The Relative Efficacies of Gastroprotective Strategies in Chronic Users of Nonsteroidal Anti-inflammatory Drugs

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http://dx.doi.org/10.1053/j.gastro.2008.01.010, How to Cite or Link Using DOI

NSAIDs, Risks, and Gastroprotective Strategies: Current Status and Future
Gastroenterology, Volume 134, Issue 4, April 2008, Pages 1240-1246
PDF (142 K)

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Background & Aims: There are numerous gastroprotective strategies recommended for reducing the risk of upper gastrointestinal (GI) complications in long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs). The relative efficacy of the different strategies alone or in combination is uncertain.

Methods: We used the Manitoba Population Health Research Data Repository to perform a population-based matched case-control analysis. All NSAID users (nonselective and cyclooxygenase [COX]-2-specific) users admitted to the hospital with a primary diagnosis for an upper gastrointestinal complication were matched to NSAID-using controls in the community. We used conditional logistic regression analysis to determine the relative efficacy of different gastroprotective strategies (proton pump inhibitors [PPIs], COX-2 inhibitors, and low-dose/high-dose misoprostol) either alone or in combination and to adjust for multiple pertinent covariates.

Results: A total of 1382 NSAID/COX-2 users with upper GI complications were matched to 33,957 age- and sex-matched controls. Cotherapy with PPIs or misoprostol or use of a COX-2 inhibitor all significantly reduced the risk of upper GI complications. COX-2 inhibitors were not statistically more likely to prevent upper GI complications than PPIs, although they were superior to low-dose misoprostol. The combination of COX-2 inhibitors with a PPI was associated with the greatest degree of upper GI complication risk reduction.

Conclusions: All of the commonly accepted gastroprotective strategies reduce the risk of upper GI complications in NSAID users, although the combination of COX-2 inhibitors with PPIs promotes the greatest risk reduction for NSAID-related upper GI complications. Celecoxib use specifically may be superior to the combination of nonselective NSAIDs with a PPI.

Abbreviations used in this paper

- CI, confidence interval;
- COX, cyclooxygenase;
- DDD, defined daily dose;
- GI, gastrointestinal;
- nsNSAID, nonselective nonsteroidal anti-inflammatory drug;
- OR, odds ratio;
- PPI, proton pump inhibitor
Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for relief of pain and inflammation associated with arthritis and musculoskeletal injury. Approximately 20% of people older than 65 years have been prescribed an NSAID, and many more have used NSAIDs purchased over the counter. While NSAIDs are well tolerated by most users, their use is associated with a significant risk of upper gastrointestinal (GI) complications, including GI bleeding, ulcer perforation, gastric outlet obstruction, and symptomatic peptic ulcer disease. Approximately 1%–2% of NSAID users will develop upper GI complications per year, a rate 3–5 times higher than in non-NSAID users. The risk of severe NSAID-related GI complications is particularly high in patients with well-established risk factors, and the case-fatality rate for patients admitted to the hospital for upper GI bleeding is approximately 5%.

Fortunately, there are strategies designed to decrease the risk of GI complications among NSAID users. Both coprescription of high-dose misoprostol as well as the use of cyclooxygenase (COX)-2 selective NSAIDs have been shown to reduce the risk of upper GI complications among long-term NSAID users. However, due to concerns about the increased risk of cardiovascular complications associated with COX-2 inhibitors and the poor tolerability of high-dose misoprostol, these specific gastroprotective strategies have fallen out of favor. Coprescription of either proton pump inhibitors (PPIs) or low-dose misoprostol has also been recommended as a gastroprotective strategy for subjects at increased risk for NSAID-induced upper GI complications. While there is evidence that concomitant therapy with either PPIs or low-dose misoprostol can reduce the incidence of asymptomatic ulcers and erosions, there are currently no randomized controlled trials showing that either of these strategies reduces the risk of upper GI complications in long-term NSAID users.

Therefore, we sought to use a large population-based health care utilization database to compare the relative efficacy of gastroprotective strategies in decreasing the risk of upper GI complications among long-term NSAID users.

Materials and Methods

Description of Data Sets

In Manitoba, the Manitoba Centre for Health Policy maintains a comprehensive health utilization data set called the Population Health Research Data Repository. This data set contains health care utilization data on all residents of Manitoba, provided by the provincial department of health. The Population Health Research Data Repository is composed of a number of distinct data sets containing information on patient demographics, all outpatient and hospital visits since April 1984 including a primary diagnosis and up to 16 secondary diagnoses, and the Drug Programs Information Network, which contains all prescription drugs dispensed outside of hospitals and personal care homes since April 1995. All pharmacies in Manitoba are required to have a direct link with the network, which allows real-time prescription information to be entered into the data set.
All data sets are linked using a deidentified personal health information number, giving researchers the ability to construct a longitudinal medical history for any person registered with Manitoba Health. The Population Health Research Data Repository is well validated and has been extensively utilized in previous clinical research. The Scientific and Ethical Advisory Board of the University of Manitoba’s Health Research Ethics Board and Manitoba Health’s Health Information and Privacy Committee approved the study.

