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Warfarin - Fluoroquinolones, Sulfonamides, or Azole Antifungals Interactions and the Risk of Hospitalization for Gastrointestinal Bleeding

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Abstract

Objective—To determine whether a potential pharmacokinetic interaction between warfarin and orally administered anti-infectives increases the risk of hospitalization for gastrointestinal (GI) bleeding in warfarin users.

Methods—We conducted a nested case-control and case-crossover study in US Medicaid data. Logistic regression was used to determine the association between GI bleeding and prior use of ciprofloxacin, levofloxacin, gatifloxacin, cotrimoxazole, or fluconazole, all versus no exposure and versus cephalexin, which would not be expected to interact with warfarin.

Results—All anti-infectives examined exhibited an elevated odds ratio (OR) vs. no exposure. Using cephalexin as the reference category, ORs for cotrimoxazole (OR:1.68 [95% CI:1.21–2.33] in the prior 6–10 days) and fluconazole (OR:2.09 [95% CI:1.34–3.26] in the prior 11–15 days) were significantly elevated.

Conclusions—Warfarin users who had received an anti-infective agent showed a substantially increased risk of GI bleeding. Nonetheless, a drug-drug interaction with warfarin was evident only for cotrimoxazole and fluconazole.

Introduction

Warfarin is widely used to prevent and treat thromboembolism, but requires frequent monitoring to avoid life-threatening complications from under- and over-coagulation. Despite its proven benefit, warfarin is vastly underused in clinical care, particularly among elderly individuals,¹ in part because of the fear of bleeding due to innumerable potential drug-drug interactions. Because the rate of major bleeding in patients receiving warfarin is about 7% to

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8% per year,² even a small improvement in the use of warfarin will have a great public impact.³

Commonly used drug-interaction compendia in the US^{4, 5} warn about interactions between warfarin and fluoroquinolones, sulfonamides, and azoles, although there is a marked disagreement about the clinical importance of these interactions.^{4, 5} This disagreement may exist because most available information about the potential interactions between warfarin and fluoroquinolones, sulfonamides, and azoles comes from uncontrolled case-reports and case-series, which are useful for generating but not confirming hypotheses.

Two different hypothesis have been postulated how fluoroquinolones can increase the bleeding risk: 1) inhibition of CYP1A2,⁶ which is one of the main enzymes responsible for metabolizing (R)-warfarin (which is responsible for 30–40% of warfarin's activity);⁷ and 2) reduction of vitamin K producing bacteria in the gut.⁸ Several small trials and observational studies in patients receiving warfarin have shown that levofloxacin and ciprofloxacin do not significantly increase the international normalized ratio (INR),^{9–13} a measure of anticoagulation intensity. Nonetheless, one small clinical trial showed that there was a small change in INR, which did not require alterations in warfarin or ciprofloxacin therapy even after 12 days of therapy.¹⁴ Further, increased INR has been reported 2–16 days after ciprofloxacin or norfloxacin was started in patients taking warfarin.¹⁵ Also, in two studies of acutely ill patients, a higher proportion of subjects treated with a fluoroquinolones or sulfonamide had an INR above range than those not receiving a fluoroquinolones or sulfonamides.^{16, 17} This observation is consistent with either a true drug-drug interaction between anti-infectives and warfarin, or with an effect on INR due to the infection itself or its sequelae, such as reduced vitamin K intake and uptake (due to diarrhea) or fever^{18–21}. While most studies have examined effects on INR rather than bleeding risk, one case-control study with 12 cases exposed to warfarin and levofloxacin found no significant increase in hospital admission rate for bleeding.¹³

A priori one might predict that fluconazole and co-trimoxazole may be more likely to potentiate warfarin than any of the fluoroquinolones²². Fluconazole and sulfamethoxazole (a component of cotrimoxazole) both inhibit CYP2C9, the main enzyme responsible for metabolizing (S)-warfarin (which is responsible for 60–70% of warfarin's activity) in the liver.⁷ One study found that warfarin users who were co-administered co-trimoxazole had an increased INR.¹⁷ Another study showed that use of cotrimoxazole in users of acenocoumarol or phenprocoumon (coumarin anticoagulants not available in US) was associated with increased risk for hospitalization for bleeding²³. However, this study did not evaluate whether warfarin users with an infection might have had an increased “baseline” bleeding risk.

Because of conflicting results about interactions between warfarin and fluoroquinolones, sulfonamides, and azoles, the severity and clinical importance of these potential interactions remains questionable. The aim of this study was to determine whether orally administered fluoroquinolones, sulfonamides, or azole antifungals (herein referred to collectively as precipitant drugs in the terminology of drug-drug interactions) have clinically important drug interactions with warfarin (the object drug) that results in an increased risk for hospital admission for gastrointestinal (GI) bleeding.

Results

In total, 308,100 warfarin users contributed a total of 234,173 person-years of observation. We identified 11,444 cases of hospitalization for GI bleeding, for an incidence rate of 4.89 per 100 person-years (95% CI: 4.80 to 4.98).

