# Hemorrhage During Warfarin Therapy Associated With Cotrimoxazole and Other Urinary Tract Anti-infective Agents

## *A Population-Based Study*

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**Background:** Some antibiotic agents, including cotrimoxazole, inhibit the metabolism of warfarin sodium and possibly increase the risk of hemorrhage. We examined the risk of upper gastrointestinal (UGI) tract hemorrhage in older patients receiving warfarin in combination with antibiotics commonly used to treat urinary tract infection, with a focus on cotrimoxazole.

**Methods:** This population-based, nested case-control study using health care databases in Ontario, Canada, between April 1, 1997, and March 31, 2007, identified residents 66 years or older who were continuously treated with warfarin. Cases were hospitalized with UGI tract hemorrhage. For each case, we selected up to 10 age- and sex-matched control subjects. We calculated adjusted odds ratios (aORs) for exposure to cotrimoxazole, amoxicillin trihydrate, ampicillin trihydrate, ciprofloxacin hydrochloride, nitrofurantoin, and norfloxacin within 14 days before the UGI tract hemorrhage.

**Results:** We identified 134 637 patients receiving warfarin, of whom 2151 cases were hospitalized for UGI tract hemorrhage. Cases were almost 4 times more likely than controls to have recently received cotrimoxazole (aOR, 3.84; 95% confidence interval [CI], 2.33-6.33). Treatment with ciprofloxacin was also associated with increased risk (aOR, 1.94; 95% CI, 1.28-2.95), but no significant association was observed with amoxicillin or ampicillin (1.37; 0.92-2.05), nitrofurantoin (1.40; 0.71-2.75), or norfloxacin (0.38; 0.12-1.26). Compared with amoxicillin or ampicillin, cotrimoxazole prescription was associated with an almost 3-fold risk (ratio of ORs, 2.80; 95% CI, 1.48-5.32).

**Conclusions:** Among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of UGI tract hemorrhage than other commonly used antibiotics. Whenever possible, clinicians should prescribe alternative antibiotics in patients receiving warfarin.

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WARFARIN SODIUM IS the oral anticoagulant of choice in North America,[1,2] with more than 30 million outpatient prescriptions in 2004 in the United States.[3] It is commonly used for the prevention and treatment of thromboembolism in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation, and mechanical heart valves.[2]

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Warfarin has a narrow therapeutic index, and the response to warfarin is influenced by pharmacogenetic and pharmacokinetic polymorphisms, vitamin K status, and multiple drug interactions.[4-8] Consequently, safe and effective treatment with warfarin poses a challenge, and it is one of the top 10 drugs cited in the Food and Drug Administration's Adverse Event Reporting System.[3]

Urinary tract infection (UTI) is the second most common infection among community-dwelling older patients.[9] It accounts for almost 25% of all infection in older adults[9] and is often treated with antibiotic agents that have significant potential for interaction with warfarin. Many antibiotics used to treat UTI disrupt gut flora, thereby reducing intestinal vitamin $K_2$ synthesis.[10] Some antibiotics also inhibit cytochrome P450 isozyme 2C9, which is responsible for metabolizing the more biologically active S-enantiomer of warfarin.[6,7] These include cotrimoxazole (trimethoprim-sulfamethoxazole), a popular antibiotic most often used to treat UTI.[6,11]

Warfarin is commonly coprescribed with antibiotics used to treat UTI. However, few observational studies[12,13] have ex-

