The Risk for Myocardial Infarction with Cyclooxygenase-2 Inhibitors: A Population Study of Elderly Adults

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Background: **Cyclooxygenase-2 (COX-2) selective inhibitors have been marketed since 1999 as safer alternatives to nonsteroidal anti-inflammatory drugs (NSAIDs). Debate about their cardiac safety has culminated in the recent withdrawal of rofecoxib. Additional studies are needed to better understand this risk and to determine whether this safety concern represents a class effect.**

Objective: **To assess the influence of various NSAIDs on the risk for a first myocardial infarction (MI).**

Design: **Population-based, retrospective cohort study analyzed using a time-matched, nested case–control approach.**

Setting: **Québec, Canada.**

Participants: **113 927 elderly persons without previous MI and newly treated with an NSAID between 1 January 1999 and 30 June 2002.**

Measurements: **NSAID exposure and occurrence of MI assessed by using Québec's administrative health databases.**

Results: **Compared with no use of NSAIDs in the year preceding the event, current use of rofecoxib was associated with an increased risk for an acute MI (rate ratio [RR], 1.24 [95% CI, 1.05 to 1.46]) that was more pronounced at higher doses (RR, 1.73 [CI, 1.09 to 2.76]). The concomitant use of aspirin appears to decrease the risk associated with low-dose rofecoxib (RR, 1.00 [CI, 0.77 to 1.28]) but not with high-dose rofecoxib (RR, 2.36 [CI, 1.27 to 4.39]). No increased risks were observed with celecoxib (RR, 0.99 [CI, 0.85 to 1.16]) or the other NSAIDs.**

Limitations: **The study could not completely account for all potential confounders, including over-the-counter use of aspirin and ibuprofen.**

Conclusions: **These results provide evidence of an increased risk for acute MI in current users of rofecoxib among elderly persons with no history of MI. This risk appears greater at higher doses. Aspirin use mitigates the risk associated with low-dose but not high-dose rofecoxib. There was no evidence of an increased risk with the other NSAIDs.**

Ann Intern Med. 2005;142:●●●-●●●. www.annals.org

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Cyclooxygenase-2 (COX-2) selective inhibitors, with their improved gastrointestinal toxicity profile, have been marketed since 1999 as safer alternatives to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) (1–3). Although these agents experienced unprecedented growth in market share, their use has not lacked controversy. Concerns regarding their potential cardiovascular toxicity were first raised in 2000 after the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (2), and then again in 2001 by the U.S. Food and Drug Administration (4) and a pooled analysis (5). However, the results of the large Celecoxib Long-term Arthritis Safety Study (CLASS) did not support the cardiotoxicity hypothesis for all COX-2 inhibitors (6). Initially, it was unclear whether the use of different comparator groups, differences between rofecoxib and celecoxib, or differences in the use of concomitant aspirin explained these divergent results. Subsequent observational studies (7–10) and meta-analyses (11–13) also reported conflicting results. Moreover, none of the studies published to date have had the power to adequately address the potentially risk-modifying effects of aspirin.

On 30 September 2004, Merck & Co., Inc., announced the worldwide voluntary withdrawal of rofecoxib after the data safety monitoring board overseeing the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial of rofecoxib, 25 mg/d, in individuals at risk for developing colon cancer recommended that the study be halted prematurely (14, 15). An interim analysis found that after 18 months of use, rofecoxib increased the risk for confirmed cardiovascular events compared with placebo. The Food and Drug Administration has since indicated that they now intend to carefully review the safety of all marketed COX-2 inhibitors (16).

Considerable uncertainty remains regarding the clinical profile of persons at risk for COX-2–mediated cardiovascular events and whether celecoxib, as well as other COX-2 selective agents, poses a similar risk. We conducted a retrospective, population-based cohort study to address these unresolved issues. Using a large and relatively unselected population of elderly persons who had no history of myocardial infarction (MI) and were initiating treatment with an NSAID, we assessed 1) whether and to what extent the use of various NSAIDs changes the risk for a first MI compared with persons who did not use these agents in the year preceding the event date and 2) how dose, concomitant therapy with aspirin, and both factors simultaneously may modify this risk.

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Context

Do risks for myocardial infarction (MI) differ among cyclooxygenase-2 (COX-2) selective inhibitors and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs)?

Contribution

This retrospective study involving 113 927 people older than age 65 years used Québec's administrative health databases to examine associations between various NSAIDs and risk for a first MI. Compared with nonuse of NSAIDs, use of rofecoxib was associated with a 1.24 higher relative risk for MI (95% CI, 1.05 to 1.46), while neither celecoxib nor other NSAIDs were associated with statistically significant increased risks.