Identification of Cases and Controls

Our patient cohort consisted of all Manitobans older than 18 years who had maintained continuous enrollment in the provincial health care plan between April 1, 1995, and March 31, 2006. The population of Manitoba is multiethnic; the majority of residents are of Northern European extraction, and approximately 15% claim either total or partial North Amerindian ancestry. We then identified all patients who had filled at least one prescription for any NSAID (both nonselective NSAIDs [nsNSAIDs] and COX-2–specific NSAIDs) during that period. Cases consisted of all subjects who were actively using an nsNSAID or COX-2 inhibitor who were admitted to the hospital with an admitting diagnosis consistent with an upper GI complication (bleeding, perforation, or symptomatic ulcer disease) between October 1, 1995, and March 31, 2004. Events that occurred between April 1, 1995, and September 30, 1995, were censored to ensure cases had at least 180 days of health care utilization data available before the index date. We included only subjects who had at least an overnight stay in the hospital to exclude patients admitted for an electively scheduled upper endoscopy or other investigation. Patients admitted for another indication who developed an upper GI complication while hospitalized for another illness were excluded. We also identified a subset of cases admitted specifically with complications of peptic ulcer disease. The administrative definitions for upper GI complications and peptic ulcer disease have been validated in other data sets and are shown in Appendix 1.

Each case was matched with as many age-matched (±3 years) and sex-matched controls as were available in the source population. We specifically excluded controls who were hospitalized for other indications on the day of the case’s event, such that all cases and controls were ambulatory in the community on the index date.
Determination of Medication Exposure for PPIs, NSAIDs, and Misoprostol

We considered a patient to be exposed to a medication in a particular class (eg, PPIs, misoprostol, H₂-receptor antagonists) from the time of the initial dispensation of a prescription to the following dispensation, so long as the calculated rate of medication use did not decrease to less than 0.7 standard doses per day. We considered a case or control to be exposed to a medication class if that patient was exposed on the 14th day before the event date. We used this 14-day cutoff to account for protopathic bias (ie, PPI or misoprostol was prescribed for early symptoms of a soon-to-be-diagnosed upper GI complication) and also to account for carryover effects associated with the medication that may persist for a time following the terminal dose. We defined a subject to be using high-dose misoprostol if he or she was using at least 600 μg of misoprostol per day, with subjects using less than this dose being defined as low-dose users. Subjects were also classified as high-intensity NSAID users if they were calculated to have used 1.00 or more defined daily doses (DDDs) on average in the 100 days before the event date. Patients were classified as high-intensity PPI users if the rate of PPI consumption equaled or exceeded 1.50 DDDs in the 100 days before the event date. Based on these definitions, all cases and controls were categorized as of the index date in the following manner: (1) nsNSAID users alone, (2) nsNSAID + PPI, (3) nsNSAID + low-dose misoprostol, (4) nsNSAID + high-dose misoprostol, (5) COX-2 inhibitor alone, (6) COX-2 inhibitor + PPI, and (7) nsNSAID + PPI + any dose misoprostol. Categories 2–5 were considered basic gastroprotective strategies, whereas categories 6 and 7 were considered combination gastroprotective strategies.

Assessment of Confounders and Covariates

Comorbid illness

To account for comorbid illnesses, we adjusted for the presence of previous cardiac disease, pulmonary disease, malignancy, renal disease, hepatic disease, autoimmune disease, previous solid organ or hematologic transplant, acute hospitalization within 6 months of the index date, admission for a GI complication before April 1, 1995, and the Johns Hopkins Aggregate Diagnostic Group score, a validated measure of overall comorbidity. A patient was considered to have disease in a specific organ system if he or she had at least 2 outpatient or inpatient health care contacts in the previous year coded for a diagnosis consistent with a disease from that organ system.

Use of other medications

We also tracked the use of other prescription medications believed to increase the risk of NSAID-related upper GI complications, including warfarin, systemic corticosteroids, clopidogrel, and selective serotonin reuptake inhibitors. Medication use was determined in methodology similar to what was used to determine PPI use. Unfortunately, the drug database is unable to track the use of
medications available without a prescription, such as aspirin. As such, we considered a prior history of cardiac disease to be a surrogate for aspirin use.

**Prior history of GI disease**

To adjust for the presence of preexisting GI disease that may be associated with adverse GI outcomes, we adjusted for the presence of any ambulatory care or inpatient visits consistent with an upper GI diagnosis as well as for the performance of an upper endoscopy in the 6 months before the index date.

**Statistics**

Univariate analyses comparing clinical characteristics of cases and controls were performed, using either the $\chi^2$ test of association or Student $t$ test where appropriate. Conditional multivariate logistic regression was then performed to identify independent variables that are associated with the outcomes of upper GI complications or peptic ulcer disease, with the relation between the predictor variables and the outcome expressed as odds ratios (ORs). All variables of interest were included in the regression, with no stepwise inclusion techniques being used. A Wald $\chi^2$ test was calculated to determine if there were significant differences in the magnitude of protection afforded by the different gastroprotective strategies.

**Results**

We identified 466,187 adults who had filled at least one NSAID prescription between April 1995 and March 2006. Within this cohort of individuals, we identified 1382 admitted with upper GI complications and 736 with peptic ulcer diseases who had hospital stays exceeding 1 day. The 1382 upper GI complication cases were matched to 33,957 age- and sex-matched controls, each of whom was also using an nsNSAID or COX-2 inhibitor within 14 days of his or her case’s event date.

