Epidemiologic Approaches to Evaluating Clinical Outcomes of Drug-Drug Interactions in Electronic Healthcare Data

EPIDEMIOLOGIC APPROACHES TO EVALUATING CLINICAL OUTCOMES OF DRUG-DRUG INTERACTIONS IN ELECTRONIC HEALTHCARE DATA

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ABSTRACT

Drug-drug interactions (DDIs) are an increasingly important clinical and public health concern as individuals with multiple chronic conditions are living longer and drug regimens are becoming more complex. Pre-marketing screening for potential DDIs is a required step in the development of new medications; however, the impact of putative interactions on patient health outcomes is usually not quantified, leading to uncertainty in clinical practice. Lack of clinically relevant DDI data has been implicated as one of the major reasons behind the failure of healthcare systems to prevent DDI-related patient harm.

Electronic healthcare databases offer a valuable opportunity to evaluate the clinical consequences of potential DDIs and to identify interactions that are not detected during pre-marketing stages. This thesis examines approaches to pharmacoepidemiologic studies of drug-drug interactions in electronic healthcare data, along with methodological challenges and potential sources of bias that can arise in this setting.

In Chapter 1, we evaluated whether the clinical impact of interaction between clopidogrel and cytochrome P450 (CYP) 2C19-inhibiting selective serotonin reuptake inhibitors (SSRIs) differed based on how patients encountered the interaction. We found that initiating CYP2C19-inhibiting SSRIs later in clopidogrel therapy was associated with a decrease in the effectiveness of clopidogrel that was of similar magnitude to the association observed among patients who

initiated clopidogrel while being treated with SSRIs, and combined the evidence using meta-analysis.

In Chapter 2, we evaluated several approaches to designing and analyzing case-crossover studies of drug-drug interactions based on two empirical DDI examples with prior evidence of harm. We found that in a case-crossover study of two drugs, a saturated model is a six-parameter model that differentiates all three ways patients can encounter an interaction. As compared to the traditional model with a product term, the saturated model can help identify heterogeneity across strata.

Finally, in Chapter 3, we developed a semi-automated, case-crossover-based screening approach for identifying clinically relevant interacting drug pairs in electronic healthcare data. The approach had high specificity and represents a promising option for generating the much-needed evidence on the relevance of drug-drug interactions in clinical practice, which was the primary motivation behind this dissertation.

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CHAPTER 1 UPDATING THE EVIDENCE OF THE INTERACTION BETWEEN CLOPIDOGREL AND CYP2C19-INHIBITING SELECTIVE SEROTONIN REUPTAKE INHIBITORS: A COHORT STUDY AND META-ANALYSIS

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ABSTRACT

Background: We previously found that patients who initiate clopidogrel while treated with a cytochrome P450 (CYP) 2C19-inhibiting selective serotonin reuptake inhibitor (SSRI) have a higher risk of subsequent ischemic events as compared to patients treated with other SSRIs. It is not known whether initiating an inhibiting SSRI while treated with clopidogrel will also increase risk of ischemic events.

Objective: To assess clinical outcomes following initiation of a CYP2C19-inhibiting SSRI versus initiation of other SSRIs among patients treated with clopidogrel and to update existing evidence on the clinical impact of clopidogrel-SSRI interaction.

Methods: Using 5 US databases (1998-2013), we conducted a cohort study of clopidogrel initiators who encountered treatment with SSRI during their clopidogrel therapy. Patients were matched by propensity score (PS) and followed for as long as they were exposed to both clopidogrel and index SSRI group. Outcomes were a composite ischemic event (myocardial infarction, ischemic stroke, or a revascularization procedure, whichever came first) and a composite major bleeding event (gastrointestinal bleed or hemorrhagic stroke, whichever came first). Results were combined via random-effects meta-analysis with previous evidence from subjects initiating clopidogrel while on SSRI therapy.

Results: The PS-matched cohort comprised 2,346 clopidogrel users starting CYP2C19-inhibiting SSRI and 16,115 starting other SSRIs (mean age 61 years; 59% female). As compared to those treated with a non-inhibiting SSRI, the hazard ratio (HR) for patients

treated with a CYP2C19-inhibiting SSRI was 1.07 (95% confidence interval (CI), 0.82 to 1.40) for the ischemic outcome and 1.00 (95% CI, 0.42 to 2.36) for bleeding. The pooled estimates were 1.11 (95% CI, 1.01 to 1.22) for ischemic events and 0.80 (95% CI, 0.55 to 1.18) for bleeding.

Conclusions: We observed similar estimates of association between the two studies. The updated evidence still indicates a small decrease in clopidogrel effectiveness associated with concomitant exposure to clopidogrel and CYP2C19-inhibiting SSRIs.

INTRODUCTION

Drug-drug interactions (DDIs) represent an increasingly important clinical and public health concern and a substantial effort has been directed at minimizing the harm associated with DDIs while ensuring that patients receive safe and effective therapy.[1] Some of this effort has been hampered by uncertainty about which potential DDIs are clinically important since we rarely have information on clinical outcomes in patients taking the interacting drugs. As such, there have been calls to improve the DDI evidence base to better inform clinical decision support (CDS) systems that generate alerts to physicians and pharmacists about potential DDIs.[2-4]

As a prodrug that is metabolized by several cytochrome P450 (CYP) enzymes, clopidogrel is a prime example of a drug that could potentially interact with multiple other drugs.[5] Prior pharmacokinetic and pharmacodynamic studies have documented reduced plasma levels of the active metabolite and impaired inhibition of platelet aggregation when clopidogrel was co-administered with CYP inhibitors.[6-9] The clinical significance of these interactions is not well understood and remains debatable, as in the case of clopidogrel-proton pump inhibitor (PPI) interaction.[10,11]

Previously, we found that patients who initiated clopidogrel while being treated with a CYP2C19-inhibiting selective serotonin reuptake inhibitors (SSRI) (fluoxetine or fluvoxamine) had a slightly increased risk of subsequent ischemic events (hazard ratio (HR), 1.12; 95% confidence interval (CI), 1.01 to 1.24) and a lower, although not statistically significant, risk of bleeding (HR, 0.76; 95% CI, 0.50 – 1.17) as compared to patients who initiated clopidogrel while being treated with a non-inhibiting SSRI.[12] However, patients may also encounter

concomitant exposure when initiating an SSRI later in the clopidogrel therapy. Since patients are at high risk of a subsequent cardiovascular event immediately following a first event,[13-15] the clinical impact of the interaction might be largest at the time of clopidogrel initiation, which often follows the first event.

Since it is not known whether initiating an inhibiting SSRI while treated with clopidogrel also decreases clopidogrel effectiveness, we evaluated the clinical impact of concomitant exposure to clopidogrel and a CYP2C19-inhibiting SSRI when it was triggered by exposure to SSRI later in clopidogrel therapy. We compared the results to those obtained from the cohort of patients who initiated clopidogrel while being treated with SSRI (clopidogrel-triggered co-exposure) and updated the evidence of the clinical impact of clopidogrel-SSRI interaction.

METHODS

Data Sources

The data for this study were drawn from five US healthcare databases: a commercial health insurance database (Optum Research Database; 2004 - 2013), a Medicaid nationwide database (Medicaid Analytic eXtract [MAX]; 2000-2006), and three Medicare databases that linked Medicare Parts A and B data to pharmacy claims data from (1) Medicare Part D plans administered by CVS Caremark (2006-2008); (2) a pharmacy assistance program in New Jersey (Pharmaceutical Assistance to the Aged and Disabled [PAAD]; 1998 - 2005); and (3) a pharmacy assistance program in Pennsylvania (Pharmaceutical Assistance Contract for the Elderly [PACE] (1998-2005). Combined, the data sources covered the period from 1998 (following clopidogrel approval in the US) through the end of 2013. All databases provide

medical claims data and pharmacy data that include a medication's National Drug Code (NDC), date of dispensing, quantity dispensed and days' supply.

Study Cohort

Findings from a cohort of patients who initiated clopidogrel during the study period (1998-2013) while being treated with an SSRI have been reported earlier.[12] In the current study, we identified patients who were not exposed to SSRI at the time of clopidogrel initiation, but encountered concomitant exposure later in clopidogrel therapy. Patients were required to have continuous insurance coverage for at least 6 months prior to clopidogrel initiation (to allow for covariate assessment and identification of new use), to be at least 18 years of age, and to be continuously exposed to clopidogrel until SSRI initiation. Continuous exposure was assessed using prescription days' supply allowing for a 7-day grace period between serial prescriptions. The first day of concomitant exposure defined the cohort entry date. The SSRI dispensing on that day was used to classify patients into either inhibiting SSRI or non-inhibiting SSRI exposure groups. Inhibiting SSRIs were fluoxetine and fluvoxamine. Citalopram, escitalopram, paroxetine and sertraline were the non-inhibiting SSRIs.[16,17] Patients were excluded if they were exposed to an SSRI at any time during the 30-day period prior to and including the clopidogrel initiation date. In addition, we excluded Medicaid beneficiaries who were 65 year of age or older as they become eligible for Medicare, or who were enrolled in comprehensive medical managed care plans, restricted benefits plans, or private insurance due to potential for incomplete claims in these patients.[18]

Outcomes and follow-up

The primary effectiveness outcome was a composite of the first admission for a major ischemic event (acute myocardial infarction [MI], or ischemic stroke) or coronary revascularization procedure (coronary artery bypass grafting [CABG], stenting, or percutaneous transluminal coronary angioplasty [PTCA]). The primary safety outcome was a composite bleeding event endpoint, comprising major upper gastrointestinal (GI) bleed and hemorrhagic stroke. Secondary outcomes included the individual components of the primary composite outcomes. All outcomes were assessed using validated claims-based algorithms (see Appendix 1.1) with high positive predicted values (PPVs), as described previously.[12]

Follow-up started on the day following the cohort entry date (**Figure 1.1**). In the primary analysis, patients were followed for the outcomes of interest for as long as they were exposed to both clopidogrel and their index SSRI group. Patients were censored at the first occurrence of an event of interest, death, disenrollment from the health plan, end of the database-specific study period, or discontinuation of either clopidogrel or their SSRI, defined as the end of days supply (plus an additional 7 days to account for variation in adherence), whichever came first. Follow-up was also censored upon a dispensing of another antiplatelet agent or of an SSRI from the other exposure group. In addition, Medicaid patients were censored when they turned 65 or when enrolled in either private, restricted benefits, or comprehensive medical managed care plans. As a secondary analysis, we used an intention-to-treat (ITT) approach where patients were followed for a maximum of 180 days, regardless of treatment changes.

Covariates

Demographic variables, including age, sex, calendar year of cohort entry, geographic region, and race where available (Medicaid and Medicare), were assessed at the time of cohort entry. We measured the duration of clopidogrel use (in days) before the initiation of SSRI and whether patients had a cardiovascular event in the 14 days prior to clopidogrel initiation (i.e., hospitalization for MI, or either inpatient or outpatient revascularization procedure (percutaneous coronary intervention [PCI] or CABG)). Exposure to concomitant medications was assessed at cohort entry and was based on whether days' supply overlapped with the cohort entry date. The remaining comorbidities, prior medications, and health care utilization variables were measured during the baseline period, defined as 180 days preceding clopidogrel initiation plus the days until and including SSRI initiation (cohort entry date) (**Figure 1.1**).

Statistical Analysis

We used variable ratio propensity score (PS) matching to account for measured differences between the exposure groups. The PSs were estimated using logistic regression predicting exposure to inhibiting vs. non-inhibiting SSRIs as a function of all pre-defined covariates (see Appendix 1.2). Patients exposed to inhibiting SSRIs were matched without replacement to patients exposed to non-inhibiting SSRIs within each database in a ratio of 1 up to 10 using a nearest neighbor algorithm with a maximum caliper of 0.025.[19] Since variable ratio matching produces covariate balance within a matched set, but not marginally in the overall matched population, to assess covariate balance achieved by PS matching, we randomly sampled one non-inhibiting SSRI-exposed patient from each matched set along with their corresponding

inhibiting SSRI-exposed patient.[19] We compared covariate distributions among this random sample using standardized differences.[20]

HRs and 95% CIs were estimated using Cox proportional hazards regression, stratified by the matching ratio and the database. We also assessed associations in subgroups of patients stratified on (1) age (< 65 years and 65 years or older) and (2) duration of clopidogrel treatment prior to SSRI initiation. Effect modification by clopidogrel duration prior to SSRI initiation was assessed based on adding the interaction term between clopidogrel duration (as a linear variable) and the exposure group to the model.

Statistical analyses were conducted using SAS version 9.4 statistical software (SAS Institute, Cary, NC).

Meta-analysis

The results from this study and the previous clopidogrel-triggered co-exposure study[12] were combined using random-effect meta-analysis. Presence of heterogeneity in associations was assessed using the Cochrane *Q* test for heterogeneity and I^2 statistic.[21] Meta-analysis was performed using STATA version 12 statistical software (Stata Corporation, College Station, TX).

RESULTS

Patients

We identified 20,117 patients who were not on an SSRI at the time of clopidogrel initiation, but were dispensed an SSRI later in clopidogrel therapy; 12% (N = 2,350) initiated a CYP2C19-inhibiting SSRI. The PS-matched cohort included 2,346 patients who were treated

with a CYP2C19-inhibiting SSRI (98% with fluoxetine and 2% with fluvoxamine) and 16,115 patients treated with other SSRIs (32% with sertraline, 28% with escitalopram, 21% with paroxetine, and 19% with citalopram). Patient baseline characteristics before and after PS matching are presented in **Table 1.1.** No covariates had a standardized difference greater than 0.1 after matching. The average age of those in the PS-matched cohort was 61 years and 59% of patients were female. The mean clopidogrel duration prior to SSRI initiation was 88 days (standard deviation [SD] 139) and the median was 37 days (interquartile range 16-98 days), with 43% of patients initiating SSRI within the first 30 days of clopidogrel treatment.

Outcomes: primary and secondary analyses

For the primary outcome of any ischemic event, patients on a CYP2C19-inhibiting SSRI contributed 424 person-years of concomitant exposure, during which 65 events were identified. Patients who initiated a non-inhibiting SSRI contributed 3,118 person-years and 433 events. The adjusted HR was of 1.07 (95% CI, 0.82 to 1.40). Mean follow-up was 72 days (SD 100 days), with 42% of patients discontinuing clopidogrel, 40% discontinuing SSRI, 5% discontinuing both drugs and 10% being censored for administrative reasons (loss of insurance eligibility or end of the study period). For the composite bleeding outcome, we observed 6 events during 432 person-years of follow-up in the group exposed to inhibiting SSRIs and 43 events during 3191 years of follow-up in the group exposed to non-inhibiting SSRIs with HR of 1.00 (95% CI, 0.42 to 2.36). **Table 1.2** shows the number of events and incidence rates in each exposure group, as well as HRs for all the outcomes.

An interaction between clopidogrel duration and exposure was not statistically significant (p-value > 0.05) for any of the outcomes (see Appendix 1.3). Results of the ITT analysis were

qualitatively similar to those of the primary analysis. The HR was 1.06 (95% CI, 0.88 to 1.28) for any ischemic event and 0.91 (95% CI, 0.49 to 1.66) for composite bleeding outcome (**Table 1.2)**.

Subgroups

Subgroup analyses suggested no heterogeneity of the association based on age for either ischemic events or bleeding, but the numbers of events were small in each age subgroup and confidence intervals were wide (see Appendix 1.4).

As compared to the overall results, HRs for the composite outcomes were similar in the subgroup of patients who were dispensed SSRI within the first month of clopidogrel therapy, but estimates for stenting and PTCA were higher (HR 1.39, 95% CI 0.88 to 2.21 and HR 1.52, 95% CI 0.94 to 2.45, respectively). Among patients who were dispensed SSRI within the first 10 days of clopidogrel therapy, the HR for any ischemic events was 1.51 (95% CI, 0.92 to 2.48) and the HRs were 2.00 (95% CI, 1.09 to 3.69) for stenting and 1.88 (95% CI, 1.00 – 3.52) for PTCA.

Meta-analysis

The HRs obtained from pooling the results of both studies were 1.11 (95% CI, 1.01 to 1.22) for any ischemic events and 0.80 (95% CI, 0.55 to 1.18) for the composite bleeding outcome. No heterogeneity was observed in these results (I^2 = 0% with Q^2 of 0.08 and p-value for heterogeneity = 0.776 for the composite ischemic event; I^2 = 0% with Q^2 of 0.30 and p-value for heterogeneity = 0.586 for bleeding). **Figure 1.2** presents the pooled results for all the outcomes, as well as the results from each study.

DISCUSSION

In this study of patients who initiated SSRIs while being treated with clopidogrel, we observed associations of similar magnitude to the associations observed in the study of patients who initiated clopidogrel while being treated with an SSRI. Following meta-analysis (total N = 72,020), the updated evidence showed an 11% increase in the rate of ischemic events among patients who were co-prescribed a CYP2C19-inhibiting SSRI as compared to a non-inhibiting SSRI and a suggestion of a possible reduction in the rate of bleeding (HR 0.80, 95% CI 0.52 – 1.24), which is consistent with the hypothesized interaction mechanism. Our results are similar to some, but not all, studies that examined the controversial association between concomitant PPI and clopidogrel exposure and cardiovascular outcomes.[22,23]

It is important to note that no association with risk of either myocardial infarction or ischemic stroke was observed in either of the studies and the increase in risk of ischemic events was driven by an increase in revascularization procedures (**Table 1.2**). The lack of information on angiographic measurements and whether a procedure was urgent or elective precluded us from further investigating this phenomenon. While unlikely, if patients with more severe depression or anxiety were more likely to undergo elective revascularization procedures and they were preferentially treated with a CYP2C19-inhibitor (fluoxetine or fluvoxamine), the increase in rates of revascularization could be attributable to confounding. However, the American Heart Association recommends sertraline and citalopram as the first-line antidepressant drugs for patients with coronary heart disease[24] and, to our knowledge, there is no evidence that fluoxetine is more efficacious than other SSRIs in treating depressive disorders or perceived as such.[25-27] Nevertheless, the lack of evidence of the interaction's association with clinical outcomes other

than revascularization should be taken into account when deciding whether and how to include an alert about this DDI in clinical decision support systems.

