Risk of Gastrointestinal Events in Patients with Rheumatoid Arthritis After Withdrawal of Rofecoxib

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ABSTRACT. ***Objective.*** To examine the incidence of gastrointestinal (GI) events in patients with rheumatoid arthritis (RA) after the removal of rofecoxib from the market.

Methods. Residents of British Columbia with a diagnosis of RA who were chronic users of cyclooxygenase 2 (COX-2) inhibitors or nonselective nonsteroidal antiinflammatory drugs (nsNSAID) as of September 30, 2004, were included. We studied the risk of GI events using incidence rates and adjusted HR from Cox proportional hazards regression using time-dependent covariates.

Results. The cohort comprised 4266 patients with a mean age of 60 years and over 72% women, of which 2034 (48%) were classified as COX-2 inhibitor users and 2232 (52%) as chronic nsNSAID users as of September 30, 2004. The 2 groups were well balanced on baseline covariates except for comorbid conditions. In the year following rofecoxib withdrawal, 174 patients (5.5%) experienced 1 or more GI events, defined as a GI-related physician visit or hospitalization. There was no statistically significant increase in the risk of a GI event between those classified as a COX-2 inhibitor or nsNSAID user at the time of withdrawal (HR 1.03, 95% CI 0.69–1.54). Considering the drug exposure at the time of the event, there was no increased risk of GI events associated with the use of either COX-2 inhibitors or nsNSAID, or with the use of oral corticosteroids, low-dose aspirin, or clopidogrel, after adjustment for potential confounders.

Conclusion. In this cohort, withdrawal of rofecoxib did not result in a significant increase in GI events among patients with RA. (J Rheumatol First Release March 15 2012; doi:10.3899/jrheum.110604)

Key Indexing Terms:
RHEUMATOID ARTHRITIS GASTROINTESTINAL RISK ROFECOXIB

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Since the withdrawal from the market of rofecoxib on September 30, 2004, due to an increased risk of cardiovascular (CV) adverse events[1], several studies have sought to describe population-level treatment changes among users of rofecoxib and other selective cyclooxygenase 2 (COX-2) inhibitors[2,3,4,5,6,7]. These studies suggest that the rofecoxib withdrawal resulted in a decrease in dispensing of all selective COX-2 inhibitors[2,3,4,7] because more COX-2 users discontinued nonsteroidal antiinflammatory drug (NSAID) therapy completely or switched to a nonselective NSAID (nsNSAID) than switched to another selective COX-2 inhibitor[5,6]. Among all users of selective COX-2 inhibitors 1 year after the withdrawal of rofecoxib, Sukel and colleagues[6] observed that although the greatest proportion (43%) discontinued NSAID use altogether, a large proportion (28%) switched to an nsNSAID. Among the users who switched to an nsNSAID, only half were also prescribed a proton pump inhibitor (PPI), indicating that the treatment change may have increased their vulnerability to a gastrointestinal (GI) adverse event. This pattern raises the concern that large-scale switching from selective COX-2 inhibitors to more gastrotoxic nsNSAID may lead to an increase in GI events at the population level.

To our knowledge, 4 studies have been published exam-

ining the effects of the withdrawal of rofecoxib on the rate of GI events at a population level[8,9,10,11], yet only 1 of these studies evaluated the difference in risk for patients switching to an nsNSAID compared to another COX-2 inhibitor[11]. Schneeweiss and colleagues[11] found a significant short-term increase in upper GI complications among rofecoxib users with osteoarthritis (OA) or rheumatoid arthritis (RA) who switched to an nsNSAID compared to those who switched to another COX-2 inhibitor. That study also showed a significantly higher proportion of rofecoxib users switched to an nsNSAID (17%) 1 month after the withdrawal than did users of any selective COX-2 inhibitor (9%)[11].

Comparing the reports of Schneeweiss, *et al*[11] and Sukel, *et al*[6], it appears that the proportion of COX-2 inhibitor users who switched to an nsNSAID may be lower within the OA/RA population than in the general population (9%[11] versus 26%[6] at 1 month). Potential differences in NSAID switching patterns between all users of selective COX-2 inhibitors and users with OA or RA suggest that the influence of NSAID switching on GI outcomes may vary depending on the population. The purpose of our study was to describe postwithdrawal changes in the use of selective COX-2 inhibitors and nonselective NSAID among patients with RA specifically. Importantly, RA patients are at an increased risk of both CV and GI adverse events, making any NSAID use challenging. Further, exposure to specific NSAID may change frequently during followup among patients with RA, making time-dependent measures of NSAID exposure, and exposure to other drugs influencing GI risk, especially important. While Schneeweiss and colleagues[11] tracked only the first treatment change within the 4 weeks following the withdrawal of rofecoxib and limited the followup of GI outcomes to 3 months, there is evidence of significant differences in treatment patterns 1 month and 1 year following the rofecoxib withdrawal[6]. Our study was therefore designed to characterize the risk of GI events in the RA population in the 12 months following the withdrawal of rofecoxib.

