

Relationship of Clinical Factors to the Use of Cox-2 Selective NSAIDs Within an Arthritis Population in a Large HMO

SCOTT A. BULL, PharmD; CAROL CONELL, PhD; and DAVID H. CAMPEN, MD

ABSTRACT

OBJECTIVE: To investigate the degree to which physicians use clinical factors to focus use of Cox-2 selective NSAIDs within an arthritis population.

METHODS: Diagnostic codes in the medical records of a large group-model HMO in northern California with approximately 3 million members were examined to identify patients with either rheumatoid arthritis (RA) or non-RA (osteoarthritis or degenerative joint disease). RA and non-RA patients were stratified in deciles of relative risk for gastrointestinal (GI) complications according to patient characteristics identified on the Standardized Calculator of Risk for Events (SCORE) that were associated with use of Cox-2 selective NSAIDs. (The SCORE tool stratifies patients by risk of serious GI complications using patient characteristics that are assigned points during an office visit, including age, health status, diagnosis of rheumatoid arthritis, corticosteroid use, and history of GI ulcer or bleed.) The second stage of analysis examined the percentage of arthritis patients in each SCORE-risk decile who received a Cox-2 selective NSAID, lower-risk NSAID, or traditional NSAID during calendar year 1999.

RESULTS: The study population consisted of 144,360 members with an arthritis diagnosis, approximately 4.8% of members in this HMO. The mean age was 62.8 years (SD = 14.1), 61% were female, 10,449 (7%) had rheumatoid arthritis (RA), and 133,911 (93%) had non-rheumatoid arthritis. A diagnosis of RA was the most significant predictor of Cox-2 NSAID use (OR=2.4; 95% CI=1.6-3.5), followed by a history of GI problems (OR=1.5; 95% CI=1.4-1.6). Female gender, chronic steroid use, and age each increased the odds of receiving a Cox-2 selective NSAID by about 35% ($P<0.001$ for all). Approximately 8.3% of patients in the highest decile of risk and 1.5% of patients in the lowest decile of risk received a Cox-2 selective NSAID.

CONCLUSIONS: Clinical characteristics of patients identified on the SCORE (GI-risk) tool were strongly associated with use of Cox-2-selective NSAIDs in this HMO. A 5.5-fold difference in utilization of Cox-2 selective NSAIDs was found among patients determined to be in the highest-risk decile versus patients in the lowest-risk decile. Future research should investigate how nonclinical factors play a role in the treatment decisions made by physicians.

KEYWORDS: Nonsteroidal anti-inflammatory drugs (NSAIDs), Cox-2 selective NSAIDs, Treatment guidelines, Prescribing behavior, Managed care, GI complications, Risk.

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NSAID-induced gastrointestinal (GI) bleed is a serious and potentially life-threatening complication, resulting in an estimated 16,500 deaths and 107,000 hospitalizations annually in the U.S. alone.¹ Rates of NSAID-related serious GI complications (i.e., gastric or duodenal perforation, gastric outlet obstruction, or upper-GI bleeding) vary depending on the population studied, ranging from 0.73-1.46% among arthritis patients.^{2,3} Many studies have demonstrated that the probability of serious GI complications rises when certain risk factors are present, including health status or disability,^{3,4} increasing age,⁵ concomitant use of systemic steroids⁶ or anticoagulants,⁷ history of a GI ulcer or bleed,⁸ diagnosis of rheumatoid arthritis,² certain patterns of prior NSAID use,⁹ history of cardiovascular disease,¹⁰ smoking status,^{3,11} and NSAID-related GI symptoms.^{1,4,7}

While meta-analyses and large, well-controlled studies have suggested that treatment with Cox-2 selective NSAIDs is associated with fewer GI complications (GI bleed, perforation, or obstruction) or symptomatic ulcers as compared to traditional NSAIDs,¹²⁻¹⁴ the clinical significance of endoscopic safety data presented in the clinical trials referenced in the celecoxib and rofecoxib labels does not allow one to compare the alleged value of Cox-2 selective NSAIDs to that of other products.^{15,16} For example, since ulcers identified by endoscopy heal and redevelop, the actual correlation between the reported prevalence in the package inserts and the true incidence of serious GI complications could be small.