Our results should be interpreted in the context of several limitations. First, the study was underpowered to detect whether patients who initiated SSRIs later in clopidogrel therapy were at a lower risk of ischemic events as compared to patients who were on an SSRI at the time of clopidogrel initiation. Second, heterogeneity statistics from our meta-analysis should be interpreted with caution as the analysis was based on only two studies. I^2 can be biased and the Q statistic has low power when the number of studies is small.[28] The power of homogeneity tests is further reduced when one of the studies is much larger than the others.[28] Thus, we cannot completely rule out heterogeneity of the association. Furthermore, although the updated results still indicate decreased effectiveness of clopidogrel associated with concomitant exposure to CYP2C19-inhibiting SSRIs, the results of the pooled analysis were primarily driven by the results from the clopidogrel-triggered co-exposure study (**Figure 1.2**).

In addition, as with any observational study based on claims data, we cannot completely rule out confounding by factors not available in the databases, such as smoking, non-prescription drug use, and CYP2C19 genotype. However, since we required all patients to be on SSRIs, we do not expect the choice of a particular SSRI agent to be driven by cardiovascular risk factors or a patient's genotype, and as the measured factors were well balanced between the two exposure groups even before PS matching, we expect that unmeasured risk factors may also be balanced and, thus, unlikely to strongly confound the results. Lastly, pharmacy claims data provide information on the drugs dispensed to patients; however, they do not contain information on whether patient took the medications. Therefore, exposure misclassification is possible. Our

strict definition of exposure (allowing maximum 7 day gaps between sequential prescriptions) likely reduced potential exposure misclassification.

This study also has important strengths, including a large nation-wide sample that was drawn from both private and public health insurance programs and a comparison group that did not differ from the exposure of interest group in baseline characteristics. Along with our previous study, this is the first population-based evaluation of the health consequences of clopidogrel-SSRI CYP-mediated interaction. While newer, more potent antiplatelets have been developed and marketed over the last decade, clopidogrel remains the most widely used prescription antiplatelet, which is also now available in generic form.

Lack of research providing evidence for the clinical outcomes of DDIs has been a major roadblock to the efficient use of health information technology, including the clinical decision support systems upon which healthcare providers in pharmacies and hospitals rely for DDI alerts.[3,29] While some potential DDIs likely do not result in observable clinical outcomes, clinical decision support systems tend to be highly inclusive and rely on package inserts or case reports for their DDI listings.[2] As a result, the large number of the alerts and the low clinical relevance of many of them have contributed to "alert fatigue," clinician frustration, and high override rates of up to 93%.[30,31] In addition, there is significant disagreement among major DDI compendia on which DDIs are significant and even on how to assess the significance of an interaction, given that little empirical evidence exists.[2,32,33] Real-world data on the clinical impact of DDIs are urgently needed for meaningful evaluations of the clinical significance of DDIs, appropriate customization of alert algorithms and evidence-based decision-making.[3,4,34]

Evaluating the health consequences of potential DDIs is challenging as elucidation of even moderate associations requires large population databases. In our investigation, we utilized 5 US databases and started with half a million clopidogrel initiators. While this sample size was large enough to detect the association in patients who initiated clopidogrel while being treated with an SSRI, the number of patients who initiated SSRI while being treated with clopidogrel was much smaller and we were underpowered to evaluate whether the interaction effect differed depending on the ordering of the drugs. Our clopidogrel duration subgroup analysis suggested that the risk might be higher closer to the initiation of clopidogrel. While the biology behind the interaction is the same regardless of how patients encounter it, clopidogrel duration prior to SSRI initiation could be a proxy for time since an event that prompted clopidogrel initiation. If the risk of subsequent ischemic events is higher immediately after the initial event,[35,36] the interaction might be of more clinical relevance during that time. However, an even larger cohort or several additional studies will be needed to further evaluate this hypothesis.

In conclusion, we observed that initiating CYP2C19-inhibiting SSRIs later in clopidogrel therapy is associated with a decrease in the effectiveness of clopidogrel that was of similar magnitude to the association observed among patients who initiated clopidogrel while being treated with SSRIs. Due to limited power to detect small differences in associations between the two studies, heterogeneity of the association cannot be completely ruled out. In the combined analysis that included all concomitantly exposed patients, concomitant use of clopidogrel and CYP2C19-inhibiting SSRIs was associated with an 11% increase in subsequent revascularization procedures that might be of relevance to patients taking these medications. Until more evidence is generated suggesting otherwise, alerts about this DDI are warranted regardless of the order in

which patients become concomitantly exposed to the drugs, and unless there are reasons to choose otherwise, selecting a non-inhibiting SSRI may be preferable when therapy is needed.

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Table 1.1: Characteristic of patients at baseline

Patient characteristic	SSRI Exposure groups: Before PS matching — Inhibitors (n = 2,350)	Before PS matching — Non-Inhibitors (n = 17,767)	After PS matching — Inhibitors (n = 2,346)	After PS matching — Non-Inhibitors* (n = 2,346 out of 16,115)
Age, *mean (SD)*, years	60.2(13.3)	62.5(14.1)	60.2(13.3)	60.1(13.5)
Female, *N (%)*	1414(60.2)	10545(59.4)	1412(60.2)	1402(59.8)
Type of insurance, *N (%):* Commercial	925(39.4)	7082(39.9)	925(39.4)	925(39.4)
Medicaid	927(39.4)	6029(33.9)	924(39.4)	924(39.4)
Medicare	498(21.2)	4656(26.2)	497(21.2)	497(21.2)
Clopidogrel Duration, mean (SD), days	83.8(136.5)	90.3(145.6)	84(136.6)	83.1(136.5)
Clopidogrel duration, *N (%):* <11 days	399(17.0)	2879(16.2)	398(17.0)	426(18.2)
11 - 30 days	632(26.9)	4778(26.9)	629(26.8)	640(27.3)
31 -60 days	475(20.2)	3339(18.8)	475(20.2)	435(18.5)
61 - 90 days	228(9.7)	1865(10.5)	228(9.7)	241(10.3)
91-180 days	336(14.3)	2524(14.2)	336(14.3)	330(14.1)
>180 days	280(11.9)	2382(13.4)	280(11.9)	274(11.7)
Year of clopidogrel initiation, *N(%):*				
1998-2001	344(14.6)	1789(10.0)	343(14.6)	345(14.7)
2002-2005	903(38.4)	7502(42.2)	902(38.4)	900(38.4)
2006-2009	776(33.0)	6193(34.9)	774(33.0)	756(32.2)
2010-2013	327(13.9)	2288(12.9)	327(13.9)	345(14.7)
Region, *N(%):* Mid West	534(22.7)	3549(20)	534(22.8)	519(22.1)
North East	517(22.0)	4853(27.3)	517(22.0)	515(22.0)
South	994(42.3)	7549(42.5)	993(42.3)	1001(42.7)
West	289(12.3)	1706(9.6)	286(12.2)	299(12.7)
Comorbidities, *N (%)*				
Atrial fibrillation	222(9.4)	2206(12.4)	222(9.5)	216(9.2)
Atherosclerosis	56(2.4)	458(2.6)	56(2.4)	54(2.3)
Coronary artery disease	1588(67.6)	12755(71.8)	1586(67.6)	1564(66.7)
Congestive heart failure	525(22.3)	4496(25.3)	525(22.4)	523(22.3)
Diabetes	997(42.4)	6813(38.3)	994(42.4)	986(42.0)
Prior hemorrhagic stroke	13(0.6)	110(0.6)	13(0.6)	15(0.6)
Hyperlipidemia	1481(63.0)	11671(65.7)	1479(63.0)	1486(63.3)
Hypertension	1855(78.9)	14594(82.1)	1853(79.0)	1842(78.5)
Prior Ischemic Stroke	438(18.6)	3373(19.0)	435(18.5)	423(18.0)
Recent MI	281(12.0)	2355(13.3)	281(12.0)	252(10.7)
Recent CABG	20(0.9)	157(0.9)	20(0.9)	18(0.8)
Recent PCI	578(24.6)	4658(26.2)	578(24.6)	549(23.4)
Peptic ulcer disease	632(26.9)	5243(29.5)	631(26.9)	612(26.1)

Table 1.1 (Continued)

Peripheral vascular disease	321(13.7)	2648(14.9)	321(13.7)	306(13.0)
Prior myocardial infarction	392(16.7)	3306(18.6)	392(16.7)	368(15.7)
Prior TIA	401(17.1)	3151(17.7)	401(17.1)	379(16.2)
Unstable angina	420(17.9)	3567(20.1)	420(17.9)	398(17.0)
Prior upper GI bleeding	23(1.0)	236(1.3)	23(1.0)	26(1.1)
Venous thromboembolism	79(3.4)	684(3.8)	79(3.4)	86(3.7)
Prior valve replacement	<11	59(0.3)	<11	<11
Combined comorbidity score, *mean (SD)*	2.0(2.5)	2.2(2.7)	2.0(2.5)	2.0(2.5)
Medication use, *N (%)*				
Prior SSRI	562(23.9)	3101(17.5)	559(23.8)	530(22.6)
Other antidepressant	569(24.2)	3742(21.1)	569(24.3)	544(23.2)
ACE Inhibitor or ARB	1426(60.7)	11194(63.0)	1425(60.7)	1404(59.8)
Beta blocker	1367(58.2)	11254(63.3)	1366(58.2)	1348(57.5)
Calcium channel blocker	747(31.8)	6081(34.2)	745(31.8)	731(31.2)
Other antihypertensive agent	1196(50.9)	8976(50.5)	1194(50.9)	1150(49.0)
H2 RA	314(13.4)	2194(12.3)	313(13.3)	305(13.0)
PPI	924(39.3)	7261(40.9)	922(39.3)	960(40.9)
Other gastroprotective agent	85(3.6)	569(3.2)	84(3.6)	72(3.1)
Statin	1503(64.0)	11675(65.7)	1500(63.9)	1484(63.3)
Other Lipid-lowering agent	413(17.6)	3284(18.5)	412(17.6)	411(17.5)
Non-selective NSAID	565(24.0)	4219(23.7)	563(24.0)	571(24.3)
COX 2 inhibitor	325(13.8)	2419(13.6)	324(13.8)	292(12.4)
Warfarin	163(6.9)	1545(8.7)	163(6.9)	160(6.8)
Other oral anticoagulant	<11	14(0.1)	<11	<11
Concomitant Inducer	0(0.0)	13(0.1)	0(0.0)	0(0.0)
Concomitant Inhibitor	283(12.0)	2232(12.6)	283(12.1)	272(11.6)
Concomitant NSAID	317(13.5)	2141(12.1)	315(13.4)	292(12.4)
Concomitant Oral Anticoagulant	73(3.1)	755(4.2)	73(3.1)	76(3.2)
Health care utilization, *mean (SD)*				
Number of distinct prescription medications	16.3(8.5)	16.1(8.1)	16.3(8.5)	16.1(8.0)
Number of hospitalizations	1.2(1.4)	1.3(1.5)	1.2(1.4)	1.2(1.3)
Number of outpatient physician visits	11.9(9.3)	12.3(10.3)	11.9(9.3)	11.8(9.9)
Number of days hospitalized	6.9(11.2)	8.1(12.7)	6.9(11.2)	7.1(11.7)
Number of days in a nursing home	8.4(50.4)	10.2(46.1)	8.4(50.4)	8.7(46.6)

*Since variable ratio propensity score matching produces covariate balance within a matched set, but not marginally, one non-inhibiting SSRI-exposed patient along with their corresponding inhibiting SSRI-exposed patient was randomly sampled from each matched set

As per Centers for Medicare and Medicaid Services cell size suppression policy, cell sizes <11 were suppressed

ARB angiotensin receptor blocker; ACE angiotensin converting enzyme; CABG coronary artery bypass grafting; COX cyclooxygenase; GI gastrointestinal; MI myocardial infarction; NSAID nonsteroidal anti-inflammatory drug; PCI percutaneous coronary intervention; PS propensity score; SD standard deviation; SSRI selective serotonin reuptake inhibitor; TIA transient ischemic attack.

Table 1.2: Association between exposure to inhibiting SSRIs vs non-inhibiting SSRIs during clopidogrel treatment and outcomes, as-treated (primary) and intention-to-treat analyses

As Treated	Inhibiting SSRIs (N = 2,346)		Non-inhibiting SSRIs (N = 16,115)		
Outcome	**Events**	**Rate / 1,000 PYs**	**Events**	**Rate / 1,000 PYs**	**HR (95% CI)**
Any Ischemic	65	153.36	433	138.88	1.07 (0.82-1.40)
AMI	11	25.48	69	21.67	1.02 (0.53-1.95)
Ischemic Stroke	11	25.52	86	27	0.87 (0.46-1.66)
Stent	34	79.69	227	72.28	1.14 (0.79-1.65)
PTCA	34	79.38	199	63.22	1.29 (0.89-1.87)
CABG	<11	16.22	46	14.42	1.08 (0.49-2.41)
Any Bleeding	<11	13.89	43	13.48	1.00 (0.42-2.36)
Hemorrhagic Stroke	<11	4.63	11	3.44	1.19 (0.26-5.47)
Upper GI Bleeding	<11	9.26	33	10.34	0.89 (0.31-2.53)

ITT analysis

Outcome	**Events**	**Rate / 1,000 PYs**	**Events**	**Rate / 1,000 PYs**	**HR (95% CI)**
Any Ischemic	130	132.06	856	118.6	1.06 (0.88-1.28)
AMI	33	32.7	163	20.16	1.30 (0.89-1.90)
Ischemic Stroke	27	26.74	168	20.83	1.09 (0.73-1.65)
Stent	60	59.9	450	59.91	0.95 (0.73-1.25)
PTCA	64	63.97	411	54.4	1.13 (0.86-1.47)
CABG	17	16.79	103	12.23	1.15 (0.68-1.92)
Any Bleeding	12	11.83	92	10.79	0.91 (0.49-1.66)
Hemorrhagic Stroke	<11	2.95	19	1.74	1.17 (0.34-3.99)
Upper GI Bleeding	<11	8.87	74	8.47	0.83 (0.41-1.66)

HRs are adjusted for a database and matching ratio. As per Centers for Medicare and Medicaid Services cell size suppression policy, cell sizes <11 were suppressed

AMI acute myocardial infarction, CABG coronary artery bypass grafting, CI confidence intervals, GI gastrointestinal, HR hazard ratio, ITT Intention-to-treat, PTCA percutaneous transluminal coronary angioplasty, PYs person years, SSRI selective serotonin reuptake inhibitor.

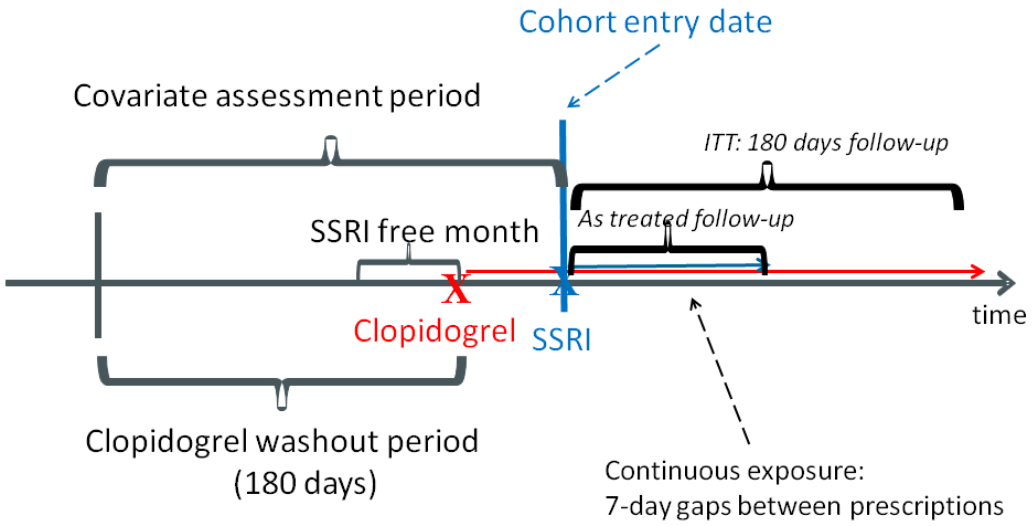

Figure 1.1: Study design

ITT intention to treat, SSRI selective serotonin reuptake inhibitor

Patients were required to be clopidogrel initiators, not on SSRI therapy at the time of clopidogrel initiation, and to initiate SSRI while exposed to clopidogrel. The day of SSRI initiation was the cohort entry date. Follow-up started the day following cohort entry and continued for as long as patients were on both drugs in as-treated analysis and for 180 days in ITT.

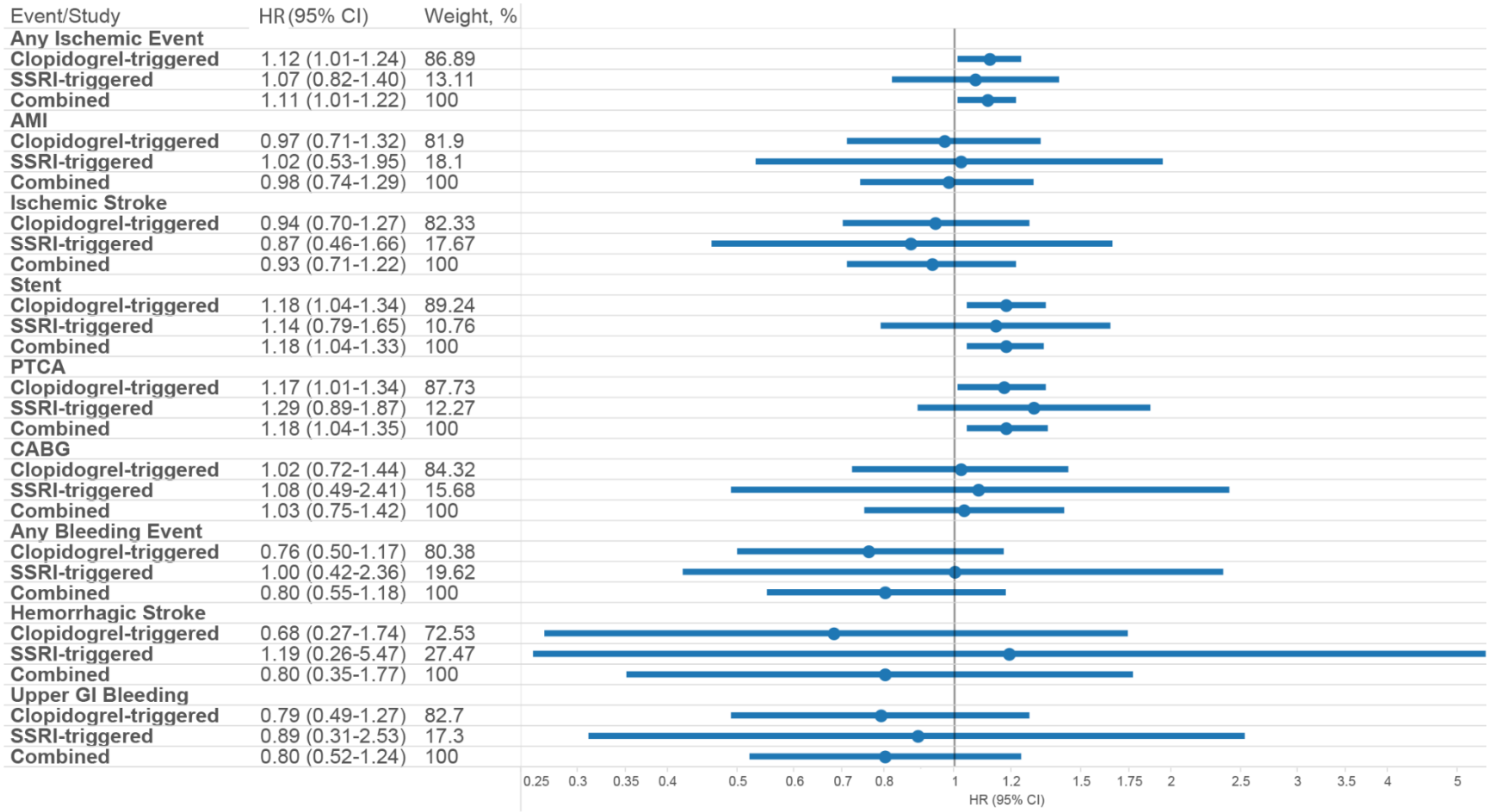

Figure 1.2: Hazard ratios for study outcomes from 1) clopidogrel-triggered co-exposure, 2) SSRI-triggered co-exposure, and 3) combined meta-analysis

Results from individual studies were combined via random effects meta-analysis. Clopidogrel-triggered study included patients who initiated clopidogrel while treated with SSRI; SSRI-triggered study included patients who initiated SSRI later in clopidogrel therapy
AMI acute myocardial infarction, CABG coronary artery bypass grafting, CI confidence intervals, GI gastrointestinal, HR hazard ratio, PTCA percutaneous transluminal coronary angioplasty.

