The COX-2 inhibitor market withdrawals and prescribing patterns by rheumatologists in patients with gastrointestinal and cardiovascular risk

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Abstract

Objective

To examine effects of the COX-2 inhibitor market withdrawals on NSAID utilization among patients at increased risk of gastrointestinal (GI) and cardiovascular (CV) toxicities.

Methods

A prospective cohort study was conducted using patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) Registry. The study population included rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients prescribed NSAIDs by rheumatologists from 1/1/2003 to 12/31/2005. Three cohorts were defined based on calendar year. The primary outcome assessed whether or not an NSAID gastroprotective strategy was prescribed. Secondary outcomes included rates of COX-2 inhibitor utilization and gastroprotective co-therapy utilization, stratified by the presence of cardiac and GI risk factors.

Results

NSAID gastroprotection utilization decreased from 65.1% in 2003 to 47.7% ($p<0.001$) in 2005. COX-2 inhibitor use decreased from 55.1% to 29.2% ($p<0.001$), whereas nonselective NSAIDs (nsNSAIDs) use increased from 50.2% to 73.9% ($p=<0.01$). Among patients with two or more risk factors for NSAID related GI bleeding, gastroprotection decreased from 74.4% in 2003 to 60.9% ($p<0.01$). For patients with two or more CV risk factors from 2003 to 2005, COX-2 inhibitor utilization decreased significantly, whereas nsNSAID utilization increased significantly.

Conclusions

The COX-2 inhibitor withdrawals resulted in a rapid decline in NSAID gastroprotection prescribed by participating U.S. rheumatologists despite the availability of other gastroprotective options. Channeling toward nsNSAID use was widespread, including among patients at increased CV risk. Longer term follow-up is required to determine the clinical significance of these changes in NSAID prescribing, particularly for NSAID-related GI and CV-related toxicities.

Key words
NSAID, utilization, gastroprotection, cardiovascular.

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Introduction

The association of traditional non-selective NSAIDS (nsNSAIDs) with serious ulcer-related gastrointestinal (GI) complications has been clearly demonstrated, and represents an important public health concern (1-3). More than 70,000 hospitalizations and over 7,000 deaths have been attributed to nsNSAIDs per year in epidemiologic studies (3). Beginning with the introduction of celecoxib in 1998 and rofecoxib in 1999, followed by the release of valdecoxib in 2001, the cyclooxygenase (COX)-2 selective inhibitor class of nonsteroidal anti-inflammatory drugs (NSAIDs) represented what was perceived as a major therapeutic advance for patients requiring analgesic and anti-inflammatory medications.

Whereas COX-2 inhibitors represented one therapeutic strategy to reduce the risk of NSAID-related gastropathy, co-therapy of nsNSAIDs with proton pump inhibitor (PPI) agents or misoprostol represented a second approach to reduce the risk of NSAID-related GI toxicities. Randomized controlled trials (RCTs) have established that either of these two strategies can reduce the risk of NSAID-related gastropathy (4, 5).

Epidemiologic studies conducted after the introduction of PPIs and the COX-2 inhibitor class reported widespread underutilization of gastroprotective measures for NSAID users, including patients with multiple GI risk factors. More recently, it has been observed that COX-2 inhibitors were prescribed in a progressively nonselective manner over time since their market introduction (6). In a prior study examining prescribing patterns of rheumatologists in the United States, we observed that the majority of patients with inflammatory arthritis who were prescribed a NSAID received a gastroprotective strategy, attributable primarily to COX-2 inhibitor utilization, not PPI co-therapy. This study, however, was conducted during 2004 prior to the COX-2 inhibitor market withdrawals (7).

Due to concerns regarding cardiovascular and skin-related toxicities, rofecoxib and valdecoxib, two of three widely prescribed COX-2 inhibitor agents, were withdrawn from the market in September 2004 and March 2005, respectively (8, 9). Despite the fact that NSAIDs remain a cornerstone of analgesic therapy for arthritis and other painful conditions, few longitudinal studies have evaluated the pattern of COX-2 inhibitor prescription and NSAID gastroprotection since the COX-2 inhibitor market withdrawals. In this study, we examine the effects of the COX-2 inhibitor market withdrawals on NSAID utilization, including among patients at increased risk of GI and cardiovascular toxicities, in a large, observational cohort of patients with inflammatory arthritis treated by rheumatologists in the United States.