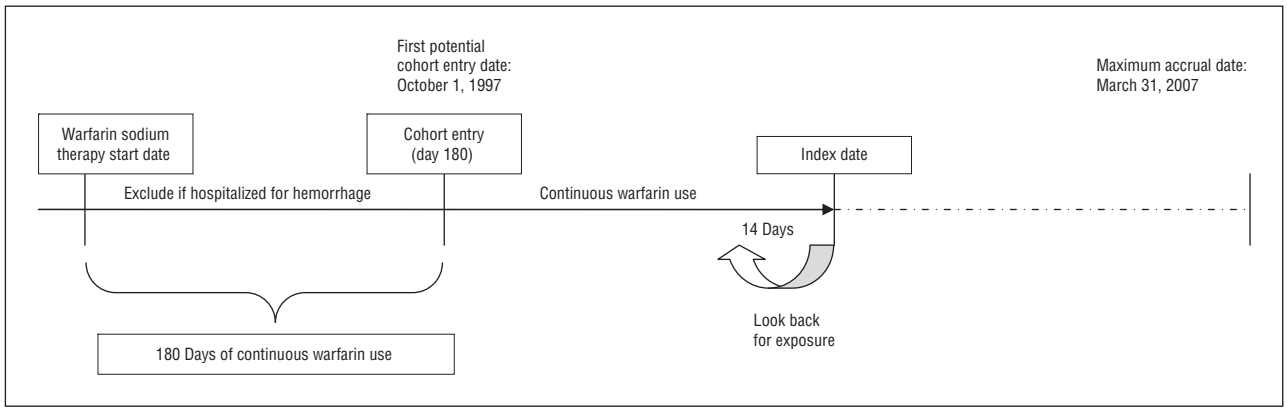


**Figure.** Description of the study design. In cases, the index date was admission to the hospital with a diagnosis of upper gastrointestinal (UGI) tract hemorrhage. In controls, the index date was eligible continuous warfarin sodium users who had not yet been hospitalized with UGI tract hemorrhage on the case index date.

amined the clinical consequences of cotrimoxazole prescription in patients receiving warfarin, and they did not focus on antibiotics indicated for UTI. Therefore, we sought to characterize the risk of upper gastrointestinal (UGI) tract hemorrhage in older patients associated with the concomitant use of warfarin and antibiotics used to treat UTI, with a primary focus on cotrimoxazole.

## METHODS

We conducted a population-based nested case-control study of health care databases in Ontario, Canada, between April 1, 1997, and March 31, 2007. This study was approved by the Ethics Review Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

The Ontario Drug Benefit Database includes data on prescription drugs reimbursed by the Ontario government for all Ontario residents 65 years or older. Hospital admissions were identified using the Canadian Institute for Health Information Discharge Abstract Database. The Ontario Health Insurance Plan Database records physician billing claims, and the Registered Persons Database provides basic demographic information. These administrative health care databases were anonymously linked using encrypted health card numbers and have been routinely used to study the clinical consequences of drug interactions.[14-18]

We assembled a cohort of Ontario residents 66 years or older who were treated with warfarin for at least 180 days, starting from the first warfarin prescription following the patient's 66th birthday (**Figure**). To identify a stable outpatient warfarin therapy population, patients who ceased warfarin therapy or who were hospitalized with any hemorrhage during the initial 180 days of therapy were excluded from analysis.

Patients were observed until hospitalization for UGI tract hemorrhage, discontinuation of warfarin therapy, the end of the study period (March 31, 2007), or death, whichever occurred first. A patient was considered to have discontinued warfarin therapy if the interval between prescription refills exceeded the days supply of the previous prescription by more than 50%. In that instance, we continued observation for 1.5 times the days supply of the final prescription to identify UGI tract hemorrhages that may have precipitated cessation of therapy.

Within the cohort of continuous warfarin users, we defined cases as those hospitalized with UGI tract hemorrhage using the *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases, 10th Revision* (eAppendix, http://www.archinternmed.com). We studied UGI tract hemorrhage because coding for the diagnosis has been validated, with positive predictive values of well above 80%.[19] The hospital admission date served as the index date for all analyses.

We selected up to 10 control subjects for each case from the cohort of patients continuously receiving warfarin therapy. Controls were matched to cases based on date of birth, sex, and warfarin use on the case's index date. Cases were eligible to serve as controls for another case whose index date occurred earlier.[20,21] We excluded cases and controls who were discharged from the hospital for any admission diagnosis within 30 days before the index date.

The primary exposure of interest was oral cotrimoxazole prescription within 14 days preceding the index date. We also examined other oral antibiotics commonly used to treat UTI, including ciprofloxacin, amoxicillin or ampicillin, norfloxacin, and nitrofurantoin. We hypothesized that these drugs would be less strongly associated with hemorrhage in patients receiving warfarin therapy because they do not inhibit metabolism of the S-enantiomer of warfarin.[6,11] To minimize the potential for confounding by indication, we did not examine other antibiotic classes. We restricted our analyses to antibiotics commonly indicated for UTI because we wanted to maximize the homogeneity of the indication for which patients were treated.