MATERIALS AND METHODS

Study design. A population-based retrospective cohort study using linked health database records of patients with RA in British Columbia (BC), Canada.

Data sources. Data on patient characteristics and health services use were obtained from the BC Medical Services Plan and Hospital Separations databases, which contain billing information on all outpatient physician visits and hospital discharges for the province of BC. Data on drug use were obtained from the BC PharmaNet database, which contains a record of the specific drug, dispensation date, and days of medication supplied for every prescription dispensed in BC. Data from these 3 databases were linked for each individual patient using a unique identifying number derived from their Personal Health Number.

Inclusion/exclusion criteria. The study cohort was derived from a population-based cohort of patients with RA from all included RA cases ≥ 18 years of age in the province of BC who had received care for their RA between 1996 and 2006, identified using physician billing data as described. We selected RA cases who had at least 1 physician visit for RA [International Classification of Diseases, 9th revision (ICD-9) code 714.X] between September 30, 2002, and September 30, 2004, and who were chronic users of a COX-2 inhibitor or nsNSAID. Chronic users were defined as patients who had filled a prescription for a selective COX-2 inhibitor or nsNSAID and who met the following criteria: (1) were taking a COX-2 inhibitor or nsNSAID as of September 30, 2004; and (2) received a supply of at least 180 days of either a COX-2 inhibitor or nsNSAID (or any combination thereof) between October 1, 2003, and September 30, 2004 (i.e., in the year prior to the withdrawal).

Sample characteristics. Patient characteristics, determined as of September 30, 2004, included age, sex, history of a previous GI event or visit to a GI specialist (practitioner's registered specialty code 56), and the number of chronic diseases identified between October 1, 2003, and September 30, 2004. The Deyo-adapted Charlson Index was used to determine the number of comorbid diseases for each patient[12,13,14]. Patients with 2 or more comorbid diseases were categorized as 1 group because of the small number of patients with comorbidities in this range[12,15]. Every patient was classified as a user of either a selective COX-2 inhibitor or nsNSAID based on the most recent dispensed prescription prior to September 30, 2004.

Followup. Patients were followed from the date of their last day's supply of rofecoxib (rofecoxib users) or from October 1, 2004 (all other patients) until a GI event (hospitalization or physician visit), death, or September 30, 2005, whichever occurred first. If a patient experienced both a physician visit and a hospitalization, the hospitalization was treated as the first event regardless of the order of events.

Assessment of drug exposure. For all drugs, exposures were assumed to begin on the dispensation date and the defined daily dose was used in the calculation of the number of days exposed to a drug. The exposure period for selective COX-2 inhibitors, nsNSAID, low-dose aspirin, PPI/misoprostol, H_2-receptor blockers, and clopidogrel was defined as 125% of the number of days of medication supplied. Exposure to warfarin was assumed to be constant until a break of 3 months from the end of 1 prescription (defined as 125% of the number of days of medication supplied) and the dispensing of a subsequent prescription. As corticosteroids are supplied in a variety of strengths (e.g., for prednisone, 1 mg, 5 mg, and 50 mg tablets) and dosage changes may occur that are not recorded in PharmaNet, the exposure period for corticosteroids was defined as 45 days from the dispensation date if no further corticosteroids were dispensed. If a prescription for a selective COX-2 inhibitor was dispensed while a patient had a supply of an nsNSAID it was assumed that the nsNSAID was stopped and the patient switched to a COX-2 inhibitor, and vice-versa. If both the number of days prescribed was fewer than 7 and the quantity dispensed of a COX-2 inhibitor or nsNSAID was to last < 7 days, it was assumed that a mistake had been made in the data entry and the prescription was excluded from the analysis (resulting in exclusion of 0.4% of COX-2 and nsNSAID prescriptions).

