ACUTE KIDNEY INJURY IN STATIN INITIATORS: PATTERNS OF INITIATION AND APPLICATIONS IN OBSERVATIONAL DRUG SAFETY RESEARCH

James Bradley Layton

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2012

Approved by:

M. Alan Brookhart

Michele Jonsson Funk

Abhijit V. Kshirsagar

Ross J. Simpson, Jr.

Til Stürmer

Abstract

J. BRADLEY LAYTON: Acute Kidney Injury in Statin Initiators: Patterns of Initiation and Applications in Observational Drug Safety Research
(Under the direction of M. Alan Brookhart)

Recent reports have suggested an increase in acute kidney injury (AKI) among users of statins, but non-experimental studies of statins face difficult, methodological challenges in estimating valid effect measure estimates. Conflictingly, some studies suggest a renal-protective effect of statins when used prior to heart surgery. To address these uncertainties, we assembled a large cohort of statin initiators and non-initiators using insurance claims from employer-based commercial and Medicare supplementary insurance plans. We investigated other medications initiated at the same time as the statin, and found that large numbers of statin users concurrently initiated other cardiovascular drugs, which may be a proxy of more severe disease risk, better medical care, better access to medical care, or increased health consciousness and behavior, all of which may be important confounding factors. We investigated the effect of statin initiation prior to heart surgery on post-surgical renal failure in a statin naïve cohort, considering concurrent medication initiation as covariates. We found a mild protective effect of statin initiation on post-surgical AKI: RR = 0.80, 95% CI 0.67, 0.96. This effect differed by age: ≥65 years, RR = 0.90 (95% CI: 0.71, 1.14); <65 years, RR = 0.69 (95% CI: 0.52, 0.91), although AKI was much more common in the older age group (8.1 vs. 3.9%). In the general population, statins were not associated with an increased risk of AKI, nor were higher-intensity statins at greater risk than lower-intensity statins, or were individual statin formulations shown to be at higher risk than others, with the exception of higher-potency simvastatin, which demonstrated a slightly higher risk of AKI. Overall, there is no need for renal concern among typical statin initiators, and there may be small renal-protective effects, as well.

For my father and mother who taught me how to work and showed me how to love

Acknowledgements

With grateful thanks for the direction, guidance, and mentoring of my doctoral advisor, Alan Brookhart whose office door was always open to my many questions. His distinguished scholarship and active mentorship have given me an example of the type of scholar I hope to become.

With gratitude for the support, encouragement, and guidance of my other distinguished dissertation committee members: Michele Jonson-Funk, Abhijit Kshirsagar, Ross Simpson, and Til Stürmer.

Many thanks for the very able assistance and technical expertise of Virginia Pate, the pharmacoepidemiology program's statistical programmer and database manager.

With deep appreciation to Ronald Falk, Susan Hogan, and all of the UNC Kidney Center who provided an amazing training experience through the renal epidemiology training grant. The funding, travel, clinical interactions, and camaraderie made this entire experience possible.

For the support, advice, occasional counseling, and constant good humor of Nancy Colvin, the Epidemiology Director of Student Services, who assured me that I didn't have to go to medical school to be a good epidemiologist. That one piece of advice saved me many years and substantial amounts of money.

For the support and encouragement of my student colleagues in the pharmacoepidemiology student group, dissertation support group, methods courses study group, and many others.

And lastly, thanks to family and friends, who put up with me throughout this entire experience.

Table of Contents

List of Tables

Table of Figures

List of Abbreviations

Abbreviation	Definition
ACEi	Angiotensin-converting enzyme inhibitors
AKI	Acute kidney injury
ARB	Angiontensin receptor blocker
ARF	Acute renal failure
BB	Beta blocker
CABG	Coronary artery bypass graft surgery
CCE	Thomson Reuters MarketScan Commercial Claims and Encounters Database
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
ENHANCE	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Athersclerosis Regression trial
ESRD	End-stage renal disease
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, 9th edition, Clinical Modification
IPTW	Inverse probability of treatment weighting
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PPI	Proton pump inhibitor
PS	Propensity score

RR	Risk ratio
SD	Standard deviation
SMRW	Standardized mortality ratio weighting
Statins	3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors
UNC	The University of North Carolina at Chapel Hill
US	United States

Chapter 1. Introduction and specific aims

1. Introduction

Statins are widely-used prescription medications for reducing serum lipoproteins, commonly used by older Americans (1) for both primary and secondary prevention of cardiovascular disease (CVD). They are prescribed over a spectrum of disease conditions including primary prevention of CVD in otherwise healthy individuals with cardiovascular risk factors, treatment of hyperlipidemia, or secondary treatment immediately post-major cardiovascular events (2-4). With such widespread use, it is critical to understand the risks associated with statin treatment (5). Although statins are generally accepted as quite safe, observational studies have suggested that statins may contribute to acute kidney injury (AKI), resulting in dialysis, loss of quality of life, or death, although these outcomes are likely rare (5, 6). Other studies have suggested that statins may be protective against renal injury in surgical settings. The disagreement between these associations may be due to and flawed study designs which fail to account for selection bias, confounding by disease severity, and the influence of the healthy user effect which may be present in epidemiologic studies of statin users. There is generally a lack of valid, population-based research on the topic, a reliable estimate of the overall risk and benefits of statin use on AKI is needed.

2. Specific aims

This study seeks to elucidate the relationship between statin initiation and AKI and describe the comparative safety of different statin formulations using contemporary pharmacoepidemiologic techniques and a large administrative claims database. A cohort of new statin users and comparison groups will be drawn from the Thomson Reuters MarketScan Research Databases which contain pharmacy and medical claims data for millions of employer-insured Americans.

To better understand the relationship between statin use and renal outcomes and observe how considering peri-initiation factors can improve epidemiologic studies of statins, the following aims will be addressed with the following methods in this study:

Aim 1: To characterize and describe new users of statin therapy in terms of other medications concurrently initiated with statins which may serve as important indicators of unmeasured clinical or behavioral characteristics. New users of statins will be identified along with their concurrently initiated medications.

Aim 2: To estimate the effect of pre-surgical statin initiation on post-coronary artery bypass graft (CABG) AKI. A cohort of statin naïve patients prior to CABG will be identified, and the risk in those initiating a statin immediately prior to CABG will be compared to those not initiating a statin.

Aim 3: To estimate the occurrence of AKI and other renal outcomes among new users of statins. A cohort of new statin users will be identified. The incidence of AKI will be estimated, and various comparison groups employed made to determine the relative hazards of renal injury in statin initiators and the comparative safety of statin formulations.

Chapter 2. Background

1. Statin Use

Statins are widely used inhibitors of 2-hydroxl-3-methyl-3-glutaryl-CoA reductase, an enzyme involved in the production of cholesterol. Statins are frequently used for the reduction of levels of low-density lipoprotein cholesterol (7) and subsequently preventing cardiovascular events (8, 9). They have been demonstrated to be highly effective in preventing serious adverse outcomes (9), giving them an important role in modern medical practice of CVD management.

Indication for statin use

With such widespread use, multiple randomized, clinical trials, both placebo controlled (10) and head-to-head (11), have been conducted investigating statins' efficacy for reducing serum lipoproteins and preventing cardiovascular events. Statins' primary indications include: the reduction of acute cardiovascular and cerbrovascular events—myocardial infarction (MI), unstable angina, stroke, or revascularization—in patients without coronary heart disease (CHD) but with other cardiovascular risk factors (12-15); the reduction of CVD events in patients with coronary heart disease (12, 16); slowing the progression of atherosclerosis (13, 14, 16); and the reduction of serum lipid levels in patients with multiple forms of hypercholesterolemia (12-17).

Recently, the indications for statin user have been expanded as rosuvastatin (marketed as Crestor®, AztraZeneca) has also recently been approved by the FDA for primary prevention of cardiovascular disease (CVD) in older Americans with normal blood lipids, but the presence of other CVD risk factors (18). Atorvastatin is also indicated for use as CVD preventives in diabetic patients with normal lipid levels (12). The expansion of statins' use into general CVD prevention has greatly increased the number of relatively healthy potential users of statins.

While multiple treatments for hyperlipidemia exist or are in development (19), statins remain the most commonly-used lipid lowering agent. The use of fibrates, another class of lipid-lowering medications, has increased in the United States over the past decade, in spite of a lack of evidence supporting their use in preference over statins (20) or even their ability to reduce incidence of coronary events (21).

As hyperlipidemia and other cardiovascular diseases increase with the American obesity and diabetes epidemics, we can expect more widespread use of anti-lipid agents and the associated adverse events in the coming future (22).

While statins are widely used for CVD, their role in renal disease and effect on renal function is less clear. Observational studies have suggested that statins may be very beneficial for kidney function; statins have demonstrated anti-inflammatory (2, 8) and renal/cardiovascular protective effects independent of their effect on lipids (3). Studies have suggested that statins may be protective to kidney function in the presence of diabetes (2), and a body of literature has emerged suggesting they may be prescribed prophylacticly to reduce or prevent renal injury (23-27) and other serious adverse events (23, 28-32) following cardiovascular surgery. However, recently epidemiologic analyses have suggested rare though serious renal adverse effects associated with statin use (33).

Prevalence of statin use

Statins are widely used throughout the United States, and are available in several popular formulations, including: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Most formulations are also available in a variety of dosages, and occasionally as combination medications with other cardiovascular drugs.

Medication dispensing and expenditure estimates from 2010 reveal massive use of lipid regulators in the United States. Lipid regulators were the most widely-dispensed class of with just less than 4 billion prescriptions, and third in the amount of spending at approximately 18.8 billion dollars. Individual statin formulations were among the most widely-used individual products: simvastatin was

the most dispensed, and Lipitor® (atorvastatin calcium, Pfizer, Inc.) was the third most-dispensed. Lipitor® hard the largest expenditure of any single drug with 7.2 billion dollars spent in 2010 (34). NHANES data from 1999-2004 estimate that 58% of older Americans (men≥50 years, women ≥60 years) have an indication for statin use, and of this indicated group, approximately 42% were prescribed statins (1).

Statin Safety

Statins are generally considered safe and effective, yet even with a favorable risk/benefit profile, there are known, rare adverse events associated with statin use. Most well-known is statin—induced muscle injury, including rhabdomyolysis—breakdown of skeletal muscle tissue resulting in muscle weakness, cramps, pain, or restricted mobility (5, 35). Indirect kidney injury can occur from rhabdomyolysis as excess muscle protein from rhabdomyolysis floods the blood stream, damaging nephrons in the kidney which may result in AKI. Statin packaging labels include warnings of muscle pain, rhabdomyolysis, elevated serum creatine kinase levels, myoglobinuria, and AKI (12-17). This effect on muscles has been observed in all statin classes, particularly those with higher dosages (36). Risk is also increased in interactions with other medications which may increase blood levels of statins, such as fibrates. The use of fibrates carries the risk of muscle and renal injury; increases in serum creatinine, an indicator of reduced renal function, have been regularly observed in fibrate monotherapy, and randomized trial data has demonstrated increased rhabdomyolysis in statin-gemfibrozil combinations (37, 38). Most rhabdomyolysis symptoms appear within a few weeks of initiating a statin (6). Rhabdomyolysis is observed both in statin monotherapy and in combination with other drugs, including fibrates, anti-fungal medications, immunosuppressants, and others (5, 6). Whether or not statins also have an independent, toxic effect on the kidney is unknown.

Non-lipid protective effects of statin

Statins have been investigated heavily for evidence of protective effects and better outcomes in the surgical setting. Studies have demonstrated statins to be associated with a reduction in post-

operative adverse events, including mortality, MI, stroke, coronary heart failure, arrhythmia, angina, and disease progression (32, 39). AKI remains a serious complication post-cardiovascular surgery, specifically resulting from the cardiopulmonary bypass occurring during and coronary artery bypass graft (CABG) surgery. It can result from many causes, including: the patient's cardiovascular risk factors and disease severity which necessitated the surgery initially (40); embolism (41); hemodynamic effects of the surgery, including changes in renal blood flow and oxygenation (40); inflammation (40, 41); and ischemia-reperfusion injury (41). Heart surgery may result in rates of AKI as high as 30% with mortality rates among AKI sufferers of approximately 15 to 30%. Post-surgery renal impairment also increases risk of hospitalization and infection (40).

It has been suggested by some epidemiologic studies that pre-operative use of statins may reduce the incidence of post-operative AKI or other serious renal events (24, 27, 29, 31), although this finding is not consistent, as additional studies have not demonstrated a protective effect (25, 41). This debated protective effect may be due, in part, to the healthy user effect (42).

Statins have also been suggested to be protective against contrast-induced nephropathy (43), a common renal adverse event of patients undergoing radiological evaluation requiring a contrast agent. While contrast-induced nephropathy may be due to a different physiologic mechanism than rhabdomyolysis or post-CABG AKI, it underscores the scrutiny which statins are receiving regarding their renal-protective effects. Statins have been credited with many protective effects through observational studies, which may be due to biases inherent in the observational study of preventive medications (44). This study seeks to address this bias in investigating statin use and renal outcomes using large, administrative databases.

2. Acute kidney injury

AKI is a syndrome characterized by a sudden, marked decrease in kidney function (45). It is a broader term than the traditionally-used "acute kidney failure," as AKI represents a spectrum of clinically-meaningful, sudden kidney dysfunction which may or may not require renal replacement

therapy (46). This potentially serious event is rare in healthy, community-dwelling individuals, but it is much more common in hospitalized patients, those undergoing procedures, those receiving medications, or those with comorbid conditions. An analysis of community-dwelling individuals in the Kaiser Permanente health system from 2002-2003 estimates the incidence of AKI not requiring dialysis as 522.4 (95% CI: 515.5-529.) / 100,000 person-years, and AKI requiring dialysis as 29.5 (95% CI: 27.9-31.1) / 100,000 person-years. These estimated incidence rates appear to have increased over time, and tend to be higher in older age groups (47). Analysis of hospital discharge summaries of Medicare recipients from 1992 to 2001 have shown rates of AKI to be approximately 23.8 cases / 1,000 discharges, again with rates increasing over time and higher rates among older age groups (48).

Consequences of AKI can be severe. Sudden decreases in renal function have been associated with higher mortality rates: the more severe the renal impairment, the higher the death rate. Patients experiencing AKI have a high mortality rate and a high cost associated with emergency department visits and dialysis sessions, ranging from one week to six months. Studies have shown that AKI requiring dialysis results in an in-hospital mortality rate of ranging from 15% to greater that 50% (49, 50). Patients with AKI who survive the initial hospitalization are at increased risk for mortality in the year following discharge (51), and may be at higher risk for the development and progression of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (52).

The etiology of AKI is complex, and may result from multiple difference pathways. The most common causes include: reduced blood flow leading to reduced renal perfusion (resulting from heart failure, renal artery stenosis, ischemia-reperfusion injury, arrthymias); volume depletion (resulting from blood loss/trauma, hypotension, dehydration); intrinsic renal factors (glomerulonephritis, autoimmunity, or other vascular causes); or urine obstruction (53). Drug-induced renal injury is a common concern of medication use, as most medication metabolites are processed through the kidneys.

While the etiology of AKI is complex, and multiple factors can contribute to its development, various prescription medications have been associated with increased incidence of AKI, both through direct effects on the kidney and indirectly through other mechanisms, such as rhabdomyolysis.

Statins & AKI

The information regarding the adverse effects of statins on the kidneys is mixed. It has been suggested that statin use may be beneficial towards overall kidney function (54), yet statins have not demonstrated the same cardiovascular protective effects on dialysis and renal transplant patients as in the general population (55). It has been suggested by one observational study that the risk of AKI may be increased in statin users (33). The association between statin use and rhabdomyolysis or other myopathies is generally clinically accepted, and rhabdomyolysis can lead to kidney and other organ failure. The molecular mechanism is not conclusively understood, although multiple hypotheses exist (6). Interestingly, rates of rhabdomyolysis seem to be increased in patients with impaired kidney function (55). However, in 2006 the Kidney Expert Panel of the National Lipid Association's Safety Task Force issued a statement that there was not evidence suggesting a link between statin exposure and renal injury (56, 57).

Whether there may also be an additional, independent toxicity of statins on kidney function remains unknown. Limited clinical evidence has suggested proteinuria as an occasional adverse event of use of certain statin formulations (58) and the previously mentioned non-experimental study suggests AKI across most statin formulations in both men and women (33).

The risk of AKI in statin use is considered rare (5, 59), with existing estimates generally around 1 case per 10,000 person-years of use (varying depending on the type of statin or interactions with other coadministered drugs). Population-based estimates are not currently available, and estimates stratified by individual statin are generally unreliable, necessitating the investigation of AKI and statin use in a large, population setting with sufficient power to accurately estimate AKI risk.

While differences in rates of AKI have been observed and interactions with other medications suggested by case reports and small studies (60) , there are few reliable estimates of comparative safety among statin potencies. Reliable estimates of increased risk due to drug interactions are even more limited, due to underpowering of epidemiologic studies and highly-selected clinical trial samples. Statin use is widespread among older Americans (1), an age group likely to be taking numerous concurrent medications (61).

3. Observational medication research

This project will utilize non-experimental data sources—administrative insurance claims—to perform secondary data analysis. While there are many benefits of large, claims data, there are also many methodological challenges which must be addressed.

Administrative claims-based pharmacoepidemiology

Large insurance claims databases can be valuable data sources for studies of rare adverse drug events. Large numbers of observed individuals, often with sizeable amounts of observable follow-up time allow for easier identification of rare events. This study will employ two such large databases, the Thomson Reuters Commercial Claims and Encounters Research Database and the MarketScan Medicare Supplementary.

Employer-based insurance coverage is the most common insurance state in the United States, with approximately 49% of the total population being covered by an employer-based health plan in 2010 [68]. While the MarketScan databases represent a very large number of unique individuals, over 65 million, from throughout the United States, there are limitations to the generalizability of the sample. Employed, insured individuals tend to be healthier than uninsured individuals (62), limiting somewhat the generalizability of findings from MarketScan-based studies to uninsured or unemployed demographics. Also, the employer-based health plans participating in MarketScan tend to be all large employers, without representation from small- or medium-sized employers (63). The employed population of MarketScan tends to be younger, not representing 65+ age groups. While the

MarketScan population is limited somewhat in population-representation, it is still a valuable tool for investigating disease-drug associations.

All claims contained within the MarketScan databases resulting from pharmacy dispensing, outpatient services, or inpatient admissions have been paid and adjudicated, ensuring a high degree of accuracy and completeness.

Prescription drug exposure information from claims

Administrative claims databases obtain prescription medication data from pharmacy billing records submitted to insurance providers for reimbursement. Accurate prescription medication dispensing information from pharmacy claims is more reliable for assessing drug exposures than patient recall (64), and allows for more accurate identification of the medication formulation, dose, duration, etc. While dispensing claims are very accurate, as they are driven by pharmacy reimbursement, claims databases do not include direct patient measures of medication consumption—such use must be assumed. Exact windows of exposure to the drug of interest can be very difficult to calculate from the dispending claims themselves. For this reason, many claims-based observational studies of medication effects generally employ an intention-to-treat, or first-exposure-carried-forward, design which assumes continuous exposure to the treatment determined during some initial window (typically the first or second prescription) until the event of interest or censoring. Intention-to-treat designs, while adding a small degree of exposure misclassification which may bias the effect measure, can also reduce the effect of informative censoring, which may be introduced if patients discontinue the use of their drug (and therefore, cease refilling the medication) due to the development of signs or symptoms of the outcome of interest. In the case of AKI which may be a condition with a sudden onset, this is a particular concern.

