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Clinical Importance of the Drug interaction Between Statins and CYP3A4 Inhibitors

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Abstract
Statins reduce the risk of major coronary outcomes and all cause mortality. They are generally well tolerated, but are associated with uncommon but serious adverse events. Pharmacokinetic studies show statins metabolized by the CYP3A4 isoenzyme (statin 3A4 substrates) are susceptible to drug interactions when concomitantly administered with drugs that inhibit the CYP3A4 isoenzyme (CYP3A4 inhibitors) - potentially increasing the risk for adverse events. Studies to evaluate the clinical importance of the statin-CYP3A4 inhibitor interaction are limited to anecdotal findings. This research endeavored to evaluate the clinical importance of the statin-CYP3A4 inhibitor drug interaction in two empiric investigations and a methodologic study.

The preliminary empiric study was an analysis of spontaneous rhabdomyolysis reports. It showed an increased rhabdomyolysis reporting rate for simvastatin (a statin 3A4 substrate) but not for pravastatin (a statin non-3A4 substrate) with a concomitant CYP3A4 inhibitor. Substantial internal validity limitations, inherent in spontaneous reporting analyses, warranted additional research.

To further assess the clinical importance of this drug interaction, we evaluated the validity of the multinomial propensity score as a confounding adjustment method in a simulated drug interaction study. The results from the simulation study provided support for using the multinomial propensity score in the second empiric study. The results showed the multinomial propensity score reduced bias, had greater coverage probability, and increased precision compared to binary propensity score methods. Investigators studying multinomial exposures, such as drug interactions, should consider the multinomial propensity score for confounding adjustment.

The second empiric study was a large retrospective cohort study. The objective was to evaluate the hazard of muscle toxicity, renal dysfunction, and hepatic dysfunction among patients exposed to statin 3A4 substrates (atorvastatin and simvastatin) compared to statin non-3A4 substrates (fluvastatin, pravastatin, and rosuvastatin) with and without CYP3A4 inhibitor concomitancy. We found no overall increased hazard of muscle toxicity, renal dysfunction, or hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with versus without a concomitant CYP3A4 inhibitor. Given the magnitude and validity of this investigation, the drug interaction between statins and CYP3A4 inhibitors therefore does not represent a substantial public health concern.

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CLINICAL IMPORTANCE OF THE DRUG INTERACTION BETWEEN STATINS AND CYP3A4 INHIBITORS

Christopher G. Rowan

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ABSTRACT

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Statins reduce the risk of major coronary outcomes and all cause mortality. They are generally well tolerated, but are associated with uncommon but serious adverse events. Pharmacokinetic studies show statins metabolized by the CYP3A4 isoenzyme (statin 3A4 substrates) are susceptible to drug interactions when concomitantly administered with drugs that inhibit the CYP3A4 isoenzyme (CYP3A4 inhibitors) - potentially increasing the risk for adverse events. Studies to evaluate the clinical importance of the statin-CYP3A4 inhibitor interaction are limited to anecdotal findings. This research endeavored to evaluate the clinical importance of the statin-CYP3A4 inhibitor drug interaction in two empiric investigations and a methodologic study.

The preliminary empiric study was an analysis of spontaneous rhabdomyolysis reports. It showed an increased rhabdomyolysis reporting rate for simvastatin (a statin 3A4 substrate) but not for pravastatin (a statin non-3A4 substrate) with a concomitant CYP3A4 inhibitor. Substantial internal validity limitations, inherent in spontaneous reporting analyses, warranted additional research.

To further assess the clinical importance of this drug interaction, we evaluated the validity of the multinomial propensity score as a confounding adjustment method in a simulated drug interaction study. The results from the simulation study provided support for using the multinomial propensity score in the second empiric study. The results showed the multinomial propensity score reduced bias, had greater coverage probability, and increased precision compared to binary propensity score methods. Investigators studying multinomial exposures, such as drug interactions, should consider the multinomial propensity score for confounding adjustment.

The second empiric study was a large retrospective cohort study. The objective was to evaluate the hazard of muscle toxicity, renal dysfunction, and hepatic dysfunction among patients exposed to statin 3A4 substrates (atorvastatin and simvastatin) compared to statin non-3A4

substrates (fluvastatin, pravastatin, and rosuvastatin) with and without CYP3A4 inhibitor concomitancy. We found no overall increased hazard of muscle toxicity, renal dysfunction, or hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with versus without a concomitant CYP3A4 inhibitor. Given the magnitude and validity of this investigation, the drug interaction between statins and CYP3A4 inhibitors therefore does not represent a substantial public health concern.

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DISSERTATION INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are extremely effective in the treatment of dyslipidemia. They have been shown to reduce the risk of major coronary outcomes and all cause mortality.[1, 2] While statins are well tolerated by the vast majority of patients, they are associated with infrequent muscle, renal, and hepatic adverse events.[3-9] Statin associated muscle and renal toxicity occur on a continuum from minor myalgias and proteinuria to severe myositis, renal failure, and fatal rhabdomyolysis.[10-12] Statin associated hepatic toxicity is characterized by transaminitis and rarely serious hepatic dysfunction or hepatic failure.[13, 14] Clinical trials, case reports, and observational studies show these adverse events are associated with all marketed statins.[9, 15-17] While the incidence of serious statin adverse events is low, muscle toxicity is a leading cause of statin discontinuation - particularly among patients treated with high-potency statin therapy.[18, 19] It has been shown that statin-related adverse events occur in a dose dependent manner. It has been hypothesized that they may be exacerbated by pharmacokinetic (PK) statin-drug interactions that increase statin system exposure.[8, 15, 20 17, 21 22-25]

However, not all statins have the same drug interaction potential. The unique physiochemical property of each statin makes certain statins more likely to interact with concomitant medications. Of particular importance is the drug interaction between statins and drugs that inhibit the CYP3A4 metabolic pathway. The CYP3A4 isoenzyme is the most prevalent isoenzyme in the cytochrome P450 enzyme system. The CYP3A4 isoenzyme metabolizes more than 50% of all marketed pharmaceuticals.[26] Statins that undergo phase I metabolism by the CYP3A4 isoenzyme are referred to as statin 3A4 substrates. Statins that do no use the CYP3A4 isoenzyme metabolic pathway are referred to as statin non-3A4 substrates. This investigation focuses on statin phase I metabolic inhibition, specifically the clinical importance of the drug interaction between statins and concomitant drugs which inhibit the CYP3A4 isoenzyme (CYP3A4 inhibitors). CYP3A4 inhibitors prevent CYP3A4 isoenzymes from metabolizing other drugs (e.g., statin 3A4 substrates). As serious statin adverse events are potency and plasma concentration related, it is recognized that plasma levels of statins 3A4 substrates may increase

with concomitant administered of CYP3A4 inhibitors.[27] Currently marketed pharmaceuticals that are CYP3A4 inhibitors are commonly used. They include calcium channel blockers, H2 receptor antagonists, antibiotics, antifungals, antidepressants, antiretrovirals, and immunosuppresants.[28]

The purpose of this investigation is to study the clinical importance of the drug interaction between statins and CYP3A4 inhibitors. Given the physiochemical properties, drug interaction potential, and prior research, we hypothesized an increased relative hazard for statin 3A4 substrates compared to statin non-3A4 substrates with CYP3A4 inhibitor concomitancy. Studies to quantify the hazard of statin-related adverse events for different statins (with different metabolism) with CYP3A4 inhibitor concomitancy have not been conducted.

We conducted two empiric investigations and a methodologic study to evaluate the clinical importance of the drug interaction between statins and CYP3A4 inhibitors. The first empiric study uses spontaneous reports of rhabdomyolysis associated with simvastatin and pravastatin to determine if the CYP3A4 mediated drug interaction results in a selective increase in rhabdomyolysis reporting rates based on different statin metabolic pathways. Given the aforementioned physiochemical characteristics of each statin, we hypothesize an increased risk for simvastatin, but not for pravastatin, with CYP3A4 inhibitor concomitancy. The project title is: Clinical importance of the drug interaction between statins and CYP3A inhibitors - analysis of spontaneous reports of rhabdomyolysis. Its specific aim is: to determine if the CYP3A4 mediated drug interaction results in a selective increase in spontaneous rhabdomyolysis reporting rates based on different statin metabolic pathways. The study's hypothesis is: because of the potential increased statin exposure when a statin 3A4 substrate is concomitantly prescribed with a 3A4 inhibitor, there will be greater spontaneous rhabdomyolysis reporting compared to patients concomitantly prescribed a statin non-3A4 substrate and a 3A4 inhibitor.

The methodologic study is a simulation study to evaluate propensity score methods in the setting of a drug-drug interaction study. In drug-drug interaction studies, such as with aforementioned empiric studies of statins and CYP3A4 inhibitors, there may be more than two non-ordered exposure categories. No applied methodologic research using simulations to evaluate different propensity score methods in multiple, non-ordered exposure categories have

been published. This study evaluated relative bias and coverage probability associated with different binary and multinomial propensity score methods. Researchers studying drug interactions may find this research informative to guide their confounding adjustment method. By evaluating each propensity score method under different scenarios, we intended to provide drug-drug interaction researchers with a broadly applicable tool that will guide their choice of PS method. Specifically, the title is: A comparison of multinomial and binary propensity score methods in a drug-drug interaction study. Its specific aim is to use Monte Carlo simulation to compare bias, precision, and coverage probability of multinomial and multiple binary propensity score methods in the setting of drug-drug interaction studies. The study's hypothesis is: the multinomial propensity score will reduce bias, increase precision, and have better empiric coverage than multiple different binary propensity score methods.

The second empiric study endeavors to evaluate the clinical importance of the drug interaction between statins and CYP3A4 inhibitors in a large retrospective cohort study using a validated electronic medical record database. In three separate cohort studies, we evaluated the relative hazard of (i) muscle toxicity, (ii) kidney dysfunction, and (iii) hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with CYP3A4 inhibitor concomitancy. The project title is: Clinical importance of the drug interaction between statins and CYP3A4 inhibitors - THIN Cohort study. Its specific aim is: to compare the relative hazard of muscle toxicity, kidney dysfunction, and hepatic dysfunction following concomitant therapy with a: [statin CYP3A4 substrate plus a CYP3A4 inhibitor] vs. [statin non-CYP3A4 substrate plus a CYP3A4 inhibitor]. The study's hypothesis is: because of the potential increased statin exposure when a statin CYP3A4 substrate is concomitantly prescribed with a CYP3A4 inhibitor, there will be greater relative hazard of muscle toxicity, renal dysfunction, and hepatic dysfunction compared to patients concomitantly prescribed a statin non-CYP3A4 substrate and a CYP3A4 inhibitor.

PROJECT 1: CLINICAL IMPORTANCE OF THE DRUG INTERACTION BETWEEN STATINS AND CYP3A4 INHIBITORS - ANALYSIS OF SPONTANEOUS REPORTS OF RHABDOMYOLYSIS (AERS)

Title of the paper: Rhabdomyolysis reports show interaction between simvastatin and CYP3A4 inhibitors

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Five key points:
1. We studied spontaneous reports of rhabdomyolysis associated simvastatin, a CYP3A4 substrate, and pravastatin, a non-CYP3A4 substrate, for evidence of CYP3A4 interaction.
2. We found 3 out of 25 pravastatin reports and 56 out of 118 simvastatin reports were associated with a concomitant CYP3A4 inhibitor
3. Fifteen percent of pravastatin and 12.5 percent of simvastatin prescriptions were concomitantly prescribed with a CYP3A inhibitor.
4. The adverse event reporting rate ratios for rhabdomyolysis (statin w/CYP3A4 inhibitor vs. statin w/o CYP3A4 inhibitor) were 0.77 and 6.34 for pravastatin and simvastatin respectively.
5. The comparison of reporting rate ratios (simvastatin/pravastatin) suggests effect modification by CYP3A4 inhibitor as predicted in FDA approved labeling for simvastatin.

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Disclaimer: The views expressed are those of the authors and do not necessarily represent those of the Food and Drug Administration or imply its endorsement.

ABSTRACT

Purpose: To assess spontaneous reports of rhabdomyolysis associated with simvastatin and pravastatin for evidence of concomitant CYP3A4 inhibitor interaction. Clinical trial results advocate for the use of cholesterol lowering in high-risk patients including diabetics and the elderly. Given the association between advancing age, metabolic, and cardiovascular disease, many patients are treated with concomitant medications upon statin initiation. Although statins are generally safe, minor and severe adverse reactions arise, especially when given to patients taking concomitant medications that inhibit the statin clearance and lead to increased statin plasma concentration.

Methods: We conducted a comparative case series of rhabdomyolysis reports associated with simvastatin and pravastatin. Domestic spontaneous reports were obtained from the FDA's Adverse Event Reporting System (AERS). Drug utilization data were obtained from IMS HEALTH and the National Ambulatory Medical Care Survey (NAMCS). Adverse event reporting rates (AER) and ratios (AERR) of rhabdomyolysis associated with simvastatin and pravastatin - stratified the presence and absence of a concomitant CYP3A4 inhibitor concomitancy were determined.

Results: Stratification by CYP3A4 inhibitor concomitancy did not change the rhabdomyolysis AER for pravastatin with versus without a CYP3A4 inhibitor (2.4 cases and 3.1 cases per 10 million Rx, respectively). However, stratification of simvastatin reports with versus without a concomitant CYP3A4 inhibitor resulted in a rhabdomyolysis AER of 38.4 and 6.0 cases per 10 million Rx. The corresponding AERR with versus without a CYP3A4 inhibitor was 0.77 for pravastatin and 6.43 for simvastatin.

Conclusions:

Spontaneous adverse event reports provide evidence of increased risk for rhabdomyolysis based on the interaction between simvastatin and selected CYP3A4 inhibitors.

INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are extremely effective in the treatment of dyslipidemias.[29, 30] They are well tolerated by the vast majority of patients, but are infrequently associated with muscle related toxicity. Statin associated muscle toxicity occurs on a continuum from minor myalgias to potentially fatal rhabdomyolysis.[10] Though rare, rhabdomyolysis has been reportedly associated with all currently marketed statins. Postmarketing reports of rhabdomyolysis resulted in the suspension of cerivastatin marketing, likely due to a drug-drug interaction.[23] However, because statins have variable physiochemical properties, certain statins may be more or less likely to interact with concomitant medications.

Due to high affinity and selectivity for the HMG-CoA reductase enzyme, statins have little potential to alter the pharmacokinetics of other drugs.[31] However, the unique pharmacokinetic (PK) characteristics of each statin may substantially impact their susceptibility to be modified by concomitant medications.[27] The PK differences between statins include: solubility, phase I and II metabolism, utilization of hepatic transporters, formation of active metabolites, bioavailability, protein binding, and excretion. Importantly, simvastatin (SV) and lovastatin (LV) are administered as lactone pro-drugs while the other statins are administered as β-hydroxy acids. SV and LV lactone undergo hydrolysis in the plasma, intestinal mucosa, and liver to form active β-hydroxy acids.[32-36] One PK characteristic shared by all statins is extensive first pass hepatic extraction.

Hepatic extraction occurs by two primary mechanisms - active transport and passive diffusion. Organic anion transporting polypeptide (OATP) is the primary membrane protein which actively transports hydrophilic statins pravastatin (PV) and rosuvastatin (RV) from portal circulation into the hepatocyte (influx). The lipophilic statins atorvastatin (AV), CV, fluvastatin (FV), LV, and SV enter mainly by passive diffusion; however, the acid forms of these statins also utilize active transport mechanisms.[27, 37-40]

Following entry into the hepatocyte each statin undergoes a unique cascade of metabolic and non-metabolic processes which ultimately results in cholesterol biosynthesis inhibition and statin elimination. The metabolic processes include phase I oxidation (mediated by cytochrome P450 (CYP) isoenzymes) and phase II glucuronidation (mediated by UDP glucuronosyl

transferase (UGT)). The CYP isoenzymes responsible for phase I statin metabolism are 3A4, 2C8, 2C9, and 2C19. Atorvastatin, LV, and SV are oxidized by the CYP3A4 isoenzyme to form both active and inactive metabolites.[41, 42] Cerivastatin (CV) is oxidized by CYP2C8 and to a lesser extent CYP3A4.[43] Fluvastatin (FV) is oxidized by CYP2C9.[39, 43] Pravastatin (PV) has no phase I metabolism and is minimally metabolized by phase II glucuronidation. Rosuvastatin (RV) also has negligible phase I metabolism (by CYP2C9 and CYP2C19) and is primarily eliminated as the unchanged parent compound.[36, 44]

Following hepatocyte entry and metabolism (phase I and II), statins exert their cholesterol inhibitory effect and are subsequently eliminated. However, a varying proportion of statin reaches systemic circulation, by efflux transport and passive diffusion.[27, 37, 38] The efflux transport proteins: P-glycoprotein (P-gp) and multidrug resistance associated protein 2 (MRP2), are believed to affect the disposition, bioavailability and elimination of all statins - primarily in the acid form.[45] For most statins, elimination occurs through biliary excretion, PV is partially eliminated by renal excretion. Inhibition of statin metabolism (phase I or II) and/or active membrane transporters (influx or efflux) may result in elevated plasma concentrations and has the potential to increase the risk for statin-related adverse events.

Gemfibrozil (GEM) and cyclosporine (CSA) have been shown to interact with statins via both metabolic and hepatic transport pathways. Shitara et al showed the drug interaction between GEM and CV occurred via GEM inhibiting CV hepatic uptake (via OATP) and oxidation (via CYP2C8).[46] Similarly, CSA has been shown to inhibit hepatic uptake (OATP), efflux transporters (P-gp and MRP2), and oxidation (via CYP3A4).[47] Olbricht et al showed a 5 and 20 fold increase in area under the curve (AUC) for PV and LV respectively in kidney transplant patients treated with CSA.[48] Given PV is not a CYP3A4 substrate, the increased AUC is the likely result of transporter mediated inhibition.

This investigation focuses on statin phase I metabolic inhibition, specifically the drug interaction between statins and concomitant drugs which inhibit CYP3A4 mediated metabolism (CYP3A4 inhibitors). As serious statin adverse events are dose and plasma concentration related, it is recognized that plasma levels of statins oxidized by the CYP3A4 isoenzyme may

increase when these statins are concomitantly administered with CYP3A4 inhibitors.[41, 49, 50] Many commonly used pharmaceuticals are CYP3A4 inhibitors.[28] Some of the drug classes that include CYP3A4 inhibitors are calcium channel blockers, antibiotics, antifungals, antidepressants, anitretrovirals, and immunosuppresants.[28]

The CYP3A4 isoenzyme metabolizes more than 50% of marketed drugs.[26] A recent investigation showed 25% of new statin initiators received a concomitant CYP3A4 inhibitor in the first year of statin therapy.[51] Case reports, risk-factor models, and clinical trials have shown concomitant administration of statins and CYP3A4 inhibitors may increase the risk for rhabdomyolysis.[52-54] Because of the potential increased risk, some statin product labels warn against concomitant administration with CYP3A4 inhibitors.

