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 thrombembolism in patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation, and mechanical heart valves. 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 adults9 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 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 studies12,13 have ex-
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.

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 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.
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 97,511 patients (7.2%) received at least 1 prescription for cotrimoxazole.

We identified 24,411 patients who were hospitalized for UGI tract hemorrhage. There were 21,511 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 21,511 cases hospitalized for UGI tract hemorrhage, almost all (21,352 [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, 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, as well as other observational studies involving warfarin. To our
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, 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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Table 3. Association Between Hospital Admission for UGI Tract Hemorrhage and Antibiotic Use in Patients Treated With Warfarin Sodium

<table>
<thead>
<tr>
<th>Exposure =≤14 d of Index Date</th>
<th>Cases (n=2151)</th>
<th>Controls (n=21434)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>Odds Ratio (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>25 (1.2)</td>
<td>56 (0.3)</td>
<td>4.53 (2.81-7.30)</td>
</tr>
<tr>
<td>Amoxicillin or ampicillin</td>
<td>30 (1.4)</td>
<td>209 (1.0)</td>
<td>1.44 (0.98-2.12)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>31 (1.4)</td>
<td>124 (0.6)</td>
<td>2.50 (1.68-3.73)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>11 (0.5)</td>
<td>64 (0.3)</td>
<td>1.71 (0.90-3.24)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>≤5 (=0.2)</td>
<td>61 (0.3)</td>
<td>0.49 (0.15-1.57)</td>
</tr>
<tr>
<td>Ocular antibiotics</td>
<td>10 (0.5)</td>
<td>81 (0.4)</td>
<td>1.23 (0.64-2.38)</td>
</tr>
</tbody>
</table>

Abbreviation: UGI, upper gastrointestinal.

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).
Online-Only Material: The eAppendix and eTable are available at http://www.archinternmed.com.

REFERENCES