While administrative claims databases can afford large numbers of participants for inclusion in studies of drug effects, they infrequently contain useful demographic or clinical information such as race/ethnicity, body mass index, smoking status. As the data generated in insurance claims is

driven by payment from insurers, claims for services and procedures will be submitted, but not necessarily the results of screening or diagnostic tests. Therefore, most claims databases will not have information on baseline kidney function, a strong predictor of AKI severity.

Clinical information from claims

In- and outpatient medical encounters by insured individuals result in bills generated by providers submitted to insurers. These bills contain documentation of procedures performed and the symptoms or diagnoses which justified the care received. These diagnoses form the source of disease information for most administrative claims-based epidemiologic studies. Diagnoses are reported as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. These codes have been adopted under the Health Insurance Portability and Accountability Act (HIPAA) as the official coding scheme for healthcare settings (65).

AKI has been studied in numerous database analyses, leading to questions regarding the validity of ICD-9-CM coding for AKI. Clinical definitions for AKI based on laboratory measurements exist (66), but the level of granularity present in precise clinical definitions may not be exhibited in diagnoses found in claims. Studies have estimated the validity of AKI definitions (see Table 2.1).

Statin-induced renal injury may be more difficult to identify in claims data, as there is the intermediate muscle-injury in many cases, or possibly an independent effect. Therefore, distinct physiologic mechanisms of statin-induced muscle injury, rhabdomyolysis, and renal toxicity may not cleanly present itself in the dataset as one of the above-mentioned ICD-9-CM code definitions. Study of this multi-faceted syndrome in administrative claims databases will require greater investigation into the patterns of coding statin-induced muscle and kidney toxicities.

The healthy user effect

Initiation of and adherence to preventive medications and behaviors such as statins or simply adherence in general (67) may me a marker of a healthy lifestyle and other behavioral characteristics

which may place one at lower risk for mortality (68) and other adverse health events (69). These characteristics are ill-defined, and cannot be accurately measured or ascertained from administrative claims data. However, these differences have been demonstrated: adherent statin users were more likely to receive screening tests and vaccinations than non-adherent statin users (44, 69). The resulting bias—the "healthy user effect—has been documented, as studies have shown of physiologically implausible associations between statin adherence and reduced risk of outcomes such as burns, motor vehicle or workplace accidents, poisoning, skin infections, drug dependency, etc. (44). Studies of preventive medications, such as statins, must take great care to avoid these biases. Some of these biases can be addressed by choosing an active-drug comparison—physiologically distinct medication with a comparable behavioral profile (preventive daily medication with regular refills) (70)—rather than simply employing drug non-users.

New user designs

Observational studies of prescription medications typically employ a new user design which requires a baseline window of observed, unexposed time. This allows ascertainment of early events of interest (which may not be observed in studies using prevalent users) (71), allows for adjustment for disease risk factors prior to drug initiations (71) and reduces biases due to differential adherence or length of follow-up in comparison groups or depletion of susceptible individuals.

These biases are particularly pronounced in older individuals where lack of preventive medication use may be more indicative of impaired health status (72). Utilizing a younger, employed, insured population for the study may reduce the influence of the healthy user effect.

Statin new users

Observational epidemiologic studies of medication use must address the confounding and bias introduced by non-randomized assignment of treatment.

Statins have a wide spectrum of indications and a wide variety of dosages and potencies, making statin initiators a heterogeneous patient population. Statins may be used as primary

preventives in otherwise healthy individuals or given in combination with other cardiovascular drugs to high cardiovascular risk (73) or immediate post-MI patients (4). The heterogeneity of risk factors in statin initiators may introduce confounding when compared with generally healthy, non-medication using comparison groups.

Statin comparative effectiveness and safety

There are multiple different statin formulations of varying potencies, dosages, chemical structures, and metabolic pathways. While as a class, statins are generally considered quite safe, these structural and pharmacokinetic differences may result in differential risk of adverse muscle and kidney events (6). For example, cerivastatin was withdrawn from the market in 2001 due to safety concerns resulting from a high number of reported cases of fatal rhabdomyolysis to the FDA.

Differing drug kinetics in statin formulations may also lead to differing muscle and kidney toxicities. Risk of toxicity seems to increase with level of statin exposure (74). Exposure level can be increased by higher dose, or differing pharmacokinetics (see Table 2.2). Statin formulations may be metabolized by different enzymes, leading to differential medication interactions which can further increase statin blood levels.

These pharmacologic differences can create important within-class variations in drug action, including risk of adverse events, and should be considered in studies of the safety of statins. Considering statins only as a class of drugs may obscure important, individual drug effects.

Individual statin formulations have exhibited unique safety profiles. Most prominent would be the withdrawal of cerivastatin from the market in 2001 due to an increased risk of fatal rhabdomyolysis. While all statins carry of risks of rhabdomyolysis, cerivastatin's was far above that shown by the other drugs. Additionally, in clinical trials of Crestor® (rosuvastatin calcium, AstraZeneca), proteinuria has developed as an occasional adverse event (58). While this may be indicative of idiopathic kidney injury, industry-sponsored studies have not shown a reliable difference in rates of rhabdomyolysis or AKI in rosuvastatin users compared to other statins (75-78). Further

investigation into the comparative safety of statin preparations is warranted, as statins have multiple formulations of varying potencies, there is a documented history of AKI in some statin classes, and observational studies of statins tend to be plagued by well-described biases.

4. Tables

Table 2.1 Validation studies of acute kidney injury ICD-9-CM billing codes

Study	Outcome	ICD-9-CM* Code	Gold Standard	Sensitivity	Specificity	PPV*	NPV*
Waikar 2006 (79)	Acute renal failure	584.5-584.9	100% change in serum creatinine	35.4	97.7	47.9	96.1
Waikar 2006	Acute renal failure	584.5-584.9	Hou definition (80)	28.3	99.0	80.2	91.0
Waikar 2006	Acute renal failure requiring dialysis	584.5-584.9 + dialysis code	Medical record review	90.4	93.8	94.0	90.0
Winterstein 2004 (abstract) (81)	Hospital-acquired acute renal failure	584.xx	Medical record review	15	83	87	--

*ICD-9-CM: International Classification of Diseases, 9th revision, Clinical modification; PPV: Positive predictive value; NPV: Negative predictive value

Table 2.2 Statin kinetics by formulation

Statin	Half-life	Distribution	Protein-bound	First pass liver extraction	Absolute bioavailability	Peak plasma levels	Metabolizing P450 enzyme
Simvastatin (17)	3 hours		95%	extensive	<5%		P450 3A4, 3A5
Rosuvastatin (13)	19 hours	134 liters	88%		20%	3-5 hours	P450 2C9
Atorvastatin (12)	14 hours	381 liters	≥98%		14%	1-2 hours	P450 3A4
Pravastatin (15)	77 hours		50%	0.66 ratio	17%	1-1.5 hours	Minimal
Lovastatin (14)	1.1–1.7 hours		>95%	extensive	<5%	2 hours	P450 3A4
Fluvastatin (16)	<3 hours	0.35 L/kg	98%		24%	<1 hour	P4540 2C9

Chapter 3. Methods

This retrospective, claims-based analysis will employ modern epidemiologic methods to address the aforementioned biases and issues using a very large, administrative claims database.

1. Study Population

This study will employ two large databases of insurance billing claims from the years 2000 to 2010, the Thomson Reuters (Thomson Reuters (Healthcare) Inc.) *MarketScan Commercial Claims and Encounters* database (CCE) and *Medicare Supplemental and Coordination of Benefit* database. Both databases contain information about beneficiary plan enrollment, and paid, adjudicated billing claims from in- and outpatient procedures, diagnoses, and outpatient pharmacy-dispensed medications (63).

MarketScan Commercial Claims and Encounters.

The MarketScan CCE database contains de-identified insurance billing data from approximately 100 large, employer-based commercial insurance providers from throughout the United States. It provides longitudinal healthcare information and individual-level data on employed individuals, their spouses, and dependents. It is limited to those under age 65. It represents primarily those employed in large employers, under-representing those in small- or medium-sized employers (63).

Approximately 49% of Americans received their health insurance coverage through an employer-sponsored health plan in 200 (63). While this database is very large (representing approximately 100 million unique lives throughout the included years), it is a non-representative sample of the general-US population, and is not representative of uninsured individuals, or those with Medicare or other governmental, or personally-purchased insurance plans.

MarketScan Medicare Supplementary and Coordination of Benefit

The MarketScan Medicare database contains information on individuals with employer-based supplemental Medicare insurance. The database contains information on all healthcare claims for the individual including the Medicare-paid, employer-paid, and out-of pocket expenses. These databases include information on Medicare-eligible individuals aged 65 and older (63).

Approximately 18% of Medicare beneficiaries received their coverage through an employer-based Medicare supplemental plan, making this database a more highly-selected sample of the general population than the CCE.

Included individuals

We have data from the years 2000 – 2010 for both the MarketScan Commercial and Medicare databases. We will restrict the analysis to individuals 18 years and older at the index date of the study, as pediatric statin-users are likely very different from the adult statin-using population (82).

2. Study design considerations

New user designs

All analyses will employ a new-user design. Non-experimental studies of prescription medications frequently employ the new user design (71) to reduce biases introduced by comparing long-term medication users to non-users. Selection bias by inability to observe early events (83) and unmeasured confounding by healthy lifestyle (69) are attenuated by restricting to new users where all person-time on the medication can be observed as follow-up. Many of the conflicting reports of statin safety and efficacy may be due to comparing prevalent users to non-users, so we have chosen to restrict all analyses to new initiators of the medications of interest.

We will define new medication use as a pharmacy dispensing claims for a specific medication or medication class following 180 days of plan enrollment (the washout period) free of claims for the medication of interest (see Figure 3.1). If an individual has multiple eligible initiation

events, either due to plan un-enrollment and subsequent re-enrollment or medication discontinuation and the restarting after an eligible washout period, only the first index event will be considered.

To ensure system utilization for pharmacy benefits, we will require all participants to have at least one medication claim for any medication other than the medication of interest during the washout period. By observing medication claims during this time, we are assured that the individuals are utilizing the insurance plan for which we have data for their prescription needs, and they are not filling their prescriptions from some other, non-observable source.

Intent-to-treat analysis

We will utilize an intent-to-treat, or first-exposure-carried-forward design, where the exposure assignment which was assigned on the index date is carried forward throughout follow-up, irrespective of subsequent prescription fills, switching, or discontinuation (84), a commonly-used technique in claims-based pharmacoepidemiology similar to those performed in randomized clinical trials. Our administrative claims databases only contain information about medication dispensing, not actual consumption, making defining periods of medication use very difficult. Also, to avoid misclassification and informative censoring introduced by non-adherence, medication discontinuation, or medication switching due to the development of adverse events, the intent-to-treat analysis considers a patient exposed or unexposed continuously from the index date. This method introduces the potential for misclassification of exposure, but reduces the potential for informative censoring, thus giving more valid effect measure estimates.

3. Innovation

This study combines novel study designs with modern pharmacoepidemiologic methods to estimate the effect of statin on AKI in a variety of settings using a large administrative claims database. The resulting studies will be among the largest conducted on the subject including representation from the complete spectrum of adult ages. It will include a geographically diverse sample from across the United States and will employ methodologic improvements over prior studies,

including the use of a new user design and more comparable non-user comparison groups. A novel approach to characterizing disease risk using concurrent medication initiation will be employed, improving over previous, limited claims-based studies. Advanced analysis methods, including multiple propensity score techniques, will be employed.

This study will substantially contribute to the fragmented literature regarding the role of statins in post-CABG surgery AKI and the small body of work on AKI in the general statin-using population. It will also introduce a new method of further characterizing baseline risk which is not explicitly hard-coded in claims data.

4. Figures

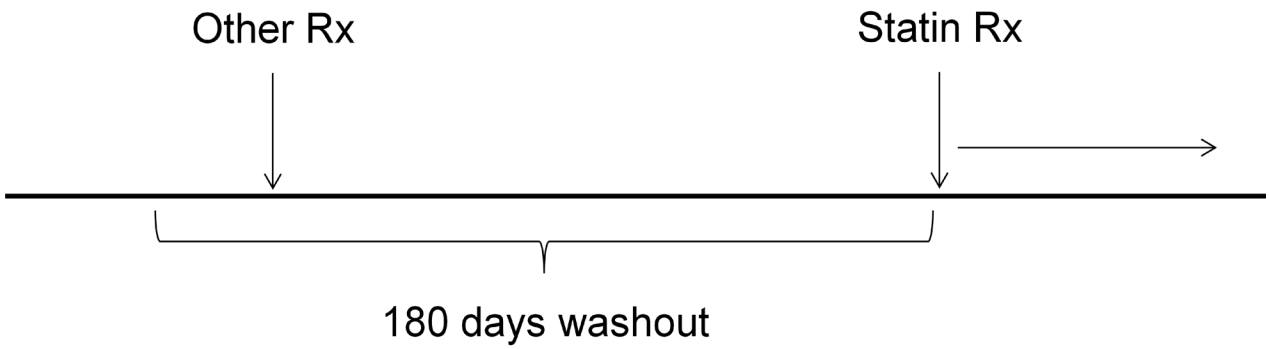

Figure 3.1 New user design with intent-to-treat exposure analysis

Chapter 4. Patterns of new statin use and concurrent medication initiation

1. Introduction

Non-experimental studies of prescription medications frequently employ the new user design (71) to reduce biases introduced by comparing long-term medication users to non-users. Selection bias by inability to observe early events (83) and unmeasured confounding by healthy lifestyle (69) are attenuated by restricting to new users where all person-time on the medication can be observed as follow-up. New-user studies of medications in administrative claims databases typically investigate claims (diagnoses, physician procedures, and dispensed medications) occurring during a 6-12 month baseline, or washout, period prior to drug initiation for evidence of conditions or procedures indicating a covariate of interest; this baseline period may or may not include the day of medication initiation, which may contain a substantial amount of information regarding relevant clinical factors which led to the patient's initiation of the medication of interest.

Medications are typically initiated in response to clinical encounters in which a patient's health status is assessed, and necessary treatments are prescribed. While diagnosis codes are reported with billing claims to payers, they are motivated by reimbursement and are not always comprehensive indicators of a patient's complete medical state. Many ICD-9-CM codes no not accurately convey relevant information about disease severity, results of laboratory measurements, or disease risk factors such as obesity, smoking, family history, etc.

To fully control for potential confounding, researchers should ascertain relevant, available clinical information about a patient which may be related to the outcome yet is unaffected by the exposure (85). This can be challenging in the setting of administrative claims, which may give an in-depth view of an individual's billable healthcare expenses, yet often do not contain laboratory

measurements, health behaviors, and basic clinical or demographic variables. Proxies for unmeasured confounding factors must be used, in many cases. Medications initiated at the same time as the medication of interest may be an important proxy for relevant, unmeasured characteristics such as disease severity, quality of healthcare care, or health-seeking behavior, potentially adding valuable covariate information in statistical models of exposure-outcome associations. Failure to account for other medications initiated on the same day as the drug of interest may result in biased estimates of drug effects.

Patterns of concurrent initiation of cardiovascular medications have not been described. This study describes the patterns of concurrent medication initiation among new statin users with related cardiovascular medications.

2. Methods

To investigate patterns of concurrent medication initiation, we identified a large cohort of new statin users using administrative billing claims.

Study population

Statin initiators were identified in Thomson Reuter's *MarketScan Commercial Claim and Encounters* and *Medicare Supplemental and Coordination of Benefits Databases* (Thomson Reuters (Healthcare) Inc., 2011) databases for the years 2000 – 2010. Paid, adjudicated outpatient pharmacy dispensing claims were searched for evidence of statin initiation, defined as a claim for a pharmacy dispensing for any statin formulation following 6-statin free months of observed plan enrollment. One additional claim for any other medication was required during the washout period to ensure system utilization for pharmacy benefits. Statin use was categorized as either higher- or lower-potency statin according to product and dosage.

Concurrent medication initiation

Initiation of other cardiovascular medication classes was assessed by identifying other medications dispensed on the same day as the index statin prescription. Medications dispensed after six months free of any other medication of the same class being dispensed were considered co-initiated (see Figure 4.1). Considered drug classes include: antihypertensives, diuretics, anti-clotting agents, and non-statin anti-cholesterol drugs. Both statin-drug combinations (e.g. statin-ezetimibe, -niacin, -calcium channel blockers) and separate prescriptions for other drug classes were considered to be co-initiated medications. Certain classes of unrelated medications were also included—proton pump inhibitors (PPIs), H_2 blockers, anti-glaucoma medications, and non-steroidal anti-inflammatory drugs (NSAIDs)—to serve as markers of patterns of medication initiation resulting from a different disease process than that of the statin.

Medication claims occurring during the washout period were considered prevalent medication use.

Clinical information

To assess cardiovascular risk, inpatient diagnosis codes were searched in the two weeks preceeding statin initiation for evidence of myocardial infarction (MI) or unstable angina. Other baseline clinical characteristics were derived from in- and outpatient diagnosis codes and procedures.

Statistical analysis

Frequencies of cardiovascular medication class concurrent initiation were calculated, and distribution by potency, data source, cardiovascular risk, and other relevant factors were investigated. Frequency of cardiovascular drug initiation by year was explored, to determine if patterns of concurrent initiation have changed over time.

Sensitivity analyses

Medications arising from the same clinical encounter may be filled on separate days due to issues of cost, supply, processing and billing practices, a physician's sample being given for one medication but not the other, etc. Therefore concurrent may not necessarily imply the exact same day. To account for this variability, sensitivity analyses were performed expanding the allowable co-initiation periods to 1, 3 and 7 days either before or after the index statin prescription.

3. Results

We identified 4,190,548 statin initiators during the time period of interest. Of the total statin initiators, 3,084,272 (73.6%) initiated a lower-potency statin, while 1,106,276 (26.4%) initiated a higher-potency statin. For clinical characteristics of the sample by statin potency, see Table 4.1.

We observed concurrent initiation of at least one additional cardiovascular medication on the same day as the statin in 31.7% of new statin users. Of those who initiated at least one other CVD medication, the majority (60.6% of co-initiators, 19.2% of the total sample) initiated only one other medication, although individuals did initiate up to 9 additional medications on the same day as the statin (see Table 4.2).

As the grace period was extended on either side of the statin index date, the proportion of patients initiating at least one other cardiovascular drug increased to 45.4% at 7 days. For some medications, increasing the grace period substantially increased the number of included initiators (angiotensin converting enzyme—ACE—inhibitors, beta blockers, thiazide diuretics), but for others, the increase was much less dramatic (see Figure 4.2).