Case-control study

Table 1 present the baseline characteristics of subjects by case-control status. Cases were older than controls and more likely to be female, African-American, to have had a prior GI bleed, chronic renal failure, and/or liver disease, and to be exposed to proton pump inhibitors (excluding omeprazole, which is a CYP1A2 inducer and therefore could reduce warfarin levels), metronidazole, acetaminophen, and prednisone.

Table 2 presents the minimally adjusted ORs for each anti-infective for each time period of interest. The ORs for the primary time period expected for a true drug-drug interaction (prescription filled 6 to 10 days prior to the index date, except for fluconazole, which was 11 to 15 days prior) ranged from 1.90 to 3.83, and were all statistically significantly elevated in the minimally adjusted model. After adjusting for the factors that changed the OR by $\geq 5\%$, all ORs were attenuated but remained statistically significantly elevated, ranging from 1.55 to 2.84 (Table 2). The ORs for amoxicillin and cephalexin, which would not be expected to interact with warfarin, were elevated in each of the exposure periods (although not statistically significantly 11 to 15 days prior to the index date). The ORs were especially elevated 0 to 5 days prior to the index date, which suggests that an increased bleeding risk might partly be due to infection or its sequelae. To examine whether the increased GI bleeding risk might be due to an interaction between warfarin and either cephalexin or amoxicillin, we also analyzed the data including only persons who filled a prescription for the reference drug on the day of or the day prior to the hospitalization for the GI bleed. This OR was statistically significant elevated for cephalexin (OR = 1.53 [95% CI: 1.09 to 2.15]), and was similar to the risk 0 to 5 days prior to the index date (Table 2). The OR for amoxicillin was not statistically significant increased (OR = 1.19 [95% CI: 0.84–1.68]), which could be due to the low number of exposed cases and widening of the 95% CI. After exclusion of cases without a principal (first) diagnosis code for GI bleeding (purportedly the diagnosis chiefly responsible for the admission) the ORs were similar but had wider 95% CIs (data not shown). Similar results were also found after exclusion of persons with a prior GI bleed (Appendix 2), and subjects with 0 or 1 prior warfarin prescription before the index date, who were less likely to have reached a stable warfarin dose (Appendix 3),

We next calculated the fully adjusted ORs for each precipitant drug using cephalexin as the reference group to try to reduce any potential confounding by indication. ORs for ciprofloxacin (OR=1.28 [95% CI: 1.00 to 1.66]) and levofloxacin (OR=1.39 [95% CI: 1.09 to 1.77]) remained statistically significant elevated 0 to 5 prior to the index date. After adjusting for the most common indications for anti-infectives that changed any of the ORs of interest by $\geq 5\%$ (i.e., cellulitis, gastroenteritis, pneumonia, and urinary tract infection) in the selected group of warfarin users who were co-administered only an anti-infective, the ORs for the fluoroquinolones and cotrimoxazole were attenuated, especially 5 days prior to the index date (Figure 1A–E). This suggests that also the indication for the type of infection (which could be a marker of the severity of the infection) influences the (“baseline”) GI bleeding risk. In the timeframes specified a priori, only the ORs for cotrimoxazole (6 to 10 prior to the index date) and fluconazole (11 to 15 days prior to the index date) remained statistically elevated. The only other statistically significant result was with warfarin and cotrimoxazole 11 to 15 days prior to the index date. After exclusion of one-day fluconazole prescriptions, the ORs of interest were similar; however, the ORs for fluconazole 6–10 days prior to the index date was now statistically significantly elevated (OR: 1.73 [95% CI: 1.07 to 1.95]). The results using amoxicillin as the reference category were very similar and are therefore not shown. The ORs were also similar when we excluded patients with a non-principal diagnosis code for GI bleeding, persons with a prior GI bleed, and subjects with 0 or 1 prior warfarin prescription prior to the index date (Appendix 2 and 3).

Case-crossover study

Table 3 presents the results from the case-crossover analyses. Because these ORs compared exposed versus unexposed to a precipitant drug of interest, the case-crossover results presented in Table 3 correspond most closely to the fully adjusted case-control results presented in Table 2. The case-crossover results were similar to the corresponding case-control results. In addition, when we extended the window interest to 21–30 days prior to the GI bleed, the risk of GI bleed was lower for the drugs of interest and the reference drugs (data not shown).

Discussion

We undertook this study to evaluate whether fluoroquinolones, sulfonamides, and azole antifungals increase the risk of hospitalization for GI bleeding in subjects receiving warfarin. We found that the risk of hospitalization for GI bleeding was increased following use of all of the anti-infectives examined, including those not believed to interact with warfarin (i.e., amoxicillin and cephalexin).^{4, 5} After trying to account for the increased “baseline” GI bleeding risk by using cephalexin or amoxicillin as reference drugs, and adjusting for the most common indications for the anti-infective (which could be a marker of the severity of the infection), the ORs for cotrimoxazole and fluconazole were still meaningfully elevated. Although the ORs for gatifloxacin versus cephalexin were also consistent with a drug-drug interaction, all of the confidence intervals include the null value, and the risk of GI bleeding was not the highest during the primary period of interest (6 to 10 days prior to the index date). Nonetheless, if the drug-drug interaction is caused by a potential reduction in vitamin K producing bacteria in the gut, the time course could be different from what we expected and would dependent on other factors, such as diet. Nonetheless, our results for gatifloxacin are equivocal.

