Risk of Upper Gastrointestinal Hemorrhage in Warfarin Users Treated With Nonselective NSAIDs or COX-2 Inhibitors

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Background: Little is known about the risk of upper gastrointestinal (GI) hemorrhage during the concomitant use of warfarin and selective cyclooxygenase (COX)-2 inhibitors. We examined the association between the concomitant use of warfarin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) or selective COX-2 inhibitors in older adults hospitalized for upper GI hemorrhage.

Methods: This nested case-control analysis of multiple linked health care databases conducted over 1 year identified a cohort of patients in Ontario, Canada, who were older than 66 years and continuously prescribed warfarin. Case patients were those admitted to the hospital with upper GI hemorrhage while taking warfarin. We compared their prescription records prior to hospitalization with those of age- and sex-matched controls who were also receiving warfarin (the control-case ratio was 4:1). Odds ratios (ORs) for the risk of hospitalization for upper GI hemorrhage while concomitantly using warfarin and celecoxib, rofecoxib, or nonselective NSAIDs were determined.

Results: During the study period, we identified 98821 elderly patients continuously receiving warfarin. Of those, 361 (0.3%) were admitted to the hospital with upper GI hemorrhage. After adjusting for other potential confounders, case patients were significantly more likely to be also taking nonselective NSAIDs (OR, 1.9; 95% confidence interval [CI], 1.4-3.7), celecoxib (OR, 1.7; 95% CI, 1.2-3.6), or rofecoxib (OR, 2.4; 95% CI, 1.7-3.6) prior to hospitalization relative to controls.

Conclusions: Patients taking warfarin concomitantly with selective COX-2 inhibitors have an increased risk of hospitalization for upper GI hemorrhage. The risk appears similar to that of patients simultaneously taking warfarin and nonselective NSAIDs.

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Warfarin is an anticoagulant commonly used for the management of patients with a variety of thromboembolic conditions but it is implicated in many drug-drug interactions. Some interactions alter warfarin pharmacokinetics and others involve drugs that directly influence hemostasis or gastrointestinal integrity. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often coprescribed to patients receiving warfarin, potentially resulting in a significantly increased risk of upper gastrointestinal (GI) hemorrhage. This increased risk may be mediated through several pathways. First, many NSAIDs are substrates for the cytochrome P450 2C9 isoenzyme. Their use may interfere with the oxidative metabolism of S-warfarin, the more active enantiomer of commercially available racemic warfarin, thereby increasing the hypoprothrombinemic response to warfarin. Second, the nonspecific inhibition of cyclooxygenase (COX) enzymes by nonselective NSAIDs leads to significant inhibition of COX-1–generated thromboxane A2, impairing platelet aggregation, which may be further compounded by the concomitant use of warfarin. Third, traditional NSAIDs can cause gastric erosion, thereby further increasing the risk of GI bleeding in patients treated with warfarin.

See also pages 158, 161, 171, and 181

The introduction of the selective COX-2 inhibitors has been met with wide acceptance given their potentially lower risk of adverse GI events relative to nonselective NSAIDs. This perception of greater safety with the selective COX-2 inhibitors may result in a higher rate of coprescription with warfarin among users of se-
the clinical consequences of this combination of drug encrypted numbers identifying patients. Registered Persons Database. The databases are linked through
tion for each Ontario resident was obtained from the Ontario hospital admissions in Ontario. Basic demographic informa-
missions for upper GI hemorrhage were identified from the
pensed to Ontario residents who are 65 years and older. Ad-
efit Program, which records prescription medications dis-
We studied elderly patients whose prescription records al-
2001) in Ontario, Canada. This research was approved by the
morbidities in the analysis, as outlined in Table 1. We included
COHOR T DEFINITION
We studied elderly patients whose prescription records al-
patient’s death, or discontinuation of warfarin, whichever oc-
curred first. We chose not to study patients during their first
year of eligibility for prescription drug coverage, ie, during their
66th year, to avoid incomplete medication records. Patients were
deemed to have discontinued warfarin treatment if more than
120 days had elapsed between prescriptions. In these cases, we
extended the observation period to 90 days after the last pre-
scription to include admissions for GI hemorrhage that may
have led to cessation of therapy. A similar method has previ-
ously been used to define periods of continuous drug use.17-19

