Statins for Secondary Prevention in Elderly Patients After Acute Myocardial Infarction

Evaluation of Class Effect and Early Initiation

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ABSTRACT

This thesis investigates two clinically important questions regarding the effectiveness of statins used in patients with acute myocardial infarction (AMI). First, is the effectiveness for secondary prevention of different statins a class effect? Second, is there an association between the timing of initiation of statins after AMI and the risk of recurrent AMI and mortality?

To study the class effect, a systematic review was conducted to compare different statins based on adjusted indirect comparison using published placebo-controlled randomized trials of statins for long-term cardiovascular prevention. This review did not find a difference in the effect among statins for reducing the risk of fatal and nonfatal cardiovascular outcomes. To further study the question, we evaluated the class effect of statins among elderly patients post-AMI using provincial-wide healthcare administrative databases. The results showed similar effects among statins for the prevention of recurrent AMI or mortality in these patients, supporting a class effect.

To study the effect associated with the timing of statin initiation, the rates of recurrent AMI and mortality were compared between patients who filled statin prescriptions at discharge and those who initiated statins between 1 to 3 months post discharge. The results showed that the effect was not associated with the time of statin initiation in the first 3-month period after discharge. Because of possible survival bias when comparing patients who differ systematically in their time of treatment initiation, a study was conducted to evaluate five different methods that can be used to characterize and control for this bias. The methods of prescription time distribution matching and time-dependent exposure appeared to be most effective in the control of survival bias.

In summary, our studies have shown that statins exhibit a class effect in secondary prevention among elderly patients post-AMI, and that difference in the time of statin initiation in the first 3 months post discharge does not lead to changes in outcome.

RÉSUMÉ

Cette thèse étudie deux questions importantes d'un point de vue clinique quant à l'efficacité des statines chez les patients ayant subi un infarctus aigu du myocarde (IAM): d'abord, l'efficacité en prévention secondaire de différentes statines est-elle un effet de classe, et enfin, y a-t-il une relation entre le délai d'initiation du traitement (après l'IAM) et le risque de deuxième IAM et/ou de mortalité?

Pour étudier l'effet de classe, nous avons d'abord effectué une revue systématique de litérature dans le but de comparer différentes statines sur la base de comparaisons indirectes ajustées en utilisant les études randomisées qui ont comparé une statine à un placebo relativement à un effet cardiovasculaire préventif à long terme. Notre analyse n'a montré aucune différence entre les différentes statines quant à la réduction du risque des événements cardiaques fatals et non-fatals. Pour approfondir la question, nous avons étudié l'effet de classe des statines chez des patients âgés ayant subi un IAM en utilisant des banques de données administratives provinciales. Nos analyses ont montré des effets similaires pour les différentes statines dans la prévention d'un second IAM et de la mortalité, en accord avec l'hypothèse d'un effet de classe.

Pour étudier l'effet du délai d'initiation du traitement, les taux de second IAM et de mortalité de patients qui ont eu une prescription de statine à la sortie de l'hôpital ont été comparés à ceux des patients qui ont commencé la prise de statine entre 1 et 3 mois après leur congé de l'hôpital. Nos analyses ont montré que l'effet du traitement n'était pas associé à la longueur du délai d'initiation dudit traitement (à l'intérieur de 3 mois après le congé). Finalements une étude de cinq méthodes permettant de mesurer et de contrôler le biais de survie sélective a été effectuée, étant donné la possibilité de ce biais lors de la comparaison de

patients différant systématiquement dans leurs longueurs respectives de délai d'initiation du traitement. Nous avons montré que l'imputation de temps de délai (dans le groupe de patients sans délai, sur la base de la distribution observée chez les patients avec délai) et l'utilisation de mesures d'exposition changeant dans le temps étaient les méthodes les plus efficaces dans le contrôle de ce biais.

En résumé, nous avons montré que les statines ont un effet de classe chez les patients âgés ayant subi un IAM et que le délai d'initiation du traitement (à l'intérieur des 3 mois suivants le congé de l'hôpital) n'induit aucune différence quant au risque de deuxième IAM et/ou de mortalité.

ABBREVIATIONS

4S	The Scandinavian Simvastatin Survival Study
ACEI	Angiotensin converting enzyme inhibitors
ACS	Acute coronary syndrome
ALLHAT-LLT	The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial
AMI	Acute myocardial infarction
ARF	Acute renal failure
ASCOT-LLA	The Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm
A to Z Trial	Early intensive versus a delayed conservative simvastatin strategy in patients with acute coronary syndrome: phase Z of the A to Z trial
CARDS	The Collaborative Atorvastatin Diabetes Study
CARE	The Cholesterol and Recurrent Events trial
CCHS	Canadian Community Health Survey
CHD	Coronary heart disease
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CRF	Chronic renal failure
CVD	Cardiovascular disease
FDA	The Food and Drug Association
GREACE	The GREek Atorvastatin and Coronary-heart-disease Evaluation study
HDL	High density lipoprotein
HPS	The MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in high risk individuals
ICD	International classification of diseases
LDL	Low density lipoprotein
LIPID	The Long-term Intervention with Pravastatin in Ischemic Disease study

MIRACL	The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study
NCEP	National Cholesterol Education Program
PPP	The Prospective Pravastatin Pooling project
PROSPER	The Prospective Study of Pravastatin in the Elderly at Risk
PROVE IT	The Pravastatin or Atorvastatin Evaluation and Infection Therapy - the intensive vs moderate lipid lowering with statin after acute coronary syndrome
RCT	Randomized controlled trial
REVERSAL	The Reversal of Atherosclerosis with Aggressive Lipid Lowering trial
WOSCOPS	The West of Scotland Coronary Prevention Study

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PREFACE

This thesis has been prepared as a manuscript-based thesis in accordance with the McGill University guidelines for thesis preparation. It consists of 6 chapters including 4 manuscripts accepted or submitted to peer reviewed medical journals. Chapter one provides an introduction in relation to the background information that contains the study rationale and the thesis objectives. Chapter two provides comprehensive literature reviews with regard to the two study questions defined in the thesis, which include a systematic review (the first manuscript) that examines the question of a class effect among statins, and a review of clinical evidence regarding the effect of early statin initiation after AMI. Chapter three describes the data source, study cohort and provides an overview of the design of the subsequent three observational studies. Chapter four includes the second manuscript that evaluates the class effect among statins for secondary prevention in elderly patients post-AMI. Chapter five consists of two manuscripts related to the study of early statin initiation. Because of possible survival bias in the study, the third manuscript focuses on the comparison of five different methods in the control of survival bias. This study provides a methodological framework for the fourth manuscript, in which we address the clinical question regarding the association between the time of statin initiation and risk of recurrent AMI and mortality in elderly patients post-AMI. Finally, chapter 6 provides a summary of the research findings and conclusions.

All manuscripts are formatted according to the requirements of the specific journals to which they have been submitted or to be submitted. As such, the

tables, figures and references for each manuscript are located at the end of the manuscript. Additional tables and figures in the text of the thesis are included in *Appendix A*. Chapters containing manuscripts introduce each manuscript with a preface and include a section of additional discussion. A complete list of references for the entire thesis, including references from all manuscripts, is included at the end of the thesis.

Ethics approval for this study has been obtained from the Faculty of Medicine Institutional Review Board of McGill University. A copy of the certification is included in *Appendix B*. All manuscript authors have approved the inclusion of all manuscripts in this thesis. A copy of the release form signed by all manuscript co-authors is included in *Appendix D*. The contributions of manuscript authors are described in the following section.

Contributions of Manuscript Authors

As PhD candidate and first author of the four manuscripts in this thesis, Zheng Zhou was primarily responsible for all phases of the research including study design, analysis, interpretation, and writing of the manuscripts. The research objectives were determined in conjunction with the candidate's thesis supervisory committee that included Dr. Louise Pilote (supervisor), Dr. Elham Rahme (co-supervisor) and Dr. Michal Abrahamowicz. All manuscripts co-authors provided guidance in their respective areas of expertise and participated in critical revision and approval of the final manuscripts. In particular, Dr. Jack V. Tu and Dr. Karin Humphries provided the databases from Ontario and British Columbia, respectively. Drs. Tu, Humphries, Mark J.

Eisenberg and Peter C. Austin participated in the development of study concept, and critical revision of the second manuscript (study of class effect among statins). Dr. Peter C. Austin also contributed to the data analysis in Ontario for the statin class effect study using the statistical programs supplied by the candidate. Dr. Michal Abrahamowicz (thesis committee member) provided guidance regarding the statistical analysis and result interpretation of the second and third manuscripts. Dr. Elham Rahme (co-supervisor) played a major role in supervising the statistical and methodological aspects of all four manuscripts. Finally, Dr. Louise Pilote (supervisor) provided the databases from Quebec, participated in defining the research questions, and supervised the methodological and clinical aspects of all four manuscripts.

Data management and programming

The candidate was responsible for cleaning and merging the source data files (Quebec and British Columbia) supplied by Hugues Richard in dataset modules. Using these source data files, the candidate independently defined and created the study cohorts and variables, and wrote programs for statistical analyses. For the second manuscript, the cohort in Ontario was assembled by Dr. Austin according to specific instructions provided by the candidate (i.e. inclusion and exclusion criteria, information regarding study variable creation). The candidate also sent programs for performing data analysis in Ontario. For the third manuscript, the candidate wrote programs for statistical analyses with respect to five different methods used to study and control for survival bias. Among these five methods, the statistical program for achieving prescription time

distribution matching (method 4) was developed with help from Youssef Toubouti and Dr. Rahme. The candidate further modified this program to accommodate changes in the design in the fourth manuscript that investigated the effect of early statin initiation.

The candidate independently performed all statistical analyses and data interpretation in all four manuscripts.

Statement of Originality

Several components of this thesis constitute original scholarship and advancement of knowledge in cardiovascular pharmacoepidemiology. In addressing the question of class effect among statins, the first manuscript represents the first systematic review to examine the relative effect of major statins based on adjusted indirect comparison using large-scale placebo controlled RCTs. The second manuscript represents the first large observational study (with data from three provinces of Canada) to compare statins head-to-head for long-term cardiovascular prevention in post AMI elderly. In addressing the question regarding the effect of early statin initiation post AMI, the third manuscript is the first to evaluate the performance of existing and new methods in the control of survival bias. Among these methods, the method of prescription time distribution matching is novel and provides a methodological solution for the fourth manuscript that examines the association between the timing of statin initiation post discharge of AMI and risk for recurrent AMI and mortality. This association, which is of large clinical interest, has not been examined previously in observational studies, partly due to the lack of effective approach to control for survival bias in the study design.

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First, I shall give my deepest gratitude to my supervisor, Dr. Louise Pilote, for giving me this research opportunity and giving me so much help during my PhD study over the past few years. Her commitment and guidance to her students is greatly appreciated. I also wish to convey my greatest appreciation to Dr. Elham Rahme, my co-supervisor, who has been extremely supportive in guiding me through my PhD research by contributing her expertise in biostatistics and pharmacoepidemiology. Both supervisors have been very generous in dedicating their time to help me achieve the objectives of my research. I am also grateful to Dr. Michal Abrahamowicz, who served as my thesis committee member, for his contribution to the study planning as well as his thoughtful criticism of my written work. I also thank Drs. Lawrence Joseph, Theresa Gyorkos for their availability as advisors, mentors to support of my academic endeavors.

My gratitude is also given to Hugues Richard, Patrick Belisle, Youssef Toubouti, Hassan Behlouli and other members of the team for providing help with computer programming, having insightful discussions and being close friends during the years of my PhD training. Their friendship will be always remembered.

I am fortunate to have been educated at the Department of Epidemiology and Biostatistics at McGill University. I thank all my professors for providing me with the foundation for my academic career in this field.

Finally, I thank my beloved wife and my family for their unconditional support and encouragement. Without them this achievement would not be possible.

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The research projects were funded in part by grants from the Canadian Institutes of Health Research (CIHR). For statin class effect, the study was funded in part by CIHR Grant No. MOP-53181 (Principal investigator: Dr. Louise Pilote). For effect of early initiation of statins, the study was funded in part by CIHR, Grant No. ATF-66669 (Principal investigator: Dr. Louise Pilote).

CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Burden of Cardiovascular Disease in Canada

Cardiovascular diseases (CVD) remain the leading cause of death and disability among Canadians, representing an enormous health and economic burden. Due to the aging of the population, such a burden is expected to increase (Manuel et al., 2003). The 2000-2001 Canadian Community Health Survey (CCHS) conducted by Statistics Canada (Statistics Canada, 2001) showed that among elderly people (≥ 70 years), almost 1 in 4 men (27%) and 1 in 5 women (21%) were diagnosed with heart disease. Although CVD mortality has been decreasing substantially over the past few decades, a report by the Heart and Stroke Foundation of Canada in 2003 showed that, between 1999–2001, still over 22,000 Canadians died each year as a result of acute myocardial infarction (AMI). Death due to CVD, including AMI, stroke and other ischemic CVD, accounts for up to 36% (~79,000) of total deaths in the country. This rate is about 8% higher than cancer related mortality. Given this disease burden, it is a priority for health care professionals and decision makers to develop effective means for CVD prevention and therapy, and to evaluate the effectiveness of existing treatments.

1.1.2 Role of Statin in the Treatment of Hypercholesterolemia and CVD Prevention

High blood cholesterol concentration (hypercholesterolemia) is one of the proven risk factors for CVD. It plays a key role in the development and progression of atherosclerosis in arteries. Because high cholesterol is a modifiable risk factor, the goal has been set to seek aggressive diagnosis and treatment of this condition. Recommendations made by the Canadian Lipid Guideline (Fodor et al., 2000) and the US National Cholesterol Education Program Adult Treatment Panel III Guideline (The NCEP ATP III, 2001) suggest a "desirable" total cholesterol level ≤ 5.2 mmol/l, and, an "optimal" low-density lipoprotein cholesterol level (LDL-cholesterol*) ≤ 2.6 mmol/l. Among people having one or more additional risk factors for CVD (Tanuseputro et al., 2003) including cigarette smoking, high blood pressure (≥ 140/90mmHg), family history of heart disease, age (men ≥ 45; women ≥ 55 years), obesity or diabetes, achieving these cholesterol level objectives becomes even more critical.

Among the therapeutic agents developed for the treatment of hypercholesterolemia, statins emerged in early 1980s as new cholesterol-lowering agents with their effect found to be much more potent than other drugs available at that time, such as resins and niacin. The functional structure of the statin molecule (hydroxy acid portion) mimics the natural substrate for HMG-CoA reductase, the rate-limiting enzyme in the pathway of cholesterol synthesis. The main mechanism for statins to lower cholesterol is thus through its competitive binding to this enzyme and inhibition of cholesterol production by the liver. Statins also induce changes in cholesterol transport

* LDL-C, so-called "bad" cholesterol, is the main source of cholesterol buildup and blockage in the arteries.

and disposition in the blood and tissues by reducing the synthesis of the LDL, and increasing the clearance of the circulating LDL-cholesterol by LDL-receptor expression in the liver. Moderate reduction of blood triglycerides and elevation of high-density lipoprotein levels (HDL-cholesterol*) are also observed (CPS 2002, Brown et al. 1985, Knopp 1999). Cholesterol lowering by statins stabilizes the vulnerable atherosclerotic plaque by reducing its lipid contents, thus rendering it less susceptible to rupture.

So far, several large-scale randomized controlled trials (RCTs) have demonstrated the benefit of cholesterol lowering by statins to reduce both fatal and non-fatal ischemic cardiovascular events. The efficacy of statins has been shown in people with and without a history of CVD, in different age groups, and people having different risk profiles for CVD (The 4S Group 1994, Shepherd et al., 1995, Sacks et al., 1996, The LIPID Study Group 1998, Sacks et al., 2000, The ALLHAT-LLT Investigators 2002, HPS Collaborative Group 2002, Shepherd et al., 2002, Sever et al., 2003).

1.1.3 Drugs in the Class of Statin and Trends in Statin Use

At least five statins are currently used in clinical practice. The prototype drug of the statin class is lovastatin, first available in 1987. Chemically modified versions of this compound have been sequentially introduced by different manufacturers in the past two decades. These include pravastatin, simvastatin, fluvastatin, and more recently,

* HDL-C, so-called "good" cholesterol that helps keep cholesterol from building up in the arteries

atorvastatin and cerivastatin*. The newest member, rosuvastatin, was approved by the US Food and Drug Administration (FDA) in 2003. With the basic mechanism of cholesterol lowering remaining the same, statins differ to a various extent in their pharmacological properties. The introduction of these statins has undoubtedly provided improvements in therapy, but the large number of these drugs has also created difficulty in terms of treatment choice.

Among the current top three prescribed cardiovascular medications in Canada, i.e. diuretics, angiotensin converting enzyme (ACE) inhibitors and statins, the largest increase in usage and costs was seen with statins, with the number of prescriptions increasing from 3.5 million in 1996 to 11 million in 2001(Heart and Stroke Foundation of Canada 2003, Jackevicius et al., 2003). This increase corresponded to prescription costs of 1 billion dollar in 2001, which are still growing at 20% annually. The surging trends in statin usage and expenditures have urged an evaluation of the appropriateness of their use and effectiveness on patient outcomes. Importantly, some of the fast growth cannot be explained by the available major clinical trial evidence and/or practice guidelines. The increase and preferential use of certain statins may have been driven by the marketing force and is not entirely evidence-based (Mamdani et al. 2001, Marwick 2003). Above all, it is for patient to provide optimal treatment by addressing the questions of whether statins are equally effective (i.e. a class effect) or whether one statin is better than the other in cardiovascular prevention.

* Cerivastatin was removed from the market in 2001 because of its association with fatal rhabdomyolysis, a severe muscle adverse reaction.

1.1.4 Concept of Class Effect and the Study of Class Effect Among Statins

A class effect implies that members of a drug class are therapeutically equivalent and can be used interchangeably (Furberg 2000, Kennedy et al., 2002). Simple membership in a class often fails to encompass all drug related actions that could have an influence on the benefit and risk of individual medications. The removal of cerivastatin from the market in 2001 due to its adverse effect in causing severe muscle damage and related symptoms while other statins do not share this problem suggest that statins may not all have the same safety and efficacy profile (Graham et al., 2004). In the absence of complete evidence of the effect of each individual drug in a class, this assumption requires evaluation.

The rationale to study the class effect among statins in this thesis can be stated as three-fold. First, although statins share the same basic structure, they differ in important functional groups and pharmacological properties (Table 1-1). These differences could potentially influence the extent to which they are beneficial. Notable differences include the need for metabolic activation, half-life ($t_{1/2}$), effect on other serum lipid components (e.g. HDL, triglycerides), liver and renal metabolism, bioavailability and potency (Compendium of Pharmaceuticals and Specialties, 2002). Second, currently there is a lack of solid evidence in support of either similar or differential efficacy of statins in cardiovascular prevention. Although many trials have compared statins with regard to surrogate endpoints, such as changes in lipid profile (Farnier et al., 2000), markers of hemostasis and inflammation (Joukhadar et al., 2001, Wiklund et al., 2002) or regression of atherotic plaques (Nissen et al., 2004), it is unclear to what extent these

results can be extrapolated to clinically relevant outcomes. To date, there has been only one trial, the PROVE-IT trial (*the intensive vs moderate lipid lowering with statin after acute coronary syndrome*) (Cannon et al., 2004), in which two statins were studied for cardiovascular prevention. However, the objective of this trial focused on comparing the intensity of treatment (i.e. aggressive treatment with atorvastatin 80 mg *versus* standard therapy with pravastatin 40 mg), rather than the two particular statins used. Third, preferential prescribing already occurs in daily practice. This is despite limited comparative data of different statins on long-term cardiovascular prevention (Jackevicius et al., 2001, Mamdani et al., 2001, Jackevicius et al., 2003). Atorvastatin, for example, has been used extensively since it was launched in 1997 and has become the number one prescribed statin in North America. On the other hand, the "reference pricing" policy adopted by some provinces in Canada (e.g. British Columbia) regulates the reimbursement to be based on the lowest price medication in a drug class to control health care costs (Schneeweiss et al., 2002). This policy encourages the use of older generation (cheaper) statins, such as lovastatin. Thus, it is important to assess the relative efficacy of different statins in order to better inform clinical and policy decision-making and ensure that patients receive the most effective treatment.

Given that the number of patients in need for statins continues to increase, evidence on the class effect among statins will have a direct impact on patient benefit as well as on health care resource utilization. To investigate the class effect of statins is the subject of the first part of this thesis.

1.1.5 Benefit of Early Initiation of Statin After Acute Coronary Syndrome – A Need for Clinical Investigations

Until recently, cholesterol-lowering therapy has been viewed exclusively as a long-term strategy to reduce cardiovascular risk, as statins are thought to promote gradual removal of lipid from the core of atherosclerotic plaques accompanied by gradual and modest regression of arterial stenoses (Archbold et al., 1998). Challenging this conventional point of view, recent experimental data have suggested that statins also act rapidly in the early period after an acute coronary syndrome (ACS)* to reverse some of the abnormalities of the arterial wall that may predispose patients to recurrent ischemic events. The mechanisms have been characterized as mainly "cholesterol-independent" (Corsini et al., 1999, Sposito et al. 2002), and include reducing local vascular inflammation, restoring the endothelial function and decreasing the tendency of blood clotting. All these mechanisms are thought to have a favorable impact in the early period following an ACS. As a result, the early introduction of statins during the acute phase of a coronary event has been highlighted as a possible therapeutic approach to improve outcomes in patients with unstable coronary disease (Olsson et al., 2002).

However, available clinical evidence that helps delineate the issue is still very limited. Results from randomized controlled trials as well as observational studies are inconsistent. Mixed results could be explained by different settings, designs, end-point definitions and analyses, but they also indicate a need for more evidence on this issue.

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* A term used to cover a group of clinical symptoms compatible with acute myocardial ischemia, including clinical conditions ranging from unstable angina to non-Q-wave or Q-wave myocardial infarction.

To further investigate the effect associated with the early initiation of statins after acute coronary events is the subject of the second part of this thesis.

1.2 Objectives of the Thesis

1.2.1 Main Objective

The main objective of this thesis is to address two clinically important questions related to the effectiveness of statins in preventing recurrent AMI and mortality in elderly survivors after AMI. The two study questions are:

1) *Class Effect.* To study the relative effectiveness of different statins in the prevention of recurrent AMI and death;
2) *Effect of early statin initiation post AMI.* To study the association between the time of statin initiation after discharge from a hospitalization for AMI and the risk of a recurrent AMI and mortality.

1.2.2 Specific Objectives

Each of these questions is addressed in two separate studies. Thus, the thesis includes four manuscripts. The specific objectives of each study are described as follows:

Class Effect

Objective of Study 1. To evaluate the possibility of a class effect among statins based on a systematic review of published placebo-controlled randomized controlled trials (RCTs) of different statins using adjusted indirect comparison methodology (manuscript #1).

Objective of Study 2. To evaluate the possibility of a class effect among statins for the secondary prevention after AMI in a population-based retrospective cohort study (manuscript #2).

Effect of Early Statin Initiation Post-AMI

Objectives of Study 3. To characterize the survival bias associated with patients' time-to-initiation of a statin, and to propose methodological solutions to control for this bias (manuscript #3).

Objective of Study 4. To study the effect of early initiation of statin post-AMI, in particular, the association between the time of statin initiation and the risk for recurrent AMI and mortality (manuscript #4).

CHAPTER 2

STATINS IN CARDIOVASCULAR PREVENTION: A REVIEW

2.1 Relative Effectiveness of Statins: A Class Effect?

2.1.1 Preface to Manuscript #1

There are major financial disincentives for drug companies to invest in costly comparative trials that test survival benefits of different drugs in a same class. Such comparative data are also not required by the regulatory agents for drug approval. Due to the lack of direct comparison trials, the current level of scientific evidence is insufficient to justify the selection of one statin over another. However, the question of "class effect" can be possibly assessed through an indirect comparison (Song et al., 2003) using the many large-scale RCTs comparing a statin to a placebo.

The following manuscript investigates the relative efficacy of three major statins (pravastatin, simvastatin and atorvastatin) by conducting a systematic review of the currently published placebo controlled RCTs of statins for long-term cardiovascular prevention. We used the adjusted indirect comparison methodology advocated by Bucher (Bucher et al., 1997).

Results from this systematic review are expected to provide preliminary evidence on the class effect of statins and serve as a basis for the second manuscript, in which we further examine the question in a population-based setting using healthcare administrative databases.

Abstract

Background The relative efficacy of different statins for long-term cardiovascular prevention remains largely undetermined.

Methods Using adjusted indirect comparison, we compared 3 statins (pravastatin, simvastatin and atorvastatin) based on published placebo controlled randomized trials (RCTs) for long-term cardiovascular prevention. A systematic literature search between 1980 and 2004 was conducted. RCTs of the 3 statins, which studied cardiovascular diseases (CVD) or death as the outcome, enrolled ≥ 1,000 participants and had ≥ 1 year follow-up were included. Trials were grouped according to the statin under study. A pooled relative risk (RR) was derived for each set of trials using a random-effects model. Adjusted indirect comparisons using pooled RR's were made between statins with regard to prespecified clinical outcomes.

Results Eight placebo-controlled trials met the inclusion criteria: 4 pravastatin trials (n= 25,572), 2 simvastatin trials (n=24,980) and 2 atorvastatin trials (n=13,143). Graphical and statistical assessments showed minimal heterogeneity in the trials' effect sizes. Adjusted indirect comparisons did not reveal a statistically significant difference between statins in reducing fatal and non-fatal myocardial infarctions (simvastatin versus pravastatin: relative risk (RR) 0.93 [95% confidence interval (CI): 0.84-1.03]; atorvastatin versus simvastatin: RR 0.84 [95% CI: 0.66-1.08]; atorvastatin versus pravastatin: RR 0.79 [95% CI: 0.61-1.02]). We were unable to detect differences also in outcomes for fatal and non-fatal strokes, all cardiovascular deaths and all cause deaths.

Conclusion Evidence from published statin RCTs suggests that pravastatin, simvastatin and atorvastatin, when used at their standard dosages, show no statistically significant difference in their effect on long-term cardiovascular prevention.

Introduction

High blood cholesterol is one of the proven risk factors for cardiovascular diseases (CVD). Large-scale randomized controlled trials (RCTs) have established that treatment with statins to lower cholesterol level may prevent future cardiovascular events in individuals with different risk profiles[1-9]. As a result, statins are among the cardiovascular medications that have seen the biggest increase of usage and reimbursement costs to the health care provider over the past decade[10-13].

Since the first statin, lovastatin, became available in the late 1980's, several statins have been introduced, including simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin and, most recently, rosuvastatin[14]. With the basic mechanism of cholesterol lowering remaining the same, statins differ to a various extent in pharmacological properties. The removal of cerivastatin from the market in 2001 due to an unusually high proportion of its users experiencing severe muscle damage suggests that statins may not all have the same safety and efficacy profile. As the number of patients in need for statin therapy continues to increase, information regarding the relative efficacy of statins is needed to better inform decision-making[15].

There have been a number of trials that directly compared statins with regard to surrogate endpoints, such as lipid reduction, changes in inflammatory markers, or reduction in atherotic plaques (e.g. *The reversal of atherosclerosis with aggressive lipid lowering trial*, REVERSAL[16]). However, it remains uncertain to what extend these results can be extrapolated to clinically relevant outcomes. Despite the many large-scale RCTs comparing statin to a placebo or usual care, there is very limited information on the relative

effect of statins for long-term cardiovascular prevention. The PROVE-IT study (*The intensive vs moderate lipid lowering with statin after acute coronary syndrome*)[17] compared intensive lipid-lowering regimen (atorvastatin 80 mg) versus standard therapy (pravastatin 40 mg). However, the objective of the study was to compare the intensity of treatment (aggressive vs. standard) rather than the particular statins used. Additional information is needed as to how atorvastatin compared to pravastatin, as well as to other major statins for long-term cardiovascular prevention.

In the absence of sufficient direct evidence, the method of adjusted indirect comparison can be used to estimate the relative effect of competing interventions[18]. In contrast to the usual method that pools findings only from the active treatment arms in the original trials, the adjusted indirect approach respects the randomization originally assigned in each trial. The indirect comparison of two treatments is made upon the adjustment of the results of their direct comparisons to a common control, thus taking into account the prognostic characteristics of participants across trials. The validity of this approach has been suggested by both theory[18, 19] and by empirical assessments[20-22].