Our results suggest that either infection or its sequelae (i.e., fever and reduced vitamin K intake and uptake or the use of nonprescription nonsteroidal anti-inflammatory drugs) may increase bleeding risk in patients receiving warfarin, and might even be more important than the pharmacokinetic interaction with cotrimoxazole and fluconazole. Our finding of no association with levofloxacin is consistent with the only previous study investigating this question,¹³ although the prior study had few warfarin users exposed to levofloxacin (only 12 cases and 16 controls). The results also supports our a priori hypothesis that of all the examined anti-infectives, cotrimoxazole and fluconazole were the most likely to have a true drug-drug interaction with warfarin.²² None of the examined drugs has a high enough plasma protein binding that would be expected to significantly displace other protein-bound drugs. Another mechanism mentioned in literature is the reduction of vitamin K producing bacteria in the gut, although the evidence for this mechanism is debatable.²⁴

This study has a number of potential limitations. One is that we did not examine the validity of the study outcome. However, diagnostic codes for hospitalization for GI bleeding, which is the most common reason for hospitalization of bleeding events (accounting for about two thirds of the bleeding events resulting in hospitalization),^{25–27} have been shown in another study to have a high positive predictive value.²⁸ Since the diagnostic codes for other types of bleeding events have not been validated in other studies, we decided a priori to include only GI bleeding events in this study, which limits the generalizability of our results. Further, we selected cephalexin and amoxicillin as comparator drugs because they would not be expected to interact pharmacologically with warfarin. Nonetheless, there is not complete certainty that these drugs do not increase the INR. However, our data showed that there was even an increased risk in warfarin users who filled a prescription for cephalexin on the day of or the day prior to the hospitalization for the GI bleed, which is most likely not due to a true drug-drug interaction. Another limitation of studies using claims data is the potential for unmeasured confounding by factors such as diet, alcohol use, warfarin dose taken at the day of the hospitalization, use

of over-the-counter medication that was not reimbursed by Medicaid, and renal function. Nonetheless, the results from the case-crossover study, which inherently adjusts for factors that do not change over time within a patient (for example, genetic makeup which could influence the half-life of warfarin²⁹), were similar to the corresponding results from the case-control study. In addition, because we used claims data, we can not determine whether persons with a diagnosis of gastroenteritis were *H. pylori* positive, which is a risk factor for GI bleeding. The risk of GI bleeding was also compared in precipitant drug users versus comparator drug users. These analyses are less likely to be biased by unmeasured confounding by factors such as over-the-counter medication since the most important deciding factor for which anti-infective to prescribe is the type of infection. Further, another limitation of this study is that we do not have information about the INR at the time of the hospitalization for GI bleeding. Furthermore, since less than 10% of our warfarin users filled after their (apparently) first prescription a subsequent prescription, we can not determine whether there might be a potential drug-drug interaction with long-term use of these drugs.

In conclusion, we found using two different study designs that patients receiving warfarin are at increased risk of serious GI bleeding immediately following receipt of an anti-infective agent, suggesting that infection itself or its sequelae may place patients at increased risk. In addition to the risk conferred by infection itself or its sequelae, cotrimoxazole and fluconazole appeared to increase this risk further. Future studies should investigate whether other azoles and sulfonamides also increase the bleeding risk in warfarin users. Patients taking warfarin who are treated for acute infections may benefit from increased clinical vigilance, including enhanced INR monitoring, to manage this increased risk of serious GI bleeding. Especially for cotrimoxazole or fluconazole, even after the infection is cured and maybe even after course has ended, increased clinical vigilance might be needed to manage the increased risk of serious GI bleeding.

Methods

Setting and design

We performed an observational case-control and case-crossover study nested within the Medicaid programs of California, Florida, New York, Ohio, and Pennsylvania from 1999 to 2002. These states comprise about 13 million Medicaid enrollees at one time, corresponding to about 35% of the United States Medicaid population. The data were obtained from the Centers for Medicare and Medicaid Services (CMS)³⁰ and consist of final-action claims that have undergone quality assurance review and editing by CMS. Because 15–17% of Medicaid beneficiaries are co-enrolled in Medicare,³¹ we obtained additional Medicare data on all dually-eligible persons. A series of quality assurance analyses of the linked Medicaid and Medicare data suggested that the data are of high quality.³² This study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings, which granted waivers of informed consent and HIPAA authorization.