Striking differences in concurrent initiation patterns were seen in Medicare patients vs. commercially insured patients, and those with recent MI or unstable angina vs. the whole sample. Medicare patients tended to have much higher prevalent use of medications, with 80.9% initiating at least one other cardiovascular medication vs. 59.1% among the commercially-insured, but much more similar concurrent initiation (36.1% vs. 29.9%) (see Table 4.3). Conversely, among those patients

with recent coronary events (2.9% of the total sample), the rates of prevalent medication use were very similar to the overall sample, but the rates of concurrent initiation were much higher than the general sample (see Table 4.3).

Higher-potency statin initiators tended to concurrently initiate slightly more cardiovascular medications than lower-potency statin users, with the notable exception of ezetimibe which is available in the common lower-potency statin-combination drug Vytorin® (ezetimibe/simvastatin, Merck & Co., Inc.).

There was a slight trend toward increasing co-initiation of most drugs over time (see Figure 4.3). Major changes were seen in the initiation of ezetimibe over time due to the introduction of a simvastatin-ezetimibe combination drug, Vytorin® in 2004. However, in 2008 the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial demonstrated no benefit of statin-ezetimibe versus statin alone (86), quickly reducing its widespread use. When time trends were investigated among non-CVD medications, a decreasing trend was observed (see Figure 4.4).

4. Conclusions and discussion

Statins are frequently initiated with other cardiovascular medications, and the majority of concurrent initiation tends to occur on the same day as the statin.

In patients recently experiencing MI or unstable angina, the overall concurrent medication initiation was higher than the overall sample (80.8% vs. 31.7%). Individual drugs classes which saw the most increase in use during this time period were ACE inhibitors (32.2%), beta blockers (54.7%), and anti-platelet agents (51.1%). These medications are all recommended for use post-MI (4) , and diagnosis or determination of high CVD risk may lead to initiation of these and other medications. This can be seen clearly in patients recently experiencing MI or unstable angina, where 80.8% of statin initiators concurrently initiated at least one other CVD medication. Among these patients, 32.2% initiated an ACE inhibitor, 54.7% a beta blocker, and 51.1% an anti-platelet agent.

Older statin initiators seemed to have much higher prevalent use of other medications than younger individuals, yet comparable concurrent initiation—likely due to the already large use of other CVD drugs prior to statin initiation.

Concurrent initiation has appeared to increase somewhat over the previous decade, perhaps in response to growing trends in diabetes, obesity, and other cardiovascular risk factors. Additionally, protocols and guidelines have consistently reinforced the control of lipids and hypertension in patients at high risk of cardiovascular disease and for secondary prevention (4, 87, 88).

Even though unrelated to the indication for statins or other cardiovascular drugs, PPIs and NSAIDs were commonly concurrently initiated with a statin. Both of these medications are commonly used, however, in frail, commonly hospitalized, or chronically medicated patient populations. Therefore, co-initiation may result from the same clinical encounter, even if the indications for the two are unrelated. However, the addition of a non-related medication will likely not convey much information regarding the patient's clinical state, and should not be included unless it can serve as a proxy for some important characteristic such as quality of care, etc.

While having accurate and complete covariate information is critical for maximum control of confounding, it is unwise to simply include all available measures as covariates in statistical models. Inclusion of instrumental variables (89)—factors which influence exposure but are independent of outcome—or causal intermediates (90)—factors affected by the exposure which then affect the outcome—in statistical models may induce bias, rather than remove it (see Figure 4.5).

Researchers have been rightfully warned against adjusting for covariates occurring after the assignment of the exposure for fear of adjusting for causal intermediates which may increase bias of the estimate (85), and therefore may systematically exclude all clinical information occurring at the same time or after the index date of medication exposure. While this may remove the potential for including causal intermediates, it may also remove potentially informative baseline variables. If researchers believe events occurring at the same time or immediately after the index prescription is unaffected by the exposure and reflective of a patient's pre-treatment state, researchers should be

explicit in their assumptions regarding the inclusion of the characteristic. Additionally, it has been suggested that in many cases, medication initiation and adherence is a proxy for better access to healthcare, preventive service utilization, or healthy lifestyle (44, 69, 91, 92). In observational claims settings, it may be impossible to disentangle the effect of the medication from these other, unmeasured factors. However, considering other medications initiated at the same time as the drug of interest may give insights into the clinical and behavioral state of patients, allowing researchers to statistically control for these factors. This practice give researchers increased ability to control confounding present in claims-based studies of, resulting in less-biased estimates of medication safety and effectiveness.

5. Tables

Table 4.1 Characteristics of the cohort by statin potency

	Lower potency (N=3,084,272)		Higher potency (N=1,106,276)	
DEMOGRAPHICS	**N**	**%**	**N**	**%**
Male	1,435,198	46.5	574,192	51.9
Database				
Commercial Claims and Encounters	2,168,777	70.3	804,084	72.7
Medicare supplementary	915,495	29.7	302,192	27.3
HEATLHCARE UTILIZATION	**Mean**	**SD**	**Mean**	**SD**
Mean Age	58.7	12.8	58.1	12.2
Lipid tests	0.83	1.01	0.82	1.05
CVD MANAGEMENT	**N**	**%**	**N**	**%**
Angiography performed	24,466	0.8	13,825	1.3
Cardiac stress test performed	273,500	8.9	119,923	10.8
Echocardiograph	360,239	11.7	151,349	13.7
CVD & COMORBID CONDITIONS	**N**	**%**	**N**	**%**
Diabetes	702,209	22.8	268,158	24.2
Chronic kidney disease	66,113	2.1	28,155	2.6
Hypertension	1,192,394	38.7	428,255	38.7
Hyperlipidemia	1,413,924	45.8	526,194	47.6
Other ischemic heart disease	375,041	12.2	193,213	17.5
Atrial fibrillation	101,890	3.3	37,740	3.4
ACUTE EVENTS IN PREVIOUS 6 MONTHS	**N**	**%**	**N**	**%**
Myocardial infarction*	65,542	2.1	35,301	3.2
Recent MI	47,471	1.5	27,140	2.5
History of MI	17,195	0.6	9,327	0.8
Unstable angina	27,170	0.9	12,952	1.2

Recent unstable angina	45,965	1.5	23,448	2.1
Stroke	170,018	5.5	63,161	5.7
Insertion of a coronary stent	60,821	2.0	37,421	3.4
Angioplasty	9,229	0.3	4,801	0.4
CABG	25,908	0.8	11,538	1.0
Heart failure	96,102	3.1	39,438	3.6

Table 4.2 Number of medications concurrently initiated with a statin

Number of medications	N	% of total sample (N=4,190,548)	% of co-initiators (N=1,329,904)
0	2,860,644	68.3	--
1	805,652	19.2	60.6
2	328,369	7.8	24.7
3	135,601	3.2	10.2
4	44,352	1.1	3.3
5	12,369	0.3	0.9
6	2,971	0.1	0.2
7	520	0.0	0.0
8	66	0.0	0.0
9	4	0.0	0.0

Table 4.3 Medication use and initiation by primary insurance type

	Prevalent Use				Concurrent Initiation			
N=4,190,548	**Commercial Claims (N=2,972,861)**		**Medicare Supplement (n=1,217,687)**		**Commercial Claims**		**Medicare Supplement**	
Drug	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Any CVD drug	1,755,901	59.1	985,582	80.9	889,996	29.9	439,908	36.1
ACE inhibitor	727,362	24.5	391,664	32.2	262,472	8.8	121,732	10.0
ARB	382,330	12.9	211,098	17.3	111,534	3.8	50,641	4.2
Alpha blocker	93,441	3.1	103,723	8.5	33,720	1.1	30,390	2.5
Beta blocker	592,342	19.9	457,700	37.6	199,531	6.7	137,283	11.3
Calcium channel inhibitor	410,632	13.8	317,317	26.1	134,344	4.5	82,766	6.8
Thiazide diuretics	693,812	23.3	350,463	28.8	176,210	5.9	75,393	6.2
Loop diuretics	121,276	4.1	165,783	13.6	31,301	1.1	40,848	3.4
Potassium-sparing diuretics	152,770	5.1	104,596	8.6	32,108	1.1	21,115	1.7
Anti-platelet agents	112,763	3.8	129,416	10.6	83,828	2.8	66,832	5.5
Fibrates	146,714	4.9	59,082	4.9	40,522	1.4	10,639	0.9
Niacin	43,932	1.5	19,856	1.6	49,516	1.7	12,922	1.1
Ezetimibe	72,037	2.4	47,968	3.9	213,180	7.2	72,763	6.0
Anti-coagulants	66,563	2.2	105,250	8.6	15,671	0.5	23,215	1.9
NSAIDs	573,770	19.3	236,183	19.4	69,001	2.3	31,078	2.6
H2 inhibitors	77,651	2.6	59,325	4.9	14,763	0.5	11,332	0.9
Proton-pump inhibitors	491,490	16.5	263,370	21.6	95,359	3.2	52,817	4.3
Anti-glaucoma	41,033	1.4	83,857	6.9	3,611	0.1	7,077	0.6

Table 4.4 Same-day concurrent medication among patients with recent myocardial infarction or unstable angina

N=122,611	Prevalent Use		Concurrent Initiation	
Drug	**N**	**%**	**N**	**%**
Any CVD drug	88,773	72.4	99,123	80.8
ACE inhibitor	34,931	28.5	39,501	32.2
ARB	16,860	13.8	3,707	3.0
Alpha blocker	9.488	7.7	11,738	9.6
Beta blocker	44,940	36.7	67,071	54.7
Calcium channel inhibitor	26,368	21.5	8,120	6.6
Thiazide diuretics	27,447	22.4	3,242	2.6
Loop diuretics	14,631	11.9	11,415	9.3
Potassium-sparing diuretics	7,788	6.4	2,725	2.2
Anti-platelet agents	18,717	15.3	62,676	51.1
Fibrates	4,726	3.9	1,385	1.1
Niacin	1,333	1.1	2,012	1.6
Ezetimibe	2,179	1.8	4,100	3.3
Anti-coagulants	6,945	5.7	5,326	4.3
NSAIDs	25,910	21.1	1,379	1.1
H2 inhibitors	5,868	4.8	3,048	2.5
Proton-pump inhibitors	27,621	22.5	11,437	9.3
Anti-glaucoma drugs	4,478	3.7	223	0.2

6. Figures

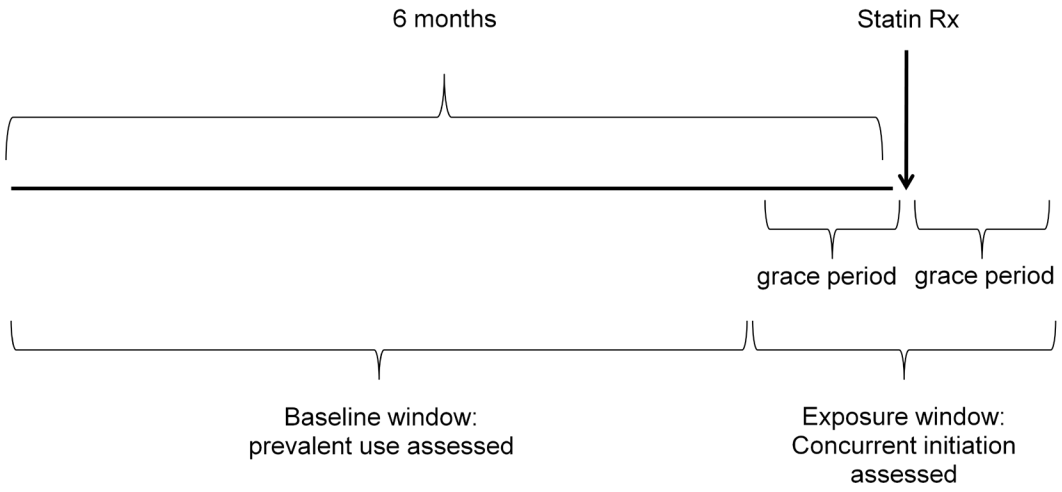

Figure 4.1 Schematic of the statin initiator cohort and concurrent initiation windows

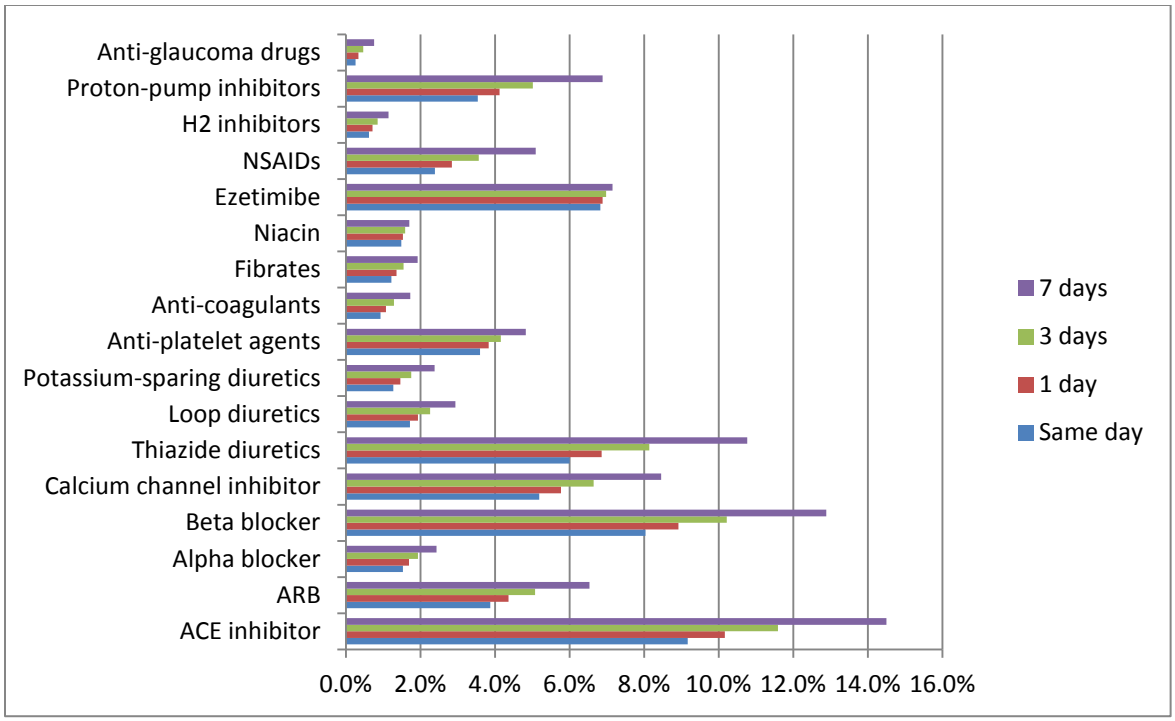

Figure 4.2 Concurrent medication initiation over varying lengths of grace periods

