Gastrointestinal Bleeding Rates Among Managed Care Patients Newly Started on COX-2 Inhibitors or Nonselective NSAIDs

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ABSTRACT

OBJECTIVE: While cyclooxygenase-2 (COX-2) inhibitors were introduced to the U.S. market with the promise of less gastrointestinal (GI) toxicity than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), additional research is needed to examine this outcome in the naturalistic setting. The objective of this study was to examine whether use of COX-2 inhibitors is associated with reduced risk of GI bleed in a managed care population.

METHODS: Adult patients in a multistate managed care organization that were initiated on a nonselective NSAID between January 1999 and August 2002 were identified and matched using propensity scoring with patients in the same managed care organization that were initiated on a COX-2 inhibitor. Matching variables included age, gender, geographical state, comorbidity index, corticosteroid use, warfarin use, arthritis indication, and history of recent GI bleed. Patients were followed until they switched or discontinued their NSAID or COX-2 inhibitor, disenrolled from the health plan, developed a GI bleed, or reached the end of the 1-year follow-up period. A GI bleed was defined as an inpatient hospitalization for GI bleed or at least 2 medical claims with a primary diagnosis for GI bleed. The relative risk (RR) of GI bleed was calculated using proportional hazards regression.

RESULTS: Overall, 35,007 pairs of COX-2 inhibitor and nonselective NSAID users were evaluated. Mean age was 63 years, and 65% were female. There were 375 cases of GI bleed among 19,201 follow-up years for COX-2 users (19.5 cases per 1,000 person-years) versus 228 cases of GI bleed among 12,680 follow-up years for NSAID users (18.0 cases per 1,000 person-years). The risk of GI bleed was not significantly different for COX-2 users compared with nonselective NSAID users (RR 1.07; 95% confidence interval [CI], 0.90-1.26). Even among high-risk patients, there was no reduction in the risk of a GI bleed among users of COX-2 inhibitors (RR 0.995; 95% CI, 0.84-1.19).

CONCLUSION: Overall, within this managed care population, COX-2 inhibitor users did not have a reduced risk of a GI bleed compared with patients with similar baseline characteristics using nonselective NSAIDs.

KEYWORDS: Cyclooxygenase, Nonsteroidal anti-inflammatory drugs, Gastrointestinal bleed, Drug therapy

J Manag Care Pharm. 2005;11(7):550-58

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Recent reports of adverse cardiovascular outcomes with two of the cyclooxygenase-2 (COX-2) inhibitors have placed the risk-benefit profile of these COX-2 inhibitors under public scrutiny; both of the COX-2 inhibitors have subsequently been withdrawn from the U.S. market).[1-3] As a result, clinicians have been encouraged to weigh the potential benefits and risks of the nonsteroidal anti-inflammatory (NSAID) medications prior to prescribing them.[4] Managed care has been particularly interested in examining the risks, benefits, and cost-effectiveness of the COX-2 inhibitors.[5-8] The present study was designed to evaluate whether the use of COX-2 inhibitor medications was beneficial in preventing gastrointestinal (GI) bleeds compared with the use of nonselective NSAIDs in the naturalistic managed care setting.

The early reported results of controlled clinical studies suggested that the COX-2 inhibitors may have less GI toxicity than nonselective NSAIDs,[9-14] but the U.S. Food and Drug Administration (FDA) permitted this claim only for rofecoxib, which was later withdrawn from the U.S. market, on September 30, 2004, due to adverse cardiovascular events.[1,15]

In actual clinical practice, patients' medication use is not monitored as closely as in clinical trials. As a result, patients may not take their COX-2 inhibitor medication under the same conditions as those studied (e.g., they may take higher doses than those prescribed or they may use COX-2 inhibitors concomitantly with gastrotoxic substances such as alcohol), which may lead to different outcomes than those observed in clinical trials. Furthermore, the population prescribed COX-2 inhibitors in clinical practice may have more risk factors for a GI bleed than the population selected to test the COX-2 inhibitors in clinical trials.

The objective of this analysis was to examine whether a managed care population of patients who used COX-2 inhibitors in a naturalistic setting actually did have a reduced occurrence of GI bleed compared with a population of patients with similar baseline characteristics who received nonselective NSAIDs.

■ Methods

This was a retrospective analysis of electronic pharmacy and medical administrative claims from a large managed care organization and Prescription Solutions, a pharmacy benefits and medical management company. Longitudinal claims data were used from health plans (private as well as Medicare+Choice [now Medicare Advantage]) within California, Oklahoma, Oregon, Texas, and Washington, which consist of approximately 2.7 million

lives. This database has been used in previous research studies.[16-20]

An estimated two thirds of members within this managed care population were subject to prior authorization for COX-2 drugs that required patients to meet certain clinical characteristics prior to receiving authorization for coverage of a COX-2 inhibitor. Prior authorization approval for a COX-2 inhibitor was more likely to be given to patients with older age, a diagnosis of rheumatoid arthritis or osteoarthritis, history of GI bleed, and/or concomitant use of oral corticosteroids or warfarin.