Cautions

Although analyses controlled for potential confounders, unmeasured factors such as over-the-counter use of aspirin and ibuprofen could have affected results.

–The Editors

METHODS

Study Sample and Data Source

We identified a cohort of individuals 66 years of age and older newly treated with an NSAID by using the computerized health insurance and vital statistics databases of the province of Québec, Canada. These administrative databases were developed as a result of the universal health care programs offered to residents and are now extensively used for research (17–23). We used the following data sources for this study: 1) the beneficiary database, managed by the Régie de l'Assurance-Maladie du Québec (RAMQ), which provided information on sociodemographic characteristics and dates of coverage; 2) the prescription drug database, which provided information on all outpatient prescriptions dispensed to residents 65 years of age and older, including drug name, strength, quantity, days supplied, and dispensing date; 3) the medical services database, which provided information on all medical visits, including the date and nature of service, with diagnostic codes, location of service, and physician's specialty; 4) the hospitalization database, which provided information on all hospitalizations, including date of admission and discharge, primary diagnosis, and up to 15 secondary diagnoses codes, and an indicator of hospital mortality when applicable; and 5) the vital statistics database, which provided information on all deaths, including date and cause. Each resident is represented in these databases by an encrypted unique identifier that enables record linkage at the level of the individual. The ethics boards of Québec (Commission d'accès à l'information du Québec) and the Royal Victoria Hospital, McGill University, approved the study.

Study Design

We conducted a retrospective, population-based cohort study that was analyzed by using a time-matched, nested case–control approach. The cohort consisted of a random sample (n = 125 000) of all residents age 66 years and older who were dispensed an NSAID between 1 January 1999 and 30 June 2002; the date of the first prescription was taken as cohort entry. We excluded persons who had not been enrolled in the health plan for at least 1 year preceding cohort entry, had been dispensed a study drug within this 1-year baseline period (n = 1193), or had received prescriptions from 2 or more NSAID categories on the day of cohort entry (n = 153). We also excluded persons hospitalized for an MI (International Classification of Diseases, Ninth Revision, codes 410 [acute] and 412 [old], all diagnostic fields) any time before cohort entry (n = 8168). We followed the remaining individuals until the earlier of one of the following dates: first hospitalization for an acute MI, end of coverage (due to death or emigration from the province), death, or end of the study (31 December 2002).

Study End Point

The case-defining event was a first hospitalization with a diagnosis of acute MI (International Classification of Diseases, Ninth Revision, code 410), nonfatal or fatal, occurring any time after cohort entry. The date of admission was used as the index date. This diagnostic code has previously been validated (24). For the MI to be considered a valid study end point, the hospital length of stay had to be at least 3 days, unless the patient had been transferred to or from another institution or had undergone percutaneous coronary angioplasty.

NSAID Exposure

All NSAIDs covered by the prescription drug benefit program during the study period were identified and classified into the following mutually exclusive categories, determined prospectively on the basis of their differential inhibition of cyclooxygenase: 1) NSAIDs (nonselective, nonaspirin NSAIDs, excluding naproxen), 2) naproxen (partially selective), 3) celecoxib (COX-2 selective), 4) rofecoxib (COX-2 selective), and 5) meloxicam (preferentially selective COX-2 inhibitor). All of these agents were available without prescribing restrictions. Valdecoxib could not be included because it was not available in Canada when the study was initiated. The accuracy and completeness of the prescription drugs database have previously been demonstrated; less than 1% of the information is out of range or missing (25).

The exposure time window of primary interest, identified a priori, was current use. However, we also evaluated use in the year preceding the index date (ever use). Individuals were considered currently exposed if the duration of the last prescription dispensed overlapped with the index date. Past users had filled at least 1 NSAID prescription in the year preceding the index date but were not currently

exposed, whereas ever users included both current and past users. Those who had not received any NSAIDs in the year preceding the index date were classified as nonusers in this time period.

We defined the following dosage categories for the COX inhibitors a priori: 200 mg/d or less (low-dose) or greater than 200 mg/d (high-dose) for celecoxib and 25 mg/d or less (low-dose) or greater than 25 mg/d (high-dose) for rofecoxib. To study the effects of aspirin on the relationship between NSAIDs and MI, we classified individuals as current users of aspirin if the duration of the last aspirin prescription dispensed before the event overlapped with the index date or ended within 30 days of this date. We used the 30-day grace period to account for aspirin's irreversible effect on platelet aggregation and the possibility of nonadherence (26, 27).

