Medication Taking Described
Compliance	General problem with medication taking	-poor execution of dosing regimen -discontinuation of therapy
Adherence	The act of conforming to recommendations made by the provider with respect to timing, dosage, and frequency of medication taking[2]	-poor execution of dosing regimen
Persistence	The act of conforming to a recommendation of continuing treatment for the prescribed length of time[3]	discontinuation of therapy
Discontinuation*	The act discontinuing therapy[3]	discontinuation of therapy

There are many methods for measuring medication compliance, encompassing both direct and indirect methods (110). Direct methods which are expensive and cumbersome include: 1) directly observing drug intake of patients or subjects; 2) measuring levels of the drug or its metabolite in blood or urine; and or 3) measuring biologic markers added to the drug formulation (110). Given the expense and the burden associated with direct methods, they are more suited to clinical studies. Indirect methods are less expensive than direct methods and depending on the measure, require varying degrees of subject burden. Examples of indirect methods that involve subject burden and are more suited to clinical trials include: 1) patient self-reported questionnaires or diaries; 2) pill counts; or 3) electronic medication monitors (110). Finally, an indirect method that does not involve subject burden and most relevant to this thesis is the use

[2] Definition from ISPOR Medication Compliance and Persistence Special Interest Group
[3] Definition proposed for purposes of thesis

of “automated databases” to measure medication-taking based on refill rates or patterns for a target drug (108). This method has been recognized as the most relevant in pharmacoepidemiologic and health services research since refill records contain specific information on timing (dispensing date), supply (quantity in days), dose for target drugs allowing for measurement of medication-taking based on timing and patterns of drug exposure (114). As a further advantage, the potential for anonymous linkage of pharmacy records with medical records including outpatient health care and hospital visits provides the capacity, as demonstrated in this thesis, to conduct studies evaluating outcomes of problems of medication compliance.

1.5.2 The Problem of Statin Discontinuation

While both problems of medication taking are relevant to statin use, of particular interest in this thesis is statin discontinuation, since therapy represents lifelong treatment (115) and with long-term therapies come potential for patients to discontinue, particularly when therapeutic effects of drugs are not readily observed, as with statins (116). It has been reported that up to 30-40% of patients on long-term therapies do not fill repeat prescriptions (116). Looking specifically at statins, it has been shown that the majority of patients for whom statins are prescribed in routine clinical practice stop taking the drug altogether (117). Thus, given high susceptibility for statin discontinuation and recognition that patterns of prescription filling represent the most accurate way of estimating actual medication use in large populations (111), emphasis on the specific problem of statin discontinuation was placed for this thesis.

Over the last decade, numerous studies have quantified the extent of statin discontinuation in real world settings. Using a variety of data sources including population-based administrative health data, data from managed care organizations, and pharmacy network records, studies have evaluated the construct as a

positive outcome of persistence with statin therapy (111, 118-120) or as a negative outcome of discontinuation of statin therapy (115, 121-127) (Table 2.5). While this highlights the historical inconsistency with description and measurement of medication compliance, altogether data suggest that statin discontinuation is frequent in real-world settings. Statin discontinuation rates range from 15% (123) to ≥75% (125), with most reports ≥50%. These high discontinuation rates are supported by persistence studies that have shown diminishing persistence with longer follow-up (118, 119). The extent of statin discontinuation in real-world settings is further magnified when compared to reported discontinuation rates in clinical trials, which have been reported to range from 2.5% to 16.5% (111). However, given the controlled nature of clinical trials along with study members encouraging and monitoring compliance, this finding is expected.

An understanding of the problem of statin discontinuation involves not only quantifying the extent of the problem but also evaluating the impact of statin discontinuation on relevant outcomes, particularly CVD and mortality, given that discontinuation of therapy implies foregone drug effects. However, there has been far less emphasis on the latter issue in the literature. Among the relevant questions include: 1) how is statin discontinuation exposure measured; 2) in what patient populations has the impact of statin discontinuation been evaluated; 3) what outcomes are evaluated; and 4) what are reported results of these studies?

Table 1.5 Studies Evaluating Statin Discontinuation

Author	Year	Patient Population	Sample Size	Setting	Follow-up	Definition of Statin Discontinuation / Persistence	Reported Rate
Statin Discontinuation Studies							
Simons	1996	General population	610	Pharmacy-network	1 yr	(D) Failure to collect scheduled dispensing	60% (121)
Andrade	2004	Hyperlipidemia	2,369	MCO	2 yr	(D) >6 mo elapsed from the last refill	15% (115)
Ellis	2004	General population	4,802	MCO	3 yr	(D) Cessation of refills prior to end of followup	50% (122)
Deambrosis	2007	General population	21,393	Pharmacy network	9 yr	(D) At least 1 statin prescription in given year	50% (124)
Chodick	2008	General population	229,917	MCO	9.5 yr	(D) Therapy gap with 30 day grace period	≥75% (125)
Foody	2008	General population	175,322	MCO	1 yr	(D) Therapy gap with 60 day grace period	50% (126)
Vinker	2008	General population	47,680	MCO	1 yr	(D) <80% of expected pills	61.1% (127)
Statin Persistence Studies							
Avorn	1998	General population	7,287	MCO	1 yr	(P) >80% expected pills during study period	64.3% (111)
Catalan	2000	General population	983	MCO	7 yr	(P) Therapy gap with 7 day grace period	33% (1 year); 13% (5 year) (118)
Perreault	2005	General population	25,733	Population-based	3 yr	(P) Therapy gap with 60 day grace period	67% (1 year); 39% (3 year) (119)
Lachaine	2006	General population	14,076	Population-based	2 yr	(P) % of patients on statin in current month	83% (120)

Abbreviations: MCO – Managed care organization

1.5.3 Understanding Statin Discontinuation in Rheumatoid Arthritis

Although compliance with medications has not been well studied in RA and other chronic rheumatic conditions (128), existing data in the literature suggest that non-compliance with medication may be a substantial problem, particularly in RA. An earlier review estimated that at least 50% of patients with RA are non-compliant with RA therapy irrespective of the intervention (129). Previous studies involving therapies for RA reported compliance rates ranging anywhere from 30% with NSAIDs, prednisone, and DMARDs (130) based on self-reports to 64% with methotrexate based on pharmacy records (131). One of the demonstrated risk factors for statin discontinuation therapy is pill burden or multiple prescription medications taken by a patient. Given the profile of medications for management of RA, it is plausible that patients are more likely to discontinue statins to alleviate pill burden (132), especially given that effects of statins are not obvious or observable when compared to those drugs taken for pain or symptom management. Using a population-based cohort of patients with RA, colleagues recently reported a 38% statin discontinuation rate over mean 8-year follow-up (133). While this finding suggests that perhaps the magnitude of statin discontinuation is less of a problem among RA patients, extension of the investigation to evaluate outcomes associated with statin discontinuation is needed.

Out of these two identified knowledge gaps – i) the need for synthesis of current knowledge on the outcomes associated with statin discontinuation and ii) the need for better understanding of the impact of statin discontinuation in RA patients – came the rationale for Theme 2 of the thesis. A logical ensuing step to better understanding statin use in RA is investigating the impact of statin discontinuation on relevant outcomes among patients prescribed with statins, in light of the problems identified with statin use in other patient populations. However, review of the literature first called for synthesis of current knowledge on outcomes associated with statin discontinuation to better inform these investigations. Thus, two-fold

objectives under this theme were: 1) to gain a better understanding of the impact of statin discontinuation on adverse outcomes through systematic review of the literature; and 2) to evaluate the outcomes of statin discontinuation among prescribed patients with RA.

1.6 Overview of Thesis Studies

In this concluding section, specific objectives addressed in each of the ensuing thesis chapters are highlighted. These chapters represent three pharmacoepidemiologic studies and one systematic review that separately and collectively contribute to addressing the overall thesis goal of gaining a better understanding of statin use in RA. Following the objectives, pertinent background to pharmacoepidemiology and systematic reviews are briefly highlighted.

1.6.1 Specific Objectives for Thesis Studies

1. To evaluate whether statin initiation has a cardioprotective effect among patients with RA.

Chapter 2 is a population-based, longitudinal study comparing AMI outcomes between statin users and non-users in a cohort of patients with RA.

2. To extend current understanding on the problem of statin discontinuation by synthesizing evidence on associations with adverse outcomes; To inform subsequent thesis studies on relevant methodologic and analytic issues on evaluating impacts of statin discontinuation.

Chapter 3 is a systematic review of pharmacoepidemiologic studies evaluating statin discontinuation on relevant adverse outcomes.

3. To evaluate the impact of statin discontinuation on risk of AMI among RA patients prescribed with statins.

Chapter 4 is a population-based, longitudinal study evaluating the association between statin discontinuation and AMI in a cohort of RA patients with incident statin use.

4. To evaluate the impact of statin discontinuation on risk of mortality among RA patients prescribed with statins.

Chapter 5 is a population-based, longitudinal study evaluating the association between statin discontinuation and all-cause mortality and CVD mortality in a cohort of RA patients with incident statin use.

1.6.2 Pharmacoepidemiologic Studies of Statins in Rheumatoid Arthritis

The three analytic chapters (Chapters 2, 4, and 5) of this thesis are pharmacoepidemiologic studies that address respective themes on cardioprotective role of statins in RA and outcomes of statin compliance in RA. Regarded by some as a relatively new science, pharmacoepidemiology is the study of the use of and effects of drugs in large populations and bridges the two disciplines of pharmacology and epidemiology (108). Methods and concepts of pharmacoepidemiology encompass a wide spectrum of studies including *hypothesis-testing studies of drug expected benefits* (108) as applicable to Theme 1 of the thesis and

assessment of patterns of drug use (pharmionics) and associated outcomes (108) as applicable to Theme 2.

1.6.2.1 Data Sources for Thesis Pharmacoepidemiologic Studies

In the past two decades, so-called "automated databases", that is, computerized databases containing medical care data have grown to be a hallmark of pharmacoepidemiologic studies in North America. These data are largely administrative in origin and generated from claims for health services (physician visits, drug prescriptions) by the population covered. Examples in the US include federal programs like Medicaid and managed care organizations like the Kaiser Permanente Medical Care Program. In Europe, medical record databases, such as the UK GPRD, developed for use by researchers are important data sources for pharmacoepidemiologic research. In Canada, provinces administer a universal and publicly funded health system. Provincial administrative health data that have become resources for pharmacoepidemiologic research as a result of this universal health care system include established databases of Saskatchewan (Health Services Databases in Saskatchewan) (108) and Quebec (Régie de l'assurance maladie du Québec [RAMQ]). Emerging resources include databases of Ontario (Ontario Health Insurance Plan, Ontario Drug Benefit), Nova Scotia, and British Columbia (Population Data BC, formerly known as the BC Linked Health Database).

The primary data sources for pharmacoepidemiologic studies in this thesis are administrative health data files from British Columbia (BC) where a provincially administered, and largely publicly funded health insurance covers acute and extended care hospitalizations, in-home care, prescription drugs for individuals 65 years and older, diagnostic tests, and fees to physicians (134). Specific data files include the Medical Services Plan (MSP), which covers information on all provincially funded health services and includes data

on date of service, practitioner, and diagnosis most closely associated with the record, using International Classification of Disease Version 9 (ICD-9). The Hospital Separations file on inpatient hospitalizations includes information on admission date, up to 10 diagnoses fields representing the reason for admission or complications during hospitalization, procedure/intervention codes (following Canadian classification of diagnostic, therapeutic, and surgical procedures), and separation date. Prescription data were drawn from BC PharmaNet, a prescription monitoring and repayment information. By law, every prescription dispensed in BC is recorded in PharmaNet, regardless of recipient or payer (135). PharmaNet claims extracts include date prescription was dispensed, drug identification number (Canadian drug identity code [CDIC]), drug name, dose, and days supplied in the prescription. Finally, information on death including date of death and underlying cause of death (ICD-10 codes) was obtained from vital statistics in the Canadian Mortality Database (136).

Specific data were drawn from a previously established population-based RA cohort in British Columbia (BC), henceforth referred to as the BC RA Cohort (137). Administrative billing data for the reimbursement of physician visits from the BC Ministry of Health were used to identify adult (≥18 years) individuals with RA who received care for their RA between January 1996 and March 2006. The case definition for RA was the same as previously published for this cohort (137); specifically, individuals met inclusion criteria if they had at least 2 physician visits more than 2 months apart with an RA diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9], 714.x). Individuals were excluded if they had at least 2 visits subsequent to the second RA visit with diagnoses of other inflammatory arthritides (systemic lupus erythematosus, other connective tissue diseases, psoriatic arthritis, ankylosing spondylitis, and otherspondylarthritides), if an RA diagnosis by a non-rheumatologist was not confirmed on a subsequent rheumatologist visit, or if they had no subsequent RA-coded physician visits over a follow-up period of 5 years or more. Complete follow-up for the cohort was available up to March 2006. Overall, this RA cohort

included 37,151 individuals and represents one of the largest cohorts of RA patients for research purposes. A prevalence rate of 0.96% was calculated for this cohort based on the number of alive prevalent cases in 2006 (n=29,417) and 2006 census data from Statistics Canada (138). This is consistent with previously reported prevalence estimates for RA (14).

1.6.3 Systematic Review of Impact of Statin Discontinuation

Chapter 3's systematic review of pharmaecoepidemioloic studies evaluating the impact of statin discontinuation on adverse outcomes falls under Theme 2 by informing analytic studies on outcomes of statin compliance in RA. Review of pharmionics literature identified the need to synthesize evidence from current literature examining the impact of statin discontinuation in order to address specific methodologic and analytic issues in thesis studies. Addressing this need called for rigorous identification of published studies, standardized appraisal and selection processes, and synthesis of all research evidence, all methods provided by a systematic review (139).

1.7 References

1. Abeles A, Pillinger M. Statins as antiinflammatory and immunomodulatory agents: A future in rheumatologic therapy? Arthritis & Rheumatism. 2006;54(2):393-407.
2. Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmunity Reviews. 2006;5(5):331.
3. Arnaud C, Mach F. Potential antiinflammatory and immunomodulatory effects of statins in rheumatologic therapy. Arthritis & Rheumatism. 2006;54(2):390-2.
4. Snow MH, Mikuls TR. Rheumatoid arthritis and cardiovascular disease: the role of systemic inflammation and evolving strategies of prevention. Current Opinion in Rheumatology. 2005;17(3):234.
5. Sattar N, McInnes IB. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. Current Opinion in Rheumatology. 2005;17(3):286.
6. McCarey DW, Sattar N, McInnes IB. Do the pleiotropic effects of statins in the vasculature predict a role in inflammatory diseases? Arthritis Research & Therapy. 2005;7(2):55.
7. Soubrier M, Roux C. Statins in rheumatology. Joint Bone Spine. 2006;73(2):159.
8. Klareskog L, Hamsten A. Statins in rheumatoid arthritis--two birds with one stone? Lancet. 2004;363(9426):2011.
9. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis & Rheumatism. 2002;46(4):862-73.
10. Pasceri V, Yeh E. A tale of two diseases: Atherosclerosis and Rheumatoid Arthritis. Circulation. 1999;100:2124-6.

11. del Rincon I, Williams K, Stern M, Freeman G, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis & Rheumatism. 2001;44(12):2737-45.

12. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107(9):1303-7.

13. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis & Rheumatism. 2005;52(2):402-11.

14. Gabriel S, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009;11 Epub 2009 May 19(3):229.

15. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Seminars in Arthritis & Rheumatism. 2006;36(3):182-8.

16. Klippel J, Stone JH, Crofford L, White P, editors. Primer on the Rheumatic Diseases 13th Edition. New York: Springer 2008.

17. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clinical & Experimental Rheumatology. 2008;26(5):S35-S61.

18. Avina-Zubieta J, Choi H, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in RA: A systematic review of observational studies. Annals of the Rheumatic Diseases. 2007;66(Supp2):320.

19. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis & Rheumatism. 2008;59(12):1690-7.

20. Nurmohamed MT. Cardiovascular risk in rheumatoid arthritis. Autoimmunity Reviews. 2009;8:663-7.

21. Park YB, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. Arthritis & Rheumatism. 2002;46(7):1714-9.

22. Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2002;46(6):1489-97.

23. O'Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. American Journal of Cardiology. 2002;90(10C):18L-21L.

24. Hermann F, Forster A, Chenevard R, Enseleit F, Hurlimann D, Corti R, et al. Simvastatin improves endothelial function in patients with rheumatoid arthritis. Journal of the American College of Cardiology. 2005;45(3):461-4.

25. Van Doornum S, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2004;63(12):1571.

26. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Practice & Research in Clinical Rheumatology. 2007;21(5):885-906.

27. Choi HK, Seeger JD. Lipid profiles among US elderly with untreated rheumatoid arthritis--the Third National Health and Nutrition Examination Survey. Journal of Rheumatology. 2005;32(12):2311-6.

28. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis & Rheumatism. 2002;46(4):862-73.

29. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation. 2003;108(24):2957-63.

30. Roubenoff R, Dellaripa P, Nadeau MR, Abad LW, Muldoon BA, Selhub J, et al. Abnormal homocysteine metabolism in rheumatoid arthritis. Arthritis & Rheumatism. 1997;40(4):718-22.

31. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. Rheumatology (Oxford). 2001;40(6):640-4.

32. Liuzzo G, Goronzy JJ, Yang H, Kopecky SL, Holmes DR, Frye RL, et al. Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. Circulation. 2000;101(25):2883-8.

33. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359(9313):1173-7.

34. Gabriel SE. Heart disease and rheumatoid arthritis: understanding the risks. Annals of the Rheumatic Diseases. 2010;69 Suppl 1:i61-4.

35. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. American Journal of Medicine. 2008;121(10 Suppl 1):S9-14.

36. Gabriel S. Heart disease and rheumatoid arthritis: Understanding the risks. Annals of the Rheumatic Diseases. 2009;69(Suppl I):i61-i4.

37. Escalante A, Haas RW, del Rincon I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Archives of Internal Medicine. 2005;165(14):1624-9.

38. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis & Rheumatism. 2004;50(11):3450-7.

39. Situnayake RD, Kitas G. Dyslipidemia and rheumatoid arthritis. Annals of the Rheumatic Diseases. 1997;56(6):341-2.

40. Park YB, Lee SK, Lee WK, Suh CH, Lee CW, Lee CH, et al. Lipid profiles in untreated patients with rheumatoid arthritis. Journal of Rheumatology. 1999;26(8):1701-4.

41. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Annals of the Rheumatic Diseases. 2009;68(4):460-9.

42. Liang K, Maradit Kremers H, Crowson CS, Snyder M, Therneau TM, Roger VL, et al. Autoantibodies and the Risk of Cardiovascular Events. Journal of Rheumatology. 2009;36:2462-9.

43. Gaw A, Packard C, Shepherd J (Ed.). Statins The HMG CoA Reductase Inhibitors in Perspective. London: Martin Dunitz Ltd; 2000.

44. Illingworth DR, Sexton GJ. Hypocholesterolemic effects of mevinolin in patients with heterozygous familial hypercholesterolemia. Journal of Clinical Investigation. 1984;74(6):1972-8.

45. Havel RJ, Hunninghake DB, Illingworth DR, Lees RS, Stein EA, Tobert JA, et al. Lovastatin (mevinolin) in the treatment of heterozygous familial hypercholesterolemia. A multicenter study. Annals of Internal Medicine. 1987;107(5):609-15.

46. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Current Controlled Trials in Cardiovascular Medicine. 2001;2(5):205-7.

47. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. New England Journal of Medicine. 1995;333(20):1301-7.

48. 4S Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9.

49. Heart Protection Study Collaborative. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.

50. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. American Journal of Cardiology. 2003;92(12):1447-51.

51. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. British Journal of Clinical Pharmacology. 2009;67(1):99-109.

52. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. Drugs. 2001;61(2):197-206.

53. Palinski W, Napoli C. Unraveling pleiotropic effects of statins on plaque rupture. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002;22:1745-50.

54. Liao JK. Isoprenoids as mediators of the biological effects of statins. Journal of Clinical Investigation. 2002;110(3):285-8.

55. Sparrow C, Burton C, Hernandez M, Mundt S, Hassing H, Patel S. Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. Arteriosclerosis, Thrombosis, and Vascular Biology. 2001;21:115-21.

56. Diomede L, Albani D, Sottocorno M, Donati MB, Bianchi M, Fruscella P, et al. In vivo anti-inflammatory effect of statins is mediated by nonsterol mevalonate products. Arteriosclerosis, Thrombosis & Vascular Biology. 2001;21(8):1327-32.

57. McKay A, Leung BP, McInnes IB, Thomson NC, Liew FY. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma. Journal of Immunology. 2004;172(5):2903-8.

58. Sasaki M, Bharwani S, Jordan P, Joh T, Manas K, Warren A, et al. The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor pravastatin reduces disease activity and inflammation in dextran-sulfate induced colitis. Journal of Pharmacology & Experimental Therapeutics. 2003;305(1):78-85.

59. Azuma RW, Suzuki J, Ogawa M, Futamatsu H, Koga N, Onai Y, et al. HMG-CoA reductase inhibitor attenuates experimental autoimmune myocarditis through inhibition of T cell activation. Cardiovascular Research. 2004;64(3):412-20.

60. Gegg ME, Harry R, Hankey D, Zambarakji H, Pryce G, Baker D, et al. Suppression of autoimmune retinal disease by lovastatin does not require Th2 cytokine induction. Journal of Immunology. 2005;174(4):2327-35.

61. Aktas O, Waiczies S, Smorodchenko A, Dorr J, Seeger B, Prozorovski T, et al. Treatment of relapsing paralysis in experimental encephalomyelitis by targeting Th1 cells through atorvastatin. Journal of Experimental Medicine. 2003;197(6):725-33.

62. Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature. 2002;420(6911):78-84.

63. Merx MW, Liehn EA, Janssens U, Lutticken R, Schrader J, Hanrath P, et al. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. Circulation. 2004;109(21):2560-5.

64. Ferrara DE, Liu X, Espinola RG, Meroni PL, Abukhalaf I, Harris EN, et al. Inhibition of the thrombogenic and inflammatory properties of antiphospholipid antibodies by fluvastatin in an in vivo animal model. Arthritis & Rheumatism. 2003;48(11):3272-9.

65. Lawman S, Mauri C, Jury EC, Cook HT, Ehrenstein MR. Atorvastatin inhibits autoreactive B cell activation and delays lupus development in New Zealand black/white F1 mice. Journal of Immunology. 2004;173(12):7641-6.

66. Leung BP, Sattar N, Crilly A, Prach M, McCarey DW, Payne H, et al. A novel anti-inflammatory role for simvastatin in inflammatory arthritis. Journal of Immunology. 2003;170(3):1524-30.

67. Katznelson S, Wilkinson A, Kobashigawa J, Wang X, Chia D, Ozawa M. The effect of pravastatin on acute rejection after kidney transplantation -- a pilot study. Transplantation. 1996;61:1469-74.

68. Tuncer M, Suleymanlar G, Ersoy FF, Yakupoglu G. Comparison of the effects of simvastatin and pravastatin on acute rejection episodes in renal transplant patients. Transplantation Proceedings. 2000;32(3):622-5.

69. Vollmer T, Key L, Durkalski V, Tyor W, Corboy J, Markovic-Plese S, et al. Oral simvastatin treatment in relapsing-remitting multiple sclerosis. Lancet. 2004;363(9421):1607-8.

70. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation. 2001;103(3):357-62.

71. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. New England Journal of Medicine. 2005;352(21):2184-92.

72. Jick H, Zornberg G, Jick S, Seshadri S, Drachman D. Statins and the risk of dementia. Lancet. 2000;356:1627-31.

73. Abud-Mendoza C, dela Fuente H, Cuevas-Orta E, Baranda L, Cruz-Rizo J, Gonzalez-Amaro R. Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. Lupus. 2003;12:607-11.

74. Mok C, Lai J, Wong C, Lam C, Lam C. Effect of rosuvastatin on homocysteine, hsCRP, and endothelial markers in systemic lupus erythematosus (SLE): A randomized controlled trial. Arthritis & Rheumatism. 2009;60(Supp10):1928.

75. Gurevich VS, Shovman O, Slutzky L, Meroni PL, Shoenfeld Y. Statins and autoimmune diseases. Autoimmunity Reviews. 2005;4(3):123-9.

76. Paraskevas KI, Tzovaras AA, Briana DD, Mikhailidis DP. Emerging indications for statins: a pluripotent family of agents with several potential applications. Current Pharmaceutical Design. 2007;13(35):3622-36.

77. Costenbader KH, Coblyn JS. Statin therapy in rheumatoid arthritis. Southern Medical Journal. 2005;98(5):534.

78. Paraskevas KI. Statin treatment for rheumatoid arthritis: a promising novel indication. Clinical Rheumatology. 2008;27(3):281-7.

79. Tandon vR, Mahajan A, Verma S. Statins and rheumatoid arthritis. Journal of Indian Rheumatology Association. 2005;13:54-9.

80. Gazi IF, Boumpas DT, Mikhailidis DP, Ganotakis ES. Clustering of cardiovascular risk factors in rheumatoid arthritis: the rationale for using statins. Clinical & Experimental Rheumatology. 2007;25(1):102-11.

81. Bisoendial RJ, Stroes ESG, Kastelein JJP, Tak PP. Targeting cardiovascular risk in rheumatoid arthritis: a dual role for statins. Nature Reviews Rheumatology. 2010;6(3):157-64.

82. Steiner G, Urowitz MB. Lipid Profiles in Patients with Rheumatoid Arthritis: Mechanisms and the Impact of Treatment. Seminars in Arthritis and Rheumatism. 2009;38(5):372-81.

83. Jury EC, Ehrenstein MR. Statins: immunomodulators for autoimmune rheumatic disease? Lupus. 2005;14(3):192-6.

84. Palinski W. New evidence for beneficial effects of statins unrelated to lipid lowering. Arteriosclerosis, Thrombosis, and Vascular Biology. 2001;21:3-5.

85. Penney CJ. Statins in rheumatology. Journal of Rheumatology. 2005;32(1):17-9.

86. Ridker PM, Solomon DH. Should patients with rheumatoid arthritis receive statin therapy? Arthritis & Rheumatism. 2009;60(5):1205-9.

87. Lee J, Choudhry R. RA - Lowering cardiovascular risk with statins. Nature Reviews Rheumatology. 2010;6:123-4.

88. Kanda H, Yokota K, Kubo K, Tateishi S, Oshima M, Kohno C, et al. Simvastatin reduces the disease activity in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2004;50(S9):S387.

89. Hochman EJ, Wolfe F, Choi H. Statins and Physical Function Among 6,265 Patients with Rheumatoid Arthritis. Arthritis & Rheumatism. 2004;50(9S):4092-3.

90. Kanda H, Hamasaki K, Kubo K, Tateishi S, Yonezumi A, Kanda Y, et al. Antiinflammatory effect of simvastatin in patients with rheumatoid arthritis. Journal of Rheumatology. 2002;29(9):2024-6.

91. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015-21.

92. Okamoto HK, K., Kamitsuji SI, E., Hara M, Tomatsu T, Kamatani N, Yamanaka H. Beneficial action of statins in patients with rheumatoid arthritis in a large observational cohort. Journal of Rheumatology. 2007;34(5).

93. Maki-Petaja KM, Booth AD, Hall FC, Wallace SML, Brown J, McEniery CM, et al. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. Journal of the American College of Cardiology. 2007;50(9):852-8.

94. Tikiz C, Utuk O, Pirildar T, Bayturan O, Bayindir P, Taneli F, et al. Effects of Angiotensin-converting enzyme inhibition and statin treatment on inflammatory markers and endothelial functions in patients with longterm rheumatoid arthritis. Journal of Rheumatology. 2005;32(11):2095-101.

95. Charles-Schoeman C, Khanna D, Furst DE, McMahon M, Reddy ST, Fogelman AM, et al. Effects of high-dose atorvastatin on antiinflammatory properties of high density lipoprotein in patients with rheumatoid arthritis: a pilot study. Journal of Rheumatology. 2007;34(7):1459-64.

96. Kanda H, Yokota K, Kohno C, Sawada T, Sato K, Yamaguchi M, et al. Effects of low-dosage simvastatin on rheumatoid arthritis through reduction of Th1/Th2 and CD4/CD8 ratios. Modern Rheumatology. 2007;17(5):364-8.

97. Shirinsky IV, Zheltova OI, Solovyova NY, Kozlov VA, Shirinsky VS. Changes in disease activity, cytokine production, and proliferation of peripheral blood mononuclear cells in patients with rheumatoid arthritis after simvastatin treatment. Scandinavian Journal of Rheumatology. 2009;38(1):23-7.

98. Jick S, Choi H, Li L, McInnes I, Sattar N. Hyperlipidemia, statin use and the risk of developing rheumatoid arthritis. Annals of the Rheumatic Diseases. 2008;68:546-51.

99. Holmqvist ME, Gallais IS, Wedren S, Klareskog L, Alfredsson L. Does statin use protect against RA or modify RA disease activity at diagnosis? Arthritis & Rheumatism. 2009;60(Supp10):1190.

100. Amittal H, Chodick G, Shalem Y, Shalev V. HMG-CoA reductase inhibitors (statins) provides primary prevention for rheumatoid arthritis. Arthritis & Rheumatism. 2009;60(Supp10):1174.

101. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: Population based cohort studying using the QResearch database. British Medical Journal. 2010;340(c2917).

102. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr., Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine. 2008;359(21):2195-207.

103. Abeles AM, Pillinger MH. Statins as antiinflammatory and immunomodulatory agents: a future in rheumatologic therapy? Arthritis & Rheumatism. 2006;54(2):393-407.

104. Gonzalez-Gay MA, Gonzalez-Juanatey C, Pineiro A, Garcia-Porrua C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. Journal of Rheumatology. 2005;32(7):1219-23.

105. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis & Rheumatism. 2005;52(8):2293-9.

106. Peters MJL, Nurmohamed MT, Kitas GD, Sattar N. Statin treatment of rheumatoid arthritis: comment on the editorial by Ridker and Solomon. Arthritis & Rheumatism. 2010;62(1):302-3.

107. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;2010(69):325-31.

108. Strom B, Kimmel S. Textbook of Pharmacoepidemiology. West Sussex: John Wiley & Sons, Ltd; 2006.

109. Haynes RB, Sackett DL. Compliance with Therapeutic Regimens. Baltimore, Maryland: Johns Hopkins University Press; 1976.

110. Osterberg L, Blaschke T. Adherence to medication. New England Journal of Medicine. 2005;353(5):487-97.

111. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, et al. Persistence of use of lipid-lowering medications: a cross-national study. Journal of the American Medical Association. 1998;279(18):1458-62.

112. Cramer JA, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: Predictors and outcomes. Value in Health. 2003;6(5):566-73.

113. International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Special Interest Group. Medication Compliance and Persistence: Terminology and Definitions; 2003.

114. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. Nature Clinical Practice Rheumatology. 2007;3(12):725-32.

115. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? New England Journal of Medicine. 1995;332(17):1125-31.

116. Tsoneva J, Shaw J. Understanding patients' beliefs and goals in medicine-taking. Professional Nurse. 2004;19(8):466-8.

117. Pedan A, Varasteh L, Schneeweiss S. Analysis of factors associated with statin adherence in a hierarchical model considering physician, pharmacy, patient, and prescription characteristics.[see comment]. Journal of Managed Care Pharmacy. 2007;13(6):487-96.

118. Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value in Health. 2000;3(6):417-25.

119. Perreault S, Blais L, Dragomir A, Bouchard MH, Lalonde L, Laurier C, et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. European Journal of Clinical Pharmacology. 2005;61(9):667-74.

120. Lachaine J, Rinfret S, Merikle EP, Tarride JE. Persistence and adherence to cholesterol lowering agents: evidence from Regie de l'Assurance Maladie du Quebec data. American Heart Journal. 2006;152(1):164-9.

121. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Medical Journal of Australia. 1996;164(4):208-11.

122. Ellis JJ, Erickson S, Stevenson J, Bernstein S, Stiles R, Fendrick M. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. Journal of General Internal Medicine. 2004;19:638-45.

123. Howell N, Trotter R, Mottram D, Rowe P. Compliance with statins in primary care. Pharmaceutical Journal. 2004;272:23-6.

124. Deambrosis P, Saramin C, Terrazzani G, Scaldaferri L, Debetto P, Giusti P, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. European Journal of Clinical Pharmacology. 2007;63(2):197-203.

125. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clinical Therapeutics. 2008;30(11):2167-79.

126. Foody JM, Joyce AT, Rudolph AE, Liu LZ, Benner JS. Persistence of atorvastatin and simvastatin among patients with and without prior cardiovascular diseases: a US managed care study. Current Medical Research & Opinion. 2008;24(7):1987-2000.

127. Vinker S, Shani M, Baevsky T, Elhayany A. Adherence with statins over 8 years in a usual care setting. American Journal of Managed Care. 2008;14(6):388-92.

128. Harrold LR, Andrade SE. Medication adherence of patients with selected rheumatic conditions: a systematic review of the literature. Seminars in Arthritis & Rheumatism. 2009;38(5):396-402.

129. Feinberg J. The effect of patient-practitioner interaction on compliance: a review of the literature and application in rheumatoid arthritis. Patient Education & Counseling. 1988;11(3):171-87.

130. Tuncay R, Eksioglu E, Cakir B, Gurcay E, Cakci A. Factors affecting drug treatment compliance in patients with rheumatoid arthritis. Rheumatology International. 2007;27(8):743-6.

131. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. American Journal of Managed Care. 2003;9(6 Suppl):S136-43.

132. Treharne GJ, Douglas KMJ, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care. 2007;5(4):175-90.

133. Goycochea-Robles M, Rahman MM, Choi H, Esdaile JM, Lacaille D. Compliance with statin therapy in rheumatoid arthritis in patients. Arthritis & Rheumatism. 2008;59(9):S877.

