Use of Nonsteroidal Antiinflammatory Drugs: Is There a Change in Patient Risk Profile After Withdrawal of Rofecoxib?

ELHAM RAHME, JEAN-PASCAL ROUSSY, JEAN-PHILIPPE LAFRANCE, HACENE NEDJAR, and SUZANNE MORIN

ABSTRACT. ***Objective.*** Use of traditional nonsteroidal antiinflammatory drugs (tNSAID) increased after rofecoxib withdrawal. tNSAID use is associated with increased gastrointestinal (GI) toxicity and cardiovascular (CV) risk similar to celecoxib. The objective of our study was to describe changes in celecoxib and tNSAID use regarding GI and CV risk and congestive heart failure (CHF) and renal risk that occurred in Quebec, Canada, between April 2005-March 2007 (the post-period) compared to April 2002-March 2004 (the pre-period).

Methods. Data were obtained from the provincial health insurance agency. All NSAID users ≥ 50 years of age were considered.

Results. Celecoxib use decreased by 23% (coxib 61%) while that of tNSAID doubled. In both periods, celecoxib users were older and included more women, and they suffered more frequently from arthritis. Users of celecoxib were more likely to have higher level of GI risk: post-period odds ratios compared to low GI risk, very high 1.79 (95% CI 1.63, 1.97), high 1.76 (95% CI 1.71, 1.81), and moderate 1.30 (95% CI 1.27, 1.33); similar results were observed in the pre-period. Celecoxib users had higher CV risk levels in the pre-period: OR compared to low CV risk, very high 1.13 (95% CI 1.08, 1.19), high 1.24 (95% CI 1.20, 1.29), and moderate 1.16 (95% CI 1.14, 1.19); and in the post-period, very high 0.85 (95% CI 0.81, 0.89), high 1.13 (95% CI 1.10, 1.16), and moderate 1.15 (95% CI 1.12, 1.17). CHF and renal risk factors did not play an important role in the choice of NSAID in either period.

Conclusion. Current NSAID use differs from that prior to 2004. Coxib utilization decreased substantially and patients at high CV risk seem less likely to receive celecoxib, while those at high GI risk seem more likely to receive it. (J Rheumatol First Release Nov 15 2010; doi:10.3899/jrheum.100332)

Key Indexing Terms:
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The cyclooxygenase-2 inhibitors (coxibs) celecoxib and rofecoxib were widely used in the years following their market introduction (October 1999-September 2004) because of their improved gastrointestinal (GI) safety profile compared to traditional nonsteroidal antiinflammatory drugs (tNSAID)[1]. In September 2004, rofecoxib was withdrawn from the market following clinical trial results that indicated its association with an increased risk of cardiovascular (CV) events compared to placebo[2]. Currently, celecoxib is the only coxib on the Canadian market and it is reimbursed by the provincial drug plan in Quebec, Canada.

Concerns about coxib-related CV events have prompted some patients and their physicians to look for alternative treatments such as tNSAID or concurrent use of acetylsalicylic acid (ASA), although none of these options has been proven to be safer than celecoxib from a CV standpoint[3]. tNSAID have also been associated with CV events[4] and, while concurrent use of ASA is known to increase risk of GI adverse events[5], its prophylactic property against NSAID-related CV adverse events has not been proven. In Canada, all NSAID product monographs currently include a CV risk warning[6]. Unless stated otherwise, "NSAID" in this report refers to both tNSAID and coxibs.

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Guidelines for NSAID prescription have recently been published[7,8,9,10,11]. According to these guidelines, tNSAID and celecoxib remain an appropriate option to relieve pain and inflammation despite concerns related to their GI, CV, congestive heart failure (CHF), and renal safety; acetaminophen alone is less effective than NSAID therapy in many patients[12,13,14], and narcotic use may be associated with sedative effects, constipation, and concerns about dependence[15]. Monitoring NSAID use in terms of patient baseline risk factors is therefore necessary to assess its risks at the population level. Current NSAID use may have changed substantially from that prior to withdrawal of rofecoxib, with increased knowledge regarding NSAID-related CV risk[4,16,17]. A study assessing utilization of NSAID in Quebec after the withdrawal of rofecoxib (October 2004-September 2007) among new users was conducted by the Conseil du Médicament[18]. That study found that older patients, women, those with GI risk factors, and those with rheumatic diseases were more likely to receive celecoxib than tNSAID. However, the study did not examine the changes that occurred in NSAID use in the period post-rofecoxib withdrawal compared to pre-rofecoxib withdrawal in terms of patients' GI, CV, CHF, and renal risk levels.

We aimed to describe the profile, including GI, CV, CHF, and renal risk levels, of patients 50 years of age or older who used celecoxib and tNSAID in Quebec between April 1, 2005, and March 31, 2007 (the post-period), compared to that of patients who used these medications between April 1, 2002, and March 31, 2004 (the pre-period).

MATERIALS AND METHODS

Data sources. Demographic, physician billing, and pharmacy records were obtained from the Régie de l'Assurance Maladie du Québec (RAMQ), the Government of Quebec health insurance agency. RAMQ coverage for outpatient and inpatient physician services is universal (7,518,473 persons in 2007). In addition, all persons aged 65 years or older, and all those younger than 65 who receive social assistance or do not have access to a group private drug insurance plan are eligible for coverage under the public drug reimbursement program administered by RAMQ[19]. In 2007, RAMQ provided prescription drug coverage to 3,177,369 individuals (42% of the population), 976,525 of whom were 65 years of age and older, 505,502 who were receiving social assistance, and 1,695,342 who were eligible for coverage (i.e., not eligible for private drug insurance). RAMQ has provided unrestricted coverage for tNSAID and celecoxib since their listing on the drug formulary. The RAMQ data have been described elsewhere[20].

