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Concurrent Use of Warfarin and Antibiotics and the Risk of Bleeding in Older Adults

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Abstract

Background—Antibiotic medications are associated with an increased risk of bleeding among patients receiving warfarin. The recent availability of data from the Medicare Part D prescription drug program provides an opportunity to assess the association of antibiotic medications and the risk of bleeding in a national population of older adults receiving warfarin.

Methods—We conducted a case-control study nested within a cohort of 38,762 patients aged 65 years and older who were continuous warfarin users, using enrollment and claims data for a 5% national sample of Medicare beneficiaries with Part D benefits. Cases were defined as persons hospitalized for a primary diagnosis of bleeding and were matched with three control subjects on age, race, gender, and indication for warfarin. Logistic regression analysis was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the risk of bleeding associated with prior exposure to antibiotic medications.

Results—Exposure to any antibiotic agent within the 15 days of the event/index date was associated with an increased risk of bleeding (aOR 2.01; 95% CI, 1.62–2.50). All six specific antibiotic drug classes examined [azole antifungals (aOR, 4.57; 95% CI, 1.90–11.03), macrolides (aOR, 1.86; 95% CI, 1.08–3.21), quinolones (aOR, 1.69; 95% CI, 1.09–2.62), cotrimoxazole (aOR, 2.70; 95% CI, 1.46–5.05), penicillins (aOR, 1.92; 95% CI, 1.21–2.07) and cephalosporins (aOR, 2.45; 95% CI, 1.52–3.95) were associated with an increased risk of bleeding.

Conclusion—Among older continuous warfarin users, exposure to antibiotic agents—particularly azole antifungals—was associated with an increased risk of bleeding.

Keywords

warfarin; antibiotics; patient safety; major bleeding; pharmacoepidemiology; older adults

Warfarin—the most widely used oral anticoagulant worldwide¹—is commonly prescribed for the treatment and prevention of thromboembolism in patients with deep vein thrombosis,

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pulmonary embolism, atrial fibrillation and mechanical heart valves.¹⁻⁴ Warfarin has a narrow therapeutic range and requires frequent monitoring to avoid potentially life-threatening complications from both under- and over-coagulation.⁵⁻⁷ A wide range of drugs has been linked to an increased risk of major bleeding in warfarin users.^{1, 6-13} Concomitant use of antibiotics is particularly common among warfarin users, and is associated with a high risk of overanticoagulation.^{4, 14} Patients receiving warfarin are generally older, have multiple comorbidities, and receive several medications concomitantly, all of which can further increase their risk of bleeding and complicate the treatment of their underlying medical conditions.⁴

The primary mechanisms by which antibiotic medications interact with warfarin to increase the risk of major bleeding is through disruption of intestinal flora that synthesize vitamin K,² and inhibition of cytochrome p450 isozymes which metabolize warfarin.^{2, 15-17} Interactions between warfarin and specific antibiotic agents have been widely assessed, primarily through case reports, case series studies,¹⁸⁻²⁰ pharmacokinetic studies,^{14, 21, 22, 23} and three population-based studies.^{2, 3, 5} Based on these investigations, quinolones, sulfonamides, macrolides, and azole antifungals are thought to carry the highest risk of warfarin toxicity, whereas amoxicillin and cephalexin are believed to have a more modest risk.¹⁴ Some of these findings, however, are inconsistent.^{2, 3, 5, 15-17, 14, 21, 22, 23}

The recent availability of prescription drug data for Medicare beneficiaries following the implementation of the Part D prescription drug program in January 2006 offers an opportunity to assess the impact of antibiotic use on warfarin toxicity in a national population of older adults. We therefore examined the risk of bleeding associated with exposure to all antibiotic agents combined as well as several specific antibiotic agents in a cohort of older patients receiving warfarin.

Methods

Data Source

We used enrollment, claims, and pharmacy data in a 5% national sample of Medicare beneficiaries.²⁴ The Centers for Medicare & Medicaid Services selected these beneficiaries based on the eighth and ninth digits of their health insurance claim number. Medicare Part A, which covers hospital expenses, begins automatically at age 65 years, whereas coverage for outpatient care (Part B) and prescription drugs (Part D) must be purchased.²⁴ Electronic data are available for parts A and B beginning in the 1990s and for Medicare Part D beginning in 2006, when the program began. Claims from the year 2007 to 2008 for 5% of Medicare beneficiaries were used, including Medicare enrollment files, Medicare Provider Analysis and Review (MEDPAR) files, Outpatient Standard Analytic Files (OutSAFs), Medicare Carrier files, and Prescription Drug Event (PDE) records.²⁵