Because absolute rates of serious GI complications are lower among nonarthritis¹ and younger, healthier populations,^{5,7,9} the expected health benefit from a Cox-2 selective NSAID in these patients is lower than for patients who may be at greater risk. In addition, less expensive NSAIDs such as salsalate and etololac have some selectivity for the Cox-2 enzyme^{17,18} and may be safer than other NSAIDs that have relatively less Cox-2 selectivity.^{2,17-19} Therefore, from the perspective of population health and quality improvement, efforts to focus Cox-2 selective NSAIDs among patients at higher risks are desirable.

Prior to the market entry of the first Cox-2 selective NSAID (celecoxib), this northern California HMO disseminated a treatment guideline for the use of NSAIDs based on the Standardized Calculator of Risk for Events (SCORE) program developed at Stanford University, Division of Immunology and Rheumatology.^{4,5,20} The SCORE tool stratifies patients by risk of developing serious GI complications using patient characteristics that are assigned points during an office visit, including age, health status, diagnosis of rheumatoid arthritis, cortico-

APPENDIX A Treatment Selection Guidelines

Risk Level	Recommended NSAID
Level 3: Greater than 21 points	celecoxib (Celebrex) rofecoxib (Vioxx)
Level 2: 16–20 points	salsalate (Disalcid) etodolac (Lodine) nabumetone (Relafen)
Level 1: 1–15 points	ibuprofen (Motrin) naproxen (Naprosyn) sulindac (Clinoril)

APPENDIX B SCORE Tool Factors

Independent Variables

Demographic Characteristics

- **Age.** Age in years as of January 1, 1999.
- **Female.** Dummy variable coded 1 for females.

Health

■ **Morbidity Score.** A continuous index created by the HMO's Department of Quality and Utilization. The index was originally developed to predict health care utilization and was created by regressing the total cost of care on information on prescriptions and inpatient visits for a variety of conditions. Since the original metric is not particularly meaningful, the decile score, normed on the total arthritis study population, was used.

■ **GI Problems.** This indicator is a dummy variable created by the Kaiser Department of Quality and Utilization. It is coded 1 if the subject probably had substantial gastrointestinal problems, based on diagnoses reported during inpatient treatment and the prescriptions filled. The scores used here are for the third quarter of 1999, which is about midway through the period during which Cox-2 selective NSAIDs were effectively introduced.

■ **Chronic Steroid Use.** A dummy variable coded 1 for individuals who either refilled a 90-day prescription for steroids during 1999 or filled two prescriptions of any duration for steroids during 1999.

■ **Rheumatoid Arthritis.** A dummy variable coded 1 if there is at least one reported diagnosis of rheumatoid arthritis in the 1998 or 1999 inpatient or outpatient automated encounter databases.

steroid use, and history of GI ulcer or bleed.

The HMO guideline recommended different NSAIDs for patients, depending on the total number of points assigned by the SCORE tool. After May 20, 1999, a Cox-2 selective NSAID, celecoxib or rofecoxib, was recommended for patients with a score of 21 or greater. Nabumetone, etodolac, or salsalate were recommended for patients with intermediate scores (16-20 points), and those with the lowest scores (1-15 points) should receive a traditional NSAID such as ibuprofen or naproxen sodium, according

to the HMO guideline (Appendix A). The clinical practice guideline was mailed to more than 3,000 physicians participating in the northern California HMO. This clinical practice guideline was reinforced by drug education pharmacists who provide academic detailing to physicians regarding treatment selection of NSAIDs and other drugs at a majority of the medical centers and outpatient clinics associated with this HMO. The purpose of this study was to determine whether patient characteristics previously shown to be associated with increased risk for serious GI complications affected prescription utilization rates for Cox-2 selective NSAIDs. We also examined the extent to which physicians used clinical factors identified on the SCORE tool to focus use of Cox-2 selective NSAIDs within the arthritis population.

Methods

Patient Identification

The study was conducted at a large, not-for-profit health maintenance organization that serves approximately 3 million members at 17 medical centers and 27 outpatient facilities in northern California. Approximately 96% of members fill their prescriptions at HMO staff pharmacies. This study and the study methods and procedures were approved by the Institutional Review Board of the HMO.