Outcome measures. The primary outcome was the occurrence of a GI event potentially related to NSAID use such as ulcerations, perforations, or bleeds in the upper or lower GI tract requiring hospitalization or physician visit. If a patient experienced both a GI-related physician visit and hospitalization, the hospitalization was treated as the GI event regardless of the order of events. GI hospitalizations were identified from the Hospital Separations database and included diagnoses of ulceration, perforation, or bleeding in the upper GI tract (ICD-9 codes 531.x, 532.x, 533.x, 534.x, 535.01, 535.31, 578.0, 578.1, 578.9, 537.83) or of a lower GI event occurring in either the small intestine (beyond the duodenum) or the colon/rectum, i.e., gross rectal bleeding, lower GI perforation, ulceration, or diverticulitis with hemorrhage (ICD-9 codes 562.02, 562.03, 562.12, 562.13, 569.3, 569.41, 569.83, 569.82, 569.85). Hospitalizations for operative gastroscopy or other invasive GI diagnostic procedures were also included (ICD-9 codes 55.0, 56.83, 56.89). Physician visits for GI events were identified from the BC Medical Services Plan physician billing data using the ICD-9 codes listed above or an appropriate fee-for-service code.

We also calculated the number of switches a patient made between

valdecoxib, celecoxib, meloxicam, and other nsNSAID in the month and year following withdrawal (or the month following the end of a rofecoxib prescription or to the end of the followup period). For patients who made at least 1 switch from 1 NSAID to another, we identified the drug dispensed that represented the first switch in the study period.

Statistical analyses. Baseline characteristics of the sample were summarized using means and standard deviations (SD) for continuous data and frequencies and percentages for categorical data. The baseline differences between those classified as a selective COX-2 inhibitor and an nsNSAID user were investigated using 2-sample t tests and Pearson chi-square for continuous and categorical data, respectively. A Cox regression model with time-dependent covariates was used to compare HR for GI events between drug exposure categories. All drug exposures were considered as time-dependent variables in the model. At any given time, the model considered a patient as belonging to the risk sets corresponding to their drug exposure categories. GI event rates were adjusted for baseline patient characteristics that could be potential confounders, including age, sex, Charlson comorbidity index, classification of a selective COX-2 inhibitor or nsNSAID user as of September 30, 2004, and history of a GI event/visit between October 1, 2003, and September 30, 2004. Statistical significance was set at 0.05 (2-tailed). To assess the robustness of the results, the definitions of drug exposures were varied in 2 sensitivity analyses. These analyses considered all GI events that occurred within 100% and 150% of the number of days of medication supplied (as opposed to within 125% of days supplied in the main analysis). We also conducted a sensitivity analysis in which we limited the outcome to only the patients with hospitalizations after September 30, 2004.

RESULTS

Baseline patient characteristics. There were 19,085 individuals who fit our definition of RA who were prescribed either a selective COX-2 inhibitor or nsNSAID in the year prior and the year following September 30, 2004. Once the inclusion criteria for chronic use were applied, the cohort comprised 4266 patients, of which 2034 (48%) were classified as COX-2 inhibitor users and 2232 (52%) as nsNSAID users as of September 30, 2004. Baseline patient characteristics for COX-2 inhibitor and nsNSAID users are shown in Table 1. Among patients classed as COX-2 inhibitor users at the time of the withdrawal, the majority were taking celecoxib (52%), followed by rofecoxib (37%). There were no significant differences between COX-2 inhibitor and nsNSAID users for previous GI event (p = 0.354); however, these groups did differ in the mean age (p = 0.032), sex (p =

Table 1. Baseline characteristics of COX-2 inhibitor and nsNSAID users. Data are mean ± SD or no. (%) unless otherwise indicated.