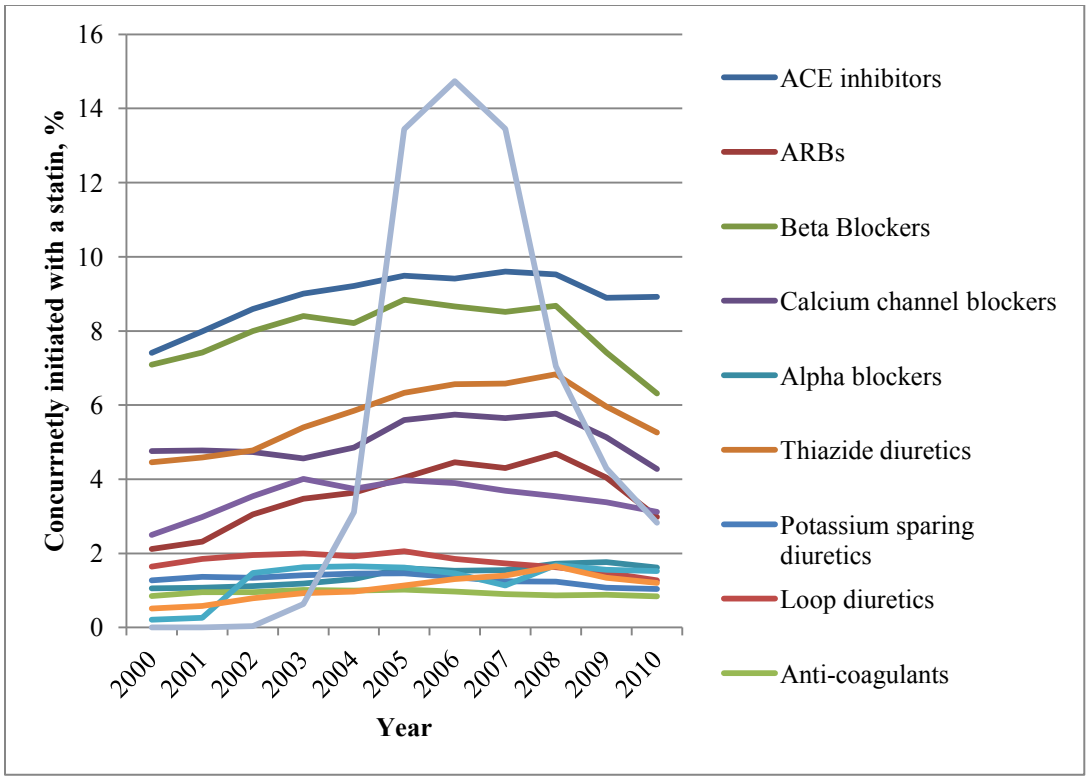

Figure 4.3 Concurrent initiation of cardiovascular medications by year

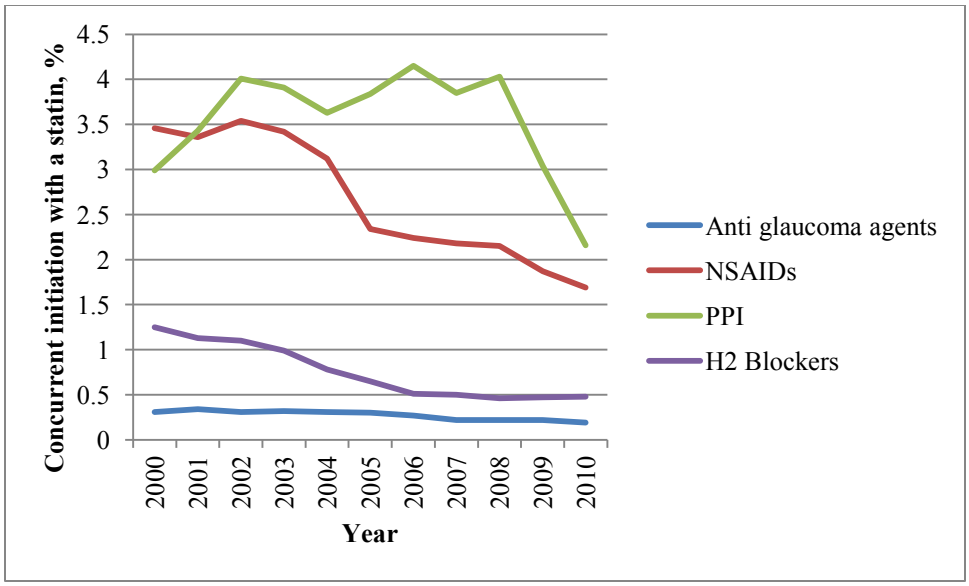

Figure 4.4 Concurrent initiation of non-cardiovascular medications by year

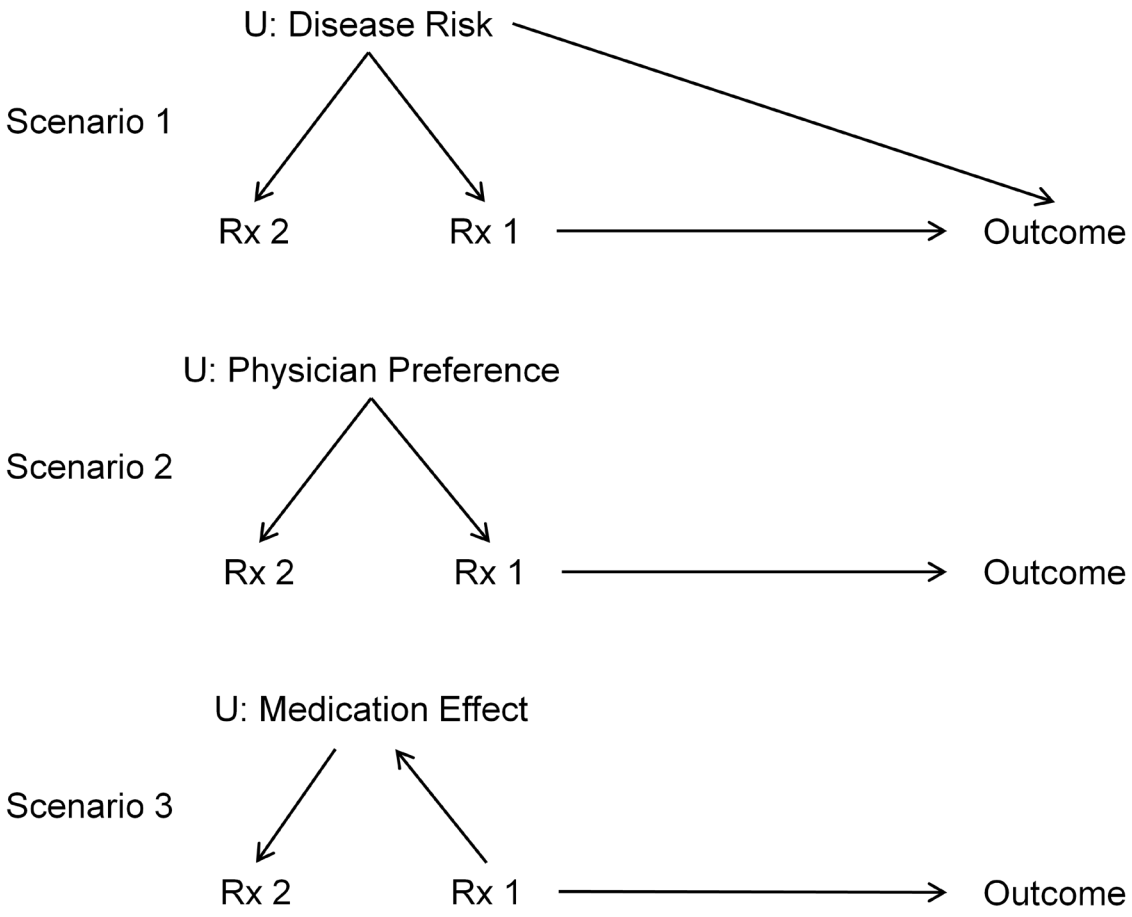

Figure 4.5 Mechanisms by which concurrent initiation may occur. 1) a proxy for an unmeasured confounder (e.g. disease severity; 2) As a proxy for an instrumental variable without effect on the outcome ; 3) Given as a result of the initial medication

Chapter 5. The effect of statin use on post-cardiac surgery acute kidney injury

1. Introduction

Acute kidney injury (AKI) is a serious complication of coronary bypass grafting (CABG) surgery. Post-surgical AKI can result in both short- and long-term consequences, including: prolonged hospital stays and cost (93); initiation of renal replacement therapy (94); development of chronic kidney disease (CKD) (95, 96) or end-stage renal disease (96, 97); or death (94, 96, 98, 99). There are currently no interventions known to attenuate the perioperative risk of AKI.

Statins, potent inhibitors of HMG co-reductase, are well known to reduce the risk of cardiovascular disease mortality and morbidity (8). A growing body of literature now suggests that statins may also attenuate the risk of perioperative kidney injury. More specifically, epidemiologic studies have found an association between statin use prior to cardiac surgery and reduced risk of post-surgical AKI (25-29, 99), dialysis (24), mortality (29, 31), and improved AKI recovery (23). These agents are postulated to have anti-inflammatory activity (100-102) and can stabilize endothelial function (103)—pleiotropic effects with potential benefits on kidney function (104).

Yet, methologic issues raise questions about the plausibility of the observed renal-protective effects of statins (30, 41, 104). Non-experimental studies have employed widely varying definitions of pre-operative statin use, such as: having any prescribed statin use at the time of surgery (27-29, 31, 41); administration the day of or the day before surgery (24, 26); or any prescribed use within the 90 days prior to CABG (25). Many of these definitions fail to consider history or length of statin use, which may introduce bias due to the healthy user effect (44, 69) whereby immeasurable differences in behavioral characteristics, e.g. healthy lifestyle, between the treated and untreated may lead to exaggerated estimates of the benefits of preventive medications. This effect has been well-described

in outcome studies comparing prevalent statin user to non-users (44). These important methodologic concerns (105) limit the ability to distinguish whether the observed results are caused by a direct beneficial effect of statins, or rather, result from unmeasured differences in patient characteristics among long-term users of statins (42).

To address these concerns, we assessed the effect of statin exposure on AKI risk using an epidemiologic design aimed at minimizing confounding bias. In patients undergoing planned CABG surgery who were not previously treated with a statin, we compare post-surgery AKI risk among patients initiating a statin immediately prior to surgery to patients not initiating statins.

2. Methods

Healthcare data

Individuals undergoing CABG surgery between the years 2000 to 2010 were identified in the *Thomson Reuters' MarketScan® Commercial Claims and Encounters* and *Medicare Supplemental and Coordination of Benefits Databases* (Thomson Reuters (Healthcare) Inc., 2011). These databases are a compilation of insurance billing data for employees, dependents and retirees from across the United States with primary or Medicare supplemental coverage through employer-based insurance plans. Adjudicated, paid inpatient, outpatient, and pharmacy claims, as well as enrollment information, are included in the databases.

Study population

All adult patients, aged ≥18 years, with inpatient procedure claims for CABG, having two-hundred days of continuous plan enrollment prior to hospital admission date for CABG were identified. If an individual had multiple eligible CABG surgeries, only the first was considered. The twenty days immediately prior to the date of hospital admission were considered the exposure window, during which statin initiation was assessed. The 180 days prior to the exposure window were considered the baseline or washout period, during which baseline characteristics and absence of statin

prescriptions were ascertained (see Figure 5.1). We required at least one pharmacy claim for any non-statin medication during the baseline window to ensure pharmacy benefit utilization.

Patients with evidence of AKI, unspecified renal failure, or end-stage renal disease before CABG were excluded. To remove individuals with emergency surgeries and restrict to planned CABG procedures, we excluded patients with inpatients claims for MI or unstable angina during the baseline period or CABG occurring after the fifth day of hospitalization.

Treatments

Statin initiation was defined as having a pharmacy dispensing claim for any statin during the exposure window without any statin claims during the preceding baseline period. A 20-day exposure window was chosen due to an observed increase in statin initiation immediately prior to CABG surgery (see Figure 5.2). Non-users had no observable statin use during the exposure or baseline windows and were required to have an outpatient physician's office visit during the exposure window to ensure healthcare utilization.

Covariates

Baseline covariates included diagnoses, procedures, prevalent medication use, and pre-operative initiation of other, non-statin medications. Racial/ethnic information was not available in the databases. Baseline diagnoses and procedures were assessed throughout the baseline and exposure windows. These covariates included: age; sex; year of surgery; number of coronary arteries bypassed; diagnoses of cardiovascular conditions; indicators of cardiovascular disease management (lipid tests, angiography, cardiac stress test, echocardiogram); acute cardiovascular events and procedures (unstable angina, myocardial infarction (MI), stroke, placement of coronary stent, angioplasty); evidence of renal conditions (chronic kidney disease, other kidney diseases, proteinuria, number of renal metabolism panels, etc.); number of emergency department visits; and number of hospitalizations. Any claims for cardiovascular medications during the baseline period were considered prevalent medication use. If the medications were initiated during the exposure window

without any use during the baseline period, the medications were considered newly-initiated and assessed separately in the analysis.

Outcomes

In-patient claims for the 15 days post-CABG were searched for evidence of AKI (ICD-9-CM codes 584.5 – 584.9). Sensitivity analyses were performed employing a broader definition of kidney failure (any of the following: acute renal failure, 584.5—584.9; end stage renal disease, 585.6; or unspecified renal failure, 586).

Statistical analysis

The association between statin initiation and AKI was estimated using multivariable Poisson regression to estimate adjusted risk ratios (RR) and 95% confidence intervals (CI) (106).

We also performed a weighted regression analysis employing stabilized inverse probability of treatment weights (IPTW) (107). Multivariable logistic regression was used to estimate the predicted probability of initiating a statin, or propensity score (PS), for each individual in the sample. Predictors of statin initiation included the pre-specified covariates described above which were believed to capture relevant clinical characteristics, healthcare utilization, and risk factors for AKI. To exclude patients treated contrary to prediction due to the concern that their extreme weights may disproportionately influence the effect measure estimate (108), we identified individuals with a PS less than the first percentile of the treated, or greater than the ninety-ninth percentile of the untreated and excluded all patients with PSs below and above these cut-points. The PS was then used to calculate the IPTW in the remaining participants, and the weights were applied to a Poisson regression model of the effect of statin initiation on post-surgical AKI.

Lastly, we performed one-to-one PS matching using a 5-to-1 greedy matching algorithm (109) where non-users were matched to statin initiators by propensity score to the 5^{th} decimal place, if possible. We then estimated RR using regression models in the matched data.

Sensitivity analyses

Sensitivity analyses were performed varying the length of the exposure window before CABG (10, 15, 25, and 30 days) to observe if the effect may be dependent on the length of time on statin prior to CABG.

To estimate the extent to which medication initiation is simply a proxy for better pre-surgical care, the entire analysis was repeated considering beta-blocker initiation as a negative control exposure (110) rather than statin initiation as the primary exposure. Like statins, beta-blockers are preventive cardiovascular medications with a similar behavioral profile and user population as statins, but they are not thought to confer a protective effect against post-operative AKI. Therefore, if a protective effect was observed among the beta-blocker initiators, it can be assumed that our study design did not adequately address the healthy user effect and other sources of confounding bias.

We performed additional analyses in pre-specified subgroups—gender, those without CKD, older vs. younger age—by stratifying by the characteristic of interest and performing the multivariable Poisson regression within the remaining subgroups.

All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

This study was exempted from further review by the University of North Carolina Institutional Review Board.

3. Results

There were 149,696 patients with CABG surgeries with at least 200 days of observable enrollment prior to surgery. Excluding those with a history of statin use and others who did not meet inclusion criteria yielded 3,798 patients who initiated a statin within 20 days prior to CABG admission, and 20,898 who did not. Distributions of demographic and clinical variables by statin initiator status are shown in Table 5.1. The sample was predominantly male. Statin initiators were predominantly commercially-insured, whereas statin non-initiators were as likely to be covered by Medicare or commercial insurance. Variables were generally well-balanced across treatment groups,

with the notable exceptions that statin initiators were more likely to have received echocardiographs and cardiac stress tests, have diagnoses of hyperlipidemia and ischemic heart disease, and were more likely to initiate other cardiovascular medications. While some of these are usually associated with increased risk for CVD outcomes, in claims data all of these factors may also be seen as markers of better disease management, preventive behavior, healthcare utilization, or pre-operative care. The propensity score distribution by statin treatment group was plotted, and we observed considerable overlap between the treatment groups (see Figure 5.3).

Post-CABG AKI occurred in 1,301 (6.2%) of the non-initiators and 140 (3.7%) of the initiators. Crude regression models yielded a highly-protective effect measure estimate, but when adjusted for clinical characteristics and other medication, the estimate attenuated to RR=0.81 (95% CI: 0.67, 0.97) (see Table 5.2).

We calculated IPTW weights from the propensity scores. The weights did not differ meaningfully between higher- and lower-potency statin formulations. When the regression analysis was performed with IPTW weighted models, the effect was very different, with RR=1.23 (95% CI: 0.86, 1.75). However, fearing the influence of large weights among individuals with residual unmeasured confounding, we trimmed PS less the 0.5^{th} percentile of treated and greater than the 99.5^{th} percentile of the untreated, yielding an effect estimate of RR=0.82 (95% CI: 0.65, 1.03) (see Table 5.2). Further trimming of the PS distribution did not yield meaningfully different estimates. PS matching also yielded similar estimates, with RR=0.75 (95% CI: 0.59, 0.93).

We observed no meaningful differences in effect estimates between male and female patients, nor when restricted to only patients without chronic kidney disease. When investigating the effect measure estimates by age, the protective effect was more pronounced in younger individuals < 65 years RR=0.69, 95% CI: 0.52, 0.91) than older individuals (RR=0.90, 95% CI: 0.71, 1.14). AKI was much more common in the older age group (8.1%) than the younger age group (3.9%).

When the exposure window before CABG was varied, the effect measure estimate tended to remain constant (see Figure 5.4). Additionally, when a wider definition of kidney failure was employed, the results remained essentially unchanged (see Table 5.2).

When the analysis was repeated considering beta-blocker initiation in the place of statin initiation, we observed no protective effect of beta blockers initiation against post-CABG AKI, with multivariable adjusted models yielding RR=0.95 (95% CI: 0.83, 1.09) and trimmed IPTW models yielding RR=1.04 (95% CI: 0.89, 1.21).

4. Discussion

In this cohort study of nearly 25,000 participants, we found that initiation of a statin just prior to CABG surgery was associated with a slightly decreased risk of post-CABG AKI compared to no statin initiation. While the crude relative risk suggested a strong protective effect of statins, after multivariable adjustment, the effect was attenuated toward the null, yielding a smiliar estimate to the PS-matched analysis. Large weights among those in the tails of the propensity score distribution may have unreasonably contributed to the IPTW analysis, so the weights were trimmed from the bottom percentiles of the treated and the top percentiles of the untreated. These trimmed propensity score weighted analyses yielded a similar effect estimate as the multivariable model, but with greater uncertainty surrounding it. The results were robust in various sensitivity analyses.

A stronger effect measure estimate was observed among those under age 65 than in the older age group. A similar trend of decreasing efficacy in older age groups for the prevention of post-surgical renal replacement therapy has been shown in previous literature (24). While the protective effect was more pronounced, younger individuals experienced many fewer post-CABG AKI events overall, suggesting that the absolute benefit of statin treatment may not be as dramatic as the relative RR suggests (111).

We adopted a design explicitly aimed at minimizing the healthy user effect, a potentially important bias in non-experimental studies of statins, and other sources of confounding bias. First, we

restricted our study to patients who initiated a statin immediately prior to surgery and compared these with patients not initiating a statin. By excluding long-term statin users from the exposed cohort, we sought to exclude patients who were likely to be healthier and more engaged in other prevention-oriented behaviors. Second, we excluded patients who were receiving CABG emergently after a hospitalization for MI or unstable angina, or late into a complex hospitalization. By doing this, we sought to create a more homogeneous group of patients. We speculated that statin initiation in these patients would be more dependent on physician preference or protocol than clinical factors, such as complexity of surgery, or patient behavioral characteristics.

Secondly, we attempted to remove remaining differences between the groups by adjusting for a wide array of clinical and prevalent characteristics. Prevalent medication use and concurrent medication initiation were considered as separate covariates in this analysis. Prevalent medication use was very similar between the two treatment groups, but statin initiators tended to initiate other medications at a much higher rate during the exposure window. Considering other pre-operative medication exposure allows us to more accurately assess pre-operative care and adjust for differences which may exist between the statin and non-statin groups.

Lastly, we also examined the effect of beta-blocker initiation on post-CABG AKI as a negative control. Beta blockers are prescribed to improve post-CABG outcomes, but are not thought to be linked with reduced AKI risk, so we would not expect an effect of beta-blocker initiation on AKI, and any observed protective effect among beta blocker initiators would suggest residual confounding rather than a physiologic effect of the drug. Beta blocker initiation did not lead to a reduction in AKI risk, suggesting that the observed effect estimate among the statin users may be a real effect, not simply unmeasured behavioral or clinical factors for which any medication initiation serves as a proxy (91).

Other published estimates of the effect of perioperative statin use on post-operative AKI have ranged from strongly protective (27), to null (41, 112). Our estimate—approximately a 20% reduction in risk with a wide confidence interval—is comparable to other studies of the subject (25, 30, 104).

Statins have been attributed with anti-inflammatory and renal- or cardio-protective effects independent of their lipid-lowering function (3). Consequently they have been investigated widely in non-experimental research for preventive effects. However, studies of statins and other preventive medications must take care to avoid study design pitfalls which can inflate protective effect measure estimates.

The findings of the study should be interpreted in the context of the following limitations. First, despite our attempts to make the treatment groups comparable, we observed some difference between groups which may indicate better health status, and thus better outcomes among statin users. Although, we controlled for these observed factors in our analysis, some of the variables, such as CKD have been shown to have poor validity (113), which would allow for some residual confounding by baseline renal impairment to remain. Similarly, the validity of AKI billing codes has been investigated, and the sensitivity has been shown to be very poor. However, the specificity of AKI coding has been shown to be very high (113). Under the assumption of nondifferential misclassification of the outcome between the statin treatment groups, the RR should be unbiased under these conditions (114, 115).

Third, these particular results may not be fully generalizable to the entire CABG population. Attempting to replicate a design similar to that of a clinical trial where a physician would have the opportunity to prescribe a statin to a previously statin-naïve patient prior to a known upcoming surgery, this analysis was restricted to only planned, non-emergency CABG surgeries among those patients without a history of statin use; the vast majority of patients undergoing CABG had evidence of prevalent statin use, and thus did not meet our inclusion criteria for this analysis. Yet, the findings were consistent through sensitivity analyses varying the time during which initiation was considered and a broader definition of kidney failure.

Statins are a mainstay of cardiovascular prevention, and are routinely prescribed to those at highest risk for cardiovascular events. However, as observational research of statins continues to suggest additional protective and beneficial effects, careful consideration must be given to the designs

of non-experimental studies to ensure that they do not fall prey to biases common to studies of preventive medications. After considering the timing of statin initiation, observing the entire length of statin treatment, measuring important markers of pre-clinical care, and matching non-users to users on healthcare utilization, our study supports the hypothesis that prescribing a statin prior to CABG may modestly attenuate the incidence of post-CABG AKI among those not already receiving statin therapy.

