1. TITLE PAGE

Project Title: Clinical importance of the drug interaction between statins and CYP3A inhibitors

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2. STRUCTURED ABSTRACT

Purpose: To compare the relative hazard of muscle toxicity, renal dysfunction, and hepatic dysfunction associated with the drug interaction between statins and concomitant medications that inhibit the CYP3A4 isoenzyme.

Scope: Although statins provide important clinical benefits related to mitigating the risk of cardiovascular events, this class of medications also has the potential for severe adverse reactions. The risk for adverse events may be potentiated by concomitant use of medications that interfere with statin metabolism.

Methods: Data from The Health Improvement Network (THIN) from 1990-2008 were used to conduct a retrospective cohort study. Cohorts were created to evaluate each outcome (muscle toxicity, renal dysfunction, and hepatic dysfunction) independently. Each cohort included new statin initiators and compared the relative hazard of the outcome. 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 the multinomial propensity score.

Results: The median follow-up time per cohort was 1.5 years. There were 7889 muscle toxicity events among 362,809 patients and 792,665 person-years. 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 and 574,584 person-years. 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 and 815,945 person-years. The adjusted hepatic dysfunction I*R was 0.78 (95% CI: 0.45-1.31). 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.

Key words: Statins, CYP3A4 inhibitors, renal dysfunction, hepatic dysfunction, muscle toxicity, myopathy, myalgia, rhabdomyolysis, drug-drug interaction, DDI, propensity score, multinomial propensity score

3. PURPOSE

The purpose of the current investigation was to detect adverse clinical outcomes associated with statins and CYP3A4 inhibitors. Our specific aim was to measure the relative hazard of muscle toxicity, kidney dysfunction, and hepatic dysfunction associated with statin 3A4 substrates compared with statin non-3A4 substrates with and without CYP3A4 inhibitor concomitancy.

4. SCOPE

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] Though statins are well tolerated by the vast majority of patients, their use can lead to infrequent muscle, renal, and hepatic adverse events.[3-9] 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 the statin's systemic exposure.[8, 15, 20 17, 21, 22-25] Of particular importance is the drug interaction between statins and drugs that inhibit the CYP3A4 metabolic pathway.

Because of unique physiochemical properties, not all statins have the same drug interaction potential. Statins that undergo phase I metabolism by the CYP3A4 isoenzyme are referred to as statin 3A4 substrates (atorvastatin and simvastatin). Statins that do not 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 a result of this interaction, it is recognized that plasma levels of statins 3A4 substrates may increase with concomitant administration of CYP3A4 inhibitors.[27] This may in turn increase the risk of significant statin toxicity. Because of the documented increased systemic statin exposure, 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.[28] Commonly prescribed CYP3A4 inhibitors include calcium channel blockers, histamine H2 receptor antagonists, antibiotics, antifungals, antidepressants, antiretrovirals, and immunosuppressants.[29]

5. METHODS

Study Design and Population

We conducted a retrospective cohort study using 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).[30] As of October 2008, THIN consisted of contributions from 415 general practices and data from more than three million actively registered patients. This study included only patients currently or once permanently registered with a general practice.[31]

Inclusion/exclusion criteria

We assembled statin-naïve cohorts with no history of the outcome event (renal dysfunction, hepatic dysfunction, or muscule injury). New statin initiators were eligible for cohort entry if they were at least 18 years old at first statin initiation and registered with a general practice for 12 consecutive months prior to the first statin drug prescription (the baseline period).

Cerivastatin initiators were excluded given the associated idiosyncratic increased risk for serious adverse events. [8, 15] For the renal dysfunction cohort, we also excluded patients with a serum creatinine (sCr) above the upper limit of normal during the baseline period. For the hepatic cohort, we excluded patients with a transaminase level (ALT or AST) greater than three times the upper limit of normal ULN during the baseline period.

We excluded patients with an organ transplant prior to statin initiation and patients with relevant chronic medical conditions. The excluded chronic medical conditions were history of dermatomyositis (for the muscle toxicity cohort), genetic kidney disease and chronic nephritis (for the renal dysfunction cohort), and a history of alcoholism and viral hepatitis (for the hepatic dysfunction cohort). We also excluded patients with these chronic medical conditions if they were identified during follow-up because of a concern that these conditions may have been present prior to the date of recording in the medical record. In a pre-specified secondary analysis, we instead censored follow-up at documentation of these specific chronic medical conditions, rather than excluding the entire patient record.