Characteristics	COX-2 Inhibitor, n = 2034	NSAID, n = 2232	p
Age, yrs	60.3 ± 13.4	59.4 ± 14.0	0.032
Female* (%)	1492 (73.4)	1575 (70.6%)	0.043
Previous GI event/visit (in prior year; %)	116 (5.7)	113 (5.1)	0.354
Charlson comorbidity index* (%)			< 0.001
0	1327 (65.2)	1289 (57.8)	
1	498 (24.5)	691 (31.0)	
2+	209 (10.3)	252 (11.3)	
Drugs taken at withdrawal (%)			
Rofecoxib	484 (23.8)		
Rofecoxib + GI**	155 (7.6)		
Rofecoxib + anticoagulant/corticosteroid***	61 (3.0)		
Rofecoxib + GI + anticoagulant/corticosteroid††	47 (2.3)		
Valdecoxib	162 (8.0)		
Valdecoxib + GI**	27 (1.3)		
Valdecoxib + anticoagulant/corticosteroid***	22 (1.1)		
Valdecoxib + GI + anticoagulant/corticosteroid††	12 (0.6)		
Celecoxib	645 (31.7)		
Celecoxib + GI**	231 (10.4)		
Celecoxib + anticoagulant/corticosteroid***	117 (5.8)		
Celecoxib + GI + anticoagulant/corticosteroid††	68 (3.3)		
Meloxicam		259 (11.6)	
Meloxicam + GI**		91 (4.1)	
Meloxicam + anticoagulant/corticosteroid***		44 (2.0)	
Meloxicam + GI + anticoagulant/corticosteroid††		21 (0.9)	
Other nsNSAID		1112 (49.8)	
Other nsNSAID + GI**		425 (19.0)	
Other nsNSAID + anticoagulant/corticosteroid***		155 (6.9)	
Other nsNSAID + GI + anticoagulant/corticosteroid††		122 (5.5)	

* Significant differences between groups (p < 0.05). ** Includes proton pump inhibitors (PPI)/misoprostol and H_2 blockers. *** Includes clopidogrel, low-dose aspirin, oral corticosteroids, and warfarin. †† Includes either PPI/misoprostol or H_2 blockers and clopidogrel or low-dose aspirin or oral corticosteroids or warfarin. GI: gastrointestinal; nsNSAID: nonselective nonsteroidal antiinflammatory drug; COX-2: cyclooxygenase 2.

0.043), and number of comorbid diseases based on the Charlson comorbidity index ($p < 0.001$).

NSAID switching in the month following rofecoxib withdrawal. Table 2 shows the number of switches between valdecoxib, celecoxib, meloxicam, and other nsNSAID in the first month following rofecoxib withdrawal, or in the month following the end of a rofecoxib prescription after the date of withdrawal. Table 3 describes the first switch among patients who switched at least once in the month following withdrawal or the end of rofecoxib prescription. Among the 750 patients who had an active prescription for rofecoxib at the time of withdrawal, 263 did not use any NSAID in the month following the end of their prescription. Among the 487 who made a switch, over half switched to another COX-2 inhibitor (38% switched to celecoxib and 27% to valdecoxib) rather than an nsNSAID (17% switched to meloxicam and 18% to another nsNSAID). Among patients taking a COX-2 inhibitor other than rofecoxib at the time of the withdrawal, only a very small percentage switched to an nsNSAID in the following month. Specifically, 1% of patients switched from valdecoxib and celecoxib, respectively, to either meloxicam or another nsNSAID.

NSAID switching in the year following rofecoxib withdrawal. Table 4 shows the number of switches between valdecoxib, celecoxib, meloxicam, and other nsNSAID in the year following the withdrawal. Table 5 outlines the first switch among patients who switched at least once in the year following withdrawal. Among the 586 patients who were taking rofecoxib at the time of withdrawal and made a switch before September 30, 2005, over half switched to another COX-2 inhibitor (37% to celecoxib and 24% to valdecoxib) as their first alternative antiinflammatory.

Gastrointestinal events. In the year following the withdrawal, 174 patients (5.5%) experienced at least 1 GI event requiring a physician visit or hospitalization. This included 119 patients (2.8%) who had a GI-related physician visit, 16 (0.4%) who were hospitalized due to a GI event, and 39 (0.9%) who had both a physician visit and a hospitalization. The results of the time-dependent multivariate Cox regression model are displayed in Table 6. In this analysis, the hazard of GI events between October 1, 2004, and September 30, 2005, was about 3 times higher among patients who experienced a GI event in the year prior to September 30, 2004, compared to those who did not (HR 3.35, 95% CI 2.22–5.07). GI events were significantly more common among patients with 1 comorbid disease relative to those with no comorbid disease (HR 1.44, 95% CI 1.03–2.01). There was no statistically significant increase in the risk of a GI event between those classified as using a COX-2 inhibitor versus nsNSAID users at the time of withdrawal (HR 1.03, 95% CI 0.69–1.54). Further, considering the drug exposure at the time of the event, there was no increased risk of GI events associated with the use of either COX-2 inhibitors or nsNSAID, or with the use of oral corticosteroids, low-dose aspirin, or clopidogrel, after adjustment for potential confounders.