Permissions from the Institutional Review Board of the Research Institute of McGill University Health Centre and from the Government of Quebec Ethics Committee, the Commission d'Accès à l'Information, were obtained to conduct this study.

Study population. We conducted a population-based, cross-sectional study using demographic, physician billing, and prescription drug records obtained from the RAMQ databases for all persons aged 50 years and older who filled at least one prescription for a tNSAID or a coxib during one or both periods (pre-period April 1, 2002, to March 31, 2004; and post-period April 1, 2005, to March 31, 2007). The tNSAID considered were: all dosages of naproxen, diclofenac, ibuprofen, and other tNSAID (diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid, and tolmetin). Patients who used rofecoxib during the pre-period were not considered in the main analyses because these patients would have been more deeply affected by the withdrawal of rofecoxib than patients taking celecoxib or tNSAID. The remaining patients were separated into 2 groups by study period. Those who used NSAID during both periods were included in both groups. For every patient in each group, respectively, the index date was the date of his/her first dispensed celecoxib or tNSAID during the corresponding period. To be included in the study in either group, patients had to be registered with the RAMQ drug plan for at least 1 year prior to their index date to assess their previous drug utilization.

Baseline characteristics. Baseline patient characteristics assessed at the index date for each study period were: demographics (age, sex, income status); specialty of the physician who prescribed the NSAID; new prescription versus refill of a previous prescription; rheumatoid arthritis (RA) or osteoarthritis (OA) status; and CV, GI, CHF, and renal risk levels as described in Appendixes 1 and 2. Four risk levels (low, moderate, high, and very high) were considered in each of the 4 conditions (GI, CV, CHF, and renal; Appendix 2). Risk categories were created based on published guidelines and expert opinion[7,8,9,10,11].

Statistical analyses. Comparison of baseline characteristics between the 2 periods. Descriptive analyses (means and standard deviations or proportions) were used as required to report patient characteristics at the index date by study period. A multivariable logistic regression model was used to identify factors associated with post- versus pre-period celecoxib use. In this analysis, only patients who received celecoxib at the index date were included. The dependent variable was a dichotomous variable where 1 indicated the post-period. The model included all patient baseline characteristics listed above. Similar analyses were used to compare baseline patient characteristics of patients who received tNSAID at the index date during the post- versus the pre-period. Multicollinearity was assessed using the variance inflation factor. A variance inflation factor ≥ 10 is an indication of multicollinearity[21]. The goodness of fit of the model was examined using the Hosmer-Lemeshow goodness of fit test. Receiver-operating characteristics curves were also plotted; a larger area under the curve indicates better fit.

Comparison of baseline patient characteristics between celecoxib and tNSAID users within the 2 periods. Two separate multivariable logistic regression models were constructed to identify baseline patient characteristics associated with celecoxib versus tNSAID utilization within the post- and pre-periods, respectively.

Subgroup analyses. Some patients may have been included in both the post- and pre-periods. Because these periods are separated by a 12-month interval, and because major decisions (withdrawal of rofecoxib and alteration of celecoxib monographs) were implemented during this interval, the choice of the NSAID medication was considered independently between these 2 periods. However, to minimize any carryover effect between the 2 periods, we conducted a first-subgroup analysis where only patients who did not use any NSAID during the previous year were included ("new users"). Also, as indicated in Appendix 2, all patients age 65 years and older were considered to be at risk of GI adverse events, therefore no patient in that age group would be at the low GI risk level[8]. To investigate the effect of this limitation on the results, we conducted a second subgroup analysis where we included only patients 50–64 years of age.

All analyses were performed using SAS version 9.2 for UNIX (SAS Institute Inc., Cary, NC, USA).

RESULTS

Comparison of NSAID users between post- and pre-periods. The number of patients using celecoxib decreased by 18.5% in the post- compared to the pre-period, while use of tNSAID increased by 106% (Table 1). Indeed, during the

Table 1. Baseline characteristics of celecoxib and traditional nonsteroidal antiinflammatory drug (tNSAID) users within each study period.