We excluded cases and controls who received amoxicillin in combination products intended for *Helicobacter pylori* elimination, as well as those who received more than 1 study antibiotic within 14 days of the index date. To test the robustness of our findings, we performed sensitivity analyses examining exposure windows of 7 days and 21 days before the index date.

We used conditional logistic regression analysis to estimate the unadjusted and adjusted odds ratio (aOR) and 95% confidence interval (CI) for the association between hospital admission for UGI tract hemorrhage during warfarin therapy and receipt of antibiotics. In each analysis, the reference group was patients not treated with antibiotics. We used multivariate analysis to adjust for numerous potential confounders (**Table 1**). We conducted a tracer analysis using ocular antibiotics because these have no plausible association with hemorrhage in patients receiving warfarin.

We compared the aOR during cotrimoxazole therapy with that of amoxicillin or ampicillin using a test of interaction as outlined by Altman and Bland.[22] This predefined comparison was based on our hypothesis that the risk of hemorrhage would not be appreciably increased during treatment with amoxicillin or ampicillin, which do not inhibit cytochrome P450 isozyme 2C9. All analyses were performed using commercially available statistical software (SAS version 9.13; SAS Institute, Cary, North Carolina).

**Table 1. Covariates Included in the Multivariate Analysis**

| Covariate |
|---|
| **History of Hemorrhage** |
| UGI tract hemorrhage <5 y before cohort enrollment |
| UGI diagnostic examination <1 y of index date |
| Any hemorrhage except UGI ≤1 y of index date |
| **Comorbidity** |
| Cirrhosis ≤5 y of index date |
| Alcoholism ≤5 y of index date |
| No. of prescription drugs ≤1 y of index date |
| Long-term care status ≤180 d of index date |
| **Concomitant Drug Use ≤120 d of Index Date** |
| Antiplatelets (aspirin [acetylsalicylic acid], ticlopidine hydrochloride, clopidogrel bisulfate, dipyridamole) |
| Anti-inflammatory medications (nonsteroidal anti-inflammatory drugs, including cyclooxygenase 2 inhibitors) |
| Other anticoagulants (vitamin K antagonists, synthetic antithrombotic agents, low-molecular-weight heparins) |
| Corticosteroids |
| Acetaminophen and combinations |
| Gastroprotective medications (histamine$_2$ antagonists, misoprostol, proton pump inhibitors, sucralfate) |
| All other systemic antibiotics |
| Selective serotonin reuptake inhibitors |
| Cytochrome P450 isozyme 2C9 |
| Inhibitor (eg, amiodarone, fenofibrate, fluconazole, fluvastatin sodium, ketoconazole, lovastatin, metronidazole, valproic acid) |
| Inducer (rifampin, secobarbital sodium, bosentan, carbamazepine, phenobarbital, phenytoin, primidone) |

Abbreviation: UGI, upper gastrointestinal.

**Table 2. Characteristics of Cases and Controls[a]**

| Characteristic | Cases (n=2151) | Controls (n=21 434) |
|---|---|---|
| Female sex | 1023 (47.6) | 10 201 (47.6) |
| Age, median (interquartile range), y | 80 (74-85) | 80 (74-85) |
| UGI tract hemorrhage <5 y before cohort enrollment | 106 (4.9) | 395 (1.8) |
| UGI diagnostic examination <1 y of index date | 469 (21.8) | 1217 (5.7) |
| Any hemorrhage except UGI ≤1 y of index date | 72 (3.3) | 331 (1.5) |
| Alcoholism ≤5 y of index date | 55 (2.6) | 466 (2.2) |
| Cirrhosis ≤5 y of index date | 34 (1.6) | 144 (0.7) |
| No. of prescription drugs ≤1 y of index date, mean (SD) | 15.36 (7.36) | 12.69 (6.66) |
| Long-term care status ≤180 d of index date | 320 (14.9) | 2332 (10.9) |
| Concomitant drug use ≤120 d of index date | | |
| Antiplatelets | 123 (5.7) | 910 (4.2) |
| Anti-inflammatory medications | 380 (17.7) | 2035 (9.5) |
| Other anticoagulants | 8 (0.4) | 181 (0.8) |
| Corticosteroids | 174 (8.1) | 1005 (4.7) |
| Gastroprotective medications | 670 (31.1) | 5128 (23.9) |
| Acetaminophen and combinations | 619 (28.8) | 4186 (19.5) |
| Selective serotonin reuptake inhibitors | 270 (12.6) | 1937 (9.0) |
| Cytochrome P450 isozyme 2C9 | | |
| Inducer | 79 (3.7) | 565 (2.6) |
| Inhibitor | 263 (12.2) | 2128 (9.9) |
| All other systemic antibiotics | 449 (20.9) | 3327 (15.5) |
| Ocular antibiotics | 56 (2.6) | 511 (2.4) |