Table 2. Number of drug changes in month following withdrawal of rofecoxib[†].

	No. Drug Changes in Month Following Withdrawal			
Drug at Withdrawal	0	1	2	Total
Rofecoxib	0	461	26	487[††]
Valdecoxib	212	11	0	223
Celecoxib	1041	17	0	1058
Meloxicam	412	6	0	418
Other nsNSAID	1786	19	2	1807*

[†] Or month following end of rofecoxib prescription if receiving rofecoxib. [††] 263 patients were not receiving a COX-2 inhibitor or nsNSAID in the month following withdrawal.* 7 patients were not receiving a COX-2 inhibitor or nsNSAID in the month following withdrawal. nsNSAID: nonselective nonsteroidal antiinflammatory drug; COX-2: cyclooxygenase inhibitor.

Table 3. First change in drug in the month following withdrawal of rofecoxib.

	Drug of 1st Switch in Month Following Withdrawal				
Drug at Withdrawal	Valdecoxib	Celecoxib	Meloxicam	Other nsNSAID	Total
Rofecoxib	131	187	83	86	487
Valdecoxib	0	1	3	7	11
Celecoxib	5	0	1	11	17
Meloxicam	1	3	0	2	6
Other nsNSAID	10	8	3	0	21

nsNSAID: nonselective nonsteroidal antiinflammatory drug.

Table 4. Number of drug changes in year following withdrawal of rofecoxib†.

Antiinflammatory at Withdrawal	No. Drug Changes in Year Following Withdrawal 0	1	2+	Total
Rofecoxib	0	344	224	568*
Valdecoxib	86	116	21	223
Celecoxib	844	154	61	1059
Meloxicam	349	46	23	418
Other nsNSAID	1740	37	36	1813

† Or to September 30, 2005, for patients finishing rofecoxib prescription after October 1, 2004. * 2 patients had a gastrointestinal event before starting a new COX-2 inhibitor or nsNSAID prescription. nsNSAID: nonselective nonsteroidal antiinflammatory drug; COX-2: cyclooxygenase inhibitor.

Sensitivity analyses. Varying the time window of exposure from 100% to 150% of the days' supply did not affect the estimates of the HR for the multivariable COX regression, suggesting that the model and the results are robust to our assumption of sporadic use of antiinflammatory drug therapy (data not shown). Further, by limiting the outcome to only patients with a GI-related hospitalization after September 30, 2004, the results were consistent, with the exception of a decreased risk of GI events associated with COX-2 inhibitor use (HR 0.32, 95% CI 0.12–0.84).

DISCUSSION

To our knowledge, this is the first study to assess the effect of the withdrawal of rofecoxib on GI events specifically in patients with RA, based on time-dependent drug exposures. The RA patient population is of particular interest given that NSAID are often used as a first-line treatment option in combination with disease-modifying antirheumatic drugs for RA, and patients with RA are already at an increased risk for both CV and GI events. In this retroprospective cohort, we found no statistically significant difference in GI events between patients who switched to an nsNSAID compared to those who switched to another COX-2 inhibitor in either the month or the year following the withdrawal of rofecoxib. In the year following the withdrawal, more than half the patients previously receiving rofecoxib switched to another COX-2 inhibitor, and the overall incidence of GI events was 5.5%. This rate was significantly higher among patients who experienced a GI event in the year prior to September 30, 2005, than among those who did not. Taking into account drug exposure at the time of the event, no increased risk was found with concomitant corticosteroid use, low-dose aspirin, or clopidogrel, after adjustment for potential confounders.

Table 6. Cox regression model with time-dependent exposure to determine the association between drug exposure and gastrointestinal events.

Variable	HR	(95% CI)	p
Nonselective NSAID	0.72	(0.52–1.14)	0.953 0.191
COX-2 inhibitor	0.67	(0.42–1.04)	0.076
Oral corticosteroid	1.14	(0.74–1.75)	0.553
Warfarin	1.72	(0.80–3.70)	0.168
Low-dose aspirin	1.55	(0.67–3.55)	0.304
Clopidogrel	1.97	(0.79–4.90)	0.145
Patient taking COX-2 inhibitor at withdrawal	1.03	(0.69–1.54)	0.869
Female	0.92	(0.66–1.27)	0.602
GI event in prior 12 months	3.35	(2.22–5.07)	<0.001
Age (per additional 10 years)	1.12	(1.00–1.25)	0.061
Charlson comorbidity index			
0 (reference)	1	—	
1	1.44	(1.03–2.01)	0.034
2+	1.43	0.92–2.23)	0.110