	Post-period (2005–07)		Pre-period (2002–04)	
	Celecoxib, No. (%)	tNSAID, No. (%)	Celecoxib, No. (%)	tNSAID, No. (%)
No. patients	145,596	249,433	178,714	120,809
Age ≥ 65 yrs	96,778 (66.5)	130,264 (52.2)	121,480 (68.0)	61,358 (50.8)
Female	95,754 (65.8)	146,519 (58.7)	119,152 (66.7)	67,129 (55.6)
Higher income	80,692 (55.4)	156,397 (62.7)	99,829 (55.9)	76,780 (63.6)
Prescriber specialty				
Rheumatologist	4,412 (3.0)	6,050 (2.4)	5,159 (2.9)	3,291 (2.7)
General practitioner	128,490 (88.3)	214,779 (86.1)	157,283 (88.0)	103,239 (85.5)
Internal medicine	1,549 (1.1)	2,592 (1.0)	2,153 (1.2)	1,523 (1.3)
Other	11,145 (7.7)	26,012 (10.4)	14,119 (7.9)	12,756 (10.6)
Renewal	37,485 (25.8)	41,691 (16.7)	52,916 (29.6)	26,235 (21.7)
Rheumatoid arthritis	3,682 (2.5)	4,160 (1.7)	4,267 (2.4)	2,400 (2.0)
Osteoarthritis	21,500 (14.8)	25,870 (10.4)	25,410 (14.2)	11,309 (9.4)
Gastrointestinal risk level				
Low	20,133 (13.8)	59,784 (24.0)	26,415 (14.8)	33,652 (27.9)
Moderate	75,603 (51.9)	132,174 (53.0)	90,289 (50.5)	61,124 (50.6)
High	49,018 (33.7)	56,354 (22.6)	60,957 (34.1)	25,497 (21.1)
Very high	842 (0.6)	1,121 (0.5)	1,053 (0.6)	536 (0.4)
Cardiovascular risk level				
Low	27,028 (18.6)	63,927 (25.6)	31,033 (17.4)	31,682 (26.2)
Moderate	79,121 (54.3)	125,881 (50.5)	95,551 (53.5)	61,395 (50.8)
High	35,785 (24.6)	52,334 (21.0)	45,963 (25.7)	23,957 (19.8)
Very high	3,662 (2.5)	7,291 (2.9)	6,167 (3.5)	3,775 (3.1)
Congestive heart failure risk level				
Low	48,091 (33.0)	102,354 (41.0)	57,321 (32.1)	51,610 (42.7)
Moderate	45,587 (31.3)	70,213 (28.2)	58,263 (32.6)	35,498 (29.4)
High	49,896 (34.3)	73,696 (29.6)	60,269 (33.7)	32,109 (26.6)
Very high	2,022 (1.4)	3,170 (1.3)	2,861 (1.6)	1,592 (1.3)
Renal risk level				
Low	24,269 (16.7)	55,928 (22.4)	29,810 (16.7)	29,268 (24.2)
Moderate	117,804 (80.9)	187,298 (75.1)	144,275 (80.7)	88,506 (73.3)
High	1,555 (1.1)	2,743 (1.1)	2,034 (1.1)	1,444 (1.2)
Very high	1,968 (1.4)	3,464 (1.4)	2,595 (1.5)	1,591 (1.3)

pre-period (April 2002-March 2004), 193,265 patients used rofecoxib at the index date, 178,717 celecoxib, and 120,809 tNSAID (42,159 naproxen, 31,202 diclofenac, 18,753 ibuprofen, 28,695 other tNSAID); and during the post-period (April 2005-March 2007) 145,596 patients used celecoxib and 249,433 tNSAID (105,715 naproxen, 78,844 diclofenac, 29,708 ibuprofen, 35,166 other tNSAID; Tables 1 to 4). Most patients had at least one risk factor for NSAID-related adverse events in both periods: for the post-period as follows, GI [celecoxib 125,463 (86%); tNSAID 189,649 (76%)], CV [celecoxib 118,568 (81%); tNSAID 185,506 (74%)], CHF [celecoxib 97,505 (67%); tNSAID 147,079 (59%)], and renal [celecoxib 121,327 (83%); tNSAID 193,505 (78%)]. Similar results were found for the pre-period (Table 1).

Comparison of baseline characteristics of celecoxib users between the post- and pre-period. Logistic regression models revealed that celecoxib users in the post- versus the pre-period were more likely to be younger, more likely to have received the prescription from a rheumatologist, and more likely to have RA and OA (Table 2). Patients using celecoxib were also less likely to have received a refill (compared to a new prescription) at the index date in the post- versus the pre-period, suggesting that more patients received celecoxib in the post-period based on a new clinical evaluation (Table 2). Logistic regression models also revealed that celecoxib users in the post- compared to the pre-period were less likely to have CV risk factors, with odds ratios (OR) compared to low CV risk, very high 0.59 (95% CI 0.56, 0.62), high 0.81 (95% CI 0.79, 0.84), and moderate 0.92 (95% CI 0.90, 0.95); and they were more likely to have GI risk factors, with OR compared to low GI risk, very high 1.30 (95% CI 1.19, 1.43), high 1.34 (95% CI 1.27, 1.35), and moderate 1.29 (95% CI 1.26, 1.32; Table 2). Prior renal and CHF risk factors did not seem to have changed between periods among celecoxib users (Table 2).

Comparison of baseline characteristics of tNSAID users between the post- and pre-period. Users of tNSAID in the post- versus the pre-period were younger, more likely to be women, and more likely to have received their prescription from a general practitioner, but less likely to have received it from an internal medicine specialist compared to rheuma-

Table 2. Comparison of baseline characteristics among celecoxib and traditional nonsteroidal antiinflammatory drug (tNSAID) users between the post- versus pre-period: logistic regression. Data are OR (95% CI).