5. Tables

Table 5.1 Baseline demographics and clinical characteristics by statin initiation status

	Statin Non-initiator (n=20,895)		Statin initiator (n=3,798)	
DEMOGRAPHICS				
Male, %	15,378	73.6	2,993	78.8
Mean age, standard deviation (SD)	65.2	10.9	62.5	10.1
MarketScan Database				
Commercial Claims and Encounters Database, %	10,759	51.5	2,402	63.2
Medicare Supplementary Database, %	10,136	48.5	1,396	36.8
HEATLHCARE UTILIZATION	**Mean**	**SD**	**Mean**	**SD**
CABG on day of hospitalization	1.36	1.47	0.79	1.24
Lipid tests*	0.63	1.06	0.83	1.11
Creatinine measurements*	0.03	0.32	0.02	0.24
Hospitalizations*	0.20	0.54	0.19	0.55
Emergency department visits*	0.14	0.49	0.19	0.55
CARDIOVASCULAR DISEASE MANAGEMENT	**N**	**%**	**N**	**%**
Angiography performed	286	1.4	108	2.8
Cardiac stress test performed	10,702	51.2	2,550	67.1
Echocardiograph	9,332	44.7	1,940	51.1
CVD & COMORBID CONDITIONS	**N**	**%**	**N**	**%**
Number of vessels bypassed during CABG				
1-2	7,400	35.4	1,166	30.7
3-5	11,681	55.9	2,198	57.9
6+	1,814	8.7	434	11.4
Diabetes	5,860	28.0	984	25.9
Chronic kidney disease	865	4.1	86	2.3
Other kidney disease	152	0.7	18	0.5
Proteinuria	87	0.4	13	0.3
Hypertension	9,962	47.7	1,887	49.7

Hyperlipidemia	5,910	28.3	1,487	39.2
Other ischemic heart disease	13,265	63.5	3,161	83.2
Atrial fibrillation	1,498	7.2	167	4.4
ACUTE EVENTS IN PREVIOUS 6 MONTHS	**N**	**%**	**N**	**%**
Myocardial infarction (MI)†	777	3.7	138	3.6
History of MI	415	2.0	92	2.4
Unstable angina†	2,544	12.2	571	15.0
Stroke	3,378	16.2	713	18.8
Insertion of a coronary stent	311	1.5	64	1.7
Angioplasty	205	1.0	53	1.4
PREVALENT MEDICATION USE DURING BASELINE	**N**	**%**	**N**	**%**
Angiotensin converting enzyme (ACE) inhibitors	6,270	30.0	1,113	29.3
Angiotensin receptor blockers (ARBs)	3,242	15.5	534	14.1
Beta blockers	7,028	33.6	1,183	31.2
Calcium channel blockers	4,797	23.0	742	19.5
Anti-platelet agents	2,086	10.0	281	7.4
Alpha blockers	1,856	8.9	248	6.5
Thiazide diuretics	4,822	23.1	841	22.1
Potassium-sparing diuretics	1,284	6.1	152	4.0
Loop diuretics	2,360	11.3	261	6.9
Niacin	358	1.7	52	1.4
Fibrates	1,391	6.7	191	5.0
Ezetimibe	911	4.4	100	2.6
Anti-coagulants	1,332	6.4	136	3.6
Non-steroidal anti-inflammatory agents	4,012	19.2	696	18.3
MEDICATIONS INITIATED DURING EXPOSURE WINDOW	**N**	**%**	**N**	**%**
ACE inhibitors	1,892	9.1	709	18.7
ARBs	760	3.6	213	5.6
Beta blockers	3,663	17.5	1,702	44.8

Calcium channel blockers	1,328	6.4	367	9.7
Anti-platelet agents	778	3.7	310	8.2
Alpha blockers	678	3.2	276	7.3
Thiazides	1,181	5.7	271	7.1
Potassium-sparing diuretics	336	1.6	57	1.5
Loop diuretics	785	3.8	142	3.7
Niacin	96	0.5	59	1.6
Fibrates	358	1.7	76	2.0
Ezetimibe	203	1.0	226	6.0
Anti-coagulants	371	1.8	58	1.5
NSAIDs	766	3.7	107	2.8

*Occurring within the 200 days prior to admission for CABG surgery

†Not including events which occurred in the 20 days prior to hospital admission for CABG as those patients were excluded

Table 5.2 The effect of statin initiation on statin on post-CABG acute kidney injury and any renal failure

			Acute kidney injury			Any renal failure		
Model	**Treatment Group**	**N**	**Events (%)**	**Risk ratio**	**95% CI***	**Events (%)**	**Risk ratio**	**95% CI**
--	Non-initiator	20,895	1,301 (6.2)	--	--	1,540 (7.4)	--	--
Crude	Statin initiator	3,798	140 (3.7)	0.59	0.50, 0.70	154 (4.1)	0.56	0.47, 0.66
Multivariable adjusted				0.81	0.67, 0.97		0.77	0.65, 0.92
IPTW*, untrimmed	Non-initiator	20,895	1,301 (6.2)	--	--	1,540 (7.4)	--	--
	Statin initiator	3,798	140 (3.7)	1.23	0.86, 1.75	154 (4.1)	1.13	0.81, 1.59
IPTW, $\leq 0.5^{th}$, $\geq 99.5^{th}$	Non-initiator	20,208	1,219 (6.0)	--	--	1,378 (6.8)	--	--
percentiles trimmed	Statin initiator	3,499	128 (3.7)	0.86	0.68, 1.09	138 (3.9)	0.82	0.66, 1.03
IPTW, $\leq 1^{th}$, $\geq 99^{th}$	Non-initiator	19,751	1,169 (5.9)	--	--	1,317 (6.7)	--	--
percentiles trimmed	Statin initiator	3,345	124 (3.7)	0.85	0.67, 1.06	134 (4.0)	0.82	0.65, 1.02
Propensity score	Non-initiator	3,547	177	--	--	193	--	--
matched	Statin initiator	3,547	132	0.75	0.59, 0.93	142	0.74	0.59, 0.91

*95% CI: 95% Confidence interval; IPTW: Inverse probability of treatment weighting

6. Figures

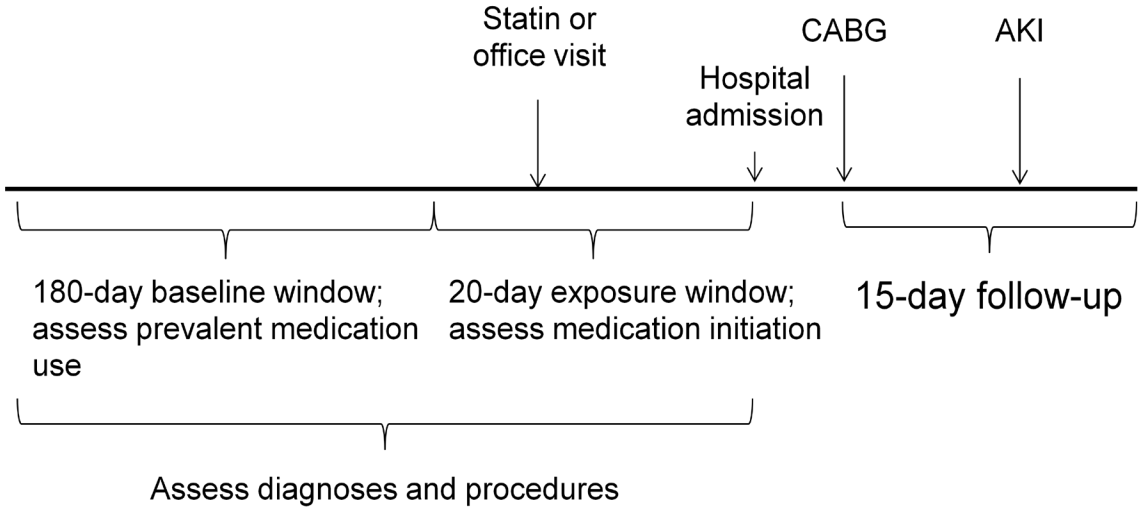

Figure 5.1 Schematics of new statin users and non-users prior to coronary artery bypass graft surgery

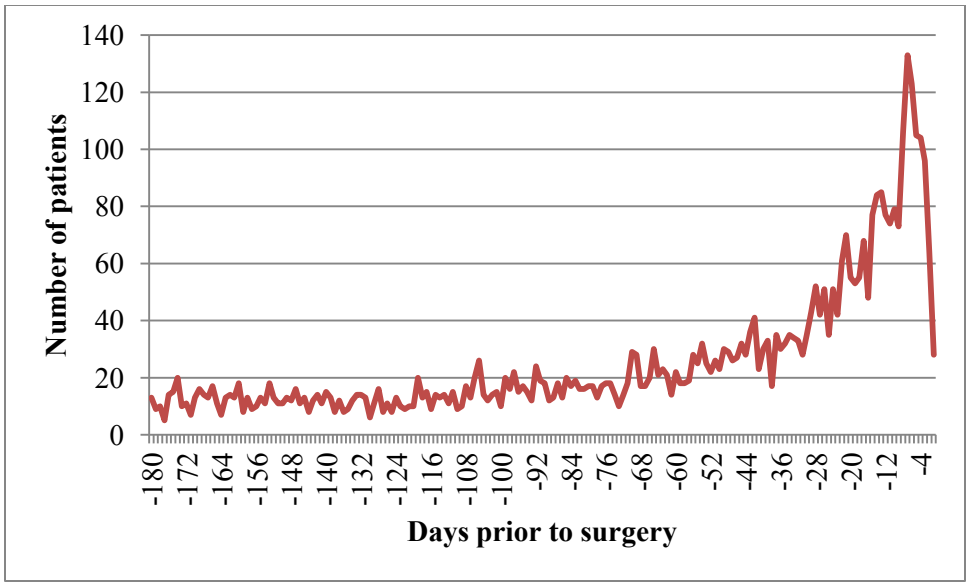

Figure 5.2 Statin initiation prior to coronary artery bypass graft surgery in commercially-insured patients

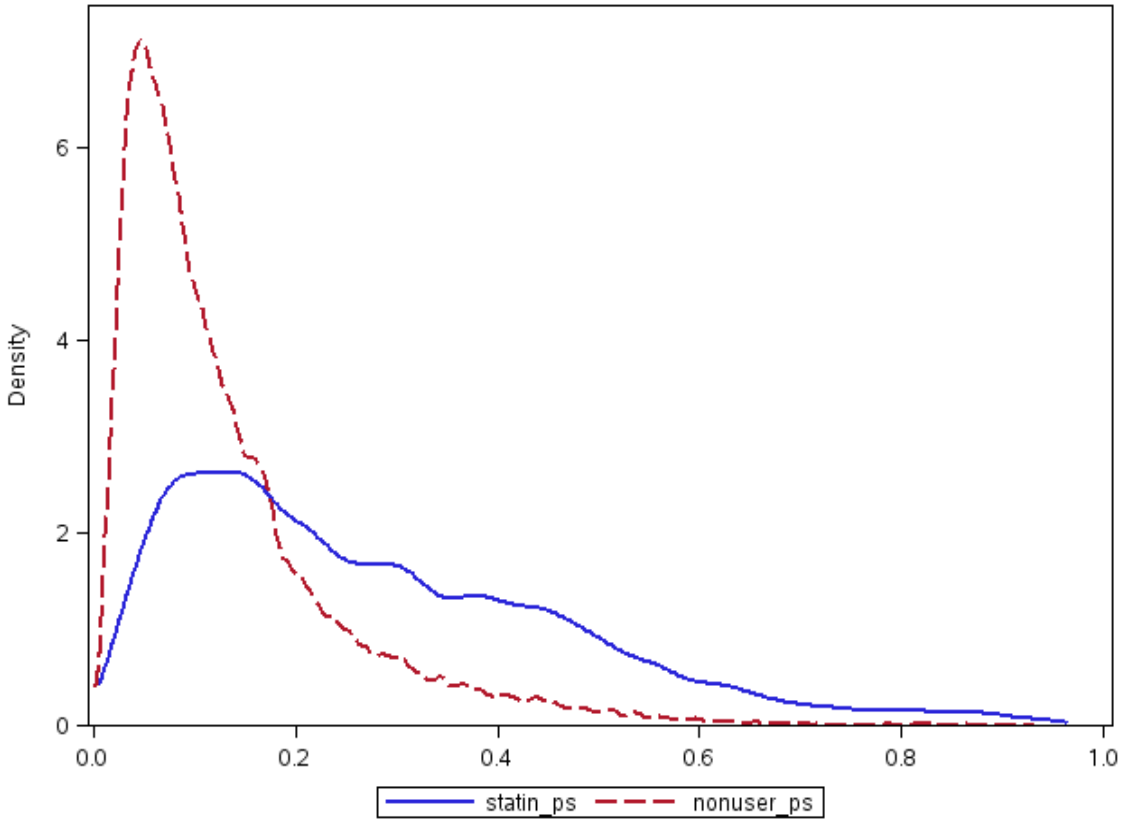

Figure 5.3 Distribution of predicted probability of pre-CABG statin treatment by treatment status

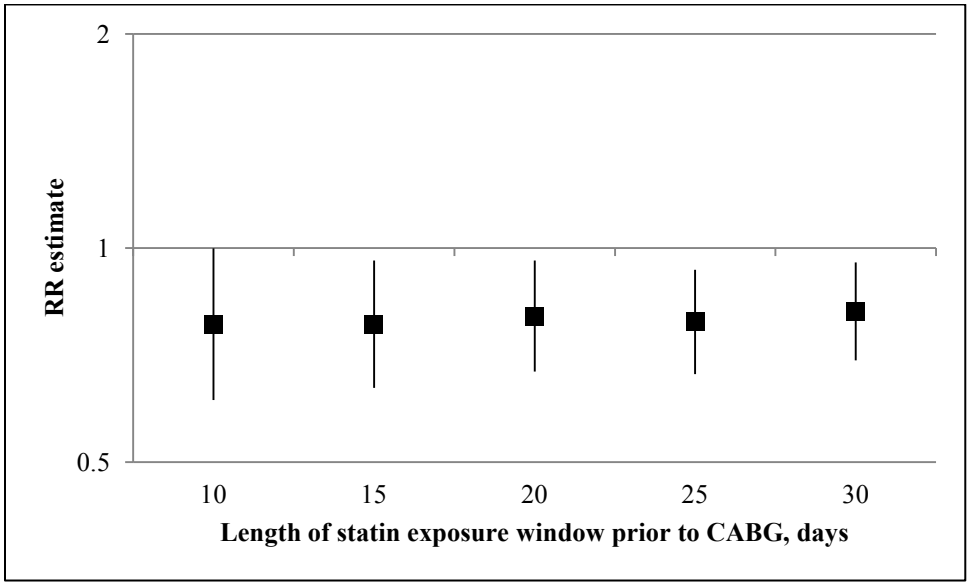

Figure 5.4 Effect measure estimates across varying exposure windows

Chapter 6. Acute kidney injury in statin initiators

1. Introduction

Use of statins has become widespread in the United States over the past decade (1, 34). They have become a mainstay of lipid management, and an integral part of both primary and secondary (4) cardiovascular disease (CVD) prevention. They are widely used by older individuals at risk of CVD (1) and are highly effective in preventing serious adverse outcomes (9). Additionally, it has been suggested that statins have anti-inflammatory (101) and other protective effects (2, 103, 116) beyond their primary lipid-lowering function. They have also begun to be used as preventives in patients at much lower CVD risk (117).

As these medications are used in younger and healthier individuals, safety and even rare adverse events have justifiably become serious considerations to ensure that potential negative effects do not outweigh the well-established cardiovascular benefits of statin use. Statins are generally accepted as safe and well-tolerated, however very real risks, including myopathies and rhabdomyolysis, have been well documented (74, 118). Additionally, recent reports have suggested that statins may carry a risk of kidney injury.

The relationship between statin use and kidney function is not well understood. It has been suggested that statin use may be beneficial towards overall kidney function (54), yet the cardiovascular protective effects of statins have not been demonstrated in dialysis and renal transplant patients as in the general population (55). It has been suggested by one observational study that the risk of AKI may be increased in both male and female statin users (33), and meta-analyzed clinical trial data showed an increased risk of proteinuria in individuals taking higher-dosages of rosuvastatin (58). However, in 2006 the Kidney Expert Panel of the National Lipid Association's Safety Task

Force issued a statement that there was not evidence suggesting a link between statin exposure and renal injury (56, 57). These reports justify increased research into the potential for statin-induced kidney injury.

Non-experimental research of statin safety is difficult owing to statins' widespread use and lack of a similar, exchangeable lipid treatment with which statins have clinical equipoise. Clinical trials or well-designed observational studies would employ a comparison group of non-users or other medication users who have a similar risk factor profile for the outcome. However, an exchangeable comparison group is difficult to identify in non-observational settings (70), particularly in administrative claims, where difficult-to-measure factors such as healthy lifestyle and behaviors, access to and utilization of healthcare, and clinical factors which would not be reflected in billing claims (obesity, smoking, family history, etc.) can all contribute to both the risk of AKI and a patient initiating a statin.

In this administrative claims-based study employing a very large cohort from the United States, we used modern epidemiologic methods and careful patient inclusion criteria to evaluate the association between statin initiation and AKI. We also evaluated and the comparative safety of individual statin formulations and higher- versus lower-potency statins.

2. Methods

Study population

We employed two large employer-based insurance claims databases: the *Thomson Reuters' MarketScan® Commercial Claims and Encounters* and *Medicare Supplemental and Coordination of Benefits Databases* (Thomson Reuters (Healthcare) Inc., 2011). These databases are compilations of insurance billing data from approximately 100 large, employer-based insurance plans and Medicare supplementary plans from across the United States. Adjudicated, paid inpatient, outpatient, and pharmacy claims, as well as enrollment information, are available in the databases for employees, dependents and retirees.

Treatment ascertainment

Statin initiators were identified from a pharmacy dispensing claim for any statin following 180 days free of a statin use. We required at least one, non-statin medication claim during the 180-day baseline period to ensure pharmacy benefit status and system utilization. The formulation of the index statin prescription was noted, and the prescription was labeled as either higher- or lower-potency based on formulation and dosage. The date of the initial statin prescription was considered the index date, and from that point forward the patient was considered a statin initiator in an intent-to-treat analysis.

Initiators of cerivastatin sodium were excluded due to its documented increased risk of myopathy and rhabdomyolysis and subsequent removal from the market (59, 119).

A cohort of non-statin users was obtained by identifying individuals with an outpatient physician's visit following 180 statin-free days. Similarly to the statin users, non-users were required to have at least one other medication dispensing during baseline.

Outcome

In- and outpatient claims in the one year following the index date were searched for *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis codes for evidence of acute renal failure (ARF) (ICD-9-CM 584.5 – 584.9). The validity of these codes has been investigated (79, 113), and while the sensitivity has been shown to be quite low, the specificity is very high. However, valid research can still be performed in situations with very high specificity under the assumption of no differential misclassification across treatment groups (114, 115).

An expanded renal failure definition was also considered, which included ARF, end-stage renal disease (ICD-9-CM 585.6), unspecified renal failure (ICD-9-CD 586), or a procedure code for dialysis (see Appendix 1).