134. Chamberlayne R, Green B, Barer M, Hertzman C, Lawrence W, Sheps S. Creating a Population-Based Linked Health Database: A New Resource for Health Services Research. Canadian Journal of Public Health. 1998;89(4):270-3.

135. Morgan S, Yan L. Income-Based Drug Coverage in British Columbia: The Impact on Private and Public Expenditures. Healthcare Policy. 2006;2(2):e129-e53.

136. Schnatter R, Acquavella J, Thompson F. An analysis of death ascertainment and follow-up through Canada's mortality database system. Canadian Journal of Public Health. 1990;81:60-5.

137. Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: a population study. Arthritis & Rheumatism. 2005;53(2):241-8.

138. Province of British Columbia. The 2006 Census of Canada in BC Stats. Available from: http://www.bcstats.gov.bc.ca/census.asp. [cited 2009 December 21, 2009]

139. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. Annals of Internal Medicine. 1997;126(5):376-80.

CHAPTER 2[4]
STATINS AND RISK OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS: A POPULATION-BASED STUDY

2.1 Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory arthritis associated with systemic inflammation and characterized by substantial disability and premature mortality. Cardiovascular disease (CVD) is a significant comorbidity (1-3), as demonstrated by studies showing increased risk for ischemic heart disease including acute myocardial infarction (AMI) among RA patients (4). CVD is also the leading cause of mortality in RA (5), with 50% higher risk of CVD death among RA patients compared to individuals in the general population (6, 7). There is evidence that RA and its associated systemic inflammation could have a direct effect on the endothelium and predispose patients to accelerated atherosclerosis and AMI (8, 9).

Statins (hydroxymethylglutaryl-coenzyme A inhibitors) are potentially excellent candidate agents to reduce CVD risks in RA patients (10, 11). Their well-established efficacy in primary and secondary prevention of vascular events in randomized trials (12-14) and observational studies (15, 16) in non-RA patient populations along with demonstrated anti-inflammatory effects (10), suggest that statins may ameliorate CVD risk in RA via classic (lipids) and novel (inflammation) mechanisms and lend to the question of whether they should comprise part of the therapeutic approach to care of patients with RA (17). Clinical studies in RA patients evaluating statin effects on intermediate correlates of CVD including arterial stiffness (18) and endothelial function (19, 20) have provided supporting evidence for this cardioprotective benefit to date, but the effect of statin therapy on hard CVD outcomes in RA patients has not been demonstrated.

[4] A version of this chapter will be submitted for publication. De Vera M, Lacaille D, Abrahamowicz M, Kopec J, Choi K. Statins and Risk of Acute Myocardial Infarction in Patients with Rheumatoid Arthritis: A Population-Based Study.

It is unknown whether results from studies of statins in non-RA populations can be directly extrapolated to RA patients (21). Population data from the Rochester Epidemiology Project of long-term outcomes in RA indicate that traditional cardiovascular risk factors including body mass index (BMI), smoking, hypertension, and diabetes, have weaker associations with heart disease in RA subjects (22, 23). Furthermore, there are observations of "paradoxical" or unexpected behaviour of these risk factors in RA patients, such as improved survival with declining BMI (24, 25), and notably precipitous decline in total and LDL-cholesterol before RA onset (23) and lower total and LDL-cholesterol levels in RA patients along with inverse association with inflammation markers (26-28). These data lend to the question of whether targeting LDL-cholesterol levels with lipid lowering agents such as statins may also yield unexpected effects in RA patients. Nevertheless, anti-inflammatory effects of statins may contribute to their CV benefits in RA patients (23). Overall, these lingering questions combined with the lack of data on effectiveness of statins on hard CVD outcomes call for an investigation of statins specifically in RA (29). To address these issues, we evaluated the cardioprotective effect of statin therapy in a longitudinal study of a population-based cohort of RA patients.

2.2 Methods

2.2.1 Data Source and Study Population

We used data from a previously established population-based RA cohort in the Canadian province of British Columbia (BC) (30). Specifically, administrative billing data for the reimbursement of physician visits from the BC Ministry of Health were used to identify adults (≥18 years) with RA who received care for their RA between January 1996 and March 2006. The case definition for RA was the same as previously published for this cohort (30); specifically, individuals met inclusion criteria if they had at least 2 physician

visits more than 2 months apart with an RA diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9], 714.x). Individuals were excluded if they had at least 2 visits subsequent to the second RA visit with diagnoses of other inflammatory arthritides (systemic lupus erythematosus, other connective tissue diseases, psoriatic arthritis, ankylosing spondylitis, and other spondylarthritides), if an RA diagnosis by a non-rheumatologist was not confirmed on a subsequent rheumatologist visit, or if they had no subsequent RA-coded physician visits over a follow-up period of 5 years or more. Complete follow-up for the cohort was available up to March 2006. Overall, this RA cohort included 37,151 individuals, yielding a prevalence rate of 0.96%, based on the number of alive prevalent cases in 2006 (n=29,417) and 2006 census data from Statistics Canada (31). This is consistent with previously reported prevalence estimates for RA (32).

For each RA case, administrative data for all provincially funded health services used since 1990 were obtained, including physician visits and hospitalizations. We also obtained information on all prescription medications dispensed since January 1996 onwards, as well as mortality and cause of death data from Vital Statistics. No personal identifying information was available on any individual and data access procedures complied with BC's Freedom of Information and Privacy Protection Act. The University of British Columbia Behavioural Research Ethics Board granted ethical approval for this study.

2.2.2 Exposure Assessment

Our primary exposure was statin initiation in RA patients, defined as the first statin prescription, at any time between January 1997 and March 2006. Individuals who had statin prescriptions in the first year of available pharmacy records data were excluded to ensure only incident statin users were considered. We also excluded individuals who initiated statin therapy before diagnosis of RA. For RA patients who initiated

statins, the date of their first statin prescription was defined as the index date, when follow-up for study outcomes began. RA patients who did not receive any statin prescription were identified as non-statin initiators. For each non-initiator, we assigned an index date corresponding to a randomly selected date between the date of their RA diagnosis and the end of follow-up[5].

Similar to a study based on The UK Health Improvement Network (THIN) Database, we allowed the possibility that statin initiators may have been non-initiators earlier in the follow-up, but eventually went on to be prescribed a statin at a later date (16). For example, a patient who was diagnosed with RA in 1997 but did not initiate a statin until 2000 contributed their person-time as a non-initiator during the elapsed period between their RA diagnosis and their first statin prescription. This approach approximates procedures in randomized trials and avoids both possibilities of assembling a biased comparison group who were not at risk of being prescribed a statin (16).

2.2.3 Outcome Assessment

The primary outcome for this study was the first AMI event during follow-up. Outcomes included both non-fatal and fatal AMI events. Non-fatal AMI events were ascertained using ICD-9 codes for AMI (410) in hospital separations data, which included up to 10 diagnoses representing either the reason for admission or complications during hospitalization. The accuracy of ICD-9 codes for AMI has been well-established in Canadian validation studies of administrative hospital discharge records, with reported positive predictive values (PPV) ranging from 89% to 96% (33-35). Fatal AMI included both AMI deaths occurring outside of hospitals based on ICD-10 codes for AMI (I21) as the cause of death in Vital Statistics death data and deaths resulting from hospitalized AMI. The validity of ICD-10 AMI codes have also been previously

[5] Subject flow of statin initiators and non-initiators in population-based RA cohort is presented in Appendix B Figure B1.1

demonstrated, with PPV of 93.5% (36). To avoid double-counting, deaths occurring within one month of a hospitalized AMI were considered as fatal AMI events. The event date was the date of hospital admission for non-fatal AMIs and date recorded on the death certificate for fatal AMIs.

2.2.4 Covariates

Factors known to influence CVD risk that were available in our data were considered as potential covariates in multivariable regression models. Fixed-in-time binary variables measured over a period of 1 year preceding the index date evaluated the presence of co-morbidities influencing cardiovascular risk and were based on diagnostic codes for physician visits or medication use. These included diabetes (use of insulin or oral hypoglycemic agents), angina (411, 413 or use of nitrates), use of cardiac medications - grouped as anti-hypertension medications (angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blocking agents, angiotensin II receptor antagonists, alpha-adrenergic blocking agents, or central alpha-agonists), congestive heart failure medications (cardiac glycosides or diuretics), and anti-arrhythmia medications (adenosine, amiodarone, disopyramide, flecainide, lidocaine, mexitelene, procainamide, propafenone, digoxin, or quinidine), as well as use of other medications known to influence AMI risk, namely hormone replacement therapy and anticoagulants. We also calculated modified Charlson Comorbidity Index over the 1-year period preceding the index date using a version adapted for administrative data (37, 38). Also considered as covariates were history of prior events of AMI and cerebrovascular accident (434, 436), at any time prior to the index date.

We also considered use of RA medications that could influence AMI risk, including glucocorticosteroids, traditional non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (Cox-2) inhibitors, and methotrexate, represented as monthly updated, time-dependent covariates.

2.2.5 Statistical Analyses

Propensity scores were calculated, at the index date, for statin initiators and non-initiators using multivariable logistic regression, with statin initiation as the binary outcome. Propensity scores estimate the probability that an individual will be prescribed a given drug, based on his or her characteristics at the time of treatment assignment (39). In principle, a causal effect of the treatment can be estimated among patients who have the same predicted propensity of treatment, as matching on propensity scores adjusts for confounding by indication related to the observed determinants of treatment choice (39). Similar to prior work by Seeger et al. (13, 40), we employed a multi-faceted approach in considering potential predictors of statin use in our propensity score model. Specifically, we considered all available variables that are identified by the National Cholesterol Education Program (NCEP) II guidelines as indications for statin use which in our dataset included presence of coronary heart disease, hypertension, and diabetes, as well as age and sex. In addition, we included healthcare utilization variables (number of prescription drugs, number of physician visits, number of lipid laboratory tests, and number of CVD-related diagnoses) as they have been previously shown to be strong predictors of statin use (15, 40). Finally, we also considered as potential variables to be included in our propensity score models, proxy indicators of RA severity, including those variables representing the number of visits to rheumatologists, number of RA related laboratory tests, and use of RA medications (including glucocorticosteroids, methotrexate, and disease modifying antirheumatic drugs). All variables considered for the propensity score model were evaluated at or up to the index date; diagnostic codes and use of medications were applied to evaluate presence of chronic diseases in the year preceding the index date. History of prior disease events (AMI, CVA, cancer) were evaluated at any time prior to the index date. Values for continuous count variables representing healthcare utilization were accumulated from available data up to the index date (40).

When building the final propensity score model, we relied on a guiding principle of maximum discrimination of exposed (statin initiation) from non-exposed (non-initiation) given observed variables (15). Thus, we opted for inclusion of even weakly predictive variables, because the potential bias due to their exclusion would tend to distort the results more than the possible loss in efficacy due to inclusion of too many variables (15). In our final propensity score model we included all potential predictor variables, which had statistically significant ($p<0.05$ for 2-tailed Wald test) unadjusted association with statin initiation in univariate logistic regression analyses. Table 2.1 lists the 46 independent variables selected into the final propensity score model, ranking variables according to univariate c-statistic[6]. The final propensity score model yielded a c-statistic of 0.87, which indicated a strong ability to differentiate between statin initiators and non-initiators. Figure 2.1 compares the distributions of calculated propensity scores for statin initiators and non-initiators.

[6] Comparison of current propensity score model with Seeger et al.'s propensity score model shown in Appendix B Table B1.1

Table 2.1 Propensity Score Variables and Association with Statin Use

Rank*	Variable	Univariate OR (95% CI)	p-value	C-statistic
1	No. of lipid-related laboratory tests	1.10 (1.09, 1.11)	<0.0001	0.78
2	No. of cardiovascular disease** (ICD9) related physician visits	1.02 (1.02, 1.03)	<0.0001	0.71
3	No. of different cardiovascular disease** (ICD9) diagnoses	1.25 (1.23, 1.26)	<0.0001	0.70
4	Use of anti-hypertension medications (y/n)	5.24 (4.87, 5.63)	<0.0001	0.69
5	No. ECG	1.19 (1.18, 1.21)	<0.0001	0.64
6	RA duration at index date (months)	1.017 (1.015, 1.018)	<0.0001	0.65
7	Charlson Score	1.25 (1.23, 1.28)	<0.0001	0.62
8	No. physician visits	1.003 (1.002, 1.003)	<0.0001	0.61
9	No. of different prescription drugs	1.012 (1.010, 1.013)	<0.0001	0.60
10	No. RA-related laboratory tests	1.011 (1.009, 1.013)	<0.0001	0.60
11	Angina (411, 413, or nitrates) (y/n)	5.88 (5.37, 6.45)	<0.0001	0.59
12	Age (years)	1.02 (1.01, 1.02)	<0.0001	0.58
13	No. of different ICD9 diagnoses	1.015 (1.013, 1.016)	<0.0001	0.59
14	No. inpatient hospitalizations	1.06 (1.05, 1.07)	<0.0001	0.59
15	Use of congestive heart failure medications (y/n)	2.22 (2.06, 2.39)	<0.0001	0.58
16	No. of cardiovascular disease** (ICD9) related hospital days	1.001 (1.001, 1.002)	<0.0001	0.56
17	Diabetes (y/n)	4.46 (4.04, 4.92)	<0.0001	0.57
18	Prior AMI (410) (y/n)	13.84 (11.87, 16.13)	<0.0001	0.55
19	Dysrrhythmia (427) (y/n)	1.88 (1.73, 2.05)	<0.0001	0.55
20	Gender (women vs. men)	1.39 (1.29, 1.49)	<0.0001	0.54
21	No. RA-related physician visits (714)	1.005 (1.004, 1.006)	<0.0001	0.54
22	CVA (434, 436) (y/n)	2.34 (2.08, 2.64)	<0.0001	0.53
23	Atherosclerosis (440) (y/n)	3.13 (2.72, 3.61)	<0.0001	0.53
24	Use of Cox2 inhibitors (y/n)	1.27 (1.18, 1.37)	<0.0001	0.53
25	Use of traditional NSAIDs (y/n)	1.33 (1.22, 1.45)	<0.0001	0.52
26	Physician visits for smoking cessation (305 or 491-6) (y/n)	1.28 (1.18, 1.39)	<0.0001	0.52
27	Use of non-statin lipid lowering drug (y/n)	5.93 (4.86, 7.25)	<0.0001	0.52

Table 2.1 Propensity Score Variables and Association with Statin Use

Rank*	Variable	Univariate OR (95% CI)	p-value	C-statistic
28	Transient ischemic attack (435) (y/n)	2.46 (2.12, 2.86)	<0.0001	0.52
29	Use of anticoagulants (y/n)	1.64 (1.45, 1.87)	<0.0001	0.52
30	Use of DMARDs (y/n)	0.92 (0.85, 0.98)	0.015	0.51
31	Visit to rheumatologist (y/n)	0.92 (0.86, 0.98)	0.017	0.51
32	Physician visits for obesity (278) (y/n)	1.52 (1.31, 1.76)	<0.0001	0.51
33	Hypertensive heart disease (402-404) (y/n)	2.66 (2.14, 3.31)	<0.0001	0.51
34	Cancer (140-208) (y/n)	1.18 (1.08, 1.32)	0.0004	0.51
35	Old MI (412) (y/n)	4.02 (3.09, 5.22)	<0.0001	0.51
36	Use of methotrexate (y/n)	0.94 (0.87, 0.99)	0.016	0.51
37	Use of anti arrhythmia medications (y/n)	2.00 (1.63, 2.45)	<0.0001	0.51
38	Circulatory disease (459) (y/n)	1.77 (1.46, 2.14)	<0.0001	0.51
39	Use of glucocorticosteroids (y/n)	1.09 (1.01, 1.17)	0.018	0.51
40	Conduction disorder (426) (y/n)	1.77 (1.44, 2.17)	<0.0001	0.51
41	No. visits to rheumatologists before index	1.008 (1.006, 1.010)	<0.0001	0.51
42	COPD (490-496, 505-506) (y/n)	1.44 (1.28, 1.63)	<0.0001	0.51
43	Attrial fibrillation (427.3) (y/n)	1.69 (1.33, 2.15)	<0.0001	0.51
44	Atherosclerotic CVD (429.2) (y/n)	5.68 (2.77, 11.62)	<0.0001	0.50
45	Cardiovascular symptoms (785.9) (y/n)	1.96 (1.16, 3.31)	0.011	0.50
46	No. different RA drugs	1.03 (1.01, 1.05)	0.0014	0.50

**Variable rank according to c-statistic in univariate logistic regression analyses;*

***ICD9 codes for cardiovascular disease (390 to 459) includes all ischemic heart disease and other heart disease, cerebrovascular diseases, hypertension, diseases of arteries and veins, and other diseases of the circulatory system (39)*

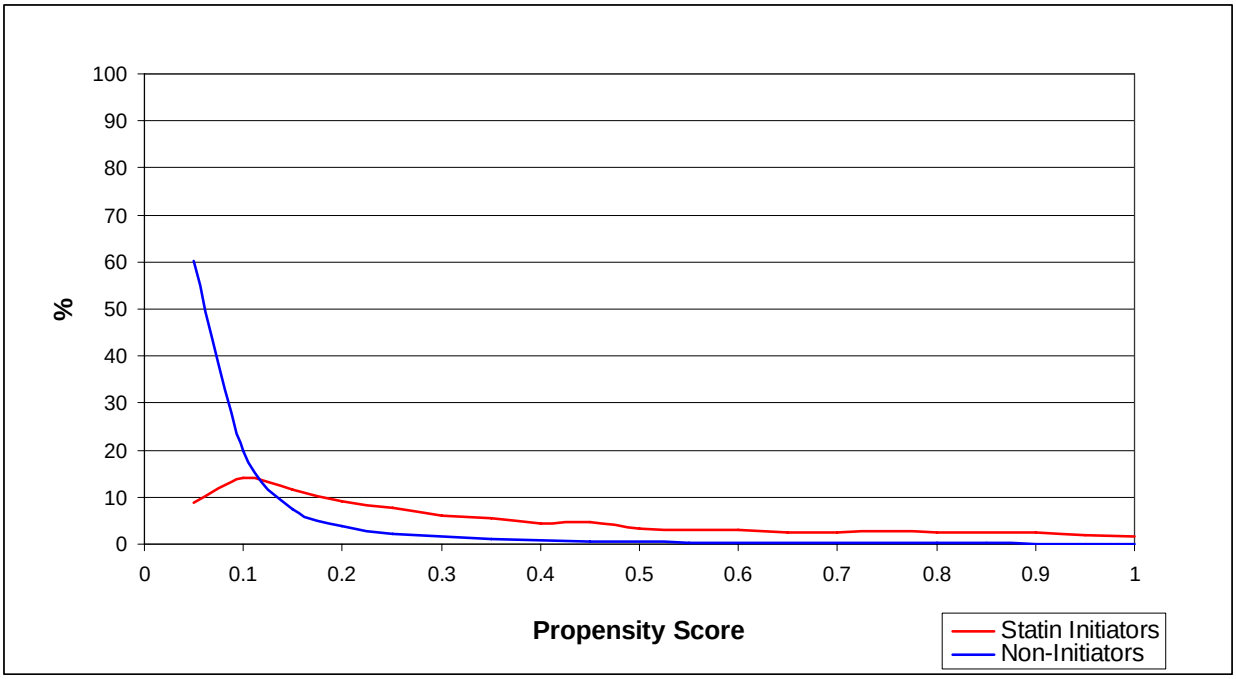


Figure 2.1 Distributions of Propensity Scores According to Statin Initiation Status Prior to Matching

We applied 'greedy matching' techniques to match statin initiators to non-initiators (42). Attempts to maximize the accuracy of matching may result in exclusion of individuals for whom exact matching is not possible. Conversely, attempts to maximize the number of matches may result in inexact matching. Thus, a 'greedy matching' approach balances potential biases associated with (i) elimination of incomplete matches *versus* (ii) inexact matching (42). Our implementation of a greedy matching algorithm involved the following steps: 1) first, statin initiators were matched to non-initiators on *n* digits of their individual propensity scores; 2) those that could not be matched in step (1) are then matched on *n-1* digits of the propensity score; 3) in each subsequent step, the matching criteria for those that remained unmatched were relaxed by further reducing the number of digits by one until the last $(k+1)^{th}$ step, with matching on only (n-k) digits, where 0<k<n. Table 2.2 summarizes the results of alternative matching algorithms, each starting with a different initial value of *n,* evaluated in this study. For illustrative purposes, we also included optimal matching algorithms on 5, 4, and 3 digits, respectively. Based on results in Table 2.2, the greedy

5→1 digit matching algorithm was selected because it balanced completeness of match (88% of statin initiators matched to non-initiators) with goodness of the matched sample (absolute difference in propensity score of matched pairs did not materially improve with 6→1 digit algorithm) (42).

Table 2.2 Summary of Algorithms for Matching on Propensity Score

Matching Algorithm	Completeness of Match	Goodness of Matched Pairs
	Statin Initiators N (% Matched)	Absolute Difference in Propensity Score of Matched Pairs
Unmatched Cohort	3,517	-
Optimal 5-digit match	1,069 (30.4)	0.0000013
Optimal 4-digit match	2,194 (62.4)	0.000024
Optimal 3-digit match	2,925 (83.2)	0.00027
Greedy 5→3 digit match	3,016 (85.8)	0.000036
Greedy 5→2 digit match	3,083 (87.7)	0.000060
Greedy 5→1 digit match	3,104 (88.3)	0.000049
Greedy 6→1 digit match	3,104 (88.3)	0.000047

To evaluate the balance achieved across variables in the propensity score model after matching, we compared statin initiators and non-initiators using independent samples t-test for continuous variables and chi square tests for categorical variables, with 2-tailed significance level set at $p < 0.05$.

We calculated person-time of follow-up from index date to AMI date, last health care service use, death or end of study period (March 31, 2006), whichever came first. To estimate the effect of statin initiation on AMI risk in the propensity-matched cohort, we used Cox's proportional hazards models, and report the adjusted hazard ratio (HR) with 95% confidence interval. Subjects were assigned their original exposure status until the end of follow-up regardless of actual use during follow-up. This provides a conservative

estimate of efficacy as intent-to-treat does in a clinical trial (40). We evaluated further multivariable Cox's proportional hazards models that included as covariate(s) both the propensity score and the variables for which residual imbalance persisted after propensity score matching. For all Cox's models, we tested the proportional hazards assumption that the hazard ratio for initiators versus non-initiators remain constant during the entire follow-up, graphically with log log plots and formally, by testing interactions with statin exposure and follow-up time.

We conducted sensitivity analyses to evaluate the robustness of our propensity score analyses, as recommended (15). Specifically, we evaluated Cox's proportional hazards models in matched cohorts resulting from four alternative greedy matching algorithms with, respectively, 5→3, 5→2, 5→1, and 6→1 digits.

We additionally repeated all aforementioned analyses using only incident RA cases (N=9,874)[7]. These were selected as individuals with a first diagnosis of RA between January 1997 and December 2001 and without a prior diagnosis of RA since 1990 (earliest available data). Use of an incident RA cohort allowed for comparison of individuals' AMI risk at the same time since date of RA diagnosis.

All hypotheses were tested using 2-tailed Wald's tests at the 0.05 significance level and the strength of the exposure effects were estimated using adjusted HRs with 95% confidence intervals (CIs). Analyses were performed using SAS (Version 9.1, SAS Institute, Cary, North Carolina).

[7] Flow of subjects in the incident RA cohort shown in Appendix B Figure B1.2;
Results of sensitivity analyses of incident RA cohort shown in Appendix B, Table B1.2 and Figure B1.3

2.3 Results

Our study included 3,517 RA cases who met inclusion criteria for statin initiation and 29,671 non-initiators, altogether contributing 93,143 person-years of follow-up between January 1996 and March 2006. Table 2.3 summarizes subject characteristics on 46 variables, ranked according to predictive value for statin initiation, included in the final propensity score model.

At index date, the unmatched statin initiators had a higher prevalence of CVD risk factors than did non-initiators. Specifically, compared to non-initiators, statin initiators were older, more likely to be men, more likely to have diabetes, hypertension, and pre-existing cardiovascular disease (angina, prior AMI, prior CVA, higher number of CVD-related physician visits). Matching on propensity score resulted in a cohort of 3,104 statin initiators and 3,104 individually matched non-initiators. Table 2.3 also summarizes characteristics of the matched cohort according to statin initiation status. Overall, propensity score matching produced good balance as the matched cohorts were significantly different ($p<0.05$) on only 2 of the 46 covariates in the propensity score model, history of angina and prior AMI.

Table 2.3 Subject Characteristics on Propensity Score Variables According to Statin Initiation in (A) Unmatched and (B) Propensity Score-Matched RA Patients

Rank	Variable	Unmatched Cohorts[A]			Propensity Score Matched Cohorts[B]		
		Non Initiators *N=29,671*	Statin Initiators *N=3,517*	P-value	Non Initiators *N=3,104*	Statin Initiators *N=3,104*	P-value
1	No. of lipid-related laboratory tests	3.9 ± 6.3	11.1 ± 9.5	<0.0001	10.1 ± 11.2	10.2 ± 8.6	0.25
2	No. of cardiovascular physician visits	7.6 ± 16.1	17.6 ± 23.6	<0.0001	16.4 ± 21.6	16.5 ± 23.1	0.85
3	No. of different cardiovascular (ICD9) diagnoses	1.6 ± 2.1	3.1 ± 2.8	<0.0001	2.9 ± 2.9	2.9 ± 2.6	0.85
4	Use of anti-hypertension medications (y/n)	7,930 (24)	2,187 (62)	<0.0001	1,878 (60)	1,828 (59)	0.20
5	No. ECG	1.1 ± 1.9	2.1 ± 2.6	<0.0001	2.1 ± 2.6	2.0 ± 2.6	0.24
6	RA duration at index date (months)	30.3 ± 27.1	44.8 ± 30.0	<0.0001	44.5 ± 32.4	43.6 ± 29.6	0.073
7	Charlson Score	0.7 ± 1.2	1.1 ± 1.4	<0.0001	1.0 ± 1.5	1.1 ± 1.3	0.29
8	No. physician visits	123.0 ± 98.7	157.5 ± 109.9	<0.0001	157.0 ± 108.2	154.0 ± 110.2	0.28
9	No. of different prescription drugs	26.4 ± 21.9	33.5 ± 24.2	<0.0001	33.5 ± 23.4	32.8 ± 24.0	0.25
10	No. RA-related laboratory tests	8.2 ± 16.4	12.5 ± 21.4	<0.0001	11.5 ± 17.8	11.8 ± 20.9	0.45
11	Angina (411, 413, or nitrates) (y/n)	1,681 (5.1)	840 (23.9)	<0.0001	575 (18.5)	649 (20.9)	0.018*
12	Age (years)	57.3 ± 17.2	62.3 ± 11.2	<0.0001	62.5 ± 13.9	62.2 ± 11.3	0.25
13	No. of different ICD9 diagnoses	35.1 ± 19.2	41.2 ± 19.6	<0.0001	41.2 ± 19.1	40.7 ± 19.7	0.26
14	No. inpatient hospitalizations	2.3 ± 3.3	3.1 ± 3.8	<0.0001	2.9 ± 3.5	3.0 ± 3.8	0.74
15	Use of congestive heart failure medications (y/n)	6,318 (19.0)	1205 (34.3)	<0.0001	1,068 (34.4)	1,046 (33.7)	0.56

Table 2.3 Subject Characteristics on Propensity Score Variables According to Statin Initiation in (A) Unmatched and (B) Propensity Score-Matched RA Patients

Rank	Variable	Unmatched Cohorts[A]			Propensity Score Matched Cohorts[B]		
		Non Initiators *N=29,671*	Statin Initiators *N=3,517*	P-value	Non Initiators *N=3,104*	Statin Initiators *N=3,104*	P-value
16	No. of cardiovascular hospital days	3.9 ± 32.1	6.2 ± 26.7	<0.0001	6.2 ± 28.1	5.7 ± 27.6	0.46
17	Diabetes (y/n)	1,638 (4.9)	661 (18.8)	<0.0001	538 (17.3)	521 (16.8)	0.57
18	Prior AMI (410) (y/n)	305 (0.9)	400 (11.4)	<0.0001	193 (6.2)	272 (8.8)	0.0001*
19	Dysrrhythmia (427) (y/n)	4,467 (13.5)	797 (22.7)	<0.0001	676 (21.8)	682 (21.9)	0.85
20	Gender (women)	22,995 (69.3)	2,174 (61.8)	<0.0001	1,981 (63.8)	1,943 (62.6)	0.32
21	No. RA-related physician visits	12.2 ± 23.2	16.2 ± 30.1	<0.0001	15.5 ± 29.8	15.4 ± 27.5	0.85
22	CVA (434, 436) (y/n)	1,532 (4.6)	358 (10.2)	<0.0001	321 (10.3)	299 (9.6)	0.35
23	Atherosclerosis (440) (y/n)	849 (2.6)	267 (7.6)	<0.0001	215 (6.9)	210 (6.8)	0.80
24	Use of Cox2 inhibitors (y/n)	10,614 (31.9)	1,316 (37.4)	<0.0001	1,185 (38.2)	1,146 (36.9)	0.31
25	Use of traditional NSAIDs (y/n)	25,224 (76)	2,843 (80.8)	<0.0001	2,520 (81.2)	2,487 (80.1)	0.29
26	Physician visits for smoking cessation (305 or 491-6) (y/n)	6,899 (20.8)	883 (25.1)	<0.0001	769 (24.8)	773 (24.9)	0.91
27	Use of non-statin lipid lowering drug (y/n)	261 (0.8)	158 (4.5)	<0.0001	129 (4.2)	123 (3.9)	0.70
28	Transient ischemic attack (435) (y/n)	889 (2.7)	223 (6.3)	<0.0001	212 (6.8)	182 (5.9)	0.12
29	Use of anticoagulants (y/n)	1,819 (5.5)	306 (8.7)	<0.0001	273 (8.8)	263 (8.5)	0.65
30	Use of DMARDs (y/n)	14,734 (44.4)	1,486 (42.3)	0.015	1,287 (41.5)	1,304 (42.0)	0.66

Table 2.3 Subject Characteristics on Propensity Score Variables According to Statin Initiation in (A) Unmatched and (B) Propensity Score-Matched RA Patients

Rank	Variable	Unmatched Cohorts[A]			Propensity Score Matched Cohorts[B]		
		Non Initiators *N=29,671*	Statin Initiators *N=3,517*	P-value	Non Initiators *N=3,104*	Statin Initiators *N=3,104*	P-value
31	Visit to rheumatologist (y/n)	17,996 (54.2)	1,833 (52.1)	0.017	1,596 (51.4)	1,605 (51.7)	0.82
32	Physician visits for obesity (278) (y/n)	1,398 (4.2)	220 (6.3)	<0.0001	195 (6.3)	190 (6.1)	0.79
33	Hypertensive heart disease (402-404) (y/n)	380 (1.1)	105 (2.9)	<0.0001	81 (2.6)	83 (2.8)	0.87
34	Cancer (140-208) (y/n)	4,183 (12.6)	517 (14.7)	<0.0001	471 (15.2)	451 (14.5)	0.48
35	Old MI (412) (y/n)	196 (0.6)	82 (2.3)	<0.0001	57 (1.8)	61 (1.9)	0.71
36	Use of methotrexate (y/n)	7,958 (23.9)	806 (22.9)	0.16	687 (22.1)	698 (22.5)	0.74
37	Use of anti arrhythmia medications (y/n)	531 (1.6)	111 (3.2)	<0.0001	81 (2.6)	92 (2.9)	0.40
38	Circulatory disease (459) (y/n)	716 (2.1)	132 (3.8)	<0.0001	128 (4.1)	104 (3.4)	0.11
39	Use of glucocorticosteroids (y/n)	13,725 (41.4)	1,527 (43.4)	<0.0001	1,329 (42.8)	1,334 (42.9)	0.90
40	Conduction disorder (426) (y/n)	612 (1.8)	113 (3.2)	<0.0001	93 (3.0)	93 (3.0)	1.00
41	No. visits to rheumatologists	6.5 ± 13.8	8.5 ± 17.9	<0.0001	7.9 ± 17.3	8.0 ± 16.9	0.91
42	COPD (490-496, 505-506) (y/n)	2,130 (6.4)	317 (9.0)	<0.0001	275 (8.9)	279 (8.9)	0.86
43	Attrial fibrillation (427.3) (y/n)	450 (1.4)	80 (2.3)	<0.0001	72 (2.3)	69 (2.2)	0.80
44	Atherosclerotic CVD (429.2) (y/n)	20 (0.06)	12 (0.3)	<0.0001	4 (0.1)	9 (0.3)	0.17
45	Cardiovascular symptoms (785.9) (y/n)	82 (0.3)	17 (0.5)	0.01	8 (0.3)	14 (0.5)	0.20

Table 2.3 Subject Characteristics on Propensity Score Variables According to Statin Initiation in (A) Unmatched and (B) Propensity Score-Matched RA Patients

Rank	Variable	Unmatched Cohorts[A]			Propensity Score Matched Cohorts[B]		
		Non Initiators *N=29,671*	Statin Initiators *N=3,517*	P-value	Non Initiators *N=3,104*	Statin Initiators *N=3,104*	P-value
46	No. different RA drugs	1.1 ± 1.8	1.2 ± 2.1	0.001	1.2 ± 2.0	1.2 ± 2.0	0.81

There were 261 AMI events in the propensity score matched cohort, during 15,271 person-years of follow-up. Incidence rates for AMI for initiators and non-initiators were 1.5 and 2.1 per 100 person-years, respectively). Statin initiation was associated with a 31% reduction in risk of AMI, which was highly significant (HR, 0.69; 95% CI, 0.54-0.90). A test of the proportional hazards assumption for this model did not result in rejection of the hypothesis (p=0.55 for the exposure-by-time interaction) indicating that the relative risk reduction of 31% associated with statin initiation remained constant over the follow-up. Additional adjustments for the propensity score (Model 2: HR 0.68; 95% CI, 0.53-0.88) or unbalanced covariates (Model 3 HR: 0.68; 95% CI, 0.52-0.88) did not materially change the hazard ratio for AMI (Table 2.4).