	Post- vs Pre-period	
	Celecoxib	tNSAID
No. patients	—	—
Age ≥ 65 yrs	0.83 (0.81, 0.85)	0.88 (0.86, 0.90)
Female	0.95 (0.93, 0.96)	1.14 (1.13, 1.16)
Higher income	0.96 (0.95, 0.98)	0.99 (0.98, 1.01)
Prescriber specialty		
Rheumatologist	1 (reference)	1 (reference)
General practitioner	0.95 (0.91, 0.99)	1.07 (1.02, 1.12)
Internal medicine	0.86 (0.79, 0.93)	0.88 (0.81, 0.95)
Other	0.91 (0.86, 0.95)	1.02 (0.97, 1.07)
Renewal prescription	0.81 (0.80, 0.83)	0.71 (0.70, 0.72)
Rheumatoid arthritis	1.09 (1.04, 1.14)	0.91 (0.86, 0.96)
Osteoarthritis	1.08 (1.05, 1.10)	1.15 (1.12, 1.17)
Gastrointestinal risk level		
Low	1 (reference)	1 (reference)
Moderate	1.29 (1.25, 1.32)	1.37 (1.34, 1.40
High	1.31 (1.27, 1.35)	1.43 (1.39, 1.47)
Very high	1.30 (1.19, 1.43)	1.34 (1.21, 1.49)
Cardiovascular risk level		
Low	1 (reference)	1 (reference)
Moderate	0.92 (0.90, 0.95)	0.89 (0.88, 0.91)
High	0.81 (0.79, 0.84)	0.86 (0.84, 0.89)
Very high	0.59 (0.56, 0.62)	0.73 (0.70, 0.77)
Congestive heart failure risk level		
Low	1 (reference)	1 (reference)
Moderate	0.98 (0.95, 1.00)	1.00 (0.98, 1.03)
High	1.10 (1.07, 1.13)	1.18 (1.15, 1.22)
Very high	1.02 (0.95, 1.08)	1.06 (0.99, 1.14)
Renal risk level		
Low	1 (reference)	1 (reference)
Moderate	1.04 (1.01, 1.06)	1.03 (1.01, 1.05)
High	0.99 (0.92, 1.07)	0.90 (0.84, 0.96)
Very high	1.06 (0.99, 1.13)	1.05 (0.98, 1.12)

Table 3. Comparison of baseline characteristics between celecoxib vs traditional nonsteroidal antiinflammatory drug (tNSAID) users within each study period: logistic regression. Data are OR (95% CI).

	Post-period (2005–07)	Pre-period (2002–04)
No. patients	—	—
Age ≥ 65 yrs	1.33 (1.30, 1.35)	1.39 (1.36, 1.42)
Female	1.28 (1.27, 1.30)	1.52 (1.50, 1.55)
Higher income	0.90 (0.89, 0.91)	0.93 (0.91, 0.94)
Prescriber specialty		
Rheumatologist	1 (reference)	1 (reference)
General practitioner	1.08 (1.04, 1.13)	1.20 (1.14, 1.26)
Internal medicine	0.92 (0.85, 0.99)	0.93 (0.86, 1.01)
Other	0.79 (0.75, 0.83)	0.88 (0.84, 0.93)
Renewal vs first prescription	1.63 (1.60, 1.65)	1.37 (1.34, 1.39)
Rheumatoid arthritis	1.27 (1.20, 1.33)	1.06 (1.00, 1.12)
Osteoarthritis	1.22 (1.19, 1.24)	1.31 (1.28, 1.34)
Gastrointestinal risk level		
Low	1 (reference)	1 (reference)
Moderate	1.30 (1.27, 1.33)	1.38 (1.34, 1.41)
High	1.76 (1.71, 1.81)	1.88 (1.82, 1.94)
Very high	1.80 (1.63, 1.97)	1.78 (1.59, 1.98)
Cardiovascular risk level		
Low	1 (reference)	1 (reference)
Moderate	1.15 (1.13, 1.18)	1.16 (1.14, 1.19)
High	1.14 (1.11, 1.17)	1.25 (1.21, 1.29)
Very high	0.85 (0.81, 0.90)	1.13 (1.08, 1.19)
Congestive heart failure risk level		
Low	1 (reference)	1 (reference)
Moderate	1.05 (1.03, 1.08)	1.07 (1.04, 1.10)
High	1.06 (1.03, 1.08)	1.13 (1.09, 1.16)
Very high	1.02 (0.96, 1.09)	1.04 (0.97, 1.11)
Renal risk level		
Low	1 (reference)	1 (reference)
Moderate	0.95 (0.93, 0.97)	0.96 (0.93, 0.98)
High	0.87 (0.81, 0.93)	0.81 (0.75, 0.87)
Very high	0.89 (0.84, 0.95)	0.92 (0.86, 0.99)

tologists (Table 2). Users of tNSAID in the post-period were also less likely to have RA, more likely to have OA, and less likely to have received a prescription refill (versus a new prescription) at the index date (Table 2). Changes similar to those described for celecoxib users were observed among tNSAID users between the 2 periods for CV, GI, CHF, and renal risk levels (Table 2).

Comparison of baseline characteristics of celecoxib and tNSAID users. Factors associated with celecoxib compared to tNSAID use at index date were similar between the 2 periods; age, female sex, having OA or RA, having a lower income, and receiving the prescription from a general practitioner versus a rheumatologist increased the likelihood of receiving a celecoxib at the index date. However, the strength of the association between these factors and the choice of celecoxib versus tNSAID seems to have changed between periods (Table 3).