The baseline characteristics of upper GI complication cases and controls are displayed in Table 1. Overall, cases were more likely to be using PPIs, COX-2 inhibitors, misoprostol, histamine-2 receptor antagonists, and medications that increase the risk of upper GI complications (warfarin, systemic corticosteroids, and clopidogrel). Cases were more likely to have severe underlying medical comorbidities, including cardiac disease, a potential surrogate for aspirin use. Cases were also more likely to have a history of a previous admission for GI disease and were much more likely to have seen a physician for a GI-related complaint in the previous 6 months.
Table 1. Baseline Characteristics of Cases and Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 1382)</th>
<th>Controls (n = 33,957)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication use ( %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nsNSAIIDs alone</td>
<td>45.1</td>
<td>36.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>nsNSAID + PPI</td>
<td>3.4</td>
<td>2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>COX-2 inhibitors alone</td>
<td>30.5</td>
<td>40.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>COX-2 inhibitors + PPI</td>
<td>6.4</td>
<td>6.9</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>nsNSAID + low-dose misoprostol</td>
<td>13.3</td>
<td>12.6</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>nsNSAID + high-dose misoprostol</td>
<td>0.1</td>
<td>0.1</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>nsNSAID + PPI + misoprostol</td>
<td>1.3</td>
<td>1.0</td>
<td>.042</td>
</tr>
<tr>
<td>H\textsubscript{2}-receptor antagonists</td>
<td>13.4</td>
<td>7.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Warfarin</td>
<td>9.0</td>
<td>3.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>4.0</td>
<td>2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>5.0</td>
<td>2.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>8.3</td>
<td>6.7</td>
<td>.011</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>34.8</td>
<td>16.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>10.9</td>
<td>6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>1.2</td>
<td>0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3.0</td>
<td>0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>12.6</td>
<td>9.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute hospitalization within 6 months</td>
<td>28.3</td>
<td>10.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous hospital admission for upper GI disease</td>
<td>7.7</td>
<td>2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Outpatient visit for upper GI diagnosis within 6 months</td>
<td>37.1</td>
<td>15.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Upper endoscopy within 6 months</td>
<td>5.6</td>
<td>1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Overall severe comorbidity (more than 7 unique ADGs in previous year)</td>
<td>24.1</td>
<td>14.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ADGs, aggregate diagnostic groups.
The adjusted ORs for each of the gastroprotective strategies in prevention of upper GI complications and peptic ulcer disease are displayed in Table 2. The COX-2i + PPI strategy was associated with the highest magnitude of risk reduction for all upper GI complications (OR, 0.36; 95% confidence interval [CI], 0.28–0.47), followed by COX-2 inhibitor alone (OR, 0.51, 95% CI, 0.43–0.60), nsNSAID + PPI + any dose misoprostol (OR, 0.58, 95% CI, 0.34–0.98), nsNSAID + PPI (OR, 0.67; 95% CI, 0.48–0.95), and nsNSAID + low-dose misoprostol (OR, 0.74, 95% CI, 0.61–0.89). The strategy of nsNSAID + high-dose misoprostol was associated with a 78% reduction in the odds of developing an upper GI complication, but the results were not statistically significant, possibly due to the low prevalence of high-intensity misoprostol use. Celecoxib use was associated with a significantly lower risk of upper GI complication than was rofecoxib (OR 0.39 vs OR 0.71; \( P < .001 \)).

Among subjects using the nsNSAID + PPI strategy, there was a trend toward a greater degree of risk reduction for patients who were using PPIs at a rate higher than 1.50 DDDs as compared with those using PPIs at a lower intensity (OR compared with nsNSAID users alone: 0.73 for <1.50 DDDs vs 0.37 for ≥1.50 DDDs), but the difference was not statistically significant (\( P = .29 \)). Furthermore, we did not detect a difference in relative effect of PPI cotherapy in patients using diclofenac, naproxen, or all other pooled nsNSAIDs.
Table 2. Conditional Logistic Regression for Predictors of Admission for Upper GI Complications and Upper GI Complications Due to Peptic Ulcer Disease