Study Design

We conducted a case-control study nested within a cohort of 38,762 Medicare beneficiaries who were continuous users of warfarin. To be included in the underlying study cohort, beneficiaries were required to: have been enrolled in Medicare parts A, B and D for all of 2007, have not enrolled in an HMO in 2007, have been prescribed warfarin for at least 180 days in 2007, and have received at least one prescription for warfarin (for any duration) in 2008. Because warfarin dosages are frequently adjusted in response to changing INR values, a given patient's supply of warfarin tablets may last beyond a defined prescription period. To account for this possibility, we defined continuous warfarin use broadly, using the aforementioned criteria. Presence and duration of warfarin use was examined by evaluating prescription data from the Medicare Part D dataset.

Continuous warfarin users were followed from January 1, 2008 until hospitalization for a bleeding event or the end of study period (December 31, 2008), whichever occurred first. Indication for warfarin use was defined based on ICD-9-CD codes (in any position using MedPAR files, Outpatient SAFs, and Medicare Carrier files) for any of the following conditions for which warfarin is used: atrial fibrillation, stroke, presence of prosthetic heart valve, and venous thromboembolism. Patients who had more than one of these conditions were classified as having multiple indications for warfarin use. This study was reviewed and approved by the institutional review board of the University of Texas Medical Branch at Galveston.

Cases

We defined cases as persons who experienced a bleeding event requiring hospitalization at any time in 2008 based on International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) codes, in the primary diagnosis position, from MEDPAR files. The ICD9 codes identifying bleeding are as follows: gastrointestinal (456.0, 531.0, 531.1, 531.4, 531.6, 532.0, 532.4, 532.6, 533.0, 534.4, 535.41, 535.51, 535.61, 537.83, 569.3, 578.0, 578.1, 578.9), non-gastrointestinal (360.43, 363.61, 364.41, 372.72, 379.32, 459.0, 568.81, 596.7, 599.7, 626.5, 626.6, 626.9, 627.0, 627.1, 719.10, 719.11, 719.12, 719.15, 719.16, 782.7, 784.7, 786.3, 998.1), intracranial (430, 431, 432.0, 432.1, 432.9) and general warfarin toxicity (E934.2, 964.2, 790.92). The date of hospital admission served as the event date for all analyses.

Controls

Controls were assigned an index month corresponding to the event date of matched cases. We selected three controls for each case from the cohort of warfarin users. We matched 92.6% of controls with cases on event month, indication for warfarin use, age, sex, race/ethnicity (white, black, Hispanic, or other), and index of multiple indications for warfarin use. 6.3% of the controls were matched with cases on event month, indication for warfarin use, sex, broad range of age (66-75, 76-85, or > 85 years), and ethnicity (white or nonwhite). The rest of the controls were matched with cases on event month, indication for warfarin use, sex, and broad range of age (66-80 or > 80 years).

Exclusion Criteria for Cases and Controls

In selecting cases and controls, we excluded persons who were hospitalized for at least one bleeding event at any time in 2007, did not received any prescriptions in the 30 days before the event/ index date, were institutionalized in a hospital or skilled nursing facility in the 30 days before the event/index date, or did not have Part D coverage in the month of and the month preceding the event/index date.

Definition of Exposure

Antibiotic exposure was determined by assessing the number of days in a given prescription period (e.g., 90 days) that followed the initial prescription date in the Medicare Part D database. Patients whose most recent prescription period for any antibiotic agent overlapped by at least one day with the 15-day period before the event/index date were defined as exposed. Among persons with antibiotic exposure, we categorized the time between the initiation of antibiotic agents and the event/index date as 0-15 days, 16-60 days, and more than 60 days before the event/index date. The date of antibiotic initiation was defined as the closest prescription to the event/index date without having a prescription for the same antibiotic in the 30 days prior. For each of these analyses, we examined the composite category 'all antibiotic medication' and each of the following specific classes of antibiotic

agents: azole antifungals, macrolides, quinolones, cotrimoxazole, penicillins, and cephalosporins.