Comparison between users of celecoxib and users of tNSAID revealed that users of celecoxib were more likely to have higher GI risk levels in both periods, with post-period OR: very high 1.79 (95% CI 1.63, 1.97), high 1.76 (95% CI 1.71, 1.81), and moderate 1.30 (95% CI 1.27, 1.33); and with pre-period OR: very high 1.77 (95% CI 1.59, 1.98), high 1.87 (95% CI 1.82, 1.94), and moderate 1.37 (95% CI 1.34, 1.41); and to have higher CV risk levels in the pre-period, with OR: very high 1.13 (95% CI 1.08, 1.19), high 1.24 (95% CI 1.20, 1.29), and moderate 1.16 (95% CI 1.14, 1.19); but lower very high CV risk levels in the post-period, with OR: very high 0.85 (95% CI 0.81, 0.89), high 1.13 (95% CI 1.10, 1.16), and moderate 1.15 (95% CI 1.12, 1.17; (Table 3). CHF risk factors alone did not play an important role in the choice between celecoxib and tNSAID in either the pre- or post-period, although the likelihood of being on celecoxib was slightly higher in patients with moderate to high levels of CHF risk. Patients using celecoxib seemed to be less likely to have prior renal risk factors in both periods (Table 3).

Further analyses revealed that patients at very high risk of CV events were 30% more likely to have received naproxen compared to celecoxib in the post-period but not in the pre-period (data not shown).

Similar but somewhat stronger associations were observed when analyses were repeated including only new users (Appendix 3). Of note, some new users (16.6%) received a prescription refill at the index date despite not having filled any NSAID prescription in the previous year, possibly reflecting the use of these medications on an as-needed basis (data not shown). Analyses restricted to patients 50 to 64 years of age revealed stronger differences in CV and GI risks among celecoxib users in the post- compared to the pre-periods; for CV, compared to low CV risk, OR: very high 0.44 (95% 0.40, 0.49), high 0.69 (95% 0.65, 0.72), and moderate 0.76 (95% 0.73, 0.79); and for GI, OR: very high 1.30 (95% 1.03, 1.62), high 1.49 (95% 1.37, 1.63), and moderate 1.33 (95% 1.29, 1.37), but otherwise with results similar to those shown in Table 3 (data not shown).

DISCUSSION

This study assessed the changes in use of celecoxib and tNSAID in terms of GI, CV, CHF, and renal risk levels between 2 similar time periods, one prior to the withdrawal of rofecoxib and one starting 6 months post-withdrawal. We found that the number of patients using celecoxib decreased by 18.5% in the post- compared to the pre-period, while use of tNSAID increased by 106%. In the post- but not the pre-period, patients with very high CV risk factors were less likely to receive celecoxib than tNSAID. Patients with GI risk factors were more likely to receive celecoxib than tNSAID in both periods. Differences in renal and CHF risk levels among celecoxib and tNSAID users overall seemed to be less important in either the pre- or post-period.

The post-period in our study started 6 months after the withdrawal of rofecoxib and was of 2 years' duration; the pre-period was the same duration as the post-period but ended 6 months prior to withdrawal of rofecoxib. We considered 6 months to be a sufficiently long period to allow the market to stabilize after the withdrawal of rofecoxib in 2004. Although valdecoxib was also withdrawn during the second period (April 2005), mainly due to skin adverse events, this is unlikely to have affected the market in Quebec as valdecoxib was never reimbursed by the Quebec drug plan. A 2-year duration, as opposed to one year, was considered for each of the 2 study periods to allow more robust estimations within subgroups with lower numbers of patients, such as those at very high risk of CV events.

Other studies that assessed NSAID use post-rofecoxib withdrawal in other countries have also reported a decrease in celecoxib utilization and an increase in tNSAID use[22,23,24,25,26,27]. Of note, most of these studies were conducted immediately after the withdrawal of rofecoxib and their results reflect utilization during a critical period when the market was still unstable. As described above, a 1-year period of market instability was removed from our study. Very few of the published studies examined NSAID use in terms of GI and CV risk levels, and none considered CHF and renal risks. Studies conducted in the United States also found that coxib use decreased following withdrawal of rofecoxib[22,28,29], likely influenced by concerns regarding CV risk[28,29]. A study in the United Kingdom also found that the number of users of coxibs declined sharply after withdrawal of rofecoxib[30]. As in our study, patients receiving coxibs post- compared to pre-rofecoxib withdrawal were younger and included more men. However, in contrast to our findings, no change in the proportion of patients with GI risk factors or high CV risk levels was found between the period post- versus pre- rofecoxib withdrawal[30]. This difference in results may be partly due to differences in the populations studied; while the UK study included patients 18 years of age or older, half of whom had no prior GI risk factor, our study included patients 50 years of age or older, most of whom (88%) were at risk of GI events. Two studies in Ireland also examined the use of NSAID following withdrawal of rofecoxib. In one study, among patients who were using rofecoxib on a chronic basis, 17.9% received no further NSAID prescription during the 12 months following withdrawal and 41% received sequential prescriptions for different NSAID[31]; whereas in the second study, female patients, those over age 65 years, and those with CV risk were more likely to receive celecoxib (in contrast to a tNSAID) in both post- and pre-rofecoxib withdrawal periods[32].

Our study is the first to examine NSAID use by GI, CV, CHF, and renal risk levels in both prevalent and new users. Although GI risk levels with NSAID utilization were extensively studied previously, CV, CHF, and renal risks have not been well examined. Whereas GI and CV risks seem to have influenced choice of NSAID, CHF and renal risks did not seem to influence that choice. CHF and renal risk factors also need to be considered when prescribing NSAID so that progression to more serious risk levels will be prevented.