Statistical Analysis

To study exposure to NSAIDs in relation to the index date (the etiologically relevant exposure time window) while simultaneously controlling for the potentially confounding effects of calendar time, we used a time-matched, nested case–control analysis (28, 29). The index date of each case-patient was used to define the risk sets from which controls were chosen. For each case-patient, we randomly selected 20 controls matched on month and year of cohort entry and age (±1 year) and assigned them the case-patient's index date. Consequently, follow-up time was identical for case-patients and controls within each risk set. We compared the risk for acute MI associated with the current use of various NSAIDs with that of "nonusers" in the year preceding the index date. Thus, we could disentangle the independent effect of individual COX inhibitors from those of naproxen and other NSAIDs since all exposure groups were compared with nonusers. We estimated crude and adjusted rate ratios (RRs) for these associations using conditional logistic regression (30, 31). These measures of association are equal to the hazard ratios that would be estimated from the corresponding Cox proportional hazards regression. All rate ratios were adjusted for the potentially confounding effects of well-established conventional risk factors, including age; sex; hypertension; coronary artery disease; cerebrovascular disease; peripheral vascular disease; congestive heart failure; diabetes; and use of antilipemic agents, anticoagulants, and aspirin. In addition, the presence of respiratory illness, gastrointestinal ulcer disease, thyroid disorders, depression or psychiatric illness, use of oral corticosteroids, 3 measures of health care utilization (the number of hospitalizations, medical outpatient visits, and visits to a cardiologist), as well as 3 measures of comorbidity (the chronic disease score [32], the number of distinct drugs dispensed [33], and the Charlson index [34]), were evaluated as possible confounders using the change-in-estimate method (35). Covariates were retained in the final model if the risk estimate changed by 10% or more. We report risk estimates adjusted for all aforementioned covariates, including nonconfounders, because a parsimonious modeling approach provided no important gain in precision. With the exception of health care utilization and indices of comorbidity, which were assessed in the year preceding the index date, all other covariates were assessed in the year before cohort entry (at baseline). We identified medications using the prescription drug database and identified comorbid conditions using both discharge diagnosis codes and specific corresponding drug treatments.

Since aspirin use is an important determinant of MI (36, 37) and may modify the association between NSAIDs and MI, we included an interaction term for the current use of aspirin in subsequent models.

Role of the Funding Source

The Canadian Institutes of Health Research funded this study and had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