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR (95% CI)</th>
<th>Overall upper GI complications</th>
<th>Upper GI complications from peptic ulcer disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastroprotective strategies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nsNSAID users alone (reference category)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>High-intensity NSAID use &gt;1.00 standard doses/day</td>
<td>1.39 (1.20–1.62)(^a)</td>
<td>1.48 (1.21–1.81)</td>
<td></td>
</tr>
<tr>
<td>nsNSAID + PPI</td>
<td>0.67 (0.48–0.95)(^b)</td>
<td>0.50 (0.31–0.82)</td>
<td></td>
</tr>
<tr>
<td>&gt;1.50 standard doses PPI/day</td>
<td>0.37 (0.10–1.23)</td>
<td>0.35 (0.07–1.66)</td>
<td></td>
</tr>
<tr>
<td>&lt;1.50 standard doses PPI/day</td>
<td>0.71 (0.51–1.02)</td>
<td>0.53 (0.32–0.88)</td>
<td></td>
</tr>
<tr>
<td>COX-2 inhibitor alone</td>
<td>0.51 (0.43–0.60)(^a)</td>
<td>0.46 (0.37–0.57)</td>
<td></td>
</tr>
<tr>
<td>Celecoxib alone</td>
<td>0.39 (0.32–0.48)(^a)</td>
<td>0.34 (0.25–0.48)</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib alone</td>
<td>0.71 (0.59–0.86)(^a)</td>
<td>0.67 (0.52–0.87)</td>
<td></td>
</tr>
<tr>
<td>nsNSAID + low-dose misoprostol</td>
<td>0.74 (0.61–0.89)(^a)</td>
<td>0.61 (0.41–0.80)</td>
<td></td>
</tr>
<tr>
<td>nsNSAID + high-dose misoprostol</td>
<td>0.23 (0.03–1.80)</td>
<td>0.42 (0.05–3.85)</td>
<td></td>
</tr>
<tr>
<td>nsNSAID + PPI + any dose misoprostol</td>
<td>0.58 (0.34–0.98)(^a)</td>
<td>0.29 (0.11–0.72)</td>
<td></td>
</tr>
<tr>
<td>COX-2 + PPI</td>
<td>0.36 (0.28–0.47)(^a)</td>
<td>0.23 (0.15–0.34)</td>
<td></td>
</tr>
<tr>
<td>H2-receptor antagonists</td>
<td>1.19 (0.99–1.43)</td>
<td>1.34 (1.06–1.70)</td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.95 (1.55–2.45)(^a)</td>
<td>1.49 (1.07–2.08)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1.40 (1.02–1.91)(^b)</td>
<td>1.51 (0.98–2.33)</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>1.48 (1.08–1.96)(^b)</td>
<td>1.28 (0.84–1.97)</td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>1.14 (0.92–1.41)</td>
<td>0.97 (0.71–1.33)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1.85 (1.60–2.14)(^a)</td>
<td>1.88 (1.54–2.29)</td>
<td></td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>1.09 (0.89–1.33)</td>
<td>1.03 (0.78–1.35)</td>
<td></td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>6.16 (3.12–11.86)(^a)</td>
<td>8.48 (3.84–18.72)</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>2.48 (1.71–3.59)(^a)</td>
<td>2.98 (1.85–4.79)</td>
<td></td>
</tr>
<tr>
<td>Active malignancy</td>
<td>1.18 (0.98–1.41)</td>
<td>1.05 (0.82–1.35)</td>
<td></td>
</tr>
<tr>
<td>Acute hospitalization within 6 months</td>
<td>1.83 (1.58–2.11)(^a)</td>
<td>1.74 (1.42–2.13)</td>
<td></td>
</tr>
<tr>
<td>Previous upper GI–related hospital admission</td>
<td>2.70 (2.11–3.45)(^a)</td>
<td>2.91 (2.10–4.03)</td>
<td></td>
</tr>
<tr>
<td>Ambulatory care visit for upper GI diagnosis within 6 months</td>
<td>2.55 (2.24–2.90)(^a)</td>
<td>2.87 (2.41–3.42)</td>
<td></td>
</tr>
<tr>
<td>Upper endoscopy within 6 months</td>
<td>2.91 (2.19–3.86)</td>
<td>3.37 (2.32–4.88)</td>
<td></td>
</tr>
<tr>
<td>Overall severe comorbidity (more than 7 unique ADGs in previous year)</td>
<td>1.02 (0.81–1.29)</td>
<td>1.03 (0.76–1.41)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) \(P<.01\).

\(^b\) \(P<.05\).
When the analysis was restricted to patients specifically with complications of peptic ulcer disease, the COX-2 inhibitor + PPI strategy had the highest magnitude in risk reduction, followed by the combination strategy of nsNSAID + PPI + any dose misoprostol. All of the basic gastroprotective strategies (nsNSAID + PPI, COX-2 inhibitor alone, nsNSAID + low-dose misoprostol) were associated with similar relative risk reduction in admissions for complications of peptic ulcer disease.

When the gastroprotective strategies were compared among themselves, COX-2 inhibitor + PPI was superior to the use of any of the basic gastroprotective strategies in isolation, both for prevention of all upper GI complications and those specifically related to peptic ulcer disease. The COX-2 inhibitor alone strategy was statistically superior to the nsNSAID + low-dose misoprostol strategy ($P = .0006$); however, there was no statistical difference between the strategies of COX-2 inhibitor alone and nsNSAID + PPI ($P = .11$). However, when celecoxib users were analyzed separately, celecoxib use was associated with a reduced risk of upper GI complication versus the strategy of nsNSAID + PPI ($P = .002$). $P$ values and ORs, and 95% CIs from the comparisons between all gastroprotective strategies, are shown in Table 3 and Table 4.