Table 2.4 Multivariable Models of Statin Initiation and Risk of Acute Myocardial Infarction in Propensity-Score Matched RA Patients

Variable	Model 1	Model 2* *(With Propensity Score)*	Model 3 *(With Unbalanced Covariates)*
	Univariate Hazard Ratio (95% CI)	Multivariable Hazard Ratio (95% CI)	Multivariable Hazard Ratio (95% CI)
Statin initiation (y vs n)	0.69 (0.54, 0.90)	0.68 (0.53, 0.88)	0.68 (0.52, 0.88)
Propensity score	--	3.08 (1.74, 5.43)	--
Prior AMI (y vs n)	--	--	1.74 (1.19, 2.54)
Angina (y vs no)	--	--	2.03 (1.54, 2.68)

As a comparison, we analyzed the unmatched cohort and in the unadjusted Cox's model, statin initiators had a 39% (HR, 1.39; 95% CI, 1.16-1.66) higher risk of AMI compared to non-initiators. A multivariable Cox's model adjusting for age, gender, comorbidities, and medication use, resulted in attenuation of the risk, which remained significant (HR, 1.36; 95% CI, 1.18-1.59). Figures 2.2 and 2.3 display cumulative incidence curves for AMI for the unmatched and propensity score matched cohorts, respectively.

When we evaluated alternative greedy matching algorithms, the results did not differ from those with 5-to-1 digit algorithm. Hazard ratios and corresponding 95% CIs for 5→3, 5→2, and 6→1 greedy matching algorithms were 0.71 (95% CI, 0.54-0.93), 0.68 (95% CI, 0.53-0.89), and 0.71 (95% CI, 0.55-0.93), respectively. To estimate the bias that would have occurred if we did not account for unexposed time before statin initiation, we repeated the analyses without this consideration and found a 9% overestimate of the protective effect (HR: 0.60; 95% CI: 0.47-0.77). Table 2.5 summarizes findings in our current study in comparison to previously reported findings in other patient populations based in observational studies and selected landmark RCTs.

Table 2.5 Comparison of Cardioprotective Effect of Statins Across Studies

Study	Patient Population	Design	Effect Estimate for AMI
Current study	RA	Observational	HR: 0.69 (0.54, 0.90)
Seeger et al., 2003	General population	Observational	HR: 0.69 (0.52, 0.93)
Smeeth et al., 2010	General population	Observational	HR: 0.87 (0.77, 0.98)
4S, 1994	CHD	RCT	RR: 0.66 (0.59, 0.75)
WOSCOPS, 1995	Hypercholesterolemia	RCT	RR: 0.69 (0.57, 0.83)
Heart Protection Study, 2002	CHD and Diabetes	RCT	RR: 0.73 (0.67, 0.91)

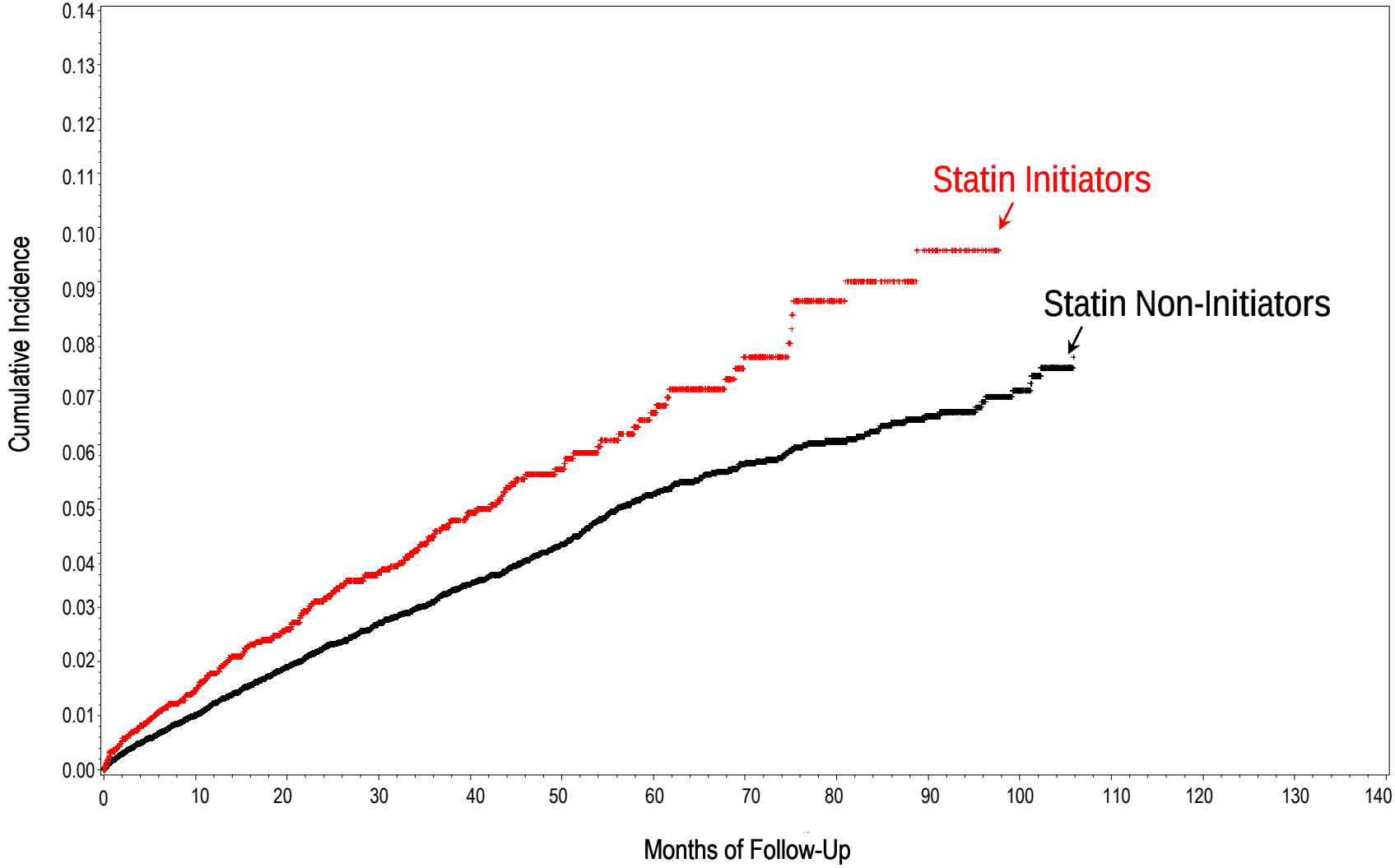


Figure 2.2 Cumulative Incidence Curves for Unmatched Cohort

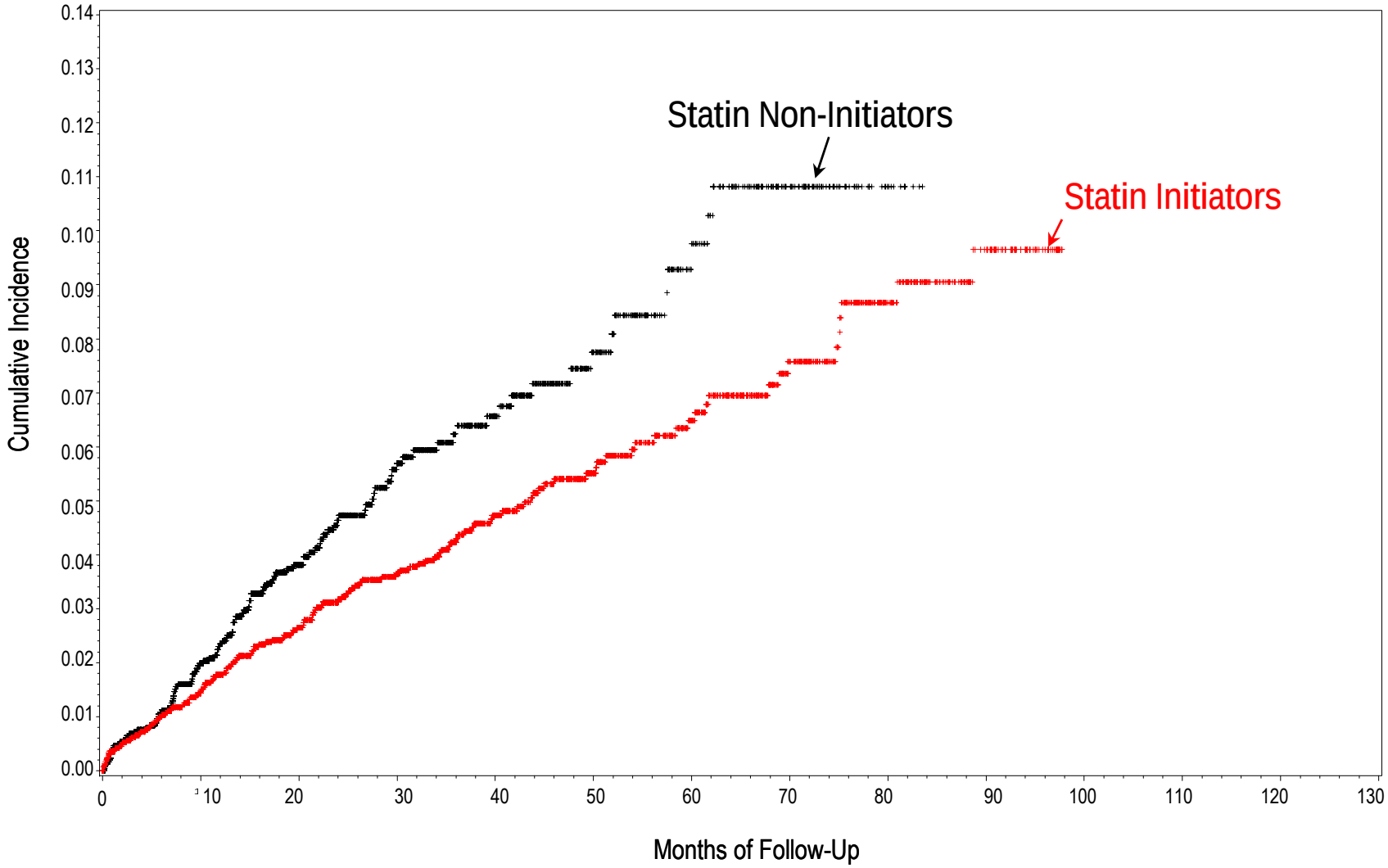


Figure 2.3 Cumulative Incidence Curves for Propensity Score Matched Cohort

2.4 Discussion

The objective of our study was to evaluate the cardioprotective effect of statins in a population-based cohort of patients with RA. Our data indicate that RA patients who initiated statins had higher prevalence of CVD risk factors. After adjusting for this confounding by indication, we found a 31% reduction in AMI risk among statin initiators compared to non-initiators. Our findings of a significant reduction of AMI risk in statin initiators are consistent with cardiovascular benefits of statins reported in RCTs such as the Heart Protection Study (HR 0.73, 95% CI, 0.67-0.79) (14) and the West of Scotland Coronary Prevention Study (HR 0.69, 95% CI, 0.57-0.83) (12); and observational studies based on a US managed care organization (HR 0.69, 95% CI, 0.52-0.93) (40) and the UK THIN database (HR 0.87, 95% CI 0.77-0.98) (16).

The increased CVD morbidity in RA and the contribution of inflammation to this risk has given rise to the considerable interest on the cardioprotective role of statins in RA. The excess CVD burden in RA is well recognized with epidemiologic studies reporting up to a 3-fold increase of AMI among RA patients compared to those without RA (2, 3). The contribution of traditional CVD risk factors such as smoking, body mass index (BMI), hyperlipidemia, to CVD risk in RA remains unclear, with some reports of similar prevalence in RA (43) and others of higher-than-usual prevalence in RA (29). Nonetheless, unexpected behaviours of these traditional risk factors may suggest the existence of a competing mechanism which imparts additional CVD risk in RA patients (23). Along with demonstrated association of inflammatory markers and markers of rheumatoid disease with CVD outcomes, findings altogether suggest the substantial contribution of systemic inflammation and immune dysregulation to CVD risk in RA (23).

To our knowledge, our study represents the first evaluation of the cardioprotective role of statins in RA on a hard clinical outcome. Our findings lend support to prior evidence for beneficial effects of statins on CVD in

RA which have been indirectly drawn from: 1) studies evaluating intermediate correlates of CVD in RA (18-20), 2) secondary findings from studies evaluating RA disease outcomes such as the Trial of Atorvastatin in Rheumatoid Arthritis (TARA) trial (44); and 3) studies evaluating statin effects in other patient populations, such as the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (45). To highlight, statin studies of intermediate CVD outcomes in RA include an open-label study of atorvastatin in 29 RA patients which demonstrated reduction in arterial stiffness, a marker of vascular dysfunction and independent risk factor for CVD (18). Another intermediate CVD outcome evaluated in previous studies of statins in RA is endothelial function; Hermann et al. reported significant improvement after 4 weeks of treatment with simvastatin compared with placebo ($5.5 \pm 0.7\%$ vs. $3.8 \pm 0.4\%$; p-value = 0.02) (19) and Tikiz et al. demonstrated that patients who received statins had significant improvement in endothelial-dependent vasodilation while no change was seen in patients who received ACE inhibitors and placebo (20). Secondary findings from studies evaluating statin effects on RA joint specific outcomes have also been drawn. Most noted is the TARA trial; along with demonstrating that RA disease activity improved significantly in the atorvastatin group compared to placebo group based on co-primary outcomes of Disease Activity Score (DAS28) (difference in DAS28 change, 0.5; p=0.004) and proportion meeting European League Against Arthritis (EULAR) response criteria (31% in atorvastatin-group vs 10% in placebo-group; p=0.006), authors also reported a 50% decline in C-reactive protein (CRP) levels relative to placebo ($p<0.0001$) (44). Finally, rationale for the cardioprotective benefit of statins in RA has also been indirectly drawn from studies in other relevant patient populations. In particular, applicability of findings in the JUPITER trial of individuals with elevated CRP levels to patients with RA has been argued on the basis of RA itself being an additional risk marker for CVD (46).

Indeed, based on their well-established cardiovascular benefits, statins are expected to have at least a similar degree of efficacy on CVD outcomes among RA patients via classic pathways (lipids). However,

given the paradoxical behaviours of CVD risk factors in RA and potential considerable contribution of inflammation of CVD risk, the exact mechanisms of statin effects on CVD risk in RA warrant further investigation. As interest in potential roles of statins in RA continue grow, so do the need for studies evaluating hard CVD outcomes (29). Initiated subsequent to our study, the Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis (TRACE RA) in the UK aims to recruit 4,000 RA patients and randomize them to atorvastatin or placebo (www.dgoh.nhs.uk/home/app/tracera). Pending results from this trial, which are anticipated in 2015 (29), our study provides an interim effect size along with contributing to a better understanding of the cardioprotective role of statins in RA. Use of population-based cohort of RA patients allows for generalizability of our findings, which reflect real-world experiences with statins in RA. Stemming from this, a clinical implication highlighted by results is the importance of monitoring and management of cardiovascular risk factors in RA patients and appropriate initiation of recommended statin therapy (47). Our ability to match a large proportion of statin initiators with non-initiators (88%), may suggest that there are RA patients who may be indicated to receive statins but are not receiving treatment. Thus, a potential problem of under treatment with statins among RA patients warrants further investigation.

Our study has strengths and limitations. Use of an established, population-based cohort of individuals with RA minimizes selection bias and increases the external validity of our findings. However, observational studies using administrative data are vulnerable to diagnostic uncertainty. For example, use of administrative diagnostic codes to define RA may potentially lead to misclassification of diagnosis. However, we used the strictest published case definition for RA, which was validated against self-report of a diagnosis of RA, yielding a positive predictive value of 0.92 (48, 49) and improved specificity with additional exclusions, as described in the Methods. In addition, the estimated prevalence of RA using this algorithm is similar to reported estimates in the literature (32). Furthermore, any misclassification of RA

would have introduced a conservative bias, such that estimates would be closer to the null. AMI outcomes in this study were also assessed using administrative data as privacy protection laws prevent access to medical records to confirm diagnosis. However, previous Canadian validation studies have shown good positive predictive values for AMI (33-35).

Observational studies assessing effects of drug exposure are also susceptible to confounding by indication, whereby patients with clinical CVD risk are more likely to receive statin therapy and may be at a higher risk for AMI. We demonstrated that traditional multivariable Cox's proportional hazards models did not mitigate this confounding by indication. Thus, to control for confounding by indication, we utilized propensity score matching in this study as an attempt to replicate the balance between exposed and non-exposed individuals that is generated with randomization (40). With this approach, matching individuals according to propensity for treatment estimated by a multivariable model removes potential confounding by variables included in the model. However, since this is an observational method of confounder control, variables that are not part of the propensity score model may remain unbalanced between the cohorts, leading to residual confounding (15). For example, lack of information on LDL levels, which has been reported as a strong predictor of statin initiation (15) would subject this study to residual confounding by this variable. However, using fee item codes for lipid-related laboratory examinations in the medical services plan database, we quantified number of lipid tests and its association with statin initiation and similarly demonstrated it as the strongest predictor for statin initiation among the propensity score variables (15, 40). Overall, the large number of predictors in our propensity score model, the high level of discrimination achieved with c-statistic = 0.87, the ability to match 88% of statin initiators to non-initiators, and the balance obtained demonstrate the utility of the database for pharmacoepidemiologic studies using propensity score methods and may suggest that other strong predictors of AMI are unlikely to be independently associated with statin initiation

in our matched cohorts. Moreover, balancing on strong, measured predictors of statin initiation may achieve balance on unmeasured predictors as these variables are likely to be correlated (50).

In conclusion, findings from our population-based, propensity score matched cohort study indicate that RA patients who initiate statins have a 31% lower risk of AMI. These data provide evidence for a postulated cardioprotective role of statins in patients with RA and suggest that effects may be similar to those previously observed in non-RA populations.

2.5 References

1. del Rincon I, Williams K, Stern M, Freeman G, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis & Rheumatism. 2001;44(12):2737-45.
2. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107(9):1303-7.
3. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis & Rheumatism. 2005;52(2):402-11.
4. Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2006;65(12):1608-12.
5. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis & Rheumatism. 2002;46(4):862-73.
6. Avina-Zubieta J, Choi H, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in RA: A systematic review of observational studies. Annals of the Rheumatic Diseases. 2007;66(Supp2):320.
7. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis & Rheumatism. 2008;59(12):1690-7.
8. Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. American Journal of Medicine. 2008;121(10 Suppl 1):S21-31.

9. Vaudo G, Marchesi S, Gerli R, Allegrucci R, Giordano A, Siepi D, et al. Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. Annals of the Rheumatic Diseases. 2004;63(1):31-5.

10. Abeles A, Pillinger M. Statins as antiinflammatory and immunomodulatory agents: A future in rheumatologic therapy? Arthritis & Rheumatism. 2006;54(2):393-407.

11. Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmunity Reviews. 2006;5(5):331.

12. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. New England Journal of Medicine. 1995;333(20):1301-7.

13. 4S Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9.

14. Heart Protection Study Collaborative. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.

15. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. Pharmacoepidemiology & Drug Safety. 2005;14(7):465-76.

16. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. British Journal of Clinical Pharmacology. 2009;67(1):99-109.

17. Paraskevas KI. Statin treatment for rheumatoid arthritis: a promising novel indication. Clinical Rheumatology. 2008;27(3):281-7.

18. Van Doornum S, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2004;63(12):1571.

19. Hermann F, Forster A, Chenevard R, Enseleit F, Hurlimann D, Corti R, et al. Simvastatin improves endothelial function in patients with rheumatoid arthritis. Journal of the American College of Cardiology. 2005;45(3):461-4.

20. Tikiz C, Utuk O, Pirildar T, Bayturan O, Bayindir P, Taneli F, et al. Effects of Angiotensin-converting enzyme inhibition and statin treatment on inflammatory markers and endothelial functions in patients with longterm rheumatoid arthritis. Journal of Rheumatology. 2005;32(11):2095-101.

21. Myasoedeva E, Gabriel S. Cardiovascular disease in rheumatoid arthritis: a step forward. Current Opinion in Rheumatology. 2010;22:342-7.

22. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. American Journal of Medicine. 2008;121(10 Suppl 1):S9-14.

23. Gabriel S. Heart disease and rheumatoid arthritis: Understanding the risks. Annals of the Rheumatic Diseases. 2009;69(Suppl I):i61-i4.

24. Escalante A, Haas RW, del Rincon I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Archives of Internal Medicine. 2005;165(14):1624-9.

25. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis & Rheumatism. 2004;50(11):3450-7.

26. Situnayake RD, Kitas G. Dyslipidemia and rheumatoid arthritis. Annals of the Rheumatic Diseases. 1997;56(6):341-2.

27. Park YB, Lee SK, Lee WK, Suh CH, Lee CW, Lee CH, et al. Lipid profiles in untreated patients with rheumatoid arthritis. Journal of Rheumatology. 1999;26(8):1701-4.

28. Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Annals of the Rheumatic Diseases. 2009;68(4):460-9.

29. Peters MJL, Nurmohamed MT, Kitas GD, Sattar N. Statin treatment of rheumatoid arthritis: comment on the editorial by Ridker and Solomon. Arthritis & Rheumatism. 2010;62(1):302-3.

30. Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: a population study. Arthritis & Rheumatism. 2005;53(2):241-8.

31. Province of British Columbia. The 2006 Census of Canada in BC Stats. Available from: http://www.bcstats.gov.bc.ca/census.asp. [cited 2009 December 21, 2009]

32. Gabriel S, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009;11 Epub 2009 May 19(3):229.

33. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. American Heart Journal. 2002;144(2):290-6.

34. Cox JL, Melady MP, Chen E, Naylor CD. Towards improved coding of acute myocardial infarction in hospital discharge abstracts: a pilot project. Canadian Journal of Cardiology. 1997;13(4):351-8.

35. Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Canadian Journal of Cardiology. 1999;15(11):1277-82.

36. Quan H, Li B, Saunders LD, Parsons GA, Nilsson CI, Alibhai A, et al. Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database. Health Services Research. 2008;43(4):1424-41.

37. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40(5):373.

38. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of Clinical Epidemiology. 1992;45(6):613.

39. Abrahamowicz M, Tamblyn R. Drug Utilization Patterns. Encyclopedia of Biostatistics. John Wiley & Sons; 2005.

40. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. American Journal of Cardiology. 2003;92(12):1447-51.

41. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007;116(8):894-900.

42. Parsons L. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. 26th Annual SAS Users Group International Conference; 2001; Long Beach, CA; 2001.

43. De Pablo P, Dietrich T, Karlson EW. Antioxidants and other novel cardiovascular risk factors in subjects with rheumatoid arthritis in a large population sample. Arthritis & Rheumatism. 2007;57(6):953-62.

44. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015-21.

45. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr., Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine. 2008;359(21):2195-207.

46. Ridker PM, Solomon DH. Should patients with rheumatoid arthritis receive statin therapy? Arthritis & Rheumatism. 2009;60(5):1205-9.

47. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;2010(69):325-31.

48. MacLean C, Louie R, Leake B, McCaffrey D, Paulus D, Brook R, et al. Quality of care for patients with rheumatoid arthritis. Journal of the American Medical Association. 2000;287(8):984-92.

49. MacLean C, Park G, Traina S, Liu H, Hahn B, Paulus H, et al. Positive predictive value (PPV) of an administrative data-based algorithm for the identification of patients with rheumatoid arthritis (RA). Arthritis & Rheumatism. 2001;44:S106.

50. Perkins S, Tu W, Underhill M, Zhou X, Murray M. The use of propensity scores in pharmacoepidemiologic research. Pharmacoepidemiology & Drug Safety. 2000;9:93-101.

CHAPTER 3 [8]
THE IMPACT OF DISCONTINUATION OF STATIN THERAPY ON ADVERSE CARDIOVASCULAR DISEASE AND MORTALITY OUTCOMES: A SYSTEMATIC REVIEW

3.1 Introduction

Statins - hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors – are a class of lipid-lowering agents whose primary physiological function is inhibition of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in the rate-limiting step of cholesterol synthesis (1). The beneficial effects of statins have been well-established in randomized clinical trials such as the West of Scotland Coronary Prevention Study (WOSCOPS), which showed reduction of cardiovascular events and mortality in middle-aged male patients with moderate hyperlipidemia but no history of cardiovascular disease (CVD) (2), the Scandinavian Simvastatin Survival Study, (4S) which showed reduction of mortality outcomes in patients with angina pectoris or previous myocardial infarct (AMI) (3), and the Heart Protection Study, which showed reduction in all cause mortality in patients with coronary heart disease (4).

In recent years, it has emerged that the effectiveness of statins observed in real-world settings is inferior to that seen in randomized controlled trials (RCTs) (5), which has been attributed to poor patient compliance with statin therapy (6). Simply prescribing statins is insufficient; it is important that patients closely follow prescribed treatment regimens to derive expected drug benefits (6). While superficially a simple concept, patient compliance with drug therapy is actually quite complex and encompasses two distinct problems: 1) poor execution of the dosing regimen, such that scheduled doses are delayed or omitted, which may lead to transient interruptions in drug action; and 2) discontinuation of the medication, which may lead to intermittent or permanent loss of drug effects (7). The literature has been plagued with misuse and

[8] A version of this chapter will be submitted for publication. De Vera M, Choi H, Bhole V, Wall-Burns L, Lacaille D. Impact of Statin Compliance on Adverse Cardiovascular Disease and Mortality Outcomes: A Systematic Review.

interchanged use of the terms “compliance”, “adherence”, and “persistence” in describing problems of medication taking (8). Recognizing the need to standardize reporting of terms and concepts, the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group proposed use of the term “adherence” to refer to the act of conforming to the recommendations made by the provider with respect to *timing, dosage, and frequency of medication taking* and the term “persistence” to refer to the act of conforming to a recommendation of continuing treatment for *the prescribed length of time* (8, 9). These terms appropriately capture and distinguish the two identified problems of medication taking. However, we additionally propose use of the term “discontinuation”, as applied throughout this systematic review, rather than persistence, as the latter term implies that the period of use is of interest rather than the problem of stopping therapy.

While both aforementioned problems of medication taking are relevant to statin use, of particular relevance is statin discontinuation, since statin therapy requires lifelong treatment for maintenance of lipid levels (5) and with long-term therapies comes potential for patients to discontinue, particularly when therapeutic effects of drugs are not readily observed, as with statins (10). Over the last decade, numerous studies have quantified the extent of statin discontinuation in real world settings (5, 6, 11-16). Using a variety of data sources including population-based administrative health databases, managed care organizations, and pharmacy network records, studies indicate a high frequency of statin discontinuation, with reported discontinuation rates ranging anywhere from 15% (5) to as high as ≥75% (11), with most reporting discontinuation rates ≥50% (12-16).

Despite numerous reports quantifying the extent of statin discontinuation in different patient populations, reports on associated adverse outcomes have only recently emerged. A comprehensive understanding of

the problem of statin discontinuation involves not only quantifying the extent of the problem but also evaluating its impact on relevant adverse outcomes, given that discontinuation of therapy implies foregone therapeutic drug effects. Relevant questions include: 1) how is statin discontinuation exposure measured; 2) in what patient populations has the impact of statin discontinuation been evaluated; 3) what outcomes are evaluated; and 4) what are reported results of these studies? To address these issues and synthesize current evidence, we conducted a systematic review of observational studies of adverse outcomes associated with discontinuation of statin therapy.

3.2 Methods

3.2.1 Literature Search Strategy

We conducted a mapped search of MEDLINE (1966–March 2010), EMBASE (1980-March 2010), and International Pharmaceutical Abstracts (1970-March 2010) databases to identify observational studies of adverse outcomes associated with statin discontinuation. We used terms that mapped to Medical Subject Headings (MeSH) in combination with keyword terms for concepts that did not map (e.g. "discontinuation," "persistence"). Given the historical interchanged use of terms to describe patient compliance with medication taking, we applied all terms, rather than those that may be regarded as specific to discontinuation to ensure the most comprehensive strategy. Table 3.1 shows the search strategy as applied in all electronic databases (conducted in March 2010). We additionally conducted a hand-search of bibliographies of articles retrieved from the electronic search to identify additional studies.

Table 3.1 MeSH Terms and Keywords Applied in Electronic Search Strategy

Concept	MeSH Terms	Keywords
statins	antilipemic agents, anticholesterolemic agents, hydroxymethylglutaryl-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin	statins
medication-taking problem	health behavior, patient compliance, medication adherence, quality of health care, guideline adherence	patient compliance, compliance, adherence, persistence, discontinuation
cardiovascular diseases	cardiovascular diseases, heart diseases, coronary artery disease, myocardial infarction, vascular diseases	acute myocardial infarction, cardiovascular disease(s)
mortality	mortality, cause of death, fatal outcome, hospital mortality, survival rate, death	mortality, death

3.2.2 Selection of Studies

Titles and abstracts were reviewed for preliminary inclusion of published studies meeting systematic review criteria of: 1) observational study design (e.g., cohort, case-control study); 2) defined patient population; 3) exposure defined as discontinuation of statins (or of a group of medications including statins); 4) defined study outcome (e.g., cardiovascular disease [CVD] or event, CVD mortality, or all-cause mortality) and 5) reporting statin-specific results. Two authors (MD and LB) independently reviewed all titles and abstracts and any discrepancies were discussed and resolved by consensus. After critical review of titles and abstracts, 22 articles were forwarded for full manuscript review.

3.2.3 Data Extraction and Quality Assessment

Descriptive information extracted from studies included: 1) year of publication, 2) country where study was conducted, 3) study design, 4) patient population and sample size, and 5) data source (e.g., administrative

health database, electronic pharmacy record, survey data). Data that were of particular importance to this systematic review were: 6) specific medication compliance problem (discontinuation vs. adherence); 7) description of how exposure (medication compliance) was measured; 8) ascertainment of study outcomes; 9) length of study follow-up; 10) analytic strategies; and 11) measure of association (e.g., odds ratio [OR], relative risk [RR], hazard ratio [HR]) and significance of results (95% confidence intervals [CI], p-values).

We assessed the quality of studies by adapting and applying the checklist developed by ISPOR's Medication Compliance and Persistence Special Interest Group for the assessment and evaluation of medication compliance studies[9] (8). Developed as consensus guidelines to meet the need for improved consistency and quality among an increasing number of studies evaluating problems of medication taking, this checklist establishes standards for data sources, operational definitions, and measurement of medication adherence and/or discontinuation, and reporting of results. We condensed the guidelines into a 20-item checklist that could be scored to evaluate whether quality criteria were met (Appendix C). The checklist was applied to each study reviewed and the number of items that met recommendations was summed to provide an overall quality score out of 20 points. A score of less than 15 points was considered to be low quality. Two authors (MD and VB) independently completed data abstraction and quality assessment. Any discrepancies were discussed and resolved by consensus. Due to the heterogeneity in patient populations and exposure definition of statin discontinuation across included studies, we were not able to conduct a formal meta-analysis; therefore, we provide a qualitative description of studies and reported outcomes.

[9] Adapted checklist as applied in systematic review is presented in Appendix C.

3.3 Results

3.3.1 Literature Search Results

Results of the literature search strategy are described in the flow of studies depicted in Figure 3.1. The electronic search strategy resulted in 1,670 potential articles, of which 1,573 were excluded due to lack of relevance to the systematic review based on title review. Articles forwarded to abstract review included the 97 remaining articles from the electronic strategy and an additional 30 articles identified from a hand search of bibliographies of the former 97 articles. Following abstract reviews, we excluded 105 articles for the following reasons: lack of relevant outcome (23 articles), lack of relevant exposure (19 articles), lack of relevant outcome and exposure (11 articles), incorrect study type (50 articles including 24 reviews, 2 economic analyses, 11 RCTs, and 13 letters/editorials), and no direct assessment of impact of exposure on outcome (2 articles). Of the 22 studies forwarded for full manuscript review and data abstraction, 15 evaluated outcomes associated with statin adherence. Given the emphasis on statin discontinuation in this thesis, adherence studies were further excluded at this stage (6, 17-30).