To study the clinical impact of this association we studied two statins with different Phase I metabolism, but similar hepatic transport mechanisms. SV (a CYP3A4 substrate) was chosen as the object drug and PV (a non-CYP3A4 substrate) as the comparator object drug. While the phase I metabolic pathways for SV and PV are different, both statins should be similarly impacted by influx and efflux hepatic transporters (via OATP, P-gp, and MRP2).[55, 56] Based on published reports by Hsiang[37] and Chen[45] et al, it is believed that hepatic transport (influx and efflux) of SV acid and PV are equally involved. Any transporter inhibition, due to co-administration of a CYP3A4 inhibitor (e.g., CSA), should impact transporter mediated shunting of SV acid and PV similarly.

Studies to quantify the hazard of rhabdomyolysis for different statins (with different metabolism) with CYP3A4 inhibitor concomitancy have not been conducted. The purpose of this investigation is to study spontaneous reports of rhabdomyolysis associated with SV and PV to determine if the CYP3A4 mediated drug interaction results in a selective increase in rhabdomyolysis reporting rates based on different statin metabolic pathways. Given the aforementioned physiochemical characteristics of each statin, we hypothesize an increased risk for SV, but not for PV, with CYP3A4 inhibitor concomitancy.

METHODS

We conducted a comparative case series of spontaneous reports of rhabdomyolysis associated with PV and SV to assess interaction with selected CYP3A4 inhibitors. To control for population exposure to each statin, we used the estimated total number of PV and SV prescriptions as denominators for each case group.

Case source: This analysis was conducted at the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). Cases consisted of domestic (U.S.) spontaneous adverse event reports of rhabdomyolysis associated with PV and SV. These reports were submitted to the FDA by pharmaceutical manufacturers or health care professionals through the MedWatch program. MedWatch reports are archived in CDER's Adverse Events Reporting System (AERS) database and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). A concise review of the history and treatment of adverse drug event reports at CDER, including epidemiological inference, has been reported seaparately.[57]

Case definition:

Spontaneous reports of rhabdomyolysis associated with PV and SV were obtained from the AERS database. We acquired all cases of rhabdomyolysis associated with these two agents from market launch (November 1991 for PV; January 1992 for SV) through July 2001. The cut-off date of July 2001 was selected to limit the effect of stimulated rhabdomyolysis reporting following the suspension of cerivastatin marketing in August 2001. Reports were selected using the MedDRA terms rhabdomyolysis, myopathy, or myalgia with further restriction for rhabdomyolysis that required hospitalization. After identification of putative cases, all reports were manually reviewed by the authors (C.R., A.B.).

A case of rhabdomyolysis was defined as a patient with a health care professional (HCP) diagnosis of rhabdomyolysis or a HCP diagnosis of myositis or myopathy with a creatine phosphokinase (CPK) > 10,000 IU/L. Exclusion criteria included non-U.S. reports, non-HCP reports, duplicate reports, "hearsay" reports, published reports, and cases with a history of: non-statin-related rhabdomyolysis, myositis, dermatomyositis, renal transplantation, or HIV infection / treatment. In order to reduce confounding by concomitant statin-fibrate exposure, reports listing

concurrent use of gemfibrozil (GEM) were excluded from the primary analysis, but were included in a secondary analysis.

Case exposure definition:

Each report was carefully reviewed for specific mention of recent administration of PV or SV and a concomitant CYP3A4 inhibitor. We further verified the temporality of the statin without a CYP3A4 inhibitor or the statin-CYP3A4 inhibitor concomitancy to the event date. We required both the statin and the CYP3A4 inhibitor to be listed (within 30 days of each other) in either the concomitant medications section or specific mention of a concomitant (statin-CYP3A4 inhibitor) therapy in the report narrative. Additionally, we required documentation of the statin-CYP3A4 inhibitor concomitancy to be no more than 30 days prior to the event date or specific mention of close temporal association between concomitant exposure and the event in the narrative.

The CYP3A4 inhibitors chosen for this investigation were: cyclosporine, clarithromycin, erythromycin, diltiazem, verapamil, mibefradil, itraconazole, ketoconazole, fluconazole, nefazodone, and fluvoxamine. Despite our attempt to study CYP3A4 inhibitors known for potent and selective CYP3A4 inhibition, some of the selected CYP3A4 inhibitors also inhibit other metabolic and uptake transport pathways.

Population exposure source:

Drug utilization data were acquired for the purpose of estimating total U.S. exposure to PV and SV with and without a CYP3A4 inhibitor during the study period (denominator data). These data were acquired from two different sources - IMS HEALTH National Prescription Audit Plus (NPA Plus) and the NAMCS. NPA Plus data were used to estimate the total number PV and SV prescriptions dispensed in the United States from November 1991 through July 2001.[15] The concomitant statin-CYP3A4 inhibitor frequency was determined using the National Ambulatory Medical Care Survey (NAMCS).

NAMCS is a national probability sample survey of office-based physicians conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. Statistics derived from NAMCS are representative of all ambulatory care visits to physicians engaged in non-federal, office-based health care. Participating physicians agree to systematic sampling and

review (via chart abstraction) of patient visits during a randomly selected week of the year. For the sampled visits, the physician provides details of specific patient information including patient demographics, reason for the visit, up to three medical diagnoses, treatments, and disposition. New and continued prescriptions are recorded as well as other treatments and recommendations. Data gathered from this survey are transcribed into standard international classification of diseases (ICD-9) nomenclature. Concomitancy data for PV and SV with a CYP3A4 inhibitor were collected from NAMCS during the time period 1993-2001. NAMCS is a practical source to estimate statin-CYP3A4 concomitancy, although it may not be representative of the overall United States concomitant frequency distribution.

In order to calculate the number of statin prescriptions with a concomitant CYP3A4 inhibitor, we multiplied the total number of PV and SV prescriptions by the concomitant frequency proportion for PV and SV with a CYP3A4 inhibitor. The remainder of each calculation is the total number of PV and SV prescriptions without a CYP3A4 inhibitor.

Measures of effect:

The adverse event reporting rate (AER), measured as number of cases per 10 million prescriptions, will be calculated using the actual number of cases of rhabdomyolysis associated with either PV or SV (as the numerator) and the estimated population exposure as the denominator. The adverse event reporting rate ratio (AERR) will also be calculated to reveal the relative effect for each statin with and without a concomitant CYP3A4 inhibitor.

The primary analysis consisted of calculating the rhabdomyolysis AER and AERR associated with PV and SV stratified by the presence or absence of a CYP3A4 inhibitor. Secondary analyses were conducted to evaluate the potential impact of statin dose and to compare the rhabdomyolysis AER and AERR with statin-GEM concomitancy.

RESULTS

A search of the AERS database MedWatch reports from 1991 through July 2001, recovered 73 and 321 potential cases of rhabdomyolysis associated with PV and SV respectively. Following hands-on review, 25 and118 reports, for PV and SV respectively, were classified as unique cases fitting the case definition. Demographic and clinical characteristics of these cases are shown in

Table 1. The median age for both groups was 66 years. Fifty-five percent and 44% of the reports were for female patients for PV and SV, respectively. The median dose reported was 20 mg for PV and 40 mg SV. The median reported time to onset of rhabdomyolysis was eight months for PV and 5.5 months for SV. A temporal dose increase was reported in zero out of 25 (0%) PV cases and 22 out of 118 (19%) SV cases. A switch from one statin to another statin within 60 days of the event was reported in one out of 25 (4%) PV cases and 11 out of 118 (9%) SV cases. Five (20%) PV and 25 (21%) SV treated patients reported acute renal failure or required dialysis. Four patients reportedly died from events presumably related to the adverse drug reaction (two (8%) patients treated with PV and two (2%) treated with SV).

Among the 25 PV and 118 SV associated cases, three (12%) and 56 (47%) reported a concomitant CYP3A4 inhibitor, respectively. The distribution of PV and SV cases with specific concomitant CYP3A4 inhibitor is shown in Table 2. Of interest, six cases associated with SV and one case associated with PV reported two concomitant CYP3A4 inhibitors.

Table 3 shows the SV dose analysis stratified by the presence or absence of a concomitant CYP3A4 inhibitor. Importantly, the median SV dose with and without a concomitant CYP3A4 inhibitor was equivalent (40 mg). However, the mean SV dose was higher (56 mg vs. 38mg) for cases reporting a concomitant CYP3A4 inhibitor than for cases not reporting a concomitant CYP3A4 inhibitor. A similar dose analysis for PV cases was not possible due to missing dose information among the three PV cases reporting a concomitant CYP3A4 inhibitor. A recent dose increase was reported was reported in 0 out of 25 (0%) PV cases and 23 out of 118 (19%) SV cases.

Reporting rate analysis: The NPA Plus audit produced 83,673,000 and 120,188,000 U.S. dispensed retail prescriptions for PV and SV from initial marketing.[15] The observed range of physician response for NAMCS was 63% (1999) to 73% (1993). Table 4 shows the NAMCS concomitant frequency data for selected CYP3A4 inhibitors and GEM. The proportion of mentions of PV and SV with a concomitant CYP3A4 inhibitor was 0.15 and 0.12 respectively. For use in the secondary analysis, the proportion of concomitant mentions of PV and SV with concomitant GEM was 0.0079 and 0.0149 respectively. Based on these data, we found the estimated US

population exposure for PV and SV to be approximately 83 million and 118.4 million U.S. dispensed prescriptions (without GEM concomitancy). The primary analysis will use these two numbers for calculating the AER and AERR.

Table 5a shows the unadjusted AER analysis for PV and SV. Twenty five cases of rhabdomyolysis associated with PV were identified among an estimated 83 million PV prescriptions yielding an AER of 3.0 cases per 10 million prescriptions. One hundred eighteen cases of rhabdomyolysis associated with SV among an estimated 118.4 million SV prescriptions yielding an AER of 10.0 cases per 10 million prescriptions. Without adjusting for CYP3A4 inhibitor concomitancy, the rhabdomyolysis AERR (SV/PV) was 3.3.

AERs and AERRs stratified by concomitant use of CYP3A4 inhibitors are shown in Table 5b. The AERs for PV with and without a concomitant CYP3A4 inhibitor are 2.4 and 3.1 cases per 10 million prescriptions (AERR = 0.77). The AERs for SV with and without a concomitant CYP3A4 inhibitor are 38.4 and 6.0 cases per 10 million prescriptions (AERR = 6.43). Table 5b also shows the relative effect of SV cases to PV cases. When stratified by CYP3A4 inhibitor, the relative effect (AERR) of SV/PV was 16.0 (38.4/2.4) with a concomitant CYP3A4 inhibitor and 1.9 (6.0/3.1) without a concomitant CYP3A4 inhibitor.

Tables 6a and 6b show the secondary analysis with concomitant statin and GEM. Twenty eight PV and 159 SV spontaneous reports of rhabdomyolysis met the prespecified inclusion criteria. Among these cases, 3 PV and 41 SV cases reported concomitant exposure to GEM. The crude AERs were 3.3 and 13.2 per 10 million prescriptions for PV and SV, respectively. Stratifying the PV cases by concomitant GEM gave AERs of 3 and 45 per 10 million prescriptions with and without GEM, respectively (AERR = 15). Stratifying the SV cases by concomitant GEM gave AERs of 229 and 10 cases per 10 million prescriptions with and without GEM, respectively (AERR = 23).

All results use the aggregate proportion of all CYP3A4 inhibitors with a concomitant statin (SV =0.1526, PV=0.1231). However, individual CYP3A4 inhibitor concomitancy with SV resulted in AER point estimates greater than the baseline AER (6.0 cases per 10 million SV Rxs without a CYP3A4 inhibitor) (data not shown).

DISCUSSION

This descriptive analysis of rhabdomyolysis AERs and AERRs associated with PV and SV reveals noteworthy effect modification by CYP3A4 inhibitor concomitancy for SV but not PV (Table 5b). The crude AERs and AERRs (Table 5a) for SV and PV are consistent with previous findings. Chang et al. reported a crude reporting rate ratio of 4 (SV/PV), which approximates our curde AERR of 3.3 (SV/PV).[15] Contrasting the crude AERR with the stratified AERR (by CYP3A4 inhibitor concomitancy) suggests a striking interaction consistent with the different pharmacokinetic clearance pathways for PV and SV.

In order to further explore the phase I interaction hypothesis, we conducted a secondary analysis among PV and SV reports with concomitant GEM as the interacting drug. GEM has been shown to inhibit Phase I metabolism (via primarily the CYP2C8 isoenzyme), Phase II metabolism (glucuronidation), and uptake transport (via OATP).[46] In contrast to CYP3A4 inhibitors, GEM minimally inhibits the phase I metabolic pathway for either PV or SV. Thus, we hypothesized no effect modification for PV and SV with concomitant GEM. Supporting this hypothesis, the results show that although PV-GEM and SV-GEM concomitancy is associated with elevated AERs (Table 6b), the relative effect (AERR) is seemingly non-differential between PV (AERR = 15) and SV (AERR = 23) with versus without GEM.

The statin-GEM findings provide another level of evidence to support the effect modification found in the primary analysis. While GEM exhibited interaction potential with cerivastatin plausibly through both metabolic (CYP2C8) and uptake transport (OATP) pathways, it does not possess PK characteristics that make it likely to differentially interact with PV or SV. Although both PV and SV rely on hepatic uptake transport via OATP, neither drug undergoes phase I metabolism by CYP2C8. Thus, the non-differential finding with concomitant GEM is expected and reassuring.

As shown in Table 3, stratification by statin dose provides inconclusive results for SV and PV associated rhabdomyolysis when adjusted for a concomitant CYP3A4 inhibitor. Despite skewed data with large variances, SV-associated cases have the same median dose regardless of CYP3A4 concomitancy. However, for PV cases, it is not possible to compare the impact of

increasing dose between the two strata due to missing dose information for cases reporting CYP3A4 concomitancy. Further analyses need to be conducted to fully evaluate the potential interaction by statin dose given missing and inconsistent data inherent to voluntary, spontaneous reports.

Although the findings from this study are consistent with a robust and selective interaction between SV and CYP3A4 inhibitors, the study has limitations which should be highlighted. Spontaneous AERs are believed to underestimate actual incidence rates substantially. This occurs because the adverse event must be: diagnosed, attributed to a drug, reported to the FDA or to the manufacturer, and documented with specific information in order to meet study inclusion criteria. Furthermore, the discrepancy between reporting rates and incidence rates may increase as physicians become more comfortable identifying and managing statin-related adverse drug reactions.

Other limitations involve the quality of case reports. Although the MedWatch form has changed little during the study period, the content of each case report may differ considerably from report to report. This difference is further complicated by the reporting source, e.g., pharmaceutical manufacturer or health care provider. In order to improve study precision, we excluded cases reported by non-health care providers and recorded the reporting source as a potential confounding variable. Fortunately, there was near perfect balance of reports reported to the FDA by the pharmaceutical manufacturers for SV and PV. However, this does not rule out differential protocols for managing adverse event reporting between the manufacturers.

Further limitations should be considered regarding the drug utilization estimates (the denominator used in calculating the adverse event reporting rates (AER)). This is particularly true for the proportion of concomitant CYP3A4 inhibitor therapy with PV (0.15) and SV (0.12). These concomitant frequency proportions were derived from NAMCS, a weighted and projected annual national survey of approximately 2,000 office-based physicians in the US. There may be substantial variability for infrequent events - such as infrequently used drug products. This variability is therefore increased in the assessment of coincident events, such as the concomitant use of two specific agents (e.g., a rarely used drug product in conjunction with a statin).

Furthermore, NAMCS may not capture drugs prescribed by non-NAMCS participating physicians, particularly specialists. Section 9 of the NAMCS survey requests information on "medications that were ordered, supplied, administered or continued during this visit." As this statement is subject to interpretation, one practice may record all patients medications while another may record only those ordered, supplied, administered or continued during that specific office visit. For example, if a NAMCS participating primary care physician records the statin therapy he initiated (or refilled), but does not record the antifungal therapy prescribed by a dermatologist, the concomitancy therapy is not recorded. This potential inconsistency may underestimate the true proportion of concomitant statin-CYP3A4 inhibitor therapy. Underestimating concomitancy (statin-CYP3A4 inhibitor or statin-GEM concomitancy) would overestimate the reporting rates and reporting rate ratios. To better understand the impact of a potential underestimation of the proportion of statin-CYP3A4 inhibitor concomitancy, we conducted a sensitivity analysis for different proportions of statin-CYP3A4 inhibitor concomitancy. Table 7 shows an inverse relationship between the concomitant frequency proportion and the AERs and AERRs. That is, if the concomitancy estimate is underestimated, the reporting rates and reporting rate ratios may be biased.

Conclusion

Despite these limitations, our findings are consistent with increased risk of rhabdomyolysis during concomitant use of SV, a CYP3A4 substrate statin, and a CYP3A4 inhibitor. Additionally, the results support observations regarding muscle toxicity in SV clinical trials with concomitant CYP3A4 inhibitors. Further analytic research is warranted to fully elucidate these findings.