Patient Identification and Matching

Adult patients (aged 18 years or older) initiated on a COX-2 inhibitor (generic product identifier [GPI] code 661005xx, which included rofecoxib, celecoxib, and valdecoxib) or a nonselective NSAID (GPI code 661000xx, which consisted of all prescription NSAIDs other than those classified as COX-2 inhibitors) during the 44-month period from January 1, 1999, through August 31, 2002 (identification period), were identified. The index date was defined as the date of each patient's first prescription fill of a COX-2 inhibitor or nonselective NSAID during the identification period. Patients were excluded from the analysis if they had a pharmacy claim for a COX-2 inhibitor or a nonselective NSAID during the 6-month period prior to their index date (i.e., the preperiod) or if they were not continuously enrolled in the health plan during the preperiod and at least 3 months after the index date. The first (earliest) patient that could have been identified would have had an index date on January 1, 1999, and a preperiod starting July 1, 1998. Hence, some patients' preperiods may have started prior to the FDA approval of celecoxib. Celecoxib, the first COX-2 inhibitor to be approved, was approved on December 31, 1998.[21]

From these identified patients, the final study cohort was obtained by matching patients who received a nonselective NSAID on the index date with those who received a COX-2 inhibitor on the index date on a 1:1 basis using the propensity score method.[22] A propensity score, which represents the likelihood of receiving a COX-2 inhibitor rather than a nonselective NSAID, was determined for each patient. Patients were matched based on their propensity score.

The independent variables that were used to calculate the propensity score included demographics (age at index date, gender, geographical state of the health plan), Charlson Comorbidity Index[23] (calculated during the preperiod using a method adapted for electronic claims databases),[24] and the following GI bleed risk factors (measured during the preperiod): a prescription fill of a corticosteroid (GPI codes 2210xx, 2220xx, 2200xx), a prescription fill of warfarin (GPI code 83200030), a medical claim representing a recent GI bleed (Table 1), history of a GI bleed-related inpatient hospitalization (i.e., an inpatient hospitalization with at least a 1-day length of stay and a diagnosis code representing a GI bleed, Table 1), and arthritis indication (osteoarthritis [*International Classification of Diseases, 9th Revision,*

TABLE 1	Diagnosis Codes Representing Gastrointestinal Bleed
ICD-9-CM Code	Description
530.2	Ulcer of esophagus
531.xx	Gastric ulcer
532.xx	Duodenal ulcer
533.xx	Peptic ulcer site unspecified
534.xx	Gastrojejunal ulcer
578.xx	Gastrointestinal hemorrhage

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.
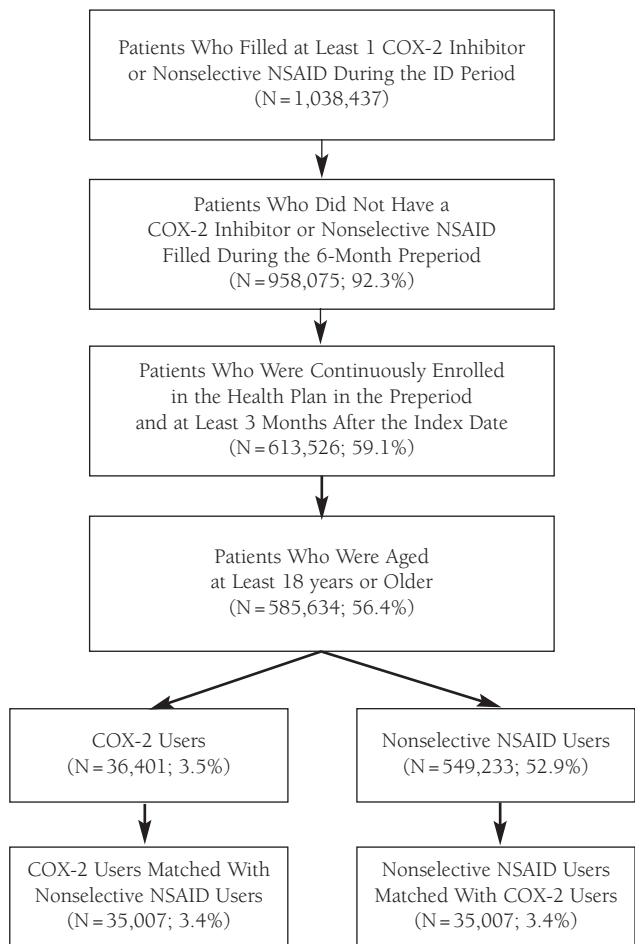
Clincial Modification (ICD-9-CM) code 715.xx], rheumatoid arthritis [ICD-9-CM code 714.xx], or neither). Patients diagnosed with both osteoarthritis and rheumatoid arthritis were classified into the rheumatoid arthritis group. If more than 1 patient who received a nonselective NSAID was identified as a match, 1 patient was selected at random to be included in the final study cohort. Patients who could not be matched were excluded from the analysis.