We conducted this study to determine the relative effect of three major statins, i.e. pravastatin, simvastatin and atorvastatin, using the adjusted indirect comparison. We used data from published large-scale RCTs that compare these statins to placebo for long-term CVD prevention.

Methods

Study Selection

We identified RCTs of pravastatin, simvastatin and atorvastatin through a systematic literature search in the *MEDLINE* and the *Cochrane Controlled Trials Register* databases (Oxford, UK: Update Software Ltd., 2004) between 1980 and 2004 for English language studies using the key words: *atorvastatin, simvastatin, pravastatin* in combination with any of the following words: *cholesterol, prevention, cardiovascular disease, myocardial infarction, coronary heart disease, ischemic heart disease, stroke, mortality* in the title or abstract. Studies were restricted to randomized trials comparing statin vs. placebo. In addition, trials that evaluated a statin vs. usual care were also identified. Use of additional medications by the trial participants was considered acceptable, if the medications were applied equally in both arms. No age, sex restrictions were applied.

Inclusion criteria

Completed RCTs were included if they measured CVD or mortality as the outcome, enrolled ≥ 1,000 participants and had a minimum follow-up of 1 year. These criteria were decided a priori in accordance with the features of long-term statin prevention trials to exclude small and short follow-up trials. Particularly true to statins to study the lipid-lowering effect on long-term cardiovascular prevention, trials having small number of subjects and short follow are not able to address the question with clinical and methodological adequacy. In addition, the publication of large studies is unlikely to depend on the magnitude or direction of their results, minimizing the chance of publication bias[23].

Outcomes

Four outcomes were compared between statins: 1) major coronary events, defined as fatal coronary heart disease and non-fatal MI; 2) major cerebrovascular events (fatal and non-fatal stroke); 3) all cardiovascular deaths (coronary and cerebrovascular causes); and 4) all cause deaths.

Data abstraction

For each study outcome, the number of events and the total number of subjects in the two treatment arms were abstracted from the original publications[1-9] and related substudies[4, 24-38]. To facilitate data combining and comparison, we calculated the relative risk (RR) from each study as the ratio of the proportion of events in the treatment group to that in the control group.

Assessment of heterogeneity of trial results

The consistency of the treatment effect across statin trials was assessed by the graphical method of L'Abbé plot[39, 40], in which the observed risk (proportion) in the treatment group for a study outcome was plotted against the risk in the control group. In addition, test for heterogeneity (a *Chi-square* statistic) was performed before the statistical pooling of the results[41].

Data analysis

The overall treatment effects of statins with regard to our study outcomes were estimated by pooling the estimates (RR) from all eligible placebo-controlled RCTs in the study using a random effect model, proposed by DerSimonian and Laird[42].

Methods of Comparison Between Statins

Placebo-controlled RCTs that met the inclusion criteria were grouped according to the statin under study. A pooled RR was derived from each set of statin trials using a random-effects model. Adjusted indirect comparison[18, 20] was made pairwise using pooled RR's of each statin with regard to the specified outcomes (Appendix).

Secondary analysis

Analyses were also performed to assess the impact of including the "usual care" controlled trials on the results. These trials were not included in the main analysis, as the usual care settings are considered to be different from using a placebo control. Also, their inclusion potentially violates the requirement for an adjusted indirect comparison, in which inference is made upon direct comparisons with a common comparator[18, 19], here, a placebo.

To examine the robustness of the results, all comparisons were repeated using pooled estimates of RR obtained from a fixed-effects model.

Statistical analyses and graphic generation were performed using SAS version 8.0 (SAS Institute Inc. Cary, NC.) and *The Cochrane Collaboration's Review Manager* software (RevMan version 4.2). Significant level of α=0.05 (2-sided) was used for all tests.

Results

The search resulted in 745 studies. Trials were excluded because they were ongoing trials (n= 56) or did not study CVD or death as the outcome (n=678); or had < 1 year follow-up (n=1, *The myocardial ischemia reduction with aggressive cholesterol lowering study*, MIRACL[43]). No trial that studied clinical outcomes (CVD or death) was excluded because of having less than 1000 subjects. Eight placebo-controlled RCTs met the inclusion criteria. These included 4 pravastatin trials (*The west of Scotland coronary prevention study,* WOSCOPS[1]; *The cholesterol and recurrent events trial*, CARE[2]; *The long-term intervention with pravastatin in ischemic disease study*, LIPID[3]; *The prospective study of pravastatin in the elderly at risk*, PROSPER; total n=25,572); 2 simvastatin trials (*The Scandinavian simvastatin survival study,* 4S[7]; *The MRC/BHF heart protection study of cholesterol lowering with simvastatin in high risk individuals*, HPS[8]; total n=24,980) and 2 atorvastatin trials (*The Anglo-Scandinavian cardiac outcomes trial - lipid lowering arm*, ASCOT-LLA[9]; *The collaborative atorvastatin diabetes study*, CARDS[44]; total n=13,143).

All these trials were double-blinded, multi-center trials with consecutive patient recruitment. Attrition rates were reported to be ≤ 3% and average non-compliance rates ≤ 15%. The average study follow-up of the eight placebo-controlled trials ranged from 3 years to 6 years. In addition to the primary (WOSCOPS, ASCOT-LLA, CARDS) and secondary prevention (4S, CARE, LIPID) studies, recent trials (HPS, PROSPER) also enrolled subjects with or without a CHD history, but all at high risk for cardiovascular events, e.g. having diabetes, hypertension and other atherosclerotic diseases (Table 1).

Some of these trials were conducted in certain population subgroups. The WOSCOPS studied simvastatin in men < 65 years. The PROSPER study evaluated pravastatin among the elderly ≥ 65 years. The study participants in the ASCOT-LLA trial all had a diagnosis of hypertension, whereas in the CARDS trial, all subjects were diabetes patients.

The baseline cholesterol level of the trial participants varied depending on the study objectives and was reflected in the inclusion criteria. For instance, the CARE and CARDS trials enrolled patients with moderate cholesterol levels, whereas the 4S and WOSCOPS trials targeted mainly hypercholesterolemic patients. The ASCOT-LLA trial included patients with total cholesterol < 6.5 mmol/L. Other trials applied fewer restrictions (Table 1).

Change of lipid levels by statin trials

All trials reported similar absolute percentage changes (percentage change in treatment group minus that in control group) in lipid levels (total cholesterol reduction > 19%; LDL-C reduction > 25%) (Table 1).

Assessment of heterogeneity in trial results

Statin treatment resulted in a significant reduction in the event rate of the primary cardiovascular outcomes. On the L'Abbé plot, a protective effect was evident for all trials (Figure 1). There was minimal variation in the effect sizes (RR's), despite different baseline patient risks (i.e. risk in the control group). Similar patterns were found in plots for outcomes of fatal and non-fatal strokes, all cardiovascular death and all cause deaths.

A test of heterogeneity for all trials and within each set of statin trials showed that the effect sizes (RR) were homogeneous with regard to different outcomes, except for the outcome of all cause mortality among the simvastatin trials (4S, HPS; χ^2 test, p=0.03, df=1). A random-effects model was used to obtain pooled estimates for all outcomes.

Effects of statins on CVD prevention

With all 8 placebo-controlled RCTs included, the overall relative risk for fatal CHD and non-fatal MI by statin therapy was 0.75 (95% CI, 0.69-0.81). For fatal and non-fatal strokes, all cardiovascular deaths and all cause deaths, the relative risks were 0.81 (95% CI, 0.73-0.89), 0.82 (95% CI, 0.75-0.89) and 0.85 (95% CI, 0.79-0.92), respectively.

Adjusted indirect comparison of statins on cardiovascular outcomes

In the main analysis including the placebo-controlled RCTs, the pooled RR's (95% CI) for major coronary events of the three statins were: pravastatin vs. placebo: RR 0.78 (95% CI: 0.72-0.83); simvastatin vs. placebo: 0.72 (0.67-0.79); atorvastatin vs. placebo: 0.61 (0.48-0.77) (Figure 2). Pairwise comparisons did not find statistically significant differences in the effect across statins, although atorvastatin appeared to be associated with a greater reduction of major coronary events compared with the two other statins: atorvastatin vs. simvastatin: 0.84 (0.66-1.08), p=0.18; atorvastatin vs. pravastatin 0.79 (0.61-1.02), p=0.06; simvastatin vs. pravastatin: 0.93 (0.84- 1.03), p=0.18. We found no evidence suggesting a difference also in outcomes for fatal and non-fatal stroke, all cardiovascular death, and all cause mortality (Table 2).

Secondary analyses

Using a fixed-effects model to obtain pooled estimates for the comparison did not materially change the results. The results were, however, affected by including the two eligible usual care-controlled trials, including 1 pravastatin trial *(The antihypertensive and lipid-lowering treatment to prevent heart attack trial*, ALLHAT-LLT[6]; n=10,355) and 1 atorvastatin trial (*The Greek atorvastatin and coronary-hart-disease evaluation study*, GREACE[45]; n=1,600). With their inclusion, the comparison favored atorvastatin for reducing major coronary events compared with simvastatin and pravastatin, i.e. atorvastatin vs. Simvastatin: RR 0.79 (95% CI: 0.63-0.99), p=0.04; atorvastatin vs. pravastatin: 0.71 (0.56-0.90), p=0.004. For other study outcomes, we did not find any statistically significant difference.

Discussion

Using the method of adjusted indirect comparison, we compared three statins based on published large placebo-controlled RCTs. Our results revealed no statistically significant difference in the three statins used at their standard dosages for long-term cardiovascular prevention. Although there appears to be a trend that atorvastatin, simvastatin have a greater reduction in the major cardiac events.

The benefit of statins as a group is unquestionable, yet comparative data regarding the relative efficacy between statins is very limited. Although two statins were studied in the PROVE-IT trial, the trial was conducted primarily to show the benefit associated with increased intensity of the treatment (aggressive vs. standard therapy) rather than to compare two statins with similar regimens. It is unclear, for example, whether similar results would have been observed if a higher dose of pravastatin was given. Other than the PROVE-IT study, no trial has directly compared statins for cardiovascular prevention[46]. Moreover, none of the previous summary studies[47-49] has examined the question regarding how statins compare to one another. Our results are among the first to address this question.

Although these trials have been conducted in populations with different prognostic characteristics, the statistical pooling of the results was appropriate for the following reasons. The statistical heterogeneity in the effect size (RR) was found to be minimal, as indicated by both the L'Abbé plots and the heterogeneity test. In addition, by using a random-effects model, the possible between-study variance was accounted for. The presence of clinical heterogeneity in these trials was evident, however results from meta-

analysis and substudies[4, 24-38], particularly those utilizing individual patient data[4, 36, 38], have shown that the relative risk reduction of cardiovascular events by statins does not depend on the patients' risk stratified by age, sex, CHD history and other cardiovascular risk factors. This consistency in the effect across different baseline characteristics is also required by the method of adjusted indirect comparison to ensure valid results[18].

Of note, the results were affected by the inclusion of usual care controlled trials in the secondary analyses. Despite some significant findings, we remained cautious because of the different clinical settings that usual care may represent compared with placebo control, and because their inclusion may have violated the basic assumption of adjusted indirect comparison. In addition, the features of these two trials caused a difficulty in the result interpretation. The ALLHAT-LLT was criticized for suboptimal trial monitoring and had a high cross-over rate. The finding of this trial was not statistically significant, however, it had a large sample size which influenced greatly the pooled estimate; whereas the GREACE, its objective was to evaluate effect of cholesterol-lowering to the national guideline goal (LDL-C < 2.6 mmol/L). Extensive dosage titration resulted in a magnitude of risk reduction very different from those observed in other trials.

There are several limitations to the study. First, although the results were drawn from published RCTs, the study was observational in nature, thus the results had a weaker interpretation than a truly randomized trial. Second, in the absence of individual patient data from the trials, aggregate data were used. This usage may have limited our ability to further address the heterogeneity issue and obtain more reliable results from a pooled analysis[50]. Third, the number of trials in the study was small. The estimated

between-study variance by the random-effects model could be less reliable[51]. Fourth, were unpublished trials sought after, the conclusions might have been different. Finally, for the trials included in the main analysis, a fixed dose of each statin was used, which were approximately cholesterol-lowering equivalent[52]. This usage of dose limited our ability to further study the effect of dosage among these trials. Our results thus pertain to the dosage used in the trials and should be interpreted accordingly. It should be noted, however, that these dosages are most commonly used in practice[53].

In summary, results from adjusted indirect comparison using published RCTs of statins suggest that the three statins, when used at their standard dosages, do not differ significantly in their effect for long-term cardiovascular prevention. The relatively wide confidence intervals in some pairwise comparisons, however, suggest that more evidence is needed. In this regard, additional results from ongoing statin trials[46] and properly designed large observational studies will help better address the question.

Appendix

Method of Adjusted Indirect Comparison

Suppose:

$ln(\text{RR}_{\text{pooled estimate of statin A vs. placebo control}})$: T_{AC} (SE_{AC})

$ln(\text{RR}_{\text{pooled estimate of statin B vs. placebo control}})$: T_{BC} (SE_{BC})

where *ln* is natural logarithm;

SE is the standard error.

The adjusted indirect estimates (statin A vs. statin B):

$$T_{AB}^* = T_{AC} - T_{BC}; \quad SE(T_{AB}) = \sqrt{SE(T_{AC})^2 + SE(T_{BC})^2}$$

its 95% confidence interval:

$$T_{AB} \pm 1.96 \times SE(T_{AB})$$

then, $RR_{AB} = exp(T_{AB})$ and 95% CI is $exp(T_{AB} \pm 1.96 \times SE(T_{AB}))$

where *exp* is the exponential function.

Hypothesis testing:

H_0: $T_{AB} = 0$; H_a: $T_{AB} \neq 0$

test statistic:

$$Z = \frac{T_{AB}}{SE(T_{AB})}$$

Note: comparisons were made on the log-scale of the pooled RR's. *ln*(RR) has been shown to be approximately normally distributed. To transform back to the original scale, we take exponential of T_{AB}.

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Table 1. Characteristics of the Statin Trials

	Simvastatin Trials		Pravastatin Trials				Atorvastatin Trials	
	4S (n=4,444)	**HPS** (n=20,536)	**WOSCOPS** (n=6,595)	**CARE** (n=4,159)	**LIPID** (n=9,014)	**PROSPER** (n=5,804)	**ASCOT-LLA** (n=10,305)	**CARDS** (n=2,838)
Year of publication	1994	2002	1995	1996	1998	2002	2003	2004
Dose (mg)	20-40	40	40	40	40	40	10	10
Year of follow-up	5.4	5	5	5	6	3.2	3.3	3.9
Mean age	59	64	55	59	61	75	63	62
> 65 yrs (%)	33	52	1	31	39	100	64	62
Men (%)	81	75	100	86	83	48	81	68
History of CHD (%)	100	65	0	100	100	44	0	0
Previous MI	79	41	0	100	64	13	0	0
Time since MI (months)	> 6	-‡	No MI	>3-20	>3-36	> 6	No MI	No MI
Risk factors (%)								
Hypertension	26	41	16	43	42	62	100	84
Diabetes	5	29	1	14	9	11	25	100
Current Smoking	26	14	35	16	10	27	33	23

Table 1 (Cont.) Characteristics of the Statin Trials

	Simvastatin Trials		Pravastatin Trials				Atorvastatin Trials	
	4S	**HPS**	**WOSCOPS**	**CARE**	**LIPID**	**PROSPER**	**ASCOT-LLA**	**CARDS**
Total-C (mmol/l)[§]								
Eligibility	5.5-8.0	≥ 3.5	>6.5	<6.2	4.0-7.0	4.0-9.0	≤ 6.5	-
Baseline (SD)	6.8 (0.7)	5.9 (1.0)	7.0 (0.6)	5.4 (0.4)	5.7 (0.7)	5.7 (0.9)	5.5 (0.8)	5.4 (0.8)
Net change by Treatment, %	-26	-20	-20	-20	-18	-	-19	-26
LDL-C								
Eligibility	-	-	4.5-6.0	3.0-4.5	No restriction	-	-	≤ 4.1
Baseline (SD)	4.9 (0.7)	3.4 (0.8)	5.0 (0.4)	3.6 (0.4)	3.9 (0.7)	3.8 (0.8)	3.4 (0.7)	3.0 (0.7)
Net change by Treatment, %	-36	-29	-26	-28	-25	-27	-29	-40
HDL-C								
Baseline (SD)	1.2 (0.3)	1.1 (0.3)	1.1 (0.2)	1.0 (0.2)	1.0 (0.2)	1.3 (0.4)	1.3 (0.4)	1.4 (0.3)
Net change by Treatment, %	+7	+3	+5	+5	+5	+5	+2	-1
Triglycerides								
Eligibility	-	-	<6.0	<4.0	<5.0	≤6.0	<4.5	≤6.8
Baseline (SD)	1.5 (0.5)	2.1 (1.4)	1.8(0.8)	1.8 (0.7)	1.8 (0.8)	1.5 (0.7)	1.7 (0.9)	1.7 (0.6)
Net change by Treatment, %	-17	-14	-12	-14	-11	-12	-13	-19

† Dosage of atorvastatin titrated to lower LDL-C to the NCEP target level (<2.6 mmol/l);

‡ "-" Unspecified in the original publication;

§ To convert values for cholesterol from *mmol/L* to *mg/L*, multiply by 38.7; for triglyceride, multiply by 88.6.

Table 2. Adjusted Indirect Comparisons Between Statins for Different Outcomes

	Point estimate of the effect difference (95% CI)	P-Value*
Major coronary events (fatal CHD and non-fatal MI)		
Simvastatin vs. Pravastatin	0.93 (0.84 - 1.03)	0.18
Atorvastatin vs. Simvastatin	0.84 (0.66 - 1.08)	0.18
Atorvastatin vs. Pravastatin	0.79 (0.61 - 1.02)	0.06
Major cerebrovascular events (fatal, non-fatal stroke)		
Simvastatin vs. Pravastatin	0.87 (0.71 - 1.07)	0.18
Atorvastatin vs. Simvastatin	0.90 (0.68 - 1.20)	0.47
Atorvastatin vs. Pravastatin	0.78 (0.57 - 1.07)	0.12
All cardiovascular deaths (coronary and cerebrovascular)		
Simvastatin vs. Pravastatin	0.96 (0.75 - 1.23)	0.73
Atorvastatin vs. Simvastatin	1.10 (0.77 - 1.58)	0.61
Atorvastatin vs. Pravastatin	1.05 (0.78 - 1.42)	0.74
All cause deaths		
Simvastatin vs. Pravastatin	0.93 (0.73 - 1.19)	0.57
Atorvastatin vs. Simvastatin	1.03 (0.79 - 1.35)	0.82
Atorvastatin vs. Pravastatin	0.96 (0.78 - 1.18)	0.71

* P-value of a test based on a null hypothesis (H_0) that the effect of the two statins are equal, i.e. *RR* of statin A vs. statin B=1.0.

Figure 1.

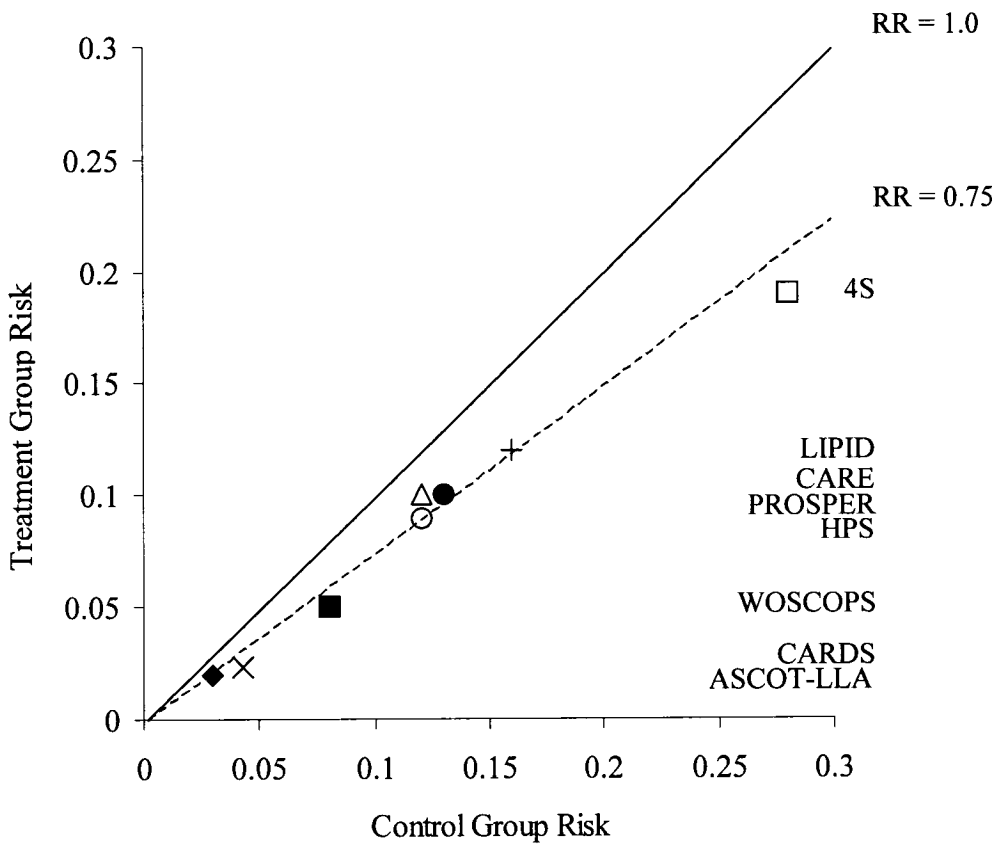
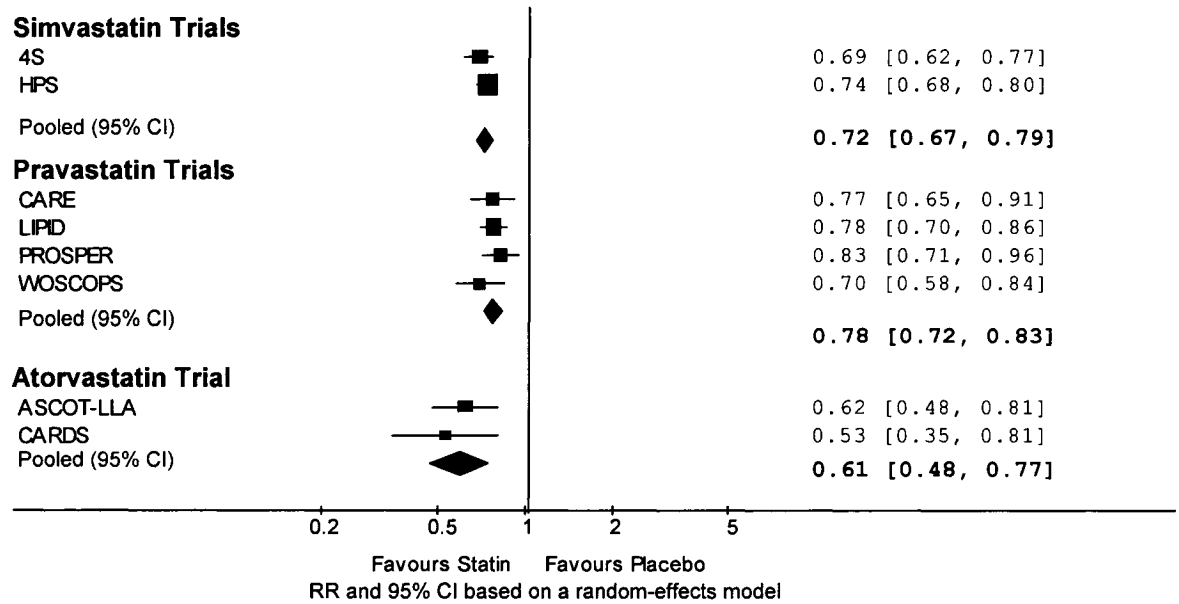

RR = 1.0
RR = 0.75
4S
LIPID
CARE
PROSPER
HPS
WOSCOPS
CARDS
ASCOT-LLA
Treatment Group Risk
Control Group Risk
0
0.05
0.1
0.15
0.2
0.25
0.3

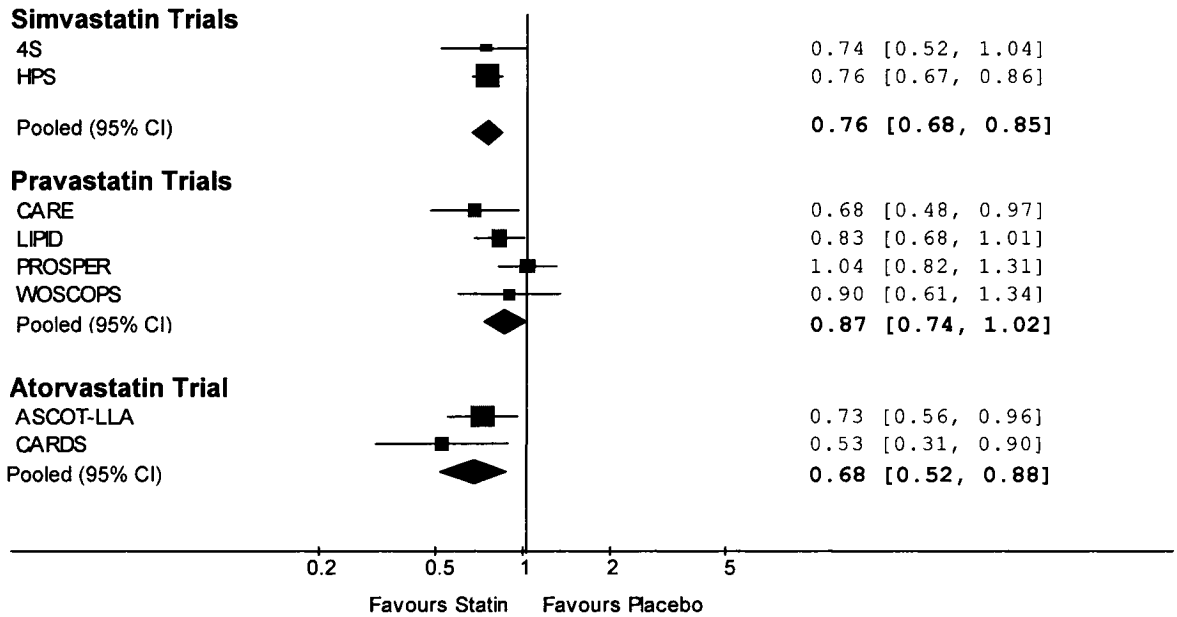
Figure 2.