Study members included all adults (18 or older) who were HMO members during 1999 and who received an arthritis diagnosis as either an inpatient or outpatient in the 2-year period between January 1, 1998, and December 31, 1999. Nonrheumatoid arthritis patients and rheumatoid arthritis (RA) patients were identified using outpatient diagnostic codes for osteoarthritis (OA), degenerative joint disease (OA/DJD) and rheumatoid arthritis. Individuals diagnosed one or more times with ICD-9 identifier code 714.0, 714.3, 716.5, 716.8, 716.9, or 716.3 were classified as having RA. Those individuals with ICD-9-CM codes 715.0-716.0 in (001-009) but without an RA diagnosis code were classified as having non-RA. Length-of-enrollment databases were used to eliminate individuals who were not HMO members during 1999. Information on birth date and gender were extracted from patient demographic databases, and age was calculated (in years) as of January 1, 1999.

Development of a Model to Predict How Patient Characteristics Relate to Prescribing of Cox-2 Selective NSAIDs

For calendar year 1999, the HMO's electronic pharmacy database was scanned for use of any of the NSAIDs listed on the treatment selection guideline: (1) a traditional NSAID: ibuprofen, sulindac, or naproxen; (2) a moderate-risk NSAID: nabumetone, salsalate, or etodolac; or (3) a Cox-2 selective NSAID: celecoxib or rofecoxib. Three different (yes/no) variables were created for each study member to identify which of the 3 NSAID categories, if any, had been used during 1999.

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TABLE 1 Sample Characteristics

	Total Sample N=144,360 (100.0%)	Rheumatoid Arthritis n=10,449 (7.24%)	Other Arthritis n=133,911 (92.76%)
DEMOGRAPHICS			
Age (mean +/- SD)	62.6 (14.2)	58.6 (14.9)	62.8 (14.1)
Female	61.9%	72.9% ¹	61.0%
HEALTH STATUS			
Morbidity score* (in deciles)	5.0 (2.9)	6.1 ¹ (3.0)	4.9 (2.8)
Patients with GI problems	9.3%	9.7%	9.3%
Patients with chronic steroid use	3.4%	29.4% ¹	1.4%
UTILIZATION OF SERVICES			
Used primary care	97.3 (16.1%)	97.7 (14.9%)	97.3 (16.2%)
Number of primary care visits (mean +/- SD)	5.8 (5.8)	8.0 ¹ (8.6)	5.6 (5.2)
Used therapy (e.g., occupational and physical therapy (SD)	25.7% (43.7)	21.7% (41.2)	26.0% (43.9)
Number of therapy visits (e.g., occupational and physical therapy) (mean +/-SD)	1.8 (4.8)	1.3 (4.3)	1.8 (4.9)
Number of specialty visits (nonprimary care physicians)† (mean +/-SD)	3.0 (7.1)	3.2 (7.4)	3.0 (7.1)
Received Cox-2 selective NSAIDS	4.0%	6.3% ¹	3.8%

*The Morbidity Score was originally developed for the purposes of predicting health care utilization.

†Includes visits to all types of specialists, including nonrheumatologists.

Significance levels: ¹.001 ².01 ³.05 (difference between "rheumatoid arthritis" and "other arthritis" patients)

Logistic regression analysis was used to determine the relationship of demographic and clinical factors (age, history of GI problems, chronic steroid use, general health, and rheumatoid arthritis) to receipt of a Cox-2 selective NSAID ("yes" for use of a category-3 NSAID). These factors are reflected in the SCORE tool that was disseminated to the HMO physicians and were developed by the HMO's Department of Quality and Utilization using northern California computerized clinical and demographic health plan databases (Appendix B).

The Degree to Which Physicians Use Clinical Factors to Focus Use of Cox-2 Selective NSAIDs

Individual patient data were applied to the resulting logistic regression equation to calculate a Cox-2 score for each study member. This score indicates how likely a patient, with given characteristics, was to receive a Cox-2 selective NSAID in 1999. The Cox-2 score reflects, in part, physician understanding and adherence to the HMO's risk stratification guideline. It does not directly assess risk for GI complications, but rather is a measure of how physicians

used clinical factors to focus use of Cox-2 selective NSAIDs. Study participants were ranked, by decile, from lowest to highest Cox-2 score. The actual percentage of patients who received a Cox-2 selective NSAID, a lower-risk NSAID, and/or a traditional NSAID was determined from the HMO's electronic pharmacy database.