TABLES

AERS TABLE 1

Table 1. Demographic and clinical attributes of domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin*

Case attributes	Pravastatin (n=25)	Simvastatin (n=118)
Age (years)	**n=16**	**n=102**
range	24 - 79	27-93
median	66	66
mean	61	64
Sex	**n=22**	**n=110**
female	12	48
male	10	62
unknown	3	8
Weight (lbs)	**n=5**	**n=48**
mean	171	181
median	181	173
Reported statin switch	**n=25**	**n=118**
number switched (%)	1	11
Concomitant meds	**n=14**	**n=106**
median number	5	4
standard deviation	3	3
Reaction onset (months)	**n=15**	**n=82**
range	0.2 - 33	0.1 - 90
median	8	5.5
mean	12	13
Outcome variables	**n=25**	**n=118**
hospitalized	25	118
death	2	2
CK median	12,300	19,240
CK range	1,076 - 700,000	761 - 625,333
acute renal failure or dialysis	5	25
Report characteristics	**n=25**	**n=118**
manufacturer report	17	81
report year (median)	1997	1999
report year range	1992-2001	1993-2001

* Excluding cases with concomitant gemfibrozil and gemfibrozil prescriptions

AERS TABLE 2

Table 2. Domestic spontaneous reports of rhabdomyolysis associated with simvastatin or pravastatin and concomitant CYP3A4 inhibitors

CYP3A4 inhibitor(s)	Number of simvastatin cases	Number of pravastatin cases
Statin plus 1 reported inhibitor		
clarithromycin	10	
mibefradil	10	
verapamil	8	
nefazodone	6	
cyclosporine	5	
diltiazem	5	2
itraconazole	3	
erythromycin	2	
ketoconazole	1	
Statin plus 2 reported inhibitors		
cyclosporine, diltiazem	1	1
cyclosporine, itraconazole	1	
cyclosporine, ketoconazole	1	
cyclosporine, mibefradil	1	
cyclosporine, verapamil	1	
mibefradil, verapamil	1	
Total	**56**	**3**

AERS TABLE 3

Table 3. Dose analysis for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin stratified by concomitant use of a selected CYP3A4 inhibitor

	All cases		w/ CYP3A4 inhibitor		w/o CYP3A4 inhibitor	
	SV	**PV**	**SV**	**PV**	**SV**	**PV**
Reports of rhabdomyolysis	**n=118**	**n=25**	**n=56**	**n=3**	**n=62**	**n=22**
Number reporting dose (%)	95 (80)	13 (52)	46 (82)	0	49 (79)	13 (52)
Dose range (mg)	5-160	20-40	5-160	n/a	5-80	20-40
Mean / median / sd (mg)	47 / 40 / 31	26 / 20 / 10	56 / 40 / 34	n/a	38 / 40 / 27	26 / 20 / 10
Reported taking max* statin dose (	32 (34)	4 (31)	20 (43)	n/a	12 (24)	4 (31)
Recent statin dose increase (%)	23 (19)	0 (0)	13 (23)	n/a	10 (16)	0 (0)

* Max dose refers to the maximum FDA approved dose in the United States (pravastatin = 40mg; simvastatin = 80mg)

AERS Table 4

Table 4. Proportion of concomitant mentions of pravastatin or simvastatin and selected CYP3A4 inhibitors or gemfibrozil in the National Ambulatory Care Survey (NAMCS), 1993-2001

Selected CYP3A4 inhibitors	Pravastatin	Simvastatin
clarithromycin	0.80%	0.01%
erythromycin	0.77%	0.19%
cyclosporine	0.52%	0.04%
mibefradil	0.06%	0.01%
verapamil	5.02%	3.80%
diltiazem	8.01%	7.53%
nefazodone	0.20%	0.27%
itraconazole/ketoconazole	0.28%	0.39%
Combined total	**15.26%**	**12.31%**
Fibrates		
gemfibrozil	0.79%	1.49%

AERS TABLE 5A

Table 5a. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin*			
	Pravastatin	**Simvastatin**	**AERR**
All cases			
Cases of Rhabdomyolysis	25	118	**3.3**
Rxs (1991-2001)	83,012,000	118,397,000	
AER (per 10^7 Rxs)	3.0	10.0	
* Excluding cases with concomitant gemfibrozil and gemfibrozil prescriptions			

AERS TABLE 5B

Table 5b. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin *stratified by concomitant use of a selected CYP3A4 inhibitor**			
	w/ CYP3A4 inhibitor	**w/o CYP3A4 inhibitor**	**AERR**
Pravastatin cases			
Cases of Rhabdomyolysis	3	22	**0.77**
Rxs (1991-2001)	12,668,000	70,344,000	
AER (per 10^7 Rxs)	2.4	3.1	
Simvastatin cases			
Cases of Rhabdomyolysis	56	62	**6.43**
Rxs (1991-2001)	14,575,000	103,822,000	
AER (per 10^7 Rxs)	38.4	6.0	
* Excluding cases with concomitant gemfibrozil and gemfibrozil prescriptions			

AERS TABLE 6A

Table 6a. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin**			
	Pravastatin	**Simvastatin**	**AERR**
All cases			
Cases of Rhabdomyolysis	28	159	
Rxs (1991-2001)	83,673,000	120,188,000	**4**
AER (per 10^7 Rxs)	3.3	13.2	
** Including cases with concomitant gemfibrozil and gemfibrozil prescriptions			

AERS TABLE 6B

Table 6b. Reporting rates (AER) and ratios (AERR) for domestic spontaneous reports of rhabdomyolysis associated with pravastatin and simvastatin *stratified by concomitant use of gemfibrozil***			
	w/ gemfibrozil	**w/o gemfibrozil**	**AERR**
Pravastatin cases			
Cases of Rhabdomyolysis	3	25	
Rxs (1991-2001)	661,000	83,012,000	**15**
AER (per 10^7 Rxs)	45.4	3.0	
Simvastatin cases			
Cases of Rhabdomyolysis	41	118	
Rxs (1991-2001)	1,791,000	118,397,000	**23**
AER (per 10^7 Rxs)	228.9	10.0	
** Including cases with concomitant gemfibrozil and gemfibrozil prescriptions			

AERS TABLE 7

Table 7. Sensitivity analysis of statin-CYP3A4 inhibitor concomitancy***

Number of prescriptions		Concomitant %	AER*		AERR**
w/ CYP3A4 inhibitor	w/o CYP3A4 inhibitor		w/ CYP3A4 inhibitor	w/o CYP3A4 inhibitor	
Pravastatin			**(n=3)**	**(n=22)**	
0	83,012,000	0%	-	2.7	-
4,150,600	78,861,400	5%	7.2	2.8	2.6
8,301,200	74,710,800	10%	3.6	2.9	1.2
12,667,631	70,344,369	15.26%	2.4	3.1	0.8
16,602,400	66,409,600	20%	1.8	3.3	0.5
20,753,000	62,259,000	25%	1.4	3.5	0.4
Simvastatin			**(n=56)**	**(n=62)**	
0	118,397,000	0%	-	5.2	-
5,919,850	112,477,150	5%	94.6	5.5	17.2
11,839,700	106,557,300	10%	47.3	5.8	8.1
14,574,671	103,822,329	12.31%	38.4	6.0	6.4
17,759,550	100,637,450	15%	31.5	6.2	5.1
23,679,400	94,717,600	20%	23.6	6.5	3.6
29,599,250	88,797,750	25%	18.9	7.0	2.7

* AER is the number of reports/ the number of estimated prescriptions (per 10 million prescriptions)

** AERR is calculated as the reporting rate w / a CYP3A4 inhibitor/ the reporting rate w /o a CYP3A4

*** excluding cases w ith concomitant gemfibrozil and gemfibrozil prescriptions

PROJECT 2: A COMPARISON OF MULTINOMIAL AND BINARY PROPENSITY SCORE METHODS IN A SIMULATED DRUG-DRUG INTERACTION STUDY

Title of the paper: A comparison of multinomial and binary propensity score methods in a simulated drug-drug interaction study

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ABSTRACT

Purpose: The propensity score was developed to control for differences in observed covariates for two treatment groups. In drug-drug interaction studies, there are usually more than two non-ordered exposure categories. The theoretical framework for the multinomial score was previously described. However, simulation studies to evaluate the performance characteristics of different propensity score methods in analyzing multiple, non-ordered exposure categories have not been published. This is important for empiric investigations where the presence and quantity of model misspecification is rarely known.

Methods: In a simulated drug-drug interaction study, we evaluated the statistical performance of multiple multinomial and binary propensity score approaches of confounding adjustment. Monte Carlo simulations were performed on a synthetic cohort with a binary outcome (Y), three binary exposure variables (A_1, A_2, A_3=A_1*A_2), and three covariates (X_1, X_2, X_3). We compared percent bias, coverage probability, and precision (MSE) of the interaction ratio parameter from four different binary propensity score adjusted models and the multinomial propensity score adjusted model. We also compared the relative performance of each propensity score approach to an unadjusted model (the null model) and the correctly specified multivariate model (the MV model). We evaluated statistical performance under a variety of scenarios typical of drug safety research. To achieve this, we determined baseline coefficient values for each parameter from those found in drug safety research. Holding baseline parameters constant, we varied individual parameters one at a time to assess performance characteristics under a variety of scenarios. We varied the sample size, the prevalence of exposure, the strength of association between exposure variables, the interaction between one exposure variable and a covariate, the outcome incidence, the strength of the interaction ratio, and propensity score form.

Results: The results from these drug interaction simulations show the multinomial propensity score adjusted model was the least biased, had the greatest coverage probability, and best precision compared to four different binary propensity score adjusted models. For all scenarios, the multinomial propensity score model demonstrated consistently superior statistical

performance - similar to the rarely identifiable MV model. The multinomial propensity score was the least biased in the presence of model misspecification.

Conclusion: Investigators conducting drug-drug interaction research should consider using the multinomial propensity score approach to adjust for confounding.

INTRODUCTION

Inferring the causal effect of one or more treatments that are not randomly assigned is often the goal of empiric observational research. However, absent random treatment assignment, the researcher has no assurance that patients receiving different treatments have similar distributions of factors that influence outcome occurrence. Therefore, researchers must make every effort to account for inter-patient differences in pre-treatment (baseline) characteristics, using appropriate statistical methodology.

One approach to account for (or balance) patient baseline characteristics is to use the propensity score, which is the predicted probability of treatment conditional on the observed (baseline) covariates.[58] The propensity score is a one dimensional covariate used to describe a multidimensional covariate matrix, and has been shown to be particularly useful when studying rare outcomes with many potential confounders, where it is not feasible to include all of the confounders in the statistical models.[59] The propensity score was originally developed to control for differences in observed covariates for two treatment groups (i.e., for a binary exposure).[58]

Methods have been described for deriving and using the propensity score for ordered exposure categories (e.g., in dose response analyses).[60-62] However, little research has been conducted using the propensity score to balance the predicted probability of treatment for more than two, non-ordered treatment categories. Imai et. al and Imbens et. al described the theoretical framework for the multinomial propensity score (PSm).[61, 63] They showed the predicted probability of more than two treatments could be derived given observed covariates. Huang and colleagues applied the PSm in a cross-sectional study of patient satisfaction with asthma care (the outcome) associated with twenty different physician groups (the multinomial exposure).[64] They showed the multinomial propensity score approach balanced the covariates among the different physician groups. While this study showed covariate balancing properties of the PSm, the authors didn't conduct simulations to investigate further PSm performance characteristics compared to other binary PS approaches or with correlated exposures.

The multinomial propensity score approach has potential applications in numerous settings where the exposure has more than two categories. A drug-drug interaction (DDI) study is one

example of a multinomial exposure. DDI studies often have more than two unordered exposure categories made up of combinations of an object drug and a precipitant drug. An object drug is a drug that is affected by a drug-drug interaction (e.g., reduced metabolism and increased bioavailability). The object drug is often a substrate for a specific hepatic enzyme. A precipitant drug is a drug that catalyzes the drug-drug interaction through inhibition of the specific hepatic enzyme. Each patient may be in one of four exposure categories. The exposure categories include: (i) the object drug only, (ii) the comparator object drug only, (iii) the object drug and the precipitant drug, and (iv) the comparator object drug and the precipitant drug. Importantly, there is no assumed ordering to these four exposure categories. Using this type of DDI study framework, we propose to evaluate the statistical performance of different propensity score methods (multinomial and binary) through simulation.

No applied methodologic research using simulations to evaluate different propensity score methods in multiple, non-ordered exposure categories have been published. This study evaluates relative bias, coverage probability, and mean squared error associated with different binary and multinomial propensity score methods. We simulated scenarios relevant to drug safety investigations. By evaluating each propensity score method under different scenarios, we provide drug-drug interaction researchers with a broadly applicable tool that will guide their choice of confounding adjustment method. The results from this study provide guidance regarding the validity of the multinomial propensity score. If the multinomial propensity score adequately reduced bias under the scenarios evaluated, we will use this method for confounding adjustment in the confirmatory drug-drug interaction cohort study.

METHODS

For the simulated drug-drug interaction study, the primary effect estimate is the interaction between the object drug and the precipitant drug. The interaction term is referred to as the interaction ratio (I*R). The I*R is a ratio of two ratios. Under the proposed DDI study, the I*R compares the association of the object drug with the precipitant drug to the association of the comparator object drug with the precipitant drug, adjusted for the effect of the object drug and comparator object drug without the precipitant drug. This contrast represents the relative effect of

the object drug with a concomitant precipitant drug compared to the comparator object drug with a concomitant precipitant drug independent of the individual effects of either the object drug or the comparator object drug alone. Since we are interested in the effect of the drug-drug interaction independent of the effects of the object/comparator object drugs alone, this investigation will focus on the I*R.

Simulation approach to creating synthetic cohorts:

We used 1,000 simulated data sets to evaluate the performance of multinomial and binary propensity score methods. We used Stata version 11.1 to perform all Monte Carlo simulations. We used the random number generator provided by Stata. The methods for generating normal (Gaussian) and uniform random numbers in Stata were derived by Knuth (1998) 65; Marsaglia, MacLaren, and Bray (1964); and Walker (1977).

Monte Carlo simulations were performed on the synthetic cohort of patients with a binary outcome (Y), three binary primary exposure variables (A_1, A_2, A_3=A_1*A_2), and three covariates (X_1, X_2, X_3). The binary outcome variable (Y), represents the presence or absence of the outcome (Y=1: outcome present; Y=0: outcome absent). The binary exposure variable A_1 represents exposure to either the object drug (A_1=1) or the comparator object drug (A_1=0). The binary exposure variable A_2 represents exposure to the precipitant drug (precipitant drug present or absent: A_2=1 or A_2=0). The binary exposure interaction variable (A_3) represents the interaction between A_1 and A_2 (A_1*A_2). When A_3=1 cohort members are exposed to the object drug (A_1=1) and the precipitant drug (A_2=1). When A_3=0 cohort members are exposed to: the object drug without the precipitant drug (A_1=1, A_2=0), the comparator object drug with the precipitant drug (A_1=0, A_2=1), or the comparator object drug without the precipitant drug (A_1=0, A_2=0).

To evaluate the multinomial propensity score, we generated a multinomial exposure variable (A_4). This non-ordered, categorical variable was derived from the four possible exposure categories for A_1 and A_2. The four categories of A_4 are: A_4=1 (A_1=1,A_2=1); A_4=2 (A_1=1,A_2=0); A_4=3 (A_1=0,A_2=1); A_4=4 (A_1=0,A_2=0). We generated the covariates X_1 and X_2 as random continuous variables (standard normal mean 0; standard deviation 1). We generated X_3 as random binary variable (1,-1) with p(1)=0.0). To compare to statistical performance of the

multinomial propensity score, we generated several binary propensity scores from A_1, A_2, and A_3 (described below).

We generated associations among the exposure variables (A_1, A_2, A_3) and covariates (X_1, X_2, X_3) to approximate those found in medical research. For the exposure variables and covariates, we varied the coefficients to evaluate statistical performance under a variety of conditions.

Description of base equations:

In simulation studies the investigator builds equations where associations among the outcome, exposure, and confounding variables are known (because these associations are determined by the investigator). We used three base equations, each with investigator determined coefficients (see base equations below). Using base equation Y as the true outcome model, we evaluated how closely each propensity score method estimated the interaction ratio (λ_3) in this model. Below we present base equations used to derive A_1 (the object drug/comparator object drug), A_2 (the precipitant drug present/absent), and Y (the binary outcome yes/no). In base equation A_1 we determined the associations among A_1 and the covariates X_1, X_2, X_3. In base equation A_2 we determined the associations among A_2 and the exposure variable A_1, the covariates X_1, X_2, X_3, and the A_1*X_1 interaction. In base equation Y we determined the association among the outcome variable (Y) and the exposure variables A_1, A_2, A_3 and the covariates X_1, X_2, X_3.

Base Equation A_1 - object/comparator drug model

Logit $p(A_1=1) = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3$

Base Equation A_2 - precipitant drug model

Logit $p(A_2=1) = \theta_0 + \theta_1A_1 + \theta_2X_1 + \theta_3X_2 + \theta_4X_3 + \theta_5(A_1*X_1)$

Base Equation Y - true outcome model

Logit $p(Y=1) = \lambda_0 + \lambda_1A_1 + \lambda_2A_2 + \lambda_3A_3 + \lambda_4X_1 + \lambda_5X_2 + \lambda_6X_3$

Baseline values:

In order to evaluate the performance of each propensity score, we first determined baseline values for each coefficient in the base equations. Baseline coefficient values were selected

based on the approximate values in an empiric drug interaction study conducted by the principal investigator (data not yet published). Holding baseline values constant, we varied specific coefficients (one at a time), to evaluate relative bias, coverage probability, and mean squared error (MSE) under a variety of conditions. The baseline sample size was set to 100,000 synthetic cohort members.

In base equation A_1, the baseline coefficients were set to the following values.

Logit $Pr(A_1=1) = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3$

Baseline coefficients: $\beta_0=1.0$; $\beta_1=1.0$; $\beta_2=0.0$; $\beta_3=1.0$

The baseline constant (β_0) was set to 1.0. This baseline value set the proportion of $A_1=1$ to 0.65 and $A_1=0$ to 0.35. The baseline associations for A_1 with X_1, X_2, and X_3 were set to $\beta_1=1.0$, $\beta_2=0.0$, $\beta_3=1.0$, respectively.

In base equation A_2, the baseline coefficients were set to the following values.

Logit $Pr(A_2=1) = \theta_0 + \theta_1A_1 + \theta_2X_1 + \theta_3X_2 + \theta_4X_3 + \theta_5(A_1*X_1)$

Baseline coefficients: $\theta_0=-1.0$; $\theta_1=0.2$; $\theta_2=0.0$; $\theta_3=1.0$; $\theta_4=1.0$; $\theta_5=0.2$

This baseline constant of -1.0 set the proportion of $A_2=1$ to 0.35 and $A_2=0$ to 0.65. The baseline association between A_1 and A_2 (θ_1) was set to 0.2. This represents a modest association between the object drug and precipitant drug. The baseline associations for A_2 with X_1, X_2, and X_3 were set to $\theta_2=0.0$, $\theta_3=1.0$, $\theta_4=1.0$, respectively. The baseline interaction between A_1 and X_1 (θ_5) was set to 0.2. This represents a weak interaction between the covariate X_1 and the object drug A_1.

In base equation Y, the coefficients were set to the following values.

Logit $p(Y=1) = \lambda_0 + \lambda_1A_1 + \lambda_2A_2 + \lambda_3A_3 + \lambda_4X_1 + \lambda_5X_2 + \lambda_6X_3$

Baseline coefficients: $\lambda_0=-2$; $\lambda_1=0.1$; $\lambda_2=0.1$; $\lambda_3=0.4$; $\lambda_4=1.0$; $\lambda_5=1.0$; $\lambda_6=1.0$

The baseline constant of -2.0 ($\lambda_0=-2.0$) set the proportion of Y=1 to 0.2 and Y=0 to 0.8. The baseline association between A_1 and Y was set to 0.1 ($\lambda_1=0.1$). The baseline association between A_2 and Y was set to 0.1 ($\lambda_2=0.1$). The baseline association between A_3 and Y was set to 0.2 ($\lambda_3=0.4$). The baseline association between the covariates (X_1, X_2, and X_3) and the outcome Y was set to1.0.

Statistical properties evaluated:

Relative bias was our primary measure of statistical performance. Relative bias reflects the difference between the estimated λ_3 value and the true λ_3 value. We expressed relative bias as a percentage [(estimated λ_3 - true λ_3)/ true λ_3)*100]. Positive (negative) percent bias indicated an overestimation (underestimation) of the association. Zero percent bias values indicated no bias. Ninety five percent confidence intervals for percent bias were derived using the bootstrap percentile method. Based on 1000 simulated λ_3 estimates, percent bias was calculated.

We also evaluated coverage probability and mean squared error (MSE) of the estimated value of λ_3. Coverage probability was estimated as the proportion of times the confidence interval for the estimated value of λ_3 included the true value of λ_3. Precision was estimated by determining the MSE value of the estimated value of λ_3 over 1000 Monte Carlo repetitions. We determined the MSE by adding the average bias squared and the average bias standard deviation squared ([average bias]^2 + [average bias standard deviation]^2).