APPENDIX

Appendix 1.1: Outcome definitions

Outcome	Algorithm
Myocardial infarction	inpatient ICD-9 diagnosis code 410.xx, excluding 410.x2, as primary; minimum 3 day stay required (unless patient died) and maximum of 180 days
Ischemic stroke	inpatient ICD-9 diagnosis code 433.x1, 434.x1, or 436.xx
Stent	ICD-9 procedure code 36.06 or 36.07 or CPT-4 code 392980, 92981 (inpatient or outpatient)
PTCA without stenting	ICD-9 procedure code 00.66, 36.01, 36.02, 36.05, 36.09 or CPT-4 code 92973, 92982, 92984, 92995, 92996 (inpatient or outpatient)
CABG	inpatient ICD-9 procedure code 36.1x or 36.2x or CPT-4 code 33510-33536, 33545, 33572
Hemorrhagic stroke	inpatient ICD-9 diagnosis code 430.x or 431.x
Severe upper GI bleed	defined by the occurrence of any one of the following: 1. inpatient ICD-9 diagnosis code 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 578.0 2. inpatient ICD-9 procedure code 44.43 3. inpatient CPT code 43255

CABG coronary artery bypass grafting; CPT-4 Current Procedure Terminology, 4th Revision; GI gastrointestinal; ICD-9 International Classification of Diseases, 9th Revision; PTCA percutaneous transluminal coronary angioplasty.

Appendix 1.2: Propensity score model covariates.

Age (years)
Race (where available, categorical)
Gender
Index year (categorical)
Region (4; categorical)
Clopidogrel duration prior to SSRI initiation (days)
Atrial fibrillation
Atherosclerosis
Coronary artery disease
Congestive heart failure
Diabetes
Prior hemorrhagic stroke
Hyperlipidemia
Hypertension
Prior ischemic stroke
Recent MI (within 2 weeks prior to clopidogrel initiation)
Recent CABG (within 2 weeks prior to clopidogrel initiation)
Recent PCI (within 2 weeks prior to clopidogrel initiation)
Peptic ulcer disease
Peripheral vascular disease
Prior myocardial infarction
Prior transient ischemic attack
Unstable angina
Prior upper GI bleeding
Venous thromboembolism
Prior valve replacement
Combined comorbidity score
Number of distinct prescription medications
Number of hospitalizations
Number of outpatient physician visits
Number of days hospitalized
Number of days in a nursing home
Prior SSRI
Other antidepressant
ACE Inhibitor or ARB
Beta blocker
Calcium channel blocker
Other antihypertensive agent
H2 receptor antagonist
PPI
Other gastroprotective agents
Statin
Other Lipid-lowering agent
Non-selective NSAID
COX 2 inhibitors
Warfarin
Other oral anticoagulant
Concomitant Inducer
Concomitant Inhibitor
Concomitant NSAID
Concomitant Oral Anticoagulant

Appendix 1.3: Parameter estimates from an interaction model

Outcome / Parameter						
Any Ischemic	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	0.166	0.169	0.326	1.18	0.85	1.64
Clopidogrel Duration (days)	-0.002	0.0005	0.000	1.00	1.00	1.00
Inhibiting SSRI*Clopidogrel duration	-0.002	0.002	0.357			
Acute Myocardial Infarction	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	0.012	0.403	0.976	1.01	0.46	2.23
Clopidogrel Duration (days)	-0.001	0.001	0.292	1.00	1.00	1.00
Inhibiting SSRI*Clopidogrel duration	0.000	0.003	0.982			
Ischemic Stroke	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	0.083	0.412	0.840	1.09	0.48	2.44
Clopidogrel Duration (days)	-0.001	0.001	0.315	1.00	1.00	1.00
Inhibiting SSRI*Clopidogrel duration	-0.004	0.005	0.438			
Stent	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	0.398	0.239	0.095	1.49	0.93	2.38
Clopidogrel Duration (days)	-0.002	0.001	0.001	1.00	1.00	1.00
Inhibiting SSRI*Clopidogrel duration	-0.005	0.003	0.143			
PTCA	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	0.412	0.243	0.089	1.51	0.94	2.43
Clopidogrel Duration (days)	-0.003	0.001	0.001	1.00	1.00	1.00
Inhibiting SSRI*Clopidogrel duration	-0.003	0.003	0.329			
CABG	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	-0.153	0.495	0.757	0.86	0.33	2.26
Clopidogrel Duration (days)	-0.002	0.002	0.163	1.00	0.99	1.00
Inhibiting SSRI*Clopidogrel duration	0.003	0.003	0.345			
Any Bleeding	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	-0.306	0.527	0.561	0.74	0.26	2.07
Clopidogrel Duration (days)	-0.003	0.002	0.061	1.00	0.99	1.00
Inhibiting SSRI*Clopidogrel duration	0.004	0.003	0.203			
Hemorrhagic Stroke	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	0.273	1.121	0.808	1.31	0.15	11.83
Clopidogrel Duration (days)	-0.016	0.008	0.058	0.98	0.97	1.00
Inhibiting SSRI*Clopidogrel duration	-0.005	0.031	0.879			
Upper GI Bleeding	Estimate	St. error	P-value	HR	95% CI	
Inhibiting SSRI	-0.499	0.637	0.433	0.61	0.17	2.12
Clopidogrel Duration (days)	-0.002	0.002	0.223	1.00	0.99	1.00
Inhibiting SSRI*Clopidogrel duration	0.004	0.003	0.157			

The model included exposure to inhibiting SSRI (vs non-inhibiting SSRI), clopidogrel duration prior to SSRI initiation in days (as a linear covariate) and a cross-product between exposure to inhibiting SSRI and clopidogrel duration

Appendix 1.4: Primary (as-treated) analyses among subgroups

Subgroup/Outcome	Inhibiting SSRIs (N = 712)		Non-inhibiting SSRIs (N = 5,271)		
Age 65+	**Events**	**Rate** / *1000 PYs*	**Events**	**Rate** / *1000 PYs*	**HR (95% CI)**
Any Ischemic	20	142.78	145	128.4	0.98 (0.60-1.60)
AMI	<11	56.83	34	29.54	1.38 (0.60-3.14)
Ischemic Stroke	<11	7.09	41	35.68	0.16 (0.02-1.23)
Stent	<11	71.2	60	52.79	1.46 (0.74-2.88)
PTCA	11	78.27	54	47.42	1.64 (0.83-3.25)
CABG	<11	7.1	13	11.29	0.49 (0.06-3.77)
Any Bleeding	<11	21.28	18	15.62	1.28 (0.37-4.41)
Hemorrhagic Stroke	<11	14.18	<11	4.34	2.77 (0.52-14.69)
Upper GI Bleeding	<11	7.09	13	11.28	0.62 (0.08-4.83)
Age < 65	**Inhibiting SSRIs (N = 1,634)**		**Non-inhibiting SSRIs (N = 10,844)**		
	Events	**Rate** / *1000 PYs*	**Events**	**Rate** / *1000 PYs*	**HR (95% CI)**
Any Ischemic	45	158.59	288	144.83	1.09 (0.79-1.51)
AMI	<11	10.31	35	17.21	0.61 (0.19-1.98)
Ischemic Stroke	<11	34.48	45	22.1	1.43 (0.71-2.86)
Stent	24	83.86	167	83.33	1.03 (0.67-1.59)
PTCA	23	79.92	145	72.18	1.16 (0.74-1.82)
CABG	<11	20.64	33	16.18	1.33 (0.55-3.20)
Any Bleeding	<11	10.31	25	12.26	0.83 (0.25-2.76)
Hemorrhagic Stroke	0	–	<11	2.94	–
Upper GI Bleeding	<11	10.31	20	9.81	1.06 (0.31-3.57)

Clopidogrel duration prior to SSRI initiation

≤ 10 days	Inhibiting SSRIs (N = 398)		Non-inhibiting SSRIs (N = 2,588)		
	Events	**Rate** / *1000 PYs*	**Events**	**Rate** / *1000 PYs*	**HR (95% CI)**
Any Ischemic	20	284.67	88	180.45	1.51 (0.92-2.48)
AMI	<11	53.39	<11	17.92	2.83 (0.83-9.67)
Ischemic Stroke	<11	40.39	17	33.93	1.45 (0.41-5.14)
Stent	14	195.79	48	97.55	2.00 (1.09-3.69)
PTCA	13	177.54	47	95.25	1.88 (1.00-3.52)
CABG	0	–	13	25.88	–
Any Bleeding	0	–	<11	17.91	–
Hemorrhagic Stroke	0	–	<11	7.95	–
Upper GI Bleeding	0	–	<11	9.95	–
>10 days	**Inhibiting SSRIs (N = 1,948)**		**Non-inhibiting SSRIs (N = 13,527)**		
	Events	**Rate** / *1000 PYs*	**Events**	**Rate** */1000 PYs*	**HR (95% CI)**
Any Ischemic	45	127.27	345	131.17	0.92 (0.67-1.27)
AMI	<11	19.62	60	22.37	0.73 (0.33-1.64)
Ischemic Stroke	<11	22.43	69	25.71	0.77 (0.36-1.62)

Appendix 1.4 (continued)

Stent	20	56.31	179	67.58	0.87 (0.54-1.38)
PTCA	21	59.14	152	57.27	1.07 (0.66-1.72)
CABG	<11	19.64	33	12.28	1.53 (0.67-3.49)
Any Bleeding	<11	16.81	34	12.65	1.27 (0.53-3.05)
Hemorrhagic Stroke	<11	5.6	<11	2.6	1.77 (0.36-8.82)
Upper GI Bleeding	<11	11.21	28	10.42	1.07 (0.37-3.07)

≤30 days	**Inhibiting SSRIs (N = 1,027)**		**Non-inhibiting SSRIs (N = 6,959)**		
	Events	**Rate** / *1000 PYs*	**Events**	**Rate** / *1000 PYs*	**HR (95% CI)**
Any Ischemic	34	209.16	221	182.76	1.06 (0.73-1.54)
AMI	<11	35.65	34	27.42	1.09 (0.45-2.61)
Ischemic Stroke	<11	29.83	39	31.46	0.76 (0.27-2.17)
Stent	22	133.98	118	96.85	1.39 (0.88-2.21)
PTCA	21	126.65	100	81.74	1.52 (0.94-2.45)
CABG	<11	11.86	28	22.56	0.50 (0.12-2.12)
Any Bleeding	<11	17.79	22	17.71	0.91 (0.27-3.10)
Hemorrhagic Stroke	<11	5.93	<11	5.63	0.81 (0.09-7.11)
Upper GI Bleeding	<11	11.86	15	12.07	0.96 (0.22-4.23)

>30 days	**Inhibiting SSRIs (N = 1,319)**		**Non-inhibiting SSRIs (N = 9,156)**		
	Events	**Rate** / *1000 PYs*	**Events**	**Rate** / *1000 PYs*	**HR (95% CI)**
Any Ischemic	31	118.65	212	111.08	1.06 (0.72-1.57)
AMI	<11	18.98	35	18.00	0.97 (0.37-2.54)
Ischemic Stroke	<11	22.78	47	24.16	0.87 (0.36-2.07)
Stent	12	45.72	109	56.70	0.87 (0.47-1.60)
PTCA	13	49.52	99	51.45	1.06 (0.57-1.95)
CABG	<11	19.01	18	9.23	1.96 (0.72-5.34)
Any Bleeding	<11	11.39	21	10.78	1.02 (0.30-3.48)
Hemorrhagic Stroke	<11	3.79	<11	2.05	1.81 (0.20-16.35)
Upper GI Bleeding	<11	7.59	18	9.24	0.79 (0.18-3.43)

Events and rates are from the variable ratio propensity score-matched cohort. HRs are adjusted for a database and matching ratio. As per Centers for Medicare and Medicaid Services cell size suppression policy, cell sizes <11 were suppressed.

AMI acute myocardial infarction; CABG coronary artery bypass grafting; CI confidence intervals; GI gastrointestinal; HR hazard ratio; PTCA percutaneous transluminal coronary angioplasty; PYs person years; SSRI selective serotonin reuptake inhibitor.

CHAPTER 2 ALTERNATIVE APPROACHES TO CASE-CROSSOVER ANALYSES OF DRUG-DRUG INTERACTIONS.

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ABSTRACT

Background: The case-crossover design may be useful for evaluating the clinical impact of drug-drug interactions (DDI) in electronic healthcare data; however, experience with the design in this context is limited.

Methods: Using US healthcare claims data (1998-2013), we evaluated two DDI examples with prior evidence of harm: (1) cytochrome P450 (CYP)3A4-metabolized statins + CYP3A4-inhibiting antibiotics (clarithromycin, erythromycin) and rhabdomyolysis; and (2) clopidogrel + CYP2C19-inhibiting selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine) and ischemic events. We conducted case-crossover analyses with (1) a 3-parameter model with a product term and a 6-parameter saturated model that distinguished initiation order of the two drugs; and (2) with or without active comparators.

Results: In the statin example, the simpler, 3-parameter model produced estimates consistent with prior evidence with the active comparator (product term odds ratio [OR] 2.05, 95% confidence interval [CI] 1.00 – 4.23) and without (OR 1.99, 95% CI 1.04 – 3.81). In the clopidogrel example, this model produced results opposite of expectation (OR 0.78, 95% 0.68 – 0.89) unless the active comparator was used (OR 1.03, 95% CI 0.90 – 1.19). The saturated model showed considerable heterogeneity across strata; strata with concordant clopidogrel exposure likely produced the least biased estimates.

Conclusion: A simpler model for interaction can be useful in evaluating outcomes of concurrent drug exposure in case-crossover studies, but a more complex saturated model can help to identify

heterogeneity across strata. Restriction to certain strata of the saturated model or use of active comparator may be necessary in the presence of time-varying confounding.

INTRODUCTION

With rising prescription drug use,[1,2] the risk of exposure to interacting medications among patients is increasing as well. More than a third of elderly patients in the US take five or more medications,[1] and drug-drug interactions (DDIs) have been estimated to cause up to 5% of all hospital admissions.[3,4] Many pharmacologic interactions, however, do not lead to adverse health outcomes, and lack of clinically relevant data has been implicated as one of the reasons behind the failure of healthcare systems to prevent DDI-related patient harm.[5,6] Thus, there have been calls for more evidence on the clinical effects of potential DDIs.[7,8] Electronic healthcare databases, which provide longitudinal information on drug utilization and patient outcomes as they occur in clinical practice, offer a valuable opportunity to evaluate and quantify the clinical consequences of exposure to interacting drugs, and thus, can help to fill existing gaps in the DDI evidence base.

While DDIs can occur by various mechanisms, we focus here on pharmacokinetic DDIs, where one drug (the precipitant) causes the interaction by affecting the absorption, distribution, metabolism, or excretion of another drug (the object). The consequence of such pharmacokinetic interaction is usually a change in bioavailability of the object drug and, subsequently, its effectiveness or toxicity. The precipitant drug itself may or may not have a direct effect on the outcome.

Whether the direct effect of the precipitant drug on the outcome is relevant depends on the causal question of interest. A pharmacologist may be interested in the effect due to interaction only, such as a departure from either additivity or multiplicity of drugs' individual effects. However, a clinician who considers prescribing a potentially interacting drug may be

more interested in the effect of adding the second drug, often relative to an alternative therapy regimen, and may therefore be concerned about the net effect of the interaction and the direct effect of the added drug on the outcome, if it exists. In addition to initiating a precipitant drug while on the object drug therapy, a patient can also encounter an interaction when initiating an object drug while taking the precipitant or when starting both drugs simultaneously. In some instances, the clinical impact of a DDI may differ according to the order in which a patient encounters the interacting drugs.[9] A study design and analytic choices should be carefully considered to ensure that they address the relevant causal question of interest (**Figure 2.1**).

The case-crossover design may be particularly useful for studying DDIs in electronic healthcare data. Because of its self-matching feature, the case-crossover inherently controls for all confounders that are stable within individuals over the observation period.[10,11] However, confounding due to outcome risk factors that change within individuals and are associated with exposure is still possible.[12] In the DDI context, both drugs may be initiated in response to a change in health status that is related to the outcome. Confounding by indication for the object drug may be particularly strong. To avoid confounding by indication for the object drug, prior DDI case-crossover studies have been designed to evaluate exposure to a precipitant within person-time exposed to the object drug.[13,14] This approach, however, restricts the study population to chronic users of the object drug and evaluates the net effect of adding a precipitant. If interest is in isolating the effect due to interaction, modeling DDI as a product of two exposures without restricting the study population would be a logical design choice. It is not known, however, how a model with the product term performs in a self-controlled analysis of two drugs in the presence of strong time-varying confounding. Moreover, in the context of DDI

case-crossover studies, a model with the interaction term represents a reduced, not saturated, model.