Potential Confounders

We also examined patients' use of potentially confounding medications known to have drug-drug interactions with warfarin. A prescription for any potential confounding drug that included at least one day in the 15 days before the event/index date was defined as use of a confounding drug. We examined the following classes of drugs: selective serotonin reuptake inhibitors (SSRIs) (citalopram hydrobromide, escitalopram oxalate, fluvoxamine maleate, fluoxetine hydrochloride, paroxetine hydrochloride, sertraline hydrochloride); serotonin norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, desvenlafaxine, duloxetine, and milnacipran); antiplatelets (clopidogrel bisulfate, prasugrel, ciltazol, and ticlopidine); corticosteroids (prednisone, dexamethasone, methylprednisolone, hydrocortisone, prednisolone, betamethasone), and cytochrome and P450 isozyme 2C9 inhibitors (amidarone, gemfibrozil, nicardipine, clofibrate, fluvastatin sodium, fenofibrate, lovastatin, zafirlukast, and fenofibric acid).

Statistical Analysis

We used logistic regression models to estimate the risk of major bleeding associated with antibiotic exposure, expressed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). In the first model, standard logistic regression was used to predict the binary outcome variable, presence vs. absence of any bleeding event that required hospitalization. In the second model, multinomial logistic regression was used to predict the three-level categorical outcome variable, GI bleeding event that required hospitalization, non-GI bleeding event that required hospitalization, and no bleeding event. All multivariable analyses were adjusted for the exposure to all above listed potentially confounding drug classes, comorbidity index, and whether or not the patient stayed in a nursing home in the 90 days before the event/index date. To test the robustness of our findings, we performed sensitivity analyses examining exposure windows of 30 and 60 days before the event/index date. All analyses were performed using SAS version 9.13 (SAS Institute, Cary, North Carolina).

Results

We identified 38,762 persons who were defined as continuous warfarin users. During 2008, 1,136 patients (2.9% of the cohort) were hospitalized with a primary diagnosis of bleeding. There were 798 patients who met our definition for a case after excluding 48 patients who were hospitalized for at least one bleeding event in 2007, one patient who did not have Medicare Part D coverage in the event month or prior month, 285 patients who were institutionalized in the 30 days before the event, and four patients who did not have at least one prescription filled in the 30 days before the event. Table 1, which presents the study characteristics for cases and matched controls, shows that most of the study variables were distributed evenly across cases and controls. However, cases were more likely to have had a higher degree of comorbidity and to have stayed in a nursing home in the 90 days before the event/index date.

Table 2 shows that continuous warfarin users exposed to any antibiotic agent were twice as likely to experience a bleeding event that required hospitalization as those who were not exposed (aOR, 2.01; 95% CI, 1.62-2.50). Assessment of specific bleeding events showed that antibiotic exposure was associated with an aOR of 2.49 (95% CI, 1.88-3.30) for non-GI bleeding and an aOR of 1.68 (95% CI, 1.28-2.21) for GI bleeding. We also examined—among all persons exposed to antibiotics—whether recency of prescription initiation was associated with major bleeding. Among all exposed persons, those whose prescription began

in the 0-15 days or 16-60 days before event/index date were more likely to have been hospitalized for bleeding compared to the referent group, patients who were not current antibiotic users (aOR, 2.37; 95% CI, 1.75-3.22; aOR, 2.11; 95% CI, 1.50-2.97). By contrast, exposed patients whose antibiotic prescription began >60 days before the event/index date did not have a statistically significant increased risk for bleeding that required hospitalization in comparison to the referent group (aOR, 1.25; 95% CI, 0.78-2.01).

We then examined the association between six specific antibiotics and hospitalization for bleeding. Treatment with azole antifungals was associated with a substantially increased risk for bleeding (aOR, 4.57; 95% CI, 1.90-11.03). Likewise, an increased risk of bleeding during warfarin therapy was also associated with treatment with macrolides (aOR, 1.86; 95% CI, 1.08-3.21), quinolones (aOR, 1.69; 95% CI, 1.09-2.62), cotrimoxazole (aOR, 2.70; 95% CI, 1.46-5.05), penicillins (aOR, 1.92; 95% CI, 1.21-2.07) and cephalosporins (aOR, 2.45; 95% CI, 1.52-3.95).

Each of the multivariable models also adjusted for the use of potentially confounding medications known to have drug-drug interactions with warfarin. These included SSRIs, SNRIs, corticosteroids, antiplatelets, and cytochrome and P450 isozyme 2C9 inhibitors. Only use of SSRIs (aOR, 1.34; 95% CI, 1.08-1.67) and corticosteroids (aOR, 2.30; 95% CI, 1.64-3.21) were associated with a statistically significant increased risk of bleeding (table 2).