RESULTS

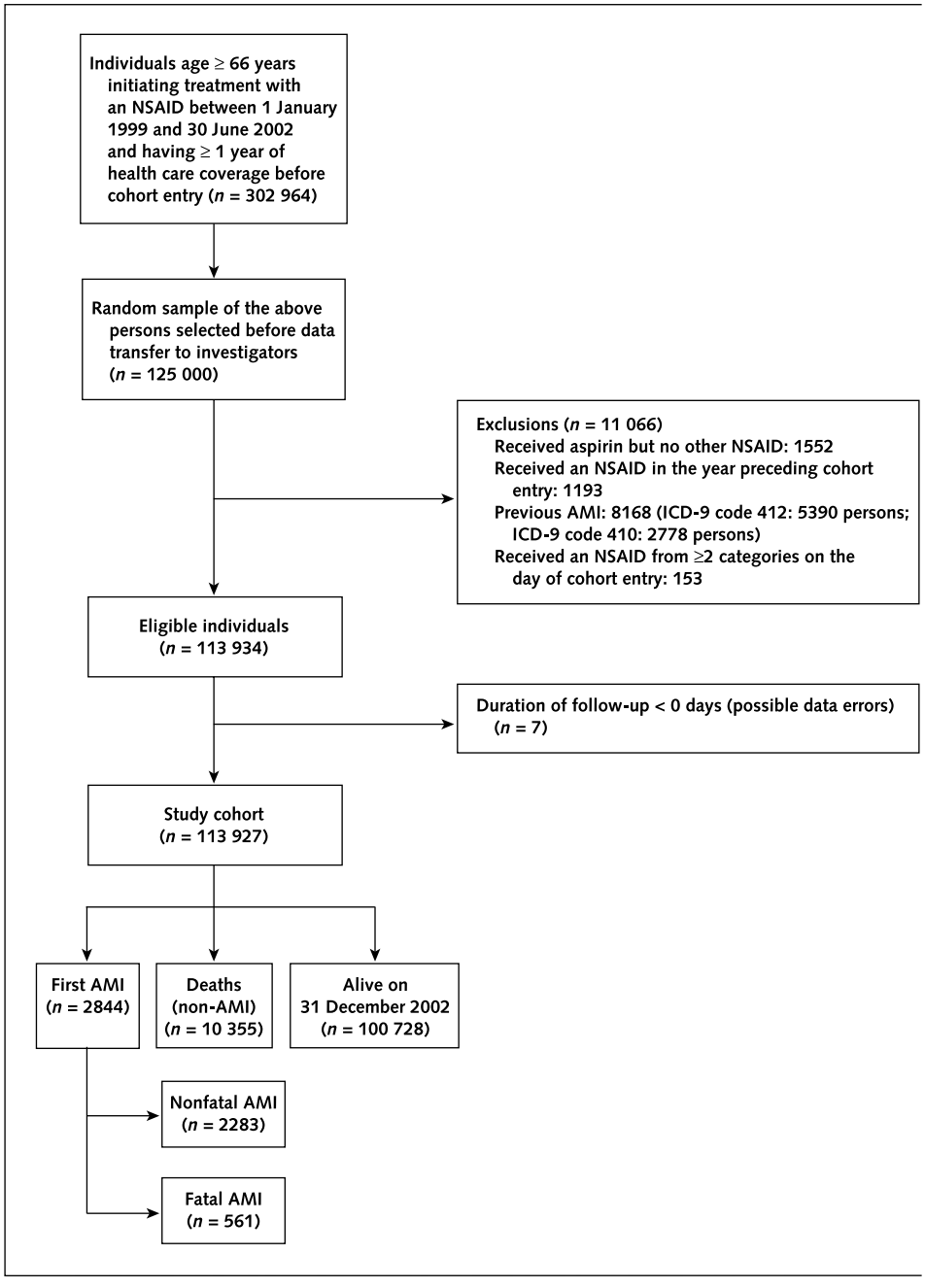
A total of 302 964 elderly persons initiated treatment with an NSAID during the study period (**Figure**). Because the provincial ethics review board considered this cohort too large, the RAMQ selected a random sample of 125 000 individuals before data transfer. After we applied the exclusion criteria, the study cohort consisted of 113 927 persons with a mean age (±SD) of 75.2 ± 5.5 years at cohort entry. This cohort was followed for an average (±SD) of 2.4 ± 0.98 years. A previous MI was the primary source of exclusions. During follow-up, 2844 individuals were hospitalized for a first MI; 561 of these patients (20%) had a fatal MI.

In the year preceding the index date, 70.7% of case-patients and controls received at least 1 NSAID prescription (ever use), of which 51.8% were past users and 18.9% were current users. Therefore, 29.3% of individuals were classified as nonusers (reference category) during this time period. Among those currently exposed, the mean (±SD) number of prescriptions dispensed in the year preceding the index date was 3.8 ± 3.3 for traditional NSAIDs, 3.0 ± 3.5 for naproxen, 6.2 ± 6.1 for celecoxib, 5.3 ± 5.7 for rofecoxib, and 4.3 ± 4.0 for meloxicam. More than 95% of persons dispensed aspirin received a daily dose of 325 mg or less.

Table 1 describes the characteristics of case-patients and controls. As expected, case-patients were more likely to be male, have traditional risk factors, have other manifestations of atherosclerosis, and be using aspirin before cohort entry. In the year preceding the index date, case-patients were also more likely to have been hospitalized and have consulted physicians, and they appeared generally sicker than controls.

After adjustment for multiple risk factors, individuals exposed to rofecoxib on the index date (current users) were

Figure. **Flow of study cohort.**



AMI = acute myocardial infarction; ICD-9 = International Classification of Diseases, Ninth Revision; NSAID = nonsteroidal anti-inflammatory drug.

at an increased risk for MI compared with those who had not used an NSAID in the year preceding the index date (RR, 1.24 [95% CI, 1.05 to 1.46]) (**Table 2**). No evidence suggested an elevated risk associated with the current use of celecoxib (RR, 0.99 [CI, 0.85 to 1.16]). Similarly, traditional NSAIDs (RR, 1.00 [CI, 0.73 to 1.37]), naproxen (RR, 1.17 [CI, 0.75 to 1.84]), and meloxicam (RR, 1.06 [CI, 0.49 to 2.30]) were not associated with a higher risk for MI. Users of NSAIDs any time in the year preceding the index date were not at increased risk for MI, including those who had taken rofecoxib (RR, 0.97 [CI, 0.85 to 1.10]) or celecoxib (RR, 1.00 [CI, 0.88 to 1.13]).