Patients in the matched COX-2 inhibitor and nonselective NSAID cohorts were further stratified according to their GI risk. Patients were considered high-risk if they met any of the following criteria: (1) age greater than 65 years; (2) GI-bleed-related inpatient hospitalization during the preperiod; (3) pharmacy claim for warfarin (GPI code 83200030) during the preperiod; or (4) pharmacy claim for a corticosteroid (GPI codes 2210xx, 2220xx, 2200xx) during the preperiod. All other patients were classified as low-risk.

Outcome Measures

The primary outcome of interest was the risk of developing a GI bleed over the follow-up period. Patients were followed until the first occurrence of one of the following events: (1) patient discontinued (as defined below) the index COX-2 inhibitor or nonselective NSAID medication; (2) crossover of medication of interest (patient filled a prescription for a study medication in a class [COX-2 inhibitor or nonselective NSAID] other than their index class of medication); (3) patient disenrolled from the health plan; (4) patient had a GI-bleed-related inpatient hospitalization; (5) patient had 2 medical claims with a primary (first-listed) diagnosis for Gl bleed (Table 1) during the follow-up period (where the event date was defined as the date of the first of the 2 claims); or (6) the end of the 1-year follow-up period. A discontinuation was defined as a gap of at least 60 days between the run-out date of the last index COX-2 inhibitor or nonselective NSAID medication fill (fill date plus the days of supply of that last prescription) and the end of the follow-up period. Patients were considered to have a GI bleed event if they experienced a GI bleed-related inpatient hospitalization (event 4 above) or had 2 medical claims with a primary diagnosis for a GI bleed (event 5 above) within the follow-up time frame.

FIGURE 1 Study Population Identification

Patients Who Filled at Least 1 COX-2 Inhibitor
or Nonselective NSAID During the ID Period
(N = 1,038,437)

↓

Patients Who Did Not Have a
COX-2 Inhibitor or Nonselective NSAID
Filled During the 6-Month Preperiod
(N = 958,075; 92.3%)

↓

Patients Who Were Continuously Enrolled
in the Health Plan in the Preperiod
and at Least 3 Months After the Index Date
(N = 613,526; 59.1%)

↓

Patients Who Were Aged
at Least 18 years or Older
(N = 585,634; 56.4%)

↓

COX-2 Users (N = 36,401; 3.5%)	Nonselective NSAID Users (N = 549,233; 52.9%)
↓	↓
COX-2 Users Matched With Nonselective NSAID Users (N = 35,007; 3.4%)	Nonselective NSAID Users Matched With COX-2 Users (N = 35,007; 3.4%)

COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

To account for the different lengths of follow-up, the number of GI bleed cases per 1,000 person years was calculated by dividing the number of patients who experienced the GI bleed event during the follow-up period by the sum of each patient's observed follow-up time (in years) and then multiplying by 1,000.

Statistical Analysis

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC). Chi-square tests and *t* tests were used to compare baseline demographics and clinical characteristics between the COX-2 inhibitor and nonselective NSAID cohorts. Propensity score calculations were conducted using logistic regression. Two-way interactions between independent variables were tested and only significant interactions ($P < 0.05$) were included in the final propensity model. The propensity score for each patient was rounded to 0.0001 for matching. Proportional

hazards regression was used to determine relative risk of a GI bleed event for the 2 cohorts, to study the relationship between the event and specific risk factors, and to adjust for baseline differences between the cohorts. Risk factors included in the model were age, gender, state of health plan, preperiod Charlson Comorbidity Index, preperiod corticosteroid use, preperiod warfarin use, preperiod diagnosis of GI bleed in any diagnostic field, and preperiod rheumatoid or osteoarthritis indication. Separate models were created for the total study population, the low-risk population, and the high-risk population. Only the main effects were included in the models (interaction terms were not tested for inclusion).

To adjust for baseline differences in the use of gastroprotective agents between the cohorts, additional proportional hazards regression models were performed after adding preperiod use of a gastroprotective agent as a variable. To assess the proportional hazards assumption, a plot of the scaled Schoenfeld residuals by transformed time for each risk factor was investigated and a test of zero slope of the plot was conducted.[25-27] Nonzero slope would indicate a violation of the proportional hazards assumption. If nonproportional hazards were found for some risk factors, then stratified proportional hazards regressions were conducted to evaluate whether the GI bleed event outcome was changed by this stratification. All statistical tests were 2-sided with an alpha of 0.05.

■ **Results**

There were 1,038,437 patients who filled at least 1 COX-2 inhibitor or nonselective NSAID during the identification period (Figure 1). Among them, 80,362 (7.7%) were excluded because they had a pharmacy claim for a COX-2 inhibitor or nonselective NSAID during the preperiod, and 344,549 were excluded because they were not continuously enrolled in the preperiod and at least 3 months after the index date. An additional 27,892 patients were excluded because they were younger than 18 years.