Definition of Exposure

The cohort included subjects exposed to statins with and without a concomitant CYP3A4 inhibitor. We categorized statin exposure by the metabolic properties of each statin. Statin 3A4 substrates, metabolized by the CYP3A4 isoenzyme, were atorvastatin and simvastatin. Statin non-3A4 substrates, not metabolized by the CYP3A4 isoenzyme, were fluvastatin, pravastatin, and rosuvastatin.

We identified CYP3A4 inhibitors from the University of Indiana's cytochrome P450 table.[29] We included concomitant exposure to the following CYP3A4 inhibitors: clarithromycin,[33] erythromycin,[34] telithromycin, norfloxacin, diltiazem,[25] verapamil,[34] mibefradil,[35] amiodarone, ketoconazole,[36] itraconazole,[37] voriconazole, fluconazole,[36] nefazodone,[38] fluvoxamine,[39] cyclosporine,[40] cimetidine, ritonavir, saquinavir, nelfinavir, indinavir, lopinavir, imatinib, and aprepitant.

To evaluate the potential drug interaction by statin metabolism, we classified the following four exposure categories: (i) statin 3A4 substrates with a concomitant CYP3A4, (ii) statin 3A4 substrates without a concomitant CYP3A4 inhibitor, (iii) statin non-3A4 substrates with a concomitant CYP3A4 inhibitor, and (iv) statin non-3A4 substrates without a concomitant CYP3A4 inhibitor. Statin exposure with and without a concomitant CYP3A4 inhibitor was evaluated in a time-varying manner. That is, subjects could contribute person-time to both the statin with a concomitant CYP3A4 inhibitor category and the statin without a concomitant CYP3A4 inhibitor category.

Statin potency was evaluated as a categorical, time-varying covariate. Statin potency categorization was based on percent low-density lipoprotein cholesterol (LDL-C) reduction in that dose range.[41] In the primary analyses, we did not account for different strengths of CYP3A4 metabolic inhibition for different CYP3A4 inhibitors. In planned secondary analyses, we stratified by the strength of CYP3A4 inhibition. A strong CYP3A4 inhibitor was defined as one that causes greater than a five-fold increase in plasma AUC values or a more than 80% decrease in clearance.[29] A moderate inhibitor was defined as one that causes a greater than two-fold increase in the plasma AUC values or a 50-80% decrease in clearance.[29]

Follow-up and Censoring

Follow-up was measured in person-years on a statin, either with or without a concomitant CYP3A4 inhibitor, beginning after the first day of the first statin drug prescription and continuing with subsequent statin prescriptions. We excluded outcomes occurring on the first day of statin exposure because of pharmacological data suggesting that a single day of statin exposure is not sufficient to cause an adverse event. Follow-up was censored at the first occurrence of (i) the end of the statin days supplied, (ii) prescription of a statin other than the one that triggered cohort entry, (iii) the outcome in question, or (iv) the end of the study (October 2008).

Definition of Outcome

Outcome definitions were derived from recently published research on statin-related adverse events.[3-7, 42, 43] 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 (analogous to ICD-9 codes). The lists of specific READ codes are available from the corresponding author.

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 (>5X 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 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.[44] 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. Records from patients with outcomes identified by READ codes but with no laboratory evidence were reviewed for additional supporting evidence. We searched physician comments associated with each READ code event. Read code-based events, in which additional physician comments supported the suspected event, were also considered confirmed. We conducted secondary analyses using confirmed outcomes only.

Outcome timing

To be classified as an outcome, the READ code or laboratory elevation must have occurred within 30 days after the end of follow-up time, consistent with the work of Graham and colleagues.[8] The 30-day period after the end of statin exposure (with no subsequent statin exposure) accounts for imperfect patient adherence and delayed outcome recording. Outcomes occurring during follow-up time

were attributed to the current exposure category. Outcomes occurring within 30 days after the included follow-up time were attributed to the prior exposure category. Outcomes occurring more than 30 days after included follow-up time were not included in the analysis, and patient follow-up was censored.