The magnitude of the risk observed for current users of rofecoxib compared with those who had not used an NSAID in the year preceding the index date appeared to be higher for individuals prescribed a dosage greater than 25 mg/d (RR, 1.73 [CI, 1.09 to 2.76]), although even low doses of rofecoxib were associated with an elevated risk (RR, 1.21 [CI, 1.02 to 1.43]) (**Table 3**). We observed no dose–response effect among users of celecoxib (RR, 0.98

Table 1. **Characteristics of Case-Patients and Controls**

Characteristic	Case-Patients (n = 2844)	Controls (n = 56 880)
Mean age ± SD, y*	78.1 ± 5.4	78.1 ± 5.4
Sex, %		
Female	53.5	68.0
Male	46.5	32.0
Comorbid conditions, %†		
Hypertension	57.0	49.8
Coronary artery disease	30.1	16.5
Cerebrovascular disease	1.4	0.7
Peripheral vascular disease	3.5	1.2
Congestive heart failure	13.5	6.7
Diabetes	23.1	11.0
Respiratory illness	24.0	18.5
Gastrointestinal ulcer disease	26.6	23.6
Thyroid disorders	16.5	17.1
Depression/psychiatric illness	14.7	14.4
Cancer	2.9	2.7
Use of concomitant therapy, %†		
Antilipemic agent	22.3	19.3
Anticoagulants	5.5	4.2
Low-dose aspirin	35.7	21.8
Oral corticosteroids	8.8	6.4
Health care utilization, %‡		
Hospitalizations		
0	62.3	62.4
≥1	37.7	23.6
Outpatient medical visits		
All physician visits		
≤12	63.0	72.5
12	37.0	27.5
Cardiologist visits		
0	75.5	85.2
≥1	24.5	14.8
Comorbidity indices‡		
Mean different drugs ± SD, n	10.9 ± 6.2	8.3 ± 5.2
Mean chronic disease score ± SD	7.2 ± 4.2	5.4 ± 3.9
Mean Charlson index score ± SD	0.73 ± 1.6	0.33 ± 1.1

* At index date.
† In the year preceding initiation of therapy with an anti-inflammatory agent (that is, cohort entry).
‡ In the year preceding the index date.

[CI, 0.83 to 1.17] for ≤200 mg/d; RR, 1.00 [CI, 0.78 to 1.29] for >200 mg/d). We could not assess the influence of meloxicam dose because there were too few current users of this drug.

The coadministration of aspirin did not modify the association for users of traditional NSAIDs (**Table 4**). Current users of naproxen combined with aspirin appeared to have a lower risk for MI (RR, 0.60 [CI, 0.24 to 1.50]) than those not receiving concomitant aspirin therapy (RR, 1.59 [CI, 0.95 to 2.65]). The association between celecoxib use, at any dose, and MI was not materially changed by aspirin. However, aspirin decreased the overall excess risk for MI associated with the current use of rofecoxib from 37% (RR, 1.37 [CI, 1.12 to 1.68]) to 7% (RR, 1.07 [CI, 0.84 to 1.36]). In addition, aspirin eliminated the excess risk for MI in persons receiving low doses of rofecoxib (RR, 1.00 [CI, 0.77 to 1.28]) but did not reduce the risk in individuals prescribed high doses of this agent (RR, 2.36 [CI, 1.27 to 4.39]). We could not evaluate the effect of aspirin on risk for MI in meloxicam users because too few persons were current users.

Discussion

Our study, with nearly 5 times as many rofecoxib-exposed case-patients with MI as reported in the recent cumulative meta-analysis (38), provides additional evidence that the use of rofecoxib is associated with an increased risk for acute MI. Our data also suggest that the risk is higher at dosages exceeding 25 mg/d. Of note, individuals who had used rofecoxib any time in the year preceding the index date did not experience an increased risk; this finding shows the need for contemporaneous exposure. In addition, the mean number of rofecoxib prescriptions dispensed in the year preceding the MI was only 5.3 ± 5.7, implying that long-term exposure may not be necessary. We have also shown that the cardiotoxic effect of rofecoxib previously observed in older and sicker populations (7, 9) extends to a healthier elderly population.