Major Coronary Events (fatal CHD, non-fatal MI)



RR and 95% CI based on a random-effects model

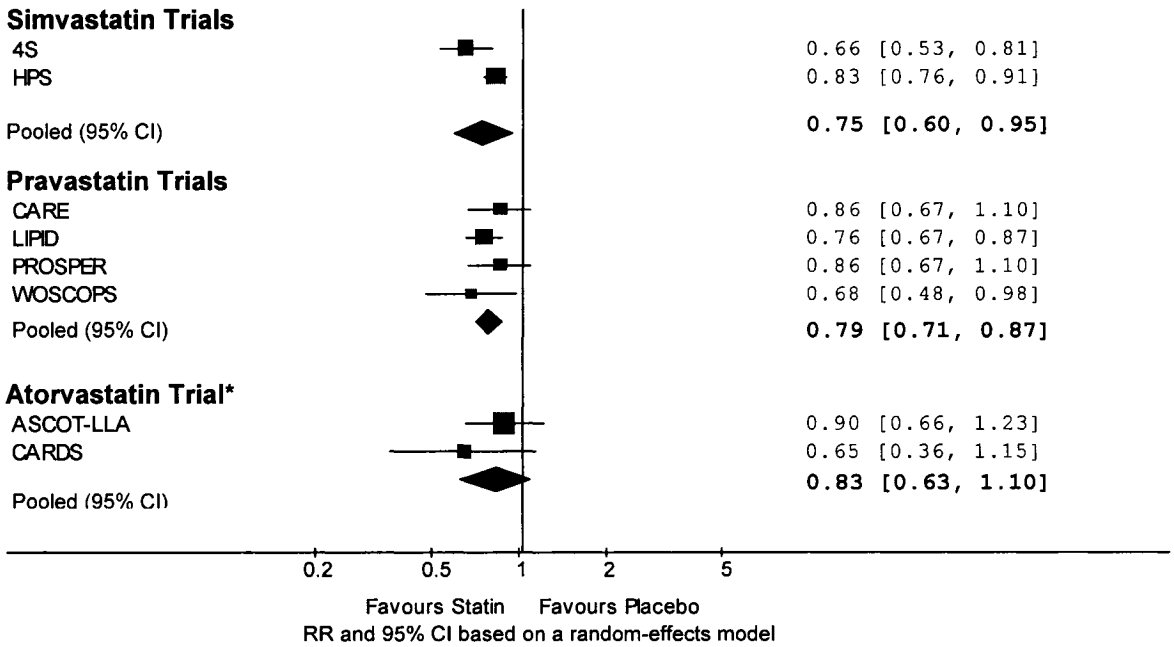
Major Cerebrovascular Events (fatal, non-fatal stroke)



RR and 95% CI based on a random-effects model

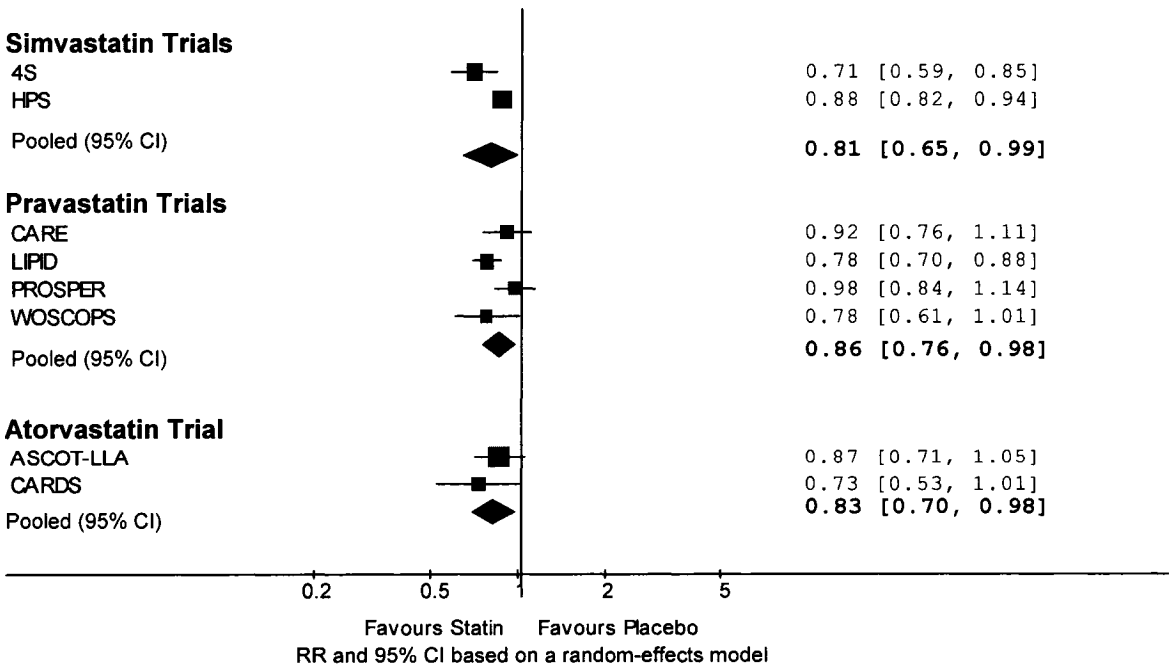
Figure 2. (Cont.)

All Cardiovascular Deaths (coronary and cerebrovascular)



RR and 95% CI based on a random-effects model

All Cause Deaths



RR and 95% CI based on a random-effects model

Figure Legend

Figure 1. L'Abbé plot of statin trials for the effect on major coronary events. The observed risk (proportion) for major coronary events (fatal and non-fatal MI) in the treatment group is plotted against the observed risk in the control group. RR's of all trials were to the right of the diagonal (RR=1.0) and were close the dotted line representing the estimated overall treatment effect (RR = 0.75). The secondary prevention trials (4S, CARE, LIPID) show higher baseline risk, whereas the primary prevention trials (WOSCOP, ASCOT-LLA, CARDS) displayed a lower risk. (□ 4S; + LIPID; • CARE; Δ PROSPER; ○ HPS; ■ WOSCOPS; ♦ ASCOT-LLA; X CARDS)

Figure 2. Effects of statin treatment on cardiovascular outcomes. Trials are grouped according to the statin under study. With regard to each outcome, the RR and 95% CI from individual studies as well as the pooled estimate of the group were shown. For each individual study, the area of the black square is proportional to the study size in each subdivision, and the width of the horizontal line indicates the 95% CI. For pooled estimates, the result and its 95% CI are represented by a diamond. Area to the left of the vertical line of unity (RR=1.0) favors treatment; area to the right of the line favors the placebo.

2.1.3 Additional Discussion

Agents within a same class are rarely compared directly in randomized controlled studies. When comparative data are necessary for decision-making, it is useful to "borrow information" from indirect evidence. McAlister and colleagues (McAlister et al., 1999) proposed a scheme of evidence levels for extrapolating drug effects within a pharmacological class. In the absence of or insufficient *Level 1* evidence that consists of head-to-head RCTs studying clinical outcomes, they suggested *Level* 2 evidence from indirect between-drug comparisons made by comparing relative risk reductions across placebo-controlled trials of different drugs. In the present study, the class effect among statins was examined based on the method of adjusted indirect comparison. There are several methodological concerns in the study that are worth discussing.

2.1.3.1 Adjusted Indirect Comparison Methodology

The usefulness of adjusted indirect comparison and its superiority over a simple indirect comparison relates to its ability to account for the differences in prognostic factors between study participants in different trials. The method uses relative effect measure (e.g. risk ratio or odds ratio) from the respective placebo-controlled trials for the indirect comparison, rather than a comparison based on the total number of events and total number of subjects from only the active treatment arms of the trials, in which case, there is no adjustment made for the baseline differences (Kunz et al. 1998). The risk ratio of the adjusted indirect comparison of *Statins A* versus *B* (RR'_{AB} is the ratio of the risk ratios $\frac{RR_{AC}}{RR_{BC}}$. Therefore,

$\ln RR'_{AB} = \ln RR_{AC} - \ln RR_{BC}$

and its variance is:

$\mathrm{Var}(\ln RR'_{AB}) = \mathrm{Var}(\ln RR_{AC}) + \mathrm{Var}(\ln RR_{BC})$

where $lnRR_{AC}$ and $lnRR_{BC}$ are the natural logarithm of the risk ratios of direct comparison of *Statin A* versus control *C* (trial 1) or *Statin B* versus control *C* (trial 2), respectively. Note that the RR_{AC} or RR_{BC} can be a relative effect measure from a single trial or a pooled estimate from a set of trials studying *Statin A* or *B* versus control.

Of importance, the statistics developed in accordance with this method of adjusted indirect comparison are based on the assumption that the relative efficacy of a treatment effect is consistent across differences in the populations' baseline characteristics (Bucher et al., 1997, Song et al., 2003), that is, for the estimate from adjusted indirect comparison of *Statin A* versus *B* to be valid, we need to assume that the results ($\ln RR_{AC}$) of trial 1 would have been observed in trial 2 if *Statin A* was used in place of *Statin B*, and vice versa. In other words, the estimated relative efficacy from the trials should be generalizable (Song et al., 2000). This is a requirement that the data themselves usually cannot fully validate, as it depends on the circumstances of each trial and the patient inclusion criteria. Therefore, clinical knowledge regarding the treatment effect in different population subgroups is usually needed before applying the method of adjusted indirect comparison. With regard to our study comparing statins, the method is justified as the assumption of consistent treatment effect is met. In fact, it has been shown that the relative risk reduction by statins in cardiovascular prevention does not depend on the patient risk stratified by age, sex, CHD history and presence or absence of high risk

factors (such as diabetes, hypertension, baseline LDL-C levels) (Sacks et al., 2000, Marschner et al., 2001, Simes et al., 2002).

2.1.3.2 A Random-Effects and A Fixed-Effects Models

As the relative risk of each statin versus placebo in the present study represents a pooled estimate from a set of trials assessing the effect of that statin, a statistical method was required to calculate a summary effect. There are two options available each requiring different assumptions – a *random-effects model* or *a fixed-effects model*. The fixed-effects approach (Mantel et al. 1959, Yusuf et al., 1985) assumes that the true treatment effect is the same in a collection of trials. The effect is then said to be homogeneous across trials. The variance seen in each trial is assumed to be due to sampling variation within the trial. Under the random-effects model, however, the assumption of a common treatment effect is relaxed. The model considers the true treatment effect in each trial to be a random variable, thus allowing for between-trial variability (in addition to within-trial variability) to be accounted for in the overall estimate and its precision (DerSimonian and Laird, 1986). The method therefore introduces a degree of statistical caution that is not present in the fixed-effect analysis.

So far, there have been arguments in favor of using either approach to obtain a summary estimate (Fisher et al., 2001, Whitehead 2002). In principle, it would seem that the random-effects model is a more appropriate choice, given that the trials are generally not run under an identical protocol, and vary in patient and other trial

characteristics. In practice, when the treatment effect is homogeneous across trials, the between study variance (τ^2) approaches "zero". The random-effects model then reduces to a fixed–effects model and both methods give the same estimate (Whitehead 2002). The concern is that when the number of trials is small, the estimated τ^2 from a random-effects model can be imprecise. This is likely to be the case in the present study, and may have affected the CI estimation of our pooled results. Given this uncertainty, we decided to repeat the analysis using a fixed-effect model to examine how much the overall conclusion changed depending on the statistical methods chosen. The use of a fixed-effect model was also justified here, because the heterogeneity between trials was found to be minimal in our study. Our results of the comparison did not change when either approach was used.

In summary, we used the adjusted indirect comparison to address the question of class effect based on available trial evidence. This method is useful in the absence of head-to-head comparisons. Our study did not find statistically significant differences in the effect of pravastatin, simvastatin and atorvastatin on long-term cardiovascular prevention. The wide confidence intervals in most comparisons, however, may suggest more evidence is needed. We further address this question in an observational study using medical administrative databases (manuscript #2).

2.2 Effect of Early Initiation of Statins After Acute Myocardial Infarction

The following section provides a review of the current clinical evidence on the early initiation of statins after an acute coronary event. To investigate the effect of this treatment strategy on cardiovascular prevention represents the next focus of this thesis.

2.2.1 An Overview of the Available Clinical Evidence

Traditionally, the benefit provided by a statin was thought to depend entirely on the control of cholesterol levels, which is itself a risk factor for CVD. This emphasizes the need for long-term treatment with statins. Therefore, although a significant therapeutic response in lowering cholesterol can be seen in the majority of patients within 2 ~ 4 weeks, for a benefit to become apparent in terms of CVD prevention, it may take up to 1~2 years (Archbold et al. 1998).

The recently observed mechanisms of statins characterized as mainly "cholesterol-independent" (Corsini et al., 1999, Sposito et al. 2002) suggest that statins may be able to reduce local inflammation and reverse the abnormality of the coronary arterial wall in a matter of days to weeks among patients with ACS. It is exactly in the early months following an acute coronary event that patients face the greatest risk of recurrence and death. Accordingly, the protective effect against cardiovascular morbidity and mortality associated with early statin treatment is expected to occur much earlier among unstable patients than was previously assumed. This could also be the reason that

previous large-scale statin RCTs (e.g. the 4S, LIPID, CARE trials), which enrolled only stable patients (survivors) 3 to 6 months after AMI, required at least 1-2 years to observe a beneficial effect.

To date, the results from clinical studies that evaluated the benefit of early statin initiation were not all consistent. In the MIRACL trial (Schwartz et al., 2001), which was the first RCT to test this hypothesis, patients were randomized to receive statin (atorvastatin 80 mg or placebo) within 24-96 hours after hospital admission for an ACS. A risk reduction for a composite end point of death, recurrent AMI, emergency hospital admissions and cardiac procedures was seen at 16 weeks, however the effect was moderate (adjusted hazard ratio, HR: 0.84, 95% CI 0.70-1.00). There were no differences when mortality alone or, combined outcome of death or recurrent AMI were studied. In addition, because the follow-up of the trial was only 16 weeks, effects beyond this study period were unclear. The recent "A to Z" trial (de Lemos et al., 2004) was the first trial that evaluated the effect of early statin initiation both in the short-term and the long-term. The trial incorporated a 4-month placebo controlled period at the beginning of the trial (simvastatin 80mg versus placebo) followed by a low dose statin controlled phase (simvastatin 40mg versus 20mg) initiated at 4 months, and patients were followed for 2 years. However, in this trial, no difference in outcome (cardiovascular death and major cardiovascular events) at both 4 months (adjusted HR: 1.01, 0.83-1.25) and 2 years (adjusted HR: 0.89, 0.76-1.04) was observed.

On the other hand, several observational studies have suggested more favorable outcomes associated with lipid-lowering therapy given at discharge from a

hospitalization for AMI. Stenestrand et al. (2001) studied 19,599 post-MI patients using the Swedish Register of Cardiac Intensive Care. The authors found a significant inverse association between statins given at discharge and 1-year mortality (adjusted HR: 0.75, 0.63-0.89) compared with no statin use at discharge. In a second study based on a post hoc analysis of clinical trials performed for other cardiac medications, Aronow et al. (2001) found a 56% reduction of mortality at 30 days post discharge in patients with discharge lipid-lowering medications (mainly statins) compared with those who did not have these medications at discharge (adjusted HR: 0.44, 0.27-0.73). This effect persisted at 6 months (adjusted HR: 0.48, 0.37-0.63). However, these favorable findings were not confirmed later by Newby et al. (2002) who also studied a retrospective cohort using data from other cardiac medication RCTs. In the study, early statin initiation after hospitalization for ACS did not confer a beneficial effect neither at 90 days nor at 1 year compared with no statin use. The adjusted HR for death or MI within 90 days was 1.08 (95% CI, 0.91-1.29), and the 1-year adjusted HR for death was 0.99 (95% CI, 0.73-1.33). Further assessment suggested that, in patients with low cholesterol levels, early statin use was even associated with an elevated risk of death or MI.

The discordance in findings may be attributed to different settings, designs, patient inclusion criteria, or different end point definitions, nonetheless there is a need for more evidence. Of note, an important aspect of the effect of early statin treatment remains largely unanswered. Most available clinical studies focus on the effect of early initiation as compared to no statin use. Very few studies have examined the effect of the timing of initiation, especially in the first few months following the acute

event. The delayed treatment phase (4 month after the start of the trial) incorporated in the "A to Z" trial aimed to examine this question, however, the results were inconclusive. The effect of a delay in statin initiation on AMI or mortality requires further assessments. However, comparing early versus delayed use in observational studies requires appropriate methodology. The fact that a patient needs to survive to fill a prescription suggests the possibility of *survival bias* when comparing two groups of subjects that differ systematically in the time of treatment initiation. In such case, the delayed users have an initial survival advantage over the early users regardless of the effect of treatment. This advantage is accentuated if the risk for outcome is high initially and decreases quickly over time (as is the case for the risk of recurrent AMI and mortality following discharge from a hospitalization for AMI). Thus, those who start treatment early in time have on average a higher risk than those who initiated late. This could obscure the potential benefit of early initiation of statin.

Furthermore, method to control for the survival bias is useful to address a limitation in the design of previous observational studies comparing early statin user versus no use. For example, in the studies by Aronow et al. (2001) and Stenestrand et al. (2001), "early use" was defined exclusively as having a statin prescription at discharge. Patients who filled a prescription in the subsequent days together with those who did not use statins were all classified as nonusers. However, this definition introduces a problem of subject misclassification, and potentially leads to an underestimation of the treatment effect.

To reduce this misclassification, an appropriate time window can be used to identify early users who initiate statins in a short period of time following discharge. However, this method may also introduce survival bias. In this case, the users must survive (event-free) up to the time of their first prescription, whereas the nonusers may have an event any time after discharge. This between-group difference in survival increases with the increased absolute level of risk following discharge as well as with the width of time window that is used to define users (Suissa, 2003). Ignoring this difference in survival can lead to a biased estimate of the treatment effect.

As the clinical interest in the early initiation of statins remains high, evaluation of the outcome of such practice is needed and the use of appropriate method to control for survival bias will help delineate and solve the question. In this thesis, methods to control for survival bias were developed and evaluated (manuscript #3). The effective methods were then applied to address our clinical question regarding the effect associated with the early initiation of statins (manuscript #4). As in the study of class effect, a retrospective cohort design using population-based information from medical administrative databases was adopted. A description of the data source, the cohort and the study design is the subject of the next chapter.

CHAPTER 3

STUDY COHORT AND OVERVIEW OF DESIGN

This chapter provides a description of the data source, an overview of the study cohort and design, as well as information regarding the definition of study variables. Methodological details specific to the objectives of each study are described within the respective manuscript.

3.1 Source of Data

Data sources used in the retrospective cohort studies included in this thesis are from provincial medical administrative databases. For the study of class effect, the data are available from three Canadian provinces including Quebec, Ontario and British Columbia. Whereas in the study of the effect of early statin initiation, we use data from Quebec only. Post-AMI elderly patients (≥ 65 years) are identified through linked hospital discharge summary data and by using international classification of disease – 9th version codes (ICD-9) for the diagnosis of MI. Patients aged 65 years and over in all three provinces have prescription coverage by their provincial health care plan, thus providing a complete history of cardiac medication prescriptions in this elderly population. A brief description of the databases in each province is given as follows:

Quebec

The Quebec hospital discharge summary database (*Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière*, Med-Echo) is used to identify AMI patients. This database records information regarding patient's primary diagnoses for hospitalization as well as demographic characteristics. Up to 14 secondary diagnoses are provided by the database. Using encrypted Medicare numbers, the above database is linked to the Quebec physician and prescription claims databases maintained by *la Régie de l'assurance maladie du Québec* (RAMQ), which contains information on Quebec in- and out-patient diagnostic and therapeutic procedures, as well as drug prescriptions. Information exists regarding type of the prescribed medication, date dispensed, dosage, quantity and number of days of supply. In a previously conducted retrospective medical chart review (Levy et al., 1999), the positive predictive value in the Med-Echo database for coding an AMI for elderly patients discharged after AMI was estimated to be 0.96 (95% CI: 0.94-0.98). Death information is available from both the Med-Echo and RAMQ databases. The Med-Echo database only records death that occurred in the hospital, whereas the RAMQ collects mortality information based on death certification that occurs in or out of hospital. Using information from both databases provides complete survival data for almost all AMI patients in the databases (Pilote et al., 2000).

Ontario

Information on patients who sustained an AMI in Ontario is obtained from Canadian Institute for Health Information (CIHI) administrative database that is created using hospital discharge abstracts. As in Quebec, this database contains information on demographic characteristics, comorbidities, procedures, and in-hospital mortality for all patients discharged from hospitals in Ontario. Coding accuracy for AMI as the most responsible diagnosis at hospital discharge was shown to have a sensitivity of 0.88, a specificity of 0.93 and a positive predictive value of 0.89 (Austin et al., 2002, Cox et al., 1997). The CIHI database is linked to the Ontario Drug Benefit Plan (ODB) database and the Ontario Registered Persons Database (RPDB) by using encrypted Ontario health card numbers that are unique to each individual. The ODB database contains information on drug prescriptions for patients aged $\geq$ 65 years; while the RPDB contains information on the vital status of all residents covered under the provincial health insurance plan. For missing death information in the RPDB, it is further identified through searching the CIHI database for death that occurred during hospitalization. The accuracy of this survival data was verified previously by data linkage to Cancer Care Ontario, and was found to have an agreement of 99.6% (Tu et al. 1999).

British Columbia

Information for AMI patients in British Columbia is obtained from the BC Patient Hospitalization Database. This database contains discharge data for all acute care hospital admissions in the province. Using the unique patient identifier, data are linked to

the Medical Services Plan database to obtain information on subsequent physician visits. Linkage with Deaths Registry of the BC Vital Statistics Agency provides data on mortality. Linkage with *PharmaCare* provides complete information on medication usage for patients ≥ 65 years of age. Measures of agreement between patient chart and BC administrative data showed that the diagnosis coding for AMI and other major comorbidities had an average sensitivity over 0.8 and a specificity of 0.95 (Humphries et al., 2000). The accuracy of survival data was ascertained by linking the BC Cardiac Registries database with the BC Vital Statistics Agency. A 95.7% to 99.8% match for 30-day and 1-year mortality was found (Ghahramani et al., 2001).

Information Regarding Prescription and Comorbidity

In addition to the previous validation studies regarding the quality of diagnosis coding and death information, we further examined the completeness of the prescription claims databases in the three provinces, particularly for the cardiac medications. Missing or out of range values in the key fields regarding the drug type, date dispensed, quantity, dosage and duration were very few, representing no more than 0 ~ 0.5% of the records. This is in agreement with the previous findings by Tamblyn (Tamblyn et al., 1995) with the RAMQ prescription database.

One potential limitation of the data however concerns comorbidity diagnoses, which is thought to be not present if not coded. Physicians may not record all comorbidities of the patient, such missing information may have an impact on the risk adjustment.

Despite the above limitation, overall, the data used in the current studies have a reasonable degree of accuracy and completeness. Such data enhances the validity of the results and their interpretations.

3.2 Overview of the Study Cohort and Design

We constructed retrospective cohorts for all observational studies included in this thesis using the medical administrative databases. Elderly patients (≥ 65 years) who had an AMI and were discharged alive between 1996 and March 2001 were identified. The follow-up information was obtained up to April 2002.

The following inclusion and exclusion criteria were used to form the cohort. Patients who had a first-recorded AMI in the study period were included at the time of their discharge. AMI was identified using ICD-9 code 410 as their most responsible diagnosis at discharge. Patients were excluded if they met one or more of the following exclusion criteria: 1) the AMI was coded as an in-hospital complication; 2) the AMI admission was a transfer from another hospital (this was to avoid counting patients twice, yet all transfers related to the initial AMI admission were counted in the total length of hospital stay); 3) the total length of hospital stay was less than 3 days (this was to exclude ruled-out AMI cases and those admitted only for procedures); 4) the patient was discharged to a long-term care institution, a rehabilitation center, or moved out of the province (as information on medication was no longer available); and 5) the health care number was invalid. Rationales for these criteria have been established previously and

has been used in multiple studies (Tu et al., 2003, Kennedy et al., 2003, Pilote et al., 2004).

The design varied slightly in each observational study. In the study of class effect of statins (manuscript #2), clinical outcomes were compared in five groups of AMI patients based on the first post-discharge statin prescription, including atorvastatin, pravastatin, simvastatin, lovastatin and fluvastatin. The atorvastatin statin group was chosen as a reference category. The primary endpoint was defined as recurrent AMI or death due to any cause, whichever occurred earlier. The follow-up for individual patients started at the time of the first statin prescription (time 0) and stopped at the occurrence of a study endpoint or the end of the study period. Outcomes were examined with and without censoring patients at the time of switching or stopping the treatment. The same study protocol was applied to the three provinces. The hazard ratios of each statin versus atorvastatin with adjustment for baseline characteristics were pooled from the three provinces.

Two studies were conducted to assess the effect associated with early initiation of statins post AMI. Manuscript #3 evaluated existing and newly developed methods that could be used to control for survival bias. This manuscript provided a methodological framework for manuscript #4, which was conducted to address the clinical question.

In manuscript #3, the study was based on an empirical assessment of five different methods that addressed survival bias in a post-AMI cohort (1996-2001) using data from the Quebec healthcare administrative databases. The clinical outcomes were

compared between the users of statins defined as those who filled a statin prescription ≤ 90 days post discharge (the users) to those who did not (the nonusers). Of the five methods, two methods were used in previous drug effectiveness studies. We illustrated how these methods introduced survival bias (method of simple grouping, and method of random selection of time of study entry). Three additional methods were employed to control for the bias at either the design level (method of prescription time distribution matching, and method of follow-up since the end of the exposure time window) or at the level of analysis (method of time-dependent exposure). Three different time origins were used in these methods, including 1) time of discharge; ii) time of first statin prescription (this time is artificially assigned to nonusers); and iii) time at the end of exposure time window, i.e. day 90. The primary outcome was a composite of recurrent AMI or death due to any cause. For each method, the outcome was studied for 6 months, 1-year post discharge, and for the full follow-up period (median of 3 years). Adjusted hazard ratios and 95% confidence intervals obtained from the five methods were compared along with the methods' performances, including statistical efficiency, advantages or disadvantages in their application to determine which method(s) offers better control for the survival bias overall.

In manuscript #4, the clinical question regarding the effect associated with the difference in the timing of statin initiation post discharge of AMI was studied. Two groups of elderly patients post-AMI, who differed in their time of statin initiation in the first 90 days after discharge were compared. Patients who started statins at discharge (early group) were compared to those who initiated statins 1 month later and up to 90

days post discharge (delayed group). Outcome of recurrent AMI or death was evaluated at 3, 6 months and at 1 year. In addition, the effect was evaluated for statins initiated during the first 90 days compared with no statin use. The method(s) that was shown to have a better control of the survival bias from manuscript #3 was used to address the clinical question.

In all studies, the reported hazard ratios were adjusted for multiple baseline characteristics, which are described in the following section.

3.3 Study Variables

In this thesis, the study variables that were considered were those related to statin exposure, outcomes and baseline characteristics (patient, physician and hospital characteristics).

Statin Exposure

Statin usage was determined based on filled prescriptions by patients. For each patient, information was obtained for the type of statin, date dispensed, quantity, dosage and duration. Prescription history was captured 1 year prior to the index AMI and for the full follow-up after discharge.

Outcomes

Outcome information was ascertained for the date of recurrent AMI or death due to any cause occurring during follow-up. The same criteria used to define the index AMI were applied to define recurrent AMI.

Baseline Patients Characteristics

The baseline patient characteristics could be broadly classified into 2 categories: 1) demographic; and 2) clinical. These characteristics have been identified as clinically plausible, and statistically significant predictors in the mortality prediction model. Similar risk-adjustment indices have been previously used to characterize illness severity and validated in several disease-specific cohorts, particularly AMI patients (Tu et al., 1999, Krumholz et al., 1999, Pilote et al., 2004, Ko et al., 2004).

1) The patients' demographics included age and sex.

2) The clinical characteristics were further divided into 4 sub-categories, including i) *Information regarding the index AMI hospitalization*: date of admission, date of discharge and length of hospital stay; ii) *Major discharge comorbidities*: hypertension, diabetes, congestive heart failure (CHF), cardiac dysrhythmia, COPD, Cerebrovascular disease, chronic renal failure (CRF), malignancy and dementia; iii) *In-hospital procedures*: date of coronary artery bypass graft surgery (CABG), catheterization and percutaneous coronary intervention (PCI); iv) *Major cardiac medications*: date of first post-discharge prescription of nitrates, beta-blockers, ACE inhibitors, antiplatelet agents, diuretics, calcium-channel blockers, warfarin and digoxin.

Physician and Hospital Characteristics.

The physician characteristics included the *specialty of the treating physician*: cardiologist, internist, general practitioners and other specialists; and hospital characteristics included: teaching or not, catheterization availability and hospital location (urban/rural). We included these characteristics for additional adjustment because these factors were likely to be potential confounders that were associated with statin selection, treatment aggressiveness and our study outcome.

A table summarizing the study variables and ICD-9 diagnostic codes is provided in *Appendix B*. The following two chapters present the results from the observational studies conducted to address the two study questions concerning statin effectiveness.

CHAPTER 4

AN EVALUATION OF STATIN CLASS EFFECT FOR SECONDARY PREVENTION IN THE POST-AMI ELDERLY

4.1 Preface to Manuscript #2

Whether a class effect could be assumed in selection of statins for cardiovascular prevention remains largely unclear. Our systematic review (manuscript #1) attempted to address this question based on adjusted indirect comparison using published statin trials. However, due to the relatively wide confidence intervals observed, the study could not reach a definitive conclusion of "a class effect".

To provide more evidence on this question, the following manuscript examines the class effect in a retrospective cohort study using medical administrative databases. Statins were compared for their relative effectiveness for secondary prevention among elderly patients post-AMI.

The data used in the study were from three provinces in Canada (Quebec, Ontario and British Columbia). Such data provides an opportunity to evaluate the relative effectiveness of statins in a large-size study.

Abstract

Background: Clinical trials have shown the benefits of statins after acute myocardial infarction (AMI). However, it is unclear whether different statins exert a similar effect in reducing the incidence of recurrent AMI and death when used in clinical practice.