Comparisons

Statin initiators were compared to the identified non-users, and the analysis was stratified by multiple clinically-relevant subgroups at higher-risk for AKI, including individuals aged 65 years and older, and those with diabetes, hypertension, recent acute coronary syndrome, or chronic kidney disease (CKD). We also compared initiators of higher-potency statins to lower-potency formulations and dosages. Lastly, we compared initiators of individual statin formulations to higher-potency atorvastatin users. In instances where formulations could exist in both higher- and lower-potency forms (e.g. atorvastatin, lovastatin, rosuvastatin, and simvastatin), the potencies were considered separately (see Table 6.1).

Covariate information

In- and outpatient claims in the 180 days prior to and including the index date were investigated for diagnosis and procedure codes for cardiovascular disease risk factors and indicators, recent acute events, healthcare utilization, and risk factors for AKI.

Pharmacy dispensing claims during the baseline window were searched for prevalent use of additional medications. Medications newly-initiated following six months free of the medication on the same day as or within one day of the statin initiation were considered concurrently initiated, and were considered as separate variables in the analysis.

Statistical analyses

Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the one-year risk of statin initiation on AKI. Follow-up began the day after statin initiation, and continued until censoring at the event of interest, plan unenrollment, one year after statin initiation, or end of the study period (December 31, 2010).

All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

Propensity score calculation and application

We estimated the predicted probability of statin initiation, or propensity score (PS), using the measured covariates in logistic regression models for each comparison in this analyses. Each distribution of the PS by treatment group was plotted to assess the exchangeability of the treatment groups with respect to the measured confounders.

Propensity score matching. Within each analysis, we matched individuals in the treatment group to individuals in the comparison group using a 5-1 greedy matching algorithm (109). The HR was estimated within the matched cohort. This method estimates the effect of the treatment only in those who received treatment rather than the entire population. In this method, individuals without a match are excluded from the analysis.

Standardized morbidity ratio weighting. The PS was also used to calculate standardized morbidity ratio weights (SMRW), in which treated individuals were unweighted, and untreated patients received a weight of [PS / (1 – PS)] . This techniques retains all individuals in the analysis, but it downweights untreated individuals with very low predicted probability of treatment, and upweights those untreated individuals with higher probability. These weights were applied to Cox proportional hazards models estimating the treatment effect in the treated.

To reduce the influence of extreme weights caused by those treated contrary to prediction (108) and to ensure positivity by restricting to portions of the PS distribution with comparable treated and untreated individuals (120), analyses were repeated with PS non-overlap extreme weights trimmed. All individuals with PS less than the 0.5^{th} percentile of the treated or the 99.5^{th}percentile of the untreated were excluded. In a series of sensitivity analyses, these cutoffs were progressively moved inward toward the median by 0.5 percentiles.

Propensity score stratification. In comparison groups with considerable non-overlap of PS distributions between the treated and non-treated, we stratified the cohort into 50 equal groups by the distribution of the propensity score. Covariates between treated and untreated individuals should be balanced within each strata (121). We estimated crude HR among each stratum and plotted them to

observe any modification of the effect measure estimate across the distribution of the propensity score.

Ethical approval

This analysis using deidentified billing claims was ruled exempt from further review by the Institutional Review Board of the University of North Carolina at Chapel Hill (UNC).

Role of the funding source

This study was funded through a training grant in renal epidemiology from the National Institutes of Health to the UNC Kidney Center (grant number 5 T32 DK007750-13). The funding source played no role in the design, analysis, or interpretation of this study.

3. Results

Statin users vs. non-users

We identified 4,146,506 statin initiators and 4,033,800 non-users eligible for the analysis. The distributions of covariates by treatment group are shown in Table 6.2. The statin users were substantially older, had more cardiovascular disease, more healthcare utilization, more comorbidities, and have more prevalent medication use and concurrent medication initiation. Analysis of the distribution of the propensity score by treatment group revealed considerable non-overlap between the statin users and non-users (see Figure 6.1), suggesting little comparability between the treatment groups.

AKI was observed during one-year of follow-up in 0.9% of the statin users and 0.3% of the non-users. Cox-proportional hazards models revealed a crude HR of 3.11 (95% CI: 3.04, 3.17). Upon multivariable adjustment, the effect estimate was attenuated to HR=0.97 (0.94, 0.99) (see Table 6.3).

Upon propensity score matching of the statin initiators to non-users, 1,522,017 matched pairs remained for analysis, resulting in HR=0.79 (95% CI: 0.76, 0.81). The vast majority of participants

were excluded from the resulting analysis due to failure to match in the non-overlapping regions of the propensity score (see Figure 6.1).

Upon SMRW weighting and trimming the most extreme 0.5^{th} and 99.5^{th} percentiles of the treated and untreated PS distributions, respectively, the estimate was HR=0.76 (95% CI: 0.76, 0.79).

When the expanded, any kidney failure outcome definition was considered, the effect measure estimates remained almost identical for all comparisons.

The cohort was divided into 50 strata of the propensity score, and the HR was calculated within each stratum. The results were plotted (see Figure 6.2), and the HR remained constant at a mild protective effect across the majority of the strata, with exceptions of the tails of the PS distribution. The risk of AKI seemed to be highly elevated among statin users at the lower fifth of the PS. We compared the covariate distributions by treatment status among select strata at the lower tail of the PS distribution to investigate potential causes of the treatment effect heterogeneity. The patients in both treatment groups in this lower tail were younger and had fewer CVD risk factors or procedures than the general sample.

We investigated the treatment effect of statin use within clinically relevant subgroups. The rates of AKI were highest in those with CKD and the elderly, as expected. The relative effect of statin initiation appeared constant over all subgroups within each estimation technique (see Table 6.4).

Higher-potency vs. lower-potency statin users

Of the statin users, 3,055,038 initiated a higher-potency statin and 1,085,202 initiated a lower-potency statin. The distribution of covariates between statin treatment groups was very similar, as evidenced by the more extensive PS overlap among the treatment groups (see Figure 6.3). All effect measure estimation techniques yielded very similar, null-to-minimal effects of higher-potency statin initiation versus lower-potency statins on AKI (see Table 6.5).

Comparative safety of statin formulations

The risks of AKI in individual statin formulations were compared to higher-potency atorvastatin. PS matching and multivariable adjusted estimates revealed very similar hazards of AKI among the various formulations groups, just slightly below the AKI rate observed in higher-potency atorvastatin. A notable exception was seen in higher-potency simvastatin, which showed a slightly increased risk of AKI compared to higher-potency atorvastatin: multivariable HR = 1.18 (95% CI 1.05, 1.11); PS-matched HR = 1.16 (95% CI: 1.00, 1.08) (see Figure 6.4).

4. Discussion

Initiation of statins was not shown to be associated with an increase in AKI in the majority of statin initiators, nor were higher-potency statins shown to be convey higher AKI risk than lower-potency statins. These findings were robust across renal failure definitions. PS-based methods may suggest a very modest protective effect of statin use against one-year risk of AKI, but the effect was very mild. The stratified analysis revealed that for many statin initiators, there appeared to be a protective effect against AKI, yet in those treated contrary to prediction in the tails of the propensity score distribution (108) appear to be a different effect.

There were some differences observed between the effect measure estimates yielded by the multivariable outcome model that showed a null effect, and the PS models that suggest a mild protective effect may be present. The multivariable adjustment considers all strata equally, while the PS matched and SMRW weighted models exclude or down-weight the individuals with extreme PS, focusing only on the treated individuals and comparable untreated individuals. The differences, therefore, between the null effect measure estimated by the outcome model and the protective estimates yielded by the PS-methods may be explained by the de-emphasis or exclusion of the untreated individuals in the lower strata of the PS distributions, or the trimming of the heavily-weighted untreated individuals at the highest strata of the PS in the SMRW analysis (122). These results suggest that for the majority of statin initiators, statin use conveys no increased risk of AKI.

However, residual unmeasured confounding by frailty, severe disease state, or other factors in the tails of the PS distribution reduce our ability to draw inference about the effect of statins in these extreme strata.

While the effect measure estimates resulting from the PS-based methods suggest a mild protective effect, this must be interpreted conservatively. The baseline rate of AKI in statin initiators was quite low (less that 1%), so the estimated absolute reduction of AKI in statin users is quite low. Additionally, the potential for unmeasured confounding and residual bias is still present, which could potentially influence the results.

This work must be interpreted in light of several important limitations. As with all administrative claims-based studies, information on kidney function, cardiovascular risk, and other covariates and outcomes is derived from submitted claims for reimbursement, rather than biomeasurements or medical records. Consequently, information on key risk factors for AKI and CVD such as glomerular filtration rate, blood lipids, obesity, smoking, and family history of CVD or renal disease may be unavailable for inclusion in analysis, leaving the possibility for residual confounding. In particular, baseline kidney function, one of the stronger predictors of AKI, can only be ascertained through the use of billing codes for chronic kidney disease, which have been shown to be very insensitive measures (113).

Additionally, due to the incomparability between the statin and non-user treatment groups, the PS-based estimates are not applicable to the entire statin initiating population. Exclusion of non-matching individuals and trimming of extreme weights limit the population to whom the estimates can be generalized. The stratified analysis suggests that for the majority of initiators, the reported effect measure estimates are valid. However, these effects were not observed in statin users with low predicted probability of statin treatment by our estimation. Investigation of the covariate distribution among the lower tail revealed that those in the lowest strata of the PS were very young adults with minimal-to-no prior cardiovascular procedures or diagnoses. The statin users appear to be initiating the medication for some unknown and unmeasured purpose, while they are being compared to

perfectly healthy young adults. We would expect these comparisons, atypical of the general statin-initiating population, to yield estimates showing statin users at higher risk of adverse events, but this effect is likely due to unmeasured confounding than an actual drug effect. When the analysis was restricted to individuals aged 65+, the heterogeneity in the lower tail of the PS disappeared, resulting in much more homogeneous treatment effect (see Figure 6.5).

There appeared to be very little difference in risk of AKI among users of higher- versus lower-potency or individual statin formulations, with the exception of higher-potency simvastatin, which demonstrated a larger AKI risk than higher-potency atorvastatin and other formulations. This finding is consistent with the prevailing safety information of high-dosage simvastatin, which has similarly demonstrated a higher risk of myalgia within the first year of therapy (123), prompting the Food and Drug Administration to limit the use of 80 mg (the highest available dose) to only those with at least 12 months free of adverse events (124).

Among the vast majority of typical statin users, we found no increased risk of AKI due to the medication initiation across subgroups and statin formulations. Non-randomized studies of statin effects must take great care in their choice of comparison groups and analysis techniques to estimate effect measures among exchangeable comparison groups to produce unbiased estimates of statin safety.

5. Tables

Table 6.1 Statin potencies by formulation and dosage

Formulation	Higher-potency dosages	Lower-potency dosages
Atorvastatin	> 10 mg	≤ 10 mg
Fluvastatin	none	all
Lovastatin	> 40 mg	≤ 40 mg
Pravastatin	none	all
Rosuvastatin	> 5mg	≤ 5 mg
Simvastatin	> 40 mg	≤ 40 mg

Table 6.2 Distribution of patient characteristics by treatment group

	Statin non-initiator (n=4,033,800)		Statin initiator (n=4,146,506)	
DEMOGRAPHICS	**N**	**%**	**N**	**%**
Male, %	1,494,210	37.0	1,984,993	47.9
Mean age, standard deviation (SD)	45.6	16.2	58.5	12.6
MarketScan Database				
Commercial Claims and Encounters Database, %	3,536,515	87.7	2,952,772	71.2
Medicare Supplementary Database, %	497,285	12.3	1,193,734	28.8
CARDIOVASCULAR DISEASE MANAGEMENT	**N**	**%**	**N**	**%**
Angiography performed, %	1,821	0.1	36,368	0.9
Cardiac stress test performed, %	39,218	1.0	385,572	9.3
Echocardiograph, %	72,859	1.8	488,892	11.8
Mean number of lipid tests, SD	0.18	0.48	0.83	1.00
Mean number of creatinine measurements, SD	0.00	0.07	0.01	0.16
CVD & COMORBID CONDITIONS	**N**	**%**	**N**	**%**
Diabetes	155,745	3.9	949,562	22.9
Chronic kidney disease	9,073	0.2	67,680	1.6
Other kidney disease	2,065	0.1	11,488	0.3
Proteinuria	727	0.0	2,401	0.1
Hypertension	485,017	12.0	1,595,038	38.5
Hyperlipidemia	245,087	6.1	1,926,172	46.5
Ischemic heart disease*	46,558	1.2	549,580	13.3
Atrial fibrillation	25,537	0.6	131,964	3.2
Chronic liver disease or cirrhosis	17,557	0.4	52,300	1.3
Multiple myeloma	723	0.0	2,759	0.1
Systemic lupus *erythematosus*	4,691	0.1	16,486	0.4
Metabolic disorders	12,257	0.3	43,320	0.8

ACUTE EVENTS	**N**	**%**	**N**	**%**
Myocardial infarction (MI) in previous 2 weeks	3,092	0.1	70,402	1.7
MI, within previous 6 months	5,607	0.1	93,491	2.3
History of MI	2,074	0.1	25,081	0.6
Unstable angina in previous 2 weeks	3,865	0.1	67,141	1.6
Unstable angina in previous 6 months	3,511	0.1	37,720	0.9
Stroke	33,198	0.8	223,446	5.4
Coronary artery bypass graft	1,259	0.0	34,345	0.8
Insertion of a coronary stent	2,270	0.1	95,306	2.3
Angioplasty	569	0.0	12,963	0.3
Heart failure	23,854	0.6	119,730	2.9
Spesis	1,258	0.0	3,289	0.1
PREVALENT MEDICATION USE DURING BASELINE	**N**	**%**	**N**	**%**
Angiotensin converting enzyme (ACE) inhibitors	367,355	9.1	1,093,563	26.4
Angiotensin receptor blockers (ARBs)	172,440	4.3	580,626	14.0
Beta blockers	352,496	8.7	1,018,742	24.6
Calcium channel blockers	257,730	6.4	706,410	17.0
Anti-platelet agents	41,140	1.0	231,225	5.6
Alpha blockers	58,389	1.5	186,631	4.5
Thiazide diuretics	400,318	9.9	1,026,844	24.8
Potassium-sparing diuretics	115,444	2.9	251,658	6.1
Loop diuretics	76,685	1.9	269,089	6.5
Niacin	9,745	0.2	62,518	1.5
Fibrates	46,217	1.2	201,658	4.9
Ezetimibe	16,641	0.4	118,049	2.9
Anti-coagulants	45,911	1.1	163,722	4.0
Non-steroidal anti-inflammatory agents (NSAIDs)	516,055	12.8	796,948	19.2
MEDICATIONS INITIATED DURING EXPOSURE WINDOW	**N**	**%**	**N**	**%**
ACE inhibitors	57,242	1.4	420,224	10.1
ARBs	18,743	0.5	180,653	4.4

Beta blockers	42,248	1.1	362,681	8.8
Calcium channel blockers	30,485	0.8	235,993	5.7
Anti-platelet agents	3,923	0.1	155,649	3.8
Alpha blockers	5,414	0.1	66,791	1.6
Thiazides	61,429	1.5	285,918	6.9
Potassium-sparing diuretics	14,904	0.4	60,332	1.5
Loop diuretics	7,638	0.2	75,779	1.8
Niacin	1,167	0.0	63,935	1.5
Fibrates	4,849	0.1	56,057	1.4
Ezetimibe	1,254	0.0	287,125	6.9
Anti-coagulants	3,574	0.1	42,556	1.0
NSAIDs	131,074	3.3	118,425	2.9

Table 6.3 Effect measure estimates of statin initiation versus non-users on acute kidney injury

			Acute kidney injury			Any renal failure		
Analysis	**Treatment group**	**N**	**Events (%)**	**HR***	**95% CI***	**Events (%)**	**HR**	**95% CI**
	Non-users	4,033,800	11,370 (0.3)	--	--	15,358 (0.4)	--	--
Crude	Statin users	4,146,506	37,542 (0.9)	3.11	3.04, 3.17	50,193 (1.2)	3.08	3.03, 3.14
Multivariable adjusted				0.97	0.94, 0.99		1.03	1.01, 1.05
Trimmed SMRW*	Non-users	2,953,843	10,726 (0.4)	--	--	14,423 (0.5)	--	--
	Statin users	3,466,441	23,569 (0.7)	0.76	0.73, 0.79	31,823 (0.9)	0.76	0.73, 0.78
Propensity score matching	Non-users	1,552,017	8,836 (0.6)	--	--	11,976 (0.8)	--	--
	Statin users	1,552,017	7,170 (0.5)	0.79	0.76, 0.81	9,928 (0.6)	0.80	0.78, 0.83

*HR, Hazard ratio; CI, Confidence interval; SMRW, standardized mortality ratio weighting

Table 6.4 Effect of statin initiation versus non-use in relevant subgroups

			Crude		Adjusted		Matched		SMRW	
Subgroup	**N**	**Events %**	**HR***	**95%CI***	**HR**	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Aged 65+	1,659,385	6.5	1.43	1.42, 1.45	0.97	0.95, 0.98	0.83	0.81, 0.84	0.82	0.80, 0.84
CKD*	76,753	16.9	1.32	1.25, 1.40	0.96	0.90, 1.01	0.93	0.86, 1.00	0.69	0.47, 1.00
Diabetes	1,105,308	4.6	1.23	1.20, 1.27	0.93	0.90, 0.95	0.78	0.75, 0.80	0.84	0.78, 0.91
Hypertension	2,080,055	3.1	1.56	1.53, 1.60	1.00	0.98, 1.03	0.90	0.87, 0.92	0.87	0.82, 0.92
Hyperlipidemia	2,171,259	1.5	1.96	1.87, 2.04	1.10	1.05, 1.15	0.98	0.93, 1.04	0.81	0.72, 0.92
Recent ACS*	178,521	6.0	1.02	0.95, 1.09	0.92	0.86, 1.00	0.72	0.65, 0.80	0.71	0.49, 1.01

*HR: Hazard ratio; CI: Confidence interval; CKD: Chronic kidney disease; ACS: Acute coronary syndrome

Table 6.5 Effect measure estimates of higher-potency versus lower-potency statin initiation on acute kidney injury

			Acute kidney injury			Any renal failure		
Analysis	**Treatment group**	**N**	**Events (%)**	**HR***	**95% CI***	**Events (%)**	**HR**	**95% CI**
	Low potency	3,055,028	26,368 (0.9)	--	--	35,235 (1.2)	--	--
Crude	High potency	1,085,202	11,091 (1.0)	1.18	1.15, 1.20	14,849 (1.4)	1.18	1.16, 1.20
Multivariable adjusted				1.09	1.07, 1.12		1.10	1.08, 1.12
Trimmed SMRW*	Low potency	3,002,718	10.693 (1.0)	--	--	34,211 (1.1)	--	--
	High potency	1,066,544	25,638 (0.9)	1.08	1.05, 1.10	14,294 (1.3)	1.06	1.04, 1.08
Propensity score matching	Low potency	1,083,310	10,931 (1.0)	--	--	14,652 (1.4)	--	--
	High potency	1,083,310	11,043 (1.0)	1.01	0.99, 1.04	12,790 (1.4)	1.01	0.99, 1.04

*HR, Hazard ratio; CI, Confidence interval; SMRW, standardized mortality ratio weighting