The objective of this study was to evaluate a 3-parameter model with the product term in the context of case-crossover drug-drug interaction studies in electronic healthcare data. As part of this exposition, we propose a novel 6-parameter saturated model that considers the order of drug initiation. Evaluations were done based on two previously established empirical examples, including one with strong confounding by indication for the object drug.

METHODS

Data

The data for this investigation came from five US healthcare databases that comprise information on ~100 million individuals covered through Medicare, Medicaid, or commercial insurance over the period of 1995 – 2013 (see **Appendix 2.1** for details). All databases provide demographic data, medical claims, and pharmacy data that include a medication's National Drug Code (NDC), date of dispensing, quantity dispensed, and days supplied.

Examples

We selected two DDI examples that had prior evidence of pharmacologic interaction and clinical outcomes (**Table 2.1**). Both examples involved inhibition of cytochrome P450 (CYP) hepatic enzymes responsible for the metabolism of the object drug. The first example evaluated the impact of the interaction between CYP3A4-metabolized statins (atorvastatin, simvastatin and lovastatin) and CYP3A4-inhibiting antibiotics (clarithromycin and erythromycin) on the outcome of rhabdomyolysis, a rare, but serious statin-related adverse effect. In a prior cohort

study, patients treated with either clarithromycin or erythromycin while on CYP3A4-metabolized statins had a two-fold higher risk of rhabdomyolysis (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.03 – 4.52) within 30 days of the antibiotic prescription, as compared to statin users who were prescribed azithromycin (a non-interacting antibiotic).[15] The second example evaluated the interaction between clopidogrel, an antiplatelet drug that is often prescribed to patients after acute coronary events for secondary cardiovascular prevention, and CYP2C19-inhibiting selective serotonin reuptake inhibitors (SSRIs; fluoxetine or fluvoxamine). By inhibiting CYP2C19, one of the enzymes responsible for conversion of clopidogrel to its active metabolite, CYP2C19 inhibitors decrease the bioavailability of the active antiplatelet agent and may therefore decrease the effectiveness of clopidogrel.[16] Previously, we found that clopidogrel users who were co-prescribed inhibiting SSRIs had a higher risk of subsequent ischemic events (hazard ratio [HR] 1.11, 95% CI 1.01 – 1.22) as compared to patients who were co-prescribed SSRIs not known to interact with CYP2C19.[17]

Population and study design

We used case-crossover design to evaluate the relation between exposure to the interacting drugs and the outcomes of interest. This design samples only individuals who experience the outcome (cases) and compares each subject's exposure in a time period prior to the outcome (hazard window) to his or her exposure during a control period (referent window).[18] For each example, we identified patients 18 years of age and older who were hospitalized for the outcome of interest and were exposed to at least one of the two interacting drugs prior to hospitalization. Outcome definitions were based on hospital discharge diagnoses or procedures

and are listed in **Appendix 2.2**. The event date was defined as the admission date. If a patient experienced more than one eligible event, only the first event was included.

For both examples, we hypothesized that there would be a short induction period following exposure and introduced a 3-day induction window immediately prior to outcome.[19] A washout period between the referent and the hazard windows was introduced to avoid auto-correlation in exposure between periods and carry-over effects.[12] **Appendix figure 2.1** depicts the overall design. In the statins-antibiotics example, we utilized a 3-day induction window, 21-day hazard and referent windows, and a 60-day washout window. Thus, the hazard window was defined as days 4 – 24 and the referent window as days 85 – 105 preceding hospital admission for the event. In the clopidogrel-SSRI example, the hazard window comprised days 4 – 31 preceding the admission for an ischemic event and the control window comprised days 92 – 119 (3-day induction, 28-day hazard and referent windows, and 60-day washout window). Shorter hazard and referent windows were utilized for statins-antibiotics interaction analysis as usual course of therapy with clarithromycin is 10-14 days. Drug exposure was defined as a binary variable and was based on a prescription dispensing occurring within a window. Only oral formulations of medications were considered.

Since prior cohort studies utilized an active comparator, comparative effects are often of interest in clinical practice, and active comparators can help address many biases in observational studies, we also conducted case-crossover analyses of negative control precipitants. In the statins example, we used azithromycin, an antibiotic from the same therapeutic class as clarithromycin and erythromycin, but without CYP enzyme-inhibiting properties. For the clopidogrel example, we used SSRIs not known to be strong inhibitors of

CYP2C19 (**Table 2.1**). The estimates obtained for the interaction of interest were compared to corresponding estimates from case-crossover analyses with negative control precipitants either qualitatively or quantitatively using case-case-time-control analysis, which has shown to reduce bias due to prognosis-related exposure trends within individuals.[20]

Statistical analysis

Conditional logistic regression, stratified on individual, was used to compare the odds of exposure during the hazard window to the odds of exposure in the referent window. We implemented two models for case-crossover analyses – a 3-parameter model with an assumed common interaction effect regardless of the order of initiation of the potentially interacting drug and a saturated 6-parameter model.

3-parameter model

To evaluate the impact of the interaction in the 3-parameter model, a product term was included:

$$\text{Logit}\,(\Pr[Y_{ij}=1]) = \alpha_i + \beta_1 \text{Object}_{ij} + \beta_2 \text{Precipitant}_{ij} + \beta_3 \text{Object}_{ij} * \text{Precipitant}_{ij} \qquad (1)$$

where Y is the outcome, *i* represents an individual, and *j* indicates the hazard or referent window.

This model evaluates concurrent use of two drugs, irrespective of their order of initiation or the duration of use of the first drug prior to initiation of the second.

To obtain estimates relative to the control precipitant, we divided the OR for the interaction (i.e., $\exp(\beta_3)$) between the drugs of interest by the OR for the interaction between the

object drug and the control precipitant drug.[20] To obtain 95% CIs, we evaluated both precipitants in one model and used the contrast statement in SAS (see **Appendix 2.3** for more details). Patients who were exposed to both the precipitant of interest and the control precipitant within the same hazard or referent windows were excluded from the analyses.

Saturated 6-parameter model

To fit a saturated model, we evaluated all possible combinations of exposure in a case-crossover analysis of two drugs that can be initiated three different ways: object drug first, precipitant drug first, or both drugs initiated simultaneously (**Table 2.2**). Only cases who are discordant on exposure between the two windows contribute to the conditional analyses. Strata with no variation in exposure drop out of the analysis. Thus, in a case-crossover analysis of two drugs, there are six informative strata that form a saturated 6-parameter model as follows:

$$\text{Logit}(\Pr[Y_{ij}=1]) = \alpha_i + \beta_1 \text{Object only}_{ij} + \beta_2 \text{Precipitant only}_{ij} + \beta_3 \text{Joint}_{ij} + \beta_4 \text{Object while on Precipitant}_{ij} + \beta_5 \text{Precipitant while on Object}_{ij} + \beta_6 \text{Switch}_{ij} \quad (2)$$

where Y is the outcome, *i* represents an individual, and *j* indicates the hazard or referent window.

This model, which is analogous to stratified analyses, was implemented for the DDI pairs of interest (CYP3A4-metabolized statins and CYP3A4-inhibiting antibiotics; clopidogrel and CYP2C19-inhibiting SSRIs), as well as for the control drug pairs (CYP3A4-metabolized statins and azithromycin; clopidogrel and noninhibiting SSRIs).

The saturated model (model 2) was compared to the 3-parameter interaction model (model 1) using a likelihood ratio test.

RESULTS

There were 21,222 patients who were hospitalized for rhabdomyolysis and were exposed to either CYP3A4-metabolized statins or macrolide antibiotics in the six months prior to the index hospitalization (mean age 65 [SD 16]; females 50%). There were 255,652 patients (mean age 66, SD 13 years; 50% females) who were hospitalized for an ischemic event and filled either clopidogrel or an SSRI within one year prior to index hospitalization.

3-parameter model results

Table 2.3 shows the estimates for the interaction obtained from the 3-parameter model. In the statins example, the OR for the product term was 1.99 (95% CI 1.04 – 3.81), indicating a positive interaction between CYP3A4-metabolized statins and CYP3A4-inhibiting antibiotics on the multiplicative scale. Case-case-time-control analysis using the negative control antibiotic (azithromycin) as a reference produced similar results (OR 2.05; 95% CI 1.00 – 4.23).

In the clopidogrel example, the OR for the interaction was 0.78 (95% CI 0.68 – 0.89) indicating an apparent protective association between concomitant exposure to clopidogrel and CYP2C19-inhibiting SSRIs and ischemic events; however, the estimate was 1.03 (95% CI 0.90 – 1.19) in the analysis with non-inhibiting SSRIs as a referent. The estimates for all parameters from the 3-parameter models, with or without a negative control precipitant, are presented in **Appendix 2.3**.

Saturated 6-parameter model results

The results from the saturated models are summarized in **Tables 2.4** and **2.5**. In the statins example (**Table 2.4**), there was no association between exposure to CYP3A-metabolized statins and rhabdomyolysis in the absence of inhibiting antibiotics (OR 1.04, 95% CI 0.99 – 1.09). Initiation of antibiotics was associated with a 1.7-fold increase in the risk of rhabdomyolysis in the absence of exposure to CYP3A-metabolized statins (OR 1.71, 95% CI 1.37 – 2.14) and 6.3-fold increase in risk among patients exposed to CYP3A-metabolized statins in both windows (OR 6.25, 95% CI 2.18 – 17.96). A positive association was also observed for the control antibiotic, azithromycin, in the absence of CYP3A-metabolized statins (OR 1.26, 95% CI 1.13 – 1.41; **Appendix 2.4**).

In the clopidogrel example (**Table 2.5**), initiation of clopidogrel was associated with a 2.3-fold increase in the risk of ischemic events (OR 2.31, 95% CI 2.27 – 2.35) in the absence of inhibiting SSRIs, a 1.8-fold increase in risk (OR 1.76, 95% CI 1.39 – 2.23) in the presence of inhibiting SSRIs, and a 1.5-fold increase when two drugs were initiated together (OR 1.51, 95% CI 1.25 – 1.82). The ORs for the association between inhibiting SSRIs and ischemic events were 1.06 (95% CI 1.01 – 1.12) in the absence of clopidogrel and 1.25 (95% CI 0.98 – 1.58) with clopidogrel exposure in both windows. The corresponding ORs for SSRIs not known to interact with clopidogrel were 1.16 (95% 1.14 – 1.19) in the absence of clopidogrel and 1.15 (1.04 – 1.27) in the presence of clopidogrel exposure (**Appendix 2.5**).

The saturated model provided a better fit to the data as compared to the reduced, 3-parameter model (likelihood ratio test p-value 0.031 in the statin example and <0.001 in the clopidogrel example).

DISCUSSION

We evaluated several approaches to designing and analyzing a case-crossover study of drug-drug interactions in electronic healthcare data. We found that in the context of two drugs, the saturated case-crossover model is a 6-parameter model while the traditional 3-parameter model with the product term represents a reduced model that assumes no effect modification by the order of drugs initiation. In our empirical statins example, the 3-parameter model with the product term produced results compatible with prior evidence and with the saturated model, both with and without the use of a control precipitant drug. However, we observed important differences in results in the clopidogrel-SSRI example. Specifically, the 3-parameter model yielded results for the product term compatible with prior knowledge only when a negative control precipitant was used as a reference, but produced results opposite of expectation without the control precipitant drug.

The primary difference between the 3-parameter and 6-parameter models is that the 3-parameter model evaluates the effect of concomitant exposure on the outcome of interest irrespective of the order in which patients encountered the interacting drugs. The product term provides the estimate for the average effect of the DDI in the population, which is often the question of interest in DDI context. The 6-parameter model, on the other hand, distinguishes all patterns of drugs initiation sequence. There is no assumption of no effect modification by order of drug initiation, and all clinical scenarios (initiating a precipitant while on object drug therapy, initiating an object drug while on precipitant drug therapy, or initiating both drugs simultaneously) are evaluated separately. There is no overall estimate for the DDI of interest and stratum-specific estimates represent the net effect (due to interaction and the direct effect) of the

added drug. From the causal inference perspective, the 6-parameter model should be preferred when effect modification by order of drug initiation is suspected, whether the heterogeneity of clinical impact is due to true underlying biological mechanism or some other factor, such as differential clinical surveillance or time on the object drug and patient's susceptibility to the outcome of interest at the time of DDI encounter (**Figure 2.1**).

In addition to combining different effects in the presence of effect modification, pooling or across-strata comparison in self-controlled analyses may introduce bias in the presence of time-varying confounding that is differential across strata. We believe that differential confounding by prognosis at the time of clopidogrel initiation was the main reason for the discrepancy we observed in the clopidogrel-SSRI example. Clopidogrel is an antiplatelet drug that is indicated for secondary prevention of cardiovascular events following a percutaneous coronary intervention or myocardial infarction,[21-23] and is often initiated when patients are at high risk of ischemic events. Both the 3-parameter model and the 6-parameter saturated model yielded highly confounded estimates for the effect of clopidogrel in the absence of inhibiting SSRIs. Both models also showed that inhibiting SSRIs modified the association between clopidogrel and ischemic events, albeit in opposite direction. Since the amount of confounding was largest among patients initiating clopidogrel in the absence of inhibiting SSRIs, and lower among patients on both drugs, the product term from the 3-parameter model yielded a protective estimate of the interaction, reflecting, most likely, a better prognosis of patients who initiate or continue an antidepressant medication at the time of clopidogrel initiation. In the statins example, we did not observe significant confounding for the association between CYP3A4-metabolized statins and rhabdomyolysis. The estimated effects of antibiotics were likely confounded by their indication (acute infection), since macrolide antibiotics (clarithromycin,

erythromycin or azithromycin) are not known to cause rhabdomyolysis.[24] Unlike in the clopidogrel example, we would not expect confounding by indication for antibiotics to be differential across strata of exposure to CYP3A4-metabolized statins, given that acute infections are usually treated regardless of other comorbidities or drugs patients are taking, although differential surveillance for muscle-related toxicity in patients exposed or unexposed to statins is possible.

Since the 6-parameter model allows a more thorough evaluation of heterogeneity across strata than the 3-parameter model, it may be preferred in scenarios where confounding by indication is of concern even if the assumption of no effect modification by the order of drugs initiation holds. Intractable confounding by indication may circumscribe the causal questions that can be validly answered with the data available and require restricting analyses to strata with no confounding or where confounding control is possible. We believe that in the clopidogrel-SSRI example, the strata in the 6-parameter model where clopidogrel exposure was concordant across hazard and referent windows were least affected by confounding and can provide valid inference about the clinical impact of adding a CYP2C19-inhibiting SSRI to clopidogrel therapy. This estimate could be further compared to the estimate of direct effect of inhibiting SSRIs in the absence of clopidogrel exposure (clopidogrel exposure = 0 across both windows) or the effect of non-interacting SSRIs among patients on clopidogrel to adjust for confounding associated with initiation of SSRIs and to isolate the effect due to interaction only.

Restriction as a method of confounding control has been previously recommended for DDI studies[9] and most prior pharmacoepidemiologic studies of DDIs have attempted to control for confounding by indication for the object drug by holding object drug exposure constant,

either within persons in self-controlled designs or across persons in cohort and case-control studies.[13,25,26] Quite often, restriction at the design stage stems from a specific clinical question of interest -- e.g., the effect of adding an interacting drug to object drug therapy (**Figure 2.1**). Restricting the study population to those with concordant object drug exposure is equivalent to one stratum of the 6-parameter saturated model fit in the overall population of cases exposed to either or both interacting drugs. Yet, the 6-parameter model additionally allows for potential evaluation and subsequent adjustment for confounding by indication for the precipitant drug or for the direct effect of the precipitant when the effect due to the interaction only is of interest. The 6-parameter model can also help to evaluate the magnitude of the confounding by indication for the object drug or the presence of effect modification by order of drug initiation.

In addition to restriction, active comparators can be used to adjust for confounding by prognosis-related treatment initiation. Using the negative control precipitant drug as an active comparator seemed to mitigate at least some bias in the estimation of the interaction term in the clopidogrel example, although residual confounding cannot be ruled out. The ability to adjust for prognosis-related confounding using an active comparator will depend on the similarity of patients and indications. In addition, a negative control precipitant drug should itself not interact with the object drug. Using an inappropriate control can lead to only partial adjustment or could even increase bias.[20] Thus, although an active comparator/reference drug-drug pair can help mitigate bias when confounding by indication is present and when appropriate for the causal question of interest, it can be difficult to identify an appropriate comparator.

Our results should be interpreted with a few points in mind. Prior evidence for the empirical examples came from cohort studies that utilized an active comparator and restricted the

study population to users of one of the interacting drugs at baseline to control for confounding.[15,17,27] Thus, estimates from cohort studies are more comparable to stratum-specific estimates from the 6-parameter saturated model. None of the prior studies utilized a model with a product term between two exposures in the overall population exposed to either or both interacting drugs. In addition, cohort and case-crossover studies focus on slightly different sub-populations and evaluate different hypotheses.[28] These differences may be immaterial with transient exposures, such as antibiotics, but may lead to differences when chronic exposures, such as SSRIs, are evaluated. However, in our clopidogrel-SSRI cohort studies, follow-up was short due to patients discontinuing at least one of the interacting drugs. It is also possible that the reference cohort studies produced biased results. While randomized clinical trials (RCTs) would be preferred, RCTs are rarely conducted for the purpose of evaluating clinical outcomes of DDIs. Some post hoc subgroup analyses of RCTs have evaluated whether the effect of an object drug varied across strata of a potentially interacting precipitant drug.[29] Aside from targeting specific strata in a manner similar to our reference cohort studies, such analyses may still be confounded since the precipitant drug was not randomized.[30]

Exposure and outcome misclassification are always of concern with studies in electronic healthcare databases. A pharmacy dispensing indicates that a patient purchased a drug in the pharmacy, but not necessarily that the patient adhered to therapy as prescribed. The degree of misclassification can increase with longer hazard and referent windows in DDI case-crossover studies as patients might stop one drug while taking the other. Lastly, we evaluated only two empirical examples; both with at least one drug representing a chronic therapy. There may be no differences between a 3- and a 6-parameter model when both drugs are used transiently or

represent point exposures, such as vaccines. Nevertheless, the question of comparability of strata in a 3-parameter model with the product term will remain.