Confounding Variables

We identified potential confounding variables associated with each outcome from previous research; these variables are listed in Table 1.[17, 19, 21, 45] Patient demographics and medical history were collected during or prior to the baseline period before statin initiation. To depict each patient's current health status, physician care, and concomitant therapies, laboratory data, patient surveillance, and pharmacotherapy confounders were collected only during the baseline period.

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

Analysis

Stata version 11.1 (Stata Corporation, College Station, Texas, USA) was used to perform all analyses. Continuous variables were described using means, and categorical variables were described using percentages.

Primary analysis

The primary effect estimates (for each outcome independently) were derived through Cox proportional hazards regression.[46] The contrast of interest is the interaction ratio (I*R). The I*R is a ratio of two hazard ratios (HRs). It represents the relative hazard of each statin type (statin 3A4 substrate vs. statin non-3A4 substrate) 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.

Secondary analyses

All secondary analyses used the same analytic method as described in the primary analysis. We conducted secondary analyses restricted to confirmed outcomes. Confirmed outcomes were determined

by obtaining additional outcome evidence in the electronic physician notes. Additionally, we evaluated the effect (I*R) of statin potency (low, medium, and high potency) and duration of response at specific time intervals (0-6, 6-12, 12-24, >24 months). We evaluated different potencies of CYP3A4 inhibition using the categorization from the University of Indiana's cytochrome P450 table. These analyses restricted concomitant exposure to CYP3A4 inhibitors exhibiting moderate and strong inhibitory characteristics. We also conducted secondary analyses stratified by chronic (e.g., calcium channel blockers) and acute (e.g., antibiotics and antifungals) concomitant CYP3A4 inhibitors. Additionally, we describe statin and CYP3A4 inhibitor concomitant person-years of exposure and events for each CYP3A4 inhibitor evaluated by statin type (statin 3A4 substrate and statin non-3A4 substrate).

Propensity score adjustment

To adjust for confounding, we used the multinomial propensity score methodology. The multinomial propensity score is the probability of being in each exposure category given baseline covariates.[47-49] Given four exposure categories, we modeled three (of the four) propensity scores in each analytic model. Using the propensity score variable selection method described by Brookhart et al.,[50] 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

For statins or CYP3A4 inhibitors missing the prescribed quantity or dosing instructions, we used median value imputation based on the 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 was 0.2 for CYP3A4 inhibitors. Baseline body mass index (BMI) and cholesterol values were imputed using multiple imputation.[51] We determined the average propensity score adjusted interaction ratio from 10 imputed datasets. Variance determination accounted for the within- and between-dataset variation.[51, 52]

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

6. RESULTS

Figure 1 displays the subjects in the cohort who were included/excluded in each analysis. The median follow-up time in each analysis was 1.5 years (Table 1). Approximately 88% of patients initiated a statin 3A4 substrate. Mean age, gender, and BMI were balanced for statin 3A4 substrate and statin non-3A4 substrate initiators. Baseline variables associated with each outcome and therefore included in the propensity score adjusted model (for that specific analysis) are listed at the bottom of each results table (Tables 2a, 2b, and 2c).

Muscle toxicity results

Table 2a shows results for muscle toxicity (primary and confirmed outcome analyses). 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, was 1.22 (95% confidence interval [CI]: 0.90-1.66).

Renal dysfunction results

Table 2b shows results for renal dysfunction (primary, confirmed outcomes, and the analysis excluding CKD outcomes). For the primary renal dysfunction analysis the adjusted I*R was 0.91 (95% CI: 0.57-1.43).

Hepatic dysfunction results

Table 2c shows results for hepatic dysfunction (primary, confirmed outcomes, and ALT/AST >10X ULN). For the primary analysis, the adjusted I*R for renal dysfunction was 0.78 (95% CI: 0.45-1.33). The confirmed hepatic dysfunction outcome (adjusted) I*R was 0.66 (95% CI: 0.38-1.14). The adjusted I*R for the ALT/AST 10X ULN was 0.85 (95% CI: 0.39-1.87).