Table 3. ORs and $P$ Values for Comparisons Between Gastroprotective Strategies for All Upper GI Complications

<table>
<thead>
<tr>
<th>Gastroprotective Strategy</th>
<th>OR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nsNSAID + low-dose misoprostol (0.74)</td>
<td>0.88 (0.52–1.49)</td>
<td>$P &gt; .20$</td>
</tr>
<tr>
<td>nsNSAID + PPI (0.67)</td>
<td>0.78 (0.46–1.34)</td>
<td>0.86 (0.47–1.57)</td>
</tr>
<tr>
<td>COX-2 inhibitor alone (0.51)</td>
<td>0.68 (0.56–0.85)</td>
<td>0.75 (0.53–1.06)</td>
</tr>
<tr>
<td>COX-2 inhibitor + PPI (0.36)</td>
<td>0.48 (0.36–0.65)</td>
<td>0.53 (0.36–0.79)</td>
</tr>
</tbody>
</table>

NOTE. ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.

a Differences are statistically significant.
Table 4. ORs and \( P \) Values for Comparisons Between Gastroprotective Strategies for Upper GI Complications Secondary to Peptic Ulcer Disease

<table>
<thead>
<tr>
<th>Strategy</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>nsNSAID + low-dose misoprostol</td>
<td>0.61 (0.48–1.38)</td>
<td>( P &gt; .20 )</td>
</tr>
<tr>
<td>nsNSAID + PPI (0.50)</td>
<td>0.81 (0.48–1.38)</td>
<td>( P &gt; .20 )</td>
</tr>
<tr>
<td>COX-2 inhibitor alone (0.46)</td>
<td>0.74 (0.55–1.00)</td>
<td>0.91 (0.55–1.50)</td>
</tr>
<tr>
<td>nsNSAID + PPI + low-dose misoprostol (0.29)</td>
<td>0.46 (0.18–1.21)</td>
<td>0.58 (0.21–1.60)</td>
</tr>
<tr>
<td>COX-2 inhibitor + PPI (0.23)</td>
<td>0.37 (0.23–0.57)</td>
<td>0.49 (0.25–0.82)</td>
</tr>
</tbody>
</table>

NOTE. ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.

\( ^a \) Differences are statistically significant.
Discussion

Based on our results, use of any of the commonly recommended basic gastroprotective strategies, including nsNSAID + PPI, nsNSAID + low-dose misoprostol, and COX-2 inhibitor alone, was associated with a significant reduction in the risk of developing an overall upper GI complication or upper GI complication secondary to peptic ulcer disease. Among the basic gastroprotective strategies, COX-2 inhibitor alone was numerically superior to nsNSAID + PPI, but the difference was not statistically significant. However, when COX-2 inhibitor users were separated into either celecoxib or rofecoxib users, we determined that celecoxib users were at lower risk for developing upper GI complications than were rofecoxib users, and the specific use of celecoxib was also superior to nsNSAID + PPI. Overall, the combination strategy of COX-2 inhibitor + PPI was the most effective form of gastroprotection, showing a statistically significant benefit over all other gastroprotective strategies.

In our analysis, we detected no statistical difference in the odds of developing an upper GI complication between patients using the strategies of COX-2 inhibitor alone and nsNSAID + PPI, which is in keeping with randomized controlled trials reporting an equivalent risk of recurrent upper GI bleeding among subjects with a recent history of upper GI bleeding receiving either the combination of a PPI with an nsNSAID or a COX-2 inhibitor. Interestingly, our analysis revealed a nonstatistically significant trend toward benefit in favor of COX-2 inhibitors over the combination of nsNSAIDs with a PPI, mirroring a nonstatistically significant trend toward a lower incidence of upper GI bleeding and development of ulcers and erosions among users of COX-2 inhibitors, specifically celecoxib, when compared with subjects using a PPI along with an nsNSAID in those same randomized controlled trials. In our analysis, we had a relatively low proportion of subjects using the NSAID + PPI strategy versus those using the COX-2 inhibitor alone strategy, and therefore it is possible that our failure to detect a statistically significant difference in the relative benefits of these 2 gastroprotective strategies may be related to a lack of statistical power, just as the lack of a statistically significant difference between these strategies in the previously reported clinical trials may be ascribed to a Type II error. Conversely, a recently published retrospective analysis of another administrative data set showed both statistical and numerical equivalence between these 2 strategies. Overall, the possibility of a significant additional benefit of COX-2 inhibitor use over the use of an nsNSAID with a PPI cannot be completely discarded and will require the performance of larger trials powered to detect a clinically significant difference in outcomes.

While our findings suggest there is no statistically significant difference between the relative efficacy of COX-2 inhibitors overall and the concomitant use of PPIs with nsNSAIDs in their ability to reduce the risk of NSAID-associated upper GI complications, we did show a statistically significant reduction in the odds of developing an upper GI complication in subjects who specifically used celecoxib versus subjects using an nsNSAID + PPI. There is evidence in the medical literature to support our assertion that celecoxib may be superior to other COX-2 inhibitors for preventing upper GI complications. Although the magnitude of risk reduction afforded by celecoxib and rofecoxib was
similar in the CLASS and VIGOR trials, the major randomized trials, [9] and [11] the high doses of celecoxib evaluated in the CLASS trial (400–800 mg daily) are not commonly used in clinical practice, whereas the dose of rofecoxib used in the VIGOR trial was more widely prescribed in the community. It is possible that the risk of upper GI complications is lower when celecoxib is taken at the lower doses (100 mg twice daily) recommended for relief of symptoms from osteoarthritis than the 400–800 mg doses used in the CLASS trial. Furthermore, other epidemiologic analyses have also shown lower risk of upper GI complications with celecoxib than is seen with rofecoxib. Current guidelines and position statements regarding the use of basic gastroprotective strategies have not differentiated between them on the basis of their relative efficacy, but only on their side effect profiles. Our findings suggest that in patients in whom COX-2 inhibitors are not contraindicated, prescribing celecoxib may be preferred over other basic gastroprotective strategies. However, because examining the COX-2 inhibitors individually was not a primary end point of our study, this conclusion should ideally be confirmed in other clinical trials or analyses of other data sets.