An important limitation of previously published studies has been the lack of information on the effects of concomitant aspirin use. A recent prospective, case–control study of COX inhibitor users (10) was the first to report MI risk stratified by aspirin use. Our study, with 10 times the sample size of that study, allows a more precise estimation of this interaction and suggests that concomitant aspirin use attenuates the nefarious cardiovascular effects of low-dose rofecoxib. A possible interaction between naproxen and aspirin requires confirmation in a larger study. However, this interaction could partly reconcile the conflicting findings of previous naproxen studies (17, 39–42) because different population mixes of these drugs may have produced results varying from a protective effect in populations with high use of concomitant aspirin to no protection in populations with low use. Reassuringly, we, like others (7, 9), found no increased risk among users of celecoxib, regardless of the dose prescribed. It is important to recognize that only 25% of current users of celecoxib received dosages greater than 200 mg/d, of which less than 0.1% received 800 mg/d or more. In addition, the confidence intervals do not rule out the possibility of a small risk or benefit with this agent. Our study also provides preliminary data on the cardiovascular safety of meloxicam. Traditional NSAIDs and naproxen were not associated with an increased cardiovascular risk or benefit.

Our findings are consistent with the results of the VIGOR study (2, 4), a cumulative meta-analysis of all randomized rofecoxib trials (38), and the APPROVe results (14–16). Indeed, our adjusted risk estimate of 2.36 (CI, 1.27 to 4.39) for high-dose rofecoxib combined with aspirin is almost identical to that reported for VIGOR participants randomly assigned to rofecoxib, 50 mg/d (RR, 2.38

Table 2. **Crude and Adjusted Rate Ratios of Acute Myocardial Infarction for Use of Various Anti-Inflammatory Agents***

Variable	Case-Patients (n = 2844), n (%)	Controls (n = 56 880), n (%)	Crude Rate Ratio	Adjusted† Rate Ratio (95% CI)
Analysis of current use				
No use‡	793 (27.9)	16 680 (29.3)	1.00	1.00 (reference)
Current use				
NSAIDs	51 (1.8)	962 (1.7)	1.17	1.00 (0.73–1.37)
Naproxen	23 (0.8)	336 (0.6)	1.52	1.17 (0.75–1.84)
Celecoxib	287 (10.1)	5598 (9.9)	1.11	0.99 (0.85–1.16)
Rofecoxib	239 (8.4)	3708 (6.5)	1.41	1.24 (1.05–1.46)
Meloxicam	7 (0.2)	132 (0.2)	1.15	1.06 (0.49–2.30)
Past use§	1444 (50.8)	29 464 (51.8)	1.05	0.93 (0.84–1.04)
Analysis of any use				
No use‡	793 (27.9)	16 680 (29.3)	1.00	1.00 (reference)
Any use‖				
NSAIDs	271 (9.5)	5532 (9.7)	1.07	0.91 (0.77–1.09)
Naproxen	106 (3.7)	2017 (3.5)	1.15	0.98 (0.78–1.24)
Celecoxib	751 (26.4)	14 898 (26.2)	1.09	1.00 (0.88–1.13)
Rofecoxib	544 (19.1)	10 990 (19.3)	1.06	0.97 (0.85–1.10)
Meloxicam	13 (0.5)	312 (0.6)	0.89	0.76 (0.43–1.36)
Combined use¶	366 (12.9)	6451 (11.4)	1.23	0.99 (0.86–1.15)

* NSAIDs = nonsteroidal anti-inflammatory drugs.
† Adjusted for age at index (continuous variable); sex, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, respiratory illness, gastrointestinal ulcer disease, thyroid disorders, depression/psychiatric illness, and cancer in the year preceding cohort entry; use of concomitant therapy, including antilipemic agents, anticoagulants, and low-dose aspirin in the year preceding cohort entry; health care utilization, including hospitalizations, outpatient visits to any physician, and outpatient cardiologist visits, in the year preceding the index date; and number of different drugs taken, chronic disease score, and Charlson index score in the year preceding the index date.
‡ No use in the year preceding the index date.
§ Past users are those who were currently unexposed but had received at least 1 prescription for an NSAID in the year preceding the index date.
‖ Any use is defined as the dispensing of at least 1 prescription in the year preceding the index date.
¶ Combined use represents the dispensing of 2 or more categories of NSAIDs in the year preceding the index date.