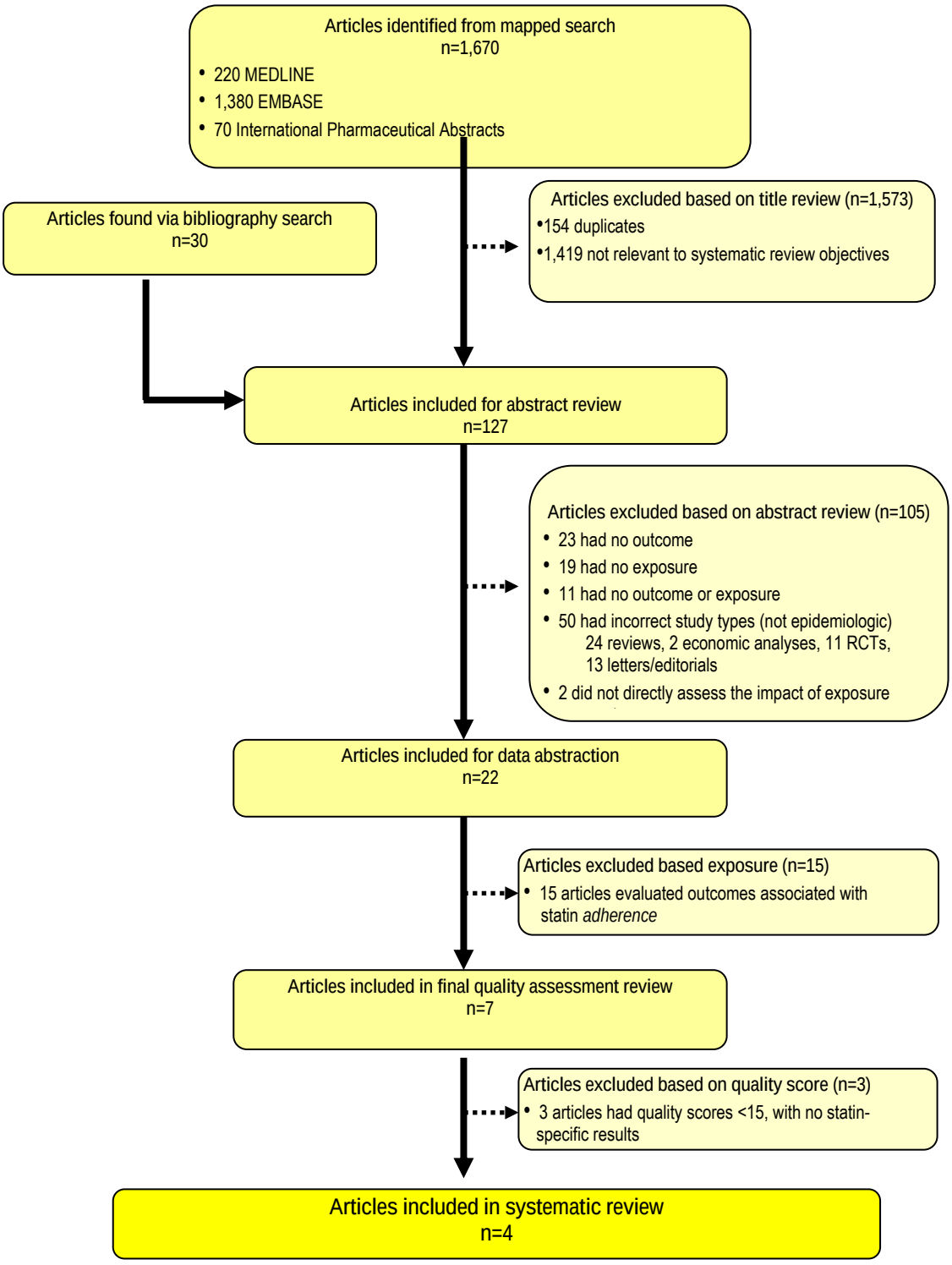


Figure 3.1 Flow Diagram of Selection of Studies

Seven studies met inclusion criteria and were thus forwarded for quality assessment. Characteristics of these studies including author, year of publication, study design, drugs evaluated, and quality assessment scores are summarized in Table 3.2. Of these, 4 studies (study IDs S1, S2, S6 and S7) evaluated discontinuation of a group of medications including statins, but 3 of these did not report statin-specific results (S2, S6, and S7) and were further excluded. Overall, 4 studies met all inclusion criteria and provided statin-specific results and were therefore included in this systematic review.

Table 3.2 Studies Evaluating Outcomes Associated with Discontinuation of Statins

Study ID	Year	Author	Title	Medications	Outcomes	Comments	Quality
S1	2006	Ho (31)	Impact of medication therapy discontinuation on mortality after myocardial infarction	Aspirin β-blockers statins	mortality		16
S2	2006	Newby (32)	Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease	ACE inhibitors aspirin β-blockers lipid-lowering agents	mortality	no statin specific result	11
S3	2007	Colivicchi (33)	Discontinuation of statin therapy and clinical outcome after ischemic stroke	statins Antiplatelet agents ACE inhibitors Calcium channel blockers Angiotensin receptor blockers β-blockers Diuretics	mortality		16
S4	2007	Penning-van Beest (34)	Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study	statins	AMI		17
S5	2008	Daskalopoulou (35)	Discontinuation of statin therapy following an acute myocardial infarction: a population-based study	statins aspirin β-blockers proton-pump inhibitors	mortality		18
S6	2008	Jackevicius (36)	Prevalence, predictors and outcomes of primary nonadherence after acute myocardial infarction	ACE inhibitors antiplatelets β-blockers calcium channel blockers lipid-lowering agents nitrates statins	mortality	no statin specific result	15

Table 3.2 Studies Evaluating Outcomes Associated with Discontinuation of Statins

Study ID	Year	Author	Title	Medications	Outcomes	Comments	Quality
S7	2008	Shaya (37)	Effect of persistence with drug therapy on the risk of myocardial re-infarction	β-blockers calcium channel blockers statins	AMI	no statin specific result	14

Abbreviations: AMI = acute myocardial infarction; ACE = angiotensin converting enzyme

3.3.2 Description of Included Studies

All 4 included studies utilized a cohort study design. These studies evaluated outcomes of statin discontinuation in specific patient populations including post-AMI [S1 and S5] and post-stroke [S3]) patients and in individuals in the general population with and without CVD (S4). Mortality was the predominant outcome evaluated in 3 of the 4 studies and only 1 study evaluated AMI outcomes. When referring to the specific problem of medication taking behaviour evaluated, 3 studies (S1, S3, and S5) correctly used the term 'discontinuation' while 1 study (S4) inappropriately used the term 'adherence.' We summarize below pertinent details from each study, with particular emphasis on measurement of statin discontinuation. Table 3.3 highlights characteristics of included studies and Table 3.4 summarizes approaches used to measure statin discontinuation in each study.

Table 3.3 Characteristics of Included Studies

Study ID	Year	Author	Country	Study Design	Patient Population	Setting	Sample Size	Follow-up (yr)	Outcomes	Adjusted for Covariates	Main Results HR or RR (95% CI)
S1	2006	Ho	USA	Cohort	Post AMI	Hospital (multi-site)	1,521	1	mortality	Yes	HR: 2.86 (1.47-5.55)
S3	2007	Colivicchi	Italy	Cohort	Post CVA	Hospital (single-site)	631	1	mortality	Yes	HR: 2.78 (1.96-3.72)
S4	2007	Penning-van Beest	Netherlands	Cohort	a. General population b. Prior CV event	Population-based	a. 46,332 b. 12,762	Not specified	AMI	Yes	1º RR: 0.70 (0.60, 0.81) 2º RR: 0.70 (0.54, 0.91)
S5	2008	Daskalopoulou	UK	Cohort	Post AMI	Population-based	9,939	1	mortality	Yes	RR: 1.88 (1.13-3.07)

*Abbreviations: * = Referent category is non-compliant group; ** = Referent category is compliant group;*

HR = hazard ratio; RR = relative risk; AMI = acute myocardial infarction

Table 3.4 Definition and Measurement of Statin Discontinuation in Included Studies

Study ID	Year	Author	Incident Statin Users	Definition	Data Source	Details of Assessment	Type of Variable	Variable Categories
S1	2006	Ho	Not specified	Medication therapy discontinuation at 1 month post discharge	Patient self-report of medication use	Patients asked to collect and read all current medications to interviewer. If not reported, then patient classified as discontinuer.	Fixed-in-time	Non-discontinuer *(ref)* Discontinuer
S3	2007	Colivicchi	Not specified	Statin discontinuation at 1, 6, and 12 months after discharge	Patient self-report of medication use	Patients asked to provide all information about their pharmacological treatments. If no statin, then patient classified as discontinuer at that point.	Time-dependent	Non-discontinuer *(ref)* Discontinuer
S4	2007	Penning-van Beest	Yes	Persistence of statin use, defined as continuous statin use in the first 2 years of treatment	Pharmacy records	Number of days of continuous statin use in the first 2 years of treatment were calculated and categorized into three categories.	Fixed-in-time	2 yr continuous 18 mo-2yr continuous <18 mo continuous *(ref)*
S5	2008	Daskalopoulou	No	Statin discontinuation in the first 90 days post-AMI.	Drug prescription data in automated health data	Pattern of statin use before AMI and 90 days after AMI were used to categorize patients.	Fixed-in-time	non-user (no statins before, no statins after AMI) *(ref)* users (statins before AMI, statins after AMI) starters (no statin before AMI, statin after AMI) stoppers (statin before AMI, no statin after AMI)

Using data from Prospective Registry Evaluation Myocardial Infarction: Event and Recovery (PREMIER) from 19 US hospitals, Ho et al. evaluated outcomes of discontinuation of statins, aspirin, and beta-blockers in 1,521 post-AMI patients following hospital discharge (31). Medication discontinuation was defined based on patient reports of medication use during telephone interviews conducted at 1, 6, and 12 months after discharge. However, associations with the primary study outcome of mortality were evaluated based on discontinuation status at the 1-month interview. Cox's proportional hazards models were used to evaluate the associations between discontinuation of each drug and mortality at one year. The study found that statin discontinuation at 1 month was associated with a 2.86-fold increased risk of mortality (hazard ratio [HR]: 2.86; 95% CI: 1.47-5.55). One limitation of this study was the short follow-up period for evaluating mortality outcomes (one year). In addition, the use of a fixed time-point to establish statin discontinuation status may have lead to potential misclassification of exposure because patients deemed as discontinuers at 1 month could potentially go on to fill their prescriptions for the remainder of the follow-up and conversely, patients deemed as continuous users at 1 month could stop taking statins in ensuing months.

Colivicchi et al. assessed the impact of discontinued statin therapy on mortality in patients discharged after an acute ischemic stroke in a single hospital setting in Italy (33). The authors prospectively selected 631 consecutive ischemic stroke survivors without clinical or laboratory evidence of coronary heart disease. All participants were discharged on statin therapy and followed for 1 year after the event. Discontinuation of statins as well as other cardiovascular therapies was assessed by telephone interviews at 1, 6, and 12 months after discharge or through information collected by contacting their primary care physicians. In cases of discontinuation of medication, the date and possible reasons for discontinuation were noted. This was the only study that used a time-dependent explanatory variable in Cox's proportional hazards models to account for changes in statin use status over time during follow-up. However, similar to the US study, study follow-up was limited to one year. The main study finding was that the risk of death was 2.78-fold

higher with statin discontinuation (HR: 2.78; 95% CI, 1.96 to 3.72) after adjustment for potential confounders.

Penning-van Beest et al. used administrative pharmacy records in the Netherlands to evaluate the impact of statin discontinuation on risk of AMI. This population-based study included a large sample size, with a total of 59,094 individuals. Of these, 46,332 without prior cardiovascular event represented a low-risk group in whom statins were prescribed for primary prevention; and 12,762 with prior cardiovascular events (i.e., AMI, CVA, or revascularization procedure) represented a high-risk group in whom statins prescription was for secondary prevention. All individuals in the study were new statin users, with the date of the first statin prescription marking the beginning of follow-up for the study. The definition of statin exposure was based on the number of days of continuous statin use in the first two years of treatment and patients were categorized according to: 1) 2-year continuous user; 2) 18-months continuous user; and 3) statin discontinuation or "non-continuous" user, defined as <18 months of continuous statin use. After defining statin use status over the first 2 years of follow-up, patients were then followed until outcome of interest or end of the study, regardless of any changes in statin use status over the remainder of the follow-up. Cox's proportional hazards models evaluated the protective effect of continuous statin use (compared to non-continuous use) on the risk of AMI. Results showed that continuous statin users had a lower risk of AMI in both the primary (HR, 0.70; 95% CI, 0.60-0.81) and secondary (HR, 0.70; 95% CI, 0.54-0.91) prevention groups. Of the four studies included, this was the only study to evaluate a non-mortality outcome, specifically the risk of AMI.

Daskalopoulou et al. conducted a population-based cohort study to estimate the extent to which different patterns of statin use before and after an index AMI event were associated with subsequent mortality outcomes. Using automated health data from the UK General Practice Research Database (GPRD), the

authors identified 9,939 patients who survived at least 90 days after their first AMI between 2002 and 2004. Patients were classified into four groups based on statin use before the index AMI and during the 90 days following the AMI: (i) non-users (patients never on statins); (ii) users (on statins before and continued statins post-AMI); (iii) starters (no statin before and started statins post-AMI); and (iv) stoppers (on statins before and stopped statins post-AMI). Patients who died in the 90-day window after AMI were excluded from the study as cohort entry (time zero) was 90 days post-AMI. Patients were followed until outcome of interest (mortality) or end of the study (1 year after AMI). It is important to note that authors used "non-users" as the reference group in their analysis, and thus caution should be taken when interpreting findings; that the 88% increased risk of mortality seen in statin stoppers is relative to individuals who did not use statins. Nonetheless, authors did not provide alternative results based on a different reference group, particularly, a more appropriate comparison of discontinuous users versus continuous users, as reported in other included studies.

3.4 Discussion

The objective of this systematic review was to gain a better understanding of the problem of statin discontinuation by synthesizing current evidence from studies that evaluated associated adverse outcomes. All studies reviewed consistently identified an increased risk of adverse AMI or mortality outcomes associated with statin discontinuation, with HRs ranging from 1.43 (95% CI, 1.09-1.85) to 2.86 (95% CI, 1.47-5.55). Other key findings of this systematic review include a paucity of studies on this topic, and a number of methodological limitations to the published studies. Most studies evaluated statin discontinuation at a specified time point, which does not account for common patterns of use in real life, such as discontinuation of statins later or intermittent use where people may temporarily discontinue statins and resume use at a later date. Furthermore, the short follow-up of one year for most studies reviewed is

particularly short for a mortality outcome. Of note, the terms used to describe persistence of statin therapy and definitions used to measure statin continuation/discontinuation were inconsistent across studies. These problems mirror historical inconsistencies in nomenclature and definitions that have plagued the literature on medication compliance.

Although the number of included studies was limited, the main finding consistently emerged that discontinuation of statins was associated with a significantly increased risk of adverse AMI or mortality outcomes. These data expand upon previous reports of a high rate of medication discontinuation among statin users (5, 6, 11-16, 38), by drawing the link between this exposure and important adverse outcomes. By lending to better understanding of the problem of statin discontinuation, findings of this systematic review have important implications for both people taking statins and health care providers prescribing them, and emphasize the importance of monitoring compliance with therapy after prescribing statins.

Issues relating to study design, particularly measurement of statin discontinuation, was perhaps the most important concern identified in this systematic review. One of the challenges in evaluating outcomes associated with statin discontinuation in a prospective cohort study is that subjects must first be followed for sufficient time to allow discontinuation, and then be followed for sufficient time to develop the outcome of interest. An additional complexity is that use may vary over time, with people potentially stopping therapy after the time when discontinuation was measured or people intermittently discontinuing statins and resuming them at later time. Therefore, use of a fixed time point to define statin discontinuation, as done in most of the reviewed studies, may potentially lead to inaccurate associations between true exposure status and outcome (35). For example, Ho et al. (S1) defined statin discontinuation exposure based on patient self-reports of medication use 1 month after hospital discharge. It is possible that the 'discontinuous' subjects may have filled their statin prescription after 1 month and remained continuous users for the

duration of follow-up, or conversely the subjects who were designated as continuous users at 1 month subsequently discontinued. Penning-van Beest et al. (S4) used a similar approach of defining statin discontinuation exposure over a fixed-period. However, the authors' use of a 2-year period to define discontinuation may have been less problematic, as stabilization of drug use patterns may have occurred during this time.

Another problem with use of a fixed time point to define statin discontinuation is potential lack of temporal link between exposure and outcome. Such a scenario would be a subject who experiences an adverse event, such as death, and thus, stop filling drug prescriptions. Without appropriate ascertainment of exposure time, then this subject may be classified as having discontinued statins, which is then associated with the adverse outcome. This would potentially result in biased risk estimates away from the null.

While methods for measuring discontinuation have been proposed, including the estimated level of persistence with therapy (ELPT) method which applies a 90 day grace periods between fills for defining discontinuation status (39), they are perhaps of greater utility when medication discontinuation is the outcome of interest, and not the exposure. In studies that quantify discontinuation as the outcome of interest, it is possible to apply different permissible gaps or grace periods before defining discontinuation with subsequent sensitivity analyses permitting evaluation of robustness of findings. In contrast, when discontinuation is the exposure of interest, a preferable methodologic solution for measuring statin discontinuation that would allow capture of real-life patterns of drug use would be to model statin discontinuation as a time-dependent variable. Of the 4 studies reviewed, only Colivicchi et al. (S3) modelled statin discontinuation as a time-dependent variable in their analyses. By modelling 'actual' statin discontinuation exposure over the entire duration of follow-up and efficiently using exposed and non-

exposed times for all subjects, time-dependent approaches provide the ability to capture real-life situations and their effects.

Another issue identified in this systematic review was the short follow-up periods in studies included. In fact, 3 of the 4 studies (S1, S3, and S5) only followed subjects up to 1 year. One study (S4) did not report median or mean follow-up periods, but given that statin discontinuation exposure was defined for each subject during the first 2 years of treatment and data covered a period over 13 years (1991-2004), this study likely had sufficiently long follow-up. Length of follow-up is particularly relevant when evaluating outcome of statin discontinuation because of issues of biologic plausibility and temporality. There must be sufficient elapsed time from statin discontinuation until changes in lipid levels can lead to atherosclerosis plaque and to thrombotic events. While data availability may explain this limitation, sufficiently long follow-up to permit discontinuation and outcomes to occur is recommended in the design of future studies. It is important to note that results of this review reflect the short-term risk associated with early statin discontinuation (within the first year post-event or post-initiation of statins).

As studies were identified for review, we noted the interchangeable and sometimes inappropriate use of terms used to describe medication compliance. Three of the four articles that met systematic review inclusion criteria appropriately used the term 'discontinuation' in their study tiles while one used the term 'nonadherence' despite the fact it was actually looking at drug discontinuation. Of the 3 other studies reviewed that were not included in the systematic review, 2 studies also used the term 'adherence' when referring to drug discontinuation. We further reviewed the nomenclature of the 17 studies that were excluded because they evaluated adherence instead of discontinuation, to determine whether the converse problem exists, that is, where the terms 'discontinuation' or 'persistence' are used to refer to 'adherence'. This problem was not generally found, although one study inappropriately used the term 'continuation' yet

evaluated adherence (30). Overall, these problems highlight the importance of applying a comprehensive search strategy in systematic reviews, as these articles may not have been found had our search strategy not accounted for potential nomenclature errors. This also further emphasizes the importance of using standard terminology in future studies evaluating medication compliance.

Strengths and limitations of our systematic review deserve comment. To our knowledge, this is the first systematic review evaluating the impact of statin discontinuation on adverse outcomes. While a previous review article on implications of statin discontinuation has been published, the authors did not employ a systematic approach to identifying all relevant articles and limited their discussion to select studies published in 2008-2009 (40). Furthermore, the scope of the review differed slightly from ours, in that the authors included studies evaluating statin adherence as well as persistence, thus failing to distinguish between the two aspects of medication-taking behaviour. By specifically focusing on the problem of statin discontinuation and following rigorous systematic review methods, our systematic review has identified gaps in knowledge and provides recommendations for future studies as described above. However, our systematic review has some limitations. The total number of published studies is small, the sample size of many of the studies included were relatively small, the outcomes evaluated varied across studies, and selection of the studies for inclusion is limited by publication bias, leading to the potential exclusion of relevant studies that may have been conducted but never published. Though our quality assessment tool has not been externally validated and the cut-off for good quality study was chosen arbitrarily, it was based on the guidelines suggested by the ISPOR checklist. Furthermore, no studies were excluded purely on the basis of a poor quality score.

Overall, despite numerous reports quantifying the magnitude of statin discontinuation, the number of studies evaluating associated adverse outcomes, as identified in this systematic review, is limited. Studies

included in this review consistently identified an increased risk of adverse outcomes, defined as AMI or mortality, associated with statin discontinuation. Findings from our systematic review suggest that future studies of adverse outcomes of statin discontinuation need to model statin discontinuation in a way that captures real-life patterns of use, must include longer follow-ups, and should use terminology that is consistent with recommendations (8). Despite the limitations observed in the studies reviewed, results consistently identify an increased risk of adverse outcomes associated with statin discontinuation. These findings have important implications for both people taking statins and health care providers prescribing them, and emphasize the importance of monitoring persistence with therapy after prescribing statins.

3.5 References

1. Statins The HMG CoA Reductase Inhibitors in Perspective. London: Martin Dunitz Ltd; 2000.
2. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. New England Journal of Medicine. 1995;333(20):1301-7.
3. 4S Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9.
4. Heart Protection Study Collaborative. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.
5. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? New England Journal of Medicine. 1995;332(17):1125-31.
6. Howell N, Trotter R, Mottram D, Rowe P. Compliance with statins in primary care. Pharmaceutical Journal. 2004;272:23-6.
7. Strom B, Kimmel S. Textbook of Pharmacoepidemiology. West Sussex: John Wiley & Sons, Ltd; 2006.
8. International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Special Interest Group. Medication Compliance and Persistence: Terminology and Definitions; 2003.
9. Cramer JA, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: Predictors and outcomes. Value in Health. 2003;6(5):566-73.

10. Tsoneva J, Shaw J. Understanding patients' beliefs and goals in medicine-taking. Professional Nurse. 2004;19(8):466-8.

11. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clinical Therapeutics. 2008;30(11):2167-79.

12. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Medical Journal of Australia. 1996;164(4):208-11.

13. Ellis JJ, Erickson S, Stevenson J, Bernstein S, Stiles R, Fendrick M. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. Journal of General Internal Medicine. 2004;19:638-45.

14. Deambrosis P, Saramin C, Terrazzani G, Scaldaferri L, Debetto P, Giusti P, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. European Journal of Clinical Pharmacology. 2007;63(2):197-203.

15. Foody JM, Joyce AT, Rudolph AE, Liu LZ, Benner JS. Persistence of atorvastatin and simvastatin among patients with and without prior cardiovascular diseases: a US managed care study. Current Medical Research & Opinion. 2008;24(7):1987-2000.

16. Vinker S, Shani M, Baevsky T, Elhayany A. Adherence with statins over 8 years in a usual care setting. American Journal of Managed Care. 2008;14(6):388-92.

17. Blackburn DF, Dobson RT, Blackburn JL, Wilson TW. Cardiovascular morbidity associated with nonadherence to statin therapy. Pharmacotherapy. 2005;25(8):1035-43.

18. Bouchard MH, Dragomir A, Blais L, Berard A, Pilon D, Perreault S. Impact of adherence to statins on coronary artery disease in primary prevention. British Journal of Clinical Pharmacology. 2007;63(6):698-708.

19. Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovascular Disorders. 2006;6:48-56.

20. Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Archives of Internal Medicine. 2006;166:1836-41.

21. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. Journal of the American Medical Association. 2007;297(2):177-86.

22. Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. American Heart Journal. 2008;155(4):772-9.

23. Perreault S, Dragomir A, Blais L, Berard A, Lalonde L, White M. Impact of adherence to statins on chronic heart failure in primary prevention. British Journal of Clinical Pharmacology. 2008;66:706-16.

24. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. British Journal of Clinical Pharmacology. 2008;66(1):110-6.

25. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. Heart. 2008;88(3):229-33.

26. Amin AP, Mukhopadhyay E, Nathan S, Napan S, Kelly RF. Association of medical noncompliance and long-term adverse outcomes, after myocardial infarction in a minority and uninsured

population. Translational Research: The Journal Of Laboratory & Clinical Medicine. 2009;154(2):78-89.

27. McGinnis BD, Olson KL, Delate TM, Stolcpart RS. Statin adherence and mortality in patients enrolled in a secondary prevention program. American Journal of Managed Care. 2009;15(10):689-95.

28. Perreault S, Dragomir A, Blais L, Berard A, Lalonde L, White M, et al. Impact of better adherence to statin agents in the primary prevention of coronary artery disease. European Journal of Clinical Pharmacology. 2009;65(10):1013-24.

29. Perreault S, Ellia L, Dragomir A, Cote R, Blais L, Berard A, et al. Effect of statin adherence on cerebrovascular disease in primary prevention. American Journal of Medicine. 2009;122:647-55.

30. Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD. Continuation of statin treatment and all-cause mortality: a population-based cohort study. Archives of Internal Medicine. 2009;169(3):260-8.

31. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Archives of Internal Medicine. 2006;166(17):1842-7.

32. Newby LK, Allen LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006;113(2):203-12.

33. Colivicchi F, Bassi A, Santini M, Caltagirone C. Discontinuation of statin therapy and clinical outcome after ischemic stroke. Stroke. 2007;38:2652-2657.

34. Penning-van Beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. European Heart Journal. 2007;28(2):154-9.

35. Daskalopoulou S, Delaney J, Filion K, Brophy J, Mayo N, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: A population-based study. European Heart Journal (advance access). 2008.

36. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008;117(8):1028-36.

37. Shaya FT, Gu A, Yan X. Effect of persistence with drug therapy on the risk of myocardial re-infarction. P & T. 2008;33(5):288-90.

38. Hahn BH, Grossman J, Ansell BJ, Skaggs BJ, McMahon M. Altered lipoprotein metabolism in chronic inflammatory states: Proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis. Arthritis Research and Therapy. 2008;10(4)(213).

39. Dezii CM. Persistence with drug therapy: a practical approach using administrative claims data. Managed Care. 2001;10(2):42-5.

40. Daskalopoulou S. When statin therapy stops: Implications for the patient. Current Opinion in Cardiology. 2009;24:454-60.

CHAPTER 4[10]
STATIN DISCONTINUATION AND RISK OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS: A POPULATION-BASED COHORT STUDY

4.1 Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory arthritis associated with systemic inflammation. Cardiovascular disease (CVD) is a significant co-morbidity, with studies reporting that individuals with RA have up to a three-fold increased risk for CVD, independent of traditional risk factors (1-3). Aside from causing significant morbidity, CVD is also the leading cause of premature mortality in RA (4). A recent meta-analysis demonstrated that the risk of CVD death among RA patients is 50% higher compared to age- and gender-matched individuals in the general population (5, 6).

Given its burden on morbidity and mortality, care for CVD is important in RA management. Clinical practice guidelines for CVD management in RA recommend regular assessment of traditional risk factors along with consideration of excess RA-associated risk (7, 8). Where an elevated risk is identified, treatment is indicated and the lipid lowering agents, statins (hydroxymethyl glutaryl-coenzyme A reductase inhibitors) are the recommended first-line therapy (7, 8). However, deriving therapeutic effect from medication depends not only on physicians prescribing treatment but also on patients following the prescribed treatment regimen reasonably closely, or in other words, being compliant with therapy (9). This is of particular concern with treatment for chronic conditions, such as statins, as it has been estimated that up to 30-40% of patients generally do not fill repeat prescriptions (10).

[10] A version of this chapter has been submitted for publication. De Vera M, Choi H, Abrahamowicz M, Kopec J, Goycochea Robles M, Lacaille D. Statin Discontinuation and Risk of Acute Myocardial Infarction in Patients with Rheumatoid Arthritis – A Population-based Cohort Study.

Indeed, reported discontinuation rates for statins which range from 15% (11) to ≥75% (12) with most reports ≥50% (13-17), indicate the magnitude of the problem in real-world patient populations. Statin discontinuation was recently shown to be considerable problem in RA by colleagues who used a population-based cohort of RA patients and reported that over 8-year mean follow-up, 38% of patients permanently discontinued therapy (18). Of equal importance to quantifying the problem of statin discontinuation is evaluating its impact on adverse outcomes. Previous studies among non-RA populations have shown that statin discontinuation has an influence on patient outcomes including increased risk of new and recurrent cardiovascular events (19). However, the impact of discontinuation of statin therapy among individuals with RA, a patient population with increased CVD risk, is not known. To address this issue, we evaluated the impact of statin discontinuation on the risk of acute myocardial infarction (AMI) in population-based cohort of patients with RA.

4.2 Methods

4.2.1 Data Source and Study Population

We used data from a previously established population-based RA cohort in the Canadian province of British Columbia (BC) (20). Specifically, administrative billing data for the reimbursement of physician visits from the BC Ministry of Health were used to identify adult (≥18 years) individuals with RA who received care for RA between January 1996 and March 2006. The case definition for RA was the same as previously published for this cohort (20); specifically, individuals met inclusion criteria if they had at least 2 physician visits more than 2 months apart with an RA diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9], 714.x). The following exclusion criteria were applied to improve specificity of the case definition: i) at least 2 visits subsequent to the second RA visit with diagnoses of

other inflammatory arthritides (systemic lupus erythematosus, other connective tissue diseases, psoriatic arthritis, ankylosing spondylitis, and other spondylarthritides); ii) if an RA diagnosis coded by a non-rheumatologist was not confirmed on a subsequent rheumatologist visit; or iii) if a subject had no subsequent RA-coded physician visits over a follow-up period of 5 years or more. Complete follow-up for the cohort was available up to March 2006. Overall, this RA cohort included 37,151 individuals, yielding a prevalence rate of 0.96%, based on the number of alive prevalent cases in 2006 (n=29,417) and 2006 census data from Statistics Canada (21). This is consistent with previously reported prevalence estimates for RA (22).

From this population-based cohort of individuals with RA, we defined a cohort of incident statin users[11] by selecting individuals who had ≥1 statin prescriptions between May 1996 and December 2003, and no prior statin prescription since January 1996 (earliest date of available prescription data) (N=4,102). The rationale for excluding individuals with a statin prescription in the first four months of prescription records was that they may have started statin therapy prior to January 1996 and therefore, would not be considered incident users.

For each RA case, administrative data for all provincially funded health services used since 1990 were obtained, including physician visits and hospitalizations. We also obtained complete information on all prescription medications dispensed by pharmacists from January 1996 onwards, as well as mortality and cause of death information from vital statistics data in the Canadian Mortality Database (23). No personal identifying information was available on any individual and data access procedures complied with BC's Freedom of Information and Privacy Protection Act. The University of British Columbia Behavioural Research Ethics Board granted ethical approval for this study.

[11] Subject flow for RA incident statin users cohort is presented in Appendix D Figure D1.1

4.2.2 Exposure Assessment

Using data on prescription dispensing date and number of days supplied, we established the statin therapy course for each subject over the entire follow-up in terms of monthly statin use. Our primary exposure was statin discontinuation, defined as at least 3 consecutive months of non-statin use, at any time during follow-up[12]. While potential contributions of lipid lowering and anti-inflammatory properties of statins to targeting CVD risk in RA remain unclear (24), we conservatively applied a rationale for the study definition of statin discontinuation based on their demonstrated lipid lowering effects. Studies have shown that it takes 2 weeks from therapy initiation for lipid lowering effects to occur and 4 to 6 weeks to achieve maximum effect (25). A similar latency likely applies to the potential impact of statin discontinuation on AMI risk; in addition, this impact may be further delayed until changes in lipid levels would lead to atherosclerotic plaque formation and thrombotic events. Therefore, we required at least 3 months of consecutive non-statin use prior to considering statin status as "discontinued." Switches from one type of statin to another were not considered as discontinuation of therapy. Statin discontinuation was evaluated over the entire follow-up and analyzed as a *monthly-updated, time-dependent variable*. If a subject filled a statin prescription after a period of discontinuation, then months for which the prescription was dispensed were classified as statin-use until discontinuation criteria were again fulfilled. Thus, our definition for statin discontinuation captured both intermittent discontinuation and permanent discontinuation of therapy.

4.2.3 Outcome Assessment

The primary outcome for this study was the first AMI event during follow-up. Outcomes included both non-fatal and fatal AMI events. Non-fatal AMI events were ascertained using ICD-9 codes for AMI (410.x) in

[12] Illustration of study definition for statin discontinuation presented in Appendix D Figure D1.2

hospital separations data, which included up to 10 diagnoses representing either the reason for admission or complications during hospitalization. The accuracy of ICD-9 codes for AMI are well-established in Canadian validation studies of administrative hospital discharge records, with reported positive predictive values (PPV) ranging from 89% to 96% (26-28). Fatal AMI included both AMI deaths occurring outside of hospitals based on ICD-10 codes for AMI (I21) as the cause of death in Vital Statistics death data and deaths resulting from hospitalized AMI. The validity of ICD-10 AMI codes have also been previously demonstrated, with PPV of 93.5% (29). To avoid double-counting, deaths occurring within one month of a hospitalized AMI were considered as fatal AMI events. The event date was the date of hospital admission for non-fatal AMIs and date recorded on the death certificate for fatal AMIs.

4.2.4 Assessment of Covariates

Factors known to influence statin discontinuation and/or cardiovascular risk that were available in our data were considered as potential covariates in multivariable regression models. Variables influencing statin discontinuation were selected based on colleagues' prior study of predictors of statin discontinuation in this study population (30). Fixed-in-time binary variables measured over a period of 1 year preceding the start of follow-up evaluated chronic co-morbid medical conditions and were based on physician visits (ICD-9 codes) or medication use. These included diabetes (use of insulin or oral hypoglycemic agents), angina (411.x, 413.x or use of nitrates), use of cardiac medications - grouped as anti-hypertension medications (angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blocking agents, angiotensin II receptor antagonists, alpha-adrenergic blocking agents, or central alpha-agonists), congestive heart failure medications (cardiac glycosides or diuretics), and anti-arrhythmia medications (adenosine, amiodarone, disopyramide, flecainide, lidocaine, mexitelene, procainamide, propafenone, digoxin, or quinidine), as well as use of other medications known to influence AMI risk, namely hormone replacement therapy and

anticoagulants. For each subject, we calculated a modified Charlson Comorbidity Score over the 1-year period preceding the beginning of follow-up using a version adapted for administrative data (31, 32). Finally, we also considered any prior AMI and cerebrovascular accident (CVA) (434.x, 436.x) event at any time between 1990 and beginning of follow-up.