Abbreviation: UGI, upper gastrointestinal.
[a] Data are given as number (percentage) unless otherwise indicated.

## RESULTS

We identified 134 637 patients with a total of 198 910 person-years of continuous warfarin treatment. During the study period, 45 972 patients (34.1%) treated with warfarin received at least 1 prescription for an antibiotic of interest, and 9751 patients (7.2%) received at least 1 prescription for cotrimoxazole.

We identified 2441 patients who were hospitalized for UGI tract hemorrhage. There were 2151 patients hospitalized for UGI tract hemorrhage who met our definition of a case after excluding 290 patients (270 who had a hospital admission within 30 days of the index date, 7 who had been prescribed more than 1 antibiotic of interest, 5 or fewer who had received combination amoxicillin-lansoprazole-clarithromycin within 14 days of the index date, and 12 who had more than 1 exclusion criteria). Of 2151 cases hospitalized for UGI tract hemorrhage, almost all (2135 [99.3%]) were matched to 10 controls. Overall, 224 cases (10.4%) died before discharge. The characteristics of cases and controls are given in **Table 2**.

Cases admitted for UGI tract hemorrhage during warfarin therapy were almost 4 times more likely than controls to have received a cotrimoxazole prescription within 14 days before hospitalization (aOR, 3.84; 95% CI, 2.33-6.33) (**Table 3**). Treatment with ciprofloxacin was also associated with an increased risk of hemorrhage during warfarin therapy (aOR, 1.94; 95% CI, 1.28-2.95). In contrast, no significant association was noted between hospitalization for UGI tract hemorrhage and the prescription of amoxicillin or ampicillin (aOR, 1.37; 95% CI, 0.92-2.05), nitrofurantoin (1.40; 0.71-2.75), or norfloxacin (0.38; 0.12-1.26). As expected, we found no association between UGI tract hemorrhage and receipt of ocular antibiotics (aOR, 0.99; 95% CI, 0.50-1.93). Sensitivity analyses using exposure windows of 7 days and 21 days revealed consistent results (eTable).

Compared with amoxicillin or ampicillin,[22] cotrimoxazole prescription was associated with an almost 3-fold increase in the risk of UGI tract hemorrhage among patients taking warfarin. The ratio of ORs was 2.80 (95% CI, 1.48-5.32).

## COMMENT

Concomitant use of cotrimoxazole in patients receiving long-term warfarin therapy was associated with an almost 4-fold increase in the risk of hospitalization for UGI tract hemorrhage, considerably higher than that with other antibiotics. Treatment with ciprofloxacin was also associated with an almost 2-fold increased risk, whereas the other antibiotics we examined were not associated with a statistically significant increased risk.

Our findings regarding cotrimoxazole are consistent with other research involving coumarin anticoagulants not widely used in North America,[23,24] as well as other observational studies[12,13] involving warfarin. To our