73

6. Figures

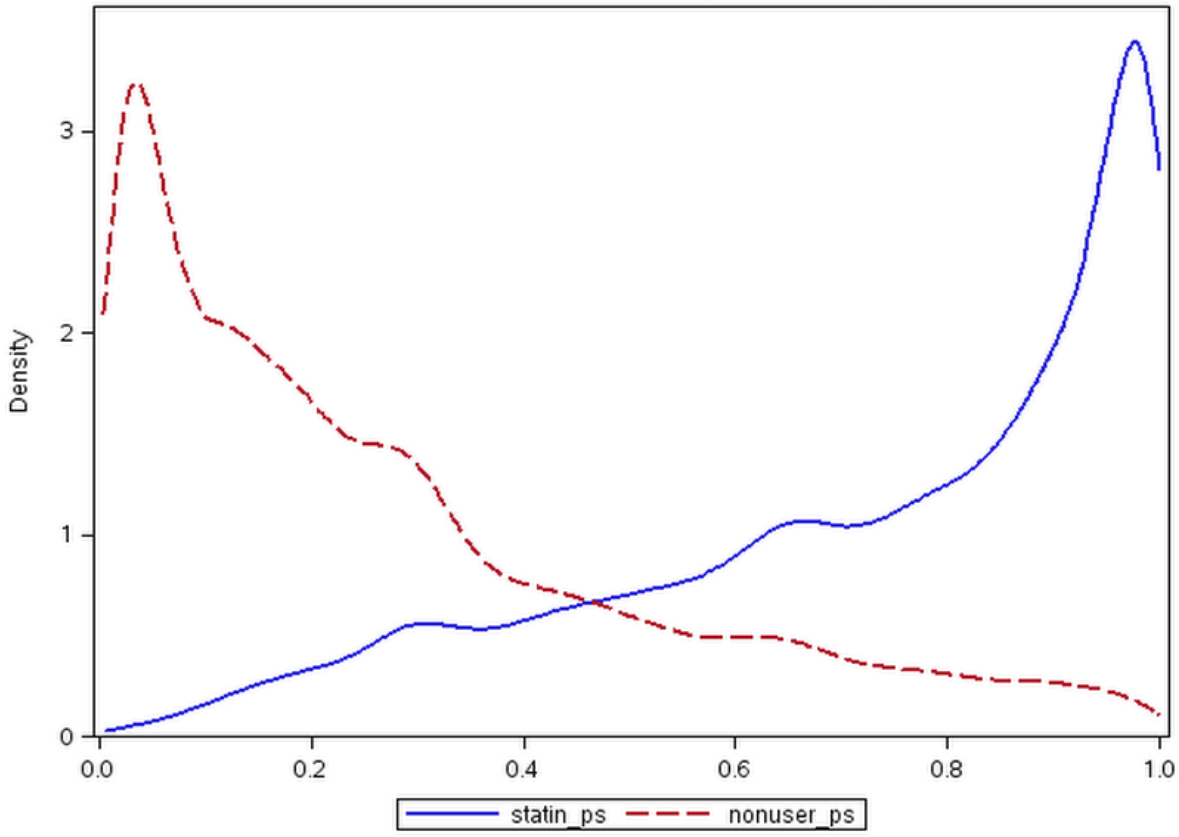

Figure 6.1 Distribution of the propensity score between statin initiators and non-user

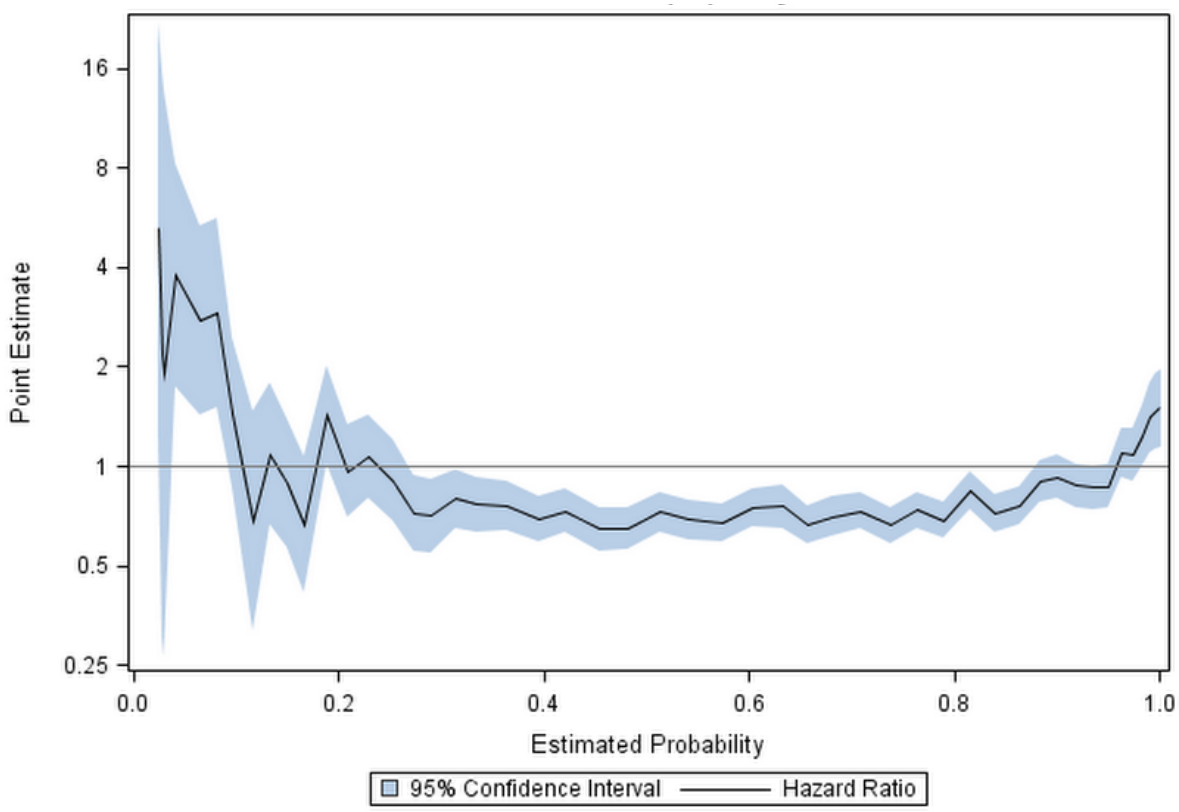

Figure 6.2 Effect of statin initiation on acute kidney injury across strata of the propensity score

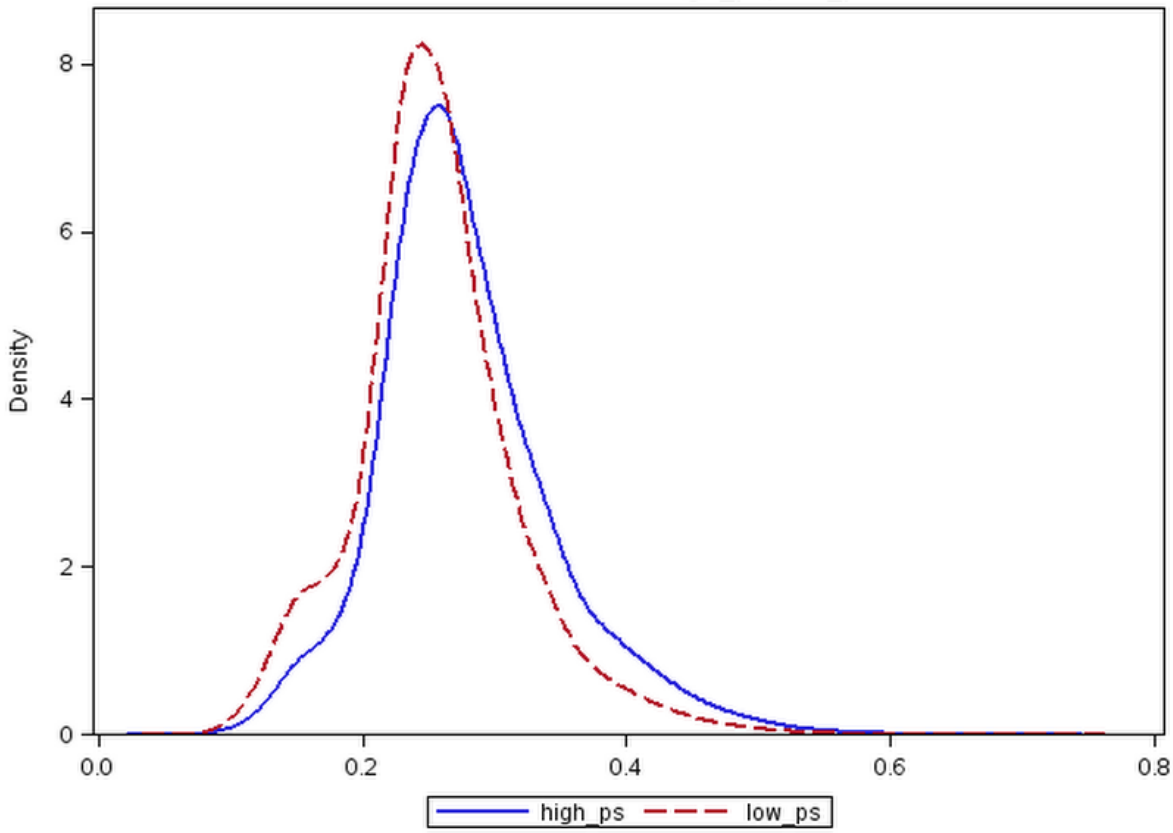

Figure 6.3 Distribution of the propensity score (PS) between higher- and lower-potency statin initiators

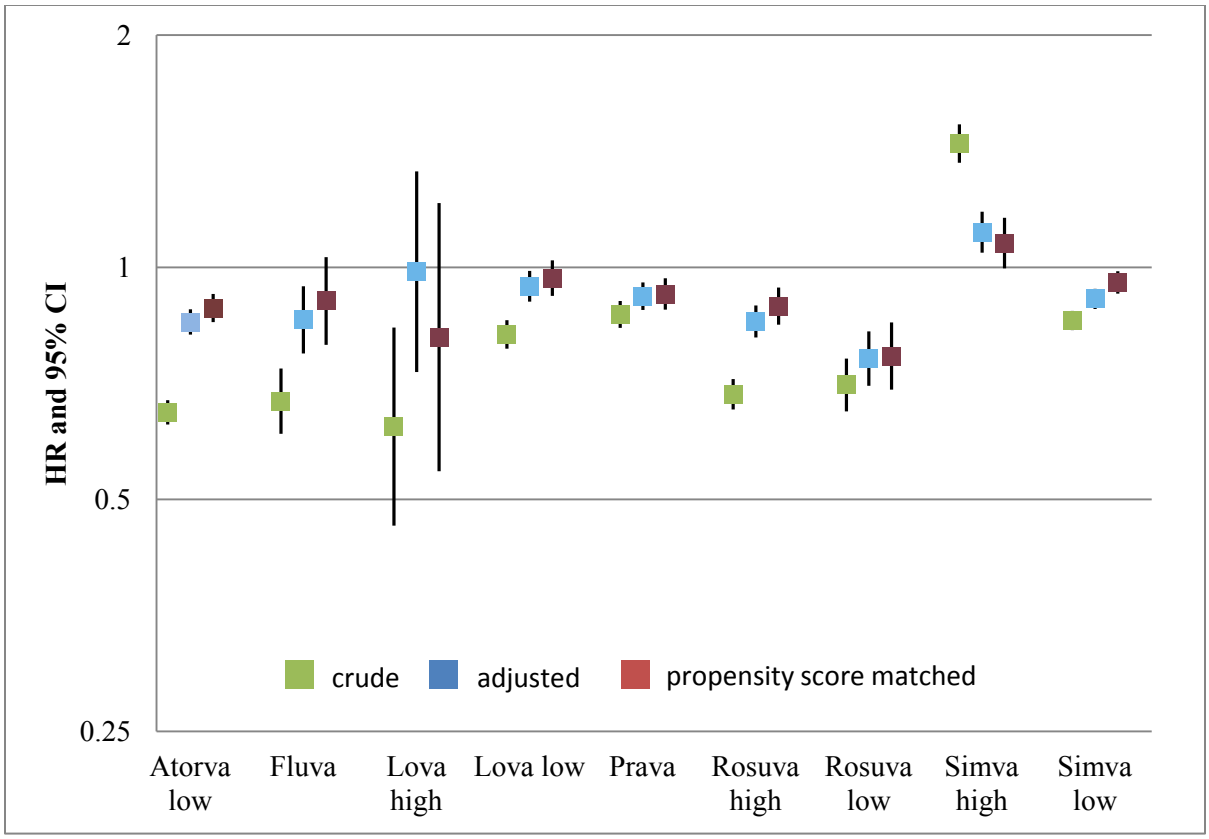

Figure 6.4 Hazard ratios and 95% confidence intervals of the risk of acute kidney injury in statin formulations versus higher-potency atorvastatin

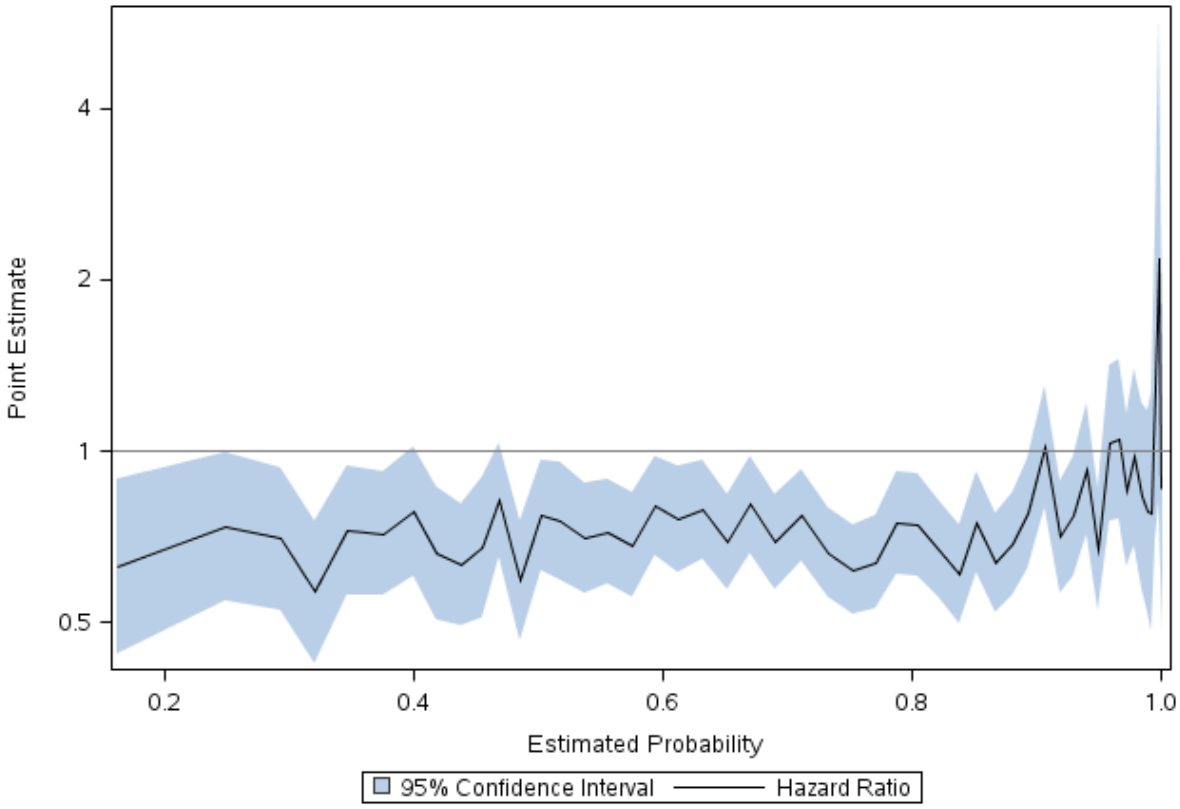

Figure 6.5 Hazard ratios and 95% confidence intervals of AKI among statin initiators vs. non-users across strata of the propensity score, ages 65+

Chapter 7. Conclusions and public health significance

Statins are widely used by a vast spectrum of Americans for primary and secondary prevention of CVD. With widespread use, particularly in relatively healthy populations, statins' safety has become a pressing concern. Numerous observational studies of statins have been conducted, and recent concerns have been raised regarding the renal safety of statin use. To investigate these effects, we performed a study of statin initiators in a large, administrative claims database of privately-insured employed individuals and Medicare retirees. We investigated what additional information about statin initiators could be ascertained from pharmacy claims for other medications at the same time as the statin initiation. We also investigated the exchangeability of various comparison groups with statin initiators.

We observed that statins were frequently initiated with other cardiovascular and non-cardiovascular medications, presumably in response to a physician's estimate of the patient's CVD risk. In many cases, the exact characteristics making up one's CVD risk may not be explicitly hard-coded in administrative claims (e.g. family history of CVD, smoking status, obesity, lack of exercise, etc.), so concurrently initiated medications may be an important proxy for unmeasured and important confounding factors. Notably, rates of concurrent initiation were higher in groups with known higher CVD and renal risk, including those with recent acute events such as myocardial infarction or unstable angina, suggesting that consideration of concurrent initiation may be a useful factor in evaluating disease risk in other patient populations with less explicit risk factors.

Medications may also be concurrently initiated as a result of better medical care. Particularly in the case of pre-CABG statin initiation, the statin may serve as a proxy for better pre-surgical evaluation and treatment. However, considering other medications initiated immediately prior to CABG allows us to control in some part for the unmeasured factors leading to statin initiation, which

may also influence the occurrence of post-CABG AKI. When considering these factors as well as other markers of CVD management, renal risk, healthcare utilization, and recent cardiovascular events, we found a mild protective effect of statin initiation on post-CABG AKI. After adjustment, we observed a protective effect of statin initiation on AKI (RR = 0.80, 95% CI 0.67, 0.96). This was robust throughout AKI definitions, varying exposure windows prior to CABG, and through most subgroups. However, this effect differed by age: ≥65 years, RR=0.90 (95% CI: 0.71, 1.14); <65 years, RR=0.69 (95% CI: 0.52, 0.91), although AKI was much more common in the older age group (8.1 vs. 3.9%). Statin initiation immediately prior to CABG may modestly reduce the risk of post-operative AKI, yet the result is small and more pronounced in younger patients with a very low baseline risk of AKI.

Lastly, we investigated the risk of AKI in a general statin-initiating population. Knowing a direct user vs. non-user design would be difficult due to the lack of an appropriate active drug comparison (e.g. another medication with a similar indication), and well described biases of statin use in primary prevention (e.g. the healthy user effect, where long-term preventive medication users are a highly-selected, healthier subgroup of medication users as compared to non-users) and secondary prevention (e.g. confounding by indication, where individuals who receive treatment are sicker and thus at higher risk of adverse events than non-users) settings, we employed multiple difference comparisons to comprehensively evaluate statins' role in AKI. We compared statin users to non-users, higher-intensity statins to lower-intensity statins, and individual statin formulations to atorvastatin. We also investigated the effect within more homogenous subgroups. We employed an array of propensity score techniques to evaluate the exchangeability of statin users with non-users, and found vast areas of minimal overlap between treated and untreated groups, making direct comparisons difficult. Propensity score matching, weighting, and stratification was employed, and all suggest no increase risk of AKI due to statin use in any individual formulation, potency, or subgroup, with the exception of higher-potency simvastatin, which has also been implicated for increased risk of muscle injury.