In conclusion, there are several approaches to designing a case-crossover study of interacting drugs in electronic healthcare data. The 3-parameter model with a product term evaluates the effect of the interaction in the population irrespective of how patients encountered the interaction, while a saturated 6-parameter model distinguishes all patterns of drugs initiation sequence and can identify heterogeneity across strata. Confounding by prognosis-related treatment initiation represents the biggest threat to validity, and can be mitigated by the use of an active comparator, if it is available, or restriction to strata of patients with constant exposure to one of the drugs, provided that the stratum-specific analyses still address a clinical question of interest.

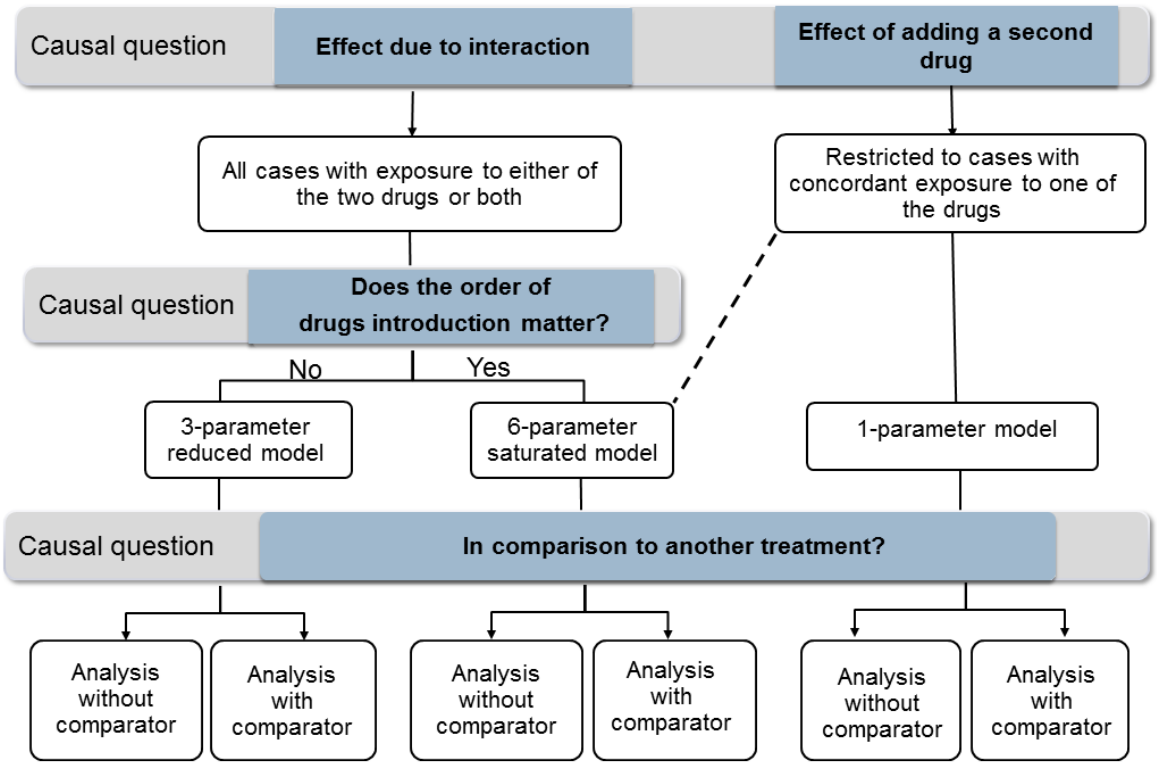

Figure 2.1: Study design decision chart

Dotted line represents a connection between models (restricted analyses are equivalent to analyses of one stratum in the saturated model).

Table 2.1: Summary of empirical examples

	Object drug	Precipitant drug	Control precipitant	Outcome	Prior evidence*
1	CYP3A4-metabolized statins: simvastatin, atorvastatin, lovastatin	CYP3A4-inhibiting antibiotics: clarithromycin, erythromycin	Azithromycin	Rhabdomyolysis	OR 2.17 (95% CI 1.03 – 4.52) within 30 days of the antibiotic prescription among patients using statins[15]
2	Clopidogrel	CYP2C19-inhibiting SSRIs: fluoxetine, fluvoxamine	Other SSRIs: citalopram, escitalopram, paroxetine, sertraline	Ischemic events: MI, ischemic stroke, or revascularization procedures	HR 1.11 (95% CI 1.01 – 1.22)[17]

*cohort studies; as compared to co-prescription with a control precipitant.

CI – confidence interval; CYP – cytochrome P450; HR – hazard ratio; MI – myocardial infarction; OR – odds ratio; SSRI – selective serotonin reuptake inhibitors

Table 2.2: Exposure patterns in case-crossover analysis of two interacting drugs and patient contributions to likelihood estimates

	Hazard window		Referent window		Contribution to the likelihood in 3-parameter model*	Contribution to the likelihood in 6-parameter model	Description
Exposure pattern	**Obj. drug**	**Prec. drug**	**Obj. drug**	**Prec. drug**			
1	1	0	0	0	β1	β1	Object drug only
2	0	0	1	0	– β1	– β1	
3	0	1	0	0	β2	β2	Precipitant drug only
4	0	0	0	1	– β2	– β2	
5	1	1	0	0	β1+β2+β3	β3	Joint exposure
6	0	0	1	1	– β1 – β2– β3	– β3	
7	1	1	0	1	β1 + β3	β4	Object drug within person-time exposed to precipitant
8	0	1	1	1	– β1 – β3	– β4	
9	1	1	1	0	β2 + β3	β5	Precipitant drug within person-time exposed to object
10	1	0	1	1	– β2 – β3	– β5	
11	1	0	0	1	β1 – β2	β6	Switch
12	0	1	1	0	– β1 + β2	– β6	
13	0	0	0	0	drops out	drops out	Always exposed to both drugs or unexposed
14	1	1	1	1	drops out	drops out	
15	1	0	1	0	drops out	drops out	Always exposed to one of the two drugs
16	0	1	0	1	drops out	drops out	

*3-parameter model with a product term; Obj. – object; Prec. – precipitant

Table 2.3: Estimates of the interaction between an object drug and a precipitant drug from a 3-parameter model

Examples	Case-crossover OR (95% CI)	Case-case time-control OR (95% CI)[a]
Statins*inhibiting antibiotics	1.99 (1.04 - 3.81)	2.05 (1.00 - 4.23)
Clopidogrel*inhibiting SSRIs	0.78 (0.68 - 0.89)	1.03 (0.90 - 1.19)

[a] as compared to the case-crossover estimate of interaction with the control precipitant drug (azithromycin in statins example and non-inhibiting SSRIs in clopidogrel example).

CI – confidence interval; OR – odds ratio; SSRI – selective serotonin reuptake inhibitors

Table 2.4: Stratified analyses (6-parameter saturated model) of interaction between CYP3A4-metabolized statins and CYP3A4-inhibiting antibiotics on the outcome of rhabdomyolysis

		Hazard period		Referent period			
Strata	**Description**	**Statin**	**Abx**	**Statin**	**Abx**	**N**	**OR (95% CI)**
1	Object drug only	1	0	0	0	3471	1.04 (0.99 – 1.09)
		0	0	1	0	3333	Reference
2	Precipitant drug	0	1	0	0	209	1.71 (1.37 – 2.14)
	only	0	0	0	1	122	Reference
3	Joint exposure	1	1	0	0	19	2.11 (0.96 – 4.67)
		0	0	1	1	<11	Reference
4	Object drug when	1	1	0	1	<11	–
	precipitant = 1	0	1	1	1	0	Reference
5	Precipitant drug	1	1	1	0	25	6.25 (2.18 – 17.96)
	when object = 1	1	0	1	1	<11	Reference
6	Switch	1	0	0	1	<11	0.19 (0.06 – 0.64)
		0	1	1	0	16	Reference

Abx – antibiotics (clarithromycin or erythromycin); CI – confidence interval; OR – odds ratio. Cells with sizes < 11 were suppressed as per Centers for Medicare and Medicaid Services.

Table 2.5: Stratified analyses (6-parameter saturated model) of interaction between clopidogrel and CYP2C19-inhibiting SSRIs on ischemic events

		Hazard period		Referent period			
Strata	**Description**	**Clo**	**SSRI**	**Clo**	**SSRI**	**N**	**OR (95% CI)**
1	Object drug only	1	0	0	0	42518	2.31 (2.27-2.35)
		0	0	1	0	18445	Reference
2	Precipitant drug	0	1	0	0	3227	1.06 (1.01-1.12)
	only	0	0	0	1	3033	Reference
3	Joint exposure	1	1	0	0	273	1.51 (1.25-1.82)
		0	0	1	1	181	Reference
4	Object drug when	1	1	0	1	188	1.76 (1.39-2.23)
	precipitant = 1	0	1	1	1	107	Reference
5	Precipitant drug	1	1	1	0	152	1.25 (0.98-1.58)
	when object = 1	1	0	1	1	122	Reference
6	Switch	1	0	0	1	118	1.64 (1.22-2.20)
		0	1	1	0	72	

CI – confidence interval; Clo – clopidogrel; OR – odds ratio; SSRI – selective serotonin reuptake inhibitors; SSRIs are CYP2C19-inhibiting SSRIs (fluoxetine and fluvoxamine)

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APPENDIX

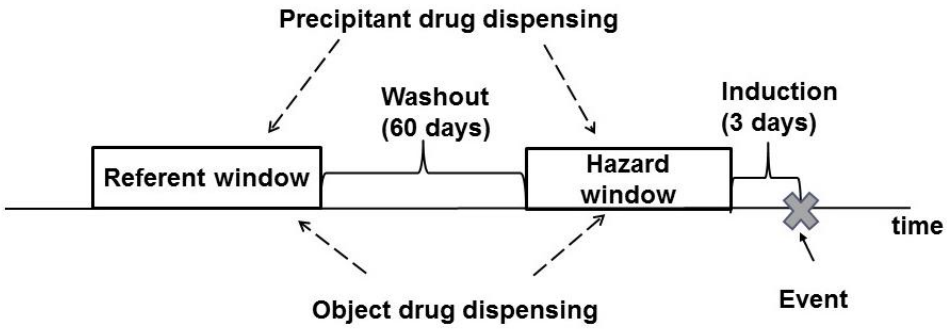
Appendix 2.1: Databases

1) Optum Research Database: 2004 – 2013
2) Medicaid Analytic eXtract (MAX): 2000-2006 for clopidogrel example and 2000 – 2010 for statins example
3) Medicare databases that linked Medicare Parts A and B data to pharmacy claims data from (1) Medicare Part D plans administered by CVS Caremark (2006-2008); (2) a pharmacy assistance program in New Jersey (Pharmaceutical Assistance to the Aged and Disabled [PAAD]; 1998 - 2005); and (3) a pharmacy assistance program in Pennsylvania (Pharmaceutical Assistance Contract for the Elderly [PACE] (1998-2005).

Appendix 2.2: Outcome definitions

Outcome	Algorithm
Ischemic events	
Myocardial infarction	inpatient ICD-9 diagnosis code 410.xx, excluding 410.x2, as primary; minimum 3 day stay required (unless patient died) and maximum of 180 days
Ischemic stroke	inpatient ICD-9 diagnosis code 433.x1, 434.x1, or 436.xx
Stent	ICD-9 procedure code 36.06 or 36.07 or CPT-4 code 392980, 92981 (inpatient or outpatient)
PTCA without stenting	ICD-9 procedure code 00.66, 36.01, 36.02, 36.05, 36.09 or CPT-4 code 92973, 92982, 92984, 92995, 92996 (inpatient or outpatient)
CABG	inpatient ICD-9 procedure code 36.1x or 36.2x or CPT-4 code 33510-33536, 33545, 33572
Rhabdomyolysis	- Primary or secondary ICD-9 diagnosis code 791.3 (myoglobinuria) -primary ICD-9 diagnosis code 728.89 (other disorder of muscle) - secondary ICD-9 diagnosis code 728.89 + claim for CK test within 7 days of hospitalization (CPT codes 82550, 82552, 82554, 80012, 80016, 80018, 80019) or a discharge code for acute renal failure (ICD-9 diagnosis code 584.x) - ICD-9 diagnosis code 728.88 (rhabdomyolysis)

CABG coronary artery bypass grafting; CPT-4 Current Procedure Terminology, 4th Revision; ICD-9 International Classification of Diseases, 9th Revision; PTCA percutaneous transluminal coronary



Appendix Figure 2.1: Study design

Hazard and referent windows were 21 days in statins-antibiotics example and 28 days in clopidogrel-SSRI example.

Appendix 2.3: Estimates from the 3-parameter interaction model, case-crossover and case-case time control analyses

Case-crossover model for a drug pair:

$$\text{Logit}(\Pr[Y_{ij}=1]) = \alpha_i + \beta_1 \text{Object}_{ij} + \beta_2 \text{Precipitant}_{ij} + \beta_3 \text{Object}_{ij} * \text{Precipitant}$$

where *i* represents an individual and *j* represents a hazard or referent window.

Case-case Time control model:

$$\text{Clogit}(\Pr[Y_{ij}=1]) = \alpha_i + \beta_1 \text{Object}_{ij} + \beta_2 \text{Ppt}_{ij} + \beta_3 \text{Object}_{ij} * \text{Ppt}_{ij} + \beta_4 \text{NonInh\_Ppt}_{ij} + \beta_5 \text{Obj}_{ij} * \text{NonInh\_Ppt}_{ij}$$

where *i* represents an individual and *j* represents a hazard or referent window, Ppt is a precipitant drug, NonInh_Ppt is a non-inhibiting (control) precipitant drug.

Since patients who were exposed to both precipitant drugs, the precipitant drug of interest and the control precipitant, within the same window were excluded, the 3-way interaction Object drug*Precipitant*NonInhibiting Precipitant is 0. SAS Contrast statement was used to obtain 95% confidence interval for the β_3 versus β_5 comparison.

Statins, inhibiting antibiotics (clarithromycin, erythromycin) and rhabdomyolysis

Case-crossover for statins, inhibiting antibiotics (clarithromycin, erythromycin) and the outcome of rhabdomyolysis

Parameter	Estimate	Standard Error	Pr > ChiSq	OR	95% Wald CI	
Statins (β_1)	0.0368	0.0242	0.128	1.04	0.99	1.09
Inhibiting antibiotics (β_2)	0.5817	0.1111	<.0001	1.79	1.44	2.22
Statins*antibiotics (β_3)	0.6859	0.3322	0.039	1.99	1.04	3.81

Case-case Time control model

Parameter	Estimate	StdErr	Prob > ChiSq	OR	LCL	UCL
Statins (β_1)	0.0368	0.0243	0.1304	1.04	0.99	1.09
Inhibiting antibiotics (β_2)	0.5836	0.1112	0.0000	1.79	1.44	2.23
NonInhibiting antibiotic (β_4)	0.2183	0.0555	0.0001	1.24	1.12	1.39
statin*Inhibiting (β_3)	0.6841	0.3322	0.0395	1.98	1.03	3.80
statin*NonInhibiting (β_5)	-0.0348	0.1612	0.8292	0.97	0.70	1.32
statin*Inhibiting (β_3) **vs** statin*NonInhibiting (β_5)	0.7188	0.7563	0.0511	2.05	1.00	4.23

Statins = CYP3A4-metabolized statins (simvastatin, atorvastatin, lovastatin); Inhibiting antibiotics = clarithromycin, erythromycin; NonInhibiting antibiotic = azithromycin.

Appendix 2.3 (Continued)

Clopidogrel, CYP2C19-inhibiting SSRIs and ischemic events

Case-crossover analysis of clopidogrel, CYP2C19-inhibiting SSRIs (fluoxetine, fluvoxamine) and ischemic events

Parameter	Estimate	Std. Err	Prob > ChiSq	OR	95% Wald CI	
Clopidogrel (β_1)	0.8321	0.00878	<.0001	2.30	2.26	2.34
Inhibiting SSRIs (β_2)	0.0703	0.0246	0.0043	1.07	1.02	1.13
clopidogrel*SSRIs (β_3)	-0.2479	0.0675	0.0002	0.78	0.68	0.89

Case-case Time control model

Variable	Estimate	Std Err	Prob > ChiSq	OR	LCL	UCL
Clopidogrel (β_1)	0.8561	0.0090	<.0001	2.35	2.31	2.40
Inhibiting SSRIs (β_2)	0.0761	0.0246	0.0020	1.08	1.03	1.13
NonInhibiting SSRIs (β_4)	0.1648	0.0111	<.0001	1.18	1.15	1.20
clopidogrel*Inhibiting (β_3)	-0.2716	0.0675	0.0001	0.76	0.67	0.87
clopidogrel*NonInhibiting (β_5)	-0.3929	0.0288	<.0001	0.68	0.64	0.71
clopidogrel*Inhibiting (β_3) **vs** clopidogrel*NonInhibiting (β_5)	0.1212	0.0820	0.0951	1.13	0.98	1.30

Inhibiting SSRIs = fluoxetine, fluvoxamine; NonInhibiting SSRIs = citalopram, escitalopram, paroxetine, sertraline.

Appendix 2.4: Stratified analyses (6-parameter saturated model) of interaction between CYP3A-metabolized statins and azithromycin on the outcome of rhabdomyolysis

		Hazard period		Referent period			
Strata	**Description**	**Statin**	**Abx**	**Statin**	**Abx**	**N**	**OR (95% CI)**
1	Object drug only	1	0	0	0	3383	1.04 (0.99-1.09)
		0	0	1	0	3268	Reference
2	Precipitant drug	0	1	0	0	681	1.26 (1.13-1.41)
	only	0	0	0	1	540	Reference
3	Joint exposure	1	1	0	0	65	1.48 (1.01-2.17)
		0	0	1	1	44	Reference
4	Object drug when	1	1	0	1	<11	0.50 (0.05-5.51)
	precipitant = 1	0	1	1	1	<11	Reference
5	Precipitant drug	1	1	1	0	32	0.94 (0.58-1.53)
	when object = 1	1	0	1	1	34	Reference
6	Switch	1	0	0	1	46	1.05 (0.69-1.58)
		0	1	1	0	44	Reference

Abx – antibiotics (azithromycin). Cells with cell sizes < 11 were suppressed as per Centers for Medicare and Medicaid Services.