[CI, 1.39 to 4.00]) (5). Since 36% of our case-patients were taking aspirin at cohort entry, our findings contradict the hypothesis that the increased risk in the VIGOR trial was due to the protocol prohibition of aspirin. In addition, our results are similar to those of 2 recent observational studies that found an increased risk for myocardial infarction among users of high-dose rofecoxib (7, 9) and confirm that this risk extends to users of low doses.

The observed pattern of risk is consistent with the pharmacologic effects of COX-2 selective inhibitors, as well as with known pharmacodynamic differences among these agents (1, 43–46). Selective COX-2–mediated inhibition of prostacyclin, a potent inhibitor of platelet aggregation, is believed to lead to a prothrombic state secondary to the unopposed activity of COX-1–mediated thromboxane A_2 (26, 47, 48). Thromboxane A_2 is proatherothrombotic because it favors the triad of platelet aggregation, vasoconstriction, and smooth-muscle proliferation. In contrast, prostacyclin counters these effects, raising the possibility that COX-2 selective inhibitors may tip this homeo-

Table 3. **Crude and Adjusted Rate Ratios of Acute Myocardial Infarction for Current Use of Celecoxib and Rofecoxib according to Dose**

Variable	Case-Patients	Controls	Adjusted* Rate Ratio (95% CI)
No use, n†	793	16 680	1.00 (reference)
Celecoxib			
Recipients, n	287	5598	
Low-dose use, n (%)‡	208 (72.5)	4176 (74.6)	0.98 (0.83–1.17)
High-dose use, n (%)§	79 (27.5)	1422 (25.4)	1.00 (0.78–1.29)
Rofecoxib			
Recipients, n	239	3708	
Low-dose use, n (%)‡	218 (91.2)	3485 (94.0)	1.21 (1.02–1.43)
High-dose use, n (%)§*	21 (9.8)	223 (6.0)	1.73 (1.09–2.76)

* Adjusted for age at index (continuous variable); sex, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, respiratory illness, gastrointestinal ulcer disease, thyroid disorders, depression/psychiatric illness, and cancer in the year preceding cohort entry; use of concomitant therapy, including antilipemic agents, anticoagulants, and low-dose aspirin in the year preceding cohort entry; health care utilization, including hospitalizations, outpatient visits to any physician, and outpatient cardiologist visits, in the year preceding the index date; number of different drugs taken, chronic disease score and Charlson index score in the year preceding the index date; and past use of nonsteroidal anti-inflammatory drugs.
† No use in the year preceding the index date.
‡ ≤200 mg/d and ≤25 mg/d for celecoxib and rofecoxib, respectively.
§ >200 mg/d and >25 mg/d for celecoxib and rofecoxib, respectively.

Table 4. **Crude and Adjusted Rate Ratios of Acute Myocardial Infarction for Current Use of Anti-Inflammatory Agents according to Concomitant Use of Aspirin and Dose of Cyclooxygenase-2 Selective Inhibitors***

Variable	No Concomitant Use of Aspirin			Concomitant Use of Aspirin			*P* Value†
	Case-Patients, *n*	Controls, *n*	Adjusted RR‡ (95% CI)	Case-Patients, *n*	Controls, *n*	Adjusted RR‡ (95% CI)	
No use	440	12 013	1.00 (reference)	353	4667	1.00 (reference)	Reference
NSAIDs	32	724	1.04 (0.71–1.54)	19	238	0.94 (0.57–1.54)	0.73
Naproxen	18	249	1.59 (0.95–2.65)	5	87	0.60 (0.24–1.50)	0.07
Celecoxib	176	4043	1.07 (0.89–1.30)	111	1555	0.88 (0.70–1.10)	0.12
Low-dose§	126	3021	1.04 (0.84–1.28)	82	1155	0.91 (0.70–1.17)	0.38
High-dose‖	50	1022	1.16 (0.85–1.57)	29	400	0.80 (0.54–1.20)	0.14
Rofecoxib	143	2586	1.37 (1.12–1.68)	96	1122	1.07 (0.84–1.36)	0.09
Low-dose§	135	2432	1.38 (1.12–1.69)	83	1053	1.00 (0.77–1.28)	0.03
High-dose‖	8	154	1.23 (0.59–2.54)	13	69	2.36 (1.27–4.39)	0.18
Meloxicam	2	92	0.59 (0.14–2.41)	5	40	1.59 (0.61–4.14)	0.25