Overall, 585,634 eligible patients were identified; 36,401 (6.2%) used COX-2 inhibitors and 549,233 (93.8%) used nonselective NSAIDs. A total of 70,014 patients (35,007 pairs of COX-2 inhibitor users and nonselective NSAID users) were matched according to propensity score and included in the final study cohort.

Demographics and clinical characteristics were similar for COX-2 inhibitor and nonselective NSAID cohorts (Table 2), with the exception of a lower percentage of COX-2 inhibitor users participating in a Medicare + Choice health plan (53.1% versus 55.7%, $P < 0.001$); health plan type was not one of the variables included in the propensity score match. When the populations were stratified according to low and high GI bleed risk, there were also statistical differences in the mean age for the COX-2 inhibitor and nonselective NSAID cohorts, which were apparently due to the large sample size since the mean

TABLE 2 Baseline Demographics and Clinical Characteristics of Study Population*

	Total Population		Low-Risk Population		High-Risk Population†	
	COX-2 Inhibitor (N = 35,007)	Nonselective NSAID (N = 35,007)	COX-2 Inhibitor (N = 14,897)	Nonselective NSAID (N = 14,650)	COX-2 Inhibitor (N = 20,110)	Nonselective NSAID (N = 20,357)
Age, mean (SD)	63.4 (16.3)	63.3 (16.3)	48.9 (10.5)‖	48.6 (10.6)‖	74.2 (10.3)‖	73.9 (10.5)‖
Female gender	22,909 (65.4)	22,906 (65.4)	9,219 (61.9)	9,142 (62.4)	13,690 (68.1)	13,764 (67.6)
State of health plan						
California	24,090 (68.8)	23,936 (68.4)	10,726 (72.0)	10,506 (71.7)	13,364 (66.5)	13,430 (66.0)
Oklahoma	1,771 (5.1)	1,756 (5.0)	951 (6.4)	902 (6.2)	820 (4.1)	854 (4.2)
Oregon	1,555 (4.4)	1,560 (4.5)	724 (4.9)	729 (5.0)	831 (4.1)	831 (4.1)
Texas	3,843 (11.0)	3,961 (11.3)	1,373 (9.2)	1,361 (9.3)	2,470 (12.3)	2,600 (12.8)
Washington	3,748 (10.7)	3,794 (10.8)	1,123 (7.5)	1,152 (7.9)	2,625 (13.1)	2,642 (13.0)
Medicare + Choice health plan (%)‡	18,574 (53.1)¶	19,488 (55.7)¶	987 (6.6)¶	1,139 (7.8)¶	17,587 (87.5)¶	18,349 (90.1)¶
Charlson Comorbidity Index, mean (SD)	0.29 (0.95)	0.30 (0.98)	0.15 (0.69)	0.15 (0.71)	0.39 (1.09)	0.40 (1.12)
Arthritis indication						
Rheumatoid arthritis§	1,040 (3.0)	1,015 (2.9)	276 (1.9)	283 (1.9)	764 (3.8)	732 (3.6)
Osteoarthritis	5,788 (16.5)	5,802 (16.6)	1,224 (8.2)	1,189 (8.1)	4,564 (22.7)	4,613 (22.7)
None	28,179 (80.5)	28,190 (80.5)	13,397 (89.9)	13,178 (90.0)	14,782 (73.5)	15,012 (73.7)
Warfarin use	2,264 (6.5)	2,262 (6.5)	0	0	2,264 (11.3)	2,262 (11.1)
Corticosteroid use	3,385 (9.7)	3,406 (9.7)	0	0	3,385 (16.8)	3,406 (16.7)
Medical claim for GI bleed (any field)	843 (2.4)	808 (2.3)	252 (1.7)	223 (1.5)	591 (2.9)	585 (2.9)
Inpatient hospitalization for GI bleed	132 (0.4)	119 (0.3)	0	0	132 (0.7)	119 (0.6)

* Values are number (%) unless specified otherwise.
† High-risk was defined as a patient with (a) age older than 65 years, or (b) recent history use of either warfarin or corticosteroid, or (c) a recent hospitalization for a GI bleed.
‡ Variable was not used in the propensity score match.
§ Includes patients with medical claims for both osteoarthritis and rheumatoid arthritis.
‖ P = 0.004 for the low-risk population and P = 0.02 for the high-risk population for the comparison of the COX-2 inhibitor cohort and the nonselective NSAID cohort.
¶ P < 0.001 for all 3 populations (total, low-risk, and high-risk) for the comparison of the COX-2 inhibitor cohort and the nonselective NSAID cohort.
COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

(± standard deviation) age was similar for the 2 cohorts (48.9 ± 10.5 years versus 48.6 ± 10.6 years, respectively, for low-risk users, P = 0.004; 74.2 ± 10.3 years versus 73.9 ± 10.5 years, respectively, for high-risk users, P = 0.02). Although statistically significant, the small difference in age between the groups probably is not clinically meaningful. During the preperiod, 17.5% of COX-2 inhibitor users and 7.8% of nonselective NSAID users filled at least 1 prescription for a GI protective agent (i.e., a proton pump inhibitor or misoprostol, GPI codes 49250030xx, 6610990220, 4927xx, 6610990242).