Appendix 2.5: Stratified analyses (6-parameter saturated model) of interaction between clopidogrel and non-inhibiting SSRIs on ischemic events

		Hazard period		Referent period			
Strata	**Description**	**Clo**	**SSRI**	**Clo**	**SSRI**	**N**	**OR (95% CI)**
1	Object drug only	1	0	0	0	39990	2.39 (2.34-2.43)
		0	0	1	0	16760	Reference
2	Precipitant drug	0	1	0	0	16697	1.16 (1.14-1.19)
	only	0	0	0	1	14357	Reference
3	Joint exposure	1	1	0	0	1579	1.59 (1.47-1.72)
		0	0	1	1	992	Reference
4	Object drug when	1	1	0	1	993	1.41 (1.28-1.55)
	precipitant = 1	0	1	1	1	704	Reference
5	Precipitant drug	1	1	1	0	854	1.15 (1.04-1.27)
	when object = 1	1	0	1	1	742	Reference
6	Switch	1	0	0	1	535	1.53 (1.34-1.75)
		0	1	1	0	349	Reference

Clo – clopidogrel; SSRI – selective serotonin reuptake inhibitors

CHAPTER 3 A CASE-CROSSOVER-BASED SCREENING APPROACH TO IDENTIFYING CLINICALLY RELEVANT DRUG-DRUG INTERACTIONS IN ELECTRONIC HEALTHCARE DATA

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ABSTRACT

Background: While many drugs interact pharmacologically, the impact of interactions on clinical outcomes is often unknown.

Objective: To develop a semi-automated approach for identifying clinically relevant interacting drug pairs in electronic healthcare data.

Methods: We evaluated two examples of drugs of interest (CYP3A4-metabolized statins and dabigatran; object drugs) and an adverse event for each (rhabdomyolysis and bleeding, respectively). Using US healthcare claims data and case-crossover design with 30-day hazard (days 4-33 preceding the outcome) and 30-day referent windows (days 64-93 preceding the outcome), we screened all co-dispensed drugs (potential precipitants) in patients who were exposed to the object drug throughout the observation period leading up to the event. Case-crossover estimates in patients with no exposure to the object drug prior to outcomes were used to adjust for associations between precipitants and outcomes that are unrelated to a potential interaction. P-values were adjusted for multiple estimation using False Discovery Rate (FDR). Drugs with FDR q-value < 0.05 and adjusted odds ratio (OR) > 1 were deemed potential signals.

Results: We identified 7,801 patients who experienced rhabdomyolysis while on CYP3A4-metabolized statins. Of 460 co-dispensed drugs screened, 1 drug (clarithromycin) was identified as a potential signal (OR 5.83). We identified 15,147 dabigatran patients with bleeding. Of 485 co-dispensed drugs screened, 2 drugs (naproxen and enoxaparin, ORs 2.50 and 2.75, respectively) were identified as signals. All 3 signals reflected known pharmacologic interactions.

Conclusions: Case-crossover-based screening has the potential to identify clinically relevant drug interactions in electronic healthcare data. Adjusting for DDI-unrelated associations between the precipitants and outcomes may be necessary to filter out signals due to bias or direct effects of precipitant drugs on the outcomes of interest.

INTRODUCTION

Patient harm due to drug-drug interactions (DDI) is a serious clinical and public health problem.[1-3] Evaluation of DDI potential is a requirement for all medications in the pre-approval stage; however, pre-approval studies are limited in the scope of interactions assessed, characteristics of patients exposed (often healthy volunteers), and outcomes evaluated (often pharmacokinetic parameters). As a result, little is known about the clinically-relevant interaction potential of new medications following their marketing approval.[3,4]

With hundreds, if not thousands, of potentially interacting drugs on the market, the lack of clinically relevant DDI data has led to substantial uncertainty and frustration in clinical practice. Electronic prescribing and pharmacy software generate an excessive number of DDI alerts, most of which are routinely overridden, although not always appropriately.[5,6] There are growing concerns that the current DDI decision support systems are failing to achieve their goal of reducing DDI-associated patient harm,[4,7] and that avoidance of interacting drugs for which no clinical outcome evidence exists might lead to underutilization of safe and effective medications.[8]

One solution to filling the existing knowledge gap is to leverage routinely-collected electronic healthcare data. Administrative claims data, which capture health utilization information for large numbers of individuals, have been utilized for drug safety research for several decades and regulatory agencies are increasingly turning to national healthcare data networks, such as the US Food and Drug Administration (FDA) Sentinel system, for real-world evidence generation and post-marketing drug safety surveillance.[9,10] While a number of *ad hoc* studies have evaluated the clinical impact of DDIs in electronic healthcare data,[11-14] evaluating

every possible drug pair via formal pharmacoepidemiologic assessments is infeasible, especially as an average of 31 drugs are approved each year in the US.[15] A semi-automated screening system capable of identifying drugs that increase the risk of a clinically relevant adverse event when used concomitantly with the main drug of interest could streamline both the identification of new interactions and quantification of risk for interactions that are suspected based on existing knowledge of pharmacology.

As healthcare databases capture information not specifically for research purposes and because drugs are not randomly allocated in usual care settings, for valid inference, assessments of clinical outcomes of DDIs in electronic healthcare data must address multiple sources of bias.[16] The need to simultaneously control for confounding across a large number of drug pairs, in particular, will present a major challenge for a DDI screening system. The case-crossover design, which makes comparisons within individuals and inherently controls for confounding factors that remain stable over the observation period,[17] would be well-suited for this purpose, and is particularly advantageous for investigations in claims databases, which often lack information on important patient characteristics. By further limiting the observation period to person-time exposed to an object drug (the drug that is affected by an interaction), confounding by indication for that drug can be mitigated. Multiple concomitantly dispensed drugs can then be efficiently screened for their association with a pre-specified outcome within this "object drug-exposed" person-time.

The objective of this investigation was to develop a semi-automated, case-crossover-based DDI screening approach in electronic healthcare data. We focused on a semi-targeted approach with a pre-specified drug of interest (object drug) and an associated adverse event, and

sought to identify concomitantly used drugs (precipitant drugs) that interacted with the object drug to increase the risk of the outcome in clinical practice.

METHODS

Data sources

We used data from seven sources that comprised US Medicare, Medicaid, or commercially-insured population over the period of 1995 – 2015 (see **Appendix 3.1** for details). All databases provide demographic data, medical claims, and pharmacy data that include a medication's National Drug Code (NDC), date of dispensing, quantity dispensed, and days supplied. All Data Use Agreements were in place. As per Centers for Medicare and Medicaid Services cell size suppression policy, cell sizes <11 were suppressed.

Test cases

Two test cases were evaluated. The first involved cytochrome P450 (CYP) 3A4-metabolized statins (atorvastatin, simvastatin and lovastatin) as the object drug and the outcome of rhabdomyolysis, a rare, but serious statin-related adverse event. The second included dabigatran, a direct oral anticoagulant approved in October 2010, as the object drug and the outcome of major bleeding. The outcome definitions were based on hospital discharge diagnoses or inpatient procedures and are listed in **Appendix 3.2**.

Monitoring framework

We used the case-crossover design to set up a screening framework. The case-crossover design samples only individuals who experience the outcome of interest (cases) and compares

each subject's exposure in a time period prior to the outcome (hazard window) to his or her exposure during a control period (referent window).[17] For both examples, we defined hazard window as days 4-33 preceding the admission for the outcome event and the reference window as days 64-93 preceding the event. Thus, the observation period prior to the event included a 3-day induction window, 30-day hazard window, 30-day washout, and 30-day referent window (**Figure 3.1**). To control for confounding by indication for the object drug, we required cases to be continuously exposed to the object drug throughout their observation period (**Figure 3.1**). Continuous exposure was determined based on days' supply with maximum gaps of 14 days in the statins example and 7 days in the dabigatran example between the end of days' supply of one dispensing and a subsequent dispensing. In the statins example, patients were allowed to switch among the three CYP3A4-metabolized statins during the observation period. In addition to continuous object drug exposure, cases were also required to be at least 18 years of age at the time of the event, have continuous insurance coverage for at least 180 days prior to the event and be free of the outcome of interest for at least 93 days (observation period) prior to their index outcome. For patients who had multiple eligible outcomes, we selected the first one.

Exposure to potential precipitant drugs was defined based on a dispensing occurring within the hazard or referent window. We evaluated all drugs that patients encountered, except topical formulations, devices, and irrigation, polyethylene glycol, or sodium chloride solutions. In addition, we excluded drugs that represented alternative therapy for the object drug of interest (other statins in the CYP3A4-metabolized statins example and other oral anticoagulants in the dabigatran examples). Screening was performed at the generic name level; thus, different formulations, salts or multi-drug combinations were evaluated as separate entities.

A concomitantly administered drug (potential precipitant) can be associated with an outcome of interest through multiple mechanisms that do not relate to the interaction (e.g., direct effect of the precipitant on the outcome, confounding, bias due to violation of assumptions). The portion of the effect that is unrelated to the interaction can be removed via a control group of cases who were exposed to the precipitant drugs in the absence of exposure to the object drug of interest (object drug-unexposed cases; **Figure 3.1, bottom panel**). The same inclusion criteria were implemented for object drug-unexposed cases as described above, except that they were required to have no exposure to any of the CYP3A4-metabolized statins in the statins-rhabdomyolysis example and no exposure to any of the oral anticoagulants (dabigatran, rivaroxaban, apixaban, or warfarin) in the dabigatran-bleeding example for at least 180 days prior to and including the hospital admission for the outcome. The same data sources were used for both case-crossover analyses in the statins example. For the dabigatran example, we did not have Medicare data on patients not exposed to oral anticoagulants; thus, we only used MarketScan data to obtain estimates of associations between precipitants and outcomes in the absence of exposure to the object drug. To evaluate the robustness of our findings, in a sensitivity analysis we limited MarketScan object drug-unexposed cases to those 65 years of age and older in order to approximate the age distribution of dabigatran-exposed cases.

The estimates obtained from the object drug-unexposed cases were used to adjust the case-crossover estimates of associations between concomitant exposure to precipitants and outcome in object drug-exposed cases using a case-case-time-control approach,[18] as described below.

Statistical analysis

Associations between exposure to precipitant drugs and the outcomes of interests were analyzed using techniques for matched data. In case-crossover analysis, the Mantel-Haenszel estimate of the odds ratio (OR) is the ratio of patients exposed in the hazard window and unexposed in the referent window to the number of patients unexposed in the hazard window but exposed in the referent window. To avoid statistically unstable estimates, we evaluated precipitant drugs with at least 5 patients with discordant exposure. P-values were estimated using McNemar's test. ORs in object drug-exposed cases were divided by the corresponding ORs in object drug-unexposed cases. Drugs that had no corresponding estimate among object drug-unexposed cases were excluded. The estimation of p-values for the ratios of ORs is described in **Appendix 3.3.**

The False Discover Rate (FDR) was used to account for multiple testing. FDR-based methods control the average proportion of positive tests that are false positives, have been extensively used in screening of genomic data, and are generally considered more appropriate for exploratory analyses as they are more powerful than family-wise error rate adjustments, such as Bonferroni and Sidak.[19-21] Following the estimation of p-value for ratios of ORs, precipitant drugs were ranked in the order of ascending nominal p-value and the FDR q-value was calculated by dividing the p-value by the number of total estimates and multiplying by the rank number.

Precipitant drugs with q-value < 0.05 and adjusted OR > 1 were deemed to be potential signals.

RESULTS

Among patients with the outcome of rhabdomyolysis, 7,801 were exposed to CYP3A4-metabolized statins for at least 93 days prior to and including the hospital admission date and 51,094 patients were not exposed to CYP3A4-metabolized statins for at least 6 months prior to index hospitalization. For the dabigatran example, we identified 15,147 patients who had a major bleeding event following at least 93 days of dabigatran exposure and 672,902 patients who were not exposed to any of the direct oral anticoagulants or warfarin for at least 6 months prior to their bleeding episode. Demographic characteristics of eligible cases are summarized in **Table 3.1**.

In the statins example, 462 drugs were screened. For two drugs estimates in the absence of exposure to CYP3A4 statins were not available; thus 460 drugs were evaluated. Prior to adjustment, nine drugs had an FDR q-value < 0.05 and all of them had ORs > 1 (**Appendix 3.4**). Two represented a known interaction (clarithromycin and gemfibrozil). Following adjustment, there was only one drug, clarithromycin, with an FDR q-value < 0.05 (**Appendix 3.7**). **Table 3.2** lists the top 15 drugs (based on ascending p-value) with ORs due to interaction with CYP3A4-metabolized statins above 1.

In the dabigatran example, 507 drugs were screened and for 22 drugs OR in the absence of exposure to oral anticoagulants was not available; thus 485 drugs were evaluated. Prior to adjustment, 29 drugs had an FDR q-value < 0.05; all with ORs > 1.0 (**Appendix 3.5**). Two out of 29 represented a known interaction (naproxen and enoxaparin). Following adjustment, there were 14 drugs with an FDR q-value < 0.05; however, only two (naproxen with adjusted OR of 2.50 and enoxaparin with adjusted OR of 2.78) with ORs > 1 (**Appendix 3.8**). **Table 3.3** lists the top 15 drugs (based on ascending p-value) that had ORs due to interaction > 1.

Sensitivity analyses

In the dabigatran example, limiting control cases (unexposed to oral anticoagulants for at least 180 days prior to their events) to patients 65 years of age or older reduced the number of control cases by half, but did not significantly alter the findings. Only enoxaparin had an FDR q-value < 0.05; for naproxen, the FDR q-value was 0.059 (see **Appendix 3.6** for demographics and screening results).

DISCUSSION

In this paper, we proposed a DDI screening approach based on the case-crossover design. The approach identified a known CYP3A4 inhibitor, clarithromycin, as a drug that interacted with CYP3A4-metabolized statins to increase the risk of rhabdomyolysis, and two drugs, naproxen and enoxaparin, that interacted with dabigatran to increase the risk of major bleeding. Both naproxen and enoxaparin can increase bleeding risk in the absence of dabigatran exposure, which was reflected in the ORs in cases unexposed to oral anticoagulants, and although neither is known to interact with dabigatran pharmacokinetically, interactions on a pharmacodynamic level are possible.[22] That the approach identified several known interactions and produced no false positive signals suggests that the case-crossover design is a viable option for DDI screening in electronic healthcare data.

Confounding by indication is the main threat to validity in studies of drug-drug interactions. In our proposed approach, confounding by indication for the object drug is inherently controlled by restricting observation period to person-time exposed to the object drug. We further filtered out associations between the precipitant drugs and the outcome of interest

that are not likely due to interactions with the object drug by comparing estimates in cases continuously exposed to the object drug to estimates in cases with no exposure to the object drug during the observation period leading up to the event date. To our knowledge, this is the first study to use the case-crossover design for DDI screening and the first to adapt this form of case-case-time-control adjustment in drug interaction studies, in general.

Other studies have evaluated other potential screening strategies for DDIs. Han *et al*. have previously evaluated a cohort design and a self-controlled case series (SCCS) design and concluded that the SCCS design was more computationally efficient and more effective in confounding control.[23,24] The SCCS design, however, operates under the assumptions of no outcome-dependent change in exposure and no outcome-related censoring.[25] Both assumptions are likely to be violated in analyses of DDIs.[26] Unlike the SCCS, the case-crossover design does not evaluate post-outcome exposure and, thus, does not require the same outcome-related assumptions. It does require an assumption of stable exposure probability in the population over time, which can be violated in the context of DDI analyses when precipitant drugs are newly marketed medications with rapid market uptake.[27] Given that no false positive signals were generated, bias due to increasing exposure probability was unlikely to have substantially affected our analyses. Nevertheless, object drug-unexposed cases could potentially be matched on calendar time with object-drug exposed cases which would further address bias due to population-level time trends in precipitant drug use. As a type of self-controlled design, the case-crossover design shares the SCCS's strength of more efficient confounding control in a screening setting as compared to a cohort or case-control design.

Another difference between our approach and the approach used by Han *et al*. is a choice of a negative control. While Han *et al*. utilized a control object drug, we used the associations between the precipitants and outcome in the absence of object drug exposure as reference. Both types of controls can potentially adjust for confounding associated with precipitant exposure and for direct effects of precipitants when only the effect due to interaction is of interest. However, utilizing a control object drug requires an assumption of no interactions with precipitants, which can never be completely guaranteed and, secondly, makes it difficult to find a suitable control object drug. Dabigatran, for example, is believed to be the least interacting drug among the oral anticoagulants;[22] thus, other oral anticoagulant drugs may not be appropriate as control object drugs for dabigatran. Even when a reasonable control object drug is available, adjustment may be limited by small number of patients using the drug (e.g., statins not metabolized by CYP3A4 are not as commonly used as CYP3A4-metabolized statins). Adjusting for associations between precipitants and an outcome in the absence of object drug exposure can circumvents these issues; however, this approach still requires an assumption that the magnitudes of the direct effects of the precipitants, confounding, and other biases are the same among those exposed and unexposed to the object drug. If cases who are exposed to a precipitant drug in the absence of object drug exposure differ from cases who were concomitantly exposed on some factor that modifies the association between the precipitant and the outcome, adjustment would lead to only partial removal of the direct effect or bias or could lead to over-adjustment. Prior to adjustment in the statin-rhabdomyolysis example, clarithromycin and gemfibrozil were identified as potential signals. Following adjustment, only clarithromycin remained significant. The adjusted OR for statins-gemfibrozil interaction was 1.71 (nominal p-value 0.03; FDR q-value 1.0). The interaction between statins and gemfibrozil is well established.[28] While it is possible that in our

cohort this interaction was managed well enough not to increase the risk of rhabdomyolysis beyond that associated with gemfibrozil alone, the possibility of a false negative either due to over-adjustment or low power cannot be ruled out.

Unfortunately, the lack of information on the clinical impact of potential DDIs, which is the motivation for this investigation, precludes us from evaluating the sensitivity of our approach. False negatives, when a true signal is not identified as such, can lead to adverse public health consequences as patients will continue using the interacting drugs or even worse, a potential interaction may get downgraded in terms of its anticipated severity. Within our two test cases, evidence for the clinical impact of dabigatran DDIs (which are primarily modulated through p-glycoprotein) is still inconclusive, but CYP enzymes and their inhibition are well characterized and evidence of clinically relevant DDI-induced harm for statins have been accumulating for a number of years.[28,29] Most strong CYP3A4-inhibitors, such as certain antiretroviral medications, ketoconazole, and itraconazole, were not among the concomitantly dispensed medications in our cohort. Others, such as diltiazem and fluconazole (both are moderate CYP3A4 inhibitors with less conclusive evidence of patient harm), were more commonly dispensed, but no alerts were generated (ORs were 0.9 for diltiazem and 1.5 for fluconazole before adjustment; 0.8 and 1.0 after adjustment, respectively). It is possible that these interactions were well managed clinically, do not lead to rhabdomyolysis requiring hospitalization, or the approach failed to identify a signal.