Limitations of our study are common to studies using data from administrative databases. Our study used physician billing records in combination with pharmacy claims records to assess the GI, CV, CHF, and renal risk factors of patients. While most risk factors were assessed using medication prescribed for the condition of interest (e.g., antidiabetic use to determine diabetes), some comorbidities were determined based on International Classification of Diseases, 9th edition (ICD-9) codes found in physician claims. Because ICD-9 codes are not mandatory for reimbursement, they are sometimes not reported. Therefore, a physician claim for a condition most likely indicates the presence of the condition but its absence does not necessarily mean the absence of the condition. A comparison of RAMQ claims data and medical chart review found that the RAMQ database does not record all cases of diagnosed illness[33]. For example, only 28% of patients with chart-documented peptic ulcer were detected using diagnostic codes in the RAMQ claims data[33]. We used several criteria to detect

prior GI risk (hospitalizations for GI bleeding ulcers, use of gastroprotective agents, and diagnostic tests such as endoscopy and radiography). Nonetheless, this study may have underestimated the level of GI risk and other diseases among NSAID recipients in Quebec. Another limitation is that some risk factors considered in the study were common to more than one condition. For example, the presence of hypertension is a CV, CHF, and renal risk factor. However, statistical tests did not indicate collinearity between the variables considered in the models. The risk categories used in this study were based on published guidelines and expert opinion. Misclassification may have occurred in particular in the moderate and high-risk categories. Such misclassification was likely nondifferential between celecoxib and tNSAID users in both periods, and therefore was unlikely to have substantially biased our results. Nonetheless, our risk categorization requires validation in a future study.

OA and RA were identified using ICD-9 codes appearing twice during the previous 2 years. While this definition seems reasonable, its validity also has not been established. To our knowledge, there is no validated definition of OA and RA using administrative databases. We conducted an ad hoc analysis to examine roughly the sensitivity of the definition in patients with severe OA and RA. Among 2143 patients hospitalized for total hip or total knee replacement that we identified in 6 Montreal hospitals, 90.3% self-reported OA and 4.1% self-reported RA. OA was confirmed in 88.5% of patients using chart review and RA in 3.8%. In a similar patient population using RAMQ databases and the OA and RA definitions used in this study, 84.9% were identified with OA and 5.5% with RA. Therefore, our definition seems to identify most of those with severe OA and RA, perhaps overestimating RA and underestimating severe OA. A more formal validation study is needed to confirm these results in the general population.

In summary, celecoxib may be more prescribed for patients in need for chronic NSAID therapy. Patients at risk of CV events were less likely to receive a NSAID (either celecoxib or tNSAID) compared to those with no CV risk factors (low CV risk) in the post- compared to the pre-period. Patients at very high CV risk were less likely to receive celecoxib than tNSAID, particularly naproxen, post-rofecoxib withdrawal, while those with GI risk factors were more likely to receive celecoxib. The influence of CHF and renal risks on the choice of celecoxib compared to tNSAID appeared not to have changed between the post- and the pre-period. tNSAID and celecoxib remain widely used by the elderly, who often have more than one risk factor. Physicians need to consider GI, CV, CHF, and renal risk factors when prescribing NSAID, so that progression to more serious levels of risk will be prevented.

APPENDIX 1. Sources of variables and definitions (ICD-9, drug, or procedure codes are available from authors upon request)

Low-income status: social assistance (yes/no) for patients aged 50-64 years and guaranteed income supplement (yes/no) for those ≥ 65 years

Prescriber specialty: rheumatologist, internist, general practitioner, or other as provided in RAMQ data

Visits to rheumatologist, cardiologists, gastroenterologists, and nephrologists: physician specialty is provided in RAMQ data

New prescription: prescriptions are written with the possibility of 3 refills. A variable taking values 1–4 is available in RAMQ data (1 indicates a first fill)

Comorbidities: Includes rheumatoid arthritis; osteoarthritis; lower or upper GI events; alcohol and drug abuse; acute myocardial infarction; congenital heart disease; hypertension; diabetes; valvular disease; arrhythmia; cardiovascular disease; congestive heart failure; chronic kidney disease; peripheral vascular disease; chronic obstructive pulmonary disease; cancer; liver disease; liver cirrhosis; renal disease (other than chronic kidney disease), reno-vascular disease, stroke; other ischemic heart disease; acute renal failure: 2 diagnostic codes (ICD-9) in the prior 2 years

Medications: Includes gastroprotective agents (proton pump inhibitor, H_2-receptor antagonist or misoprostol); antidiabetics; antihypertensives; lipid-lowering agents; nitrates; digoxin; clopidogrel; antiarrhythmics; estrogen, serotonin reuptake inhibitors; diuretics, cardiotonic, vasodilators, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, hydralazine, beta-blockers, glitazones; antiplatelets, lipid-lowering agents, raloxifene or tamoxifene; nephrotoxic drugs: angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, calcineurin inhibitors, diuretics, aminoglycosides, sulfas, acyclovir, indinavir, triamterene, allopurinol, amphotericin, bisphosphonates, cimetidine, cisplatin, gold, ifosfamide, lithium, methotrexate, penicillamine, phospho soda enema (over the counter), tetracyclines]: Drug code in the prior year