Subjects in the nonselective NSAID cohort had a shorter follow-up time (average 4.3 months per patient or 12,680 person-years, Table 3) than subjects in the COX-2 inhibitor cohort (average 6.6 months per patient or 19,201 person-years).

A GI bleed event (defined as a GI-bleed-related inpatient hospitalization or at least 2 medical claims with a primary diagnosis for GI bleed) was noted in 19.5 patients per 1,000 person years in the COX-2 inhibitor cohort and 18.0 patients per 1,000 person years in the nonselective NSAID cohort (Table 3). The time to GI bleed event (median and mean) was shorter for the nonselective NSAID cohort than for the COX-2 inhibitor cohort.

The proportions of patients in each cohort whose follow-up period ended due to reasons other than a GI bleed event are described below. Compared with COX-2 inhibitor users, a greater percentage of nonselective NSAID users discontinued their index medication (82.2% versus 63.6%), while a smaller percentage of nonselective NSAID users had a crossover of medication of interest (1.2% versus 4.6%). Nonselective NSAID users were also less likely than COX-2 inhibitor users to disenroll from the health plan (15.8% versus 30.1%) but were less likely to reach the end of the 1-year follow-up period than COX-2 inhibitor users (0.2% versus 0.6%).

Patients who had a GI bleed event had a mean age of 75.1 ± 11.3 years and 61% were female. The mean Charlson Comorbidity Index was 0.84 ± 1.57. Among these patients, 15.3% used warfarin and 13.1% used corticosteroids during the preperiod. During the preperiod, 16.1% of these patients had a medical claim for a GI bleed (any field), and 3.6% had an inpatient hospitalization for a GI bleed. At the end of follow-up, use of a GI protective agent was observed in 21.1% of COX-2 inhibitor and 8.8% of nonselective NSAID users who had a GI bleed event compared with 8.1% of COX-2 inhibitor and 4.0%

TABLE 3 GI Bleed Events, Number of Cases per 1,000 Person Years

		Total Population		Low-Risk Population		High-Risk Population*	
		COX-2 Inhibitor (N = 35,007)	Nonselective NSAID (N = 35,007)	COX-2 Inhibitor (N = 14,897)	Nonselective NSAID (N = 14,650)	COX-2 Inhibitor (N = 20,110)	Nonselective NSAID (N = 20,357)
Sum of patients' follow-up years		19,201	12,680	6,605	5,003	12,596	7,677
Inpatient hospitalization or primary diagnosis for GI bleed on 2 medical claims	Number of cases	375	228	51	19	324	209
	Number of cases per 1,000 person-years	19.5	18.0	7.7	3.8	25.7	27.2
	Median time to event (days)†	84.0	61.5	102.0	78.0	77.0	61.0
	Mean time to event (days)†	111.5	100.9	117.3	110.6	110.6	100.0

* High-risk was defined as a patient with (a) age older than 65 years, or (b) recent history use of either warfarin or corticosteroid, or (c) a recent hospitalization for a GI bleed.
† Median and mean time to event were measured among those patients who had a GI bleed event during the follow-up period.
COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

of nonselective NSAID users who did not have a GI bleed event.

Proportional hazards regression was conducted to determine the relative risk of a GI bleed event for the 2 cohorts (accounting for different patient follow-up times and adjusting for baseline characteristics) and to study the relationship between the event and specific risk factors (Table 4). Among the total study population and the high-risk population, patients who received a COX-2 inhibitor did not have a lower relative risk of having a GI bleed event (defined as an inpatient hospitalization for GI bleed or at least 2 medical claims with a primary diagnosis for GI bleed) compared with patients who received a nonselective NSAID. Other factors that were significant predictors of a GI bleed event were older age, male gender, state of health plan (California versus Texas), higher Charlson Comorbidity Index, use of warfarin, and a history of GI bleed. For low-risk patients, those who received a COX-2 inhibitor had a higher relative risk of a GI bleed event compared with patients who received nonselective NSAIDs. Male gender, higher Charlson Comorbidity Index, history of GI bleed, and diagnosis of osteoarthritis were found to be additional risk factors, but age and state of health plan were not.

Within the total study population and the high-risk population, the test of the proportional hazards assumption (using the plot of the scaled Shoenfeld residuals by transformed time for each risk factor) revealed significant evidence of nonproportional hazards for the risk factor of a preperiod history of GI bleed. Stratification by preperiod history of GI bleed did not significantly alter the hazard ratio for the comparison between COX-2 inhibitors and nonselective NSAIDs or for the other specific risk factors in the model. Within the low-risk population, the test of the proportional hazards assumption found significant evidence of nonproportional hazards for the risk factor of arthritis indication on a medical claim. Stratification by arthritis indication did not significantly alter the other hazard ratios in the model.