Propensity score methods to be compared:

We evaluated the performance of the multinomial propensity score and other binary propensity scores methods in the setting of a hypothetical drug interaction study. Because we are interesting in studying a four level, non-ordered exposure; the multinomial propensity score was derived using multinomial logistic regression (MLR).[63] MLR is an adaption of binary logistic regression for multiple, non-ordered outcomes. Using MLR, the multinomial propensity score was derived by regressing the covariates X_1, X_2, & X_3 on the categorical (four level) exposure variable A_4. MLR compares each exposure category of A_4 (1, 2, 3, and 4) through a combination of binary logistic regressions. As with traditional propensity score methods, MLR is followed by arithmetic transformation of odds (probability/1-probability) into the predicted probability (odds/1+odds) of being in one of the following exposure categories: 1 vs 4, 2 vs 4, and 3 vs 4. Category 4 was set as the base level for MLR. The probability of being in a particular exposure category (1, 2, 3, or 4) is a quantitative representation of the joint distribution of each exposure category given the set of covariates. We derived the multinomial propensity score (PS4) by determining the predicted probability of each A_4 category given X_1, X_2, & X_3. Functionally this equates to estimating the

following conditional probabilities (i) $Pr(A_4=1| X_1, X_2, X_3)$, (ii) $Pr(A_4=2| X_1, X_2, X_3)$, (i) $Pr(A_4=3| X_1, X_2, \& X_3)$, (iii) $Pr(A_4=4| X_1, X_2, \& X_3)$. Because the cumulative sum of these four probabilities is one, confounding adjustment with PS4 uses three of the four probabilities.

For comparison with the multinomial propensity score (PS4), we used logistic regression to derive the predicted probability of other binary exposure variables A_1, A_2, and A_3 given X_1, X_2, and X_3. Functionally this equates to estimating the following conditional probabilities: $Pr(PS1: A_1=1| X_1, X_2, X_3)$, $Pr(PS2: A_2=1| X_1, X_2, X_3)$, and $Pr(PS3: A_3=1| X_1, X_2, X_3)$. Below is a summary derivation of each propensity score evaluated included in this investigation.

PS1: logit $Pr(A_1=1) = \rho_{01} + \rho_{11}X_1 + \rho_{21}X_2 + \rho_{31}X_3$

PS2: logit $Pr(A_2=1) = \rho_{02} + \rho_{12}X_1 + \rho_{22}X_2 + \rho_{32}X_3$

PS3: logit $Pr(A_3=1) = \rho_{03} + \rho_{13}X_1 + \rho_{23}X_2 + \rho_{33}X_3$

PS4: mlogit $Pr(A_{4=1}): \rho_{041} + \rho_{141}X_1 + \rho_{241}X_2 + \rho_{341}X_3$

mlogit $Pr(A_{4=2}): \rho_{042} + \rho_{142}X_1 + \rho_{242}X_2 + \rho_{342}X_3$

mlogit $Pr(A_{4=3}): \rho_{043} + \rho_{143}X_1 + \rho_{243}X_2 + \rho_{343}X_3$

mlogit $Pr(A_{4=4}): \rho_{044} + \rho_{144}X_1 + \rho_{244}X_2 + \rho_{344}X_3$

PS12: PS1 & PS2

We evaluated each of these models in the presence of weak model misspecification. Evaluating statistical performance in the presence known model misspecification, informs us about the effectiveness of the different confounding adjustment approaches under this common (and often unknown) condition. It is often the case in empiric research that model misspecification occurs. Under model misspecification we did not account for the weak interaction between A_1 and X_1 (A_1*X_1). The A_1*X_1 interaction is depicted in base equation A_2.

Propensity score form:

We evaluated each propensity score using three approaches: spline, categorical, and continuous covariates. Categorical propensity scores were derived using quintiles of the predicted probabilities. Spline propensity scores were derived through cubic spline regression with five interior knot points placed at quintiles of the estimated propensity score. Continuous propensity scores used the linear form of the predicted probabilities. In general, spline and categorical

covariates are useful when the relationship between the dependent variable (Y) and the independent variables is not linear. Regression splines also provide flexibly to model a nonparametric relationship between the propensity score and outcome variable. We used the spline propensity score adjustment as the baseline form. While propensity scores stratification and matching are commonly used methods, applications of these methods with a multinomial exposure have not been developed.

Outcome models:

All propensity score adjusted outcome models used logistic regression with three exposure variables (A_1, A_2, A_3) and the propensity score (E[Y| A_1, A_2, A_3, PS]). We refer to propensity score outcome models using PS* to indicate that we evaluated each propensity score (described above). We compared each propensity score outcome model to an unadjusted model (the null model) and a correctly specified multivariable (MV) model. The null model included only exposure variables regressed on Y (E[Y| A_1, A_2, A_3]). The null model allowed us to quantify bias without covariate adjustment. The MV model included each exposure variable and the three covariates regressed on Y (E[Y| A_1, A_2, A_3, X_1, X_2, X_3]). In empiric research, the correctly specified MV model is rarely known. It is presented in this study to illustrate the relative performance of the propensity score methods to the performance of the correctly specified model. We present bias, coverage probability, and MSE for the interaction ratio (the estimated value of λ_3) from the null model, the MV model, and each propensity score model. The five propensity score models were independently evaluated in PS*. The outcome models are presented below.

Null outcome model: Logit $Pr(Y=1) = \xi_0 + \xi_1 A_1 + \xi_2 A_2 + \xi_3 A_3$

MV outcome model: Logit $Pr(Y=1) = \omega_0 + \omega_1 A_1 + \omega_2 A_2 + \omega_3 A_3 + \omega_4 X_1 + \omega_5 X_2 + \omega_6 X_3$

PS* outcome model: Logit $Pr(Y=1) = \varphi_0 + \varphi_1 A_1 + \varphi_2 A_2 + \varphi_3 A_3 + \varphi_4 PS^*$

Diagnostic evaluation of propensity score balance:

In empiric investigations, with one "real" dataset, researchers commonly evaluate the distribution of propensity scores for each treatment group. This is done to evaluate balance between exposed and unexposed individuals given their respective vector of covariates. The primary reason to check propensity score balance is to evaluate the assumption of positivity.

Positivity exists when exposed and unexposed individuals exist at every level of each confounder. While the propensity score does not tell you if there are exposed and unexposed at every level of each confounder, it provides a composite covariate vector which summarizes the probability of treatment. Assuming no gross positivity violations, one expects the PS distributions (for exposed and unexposed) to have some degree of overlap. The proportion of overlap informs the investigator about the heterogeneity of the composite covariate vector in each treatment group. In an extreme example, if the distributions of propensity scores, for exposed and unexposed, have no overlap, an excess in covariate heterogeneity suggests these two groups are not comparable.

In order to evaluate PS balance, we present quintile box plots for each derived propensity score quintile. Visual inspection of quintile box plots depicts the composite covariate overlap at each propensity score quintile for each exposure category. For the binary propensity scores (PS1, PS2, PS3), this equates to evaluating the composite covariate distribution at each propensity score quintile for exposed and unexposed synthetic cohort members. For the multinomial propensity score (PSm), this equates to evaluating the composite covariate distribution for each propensity score quintile at each of the four exposure categories. Because PSM is comprised of the predicted probability of four exposure categories (i.e., $Pr(A_4=1)$, $Pr(A_4=2)$, $Pr(A_4=3)$, and $Pr(A_4=4)$), we present quintile box plots for each exposure category.

Scenarios evaluated (seven simulation studies):

To evaluate the statistical performance of different propensity score methods, we varied seven different parameters - holding the other baseline values constant. The parameters we varied are described below.

Confounding: We evaluated statistical performance over a spectrum of confounding by changing the associations between the covariates (X_1, X_2, and X_3) and the outcome (Y). In the true outcome model (base equation Y), we evaluated beta coefficients at 0.0, 0.4, 0.7, 1.0, and 1.39. These values range from no confounding to very strong confounding. For all confounding strengths, the associations among the exposure variables (A_1 and A_2) and the covariates (X_1, X_2, and X_3) were fixed at the baseline values.

Sample size: We evaluated three sample sizes of 50,000, 100,000, and 150,000 synthetic cohort members. These sample sizes were chosen to emulate typical drug safety data, to avoid finite sample bias, as well as to permit the study of both common and rare events.

Prevalence of exposure to the precipitant drug: We evaluated three scenarios for the prevalence of exposure to the precipitant drug (A_2=1). By varying the θ_0 coefficient (from base equation A_2), we determined the proportion of the synthetic cohort exposed to the precipitant drug A_2 (A_2=1). We evaluated the following three proportions: 0.35 (θ_0= -1.0), 0.20 (θ_0= -2.0), and 0.10 (θ_0= -3.0).

Association between object drug and precipitant drug: We varied the association between the object drug (A_1) and the precipitant drug (A_2) using θ_1 (from base equation A_2). This allowed us to evaluate each propensity score method in the presence of a null (θ_1=0), a moderate (θ_1=0.7), and a strong (θ_1=1.39) association. This is equivalent to evaluating different proportions of concomitant exposure to A_1 and A_2.

Interaction between the object drug and the covariate: We varied the interaction between the object drug (A_1) and the covariate X_1 using θ_5 from base equation A_2. Varying this association allowed us to understand how each propensity score method performed in the presence of a null (θ_5=0), a moderate (θ_5=0.4), or strong (θ_5=0.7) model misspecification.

Incidence of the outcome: We varied the proportion of synthetic cohort members having the outcome (Y=1). This allowed us to understand how each propensity score method performed under different incidences of the outcome. We evaluated each method with the outcome incidence (Y=1) set at 0.2 (λ_0= -2.0), 0.1 (λ_0= -3.0), and 0.05 (λ_0= -4.0). Given the work by Cepeda et. al. (ref), the incidence of the outcome may be an important characteristic in determining the performance of each method.

Association between the interaction ratio with the outcome: We varied the strength of association between the interaction term (λ_3) and the outcome (Y). This allowed us to understand how each propensity score method performed in the presence of a weak (λ_3=0.3), a moderate (λ_3=0.6), or a strong (λ_3=0.9) association. Depending on the strength of the association between

the interaction term and the outcome; it is plausible that the performance of each propensity score method will vary based on this association.

Propensity score form: Using the baseline coefficient values describe above, we evaluated the performance of each propensity score as a continuous, spline, and categorical covariate.

RESULTS

The results from the seven simulation studies are presented in Figures and Tables 1-7. Under each scenario evaluated, the multinomial propensity score model (PS4) demonstrated superior statistical performance compared to the binary propensity score models (PS1, PS2, PS3, PS12). Statistical performance of the PS4 model was similar to that of the MV model. As previously mentioned, it is rarely feasible to fit the MV model. Thus, the ability of the PS4 model to achieve similar performance is important.

Confounding scenarios: Figures 1a, 1b, and Table 1 show the performance of each model over the spectrum of confounding (no confounding to very strong confounding). The null model is increasingly biased, with worsening coverage probability, and less precision (increased MSE) as the strength of confounding increased. The MV model is consistently unbiased, with excellent coverage probability, and consistent precision over the spectrum of confounding. The binary propensity score models (PS1, PS2, PS3, and PS12) were increasingly biased, had worsening coverage probability, and became less precise as the strength of confounding increased. Over the spectrum of confounding, the PS4 model demonstrated superior statistical performance compared to the binary propensity score models. The PS4 model had similar percent bias, coverage probability, and precision to the MV model.

Sample size variation: Figure 2 and Table 2 show the statistical performance for the three different sample sizes (50,000, 100,000, and 150,000). For all models evaluated, percent bias was consistent with narrowing 95% confidence intervals as sample size increased. The null model and propensity scores models PS1, PS2, PS3, and PS12 revealed excess percent bias for each sample size. The MV and PS4 models remained consistently unbiased for each sample size. Coverage probability for the MV and PS4 models remained consistently at 0.95. Coverage probability for the null and PS1, PS2, PS3, and PS12 models reduced as sample size increased.

The precision (MSE) of the MV and PS4 models was at least twice as precise as the binary propensity score models. All models show increased precision with larger sample sizes.

Prevalence of exposure to the precipitant drug: Figure 3 and Table 3 show statistical performance for three different proportions (0.35, 0.2, 0.1) of synthetic cohort members exposed to the precipitant drug (A_2=1). The null and binary propensity score models (PS1, PS2, PS3, and PS12) show increasing percent bias as the frequency of precipitant drug exposure decreases. The MV and PS4 models remained consistently unbiased for each proportion of precipitant drug exposure. Coverage probability increased for binary propensity score models PS1, PS2, and PS12 and increased as the proportion of precipitant drug exposure decreased. Coverage probability for the MV and PS4 models remained consistent across each proportion of precipitant drug exposure. For all models, precision was reduced as the proportion of precipitant drug exposure decreases (i.e., MSE was increased as the proportion of precipitant drug exposure decreased).

Association between the object drug and the precipitant drug: Figure 4 and Table 4 show the statistical performance for three different associations (null, moderate, strong) between the object drug (A_1) and the precipitant drug (A_2). Across each strength of association between the object drug and precipitant drug, the MV and PS4 models remained unbiased, had approximately 95% coverage probability, and maintained a consistent level of precision (MSE). With the strengthening association between the object drug and precipitant drug, percent bias and coverage probability for the null and the binary propensity models score trended toward decreasing bias and increased coverage probability. These models also showed better precision (reduced MSE) as the object drug and precipitant drug association strengthened.

Interaction between object drug and covariate: Figure 5 and Table 5 show statistical performance for the null, moderate, and strong interaction between the object drug (A_1) and one of the covariates (X_1). The strength of this interaction represents the amount of model misspecification. Under model misspecification, only the MV model is correctly specified. For each interaction level, the MV and PS4 models remained similarly unbiased, with near 95% coverage probability, and maintained a consistent level of precision. The null model showed less

bias, better coverage probability, and greater precision with increasing A_1*X_1 interaction strength. The binary propensity score models show varied performance across interaction levels, all with substantial bias and inferior coverage probability.

Incidence of the outcome: Figure 6 and Table 6 show statistical performance under three incidences of outcome occurrence (Y=1). For each outcome incidence, the MV and PS4 models remained unbiased, with near 95% coverage probability. The null, PS1, PS2, PS3, and PS4 models remained consistently biased over each outcome incidence. Coverage probability for the null and binary propensity score models was greater as the incidence of the outcome decreased. As evidenced by increasing MSE, precision for all models decreased with lower outcome incidence.

Strength of the interaction ratio: Figure 7 and Table 7 show statistical performance for three interaction ratio strengths. The MV and PS4 models showed negligible bias, excellent coverage probabilities, and consistent precision for varied strengths of interaction ratio. Percent bias decreased for the null and binary propensity score models as the strength of the interaction ratio increased. For PS2, PS3, and PS12 coverage probability increased as the strength of the interaction increased. PS1 showed reduced coverage probability with increasing interaction ratio strength. Precision was increased (i.e., MSE decreased) for the null and binary propensity score models as the strength of the interaction ratio increased.

Propensity score form: Figure 8 and Table 8 show statistical performance for the continuous, spline, and categorical propensity score forms. For PS4, the spline form was less biased but had similarly good coverage probability and precision compared to the continuous and categorical forms.

Balance diagnostic: The results from propensity score balance diagnostics are presented in Figures 9, 10, 11, 12a, 12b, 12c, and 12d. For all propensity scores evaluated, the propensity score quintile box plots show sufficient covariate balance for each propensity score method to support the assumption of positivity. This represents similar composite covariate distributions for each level of the propensity score.

Model convergence for each model evaluated was more than 99%.

DISCUSSION

The results from these drug interaction simulations show the multinomial propensity score (PS4) was the least biased, had the greatest coverage probability, and best precision compared to binary propensity score methods. For all scenarios, the multinomial propensity score model demonstrated consistently superior statistical performance - similar to the rarely identifiable MV model. The multinomial propensity score was the least biased in the presence of model misspecification. This is important for empiric investigations where the presence and quantity of model misspecification is rarely known. Superior performance of the multinomial propensity score was expected since each of the conditional probabilities of exposure, four each of the four exposure categories, given the set of covariates is determined using multinomial logistic regression. Binary propensity score methods are limited since they do not account for each of the four exposure categories simultaneously.

This applied simulation project builds on the theoretical approaches to the multinomial propensity score described by Imai et al. and Imbens et al.[61, 63] In addition, these results are concordant with the findings of Huang et al. who showed the multinomial propensity score improved covariate distribution balance across twenty exposure categories compared to conventional methods.[64] Researchers evaluating multi-level, non-ordered exposure categories, particularly in the setting of drug-drug interaction studies, should consider confounding adjustment with the multinomial propensity score.

The simulated cohort in this investigation was nested in a cohort of object drug and comparator object drug users. We did not consider scenarios where synthetic cohort members were truly unexposed. However, investigators may extrapolate these results to other scenarios where the comparator object drug group alone (A_1=0, A_2=0) represents an unexposed group.

The results of this investigation are generalizable to other studies under similar scenarios as those investigated in this study. While we attempted to evaluate broadly applicable scenarios found in drug safety research, there may be other situations where these results will not be applicable. For example, we studied statistical performance using a spectrum of confounding,

three incidences of the outcome, three associations between the object drug and the precipitant drug, three strengths of the covariate-drug interaction (A_1*X_1), and three associations of the drug interaction (A_1*A_2) with the outcome Y. Despite our efforts to study associations commonly found in drug safety research, additional research is warranted to evaluate scenarios substantially different from those we studied.

We evaluated three covariates to estimate statistical performance of different propensity score methods. As demonstrated by Cepeda et al. [59], the propensity score is most advantageous, with regard to bias reduction, when the number of covariates is large compared to the number of outcomes. Using three covariates adequately demonstrated relative statistical performance; however, future studies of scenarios with additional covariates with more complex distributions, interactions, and transformations may be beneficial for drug-drug interaction researchers.

Matching and stratification on the propensity score are commonly used methods to adjust for confounding. The complexity of the multinomial propensity score does not extrapolate directly to either matching or stratification. Methods for matching on a four level categorical exposure have not been developed. This is an area for future research. Likewise, propensity score stratification does not have a multinomial equivalent. Given the multinomial propensity score approach includes three propensity scores used in the final model, propensity score stratification would not provide a single overall estimate. This strategy may not be applicable to the multinomial approach.

The results from this investigation presume the assumptions for causal inference are not violated. These assumptions include no unmeasured confounding, positivity, and no model misspecification.[66] We make the assumption that, given measured covariates (X_1, X_2, and X_3), there are no additional covariates that influence the association among the multi-level exposure and the outcome. Investigators must make every effort to evaluate all potential covariates associated with the exposure and the outcome. This is not a testable assumption. Positivity, on the other hand, is a testable assumption. As previously stated, positivity exists when exposed and unexposed individuals exist at every level of each covariate. While this is difficult to test for

continuous covariates, one may evaluate positivity by examining the composite covariate distribution for exposed and unexposed individuals. If the distributions are similar, it may be assumed that positivity is achieved. We evaluated the quintile box plots for all exposure categories within each propensity score quintile (for each covariate).