Methods: We conducted a retrospective cohort study (1997-2002) to compare 5 statins using medical administrative databases in 3 provinces (Quebec, Ontario and British Columbia). We included patients aged 65 years and over who were discharged alive after their first AMI-related hospital stay and who began statin treatment within 90 days after discharge. The primary endpoint was recurrent AMI or death from any cause. The secondary endpoint was death from any cause. Adjusted hazard ratios (HRs) for each statin compared with atorvastatin were estimated using Cox proportional hazards models.

Results: A total of 18,637 patients were prescribed atorvastatin (n=6,420), pravastatin (n=4,480), simvastatin (n=5,518), lovastatin (n=1,736) or fluvastatin (n=483). Users of different statins showed similar baseline characteristics and patterns of statin use. The adjusted HRs (and 95% confidence intervals) for the combined outcome of AMI or death showed that each statin had similar effects when compared with atorvastatin: pravastatin 1.00 (0.90-1.11), simvastatin 1.01 (0.91-1.12), lovastatin 1.09 (0.95-1.24), and fluvastatin 1.01(0.80-1.27). The results did not change when death alone was the end point, nor did they change after adjustment for initial daily dose or after censoring of patients at their time of switching or stopping the initial statin treatment.

Conclusion: Our results suggest that, under current usage, statins are equally effective for the secondary prevention in elderly patients post-AMI.

Introduction

Randomized controlled trials (RCTs) have shown that the use of statins after acute myocardial infarction (AMI) are effective in reducing both fatal and non-fatal cardiovascular events[1-8]. Although these trials have significantly influenced post-AMI treatment[9-12], it remains unclear whether all statins are equally effective in preventing recurrent AMI and death. Drugs in the same class are generally thought to be therapeutically equivalent because of similar mechanisms of action (*a class effect*)[13-15]. However, in the absence of comparative data, this assumption requires evaluation. Statins differ in multiple characteristics, including liver and renal metabolism, half-life, effect on other serum lipid components, bioavailability and potency[16-19]. These differences could potentially influence the extent to which the drugs are beneficial. Despite limited evidence in support of a differential benefit of statins for secondary prevention, preferential prescribing already occurs in practice and can not be fully explained by the existing evidence or guidelines[20]. Comparative data of statins are thus required to inform health care decision-making.

A number of RCTs have directly compared statins using surrogate endpoints, such as lipid reduction[21-23], markers of hemostasis and inflammation[24-26] or reduction in number of atherotic plaques[27]. Nonetheless, the extent to which these results can be extrapolated to clinically relevant outcomes remains to be established. The newly released PROVE-IT trial[28] was the first trial to compare 2 statins for cardiovascular prevention. The study showed that atorvastatin used at maximal dose of 80 mg (intensive therapy) was better than pravastatin 40 mg (standard therapy) in decreasing the incidence

of cardiovascular events and procedures. The study was, however, conducted to show the benefit associated with increased treatment intensity. The two statins were not compared by milligram or cholesterol-lowering equivalent dosages. Moreover, no difference was detected when death alone or the combined outcome of death or AMI was evaluated. Other than the PROVE-IT trial, few data are currently available from RCTs that compare statins for cardiovascular prevention[29].

We conducted a population-based study to examine the relative effectiveness of different statins for long-term secondary prevention after AMI. We used retrospective cohorts of elderly patients prescribed statins after AMI in 3 provinces. Five statins were studied: atorvastatin, pravastatin, simvastatin, lovastatin and fluvastatin. The newest statin, rosuvastatin, was not available during the study period and was not considered in this study.

Methods

Study Population and Data Sources

Three comparable AMI cohorts were created by using the linked hospital discharge databases and the physician and prescription claims databases in Quebec (QC), Ontario (ON) and British Columbia (BC). We used standardized inclusion and exclusion criteria as well as comorbidity information across provinces according to concurrent collaborations at the national level in cardiovascular outcome research[30, 31]. Several validation studies have ensured the accuracy of coding in each province[30, 32, 33].

Information regarding outpatient prescriptions, as well as therapeutic procedures, was obtained from the physician and prescription claims databases (the *Ontario Drug Benefits* database, the BC *PharmaCare Program* and the *Régie de l'Assurance Maladie du Québec* [RAMQ]). All patients aged 65 years and over receive prescription coverage in Canada. Available prescription information included type, dosage, quantity and days of supply. Death information was obtained from provincial registry databases (Ontario Registered Persons, BC Vital Statistics and RAMQ). All data were linked by the patients' unique, encrypted health care insurance number.

Inclusion and Exclusion Criteria

Patients were included if they were 65 years and older, had their first recorded AMI hospitalization and were discharged alive between 1997 and 2001, and filled a statin prescription within 90 days after discharge. The 90-day time window was chosen because most of the statin prescriptions post-discharge occur in this period. All patients had AMI (ICD-9 code 410) recorded as the most responsible diagnosis in the hospital discharge

database (*Canadian Institute for Health Information* for Ontario and BC data, and Med-Echo [*Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière*] for Quebec data).

We excluded patients if they met any of the following criteria: 1) the AMI was coded as an in-hospital complication; 2) the AMI-related hospital admission was a transfer from another hospital (to avoid counting patients twice, yet all transfers related to the initial AMI admission were counted in the total length of hospital stay); 3) the total length of hospital stay was less than 3 days (to exclude ruled-out AMI cases and those admitted only for procedures); 4) the patient was discharged to a long-term care institution or a rehabilitation center or moved out of the province; and 5) the health care number was invalid. More details of the rationale for these criteria can be found elsewhere[30,34].

Design and Statin Use

Cohort enrolment began on April 1, 1997 and ended on March 31, 2001 (1 year before the end of the study to ensure a potential for at least 1-year follow-up for every patient). Follow-up for each patient was from the time of the first statin prescription (time 0) to the occurrence of a study end point or the end of the study period. On the basis of the first statin prescribed, 5 statin groups were formed (atorvastatin, pravastatin, simvastatin, lovastatin and fluvastatin). For statin usage pattern, we recorded the number of patients who switched or stopped the initially prescribed statin treatment. Stopping treatment was defined as discontinuation of the initial statin or the absence of a prescription for the initial statin 15 or more days after the end of the previous prescription. To indicate patient

persistence on the treatment, we calculated the ratio of the total number of days supplied for the initial statin divided by the total number of follow-up days.

Baseline Characteristics

Patient demographic characteristics and comorbidities at discharge were determined from the hospital discharge databases. Comorbidities included coexisting cardiovascular and lung diseases, chronic kidney or liver conditions as well as diabetes, dementia and malignant disease. Concurrent use of major cardiac medications was also recorded. These drugs included beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, antiplatelet drugs (aspirin, clopidogrel), calcium-channel blockers, diuretics, warfarin and digoxin. Use of statins during the year before the index AMI was also included as a baseline covariate. Information was obtained regarding in-hospital procedures performed (catheterization, percutaneous coronary intervention, coronary artery bypass graft surgery), length of stay, time to first statin prescription, year of AMI, specialty of the treating physician (cardiologist, internist, general practitioner or other specialist), type of hospital (teaching or not), hospital volume, hospital location (urban or rural) and availability of cardiac catheterization facility in the hospital.

Outcomes

The primary endpoint was defined as a combined outcome of recurrent AMI or death from any cause, whichever occurred earlier. The secondary outcome was death from any cause.

Statistical Analysis

Descriptive statistics were used to compare baseline patient characteristics between statin groups. A multivariate Cox proportional hazards model was used to assess

the associations between type of statin used and time to study outcome. The proportional hazard assumption was assessed by a plot of log(-log(survival function)) versus time for both primary and secondary outcomes. The linearity assumption was assessed for continuous variables in the model, including age, length of hospital stay and time to first statin prescription. These variables were categorized if the linearity assumption was not met.

Analyses were performed in 2 ways. First, in an intention-to-treat analysis, patients were assumed to be taking the initial statin throughout follow-up. In a second analysis, patients were censored at the time of switching or stopping the initial statin. Adjusted hazard ratios and 95% confidence intervals (CIs) were reported for each statin compared with atorvastatin, the most frequently used statin, as a reference drug. The model was adjustment for baseline characteristics and potential confounders. To examine the robustness of our results, we did several additional analyses. First, to assess the impact of statin dose, we adjusted for the initial daily dose of each statin by creating a binary variable "at or above target dose". We determined the target dose by referring to the cholesterol-lowering equivalent dose[21, 35] as well as the dose tested in the large-scale RCTs of each statin for long-term cardiovascular prevention[1, 2, 5, 8, 36-39]. The target dose was set as 10 mg for atorvastatin, 40 mg for the other statins. The binary variable "at or above target dose" was subsequently adjusted in the Cox model. Second, results were stratified according to statin use status (yes or no) before the index AMI to examine whether the effect depended on the history of statin use. Finally, to ensure that the results did not depend on the choice

of the reference statin, a likelihood ratio test with 4-degree of freedom (df) was performed with the hypothesis that all statins have the same effects.

We applied the same methods to the data from each of the 3 provinces. We then pooled the HRs for each statin (compared with atorvastatin) using a fixed-effects model, with weight being the inverse of the variance of the province-specific parameter estimate, ln(HR)[40]. A test of heterogeneity was performed to examine the appropriateness of using a fixed-effects model to pool the estimates[41]. All analyses were done using SAS version 8.0 (SAS Institute Inc. Cary, NC.).

Results

Study Population

Of the 56,408 identified AMI patients, 18,637 (33.0%) had filled a statin prescription within 90 days after discharge for atorvastatin (n=6,420), pravastatin (n=4,480), simvastatin (n=5,518), lovastatin (n=1,736) or fluvastatin (n=483). The median follow-up was 2.3 years (IQR: 1.6 - 3.2 years; range 1 to 5 years).

A comparison of baseline demographic and clinical characteristics did not reveal any major differences across statin groups (Table 1). Notable exceptions were that (a) lovastatin users tended to have more comorbidities and possibly a longer cardiac history as suggested by greater use of diuretics and calcium channel blockers and higher prevalence of congestive heart failure; and (b) fluvastatin was found to be prescribed more by general practitioners and less by cardiologists, and fluvastatin users were more often treated in rural hospitals and less often underwent revascularization procedures during the hospital stay. Nevertheless, a pattern of preferential prescribing of a particular statin to sicker or healthier patients did not emerge.

Statin Usage Patterns

Use of any statin within 1 year before the index AMI was similar for atorvastatin, pravastatin and simvastatin users but was more frequent among lovastatin and fluvastatin users (Table 2). No apparent delay in filling a first prescription was associated with any particular statin. The median duration of use of the initial statin during the first year of follow-up was similar across the statin groups (330-365 days), except for fluvastatin (307 days). This difference in duration could be explained by the higher

switching rates among fluvastatin users. On average, more than 85% of the patients in each group had initial statin prescriptions that covered at least 80% of the follow-up period.

The overall proportion of patients who switched to a different statin during the first year of follow-up was low (7%), but increased to 21% by the end of follow-up. Among patients who switched, 55% switched to atorvastatin. Fluvastatin and lovastatin users had the highest percentages of switching (Table 2). To assess whether switching to atorvastatin was related to a change in disease state, we examined the rates of hospital readmission because of cardiovascular causes and the rates of cardiac medication use from the first prescription to the time of switching and compared them between patients who switched to atorvastatin and those who switched to another statins. No significant difference in these rates was found. The overall proportion of patients who stopped statin treatment during follow-up was 11%, with similar percentages across statin groups.

In terms of the distribution of daily doses, we found that statins were mostly prescribed at their lower doses (10-20mg) (Table 2), which are approximately equivalent in lowering cholesterol level[21]. Very few subjects (0.7%) were prescribed the highest dose of each statin. For example, among atorvastatin users, only 0.5% of them were prescribed an 80-mg dose. The proportion of patients who changed dosage was low and was similar in the atorvastatin, pravastatin and simvastatin groups. The doses of fluvastatin and lovastatin changed less frequently.

Survival Analysis

A total of 2924 patients either had an AMI or died. The unadjusted cumulative incidences of each outcome for each statin group are shown in Table 3. Patients

in the lovastatin group appeared to be at higher risk of recurrent AMI or death compared with those in the other statin groups, although the difference was not statistically significant.

The results of the multivariate survival analysis are summarized in Table 4. Older age, male sex and most major comorbidities were associated with increased risk, whereas cardiac procedures and use of some cardiac medications showed protection. Patients using diuretics, calcium channel blockers and digoxin and patients who were using statins before the index AMI were at increased risk of recurrent AMI or death. This effect could be an indication of greater disease severity associated with use of these medications[42]. Hypertension did not appear to be a significant risk factor. This could be due to the inclusion of anti-hypertensive medications in the risk adjustment model. A delay in initiating statin therapy appeared to be "protective"; however, this effect was due to a decreasing risk over time after discharge, which was independent of statin treatment effect. None of the physician and hospital characteristics were significantly associated with outcome. No apparent secular trend in the event rate was detected.

For all statins, the heterogeneity test of estimates (HRs) from the 3 provinces suggested a homogenous effect (all p-values >0.62, x^2 <0.95, 2 df). The pooled adjusted HRs and 95% CIs for the combined outcome of recurrent AMI or death showed that each statin had similar effects when compared with atorvastatin (Figure 1). Provincial specific results were shown in Figure 2. Adjustment for initial daily dose of each statin according to whether it was "at or above target dose" did not materially change the results. Stratified analyses according to prior statin use did not affect the results, nor did restricting

the outcome to death or censoring patients when switching or stopping the initial statin treatment. The likelihood ratio test confirmed the absence of any statistically significant difference in risk between patients prescribed different statins ($p>0.41$, $df=4$). Finally, we performed *post hoc* comparisons of (a) atorvastatin versus the other statins and (b) lovastatin versus the other statins. The latter comparison was done because lovastatin group showed a slightly increased incidence of clinical end points. The results were unchanged in each comparison: HR for recurrent AMI or death was 0.98 (95% CI, 0.90 – 1.07) for the comparison of atorvastatin with the other statins and 1.09 (95% CI, 0.98– 1.22) for the comparison of lovastatin with the other statins.

Discussion

The results of our population-based study of commonly used statins suggest that individual drugs in the statin class exhibit a similar effect in reducing the incidence of recurrent AMI or death among elderly patients.

Individually, statins have been shown to reduce recurrent AMI and death among patients who sustained an AMI. These studies includes the 4S trial[1](simvastatin), the CARE[2] and the LIPID trials[5] (pravastatin), and the GREACE[8] trial (atorvastatin). The benefit has been also evident in recent trials that enrolled subjects with and without prior cardiovascular diseases but who were at high risk of future cardiovascular events, including the HPS trial[37](simvastatin) and the PROSPER trial[43](pravastatin). In each trial, the statin was compared with a placebo. It is not evident whether the effect size observed across trials varied because of different trial characteristics or because the statins had truly different effects. The result of the PROVE-IT trial suggested that a statin used at high dose could provide additional benefits, yet 80 mg of atorvastatin was not frequently prescribed in practice during our study period. Compared with the patients in our study, those in the PROVE-IT trial were younger (mean age 58 years), mostly male (78%) and had less comorbidity and thus were more likely to tolerate a high dose of statin and experience the benefit. In our head-to-head comparison of 5 statins, we examined the relative effectiveness of the drugs in older patients with a more diverse risk profile, a population-based setting that is representative of daily practice.

Our study was a retrospective analysis of administrative databases, and thus several limitations merit discussion. First, because the patients in the study were all on

statin therapy, there is a lower likelihood of confounding by indication[44]. However, we could not control for all patient characteristics that may influence physicians' choice of statin. Unmeasured comorbidity as well as missing clinical information (e.g. cholesterol levels, location of MI) could confer residual confoundings effect; however, there is no obvious reason that prescribing of different statins would be strongly influenced by these unmeasured characteristics. The analysis of available baseline characteristics did not suggest a preferential prescribing of a particular statin to sicker patients. In addition, we controlled for the specialty of treating physician and the type of hospital, which could be associated with statin selection and intensity of therapy.

Second, unlike patients in RCTs, those in actual practice start statin treatment at different points in time after discharge and may experience more changes in use over time. Our analysis showed a similar time-to-first prescription across the 5 statin groups. This similarity reduced concerns about a potential initial survival advantage associated with a particular statin. In addition, patients were observed to have a high persistence on the statin initially prescribed. To account for switching and stopping treatment, we censored patients at the time they changed exposure status, and the results were unchanged. Nevertheless, the concern would be whether an excess proportion of this switching was related to worsening of clinical status. Our comparison of patients who switched to atorvastatin and to another statin by rates of hospital readmission and cardiac medications use before switching did not suggest a "channeling over time" due to a change of disease state[45].

Third, statins were used at low doses all within the range of the starting and maintenance dose recommended in the *Compendium of Pharmaceuticals and Specialties*. These doses were comparable based on cholesterol-lowering equivalents[21]. Our adjustment for initial daily dose according to whether it was "at or above target dose" did not affect the results. This adjustment reduced the likelihood of confounding by dose. However, the lack of information on patients' cholesterol levels limited our ability to study the effect of statin dose condition on cholesterol levels. The pattern of prescribing low doses also limited our ability to compare statins at their upper dose limits[28]. Due to observed close relation between degree of LDL reduction and risk of cardiovascular events[46], more potent statins used at their high end dose could offer incremental benefit. With possible practice change to achieve lower cholesterol level by using statins at higher doses, the latter question could be better addressed.

Fourth, our follow-up period was shorter than that in most large-scale RCTs of statin therapy. However, the RCTs would have required a longer follow-up to see an effect because they enrolled only stable patients 3-6 months after AMI. Our study patients were included immediately after their discharge from hospital and thus were at higher risk of recurrent AMI or death. Early initiation of statins after AMI has been suggested to be beneficial[47]. The PROVE-IT trial, which enrolled patients within 10 days after experiencing an acute coronary syndrome and randomly assigned them to receive either standard or intensive statin therapy, observed a difference between the 2 treatment arms after 6 months and at the end of the trial (follow-up 1.5 to 3 years, mean 2 years).

Accordingly, our median follow-up of 2.3 years and a maximum of 5 years is of reasonable length to detect possible difference in outcomes.

Fifth, as we studied all cause mortality in an elderly cohort followed for several years, death from other causes may have been an issue. However, since most of the deaths in the study population occurred relatively soon after the index AMI, we were more likely to capture cardiac-related deaths. Also, we adjusted for major morbid conditions in the elderly including dementia, malignancy, congestive heart failure and chronic renal failure.

Sixth, we used prescription claims as a proxy for actual statin use. However, given that the data represented filled prescriptions instead of written prescriptions, and that the patients refill regularly, it was likely that the patients were compliant.

Finally, although the conclusion towards the effect of lovastatin and fluvastatin should be more conservative because of the relatively low number of patients prescribed these agents, the point estimates of the relative effects between statins were all in the neighborhood of 1.0, and the accompanying 95% CIs were narrow. If we consider a range of ± 10-20% relative difference in hazard ratios as the region of clinical equivalence[48, 49], we have good evidence to declare equivalence among these statins.

In conclusion, our study provides evidence that, under current usage, statins are equally effective for the secondary prevention of recurrent AMI and death in post-AMI elderly.

Appendix

Method of Pooling

Suppose for the ith parameter the true value of the parameter is θ_i, estimated by y_i, with estimated sampling variance v_i. Define the weight $w_i=1/v_i$. Then, if all the θ_i are equal to some common value θ, a suitable estimate of θ is the weighted mean

$$\bar{y} = \frac{\sum w_i y_i}{\sum w_i}$$

and $\text{var}(\bar{y})=1/\sum w_i$. Here, $y_i = Ln(\text{HR})$, $v_i = [\text{SE}_{ln(\text{HR})}]^2$. Once the pooled parameter and its confidence interval are calculated, convert it back to the original scale: $exp(\bar{y} \pm 1.96 SE_{\bar{y}})$, where *exp* is the exponential function.

Test of Heterogeneity

The assumption that the θ_i are constant may be tested by the heterogeneity statistic

$$Q = \sum w_i (y_i - \bar{y})^2 = \sum w_i y_i^2 - (\sum w_i y_i)^2 / \sum w_i$$

distributed approximately as χ^2_{k-1}.

Figure Legend

Figure 1. Pooled Adjusted Hazard Ratios and 95% Confidence Intervals of the Combined Outcome among Patients Given a Statin Compared to Those Given an Atorvastatin. Atorvastatin is the reference category. Hazard ratios were adjusted for age, sex, prior statin use, comorbidities (hypertension, diabetes, CHF, COPD, cerebrovascular disease, CRF, dementia, malignancy); in-hospital procedures (catheterization, PCI, CABG); cardiac medications (β-blockers, ACE inhibitors, nitrates, antiplatelet agents, calcium channel blockers, diuretics, warfarin, digoxin, fibrates); specialty of treating physician, hospital type, length of hospital stay, time to first prescription, and the year of index AMI.

Figure 2. Provincial Specific Adjusted Hazard Ratios and 95% Confidence Intervals of the Combined Outcome among Patients Given a Statin Compared to Those Given an Atorvastatin. Atorvastatin as the reference category. Hazard ratios were adjusted for age, sex, prior statin use, comorbidities (hypertension, diabetes, CHF, COPD, cerebrovascular disease, CRF, dementia, malignancy); in-hospital procedures (catheterization, PCI, CABG); cardiac medications (β-blockers, ACE inhibitors, nitrates, antiplatelet agents, calcium channel blockers, diuretics, warfarin, digoxin, fibrates); specialty of treating physician, hospital type, length of hospital stay, time to first prescription, and the year of index AMI.

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Figure 1.

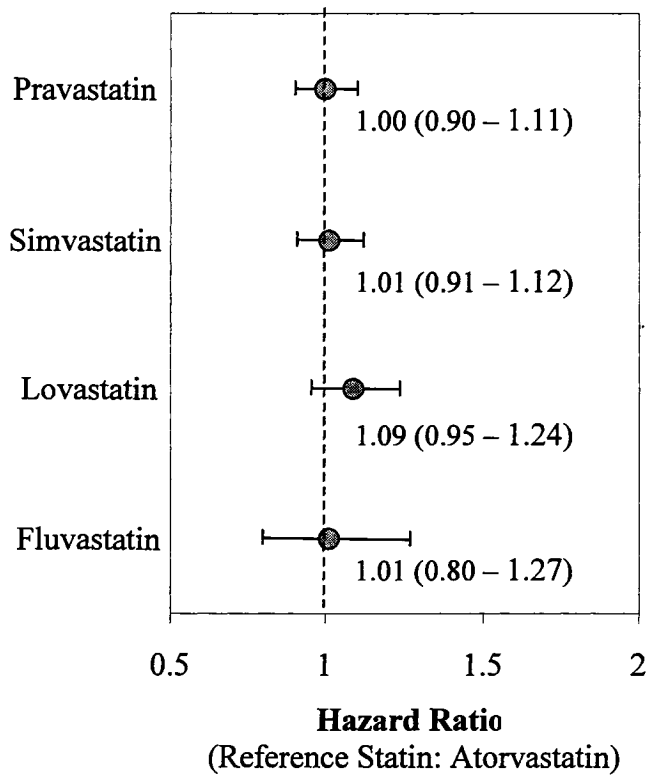
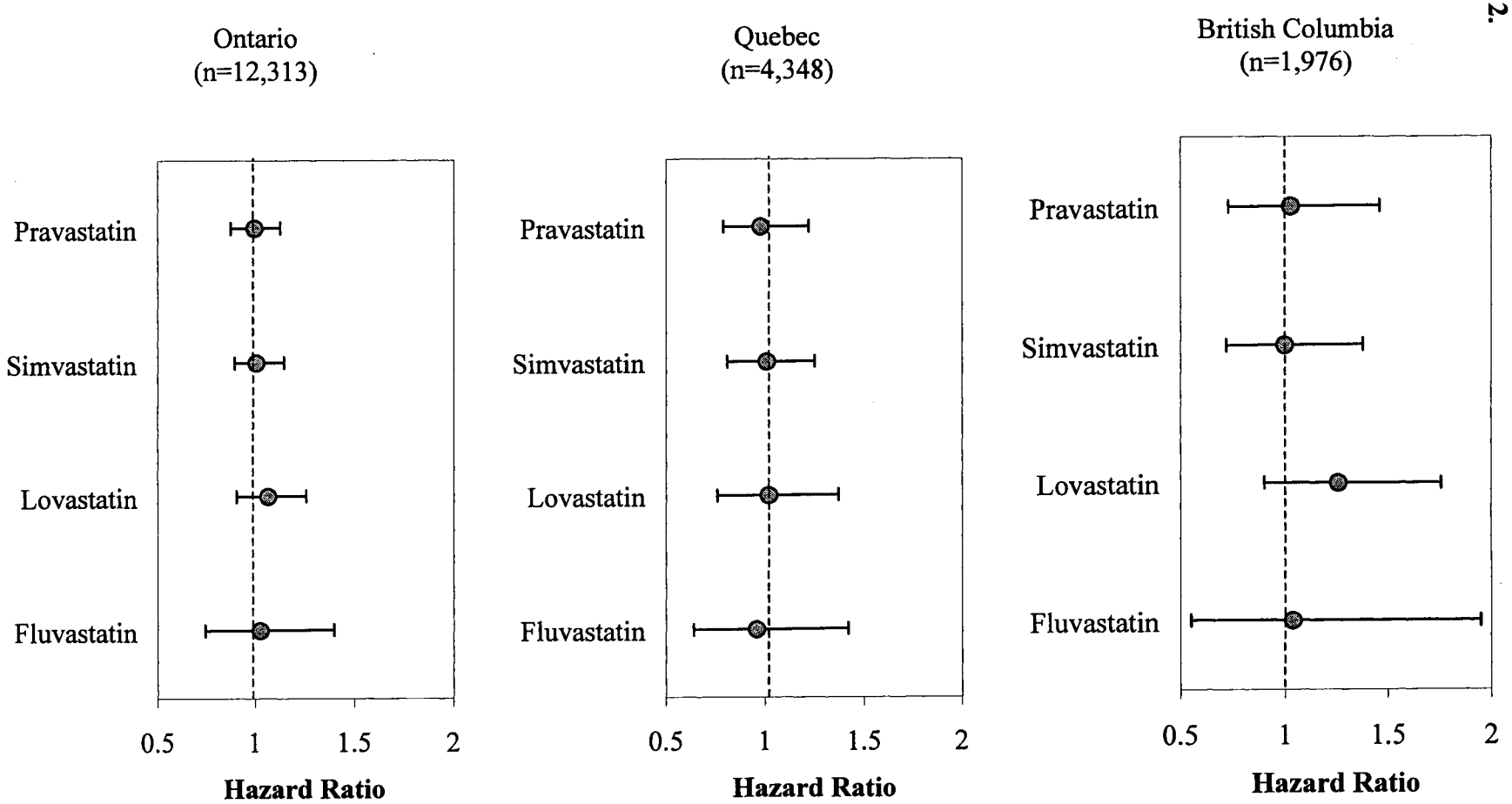

Pravastatin
1.00 (0.90 – 1.11)
Simvastatin
1.01 (0.91 – 1.12)
Lovastatin
1.09 (0.95 – 1.24)
Fluvastatin
1.01 (0.80 – 1.27)
0.5
1
1.5
2
Hazard Ratio
(Reference Statin: Atorvastatin)

Figure 2.