Results

Study Population

Table 1 shows the characteristics of the study population, including demographic information, relevant health information, and health services utilization. There were 144,360 individuals in the study population, of which 10,449 (7.2%) had rheumatoid arthritis. About three-fifths were female. The mean age of the study population was 63. Patients with rheumatoid arthritis were significantly more likely than other arthritic subjects ($P < 0.001$) to be female, in poorer health, chronic steroid users, and to have received a Cox-2 selective NSAID during 1999. RA patients also

TABLE 2 Impact of Patient Characteristics on the Chance of Receiving a Cox-2 Selective NSAID

VARIABLE	Odds Ratio (Confidence Interval)	
	UNIVARIATE	MULTIVARIATE
Age (in decades)		
Other—arthritis	1.24 ¹ (1.22–1.27)	1.12 ¹ (1.10–1.15)
Rheumatoid	1.22 ¹ (1.15–1.29)	1.19 ¹ (1.13–1.27)
Female		
Other—arthritis	1.52 ¹ (1.43–1.62)	1.35 ¹ (1.27–1.43)
Rheumatoid	1.10 (0.92–1.33)	
Morbidity score*		
Other—arthritis	1.16 ¹ (1.15–1.18)	1.11 ¹ (1.10–1.13)
Rheumatoid	1.09 ³ (1.06–1.12)	
GI problems	2.00 ¹ (1.86–2.15)	1.47 ¹ (1.36–1.59)
Chronic use of steroids	1.56 ¹ (1.32–1.83)	1.36 ¹ (1.20–1.53)
Rheumatoid arthritis	1.68 ¹ (1.54–1.83)	2.39 ¹ (1.60–3.54)

*The Morbidity Score was originally developed for the purposes of predicting health care utilization.

Significance levels: ¹.001, ².01, ³.05

For each variable, the odds ratio is presented for the characteristic being present as compared to not present.

used significantly more primary care services ($P < 0.001$). RA patients versus other arthritis patients did not differ significantly in age, probability of having a history of GI problems, or utilization of specialty and rehabilitation services. Almost all patients (97–98%) had at least one office visit with a primary care physician during the one-year study period. In addition, the patients averaged a total of 10.6 visits during the year, of which 5.8 (55%) were made to primary care providers, 3.0 (28%) to specialists (included all specialists, i.e., nonrheumatologists), and 1.8 (17%) to occupational or physical therapists. This visit rate is higher than for the general adult population of this northern California HMO but consistent with the demographics of the study population.

Patient Characteristics Associated with Receiving a Cox-2 Selective NSAID

The first column in Table 2 indicates the univariate impact of each factor on the odds of receiving a Cox-2 selective NSAID. The second column shows the impact of each factor while controlling for the other factors. For the dichotomous variables in Table 2, the effect is defined as the odds ratio for those who have the characteristic compared to those who do not. For example, a patient with a history of GI problems was 1.47 times as likely (or about 47% more likely) to receive a Cox-2 selective NSAID compared to an otherwise similar individual with no such history. For continuous predictor variables, the effect is defined as the odds ratio for an individual who scores one standard deviation above the mean of

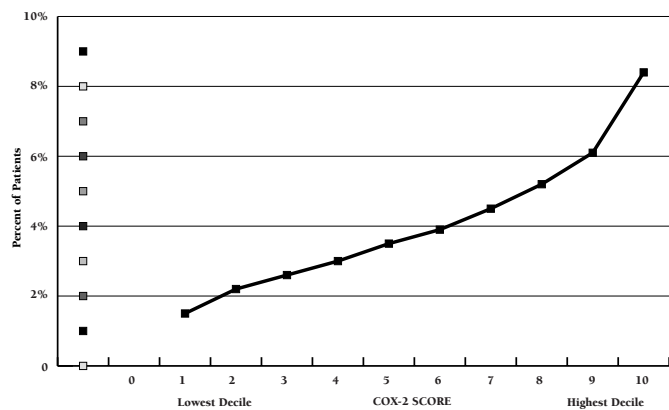
the predictor variable compared to an individual who scored one standard deviation below the mean.

Rheumatoid arthritis had, by far, the largest impact on the chance of receiving a Cox-2 selective NSAID (OR=2.39; 95% CI=1.60–3.54; $P < 0.001$), followed by a history of GI problems (OR=1.47; 95% CI=1.36–1.59; $P < 0.001$). Being female, having a history of chronic steroid use, and being older for non-RA patients (each of which multiplied the odds by approximately 1.3) also had a significant impact ($P < 0.001$ for all). For all factors except gender, which was not included in the SCORE tool,^{5,20} higher use of Cox-2 selective NSAIDs correlated to risk factors contained in the SCORE tool.