Statin potency results

Table 3 shows the results for the statin potency analyses. The test for trend among the muscle toxicity potency strata was not significant (p=0.46). For renal dysfunction, because of 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 results

Duration of response analyses are presented in Table 4. Because of sparse events in the statin non-3A4 substrate with a CYP3A4 inhibitor exposure category, we could not obtain stable interaction ratios earlier than 6 months after 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. We found a nonsignificant increased hazard of muscle toxicity for statin 3A4 substrates with a CYP3A4 inhibitor compared with statin non-3A4 substrates with a CYP3A4 inhibitor in the 0-6--month strata (adjusted I*R = 2.07 [95% CI: 0.95-4.49]).

Other secondary analysis results

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). Results from the moderate/strong CYP3A4 inhibitor analyses and the short/long duration use CYP3A4 inhibitor analyses showed no increased hazard for statin 3A4 substrates compared with statin non-3A4 substrates (data not shown).

Our analyses showed no significant increased hazard associated with statin 3A4 substrates compared with statin non-3A4 substrates with a concomitant CYP3A4 inhibitor, adjusted for the hazard of each statin type without a concomitant CYP3A4 inhibitor. Unlike previous research of the statin-CYP3A4 inhibitor interaction, this study was well powered (except for the first statin course with and without a concomitant CYP3A4 inhibitor); had detailed information on comorbidities and confounders; used propensity score adjustment; and used the interaction ratio (I*R) to control for the hazard associated with each statin type alone, thus focusing on the effect on the differential hazard due to the statin-CYP3A4 inhibitor interaction. 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-time in each of the four exposure categories was sufficient 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 higher systemic statin exposure with co-administration of statin 3A4 substrates and a CYP3A4 inhibitor compared with statin 3A4 substrates alone.[35, 53-55] However, the long-term effect and clinical importance of elevated statin exposure are not well characterized. The results of this study suggest the increased systemic statin exposure may not translate into an increased hazard for statin-related adverse events. However, in the duration-response analysis for muscle toxicity, the I*R showed a nonsignificantly increased hazard in the first 6 months after statin initiation (I*R=2.07 [0.95-4.48]) and for the first statin course with and without a concomitant CYP3A4 inhibitor (data not shown). Additional investigation of muscle toxicity is warranted to evaluate the early effect of joint exposure to statins and CYP3A4 inhibitors.

Previous research suggests statin potency is associated with muscle toxicity.[19, 21] Consistent with previous findings, we saw a significant increased hazard of all three outcomes for each successive increase in statin potency; however, the change was not quite statistically significant for renal dysfunction (data not shown). Although the continuous statin potency analyses, not accounting for the potential interaction with CYP3A4 inhibitor concomitancy, depict the relationship between statin potency and the outcome, they do not reveal the differential effect for each statin type with a CYP3A4 inhibitor compared with each statin type without a CYP3A4 inhibitor at each potency level. This contrast (i.e., the I*R) is depicted in the stratified potency analyses, in which the I*Rs show a nonsignificantly increasing hazard of muscle toxicity with increasing statin potency but no difference for renal or hepatic dysfunction with increasing statin potency. Additional evaluation of the muscle toxicity I*R for highly potent statin doses with CYP3A4 inhibitor concomitancy may be warranted. That said, the muscle toxicity I*R (I*R 2.85; 95% CI: 0.70-11.62) for highly potent statins was derived from a large sample size (277,371 person-years of statin exposure) and many muscle toxicity events (3048). It would take a much larger sample size to improve I*R precision.

Our results must be placed into the context of other observational studies showing an increased risk of statin-associated adverse events with concomitant CYP3A4 inhibitors. Cziraky and colleagues reported a six-fold relative risk (RR=6.01; 95% CI: 2.08-17.38) of muscle toxicity for statins with CYP3A4 inhibitors compared with atorvastatin alone.[9] However, statin plus concomitant CYP3A4 inhibitor exposure was

aggregated among all person-years attributed to cerivastatins, 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 of the concomitant CYP3A4 inhibitor (or the indication for the concomitant CYP3A4 inhibitor) from the risk from the drug interaction. In the present study, the interaction ratio separates the effect associated with each statin type with a CYP3A4 inhibitor from the effect associated with each statin type without a CYP3A4 inhibitor.