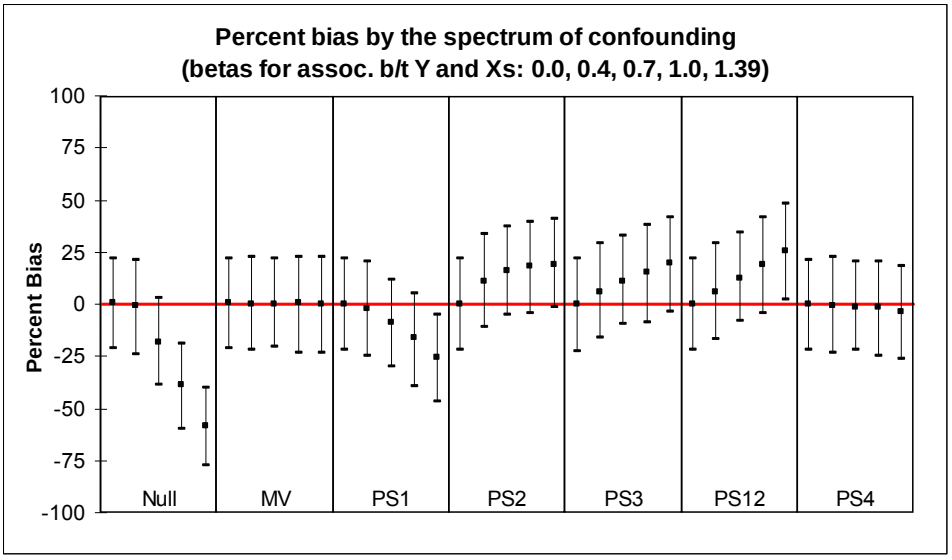
Correct model specification (for logistic regression) means the relationship between the independent variables and the dependent variable is linear on the log scale.[67] However, as previously described, we intentionally created weak model misspecification through the A_1*X_1 interaction variable. This was done to evaluate propensity score performance with known model misspecification. In empiric investigations, model misspecification may often exist, yet be unknown to the researcher. To provide a comprehensive evaluation (with and without model misspecification), we evaluated performance with a null, moderate, and strong A_1*X_1 interaction. Under all scenarios evaluated, with our without model misspecification, the multinomial propensity score showed superior statistical performance to binary propensity score methods.

Conclusion

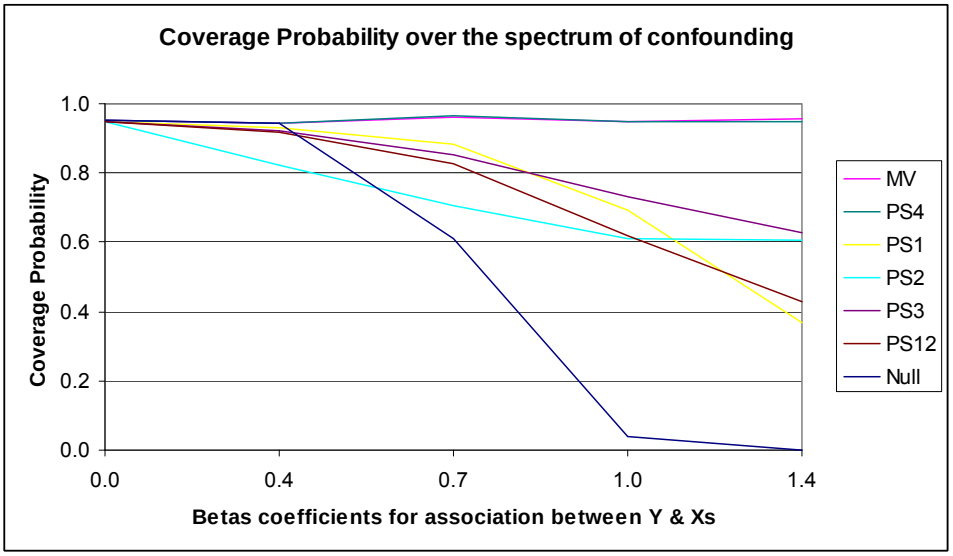
The results from these simulation studies show the multinomial propensity score eliminated most bias, had greater coverage probability, and increased precision than comparator binary propensity score methods. The results were essentially comparable to the correctly specified MV model, which is rarely attainable in empiric research. Based on these results, Investigators studying drug-drug interactions should consider using the multinomial propensity score approach to adjust for confounding.

TABLES

METHODS FIGURE 1 PERCENT BIAS (SPECTRUM OF CONFOUNDING)



METHODS FIGURE 1A COVERAGE PROBABILITY (SPECTRUM OF CONFOUNDING)

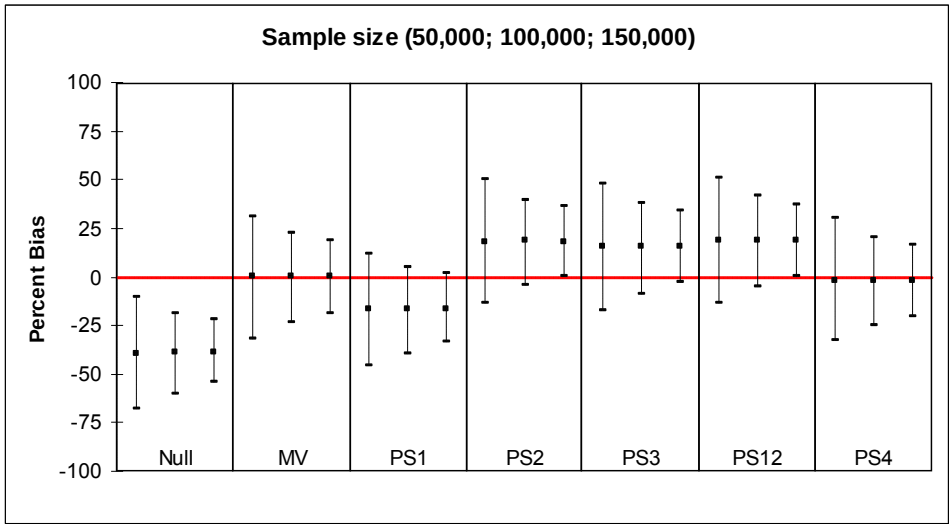


METHODS TABLE 1 COVERAGE PROBABILITY AND MSE (SPECTRUM OF CONFOUNDING)

Methods Table 1 (coverage probability and MSE)

confounding	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
0.0	0.953	0.953	0.949	0.950	0.950	0.950	0.954
0.4	0.944	0.945	0.932	0.822	0.920	0.917	0.945
0.7	0.611	0.960	0.883	0.705	0.853	0.825	0.964
1.0	0.041	0.948	0.693	0.612	0.731	0.621	0.950
1.4	0.000	0.958	0.369	0.607	0.627	0.429	0.950
	Mean squared error (bias)						
0.0	0.002	0.002	0.002	0.002	0.002	0.002	0.002
0.4	0.002	0.002	0.002	0.004	0.003	0.003	0.002
0.7	0.007	0.002	0.003	0.006	0.004	0.004	0.002
1.0	0.026	0.002	0.006	0.007	0.006	0.008	0.002
1.4	0.055	0.002	0.012	0.008	0.008	0.013	0.002

METHODS FIGURE 2: PERCENT BIAS (SAMPLE SIZE)

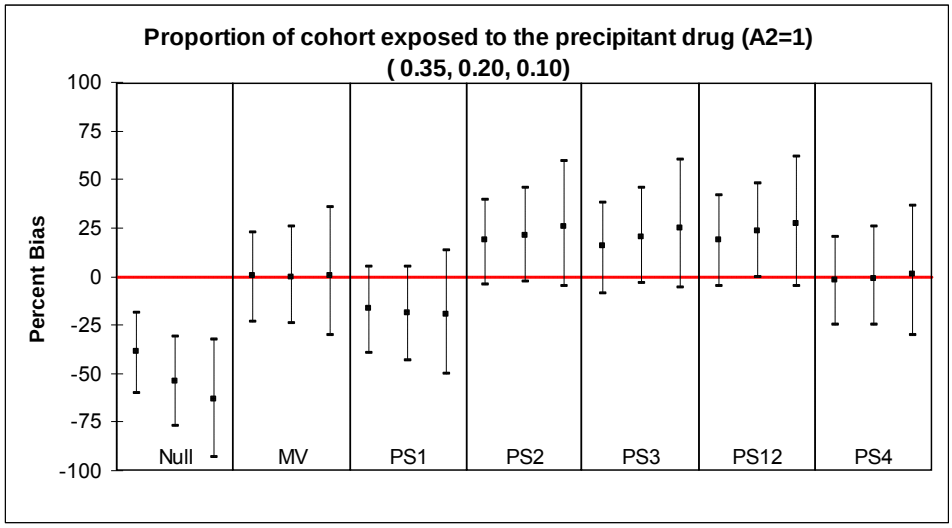


METHODS TABLE 2: COVERAGE PROBABILITY AND MSE (SAMPLE SIZE)

Methods Table 2 (coverage probability and MSE)

Sample size	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
50,000	0.246	0.955	0.817	0.776	0.827	0.771	0.956
100,000	0.041	0.948	0.693	0.612	0.731	0.621	0.950
150,000	0.002	0.951	0.558	0.488	0.628	0.484	0.945
	Mean squared error (bias)						
50,000	0.028	0.004	0.008	0.010	0.008	0.010	0.004
100,000	0.026	0.002	0.006	0.007	0.006	0.008	0.002
150,000	0.025	0.001	0.005	0.007	0.005	0.007	0.001

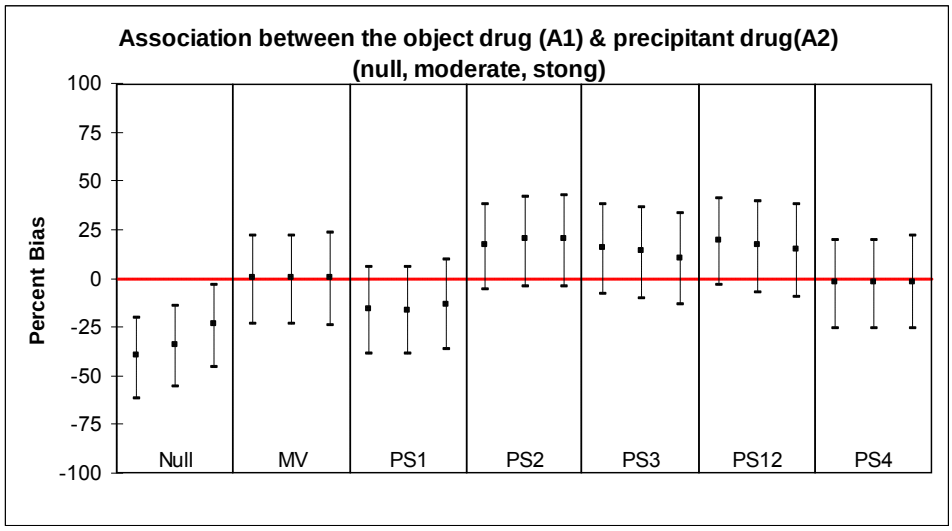
METHODS FIGURE 3: PERCENT BIAS (PROPORTION A2=1)



METHODS TABLE 3: COVERAGE PROBABILITY AND MSE (PROPORTION A2=1)

Methods Table 3 (coverage probability and MSE)							
Proportion A2 =1	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
0.35	0.041	0.948	0.693	0.612	0.731	0.621	0.950
0.20	0.001	0.961	0.682	0.624	0.671	0.583	0.963
0.10	0.021	0.959	0.767	0.677	0.704	0.658	0.959
	Mean squared error (bias)						
0.35	0.026	0.002	0.006	0.007	0.006	0.008	0.002
0.20	0.050	0.003	0.008	0.010	0.009	0.011	0.003
0.10	0.068	0.005	0.010	0.015	0.015	0.017	0.005

METHODS FIGURE 4: PERCENT BIAS (ASSOC. BETWEEN THE OBJECT AND PRECIPITANT DRUGS)

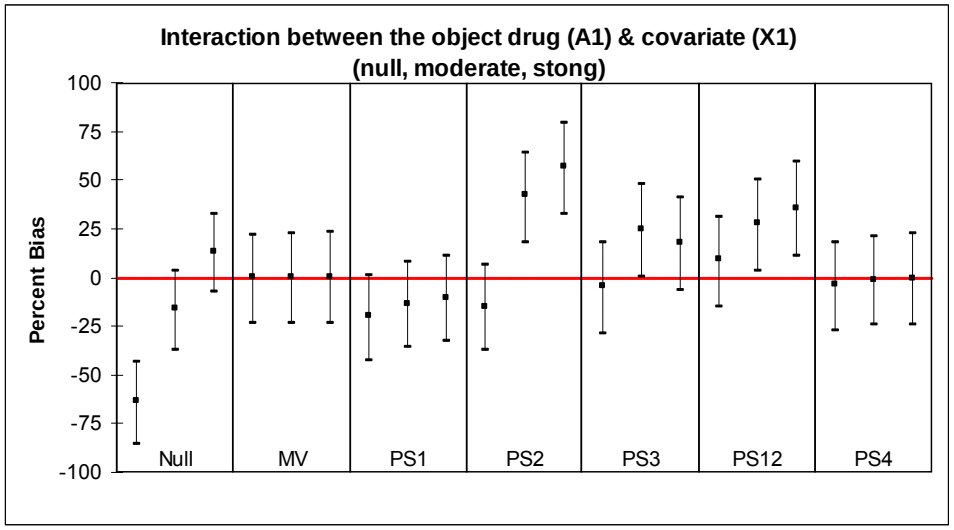


METHODS TABLE 4: COVERAGE PROBABILITY AND MSE (ASSOC. BETWEEN THE OBJECT AND PRECIPITANT DRUGS)

Methods Table 4 (coverage probability and MSE)

A1 & A2 assoc.	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
null	0.023	0.952	0.705	0.655	0.725	0.594	0.955
weak	0.103	0.950	0.700	0.575	0.782	0.675	0.953
stong	0.411	0.945	0.796	0.586	0.870	0.752	0.941
	Mean squared error (bias)						
null	0.027	0.002	0.006	0.007	0.006	0.008	0.002
weak	0.020	0.002	0.006	0.008	0.005	0.007	0.002
stong	0.011	0.002	0.005	0.009	0.004	0.006	0.002

METHODS FIGURE 5: PERCENT BIAS (STRENGTH OF A1*X1 INTERACTION)

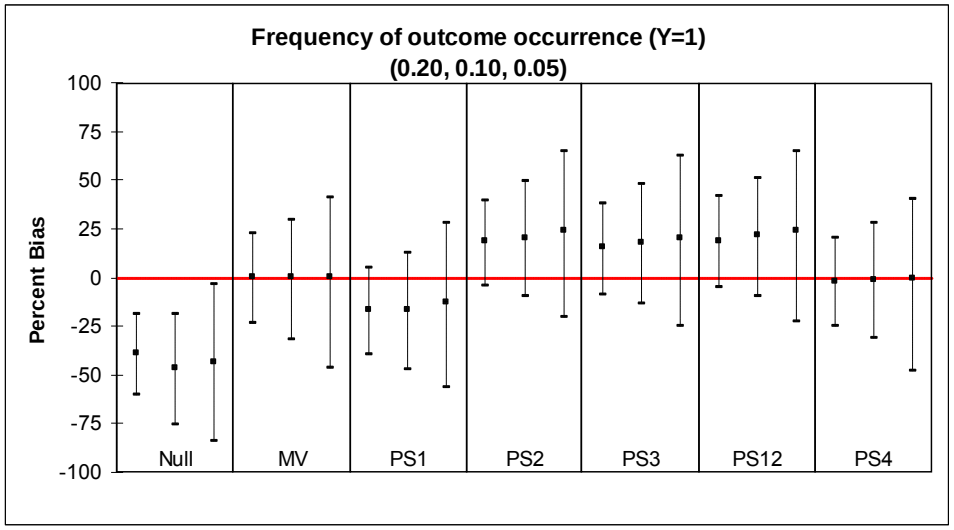


METHODS TABLE 5: COVERAGE PROBABILITY AND MSE (STRENGTH OF A1*X1 INTERACTION)

Methods Table 5 (coverage probability and MSE)

A1 & X1 interaction	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
null	0.000	0.952	0.577	0.745	0.933	0.874	0.942
weak	0.685	0.955	0.791	0.046	0.418	0.334	0.956
stong	0.745	0.945	0.863	0.001	0.668	0.133	0.949
	Mean squared error (bias)						
null	0.066	0.002	0.008	0.005	0.002	0.004	0.002
weak	0.006	0.002	0.005	0.031	0.012	0.014	0.002
stong	0.005	0.002	0.004	0.054	0.007	0.022	0.002

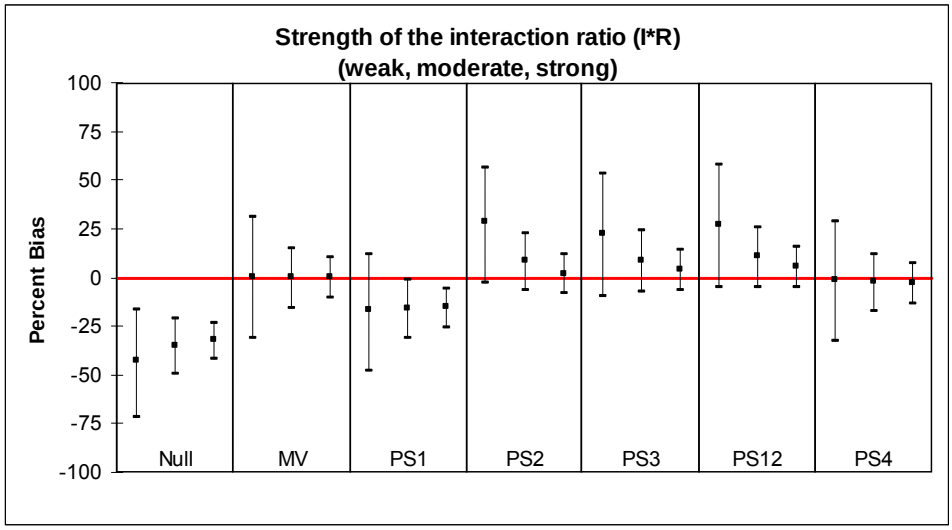
METHODS FIGURE 6: PERCENT BIAS (FREQUENCY OF OUTCOME OCCURRENCE (Y=1))



METHODS TABLE 6: COVERAGE PROBABILITY AND MSE (FREQUENCY OF OUTCOME OCCURRENCE (Y=1))

Methods Table 6 (coverage probability and MSE)							
Outcome frequency	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
0.20	0.041	0.948	0.693	0.612	0.731	0.621	0.950
0.10	0.086	0.950	0.806	0.732	0.788	0.701	0.953
0.05	0.474	0.953	0.916	0.808	0.853	0.801	0.950
	Mean squared error (bias)						
0.20	0.026	0.002	0.006	0.007	0.006	0.008	0.002
0.10	0.037	0.004	0.008	0.010	0.009	0.011	0.004
0.05	0.037	0.008	0.010	0.017	0.015	0.017	0.008

METHODS FIGURE 7: PERCENT BIAS (STRENGTH OF THE INTERACTION RATIO (I*R))