Eligible person time

The person-time eligible for inclusion in the case-control and case-crossover study was all person-time exposed to an outpatient prescription for warfarin in those 18 years and older between January 1st, 1999 and December 1st, 2002. We assumed that warfarin users took one tablet per day, and thus that the duration of a warfarin prescription was equivalent to the number of tablets dispensed. Further, the maximum prescription length was assumed to be 30 days, since Medicaid prescriptions for warfarin tend to be dispensed in 30-day increments. Both assumptions were confirmed by examining the frequency distribution of the number of pills supplied and the number of days between subsequent prescriptions for the same enrollee. The

observation period ended with either a hospitalization for GI bleeding or the end of the prescription period, whichever occurred first.

Identification of cases

Cases consisted of all individuals who had a hospitalization with a diagnosis code (ICD-9) for gastrointestinal bleeding. ICD-9 codes used to identify gastrointestinal bleeding were: ulcer of oesophagus with haemorrhage (530.21), gastric ulcer with haemorrhage (531.1*, 531.2*, 531.4*, 531.6*), duodenal ulcer with haemorrhage (532.1*, 532.2*, 532.4*, 532.6*), peptic ulcer with hemorrhage (533.1*, 533.2*, 533.4*, 533.6*), gastrojejunal ulcer with haemorrhage (534.1*, 534.2*, 534.4*, 534.6*), gastritis and duodenitis with hemorrhage (535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61), angiodysplasia of stomach and duodenum with hemorrhage (537.83), dieulafoy lesion (haemorrhagic) of stomach and duodenum with hemorrhage (537.84), diverticul of intestine with haemorrhage (562.02, 562.03, 562.12, 562.13), angiodysplasia of intestine with hemorrhage (569.85), dieulafoy lesion (hemorrhagic) of intestine with hemorrhage (569.86), and gastrointestinal hemorrhage (578.*). The index date for a case was the date of the event. In the case-crossover study, the case day (which was selected so as to be exposed to warfarin) was the day of the event.

Identification of controls

In the case-control study, we randomly selected up to 50 controls for each case, matching on index year and state, using incidence density sampling.³³ The index date for a control was the event date of the matched case. In the case-crossover study, eligible control days (which were selected so as to be exposed to warfarin) began 13 months prior and ended 1 month prior to the event date of each case.³⁴ We opted for the ending the time window 1 month prior to the index date, because we assumed that the effect of the precipitant drug (and potentially the infection or its sequelae) prescribed 31 days prior to the index date would have no longer increase the risk of GI bleeding on the index day. In addition, a case can have only up to 365 control days exposed to warfarin to minimize the effect of changing practice behavior (for example, due to a wider spectrum of indications, decrease recognition of the drug's benefits, or increasing patient reliance on the drug).

Exposure to precipitant drug

We assessed exposure based on filling of an orally administered precipitant drug 0 to 5 days, 6 to 10 days, 11 to 15 days, and 16 to 20 days prior to the index date. A priori, we assumed that the primary time period for a true pharmacologic interaction for an oral prescription for the precipitant drug was a prescription filled 6 to 10 days prior to the index date for precipitant drugs that reach steady state concentration within 5 days (fluoroquinolones and cotrimoxazole) and 11 to 15 days for precipitant drugs that reach steady state phase after 5 days (fluconazole). In addition, we expected that a true pharmacokinetic interaction would not significantly increase the bleeding risk 0 to 5 days prior to the index date, because to increase the INR it takes more than one dose of an anti-infective, which may be due to the long half-lives of some of the anticoagulation factors. Therefore, it would probably take 3 days or more after a prescription was filled before the bleeding risk would be increased. To avoid having an insufficient number of events in multivariable models, we did not examine precipitant drugs with fewer than 7 exposed cases for any examined time period.

To distinguish the effect of a particular anti-infective (i.e., a true drug-drug interaction) from an effect of infection or its sequelae, we examined whether orally administered cephalexin and amoxicillin were associated with serious GI bleeding in patients receiving warfarin. We have chosen these reference drugs for which the consensus of clinical opinion indicates that they do not produce a clinically significant interaction. In particular, commonly used drug-drug interaction compendia^{4,5} do not classify cephalexin as a potentially interacting drug. An

increased GI bleeding risk with these comparator drugs would therefore suggest that infection or its sequelae may place patients at increased risk of GI bleeding. The use of another anti-infective as the reference drug can reduce a bias which could be introduced when the underlying diagnosis which triggers the use of a certain drug is also related to patient outcome (i.e., confounding by indication). For example, if a warfarin user with an infection has already an increased “baseline” risk of GI bleeding, which might be caused by a reduction of vitamin K intake and uptake, then comparing that person to a warfarin user without an infection would result in a positive association, regardless of whether there is a true drug-drug interaction. By comparing a warfarin user who is prescribed an anti-infective to a warfarin user who is also prescribed a different anti-infective, we try to study subjects whose baseline (GI bleeding) risk is more comparable. We assumed that the effect of the infection would be present when a prescription was filled (day 0 prior to the index date) and that primary time period for the effect of an infection would be 0 to 5 days prior to the index date. In addition, to test this hypothesis we also evaluated the risk of hospitalization in subjects receiving a comparator drug either on the day of or the day prior to the hospitalization of the GI bleed. If this similar to the results in the 0 to 5 days prior to the index date, this supports that the infection or its sequelae increases the risk GI bleed, and not a true drug-drug interaction.