(Reference Statin : Atorvastatin)

Table 1. Characteristics of Elderly Patients Receiving Statins After Acute Myocardial Infarction

Characteristics	Atorvastatin	Pravastatin	Simvastatin	Lovastatin	Fluvastatin
Number of patients	**6420**	**4480**	**5518**	**1736**	**483**
Median age, years	72 (72, 72)*	72 (71, 73)	73 (71, 73)	73 (72, 73)	72 (72, 73)
Males, %	59 (59, 62)	61 (59, 63)	61 (60, 64)	56 (50, 61)	57 (56, 59)
Baseline comorbidities, %					
Hypertension	32 (27, 39)	31 (24, 37)	31 (29, 36)	32 (28, 41)	29 (26, 31)
Diabetes	25 (20, 27)	23 (19, 25)	23 (17, 24)	24 (20, 26)	25 (20, 29)
CHF	20 (15, 21)	19 (13, 20)	20 (14, 22)	23 (17, 28)	18 (16, 22)
Cardiac dysrhythmia	15 (12, 18)	15 (12, 17)	15 (12, 18)	15 (13, 19)	13 (11, 16)
COPD	10 (6, 16)	11 (9, 17)	10 (9, 16)	11 (9, 16)	11 (6, 19)
Cerebrovascular disease	4 (1, 7)	5 (2, 8)	4 (2, 8)	5 (2, 8)	5 (2, 6)
Chronic renal failure	4 (1, 7)	5 (1, 7)	4 (1, 7)	4 (1, 9)	4 (1, 9)
Malignancy	2 (1, 2)	2 (1, 2)	2 (1, 3)	2 (1, 2)	2 (1, 3)
Dementia	1 (1, 1)	1 (0, 1)	1 (0, 1)	1 (1, 1)	1 (0, 2)
In-hospital procedures					
Catheterization	30 (24, 47)	29 (21, 45)	28 (22, 42)	29 (17, 43)	26 (23, 33)
PCI	12 (8, 25)	12 (7, 22)	11 (6, 22)	12 (6, 23)	9 (5, 19)
CABG	4 (2, 11)	3 (1, 6)	4 (2, 8)	5 (2, 12)	5 (4, 6)
Cardiac medications (before first statin prescription)					
Nitrates	71 (62, 73)	71 (66, 74)	72 (68, 74)	69 (61, 74)	67 (66, 70)
Beta-blockers	71 (65, 73)	67 (65, 67)	67 (62, 69)	63 (61, 64)	64 (55, 69)
ACE Inhibitors	56 (45, 60)	52 (47, 55)	53 (45, 57)	49 (42, 51)	48 (42, 51)
Antiplatelet agents**	54 (51, 64)	57 (54, 63)	54 (51, 61)	50 (47, 59)	55 (54, 57)
Diuretics	28 (22, 28)	28 (23, 29)	28 (23, 29)	33 (27, 35)	26 (23, 28)
Calcium-channel blockers	24 (22, 25)	24 (19, 24)	25 (19, 26)	30 (18, 35)	24 (22, 26)
Warfarin	12 (7, 16)	13 (12, 13)	13 (9, 13)	14 (11, 15)	14 (7, 20)
Digoxin	11 (9, 16)	12 (8, 14)	11 (10, 13)	14 (12, 17)	10 (6, 12)

Table 1 (Cont.) Characteristics of Elderly Patients Receiving Statins After Acute Myocardial Infarction

Characteristics	Atorvastatin	Pravastatin	Simvastatin	Lovastatin	Fluvastatin
Specialty of treating physicians	39 (36, 48)	42 (37, 50)	40 (35, 48)	38 (34, 45)	27 (20, 32)
Cardiologist	39 (36, 48)	42 (37, 50)	40 (35, 48)	38 (34, 45)	27 (20, 32)
Internist †	35 (10, 41)	30 (9, 40)	36 (14, 43)	31 (10, 38)	35 (20, 44)
GP and other specialists	26 (22, 41)	28 (23, 40)	24 (19, 37)	31 (21, 44)	38 (26, 41)
Hospital characteristics					
Teaching hospital	21 (5, 23)	17 (5, 20)	23 (7, 25)	21 (8, 27)	11 (4, 18)
Catheterization availability	18 (14, 31)	23 (16, 37)	21 (18, 27)	25 (22, 34)	12 (10, 19)
Hospital rural locations ‡	4 (4,6)	5 (4, 8)	4 (3, 6)	5 (5, 6)	11 (7, 15)
Length of hospital stay, median days	7 (7, 9)	8 (7, 9)	8 (7, 9)	8 (7, 10)	8 (7, 9)

* Weighted percentage or median; figures in parentheses represent the lowest and the highest value of the three provinces;
** Includes ASA and clopidogrel;
† Excludes cardiologist;
‡ Defined as having 0 in the middle of the first 3 digits of the postal code (as per Canada Post definition);
AMI=Acute Myocardial Infarction; CHF=Congestive Heart Failure; COPD=Chronic Obstructive Pulmonary Disease;
PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Graft surgery; GP= General Practitioner.

Table 2. Statin Usage Pattern

	Atorvastatin	Pravastatin	Simvastatin	Lovastatin	Fluvastatin
Statin use prior to index MI, %	33 (27, 37)*	37 (32, 38)	35 (32, 40)	53 (37, 58)	42 (37, 50)
Time to first statin prescription after discharge, median, days	3 (1, 4)	6 (1, 14)	3 (0, 15)	6 (0, 11)	9 (0, 12)
Duration of use in the first year, median, days	364 (360, 365)	352 (330, 360)	360 (350, 365)	353 (330, 360)	307 (240, 342)
Persistence†	0.94 (0.87, 0.99)	0.94 (0.87, 1)	0.94 (0.87, 0.99)	0.94 (0.89, 1)	0.95 (0.88, 1)
Switching during first year, %	3 (3, 3)	9 (8, 9)	6 (6, 7)	13 (12, 15)	17 (14, 23)
Switching during follow-up	8 (8, 9)	29 (24, 31)	22 (22, 26)	41 (36, 43)	50 (42, 56)
Treatment stopped during follow-up	10 (9, 12)	10 (10, 12)	11 (10, 12)	12 (9, 13)	13 (10, 18)
Daily dose (median, mg)‡	10 (10, 10)	20 (20, 20)	20 (20, 20)	20 (20, 20)	20 (20, 20)
Dose distribution, % 10 mg	66	12	46	2	0.2
20 mg	28	71	47	82	75
40 mg	5	16	7	15	24
80 mg	0.5	0.6	0.4	1	0.8
Dose increased, %	13 (11, 14)	13 (11, 15)	13 (11, 14)	10 (10, 11)	11 (9, 11)
Dose decreased	5 (5, 6)	5 (4, 6)	6 (4, 6)	4 (3, 4)	3 (1, 4)

* Unless specified otherwise, numbers are weighted percentage or median, numbers in parentheses represent the lowest and highest values for the 3 provinces;

† Defined as the ratio of total number of days supplied for the initial statin divided by the total number of follow-up days;

‡ Median daily dose of the initial statin prescription post AMI.

Starting and maintenance dose as recommended by the Compendium of Pharmaceuticals and Specialties (CPS) Canada 2002:

Atorvastatin 10~20mg; Pravastatin 20~40mg; Simvastatin 10~40mg; Lovastatin 20~40mg; Fluvastatin 20~40mg

Table 3. Unadjusted Cumulative Incidence and Incidence Rate for Recurrent AMI and Death during Follow-up

Outcome	Atorvastatin	Pravastatin	Simvastatin	Lovastatin	Fluvastatin
Length of follow-up, median, yr	2.0	2.4	2.3	2.4	2.5
Recurrent AMI and Death, %*	19 (14, 21)	22 (16, 24)	23 (16, 25)	27 (20, 31)	21 (17, 23)
Rate (per 100 patient-years)	11 (8, 12)	11 (7, 11)	11 (7, 11)	12 (9, 14)	10 (7, 10)
Death alone, %	13 (9, 15)	16 (10, 19)	16 (10, 18)	22 (12, 28)	13 (8, 17)
Rate (per 100 patient-years)	7 (5, 7)	7 (4, 7)	7 (4, 7)	9 (7, 10)	6 (4, 7)

* Weighted percentages and rates; figures in parentheses represent the lowest and the highest value of the three provinces.

Table 4. Multivariable Model Comparing Recurrent AMI and Mortality among Statin Users. Adjusted Hazard Ratios and 95% Confidence Intervals for Statins and Covariates*

	Hazard Ratio	95% Confidence Interval of the Hazard Ratio
Statin Prescriptions		
Atorvastatin (reference)	-	- -
Pravastatin	1.00	(0.90 , 1.11)
Simvastatin	1.01	(0.91 , 1.12)
Lovastatin	1.09	(0.95 , 1.24)
Fluvastatin	1.01	(0.80 , 1.27)
Baseline Demographic and Comorbidities		
Age**	1.04	(1.04 , 1.05)
Male	1.19	(1.10 , 1.28)
Prior Statin Use†	1.26	(1.16 , 1.36)
Length of Hospital Stay‡	1.06	(0.98 , 1.15)
Time to First Statin Prescription§	0.70	(0.64 , 0.77)
Hypertension	1.01	(0.93 , 1.09)
Diabetes	1.60	(1.46 , 1.75)
CHF	1.51	(1.38 , 1.65)
Cardiac Dysrhythmia	1.09	(0.98 , 1.20)
COPD	1.18	(1.06 , 1.32)
Cerebrovascular Diseases	1.30	(1.12 , 1.51)
Chronic Renal Failure	1.71	(1.49 , 1.97)
Malignancy	1.97	(1.59 , 2.44)
Dementia	1.29	(0.93 , 1.80)
Procedures During Index Admission		
Catheterization	0.76	(0.67 , 0.87)
PCI	0.60	(0.48 , 0.74)
CABG	0.33	(0.23 , 0.47)
Other Cardiac Prescriptions		
Nitrates	1.00	(0.92 , 1.09)
Beta-blockers	0.83	(0.77 , 0.90)
ACE Inhibitors	1.08	(0.99 , 1.16)
Antiplatelet agents (*aspirin* and *clopidogrel*)	0.88	(0.82 , 0.94)
Diuretics	1.46	(1.34 , 1.59)
Calcium-channel blockers	1.21	(1.12 , 1.32)
Warfarin	1.03	(0.92 , 1.14)
Digoxin	1.28	(1.16 , 1.42)

Table 4. (Cont.) Multivariable Model Comparing Recurrent AMI and Mortality among Statin Users. Adjusted Hazard Ratios and 95% Confidence Intervals for Statins and Covariates*

	Hazard Ratio	95% Confidence Interval of the Hazard Ratio
Physician and Hospital Characteristics		
Cardiologist	0.98	(0.90 , 1.07)
Teaching Hospital	1.08	(0.95 , 1.22)
Cath. Lab. Availability	0.98	(0.87 , 1.10)
Hospital Volume¶	0.87	(0.41 , 1.85)
Year of Index AMI Admission		
97-98 (reference)	-	- -
98-99	1.04	(0.95 , 1.15)
99-00	1.06	(0.95 , 1.18)
00-01	1.05	(0.92 , 1.20)

* Adjusted hazard rates and 95% CIs pooled from the estimates of the 3 provinces, with weight being the inverse of the variance of the estimates;

** Effect of age was linearly related to the outcome, hence "Age" was modeled as a continuous variable;

† Any statin use within 1 year before the index AMI admission;

‡ Length of hospital stay dichotomized at 7 days, with (< 7 days) as a reference category

§ Time to first statin prescription since discharge dichotomized at 30 days post discharge, with (< 30 days) as a reference category

¶ Hospital volume dichotomized at the third quartile (Q3), with (Q1-Q3) as a reference category.

CHF=Congestive Heart Failure; COPD=Chronic Obstructive Pulmonary Disease;
PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Graft surgery.

4.3 Additional Discussion

In this study, we reported a similar effect between statins for secondary prevention in an elderly population post-AMI. There are several issues related to the result interpretation and method of analysis, which deserve further discussion.

4.3.1 Determination of Clinical Equivalence

The claim for *equivalence* between treatments should be made upon careful examination. A misinterpretation may lead to harmful decision regarding patient care (Greene et al., 2000), as clinically inferior treatments might be used, or a potentially superior therapy might be discarded. To declare equivalence based on a failed hypothesis testing ($p>0.05$) with a null hypothesis (H_0: effects of treatment A and B are the same) and an alternative hypothesis (H_a: effects of treatment A and B are different) might be misleading because (Altman et al. 1995, Jones et al., 1996). The failure to reject the null hypothesis may indicate inadequate evidence (Greene et al., 2000).

In the context of statistical testing, however, "equivalence" exists only as a theoretical entity, because it would require an infinitely large sample size to establish no difference between compared groups. In practice, the strategy is to specify some value for the difference (δ), such that a difference in the effect between two treatments, if less than this value, can be considered as clinically unimportant (Friedman et al., 1998). The two treatments then can be treated as being equally effective. Such a difference can be formulated into an *Equivalence Test* (H_0: difference in effect between treatment A and B is greater than a pre-specified value δ; H_a: difference in effect between treatment A and

B is less than the value δ) (Ware et al. 1997), or more conveniently, can be considered in terms of a region of clinical equivalence (i.e. unity ± δ). Depending on how the confidence interval (CI) of the estimated comparative effect falls in relation to the predefined region of clinical equivalency, different interpretations apply (Alderson 2004) (Figure 4-1).

There is, however, no standard method or criteria to determine what would be a "large" or an important difference. The δ is, therefore, an arbitrary threshold to be decided upon according to clinical situations. For example, in the post-AMI treatment, the *Global Use of Strategies to Open Occluded Arteries Trials* (GUSTO/GUSTO III) (The GUSTO investigators 1993, The GUSTO III investigators 1997) considered a relative difference of 20%, or an incremental difference of 1% in mortality rates as potentially important thresholds to declare difference between thrombolytic treatment groups. In the present study comparing statins, if a ± 20% relative difference is chosen to form the region of clinical equivalence, an equal effectiveness can be established among statins according to their estimated relative effect and 95% CI's. With a more stringent threshold of ± 10%, we can still reasonably declare equivalence for pravastatin and simvastatin compared with atorvastatin, although the conclusion turns to be more conservative for lovastatin and fluvastatin.

4.3.2 Issues with Censoring at Switching and Channeling Over Time

When comparing drugs from the same therapeutic class, switching between drugs poses a difficulty in outcome interpretation. There is a question about which drug should be responsible for the effect if frequent switching occurs.

Currently, there is a lack of an optimal method to deal with switching in the evaluation of treatment effect (Blais et al., 1998, Suissa et al., 2000, Pilote et al., 2004). In the present study, we censored patients at switching to account for the discontinuation of the initial statin, and kept the person-time follow-up until the time of switching in the analysis. The result was compared to that from the main analysis by the "intention-to-treat" approach, in which patients were considered to be on the initial statin until the end of follow-up or the occurrence of a study outcome. We examined how results would change depending on the analytical approaches with and without considering switching. However, there is a concern whether an excessive amount of these censorings carries information for patients' prognosis, i.e. censoring is informative. For the model estimates to be unbiased in the presence of censored data, it is essential that censoring is random and noninformative, that is, the censored subjects are "representative" of those still under observation at the same time, given the covariates. Patients are not censored because of having a higher or lower risk than the average patients (Leung et al., 1997).

The rates of switching in this study were found to be very different across different statins, with lovastatin and fluvastatin users having the highest rate of switching (40%-50%) and atorvastatin users the lowest (8%). Among those who switched, close to

half of them switched to atorvastatin. Whether the switching was associated with unsatisfactory control of cholesterol levels, or merely because of the enthusiasm towards the newly released atorvastatin at that time, or both, is very difficult to assess, especially in the absence of patients' cholesterol information in the database. Particularly for those who switched to atorvastatin, if the switch is related to less well-controlled disease, censoring is likely to be informative, as these patients might be associated with a higher risk for outcomes. Preferential prescribing in the follow-up due to the change of disease status has been previously described - a phenomenon termed "channeling over time". It suggests that even if the initial choice between drugs is independent of the severity of disease at baseline, preferential selection of a drug could occur in the follow-up. This emphasizes the fact that the direction of the switch could be associated with disease severity.

To assess the possibility of "channeling over time", we compared "switchers to atorvastatin" with "switchers to other statins" for the rates of hospitalization for CHF and angina, and cardiac medication use (β-blocker, ACE inhibitor, diuretics, nitrates and digoxin) since the first statin prescription until the date of switching. These rates were used as a proxy to indicate the disease state prior to switching. No statistically significant difference in these rates between the two groups was detected. However, this approach together with other approaches (Blais et al., 1996) are still preliminary in studying the cause and direction of switching. In the present study, it remains possible that some of the switching were due to unsatisfactory control of cholesterol levels, which could be associated with increased risk for outcomes. In such case, censoring at switching

would positively impact the statin switched from. The results based on the approach to censor patients at switching, therefore, need to be interpreted with caution.

In summary, in the absence of sufficient patient (e.g. cholesterol levels) or physician information, it remains difficult to fully understand switching and to account for it with appropriate statistical techniques.

4.3.3 "Time to First Statin Prescription" – The Earlier The Better?

There is a notable finding in the Cox multivariate regression model studying the class effect of statins on survival. The parameter estimate for "time to first statin prescription" adjusted as one of the baseline covariates was less than "1" and was statistically significant (HR: 0.70, 95% CI: 0.64-0.77). A naïve interpretation would be that there is a protective effect associated with a delay in treatment initiation – the later the better. Intuition suggests that this interpretation must be incorrect, as one could otherwise infinitely postpone statin use to achieve the "best" outcome.

This estimate, in fact, indicates a decrease of risk for outcome occurrence over time after an AMI, independent of treatment effect, and it closely relates to the survival bias that is studied in the following two chapters assessing the effect associated with the timing of statin initiation post-AMI.

CHAPTER 5

AN EVALUATION OF THE EFFECT ASSOCIATED WITH EARLY INITIATION OF STATIN AFTER ACUTE MYOCARDIAL INFARCTION

As a second focus of this thesis, Chapter 5 and 6 are devoted to the study of the effect associated with early initiation of statin among elderly patients post-AMI. There is, however, a possibility of having survival bias in this evaluation, and to control for this bias represents a methodological challenge. In Chapter 5, I will characterize this bias and propose methodological solutions. Methods determined to be effective in the control of survival bias will be used in Chapter 6 to address the clinical question.

5.1 Survival Bias: Characterization and Proposed Methodological Solutions

5.1.1 Preface to Manuscript #3

In assessing the effect of early initiation of statin after AMI, survival bias may affect the validity of the results. Generally, the bias occurs when subjects' survival affects the classification of two comparison groups. This could be a classification of "exposed" and "unexposed" subjects to a treatment, or among the exposed subjects, those who differ systematically in their time of treatment initiation, e.g. "early" and "delayed" users.

Using real-life data, the current manuscript compares 5 different methods in the study and control of survival bias. Two of these methods have been used in

previous drug effectiveness studies that suffered from survival bias (Sin et al. 2001, Mamdani et al., 2002). Three additional methods are proposed to control for this bias, including a newly proposed method using prescription time distribution matching. To replicate previous designs and facilitate result comparison among existing and new methods, in this manuscript, survival bias is studied through an evaluation of early statin initiation ($\leq$ 90 days post discharge after AMI) compared with no statin treatment.

This study is the first to compare the performance of different methods to control for survival bias in the drug effectiveness evaluation. Upon evaluation of their performance in controlling for survival bias, optimal method(s) will be used in studying the effect associated with a difference in the timing of statin initiation after AMI.

Abstract

Objective To characterize the survival bias associated with subjects' time-to-treatment initiation in drug effectiveness evaluation and assess the performance of different methods in the control of this bias.

Study Design and Setting We studied survival bias in the context of evaluating effectiveness of statins in elderly patients discharged from a hospitalization for acute myocardial infarction (AMI). We used a retrospective cohort (1996-2002) to compare the risk of recurrent AMI or death among patients who initiated statins ≤ 90 days after discharge (users) and those who did not (nonusers). Five methods were evaluated. In *method 1,* patients are dichotomized into statin users and nonusers and are followed since discharge. In *method 2,* users are followed from the time of the first statin prescription, while nonusers are followed from a randomly chosen time between 0-90 days post discharge. In *method 3,* all patients are followed from the end of the 90-day time window used to define "users". In *method 4*, users are followed from the time of the first statin prescription, while each nonuser is assigned a follow-up starting time that is randomly selected from the observed distribution of the users' time of first prescription. Finally, in *method 5*, a time-dependent variable is used to represent statin initiation. Patients are all followed from discharge and they are classified as nonusers until the dispensing time of their first prescription when they become users. In all 5 methods, a multivariate Cox regression model is used to analyze the failure time.

Results The cohort comprised 6,235 patients who initiated a statin in the 90 days post discharge and 15,286 patients who did not. Method 1 introduced an artificial survival advantage associated with the user group, leading to an overestimation of the benefit of statins (38% relative risk reduction at 1-year). In method 2, nonusers were selected by design to have

on average a longer survival time than the users. This attenuated the effect of statins towards the null (10% relative risk reduction). Method 3 controlled for the survival bias by including only 90-day survivors from both groups, however it suffered a loss of statistical efficiency and precision. Method 4 and 5 controlled for the survival bias that occurred in method 2 and 1 respectively, without apparent loss of statistical efficiency. The two methods gave the same estimates, suggesting a 20% relative risk reduction by statin treatment.

Conclusion The method using prescription time distribution matching at study entry (method 4) and the method using a time-dependent variable for treatment initiation (method 5) showed better performances in the control of survival bias. The two methods controlled for the bias at the design and the analysis level, respectively, and have better statistical efficiency compared with other methods assessed in the study.

Introduction

Survival bias occurs in studies that assess the effect of a treatment on survival or any other failure time, when the classification of "exposed" subjects requires that a person survives or remains event free until the date he/she receives the treatment. Subjects who die shortly after the start of follow-up may not have had the opportunity to become exposed, and are "unexposed" by definition. This artificially introduces a survival advantage associated with the exposed subjects regardless of treatment effectiveness. Typically, survival bias arises when a time window from start of follow-up to start of exposure is used to define users of a medication, and subsequent analyses fail to account for the fact that the users' time-to-treatment initiation represents unexposed survival time. The magnitude of this bias depends on both the length of the time window used to define the users and the risk for outcome within this time window[1]. The treatment effect will be much more distorted if an excessive number of early deaths are classified into the unexposed group or if a longer time window captures more late users who, by definition, survive longer.

Some previous observational studies of drug effectiveness may have failed to recognize and effectively control for such survival bias. This lack of control could have resulted in biased estimates. In practice, patients discharged from a hospitalization for a disease condition, such as acute myocardial infarction (AMI), exacerbation of chronic obstructive pulmonary disease (COPD) or asthma, are at high risk of hospital readmission due to event recurrence or mortality[2]. Studies evaluating medication effectiveness in these patients are prone to survival bias. For example, in a study assessing the effect of inhaled corticosteroids use on the risk of mortality and hospital readmission in COPD patients[3], the authors defined the users as those who filled a prescription of inhaled corticosteroids in the 90-day period following

discharge. Nonusers were those who did not fill a prescription for the medication in the same time period. Both groups were followed for 1 year from the date of discharge. The study reported a 26% reduction in mortality and hospital readmission for COPD associated with inhaled corticosteroids use. However, the benefit may have been overestimated because of survival bias. The higher event rate, likely driven by rehospitalization in the early period following discharge, may have forced a majority of the early events to be classified into the nonuser group, because most of these subjects may not yet have an opportunity to receive the medication. A subsequent analysis in a similar setting using a time-dependent variable to represent treatment initiation[1] revealed that there was indeed no effect of the treatment (RR: 1.00, 95% CI: 0.79-1.26). Similar examples of survival bias can be found in several other studies of drug effectiveness[4-8].

In order to control for survival bias, some studies have used an alternative time 0, such as to follow patients from the time of the first prescription rather than the date of discharge. The difficulty however is that, among nonusers, there is no actual prescription time of the study drug. Several approaches have been used in the literature to define time 0 for the nonusers. Some authors used a method that randomly assigns a prescription time to the nonusers as time 0 for the follow-up[9], while others chose the prescription time of another drug filled by the nonusers during the same period for user identification[10]. However, survival bias may still be present in these methods. For example, random assignment of prescription time to nonusers may not lead to equalization of the survival pattern between the two groups, and the survival difference may remain. In the case of using a prescription time of another drug among nonusers, that drug may be associated with the study outcome and may confound the treatment effect under study. Finally, the method that dichotomizes subjects into "users" and "nonusers"

based on discharge prescriptions leads to misclassification. A considerable number of subjects who fill the prescription in the subsequent days are misclassified as "nonusers"[11]. This may attenuate the treatment effect towards the null.

Despite the many methods that are used in different studies, there is a lack of an optimal approach that adequately controls for the survival bias. The current study was conducted to compare the performance of different methods in the control of this bias. We proposed a new "prescription time distribution matching" method and compared its performance with other methods. We applied these different methods to evaluate the effectiveness of statins among elderly patients after AMI.

Methods

Data Source

The Quebec hospital discharge summary database and the physician and prescription claims databases were linked to identify patients hospitalized for AMI and to determine their comorbidity. Up to 15 diagnoses of comorbidity are recorded in the hospital discharge database. In- and out-patient physician visits and diagnoses and prescribed medications are recorded in the physician and prescription claims databases. Prescription information includes type of medication, dosage, quantity and duration. In- and out-of-hospital death information is available from provincial registry databases. All databases were linked with patients' unique, encrypted healthcare insurance number. Several validation studies have been conducted previously to assess the accuracy of the coding[12-14].

Study Cohort

We created a retrospective cohort. Eligible subjects were Quebec elderly (≥ 65 years) who were admitted to hospital with a diagnosis of AMI between 1996 and March, 2000. Survival data was available for these patients until April, 2002.

Inclusion and exclusion criteria

Patients were included if they had an AMI (ICD-9 code 410) coded as their most responsible diagnosis and were discharged alive. Patients were excluded if they met one or more of the following exclusion criteria: 1) the AMI was coded as an in-hospital complication; 2) the AMI admission was a transfer from another hospital (this is to avoid counting patients twice, yet all transfers related to the initial AMI admission are counted in the total length of hospital stay); 3) the total length of hospital stay was less than 3 days (this is to exclude ruled-out AMI cases and those admitted only for procedures); 4) the patient was discharged to a long-

term care institution, a rehabilitation center, or move out of the province (as information on medication was not available in these cases); and 5) the health care number was invalid.

Exposure definition

Patients who filled at least one statin prescription ≤ 90 days after discharge were defined as statin users. Patients who did not have a prescription ≤ 90 days were nonusers (the latter included a small number of subjects who had a first statin prescription after 90 days post discharge).

Outcome

The study outcomes were defined as a combination of recurrent AMI or death due to any cause, whichever occurred first.

Follow-up

All patients were followed for the earliest of 1-year post discharge, the occurrence of a study outcome. In addition, follow-up at 6-month post discharge and full follow-up (until April, 2002) were also studied.

Baseline Characteristics

Patients' characteristics included age, sex and comorbidity at discharge (i.e. coexisting cardiovascular and lung diseases, chronic kidney or liver conditions as well as other diseases, such as diabetes, dementia and malignancy). Concurrent use of β-blockers, angiotensin converting enzyme (ACE) inhibitors, antiplatelet drugs (aspirin, clopidogrel), calcium channel blockers, diuretics, warfarin, digoxin and fibrates as well as statin use during the year before the index AMI was also included as baseline covariates. In addition, we obtained information for each patient regarding in-hospital procedures (catheterization,

percutaneous coronary intervention, coronary artery bypass graft surgery), specialty of the treating physician and the type of hospital, length of hospital stay and the year of AMI.

Description of Study Methods

We compared five methods (Table 1). The first two methods illustrated how survival bias could be introduced in the drug effectiveness studies. Three additional methods were considered to control for this bias, including a newly proposed method of the prescription time distribution matching. We compared it to other available methods. In all five methods, a 90-day post discharge period was used to define users of statins.

I) Methods introducing survival bias

Method 1 (Simple grouping)[3] Statin use is represented by a binary variable taking the value 1 for those who initiated a statin within 90 days post discharge and 0 for those who did not. Both groups are followed from the date of discharge until the earliest of recurrent AMI or death occurrence or the end of study follow-up.

Method 2 (Random selection of prescription time)[9] Statin use is represented by a binary variable taking the value 1 for those who initiated statins within 90 days post discharge and 0 for those who did not. The nonusers are assigned a time 0 that is randomly selected between 0 and 90 days post discharge. Nonusers who had an event before the assigned time 0 are excluded from the analysis. Time 0 for a user is the time of his/her first prescription. Both groups are then followed from time 0 until the earliest of recurrent AMI or death occurrence or the end of study follow-up.

II) Methods to control for survival bias

Method 3 (Follow-up begins at day 90) Statin use is represented by a binary variable taking the value 1 for those who initiated a statin within 90 days post discharge and 0 for those who did not. Users and nonusers of statins are followed from the end of the exposure time window (i.e. 90 days post discharge) until the earliest of recurrent AMI or death occurrence or the end of study follow-up. Accordingly, patients who sustain an event during the first 90 days are excluded from the analysis.

Method 4 (Prescription time distribution matching) Statin use is represented by a binary variable (1 for users and 0 for nonusers). The number of days from discharge to the dispensing time of the first prescription is assessed for the users. For each nonuser, a time 0 is randomly selected from this set and assigned to him/her. Therefore, the overall distribution of time 0 of the nonusers is matched to that of the users' time of first prescription (time 0). Both groups are followed from time 0 until the earliest of recurrent AMI or death occurrence or the end of study follow-up. Nonusers who had an event before the assigned time 0 are excluded from the analysis.