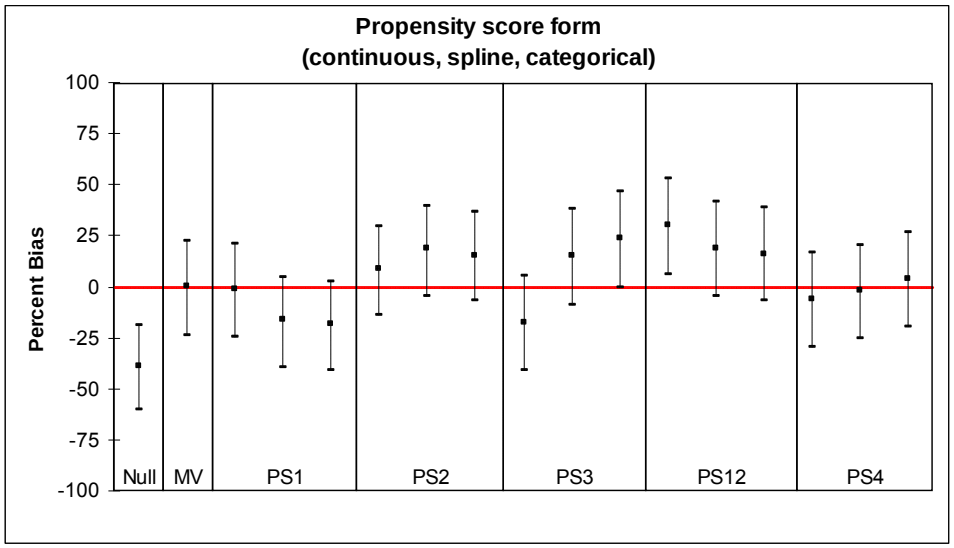


METHODS TABLE 7: COVERAGE PROBABILITY AND MSE (STRENGTH OF THE INTERACTION RATIO (I*R))

Methods Table 7 (coverage probability and MSE)

Interaction Ratio	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
weak	0.140	0.946	0.791	0.513	0.701	0.574	0.953
moderate	0.002	0.954	0.459	0.796	0.800	0.712	0.939
strong	0.000	0.951	0.136	0.929	0.869	0.822	0.923
	Mean squared error (bias)						
weak	0.018	0.002	0.005	0.009	0.007	0.009	0.002
moderate	0.045	0.002	0.011	0.005	0.005	0.006	0.002
strong	0.084	0.002	0.020	0.002	0.004	0.005	0.003

METHODS FIGURE 8: PERCENT BIAS (COVARIATE FORM)

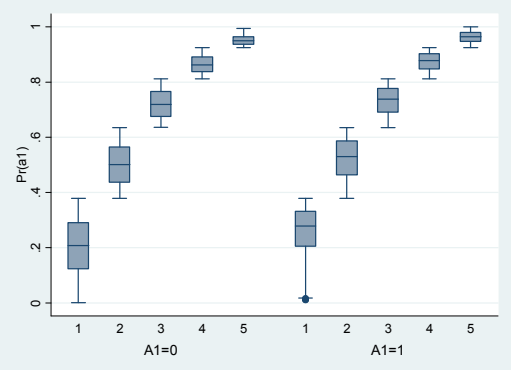


METHODS TABLE 8: COVERAGE PROBABILITY AND MSE (COVARIATE FORM)

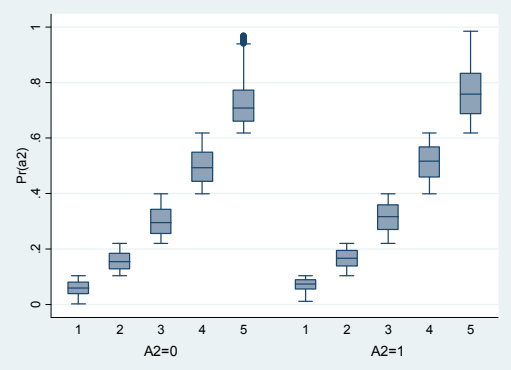
Methods Table 8 (coverage probability and MSE)

Propensity score form	Null	MV	PS1	PS2	PS3	PS12	PS4
	Coverage probability						
continuous	0.041	0.948	0.942	0.877	0.683	0.267	0.918
spline	-	-	0.693	0.612	0.731	0.621	0.950
categorical	-	-	0.633	0.724	0.440	0.698	0.932
	Mean squared error (bias)						
continuous	0.026	0.002	0.002	0.003	0.007	0.017	0.003
spline	-	-	0.006	0.007	0.006	0.008	0.002
categorical	-	-	0.007	0.006	0.011	0.006	0.002

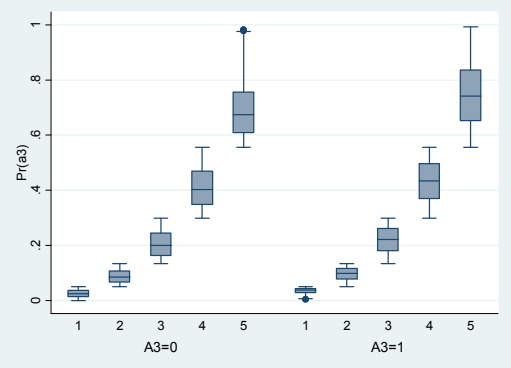
METHODS FIGURE 9 (PS1 BALANCE DIAGNOSTIC)



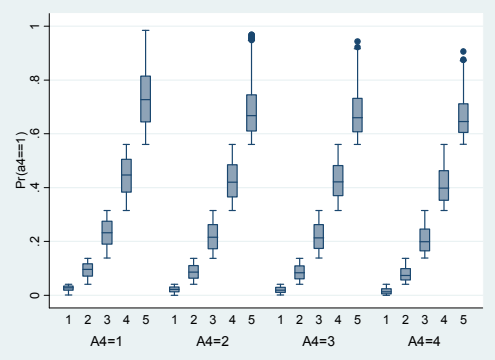
METHODS FIGURE 10 (PS2 BALANCE DIAGNOSTIC)



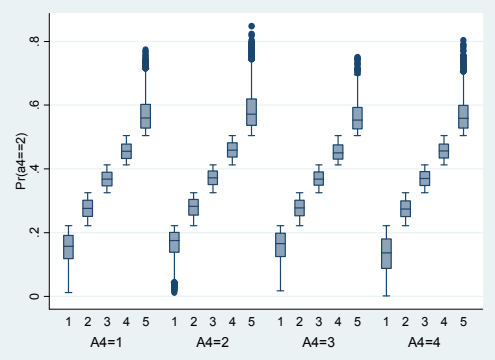
METHODS FIGURE 11 (PS3 BALANCE DIAGNOSTIC)



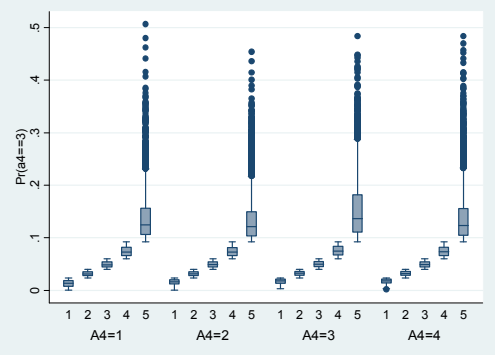
METHODS FIGURE 12A (PS4A BALANCE DIAGNOSTIC)



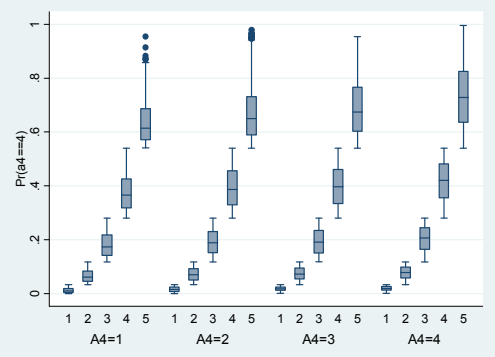
METHODS FIGURE 12B (PS4B BALANCE DIAGNOSTIC)



METHODS FIGURE 12C (PS4C BALANCE DIAGNOSTIC)



METHODS FIGURE 12D (PS4D BALANCE DIAGNOSTIC)



PROJECT 3: CLINICAL IMPORTANCE OF THE DRUG INTERACTION BETWEEN STATINS AND CYP3A4 INHIBITORS - A RETROSPECTIVE COHORT STUDY IN THE HEALTH IMPROVEMENT NETWORK (THIN)

Title of the paper: Statins and concomitant CYP3A4 inhibitors show no difference in statin-related adverse events based on statin metabolism

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Five key points:
1. We studied the relative hazard of muscle toxicity, renal dysfunction, and hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with a concomitant CYP3A4 inhibitor
2. We found no overall difference in muscle toxicity, renal dysfunction, and hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with a concomitant CYP3A4 inhibitor

3. The stratified dose response analysis showed a non-significant increased hazard of muscle toxicity for high dose statin 3A4 substrates with a CYP3A4 inhibitor compared to high dose statin non-3A4 substrates with a CYP3A4 inhibitor
4. The duration of response analysis showed a non-significant increased hazard of muscle toxicity in the first six months for statin 3A4 substrates with a CYP3A4 inhibitor compared to statin non-3A4 substrates with a CYP3A4 inhibitor
5. In this large drug interaction study of statins and CYP3A4 inhibitors, the overall results show no evidence of increased hazard of statin-related adverse events based on statin metabolism

Requests for reprints should be sent to:
crowan@mail.med.upenn.edu

ABSTRACT

Title: Statins and concomitant CYP3A4 inhibitors show no difference in statin-related adverse events based on statin metabolism

Background: Although generally safe, statins have the potential for severe adverse reactions.

Objective: To compare the relative hazard of muscle toxicity, renal dysfunction, and hepatic dysfunction between patients initiating statins metabolized by the CYP3A4 isoenzyme (statin-3A4 substrates (atorvastatin & simvastatin)) to patients initiating statins not metabolized by the CYP3A4 isoenzyme (statin non-3A4 substrates (fluvastatin, pravastatin, and rosuvastatin)) with and without CYP3A4 inhibitor concomitancy.

Methods: The Health Improvement Network (THIN) was used to conduct a retrospective cohort study from 1990-2008. Each cohort included new statin initiators and compared the relative hazard of statin-related adverse events. The interaction ratio (I*R) was the primary contrast of interest. The I*R represents the relative effect of each statin type (statin 3A4 substrate vs. statin non-3A4 substrate) with a CYP3A4 inhibitor, independent of the effect of the statin type without a CYP3A4 inhibitor. We adjusted for confounding variables using propensity scores.

Results: The median follow-up time per cohort was 1.5 years. There were 7889 muscle toxicity events among 362,809 patients. The adjusted muscle toxicity I*R was 1.22 (95% CI: 0.90-1.66). There were 1449 renal dysfunction events among 272,099 patients. The adjusted renal dysfunction I*R was 0.91 (95% CI: 0.58-1.44). There were 1434 hepatic dysfunction events among 367,612 patients. The adjusted hepatic dysfunction I*R was 0.78 (95% CI: 0.45-1.31).

Conclusions: Overall, this study found no difference in the relative hazard of muscle toxicity, renal dysfunction, or hepatic dysfunction for patients prescribed a statin-3A4 substrate versus a statin non-3A4 substrate with CYP3A4 inhibitor concomitancy.

INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are effective in the treatment of dyslipidemia, and have been shown to reduce the risk of major coronary outcomes and all cause mortality.[1, 2] While statins are well tolerated by the vast majority of patients, they are associated with infrequent muscle, renal, and hepatic adverse events.[3-9] Statin associated muscle and renal toxicity occur on a continuum from minor myalgias and proteinuria to severe myositis, renal failure, and fatal rhabdomyolysis.[10-12] Statin associated hepatic toxicity is characterized by transaminitis and rarely serious hepatic dysfunction or hepatic failure.[13, 14] Clinical trials, case reports, and observational studies show these adverse events are associated with all marketed statins.[9, 15-17] While the incidence of serious statin adverse events is low, muscle toxicity is a leading cause of statin discontinuation.[18, 19] It has been shown that statin-related adverse events occur in a potency dependent manner and therefore may be exacerbated by pharmacokinetic (PK) statin-drug interactions that increase statin system exposure.[8, 15, 20 17, 21 22-25]

Statin-drug interactions occur via inhibition of statin metabolic and/or non-metabolic (i.e., hepatic transport) pathways. Statin metabolism involves phase I oxidation (mediated by cytochrome P450 isoenzymes (CYP)) and phase II glucuronidation (mediated by UDP glucuronosyl transferase (UGT)). The specific hepatic isoenzymes mediating phase I statin metabolism are CYP3A4 (for atorvastatin and simvastatin), CYP2C8 (for cerivastatin), CPY2C9 (for fluvastatin), and CYP2C19 (rosuvastatin). [41, 42] Pravastatin undergoes negligible metabolism by CYP isoenzymes. It is primarily metabolized by glucuronidation (phase II). The non-metabolic statin pathways are mediated by influx and efflux transport proteins. Inhibition of statin metabolism (phase I or II) and/or hepatic transport (influx or efflux) results in elevated statin plasma concentrations and prolonged systemic exposure, which has the potential to increase the risk for statin-related adverse events.

Not all statins have the same drug interaction potential. The unique physiochemical property of each statin makes certain statins more likely to interact with concomitant medications. Of particular importance is the drug interaction between statins and drugs that inhibit the CYP3A4

metabolic pathway. The CYP3A4 isoenzyme is the most prevalent isoenzyme in the cytochrome P450 enzyme system. The CYP3A4 isoenzyme metabolizes more than 50% of marketed pharmaceuticals.[26] Statins that undergo phase I metabolism by the CYP3A4 isoenzyme are referred to as statin 3A4 substrates (atorvastatin and simvastatin). Statins that do no use the CYP3A4 isoenzyme metabolic pathway are referred to as statin non-3A4 substrates (pravastatin, fluvastatin, and rosuvastatin). CYP3A4 inhibitors prevent CYP3A4 isoenzymes from metabolizing other drugs (e.g., statin 3A4 substrates). As serious statin adverse events are potency and plasma concentration related, it is recognized that plasma levels of statins 3A4 substrates may increase with concomitant administration of CYP3A4 inhibitors.[27] Due to the documented increased systemic statin exposure (demonstrated through PK studies) and increased potential for adverse events, statin 3A4 substrate product labels warn against concomitant administration of these statins with CYP3A4 inhibitors. Despite these warnings, statin 3A4 substrates and CYP3A4 inhibitors are frequently co-prescribed.[51] Commonly used CYP3A4 inhibitors include calcium channel blockers, H2 receptor antagonists, antibiotics, antifungals, antidepressants, antiretrovirals, and immunosuppresants.[28]

Studies quantifying the relative hazard of statin adverse events for different statins (with different metabolism) with CYP3A4 inhibitor concomitancy are limited. The clinical importance of this drug interaction was described in an preliminary analysis of spontaneous adverse event reports associated with statin use.[22] In this investigation, we compared the adverse event reporting rate (AER) and ratio (AERR) of rhabdomyolysis reports for simvastatin (a statin 3A4 substrate) and pravastatin (a statin non-3A4 substrate) with versus without a CYP3A4 inhibitor. This study showed a six fold increase in the AERR for simvastatin (with vs. without a CYP3A4 inhibitor) and no increase for pravastatin (with vs. without a CYP3A4 inhibitor).[22] Given the limitations of spontaneous report analyses, further research was warranted to fully elucidate these findings.

The purpose of the current investigation was to study the clinical importance of the drug interaction between statins and CYP3A4 inhibitors in a large retrospective cohort study. Our specific aim was to determine the relative hazard of muscle toxicity, kidney dysfunction, and

hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with and without CYP3A4 inhibitor concomitancy. Given the physiochemical properties, drug interaction potential, and prior research, we hypothesized an increased relative hazard for statin 3A4 substrates compared to statin non-3A4 substrates with CYP3A4 inhibitor concomitancy.

METHODS

Study Population

The study population was drawn from The Health Improvement Network (THIN) from 1990 through October 2008. THIN is an anonymized electronic medical record database of primary care medical records from the United Kingdom (UK). The database consists of contributions from 415 general practices and data from more than three million actively registered patients (as of mid-year 2007). Record selection was restricted to acceptable medical records, ensuring that only patients currently or once permanently registered with a general practice were included.[68]

Statin initiators were eligible for cohort entry if they were eighteen years of age (at statin initiation) and registered with a general practice for twelve months prior to the first statin drug code. The twelve month period prior to statin initiation is referred to as the baseline period. The rationale for requiring a twelve month baseline period prior to statin initiation is to collect baseline medical, therapy, outcome, and confounder data.

Exclusion criteria were implemented based on information obtained prior to statin initiation. We excluded patients not continuously registered during the baseline period and those with a statin drug code prior to or during the baseline period. Cerivastatin initiators were excluded given the idiosyncratic increased risk for serious adverse events. We excluded patients with an organ transplant.

Definition of Exposure

As noted, the cohort included subjects exposed to statins. We categorized statin exposure by the metabolic properties of each statin with and without a concomitant CYP3A4 inhibitor. Statin 3A4 substrates, metabolized by the CYP3A4 isoenzyme, included atorvastatin and simvastatin. Statin non-3A4 substrates, not metabolized by the CYP3A4 isoenzyme, included fluvastatin, pravastatin, and rosuvastatin. Statin potency was evaluated as a categorical, time varying

covariate. Statin potency categorization was based on percent low density lipoprotein cholesterol (LDL-C) reduction.[69]

The four exposure categories included: statin 3A4 substrates with and without a concomitant CYP3A4 inhibitor and statin non-3A4 substrates with and without a concomitant CYP3A4 inhibitor. We identified CYP3A4 inhibitors from the University of Indiana's cytochrome P450 table.[28] We included concomitant exposure to the following CYP3A4 inhibitors: clarithromycin,[52] erythromycin,[70] telithromycin, norfloxacin, diltiazem,[25] verapamil,[70] mibefradil[71], amiodarone, ketoconazole,[72] itraconazole,[50] voriconazole, fluconazole[72], nefazodone,[73] fluvoxamine,[74] cyclosporine,[47] cimetidine, ritonavir, saquinavir, nelfinavir, indinavir, lopinavir, imatinib, and aprepitant. For use in secondary analyses, a strong inhibitor was defined as one that causes greater than 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.[28] A moderate inhibitor was defined as one that causes a greater than 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.[28]

Follow-up was measured in person-time on a statin, either with or without a concomitant CYP3A4 inhibitor, beginning after the first day of the first statin drug code and continued with subsequent statin drug codes. Due to the pharmacology of the drug interaction, we excluded outcomes occurring on the first day of statin exposure. Follow-up was censored at the first occurrence of: (i) the end of the statin days supplied (and no subsequent statin drug code), (ii) a drug code for a different statin (other than the one they initiated), (iii) the outcome in question, or (iv) the end of the study (October 2008). Each statin-exposed person-day was attributed to one of four exposure categories: (i) a statin 3A4 substrate with a CYP3A4 inhibitor, (ii) a statin 3A4 substrate without a CYP3A4 inhibitor, (iii) a statin non-3A4 substrate with a CYP3A4 inhibitor, and (iv) a statin non-3A4 substrate without a CYP3A4 inhibitor.

Definition of Outcome

To be classified as an outcome, the READ code or laboratory elevation must have occurred during or within thirty days following the end of included follow-up time, consistent with the work of Graham and colleagues.[8] The thirty day period following the end of statin exposure (with no subsequent statin exposure) accounts for imperfect patient adherence and delayed outcome

recording. Outcomes were attributed to one of the four exposure categories. If an outcome occurred more than thirty days following included follow-up time, patient follow-up was censored.