CASE PATIENTS
Within the cohort of continuous warfarin users, we defined as
case patients those registered in the CIHI DAD as having been
admitted to the hospital with any diagnosis of upper GI hem-
orrhage between April 17, 2000, and March 31, 2001. The most
commonly found International Classification of Diseases, Ninth
Revision (ICD-9) Clinical Modification diagnostic codes were
531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0,
533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 578.0, 578.1,
and 578.9,20 and these codes have been shown to have a posi-
tive predictive value of 86% for upper GI hemorrhage.21 These
date were chosen because both celecoxib and rofecoxib were made available on the provincial formulary on April
17, 2000, and our hospital database, the CIHI DAD, was com-
plete until March 31, 2001, at the time of the study. The date
of admission for upper GI hemorrhage served as the index date
for all analyses.

CONTROL PATIENTS
From the cohort of continuous warfarin users, we randomly
selected 50 controls for each case, matching for age (born within
1 year of the case patient) and sex. When numerous controls
 existed for each case patient, we randomly selected 4 matched
controls for analysis. When fewer than 4 potential controls were
available, we analyzed only those controls and did not alter the
matching process. A case patient could serve as a control for a
different case patient prior to his or her admission date, and
each control could be used for multiple case patients.22,23

EXPOSURE TO INTERACTING MEDICATIONS
AND COVARIATES
We identified prescriptions for any COX-2 inhibitor and any
prescription for an NSAID in the 90 days prior to the index date.
As a test of robustness, we also examined any prescriptions for
ocular antibiotics in our cohort of warfarin users to test if no
association was observed where none was expected.
To adjust for potential confounders we included several co-
morbidities in the analysis, as outlined in Table 1. We included
hospitalizations for upper GI hemorrhage in the 3 years prior
to the index date using the CIHI DAD. For procedures such as
doscopy and upper GI radiologic studies, we examined the data
of the Ontario Health Insurance Plan, which records all phy-
sician claims for diagnostic and therapeutic procedures. We also
examined drug use patterns during the 120 days prior to the in-
dex date as markers for conditions that may be associated with
an increased risk for upper GI hemorrhage or as drugs that could
interfere with the metabolism of warfarin (Table 1).24,25 We also
identified residence in a long-term care institution, since this may
be an indicator of comorbidity.30 Finally, we adjusted for the
number of different drugs prescribed in the year prior to the in-
dex date as a recently validated measure of comorbidity.31

STUDY DESIGN AND DATA SOURCES
We conducted a nested case-control analysis of multiple linked
health care databases over 1 year (April 1, 2000, to March 31,
2001) in Ontario, Canada. This research was approved by the
ethics review board of Sunnybrook and Women’s College Health
Sciences Center.

Prescriptions were identified from the Ontario Drug Bene-
fit Program, which records prescription medications dis-
pensed to Ontario residents who are 65 years and older. Ad-
missions for upper GI hemorrhage were identified from the
Canadian Institute for Health Information Discharge Abstract
Database (CIHI DAD), which contains a detailed record of all
hospital admissions in Ontario. Basic demographic informa-
tion for each Ontario resident was obtained from the Ontario
Registered Persons Database. The databases are linked through
crypted numbers identifying patients.

METHODS

TABLE 1. Potential Confounders Accounted for
in the Analysis of Elderly Patients Taking Warfarin
and Either a COX-2 Inhibitor or NSAIDs

| Causes for hospitalization in the 3 years prior to the index date |
| Upper GI hemorrhage |
| Medical/surgical procedures in the 3 years prior to the index date |
| Upper GI endoscopic or radiologic examinations |
| Drugs used in the 120 days before the index date and to the end of follow-up |
| CYP 2C9 inhibitors (amiodarone, losartan, tolbutamide, cimetidine, fluvalastin, fluconazole) |
| Antibiotics |
| CYP 2C9 inducers (rifampin, phenytoin) |
| Glucocorticoids |
| Antiplatelet agents (aspirin, ticlopidine, clopidogrel) |
| Oral hypoglycemic agents or insulin* |
| Gastroprotective agents (misoprostol, proton pump inhibitors, H2 antagonists, sucralfate) |
| No. of different drugs prescribed in the preceding year |
| Other |
| Residence in a long-term care facility |