In addition to confounding and low power, failure to identify a signal can arise from suboptimal selection of hazard and referent windows in case-crossover analyses, which are highly sensitive to assumptions about the length of the exposure time window.[30] To semi-

automate and scale the approach, we implemented the same 30-day windows for all precipitants; however, these windows are almost certainly not optimal for every drug. Customizing windows for specific precipitants or groups of precipitants should be explored in subsequent developments.

Furthermore, clinical outcomes of DDIs may only manifest in specific populations, such as older patients, patients with impaired renal or hepatic function, patients with certain genotypes or on multiple interacting drugs. The impact of an interaction may also be dose-dependent. Since the objective of our study was to evaluate the feasibility of a case-crossover-based DDI screening approach, not to formally examine the clinical impact of specific DDIs in the two examples we evaluated, we did not undertake any subgroup or dose-response analyses. Nevertheless, analyses can easily be extended to identification of additional risk factors (another area in urgent need of more research[4]), provided information needed to identify subgroups is available, and our results certainly do not exclude clinically relevant interactions in subgroups or with higher doses.

Additional limitations include known limitations of electronic healthcare data.[31] Claims-based screening will often be restricted to outcomes that can be accurately measured in claims data. To improve specificity of outcome algorithms we required patients to be hospitalized; however, the validity of hospital discharge codes may still be imperfect.[32] Furthermore, by restricting outcomes to hospitalizations, we were not able to evaluate adverse events that were managed in outpatient settings (e.g., mild myopathies). Exposure misclassification is also of concern. While we know that patients were dispensed a medication, we do not know how and when they took it. In situations of a suspected drug interaction, patients may have been instructed to stop or reduce the dose of object drug therapy.

Finally, we applied our approach to only two examples. One example included drugs with strong interaction potential through CYP3A4 enzyme inhibition (CYP3A4-metabolized statins) and some prior evidence of clinically relevant adverse events.[14,29] The other included a relatively new drug (dabigatran) with limited and largely conflicting evidence of DDI-related patient harm.[33-37] Additional empirical evaluations are needed to ensure that the approach has acceptable performance across a range of object drugs and outcomes, although estimating sensitivity will remain a challenge.

In conclusion, using two test cases, we found that a case-crossover-based approach is a viable option for semi-automated DDI screening in electronic healthcare data. The approach inherently controls for confounding by indication for the object drug, and we utilized cases exposed to precipitants in the absence of object drug exposure to control for direct effects, confounding, and other biases associated with concomitantly dispensed drugs. The approach identified three known DDIs as being associated with increases in adverse clinical outcomes and did not generate any false positives. Further research should concentrate on evaluating the trade-off between false positives and false negatives with the proposed confounding adjustment approach and the automated nature of risk window selection.

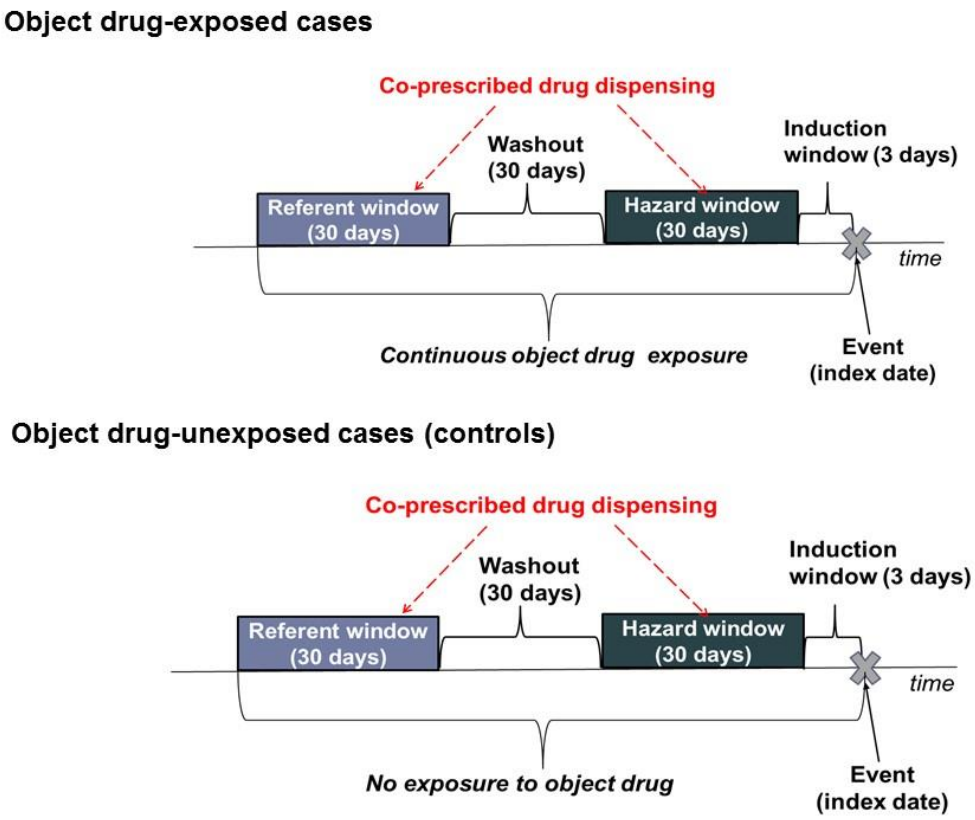

Figure 3.1: Screening framework

Object drug-unexposed cases were used to isolate the effect due to interaction only and to control for confounding by indication for co-dispensed drugs. Object drugs were CYP3A4-metabolized statins in the statins example and dabigatran in the dabigatran example.

Table 3.1: Patient characteristics

	CYP3A4-metabolized statins-exposed cases	**CYP3A4-metabolized statins-unexposed cases**	**Dabigatran-exposed cases**	**Dabigatran-unexposed cases***
Number	7,801	51,094	15,147	672,902
Female, %	50.3	44.8	52.9	56.5
Age (years), mean (SD)	70.4 (13.1)	61.0 (19.7)	79.2 (8.7)	61.1 (17.7)
Precipitant drugs evaluated, N	460		485	

*Dabigatran-unexposed cases were also required to have no exposure to any other direct oral anticoagulants or warfarin; SD – standard deviation.

Table 3.2: Top 15 drugs dispensed to patients on CYP3A4-metabolized statins therapy with odds ratio for the association between interaction and rhabdomyolysis > 1.0

Drug	CYP3A-statins-exposed cases		CYP3A4-statins-unexposed cases				
	N	OR	N	OR	Adjusted OR	Nominal p-value	FDR q-value
clarithromycin	60	7.57	216	1.30	5.83	0.00003	0.015†
sulfamethoxazole/trimethoprim	275	2.35	1289	1.61	1.46	0.008	1.0
meclizine	91	1.60	228	0.84	1.91	0.011	0.99
gemfibrozil	108	2.18	191	1.27	1.71	0.035	1.0
megestrol acetate	66	3.13	235	1.64	1.90	0.042	1.0
diphenoxylate /atropine sulfate	48	2.20	269	1.15	1.91	0.053	1.0
haloperidol	38	2.45	297	1.25	1.96	0.073	1.0
albuterol sulfate	339	1.40	1228	1.12	1.25	0.074	1.0
carbidopa/levodopa	82	1.41	302	0.90	1.57	0.074	1.0
phenobarbital	<11	7.00	70	1.00	7.00	0.076	1.0
metformin	495	1.07	988	0.88	1.21	0.078	1.0
ergocalciferol (vitamin d2)	43	1.87	160	1.00	1.87	0.080	1.0
clozapine	<11	1.67	47	0.42	3.93	0.086	1.0
labetalol	33	2.00	142	1.00	2.00	0.088	1.0
methylprednisolone	88	1.75	483	1.17	1.50	0.090	1.0

† denotes potential signal; N - number of patients contributing to analyses (patients with discordant exposure); OR – odds ratio; Adjusted OR is a ratio of OR in cases exposed to CYP3A4-metabolized statins to OR in cases unexposed to CYP3A4-metabolized statins; FDR – False Discovery Rate.

Table 3.3: Top 15 drugs dispensed to patients on dabigatran with odds ratio for the association between interaction and major bleeding > 1.0

Drug	Dabigatran-exposed cases		Dabigatran-unexposed cases*				
	N	OR	N	OR	Adjusted OR	Nominal p-value	FDR q-value
naproxen	92	3.00	7419	1.20	2.50	0.0002	0.0084†
enoxaparin sodium	215	14.36	5507	5.22	2.75	0.0003	0.011†
nortriptyline	37	2.36	1455	1.05	2.26	0.025	0.275
diazepam	90	2.60	7765	1.57	1.66	0.033	0.341
clonazepam	85	2.04	7183	1.26	1.62	0.039	0.348
aclidinium bromide	13	12.00	122	1.39	8.62	0.042	0.347
bimatoprost	96	1.53	1822	1.03	1.48	0.065	0.440
mirtazapine	184	1.67	3639	1.25	1.33	0.066	0.441
mupirocin	366	2.49	6	0.50	4.97	0.066	0.435
torsemide	193	1.64	1722	1.24	1.32	0.073	0.447
fluoxetine	117	1.49	6321	1.08	1.38	0.089	0.497
fluocinolone acetonide	12	3.00	83	0.93	3.23	0.095	0.513
meloxicam	197	1.21	12464	0.96	1.27	0.098	0.519
fesoterodine fumarate	26	2.25	614	1.13	1.99	0.112	0.561
bromfenac sodium	24	1.67	595	0.87	1.93	0.127	0.592

*Dabigatran-unexposed cases were also required to be unexposed to any other direct oral anticoagulants or warfarin; † denotes potential signal; N - number of patients contributing to analyses (patients with discordant exposure); OR – odds ratio; Adjusted OR is a ratio of OR in dabigatran-exposed cases to OR in unexposed cases; FDR – False Discovery Rate.

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APPENDIX

Appendix 3.1: Databases

Statins-rhabdomyolysis example

1) Optum Research Database: 2004 – 2013
2) Medicaid Analytic eXtract (MAX): 2000 – 2010
3) Medicare databases that linked Medicare Parts A and B data to pharmacy claims data from (1) Medicare Part D plans administered by CVS Caremark (2006-2008); (2) a pharmacy assistance program in New Jersey (Pharmaceutical Assistance to the Aged and Disabled [PAAD]; 1998 - 2005); and (3) a pharmacy assistance program in Pennsylvania (Pharmaceutical Assistance Contract for the Elderly [PACE] (1998-2005).

Dabigatran-bleeding example

1) Optum Research Database: 2009 – September 2015
2) Truven Research Database: 2009 – 2014
3) Medicare dabigatran patients: 2010 – 2014

Appendix 3.2: Outcome definitions

Outcome	Algorithm
Rhabdomyolysis	- ICD-9 diagnosis code 791.3 (myoglobinuria) -primary ICD-9 diagnosis code 728.89 (other disorder of muscle) - ICD-9 diagnosis code 728.89 + claim for CK test within 7 days of hospitalization (CPT codes 82550, 82552, 82554, 80012, 80016, 80018, 80019) or a discharge code for acute renal failure (ICD-9 diagnosis code 584.x) OR - ICD-9 diagnosis code 728.88 (rhabdomyolysis)
Bleeding	
Major intracranial bleeding	ICD-9 diagnosis (any): 430.x, 431.x, 432.x
Major upper GI bleed	ICD-9 diagnoses (any): 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 578.0 OR ICD-9 procedure code 44.43 (endoscopic control of gastric or duodenal bleeding) OR CPT code 43255 (happen during hospitalization, doesn't have to be IP)
Major lower GI bleeding	ICD-9 diagnosis (any): 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9
Major urogenital bleed	ICD-9 Dx: 599.7 (hematuria) OR ICD-9 Dx 626.2x (excessive menstruation) AND at least one of these: 280.0, 285.1, 285.9 (anemia)
Other major bleeds	ICD-9 Dx (any): 719.1x (hemathrosis 423.0x (hemopericardium) 786.3x (hemoptysis) 784.7x (epistaxis) 459.0x (hemorrhage not specified) 285.1x (acute posthemorrhagic anemia)

CPT-4 Current Procedure Terminology, 4th Revision; ICD-9 International Classification of Diseases, 9th Revision; PTCA percutaneous transluminal coronary

Appendix 3.3: Odds ratio and p-value estimation for the ratio of odds ratios (ORs)

		Referent window	
		Exposed	Unexposed
Hazard Window	Exposed	a	c
	Unexposed	b	d

OR = c/b

OR_1 = OR for precipitant among patients exposed to the object drug throughout the study period

OR_2 = OR for precipitant in the absence of exposure to the object drug

Final OR = OR_1 / OR_2

Var [ln(OR_1 / OR_2)] = $\frac{1}{c_1} + \frac{1}{b_1} + \frac{1}{c_2} + \frac{1}{b_2}$

Test statistic = $^2 = \frac{\left(\ln\left(\frac{OR_1}{OR_2}\right) - 0\right)^2}{\frac{1}{c_1}+\frac{1}{b_1}+\frac{1}{c_2}+\frac{1}{b_2}} \sim \ ^2_1$

Appendix 3.4: Screening results for drugs co-dispensed with CYP3A4-metabolized statins and increasing the risk of rhabdomyolysis, prior to adjustment (drugs with FDR q-value < 0.10 are presented)

Drug	N	OR	P-value	FDR q-value
sulfamethoxazole/trimethoprim	275	2.35	< 0.00001	< 0.00001
clarithromycin	60	7.57	< 0.00001	< 0.00001
morphine sulfate	130	2.25	0.00001	0.0018
megestrol acetate	66	3.13	0.00003	0.0033
gemfibrozil	108	2.18	0.00012	0.0110
levofloxacin	233	1.65	0.00019	0.0145
oxycodone hcl	169	1.77	0.00030	0.0198
hydrocodone bitartrate/acetaminophen	644	1.32	0.00039	0.0225
diazepam	94	2.03	0.00096	0.0495

N represents the number of patients contributing to the analyses (patients with discordant exposure); OR – odds ratio; FDR – False Discovery Rate; FDR q-value = p-value*number of tests/p-value rank.

Appendix 3.5: Screening results for drugs co-dispensed with dabigatran and increasing the risk of major bleeding, prior to adjustment (drugs with FDR q-value < 0.10 are presented)

Drug	N	OR	P-value	FDR q-value
enoxaparin sodium	215	14.36	< 0.0001	< 0.0001
hydrocodone bitartrate/acetaminophen	1283	1.59	< 0.0001	< 0.0001
mupirocin	366	2.49	< 0.0001	< 0.0001
sulfamethoxazole/trimethoprim	545	2.04	< 0.0001	< 0.0001
ciprofloxacin hcl	878	1.71	< 0.0001	< 0.0001
oxycodone hcl/acetaminophen	406	2.08	< 0.0001	< 0.0001
levofloxacin	590	1.51	< 0.0001	0.0001
ondansetron hcl	160	2.27	< 0.0001	0.0001
naproxen	92	3.00	< 0.0001	0.0001
diazepam	90	2.60	< 0.0001	0.0013
oxycodone hcl	145	2.02	< 0.0001	0.0022
tramadol hcl	703	1.36	0.0001	0.0023
amoxicillin/potassium clavulanate	356	1.51	0.0001	0.0053
prednisone	772	1.31	0.0002	0.0066
fluconazole	152	1.81	0.0004	0.0121
albuterol sulfate	597	1.34	0.0004	0.0117
fentanyl	91	2.14	0.0005	0.0161
cephalexin	577	1.34	0.0005	0.0155
dexamethasone	50	2.85	0.0007	0.0184
mirtazapine	184	1.67	0.0007	0.0176
promethazine hcl	126	1.86	0.0007	0.0172
torsemide	193	1.64	0.0007	0.0165
ondansetron	82	2.15	0.0009	0.0204
metoclopramide hcl	112	1.87	0.0013	0.0278
clonazepam	85	2.04	0.0017	0.0336
metolazone	309	1.43	0.0018	0.0342
alprazolam	282	1.45	0.0020	0.0368
aclidinium bromide	13	12.00	0.0023	0.0413
lidocaine hcl	62	2.26	0.0023	0.0403
glyburide/metformin hcl	30	0.30	0.0035	0.0589
lorazepam	186	1.51	0.0053	0.0872
mupirocin calcium	52	2.25	0.0055	0.0879
methylprednisolone	282	1.39	0.0062	0.0946
neomycin sulfate	11	10.00	0.0067	0.0992

N - number of patients contributing to analyses (patients with discordant exposure); OR – odds ratio; FDR – False Discovery Rate.

Appendix 3.6: Limiting control cases (unexposed to oral anticoagulants for 180 days prior to outcome) to patients 65 years of age or older in the dabigatran-bleeding example

Demographics table

	N	Age (years), mean (SD)	Age (years), median (25% Q1 – 75% Q3)	Female, %
Dabigatran cases	15,147	79.2 (8.7)	80.1 (73.7 – 85.5)	52.9
Control cases	268,563	78.3 (8.2)	78.1 (71.4 – 84.6)	53.8

Screening results table (top 15 drugs with adjusted OR > 1.0)

	Dabigatran-exposed cases		Oral anticoagulant-unexposed cases				
Drug	**N**	**OR**	**N**	**OR**	**Adjusted OR**	**Nominal p-value**	**FDR q-value**
enoxaparin sodium	215	14.36	1602	5.02	2.86	0.000	0.027
naproxen	92	3.00	2247	1.31	2.28	0.001	0.059
nortriptyline	37	2.36	592	0.94	2.51	0.013	0.302
clonazepam	85	2.04	2270	1.17	1.74	0.018	0.345
diazepam	90	2.60	2427	1.50	1.73	0.022	0.394
aclidinium bromide	13	12.00	81	1.25	9.60	0.034	0.463
bimatoprost	96	1.53	1492	1.02	1.50	0.060	0.605
clobetasol propionate	106	1.41	252	0.91	1.55	0.061	0.601
torsemide	193	1.64	1159	1.22	1.34	0.065	0.629
fluocinolone acetonide	12	3.00	48	0.85	3.55	0.082	0.678
lidocaine	62	2.26	586	1.37	1.65	0.082	0.662
fluoxetine	117	1.49	2075	1.06	1.40	0.083	0.656
vilazodone hydrochloride	< 11	7.00	54	1.08	6.50	0.090	0.687
fesoterodine fumarate	26	2.25	453	1.13	2.00	0.112	0.750
celecoxib	191	1.48	4109	1.17	1.27	0.116	0.758

N - number of patients contributing to analyses (patients with discordant exposure); OR – odds ratio; Adjusted OR is a ratio of OR in dabigatran-exposed cases to OR in cases unexposed to oral anticoagulants for at least 180 days prior to outcome; FDR – False Discovery Rate; FDR q-value = p-value x number of tests/p-value rank.