Ascertainment of potential confounding factors

Potential confounding factors were ascertained based on the index date. We defined five types of potential confounding factors: demographic factors; chronic diseases, defined as diagnosis ever before the index date; current use of drugs that could potentially increase or decrease the bleeding risk, defined as a prescription in the 30 days prior to the index date; current use of drugs that could potentially interact with warfarin (class 1 and 2 of Drug Facts & Comparisons⁵), defined as a prescription in the 30 days prior to the index date; current use of drugs that could potentially inhibit or induce CYP2C9, CYP3A4, and/or CYP1A2 enzymes, defined as a prescription in the 30 days prior to the index date. Only variables with more than 25 cases in our database were considered as potential confounding factors to avoid model instability. In addition, in the analyses with only subjects receiving an anti-infective and with cephalexin and amoxicillin as reference drugs, the indication for an anti-infective, defined as a diagnosis of infection in the 30 days prior to the index date, was considered as a potential confounder. All potential confounding factors are listed in the appendix. List of specific diagnostic and drug codes are available from the authors.

Statistical analysis

First, the incidence rate for the outcome of interest in our cohort of warfarin users was calculated. For the case-control analyses, conditional logistic regression was used to estimate the matched odds ratios (ORs) and 95% confidence intervals (CIs) for the association between use of precipitant drugs and hospital admission for GI bleeding in users of warfarin. We then examined the need to retain the matching in the analysis by calculating the matched OR using conditional logistic regression and unmatched OR using unconditional logistic regression. Because the matched and unmatched ORs were nearly identical, we did not retain the matching in the subsequent analyses. Next we used unconditional logistic regression to estimate the ORs of interest adjusting for age, sex, state, and race, referred to as the minimally adjusted model. We then examined each potential confounding factor individually; if a factor changed any of the ORs of interest by 5% or more, it was retained in the fully-adjusted model.³⁵ To try to discern a true drug-drug interaction, we estimated the risk of hospitalization for GI bleeding, using comparator drugs as reference group, and adjusting for the indication for the anti-infective (marker of disease severity; defined as a diagnosis in the prior 30 days), in the selected group of warfarin users who were co-administered an anti-infective drug prior to the index date.

For the case-crossover analyses, we used conditional logistic regression to estimate the OR and 95% CIs for association between the precipitant drugs and the study outcome. All potential confounders that changed any of the ORs of interest by 5% or more were retained in the fully-adjusted model.³⁵ All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

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Abbreviations

GI	Gastrointestinal
OR	Odds ratio
INR	International normalized ratio
CMS	Centers for Medicare and Medicaid Services
ICD-9	International classification of diseases, 9 th edition
95% CI	95% Confidence intervals

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Appendix 1

Table 4
All potential confounding factors that were considered in this study

Demographic factors		
Age	Gender	Sex
Calendar year	Nursing home resident	
Chronic Diseases		
Prior history of GI bleed	Chronic renal failure	Liver disease
Obesity		
Drugs that could potentially increase or decrease the bleeding risk		
Aspirin NSAIDs	Histamine H-2 antagonists	Proton pump inhibitors (excluding omeprazole)
Drugs that could potentially interact with warfarin [*]		
Azithromycin	Acetaminophen	Amiodarone
Butalbital	Carbamazepine	Clarithromycin
Doxycycline	Erythromycin	Fenofibrate
Fluvastatin	Gemfibrozil	Levothyroxine
Lovastatin	Methylprednisolone	Metronidazole
Phenobarbital	Phenytoin	Prednisone
Primidone	Quinidine	Quinine
Sertraline	Simvastatin	Trazodone
Troglitazone		
Potential CYP2C9, CYP3A4, and/or CYP1A2 inhibitors or inducers [†]		
Nefazodone	Omeprazole	Pioglitazone
Verapamil		
Indications for an anti-infective therapy [‡]		
Cellulitis	Gastroenteritis	Pneumonia
Upper respiratory tract infection	Urinary tract infection	Vaginal candidiasis

^{*}Based on potentially interacting drugs according to Drug Facts and Comparison (Class 1 and 2 drugs)

[†]Only CYP2C9, CYP3A4, and/or CYP1A2 inhibitors or inducers that were not listed as drugs that could potentially interact with warfarin in Drug Facts and Comparison

[‡]Only in the analysis including warfarin users and concomitant use of an anti-infective

Appendix 2

Table 5
Association between drugs of interest (versus no exposure) and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study; excluding patients with a prior GI bleed