Concomitant use of: low-dose acetylsalicylic acid (≤ 325 mg/day), systemic corticosteroid, anticoagulant, and multiple NSAID: drug supply overlapping the index date

Procedures: Procedures in the prior year: Upper digestive tract examination; coronary angiography or revascularization procedure; contrast media procedures (in the prior 30 days); electrocardiogram and electrophysiology; catheterization; coronary bypass surgery; anti-arrhythmic surgery; and cardiac surgery: Claim for an endoscopic or barium examination in the prior year

Hospitalization: For gastric or duodenal perforation, ulcer or bleeding, acute myocardial infarction or congestive heart failure: ICD-9 code for one of these conditions on a claim filed from a hospital center in the prior year

APPENDIX 2. Criteria of gastrointestinal, cardiovascular, congestive heart failure, and renal risk levels (as defined in Appendix 1) according to clinical practice guidelines. Risk level categories are mutually exclusive for each disease; patients were considered at the highest risk level for which they fulfilled the criteria.

Gastrointestinal Risk Level

Low. Criteria: No identified GI risk factor

Moderate. Criteria: One or more of the following: age 65-74 years; GI symptoms (dyspepsia, heartburn, esophageal reflux, gastritis, and duodenitis); upper GI diagnostic test (endoscopy or barium swallow); lower GI diagnostic test; dispensing of a proton pump inhibitor, H_2 receptor antagonist, misoprostol in the prior year; use of HP-Pack in the prior year; serious comorbid conditions (chronic obstructive pulmonary disease, diabetes, cancer, liver disease; hospitalization in an intensive care unit in the prior year); hospitalization in the cardiac ward in the prior year; concomitant use of ASA (low-dose); use of ≥ 2 NSAID concurrently; concomitant use of corticosteroid, clopidogrel, or SSRI

High. One or more of the following criteria: Age ≥ 75 years; concomitant anticoagulant use; concomitant use of ASA and clopidogrel; gastric or GI ulcer without bleeding or perforation; history of lower GI bleed; and liver cirrhosis

Very high. One or more of the following criteria: GI ulcer with bleeding or perforation (bleeding, perforation or rupture of esophagus)

Cardiovascular Risk Level

Low. Criteria: No identified CV risk factors

Moderate. One or more of the following criteria: Hypertension; diabetes;

use in the prior year of anticoagulants, antiplatelets, lipid-lowering agents, estrogen, raloxifene or tamoxifen; procedures in prior year (coronary angiogram; electrocardiogram and electrophysiology)
High. One or more of the following criteria: Both hypertension and diabetes; angina or other ischemic heart disease (other than acute myocardial infarction); peripheral vascular disease; congestive heart failure (CHF; no hospitalization); use in the prior year of antiarrhythmic drugs, nitrates, or cardiotonic drugs; and cardiac stimulator
Very high. Criteria: Acute myocardial infarction (hospitalization in prior 2 years); CHF (hospitalization in prior 2 years); procedures in the prior 2 years (catheterization; coronary bypass surgery; anti-arrhythmic surgery; cardiac surgery)

Congestive Heart Failure Risk Level
Low. Criteria: No identified risk factor
Moderate. One or more of the following criteria: Congenital heart disease; hypertension; diabetes; alcohol or drug abuse; use in the prior year of at least one medication from the following: diuretics, cardiotonic, vasodilators, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, hydralazine, beta-blockers, and glitazones
High. One or more of the following criteria: Valvular disease (mitral stenosis, mitral regurgitation, aortic stenosis and regurgitation); arrhythmia; CV disease; CHF (with no hospitalization), chronic kidney disease; and peripheral vascular disease
Very high. One or more of the following criteria: CHF hospitalization in the prior 2 years; acute myocardial infarction hospitalization in the prior 6 months; use of carvedilol, spironolactone in combination with another diuretic in the absence of a diagnosis of liver disease; use of a combination of diuretic + angiotensin converting enzyme inhibitors/angiotensin II receptor blockers/beta-blocker; and implantable cardioverter defibrillator with use of diuretic + angiotensin converting enzyme inhibitors/angiotensin II receptor blockers
Renal Risk Level
Low. Criteria: No identified renal risk factor
Moderate. One or more of the following criteria: Use in the prior year of angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers, diuretics, or nephrotoxic drugs (as defined in Appendix 1); diabetes; peripheral vascular disease; alcohol or drug abuse; contrast media procedures (in the prior 30 days); visit to a nephrologist (1-2 visits in prior 2 years); hypertension; age > 75 years; recent hospitalization (< 30 days)
High. One or more of the following criteria: Visit to a nephrologist (≥ 3 visits in prior 2 years); renal disease without chronic kidney disease; renovascular disease
Very high. One or more of the following criteria: Chronic kidney disease; acute renal failure; CHF; chronic liver disease

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APPENDIX 3. Comparison of patient baseline characteristics of naproxen, diclofenac, and ibuprofen compared to celecoxib new users in the post- and pre-periods, respectively: logistic regression. Data are OR (95% CI).