**Table 3. Association Between Hospital Admission for UGI Tract Hemorrhage and Antibiotic Use in Patients Treated With Warfarin Sodium**

| Exposure ≤14 d of Index Date | No. (%) | | Odds Ratio (95% Confidence Interval) | |
|---|---|---|---|---|
| | Cases (n=2151) | Controls (n=21 434) | Univariate | Multivariate[a] |
| Cotrimoxazole | 25 (1.2) | 56 (0.3) | 4.53 (2.81-7.30) | 3.84 (2.33-6.33) |
| Amoxicillin or ampicillin | 30 (1.4) | 209 (1.0) | 1.44 (0.98-2.12) | 1.37 (0.92-2.05) |
| Ciprofloxacin | 31 (1.4) | 124 (0.6) | 2.50 (1.68-3.73) | 1.94 (1.28-2.95) |
| Nitrofurantoin | 11 (0.5) | 64 (0.3) | 1.71 (0.90-3.24) | 1.40 (0.71-2.75) |
| Norfloxacin | ≤5 (≤0.2) | 61 (0.3) | 0.49 (0.15-1.57) | 0.38 (0.12-1.26) |
| Ocular antibiotics | 10 (0.5) | 81 (0.4) | 1.23 (0.64-2.38) | 0.99 (0.50-1.93) |

Abbreviation: UGI, upper gastrointestinal.
[a]Multivariate analysis adjusts for history of UGI hemorrhage, UGI diagnostic examination, any hemorrhage except UGI; history of cirrhosis and alcoholism; number of prescription drugs within 1 year of the index date, long-term care status, other antibiotics of interest, and other concomitant drug use (see Table 1).

knowledge, this study is the first to focus on the specific risks associated with UTI antibiotics, a leading reason for antibiotic therapy in older patients receiving warfarin.

We observed a less dramatic increase in the risk of hemorrhage with ciprofloxacin therapy. This may be related to a heterogeneous patient population with a greater burden of illness, because ciprofloxacin is more commonly used for a wider variety of indications beyond UTI compared with the other antibiotics that were studied. The small statistically nonsignificant elevated aORs associated with the use of amoxicillin or ampicillin and nitrofurantoin may indicate residual confounding. However, the much higher aOR associated with cotrimoxazole therapy strongly indicates that it has a much greater effect on the risk of UGI tract hemorrhage than the other antibiotics studied.[13]

Some limitations of our study merit emphasis. First, our analyses were confined to older patients, and we have no direct measure of coagulation status. Second, the mean duration that patients were taking warfarin (slightly >1 year) may seem shorter than expected. However, the cohort consisted of prevalent warfarin users, some of whom would have been receiving warfarin before their 66th birthday. Also, patients had to have received 6 months of continuous warfarin therapy before enrolling in the cohort, and these 6 months are excluded from the study follow-up. We also used a rigorous definition of adherence, which may have led us to censor some patients who actually continued warfarin therapy. Third, although we adjusted for many potential confounders, we could not adjust for unmeasured confounders such as the use of nonprescription drugs, foods, or herbal supplements. However, these are not expected to differ among antibiotic groups. Fourth, we had no information about the indication for antibiotic therapy and cannot exclude the possibility that patients who were prescribed various antibiotics were systematically different from one another.

Our findings provide strong evidence that treatment with cotrimoxazole is associated with an important increase in the risk of UGI tract hemorrhage during warfarin therapy and that this risk is considerably higher than the risk associated with other commonly used antibiotics. In addition to the morbidity associated with hospitalization for UGI tract hemorrhage (including endoscopy, blood transfusion, and nosocomial infection), approximately 10% of cases hospitalized for UGI tract hemorrhage died before hospital discharge. This finding is important in view of the tens of millions of warfarin prescriptions dispensed annually in the United States.[3] Our observations suggest that clinicians should consider antibiotics other than cotrimoxazole in patients receiving warfarin. If alternatives are inappropriate, close monitoring of anticoagulation control is necessary, and temporary reductions in the dosage of warfarin may be required.

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**Author Contributions:** Dr Fischer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Fischer, Juurlink, Mamdani, and Laupacis. *Acquisition of data:* Kopp. *Analysis and interpretation of data:* Fischer, Juurlink, Mamdani, Kopp, and Laupacis. *Drafting of the manuscript:* Fischer, Juurlink, Mamdani, and Laupacis. *Critical revision of the manuscript for important intellectual content:* Fischer, Juurlink, Mamdani, Kopp, and Laupacis. *Statistical analysis:* Fischer, Juurlink, Mamdani, and Kopp. *Obtained funding:* Juurlink. *Administrative, technical, and material support:* Fischer. *Study supervision:* Laupacis.
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**Online-Only Material:** The eAppendix and eTable are available at http://www.archinternmed.com.

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