Abbreviations: COX-2, cyclooxygenase-2; CYP, cytochrome P450; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.
*These medications are used as markers for diabetes.
Table 2. Baseline Characteristics of Elderly Patients Using Nonselective NSAIDs and COX-2 Inhibitorsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case Patients</th>
<th>All Potential Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patients</td>
<td>361 (51.5)</td>
<td>65 653 (51.2)</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>79.8 (6.9)</td>
<td>77.6 (5.5)</td>
</tr>
<tr>
<td>Residence in long-term care facility</td>
<td>58 (16)</td>
<td>5 124 (8)</td>
</tr>
<tr>
<td>Mean (SD) of prescription drugs in the past year</td>
<td>15.7 (7.7)</td>
<td>12.6 (6.8)</td>
</tr>
<tr>
<td>Hospitalization/procedures in the past 3 years</td>
<td>22 (6)</td>
<td>751 (1)</td>
</tr>
<tr>
<td>Upper GI hemorrhage</td>
<td>22 (6)</td>
<td>751 (1)</td>
</tr>
<tr>
<td>GI endoscopy or radiologic examinations</td>
<td>117 (32)</td>
<td>14 557 (22)</td>
</tr>
<tr>
<td>Drug use in the 120 days before the index date and to the end of follow-up</td>
<td>2 (&lt;1)</td>
<td>763 (1)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>68 (19)</td>
<td>11 298 (17)</td>
</tr>
<tr>
<td>Antihyperglycemic agents</td>
<td>41 (11)</td>
<td>4 734 (7)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>170 (47)</td>
<td>19 283 (29)</td>
</tr>
<tr>
<td>Gastroprotective agents†</td>
<td>22 (6)</td>
<td>1 606 (2)</td>
</tr>
<tr>
<td>Heparins</td>
<td>173 (20)</td>
<td>12 697 (19)</td>
</tr>
<tr>
<td>CYP 2C9 inhibitors</td>
<td>73 (20)</td>
<td>12 697 (19)</td>
</tr>
<tr>
<td>CYP 2C9 inducers</td>
<td>6 (2)</td>
<td>735 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: COX-2, cyclooxygenase-2; CYP, cytochrome P450; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 3. Association Between Hospitalization for Upper Gastrointestinal Hemorrhage Among Elderly Warfarin Users and Exposure to Potential Interacting Drugs in the Preceding 90 Days

<table>
<thead>
<tr>
<th>Drug Taken</th>
<th>Case Patients (n = 361)</th>
<th>Controls (n = 1437)</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysisa</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>24</td>
<td>337</td>
<td>2.3 (1.8-3.2)</td>
<td>1.9 (1.4-3.7)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>22</td>
<td>339</td>
<td>1.9 (1.4-2.4)</td>
<td>1.7 (1.2-3.6)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>25</td>
<td>336</td>
<td>2.6 (2.0-3.7)</td>
<td>2.4 (1.7-3.6)</td>
</tr>
<tr>
<td>Ocular antibiotics</td>
<td>17</td>
<td>344</td>
<td>1.1 (0.9-1.5)</td>
<td>0.9 (0.7-1.3)</td>
</tr>
</tbody>
</table>

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

*Multivariate analysis adjusts for other potential interacting medications (Table 1), a history of previous gastrointestinal bleeding in the 3 years preceding the index date, comorbidities as estimated by the number of medications prescribed during the previous year, and use of other gastrointestinal medications and antulcer agents.

1.7-3.6) in the preceding 90 days (Table 3). As expected, no significant association was observed for ocular antibiotics (OR, 0.9; 95% CI, 0.7-1.3).