Drugs of interest	Fully adjusted OR (95% CI) 0 to 5 days	Fully adjusted OR (95% CI) 6 to 10 days	Fully adjusted OR (95% CI) 11 to 15 days	Fully adjusted OR (95% CI) 16 to 20 days
Ciprofloxacin	2.14 (1.76 to 2.62)	1.58 (1.22 to 2.04)	1.36 (1.04 to 1.78)	1.38 (1.05 to 1.81)
Levofloxacin	2.48 (2.10 to 2.93)	1.64 (1.31 to 2.04)	1.65 (1.33 to 2.06)	1.55 (1.23 to 1.96)
Gatifloxacin	3.02 (1.81 to 5.03)	2.10 (1.07 to 4.11)	3.04 (1.72 to 5.37)	1.37 (0.56 to 3.36)
Cotrimoxazole	1.56 (1.19 to 2.06)	2.70 (2.14 to 3.41)	2.34 (1.82 to 3.00)	1.26 (0.89 to 1.77)

Drugs of interest	Fully adjusted OR (95% CI) 0 to 5 days	Fully adjusted OR (95% CI) 6 to 10 days	Fully adjusted OR (95% CI) 11 to 15 days	Fully adjusted OR (95% CI) 16 to 20 days
Fluconazole	1.66 (1.09 to 2.53)	2.23 (1.49 to 3.33)	2.86 (1.99 to 4.12)	1.60 (0.98 to 2.61)
Cephalexin	1.72 (1.38 to 2.16)	1.37 (1.05 to 1.80)	1.25 (0.94 to 1.66)	1.27 (0.95 to 1.70)
Amoxicillin	1.47 (1.17 to 1.84)	1.28 (0.99 to 1.65)	1.11 (0.84 to 1.48)	1.48 (1.16 to 1.90)

Table 6

Association between drugs of interest and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study after adjustment for confounders with cephalexin as the reference group; excluding patients with a prior GI bleed

Drugs of interest versus Cephalexin	Fully adjusted OR (95% CI) 0 to 5 days	Fully adjusted OR (95% CI) 6 to 10 days	Fully adjusted OR (95% CI) 11 to 15 days	Fully adjusted OR (95% CI) 16 to 20 days
Ciprofloxacin	1.04 (0.75 to 1.44)	1.06 (0.71 to 1.59)	0.90 (0.59 to 1.38)	0.96 (0.62 to 1.48)
Levofloxacin	0.97 (0.71 to 1.32)	0.92 (0.63 to 1.34)	0.99 (0.67 to 1.46)	0.97 (0.65 to 1.46)
Gatifloxacin	1.51 (0.84 to 2.72)	1.13 (0.52 to 2.45)	2.42 (1.25 to 4.70)	0.92 (0.35 to 2.44)
Cotrimoxazole	0.85 (0.58 to 1.25)	2.04 (1.38 to 3.01)	1.95 (1.30 to 2.95)	0.94 (0.58 to 1.53)
Fluconazole	1.26 (0.74 to 2.14)	1.86 (1.07 to 3.25)	2.74 (1.64 to 4.58)	1.59 (0.85 to 2.94)

Appendix 3

Table 7

Association between drugs of interest (versus no exposure) and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study; excluding patients with no or only 1 prior warfarin prescription prior to the index date

Drugs of interest	Fully adjusted OR (95% CI) 0 to 5 days	Fully adjusted OR (95% CI) 6 to 10 days	Fully adjusted OR (95% CI) 11 to 15 days	Fully adjusted OR (95% CI) 16 to 20 days
Ciprofloxacin	2.03 (1.67 to 2.48)	1.52 (1.18 to 1.94)	1.29 (1.00 to 1.67)	1.34 (1.03 to 1.75)
Levofloxacin	2.37 (2.02 to 2.78)	1.68 (1.37 to 2.05)	1.62 (1.32 to 2.00)	1.33 (1.05 to 1.67)
Gatifloxacin	2.56 (1.55 to 4.22)	2.64 (1.54 to 4.53)	2.30 (1.30 to 4.07)	1.31 (0.61 to 2.81)
Cotrimoxazole	1.58 (1.21 to 2.05)	2.76 (2.20 to 3.46)	2.00 (1.55 to 2.58)	1.14 (0.81 to 1.59)
Fluconazole	1.73 (1.17 to 2.57)	1.70 (1.11 to 2.58)	2.05 (1.38 to 3.04)	1.21 (0.71 to 2.08)
Cephalexin	1.81 (1.45 to 2.27)	1.44 (1.10 to 1.87)	1.35 (1.03 to 1.76)	1.37 (1.05 to 1.80)
Amoxicillin	1.43 (1.15 to 1.78)	1.24 (0.96 to 1.59)	1.27 (0.98 to 1.64)	1.40 (1.10 to 1.78)

Table 8

Association between drugs of interest and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study after adjustment for confounders with cephalexin as the reference group; excluding patients with no or only 1 prior warfarin prescription prior to the index date