To our knowledge, this study is also the first to show that the concomitant use of low-dose misoprostol with nsNSAIDs reduces the risk of upper GI complications. There is strong evidence that high-dose misoprostol (>600 mg/d) can reduce the risk of upper GI complications in long-term NSAID users. Although lower doses of misoprostol have been shown to decrease the incidence of asymptomatic endoscopically visualized ulcers in NSAID users, [17] and [36] there are no clinical trial data showing a reduction in the risk of upper GI complications with low-dose misoprostol. [15] [36] and [37] Our discovery of a clinical benefit to the use of low-dose misoprostol is important for several reasons. Firstly, high-dose misoprostol is poorly tolerated, both because of the presence of side effects, which necessitates discontinuation or dose reduction in approximately one fourth of users, [10] and [17] and because its dosing 4 times daily likely interferes with adherence. Conversely, low-dose misoprostol is better tolerated than the high-dose regimen and is given twice daily. This is borne out in our analysis, which reveals that high-dose misoprostol use, although associated with a large magnitude risk reduction in upper GI complications, made up a very small proportion of all misoprostol use. Secondly, most misoprostol used in our study was in the form of Arthrotec (Pfizer Inc, New York, NY), a formulation containing both the nsNSAID diclofenac along with 200 μg of misoprostol, which is generally dosed as a twice-daily regimen. Third, due to concerns about their cardiovascular safety, there is a limited population in whom COX-2 inhibitors can be prescribed, which means that physicians will be considering alternate gastroprotective strategies. Because the use of Arthrotec involves ingesting one pill containing both the NSAID and its gastroprotective agent, and the use of concomitant PPIs currently requires providing 2 separate prescriptions, low-dose misoprostol use may once again come into vogue. Last, there are emerging concerns about the long-term safety of PPI use, with studies reporting relationships between PPI use and the development of community-acquired pneumonia, [38] and [39] Clostridium difficile–associated diarrhea, [40] and [41] and hip fracture, and it is possible that PPI use in populations at high risk for these adverse outcomes may be particularly deleterious. Therefore, there may exist clinical scenarios in which misoprostol may be the preferred gastroprotective strategy. Given our results, the addition of low-dose misoprostol to nsNSAID therapy may be a reasonable option for prevention of upper GI complications.
We also determined that the combination of a COX-2 inhibitor and a PPI was the optimal strategy for preventing upper GI complications in NSAID users. This mirrors the results of clinical studies showing that the addition of the combination of COX-2 inhibitors (specifically celecoxib) and the PPI esomeprazole was superior to using the COX-2 inhibitor celecoxib alone among patients with a recent history of upper GI bleeding, with no patients using both a COX-2 inhibitor and a PPI developing recurrent bleeding after a median follow-up of 13 months. Our study confirms that the risk of upper GI complications is low in all users of COX-2 inhibitors with a PPI. We also determined the combination of misoprostol, a PPI, and an nsNSAID was associated with a nonsignificant benefit over using an nsNSAID with either a PPI or misoprostol alone in prevention of upper GI complications. However, there were relatively few subjects using this combination, and thus this study was underpowered to detect a statistically significant difference. However, this combination may be useful in subjects at very high risk in whom use of a COX-2 inhibitor is contraindicated.

There are several important limitations to our study that deserve mention. Because we used an administrative claims database to determine both outcomes and exposure, we could not directly confirm whether included cases truly were admitted with an upper GI complication. However, our case identification algorithm is similar to those used in other database studies and has been extensively validated. Furthermore, although the Drug Programs Information Network has been validated to be accurate for tracking drug dispensation, we cannot be certain whether dispensed medications were ingested. Moreover, because the Drug Programs Information Network only tracks dispensations of prescription medication, we cannot determine whether included subjects were using over-the-counter NSAIDs or aspirin. While the combination of aspirin with an NSAID is associated with a higher risk of upper GI complications, there are no data to suggest that users of the combination of aspirin with an NSAID are more likely to be prescribed a PPI than users of an NSAID alone, thereby mitigating against the potential for confounding. We also adjusted for the presence of a history of underlying cardiac disease, which is a surrogate for aspirin use. Therefore, our inability to completely classify over-the-counter aspirin use does not likely have a significant effect on our findings. In addition, any observational study must account for channeling bias, the possibility that subjects at higher baseline risk for developing an upper GI complication will be more likely to be prescribed a gastroprotective strategy. We mitigated against channeling bias by accounting for underlying risk factors for upper GI complications, the overall existing burden of illness, preexisting GI disease, and socioeconomic status. We accept that our measures of comorbidity may be imperfect, but all our determinants designed to measure underlying upper GI complication risk were associated with the development of upper GI complications, suggesting that they are valid.