The following variables, evaluated over study follow-up, were considered as proxy indicators of RA severity: disease modifying anti-rheumatic drug (DMARD) use, rate of RA-related physician visits, and any orthopedic procedure. DMARD use over the follow-up was categorized as an ordinal variable, corresponding to increasing RA severity: no DMARD use (group 1); anti-malarial drugs or sulfasalazine (group 2); methotrexate or intramuscular gold (group 3); leflunomide, cyclosporin-A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil (group 4); and biologics (group 5). These categories were mutually exclusive and we used the highest rank ever attained during the follow-up. We quantified the rate of RA-related physician visits (to family physicians and rheumatologists) as a time-dependent covariate representing the cumulative rate of visits for each patient since RA onset, updated monthly. Finally, we determined use of RA medications that could influence AMI risk, including glucocorticosteroids, traditional non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (Cox-2) inhibitors, and methotrexate, as monthly updated, time-dependent covariates.

4.2.5 Statistical Analysis

The timing of the first statin prescription relative to RA diagnosis was used to assign the index date, the date at which an individual was considered 'at risk' and follow-up for study outcome began. Specifically, the index date for individuals whose first statin prescription was dispensed on or after RA diagnosis was the date of the first statin prescription; whereas the index date for individuals whose first statin was dispensed

before RA diagnosis was the date of RA diagnosis. The rationale for applying different index dates was that, in order to assess the impact of statin discontinuation in RA, individuals were considered eligible only after they had met both criteria of i) being diagnosed with RA and ii) initiating statin therapy.

For all individuals in the cohort, person-time of follow-up was computed from the index date to the first AMI event, last health care service use, death, or end of study period (March 31, 2006), whichever came first. To estimate the effect of statin discontinuation on AMI risk, we used Cox's proportional hazards models with delayed entry and time-varying covariates (33, 34). Since both the probability of statin discontinuation and its impact on AMI risk may depend on the time since initiation of statin therapy, we ensured that individual subjects' AMI risks were compared at the same time since therapy initiation. This implied using time since statin therapy initiation as the time axis so that the time origin corresponded to the date of the first statin prescription. However, as stated above, follow-up for the study outcome started only at the index date, when an individual subject met both criteria for study entry (i.e., RA diagnosis and statin initiation). This implied delayed entry for subjects who initiated statin therapy before their RA diagnosis. Since these subjects met our inclusion criteria only after they were diagnosed with RA, they were not considered 'at risk' for the study outcome in the elapsed time between their first statin prescription and their RA diagnosis at follow-up. If these subjects entered the study at the time of their first statin prescription, the results would be affected by survival bias, also known as immortal time bias (35).

We modelled statin discontinuation, the exposure variable of primary interest, as a binary time-dependent covariate, updated monthly. Accordingly, the hazard ratio (HR) represented the independent risk of AMI associated with statin discontinuation in the current month. All multivariable Cox's models were adjusted for age at index date and sex. Fixed-in-time variables representing RA duration at index date (months), statin duration at index date (months), and a binary indicator of whether subjects initiated statin therapy

before RA diagnosis (yes/no) were forced in the final multivariable model. All other aforementioned time-fixed and time-varying covariates were initially considered as candidates for inclusion in multivariable regression models. A forward selection procedure, with $p<0.05$ criterion for entry, was employed to select covariates with statistically significant independent associations with AMI outcome into the final model.

We considered the possibility that a longer time since statin discontinuation may be associated with increased cardiovascular risk. Therefore, we repeated the analyses to model statin discontinuation as a continuous time-dependent variable that increased with every month since discontinuation, thus representing time since discontinuation. To assess whether timing of first statin prescription relative to RA diagnosis modified the risk of AMI, we added the interaction term between discontinuation status and the indicator variable representing timing of first statin prescription (before vs after RA diagnosis), and tested its statistical significance in the multivariable model. Similarly, we tested potential interactions between discontinuation and i) prior AMI status (no vs yes), ii) sex (women vs men), and iii) age group (<65 years vs ≥65 years). Finally, we conducted sensitivity analyses of our definition of statin discontinuation by repeating the analyses on varying durations of consecutive non statin-use (1 month, 2 months) required prior to defining the subject as having discontinued statin therapy and evaluated impact on our results. All hypotheses were tested using 2-tailed Wald's tests at the 0.05 significance level and the strength of the exposure effects were estimated using adjusted HRs with 95% confidence intervals (CIs). Analyses were performed using SAS (Version 9.1, SAS Institute, Cary, North Carolina).

4.3 Results

Our cohort included 4,102 individuals with RA who were incident statin users, contributing 15,669 person-years of follow-up between May 1996 and March 2006. Subject characteristics are summarized in Table 4.1. Women comprised 60% of the cohort and at index date, mean age was 66.6 ± 10.4 years.

Table 4.1 Characteristics of the RA Cohort of Incident Statin Users (N = 4,102)

Characteristic	
Demographics	
Age (years), *mean (SD)*	66.6 (10.4)
Women	2,460 (60)
RA Characteristics	
RA duration at index date (months), *mean (SD)*	19.0 (25.5)
Rate of RA-related medical visits (visits/person yr follow-up), *mean (SD)*	2.5 (6.7)
RA-related orthopedic procedure (over follow-up)	621 (15.1)
Use of RA prescription medications (over follow-up)	
Traditional non-steroidal anti-inflammatory drugs	2,364 (57.6)
Cox-2 inhibitors	1,347 (32.8)
Glucocorticosteroids	1,723 (42.0)
Disease modifying anti-rheumatic drug categories*	
Group 1	2,500 (60.9)
Group 2	489 (11.9)
Group 3	818 (19.9)
Group 4	171 (4.2)
Group 5	124 (3.0)
Co-morbid Medical Conditions	
Prior acute myocardial infarction§	441 (10.8)
Prior cerebrovascular accident§	117 (2.9)
Use of anti hypertension medication†	2,528 (61.6)
Use of congestive heart failure medication†	1,344 (32.8)
Angina†	903 (22.0)
Diabetes†	730 (17.8)
Use of anti arrhythmia medication†	94 (2.3)
Charlson Comorbidity Score†, *mean (SD)*	1.0 (1.3

Table 4.1 Characteristics of the RA Cohort of Incident Statin Users (N = 4,102)[13]

Characteristic (continued)	
Other Medications Affecting Cardiovascular Risk	
Use of hormone replacement therapy†	506 (12.3)
Use of anticoagulants†	266 (6.5)

Values represent the number (percentage) of cases unless otherwise indicated;

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; SD: Standard deviation;

**DMARD categories: 1 – no DMARD use; 2 – anti-malarial drugs, sulfasalazine; 3 – methotrexate, intramuscular gold; 4 - leflunomide, cyclosporin-A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil; 5 – biologics;*

§ Evaluated prior to start of follow-up (index date) since 1990 (earliest available data);

†Evaluated over 1 year preceding start of follow-up (index date);

***Anti hypertension medications included: angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blocking agents, angiotensin II receptor antagonists, alpha-adrenergic blocking agents, or central alpha-agonists;*

****Congestive heart failure medications included cardiac glycosides or diuretics;*

*****Anti arrhythmia medications included: adenosine, amiodarone, disopyramide, flecainide, lidocaine, mexitelene, procainamide, propafenone, digoxin, or quinidine.*

[13] Characteristics of the RA cohort of incident statin users according to whether individuals met study definition of statin discontinuation at least once over follow-up is shown in Appendix D TableD1.1.

Table 4.2 Frequency of Statin Prescriptions Among RA Cohort of Incident Statin Users

Type of Statin	% of RA Patients with Prescription
Atorvastatin	47.9
Simvastatin	21.9
Pravastatin	12.2
Lovastatin	5.1
Rosuvastatin	4.9
Cerivastatin	4.7
Fluvastatin	3.3

Over mean 4 years follow-up (median 3.5 years), we identified 264 AMI outcomes; 196 (74%) were first AMI events and 68 (26%) were new events that occurred in patients with a history of AMI prior to their index date. Incidence rates of AMI were 1.7 and 4.7 per 100 person-years in individuals without and with a prior AMI, respectively.

When we modelled statin discontinuation as a categorical time-dependent variable, univariate Cox's regression analysis showed that statin discontinuation was associated with an almost 50% increased risk of AMI (unadjusted HR: 1.46; 95% CI: 1.09-1.95)[14]. After adjusting for covariates included in the final multivariable Cox's model, shown in Table 4.3, the statistical association remained highly significant (adjusted HR: 1.67; 95% CI: 1.24-2.26, $p<0.001$). Other significant predictors of increased AMI risk included older age, male sex, history of prior AMI, presence of diabetes, use of anti-hypertension or congestive heart failure medications, as well as current glucocorticosteroid use, and cumulative rate of RA visits measured as time-dependent covariates (Table 4.3).

[14] Univariate hazard ratios for risk of AMI for all considered covariates are presented in Appendix D, Table D1.2

Table 4.3 Final Multivariable Model for Statin Discontinuation and Risk of AMI, with Statin Discontinuation Modelled as a Categorical, Time-Dependent Variable

	Multivariable Hazard Ratio (95% CI)
Primary Exposure (Time-Dependent)	
Statin Discontinuation *(yes vs no)*	1.67 (1.24, 2.25)
Fixed-in-Time Covariates	
Age	1.06 (1.04, 1.07)
Sex *(men vs women)*	1.68 (1.31, 2.17)
Initiation of first statin before RA† *(yes vs no)*	1.27 (0.81, 2.00)
RA duration at index date†	1.00 (0.99, 1.01)
Statin duration at index date†	0.99 (0.98, 1.00)
Prior AMI *(yes vs no)*	2.16 (1.59, 2.93)
Diabetes *(yes vs no)*	1.50 (1.11, 2.06)
Use of anti-hypertension medication *(yes vs no)*	1.42 (1.03, 1.95)
Use of congestive heart failure medication *(yes vs no)*	1.56 (1.20, 2.04)
RA-related orthopaedic procedure *(yes vs no)*	0.57 (0.39, 0.83)
Time-Dependent Covariates	
Current use of glucocorticosteroid *(yes vs no)*	1.61 (1.21, 2.16)
Cumulative rate of RA medical visits	1.45 (1.02, 2.06)

†Variables forced into final multivariable model.

When we modelled statin discontinuation as a continuous time-dependent variable, the value of which increased with each additional month since discontinuation, we found similar, statistically significant associations in both univariate and multivariable Cox's models. Specifically, with each additional month of statin therapy discontinuation, the risk of AMI increased by about 2% (crude HR: 1.017; 95% CI: 1.008-1.026 and adjusted HR: 1.020; 95% CI: 1.011-1.029). Table 4.4 shows the final multivariable model for statin discontinuation and risk of AMI, when statin discontinuation was modelled as a continuous time-

dependent variable. Associations between other covariates and AMI risk were similar in multivariable models whether statin discontinuation was modelled as a categorical variable (Table 4.3) or as a continuous variable (Table 4.4).

Table 4.4 Final Multivariable Model for Statin Discontinuation and Risk of AMI, with Statin Discontinuation Modelled as a Continuous, Time-Dependent Variable

	Multivariable Hazard Ratio (95% CI)
Primary Exposure (Continuous Time-Dependent)	
Statin Discontinuation	1.02 (1.01, 1.03)
Fixed-in-Time Covariates	
Age	1.05 (1.04, 1.07)
Sex *(men vs women)*	1.69 (1.31, 2.18)
Initiation of first statin before RA† *(yes vs no)*	1.24 (0.79, 1.95)
RA duration at index date†	1.00 (0.99, 1.00)
Statin duration at index date†	0.99 (0.98, 1.00)
Prior AMI *(yes vs no)*	2.18 (1.61, 2.97)
Diabetes *(yes vs no)*	1.52 (1.12, 2.06)
Use of anti-hypertension medication *(yes vs no)*	1.43 (1.04, 1.96)
Use of congestive heart failure medication *(yes vs no)*	1.58 (1.21, 2.05)
RA-related orthopaedic procedure *(yes vs no)*	0.57 (0.39, 0.83)
Time-Dependent Covariates	
Current use of glucocorticosteroid *(yes vs no)*	1.62 (1.21, 2.17)
Cumulative rate of RA medical visits	1.45 (1.02, 2.05)

†Variables forced into final multivariable model.

In subgroup analyses, we found that the impact of statin discontinuation did not depend on the timing of first statin use (before vs after RA diagnosis), prior AMI status, sex, or age, as none of the corresponding interactions approached statistical significance (p-values for interactions: >0.17) (Table 4.5).

Table 4.5 Multivariable Hazard Ratios (95% CIs) of AMI Associated with Statin Discontinuation Stratified by Initiation of First Statin Before RA, Prior AMI, Sex, and Age Group

	No. of AMI (in each stratum)	Hazard Ratio (95% CI)	p-value for interaction*
Initiation of First Statin Before RA			
Yes	78	2.13 (1.29, 3.52)	0.18
No	186	1.53 (1.06, 2.21)	
Prior AMI			
Yes	68	1.55 (1.07, 3.36)	0.37
No	196	1.61 (1.16, 2.22)	
Sex			
Men	136	1.79 (1.16, 2.77)	0.68
Women	128	1.51 (1.01, 2.28)	
Age Group			
<65 years	62	2.19 (1.20, 3.99)	0.40
≥65 years	202	1.48 (1.05, 2.09)	

**P-value for the 2-tailed Wald test of the interaction between a given stratification variable (shown in the 1st column) and statin discontinuation*

Finally, in sensitivity analyses of our statin discontinuation definition, we found that the association between statin discontinuation and AMI remained statistically significant regardless of whether statin discontinuation was defined as requiring 1 or 2 months of persistent non-use. Specifically, adjusted HRs ranged from 1.47 (95% CI: 1.10-1.97) for 1 month to 1.62 (95% CI: 1.21-2.17) for 2 months, and all 95% confidence intervals excluded 1.0.

4.4 Discussion

In this population-based study of a Canadian cohort of individuals with RA prescribed with statins, we found a significant negative impact of discontinuation of statin therapy on the risk of AMI. Specifically, our findings indicate a 67% increased risk of AMI associated with discontinuation of statin therapy. Each additional month since statin discontinuation, the risk of AMI is increased by about 2%. This increased risk is independent of age, sex, proxy indicators of RA severity, prior MI, cardiovascular risk factors, and use of RA medications. Moreover, findings persisted across different subgroups evaluated based on sex, age group, prior AMI status, and timing of first statin use. Overall, these results emphasize the need to raise awareness, among physicians and patients with RA, about the importance of compliance with statin therapy in RA.

Evaluating adverse outcomes associated with statin discontinuation is particularly relevant in individuals with RA, given the established risk and burden of CVD in this population. Both the Nurses' Health Study (adjusted relative risk [RR] 2.00; 95% CI: 1.23-3.29) (2) and the Rochester Epidemiology Project (adjusted HR, 2.13; 95% CI: 1.13-4.03) (3) found a two-fold increase in AMI in individuals with RA compared to individuals without RA. More recently, the Cardiovascular Research and Rheumatoid Arthritis study confirmed the two-fold higher risk of CVD in RA compared to the general population (36). Given the recent emphasis on the management of cardiovascular risk factors in RA, as outlined in recent guidelines (7), our findings have implications for the care of people with RA. Not only is it important to assess and establish CVD risk among patients and to initiate statins when appropriate (37) but it is also essential to monitor and ensure compliance with the prescribed treatment regimen. Overall, findings of our study provide physicians and individuals with RA relevant and specific information on the risks associated with statin discontinuation.

Although compliance with medications has not been well studied in RA and other chronic rheumatic conditions (38), existing data in the literature suggest that non-compliance with medication may be a substantial problem, particularly in RA. An earlier review estimated that at least 50% of patients with RA are non-compliant with RA therapy irrespective of the intervention (39). Previous studies involving therapies for RA reported compliance rates ranging anywhere from 30% with NSAIDs, prednisone, and DMARDs (40) based on self-reports to 64% with methotrexate based on pharmacy records (41). Using the same population-based RA cohort, colleagues found an overall permanent discontinuation rate of statin therapy of 38% (18). They also identified factors associated with reduced risk of statin discontinuation including older age, history of AMI or CVA, diabetes, and anti-hypertension medication use (30). Other studies have also shown the association between presence of CVD risk factors and better statin compliance (42, 43).

To our knowledge, this is the first study to evaluate the impact of statin discontinuation on cardiovascular outcomes among individuals with RA. Our results corroborate findings in the growing literature on morbidity and mortality outcomes associated with statin discontinuation in other populations. Penning-van Beest et al. used administrative data in the Netherlands to evaluate the impact of statin discontinuation within the first 2 years of follow-up on the risk of AMI among individuals with no prior CVD (low risk) and prior CVD (high risk) (19). Authors reported a reduction in AMI risk among individuals who continuously used statins in the first 2 years of treatment compared to those who discontinued therapy in both low risk (RR: 0.70; 95% CI: 0.60-0.81) and high risk groups (RR: 0.70; 95% CI: 0.54-0.91) (19). A multi-centre cohort study of post-AMI patients in the US showed that statin discontinuation was associated with increased risk of 1-year all-cause mortality (HR: 2.86; 95% CI: 1.47-5.55) (44). A similar association between statin discontinuation and risk of 1-year all cause mortality (HR:1.88; 95% CI: 1.13-3.07) was also shown in post-AMI patients using the UK General Research Practice Database (45). These studies evaluated statin discontinuation at a fixed

time point and both the US (44) and UK (45) studies had follow-up periods of only 1 year. In contrast, our study evaluated impact of statin discontinuation on AMI outcomes up to 10 years of follow-up (mean, 4 years). Furthermore, application of time-dependent modelling techniques allowed us to capture the effects of both intermittent and permanent discontinuation, thereby reflecting more accurately real world patterns of statin use.

A number of postulated mechanisms may explain the association between statin discontinuation and AMI risk observed in this study. Aside from the loss of cholesterol lowering effect of statins, potential biological mechanisms based on statin anti-inflammatory effects may also play a role. For example, discontinuation may lead to loss of statin anti-rheumatic effects shown in a randomized trial of RA patients (46). Statin discontinuation studies have demonstrated deterioration of endothelial function (47, 48) and increased levels of C-reactive protein to pre-treatment levels (49). Finally, associations observed in this study could also be potentially explained by a behavioral or 'healthy adherer' effect, whereby individuals who are more compliant (less likely to discontinue therapy) are those who exhibit healthier behaviors. Indeed observations that good compliance with drug therapy and placebo are similarly associated with mortality may suggest that compliance to any therapy may be a surrogate marker for overall healthy behaviour (50). However, there is also contrasting evidence to the 'healthy adherer' effect. A study evaluating the association between adherence to statin, aspirin, or both and CVD showed that in subjects taking both drugs, adherence to statins but not aspirin was associated with lower risk of CVD recurrence (RR 0.64; 95% CI: 0.49-0.82) but the same was not observed with adherence to aspirin but not statins (RR 0.91; 95% CI: 0.72-1.15) (51). Based on these findings, authors suggested that poor health behaviour may not adequately explain of adverse outcomes in poorly adherent patients and that unfavourable outcomes are more likely to be driven by foregone drug benefits resulting from discontinuation of use (51). When we

evaluated the impact of aspirin discontinuation in our cohort, we found a similar lack of association with AMI outcomes.

Study strengths and limitations deserve comment. The universal nature of the Canadian health care system has provided a population-based cohort of individuals with RA, free of selection bias, thus increasing external validity of our findings. However, observational studies using administrative data are vulnerable to diagnostic uncertainty. Specifically, because we used administrative diagnostic codes to define RA, some misclassification of diagnosis likely occurred. However, inclusion of non-RA cases would likely bias results towards the null, given the increased risk of AMI in RA. Furthermore, we used the strictest published case definition for RA, which was validated against self-report of a diagnosis of RA, yielding a positive predictive value of 0.92 (52, 53) and improved specificity with additional exclusions, as described in the Methods. As demonstrated in a simulation study, high specificity of the diagnostic criteria minimizes the risk of biases that might occur if the association of interest and/or the risk vary depending on the subjects true diagnostic status (54). While the use of administrative pharmacy records and registries have been well established in pharmacoepidemiologic studies (55) and our data has the advantage of including all medications dispensed to the entire RA population in BC, data are limited to prescriptions dispensed and we did not have information on whether pills were actually taken or reasons for statin discontinuation. For example, patients may discontinue due to unfavourable side effects, which may have an impact on patients' willingness to continue with therapy (56). Finally, although we adjusted for all known risk factors for discontinuation (exposure) and AMI (outcome) available in our data, unmeasured or unknown confounders including lifestyle factors for AMI could still affect results.

In conclusion, our population-based data indicate that patients with RA who discontinue statin therapy have a 67% increased risk of AMI. Given the established risk and burden of cardiovascular disease in RA, these

findings emphasize the need to raise awareness, among health professionals and people with RA, of the importance of compliance with statin therapy.

4.5 References

1. del Rincon I, Williams K, Stern M, Freeman G, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis & Rheumatism. 2001;44(12):2737-45.
2. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107(9):1303-7.
3. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis & Rheumatism. 2005;52(2):402-11.
4. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis & Rheumatism. 2002;46(4):862-73.
5. Avina-Zubieta J, Choi H, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in RA: A systematic review of observational studies. Annals of the Rheumatic Diseases. 2007;66(Supp2):320.
6. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis & Rheumatism. 2008;59(12):1690-7.
7. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;2010(69):325-31.

8. Pham T, Gossec L, Constantin A, Pavy S, Bruckert E, Cantagrel A, et al. Cardiovascular risk and rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. Joint Bone Spine. 2006;73(4):379-87.

9. Osterberg L, Blaschke T. Adherence to medication. New England Journal of Medicine. 2005;353(5):487-97.

10. Tsoneva J, Shaw J. Understanding patients' beliefs and goals in medicine-taking. Professional Nurse. 2004;19(8):466-8.

11. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? New England Journal of Medicine. 1995;332(17):1125-31.

12. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clinical Therapeutics. 2008;30(11):2167-79.

13. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Medical Journal of Australia. 1996;164(4):208-11.

14. Ellis JJ, Erickson S, Stevenson J, Bernstein S, Stiles R, Fendrick M. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. Journal of General Internal Medicine. 2004;19:638-45.

15. Deambrosis P, Saramin C, Terrazzani G, Scaldaferri L, Debetto P, Giusti P, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. European Journal of Clinical Pharmacology. 2007;63(2):197-203.

16. Foody JM, Joyce AT, Rudolph AE, Liu LZ, Benner JS. Persistence of atorvastatin and simvastatin among patients with and without prior cardiovascular diseases: a US managed care study. Current Medical Research & Opinion. 2008;24(7):1987-2000.

17. Vinker S, Shani M, Baevsky T, Elhayany A. Adherence with statins over 8 years in a usual care setting. American Journal of Managed Care. 2008;14(6):388-92.

18. Goycochea-Robles M, Rahman MM, Choi H, Esdaile JM, Lacaille D. Compliance with statin therapy in rheumatoid arthritis in patients. Arthritis & Rheumatism. 2008;59(9):S877.

19. Penning-van Beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. European Heart Journal. 2007;28(2):154-9.

20. Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: a population study. Arthritis & Rheumatism. 2005;53(2):241-8.

21. Province of British Columbia. The 2006 Census of Canada in BC Stats. Available from: http://www.bcstats.gov.bc.ca/census.asp [cited 2009 December 21, 2009].

22. Gabriel S, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009;11 Epub 2009 May 19(3):229.

23. Schnatter R, Acquavella J, Thompson F. An analysis of death ascertainment and follow-up through Canada's mortality database system. Canadian Journal of Public Health. 1990;81:60-5.

24. Peters MJL, Nurmohamed MT, Kitas GD, Sattar N. Statin treatment of rheumatoid arthritis: comment on the editorial by Ridker and Solomon. Arthritis & Rheumatism. 2010;62(1):302-3.

25. Chong PH, Seeger JD, Franklin C. Clinically relevant differences between the statins: implications for therapeutic selection. American Journal of Medicine. 2001;111(5):390-400.

26. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. American Heart Journal. 2002;144(2):290-6.

27. Cox JL, Melady MP, Chen E, Naylor CD. Towards improved coding of acute myocardial infarction in hospital discharge abstracts: a pilot project. Canadian Journal of Cardiology. 1997;13(4):351-8.

28. Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Canadian Journal of Cardiology. 1999;15(11):1277-82.

29. Quan H, Li B, Saunders LD, Parsons GA, Nilsson CI, Alibhai A, et al. Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database. Health Services Research. 2008;43(4):1424-41.

30. Goycochea-Robles M, Rahman MM, Choi H, Esdaile JM, Lacaille D. Compliance with statin therapy and predictors of compliance in rheumatoid arthritis (RA). Journal of Rheumatology. 2009;36:2575.

31. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40(5):373.

32. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of Clinical Epidemiology. 1992;45(6):613.

33. Allison P. Survival Analysis Using the SAS System: A Practical Guide. Cary, NC, USA: SAS Institute Inc; 1995.

34. Abrahamowicz M, Tamblyn R. Drug Utilization Patterns. Encyclopedia of Biostatistics. John Wiley & Sons, 2005.

35. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. American Journal of Epidemiology. 2005;162(10):1016-23.

36. Peters MJ, Van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF, et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease: A prospective study. Arthritis & Rheumatism. 2009;61(11):1571-9.

37. Toms TE, Panoulas VF, Douglas KMJ, Griffiths H, Sattar N, Smith JP, et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? Annals of the Rheumatic Diseases. 2010;69(4):683-8.

38. Harrold LR, Andrade SE. Medication adherence of patients with selected rheumatic conditions: a systematic review of the literature. Seminars in Arthritis & Rheumatism. 2009;38(5):396-402.

39. Feinberg J. The effect of patient-practitioner interaction on compliance: a review of the literature and application in rheumatoid arthritis. Patient Education & Counseling. 1988;11(3):171-87.

40. Tuncay R, Eksioglu E, Cakir B, Gurcay E, Cakci A. Factors affecting drug treatment compliance in patients with rheumatoid arthritis. Rheumatology International. 2007;27(8):743-6.

41. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. American Journal of Managed Care. 2003;9(6 Suppl):S136-43.

42. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. Heart. 2002;88(3):229-33.

43. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, et al. Persistence of use of lipid-lowering medications: a cross-national study. Journal of the American Medical Association. 1998;279(18):1458-62.

44. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Archives of Internal Medicine. 2006;166(17):1842-7.

45. Daskalopoulou S, Delaney J, Filion K, Brophy J, Mayo N, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: A population-based study. European Heart Journal (advance access). 2008.

46. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015-21.

47. Taneva E, Borucki K, Wiens L, Makarova R, Schmidt-Lucke C, Luley C, et al. Early effects on endothelial function of atorvastatin 40 mg twice daily and its withdrawal. American Journal of Cardiology. 2006;97(7):1002-6.

48. Westphal S, Abletshauser C, Luley C. Fluvastatin treatment and withdrawal: effects on endothelial function. Angiology. 2008;59(5):613-8.

49. Lee KT, Lai WT, Chu CS, Tsai LY, Yen HW, Voon WC, et al. Effect of withdrawal of statin on C-reactive protein. Cardiology. 2004;102(3):166-70.

50. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. British Medical Journal. 2006;333(7557):15.

51. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. British Journal of Clinical Pharmacology. 2008;66(1):110-6.

52. MacLean C, Louie R, Leake B, McCaffrey D, Paulus D, Brook R, et al. Quality of care for patients with rheumatoid arthritis. Journal of the American Medical Association. 2000;287(8):984-92.

53. MacLean C, Park G, Traina S, Liu H, Hahn B, Paulus H, et al. Positive predictive value (PPV) of an administrative data-based algorithm for the identification of patients with rheumatoid arthritis (RA). Arthritis & Rheumatism. 2001;44:S106.

54. Abrahamowicz M, Xiao Y, Ionescu-Ittu R, Lacaille D. Simulations showed that validation of database-derived diagnostic criteria based on a small subsample reduced bias. Journal of Clinical Epidemiology. 2007;60(6):600-9.

55. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. Nature Clinical Practice Rheumatology. 2007;3(12):725-32.

56. Daskalopoulou S. When statin therapy stops: Implications for the patient. Current Opinion in Cardiology. 2009;24:454-60.

CHAPTER 5[15]
IMPACT OF STATIN DISCONTINUATION ON MORTALITY IN PATIENTS WITH RHEUMATOID ARTHRITIS: A POPULATION-BASED STUDY

5.1 Introduction

Affecting approximately 1% of the population (1), rheumatoid arthritis (RA) is a chronic, inflammatory arthritis associated with increased mortality, with death rates in RA 1.5-fold higher than in the general population (2). Cardiovascular disease (CVD) is the leading cause of mortality in RA (3). A recent meta-analysis demonstrated a 50% increased risk of CVD death in RA patients compared to individuals in the general population (4).

Considering its impact on RA mortality, care for CVD is important in management of RA patients (5, 6). Statins (hydroxyl-methyl-glutaryl-coenzyme A reductase inhibitors) are recommended therapy for management of hypercholesterolemia and ischemic heart disease in RA (5, 6). However, simply prescribing statins is insufficient; it is important that patients closely follow prescribed treatment regimens to derive expected drug benefits (7). Since statin therapy represents 'chronic' or long-term treatment (8) in which therapeutic effects are not readily observed (9), discontinuation is of particular concern (9). This is supported by numerous reports of statin discontinuation rates of ≥50% in studies in the general population (10-14). Using an established population-based RA cohort, colleagues reported that over 8-year mean follow-up, 38% of RA patients discontinued statins permanently (15). Applying time-dependent approaches that accounted for both intermittent and permanent statin discontinuation, we subsequently showed that discontinuation of statins at any time during the course of therapy was associated with a 67% increased risk for acute myocardial infarction (AMI) (16), corroborating previous reports of the negative CVD impact of

[15] A version of this chapter has been submitted for publication. De Vera M, Choi H, Abrahamowicz M, Kopec J, Lacaille D. Impact of Statin Discontinuation on Mortality in Patients with Rheumatoid Arthritis – A Population-Based Study

statin discontinuation among non-RA populations (17). Since statin discontinuation has also been shown to have a negative impact on mortality outcomes (18-20), we extended our investigation to evaluate the impact of statin discontinuation on the risk of mortality using the same population-based cohort of RA patients.

5.2 Methods

5.2.1 Data Source and Study Population

We used data from a previously established population-based RA cohort (N=37,151) in the Canadian province of British Columbia (BC) (21). Administrative data for the reimbursement of physician visits from the BC Ministry of Health were used to identify adult (≥18 years) individuals with RA who received care for their RA between January 1996 and March 2006. The case definition for RA was the same as previously published for this cohort (16, 21); inclusion criteria were at least 2 physician visits >2 months apart with an RA diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9], 714) and exclusion criteria were at least 2 visits subsequent to the second RA visit with diagnoses of other inflammatory arthritides, an RA diagnosis by a non-rheumatologist that was not confirmed on subsequent rheumatologist visit, or no subsequent RA-coded physician visits over a period of ≥5 years. Using the number of alive prevalent cases in our cohort in 2006 (n=29,417) and census data from Statistics Canada (22), we estimated a prevalence rate of 0.96% for BC, consistent with reported prevalence estimates for RA (1).

From this population-based cohort of RA patients, we identified a cohort of incident statin users defined as those who had ≥1 statin prescriptions between May 1996 and December 2003, and no prior statin prescriptions since January 1996 (earliest date of available prescription data). The purpose of excluding

individuals with a statin prescription in the first four months of prescription records was to ensure incident statin use (16).

For each cohort member, information on all provincially funded health services used including physician visits and hospitalizations since 1990, as well as all prescriptions dispensed regardless of source of funding since 1996 was obtained. As well, information on mortality, including date and primary cause of death, was obtained from vital statistics data in the Canadian Mortality Database (23). No personal identifying information was available on any individual and data access procedures complied with BC's Freedom of Information and Privacy Protection Act. The University of British Columbia Behavioural Research Ethics Board granted ethical approval for this study.

5.2.2 Exposure Assessment

Similar to our study of statin discontinuation and AMI risk (16), we established the statin therapy course for each subject over the entire follow-up in terms of monthly statin use. Our primary exposure was statin discontinuation, defined as at least 3 consecutive months of non-statin use, which takes into account a potential biological effect of statin discontinuation on mortality risk, namely a delayed effect until changes in lipid levels would lead to increased atherosclerosis and to thrombotic events that mediate mortality risk (16). This definition also avoids classifying periods of low adherence or transient interruptions as therapy discontinuation. Switches between different types of statins were not considered as discontinuation. Months with resumed statin prescriptions after a period of discontinuation were classified as "statin-use" until discontinuation criteria were again met, thereby allowing capture of both intermittent and permanent discontinuation of therapy.

5.2.3 Outcome Assessment

Death outcomes for this study was mortality ascertained using vital statistics data in the Canadian Mortality Database; vital status ascertainment through this database is 97.6% complete for deaths in Canada (23). The primary study outcome was deaths due to all CVD and the secondary outcome was deaths due to all causes. Similar to a Canadian study of national trends in CVD mortality using vital statistics data (24), we ascertained deaths due to all CVD using International Classification of Diseases (ICD-10) 10th Revision codes (I00-I99) in the primary cause of death data by including codes for ischemic heart disease and other heart diseases, cerebrovascular disease, hypertension, diseases of arteries and veins, and other diseases of the circulatory system.

5.2.4 Assessment of Covariates

Factors known to influence statin discontinuation in our cohort (25), CVD, or mortality, were considered as potential covariates in multivariable regression models. Fixed-in-time binary variables measured over a period of 1 year preceding the start of follow-up evaluated the presence of chronic co-morbid conditions and were based on diagnostic codes for physician visits (ICD-9 codes) or medication use. These included: i) diabetes (use of insulin or oral hypoglycemic agents) (16); ii) angina (ICD-9 411, 413 or use of nitrates) (16); iii) chronic obstructive pulmonary disease (ICD-9 490-496, 505-506) (26); iv) gastrointestinal (GI) diseases including gastric/gastrojejunal ulcer, duodenal ulcer, peptic ulcer, and GI hemorrhage (ICD-9 531-534, 578) (27); and v) renal disease (ICD-9 403.11, 403.91, 404.12, 585-586) (26); vi) anti-hypertension medications; vii) congestive heart failure medications; and viii) anti-arrhythmia medications. We considered other medications known to influence risk of CVD, namely hormone replacement therapy and anticoagulants, and calculated a modified Charlson Comorbidity Index over the 1-year period preceding the

start of study follow-up using a version adapted for administrative data (28, 29). We also evaluated occurrences of the following disease events at any time from 1990 to index date: AMI (ICD-9 410), cerebrovascular accident (CVA) (ICD-9 434, 436), malignancy (30), and infection requiring hospitalization as defined in a previous publication using this cohort (31).