The results of the present study are also discordant from a spontaneous report study in which a six-fold adverse event reporting rate ratio (AERR) for simvastatin reports with a concomitant CYP3A4 inhibitor compared with simvastatin reports without a concomitant CYP3A4 inhibitor was reported.[22] The current study, however, has substantial advantages in design and execution. 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.[56] 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.[31, 57, 58] THIN is a powerful tool for studying drug interactions, because the population included is large, diverse, and well characterized. Despite this, practice patterns, patient populations, prescribing patterns, and patient surveillance may be systematically different in the UK than in other countries. We compared the baseline patient characteristics in this study with those in other recent statin safety investigations.[3-7, 9, 42, 45, 59, 60] These baseline patient characteristics were consistent with the baseline patient characteristics from other US, Canadian, and European statin safety cohorts (data not shown).

Regarding confounding, we could not control for variables that 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.

To minimize exposure misclassification, we defined precise exposure criteria for each exposure category, used up-to-date drug codes, and carefully constructed exposure episodes. These methods, of course, do not eliminate the possibility of poor medication adherence. However, we would not expect medication adherence to be different for users of statin 3A4 substrates compared with statin non-3A4 substrates.

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. These secondary analyses were consistent with our primary results.

This large retrospective cohort study showed no overall increased hazard for muscle toxicity, renal dysfunction, or hepatic dysfunction associated with statin 3A4 substrates compared with statin non-3A4 substrates with versus without a concomitant CYP3A4 inhibitor. Additional research could evaluate the nonsignificant yet increased muscle toxicity interaction ratio we observed for highly potent statin dosages and within 6 months after statin initiation. However, it is clear that the drug interaction between statins and CYP3A4 inhibitors does not represent an important public health concern.

Figure 1

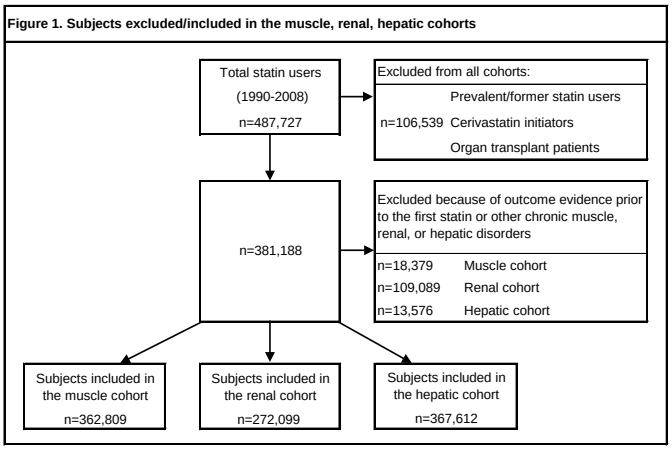
Figure 1. Subjects excluded/included in the muscle, renal, hepatic cohorts
Total statin users
(1990-2008)
n=487,727
Excluded from all cohorts:
Prevalent/former statin users
n=106,539 Cerivastatin initiators
Organ transplant patients
n=381,188
Excluded because of outcome evidence prior to the first statin or other chronic muscle, renal, or hepatic disorders
n=18,379 Muscle cohort
n=109,089 Renal cohort
n=13,576 Hepatic cohort
Subjects included in the muscle cohort
n=362,809
Subjects included in the renal cohort
n=272,099
Subjects included in the hepatic cohort
n=367,612

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 (within 12 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) (mol/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	8827	109,144	6195	151,670	8887
% 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	1120	11,625	800	17,012	1172
% 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%