Ideally, the final word on the relative effectiveness of gastroprotective strategies will come from well-designed randomized clinical trials. However, because it is unlikely that these large trials will be performed, large observational studies will likely provide the majority of evidence in determining the proper role for the different gastroprotective strategies in the prevention of upper GI complications. In the interim, we believe that the use of celecoxib alone is the optimal basic gastroprotective strategy, although the combination strategy of a COX-2 inhibitor with a PPI provides the highest level
of gastroprotection. For patients in whom COX-2 inhibitors are contraindicated due to an increased risk of cardiac disease (or in whom the cost of both celecoxib and a PPI in combination is deemed prohibitive), gastroprotection, coprescription of an nsNSAID with either a PPI or low-dose misoprostol, while less effective, still is superior to using an nsNSAID alone. In light of these new data, further study is required to confirm the relative efficacy, specifically of celecoxib, and to determine the cost-effectiveness of the various gastroprotective strategies in clinical practice.

Acknowledgements

The authors thank the Canadian Institutes of Health Research and the Health Sciences Centre Foundation (Winnipeg) for their financial support of this project.

Appendix 1. Admission Definitions

I Upper Gastrointestinal Complication

A Most Responsible Admitting Diagnosis with any of the following ICD-9 codes

a 530.1x: Esophagitis
b 530.2x: Esophageal Ulcer
c 530.7x: Mallory-Weiss Syndrome
d 578.0: Hematemesis
e 531.xx: Gastric Ulcer
f 532.xx: Duodenal Ulcer
g 533.xx: Peptic Ulcer
h 534.xx: Gastrojejunal Ulcer
i 535.01: Acute Gastritis With Hemorrhage
j 535.11: Atrophic Gastritis With Hemorrhage
k 535.31: Alcoholic Gastritis With Hemorrhage
l 535.51: Unspecified Gastritis With Hemorrhage
m 535.61: Duodenitis with Hemorrhage
or

B Most Responsible Admitting Diagnosis for Gastritis/Duodenitis (ICD-9 code 535.xx) and any of the following upper endoscopy procedure codes

a 42.23: Esophagoscopy
b 42.24: Esophagoscopy With Biopsy
c 42.41: Endoscopic Excision or Destruction of Lesion or Tissue of Stomach
d 44.13: Gastroscopy
e 44.14: Gastroscopy With Biopsy
f 44.43: Endoscopic Control of Gastric or Duodenal Bleeding
g 45.13: Other Endoscopy of Small Intestine
h 45.14: Other Endoscopy of Small Intestine With Biopsy
i 45.16: Esophagogastroduodenoscopy With Closed Biopsy
or any of the following physician tariff codes:

Manitoba Tariff 3185: Esophagogastroduodenoscopy

or

C Most Responsible Admitting Diagnosis for Melena (ICD-9 code 578.1) or Gastrointestinal Bleeding Not Otherwise Specified (ICD-9 code 578.9)

and

A Secondary Admitting Diagnosis for any diagnosis listed under “A” or both

1 An upper endoscopy procedure code listed in “B” and

2 The absence of a procedure code or tariff consistent with colonoscopy

II Peptic Ulcer Disease

A Most Responsible Admitting Diagnosis of

a 531.xx: Gastric Ulcer

b 532.xx: Duodenal Ulcer

c 533.xx: Peptic Ulcer

d 534.xx: Gastrojejunal Ulcer

or

B Most Responsible Admitting Diagnosis for Hematemesis (ICD-9 code 578.0), Melena (ICD-9 code 578.1), or Gastrointestinal Bleeding Not Otherwise Specified (ICD-9 code 578.9)

and

A Secondary Admitting Diagnosis for any diagnosis listed under “A”

References

1 N. Kasman, E. Badley

Chapter 5: Arthritis-related prescription medications


2 A. Lanas, P. Serrano, E. Bajador et al.

Evidence of aspirin use in both upper and lower gastrointestinal perforation

Gastroenterology, 112 (1997), pp. 683–689

Article | PDF (331 K) | View Record in Scopus | Cited By in Scopus (148)

3 L.A. Garcia Rodriguez, H. Jick

Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs


Article | PDF (527 K) | View Record in Scopus | Cited By in Scopus (733)

4 M.J. Langman, J. Weil, P. Wainwright et al.

Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs


Article | PDF (553 K) | View Record in Scopus | Cited By in Scopus (634)

5 S.E. Gabriel, L. Jaakkimainen, C. Bombardier

Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs A meta-analysis


View Record in Scopus | Cited By in Scopus (859)

6 M.R. Griffin, J.M. Piper, J.R. Daugherty et al.

Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons


View Record in Scopus | Cited By in Scopus (487)

7 L.E. Targownik, A. Nabalamba

8 T.J. Schnitzer, G.R. Burmester, E. Mysler et al.
Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial

9 C. Bombardier, L. Laine, A. Reicin et al.
Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis
VIGOR Study Group

10 F.E. Silverstein, D.Y. Graham, J.R. Senior et al.
Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs
A randomized, double-blind, placebo-controlled trial