We conducted sensitivity analyses using exposure times of 30 and 60 days. The adjusted odds ratios for the 30- and 60-day exposure periods were both similar to those for the 15-day period reported in table 1. As a control, we also assessed the relative proportion of cases and controls who were prescribed angiotensin-converting enzyme (ACE) inhibitors. Patients prescribed ACE inhibitors did not have an increased risk of bleeding that required hospitalization (aOR, 1.00; 95% CI, 0.82-1.20). In addition, to verify that our methodology for defining continuous warfarin use did not underestimate warfarin exposure, we assessed the proportion of cases and controls that had an active warfarin prescription in the 30 days and 60 days before the event/index date. Our analysis showed that in the 60-day period, 96% of cases and 95% of controls had an active prescription of warfarin and in the 30-day period, 93% of cases and 92% of controls had an active prescription of warfarin. Moreover, when we restricted our multivariable analyses to patients who had an active warfarin prescription within 30 days of the event/index date, our results were not substantially altered.

Discussion

We found that the exposure to any antibiotic agent was associated with a two-fold increased risk of bleeding that required hospitalization among older continuous warfarin users. All six specific antibiotic drug classes examined (azole antifungals, macrolides, quinolones, cotrimoxazole, penicillins, and cephalosporins) were associated with an increased risk of bleeding. Our finding that patients who were prescribed azole antifungals and cotrimoxazole had the highest risks of hospitalization for bleeding is consistent with previous studies.^{2, 5} In their nested case-control study of U.S. Medicaid patients (n=580,188) receiving warfarin, Schelleman et al⁵ reported that of the seven antibiotic agents evaluated, cotrimoxazole and fluconazole (an azole antifungal) demonstrated the highest risk of GI bleeding. Likewise, in their nested case-control study of older adult warfarin users in Ontario, Canada (n=23,585) Fischer et al² reported that cotrimoxazole carried the highest risk of GI bleeding of the seven antibiotic agents evaluated. The increased risk associated with azole antifungals and cotrimoxazole may be attributable to their inhibitory effects on CYP2C9—one of the main enzymes responsible for metabolizing warfarin. Additionally, our finding that cephalosporins carried a modest increased risk of major bleeding was consistent with

Schelleman et al's⁵ report for cephalexin (aOR, 1.72; 95% CI, 1.41-2.09), and with Zhang et al's³ report for cephalosporins (aOR, 1.16; 95% CI, 1.04-1.29),

Our finding that quinolones carried an increased risk for bleeding was inconsistent with that of Fischer et al,² who reported an aOR of 0.38 (95% CI, 0.12-1.26) for norfloxacin (a quinolone), as well as with several pharmacokinetics studies,¹⁵⁻¹⁷ which reported that exposure to quinolones was not associated with increased INRs among continuous warfarin users. Smaller retrospective studies have demonstrated increased INR and bleeding risk with levofloxacin use^{21, 26} but a systematic review of the effect of ciprofloxacin, levofloxacin, or moxifloxacin among warfarin users reported that findings were inconsistent across studies.²⁷ In view of this, this association should be further investigated in future studies.

Numerous studies have reported that interactions between warfarin and antibiotic agents may result in increased INRs.^{14, 21} As a result, frequent monitoring of INR has been recommended for patients who are concurrently taking warfarin and antibiotic agents.¹⁴ Given that inhibition of vitamin K synthesis by alteration of gut flora or inhibition of cytochrome P450 enzymes can lead to an increased INR and hence increased bleeding within a one to two-week period, a prudent strategy is to monitor INR one week after initiating antibiotic therapy. More frequent monitoring should be considered for patients at higher risk for bleeding.

Finally, we found that hospitalization for bleeding was more likely to occur in patients whose antibiotic exposure began in the 60 days before the event/index date. Given the mechanism of drug-drug interactions between antibiotic agents and warfarin, exposure more than 60 days prior to an event should not be associated with increased risk, and our analysis confirmed this.