STATISTICAL ANALYSIS

Conditional logistic regression was used to estimate the odds ratios (ORs) for the association between hospital admission for upper GI hemorrhage and receipt of COX-2 inhibitors or nonselective NSAIDs. The 95% confidence intervals (CIs) were constructed using nonparametric bootstrap methods with resampling of controls over 1000 iterations. To avoid the extreme OR estimates that may occur with low exposure rates, for each interaction we examined the comparative safety of the COX-2 inhibitors celecoxib and rofecoxib in patients receiving warfarin. Previous studies of this potential interaction have been conducted in healthy volunteers and have relied on small samples and surrogate outcome rather than actual bleeding episodes. Furthermore, in the Celecoxib Long-term Arthritis Safety Study (CLASS), the comparison of patients receiving celecoxib and aspirin with patients receiving standard NSAID therapy demonstrated no difference in ulcer complications. This may suggest that a COX-2 inhibitor taken with an agent that increases the risk of bleeding may not be safer than NSAIDs alone. A small nested case-control study recently observed differences in the results of exposure to nabumetone or meloxicam when compared with nonselective NSAIDs in patients with or without bleeding complications who were concomitantly using coumarine. However, this study was questionnaire-based with a significant differential in response rates between case patients (approximately 70%) and controls (approximately 31%) and it lacked sufficient information on celecoxib and rofecoxib. Furthermore, patients in this study received phenprocoumon or acenocoumarol, whereas in our study patients only received warfarin. These differences would preclude direct comparisons between this study and ours.

Several limitations of our study deserve mention. First, although we controlled for many important confound-

We identified 98 821 elderly patients treated continuously with warfarin for a total of 65 064 patient-years of therapy. Their mean (SD) age at entry was 77 (6.8) years and approximately 50% were women.

During the study period, 361 elderly patients were admitted to the hospital with GI hemorrhage. Their mean (SD) age at entry was 79.8 (6.9) years and 51.5% were women (Table 2). Of these 361 case patients, 24 (6.6%) had received a prescription for a nonselective NSAID within the preceding 90 days, while 23 (6.1%) had received celecoxib and 25 (6.9%) had received rofecoxib. After adjusting for other potential interacting medications and comorbidities, we found that patients receiving warfarin who were admitted with GI hemorrhage were more likely to have been treated with celecoxib (OR, 1.7; 95% CI, 1.2-3.6), nonselective NSAIDs (OR, 1.9; 95% CI, 1.4-3.7), or rofecoxib (OR, 2.4; 95% CI,
ers, we were unable to account for some potentially important factors such as smoking, alcohol consumption, and the use of nonprescription analgesics. In our study, case patients presented with a higher prevalence of GI comorbidity. Previous research also suggests that COX-2 inhibitors also typically present with greater GI comorbidity relative to control populations or nonselective NSAID users. The implications of these discrepancies in comorbidity profiles between groups could result in an overestimation of true risk. Second, the low absolute number of events in the study groups precluded reliable subgroup analyses such as comparisons among users of specific NSAIDs. Third, the generalizability of our findings to younger patients or settings with different drug policies over longer durations of follow-up is uncertain. Fourth, we were not able to examine international normalized ratios in any patients, making it difficult to determine whether patients with GI hemorrhage had supratherapeutic international normalized ratios. Furthermore, the incidence of GI hemorrhage in patients taking warfarin in our study was surprisingly low (0.3%) compared with a prediction model based on different risk factors (high, middle, and low) in which the proportion of bleeding events was 7%, 4%, and 1%, respectively, after 3 months of therapy. Our lower incidence of GI hemorrhage may be secondary to intermittent dosing of anti-inflammatory agents or other patient-level factors. Finally, we did not examine the interaction between COX-2 inhibitors and aspirin use.

Our findings suggest that the risk of upper GI hemorrhage is similarly heightened in warfarin users treated with either selective COX-2 inhibitors or nonselective NSAIDs. Given the observational nature of this study, our findings should be viewed as preliminary and require confirmation through well-designed clinical trials. Regardless, physicians and pharmacists who care for elderly patients taking warfarin should be aware of the potential risks of concomitant therapy with NSAIDs or COX-2 inhibitors, particularly because the latter are among the fastest-growing class of prescription medications and have rapidly gained acceptance in clinical practice.

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REFERENCES


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