The following variables, evaluated over study follow-up, were considered as proxy indicators of RA severity: disease modifying anti-rheumatic drug (DMARD) use, rate of RA-related physician visits, and having received any orthopedic procedure for RA. DMARD use over the follow-up was categorized to reflect increasing RA severity: no DMARD use (group 1); anti-malarial drugs or sulfasalazine (group 2); methotrexate or intramuscular gold (group 3); leflunomide, cyclosporin-A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil (group 4); and biologics (group 5). These categories were mutually exclusive and we used the highest rank ever attained during the follow-up. We quantified rate of RA-related physician visits as a cumulative rate of visits since RA onset, updated monthly. Finally, we determined use of RA medications that could influence mortality risk, including glucocorticosteroids, traditional non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (Cox-2) inhibitors, and methotrexate, as monthly updated, time-dependent covariates.

5.2.5 Statistical Analysis

In order to assess the impact of statin discontinuation on mortality in RA, individuals were considered 'at risk' only after they had met both criteria of i) being diagnosed with RA and ii) initiating statin therapy (16) and thus, we set the index date for individuals whose first statin prescription was dispensed on or after RA diagnosis as the date of the first statin prescription and for individuals whose first statin was dispensed before RA diagnosis as the date of RA diagnosis. We computed person-time of follow-up from the index

date to death outcome, last health care service, or end of study period (March 31, 2006), whichever came first.

To estimate the effect of statin discontinuation on mortality risk, we used Cox's proportional hazards models with delayed entry (32, 33). Since both probability of statin discontinuation and its impact on mortality may depend on the time since statin initiation, we ensured that subjects' mortality risks were compared at the same time. Thus we used time since statin initiation as the time axis, with the origin (time zero) corresponding to the date of the first statin prescription. However, since follow-up for the study outcome started at the index date, subjects who initiated statin therapy before RA diagnosis had delayed entry into the risk set. Specifically, since these subjects met our inclusion criteria only after they were diagnosed with RA, they were not considered 'at risk' for the study outcome until their RA diagnosis. Had subjects entered the study at the time of their first statin prescription, results could be affected by survival bias (34).

Statin discontinuation, the exposure of primary interest, was modelled as a binary time-dependent variable, updated monthly. Accordingly, the hazard ratio (HR) represented the independent risk of mortality associated with statin discontinuation in the current month. All multivariable Cox's models were adjusted for age at index date and sex. Fixed-in-time variables representing RA duration at index date (months), statin duration at index date (months), and a binary indicator of whether subjects initiated statin therapy before RA diagnosis (yes/no) were forced into final multivariable models. Established risk factors for mortality in RA (e.g., prior AMI, malignancy) were forced into final multivariable models and for putative risk factors, a forward selection procedure, with $p \leq 0.20$ criterion for entry, was employed.

We repeated the analyses to model statin discontinuation as a continuous time-dependent variable that increased with every month since discontinuation to account for the possibility that a longer time since statin discontinuation may be associated with increased mortality risk. We tested potential interactions of statin discontinuation with timing of first statin prescription (before/after RA diagnosis), sex (women/men), and age (<65/≥65 years) with likelihood ratio tests. Finally, we conducted sensitivity analyses of our definition of statin discontinuation by evaluating the impact of varying the duration of persistent non statin-use (1 month, 2 months) required prior to declaring an individual as having discontinued statin therapy. All hypotheses were tested using 2-tailed Wald's tests at the 0.05 significance level and analyses were performed using SAS (Version 9.1, SAS Institute, Cary, North Carolina).

5.3 Results

Our cohort included 4,102 individuals with RA who were incident statin users, contributing 16,144 person-years of follow-up between May 1996 and March 2006. Subject characteristics are summarized in Table 5.1. Women comprised 60% of the cohort and at index date, mean age was 66.6 ± 10.4 years.

Table 5.1 Characteristics of RA Incident Statin Users Cohort (N = 4,102)

Characteristic	
Demographics	
Age (years), *mean (SD)*	66.6 (10.4)
No. of women	2,460 (60)
RA Characteristics	
RA duration at index date (months), *mean (SD)*	19.0 (25.5)
Rate of RA-related medical visits/person yr follow-up, *mean (SD)*	2.8 (4.3)
RA-related orthopedic procedure (over follow-up)	636 (15.5)
Use of RA prescription medications (over study follow-up)	
Traditional non-steroidal anti-inflammatory drugs	2,364 (57.6)
Glucocorticosteroids	1,723 (42.0)
Cox-2 inhibitors	1,347 (32.8)
Methotrexate	959 (23.4)
Disease modifying anti-rheumatic drug categories*	
Group 1	2,481 (56.8)
Group 2	492 (13.3)
Group 3	825 (21.9)
Group 4	172 (4.9)
Group 5	132 (3.1)
Co-morbid Medical Conditions	
Prior malignancy§	884 (21.6)
Prior acute myocardial infarction§	441 (10.8)
Prior infection requiring hospitalization§	347 (8.5)
Prior cerebrovascular accident§	117 (2.9)
Use of anti hypertension medication†	2,528 (61.6)
Use of congestive heart failure medication†	1,344 (32.8)
Angina†	903 (22.0)
Diabetes†	730 (17.8)
Chronic obstructive pulmonary disease†	508 (12.4)

Table 5.1 Characteristics of RA Incident Statin Users Cohort (N = 4,102)[16]

Characteristic (continued)	
Gastrointestinal disease†	148 (3.6)
Use of anti arrhythmia medication†	94 (2.3)
Renal disease†	83 (2.0)
Charlson Comorbidity Score†, *mean (SD)*	1.0 ± 1.3
Other Medications Affecting Cardiovascular Risk	
Use of hormone replacement therapy†	506 (12.3)
Use of anticoagulant†	266 (6.5)

Values represent the number (percentage) of cases unless otherwise indicated;

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; SD: Standard deviation;

**DMARD categories: 1 – no DMARD use; 2 – anti-malarial drugs, sulfasalazine; 3 – methotrexate, intramuscular gold; 4 - leflunomide, cyclosporin-A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil; 5 – biologics;*

§ Evaluated prior to start of follow-up (index date) since 1990 (earliest available data);

†Evaluated over 1 year preceding start of follow-up (index date);

***Anti hypertension medications included: angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blocking agents, angiotensin II receptor antagonists, alpha-adrenergic blocking agents, or central alpha-agonists;*

****Congestive heart failure medications included cardiac glycosides or diuretics;*

*****Anti arrhythmia medications included: adenosine, amiodarone, disopyramide, flecainide, lidocaine, mexitelene, procainamide, propafenone, digoxin, or quinidine.*

The frequency of statin prescriptions at initiation of statin therapy according to each different type for the cohort are shown in Table 5.2. Overall, atorvastatin was the most commonly prescribed type of statin in 47.9% of patients in the cohort. This is followed by simvastatin with 21.9%, and then pravastatin with

[16] Characteristics of the RA cohort of incident statin users according to whether individuals met study definition of statin discontinuation at least once over follow-up is shown in Appendix E TableE1.2.

12.2% of patients in the cohort prescribed respective drugs. Overall, 1,862 (45.4%) individuals in the cohort met the study definition for statin discontinuation at least once during study follow-up.

Table 5.2 Frequency of Statin Prescriptions

Type of Statin	% of RA Patients with Prescription
Atorvastatin	47.9
Simvastatin	21.9
Pravastatin	12.2
Lovastatin	5.1
Rosuvastatin	4.9
Cerivastatin	4.7
Fluvastatin	3.3

Over mean 4 years follow-up (median 3.6 years), we documented 467 deaths overall (2.9 per 100 PY), with 198 deaths due to CVD (1.2 per 100 PY). In univariate Cox's regression analysis, statin discontinuation was associated with a 41% increased risk of CVD mortality (unadjusted HR 1.41; 95% CI 1.02-1.96) (Table 5.3). Significant univariate predictors of CVD mortality included older age, male sex, prior AMI, diabetes, infection requiring hospitalization, as well as higher Charlson comorbidity score, use of anti-hypertension and congestive heart failure medications, and time-dependent indicators of current use of glucocorticosteroids and methotrexate. After adjusting for covariates included in the final multivariable Cox's model, shown in Table 5.3, statin discontinuation was associated with a 60% increased risk in CVD mortality (adjusted HR: 1.60; 95% CI: 1.15-2.23). Other significant predictors of increased CVD mortality risk included older age, male sex, prior AMI, use of anti-hypertension or congestive heart failure medications, as well as current glucocorticosteroid use, which was associated with a 50% increased risk of CVD mortality (HR, 1.51; 95% CI, 1.09-2.09).

When we modelled time since statin discontinuation as a continuous time-dependent variable, the value of which increased with each additional month since discontinuation, we also found significant associations for statin discontinuation and mortality outcomes in both univariate and multivariable Cox's models (crude HR = 1.004; 95% CI: 1.001-1.016, adjusted HR = 1.004; 95% CI: 1.001-1.016), indicating a 0.4% increase in risk of CVD mortality per month since discontinuation[17].

[17] Final multivariable model for statin discontinuation, modelled as a continuous time-dependent variable, and CVD mortality presented in Appendix E, Table E1.4

Table 5.3 Unadjusted and Adjusted Hazard Ratios and 95% Confidence Intervals for Risk of Death from All Cardiovascular Diseases

	Unadjusted Hazard Ratio (95% Confidence Interval)	p-value§	Adjusted Hazard Ratio (95% Confidence Interval)	p-value§
Primary Exposure (Time-Dependent)				
Statin discontinuation *(yes vs no)*	1.41 (1.02, 1.96)	0.04	1.60 (1.15, 2.23)	0.005
Fixed-in-Time Covariates				
Age	1.08 (1.07, 1.10)	<0.0001	1.07 (1.05, 1.09)	<0.0001
Sex *(men vs women)*	1.49 (1.12, 1.97)	0.006	1.53 (1.15, 2.04)	0.004
Prior AMI *(yes vs no)*	2.94 (2.12, 4.06)	<0.0001	1.47 (1.03, 2.09)	0.03
Prior infection requiring hospitalization *(yes vs no)*	2.37 (1.62, 3.46)	<0.0001	1.49 (1.01, 2.23)	0.05
Diabetes *(yes vs no)*	1.54 (1.10, 2.15)	0.01	1.25 (0.88, 1.77)	0.2
Use of anti hypertension medication *(yes vs no)*	3.36 (2.32, 4.86)	<0.0001	1.87 (1.26, 2.78)	0.002
Use of congestive heart failure medication *(yes vs no)*	3.04 (2.29, 4.03)	<0.0001	1.79 (1.31, 2.45)	0.0002
Use of anticoagulant *(yes vs no)*	2.88 (1.94, 4.27)	<0.0001	1.29 (0.85, 1.96)	0.2
Charlson comorbidity score	1.37 (1.27, 1.47)	<0.0001	1.15 (1.09, 1.26)	0.004
Time-Dependent Covariates				
Current use of glucocorticosteroid *(yes vs no)*	1.98 (1.45, 2.72)	<0.0001	1.51 (1.09, 2.09)	0.01
Current use of methotrexate *(yes vs no)*	0.79 (0.50, 0.90)	0.009	0.68 (0.43, 1.08)	0.1

§ p-value for 2-tailed Wald test

Unadjusted and adjusted HRs for all-cause mortality are summarized in Table 5.4. In univariate analyses, statin discontinuation was associated with a statistically significant increase in the risk of death from all causes (HR = 1.70; 95% CI: 1.39-2.08). Older age, male sex, several comorbidities - including AMI, diabetes, cancer, and infection requiring hospitalization, as well as higher Charlson comorbidity score, use of anti-hypertension and congestive heart failure medications, and time-dependent indicators of current use of glucocorticosteroids and methotrexate also had significant unadjusted associations with all cause mortality. In the final multivariable model, the association between statin discontinuation and all cause mortality remained significant (HR, 1.79; 95% CI, 1.46-2.20). Other significant predictors of increased mortality risk included older age, male sex, higher Charlson comorbidity score, infection requiring hospitalization, and use of anti-hypertension and congestive heart failure medications. In addition, current use of glucocorticosteroids was associated with a two-fold increased mortality risk (adjusted HR, 2.28; 95% CI, 1.87-2.79) while current methotrexate use was associated with approximately 50% reduction in mortality risk (adjusted HR, 0.54; 95% CI, 0.39-0.74). Hazard ratios for AMI, diabetes, and cancer did not retain their statistical significance when Charlson comorbidity score was entered into the model, likely due to the fact that these comorbidities are components of the score. However, given that they are established risk factors for death in RA, these variables were forced in the final multivariable model.

When we modelled time since statin discontinuation as a continuous time-dependent variable, the value of which increased with each additional month since discontinuation, we also found significant associations for statin discontinuation and mortality outcomes in both univariate and multivariable Cox's models (crude HR

= 1.011; 95% CI: 1.004-1.018, adjusted HR = 1.010; 95% CI: 1.002-1.015), indicating a 1% increase in risk of death for every month since statin discontinuation[18].

[18] Final multivariable model for statin discontinuation, modelled as a continuous time-dependent variable, and all cause mortality presented in Appendix E, Table E1.5

Table 5.4 Unadjusted and Adjusted Hazard Ratios and 95% Confidence Intervals for Risk of Death from All Causes

	Unadjusted Hazard Ratio (95% Confidence Interval)	p-value§	Adjusted Hazard Ratio (95% Confidence Interval)	p-value§
Primary Exposure (Time-Dependent)				
Statin discontinuation *(yes vs no)*	1.70 (1.39, 2.08)	<0.0001	1.79 (1.46, 2.20)	<0.0001
Fixed-in-Time Covariates				
Age	1.08 (1.06, 1.09)	<0.0001	1.07 (1.05, 1.08)	<0.0001
Sex *(men vs women)*	1.30 (1.08, 1.56)	0.0048	1.40 (1.17, 1.69)	0.0004
Prior AMI *(yes vs no)*	2.21 (1.76, 2.79)	<0.0001	1.16 (0.91, 1.49)	0.2
Prior malignancy *(yes vs no)*	1.66 (1.36, 2.04)	<0.0001	1.07 (0.86, 1.34)	0.5
Prior infection requiring hospitalization *(yes vs no)*	2.08 (1.60, 2.69)	<0.0001	1.36 (1.03, 1.78)	0.02
Diabetes *(yes vs no)*	1.43 (1.15, 1.78)	0.002	1.23 (0.97, 1.54)	0.08
Use of anti-hypertension medication *(yes vs no)*	2.60 (2.08, 3.24)	<0.0001	1.64 (1.29, 2.08)	<0.0001
Use of congestive heart failure medication *(yes vs no)*	2.51 (2.09, 3.01)	<0.0001	1.59 (1.31, 1.94)	<0.0001
Charlson comorbidity score	1.36 (1.29, 1.43)	<0.0001	1.18 (1.10, 1.25)	<0.0001
Time-Dependent Covariates				
Current use of glucocorticosteroid *(yes vs no)*	2.81 (2.32, 3.40)	<0.0001	2.28 (1.87, 2.78)	<0.0001
Current use of methotrexate *(yes vs no)*	0.66 (0.49, 0.90)	0.009	0.54 (0.39, 0.74)	0.0001

§p-value for 2-tailed Wald test

Results of subgroup analyses indicate that the impact of statin discontinuation did not depend on: i) timing of first statin use (before vs. after RA diagnosis), ii) gender, and iii) age, for either all-cause mortality (all p-values for interactions: ≥0.29) (Table 5.5) or CVD mortality outcomes (all p-values for interactions: ≥0.61).

Table 5.5 Multivariate Hazard Ratios for Statin Discontinuation and Risk of All Cause and Cardiovascular Disease (CVD) Mortality Stratified by Initiation of First Statin Before RA, Sex, and Age Group

Subgroup	Number of Deaths	HR (95% CI)	P value for interaction*
CVD Mortality			
First statin before RA diagnosis	58	1.69 (1.02, 3.11)	0.65
First statin after RA diagnosis	140	1.53 (1.01, 2.28)	
Women	101	1.43 (1.04, 2.26)	0.61
Men	97	1.74 (1.06, 2.85)	
<65 years	37	1.29 (0.59, 2.82)	0.82
≥65 years	161	1.63 (1.12, 2.35)	
All Cause Mortality			
First statin before RA diagnosis	127	1.67 (1.10, 2.53)	0.93
First statin after RA diagnosis	340	1.84 (1.45, 2.34)	
Women	252	1.67 (1.27, 2.20)	0.29
Men	215	2.02 (1.48, 2.77)	
<65 years	94	1.70 (1.09, 2.67)	0.29
≥65 years	373	1.84 (1.46, 2.32)	

**P-value for the 2-tailed Wald test of the interaction between a given stratification variable (shown in the 1st column) and statin discontinuation*

Finally, in sensitivity analyses, we found that the association between statin discontinuation and all cause mortality and CVD mortality remained statistically significant regardless of whether statin discontinuation

was defined as requiring 1 or 2 months of persistent non-use, rather than 3 months as in the main analyses. Specifically, for CVD mortality and all cause mortality adjusted HRs were 1.47 (95% CI: 1.22-2.29) and 1.69 (95% CI: 1.65-2.43), respectively when using a definition based on 1 month of non-use, and for they were 1.57 (95% CI: 1.13-2.18) and 1.72 (95% CI: 1.58-2.35) when using a definition based on 2 months of consecutive non-use.

5.4 Discussion

We conducted a population-based study of an RA cohort of incident statin users followed up to 10 years to determine the impact of statin discontinuation on risk of cardiovascular and all-cause mortality. To our knowledge, this is the first study to evaluate the association of statin discontinuation with mortality outcomes specifically in RA, a patient population in whom it is particularly relevant given their increased risk of CVD death (4). We found that statin discontinuation was associated with a 60% increased risk of cardiovascular mortality and 79% increase risk of all cause mortality. These associations were independent of age, sex, comorbid medical conditions, and prescription medication use. Findings also persisted across different subgroups evaluated based on sex, age, and timing of first statin use. Given the recent emphasis on the management of cardiovascular risk factors in RA as outlined in newly-released recommendations (5), our findings have implications for the care of people with RA. Not only is it important to assess CVD risk and initiate recommended statin therapy in patients (5), but it is also essential to monitor patient compliance to the prescribed therapy regimen.

The mortality risk associated with RA has been evaluated across different populations and clinical settings, and studies have consistently shown that RA is associated with increased mortality, with death rates in RA 1.5 to 1.6 fold higher than in the general population (2). Furthermore, studies have shown that CVD is the

main cause of excess of mortality in RA. A meta-analysis by colleagues showed a 50% increased risk of CVD death in RA patients (meta-standardized mortality ratio [SMR] 1.50, 95% CI, 1.39-1.69) (4). Given its burden on RA mortality, care for CVD is important in the management of RA and clinical practice guidelines recommend regular assessment of cardiovascular risk factors including lipid tests and treatment with statins as first-line therapy for high-risk patients (5, 6). By demonstrating the impact of statin discontinuation for both specific CVD and overall mortality outcomes, our study additionally suggests the importance of ensuring compliance with statin treatment among those RA patients prescribed with statins. Furthermore, RA-specific findings from our study will allow physicians to inform individuals with RA of the risks associated with discontinuing statin therapy, thus helping them to weigh the pros and cons of remaining on therapy.

The problem of statin discontinuation in the general population has become well-recognized over the last decade, with earlier studies pointing out that in real-life settings discontinuation of statins is more frequent than in RCTs (8, 35) and subsequent studies reporting high statin discontinuation rates (7, 8, 10-14, 36). Equally important to quantifying the magnitude of the problem is evaluating associated adverse outcomes. However, the literature on impact of statin discontinuation on health outcomes is still limited, and there is need for studies across different patient populations. Nonetheless, our results corroborate previously reported findings. Specifically, statin discontinuation was associated with an increased risk of 1-year all cause mortality in post AMI patients using data from the UK General Research Practice Database (adjusted relative risk [RR], 1.88; 95% CI, 1.13-3.07) (18) and a US managed care organization (HR, 2.86; 95% CI, 1.47-5.55) (20). Aside from extending evidence for the adverse impact of statin discontinuation to a specific RA population, our study additionally evaluated specific outcomes of CVD mortality along with all-cause mortality. Furthermore, follow-up for our study was longer (mean 4 years) and use of time-

dependent modeling techniques permitted capture of real life patterns of statin use by evaluating the effects of both intermittent and permanent discontinuation.

Both potential biological effects and behavioral factors may explain the association between statin discontinuation and increased mortality risk observed in this study. Potential biological mechanisms include the loss of cholesterol lowering effect of statins as well as loss of anti-inflammatory, immumodulatory effects, which have been postulated to mediate beneficial effects of statins on CVD in inflammatory diseases such as RA. Potential behavioral factors are those described as a 'healthy adherer' effect whereby individuals who tend to closely follow prescribed medication regimens then to also who exhibit healthier behaviors such as better diets, more exercise, and less smoking (37). A recent meta-analysis reported associations between i) good compliance with drug therapy and mortality and ii) good compliance with placebo and mortality and suggested that findings may provide evidence for the 'healthy adherer' effect, whereby compliance to therapy, regardless of active or inactive substance, may be a surrogate marker for overall healthy behaviors (38). However, there is also contrasting evidence to the 'healthy adherer' effect. For example, a study evaluating the association between adherence to statin, aspirin, or both and CVD showed that in subjects taking both drugs, adherence to statins but not aspirin was associated with lower risk of CVD recurrence (RR 0.64; 95% CI: 0.49-0.82) but the same was not observed with adherence to aspirin but not statins (RR 0.91; 95% CI: 0.72-1.15) (39). Authors argued that these results suggest that poor health behavior does not adequately explain of adverse outcomes in poorly adherent patients and that unfavourable outcomes are more likely to be driven by foregone drug benefits resulting from discontinuation of use (39). We replicated Wei et al.'s analyses in our cohort and similarly found that aspirin discontinuation did not have an impact on mortality outcomes.

Although evaluating the impact of RA medications on mortality was not the primary intent of this study, it is nonetheless noteworthy that current use of glucocorticosteroids was associated with increased risk of mortality and current use of methotrexate was associated with decreased mortality risk. These findings confirm previous reports of the beneficial effects of methotrexate on RA mortality (40) and add to the literature cautioning clinicians of the risks associated with glucocorticosteroid use (41, 42).

Strengths and limitations of our study deserve comment. Use of a population-based cohort of RA patients diminishes selection bias and increases external validity. Universal data on all prescriptions, health services, and vital statistics for a cohort of incident statin users ensured complete capture of statin discontinuation and death outcomes over a long period of observation (up to 10 years of follow-up). However, our study is subject to limitations inherent to administrative data and observational studies. For example, because we used an algorithm based on diagnostic codes for physician visits to define RA, some misclassification of diagnosis likely occurred. However, inclusion of non-RA cases would likely bias results towards the null, given the increased risk of mortality in RA. Furthermore, we used the strictest published case definition for RA (21), which was validated against self-report of a diagnosis of RA, yielding a positive predictive value of 0.92 (43, 44) and improved specificity with additional exclusions, as described in the Methods. As demonstrated in a simulation study, high specificity of the diagnostic criteria minimizes the risk of biases that might occur if the association of interest and/or the risk vary depending on the subjects true diagnostic status (45). The use of administrative pharmacy records is well established in pharmacoepidemiologic studies (46) and our data has the advantage of including all medications dispensed to the entire RA population in BC. However, we did not have information on whether pills were actually taken or reasons for statin discontinuation. For example, patients may discontinue due to unfavourable side effects, which may have an impact on patients' willingness to continue with therapy (47). Despite this, it has been reported that evaluation of prescription fill patterns represent the most accurate way of estimating

actual medication use in large populations (48). Finally, although we adjusted for all known risk factors for discontinuation (exposure) and mortality (outcome) available in our data, unmeasured or unknown confounders could still affect results.

In conclusion, our population-based study of RA patients with incident statin use demonstrated an increased risk of cardiovascular and all cause mortality associated with statin discontinuation. Given the increased mortality risk from CVD in RA, findings provide support for raising awareness among health professionals and people with RA of the importance of compliance with statin therapy.

5.5 References

1. Gabriel S, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009;11 Epub 2009 May 19(3):229.
2. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clinical & Experimental Rheumatology. 2008;26(5):S35-S61.
3. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis & Rheumatism. 2002;46(4):862-73.
4. Avina-Zubieta J, Choi H, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in RA: A systematic review of observational studies. Annals of the Rheumatic Diseases. 2007;66(Supp2):320.
5. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;2010(69):325-31.
6. Pham T, Gossec L, Constantin A, Pavy S, Bruckert E, Cantagrel A, et al. Cardiovascular risk and rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. Joint Bone Spine. 2006;73(4):379-87.
7. Howell N, Trotter R, Mottram D, Rowe P. Compliance with statins in primary care. Pharmaceutical Journal. 2004;272:23-6.
8. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? New England Journal of Medicine. 1995;332(17):1125-31.

9. Tsoneva J, Shaw J. Understanding patients' beliefs and goals in medicine-taking. Professional Nurse. 2004;19(8):466-8.

10. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clinical Therapeutics. 2008;30(11):2167-79.

11. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Medical Journal of Australia. 1996;164(4):208-11.

12. Deambrosis P, Saramin C, Terrazzani G, Scaldaferri L, Debetto P, Giusti P, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. European Journal of Clinical Pharmacology. 2007;63(2):197-203.

13. Foody JM, Joyce AT, Rudolph AE, Liu LZ, Benner JS. Persistence of atorvastatin and simvastatin among patients with and without prior cardiovascular diseases: a US managed care study. Current Medical Research & Opinion. 2008;24(7):1987-2000.

14. Vinker S, Shani M, Baevsky T, Elhayany A. Adherence with statins over 8 years in a usual care setting. American Journal of Managed Care. 2008;14(6):388-92.

15. Goycochea-Robles M, Rahman MM, Choi H, Esdaile JM, Lacaille D. Compliance with statin therapy in rheumatoid arthritis in patients. Arthritis & Rheumatism. 2008;59(9):S877.

16. De Vera M, Choi H, Abrahamowicz M, Rahman MM, Goycochea M, Lacaille D. Non-compliace with statin therapy and risk of acute myocardial infarction in patients with rheumatoid arthritis. Canadian Arthritis Network Annual Scientific Conference; 2009; Vancouver, Canada; 2009.

17. Penning-van Beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. European Heart Journal. 2007;28(2):154-9.

18. Daskalopoulou S, Delaney J, Filion K, Brophy J, Mayo N, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: A population-based study. European Heart Journal (advance access). 2008.

19. Colivicchi F, Bassi A, Santini M, Caltagirone C. Discontinuation of statin therapy and clinical outcome after ischemic stroke. Stroke. 2007;38(10):2652-7.

20. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction.[see comment]. Archives of Internal Medicine. 2006;166(17):1842-7.

21. Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: a population study. Arthritis & Rheumatism. 2005;53(2):241-8.

22. Province of British Columbia. The 2006 Census of Canada in BC Stats. Available from: http://www.bcstats.gov.bc.ca/census.asp [cited 2009 December 21, 2009].

23. Schnatter R, Acquavella J, Thompson F. An analysis of death ascertainment and follow-up through Canada's mortality database system. Canadian Journal of Public Health. 1990;81:60-5.

24. Tu JV, Nardi L, Fang J, Liu J, Khalid L, Johansen H, et al. National trends in rates of death and hospital admissions related to acute myocardial infarction, heart failure and stroke, 1994-2004. CMAJ Canadian Medical Association Journal. 2009;180(13):E118-25.

25. Goycochea-Robles M, Rahman MM, Choi H, Esdaile JM, Lacaille D. Compliance with statin therapy and predictors of compliance in rheumatoid arthritis (RA). Journal of Rheumatology. 2009;36:2575.

26. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Medical Care. 1998;36(1):8-27.

27. Andrade SE, Gurwitz JH, Chan KA, Donahue JG, Beck A, Boles M, et al. Validation of diagnoses of peptic ulcers and bleeding from administrative databases: a multi-health maintenance organization study. Journal of Clinical Epidemiology. 2002;55(3):310-3.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40(5):373.

29. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of Clinical Epidemiology. 1992;45(6):613.

30. Smitten A, Simon T, Qi K, Suissa S, Askling J, Franklin J, et al. Malignances in the Abatacept RA Clinical Development Program: An epidemiological assessment with >10,000 person-years of exposure. Arthritis & Rheumatism. 2008;59(9(Suppl)):S786.

31. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis & Rheumatism. 2008;59(8):1074-81.

32. Allison P. Survival Analysis Using the SAS System: A Practical Guide. Cary, NC, USA: SAS Institute Inc; 1995.

33. Abrahamowicz M, Tamblyn R. Drug Utilization Patterns. Encyclopedia of Biostatistics. John Wiley & Sons, 2005.

34. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. American Journal of Epidemiology. 2005;162(10):1016-23.

35. Insull W. The problem of compliance to cholesterol altering therapy. Journal of Internal Medicine. 1997;241(4):317-25.

36. Ellis JJ, Erickson S, Stevenson J, Bernstein S, Stiles R, Fendrick M. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. Journal of General Internal Medicine. 2004;19:638-45.

37. The Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. New England Journal of Medicine. 1980;303:1038-41.

38. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. British Medical Journal. 2006;333(7557):15.

39. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. British Journal of Clinical Pharmacology. 2008;66(1):110-6.

40. Choi H, Herman M, Seeger J, Robins J, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: A prospective study. The Lancet. 2002;359:1173-7.

41. Caplan L, Russell AS, Wolfe F. Steroids for rheumatoid arthritis: the honeymoon revisited (once again). Journal of Rheumatology. 2005;32(10):1863-5.

42. Ramos-Remus C, Sibley J, Russell AS. Steroids in rheumatoid arthritis: the honeymoon revisited. Journal of Rheumatology. 1992;19(5):667-70.

43. MacLean C, Louie R, Leake B, McCaffrey D, Paulus D, Brook R, et al. Quality of care for patients with rheumatoid arthritis. Journal of the American Medical Association. 2000;287(8):984-92.

44. MacLean C, Park G, Traina S, Liu H, Hahn B, Paulus H, et al. Positive predictive value (PPV) of an administrative data-based algorithm for the identification of patients with rheumatoid arthritis (RA). Arthritis & Rheumatism. 2001;44:S106.

45. Abrahamowicz M, Xiao Y, Ionescu-Ittu R, Lacaille D. Simulations showed that validation of database-derived diagnostic criteria based on a small subsample reduced bias. Journal of Clinical Epidemiology. 2007;60(6):600-9.

46. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. Nature Clinical Practice Rheumatology. 2007;3(12):725-32.

47. Daskalopoulou S. When statin therapy stops: Implications for the patient. Current Opinion in Cardiology. 2009;24:454-60.

48. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, et al. Persistence of use of lipid-lowering medications: a cross-national study. Journal of the American Medical Association. 1998;279(18):1458-62.

CHAPTER 6
CONCLUSIONS

*The body of work comprising this thesis is unified by the common goal of gaining a better understanding of statin use in RA through guiding themes of "**Statins as Cardioprotective Agents in RA**" and "**Outcomes of Statin Compliance in RA**" and represents a comprehensive epidemiologic evaluation of statin use and relevant outcomes in RA. In this concluding chapter, key results from each study are highlighted and discussed within the thesis as well as relevant context. Strengths and limitations of the collective work are further discussed along with some recommendations for future research on this important topic.*

6.1 Key Findings

Addressing the goal of gaining a better understanding of statin use in RA first called for an evaluation of their cardioprotective effect in this specific patient population. Despite considerable interest in the field (1-3), there is a lack of studies evaluating hard CVD outcomes along with debate on whether extrapolation of existing data on intermediate CVD outcomes and findings in non-RA patient populations to patients with RA is sufficient evidence for this effect (4, 5). Chapter 2's population-based longitudinal study using the BC RA cohort addressed these issues by comparing incidence of AMI outcomes between statin users and non-users. The key study finding of a 31% lower risk of AMI associated with statin use among RA patients provides evidence for the postulated cardioprotective role of statins in patients with RA in a generalizable, population-based setting. The application of propensity score methods in this study mitigated effects of confounding by indication by allowing comparison of statin users with non-users with balanced distributions of observed covariates.

An ensuing step to better understanding statin use in RA involved looking specifically at patients who have been *prescribed* with statins and evaluating whether poor compliance - namely therapy discontinuation – have an impact on adverse CVD and mortality outcomes. Chapter 4 was a population-based cohort study evaluating the impact of statin discontinuation on risk of AMI among RA patients prescribed with statins. Findings indicate a 67% increased risk of AMI associated with statin discontinuation that is independent of age, sex, proxy indicators of RA severity, prior AMI, cardiovascular risk factors, and use of RA medications. Moreover, with each additional month since statin discontinuation, the risk of AMI is increased by about 2%. An extension of the work in Chapter 4, Chapter 5 was a population-based study evaluating the impact of statin discontinuation on outcomes of CVD mortality and all cause mortality. Results of this study indicate a 60% and 79% increased risk for CVD mortality and all cause mortality, respectively independent of age, sex, comorbid medical conditions, and prescription medication use. Altogether, Chapters 4 and 5 represent a comprehensive evaluation of the adverse impact of statin discontinuation in RA.