Materials and methods

Study population and cohort definitions

We examined a prospective cohort of patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) Registry. A total of 76 rheumatology practices across the U.S. participated in the registry during the study period, including 56 community-based sites and 20 academic sites. The study was approved by the Institutional Review Boards of participating academic sites and a central Institutional Review Board for community-based private sites. Details of the CORRONA registry have been previously published (10). The study population included patients identified as having rheumatoid arthritis (RA) and psoriatic arthritis (PsA) by their treating rheumatologists, who were enrolled in the CORRONA Registry over a three-year period from January 1, 2003 through December 31, 2005 and had been prescribed a NSAID. Patients were divided into three cohorts based on calendar year for the purposes of this study: the 2003 cohort, 2004 cohort and 2005 cohort.

Study outcomes

The primary study outcome was defined as whether or not NSAID gastroprotection was prescribed for each patient. NSAID gastroprotection was defined as either utilization of a COX-2 inhibitor or a nsNSAID plus gastroprotective agent (GPA) co-therapy (proton pump inhibitors or misoprostol). This

definition was based on the American College of Rheumatology guidelines for the management of RA and OA (11, 12). Secondary study outcomes included rates of nsNSAID, COX-2 inhibitor and GPA utilization.

Drug exposure definitions

Data were prospectively collected during the study period from patient and physician questionnaires obtained during routine clinical encounters. All medication data were obtained from patient questionnaires that were completed during clinical encounters. Specifically, prescription NSAIDs including nsNSAIDs, COX-2 inhibitors, PPI agents, misoprostol, oral corticosteroids, warfarin and aspirin use were reported on the patient questionnaires. The COX-2 inhibitor class included celecoxib, rofecoxib and valdecoxib from January to September 2004, celecoxib and valdecoxib from October 2004 to March 2005 and celecoxib alone from April to December 2005. Meloxicam was categorized as an nsNSAID for the purposes of this study, distinct from the COX-2 inhibitor class. In addition, over-the-counter (OTC) nsNSAIDs including ibuprofen and naproxen and OTC omemprazole were reported in the patient questionnaire.

Data analysis

First, we compared demographic and clinical characteristics of the study cohorts for calendar year 2003, 2004 and 2005. Next, we calculated the proportion of patients for each calendar year who were prescribed each of the following: i) any NSAID; ii) a COX-2 inhibitor agent; iii) a nsNSAID; iv) a gastroprotective cotherapy agent (PPI or misoprostol). In secondary analyses, we further categorized the ns NSAIDs into the following: i) naproxen ii) ibuprofen iii) meloxicam and iv) other ns NSAIDs. Finally, we stratified patients in each NSAID cohort based on the number of gastrointestinal (GI) risk factors. We defined these risk factors for NSAID-related gastropathy based on published meta-analyses, consensus guidelines, and quality indicators (1-3, 13). We selected the following risk factors: patient age greater than 65 years, lifetime history of peptic ulcer disease and/or GI bleeding, concomitant warfarin use, concomitant steroid use, and lifetime history of serious cardiovascular comorbidities. Each patient was also stratified based on the number of cardiacvascular (CV) disease risk factors. CV risk factors were determined based on the National Cholesterol Education Program Adult Treatmant Panel (NCEP ATP) III guidelines (14). We selected the following risk factors: hypertension, diabetes, current smoking, and age greater than or equal to 45 years for men and 55 years for women. Risk factors were assessed from physician-reported diagnoses recorded at study entry and visits prior to the index date.

Table I. Demographic and risk factors of the study cohorts.