Appendix 3.7: Top (based on ascending p-value) 100 screening results (out of 460) for CYP3A-metabolized statin drug interactions and rhabdomyolysis

Drug	CYP3A4-statin exposed cases		Controls		Adjusted OR	p-value	FDR q-value
	N	OR	N	OR			
clarithromycin	60	7.57	216	1.30	5.83	0.0000	0.015
lisinopril	771	0.94	2145	1.22	0.77	0.0018	0.420
sulfamethoxazole/trimethoprim	275	2.35	1289	1.61	1.46	0.0082	1.0
hydrochlorothiazide	354	0.86	1219	1.19	0.73	0.0083	0.950
meclizine hcl	91	1.60	228	0.84	1.91	0.0107	0.988
gentamicin sulfate	22	0.57	44	2.14	0.27	0.0160	1.0
duloxetine hcl	124	0.63	523	0.99	0.64	0.0281	1.0
isosorbide dinitrate	31	0.35	69	0.97	0.36	0.0309	1.0
lorazepam	146	0.92	995	1.34	0.69	0.0344	1.0
gemfibrozil	108	2.18	191	1.27	1.71	0.0345	1.0
pregabalin	123	0.92	459	1.40	0.66	0.0393	1.0
glyburide,micronized	<11	0.17	15	2.00	0.08	0.0402	1.0
fenofibrate nanocrystallized	82	1.00	157	1.75	0.57	0.0419	1.0
megestrol acetate	66	3.13	235	1.64	1.90	0.0421	1.0
diclofenac potassium	<11	0.17	<11	2.50	0.07	0.0475	1.0
diphenoxylate hcl/atropine sulfate	48	2.20	269	1.15	1.91	0.0531	1.0
alendronate sodium	133	0.64	360	0.96	0.67	0.0536	1.0
cilostazol	32	0.68	65	1.60	0.43	0.0541	1.0
metoprolol succinate	346	0.93	856	1.18	0.79	0.0621	1.0
irbesartan	30	0.43	78	1.00	0.43	0.0645	1.0
fexofenadine hcl	49	0.69	158	1.26	0.55	0.0704	1.0
haloperidol	38	2.45	297	1.25	1.96	0.0729	1.0
levetiracetam	58	0.71	287	1.19	0.59	0.0731	1.0
albuterol sulfate	339	1.40	1228	1.12	1.25	0.0736	1.0
carbidopa/levodopa	82	1.41	302	0.90	1.57	0.0736	1.0
phenobarbital	<11	7.00	70	1.00	7.00	0.0757	1.0
nebivolol hcl	27	0.42	66	1.00	0.42	0.0764	1.0
hydralazine hcl	98	0.81	210	1.26	0.65	0.0775	1.0
metformin hcl	495	1.07	988	0.88	1.21	0.0779	1.0
ergocalciferol (vitamin d2)	43	1.87	160	1.00	1.87	0.0803	1.0
amlodipine besylate/benazepril hcl	44	0.69	202	1.24	0.56	0.0825	1.0
clozapine	<11	1.67	47	0.42	3.93	0.0860	1.0
labetalol hcl	33	2.00	142	1.00	2.00	0.0875	1.0
methylprednisolone	88	1.75	483	1.17	1.50	0.0902	1.0
lactulose	57	0.84	308	1.37	0.61	0.0909	1.0
diazepam	94	2.03	604	1.37	1.48	0.0916	1.0
oxycodone hcl	169	1.77	748	1.32	1.35	0.0924	1.0
beclomethasone dipropionate	11	2.67	63	0.80	3.33	0.0958	1.0
triamterene/hydrochlorothiazide	90	0.61	433	0.90	0.68	0.0987	1.0
nitrofurantoin/nitrofurantoin macrocrystal	<11	2.50	31	0.55	4.55	0.0987	1.0
glipizide/metformin hcl	<11	0.50	<11	3.50	0.14	0.0992	1.0
diclofenac sodium/misoprostol	<11	0.25	42	1.00	0.25	0.1024	1.0
darifenacin hydrobromide	22	2.67	50	1.08	2.46	0.1053	1.0
sodium polystyrene sulfonate	13	3.33	30	1.00	3.33	0.1097	1.0
spironolactone	131	1.38	467	1.00	1.38	0.1102	1.0
bimatoprost	48	1.67	107	0.95	1.76	0.1107	1.0
rabeprazole sodium	29	0.81	131	1.57	0.52	0.1122	1.0
letrozole	<11	4.00	14	0.56	7.20	0.1141	1.0
triazolam	<11	0.20	46	1.19	0.17	0.1160	1.0

Appendix 3.7 (Continued)

metolazone	93	1.21	224	1.80	0.67	0.1164	1.0
cyclosporine	26	0.63	47	1.35	0.46	0.1232	1.0
ramipril	89	0.65	183	0.97	0.67	0.1269	1.0
guaifenesin/pseudoephedrine hcl	<11	2.00	32	0.60	3.33	0.1303	1.0
colchicine	64	1.67	173	1.06	1.57	0.1306	1.0
ezetimibe	68	0.62	176	0.96	0.65	0.1365	1.0
bethanechol chloride	<11	5.00	27	0.93	5.38	0.1471	1.0
metaxalone	21	2.50	138	1.19	2.10	0.1476	1.0
mycophenolate mofetil	<11	0.50	31	1.58	0.32	0.1483	1.0
esomeprazole magnesium	173	0.92	693	1.17	0.79	0.1584	1.0
olmesartan /hydrochlorothiazide	29	0.71	105	1.28	0.55	0.1602	1.0
bumetanide	45	0.73	125	1.19	0.61	0.1629	1.0
olanzapine	74	0.76	635	1.08	0.71	0.1644	1.0
minocycline hcl	14	2.50	46	1.00	2.50	0.1657	1.0
polymyxin b sulfate/trimethoprim	<11	0.17	29	0.81	0.21	0.1657	1.0
valsartan	132	0.83	362	1.10	0.75	0.1672	1.0
enalapril maleate	104	0.76	411	1.03	0.74	0.1679	1.0
sitagliptin phosphate	74	1.47	104	0.96	1.52	0.1705	1.0
mirtazapine	87	0.85	540	1.17	0.73	0.1713	1.0
tobramycin/dexamethasone	18	0.64	61	1.35	0.47	0.1719	1.0
diphtheria,pertussis(acellular),tetanus vaccine	<11	6.00	20	1.22	4.91	0.1738	1.0
bisacodyl	<11	0.60	39	1.79	0.34	0.1744	1.0
ofloxacin	22	1.75	58	0.87	2.01	0.1759	1.0
salmeterol xinafoate	<11	3.50	42	1.10	3.18	0.1780	1.0
cephalexin monohydrate	18	0.38	125	0.81	0.47	0.1793	1.0
lithium carbonate	31	1.58	231	0.94	1.68	0.1840	1.0
morphine sulfate	130	2.25	593	1.71	1.32	0.1854	1.0
ranitidine hcl	159	1.18	524	0.93	1.27	0.1858	1.0
acyclovir	22	1.75	157	0.94	1.87	0.1858	1.0
oseltamivir phosphate	15	0.88	66	1.87	0.47	0.1893	1.0
loratadine	40	0.67	250	1.05	0.64	0.1908	1.0
cefadroxil	<11	4.00	24	0.85	4.73	0.1921	1.0
topiramate	51	0.70	286	1.04	0.67	0.1958	1.0
hyoscyamine sulfate	15	0.50	95	1.07	0.47	0.1960	1.0
trospium chloride	<11	0.50	22	1.75	0.29	0.1978	1.0
rosiglitazone maleate/metformin hcl	<11	0.33	19	1.11	0.30	0.1988	1.0
amitriptyline hcl	122	1.00	668	1.29	0.78	0.1997	1.0
metronidazole	50	2.13	366	1.41	1.51	0.1999	1.0
levofloxacin	233	1.65	1116	1.36	1.21	0.2026	1.0
nabumetone	27	1.45	131	0.85	1.72	0.2057	1.0
captopril	18	0.50	78	1.00	0.50	0.2067	1.0
tizanidine hcl	49	0.81	310	1.20	0.68	0.2117	1.0
montelukast sodium	88	0.80	426	1.07	0.75	0.2118	1.0
amoxicillin	193	1.38	885	1.13	1.22	0.2141	1.0
lubiprostone	<11	3.00	34	1.00	3.00	0.2148	1.0
trandolapril/verapamil hcl	<11	4.00	19	0.90	4.44	0.2172	1.0
doxazosin mesylate	70	0.79	187	1.13	0.71	0.2176	1.0
estrogens,conjugated	12	1.00	73	0.46	2.17	0.2177	1.0
benzonatate	22	0.83	148	1.47	0.57	0.2188	1.0
calcium carbonate/cholecalciferol (vitamin d3)	17	0.70	78	1.36	0.51	0.2198	1.0
alfuzosin hcl	12	3.00	26	1.17	2.57	0.2224	1.0

N - number of patients contributing to analyses (patients with discordant exposure); OR – odds ratio; FDR – False Discovery Rate.

Appendix 3.8: Top (based on ascending p-value) 100 screening results (out of 485) for dabigatran drug interactions and the outcome of major bleeding

	Dabigatran-exposed cases		Controls				
Drug	**N**	**OR**	**N**	**OR**	**Adjusted OR**	**p-value**	**FDR q-value**
potassium chloride	1724	0.97	21794	1.37	0.71	0.0000	0.0000
erythromycin base	73	1.15	1683	5.95	0.19	0.0000	0.0000
carvedilol	1061	0.87	12552	1.29	0.68	0.0000	0.0000
nitroglycerin	394	1.08	8062	1.93	0.56	0.0000	0.0000
amiodarone hcl	691	1.11	2269	1.64	0.67	0.0000	0.0007
metoprolol succinate	1211	1.04	22341	1.34	0.78	0.0000	0.0017
furosemide	2590	1.09	28271	1.28	0.85	0.0001	0.0047
amlodipine besylate	844	0.91	28944	1.18	0.77	0.0002	0.0093
naproxen	92	3.00	7419	1.20	2.50	0.0002	0.0084
diltiazem hcl	981	0.92	7562	1.18	0.78	0.0003	0.0134
sotalol hcl	323	0.81	778	1.32	0.62	0.0003	0.0122
enoxaparin sodium	215	14.36	5507	5.22	2.75	0.0003	0.0114
finasteride	286	0.79	4297	1.19	0.66	0.0008	0.0310
amoxicillin	513	1.00	18638	1.35	0.74	0.0009	0.0295
nifedipine	85	0.60	4424	1.23	0.49	0.0017	0.0544
digoxin	1128	0.92	3660	1.14	0.81	0.0019	0.0581
pravastatin sodium	549	0.87	11283	1.14	0.76	0.0022	0.0626
metronidazole	185	1.40	10566	2.19	0.64	0.0032	0.0856
simvastatin	1335	0.93	33858	1.09	0.85	0.0035	0.0905
metoprolol tartrate	1214	1.11	19495	1.32	0.84	0.0036	0.0866
levothyroxine sodium	1480	0.99	36395	1.15	0.86	0.0039	0.0897
allopurinol	511	0.91	8988	1.19	0.77	0.0040	0.0889
chlorhexidine gluconate	90	1.31	27	8.00	0.16	0.0052	0.1098
glyburide/metformin hcl	30	0.30	1275	1.02	0.30	0.0053	0.1075
atenolol	403	0.90	13213	1.19	0.75	0.0054	0.1040
indapamide	20	0.25	680	1.13	0.22	0.0075	0.1390
morphine sulfate	52	1.00	3298	2.10	0.48	0.0082	0.1464
chlorthalidone	30	0.43	1118	1.24	0.35	0.0086	0.1485
paroxetine hcl	113	0.69	4700	1.14	0.60	0.0094	0.1573
losartan potassium	581	0.96	11786	1.20	0.80	0.0099	0.1603
diphenoxylate hcl/atropine sulfate	91	0.90	3202	1.55	0.58	0.0101	0.1586
propafenone hcl	121	0.73	409	1.25	0.58	0.0102	0.1546
influenza virus vaccine trivalent 2014-2015 (65 yr+)/pf	<11	0.17	96	2.69	0.06	0.0118	0.1727
varenicline tartrate	19	0.36	1245	1.33	0.27	0.0123	0.1750
spironolactone	568	1.09	7178	1.35	0.81	0.0145	0.2005
ropinirole hcl	106	0.68	2520	1.11	0.62	0.0169	0.2278
hydrocodone bitartrate/acetaminophen	1283	1.59	65795	1.83	0.87	0.0171	0.2243
ibandronate sodium	47	0.52	1502	1.08	0.48	0.0180	0.2292
valsartan	315	0.85	6357	1.12	0.76	0.0188	0.2335
megestrol acetate	121	1.37	2829	2.14	0.64	0.0189	0.2292
glipizide	297	0.84	6492	1.12	0.76	0.0193	0.2288
clotrimazole	53	0.83	768	1.59	0.52	0.0217	0.2508
glyburide	93	0.75	3147	1.23	0.62	0.0222	0.2498
nortriptyline hcl	37	2.36	1455	1.05	2.26	0.0250	0.2753
lisinopril	1352	1.05	34819	1.18	0.88	0.0252	0.2716
budesonide	43	0.72	1983	1.43	0.50	0.0276	0.2910
diazepam	90	2.60	7765	1.57	1.66	0.0330	0.3405
colchicine	151	0.86	2315	1.24	0.70	0.0334	0.3372

Appendix 3.8 (Continued)

nebivolol hcl	135	0.80	2870	1.16	0.69	0.0342	0.3381
buspirone hcl	48	0.66	1890	1.23	0.53	0.0359	0.3484
travoprost	101	0.74	1461	1.15	0.65	0.0365	0.3468
famotidine	142	1.09	3469	1.55	0.70	0.0377	0.3512
methyldopa	<11	0.20	276	1.97	0.10	0.0382	0.3492
clonazepam	85	2.04	7183	1.26	1.62	0.0387	0.3478
levetiracetam	78	1.11	2809	1.78	0.62	0.0398	0.3511
nystatin	274	1.17	4470	1.52	0.77	0.0401	0.3469
atorvastatin calcium	1248	1.05	27642	1.18	0.89	0.0408	0.3474
aclidinium bromide	13	12.00	122	1.39	8.62	0.0415	0.3474
lisinopril/hydrochlorothiazide	102	0.76	8412	1.14	0.67	0.0426	0.3506
latanoprost	231	0.83	4133	1.10	0.76	0.0437	0.3531
trazodone hcl	207	0.92	7224	1.21	0.76	0.0470	0.3739
ampicillin trihydrate	32	0.78	626	1.58	0.49	0.0534	0.4179
fluorouracil	38	0.52	43	1.26	0.41	0.0535	0.4116
loratadine	<11	0.29	243	1.34	0.21	0.0575	0.4356
tobramycin	20	0.54	605	1.33	0.41	0.0581	0.4335
meclizine hcl	119	0.89	2464	1.27	0.70	0.0596	0.4382
prednisone	772	1.31	26158	1.51	0.87	0.0617	0.4466
colchicine/probenecid	<11	0.14	94	1.09	0.13	0.0621	0.4431
acetaminophen with codeine phosphate	200	1.22	7679	1.60	0.76	0.0624	0.4383
dronedarone hcl	249	0.75	323	1.03	0.73	0.0642	0.4448
glimepiride	210	0.88	5109	1.14	0.77	0.0645	0.4405
bimatoprost	96	1.53	1822	1.03	1.48	0.0653	0.4396
mirtazapine	184	1.67	3639	1.25	1.33	0.0664	0.4410
mupirocin	366	2.49	6	0.50	4.97	0.0664	0.4354
calcitriol	69	0.68	1525	1.08	0.63	0.0670	0.4332
irbesartan	70	0.67	1939	1.05	0.64	0.0674	0.4299
insulin aspart protamine human/insulin aspart	27	0.50	862	1.06	0.47	0.0687	0.4326
insulin aspart	176	0.93	3984	1.23	0.76	0.0726	0.4514
torsemide	193	1.64	1722	1.24	1.32	0.0728	0.4468
potassium citrate	17	0.42	570	1.10	0.38	0.0728	0.4413
ranitidine hcl	202	1.04	5144	1.34	0.78	0.0767	0.4593
mesalamine	31	0.82	3025	1.56	0.53	0.0779	0.4606
clonidine hcl	151	0.91	5334	1.21	0.75	0.0850	0.4968
zolpidem tartrate	442	1.14	16231	1.34	0.85	0.0856	0.4941
isosorbide mononitrate	399	1.23	7453	1.47	0.84	0.0869	0.4956
estrogens, conjugated	71	0.73	2353	1.11	0.66	0.0884	0.4988
fluoxetine hcl	117	1.49	6321	1.08	1.38	0.0892	0.4975
amlodipine besylate/olmesartan medoxomil	12	0.33	739	1.03	0.32	0.0925	0.5098
ciprofloxacin hcl	878	1.71	31367	1.93	0.89	0.0926	0.5046
fluocinolone acetonide	12	3.00	83	0.93	3.23	0.0953	0.5135
azathioprine	14	0.56	1012	1.41	0.39	0.0972	0.5182
meloxicam	197	1.21	12464	0.96	1.27	0.0984	0.5188
loteprednol etabonate	47	0.57	671	0.95	0.60	0.0986	0.5145
neomycin sulfate/polymyxin b sulfate/hydrocortisone	39	0.70	1164	1.18	0.59	0.1080	0.5573
rosuvastatin calcium	421	0.95	10660	1.11	0.85	0.1099	0.5610
cyanocobalamin/folic acid/pyridoxine	11	0.38	587	1.11	0.34	0.1111	0.5615
fesoterodine fumarate	26	2.25	614	1.13	1.99	0.1122	0.5611
gemfibrozil	55	0.67	2163	1.04	0.64	0.1130	0.5592
glyburide,micronized	<11	0.20	212	1.14	0.18	0.1147	0.5618
amlodipine besylate/benazepril hcl	67	0.72	4315	1.06	0.68	0.1170	0.5676