Findings from Chapter 3's systematic review of observational studies evaluating adverse outcomes associated with statin discontinuation contributed towards achievement of the thesis goal by informing study design and analytic issues for studies in Chapter 4 and 5, while synthesizing current evidence on negative impacts of discontinuation of statin therapy. Studies included in this review consistently identified an increased risk of adverse outcomes associated with statin discontinuation, highlighting the importance of ensuring adequate persistence in patients that are prescribed statins for primary or secondary prevention.

6.2 Integration and Implications of the Research

Addressing the two themes of this thesis called for synthesis of a wide range of literature for establishing background and rationale, developing study designs, applying analytical solutions, and interpreting findings. In turn, as stand-alone studies or as a collective work, this thesis provides potential contributions across a number of fields including rheumatology, pharmacoepidemiology, health services research, and pharmionics.

As the first study to demonstrate a cardioprotective role of statins in RA using a hard CVD outcome of AMI, Chapter 2 represents a contribution to rheumatologic literature on the potential roles of statins in RA. Specifically, this study adds to the evidence base for a cardioprotective effect of statins, which to date, has been largely based on studies in RA patients evaluating intermediate CVD outcomes (6-8), studies primarily evaluating RA joint-specific outcomes but also reporting secondary outcomes on inflammatory markers with known links to CVD (9), and RCT data in other patient populations (10). At conceptualization stages of the thesis, access to population-based data for BC RA Cohort, the largest RA cohort for research purposes with longitudinal follow-up for 10 years, provided the opportunity to address the question on the cardioprotective effect of statins utilizing pharmacoepidemologic observational study methods. It is important to acknowledge the currently ongoing Trial of Atorvastatin for the primary prevention of Cardiovascular Events in Rheumatoid Arthritis (TRACE RA), a multi-centre trial evaluating the impact of atorvastatin on CVD endpoints including AMI and stroke (www.dgoh.nhs.uk/home/app/tracera). Pending results from this trial, anticipated in 2015, current findings from Chapter 2 provide an interim effect size for the cardioprotective role of statins in RA. Beyond this contribution, this study provides real-world generalizable information on statin use in RA.

Aside from contributing to rheumatologic literature on the cardioprotective role of statins in RA, Chapter 2 also provides contributions to pharmacoepidemiologic literature on applications of the propensity score method as well as observational studies evaluating anticipated benefits of statins. Previous studies using propensity score methods for statin research in non-RA populations included Seeger et al.'s study using US managed care organization data (11) and Smeeth's et al.'s study using UK THIN data (12).

Finally, it is important to consider clinical implications of findings in Chapter 2. By demonstrating that statin initiators have a lower risk of AMI compared to non statin-initiators, results highlight the importance of monitoring and management of cardiovascular risk factors in RA patients and appropriate initiation of recommended statin therapy (13). Our ability to match a large proportion of statin initiators with non-initiators (88%), may suggest that there are RA patients who may be indicated to receive statins but are not receiving treatment. Thus, a potential problem of under treatment with statins among RA patients warrants further investigation.

Chapter 3's systematic review of observational studies on adverse impacts of statin discontinuation addressed a limitation identified in review of relevant pharmionics literature. While the past decade has seen the magnitude of statin discontinuation quantified in numerous reports in different patient populations (14-20), reports on adverse outcomes associated with statin discontinuation have only recently emerged. Thus, before conducting studies of statin discontinuation in RA, an objective summary of the literature evaluating adverse outcomes of statin discontinuation was performed. Recommendations set forth based on systematic review findings directly informed subsequent thesis topics on the clinical impact of statin discontinuation in RA and included: 1) modelling statin discontinuation in a way that captures real-life patterns of use; 2) longer follow-up period, and 3) use terminology that is consistent with recommendations (21). Aside from direct impacts on the thesis, this systematic review represents potential contributions to

pharmionics literature – both specifically in terms of future studies of statin discontinuation and broadly in terms of relevant studies of other chronic medications and subsequent impact on relevant outcomes.

Thesis studies evaluating the impact of statin discontinuation on outcomes of AMI (Chapter 4) and CVD mortality and all cause mortality (Chapter 5) provide contributions to rheumatologic literature by informing risks of statin discontinuation among individuals with RA. Given the limited number of studies on statin discontinuation and adverse impacts, as identified in our systematic review, they also contribute to pharmacoepidemiologic and pharmionics literature on this issue.

Aside from potential contributions to research, it is also important to consider potential contributions to policy or practice. Perhaps of the thesis chapters, Chapters 4 and 5 represent the most potential for direct relevance and implications for current management of RA. Recent attention on the management of cardiovascular risk factors in RA has been highlighted by newly-published guidelines (13) and a shift in emphasis from quantification of cardiovascular burden in RA to identification of effective means of reducing CVD risk (22). By identifying a relevant quality of care issue, that is, the adverse impact of discontinuation of statin therapy among prescribed RA patients, Chapters 4 and 5 highlight the importance of monitoring and ensuring compliance with prescribed therapy. These findings are especially relevant given that they provide physicians and individuals with RA relevant and *specific* information on the risks associated with discontinuation of statin therapy.

Although studies were not specifically designed to address this purpose, it was notable that findings from Chapters 4 and 5 were consistent with those from Chapter 2. As described in Chapter 2, confounding by indication is a common problem in pharmacoepidemiologic studies of expected drug benefits, which may occur when predictors of treatment also have prognostic value for the outcome of interest (23). Propensity

scores, as applied in Chapter 2, provide a useful approach to help mitigating this bias by balancing observed risk factors between exposed and non-exposed groups when traditional multivariable modelling methods fail to attenuate this bias, also shown in Chapter 2. Statin discontinuation studies in Chapters 4 and 5 may also offer an effective way of dealing with confounding by indication; since all subjects included were those who initiated statin therapy. Thus, in these studies statin discontinuation essentially represents a "non-exposed" status, while continuous use essentially represents an "exposed" status. While this potential application of drug discontinuation studies has not been acknowledged in such studies, it establishes a link between otherwise independent objectives of respective thesis studies.

6.3 Strengths and Limitations of the Research

As each manuscript chapter provided its own discussion of study-specific strengths and limitations, this examination of strengths and limitations will focus on the collective thesis work, with particular emphasis on pharmacoepidemiologic studies. Where applicable, issues that were consistent across studies will be highlighted.

Consistent across analytic studies in the thesis was the application of novel methodological approaches in addressing important study issues related to measurement of statin exposure, whether the purpose was to mitigate confounding by indication (Chapter 2) or to appropriately measure the impact of statin discontinuation (Chapters 4 and 5). To highlight, in Chapter 2, methods used to address several important issues included: 1) propensity scores to mitigate confounding by indication; 2) greedy matching algorithms on individual propensity scores for statin users and non-users to balance incomplete matching and inexact matching; 3) defining statin initiation to allow "late initiators" to contribute non-exposed time to avoid both

possibilities of assembling a biased comparison group who were not at risk of being prescribed a statin and inappropriately assigning exposure time to statin initiators (12).

Methodological strengths in Chapters 4 and 5 were the application of time-dependent statistical techniques to measure statin discontinuation exposure that allowed capture of both intermittent and permanent discontinuation. As identified in Chapter 3's systematic review, measurement of statin discontinuation in prior studies has been inconsistent and largely based on fixed time points to determine discontinuation status. Measuring statin discontinuation exposure in a cohort study must take into consideration two analytic issues: that follow-up time in the cohort study is used to define exposure and time to statin discontinuation must occur before time to outcome. Moreover, patterns of statin use may vary across patients and a definition for statin discontinuation would need to account for both permanent discontinuation of therapy and intermittent gaps in treatment.

Data sources play a particularly important role in pharmacoepidemiologic research; thus further comment on data used for the thesis analytic studies are warranted. As described in Chapter 1 and methods sections for Chapters 2, 4, and 5, we used population-based administrative health data for a cohort of RA patients in BC. With capture of health care utilization data for 37,151 individuals with RA, this data source represents one of the largest RA cohorts for epidemiologic and health services research. In particular, complete information on all dispensed prescription medications for the cohort makes it an excellent resource for pharmacoepidemiologic research. Available information in each database (i.e., MSP, Hospital Separations, PharmaNet) lends to the richness of the data - for example date of prescription and number of drug days' dispensed in pharmacy records - and provides potential for application of novel methods to mine important and relevant information, as done in this thesis.

It is important to acknowledge limitations of administrative health data. A fundamental limitation is the fact that data is collected for billing purposes or reimbursement for health services incurred and not primarily meant for research. Given this problem, one important limitation as discussed in Chapters 2, 4, and 5, is that studies may be vulnerable to diagnostic uncertainty of RA. However, as with prior publications on this cohort, for all thesis studies the strictest published case definition for RA was used. A validation study of this definition reported a positive predictive value of 0.92 (24, 25). Furthermore, additional exclusions attempted to improve specificity for RA, as described in the Methods sections for respective chapters. Using this definition, the prevalence of RA in BC was estimated as 0.96%, which is similar to the reported estimates in the literature (26). Diagnostic uncertainty for outcomes (AMI, CVD mortality, and all cause mortality) is another shared limitation across thesis studies. However, previous Canadian validation studies of hospital discharge data have demonstrated good positive predictive values for AMI, from 89% in Ontario (27) to 96% in Quebec (28). Capture of mortality data in the Canadian Mortality Database is also well established (29). Aside from diagnostic uncertainty, another important limitation of administrative health data is the vulnerability to potential unmeasured and/or unobserved confounders. By failing to capture information on risk factors such as cigarette smoking and alcohol exposure, family histories, diet, and physical activity, their confounding effects may persist and should be acknowledged.

Overall, in considering their potential and acknowledging their limitations, administrative health data sources such as BC health data for the BC RA Cohort, will continue to be a resource for pharmacoepidemiologic research. Overall, thesis studies demonstrating use of the BC RA Cohort to measure anticipated drug effects (Chapter 2) as well as adverse outcomes of statin discontinuation (Chapters 4 and 5) potentially contribute to growing capacity for research with BC health data.

6.4 Future Research and Recommendations

Work from this thesis gives rise to future research directions and recommendations. Stemming from Chapter 2 is evaluation of other hard CVD outcomes with demonstrated validity in administrative health data. An example is stroke; definition for this outcome based on ICD-9 codes has been shown to have PPV of 0.96 (30). Deaths – including all cause mortality and mortality from cardiovascular causes – represent other hard outcomes that are established in administrative health data. Investigations of these outcomes by members of our research group are currently underway. Results from Chapter 2 may also be applied to extend a current decision analytic model based on data from the TARA trial, developed by members of our group (31), on the role of statin therapy in RA management. Specifically by providing longer follow-up data as compared to the 6 month follow-up data from the TARA trial along with information on CVD end points, Chapter 2 provides generalizable input variables for projecting long-term net health outcomes with statins in RA.

Stemming from work in Chapters 3, 4, and 5 is recommendation for further studies evaluating outcomes of statin discontinuation in other patient populations. Despite a limited number of studies identified in Chapter 3's systematic review, they consistently reported a significant association between statin discontinuation and adverse outcomes of AMI and mortality. Corroboration of these studies by results in thesis studies (Chapters 4 and 5) suggests that statin discontinuation is an important quality of care issue. Further confirmation in greater number of studies and in other patient populations, particularly those with established CVD risk as in RA, would be valuable. Aside from confirmatory studies, there is also potential for future investigations evaluating why RA patients discontinue statins (and perhaps other chronic medications) in order to identify appropriate interventions and/or policies to ensure maintenance of quality of care.

Chapter 3's systematic review outlined recommendations for future studies on the impact of statin discontinuation on adverse CVD and mortality outcomes. These recommendations are not necessarily limited to studies of statin alone, but may also be extended to studies of adverse outcomes of discontinuation of other chronic medications. While this thesis specifically focused on problems with use of a specific drug (statins) in a specific patient population (RA), similar problems may exist with other chronic drugs and in other patient populations, given that with lifelong therapies comes the risk for patient discontinuation.

6.5 Conclusion

In this pharmacoepidemiologic evaluation of statin use in RA, several concluding points are emphasized. First, in a population-based comparison of statin-users and non-statin users, statin use among RA patients was associated with lower risk of AMI. Second, when evaluating real-life patterns of statin use in the RA cohort, statin discontinuation was associated with increased risk of AMI, CVD mortality, and all-cause mortality. Altogether as a collective work, this thesis supports a substantial role of statins in management of CVD, a key comorbidity in RA, and additionally highlights the importance of patient compliance in achieving therapeutic goals of treatment.

6.6 References

1. Abeles A, Pillinger M. Statins as antiinflammatory and immunomodulatory agents: A future in rheumatologic therapy? Arthritis & Rheumatism. 2006;54(2):393-407.
2. Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmunity Reviews. 2006;5(5):331.
3. Costenbader KH, Coblyn JS. Statin therapy in rheumatoid arthritis. Southern Medical Journal. 2005;98(5):534.
4. Ridker PM, Solomon DH. Should patients with rheumatoid arthritis receive statin therapy? Arthritis & Rheumatism. 2009;60(5):1205-9.
5. Peters MJL, Nurmohamed MT, Kitas GD, Sattar N. Statin treatment of rheumatoid arthritis: comment on the editorial by Ridker and Solomon. Arthritis & Rheumatism. 2010;62(1):302-3.
6. Van Doornum S, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2004;63(12):1571.
7. Tikiz C, Utuk O, Pirildar T, Bayturan O, Bayindir P, Taneli F, et al. Effects of Angiotensin-converting enzyme inhibition and statin treatment on inflammatory markers and endothelial functions in patients with longterm rheumatoid arthritis. Journal of Rheumatology. 2005;32(11):2095-101.
8. Hermann F, Forster A, Chenevard R, Enseleit F, Hurlimann D, Corti R, et al. Simvastatin improves endothelial function in patients with rheumatoid arthritis. Journal of the American College of Cardiology. 2005;45(3):461-4.
9. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015-21.

10. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr., Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine. 2008;359(21):2195-207.

11. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. American Journal of Cardiology. 2003;92(12):1447-51.

12. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. British Journal of Clinical Pharmacology. 2009;67(1):99-109.

13. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Annals of the Rheumatic Diseases. 2010;2010(69):325-31.

14. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. Medical Journal of Australia. 1996;164(4):208-11.

15. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? New England Journal of Medicine. 1995;332(17):1125-31.

16. Ellis JJ, Erickson S, Stevenson J, Bernstein S, Stiles R, Fendrick M. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. Journal of General Internal Medicine. 2004;19:638-45.

17. Deambrosis P, Saramin C, Terrazzani G, Scaldaferri L, Debetto P, Giusti P, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. European Journal of Clinical Pharmacology. 2007;63(2):197-203.

18. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clinical Therapeutics. 2008;30(11):2167-79.

19. Foody JM, Joyce AT, Rudolph AE, Liu LZ, Benner JS. Persistence of atorvastatin and simvastatin among patients with and without prior cardiovascular diseases: a US managed care study. Current Medical Research & Opinion. 2008;24(7):1987-2000.

20. Vinker S, Shani M, Baevsky T, Elhayany A. Adherence with statins over 8 years in a usual care setting. American Journal of Managed Care. 2008;14(6):388-92.

21. International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Special Interest Group. Medication Compliance and Persistence: Terminology and Definitions; 2003.

22. Myasoedeva E, Gabriel S. Cardiovascular disease in rheumatoid arthritis: a step forward. Current Opinion in Rheumatology. 2010;22:342-7.

23. Abrahamowicz M, Tamblyn R. Drug Utilization Patterns. Encyclopedia of Biostatistics. John Wiley & Sons, 2005.

24. MacLean C, Louie R, Leake B, McCaffrey D, Paulus D, Brook R, et al. Quality of care for patients with rheumatoid arthritis. Journal of the American Medical Association. 2000;287(8):984-92.

25. MacLean C, Park G, Traina S, Liu H, Hahn B, Paulus H, et al. Positive predictive value (PPV) of an administrative data-based algorithm for the identification of patients with rheumatoid arthritis (RA). Arthritis & Rheumatism. 2001;44:S106.

26. Gabriel S, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009;11 Epub 2009 May 19(3):229.

27. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. American Heart Journal. 2002;144(2):290-6.

28. Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Canadian Journal of Cardiology. 1999;15(11):1277-82.

29. Schnatter R, Acquavella J, Thompson F. An analysis of death ascertainment and follow-up through Canada's mortality database system. Canadian Journal of Public Health. 1990;81:60-5.

30. Birman-Deych E, Waterman A, Yan Y, Nisalena D, Radford M, Gage B. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Medical Care. 2005;43:480-5.

31. Bansback N, Ara R, Ward S, Anis AH, Choi H. Statin therapy in rheumatoid arthritis: A cost-effectiveness and value-of-information analysis. Pharmacoeconomics. 2009;27:25-37.

APPENDIX A: UBC BEHAVIOURAL RESEARCH ETHICS BOARD CERTIFICATES OF APPROVAL

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Hyon Choi	UBC/Medicine, Faculty of/Medicine, Department of/Rheumatology - Med	H07-03110

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
Vancouver Coastal Health (VCHRI/VCHA)	Mary Pack Arthritis Centre

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):

Mahyar Etminan
Nick Bansback
Aslam H. Anis
Diane Lacaille
Mary A. De Vera

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR)

PROJECT TITLE:
Role of Statins in Prevention and Management of Rheumatoid Arthritis

EXPIRY DATE OF THIS APPROVAL: November 3, 2010

APPROVAL DATE: November 3, 2009

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Anita Ho, Associate Chair

The University of British Columbia
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Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Diane Lacaille	UBC/Medicine, Faculty of/Medicine, Department of/Rheumatology - Med	H07-00628

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
N/A	N/A

Other locations where the research will be conducted:
Arthritis Research Centre of Canada

CO-INVESTIGATOR(S):

Aslam Anis

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR)

PROJECT TITLE:
IMPACT OF NON COMPLIANCE WITH STATINS ON CARDIOVASCULAR MORBIDITY AND MORTALITY OF RHEUMATOID ARTHRITIS PATIENTS.

EXPIRY DATE OF THIS APPROVAL: January 14, 2011

APPROVAL DATE: January 14, 2010

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Anita Ho, Associate Chair

APPENDIX B: SUPPLEMENTARY MATERIAL FOR CHAPTER 2

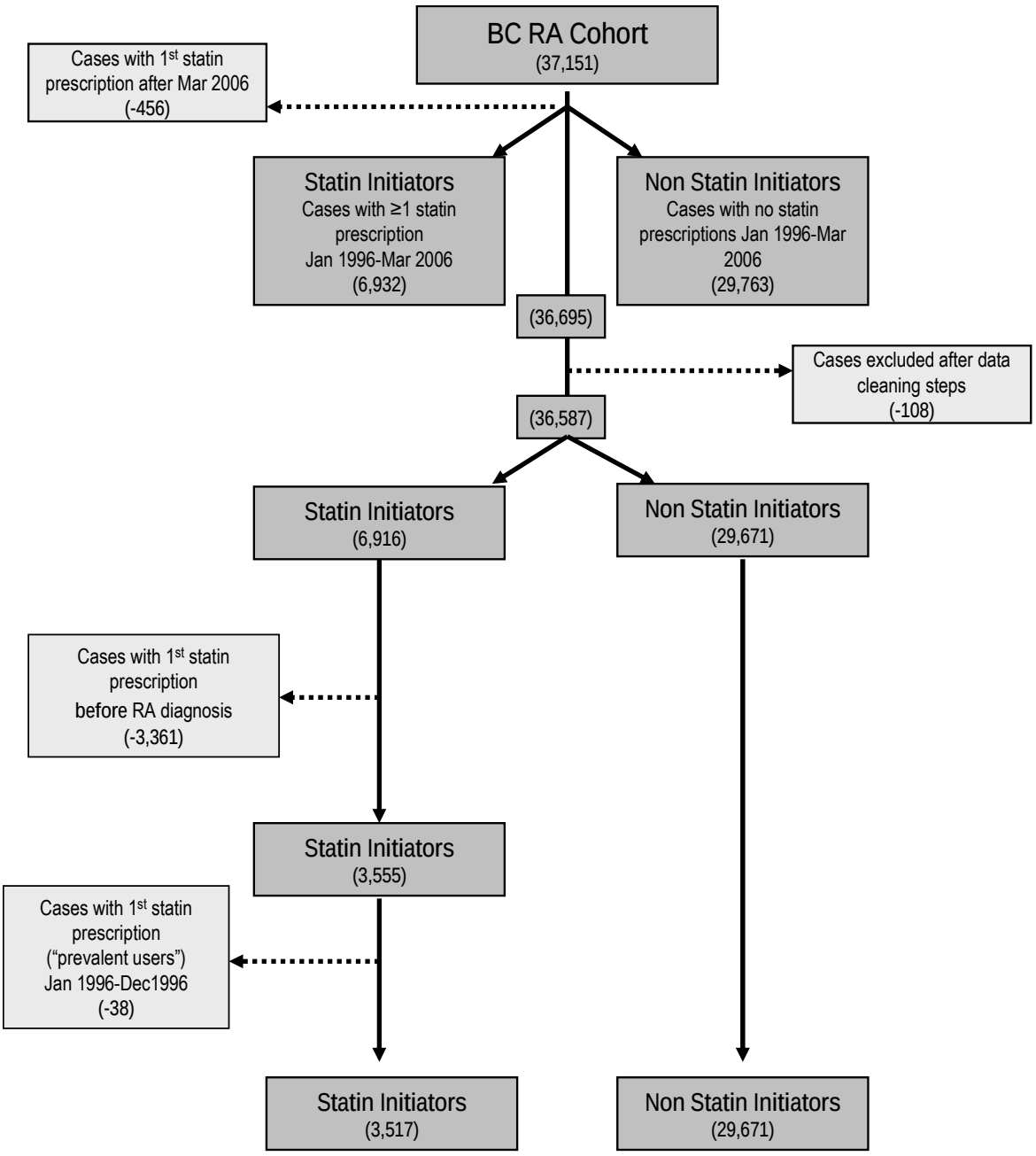

Figure B.1 Subject Flow for Pharmacoepidemiologic Study of Cardioprotective Effect of Statins in Rheumatoid Arthritis[19]

[19] Study Flow for Chapter 2

Table B.1 Comparison of Ranking of Variables in Propensity Score Model with Previous Study[20]

Variable	De Vera et al.			Seeger et al.		
	Rank	Univariate OR (95% CI)	C-statistic	Rank	Univariate OR (95% CI)	C-statistic
No. of lipid-related laboratory tests	1	1.10 (1.09, 1.11)		1	1.13 (0.98, 1.31)	
No. of cardiovascular disease** (ICD9) related physician visits	2	1.02 (1.02, 1.03)		6	1.25 (1.10, 1.42)	
No. of different cardiovascular disease** (ICD9) diagnoses	3	1.25 (1.23, 1.26)		11	1.92 (1.46, 2.53)	
Use of anti-hypertension medications (y/n)	4	5.24 (4.87, 5.63)		17		
No. ECG	5	1.19 (1.18, 1.21)		25	1.17(0.94, 1.46)	
RA duration at index date (months)	6	1.017 (1.015, 1.018)		NA		
Charlson Score	7	1.25 (1.23, 1.28)		NI		
No. physician visits	8	1.003 (1.002, 1.003)		8	1.04 (1.01, 1.07)	
No. of different prescription drugs	9	1.012 (1.010, 1.013)		2	1.20 (1.13, 1.27)	
No. RA-related laboratory tests	10	1.011 (1.009, 1.013)		NA		
Angina (411, 413, or nitrates) (y/n)	11	5.88 (5.37, 6.45)		14		
Age (years)	12	1.02 (1.01, 1.02)		7	1.26 (1.25, 1.27)	
No. of different ICD9 diagnoses	13	1.015 (1.013, 1.016)		23	1.15 (1.14, 1.16)	
No. inpatient hospitalizations	14	1.06 (1.05, 1.07)		19	1.55 (1.21, 1.98)	
Use of congestive heart failure medications (y/n)	15	2.22 (2.06, 2.39)		27		

[20] Reference: Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. American Journal of Cardiology. 2003;92(12):1447-51.

Table B.1 Comparison of Ranking of Variables in Propensity Score Model with Previous Study

Variable	De Vera et al.			Seeger et al.		
	Rank	Univariate OR (95% CI)	C-statistic	Rank	Univariate OR (95% CI)	C-statistic
No. of cardiovascular disease** (ICD9) related hospital days	16	1.001 (1.001, 1.002)		12		
Diabetes (y/n)	17	4.46 (4.04, 4.92)				
Prior AMI (410) (y/n)	18	13.84 (11.87, 16.13)		13		
Dysrrhythmia (427) (y/n)	19	1.88 (1.73, 2.05)		29		
Gender (women vs. men)	20	1.39 (1.29, 1.49)		20		
No. RA-related physician visits (714)	21	1.005 (1.004, 1.006)		NA		
CVA (434, 436) (y/n)	22	2.34 (2.08, 2.64)		35		
Atherosclerosis (440) (y/n)	23	3.13 (2.72, 3.61)		43		
Use of Cox2 inhibitors (y/n)	24	1.27 (1.18, 1.37)		NA		
Use of traditional NSAIDs (y/n)	25	1.33 (1.22, 1.45)		NA		
Physician visits for smoking cessation (305 or 491-6) (y/n)	26	1.28 (1.18, 1.39)		16		
Use of non-statin lipid lowering drug (y/n)	27	5.93 (4.86, 7.25)		31		
Transient ischemic attack (435) (y/n)	28	2.46 (2.12, 2.86)		39		
Use of anticoagulants (y/n)	29	1.64 (1.45, 1.87)		NI		
Use of DMARDs (y/n)	30	0.92 (0.85, 0.98)		NA		
Visit to rheumatologist (y/n)	31	0.92 (0.86, 0.98)		NA		
Physician visits for obesity (278) (y/n)	32	1.52 (1.31, 1.76)		42		

Table B.1 Comparison of Ranking of Variables in Propensity Score Model with Previous Study

Variable	De Vera et al.			Seeger et al.		
	Rank	Univariate OR (95% CI)	C-statistic	Rank	Univariate OR (95% CI)	C-statistic
Hypertensive heart disease (402-404) (y/n)	33	2.66 (2.14, 3.31)		34		
Cancer (140-208) (y/n)	34	1.18 (1.08, 1.32)		46		
Old MI (412) (y/n)	35	4.02 (3.09, 5.22)		30		
Use of methotrexate (y/n)	36	0.94 (0.87, 0.99)		NA		
Use of anti arrhythmia medications (y/n)	37	2.00 (1.63, 2.45)				
Circulatory disease (459) (y/n)	38	1.77 (1.46, 2.14)		41		
Use of glucocorticosteroids (y/n)	39	1.09 (1.01, 1.17)		NA		
Conduction disorder (426) (y/n)	40	1.77 (1.44, 2.17)		40		
No. visits to rheumatologists before index	41	1.008 (1.006, 1.010)		NA		
COPD (490-496, 505-506) (y/n)	42	1.44 (1.28, 1.63)		NI		
Attrial fibrillation (427.3) (y/n)	43	1.69 (1.33, 2.15)		33		
Atherosclerotic CVD (429.2) (y/n)	44	5.68 (2.77, 11.62)		24		
Cardiovascular symptoms (785.9) (y/n)	45	1.96 (1.16, 3.31)		38		
No. different RA drugs	46	1.03 (1.01, 1.05)		NA		

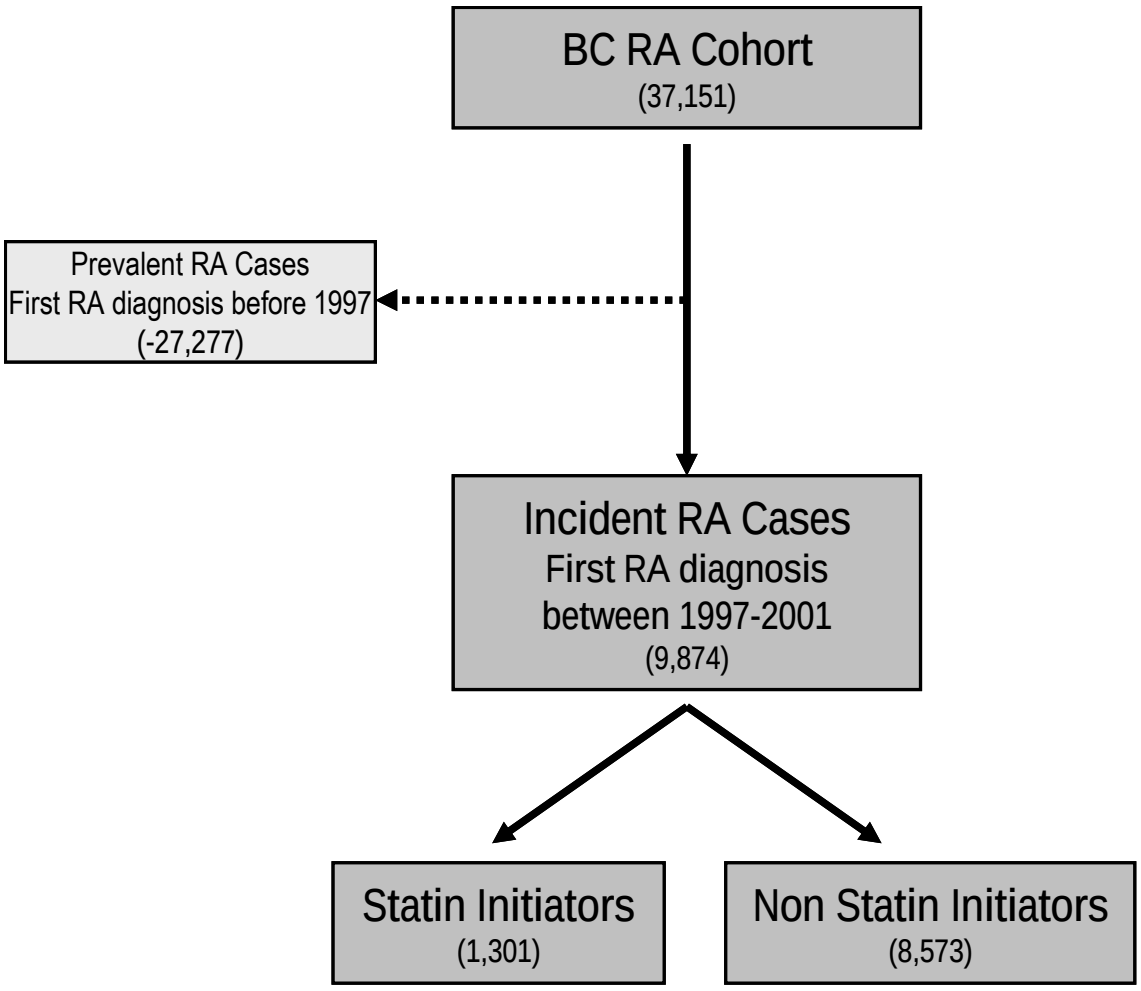

Figure B.2 Subject Flow for Pharmacoepidemiologic Study of Cardioprotective Effect of Statins in Incident Rheumatoid Arthritis Cohort21

[21] Incident RA cohort used in sensitivity analyses for Chapter 2

Results of Sensitivity Analyses of Cardioprotective Effect of Statins in Incident Rheumatoid Arthritis Cohort

The cohort of individuals with incident RA included 1,301 patients who met inclusion criteria for statin initiation and 8,573 non-initiators, altogether contributing 64,354 person-years of follow-up between January 1997 and March 2006. Matching on propensity score resulted in a cohort of 1,119 statin initiators and 1,119 individually matched non-initiators. Table B.2 summarizes Cox's proportional hazards models before and after propensity score matching. Figure B.3A and B display cumulative incidence curves for AMI for the unmatched and propensity score matched incident RA cohorts, respectively. While the association between statin initiation and AMI did not reach statistical significance after propensity score matching, the point estimate indicate a protective effect of statin initiation, similar to findings in primary analyses with prevalent RA cases.