Drugs of interest versus Cephalexin	Fully adjusted OR (95% CI) 0 to 5 days	Fully adjusted OR (95% CI) 6 to 10 days	Fully adjusted OR (95% CI) 11 to 15 days	Fully adjusted OR (95% CI) 16 to 20 days
Ciprofloxacin	0.68 (0.43 to 1.10)	0.85 (0.50 to 1.43)	1.09 (0.58 to 2.05)	0.94 (0.53 to 1.68)
Levofloxacin	0.73 (0.47 to 1.12)	0.72 (0.44 to 1.17)	1.19 (0.66 to 2.15)	0.71 (0.40 to 1.24)
Gatifloxacin	1.14 (0.49 to 2.64)	0.38 (0.09 to 1.63)	2.39 (0.90 to 6.34)	1.01 (0.33 to 3.08)
Cotrimoxazole	0.80 (0.48 to 1.34)	1.66 (1.01 to 2.74)	2.05 (1.10 to 3.80)	0.95 (0.50 to 1.80)
Fluconazole	1.05 (0.51 to 2.16)	1.36 (0.64 to 2.88)	2.59 (1.18 to 5.69)	1.21 (0.50 to 2.92)

Figure 1. Association between drugs of interest and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study after adjustment for confounders with cephalexin as the reference group

Each diamond represents the OR of interest versus cephalexin and the vertical line the 95% CI. All analyses are adjusted for age, gender, race, state, use of proton pump inhibitors, metronidazole, acetaminophen, and prednisone, prior GI bleed, chronic renal disease, liver disease, cellulitis, gastroenteritis, pneumonia, and urinary tract infection.

Table 1

Characteristics of cases and controls exposed to the precipitant drugs on the index date

Variable	Cases (11,444) N (%)	Controls (568,744) N (%)	Unadjusted OR and 95% CI
Ciprofloxacin [*]	150 (1.3%)	3,069 (0.5%)	2.45 (2.08–2.89)
Levofloxacin [*]	214 (1.9%)	3,737 (0.7%)	2.88 (2.51–3.31)
Gatifloxacin [*]	21 (0.2%)	330 (0.1%)	3.17 (2.04–4.92)
Cotrimoxazole [*]	75 (0.7%)	2,226 (0.4%)	1.68 (1.33–2.12)
Fluconazole [*]	35 (0.3%)	865 (0.2%)	2.02 (1.44–2.83)
Cephalexin [*]	104 (0.9%)	3,022 (0.5%)	1.72 (1.41–2.09)
Amoxicillin [*]	112 (1.0%)	3,907 (0.7%)	1.43 (1.19–1.73)
Male sex	3,685 (32.2%)	191,604 (33.7%)	0.94 (0.90–0.97)
Race			
Caucasian	7,267 (63.5%)	368,416 (64.8%)	Reference
African-American	1,736 (15.2%)	74,378 (13.1%)	1.18 (1.12–1.25)
Other	2,441 (21.3%)	125,950 (22.1%)	0.98 (0.94–1.03)
Age			
<60 years	1,924 (16.8%)	150,426 (26.4%)	Reference
60–69 years	1,993 (17.4%)	106,282 (18.7%)	1.47 (1.38–1.56)
70–79 years	3,431 (30.0%)	150,802 (26.5%)	1.78 (1.68–1.88)
≥ 80 years	4,096 (35.8%)	161,234 (28.3%)	1.99 (1.88–2.10)
State			
California	3,073 (26.9%)	152,519 (26.8%)	Reference
Florida	2,232 (19.5%)	110,900 (19.5%)	1.00 (0.95–1.06)
New York	2,292 (20.0%)	113,936 (20.0%)	1.00 (0.95–1.05)
Ohio	2,201 (19.2%)	109,373 (19.2%)	1.00 (0.95–1.06)
Pennsylvania	1,646 (14.4%)	82,016 (14.4%)	1.00 (0.94–1.06)
Prior GI bleed [‡]	3,473 (30.3%)	67,634 (11.9%)	3.23 (3.10–3.36)
Chronic Kidney Disease [‡]	2,702 (23.6%)	58,786 (10.3%)	2.68 (2.57–2.80)
Liver Disease [‡]	2,166 (18.9%)	65,090 (11.4%)	1.81 (1.72–1.89)
Proton Pump Inhibitors (excluding omeprazole) [†]	1,940 (17.0%)	62,736 (11.0%)	1.65 (1.57–1.73)
Metronidazole [†]	166 (1.5%)	2,581 (0.5%)	3.23 (2.76–3.78)
Acetaminophen [†]	2,830 (24.7%)	103,060 (18.1%)	1.49 (1.42–1.55)
Prednisone [†]	850 (7.4%)	22,736 (4.0%)	1.93 (1.80–2.07)

* Currently exposed, defined as a prescription in the 5 days prior to the index date

† Currently exposed, defined as a prescription in the 30 days prior to the index date

‡ Ever in the past

Table 2

Association between drugs of interest (versus no exposure) and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study