Since a higher proportion of patients treated with a COX-2 inhibitor used a gastroprotective agent during the preperiod,

additional proportional hazards regression models were performed to evaluate whether the GI bleed outcome changed after adjusting for differences in preperiod use of a gastroprotective agent (Table 5). In the total study population and the high-risk population, the hazard ratios changed slightly, but the overall study findings and level of significance were not altered. However, in the low-risk population, patients who received a COX-2 inhibitor no longer had a significantly greater risk of having a GI bleed event compared with patients who received a nonselective NSAID after adjusting for preperiod use of a gastroprotective agent. In all 3 study populations (total population, low-risk, and high-risk), preperiod use of gastroprotective agents was a factor associated with a higher risk of a GI bleed during follow-up. Similar to the previous models, stratified models were performed because there was evidence of nonproportional hazards for the risk factor of history of GI bleed for the total population and the high-risk population and for the risk factor of arthritis indication for the low-risk population. The stratified models did not significantly alter the hazard ratios.

■ Discussion

In this retrospective study of a population of COX-2 inhibitor users who were matched to nonselective NSAID users with similar baseline characteristics, a lower risk of having a GI bleed was not observed among patients receiving COX-2 inhibitors. Despite the fact that the early controlled clinical trials of the COX-2 inhibitors suggested a lower risk of GI bleed, particularly for rofecoxib,[9-15] similar results were not demonstrated at the population level within this managed care setting.

The results from the present study expand on those from a cross-sectional time series analysis from 1994 through 2002 among patients older than 66 years in Ontario, Canada, where a 41% increase in NSAID utilization (resulting from the increased use of COX-2 inhibitors) was accompanied by a 10% increase in hospitalization rates for upper GI bleed.[28] Although causation was not proven, adverse outcomes may result when

high-risk patients who would normally not be prescribed nonselective NSAIDs are treated with COX-2 inhibitors because these medications are perceived to be safer. In the present study, the use of COX-2 inhibitors was not associated with higher rates of GI bleed for the high-risk population, and there was no measurable reduction in the risk of GI bleed for COX-2 inhibitor users compared with nonselective NSAID users.

Contrary to the findings of the present study, an earlier observational study published in 2002 examining an administrative health care database in Ontario, Canada, found a higher risk of hospitalization for a GI hemorrhage with the nonselective NSAIDs than with the COX-2 inhibitors (12.6 GI hemorrhages per 1,000 person years for nonselective NSAIDs versus 3.6 to 7.3 GI hemorrhages per 1,000 person years for COX-2 inhibitors, adjusted rate ratio ranged from 1.9 to 4.4 for nonselective NSAIDs versus COX-2 inhibitors).[29] While this study was similar in concept to the present study, the 2 studies used different study populations and health systems, different cohort matching techniques, different model covariates, and different definitions of a GI bleed. The Canadian study evaluated a high-risk population (patients aged 66 years and older), while the present evaluated both low- and high-risk patients. In the Canadian study, the GI bleed outcome was limited to hospitalizations for a GI bleed, but the present study examined hospitalizations as well as outpatient claims for a GI bleed because many GI bleeds are treated in the outpatient setting (hence, the absolute rate of GI bleeds was lower in the Canadian study compared with the present study).

The Canadian study did not match nonselective NSAID users to COX-2 inhibitor users but, instead, adjusted for covariates using a Cox proportional hazards model. The covariates used within the Canadian 2002 study were different than those used in the present study. One noteworthy difference was that the Canadian study measured past history of a GI bleed over the prior 5-year period, while the present study limited this look-back period to 6 months since the frequent turnover of patients in U.S. managed care plans would not allow for a longer evaluation without significantly reducing the study sample size. While the differences in study design prohibit a direct comparison of the 2 studies, the contrasting results between the studies indicate a need for additional research to further understand the risk of GI bleed among users of COX-2 inhibitors and nonselective NSAIDs.

Whether COX-2 inhibitors are cost effective at the population level remains a controversial issue.[5-8, 30-32] Based on data from this managed care organization during the fourth quarter of 2004, the average pharmacy ingredient cost per 30 days for a COX-2 inhibitor prescription was $95.70, which, if filled regularly for a 1-year period, would have an annual drug cost of $1,148 per patient. In comparison, the average pharmacy ingredient cost per 30 days for a nonselective NSAID was $16.56, or $199 per patient per year. In other words, it would be possible to treat