Method 5 (Time-dependent exposure)[1] A time-dependent variable for statin initiation within first 90 days is used to define current users and nonusers. Follow-up starts at discharge until the earliest of recurrent AMI or death occurrence or the end of study follow-up. For users, the value of the time-dependent variable is 0 before the time of first statin prescription. This value changes to 1 when the prescription is filled and onward. For nonuser, the value remains as 0 throughout the follow-up.

Schematic diagrams of these 5 methods are given in *Appendix 1.*

Data Analysis

Descriptive analyses were used to compare patient characteristics at discharge between statin users and nonusers. The rate of recurrent AMI and mortality were determined during the 1-year follow-up after discharge. A multivariate Cox proportional hazards model[16] was used to analyze the time to recurrent AMI or death in all methods, except that, in method 5, a multivariate Cox model with a time-dependent variable for statin initiation was used. For each method, an adjusted hazard ratio (HR) of statin use was reported for recurrent AMI or death during 1-year post discharge. In supplement analyses, adjusted HR's for outcome at 6-month and full follow-up (until April, 2002) were reported.

Comparison of the Methods

The five methods were compared to determine: 1) the source of bias and/or their ability to control for it; 2) the differences in point estimates of the adjusted HR's and the width of corresponding 95% confidence intervals (CI's); 3) the statistical efficiency in terms of number of subjects excluded from the analysis; 4) advantages and limitations in their applications.

All analyses were done using SAS version 8.0 (SAS Institute Inc. Cary, NC.). Significant level of 0.05 (2-sided) was used for all tests.

Results

Study Subjects

The cohort included 21,521 elderly patients (92% of the original cohort) who met the inclusion criteria. Among them, 6,235 patients (29% of the cohort) filled a statin prescription during the first 90 days following discharge. The median follow-up time of the cohort was 3.0 years (25th. – 75th. percentile: 1.6 – 4.4 years).

We observed that users and nonusers differed in several baseline characteristics (Table 2). Overall, users appeared to be younger and had less comorbidity than nonusers. Differences in these baseline characteristics were adjusted for using the multivariate Cox regression analysis.

Time to First Statin Prescription and Statin Use

The 90-day exposure time window captured 92% of all first post-AMI statin prescriptions during the first year. The distribution of time of the first statin prescription was skewed (median: 1 day; 25^{th} – 75^{th} percentile: 0 – 24 days) (Figure 1). Close to one half of all the prescriptions (n=3,075) were dispensed at discharge, and 81% were dispensed within the first month. One-year persistence (defined as the ratio of total number of supplied days during 1-year divided by 365 days) was high among users of statin (median: 95%; 25^{th} – 75^{th} percentile: 87% – 100%).

Risk of Recurrent AMI and Mortality Within the First Year Post Discharge

By the end of 1 year, 4,168 subjects (19% of all subjects) had a recurrent AMI or death. Among them, 1,930 subjects (46%) had their first event during the first 90 days post discharge, which coincided with the time window used to define users. The event rate peaked

during the first 30 days, when it reached 1.1–1.3 per 1000 patients-day. It then decreased to about 0.6–0.7 per 1000 patient-day by the 90–100 days after discharge, and remained stable thereafter (Figure 2).

Results from Different Methods Evaluating Statin Effectiveness

In method 1 (*simple grouping*), statin use appeared to reduce the risk of recurrent AMI or death by 38% (adjusted HR at 1-year post discharge: 0.62; 95% CI: 0.55-0.69). The effect was overestimated, however, because the design and analysis introduced an artificial survival advantage to users. A total of 254.4 person-years representing users' survival time since discharge to their first prescription were misclassified as exposed person-time. These, by definition, "event-free" person-times inflated the denominator of the event rate in the user group and led to an artificially small rate ratio.

In method 2 (*random selection of prescription time*), simple random assignment of prescription time to the nonusers gave rise to a uniform distribution of time 0 with a median of 45 days (Figure 1). A total of 1,018 (6.7%) nonusers were excluded because of having an event before their assigned time 0. The method showed that statin use was associated with a marginal, non-significant beneficial outcome (adjusted HR: 0.90; 95% CI: 0.80-1.01). However, this effect could be also due to survival bias. Because of the uniform distribution of time 0, nonusers had on average longer survival time than users. The bias was induced by the combination of (i) systematic difference in the time to first prescription between users and nonusers; and (ii) the substantial change in the absolute level of risk during the first 90 days. The median time of 45 days indicated that half of the nonusers survived and were followed after 45 days post discharge when the risk of recurrence was lower than that immediately following discharge, whereas half of the users were followed since day 1 (users' median time

of first prescription) when the risk was the highest. As a result, the nonusers who remained in the study were by design at lower risks for outcomes.

In method 3 (*follow-up begins at 90 days*), following patients from the end of 90-day time window led to the exclusion of 294 (4.7%) users and 1,622 (10.6%) nonusers who had an event in this period. Statin treatment was associated with a 22% reduction of recurrent AMI or death (adjusted HR: 0.78; 95% CI: 0.67-0.90). However, due to exclusion of a large number of events, this method suffered a loss of study information and statistical efficiency.

In method 4 (*prescription time distribution matching*), after matching on the prescription time distribution between user and nonuser groups, there were 364 (2.4%) nonusers excluded because of having an event before assigned time 0. The estimated risk reduction for recurrent AMI or death associated with statin use was 20% (adjusted HR: 0.80, 95% CI: 0.72-0.89). The point estimate was very close to that of method 3, but the CI was narrower, indicating a better precision. Distribution matching of the time at study entry avoided introducing differences in survival patterns between users and nonusers as oppose to method 2 using random selection of prescription time.

In the method 5 (*time-dependent exposure*), a time-dependent representation of statin initiation reduced misclassification of users' survival time before their first prescription as exposed follow-up time. No subject was excluded from the analysis. This method showed that statin use reduced the risk of recurrent AMI or death by 20% (adjusted HR: 0.80, 95% CI: 0.73-0.89). This estimated HR and the 95% CI were the same as those estimated from method 4, and the HR reduction was significantly smaller than that from method 1 of simple grouping (non-overlapping 95% CI).

Overall, method 1 (simple grouping) overestimated the benefit, whereas method 2 (random selection of prescription time) attenuated the estimate towards the null. The other three methods (method 3-5) appeared to be effective in controlling for the bias and provided similar results. This pattern of estimates from different methods was not limited to the outcome by 1-year. A similar pattern was observed in outcomes at 6-month and full follow-up (Table 3).

Discussion

We have demonstrated that survival bias occurs in the study of treatment effectiveness and its impact on the results is substantial. In the present study, artificial survival advantage associated with either users (in method 1, simple grouping) or nonusers (in method 2, random selection of prescription time) distorted the results. The same data analyzed by methods 3-5 that controlled for the bias, suggested that statin use was associated with 20%-22% hazard reduction. This is very different from either a 38% reduction, or statistically non-significant 10% reduction as estimated, respectively, by the first two methods.

Bias due to 'Survival' in Epidemiology

Bias resulting from the subjects' survival is common in clinical epidemiology. In cross sectional studies of patients having rapidly progressive illnesses, a person's survival affects his/her probability to be included in a study (*length bias sampling*)[17, 18], whereas in the current study of treatment effectiveness, a person's survival affects his/her probability to become exposed. Similarly, in the study of cancer recurrence and mortality, the role of "late recurrence" as a predictor for longer survival could be misinterpreted, if one ignores the fact that to have a late recurrence, a patient has to survive a longer period of time[19-21]. Another example, from the transplantation literature, is the duration of the waiting time a patient has lived before transplantation. This length of time should not be interpreted as the effectiveness of transplantation to improve survival[22]. From these perspectives, the survival bias characterized here is not new. The occurrence of this bias can be characterized in a more general situation where subjects' survival affects the classification of two comparison groups.

Performance of Different Methods

The methods we evaluated had 3 different types of time 0: i) the time of discharge (method 1 and 5); ii) the time of first statin prescription (method 2 and 4), and iii) the time at the end of exposure time window (method 3). The occurrence of survival bias associated with *misclassification* of survival time is possible only when using the time of discharge as time 0, because it precedes the time of the first prescription. Unless the prescription is filled on the date of discharge, a subject is unexposed and should be considered as such until the day he/she fills the prescription. This was ignored in the method 1 that involved simple grouping. Such misclassification was reduced by using a time-dependent variable for treatment initiation (method 5) or by starting the follow-up at the time of first prescription (method 2 and 4), or the time where all the first prescriptions have occurred as specified by the design (method 3), here, the end of 90-day time window.

However, using the time of first prescription as the study entry may still introduce survival bias through *selection*. In the method of random selection of prescription time (method 2), the uniform distribution led to the inclusion of a large proportion of nonusers having an assigned time 0 late in time compared to users. Furthermore, because the risk for outcome decreased considerably over time, the nonusers appeared to have an overall lower risk than the users. This differential selection did not occur in the prescription time distribution matching design (method 4), where the proportion of subjects starting at different points in time in the 90 days was similar between users and nonusers. Similarly, there was no "imbalance" in survival time, when subjects were all followed from the same point in time (method 3).

Compared with other methods, the time-dependent approach (method 5) showed several advantages. First, with regard to statistical efficiency, no subject was excluded from the

analysis, whereas this number was 1,916 and 364 in method 3 (follow-up since day 90) and method 4 (prescription time distribution matching), respectively (Table 4). The substantial exclusion also raises the concern of limited generalizability, for example, in method 3, the results may apply only to those 90-day survivors who are included in the study. Second, the time-dependent method is capable of providing effect estimation at any time point post discharge. A subject is allowed to be in the risk set as a nonuser early on and becomes a user later. In other methods, treatment effect cannot be reliably evaluated for the initial time period when users are still being defined.

Despite these advantages, the time-dependent method relies on additional assumptions. The time-dependent representation of statin initiation usually implies that the first prescriptions occur at unpredictable (random) times[22, 23]. This assumption is difficult to assess in this case, as physician's decision to prescribe statins may be influenced by the severity of a patient's condition and life expectancy. Physicians may withhold statins from patients until their condition becomes stable. Thus, receiving a statin may indicate a lower risk status independent of the treatment effect of statins. In such case, survival bias remains, despite the use of time-dependent approach (method 5). Similarly, this assumption also affects the ability of method 4 (prescription time distribution matching) to control for survival bias, as the matching is based on the observed pattern of prescription time.

Notably, method 4 and 5 gave almost identical estimates and 95% CI's, suggesting their similar effectiveness in the control of survival bias. One advantage associated with the method of prescription time distribution matching (method 4) is that it is useful where the comparison is made among users only, for example, in the study of early vs delayed treatment initiation. Survival bias is possible, because the two groups differ systematically in

the time of treatment initiation. The time-dependent approach that compares treatment vs no treatment may have limited application in this case.

Effectiveness of Statins in Elderly Patients Post-AMI

Despite the control for survival bias, the estimated treatment effect of statins is still susceptible to other common biases in observational studies, especially confounding by indication[24]. In practice, statins are prescribed more often to patients perceived to experience the benefit[25]. Older patients and patients with severe coexisting diseases are less likely to receive statin prescriptions. Despite adjusting for a wide spectrum of characteristics, it is possible that we cannot control for all the factors that may affect a physician's decision to prescribe a statin or not. Therefore, even after controlling for survival bias, our results still need to be interpreted with caution.

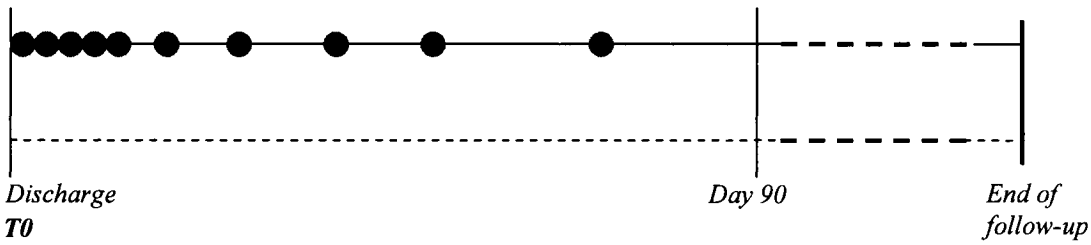
Conclusion

We have shown that the effective control for survival bias relies on the correct use of study design and analysis. Our empirical assessment using real-life data suggests that the method of prescription time distribution matching and the method using a time-dependent variable for treatment initiation provide very similar results and exhibit better performance. This is determined based on their ability to control for the survival bias, statistical efficiency and advantages in their applications.

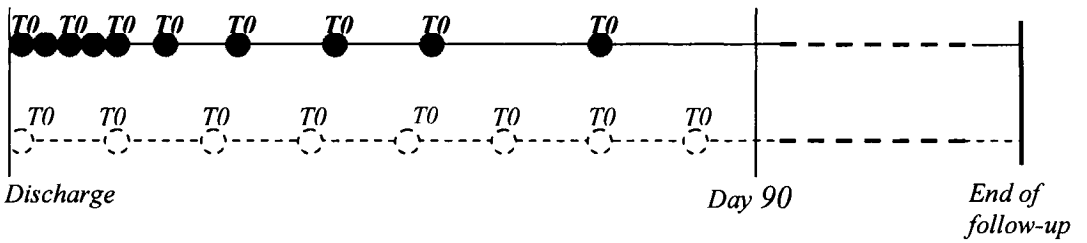
Appendix 1

Schematic Diagrams of Different Designs

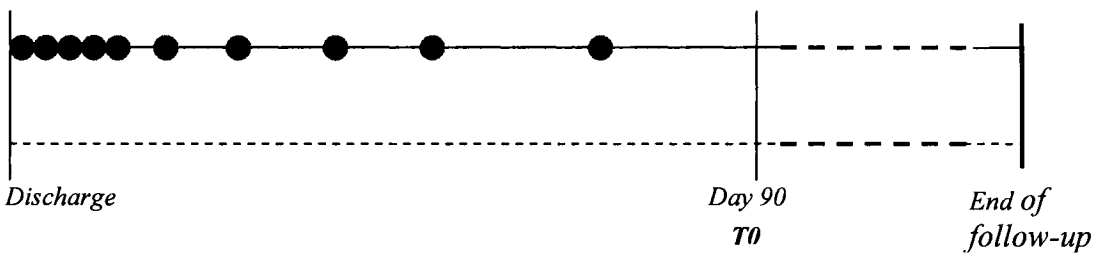
Method 1: *Simple grouping*



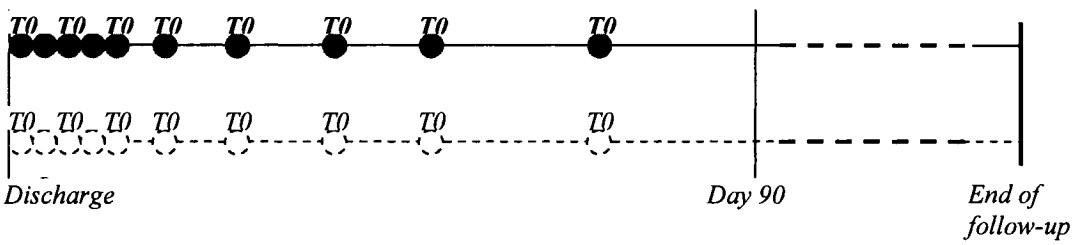
Method 2: *Random selection of prescription time*



Method 3: *Follow-up begins at 90 days (End of exposure time window)*



Method 4: *Prescription time distribution matching*

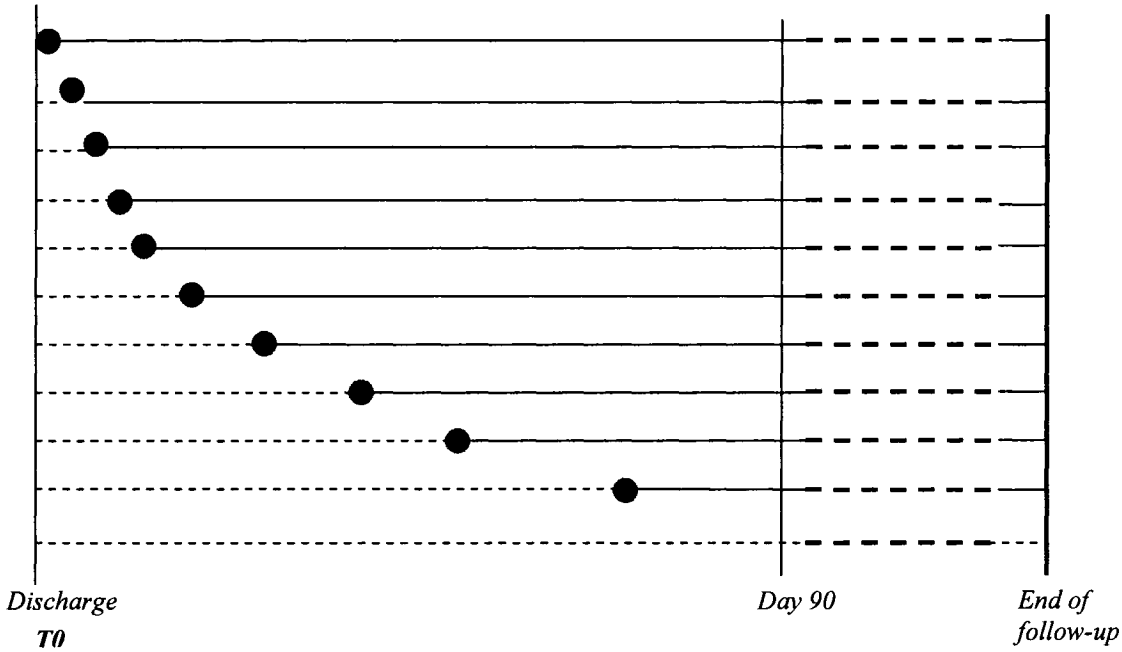


— *Follow-up of user group* - - - *Follow-up of nonuser group* – – – *Follow-up omitted to show*

● *Users' time of first statin prescription during the 90-day time window* ◌ *Nonusers' assigned time of first statin prescription during the 90-day time window*

T0: *time 0 for follow-up*

Method 5: *Time dependent exposure representing treatment initiation*



------ *Unexposed person-time* — *Exposed person-time* - - - *Follow-up omitted to show*

● *Users' time of first statin prescription during the 90-day time window*

T0: *time 0 for follow-up*

Figure Legend

Figure 1. Distribution of time of first statin prescription during 90-day period post discharge. For users, these are their actual prescription time. For nonusers, this time is randomly selected between 0-90 days and follows a uniform distribution.

Figure 2. Rate of recurrent AMI or death occurring within 1-year after hospital discharge.

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Table 1. Description of Different Methods

	T_0 (time 0) for the follow-up	Variable representing statin exposure	Method of analysis
Method 1 *Simple grouping*	Hospital discharge	Fixed-in-time dummy variable (1= users; 0= nonusers)	Cox proportional hazards model
Method 2 *Random selection of prescription time*	*Users**: time of the first prescription; *Nonusers***: randomly selected time between 0- 90 days	Fixed-in-time dummy variable (1= users; 0= nonusers)	Cox proportional hazards model
Method 3 *Follow-up since the end of the exposure time window*	Day 90 post discharge	Fixed-in-time dummy variable (1= users; 0= nonusers)	Cox proportional hazards model
Method 4 *Prescription time distribution matching*	*Users:* time of the first prescription; *Nonusers:* time assigned according to the distribution of users' time to the first statin prescription	Fixed-in-time dummy variable (1= users; 0= nonusers)	Cox proportional hazards model
Method 5 *Time-dependent exposure*	Hospital discharge	Time dependent variable for statin initiation (0= before use; 1= after use)	Time-dependent Cox model

* Users are defined as those who filled a statin prescription in the first 90 days post discharge;

** Nonusers are defined as those who without any statin prescription in the first 90 days post discharge.

Table 2. Characteristics of Statin Users and Nonusers at Discharge from a First Hospitalization for Acute Myocardial Infarction

Characteristics	Users	Non-users
Number of Patients	6,235	15,286
Median age, years (IQR)	72 (68, 76)	76 (70, 81)
Males, %	60	56
Baseline co-morbidities, %		
Hypertension	36	33
Diabetes	23	25
CHF	20	28
Cardiac dysrhythmia	17	20
COPD	16	21
Cerebrovascular disease	7	8
Chronic renal failure	7	10
Malignancy	2	3
Dementia	1	3
Hyperlipidemia	52	10
In-hospital Procedures, %		
Catheterization	40	22
PCI	19	10
CABG	8	5
Cardiac medications (prescriptions at discharge), %		
Nitrates	54	53
Beta-blockers	52	38
ACE Inhibitors	35	33
Antiplatelet agents*	48	43
Diuretics	19	27
Calcium-channel blockers	17	17
Warfarin	11	11
Digoxin	10	14

Table 2 (cont.) Characteristics of Statin Users and Nonusers at Discharge from a First Hospitalization for Acute Myocardial Infarction

Characteristics	Users	Non-users
Specialty of treating physicians, %		
Cardiologist	48	44
Internist †	11	9
GP and other specialists	40	45
Hospital Characteristics		
Teaching hospital	18	14
Catheterization availability	30	26
Hospital rural locations‡	5	5
Length of hospital stay, median days	9 (7, 15)	10 (7, 15)

* Anti-platelet agents include aspirin and clopidogrel;

† Internist excluding cardiologist;

‡ Rural location: with 0 in the middle of the first 3 digits of the postal code (defined by Census Canada)

CHF=Congestive Heart Failure; COPD=Chronic Obstructive Pulmonary Disease; PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Graft surgery; GP=General Practitioner.

Table 3. Adjusted Hazard Ratios (HR)* of Statin Use for Recurrent AMI or Mortality From Different Methods

	HR (95% CI) at 1 Year**	Change in HR relative to method 4 or 5†	HR (95% CI) at 6 months	HR (95% CI) Full follow-up‡
Method 1§ *Simple grouping*	0.62 (0.55, 0.69)	-0.23	0.58 (0.50, 0.66)	0.68 (0.63, 0.72)
Method 2 *Random assignment of prescription time*	0.90 (0.80, 1.01)	+0.13	1.01 (0.87, 1.17)	0.80 (0.74, 0.86)
Method 3 *Follow-up begins at day 90*	0.78 (0.67, 0.90)	-0.03	0.93 (0.75, 1.16)	0.75 (0.69, 0.81)
Method 4 *Prescription time distribution matching*	0.80 (0.72, 0.89)	-	0.84 (0.74, 0.98)	0.76 (0.71, 0.81)
Method 5 *Time-dependent exposure*	0.80 (0.73, 0.89)	-	0.86 (0.76, 0.98)	0.76 (0.71, 0.81)

* Multivariate Cox regression model adjusted for demographic, clinical characteristics, physician and hospital type;
** Follow-up time since discharge;
† Relative change in the adjusted HR calculated as: (HR of a given method - HR of method 4)/HR of method 4;
‡ Median follow-up of 3.0 years (25th – 75th percentile: 1.6 – 4.4 years);
§ Refer to Table 1 and corresponding comments in Methods section for descriptions of the respective methods.

Table 4. Comparison of Different Methods in the Control of Survival Bias

	Source of Bias	Study Efficiency (Number excluded)	Advantages	Limitations
Method 1 *Simple grouping*	Misclassification of unexposed follow-up of users before treatment initiation	0	–	1) Overestimation of treatment effect
Method 2 *Random assignment of prescription time*	Preferential selection of nonusers having longer survival and underlying risk change	1,018 nonusers	–	1) Treatment effect biased towards the null; 2) Loss of statistical efficiency and precision.
Method 3 *Follow-up begins at day 90*	– All patients survived 90 days	294 users 1,622 nonusers	–	1) Major loss of study information, efficiency and precision; 2) Effect during the first 90 days ignored; 3) Large exclusion results in limited generalizability.
Method 4 *Prescription time distribution matching*	– Similar survival pattern	364 nonusers	1) No apparent loss of study efficiency; 2) Useful when comparing users only (e.g. early vs. delayed use)	1) Effect estimation not available during the period when users are being defined; 2) Assumption the prescription occur at random unlikely to be met.
Method 5 *Time-dependent exposure*	– Remain as a nonuser until filled a prescription	0	1) Best statistical efficiency; 2) Allow effect estimation at any point in time after discharge;	1) Comparison is limited to between use vs. no use; 2) Assumption that prescription occur at random unlikely to be met.

Figure 1.

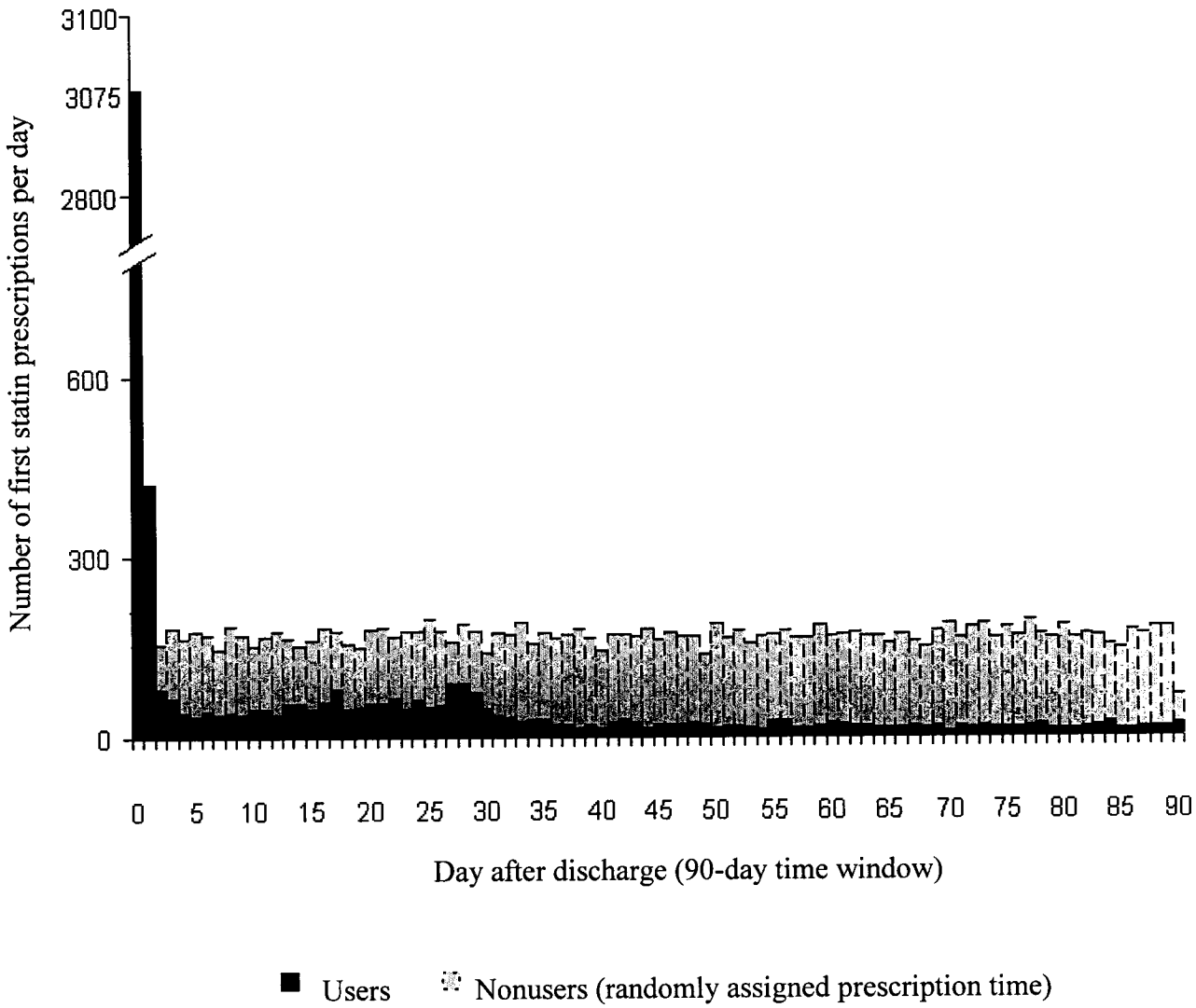
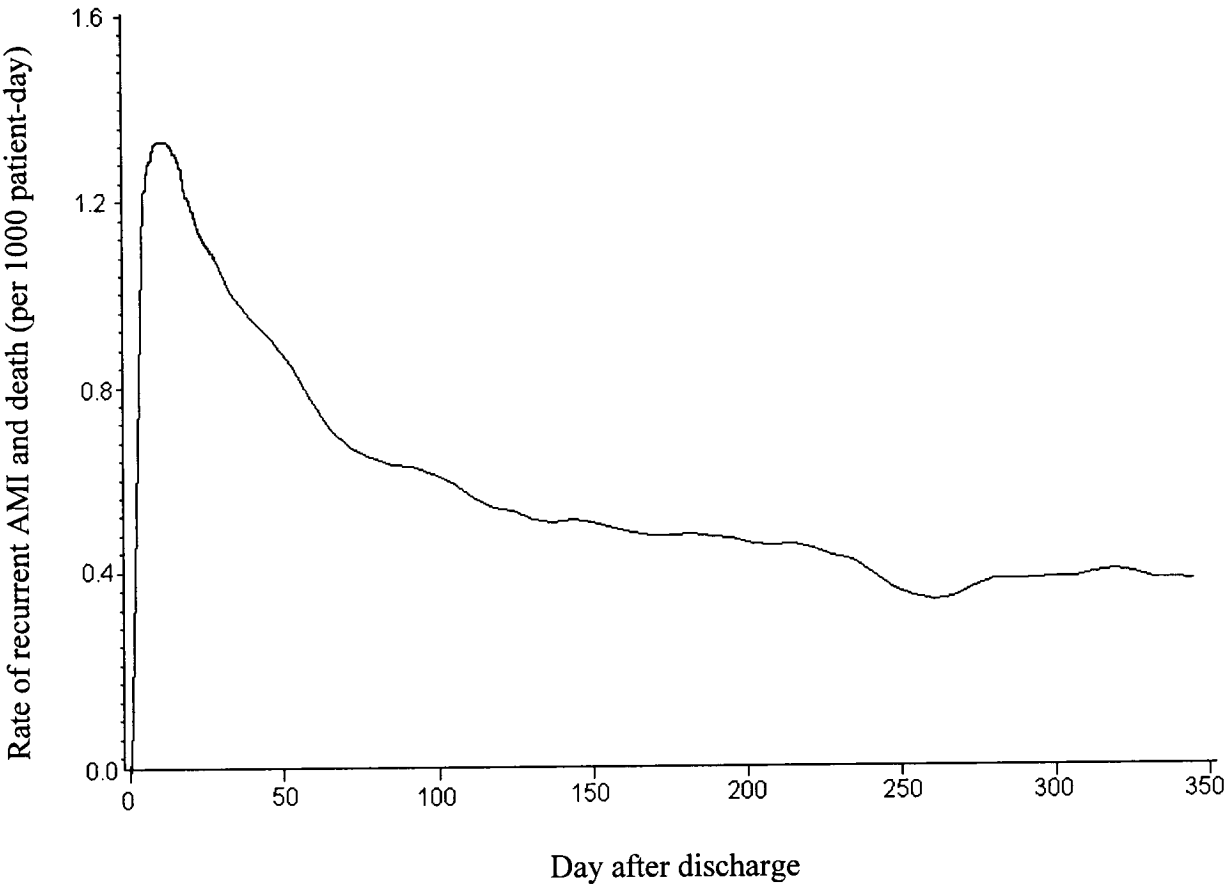

3100
3075
2800
600
300
0
Number of first statin prescriptions per day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Day after discharge (90-day time window)
Users
Nonusers (randomly assigned prescription time)

Figure 2.