Drugs of interest	Model adjustments	OR (95% CI) 0 to 5 days	OR (95% CI) 6 to 10 days	OR (95% CI) 11 to 15 days	OR (95% CI) 16 to 20 days
Ciprofloxacin	Minimally [*] Fully [†]	2.39 (2.02 to 2.82) 2.05 (1.74 to 2.43)	1.90 (1.55 to 2.33) 1.62 (1.31 to 1.99)	1.55 (1.24 to 1.93) 1.30 (1.04 to 1.62)	1.63 (1.30 to 2.04) 1.35 (1.08 to 1.69)
Levofloxacin	Minimally [*] Fully [†]	2.79 (2.43 to 3.21) 2.23 (1.94 to 2.57)	1.99 (1.67 to 2.38) 1.55 (1.30 to 1.86)	1.99 (1.66 to 2.38) 1.56 (1.31 to 1.87)	1.87 (1.55 to 2.26) 1.44 (1.18 to 1.74)
Gatifloxacin	Minimally [*] Fully [†]	3.23 (2.08 to 5.03) 2.43 (1.55 to 3.81)	3.83 (2.45 to 5.98) 2.84 (1.79 to 4.49)	2.93 (1.77 to 4.87) 2.17 (1.30 to 3.64)	1.87 (0.96 to 3.64) 1.33 (0.68 to 2.62)
Cotrimoxazole	Minimally [*] Fully [†]	1.64 (1.30 to 2.07) 1.46 (1.16 to 1.85)	2.86 (2.34 to 3.48) 2.54 (2.08 to 3.10)	2.36 (1.91 to 2.93) 2.04 (1.64 to 2.54)	1.41 (1.06 to 1.87) 1.18 (0.89 to 1.57)
Fluconazole	Minimally [*] Fully [†]	2.01 (1.43 to 2.83) 1.55 (1.10 to 2.20)	2.55 (1.83 to 3.54) 1.89 (1.35 to 2.64)	2.95 (2.14 to 4.05) 2.32 (1.68 to 3.20)	1.74 (1.13 to 2.66) 1.35 (0.88 to 2.08)
Cephalexin	Minimally [*] Fully [†]	1.75 (1.44 to 2.13) 1.61 (1.32 to 1.96)	1.59 (1.27 to 1.99) 1.38 (1.10 to 1.73)	1.37 (1.08 to 1.74) 1.22 (0.96 to 1.55)	1.54 (1.23 to 1.94) 1.33 (1.06 to 1.68)
Amoxicillin	Minimally [*] Fully [†]	1.50 (1.24 to 1.81) 1.36 (1.12 to 1.64)	1.40 (1.14 to 1.74) 1.28 (1.03 to 1.58)	1.32 (1.05 to 1.65) 1.20 (0.96 to 1.51)	1.64 (1.33 to 2.01) 1.44 (1.17 to 1.77)

^{*} Adjusted for age, gender, race, and state.

[†] Adjusted for age, gender, race, state, prior GI bleed, chronic renal disease, liver disease, and use of proton pump inhibitors, metronidazole, acetaminophen, and prednisone.

Association between drugs of interest and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-crossover study after adjustment for confounders

Table 3

Drugs of interest	Case days (9,284) N (%) 0 to 5 days	Control days (1,551,425) N (%) 0 to 5 days	Fully adjusted OR (95% CI) 0 to 5 days *	Fully adjusted OR (95% CI) 6 to 10 days *	Fully adjusted OR (95% CI) 11 to 15 days *	Fully adjusted OR (95% CI) 16 to 20 days *
Ciprofloxacin	117 (1.26%)	10,338 (0.67%)	1.77 (1.45 to 2.17)	1.27 (0.99 to 1.63)	1.24 (0.96 to 1.60)	1.19 (0.91 to 1.54)
Levofloxacin	180 (1.94%)	12,398 (0.80%)	2.38 (2.02 to 2.82)	1.68 (1.37 to 2.06)	1.62 (1.32 to 2.00)	1.43 (1.15 to 1.80)
Gatifloxacin	18 (0.19%)	976 (0.06%)	3.83 (2.28 to 6.42)	3.97 (2.26 to 6.96)	3.53 (1.94 to 6.42)	1.73 (0.78 to 3.82)
Cotrimoxazole	60 (0.65%)	6,288 (0.41%)	1.43 (1.08 to 1.90)	3.06 (2.41 to 3.88)	2.62 (2.03 to 3.38)	1.29 (0.92 to 1.81)
Fluconazole	29 (0.31%)	2,341 (0.15%)	1.63 (1.07 to 2.48)	2.06 (1.35 to 3.13)	2.50 (1.68 to 3.73)	0.82 (0.44 to 1.53)
Cephalexin	85 (0.92%)	9,660 (0.62%)	1.34 (1.06 to 1.70)	1.29 (0.99 to 1.67)	1.20 (0.91 to 1.58)	1.26 (0.96 to 1.67)
Amoxicillin	90 (0.97%)	10,486 (0.68%)	1.36 (1.08 to 1.70)	1.25 (0.97 to 1.62)	1.16 (0.89 to 1.52)	1.55 (1.21 to 1.97)

* Adjusted for prednisone use (only factor that changed any of the ORs of interest by 5%)