	2003	2004	2005
CORRONA patients with inflammatory arthritis	n=3661	n=7092	n=8708
Patients taking NSAIDs	n=2797	n=4199	n=4643
Baseline characteristics			
Age (mean ± SD)	56.7 ± 13.2	57.4 ± 12.8	56.9± 13.0
Female	2068 (74.9)	3068 (74.6)	3392 (74.0)
Race White	2332 (85.1)	3495 (85.6)	3939 (86.2)
Ethnicity Hispanic	199 (7.3)	333 (8.2)	316 (7.0)
RA diagnosis (versus PsA)*	2489 (89.0)	3776 (89.9)	4046 (87.1)
Gastroesophageal reflux	537 (19.2)	813 (19.4)	864 (18.6)
Traditional GI risk factors			
Peptic ulcer disease history*	278 (9.9)	403 (9.6)	381 (8.2)
Cardiovascular disease	204 (7.3)	323 (7.7)	306 (6.6)
Current aspirin use	384 (13.7)	558 (13.3)	670 (14.4)
Current steroid use*	991 (35.4)	1454 (34.6)	1473 (31.7)
Mean daily prednisone dose†	6.21	5.94	6.09
Traditional CV risk factors			
Hypertension*	868 (31.0)	1293 (30.8)	1316 (28.3)
Diabetes	219 (7.8)	306 (7.3)	324 (7.0)
Current smoker	429 (15.6)	646 (15.7)	676 (14.7)
Males age ≥45 years	585 (21.6)	908 (22.3)	1009 (22.2)
Females age ≥55 years	1113 (41.1)	1762 (43.3)	1902 (41.8)

All values are expressed as frequencies with percentages in parentheses, except where indicated.
No statistical differences across the 3 calendar years were noted, except for variables with an asterisk (*) with $p<0.05$.
† Mean daily dose for those patients taking prednisone.

Results

We identified 2,797 patients prescribed NSAIDs in calendar year 2003, defined as the baseline year and comparator cohort for the study. There were 4,199 patients prescribed NSAIDs in 2004 and 4,643 patients prescribed NSAIDs in 2005. Baseline demographic and clinical characteristics of patients in the study cohorts are described in Table I. For each of the cohorts, approximately one-third of the patients were greater than 65 years of age, and more than two-thirds were female. There were no clinically meaningful differences in GI risk factors across the three calendar years, with the exception of a modest difference in the prevalence of peptic ulcer disease and proportion of patients prescribed corticosteroids. Among CV risk factors, the only difference was the proportion of patients with hypertension which declined from 31.0% in 2003 to 28.3% in 2005 ($p<0.05$).

Longitudinal trends in rates of NSAID gastroprotective prescribing are summarized in Table II, using 2003 as the baseline year. Compared to 65.1% of NSAID users in 2003 prescribed any NSAID gastroprotective strategy, there was a modest decline to 62.9% of patients in 2004 ($p=0.018$) and a marked decline to 47.7% in 2005 ($p<0.001$). This decline in NSAID gastroprotection was observed across all levels of GI risk, as defined by number of risk factors. We also examined utlilization patterns over the 3-year period of the individual gastroprotective strategies. COX-2 inhibitor utilization declined

from 55.1% in 2003 to 29.2% in 2005 (p<0.001). These declines were associated with a small increase in utilization of gastroprotective co-therapies (PPI or misoprostol), increasing from 26.5% in 2003 to 28.3% in 2005 (p=0.052). Utilization rates stratified by number of GI risk factors are also summarized in Table II. Among patients with two or more risk factors, COX-2 inhibitor use decreased markedly from 58.9% in 2003 to 35.3% in 2005 (p<0.01). There was no significant change in GPA co-therapy during this time for patients with two or more risk factors.

Next, we examined rates of nsNSAID and COX-2 inhibitor utilization, stratified by number of CV risk factors (Table III). Among patients with pre-existing CV disease, 60.3% were prescribed a COX-2 inhibitor in 2003. There was no significant change in COX-2 inhibitor use (57.0%) in this high-risk group in 2004. However, COX-2 inhibitor use in patients with established CV disease declined to 34.0% (p<0.001) in 2005. During the same time period, among patients with established CV disease, there was a significant increase in the proportion of patients prescribed an nsNSAID from 49.0%in 2003 to 69.3% (p<0.001) in 2005. The trends were similar in stratified analyses with different numbers of CV risk factors. During this same time period, nsNSAID use increased overall, from 50.2% in 2003 to 73.9%(p<0.001) in 2005.

Trends in the use of specific nsNSAIDs and COX-2 inhibitors among patients with established CV disease, including stratified analyses by aspirin use, are shown in Table IV. Among all patients with established CV disease, naproxen use increased almost two-fold from 9.3% in 2003 to 17.7% in 2005 (p=0.003). In contrast, there were no significant changes in the use of ibuprofen, meloxicam, or other nsNSAIDs during the period from 2003 to 2005. In addition, there was no significant change in the use of celecoxib from 2003 to 2005. As expected, based on the timing of the market withdrawals, the rates of rofecoxib and valdecoxib declined from 2003 to 2005.