The results of this study may have been influenced by several limitations. First, the study outcome was defined as hospitalization for a bleeding event based on ICD-9-CM codes. Such codes are not always accurate or complete.²⁸ Previous research has shown that a number of ICD9 bleeding codes, particularly those corresponding to non-gastrointestinal bleeds, have demonstrated poor positive predictive value.²⁹ It is possible, therefore, that some of the cases we identified may have been based on misclassified data. Second, Part D plans do not cover over-the-counter (OTC) medications and thus contain no information on co-administration of these drugs. Many OTC medications, including aspirin and non-steroidal anti-inflammatory drugs, interact with warfarin to increase the risk of bleeding. Third, reliance on claims data precluded assessment of a number of potential confounding factors such as diet, alcohol, and use of herbal supplements. Fourth, although Medicare Part D data provides information on the strength of warfarin tablet prescribed, accurate information on daily dose of medication was not available. Consequently, we did not have complete information on the intensity of anticoagulation therapy. Fifth, Medicare Part D data provides information on the date the prescription was filled but not on the date it was purchased or picked up by the patient. It is possible, therefore, that some of the drug exposure periods used in this study underestimated the true medication exposure period. Sixth, to identify a cohort of continuous warfarin users, we assessed the number of days the medication was prescribed. Given that the weekly dosing schedules for warfarin may change based on INR response, this value may also have been underestimated. Additionally, we assumed that patients adhered to their prescribed medication regimen. It is possible, however, that some patients did not take all or any of their prescribed medication. Finally, we were not able to assess the extent to which the sequelae of infection, such as fever and changes in diet may have contributed to increased risk of bleeding among patients with antibiotic exposure.

Using newly available Medicare Part D data, we have documented the risk of exposure to all antibiotic agents as well as to specific classes of antibiotics. Based on our findings and those of previous studies, clinicians should consider choosing antibiotics with low-risk profiles if appropriate based on a patient's clinical situation. If such therapeutic substitution is not permissible, close INR monitoring is imperative to reduce the risk of bleeding.

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Appendix A

Specific antibiotic medications corresponding to each major class of antibiotics

Azole Antifungals	Fluconazole, Itraconazole, Ketoconazole, Miconazole, Posaconazole, Voriconazole
Cephalosporins	Cefaclor, Cefadroxil, Cefamandole, Cefdinir, Cefazolin, Cefixime, Cefmetazole, Cefonicid, Cefoperazone, Cefotaxime, Cefotetan, Cefoxitin, Cefprozil, Ceftazidime, Ceftizoxime, Cefpodoxime Proxetil, Ceftriaxone, Cefibuten, Cefuroxime, Ceftaroline, Cephalixin, Cephalothin Sodium, Cephapirin Sodium, Cephadrine, Cefditoren, Cefepime HCl
Macrolides	Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Telithromycin, Troleandomycin
Penicillins	Amoxicillin, Ampicillin, Bacampicillin, Carbenicillin, Cloxacillin, Dicloxacillin Sodium, Methicillin Sodium, Mezlocillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin Sodium, Ticarcillin
Quinolones	Ciprofloxacin, Gemifloxacin, Enoxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin, Gatifloxacin
Cotrimoxazole	Cotrimoxazole

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Table 1

Baseline characteristics for cases and matched controls

Characteristic	Matched Controls ^a	Cases	p value [†]
	No. (%)	No. (%)	
All	2394(100)	798 (100)	
Indication for Warfarin use in 2007			
Afib	1302 (54.4)	434 (54.4)	1.000
Other	597 (24.9)	199 (24.9)	
Prosthetic heart valve	207 (8.7)	69 (8.7)	
Stroke	87 (3.6)	29 (3.6)	
Venous thromboembolism	201 (8.4)	67 (8.4)	
Multiple Indication for Warfarin use			
N	1890 (79.0)	614 (76.9)	0.233
Y	504 (21.0)	184 (23.1)	
Age at 2008, y			
66-70	247 (10.3)	86 (10.8)	0.973
71-75	465 (19.4)	152 (19.1)	
76-80	536 (22.4)	171 (21.4)	
81-85	539 (22.5)	183 (22.9)	
>85	607 (25.4)	206 (25.8)	
Race			
White	2109 (88.1)	698 (87.5)	0.517
Black	168 (7.0)	61 (7.6)	
Hispanic	83 (3.5)	23 (2.9)	
Other/unknown	34 (1.4)	16 (2.0)	
Sex			
Male	837 (35.0)	279 (34.5)	1.000
Female	1557 (65.0)	519 (65.0)	
Charlson Comorbidity Index^b			
0	1129 (47.2)	319 (40.0)	<0.001
1	601 (25.1)	173 (21.7)	
2	319 (13.3)	128 (16.0)	
3	172 (7.2)	78 (9.8)	
4	173 (7.2)	100 (12.5)	
Resided in a nursing home within 90 days before event/index date			
N	2160 (90.2)	623 (86.3)	<0.002
Y	234 (9.8)	104 (13.7)	

^aWe matched 92.6% of controls with cases on event month, major indication of warfarin use, age, sex, ethnicity, and index of multiple indications of warfarin use. 6.3% of the controls were matched with cases on event month, major indication of warfarin use, sex, broad range of age (66-75, 76-85, or > 82 years), and ethnicity (white or nonwhite). The rest of the controls were matched with cases on event month, major indication of warfarin use, sex, and broad range of age (66-80 or > 80 years).