Outcome definitions were derived from recently published research on statin-related adverse events. [3-7, 75, 76] Each outcome was analyzed independently. We utilized medical diagnoses or laboratory evidence to identify incident outcomes. Medical diagnoses are recorded in THIN using READ codes which are analogous to ICD-9 codes. All READ codes and laboratory criteria were independently reviewed and verified by the study authors to identify muscle toxicity, renal dysfunction, and hepatic dysfunction (CR, SB, PR, JM, and JF).

Muscle toxicity was defined by a READ code for muscle symptoms (e.g., myalgia, myopathy, myositis, and muscle pain) or a creatine kinase (CK) elevation greater than five times the upper limit of normal (>5 X ULN).

Renal dysfunction was defined by a READ code for acute kidney injury, chronic kidney disease, end stage renal disease, dialysis, or a doubling of serum creatinine (sCr) (elevated to at least above the sCr upper limit of normal) over the baseline sCr or a single sCr value greater than twice the ULN (>2X ULN). The baseline sCr measurement was the lowest sCr value occurring within 365 days before the elevated sCr measurement. A secondary analysis excluded patients with a READ code for chronic kidney disease.

Hepatic dysfunction was defined as the first READ code for hepatic failure, toxic liver disease, acute liver necrosis, acute hepatitis, jaundice, or an ALT/AST measurement greater than five times the upper limit of normal (>5X ULN). We utilized the 5X ULN ALT/AST outcome threshold, consistent with the Drug-Induced Liver Injury Network criteria.[77] Additionally, we conducted a secondary analysis of severe transaminitis (using the ALT/AST threshold of 10X ULN).

Outcomes identified by laboratory evidence were considered confirmed. Outcomes identified by READ codes with no laboratory evidence but with additional outcome evidence from physician comments in the electronic medical record were also considered confirmed. We conducted secondary analyses using confirmed outcomes only.

Confounding Variables

We evaluated potential confounding variables associated with each outcome from previous research.[17, 19, 21, 78] Patient demographics and medical history were collected during or prior to the twelve month baseline period prior to statin initiation. Laboratory, patient surveillance, and pharmaceutical therapy data were collected only during the baseline period. Table 1 shows the specific potential confounding variables we evaluated.

Due to incomplete baseline laboratory data (e.g., cholesterol, CK, sCr, and ALT/AST), only baseline cholesterol was evaluated as a potential confounder. The other laboratory measures were used to evaluate the patient surveillance rate. That is, the number of normal (below the threshold for outcome/exclusion from the specific cohort) measurements during the baseline period.

Analysis

For each analysis, patients with documented evidence of the outcome prior to statin initiation were excluded, as were patients with chronic medical conditions related to that outcome. For the analyses of muscle outcomes, we excluded those with prior codes for that outcome, and also those who ever had a code for dermatomyositis or myositis specifically attributed to another disorder. For the analyses of the renal dysfunction outcome, we excluded those with prior codes for that outcome, patients with a sCr above the upper limit of normal within the twelve months prior to statin initiation, and also those who ever had codes for genetic kidney disease and chronic nephritis. For the analyses of the hepatic outcomes, we excluded patients with prior codes for that outcome, with an ALT or AST greater than 3X ULN within twelve months prior to statin initiation, and those who ever had a history of alcoholism and viral hepatitis. As noted, patients with chronic conditions (e.g., dermatomyositis, chronic nephritis, and alcoholism) were excluded, even if those chronic conditions were first diagnosed after cohort entry; since these were chronic conditions, we felt their appearance after cohort entry was simply a reflection of when the disease was recorded in the medical record, rather than the true onset of the condition. In a planned secondary analysis, we censored follow-up at documentation of these specific conditions, rather than excluding the entire patient record.

In descriptive analyses, continuous variables were described using means and categorical variables were described using percentages.

The primary effect estimates were derived through Cox proportional hazards regression.[79] Statin potency was included as a time varying covariate in each analytic model. The contrast of interest is the interaction ratio (I*R). The I*R is a ratio of two hazard ratios (HR). It represents the relative hazard of each statin type with a concomitant CYP3A4 inhibitor adjusted for the hazard of each statin type without a CYP3A4 inhibitor. This method controls for the hazard of the outcome associated with each statin type alone, thus, focusing on the effect on the differential hazard due to the statin-CYP3A4 inhibitor interaction.

In addition to the primary analyses, we conducted secondary analyses of those with confirmed outcomes. Other secondary analyses evaluated the effect of statin potency and duration of response.

In order to evaluate different CYP3A4 inhibitor potencies, we conducted secondary analyses restricted to CYP3A4 inhibitors exhibiting moderate and strong inhibitory characteristics. We also conducted secondary analyses based on duration of CYP3A4 inhibitor use. We evaluated the I*R for antibiotics and antifungals as short duration CYP3A4 inhibitors and other long duration use drugs (e.g., antihypertensives) as chronically used CYP3A4 inhibitors. We also present an analysis with specific concomitant CYP3A4 inhibitors.

To control for confounding we used the multinomial propensity score. Multinomial propensity score methodology was described by Imai and Imbens and applied by Huang.[61, 63, 64] The multinomial propensity score determines the probability of being in each exposure category given baseline covariates. Using the propensity score variable selection method described by Brookhart,[80] we included only baseline variables associated ($p<0.1$) with the outcome. This confounder selection procedure was conducted independently for each outcome. To assess baseline covariate balance we graphically evaluated the distribution of propensity scores for each of the four exposure categories. Graphic representation of propensity score distributions showed ample overlap to permit valid comparison among the four exposure categories (data not shown).

Missing data was handled using median value imputation and multiple imputation. For statins or CYP3A4 inhibitors missing the prescribed quantity or dosing instructions, we used median value imputation based on the derived median prescription duration for statins or CYP3A4 inhibitors with available prescribed quantity and dosing instructions. The proportion of statin and CYP3A4 inhibitor drug codes missing either the prescribed quantity or dosage instructions was 0.1 for statins and 0.2 for CYP3A4 inhibitors. Baseline body mass index (BMI) and cholesterol values were imputed using multiple imputation.[81] We determined the average propensity score adjusted interaction ratio from ten imputed datasets. Rubin's method was used to determine the variance; this method accounts for the within and between dataset variation.[81, 82]

Monte Carlo simulation was used to estimate empiric power. Based on an estimated 600,000 and 50,000 statin person-years with and without a concomitant CYP3A4 inhibitor (respectively), our empiric power simulations determined there was more than 80% power to detect an I*R of 2.0 (or above), for each outcome.

Stata version 11.1 was used to perform all analyses.

This study was approved by the Institutional Review Board at the University of Pennsylvania and registered with the National Health Service - Central Office for Research Ethics Committees (COREC), United Kingdom.

RESULTS

Figure 1 displays the subjects in the cohort who were excluded/included in each analysis. The median follow-up time in each analysis was 1.5 years (see Table 1). Approximately 88% of patients initiated a statin 3A4 substrate. Mean age, proportion of males, and BMI were balanced within between statin 3A4 substrate and statin non-3A4 substrate initiators.

The results for muscle toxicity (primary and confirmed outcome analyses) are presented in Table 2a. Baseline variables associated with muscle toxicity and therefore included in the propensity score adjusted model are listed at the bottom of Table 2a. The adjusted relative hazard of muscle toxicity for each statin type with a concomitant CYP3A4 inhibitor, adjusted for the effect of each statin type without a CYP3A4 inhibitor is depicted by the I*R. The primary muscle toxicity adjusted I*R (95% CI) was 1.22 (0.90-1.66). The confirmed muscle toxicity I*R

(adjusted) was 0.90 (0.53-1.52). Muscle toxicity hazard ratios for each statin type with versus without a CYP3A4 inhibitor are presented in Table 2a.

The results for renal dysfunction (primary analysis, confirmed outcome analysis, and CKD exclusion analyses) are presented in Table 2b. The baseline variables included in the propensity score adjusted model are listed at the bottom of Table 2b. For the primary renal dysfunction analysis the adjusted I*R was 0.91 (0.57-1.43). The confirmed renal dysfunction outcome I*R (adjusted) was 0.86 (0.50-1.45). The adjusted I*R excluding CKD outcomes was 0.91 (0.55-1.49). Renal dysfunction hazard ratios for each statin type with versus without a CYP3A4 inhibitor are presented in Table 2b.

The results for hepatic dysfunction (primary, confirmed, and ALT/AST >10X ULN) are presented in Table 2c. The baseline variables included in the propensity score adjusted model are listed at the bottom of Table 2c. For the primary analysis the adjusted I*R for renal dysfunction was 0.78 (0.45-1.33). The confirmed hepatic dysfunction outcome (adjusted) I*R was 0.66 (0.38-1.14). The adjusted I*R for the ALT/AST 10X ULN was 0.85 (0.39-1.87). Hepatic dysfunction hazard ratios for each statin type with versus without a CYP3A4 inhibitor are presented in Table 2c.

Statin potency analyses are presented in Table 3. The table shows specific statin dosages included in each category. The test for trend among the muscle toxicity potency strata was not significant (p=0.46). For renal dysfunction, due to sparse events (and person-years) in the statin non-3A4 substrate with a CYP3A4 inhibitor exposure category, we could not obtain an interaction ratio in the high potency strata.

Duration of response analyses are presented in Table 4. Due to sparse events in the statin non-3A4 substrate with a CYP3A4 inhibitor exposure category, we could not obtain stable interaction ratios earlier than six months following statin initiation. We also attempted to determine the I*R during the first course of statin therapy, but there were insufficient person-years and events to obtain stable I*R estimates. Given this, we stratified the duration of follow-up as follows: 0-6 months, 6-12 months, 12-24 months, and >24 months.

Table 5 describes the person-years and events for specific CYP3A4 inhibitors jointly prescribed with statins. Overall, the concomitant statin-CYP3A4 inhibitor person-years and events were similarly distributed for patients exposed to statin 3A4 substrates and statin non-3A4 substrates. For each cohort, diltiazem, verapamil, and amiodarone make up nearly 85% of all CYP3A4 inhibitor concomitancy among statin users.

The results from the secondary analysis censoring follow-up for patients with specific chronic medical conditions identified after statin initiation rather than excluding the entire patient record were consistent with the primary findings (data not shown). For each outcome, the I*R from the moderate/strong CYP3A4 inhibitor analysis and the short/chronic CYP3A4 inhibitor analysis were consistent from the primary analysis findings (data not shown).

DISCUSSION

For each outcome, the primary and confirmed analyses show no significant increased hazard associated with statin 3A4 substrates compared to statin non-3A4 substrates with a concomitant CYP3A4 inhibitor, adjusted for the hazard of each statin type without a concomitant CYP3A4 inhibitor. The I*R is an appropriate effect estimate for evaluating the clinical importance of drug interactions provided a suitable comparator group is available. For the primary and confirmed outcome analyses, statin person-years in each of the four exposure categories contributed sufficient person-years to allow I*R estimation. The results from this investigation indicate the clinical implications of this well documented drug interaction may be of less importance than suggested by pharmacokinetic studies, case reports, and analyses of spontaneous reports.

Pharmacokinetic studies consistently show rapidly increased systemic statin exposure with co-administration of statin 3A4 substrates and a CYP3A4 inhibitor compared to statin 3A4 substrates alone.[71, 83-85] The results of this study suggest the short term increased systemic statin exposure does not translate into increased hazard for statin-related adverse events. We evaluated the early effect this drug interaction by conducting a duration-of-response analysis. For renal and hepatic dysfunction, the I*R showed no increased hazard in the first six months following statin initiation. For muscle toxicity, the I*R showed a non-significant increased hazard

in the first six months following statin initiation (I*R=2.07 (0.95-4.48)). Further evaluation of muscle toxicity may be warranted within six months following the joint exposure to statins and CYP3A4 inhibitors.

Previous research shows statin potency is associated with muscle toxicity.[19, 21] As expected, we saw an increase in the hazard of all three outcomes for each successive increase in statin potency, not quite statistically significant for renal dysfunction (data not shown). However, the continuous potency analysis shows the association between statin potency and the outcome, but does not address the differential hazard for each statin type with a CYP3A4 inhibitor, compared to each statin type without a CYP3A4 inhibitor. This contrast (i.e., the I*R) is depicted in the stratified potency analyses, where the interaction ratios show no increasing effect in subsequent potency strata.

Other recent observational studies evaluated statin-associated adverse events with concomitant CYP3A4 inhibitors. Cziraky and colleagues reported a six fold (RR=6.01 95% CI (2.08-17.38)) increased risk of muscle toxicity for statins with CYP3A4 inhibitors compared to atorvastatin alone.[9] However, statin exposure was aggregated among all person-years attributed to cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin with a concomitant CYP3A4 inhibitor. Stratification of statin exposure by oxidative metabolism was not evaluated, so they could not disaggregate the independent risk from the CYP3A4 inhibitor from the risk from the drug interaction. In the present study, the interaction ratio separates the effect of the statin type with a CYP3A4 inhibitor from the effect of each statin type without a CYP3A4 inhibitor.

The results from the present study are also discordant from our preliminary spontaneous report study in which we found a six fold increased adverse event reporting rate ratio (AERR) for simvastatin reports with a concomitant CYP3A4 inhibitor compared to simvastatin reports without a concomitant CYP3A4 inhibitor.[22] Substantial methodologic differences favoring validity in the present study likely drive the inconsistent finding. The present study included only new statin initiators, excluded patients with prior outcomes, excluded organ transplant patients, used a validated electronic medical record database, adjusted for potential confounding variables, had a

true denominator of statin person-years with and without CYP3A4 inhibitor concomitancy, was not dependent on external outcome reporting, and used Cox proportional hazards regression to estimate the interaction ratio with 95% confidence intervals. Spontaneous report analyses are critical for signal generation. However, the conclusiveness of their findings is limited.[86] The present study is the largest observational study specifically designed to evaluate the clinical importance of the statin-CYP3A4 inhibitor drug interaction.

THIN has been used in many epidemiologic studies and has been validated for numerous medical conditions including studies of statin-related side effects.[87-89] Despite this, practice patterns, patient populations, prescribing patterns, and patient surveillance may be systematically different in the UK from in other countries. We compared the baseline patient characteristics in this study to those in other recent statin safety investigations.[3-7, 9, 75, 78, 90, 91] These baseline patient characteristics were consistent with the baseline patient characteristics from other US, Canadian, and European statin safety cohorts.

Regarding confounding, we did not control for variables which we could not identify or could not measure. However, we captured important variables previously shown to be risk factors for each outcome. We also separately controlled for confounding by chronic diseases, whether they were diagnosed before or after the initiation of the statin; the results were the same.

We addressed potential bias associated with depletion of susceptibles by including only new statin initiators. The rationale for employing the new user design is to circumvent under-ascertainment of outcomes occurring early in therapy and to evaluate potential confounders prior to statin exposure. This is important because some potential confounders (e.g., cholesterol) may change as a result of statin exposure. Furthermore, if outcomes occurred rapidly following statin initiation, as was expected with muscle toxicity and hepatic dysfunction, and if the occurrence of these early outcomes were associated with statin type, our estimates would be biased. The new user design diminishes this risk of this potential bias.

In order to minimize exposure misclassification, we defined precise exposure criteria for each exposure category, used up to date drug codes, and carefully constructed exposure episodes. Use of THIN diminishes the possibility of poor medication adherence, since in the UK

patients are given only a 28-day prescription at a time. Regardless, we would not expect medication adherence to differ by statin type.

One noteworthy class of CYP3A4 inhibitors not represented in this investigation is antiretroviral therapy (e.g., ritonavir, saquinavir, nelfinavir, indinavir, and lopinavir). This investigation included person-years of concomitant exposure to statins and antiretrovirals, but there was negligible use included in THIN. In the UK, antiretroviral treatment is given mainly by specialized genitourinary medical clinics, not by physicians in general practice. The results from this investigation may or may not extrapolate to statins with concomitant antiretroviral therapy.

Outcome misclassification threatens the validity of all retrospective cohort studies. To evaluate potential outcome misclassification, we conducted secondary analyses restricted to confirmed outcomes. This provided a sensitivity analysis to reveal the accuracy of our original outcome classification; the findings from the confirmed outcome analyses were consistent with the primary analyses.

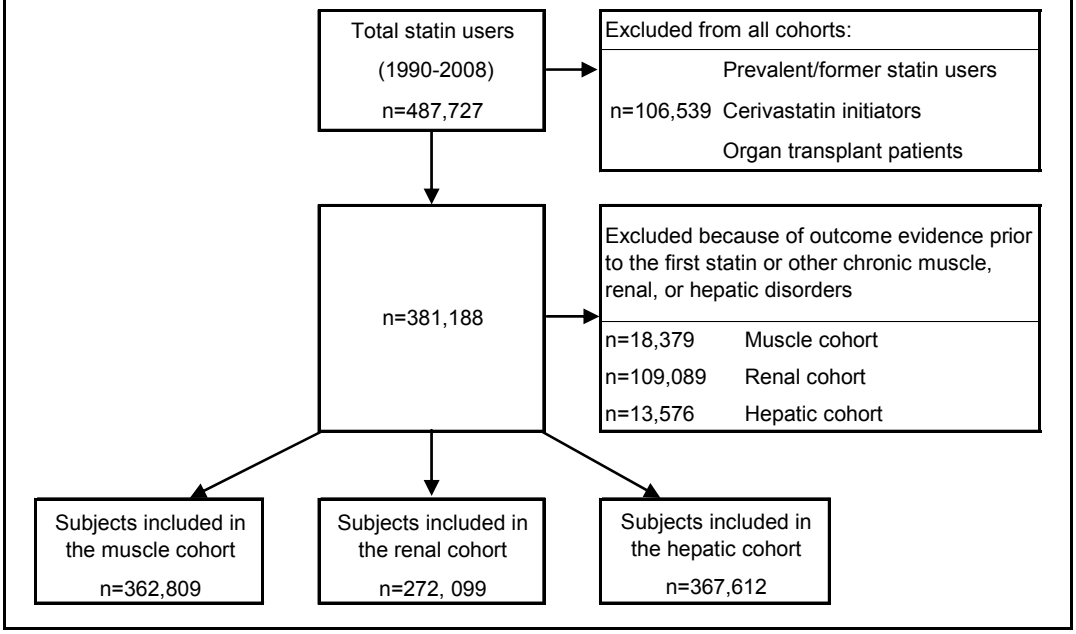
Conclusion

This large retrospective cohort study showed no overall increased hazard for muscle toxicity, renal dysfunction, or hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with versus without a concomitant CYP3A4 inhibitor. Additional research could further evaluate the non-significant yet increased muscle toxicity interaction ratio we observed for highly potent statin dosages and within six months following statin initiation. However, it is clear that the drug interaction between statins and CYP3A4 inhibitors does not represent an important public health concern.