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	50,608	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	657,276	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	77,555	9.10				
Totals	**7889**	**792,665**	**9.95**				
Confirmed outcomes							
statin 3A4 substrate + CYP3A4X	131	50,608	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	657,276	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	77,555	2.73				
Totals	**2718**	**792,665**	**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, ALT/AST measurements during the baseline period, and 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 HR (95% CI)	Adjusted† HR (95% CI)	Unadjusted I*R (95% CI)	Adjusted† I*R (95% CI)
Primary							
statin 3A4 substrate + CYP3A4X	175	33,543	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	478,830	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	57,339	2.27				
Totals	**1449**	**574,584**	**2.52**				
Confirmed outcomes							
statin 3A4 substrate + CYP3A4X	131	33,543	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	478,830	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	57,339	1.43				
Totals	**934**	**574,584**	**1.63**				
Excluding chronic kidney disease outcomes							
statin 3A4 substrate + CYP3A4X	152	33,543	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	478,847	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	57,339	1.94				
Totals	**1220**	**574,601**	**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, and statin potency (as a time-varying covariate)

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 HR (95% CI)	Adjusted† HR (95% CI)	Unadjusted I*R (95% CI)	Adjusted† I*R (95% CI)
Primary analysis							
statin 3A4 substrate + CYP3A4X	116	52,957	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	675,312	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	80,052	1.46				
Totals	**1434**	**815,945**	**1.76**				
Confirmed outcomes							
statin 3A4 substrate + CYP3A4X	97	52,957	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	675,312	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	80,052	1.27				
Totals	**1241**	**815,945**	**1.52**				
ALT/AST 10X ULN OR med codes							
statin 3A4 substrate + CYP3A4X	62	52,961	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	675,358	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	80,056	0.71				
Totals	**754**	**816,000**	**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)

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	166,470	8.63	1.06	(0.87-1.12)
	medium[2]	3405	348,824	9.76	1.28	(0.77-2.11)
	high[3]	3048	277,371	10.99	2.85	(0.70-11.62)
Renal dysfunction	low	291	120,934	2.41	0.84	(0.39-1.83)
	medium	620	251,108	2.47	0.78	(0.42-1.45)
	high	538	202,542	2.66	-	-
Hepatic dysfunction	low	257	171,580	1.50	0.51	(0.22-1.15)
	medium	609	359,195	1.70	1.27	(0.97- 1.67)
	high	568	284,086	2.00	0.97	(0.13-7.45)

† Statin potency standardization

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

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

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

‡ Models adjusted for the same variables in the primary analysis. See tables 2a, 2b, and 2c for specific variables.

TABLE 4

Table 4. Duration of response analyses 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	104,377	1019	11,781	123,685			
	6-12	events	63	1082	10	89	1244	9.89	**0.72**	(0.36-1.44)
		p-years	6678	106,370	1018	11,772	125,838			
	12-24	events	78	1264	8	137	1487	7.77	**1.37**	(0.65-2.89)
		p-years	10,988	160,601	1629	18,213	191,431			
	>24	events	183	1822	24	269	2298	6.54	**1.20**	(0.79-1.87)
		p-years	26,433	285,624	3561	35,789	351,408			
Renal dysfunction	0-6	events	22	198	3	19	242	2.63	**0.96**	(0.26-3.51)
		p-years	4363	78,150	710	8959	92,183			
	6-12	events	17	153	3	12	185	2.00	**0.60**	(0.15-2.33)
		p-years	4454	78,550	699	8821	92,524			
	12-24	events	30	210	5	25	270	1.94	**0.89**	(0.32-2.51)
		p-years	7236	117,080	1097	13,524	138,937			
	>24	events	106	558	14	74	752	3.00	**0.99**	(0.54-1.82)
		p-years	17,489	205,049	2366	26,035	250,939			
Hepatic dysfunction	0-6	events	17	296	4	23	340	2.71	**0.43**	(0.13-1.38)
		p-years	6702	105,868	1061	11,982	125,614			
	6-12	events	11	172	2	15	200	1.56	**0.65**	(0.13-3.19)
		p-years	6904	108,304	1063	12,035	128,305			
	12-24	events	21	259	4	25	309	1.58	**0.67**	(0.21-2.09)
		p-years	11,387	164,342	1704	18,696	196,130			
	>24	events	67	456	8	54	585	1.60	**1.08**	(0.49-2.36)
		p-years	27,964	296,798	3796	37,339	365,897			

‡ Models adjusted for the same variables in the primary analysis. See tables 2a, 2b, 2c for specific variables.

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