Heterogeneous treatment effects across the propensity score merit further exploration, as statin users come from a wide array of disease risk groups, and the reason for statin initiation is not always evident in claims data. Restriction to disease risk groups (e.g. older age, hypertension, recent acute events, etc.) removed much of this heterogeneity, but in younger, relatively healthier statin users, there appears to be an increased risk on AKI not seen in the vast majority of typical statin users. This is likely due to unmeasured confounding, and should not be generalized to the entire statin-initiating population.

Overall, statins do not appear to increase the risk of AKI in most cases, and may in fact, slightly reduce the incidence of AKI in pre-surgical settings. Lingering methodological concerns of non-randomized studies of statin use require that careful attention be paid to study design and analysis methods to estimate valid measures of statin safety and effectiveness.

Appendix 1

Procedure codes for dialysis:

V451, V56, V560, V560, V568, E8791, E8702, E8712, E8722, E8742, V5632, 0505F, 0507F, 3995, 4052F, 4053F, 4054F, 4055F, 5498, 50360, 50365, 5569, 90935, 90937, 90940, 90945, 90947, 90951, 90952, 90953, 90954, 90955, 90956, 90957, 90958, 90959, 90960, 90961, 90962, 90963, 90964, 90965, 90966, 90967, 90968, 90969, 90970, 90999, 99512

Works Cited

1. Spatz ES, Canavan ME, Desai MM**.** From here to JUPITER: identifying new patients for statin therapy using data from the 1999-2004 National Health and Nutrition Examination Survey. Circ Cardiovasc Qual Outcomes. 2009;2(1):41-8.

2. McFarlane SI, Muniyappa R, Francisco R, Sowers JR**.** Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond. J Clin Endocrinol Metab. 2002;87(4):1451-8.

3. Kostapanos MS, Liberopoulos EN, Elisaf MS**.** Statin pleiotropy against renal injury. J Cardiometab Syndr. 2009;4(1):E4-9.

4. Lin V, Holman JR**.** Which drugs should post-MI patients routinely receive? The Journal of Family Practice. 2010;59(9):527-9.

5. Bellosta S, Paoletti R, Corsini A**.** Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation. 2004;109(23 Suppl 1):III50-7.

6. Buetner C, Lecker SH**.** Molecular basis for statin-induced muscle toxicity: implications and possibilities. Pharmacogenomics. 2008;9(8):1133-42.

7. Thompson PD, Clarkson P, Karas RH**.** Statin-associated myopathy. JAMA. 2003;289(13):1681-90.

8. Maron DJ, Fazio S, Linton MF**.** Current perspectives on statins. Circulation. 2000;101:207-13.

9. Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM. 2011;104(2):109-24.

10. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207.

11. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E**.** Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. J Am Coll Cardiol. 2009;54(25):2358-62.

12. Highlights of prescribing information: Lipitor (atorvastatin calcium). In: Parke-Davis, ed. New York, NY: Parket-Davis; 2009.

13. Highlights of prescribing information: Crestor (rosuvastatin calcium). In: AstraZeneca, ed. Wilmington, DE: AstraZeneza; 2011.

14. Mevacor (Lovastatin). In: ULC MP, ed. Morgantown, WV: Mylan Pharmaceuticals ULC; 2010.

15. Pravachol (pravastatin sodium) tablets. In: Company B-MS, ed. Princeton, NJ: Bristol-Myers Squibb Company; 2010.

16. Lescol (fluvastatin sodium) Prescribing Information. In: Corporation NP, ed. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2006.

17. Highlights of prescribing information: Simcor (niacin extended-release/simvastatin). In: Laboratories A, ed. North Chicago, IL: Abbott Laboratories; 2008.

18. Administration UFaD**.** Questions and Answers for Healthcare Professionals: CRESTOR and the JUPITER Trial. 2010.

19. Rozman D, Monostory K**.** Perspectives of the non-statin hypolipidemic agents. Pharmacol Ther. 2010;127(1):19-40.

20. Jackevicius CA, Tu JV, Ross JS, Ko DT, Carreon D, Krumholz HM**.** Use of fibrates in the United States and Canada. JAMA. 2011;305(12):1217-24.

21. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010;375:1875-84.

22. Grundy SM**.** The issue of statin safety: where do we stand? Circulation. 2005;111(23):3016-9.

23. Welten GM, Chonchol M, Schouten O, Hoeks S, Bax JJ, van Domburg RT, et al. Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome. Nephrol Dial Transplant. 2008;23(12):3867-73.

24. Huffmyer JL, Mauermann WJ, Thiele RH, Ma JZ, Nemergut EC**.** Preoperative statin administration is associated with lower mortality and decreased need for postoperative hemodialysis in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2009;23(4):468-73.

25. Molnar AO, Coca SG, Devereaux PJ, Jain AK, Kitchlu A, Luo J, et al. Statin use associates with a lower incidence of acute kidney injury after major elective surgery. J Am Soc Nephrol. 2011;22(5):939-46.

26. Tabata M, Khalpey Z, Pirundini PA, Byrne ML, Cohn LH, Rawn JD**.** Renoprotective effect of preoperative statins in coronary artery bypass grafting. Am J Cardiol. 2007;100(3):442-4.

27. Virani SS, Nambi V, Polsani VR, Lee VV, Elayda M, Kohsaka S, et al. Preoperative statin therapy decreases risk of postoperative renal insufficiency. Cardiovasc Ther. 2010;28(2):80-6.

28. Ali IS, Buth KJ**.** Preoperative statin use and in-hospital outcomes following heart surgery in patients with unstable angina. Eur J Cardiothorac Surg. 2005;27(6):1051-6.

29. Clark LL, Ikonomidis JS, Crawford FA, Jr., Crumbley A, 3rd, Kratz JM, Stroud MR, et al. Preoperative statin treatment is associated with reduced postoperative mortality and morbidity in patients undergoing cardiac surgery: an 8-year retrospective cohort study. J Thorac Cardiovasc Surg. 2006;131(3):679-85.

30. Liakopoulos OJ, Choi YH, Haldenwang PL, Strauch J, Wittwer T, Dorge H, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. Eur Heart J. 2008;29(12):1548-59.

31. Pan W, Pintar T, Anton J, Lee VV, Vaughn WK, Collard CD**.** Statins are associated with a reduced incidence of perioperative mortality after coronary artery bypass graft surgery. Circulation. 2004;110(11 Suppl 1):II45-9.

32. Winchester DE, Wen X, Xie L, Bavry AA**.** Evidence of pre-procedural statin therapy a meta-analysis of randomized trials. J Am Coll Cardiol. 2010;56(14):1099-109.

33. Hippisley-Cox J, Coupland C**.** Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. Bmj. 2010;340(may19 4):c2197-c.

34. U.S. spending and prescription information. IMS Health; 2010.

35. Corsini A**.** Statin-related muscle complaints: an underestimated risk. Cardiovasc Drugs Ther. 2005;19(6):379-81.

36. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B**.** Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther. 2005;19(6):403-14.

37. Wierzbicki AS**.** Fibrates: no ACCORD on their use in the treatment of dyslipidaemia. Curr Opin Lipidol. 2010;21(4):352-8.

38. Shek A, Ferril MJ**.** Statin-fibrate combination therapy. Ann Pharmacother. 2001;35:908-17.

39. Williams TM, Harken AH**.** Statins for surgical patients. Ann Surg. 2008;247(1):30-7.

40. Rosner MH, Okusa MD**.** Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol. 2006;1(1):19-32.

41. Argalious M, Xu M, Sun Z, Smedira N, Koch CG**.** Preoperative statin therapy is not associated with a reduced incidence of postoperative acute kidney injury after cardiac surgery. Anesth Analg. 2010;111(2):324-30.

42. Beattie WS, Wijeysundera DN**.** Statins and the "healthy user bias" in cardiac surgery. Anesth Analg. 2010;111(2):261-3.

43. Zhang T, Shen LH, Hu LH, He B**.** Statins for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Am J Nephrol. 2011;33(4):344-51.

44. Dormuth CR, Patrick AR, Shrank WH, Wright JM, Glynn RJ, Sutherland J, et al. Statin adherence and risk of accidents: a cautionary tale. Circulation. 2009;119(15):2051-7.

45. D C**.** Acute kidney injury: current perspectives. Postgraduate Medicine. 2010;122(6):29-40.

46. Gunaratnam L, Bonventre JV**.** Pathophysiology of acute kidney injury. In: Greenberg A, Cheung AK, Coffman TM, Falk RJ, Jennette JC, eds. Primer on Kidney Diseases. 5th ed; 2009:270-6.

47. Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS**.** Community-based incidence of acute renal failure. Kidney Int. 2007;72(2):208-12.

48. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol. 2006;17(4):1135-42.

49. Omar MA, Wilson JP, Cox TS**.** Rhabdomyolysis and HMG-CoA reductase inhibitors. Annals of Pharmacotherapy. 2001;15:1096-107.

50. Waikar SS, Liu KD, Chertow GM**.** Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol. 2008;3(3):844-61.

51. Van Berendoncks AM, Elseviers MM, Lins RL**.** Outcome of acute kidney injury with different treatment options: long-term follow-up. Clin J Am Soc Nephrol. 2010;5(10):1755-62.

52. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK**.** Acute kidney injury: a springboard for progression in chronic kidney disease. Am J Physiol Renal Physiol. 2010.

53. Holley JL**.** Clinical approach to the diagnosis of acute renal failure. In: Greenberg A, ed. Primer on Kidney Diseases. 5 ed. Philadelphia, PA: Saunders Elsevier; 2009:277-83.

54. Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol. 2004;57(7):728-34.

55. Olyaei A, Greer E, Delos Santos R, Rueda J**.** The efficacy and safety of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors in chronic kidney disease, dialysis, and transplant patients. Clin J Am Soc Nephrol. 2011;6(3):664-78.

56. Kasiske BL, Wanner C, O'Neill WC**.** An assessment of statin safety by nephrologists. Am J Cardiol. 2006;97(8A):82C-5C.

57. McKenney JM, Davidson MH, Jacobson TA, Guyton JR**.** Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97(8A):89C-94C.

58. Gray J, Edwards SJ, Lip GY**.** Comparison of sequential rosuvastatin doses in hypercholesterolaemia: a meta-analysis of randomised controlled trials. Curr Med Res Opin. 2010;26(3):537-47.

59. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292(21):2585-90.

60. Omar MA, Wilson JP**.** FDA adverse event reports on statin-associated rhabdomyolysis. Annals of Pharmacotherapy. 2002;36:288-95.

61. Kaufman DW. Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States: The Slone Survey. JAMA: The Journal of the American Medical Association. 2002;287(3):337-44.

62. Kasper JD, Giovannini TA, Hoffman C. Gaining and losing health insurance: strengthening the evidence for effects on access to care and health outcomes. Med Care Res Rev. 2000;57(3):298-318; discussion 9-25.

63. Hansen LG, Chang S. Health research data for the real world: the Thomson Reuters MarketScan databases. Thomson Reuters; 2011.

64. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37.

65. ICD-9-CM Official guidelines for coding and reporting. Centers for Disease Control and Prevention; 2011.

66. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204-12.

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

68. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007;7(10):658-66.

69. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. 2007;166(3):348-54.

70. Schneeweiss S, Patrick AR, Sturmer T, Brookhart MA, Avorn J, Maclure M, et al. Increasing levels of restriction pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Med Care. 2007;45:S131-S42.

71. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology. 2003;158(9):915-20.

72. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology. 2001;12(6):682-9.

73. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med. 2003;163:553-64.

74. Hedenmalm K, Alvan G, Ohagen P, Dahl ML. Muscle toxicity with statins. Pharmacoepidemiol Drug Saf. 2010;19(3):223-31.

75. McAfee AT, Ming EE, Seeger JD, Quinn SG, Ng EW, Danielson JD, et al. The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48,000 initiators of statin therapy. Pharmacoepidemiol Drug Saf. 2006;15(7):444-53.

76. Goettsch WG, Heintjes EM, Kastelein JJ, Rabelink TJ, Johansson S, Herings RM**.** Results from a rosuvastatin historical cohort study in more than 45,000 Dutch statin users, a PHARMO study. Pharmacoepidemiol Drug Saf. 2006;15(7):435-43.

77. Garcia Rodriguez LA, Herings R, Johansson S**.** Use of multiple international healthcare databases for the detection of rare drug-associated outcomes: a pharmacoepidemiological programme comparing rosuvastatin with other marketed statins. Pharmacoepidemiol Drug Saf. 2010;19(12):1218-24.

78. Garcia-Rodriguez LA, Gonzalez-Perez A, Stang MR, Wallander MA, Johansson S**.** The safety of rosuvastatin in comparison with other statins in over 25,000 statin users in the Saskatchewan Health Databases. Pharmacoepidemiol Drug Saf. 2008;17(10):953-61.

79. Waikar SS, Wald R, Chertow GM, Curhan GC, Winkelmayer WC, Liangos O, et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. J Am Soc Nephrol. 2006;17(6):1688-94.

80. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT**.** Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983;74(2):243-8.

81. Winterstein AG, Weiner ID, Johns TE, Hatton RC**.** Validation of automated database algorithms to identify hospital-acquired acute renal failure. Value Health. 2004;7:PUK13.

82. Daniels SR, Gidding SS, de Ferranti SD**.** Pediatric aspects of familial hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S30-7.

83. Moride Y, Abenhaim L**.** Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol. 1994;47(7):731-7.

84. Weiss NS**.** Clinical epidemiology. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology. 3 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:641-51.

85. Glymour MM, Greenland S**.** Causal Diagrams. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology. 3rd ed. New York: Lippincott Williams & Wilkins; 2008:183-209.

86. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431-43.

87. Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006;113(19):2363-72.

88. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-

elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation. 2007;116(7):e148-304.

89. Patrick AR, Schneeweiss S, Brookhart MA, Glynn RJ, Rothman KJ, Avorn J, et al. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. Pharmacoepidemiol Drug Saf. 2011;20(6):551-9.

90. Rothman KJ, Greenland S, Lash TL**.** Validity in Epidemiologic Studies. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology. 3rd ed. Baltimore: Lippincott Williams & Wilkins; 2008:128-67.

91. Patrick AR, Shrank WH, Glynn RJ, Solomon DH, Dormuth CR, Avorn J, et al. The association between statin use and outcomes potentially attributable to an unhealthy lifestyle in older adults. Value Health. 2011;14(4):513-20.

92. Simpson RJ, Jr., Mendys P**.** The effects of adherence and persistence on clinical outcomes in patients treated with statins: a systematic review. J Clin Lipidol. 2010;4(6):462-71.

93. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT**.** Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med. 1998;128(3):194-203.

94. Coleman MD, Shaefi S, Sladen RN**.** Preventing acute kidney injury after cardiac surgery. Curr Opin Anaesthesiol. 2011;24(1):70-6.

95. Coca SG, Singanamala S, Parikh CR**.** Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442-8.

96. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med. 2011;171(3):226-33.

97. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20(1):223-8.

98. Li SY, Chen JY, Yang WC, Chuang CL**.** Acute kidney injury network classification predicts in-hospital and long-term mortality in patients undergoing elective coronary artery bypass grafting surgery. Eur J Cardiothorac Surg. 2011;39(3):323-8.

99. Le Manach Y, Ibanez Esteves C, Bertrand M, Goarin JP, Fleron MH, Coriat P, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing vascular surgery. Anesthesiology. 2011;114(1):98-104.

100. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV**.** Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol. 2006;47(2):332-7.

101. Albert MA, Danielson E, Rifai N, Ridker PM**.** Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA. 2001;286(1):64-70.

102. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med. 2005;352(1):20-8.

103. Giusti-Paiva A, Martinez MR, Felix JV, da Rocha MJ, Carnio EC, Elias LL, et al. Simvastatin decreases nitric oxide overproduction and reverts the impaired vascular responsiveness induced by endotoxic shock in rats. Shock. 2004;21(3):271-5.

104. Mithani S, Kuskowski M, Slinin Y, Ishani A, McFalls E, Adabag S**.** Dose-dependent effect of statins on the incidence of acute kidney injury after cardiac surgery. Ann Thorac Surg. 2011;91(2):520-5.

105. Waikar SS, Brunelli SM**.** Peri-surgical statins lessen acute kidney injury. J Am Soc Nephrol. 2011;22(5):797-9.

106. Zou G**.** A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.

107. Cole SR, Hernan MA**.** Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656-64.

108. Sturmer T, Rothman KJ, Avorn J, Glynn RJ**.** Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. Am J Epidemiol. 2010;172(7):843-54.

109. Parsons LS**.** Reducing bias in a propensity score matched-pair sample using greedy matching techniques. 2001. SAS Institute Inc.: 214-26.

110. Brookhart MA, Patrick AR, Shrank WH, Dormuth CR**.** Validating studies of adherence through the use of control outcomes and exposures. Am J Hypertens. 2010;23(2):110.

111. Rothman KJ, Poole C**.** A strengthening programme for weak associations. Int J Epidemiol. 1988;17(4):955-9.

112. Kor DJ, Brown MJ, Iscimen R, Brown DR, Whalen FX, Roy TK, et al. Perioperative statin therapy and renal outcomes after major vascular surgery: a propensity-based analysis. J Cardiothorac Vasc Anesth. 2008;22(2):210-6.

113. Vlasschaert ME, Bejaimal SA, Hackam DG, Quinn R, Cuerden MS, Oliver MJ, et al. Validity of administrative database coding for kidney disease: a systematic review. Am J Kidney Dis. 2011;57(1):29-43.

114. Chubak J, Pocobelli G, Weiss NS**.** Tradeoffs between accuracy measures for electronic health care data algorithms. J Clin Epidemiol. 2012;65(3):343-9 e2.

115. Greenland S, Lash TL**.** Bias analysis. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology. 3rd edition ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

116. Haslinger-Loffler B**.** Multiple effects of HMG-CoA reductase inhibitors (statins) besides their lipid-lowering function. Kidney Int. 2008;74(5):553-5.

117. Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, Hemmelgarn B, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. CMAJ. 2011;183(16):E1189-202.

118. Ahn SC**.** Neuromuscular complications of statins. Phys Med Rehabil Clin N Am. 2008;19(1):47-59, vi.

119. Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, et al. Statin safety: an assessment using an administrative claims database. Am J Cardiol. 2006;97(8A):61C-8C.

120. Westreich D, Cole SR, Funk MJ, Brookhart MA, Stürmer T**.** The role of the c-statistic in variable selection for propensity score models. Pharmacoepidemiol Drug Saf. 2011;20(3):317-20.

121. Glynn RJ, Schneeweiss S, Sturmer T**.** Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol. 2006;98(3):253-9.

122. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol. 2006;163(3):262-70.

123. Backes JM, Howard PA, Ruisinger JF, Moriarty PM**.** Does simvastatin cause more myotoxicity compared with other statins? Ann Pharmacother. 2009;43(12):2012-20.

124. Administration USFaD**.** FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Rockville, MD; 2011.