TABLES

THIN FIGURE 1

Figure 1. Subjects excluded/included in the muscle, renal, hepatic cohorts



THIN TABLE 1

Table 1. Subject characteristics - (at or prior to the first statin)						
	Muscle cohort		Renal cohort		Hepatic cohort	
Baseline characteristics	**Statin 3A4 substrate**	**Statin non-3A4 substrate**	**Statin 3A4 substrate**	**Statin non-3A4 substrate**	**Statin 3A4 substrate**	**Statin non-3A4 substrate**
# of statin initiators	325,460	37,349	243,707	28,392	329,668	37,944
Age (mean)	63	64	62	62	64	63
<54	22%	22%	26%	27%	21%	22%
55-64	29%	30%	32%	32%	29%	30%
65-74	30%	32%	28%	29%	30%	32%
>75	20%	17%	14%	13%	20%	17%
Male	54%	54%	56%	56%	53%	53%
BMI (mean)	28	28	28	28	28	28
Alcoholism	1.6%	1.3%	1.9%	1.5%	excluded	excluded
Current smoker	11%	6%	12%	6%	11%	6%
Medical diagnoses (anytime prior to statin initiation)						
CHF	4%	5%	2%	3%	4%	5%
Previous MI	28%	37%	26%	35%	28%	37%
Previous Stroke	4%	5%	4%	4%	4%	5%
Diabetes	21%	19%	19%	16%	21%	19%
Hypertension	52%	49%	47%	45%	52%	49%
Hypothyroidism	4%	4%	4%	3%	5%	4%
Acute kidney disease	0.5%	0.4%	excluded	excluded	0.5%	0.4%
Chronic kidney disease	3.4%	1.2%	excluded	excluded	3.4%	1.2%
Acute liver disease	0.4%	0.3%	0.3%	0.3%	excluded	excluded
Chronic liver disease	0.3%	0.2%	0.3%	0.3%	excluded	excluded
Subject Surveillance Rate (within 12 months prior to statin initiation)						
Office visits	2.0	1.7	1.8	1.6	2.0	1.7
Serum creatinine	1.0	0.6	0.9	0.6	1.0	0.6
ALT or AST	0.7	0.4	0.7	0.4	0.7	0.4
Baseline labs (within12 months prior to statin initiation)						
Total cholesterol (mmol/L)						
n	273,245	26,734	202,169	19,707	276,993	27,150
% w/measurement	84.0	71.6	83.0	69.4	84.0	71.6
mean cholesterol	6.3	6.4	6.3	6.5	6.3	6.4
Serum creatinine (sCr) (µmol/L)						
n	235,183	18,122	166,387	12,124	238,169	18,395
% w/measurement	72.3	48.5	68.3	42.7	72.2	48.5
mean sCr	93.1	95.1	83.9	84.9	93.1	95.1
ALT or AST (U/L)						
n	150,614	8,827	109,144	6,195	151,670	8,887
% w/measurement	46.3	23.6	44.8	21.8	46.0	23.4
mean ALT	28.8	29.1	30.1	30.1	27.3	27.3
Creatine Kinase (CK) (U/L)						
n	16,090	1,120	11,625	800	17,012	1,172
% w/measurement	4.9	3.0	4.8	2.8	5.2	3.1
mean CK	112.1	112.0	126.0	131.2	122.8	124.3
First statin						
Atorvastatin	26%	-	25%	-	26%	-
Simvastatin	74%	-	75%	-	74%	-
Fluvastatin	-	17%	-	17%	-	17%
Pravastatin	-	64%	-	63%	-	64%
Rosuvastatin	-	19%	-	20%	-	19%
Standardized statin potency category (at statin initiation)						
Low	20%	59%	20%	59%	20%	59%
Medium	49%	23%	49%	22%	49%	23%
High	31%	18%	31%	19%	31%	18%
Pharmacotherapy (at statin initiation)						
CYP3A4 inhibitor	6%	8%	5%	7%	6%	8%
Diabetes drug	11%	10%	10%	8%	11%	10%
Hypertension drug	63%	64%	57%	60%	63%	65%
Thyroid drug	7%	7%	6%	6%	7%	7%
Gemfibrozil	0.1%	0.1%	0.1%	0.2%	0.1%	0.1%
Other fibrate	1.1%	1.8%	1.0%	1.8%	1%	2%
Niacin	0.0%	0.0%	0.0%	0.0%	0.01%	0.01%
Vitamin D	2.0%	1.4%	1.6%	1.1%	0%	0%

THIN TABLE 2A

Table 2a. Muscle toxicity analyses: number of events (events), person-years (p-y), incidence rates per 1000 person years (IR), unadjusted and adjusted hazard ratios (HR), and unadjusted and adjusted interaction ratios (I*R)

	Events	p-y	IR	Unadjusted HR (95% CI)	Adjusted† HR (95% CI)	Unadjusted I*R (95% CI)	Adjusted† I*R (95% CI)
Primary analysis							
statin 3A4 substrate‡ + CYP3A4X↑	446	50608	8.81	0.93 (0.85-1.03)	0.97 (0.88-1.07)	1.20 (0.89-1.63)	**1.22 (0.90-1.66)**
statin 3A4 substrate*	6688	657276	10.18				
statin non-3A4 substrate + CYP3A4X	49	7227	6.78	0.76 (0.57-1.01)	0.75 (0.56-1.00)		
statin non-3A4 substrate	706	77555	9.10				
Totals	**7889**	**792665**	**9.95**				
Confirmed outcomes							
statin 3A4 substrate + CYP3A4X	131	50608	2.59	0.79 (0.66-0.94)	0.88 (0.74-1.06)	0.87 (0.52-1.48)	**0.90 (0.53-1.52)**
statin 3A4 substrate	2358	657276	3.59				
statin non-3A4 substrate + CYP3A4X	17	7227	2.35	0.89 (0.54-1.46)	0.94 (0.57-1.55)		
statin non-3A4 substrate	212	77555	2.73				
Totals	**2718**	**792665**	**3.43**				

†Model adjusted for the following baseline variables (i.e., at or prior to statin initiation): age, sex, cholesterol, year at statin initiation, CHF, stroke, diabetes, hypothyroidism, fluoroquinolone antibiotics, diabetes drugs, thyroid drugs, number of office visits, sCr measurements, and ALT/AST measurements during the baseline period, statin potency (as a time varying covariate)

THIN TABLE 2B

Table 2b. Renal dysfunction analyses: number of events (events), person-years (p-y), incidence rates per 1000 person years (IR), unadjusted and adjusted hazard ratios (HR), and unadjusted and adjusted interaction ratios (I*R)

	Events	p-y	IR	Unadjusted	Adjusted†	Unadjusted	Adjusted†
				HR (95% CI)		I*R (95% CI)	
Primary							
statin 3A4 substrate + CYP3A4X	175	33543	5.22	2.10 (1.79-2.46)	1.69 (1.43-1.99)	0.95 (0.60-1.50)	**0.91 (0.57-1.43)**
statin 3A4 substrate	1119	478830	2.34				
statin non-3A4 substrate + CYP3A4X	25	4872	5.13	2.21 (1.44-3.39)	1.80 (1.16-2.79)		
statin non-3A4 substrate	130	57339	2.27				
Totals	**1449**	**574584**	**2.52**				
Confirmed outcomes							
statin 3A4 substrate + CYP3A4X	131	33543	3.91	2.53 (2.09-3.05)	2.15 (1.77-2.60)	0.90 (0.51-1.46)	**0.86 (0.50-1.45)**
statin 3A4 substrate	701	478830	1.46				
statin non-3A4 substrate + CYP3A4X	20	4872	4.10	2.80 (1.71-4.56)	2.23 (1.35-3.69)		
statin non-3A4 substrate	82	57339	1.43				
Totals	**934**	**574584**	**1.63**				
Excluding chronic kidney disease outcomes							
statin 3A4 substrate + CYP3A4X	152	33543	4.53	2.20 (1.85-2.62)	1.75 (1.46-2.08)	0.96 (0.59-1.57)	**0.91 (0.55-1.49)**
statin 3A4 substrate	935	478847	1.95				
statin non-3A4 substrate + CYP3A4X	22	4872	4.52	2.27 (1.44-3.60)	1.79 (1.12-2.86)		
statin non-3A4 substrate	111	57339	1.94				
Totals	**1220**	**574601**	**2.12**				

†Model adjusted for the following baseline variables (i.e., at or prior to statin initiation): age, sex, BMI, cholesterol, alcoholism, year at statin initiation, CHF, MI, stroke, diabetes, hypertension, vitamin D, diabetes drug use, hypertension drug use, # of office visits during the baseline period, statin potency (as a time varying covariate)

THIN TABLE 2C

Table 2c. Hepatic dysfunction analyses: number of events (events), person-years (p-y), incidence rates per 1000 person years (IR), unadjusted and adjusted hazard ratios (HR), and unadjusted and adjusted interaction ratios (I*R)

	Events	p-y	IR	Unadjusted	Adjusted†	Unadjusted	Adjusted†
				HR (95% CI)		I*R (95% CI)	
Primary analysis							
statin 3A4 substrate + CYP3A4X	116	52957	2.19	1.25 (1.03-1.52)	1.19 (0.97-1.44)	0.78 (0.46-1.32)	**0.78 (0.46-1.33)**
statin 3A4 substrate	1183	675312	1.75				
statin non-3A4 substrate + CYP3A4X	18	7624	2.36	1.62 (0.99-2.66)	1.64 (0.98-2.72)		
statin non-3A4 substrate	117	80052	1.46				
Totals	**1434**	**815945**	**1.76**				
Confirmed outcomes							
statin 3A4 substrate + CYP3A4X	97	52957	1.83	1.21 (0.98-1.50)	1.20 (0.97-1.49)	0.65 (0.37-1.11)	**0.66 (0.38-1.14)**
statin 3A4 substrate	1024	675312	1.52				
statin non-3A4 substrate + CYP3A4X	18	7624	2.36	1.86 (1.12-3.07)	2.01 (1.20-3.36)		
statin non-3A4 substrate	102	80052	1.27				
Totals	**1241**	**815945**	**1.52**				
ALT/AST 10X ULN OR med codes							
statin 3A4 substrate + CYP3A4X	62	52961	1.17	1.27 (0.97-1.65)	1.14 (0.87-1.49)	0.86 (0.39-1.88)	**0.85 (0.39-1.87)**
statin 3A4 substrate	627	675358	0.93				
statin non-3A4 substrate + CYP3A4X	8	7625	1.05	1.47 (0.70-3.09)	1.34 (0.63-2.86)		
statin non-3A4 substrate	57	80056	0.71				
Totals	**754**	**816000**	**0.92**				

†Model adjusted for the following baseline variables (i.e., at or prior to statin initiation): age, sex, cholesterol, year at statin initiation, CHF, MI, stroke, diabetes, hypertension, hypothyroidism, diabetes drugs, hypertension drugs, # of office visits, sCr measurements, ALT/AST measurements in the 12 months prior to statin initiation, statin potency (as a time varying covariate)

THIN TABLE 3

Table 3. Standardized potency† analysis

Outcome	Statin Potency†	# of Events	Person-years	IR/1000 p-y	Adjusted‡ I*R	95% CI
Muscle toxicity	low[1]	1436	166470	8.63	1.06	(0.87-1.12)
	medium[2]	3405	348824	9.76	1.28	(0.77-2.11)
	high[3]	3048	277371	10.99	2.85	(0.70-11.62)
Renal dysfunction	low	291	120934	2.41	0.84	(0.39-1.83)
	medium	620	251108	2.47	0.78	(0.42-1.45)
	high	538	202542	2.66	-	-
Hepatic dysfunction	low	257	171580	1.50	0.51	(0.22-1.15)
	medium	609	359195	1.70	1.27	(0.97- 1.67)
	high	568	284086	2.00	0.97	(0.13-7.45)

† Statin potency standardization

[1] Low potency: < 25% LDL-C reduction (atorvastatin <=5mg, simvastatin <=10mg, fluvastatin <=20mg, pravastatin <=20)

[2] Medium potency: 25-30% LDL-C reduction (atorvastatin 10mg, simvastatin 20mg, fluvastatin 80mg, pravastatin 40)

[3] High potency: is >30% LDL-C reduction (atorvastatin >=20mg, simvastatin >=40mg, fluvastatin 160mg, pravastatin >=80, rosuvastatin >=5mg)

‡ Models adjusted for the same variables in the primary analysis. See tables 3a, 3b, 3c for specific variables.

THIN TABLE 4

Table 4. Duration of response analysis for muscle toxicity, renal dysfunction, and hepatic dysfunction stratified by statin 3A4 substrates and statin non-3A4 substrates with and without a CYP3A4 inhibitor (cyp).

Outcome	Months	Events & P-years	Statin 3A4 substrate		Statin non-3A4 substrate		Totals	IR/1000 p-y	Adjusted‡ I*R	95% CI
			cyp +	cyp -	cyp +	cyp -				
Muscle toxicity	0-6	events	122	2520	7	211	2860	23.12	**2.07**	(0.95-4.49)
		p-years	6509	104377	1019	11781	123685			
	6-12	events	63	1082	10	89	1244	9.89	**0.72**	(0.36-1.44)
		p-years	6678	106370	1018	11772	125838			
	12-24	events	78	1264	8	137	1487	7.77	**1.37**	(0.65-2.89)
		p-years	10988	160601	1629	18213	191431			
	>24	events	183	1822	24	269	2298	6.54	**1.20**	(0.79-1.87)
		p-years	26433	285624	3561	35789	351408			
Renal dysfunction	0-6	events	22	198	3	19	242	2.63	**0.96**	(0.26-3.51)
		p-years	4363	78150	710	8959	92183			
	6-12	events	17	153	3	12	185	2.00	**0.60**	(0.15-2.33)
		p-years	4454	78550	699	8821	92524			
	12-24	events	30	210	5	25	270	1.94	**0.89**	(0.32-2.51)
		p-years	7236	117080	1097	13524	138937			
	>24	events	106	558	14	74	752	3.00	**0.99**	(0.54-1.82)
		p-years	17489	205049	2366	26035	250939			
Hepatic dysfunction	0-6	events	17	296	4	23	340	2.71	**0.43**	(0.13-1.38)
		p-years	6702	105868	1061	11982	125614			
	6-12	events	11	172	2	15	200	1.56	**0.65**	(0.13-3.19)
		p-years	6904	108304	1063	12035	128305			
	12-24	events	21	259	4	25	309	1.58	**0.67**	(0.21-2.09)
		p-years	11387	164342	1704	18696	196130			
	>24	events	67	456	8	54	585	1.60	**1.08**	(0.49-2.36)
		p-years	27964	296798	3796	37339	365897			

‡ Models adjusted for the same variables in the primary analysis. See tables 3a, 3b, 3c for specific variables.

THIN TABLE 5

Table 5. Descriptive analysis of statin person-years and events with and without specific concomitant CYP3A4 inhibitors for muscle toxicity, renal dysfunction, and hepatic dysfunction stratified by statin 3A4 substrates and statin non-3A4 substrates.

	Muscle toxicity						Renal dysfunction						Hepatic dysfunction					
	Statin 3A4 substrate			Statin non-3A4 substrate			Statin 3A4 substrate			Statin non-3A4 substrate			Statin 3A4 substrate			Statin non-3A4 substrate		
	p-years	%†	Events	p-years	%†	Events	p-years	%†	Events	p-years	%†	Events	p-years	%†	Events	p-years	%†	Events
Statin w/o CYP3A4 inhibitor	657726	-	6688	77555	-	706	478830	-	1119	57339	-	130	675312	-	1183	80052	-	117
Statin w/ CYP3A4 inhibitor	50608	-	446	7227	-	49	33543	-	175	4872	-	25	52957	-	116	7624	-	18
Specific concomitant CYP3A4 inhibitors																		
Diltiazem	36770	72.75	330	5083	70.65	36	25835	77.04	85	3644	74.88	9	38558	73.05	57	5318	70.89	11
Amiodarone	7644	15.11	57	1214	16.78	7	3548	10.58	67	623	12.81	11	7807	14.79	42	1243	16.57	7
Cimetidine	3218	6.37	22	483	6.71	1	2048	6.11	10	309	6.35	1	3361	6.37	9	500	6.66	1
Verapamil	2111	4.18	29	283	3.93	2	1481	4.42	7	198	4.08	1	2211	4.19	4	288	3.84	-
Erythromycin	777	1.54	9	98	1.36	-	545	1.63	2	72	1.48	-	816	1.55	2	104	1.39	-
Clarithromycin	447	0.88	4	70	0.98	-	321	0.96	6	51	1.06	2	474	0.90	1	74	0.99	-
Cyclosporine	183	0.36	2	66	0.92	3	63	0.19	2	29	0.59	1	179	0.34	1	65	0.87	-
Fluconazole	101	0.20	1	13	0.18	-	76	0.23	1	8	0.17	-	106	0.20	1	13	0.18	-
Fluvoxamine	80	0.16	1	9	0.13	-	68	0.20	-	8	0.17	-	75	0.14	-	9	0.13	-
Nefazadone	42	0.08	-	16	0.22	-	33	0.10	-	13	0.26	-	48	0.09	-	15	0.19	-
Itraconazole	34	0.07	-	5	0.07	-	27	0.08	-	3	0.06	-	34	0.07	-	5	0.07	-
Norfloxacin	23	0.05	-	3	0.04	-	18	0.05	-	2	0.04	-	27	0.05	-	3	0.04	-
Ketoconazole	3	0.01	-	1	0.01	-	3	0.01	-	0	0.00	-	3	0.01	-	1	0.01	-
Mibefradil	2	0.00	-	4	0.05	-	1	0.00	-	3	0.06	-	2	0.00	-	4	0.05	-
Imatinib	0	0.00	-	-	-	-	0	0.00	-	-	-	-	0	0.00	-	-	-	-
Voriconazole	0	0.00	-	0	0.00	-	0	0.00	-	-	-	-	0	0.00	-	0	0.00	-

† percent of total concomitant statin plus CYP3A4 inhibitor person-years

DISSERTATION CONCLUSION

This research endeavor evaluated the clinical importance of the drug interaction between statins and CYP3A4 inhibitors. Two empiric investigations and a methodologic study were conducted. The preliminary empiric study (the AERS study) showed an increased adverse event reporting rate of rhabdomyolysis for simvastatin, a statin 3A4 substrate statin, with a concomitant CYP3A4 inhibitor. There was no increased adverse event reporting rate for pravastatin, a statin non-3A4 substrate, with a concomitant CYP3A4 inhibitor. These results supported observations in clinical trials and case reports regarding increased risk of muscle toxicity for statin 3A4 substrates with concomitant CYP3A4 inhibitors. However, substantial limitations of internal validity, inherent in spontaneous report analyses, warranted additional research to fully elucidate these findings.

To assess the validity of the multinomial propensity score, we evaluated the statistical performance of different propensity score methods in the setting of a simulated drug interaction study. The results from this methodologic investigation showed the multinomial propensity score reduced bias, had greater coverage probability, and increased precision than comparator binary propensity score methods. Investigators studying drug-drug interactions may consider the multinomial propensity score approach for confounding adjustment.

To further address the clinical importance of this drug interaction, we conducted a retrospective cohort study in the THIN database (the THIN study). This was the largest study specifically designed to evaluate statin-related adverse events based on statin metabolism with CYP3A4 inhibitor concomitancy. We used a multinomial propensity score to control confounding. The results of this study showed no overall increased hazard for muscle toxicity, renal dysfunction, or hepatic dysfunction associated with statin 3A4 substrates compared to statin non-3A4 substrates with versus without a concomitant CYP3A4 inhibitor. We only identified a non-significant increased hazard of muscle toxicity for highly potent statin dosages and within six months following statin initiation for statin 3A4 substrates compared to statin non-3A4 substrates. Given the magnitude of this investigation, the drug interaction between statins and CYP3A4 inhibitors does not represent a substantial public health concern.

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