The Degree to Which Clinical Factors Were Used to Focus Use of Cox-2 Selective NSAIDs

Figure 1 provides a graphic illustration of the percentage of patients who received a Cox-2 selective NSAID based on the calculated Cox-2 score (by decile). Approximately 8.3% of patients in the highest decile of the Cox-2 score and 1.5% of patients in the lowest decile received a Cox-2 selective NSAID. Figure 2 illustrates the percentage of patients (by decile) who had received either a traditional NSAID, lower-risk NSAID, or Cox-2 selective NSAID based on their Cox-2 score. Use of traditional NSAIDs tended to be lower among patients with the highest Cox-2 score, while use of lower-risk NSAIDs (etodolac, nabumetone, and salsalate) was similar to the utilization of the Cox-2 selective NSAIDs in the group of patients with the highest Cox-2 score.

FIGURE 1 Percent of Patients Who Received a Cox-2 NSAID by "Cox-2 Score"



Discussion

The goal of this study was to evaluate utilization of 3 categories of NSAIDs: traditional NSAIDs, lower-risk NSAIDs, and Cox-2 selective NSAIDs in relation to patient-specific factors identified in the SCORE tool that have been shown to predict risk for serious GI complications. We found that the utilization of Cox-2 selective NSAIDs was stratified according to these factors. We also found that gender, which was not included in the SCORE guideline, was associated with use of Cox-2 selective NSAIDs.

A 5.5-fold difference in the use of Cox-2 selective NSAIDs was observed between the 10% of patients with the lowest risk and the 10% of patients with the highest calculated risk (decile). This pattern of use of Cox-2 selective NSAIDs among physicians employed by this northern California HMO follows regional guidelines recommending that these agents be reserved for patients at the highest risk for serious GI complications. Treatment selection guidelines based on risks for complications are intended to maximize the cost-effectiveness of NSAID utilization by recommending treatment with less expensive NSAIDs for patients who are at lower risk for serious GI complications. Concentrating the use of Cox-2 selective NSAIDs among patients at higher risk for GI complications can potentially prevent a larger number of serious GI complications among NSAID users and improve the cost-effectiveness of the use of Cox-2 drugs. For example, risk-stratification models used in developing the SCORE tool predict that risk of hospitalization or death due to NSAID-related GI complications decreases by approximately 4-fold between arthritis patients in higher and lower risk strata.^{5,20} This pattern is consistent with other reports of NSAID-related GI complication rates for high-risk and low-risk populations^{9,21} and suggests that the cost-effectiveness of Cox-2 selective NSAIDs is likely to be lower in populations at lower risk for GI complications.

Although sometimes controversial,²² a step-care approach to therapy has also been shown to be an effective intervention for

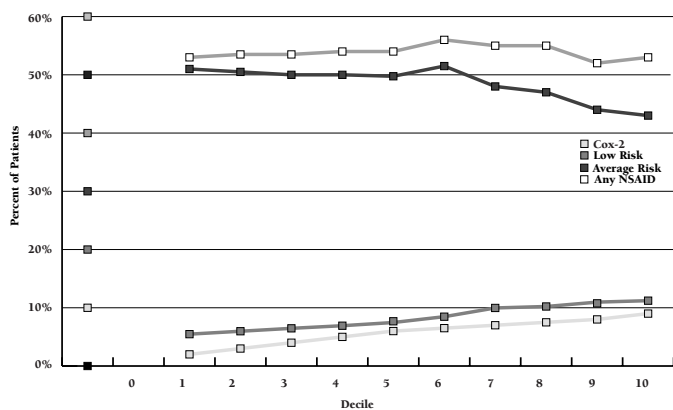
containing the costs of Cox-2 selective NSAIDs.²³ However, because symptomatic adverse events do not appear in up to 91% of patients who experience serious GI complications,^{24,25} step-care strategies that rely solely on the presence of side effects to identify treatment failure would appear to be inadequate.^{2,25}

Of the patient-specific factors measured in this study, the presence of rheumatoid arthritis had the largest impact on the chance of receiving a Cox-2 selective NSAID, more than doubling prescription rates. Patients with rheumatoid arthritis were substantially sicker than the non-RA patients, as indicated by greater use of primary care office visits, use of steroids, and higher morbidity scores.¹ An interesting finding of our study was that female gender and having non-RA¹ were positively correlated to receiving a Cox-2 selective NSAID. Gender was not included in the SCORE tool and is not known to be a risk factor for serious GI complications. The adjusted odds ratio indicates that women were more likely to be prescribed a Cox-2 selective NSAID than men with otherwise similar characteristics. It is possible that women are either more likely to request treatment with a specific agent, or because physicians see a higher incidence of RA among their female patients, they perhaps expect women to require higher dosages and/or more chronic use of NSAIDs.