Among patients with established CV disease prescribed aspirin, naproxen

Table II. Gastroprotection strategies for patients prescribed NSAIDs with number of risk factors.

	2003 n=2797	2004 n=4199	2005 n=4643
Any gastroprotective strategy			
No GI risk factors	692 (58.8)	968 (55.8)*	811 (39.4)†
One GI risk factor	751 (67.5)	1112 (66.6)	931 (51.5)†
Two or more GI risk factors	378 (74.4)	561 (70.7)	473 (60.9)†
Overall (regardless of # of GI risk factors)	1821 (65.1)	2641 (62.9)*	2215 (47.7)†
Coxib utilization			
No GI risk factors	611 (51.9)	802 (46.2)†	531 (25.8)†
One GI risk factor	632 (56.8)	892 (53.4)*	549 (30.4)†
Two or more GI risk factors	299 (58.9)	435 (54.8)	274 (35.3)†
Overall	1541 (55.1)	2129 (50.7)†	1356 (29.2)†
Gastroprotective co-therapy			
No GI risk factors	234 (19.9)	352 (20.3)	428 (20.8)
One GI risk factor	314 (28.2)	494 (29.6)	566 (31.3)
Two or more GI risk factors	194 (38.2)	298 (37.5)	321 (41.3)
Overall	741 (26.5)	1146 (27.3)	1314 (28.3)

All comparisons are versus 2003 designated as the baseline year.
Any gastroprotective strategy is defined as either coxib use or concomitant gastroprotective co-therapy.
Gastroprotective co-therapy is defined as any proton pump inhibitor or misoprotol.
*Denotes p<0.05 but >0.01; † denotes p<0.01

Table III. NSAID and coxib utilization in patients with traditional CV risk factors.

	2003 n=2797	2004 n=4199	2005 n=4643
All NSAID use			
No CV risk factors	713 (25.5)	974 (23.2)	1151 (24.8)
One CV risk factor	1152 (41.2)	1814 (43.2)	2038 (43.9)
Two or more CV risk factors	934 (33.4)	1411 (33.6)	1453 (31.3)*
Established CV disease	204 (7.3)	323 (7.7)	305 (6.6)
Overall	2797 (100)	4199 (100)	4643 (100)
COX-2 inhibitors			
No CV risk factors	339 (47.6)	413 (42.4)†	258 (22.4)†
One CV risk factor	649 (56.4)	960 (53.0)*	620 (30.4)†
Two or more CV risk factors	554 (59.3)	754 (53.4)†	478 (32.9)†
Established CV disease	123 (60.3)	184 (57.0)	104 (34.0)†
Overall	1541 (55.1)	2129 (50.7)†	1356 (29.2)†
Non-selective NSAIDs			
No CV risk factors	414 (58.1)	612 (62.8)*	932 (81.0)†
One CV risk factor	558 (48.5)	933 (51.5)*	1484 (72.8)†
Two or more CV risk factors	433 (46.4)	712 (50.4)*	1013 (69.7)†
Established CV disease	100 (49.0)	147 (45.5)	212 (69.3)†
Overall	1404 (50.2)	2259 (53.6)†	3431 (73.9)†
Naproxen users			
No CV risk factors	90 (12.6)	159 (16.3)*	273 (23.7)†
One CV risk factor	107 (9.3)	223 (12.3)†	428 (21.0)†
Two or more CV risk factors	82 (8.8)	188 (13.3)†	268 (18.4)†
Established CV disease	19 (9.3)	30 (9.3)	54 (17.6)†
Overall	280 (10.0)	571 (13.6)†	966 (20.8)†
Non-naproxen Non-selective NSAIDs ‡			
No CV risk factors	324 (45.5)	453 (46.5)	660 (57.3)†
One CV risk factor	451 (39.2)	712 (39.3)	1058 (51.9)†
Two or more CV risk factors	351 (37.6)	522 (37.0)	746 (51.3)†
Established CV disease	81 (39.7)	117 (36.2)	158 (51.6)†
Overall	1127 (40.3)	1688 (40.2)	2461 (53.0)†

*Denotes p<0.05; †denotes p<0.01; ‡includes ibuprofen, meloxicam and "other non-selective NSAIDs"

Table IV. NSAID and COX-2 inhibitor utilization in patients with established cardiovascular disease.