The effect of the withdrawal of rofecoxib on GI outcomes in chronic COX-2 inhibitor users has been described in the general population and within a group of patients with OA or RA. Taha and colleagues noted a slight increase between 2002 and 2005 in the rate of GI bleeds in Scotland, yet they found this increase to be associated with an increase in the use of low-dose aspirin, other antithrombotics, and alcohol, and not significantly associated with nsNSAID use[8]. In the United Kingdom, Wheeler and colleagues noted a slight increase in the rate of hospitalizations for GI hemorrhage after 2002, but noted that this predated the withdrawal of rofecoxib[10]. In an international comparison of mortality rates due to myocardial infarction and GI hemorrhage, Metcalfe, *et al* found no effect of the rofecoxib withdrawal on mortality, and in fact noted an apparent reduction in mortality due to GI hemorrhage and acute myocardial infarction after 2004[9]. Among patients with OA or RA, Schneeweiss, *et al* found no increase in the rates of GI-relat-

Table 5. First change in drug in the year following withdrawal of rofecoxib†.

Antiinflammatory at Withdrawal	Drug of 1st Switch in Year Following Withdrawal Valdecoxib	Celecoxib	Meloxicam	Other nsNSAID	Total
Rofecoxib	136	208	98	126	568
Valdecoxib	0	35	29	73	137
Celecoxib	16	0	30	169	215
Meloxicam	5	12	0	52	69
Other nsNSAID	14	40	19	0	73

† Or to September 30, 2005, for patients finishing rofecoxib prescriptions after October 1, 2004. nsNSAID: nonselective nonsteroidal antiinflammatory drug; COX-2: cyclooxygenase inhibitor.

ed hospitalizations in people switching from rofecoxib to nsNSAID, but did find an increase in outpatient visits for peptic ulcer disease[11].

The following limitations of our study should be considered when interpreting the results. First, although hospitalizations for GI events and endoscopy have been validated as outcome measures[16], physician visits for GI symptoms may not always be recorded as such, potentially resulting in underestimation of outpatient GI events. Second, the database used to determine drug exposure does not include data regarding nonprescription use of other available NSAID (e.g., ibuprofen) and thus this potential exposure is not accounted for. Third, there is inherent difficulty in characterizing the duration of use of warfarin and corticosteroids due to the nature of the treatment course, which often involves frequent dosing changes, as well as tapering schedules that are not always recorded in the PharmaNet database. This may have resulted in misclassification of a proportion of patients in the regression analysis. Fourth, in the event that patients had overlapping nsNSAID and COX-2 inhibitor prescriptions, we assumed that the first prescription was discontinued, which may underestimate exposures in some patients. Also, although there is an accepted classification scheme for NSAID as either COX-2-selective or nonselective, these drug entities in fact make up a spectrum of enzyme selectivity, and we were unable to account for this variability. Finally, there is some possibility that cotherapy with GI drugs (PPI, H_2 antagonists, or misoprostol) or lower doses or intermittent use of NSAID could lead to a reduction in events, thus accounting for a lack of difference between the groups. From Table 1, it appears that patients prescribed nsNSAID have a higher use of concomitant GI drugs than those taking COX-2 inhibitors.

The latter information is supported by the recently published CONDOR trial results, which demonstrated in a straightforward randomized controlled trial of celecoxib versus NSAID that most of the noted adverse events were of bleeding and not ulcers or other complications of ulcers. This information might be helpful for the discussion.

Our report has several strengths, including the methodology used for determining GI events, which has been shown to have high validity[16,17]. In our statistical analysis, a time-dependent Cox model was used, allowing the exposure status to vary with time and thus more accurately represent an individual's changing exposure status[18]. Finally, we conducted sensitivity analyses to measure potential effects of our chosen 125% exposure time estimate. These analyses showed no effect on HR, indicating that our model was robust with regard to the estimated duration of drug exposure. In terms of generalizability, the databases used for determining drug exposures record all individuals enrolled in the publicly funded BC health insurance program, effectively identifying all patients with RA in the province regardless of source of funding for medications.

We conclude that in this cohort of patients with RA the withdrawal of rofecoxib from the market resulted in a prescribing shift mainly to other COX-2 inhibitors, and did not result in a significant increase in GI events over the following month or year.

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