Nonclinical factors, such as physicians' and patients' attitudes about an acceptable level of risk or the consideration of the relative cost of alternative therapies, may also account for differences in the use of Cox-2 selective NSAIDs among patients in the highest and lowest risk strata. For example, the rationale behind prescribing guidelines may be perceived by some physicians to be intrusive and not in the best interest of an individual patient. From the patient's perspective, "risk" for a life-threatening event may be difficult to comprehend or may be perceived differently from patient to patient. A patient who is highly averse to risk may feel perfectly justified seeking treatment with the absolute safest treatment available even if he or she could safely be treated with a traditional NSAID. It is likely that such patient requests for specific agents have increased in recent years due to more frequent direct-to-consumer advertising by drug manufacturers.²⁶

Other researchers have concluded that multiple factors, such as educational campaigns and patient cost-sharing requirements, can simultaneously influence prescribing rates of NSAIDs.²⁷ Similarly, variation in prescription rates for Cox-2 selective NSAIDs at this northern California HMO are likely to be influenced by additional factors that include formulary status, the dissemination of treatment guidelines, and physician incentives that are specific to this HMO. For example, this HMO does not have a tier-copay formulary, and Cox-2 selective NSAIDs were not on the formulary during the calendar year that prescription rates were analyzed. Prescriptions for Cox-2 selective NSAIDs were required to have prior authorization (a 4-digit medical necessity code written on the prescription by the prescribing physician) in order to be covered by the pharmacy benefit; otherwise, members paid 100% of

FIGURE 2 Percent of Patients Receiving Different Risk NSAIDs by "Cox-2 Score"



the cost of Cox-2 selective NSAIDs.

Some patients may have had risk factors not measured in our study (e.g., smoking or coincident warfarin use), which could partially explain why some patients in the lowest-risk decile received a Cox-2 selective NSAID. A potential limitation of the study is extent to which the factors derived from the health plan's computerized databases depart from the actual self-report variables identified in the SCORE tool. Although these factors were not calibrated exactly to those in the SCORE tool, they served as useful markers for identifying characteristics of study members that may be likely to increase their risk for a serious GI complication. As evidenced by lower utilization of traditional NSAIDs in relation to higher Cox-2 scores, we believe the variables were, in fact, valid indicators of individuals' level of risk for serious GI complications. The actual SCORE tool²⁰ may be useful for other managed care organizations attempting to balance cost and quality in the delivery of pharmaceutical care.

This study has limitations. First, there were no outcome measures in this study other than the receipt (dispensing) of NSAIDs by type. It is up to other researchers to tie predicted risk with receipt of NSAIDs by type and ultimate patient outcomes (e.g., GI bleeding incidents sufficient to warrant medical intervention). Second, this group-model HMO is probably not typical of other environments, managed care or otherwise. As previously mentioned, several factors make the environment of this study unique, including the use of clinical practice guidelines and the support of these guidelines by drug education pharmacists.

Conclusions

In summary, we found that patient characteristics identified on the SCORE tool were strongly associated with receiving a Cox-2 selective NSAID among patients with rheumatoid arthritis (RA) and patients with non-RA. These characteristics included increasing

age and morbidity, diagnosis of rheumatoid arthritis (vs. non-RA), history of GI problems, and chronic use of systemic steroids. Use of Cox-2 selective NSAIDs was moderately concentrated among patients with observable risk factors for GI complications. Future research should investigate how nonclinical factors play a role in the treatment decisions made by physicians and the value of risk-stratification in maximizing the cost-effectiveness of use of Cox-2 selective NSAIDs.

DISCLOSURES

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Bull served as principal author of the study. Study concept and design were contributed primarily by Bull and author Carol Conell. Analysis and interpretation of data were contributed primarily by Bull and Conell. Drafting of the manuscript was primarily the work of Bull. Critical revision of the manuscript was primarily the work of Bull, Conell, and author David H. Campen. Statistical expertise was contributed primarily by Conell. Administrative, technical, and/or material support was provided by Kaiser Permanente.

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