	2003	2004	2005
Overall			
(All NSAID users with CV disease)	n=204	n=323	n=306
Ibuprofen	39 (19.12)	45 (13.93)	70 (22.88)
Naproxen	19 (9.31)	30 (9.29)	54 (17.65)†
Meloxicam	16 (7.84)	24 (7.43)	42 (13.73)*
Other non-selective NSAID	38 (18.63)	60 (18.58)	61 (19.93)
Celecoxib	57 (27.94)	108 (33.44)	84 (27.45)
Valdecoxib	27 (13.24)	34 (10.53)	19 (6.21)†
Rofecoxib	46 (22.55)	42 (13.00)†	1 (0.33)†
Aspirin users with CV disease	n=97	n=136	n=131
Ibuprofen	20 (20.62)	19 (13.97)	30 (22.90)
Naproxen	12 (12.37)	19 (13.97)	31 (23.66)*
Meloxicam	7 (7.22)	10 (7.35)	15 (11.45)
Other non-selective NSAID	7 (7.22)	29 (21.32)†	22 (16.79)*
Celecoxib	30 (30.93)	38 (27.94)	31 (23.66)
Valdecoxib	14 (14.43)	13 (9.56)	13 (9.92)
Rofecoxib	25 (25.77)	16 (11.76)†	0 (0.00)†
Non-aspirin users with CV disease	n=107	n=187	n=175
Ibuprofen	19 (17.76)	26 (13.90)	40 (22.86)
Naproxen	7 (6.54)	11 (5.88)	23 (13.14)
Meloxicam	9 (8.41)	14 (7.49)	27 (15.43)
Other non-selective NSAID	31 (28.97)	31 (16.58)†	39 (22.29)
Celecoxib	27 (25.23)	70 (37.43)†	53 (30.29)
Valdecoxib	13 (12.15)	21 (11.23)	6 (3.43)*
Rofecoxib	21 (19.63)	26 (13.90)	1 (0.57)†

The group of aspirin users with CV disease is defined as aspirin users with CV disease within NSAID users. *Denotes $p<0.05$; † denotes $p<0.01$.

use increased significantly from 2003 to 23.7% (p=0.011) in 2005. Ibuprofen and meloxicam use did not change among this group during the time period studied, but the use of other nsNSAIDs increased from 7.2% in 2003 to 16.8% (p=0.02) in 2005.

Discussion

Since the withdrawal of rofecoxib and valdecoxib from the U.S. market, there has been limited data on changes in utilization patterns of NSAIDs and gastroprotective agents (GPA), particularly among rheumatologists. In this study, we examined changes in utilization patterns, focusing specifically on changes in prescribing patterns among patients at increased risk of NSAID-related GI and CV toxicities.

The first observation of this study was the marked decrease in overall gastroprotection among patients prescribed NSAIDs since the COX-2 inhibitor market withdrawals. In our study, this decline in NSAID gastroprotection was primarily attributable to decreased utilization of COX-2 inhibitor agents. Prior to the widespread adoption of COX-2 inhibitor prescribing, multiple studies demonstrated under-utilization of NSAID gastroprotection. Smalley and colleagues examined gastroprotection among recurrent NSAID users using data from the Tennessee Medicaid program shortly after the introduction of the first two COX-2 inhibitors (15). They found that fewer than one-third of patients with 2 or more risk factors also received a GPA. Sturkenboom *et al*. also examined gastroprotective cotherapy at the time of new NSAID initiation in a large retrospective, observational study, similarly establishing underutilization of gastroprotection (16). However, both of these studies were completed soon after the introduction of the COX-2 inhibitors. Similarly, our previously published work examining NSAID prescribing patterns was conducted in 2004, prior to the market withdrawals (7).

Our study represents the first published assessment of U.S. rheumatologist prescribing patterns of NSAIDs and gastroprotection after the COX-2 market withdrawals. Similar findings were recently documented from a U.S. pharmacy claims database, but this may or may not reflect the practice patterns of U.S. rheumatologists (17). Moreover, Sun and colleagues did not examine utilization patterns among high-risk patients for GI and CV adverse outcomes. Although our study documents a steep decline in NSAID gastroprotection among patients including high-risk patients, the clinical significance of this trend is only beginning to be examined. Singh and colleagues recently reported a marked increase in ulcer-related complications among elderly NSAID users since the COX-2 inhibitor market (18).