	Individual tNSAID vs Celecoxib					
	Post-period (2005–07)			Pre-period (2002–04)		
	Naproxen	Diclofenac	Ibuprofen	Naproxen	Diclofenac	Ibuprofen
No. patients*	78,802	49,484	22,257	29,117	16,491	13,578
Age ≥ 65 vs < 65 yrs	0.61 (0.59, 0.63)	0.82 (0.79, 0.84)	0.65 (0.62, 0.68)	0.52 (0.50, 0.54)	0.73 (0.70, 0.77)	0.63 (0.60, 0.67)
Female	0.73 (0.72, 0.75)0	0.79 (0.77, 0.80)	0.67 (0.65, 0.69)	0.61 (0.59, 0.63)	0.65 (0.63, 0.68)	0.63 (0.61, 0.66)
Higher vs lower income	1.10 (1.08, 1.11)	1.15 (1.12, 1.18)	0.99 (0.96, 1.03)	1.01 (0.98, 1.04)	1.16 (1.12, 1.20)	1.03 (0.98, 1.07)
Prescriber specialty						
Rheumatologist	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
General practitioner	1.76 (1.58, 1.96)	1.02 (0.92, 1.13)	2.39 (1.93, 2.94)	1.80 (1.51, 2.15)	0.93 (0.80, 1.10)	2.36 (1.76, 3.13)
Internal medicine	2.34 (2.01, 2.73)	1.22 (1.04, 1.43)	2.91 (2.22, 3.81)	2.19 (1.75, 2.74)	0.99 (0.78, 1.25)	2.37 (1.67, 3.35)
Other	2.57 (2.29, 2.88)	1.15 (1.03, 1.28)	5.30 (4.28, 6.56)	2.52 (2.11, 3.02)	1.14 (0.96, 1.35)	4.90 (3.69, 6.52)
Renewal vs first prescription	0.39 (0.36, 0.43)	0.67 (0.62, 0.73)	0.38 (0.33, 0.43)	0.75 (0.68, 0.82)	1.43 (1.31, 1.56)	0.62 (0.54, 0.71)
Rheumatoid arthritis	0.74 (0.65, 0.83)	0.76 (0.67, 0.86)	0.64 (0.52, 0.79)	1.00 (0.82, 1.21)	1.13 (0.92, 1.40)	0.79 (0.59, 1.06)
Osteoarthritis	0.68 (0.65, 0.71)	0.91 (0.88, 0.95)	0.59 (0.55, 0.63)	0.63 (0.59, 0.67)	0.91 (0.85, 0.98)	0.53 (0.48, 0.58)
Gastrointestinal risk level						
Low	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Moderate	0.75 (0.72, 0.77)	0.77 (0.74, 0.80)	0.67 (0.64, 0.70)	0.71 (0.68, 0.74)	0.74 (0.70, 0.78)	0.70 (0.66, 0.74)
High	0.49 (0.46, 0.51)	0.56 (0.54, 0.59)	0.47 (0.44, 0.51)	0.41 (0.39, 0.44)	0.52 (0.49, 0.56)	0.45 (0.41, 0.48)
Very high	0.50 (0.43, 0.57)	0.43 (0.36, 0.51)	0.49 (0.39, 0.59)	0.52 (0.42, 0.64)	0.32 (0.23, 0.44)	0.57 (0.44, 0.74)
Cardiovascular risk level						
Low	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Moderate	0.87 (0.84, 0.90)	0.94 (0.90, 0.97)	0.75 (0.72, 0.79)	0.88 (0.84, 0.91)	0.90 (0.86, 0.95)	0.79 (0.74, 0.84)
High	0.91 (0.87, 0.95)	0.96 (0.91, 1.01)	0.81 (0.75, 0.86)	0.83 (0.78, 0.88)	0.80 (0.76, 0.85)	0.75 (0.70, 0.81)
Very high	1.30 (1.20, 1.40)	1.06 (0.97, 1.15)	1.02 (0.91, 1.13)	0.98 (0.89, 1.08)	0.88 (0.78, 1.00)	0.83 (0.73, 0.95)
Congestive heart failure risk level						
Low	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Moderate	0.94 (0.90, 0.97)	0.99 (0.95, 1.03)	0.71 (0.68, 0.75)	0.94 (0.90, 0.98)	1.02 (0.98, 1.07)	0.70 (0.66, 0.73)
High	0.90 (0.87, 0.94)	0.97 (0.93, 1.02)	0.67 (0.64, 0.71)	0.84 (0.79, 0.89)	0.96 (0.90, 1.03)	0.58 (0.54, 0.62)
Very high	0.90 (0.81, 1.01)	0.99 (0.89, 1.11)	0.68 (0.58, 0.79)	0.86 (0.75, 0.99)	0.96 (0.81, 1.14)	0.52 (0.43, 0.63)
Renal risk level						
Low	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Moderate	1.00 (0.97, 1.04)	0.95 (0.91, 0.98)	2.18 (2.08, 2.29)	0.94 (0.91, 0.98)	0.87 (0.83, 0.92)	2.25 (2.12, 2.37)
High	1.05 (0.94, 1.16)	1.02 (0.91, 1.15)	2.78 (2.41, 3.21)	0.94 (0.81, 1.08)	1.10 (0.94, 1.30)	2.54 (2.12, 3.03)
Very high	1.11 (1.01, 1.22)	0.94 (0.84, 1.05)	2.77 (2.42, 3.16)	1.16 (1.02, 1.32)	0.92 (0.78, 1.09)	2.94 (2.49, 3.47)

* New users of celecoxib at index date: post-period 77,051 patients, pre-period 86,425 patients. tNSAID: traditional nonsteroidal antiinflammatory drugs.

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