Rate of recurrent AMI and death (per 1000 patient-day)
1.6
1.2
0.8
0.4
0.0
0
50
100
150
200
250
300
350
Day after discharge

5.1.3 Additional Comments

5.1.3.1 Time of Cohort Entry and the Underlying Risk

In observational studies evaluating treatment effectiveness, one of the challenges is to make comparison groups as similar as possible, except for the intervention. Our study showed that differences in patients' initial survival and associated underlying risk for outcomes should be an important consideration when trying to achieve such a "similarity". Ignoring this difference will lead to survival bias.

The occurrence of survival bias is a result of both pathophysiologic process (changes in the absolute level of underlying risk in the period used to define the comparison groups) and erroneous study design and analysis. Notably, depending on the choice of the time of cohort entry (time 0), survival bias can occur through 1) *misclassification* of time-to-treatment initiation as exposed person-time, if time 0 is the date of discharge. This occurred in the method of simple grouping (method 1), where users were defined on the basis of their future exposure, but followed from discharge. 2) Survival bias can occur through *selection*, when time 0 is chosen to be the date of first prescription. This occurred in the method of random selection of prescription time (method 2), where nonusers were included in the analysis provided that they did not have an event before their assigned time 0's.

The methods of time-dependent exposure (method 5) and prescription time distribution matching (method 4) are used to control the survival bias that have occurred in method 2 and 1, respectively. Our empirical assessment using real-life data showed that both methods appear to be effective in the control of this bias and give the

same estimates. However, a more rigorous statistical comparison of these methods may require a theoretical proof. This is, however, beyond the objective of this thesis.

In the following chapter, the two methods were used to address the clinical question regarding the effect associated with the early initiation of statins.

5.2 Early Initiation of Statins and Associated Outcomes

5.2.1 Preface to Manuscript #4

The current manuscript is to address the clinical question regarding the association between the timing of statin initiation after AMI and risk of recurrence and mortality. To control for survival bias in comparing outcomes among patients who differ in their time of treatment initiation, we used prescription distribution matching method. In particular, it has the advantage of being able to control for survival bias in situations where all subjects have a treatment, but only differ in time of treatment initiation. A time-dependent approach, which is best to control survival bias when comparing treatment vs no treatment, may have limited use in this case.

We created a retrospective cohort (1996-2001) using Quebec healthcare administrative databases to study the risk of recurrence and mortality among post-AMI patients (≥ 65 years), who differ in their time of statin initiation in the first 90 days post discharge.

Abstract

Background Clinical studies have shown the benefit of statin utilization after acute myocardial infarction (AMI). However, it is unclear how this beneficial effect relates to the timing of statin initiation after AMI.

Methods We created a retrospective cohort (1996-2001) using healthcare databases in Quebec, Canada to study post-AMI patients (≥ 65 years) who differ in their time of statin initiation in the first 90 days post discharge. The rate of recurrent AMI and mortality was compared between patients who initiated statin at discharge (early group) and those who initiated statin at least 1 month later and up to 90 days post discharge (delayed group). A multivariate Cox regression model was used in the comparison. We used prescription time distribution matching to control for survival bias.

Results The early and delayed group consisted of 3,075 and 1,187 patients, respectively. During the 1-year follow up, no statistically significant difference in the outcome was detected between the early and delayed statin group. The adjusted hazard ratio (HR) for initiation at discharge versus between 30-90 days later was 1.03 (95% CI, 0.56-1.87) at 3 months and was 1.24 (95% CI, 0.96-1.62) at 1 year. Analyses restricted to first time users after AMI or excluding patients with severe comorbidity or those ≥ 85 years did not change the results. Our findings were not affected by changes in the definition of delayed use within the 90-day period.

Conclusion A delay of statin initiation up to 30-90 days post discharge following AMI does not appear to lead to a difference in the rates of recurrent AMI and mortality compared with statin initiation at discharge.

Introduction

Early initiation of statin treatment during the acute phase of a coronary event has been highlighted as a possible therapeutic approach to improve clinical outcomes in patients having an acute coronary syndrome (ACS)[1]. Experimental data have characterized the mechanisms as both cholesterol-dependent and independent[2-4]. In addition to a cholesterol-lowering effect, statin may reduce vascular inflammation[5-8], decrease thrombus formation[9-11], and improve endothelial function[12-14]. Taken together, these mechanisms are expected to act rapidly to minimize the risk for recurrent ischemic events and mortality, and therefore the benefit from statin treatment may manifest much earlier.

Several randomized trials (RCTs)[15, 16] and observational studies[17-21] have suggested favorable outcomes associated with early statin initiation after ACS. However, there is limited information with regard to how this effect is related to the timing of statin initiation, particularly in the first few months following the acute event. It would be important to know whether a short delay in time of initiation will result in a significant change in benefit. Almost all available clinical studies, focused on early use versus no use of statins after ACS. Among the observational studies, this "early use" is often defined as having a statin prescription at hospital discharge after ACS. Patients who fill a prescription during the subsequent days along with those who do not use statins are classified together as nonusers[17, 18]. Such a definition misses the opportunity to discern the effect that could result from a difference in the timing of treatment initiation. This definition also introduces

a problem of subject misclassification, which potentially leads to an underestimation of the treatment effect of statins.

We constructed a retrospective cohort (1996-2001) using Quebec healthcare administrative databases to study the association between time of statin initiation within the first 90-day period after discharge from a hospitalization for AMI and the risk of recurrent AMI and mortality among elderly patients.

Methods

Data Source

Data were obtained from the Quebec hospital discharge summary database and the physician and prescription claims databases. The principle diagnosis and up to 14 secondary diagnoses are recorded in the hospital discharge database. The physician and prescription claims databases contain information regarding in- and out-patients physician encounters and dispensed medications. Prescription information includes type of medication, dosage, quantity and number of supplied days. In- and out-of-hospital death information was obtained from provincial registry databases. All data were linked by patients' unique, encrypted healthcare insurance number.

Study Cohort

We created a retrospective cohort. Eligible patients were Quebec elderly (≥ 65 years) who were discharged alive from a hospitalization for AMI (ICD-9 code 410) between January 1996 and March 2000. Survival data was obtained for these patients until April, 2001.

Inclusion and Exclusion Criteria

Patients discharged from their first recorded hospitalization for AMI in the study period were included. All included patients had AMI coded as their most responsible diagnosis and were discharged alive. Patients were excluded if they met one or more of the following exclusion criteria: 1) the AMI was coded as an in-hospital complication; 2) the AMI admission was a transfer from another hospital; 3) the total length of hospital stay was less than 3 days; 4) the patient was discharged to a long-term care institution, a

rehabilitation center, or moved out of the province; and 5) the health care number was invalid. The rationale for these criteria has been previously documented[22, 23].

Exposure Group Definition

Patients who filled at least one statin prescription ≤ 90 days after discharge were identified as statin users. Statin users were separated into 2 groups. Those who had a prescription dispensed at discharge formed the *early* group, and those who filled a prescription between 30-90 days, inclusive, after discharge formed the *delayed* group. We varied the definition of the delayed group to include those who filled their first prescription between 1) 15-90 days; 2) 7-90 days; and 3) 1-90 days after discharge.

Outcome

The study outcome was defined as a combination of recurrent AMI or mortality due to any cause, whichever occurred earlier.

Follow-up

All patients were followed for the earliest of the occurrence of a study outcome or 1-year post discharge.

Baseline Characteristics

Information recorded included patients' age, sex, comorbidity at discharge, including coexisting cardiovascular and lung diseases, chronic kidney or liver conditions as well as diabetes, dementia and malignancy diseases. Concurrent use of major cardiac medications was recorded for β-blockers, angiotensin converting enzyme (ACE) inhibitors, nitrates, antiplatelet drugs (aspirin, clopidogrel), calcium channel blockers, diuretics, warfarin and digoxin. Information regarding statin use during the year prior to the index

AMI was also recorded. In addition, the data included information for each patient regarding date of cardiac procedures after AMI admission (catheterization, percutaneous coronary intervention, coronary artery bypass graft surgery), length of hospital stay, specialty of the treating physician (cardiologist or other) and the type of hospital (teaching or not; urban or rural location), as well as the year of AMI.

Methods to Control for Survival Bias

Patients initiated statins 30-90 days post discharge (delayed group) have all survived at least the first month and up to 90 days, while patients initiated statins at discharge (early group) may have had an event anytime after discharge. The risk of AMI or death is high following discharge. Therefore, an excessive amount of early events is expected to occur in the early group. This systematic difference in time of treatment initiation may result in biased estimates if not corrected for either at the design or analysis level.

To address this between-group survival difference at the design level, we used the method of *prescription time distribution matching* to define the time of study entry (T_0). The method considered the dispensing date of the first statin prescription to be the time of study entry of the delayed users. Early users were assigned a T_0 selected at random from the observed prescription time distribution of the delayed users. Those who had an event before their assigned T_0 were excluded. Both groups were then followed since their T_0 and onwards.

Data Analyses

Descriptive statistics were used to compare baseline patient characteristics between groups. Patients' persistence on statins was defined as a ratio of the total duration of post-discharge statin prescriptions divided by the time of follow-up.

To exclude the possibility that the delayed users were late to fill the prescription because they experienced more post discharge procedures or hospital readmissions, we examined the period between discharge and matched prescription time for rates of cardiac procedures (including percutaneous coronary intervention, PCI; coronary artery bypass graft surgery, CABG and catheterization) and hospital admissions for CHF or unstable angina. This is relevant, as information regarding medication use during hospitalized period is not recorded in the database, and patients may appear not to have prescriptions due to excessive hospital readmissions.

A multivariate Cox regression model was used to obtain hazard ratio (HR) of recurrent AMI and mortality between the early and delayed (reference) groups with adjustment for patient baseline characteristics. The outcomes were evaluated at 3, 6 months and 1 year post discharge.

We repeated the analysis to examine the effect in several subgroups of interest. First, we restricted analysis among first time users of statins after discharge (no statin use in the year prior to the index AMI). Second, we excluded patients with severe comorbidities (congestive heart failure (CHF), chronic renal failure, dementia or malignancy) or those aged ≥ 85 years. These patients were frail and likely to have a short life expectancy, which may obscure the effect associated with statin treatment. To further

test for effect modification in these subgroups, we included interaction terms between statin treatment and these characteristics (prior statin use, presence of severe comorbidity, and senior age) in the Cox regression model.

Finally, we repeated the analyses by changing the definition of delayed use to include patients having a prescription between 15-90 days, 7-90 days and 1-90 days, respectively.

All analyses were done using SAS version 8.0 (SAS Institute Inc. Cary, NC.). Significant level of 0.05 (2-sided) was used for all tests.

Results

Cohort and Baseline Characteristics

Our cohort comprised 21,521 elderly patients. Among them, 6,235 patients (29% of the cohort) filled a statin prescription during the first 90 days after discharge. The 90-day time window captured 92% of all first statin prescriptions during the first year. There were 3,075 patients who filled a statin prescription at discharge (early group) and 1,187 patients who initiated statins between 30–90 days post discharge (delayed group).

After matching the assigned T_0 of the early users to the prescription time of the delayed users, the early users had a distribution of T_0 identical to that of the delayed users (median: 55 days, interquartile range: 40–72 days) (Figure 1). There were 134 subjects excluded from the early group because of having an outcome before their assigned T_0.

A comparison between the early and the delayed users showed similar demographic and clinical characteristics (Table 1), except that delayed users were more likely to be men, and were more likely treated by a general practitioner and in a non-teaching hospital. Both early and delayed groups had a high persistence on statin treatment during the follow-up. The median persistence was above 94% in both groups. Notably, more patients in the early group (36%) than those in the delayed group (25%) used statins in the year prior to the index AMI. No difference in statin dosages used was found between early and delayed user groups.

Treatment Rates after Discharge and Up to the Matched Prescription Time

A comparison between the early and delayed groups suggested there was no significant difference in the rates of post-discharge cardiac procedures (PCI, CABG, catheterization) and hospital admissions for CHF or unstable angina up to their matched T_0. For post-discharge cardiac procedures, rates in early and delayed group were 9% versus 10% (p=0.32). For post-discharge hospital admissions, rates in early and delayed group were 6% versus 7% (p=0.26).

Effect Associated with the Difference in the Timing of Statin Initiation

Survival analysis using a multivariate Cox regression model found no evidence that there was a difference in outcome resulting from a delay of statin initiation up to 30-90 days post discharge compared with initiation at discharge. The adjusted HR for recurrent AMI and mortality for early versus delayed initiation was 1.03 (95% CI, 0.56-1.87) at 3 months post discharge, 1.13 (0.80-1.60) at 6 months and 1.24 (0.96-1.62) at 1 year (Table 2).

In subgroup analyses, no difference in the outcome between early and delayed initiation was found when analysis was restricted to first time users of statin after discharge (Table 2). Our finding did not change when we excluded patients with severe comorbidities (CHF, chronic renal failure, dementia and malignancy) or those who were ≥ 85 years from the analyses. Including these characteristics (prior statin use, presence of severe comorbidity, and older age) as interaction terms with the treatment (early/delayed) in the Cox regression model did not show any effect modification (p>0.19 for all interaction terms). Finally, our finding was not affected by changes in the definition of delayed use (Table 2).

Discussion

Our results suggest that a delay in statin initiation between 30-90 days post discharge of AMI does not lead to a difference in outcome compared with statin initiation at discharge.

The effect associated with the difference in the timing of statin initiation in the early period after AMI remains largely unclear. So far, the results from clinical studies are not all consistent. The recent "A to Z trial"[24] (*Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndrome*) is the first trial to examine the effect associated with the difference in the timing of initiation. However, the study did not detect a difference in outcome between early and delayed initiation at the end of 2-year follow-up (adjusted HR: 0.89, 95% CI 0.76-1.04). No difference was also evident during

the first 4 months placebo-controlled phase prior to the start of the delayed treatment (adjusted HR: 1.01, 0.83-1.25). This finding is inconsistent with the MIRACL trial[15] (*The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study*), which demonstrated a moderate benefit at 16 weeks between early treatment versus placebo (adjusted HR: 0.84, 0.70-1.00). In addition, both short-term (4 months) and long-term (2 years) outcomes of the A to Z trial disagree with the PROVE-IT trial[16] (*The intensive versus moderate lipid lowering with statins after acute myocardial syndrome*), in which atorvastatin and pravastatin started early after an ACS showed a difference in outcome favoring atorvastatin at 6 months and after 2 years.

Our study evaluated the effectiveness of early statin utilization in a population-based setting. In contrast to the A to Z trial that compared the early and delayed initiation by 4 months, the "delay" in our study was 1 month and up to 90 days post discharge. All users were defined within the first 90 days, which is a period that was considered as "early" in the A to Z trial. Reasons for this design are two-folds. First, it is a reflection of the actual prescription pattern of statins. The first 90-day time window captured 92% of all first statin prescriptions in the first year. In addition, the first scheduled physician visit after discharge is usually in the 4-6 weeks post discharge, this gives patients an opportunity to receive prescriptions. In fact, we observed a small increase of prescription volume around 30 days (Figure 1). Second, the risk of recurrent events after AMI is the highest in the first month post discharge[25] (Figure 2). If the disease process is believed to be modulated by statin treatment at an early stage, it is then clinically important

to study the outcome associated with a delay of statin initiation with 1 month or more as compared to initiation at discharge.

Despite adequate design and analyses, our study still has several limitations. First, the study is prone to biases because of its observational nature. Although the bias resulting from confounding by indication[26] is minor as all subjects are statin users, there are likely uncharacterized factors that may confound the timing of initiation. Some of them could be related to the clinical practice. In addition, the unobserved characteristics associated with the delayed users who remained event-free before treatment initiation may predict their better prognosis. This could obscure the possible benefit associated with early statin initiation. Despite adjustment for a wide spectrum of characteristics, it is still possible to have residual confounding in the comparisons.

Second, survival bias in the comparison of early vs. delayed statin initiation may affect the validity of the results. We used prescription time distribution matching method to control for this bias by equalizing the pattern of time of initiation (i.e. survival time) between the two groups.

Third, our study is also limited by the data and clinical practice in the study period. Initiation of statins is considered to be the date of prescription dispensing not the time of consumption. In the current study where the actual time of statin initiation is crucial, this approximation may have been imprecise. The overall statin usage was low (29%) in this post-AMI elderly population. The practice in the study period (1996-2000) already exhibited a trend towards early initiation of statins post discharge. This gave rise to

a relatively small delayed user group, which limited the statistical power and, therefore, the ability of the study to detect a difference.

In summary, our results suggest no evidence that a delay of statin initiation between 30-90 days post discharge can lead to a difference in the rates of recurrent AMI and mortality compared with statin initiation at discharge. Given that this study is a retrospective, observational study, the results need to be confirmed in a well-designed large randomized controlled trial.

Figure Legend

Figure 1. Distribution of time of first statin prescription during 90-day period post discharge.

Figure 2. Rate of recurrent AMI or death during 1-year after hospital discharge.

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Table 1. Characteristics of Statin Users Discharged from a First Hospitalization for Acute Myocardial Infarction

Characteristics	Early Users	Delayed Users
Number of Patients	**2,941***	**1,187****
Median age, years (IQR)	72 (68, 76)	71 (68, 75)
Males, %	59	62
Baseline co-morbidities, %		
Hypertension	36	33
Diabetes	22	20
CHF	20	21
Cardiac dysrhythmia	18	17
COPD	15	17
Cerebrovascular disease	7	6
Chronic renal failure	7	5
Malignancy	2	1
Dementia	1	0
Hospital Procedures***, %		
Catheterization	44	41
PCI	24	23
CABG	10	12
Cardiac medications†, %		
Nitrates	75	73
Beta-blockers	71	70
ACE Inhibitors	50	48
Antiplatelet agents	71	74
Diuretics	32	31
Calcium-channel blockers	28	28
Warfarin	16	15
Digoxin	16	17

Table 1 (cont.) Characteristics of Statin Users Discharged from a First Hospitalization for Acute Myocardial Infarction

Characteristics	Early Users	Delayed Users
Specialty of treating physician, %		
Cardiologist	51	43
Internist	13	8
GP and other specialists	35	49
Hospital Characteristics, %		
Teaching hospital	21	15
Catheterization availability	31	26
Hospital rural locations‡	6	6
Length of hospital stay, median days	10 (7, 15)	9 (7, 15)
Statin usage		
Days to first statin prescription, median (IQR)	0 (0, 0)¶	55 (40, 72)
Prior statin use§, %	36	25
Persistence (IQR)#	0.95 (0.88, 1)	0.94 (0.85, 0.99)

* Users who initiated statin at discharge; Number after exclusion of 134 patients who had an event before assigned prescription time;

** Users who filled a statin prescription between 30-90 days post discharge; Users who initiated statin during the first month were not shown.

*** Hospital procedure rates for catheterization, PCI and CABG up to the matched time of first statin prescription;

† Rates of cardiac medication use up to the matched time of first statin prescription;

‡ Rural location: with 0 in the middle of the first 3 digits of the postal code (defined by Census Canada)

§ Any statin prescription during the year before the index AMI;

¶ Median time before prescription time matching; Both groups (early and delayed) has the same median and IQR after matching;

Defined as a ratio of total days of supply of statin prescriptions divided by the days of follow-up;

IQR=Interquartile Range, CHF=Congestive Heart Failure; COPD=Chronic Obstructive Pulmonary Disease;
PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Graft surgery; GP=General Practitioner.

Table 2. Adjusted Hazard Ratios* for Outcomes Associated With Early Statin Initiation

	3 month	6 month	1 year
Early vs. delayed initiation (0 vs. 30-90 days)**			
	1.03 (0.56, 1.87)	1.13 (0.80, 1.60)	1.24 (0.96, 1.62)
Subgroup Analyses			
First time users only†	0.79 (0.36, 1.74)	1.05 (0.68, 1.63)	1.28 (0.91, 1.81)
Exclusion of patients with severe diseases‡	0.91 (0.38, 2.18)	0.93 (0.57, 1.50)	1.10 (0.76, 1.57)
Exclusion of patients >= 85 years	0.98 (0.53, 1.79)	1.12 (0.78, 1.60)	1.27 (0.97, 1.67)
With different definitions of delayed use			
0 vs. 15-90 days	1.05 (0.73, 1.50)	1.08 (0.84, 1.37)	1.10 (0.91, 1.33)
0 vs. 7-90 days	0.98 (0.71, 1.37)	0.99 (0.79, 1.24)	1.05 (0.88, 1.25)
0 vs. 1-90 days	1.09 (0.83, 1.44)	1.07 (0.88, 1.31)	1.06 (0.90, 1.24)

* Multivariate Cox regression model adjusted for demographic, clinical characteristics, physician and hospital type;

** Delayed initiation as a reference category; Comparison controlled for survival bias by method of prescription time distribution matching;

† No statin use during 1-year prior to the index AMI;

‡ Exclusion of patients having a diagnosis of CHF, chronic renal failure, dementia or malignancy;

Figure 1.

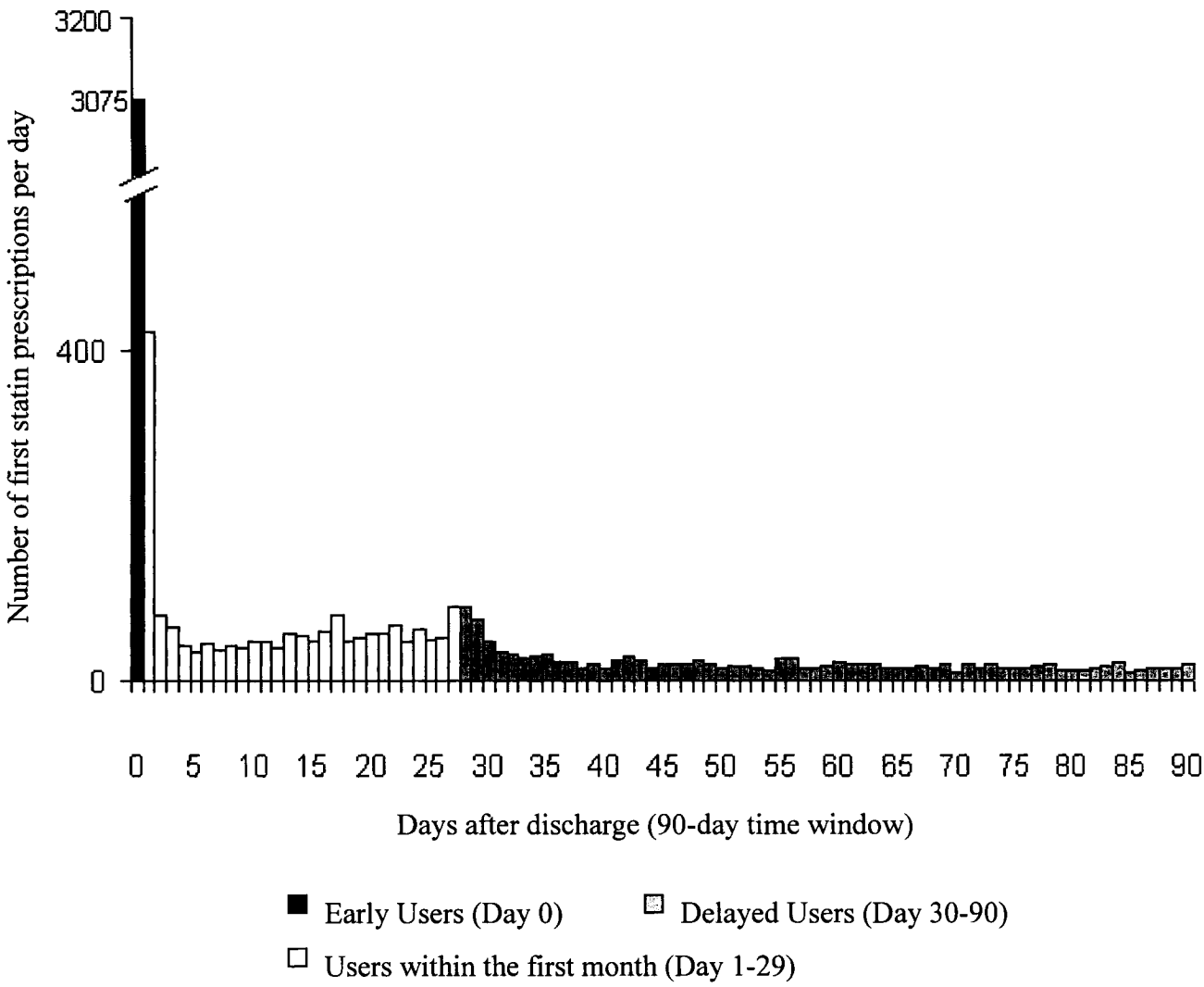
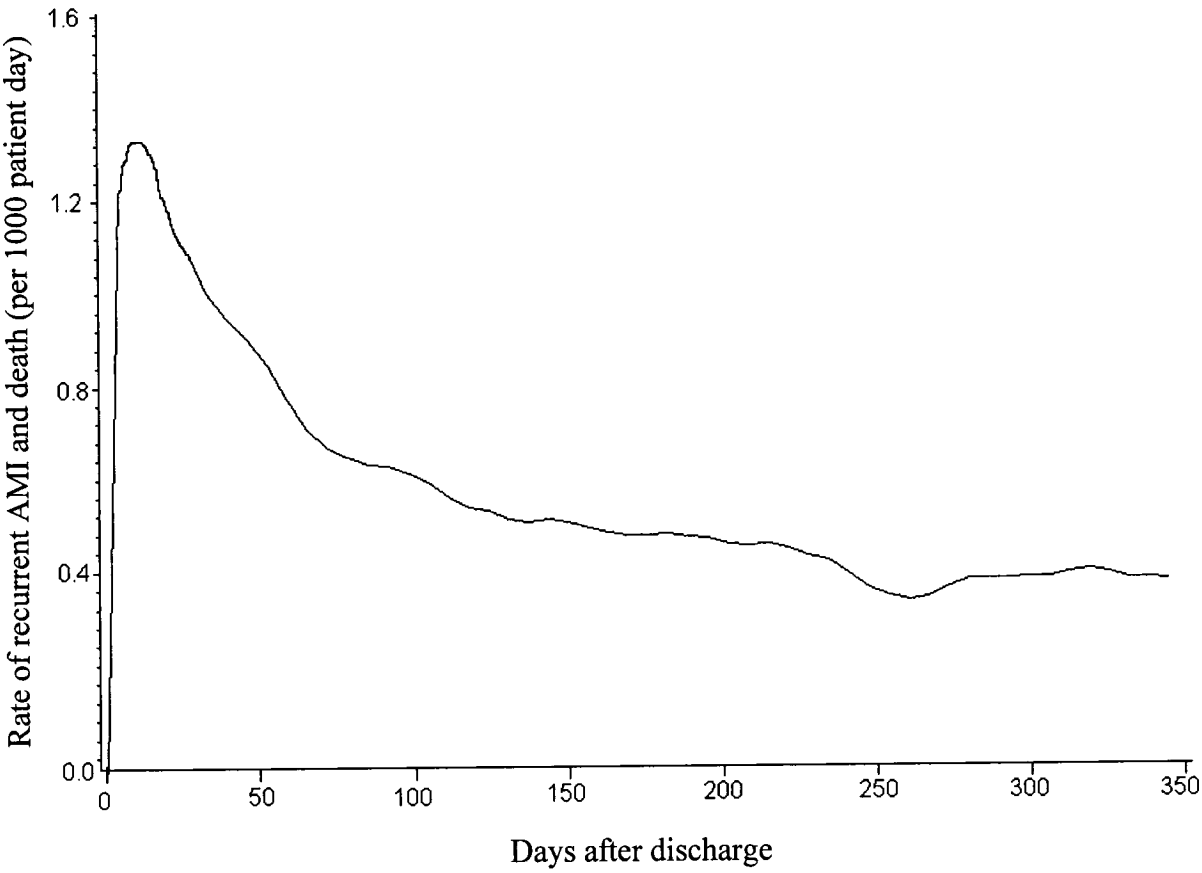

3200
3075
400
0
Number of first statin prescriptions per day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Days after discharge (90-day time window)
Early Users (Day 0)
Delayed Users (Day 30-90)
Users within the first month (Day 1-29)

Figure 2.