Table B.2 Cox's Proportional Hazards Models of Statin Initiation and Risk of Acute Myocardial Infarction in Propensity-Score Matched Incident RA Patients

Variable	Model 1 *(Before Propensity Score Matching)*	Model 2 *(After Propensity Score Matching)*	Model 3* *(After Propensity Score Matching Adjusted for Propensity Score)*
	Univariate Hazard Ratio (95% CI)	Univariate Hazard Ratio (95% CI)	Multivariable Hazard Ratio (95% CI)
Statin initiation (y vs n)	1.51 (1.11, 2.05)	0.73 (0.48, 1,10)	0.71 (0.47, 1.07)
Propensity score		--	4.31 (1.93, 9.61)

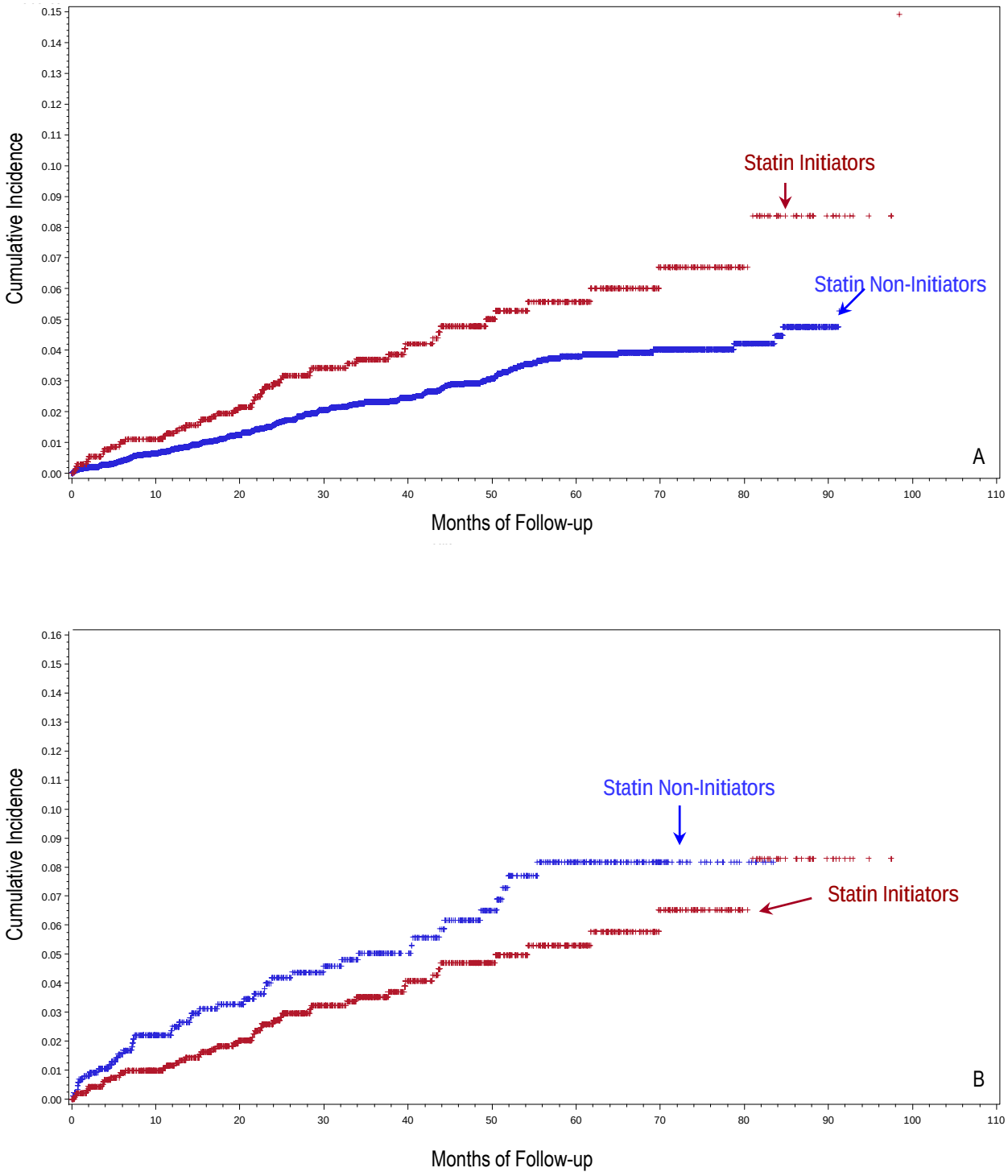

Figure B.3 Cumulative Incidence of AMI in (A) Unmatched and (B) Propensity-Score Matched Incident RA Cohorts

APPENDIX C: SUPPLEMENTARY MATERIAL FOR CHAPTER 3

Data Extraction and Quality Assessment Form for Systematic Review[22]

Section 1. Study Information			
Study Title		Year	
Journal		Reviewer	
First Author		Country	
Section 2. Quality Assessment			
Item No		Score 0=no 1=yes	Notes
1	Objective(s) stated		
Non-scoring	Compliance/persistence is primary outcome of the study		
2	Study design appropriate for objectives		
3	Data sources adequately described		
4	Evidence provided for reliability/accuracy of data		
5	Sampling methods described		
6	Well-described patient population and subject inclusion/exclusion criteria stated		
7	Sufficient data to make valid estimate of compliance (i.e. continuous eligibility for drug during study period verified)		
8	Sufficient pre-enrolment period to ensure drug naivety		
9	Explanation of how patients who switched drugs within or between therapeutic classes were handled		
10	Explicit definition of compliance/persistence based on published, accepted definition?		
Non-Scoring	Definition of compliance: Discontinuation (persistence, discontinuation rate) or Adherence (i.e, PDC)		
11	Methods for calculating compliance / persistence clearly described		
Non-Scoring	If atypical method for calculating compliance used, rationale and formula provided		
12	Handling of medication gaps described		
Non-Scoring	Type of data (categorical, continuous)		
Non-Scoring	If converted to categorical, rationale for cut-points provided, and consistent with evidence		
13	Study outcomes are explicitly defined using appropriate data (i.e. mortality from Vital Statistics, CVD outcomes from hospitalizations)		
14	Follow-up period specified		
15	Statistical tests appropriate to design and data		
16	Appropriate adjustments made (i.e., multiple comparisons, confounders)		
17	Test statistics are reported appropriately (i.e. CIs, p-values reported)		
18	Sensitivity analyses conducted		
19	Appropriate descriptive data on study sample are presented		
20	Distribution of compliance/persistence variable is presented (i.e. proportion of discontinuers)		
Non-Scoring	Statin specific result reported		
Final Quality Assessment Score (/20)			

[22] Adapted from International Society for Pharmacoeconomics and Outcomes Research (ISPOR): A Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases

APPENDIX D: SUPPLEMENTARY MATERIAL FOR CHAPTER 4

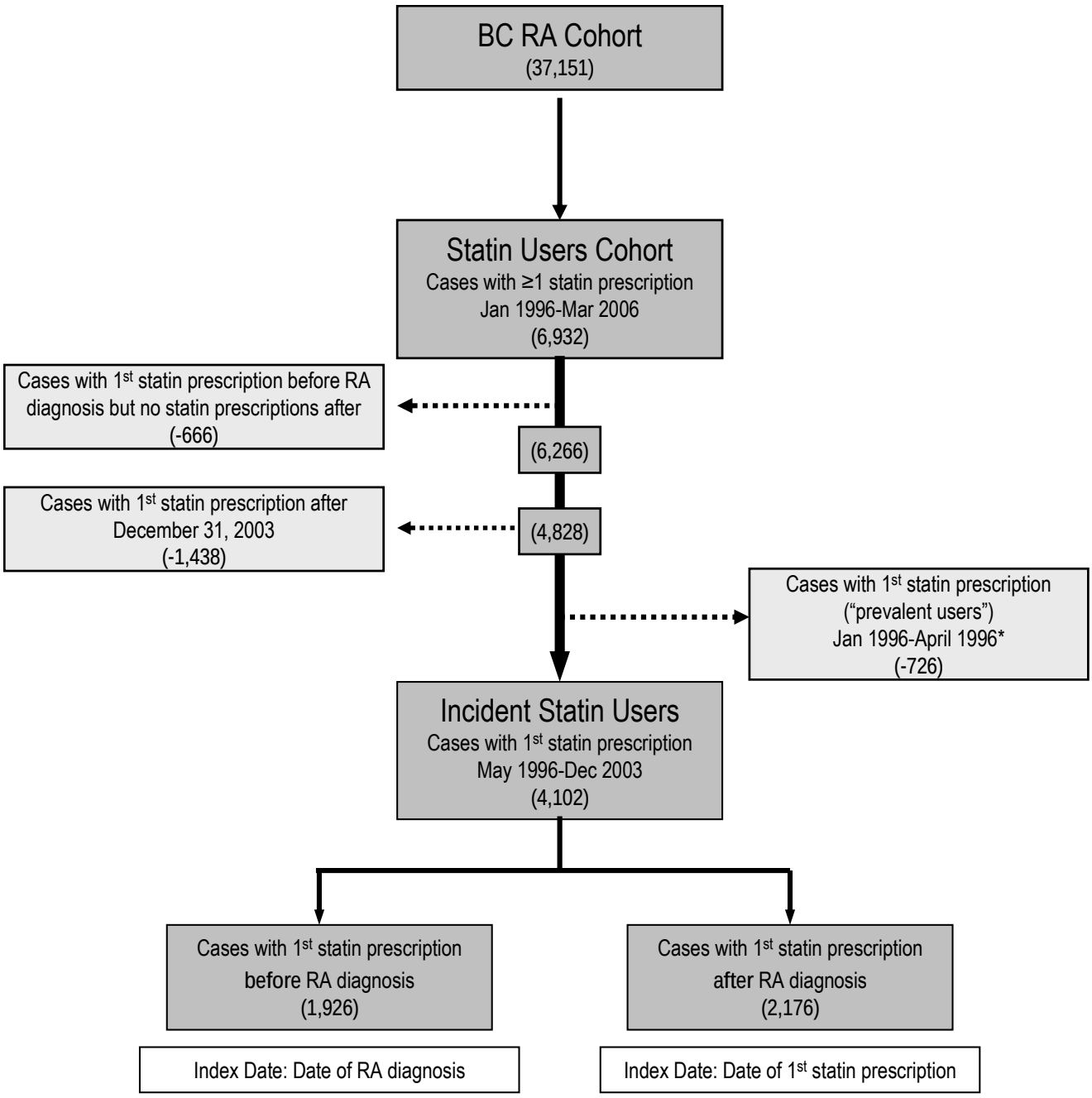

Figure D.1 Subject Flow for Pharmacoepidemiologic Studies of Impacts of Statin Discontinuation[23]

[23] Subject flow applies to both Chapter 4 and Chapter 5

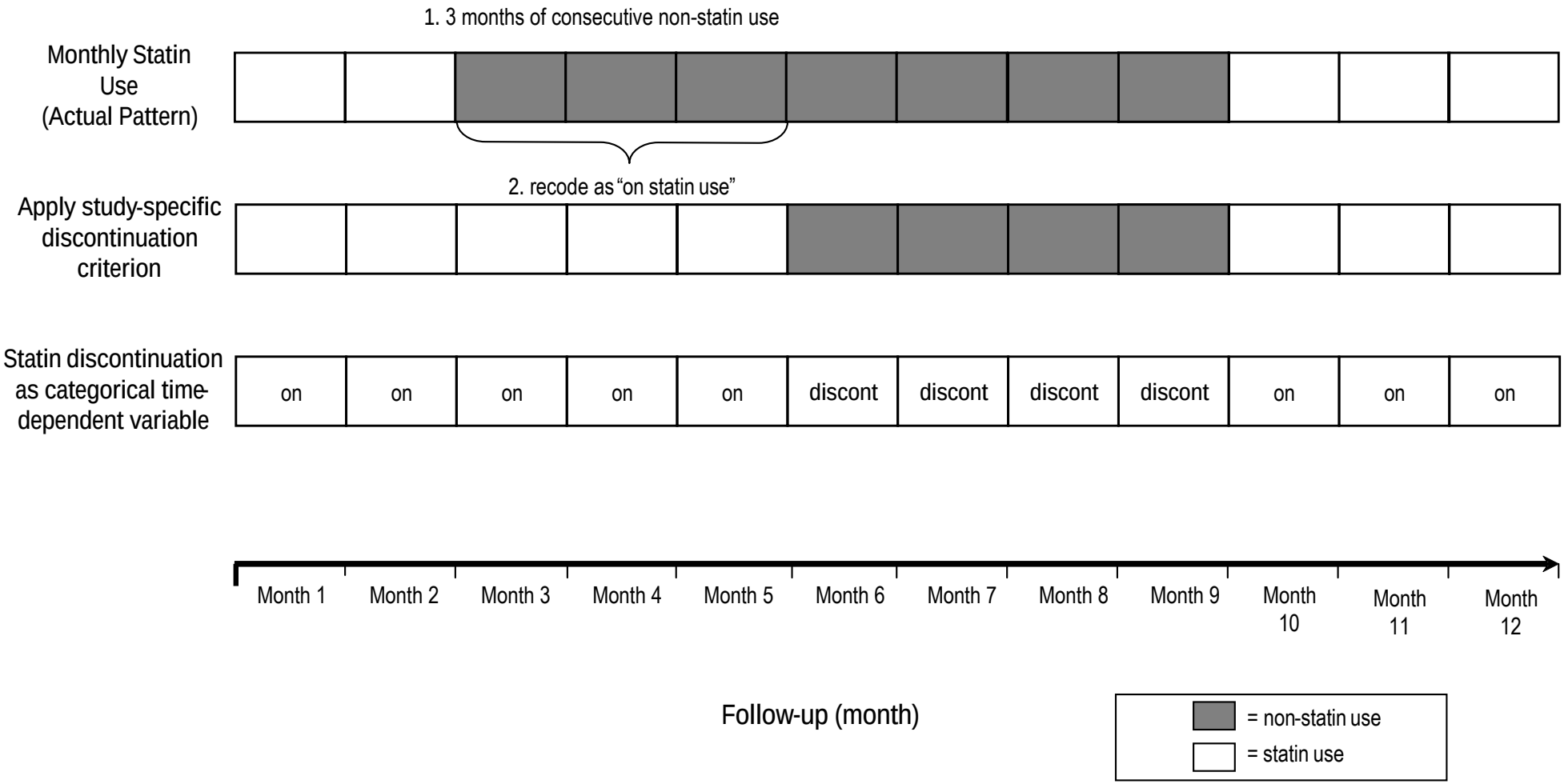

Figure D.2 Definition of Statin Discontinuation Applied in Pharmacoepidemiologic Studies of Impacts of Statin Discontinuation[24]

[24] Definition for statin discontinuation applies to both Chapter 4 and Chapter 5

Table D.1 Characteristics of the RA Cohort of Incident Statin Users According to Whether They Met Discontinuation Definition at Least Once Over Study Follow-Up

Characteristic	Did Not Meet Discontinuation Criteria	Met Discontinuation Criteria	P-value
Demographics			
Age (years), *mean (SD)*	67. 6 (9.9)	65.4 (10.8)	<0.0001
Women	1,300 (57.3)	1,160 (63.3)	<0.0001
RA Characteristics			
RA duration at index date (months), *mean (SD)*	18.3 (25.9)	19.9 (24.9)	0.057
Rate of RA-related medical visits (visits/person yr follow-up), *mean (SD)*	1.91 (6.71)	2.61 (4.99)	<0.0001
RA-related orthopedic procedures (over follow-up)	337 (14.9)	284 (15.5)	0.57
Use of RA prescription medications (over follow-up)			
Traditional NSAIDs	1,209 (53.3)	1,155 (63.0)	<0.0001
Cox-2 selective NSAIDs	691 (30.5)	656 (35.8)	0.0003
Glucocorticosteroids	934 (41.2)	789 (43.0)	0.23
Disease modifying anti-rheumatic drug categories*			
Group 1	1,247 (54.9)	1,084 (59.1)	0.023
Group 2	311 (13.7)	233 (12.7)	
Group 3	538 (23.7)	364 (19.9)	
Group 4	105 (4.6)	94 (5.1)	
Group 5	68 (3.0)	58 (3.2)	
Co-morbid Medical Conditions			
Prior acute myocardial infarction§	311 (13.7)	130 (7.1)	<0.0001
Prior cerebrovascular accident§	64 (2.8)	53 (2.9)	0.89
Use of anti hypertension medication†**	1,558 (68.7)	970 (52.9)	<0.0001
Use of congestive heart failure medication†***	833 (36.7)	511 (27.9)	<0.0001
Angina†	553 (24.4)	350 (19.1)	<0.0001
Diabetes†	448 (19.7)	282 (15.4)	0.0003

Table D.1 Characteristics of the RA Cohort of Incident Statin Users According to Whether They Met Discontinuation Definition at Least Once Over Study Follow-Up

Characteristic (continued)	Did Not Meet Discontinuation Criteria	Met Discontinuation Criteria	P-value
Use of anti arrhythmia medication† ****	61 (2.7)	33 (1.8)	0.059
Charlson Comorbidity Score†, *mean (SD)*	1.11 (1.31)	0.90 (1.22)	<0.0001
Other Medications Affecting Cardiovascular Risk			
Use of hormone replacement therapy†	279 (12.3)	227 (12.4)	0.93
Use of anticoagulants†	173 (7.6)	93 (5.1)	0.001

Values represent the number (percentage) of cases unless otherwise indicated. P-values for chi-square tests for categorical variables and independent samples t-test for continuous variables;

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; SD: Standard deviation;

**DMARD categories: 1 – no DMARD use; 2 – anti-malarial drugs, sulfasalazine; 3 – methotrexate, intramuscular gold; 4 - leflunomide, cyclosporin-A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil; 5 – biologics;*

§ Evaluated prior to start of follow-up (index date) since 1990 (earliest available data);

†Evaluated over 1 year preceding start of follow-up (index date);

***Anti hypertension medications included: angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blocking agents, angiotensin II receptor antagonists, alpha-adrenergic blocking agents, or central alpha-agonists;*

****Congestive heart failure medications included cardiac glycosides or diuretics;*

*****Anti arrhythmia medications included: adenosine, amiodarone, disopyramide, flecainide, lidocaine, mexitelene, procainamide, propafenone, digoxin, or quinidine.*

Table D.2 Univariate Hazard Ratios for Risk of AMI in RA Incident Users Cohort

	Univariate HR (95% CI)	p-value
PRIMARY EXPOSURE (Time-Dependent)		
Discontinuation (categorical)	1.46 (1.09, 1.95)	0.0110
Discontinuation (continuous)	1.017 (1.008, 1.026)	<0.0001
DEMOGRAPHICS		
Age	1.06 (1.05, 1.07)	<0.0001
Sex *(men vs women)*	1.64 (1.28, 2.11)	<0.0001
Initiation of first statin before RA (*yes vs no)*	1.53 (1.12, 2.07)	0.0069
RA duration at index date *(mo)*	1.006 (1.001, 1.011)	0.0254
Statin duration at index date *(mo)*	0.989 (0.981, 0.998)	0.0143
COVARIATES		
Fixed-in-Time Covariates		
Comorbid Medical Conditions		
Prior AMI (*yes vs no)*	3.083 (2.305, 4.124)	<0.0001
Prior cerebrovascular accident (*yes vs no)*	1.460 (0.774, 2.752)	0.2423
Angina (*yes vs no)*	1.831 (1.409, 2.378)	<0.0001
Diabetes (*yes vs no)*	1.524 (1.131, 2.053)	0.0056
COPD (*yes vs no)*	1.324 (0.681, 2.577)	0.4080
Charlson Score	1.266 (1.176, 1.362)	<0.0001
Use Cardiac Medications		
Use of anti hypertension medication (*yes vs no)*	2.280 (1.702, 3.054)	<0.0001
Use of anti arrhythmia medication (*yes vs no)*	1.808 (0.960, 3.405)	0.0666
Use of congestive heart failure medication (*yes vs no)*		
Use of Other Medications Affecting CVD Risk		
Use of HRT (*yes vs no)*	0.619 (0.400, 0.960)	0.0320
Use of anticoagulants (*yes vs no)*	1.365 (0.855, 2.179)	0.1925
Proxy Measures of RA Severity		
Rheumatologist care (*yes vs no)*	1.111 (0.865, 1.426)	0.4102
RA-related orthopaedic procedures	0.670 (0.460, 0.976)	0.0371
DMARD ranking		
1	1.000	
2	0.934 (0.624, 1.397)	0.7388
3	1.391 (1.046, 1.850)	0.0233
4	0.917 (0.495, 1.699)	0.7838
5	0.520 (0.213, 1.271)	0.1515
Time-Dependent Covariates		
Proxy Measures of RA Severity		
RA-related medical visits (visits/person yr follow-up)	1.046 (1.031, 1.062)	<0.0001
Use of RA Drugs		
Glucocorticosteroids	2.122 (1.607, 2.802)	<0.0001
NSAIDs	1.093 (0.795, 1.502)	0.5830
Methotrexate	1.540 (1.123, 2.111)	0.0073
COX2	0.894 (0.572, 1.399)	0.6251
Biologics	1.612 (0.664, 3.916)	0.2918

APPENDIX E: SUPPLEMENTARY MATERIAL FOR CHAPTER 5

Table E.1 Definition of Mortality Outcomes Using ICD10 Codes in Vital Statistics Data

Outcome	ICD10 Codes	Details of ICD10 Codes
1º: CVD mortality[25]	I00-I99	I00-I02 acute rheumatic fever I05-I09 chronic rheumatic heart disease I10-I15 hypertensive diseases I20-I25 ischemic heart diseases I26-I28 pulmonary heart disease and diseases of pulmonary circulation I30-I52 other forms of heart disease I60-I69 cerebrovascular diseases I70-I79 diseases of arteries, arterioles, and capillaries I80-I89 diseases of veins, lymphatic vessels, lymph nodes I95-I99 other and unspecified disorders of the circulatory system
2 º: All cause mortality	All	All

[25] Reference: Tu et al. National trends in rates of date and hospital admissions related to acute myocardial infarction, heart failure, and stroke, 1994-2004. Canadian Medical Association Journal. 2009; 180:E118-25.

Table E.2 Characteristics of the RA Cohort of Incident Statin Users According to Whether They Met Discontinuation Definition at Least Once Over Study Follow-Up

Characteristic	Did Not Meet Discontinuation Criteria	Met Discontinuation Criteria	P-value
Demographics			
Age (years), *mean (SD)*	67. 6 (9.9)	65.4 (10.8)	<0.0001
Women	1,300 (57.3)	1,160 (63.3)	<0.0001
RA Characteristics			
RA duration at index date (months), *mean (SD)*	18.3 (25.9)	19.9 (24.9)	0.057
Rate of RA-related medical visits (visits/person yr follow-up), *mean (SD)*			
RA-related orthopedic procedures (over follow-up)	344 (15.4)	292 (15.7)	0.77
Use of RA prescription medications (over follow-up)			
Traditional NSAIDs	1,191 (53.2)	1,173 (63.0)	<0.0001
Cox-2 selective NSAIDs	681 (30.4)	666 (35.8)	0.0003
Glucocorticosteroids	915 (40.9)	808 (43.4)	0.10
Disease modifying anti-rheumatic drug categories*			
Group 1	1,304 (58.2)	1,177 (63.2)	0.007
Group 2	291 (12.9)	201 (10.8)	
Group 3	484 (21.6)	341 (18.3)	
Group 4	91 (4.1)	81 (4.4)	
Group 5	70 (3.1)	62 (3.3)	
Co-morbid Medical Conditions			
Prior malignancy§	536 (23.9)	348 (18.7)	<0.0001
Prior acute myocardial infarction§	311 (13.7)	130 (7.1)	<0.0001
Prior infection requiring hospitalization§	186 (8.3)	161 (8.7)	0.69
Prior cerebrovascular accident§	64 (2.8)	53 (2.9)	0.89
Use of anti hypertension medication†**	1,558 (68.7)	970 (52.9)	<0.0001
Use of congestive heart failure medication†***	833 (36.7)	511 (27.9)	<0.0001
Angina†	553 (24.4)	350 (19.1)	<0.0001

Table E.2 Characteristics of the RA Cohort of Incident Statin Users According to Whether They Met Discontinuation Definition at Least Once Over Study Follow-Up

Characteristic (continued)	Did Not Meet Discontinuation Criteria	Met Discontinuation Criteria	P-value
Diabetes†	448 (19.7)	282 (15.4)	0.0003
Chronic obstructive pulmonary disease†	266 (11.9)	242 (13.0)	0.28
Gastrointestinal disease†	82 (3.7)	66 (3.5)	0.84
Use of anti arrhythmia medication† ****	61 (2.7)	33 (1.8)	0.059
Renal disease†	53 (2.4)	30 (1.6)	0.087
Charlson Comorbidity Score†, *mean (SD)*	1.11 (1.31)	0.90 (1.22)	<0.0001
Other Medications Affecting Cardiovascular Risk			
Use of hormone replacement therapy†	279 (12.3)	227 (12.4)	0.93
Use of anticoagulants†	173 (7.6)	93 (5.1)	0.001

Values represent the number (percentage) of cases unless otherwise indicated. P-values for chi-square tests for categorical variables and independent samples t-test for continuous variables;

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; SD: Standard deviation;

**DMARD categories: 1 – no DMARD use; 2 – anti-malarial drugs, sulfasalazine; 3 – methotrexate, intramuscular gold; 4 - leflunomide, cyclosporin-A, azathioprine, cyclophosphamide, chlorambucil or mycophenolate mofetil; 5 – biologics;*

§ Evaluated prior to start of follow-up (index date) since 1990 (earliest available data);

†Evaluated over 1 year preceding start of follow-up (index date);

***Anti hypertension medications included: angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blocking agents, angiotensin II receptor antagonists, alpha-adrenergic blocking agents, or central alpha-agonists;*

****Congestive heart failure medications included cardiac glycosides or diuretics;*

*****Anti arrhythmia medications included: adenosine, amiodarone, disopyramide, flecainide, lidocaine, mexitelene, procainamide, propafenone, digoxin, or quinidine.*

Table E.3 Univariate Hazard Ratios for Risk of CVD Mortality in RA Incident Users Cohort

	Univariate HR (95% CI)	p-value
PRIMARY EXPOSURE (Time-Dependent)		
Discontinuation (categorical)	1.41 (1.02, 1.96)	0.04
Discontinuation (continuous)	1.004 (1.001, 1.016)	0.05
DEMOGRAPHICS		
Age	1.08 (1.07, 1.10)	<0.0001
Sex *(men vs women)*	1.49 (1.12, 1.97)	0.006
Initiation of first statin before RA (*yes vs no)*	2.00 (1.42, 2.82)	<0.0001
RA duration at index date *(mo)*	1.010 (1.004, 1.016)	0.0008
Statin duration at index date *(mo)*	0.99 (0.98, 0.99)	0.002
COVARIATES		
Fixed-in-Time Covariates		
Comorbid Medical Conditions		
Prior AMI (*yes vs no)*	2.94 (2.12, 4.06)	<0.0001
Prior malignancy (*yes vs no)*	1.34 (0.96, 1.86)	0.06
Prior cerebrovascular accident (*yes vs no)*	1.97 (1.26, 3.06)	0.003
Prior infection requiring hospitalization (*yes vs no)*	2.37 (1.62, 3.46)	<0.0001
Angina (*yes vs no)*	2.04 (1.53, 2.72)	<0.0001
Diabetes (*yes vs no)*	1.54 (1.10, 2.15)	0.01
COPD (*yes vs no)*	1.07 (0.71, 1.62)	0.7
GI diseases	1.66 (0.90, 3.05)	0.1
Renal disease	4.83 (2.79, 8.33)	<0.0001
Charlson Score	1.37 (1.27, 1.47)	<0.0001
Use Cardiac Medications		
Use of anti hypertension medication (*yes vs no)*	3.36 (2.32, 4.86)	<0.0001
Use of anti arrhythmia medication (*yes vs no)*	2.51 (1.36, 4.61)	0.003
Use of congestive heart failure medication (*yes vs no)*	3.04 (2.29, 4.03)	<0.0001
Use of Other Medications Affecting CVD Risk		
Use of HRT (*yes vs no)*	0.57 (0.34, 0.95)	0.03
Use of anticoagulants (*yes vs no)*	2.88 (1.94, 4.27)	<0.0001
Proxy Measures of RA Severity		
Rheumatologist care (*yes vs no)*	0.97 (0.74, 1.29)	0.8
RA-related orthopaedic procedures	0.80 (0.54, 1.19)	0.3
DMARD ranking		
1	1.00	
2	1.00 (0.65, 1.56)	1.00
3	1.12 (0.79, 1.57)	0.5
4	2.12 (1.31, 3.43)	0.002
5	0.37 (0.12, 1.18)	0.09

Table E.3 Univariate Hazard Ratios for Risk of CVD Mortality in RA Incident Users Cohort

	Univariate HR (95% CI)	p-value
Time-Dependent Covariates		
Proxy Measures of RA Severity		
RA-related medical visits (visits/person yr follow-up)	1.14 (0.73, 1.79)	0.6
Use of RA Drugs		
Glucocorticosteroids	1.98 (1.45, 2.72)	<0.0001
NSAIDs	0.75 (0.50, 1.13)	0.1
Methotrexate	0.79 (0.50, 1.22)	0.2
COX2	0.76 (0.44, 1.31)	0.3
Biologics	0.37 (0.05, 2.64)	0.3

Table E.4 Univariate Hazard Ratios for Risk of All Cause Mortality in RA Incident Users Cohort

	Univariate HR (95% CI)	p-value
PRIMARY EXPOSURE (Time-Dependent)		
Discontinuation (categorical)	1.70 (1.39, 2.08)	<0.0001
Discontinuation (continuous)	1.011 (1.004, 1.018)	0.001
DEMOGRAPHICS		
Age	1.08 (1.06, 1.09)	<0.0001
Sex *(men vs women)*	1.30 (1.08, 1.56)	0.005
Initiation of first statin before RA (*yes vs no)*	2.27 (1.82, 2.84)	<0.0001
RA duration at index date *(mo)*	1.011 (1.007, 1.015)	<0.0001
Statin duration at index date *(mo)*	0.98 (0.97, 0.99)	<0.0001
COVARIATES		
Fixed-in-Time Covariates		
Comorbid Medical Conditions		
Prior AMI (*yes vs no)*	2.21 (1.76, 2.79)	<0.0001
Prior malignancy (*yes vs no)*	1.66 (1.36, 2.04)	<0.0001
Prior cerebrovascular accident (*yes vs no)*	1.96 (1.47, 2.62)	<0.0001
Prior infection requiring hospitalization (*yes vs no)*	2.08 (1.60, 2.69)	<0.0001
Angina (*yes vs no)*	1.79 (1.48, 2.16)	<0.0001
Diabetes (*yes vs no)*	1.43 (1.15, 1.78)	0.002
COPD (*yes vs no)*	1.38 (1.08, 1.76)	0.01
GI diseases	1.59 (1.06, 2.38)	0.02
Renal disease	4.31 (2.97, 6.24)	<0.0001
Charlson Score	1.36 (1.29, 1.43)	<0.0001
Use Cardiac Medications		
Use of anti hypertension medication (*yes vs no)*	2.60 (2.08, 3.24)	<0.0001
Use of anti arrhythmia medication (*yes vs no)*	1.69 (1.06, 2.71)	0.03
Use of congestive heart failure medication (*yes vs no)*	2.51 (2.09, 3.01)	<0.0001
Use of Other Medications Affecting CVD Risk		
Use of HRT (*yes vs no)*	0.73 (0.54, 0.98)	0.04
Use of anticoagulants (*yes vs no)*	2.29 (1.74, 3.04)	<0.0001
Proxy Measures of RA Severity		
Rheumatologist care (*yes vs no)*	1.13 (0.94, 1.35)	0.2
RA-related orthopaedic procedures	0.87 (0.67, 1.11)	0.3
DMARD ranking		
1	1.00	
2	0.93 (0.69, 1.24)	0.6
3	1.00 (0.80, 1.26)	0.9
4	1.64 (1.17, 2.31)	0.005
5	0.66 (0.38, 1.15)	0.1

Table E.4 Univariate Hazard Ratios for Risk of All Cause Mortality in RA Incident Users Cohort

	Univariate HR (95% CI)	p-value
Time-Dependent Covariates		
Proxy Measures of RA Severity		
RA-related medical visits (visits/person yr follow-up)	1.06 (0.77, 1.44)	0.7
Use of RA Drugs		
Glucocorticosteroids	2.81 (2.32, 3.40)	<0.0001
NSAIDs	0.78 (0.59, 1.01)	0.06
Methotrexate	0.66 (0.49, 0.90)	0.009
COX2	0.95 (0.69, 1.30)	0.7
Biologics	1.28 (0.63, 2.57)	0.5

Table E.5 Final Multivariable Model for Statin Discontinuation, as a Time-Dependent Continuous Variable, and Risk of CVD Mortality

	Adjusted Hazard Ratio (95% Confidence Interval)	p-value§
Primary Exposure (Time-Dependent)		
Statin discontinuation *(yes vs no)*	1.004 (1.001, 1.016)	0.04
Fixed-in-Time Covariates		
Age	1.07 (1.05, 1.09)	<0.0001
Sex *(men vs women)*	1.50 (1.12, 2.00)	0.006
Prior AMI *(yes vs no)*	1.45 (1.02, 2.07)	0.04
Prior infection requiring hospitalization *(yes vs no)*	1.53 (1.03, 2.28)	0.04
Diabetes *(yes vs no)*	1.25 (0.89, 1.77)	0.20
Use of anti hypertension medication *(yes vs no)*	1.82 (1.22, 2.69)	0.003
Use of congestive heart failure medication *(yes vs no)*	1.78 (1.31, 2.44)	0.0003
Use of anticoagulant *(yes vs no)*	1.27 (0.83, 1.93)	0.26
Charlson comorbidity score	1.14 (1.04, 1.25)	0.006
Time-Dependent Covariates		
Current use of glucocorticosteroid *(yes vs no)*	1.52 (1.09, 2.11)	0.01
Current use of methotrexate *(yes vs no)*	0.66 (0.42, 1.05)	0.07

§p-value for 2-tailed Wald test

Table E.6 Final Multivariable Model for Statin Discontinuation, as a Time-Dependent Continuous Variable, and Risk of All Cause Mortality

	Adjusted Hazard Ratio (95% Confidence Interval)	p-value§
Primary Exposure (Time-Dependent)		
Statin discontinuation *(yes vs no)*	1.01 (1.01, 1.02)	0.01
Fixed-in-Time Covariates		
Age	1.07 (1.05, 1.08)	<0.0001
Sex *(men vs women)*	1.37 (1.13, 1.65)	0.001
Prior AMI *(yes vs no)*	1.14 (0.89, 1.47)	0.29
Prior malignancy *(yes vs no)*	1.07 (0.86, 1.33)	0.57
Prior infection requiring hospitalization *(yes vs no)*	1.39 (1.07, 1.83)	0.01
Diabetes *(yes vs no)*	1.23 (0.97, 1.54)	0.08
Use of anti-hypertension medication *(yes vs no)*	1.64 (1.29, 2.08)	<0.0001
Use of congestive heart failure medication *(yes vs no)*	1.57 (1.29, 1.92)	<0.0001
Charlson comorbidity score	1.17 (1.10, 1.25)	<0.0001
Time-Dependent Covariates		
Current use of glucocorticosteroid *(yes vs no)*	2.29 (1.89, 2.80)	<0.0001
Current use of methotrexate *(yes vs no)*	0.52 (0.38, 0.72)	<0.0001

§p-value for 2-tailed Wald test