^bComorbidity was measured with a score developed by Klabunde et al³⁰

Table 2

Association between specific antibiotic agent exposure and hospitalization for bleeding in older patients receiving warfarin

Drug	Controls ^a	Cases	Univariate OR ^b (95% CI) ^c	Multivariable ^d OR (95% CI)
	No. (%)	No. (%)		
Use of any antibiotic agent^e				
All bleeding requiring hospitalization				
No	2,130 (88.9)	628 (78.7)	Referent	Referent
Yes	264 (11.1)	170 (21.3)	2.18 (1.77-2.70)	2.01 (1.62-2.50)
GI bleeding requiring hospitalization				
No	2,130 (88.97)	367 (81.19)	Referent	Referent
Yes	264 (11.03)	85 (18.81)	1.86 (1.43-2.44)	1.68 (1.28-2.21)
Non-GI bleeding requiring hospitalization^f				
No	2,130 (88.97)	261 (75.43)	Referent	Referent
Yes	264 (11.03)	85 (24.57)	2.63 (1.99-3.46)	2.49 (1.88-3.30)
Days since initiation of prescription^g				
All Major Bleeding				
No Exposure	2,130 (88.97)	628 (78.70)	Referent	Referent
0-15 days	112 (4.68)	81 (10.15)	2.45 (1.82-3.31)	2.37 (1.75-3.22)
16-60 days	91 (3.80)	62 (7.77)	2.31 (1.65-3.23)	2.11 (1.50-2.97)
> 60 days	61 (2.55)	27 (3.38)	1.50 (0.95-2.38)	1.25 (0.78-2.01)
Use of other medications				
SSRI	343 (14.33)	156 (19.55)	1.45 (1.18-1.79)	1.34 (1.08-1.67)
SNRI	61 (2.55)	27 (3.38)	1.34 (0.85-2.12)	1.17 (0.73-1.90)
Corticosteroid	86 (3.59)	70 (8.77)	2.58 (1.86-3.58)	2.30 (1.64-3.21)
Antiplatelet	96 (4.01)	49 (6.14)	1.57 (1.10-2.23)	1.43 (1.00-2.07)
CYP2CP	271 (11.32)	99 (12.41)	1.11 (0.86-1.42)	1.07 (0.83-1.37)

^aSee Table 1

^bOR, odds ratio

^cCI, confidence interval

^dMultivariate analyses were adjusted for: all drug groups; comorbidity index; having stayed in a nursing home in the 90 days before event/index date

^ePatients whose most recent prescription period for any antibiotic agent overlapped by at least one day with the 15 day period before the event/index date were defined as exposed.

^fIncludes intracranial bleed

^gAmong patients who met this criterion, we examined the duration since the initiation of current antibiotic agents.

Table 3

Association between specific antibiotic agent exposure and hospitalization for bleeding in older patients receiving warfarin

Antibiotic Drug	Matched Controls ^a	Cases	Univariate OR ^b (95% CI) ^c	Multivariable ^d OR (95% CI)
	No. (%)	No. (%)		
Azole Antifungals	8 (0.33)	17 (2.13)	6.49 (2.79-15.10)	4.57 (1.90-11.03)
Macrolides	35 (1.46)	24 (3.01)	2.09 (1.24-3.54)	1.86 (1.08-3.21)
Quinolones	56 (2.34)	40 (5.01)	2.20 (1.46-3.33)	1.69 (1.09-2.62)
Cotrimoxazole	22 (0.92)	22 (2.76)	3.06 (1.68-5.55)	2.70 (1.46-5.05)
Penicillins	50 (2.09)	31 (3.88)	1.89 (1.20-2.99)	1.92 (1.21-2.07)
Cephalosporins	39 (1.63)	36 (4.51)	2.85 (1.80-4.52)	2.45 (1.52-3.95)

^aSee Table 1

^bOR, odds ratio

^cCI, confidence interval;

^dMultivariable analyses were adjusted for: all drug groups; comorbidity index; having stayed in a nursing home in the 90 days before event/index date