Rate of recurrent AMI and death (per 1000 patient day)
1.6
1.2
0.8
0.4
0.0
0
50
100
150
200
250
300
350
Days after discharge

5.2.3 Additional Comments

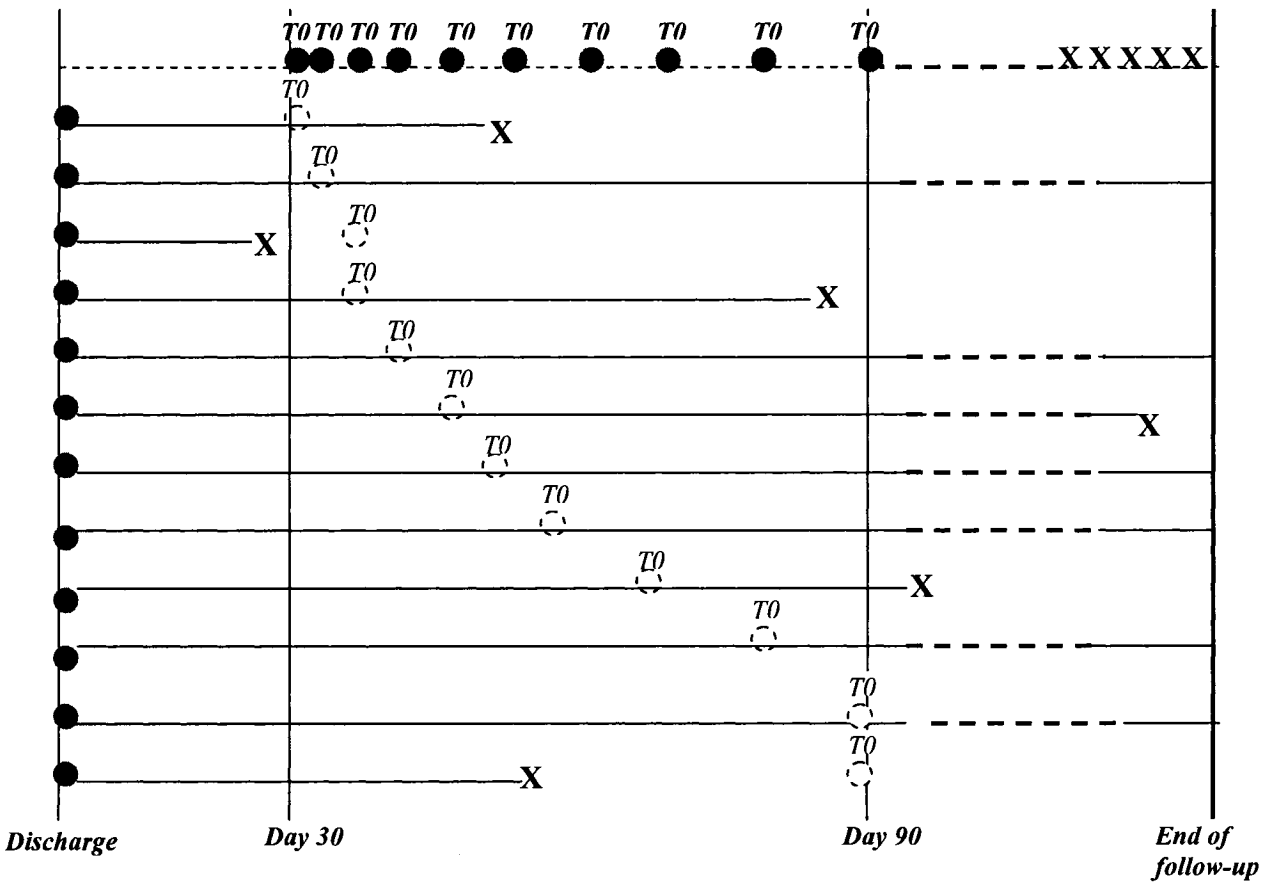
5.2.3.1 Effect of Survival Bias in Comparing Early versus Delayed Statin Initiation

In the comparison of early versus delayed statin initiation, survival difference originated from the difference in the time of treatment initiation and the change of underlying risk in this period used to define statin users. The method of prescription time distribution matching minimized this survival difference between groups by matching on the distribution of prescription time (i.e. survival time).

To show the effect of survival bias when such a difference is ignored by the study design and analysis, we repeated the analysis using the method of simple group (*Method 1* in manuscript #3), in which the early and the delayed groups were represented by a fixed-in-time binary variable ("1" for early users; "0" for delayed users) and both groups were followed since the date of discharge (T_0). Results were compared with those from the prescription time distribution matching method that controlled for the survival bias.

The adjusted HR for early versus delayed use from the method of simple grouping was: 4.31 (95% CI: 2.54-7.32) at 3 months, 2.29 (1.65-3.19) at 6 months, and 1.98 (1.54-2.56) at 1 year post discharge. Compared to the corresponding estimates from the method of prescription time distribution matching, i.e. 1.03 (0.56-1.87) at 3 months, 1.13 (0.80-1.60) at 6 months, and 1.24 (0.96-1.62) at 1 year, there is an average 2.60 times inflation of the estimates using the biased method, which showed an artificially inflated protective effect associated with delayed statin initiation.

Schematic Diagram: Prescription Time Distribution Matching Method for the Comparison of Early vs Delayed Statin Initiation



- - - *Follow-up of delayed users* — *Follow-up of early users* — - - *Follow-up omitted to show*

● *Actual first prescription time* ◌ *Assigned prescription time among the early users (distribution matched to that of the delayed users)*

T0: *time 0 for follow-up* **X:** *Event*

5.2.3.2 Effect of Statin Initiated During the First 90 days Post Discharge Compared With No Statin Use

We additionally evaluated the effect of statins initiated during the first 90-day period post discharge compared with no statin use. The inclusion of this comparison of early versus no statin use has the following considerations. First, we were concerned with the effect in the first month post-discharge, which is the period prior to the initiation of statins among the delayed users. Second, we concern with the effect of statin initiation in the first 90 days versus no treatment, as this period includes all users as we defined, both early and delayed.

To control for the survival bias in this case, a Cox regression model with a time-dependent variable representing statin initiation was used. The time-dependent method was shown in our previous study (manuscript #3) to be effective in the control of survival bias. Moreover, the method allows effect estimation at any point in time since discharge, which is particularly useful in the evaluation of the treatment effect during the first month. The prescription time distribution matching method may have limited application in this case, because, with this method, the effect of statins can only be reliably assessed from the matched time 0 and onwards (i.e. $\geq$ 1 month).

Using the time-dependent approach, we specifically examined the risk of recurrent AMI and mortality during 1 month post discharge. In addition, we reported outcomes at 3, 6 months and 1 year post discharge for statins initiated anytime during the first 90 days compared with no statin treatment. We found that, compared with no use of statins, statins initiated early after discharge was not associated with a significant risk

reduction at 1 month post discharge (adjusted HR for recurrent AMI or mortality: 0.88; 95% CI, 0.71-1.10). However, a significant risk reduction was seen at 3 months post discharge (adjusted HR: 0.84, 0.72-0.98) and persisted through the rest of follow-up (adjusted HR at 1 year: 0.80, 0.73-0.89).

The use of the time-dependent approach also represents a notable improvement in methodology compared with previous observational studies examining early statin use versus no use (Stenestrand et al., 2001; Aronow et al., 2001). Dichotomizing subjects according to discharge prescriptions in these studies introduces misclassification. This biases the effect towards the null. In our case, half of the statin users in the first 90 days would otherwise have been misclassified as nonusers. The time-dependent definition reduces such a misclassification and allows effect estimation at any point in time after discharge. We did not found statistically significant benefits associated with early use versus no use of statin in the first month. This result is different from the finding by Aronow et al. (2001), who reported a 56% risk reduction in mortality at 30 days (adjusted HR: 0.44, 0.27-0.73) with lipid-lowering therapy initiated at discharge. Of note, our estimate at 1 year comparing early versus no statin use is close to that reported by Stenestrand et al. (2001) (adjusted HR for mortality at 1-year: 0.75, 0.63-0.89).

In summary, despite there is no evidence suggesting a difference in outcome associated with the timing of statin initiation early after discharge, our results show that compared to no statin treatment, patients who initiate statins in the first 90 days post discharge after AMI have a significant risk reduction. The benefit occurred as early as at 3 months post discharge and persisted through the rest of follow up.

CHAPTER 6

GENERAL DISCUSSION

6.1 Summary

Two clinically important questions were investigated in this thesis concerning the effect of statins in medical practice. In the first question, we examined whether different statins exhibited a similar effect in reducing the risk for recurrent AMI or mortality among post-AMI patients (a class effect). Using the method of adjusted indirect comparison, a systematic review was first conducted to compare statins based on published placebo-controlled RCTs of statins for CVD prevention. The adjusted indirect comparison allowed different statins to be compared through their relative effect against a common comparator (the placebo), while taking into account the differences in prognostic factors between study participants across trials. Our results using this method showed no statistically significant difference in the effect between statins for cardiovascular prevention. However, relatively wide 95% CI's in some comparisons precluded definitive conclusions. To further study this question, we conducted a retrospective cohort study to compare statins head-to-head using data from provincial healthcare administrative databases. The relative effectiveness of five statins was evaluated in a large cohort of elderly patients post-AMI. After adjusting for risk factors and potential confounders among users of different statins, the results showed that statins exhibit a similar effect in reducing recurrent MI or death. The point estimates of the relative effect (HR) between statins were in the neighborhood of 1.0, and the concomitant

95% CI's were narrow, supporting the assumption of therapeutic equivalence among these statins for long-term secondary prevention.

In the second question, we examined the effect associated with the early initiation of statins among post-AMI patients, in particular, the association between time of initiation after discharge of AMI and risk of recurrence and mortality. Because of possible survival bias in comparing patients who differ in time of treatment initiation, a study was conducted to characterize this bias and propose methodological solutions to control for it before addressing the clinical question. We found that the methods of prescription time distribution matching and time-dependent exposure were most effective in the control of survival bias. The method of prescription time distribution matching has an advantage of being able to control for this bias in a study that include only "exposed" subjects, but who differ in the time of treatment initiation; whereas the method of time-dependent exposure can be used to control for survival bias when studying the effect of treatment versus no treatment. In assessing the effect associated with the difference in the timing of statin initiation, we did not find that a delay of statin initiation within this 90-day period could lead to a difference in outcomes compared with initiation at discharge. The effect of early statin initiation compared with no statin use was additionally evaluated using the method of time dependent exposure. Our results showed that statins initiated early after discharge of AMI ($\leq$ 90 days) was associated with an early (as early as 3 month) and sustained benefit compared with no statin treatment.

6.2 Limitations

The studies in this thesis are based on a retrospective analysis of data derived from medical administrative databases. Although these databases allow for access to a wide variety of information on very large number of patients, studies using these databases may be still subject to bias. Several important sources of bias pertaining to our studies are discussed as follows:

Confounding

An important limitation of our studies and most observational studies assessing intended treatment effect using administrative databases is the possibility of *confounding by indication.* Unlike in randomized controlled trials where treatment allocation is independent of disease manifestation, treatment assignment in observational studies can be determined by the patient's disease presentation, and often, by physician's perception of the patient's prognosis (Salas et al., 1999, Walker 1996). For example, a patient not receiving a medication could be due to either not having the disease diagnosis (indication) or being considered too frail to benefit from the treatment. In this regard, it has been shown that, in practice, older patients and patients with severe coexisting diseases are less likely to receive statin prescriptions (Ko et al., 2004). In our study of early use versus no statin treatment among post-AMI patients, confounding by indication may have been present. This was depsite the adjustment for a wide variety of observed patient's characteristics.

On the other hand, although it can be argued that confounding by indication was minor in studies comparing different statins or comparing early versus delayed initiation where all subjects were statin users, this does not preclude the possibility of *confounding by severity*. In practice, preferential prescribing of certain statins to patients with severe disease is possible. This could involve the physician's knowledge, or sometimes, their belief, as well as many other factors that are not entirely evidence-based. Likewise, these factors could have a role in our study assessing the effect associated with the timing of statin initiation. Physicians may withhold statins from patients until their disease becomes stable; on the other hand, physicians who prescribe statins early after discharge may have done so for patient to continue their previous treatment, indicating a history of hyperlipidemia among these early users. In addition, preferential selection of statin can also occur over the course of follow-up (characterized by "switching") due to change of disease state, such as less well-controlled cholesterol levels. This emphasizes the possibility of confounding resulting from factors that may also vary over time.

Because of the many unobserved risk factors that could affect the physician's selection of statin both at the baseline and over the course of follow-up, it remains difficult to measure and sufficiently control for confounding by indication and/or severity in our study. Furthermore, because these factors often act in different directions, it is also difficult to predict their impact on the results (Collet et al., 2000).

Information Bias

Misclassification of exposure or outcome in the study, either differential or non-differential, can lead to information bias. With regard to the exposure, although provincial drug claim data have been found to be comprehensive and reliable (Miller et al., 1996, Tamblyn et al., 1995), we relied on the assumption that dispensed medications were actually consumed by the patients according to instructions. This assumption appears to be crucial in the evaluation of early versus delayed statin initiation, where the classification of the two groups was based on the time of prescription filling, not the time of actual consumption. However, given that the data included filled prescriptions instead of written prescriptions, and that refills occurred regularly, patients were likely to be compliant. Noncompliance with supplied statin occurs across different treatment groups and is most likely non-differential between these groups, which could attenuate the effect towards the null. This represents a potential limitation in the interpretation of our findings, where the effects of statins were not statistically different. However, in our study, post-AMI patients were found to have good persistence to statins during the follow-up. This reduces the possibility of exposure misclassification. In addition, in a supplement analysis, we terminated follow-up at switching or stopping statin treatment to assess the impact on the results when these changes in exposure status were taken into account. The results did not change substantially.

With regard to the outcome, hospitalization for recurrent AMI was ascertained using the same criteria used to identify the index AMI. These criteria have been shown to be reliable in ascertaining AMI as the most responsible diagnosis for the

hospitalization. Patient's death was identified based on information from both in- and out of hospital death records. Therefore, the two outcomes were unlikely subject to misclassification in our study. However, there was a possibility that some patients may have sustained silent MI that did not necessitate a hospitalization. In such case, the misclassification was more likely to be of similar magnitudes in different statin groups. Unless one statin is more effective in preventing silent MI than another statin, the estimated relative effect is unlikely to be biased in this case.

6.3 Significance and Future Research Implications

Despite the limitations discussed, the findings from our studies are important from both clinical and epidemiological perspectives. Our studies are among the first to examine the effectiveness of statins with respect to the questions of class effect and the effect associated with the timing of statin initiation post-AMI. Both questions have generated great interest and debates in recent cardiovascular outcome research. Given the current wide use of statins, our results thus provide valuable information in assisting clinical decision-making and promoting better patient care.

From an epidemiological perspective, survival bias associated with time-to-treatment initiation in the study of early initiation of statins represents a common issue encountered in drug effectiveness evaluation. The ability to control for survival bias holds extremely important implications for pharmacoepidemiologic research. The methods developed and evaluated in our study are broadly applicable to observational

health services research concerned with the effectiveness of drug therapy or other medical treatments where there is an involvement of survival bias.

As to the future research implications, because the two studies assessed the effectiveness of statins in a real-life situation, they highly depend on the practice pattern observed during the study period. With accumulation of more recent data and updates of treatment guidelines concerning the statin use, revisiting the two questions in the future is indicated. This is worthwhile, because, for example, in the present study of class effect, statins were prescribed at cholesterol-lowering equivalent dosages. With the new evidence supporting benefits associated with aggressive lipid lowering (Cannon et al., 2004), we will be able to compare statins at their high end of dosages if the practice changes accordingly. Moreover, in the evaluation of early statin initiation, our study period (1996-2001) was before any clinical evidence on the benefit of early statin use was available (the first RCT in this regard, the MIRACL trial, was published in 2001). It is likely that most of the early initiation was for the continuation of a previous therapeutic regimen, thus indicating a history of hyperlipidemia in these patients. This may have impacted negatively on the early user group. Using more recent data reflecting the practice change in light of the new evidence, reexamination of this question will provide additional information.

With regard to future research in methodology, efforts should be directed to establish appropriate methods to account for switching medications in the evaluation of their effectiveness. It is also of priority to consider issues such as clustering effect (by hospital or physician) and possible confounding from concurrent cardiac medication use

over time. Finally, in addition to our empirical assessment, a simulation study is needed to systematically evaluate the performance of the methods in the control of survival bias. Addressing these methodological issues will improve the validity of the results.

6.4 Conclusion

Our studies show that statins exhibit a similar effect in secondary prevention among elderly patients post AMI. These medications initiated during the first 3 months following discharge of AMI have a significant protective effect compared with no statin treatment in reducing the risk of recurrent AMI and mortality. However, we did not find that this benefit is associated with a difference in the time of initiation during the first 3-month period post discharge. With regard to the methodology applied in this thesis, the method of adjusted indirect comparison is useful to assess the relative effect of competing interventions, where evidence from direct comparisons is limited or absent. In studying the effect of early initiation of statins, the methods of prescription time distribution matching and time-dependent exposure appeared to be most effective in the control of survival bias associated with time-to-treatment initiation. The two methods should be considered in the treatment effectiveness studies where this bias might otherwise occur.

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APPENDIX A

Additional Tables and Figures

Table 1-1 Characteristics of Statins*

Characteristics	Atorvatatin	Pravastatin	Simvastatin	Fluvastatin	Lovastatin
Maximal daily dose (mg)	80	40†	80	40	80
Serum LDL cholesterol reduction produced (%)‡	50	34	41	24	34
Serum triglyceride reduction produced (%)‡	29	24	18	10	16
Serum HDL cholesterol increase produced (%)‡	6	12	12	8	8.6
Cholesterol-lowering equivalent dose (mg)§	10	20	20	20-40	20
Plasma half life (hr)	14	1-2	1-2	1.2	2
Effect of food on absorption of drug	None	Decrease	None	Minimal	Increase
Requirement for liver metabolic activation	No	No	Yes	No	Yes
Penetration of CNS	No	No	Yes	No	Yes
Mechanism of liver metabolism	Cytochrome P-450 3A4	Sulfation	Cytochrome P-450 3A4	Cytochrome P-450 2C9	Cytochrome P-450 3A4
Renal excretion of absorbed dose (%)	2	20	13	<6	10

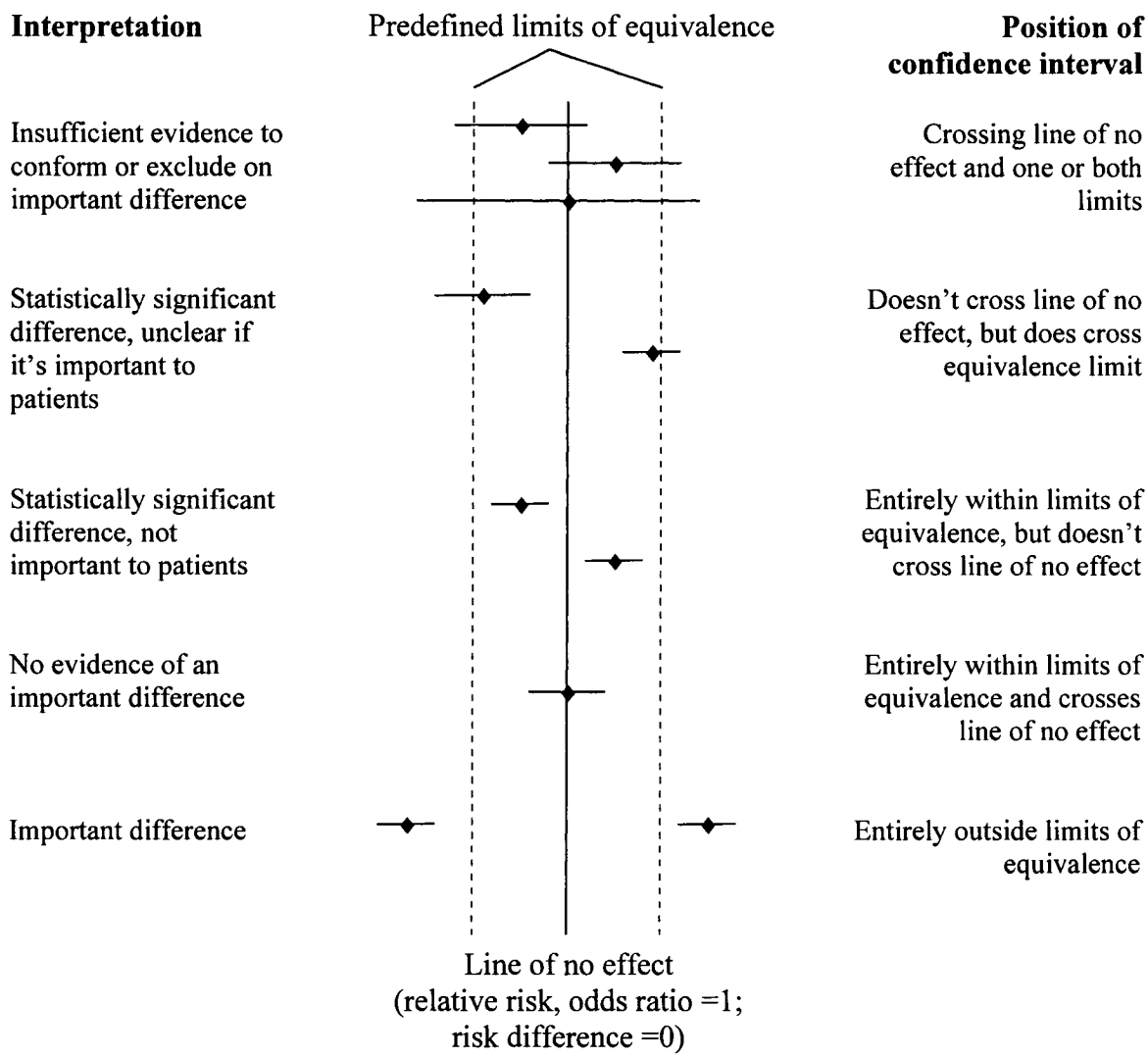
* Information from *Compendium of Pharmaceuticals and Specialities, Canada*: Canadian Pharmacist Association 2002;

† Approved maximal dose. An 80 mg dose has also been studied, which reduces serum LDL-C by 38-39 % and is safe;

‡ Effect produced by a daily dose of 40 mg of atorvastatin, pravastatin, simvastatin, fluvastatin and lovastatin in hypercholesterolemia patients;

§ Dosages which produce equal % reduction of total cholesterol.

Figure 4-1.



Interpretations of equivalence based on the position of confidence interval of the estimated effect in relation to the region of clinical equivalence (modified from Armitage, Berry and Matthews (Armitage et al., 2002)).

APPENDIX B

Ethics and IRB Approval

APPENDIX C

A List of Study Variables and ICD-9 Diagnostics Codes

Baseline Characteristics

1) Demographic

Variable Name	Type	Label
ID	Char	Patient ID; scrambled healthcare card number
Sex	Num	Sex
Age	Num	Age at the time of hospital admission for index MI

2) Clinical Characteristics

Variable Name	Type	Label (ICD-9 Codes)
AMI Hospitalization		
Adm	Num	Date of Index AMI admission
Exit	Num	Date of hospital discharge including all transfers
LOS	Num	Length of hospital stay (time between admission - exit)
Discharge Comorbidities		
HT	Num	Hypertension: (ICD-9: 401 & 405)
Diab	Num	Diabetes with or without complications: (250)
CHF	Num	Congestive heart failure: (428)
Carddys	Num	Cardiac dysrhythmia: (427)
COPD	Num	COPD (490 - 496)
CVD	Num	Cerebrovascular diseases: (430-438)
CRF	Num	Chronic renal failure (403, 404, 585, V451)
Malig	Num	Malignancy: (140 - 2089)
Dem	Num	Dementia (290, 3310, 3311, 3312)
Pulmoned	Num	Pulmonary edema (5184, 514)
ARF	Num	Acute renal failure (584, 586, 7885)
Shock	Num	Shock: (7855)
HLIP	Num	Hyperlipidemia (2720-2724, 2728-2729)
LIV	Num	Liver disease (mild & severe) (5712, 5714-5716, 5718-5719, 5722-5724, 4560-4562)

** N.B. 3-digit ICD-9 code includes all its 4th digit sub-strings (e.g. 111 includes 1110, 1111, 1112...)*

In-hospital procedure		
CABG_date	Num	Date of first CABG post index MI
Cath_date	Num	Date of first Catheterization post index MI
PTCA_date	Num	Date of first PTCA post index MI

Cardiac Medications		
NITR	Num	Nitrates
BETA	Num	Beta-blocker
ACEI	Num	Angiotensin converting enzyme inhibitors
ASA_	Num	Antiplatelet agents (Aspirin & Clopidogrel)
DIUR	Num	Diuretics
CCBK	Num	Calcium channel blocker
WARF	Num	Warfarin
DIGX	Num	Digoxin

3) Physician & Hospital Characteristics

Variable Name	Type	Label
Physicians		
Cardiol	Num	Cardiologist
Internist	Num	Internist (excluding cardiologist)
GenPrac	Num	General Practitioner and other specialists
Hospital Characteristics		
Teaching	Num	Indicator of teaching hospital
Urban		Hospital urban location
	Num	(rural, if middle digit=0 of the first 3 postal code digits)
Hosp_cath	Num	Hospital availability of Cath. Lab.

Outcomes

Variable Name	Type	Label
Reami	Num	Date of hospital readmission due to recurrent MI (ICD-9: 410)
Death	Num	Date of death

APPENDIX D

Manuscript Author Release forms