TABLE 4	Hazard Ratio (95% Confidence Interval) of a GI Bleed Event*		
	Total Population (N = 70,014)	Low-Risk Population (N = 29,547)	High-Risk Population† (N = 40,467)
NSAID Selection			
COX-2 inhibitor vs. nonselective NSAID	1.07 (0.90-1.26)	2.05 (1.21-3.48)‡	0.995 (0.84-1.19)
Other Factors			
Age	1.61 (1.50-1.72)‡	1.25 (0.97-1.62)	1.53 (1.39-1.68)‡
Gender (male vs. female)	1.34 (1.13-1.58)‡	1.64 (1.02-2.63)‡	1.31 (1.09-1.56)‡
State of health plan			
Washington vs. California	0.93 (0.69-1.24)	0.55 (0.17-1.77)	0.94 (0.69-1.26)
Texas vs. California	0.68 (0.50-0.92)‡	0.75 (0.30-1.87)	0.66 (0.48-0.91)‡
Oregon vs. California	0.79 (0.49-1.29)	0.55 (0.14-2.28)	0.81 (0.48-1.36)
Oklahoma vs. California	0.69 (0.43-1.09)	0.38 (0.09-1.54)	0.77 (0.47-1.25)
Charlson Comorbidity Index	1.11 (1.04-1.18)‡	1.26 (1.08-1.49)‡	1.10 (1.03-1.17)‡
Corticosteroid use (yes vs. no)	1.27 (0.99-1.61)	–	1.20 (0.94-1.54)
Warfarin use (yes vs. no)	1.75 (1.39-2.19)‡	–	1.68 (1.33-2.12)‡
History of GI bleed (yes vs. no)	5.35 (4.00-7.15)‡	10.30 (5.19-20.45)‡	4.82 (3.52-6.60)‡
Arthritis indication			
Rheumatoid arthritis vs. none	1.05 (0.69-1.61)	1.44 (0.45-4.65)	0.98 (0.62-1.55)
Osteoarthritis vs. none	1.10 (0.91-1.32)	2.01 (1.10-3.67)‡	1.03 (0.85-1.26)

* A separate regression model was performed for each of the 3 populations: the total study population, low-risk population, and high-risk population.
† High-risk was defined as a patient with (a) age older than 65 years, or (b) recent history use of either warfarin or corticosteroid, or (c) a recent hospitalization for a GI bleed.
‡ Indicates a level of significance of P < 0.05.

COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

6 patients with nonselective NSAIDs for the same drug cost incurred for 1 patient taking a COX-2 drug.

Since patients using the COX-2 inhibitors did not demonstrate a reduction in GI bleeding in the present study, the cost benefit of the COX-2 inhibitors is questionable. Previous research has shown that use of COX-2 inhibitors may not be cost effective among patients with low or average GI risk,[30] and the findings from the current study suggest that COX-2 inhibitors may not be cost effective even in high-risk populations. While the use of nonselective NSAIDs for high-risk patients may not be appropriate, the use of COX-2 inhibitors within high-risk populations must also be questioned. The use of COX-2 inhibitors may be appropriate for some patients; however,

TABLE 5 Hazard Ratio (95% Confidence Interval) of a GI Bleed Event, Adjusting for Preperiod Use of a Gastroprotective Agent*

	Total Population (N = 70,014)	Low-Risk Population (N = 29,547)	High-Risk Population† (N = 40,467)
NSAID Selection			
COX-2 inhibitor vs. nonselective NSAID	1.01 (0.85-1.19)	1.65 (0.96-2.85)	0.96 (0.80-1.14)
Other Factors			
Age	1.61 (1.51-1.73)‡	1.22 (0.94-1.57)	1.54 (1.40-1.70)‡
Gender (male vs. female)	1.35 (1.15-1.60)‡	1.63 (1.02-2.62)‡	1.32 (1.10-1.57)‡
State of health plan			
Washington vs. California	0.95 (0.71-1.28)	0.56 (0.18-1.79)	0.96 (0.71-1.30)
Texas vs. California	0.69 (0.51-0.92)‡	0.74 (0.30-1.86)	0.67 (0.49-0.92)‡
Oregon vs. California	0.81 (0.50-1.32)	0.54 (0.13-2.22)	0.83 (0.50-1.40)
Oklahoma vs. California	0.68 (0.43-1.08)	0.38 (0.09-1.58)	0.76 (0.47-1.24)
Charlson Comorbidity Index	1.10 (1.04-1.17)‡	1.30 (1.11-1.51)‡	1.09 (1.02-1.17)‡
Corticosteroid use (yes vs. no)	1.23 (0.97-1.57)	–	1.18 (0.92-1.52)
Warfarin use (yes vs. no)	1.78 (1.42-2.23)‡	–	1.70 (1.35-2.15)‡
History of GI bleed (yes vs. no)	4.70 (3.50-6.30)‡	6.41 (3.17-12.95)‡	4.40 (3.20-6.04)‡
Arthritis indication			
Rheumatoid arthritis vs. none	1.03 (0.68-1.58)	1.38 (0.43-4.45)	0.97 (0.62-1.53)
Osteoarthritis vs. none	1.10 (0.91-1.32)	1.98 (1.08-3.60)‡	1.03 (0.85-1.26)
Preperiod gastroprotective agent use (yes vs. no)	1.58 (1.30-1.91)‡	2.85 (1.70-4.80)‡	1.43 (1.15-1.76)‡

*A separate regression model was performed for each of the 3 populations: the total study population, low-risk population, and high-risk population.

† High-risk was defined as a patient with (a) age older than 65 years, or (b) recent history use of either warfarin or corticosteroid, or (c) a recent hospitalization for a GI bleed.