11 F.E. Silverstein, G. Faich, J.L. Goldstein et al.
Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial
Celecoxib Long-term Arthritis Safety Study
JAMA, 284 (2000), pp. 1247–1255

12 R.S. Bresalier, R.S. Sandler, H. Quan et al.
Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial

13 S.D. Solomon, J.J. McMurray, M.A. Pfeffer et al.
Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention
Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery 

15. T.S. Bocanegra, A.L. Weaver, E.A. Tindall et al. 
Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial
Arthrotec Osteoarthritis Study Group

Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study
NSAID-Associated Gastric Ulcer Study Group

Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs
Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group

18. N.D. Yeomans, Z. Tulassay, L. Juhasz et al. 
A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs
Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group

19. N.P. Roos 
Establishing a population data-based policy unit 
Med Care, 37 (1999), pp. JS15–JS26
20 N.P. Roos, E. Shapiro
Revisiting the Manitoba Centre for Health Policy and Evaluation and its population-based health information system
Med Care, 37 (1999), pp. JS10–JS14

21 J.R. Robinson, T.K. Young, L.L. Roos et al.
Estimating the burden of disease: Comparing administrative data and self-reports
Med Care, 35 (1997), pp. 932–947

22 L. Huzel, L.L. Roos, N.R. Anthonisen et al.
Diagnosing asthma: the fit between survey and administrative database

23 C. Metge, C. Black, S. Peterson et al.
The population’s use of pharmaceuticals
Med Care, 37 (1999), pp. JS42–JS59

24 C.J. Metge, J.F. Blanchard, S. Peterson et al.
Use of pharmaceuticals by inflammatory bowel disease patients: a population-based study
Am J Gastroenterol, 96 (2001), pp. 3348–3355

25 L.E. Targownik, C. Metge, L. Roos et al.
The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use
Am J Gastroenterol, 102 (2007), pp. 942–950

26 G.S. Cooper, A. Chak, L.E. Lloyd et al.
The accuracy of diagnosis and procedural codes for patients with upper GI hemorrhage
27D.S. Raiford, S. Perez Gutthann, L.A. Garcia Rodriguez
Positive predictive value of ICD-9 codes in the identification of cases of complicated peptic ulcer disease in the Saskatchewan hospital automated database
Epidemiology, 7 (1996), pp. 101–104

28E. Rahme, M. Bardou, K. Dasgupta et al.
Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study

29B. Starfield, J. Weiner, L. Mumford et al.
Ambulatory care groups: a categorization of diagnoses for research and management
Health Serv Res, 26 (1991), pp. 53–74

Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications

Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial
Gastroenterology, 127 (2004), pp. 1038–1043

Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis
W.A. Ray, C.P. Chung, C.M. Stein et al.  
Risk of peptic ulcer hospitalizations in users of NSAIDs with gastroprotective cotherapy versus coxibs  
Gastroenterology, 133 (2007), pp. 790–798

C.M. Wilcox, J. Allison, K. Benzuly et al.  
Consensus development conference on the use of nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin  

H. Tannenbaum, C. Bombardier, P. Davis et al.  
An evidence-based approach to prescribing nonsteroidal antiinflammatory drugsThird Canadian Consensus Conference  

J.B. Raskin, R.H. White, R. Jaszewski et al.  
Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: a prospective, double-blind, multicenter study  

N.M. Agrawal, J. Caldwell, A.J. Kivitz et al.  
Comparison of the upper gastrointestinal safety of Arthrotec 75 and nabumetone in osteoarthritis patients at high risk for developing nonsteroidal anti-inflammatory drug-induced gastrointestinal ulcers  
Clin Ther, 21 (1999), pp. 659–674
Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study

Arch Intern Med, 167 (2007), pp. 950–955

View Record in Scopus

39 R.J. Laheij, M.C. Sturkenboom, R.J. Hassing et al.

Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs


View Record in Scopus

40 S. Dial, J.A. Delaney, A.N. Barkun et al.

Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease

JAMA, 294 (2005), pp. 2989–2995

View Record in Scopus

41 S. Dial, J.A. Delaney, V. Schneider et al.

Proton pump inhibitor use and risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy

CMAJ, 175 (2006), pp. 745–748

View Record in Scopus

42 Y.X. Yang, J.D. Lewis, S. Epstein et al.

Long-term proton pump inhibitor therapy and risk of hip fracture

JAMA, 296 (2006), pp. 2947–2953

View Record in Scopus

43 F.K. Chan, V.W. Wong, B.Y. Suen et al.

Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial


Article | PDF (127 K) | View Record in Scopus

44 Supported by grants from the Manitoba Medical Services Foundation, the Health Sciences Centre Foundation (Winnipeg), and the Canadian Institutes of Health Sciences Regional Partnership
Program. This study was not funded in any part by private industry. L.T. is the recipient of the University of Manitoba Rudy Falk Clinical Scholar Award and has previously received grant support from Astra-Zeneca Canada, Janssen-Ortho Canada, and Altana Canada.

The results and conclusions are those of the authors, and no official endorsement by Manitoba Health or the Manitoba Centre for Health Policy is intended or should be inferred.

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1 L.T. has served on advisory panels for Janssen-Ortho Canada and Novartis Canada. The other authors have no financial conflicts of interest to disclose.