Our second major finding in the study was the parallel increase in utilization of nsNSAIDs in patients with established CV disease that accompanied the decline in COX-2 inhibitor utilization. Although the discontinuation of COX-2 inhibitor agents in patients with established coronary artery disease is supported by a number of RCTs and observational studies (4, 19-21), there is ample evidence to suggest individual nsNSAIDs, with the possible exception of naproxen, may also predispose to CV events. In a post-hoc analysis of a study of a COX-2 inhibitor lumiracoxib that has not yet received FDA approval (TARGET), which assessed patients at high CV risk, Farkouh and colleagues found that patients prescribed ibuprofen had a higher risk of ischemic CV events compared to supratherapeutic doses of lumiracoxib (22). Indeed, large observational studies have also found increased risk of CV events associated with most nsNSAIDs, with the possible exception of naproxen (23-26). In this respect, the increase in naproxen prescribing among high risk CV patients in our study may indicate rheumatologist awareness of the emerging evidence that naproxen may indeed confer a smaller CV risk than other nsNSAIDs.

Our third major objective was to specifically examine NSAID prescribing patterns among patients with established CV disease who were also prescribed low-dose aspirin. Evidence of a possible interaction of aspirin and nsNSAIDs, particularly ibuprofen, has raised concern regarding nsNSAID

prescribing in this high-risk patient population. This concern has been supported by work by Catella-Lawson and colleagues who demonstrated that inhibition of platelet aggregation by aspirin was diminished in the presence of ibuprofen, but not diclofenac or rofecoxib (27). A putative mechanism may be interference with aspirin acetylation at the COX-1 binding site on the platelet. The potential clinical relevance of this interaction was demonstrated by a retrospective cohort study by MacDonald and colleagues which indicated that patients taking aspirin and ibuprofen had an increase in both all cause and cardiovascular mortality as compared with patients taking aspirin alone (28). In contrast, naproxen and meloxicam have been shown to lack the inhibiting effect on the anti-platelet effect of aspirin (29, 30). Additional evidence of a possible interaction between aspirin and nsNSAIDs includes the work of Kurth and colleagues in a subanalysis of the Nurses Health Study, among other studies (31-34).

Based on these data, the channeling of high risk CV patients on aspirin who were previously on a COX-2 inhibitor agent to nsNSAIDs including ibuprofen may not entirely reduce CV risk in these patients. Ultimately, a randomized controlled trial may be the only approach to more definitively resolve whether aspirin interacts with specific nsNSAIDs in a clinically relevant manner.

The strengths of this study include the prospective longitudinal nature of the CORRONA registry with large numbers of patients enrolled from over 200 participating U.S. rheumatologists In addition, registries such as CORRONA that capture lifetime medical histories such as remote peptic ulcer and CV disease provide valuable tools for assessing utilization patterns in high risk GI and CV patients. In addition, over-the-counter (OTC) omeprazole, aspirin, ibuprofen and naproxen are specifically collected in the CORRONA dataset and these OTC drugs are frequently under-reported or missing in administrative databases. As a result, this registry-based study provides valuable insights into the decision-making and prescribing patterns of rheumatologists in the aftermath of the COX-2 inhibitor market withdrawals in the United States.

There are limitations in our analysis as well. Although the CORRONA registry does not apply any exclusion criteria for enrollment for patients with RA and PsA, participation in the registry is voluntary, and it is possible that certain types of patients may be under-represented. Lipid measurements were not collected during the study period in the CORRONA registry during the entire study period, although other NCEP ATP III risk factors for CV disease were recorded. Finally, we limited our analysis to the interval immediately before and after the COX-2 inhiibitor withdrawals and it is possible that the utilization trends may further evolve. Despite these limitations, CORRONA is one of the few multi-centered registries of inflammatory arthritis patients in the United States, and the largest RA registry that includes physician data captured longitudinally.

In conclusion, our data indicate that the COX-2 market withdrawals led to an overall decline in NSAID gastroprotection prescribed by rheumatologists. The underutilization of gastroprotective cotherapies in patients at increased GI risk represents an opportunity to improve the quality of care and patient outcomes. While the discontinuation of COX-2 inhibitors in high CV risk patients is appropriate, recent evidence suggests that the channeling of these patients to nsNSAIDs observed in our study may also increase CV risk. Ongoing clinical vigilance for NSAID-related GI and CV-related toxicities is required.

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