‡ Indicates a level of significance of P < 0.05.

COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

cohort. Because patients were not randomized to treatment group, there exists the potential for selection bias between the COX-2 inhibitor and nonselective NSAID cohorts. Physicians may have decided to prescribe COX-2 inhibitors instead of nonselective NSAIDs for their higher-risk patients.

In many of the health plans within this managed care population, COX-2 inhibitors were subjected to prior authorization, which required patients to meet certain clinical characteristics prior to receiving an authorization for coverage of a COX-2 inhibitor. Such criteria commonly include age, diagnosis, GI bleed history, and concomitant medication use. Thus, patients receiving COX-2 inhibitors may have had different GI risk factors than those receiving nonselective NSAIDs. Due to database limitations, it was not possible to determine the proportion of subjects within each cohort that required prior authorization to obtain a COX-2 inhibitor. However, propensity matching was used to minimize demographic, clinical, and geographical differences between the cohorts.

The percentage of patients in the Medicare + Choice health plan was statistically different for the COX-2 inhibitor group and the nonselective NSAID group (53.1% versus 55.7%). The practical significance of this 2.6-point absolute difference is not clear, but the Medicare + Choice health plan may have had a maximum annual pharmacy benefit ranging from $500 to $2,000 and generic-only benefits (with or without limits), depending on the benefit year and the geographical county of the member.

The 6-month preperiod may not have been long enough to capture the patient's entire past history. For example, if a patient had a GI bleed prior to the preperiod, his or her history of GI bleed would not have been captured. All of the potential risk factors for a GI bleed could not be captured in this claims database, including use of alcohol, tobacco, aspirin or over-the-counter nonselective NSAIDs. Patients may have had other risk factors for GI bleed (e.g., bleeding disorders) that were not considered in this analysis. As a result, some high-risk patients could have been mismatched or incorrectly classified as low-risk patients because of missing data. Within the low-risk population, the higher rate of GI bleed among patients receiving COX-2 inhibitors versus patients receiving nonselective NSAIDs may be the result of incorrect (false assignment) classification of high-risk patients into the low-risk population. In contrast, patients in the high-risk population were more likely to be correctly classified since they were required to have a high-risk condition (i.e., age older than 65 years, recent history of warfarin or corticosteroid use, or a recent hospitalization for a GI bleed) to be included in this population.

Since these results were obtained among health maintenance organizations and Medicare + Choice patients in 3 western states, Texas, and Oklahoma, similar results may not be observed among populations with different demographic or socioeconomic characteristics (such as the Medicaid population). These results were

further research is warranted to determine the specific patient populations where the COX-2 inhibitors are cost effective.

Limitations

Potential study limitations should be considered when generalizing these results to other populations. Although patients were matched by propensity score to control for possible selection bias, the matching may not have accounted for all of the factors that could have led to adverse selection for the COX-2 inhibitor

subject to the definition used to identify a case of GI bleed. A GI bleed event was defined as an inpatient hospitalization with a diagnosis representing GI bleed or at least 2 medical claims with a primary (first-listed) diagnosis representing a GI bleed. Medical records could be used to validate this definition of a GI bleed; however, examination of patient medical records was beyond the scope of this study. Further study of the accuracy of medical claims diagnoses in identifying actual GI bleeds would add to the literature. Applying a less stringent or more stringent definition for a GI bleed could have changed the study outcomes.

In order to be included in the analysis, patients were only required to have 3 months of continuous enrollment in the health plan following their fill of a COX-2 inhibitor or nonselective NSAID. While some patients could have been followed for a maximum of 1 year, others were followed for a shorter period if they disenrolled from the health plan, switched or discontinued their index class of medication (COX-2 inhibitor or nonselective NSAID), or had a GI bleed. Further research is needed to understand whether these results would have been different if patients were studied over a longer follow-up period.

While rates of concomitant use of proton pump inhibitors or other gastrointestinal protective agents were reported, an evaluation of the impact of gastroprotective agents on GI outcomes was beyond the scope of this study, which was designed to examine the relative risk of having a GI bleed among patients using COX-2 inhibitors or nonselective NSAIDs within this managed care population. Introducing the use of gastroprotective agents as a variable within the analysis could have confounded the results since the use of gastroprotective agents can represent either a risk factor or a study outcome. While the use of gastroprotective agents in combination with COX-2 inhibitors or nonselective NSAIDs merits further research, a study designed specifically to measure the concomitant use of gastroprotective agents such as a case-control study could help eliminate some of the confouning associated with this measure.

■ Conclusion

This study provides insight into the rates of GI bleeding among a large population of managed care patients initiated on COX-2 inhibitors or nonselective NSAIDs. Patients using a COX-2 inhibitor did not have a reduced risk of a GI bleed compared with patients with similar baseline characteristics who were using nonselective NSAIDs. With the high direct-drug cost of COX-2 inhibitors and the uncertain risk of adverse cardiovascular events, further research is needed to reevaluate the appropriate patient populations for cost-effective treatment with COX-2 inhibitors.

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