* NSAID = nonsteroidal anti-inflammatory drug; RR = rate ratio.
† *P* value for 2-sided test of interaction comparing use and nonuse of aspirin at a significance level of $\alpha = 0.05$.
‡ Adjusted for age at index (continuous variable); sex, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, respiratory illness, gastrointestinal ulcer disease, thyroid disorders, depression/psychiatric illness, and cancer in the year preceding cohort entry; use of concomitant therapy, including antilipemic agents, anticoagulants, and low-dose aspirin in the year preceding cohort entry; health care utilization, including hospitalizations, outpatient visits to any physician, and outpatient cardiologist visits, in the year preceding the index date; number of different drugs taken, chronic disease score, and Charlson index score in the year preceding the index date; and past use of NSAIDs. Rate ratios are for current users compared with nonusers.
§ ≤200 mg/d and ≤25 mg/d for celecoxib and rofecoxib, respectively.
‖ >200 mg/d and >25 mg/d for celecoxib and rofecoxib, respectively.

static balance in favor of atherothrombosis. This hypothesis could also explain why rofecoxib, at least at low doses, appears to be susceptible to the cardioprotective effects of aspirin, a potent and irreversible inhibitor of thromboxane A_2. The COX-2 inhibiting potency of rofecoxib is nearly 10 times greater than that of celecoxib or meloxicam, thereby possibly explaining the observed differences in risk between these COX inhibitors (44, 45). The unopposed prothrombic activity of thromboxane A_2 associated with rofecoxib is likely to be considerably greater than that of celecoxib or meloxicam because of these differences in COX-2 selectivity. Finally, the absence of an increased risk with ever use of rofecoxib, in contrast to the elevated risk in current users, is consistent with the reversible nature of COX-2 inhibition exhibited by this agent (27).

Our study had some limitations. First, while we did not observe any increased risk with the use of meloxicam, traditional NSAIDs, or naproxen, our power to detect meaningful differences was limited by the unexpectedly low use of these agents. Second, only case-patients admitted to the hospital were included in our analysis. Missing events due to silent myocardial infarctions and sudden death could have resulted in incomplete case ascertainment. In addition, the intermittent use that occasionally accompanies NSAID therapy may have lead to misclassification of exposure. However, there is no reason to believe that ascertainment or exposure errors would have occurred differentially across drug groups. Consequently, any resulting bias would be toward the null. Third, we did not have information on smoking status, obesity, physical activity, family history, and socioeconomic status. If the distribution of these risk factors varied significantly across exposure groups, our results could be biased because of confounding by indication. Several studies have evaluated the potential for and magnitude of such bias and have demonstrated that any resulting bias would be negligible and directed toward the null (9, 42, 49, 50).

While a major strength of this study has been our accounting of the risk-modifying effects of aspirin, concern may exist about the possibility of misclassification due to missing information on over-the-counter use of aspirin, as well as ibuprofen (the only NSAID available over-the-counter in Canada). However, we expect the frequency of aspirin misclassification to be low because 1) a systematic campaign in Québec has been conducted to assure that all cardioprotective use of aspirin be formalized with written prescriptions (51), 2) low-dose aspirin is covered by the universal drug program, and 3) procurement of over-the-counter NSAIDs would be costlier. In addition, studies in similar populations but different jurisdictions have reported that self-medication with aspirin is low (≤10%) (9, 42, 49, 50). Finally, previous research conducted in Québec has shown that this prescription drug database captures almost all secondary cardioprotective aspirin use (18). Nevertheless, even if we accept that some degree of misclassification of aspirin use is possible, our data indicate that it would be nondifferential across the groups in comparison to the reference group (**Table 4**). The resulting bias would therefore be toward the null, meaning that our findings represent an underestimate of the true risk. Similar reasoning applies to over-the-counter use of ibuprofen.

It is important to consider the potential public health impact of our findings given the high prevalence of COX inhibitor use. A baseline rate of 10.6 MIs per 1000 person-years was observed in this cohort of elderly adults with no history of MI. This rate increased to 12.8 and 18.3 per 1000 persons per year among those receiving low and high doses of rofecoxib, respectively. Assuming causality, this

corresponds to an excess rate attributable to rofecoxib of 2.2 and 7.7 MIs per 1000 exposed elderly adults per year.

In conclusion, our results provide evidence of an increased risk for myocardial infarction, nonfatal and fatal, with current use of rofecoxib, even in individuals with no history of myocardial infarction. The concomitant use of aspirin in persons using low-dose rofecoxib appears to mitigate this risk. Although the observational nature of our study limits the ability to assign causality, the totality of the current evidence confirms the increased cardiovascular risk associated with rofecoxib and the sagacity of its withdrawal. Of equal importance, we provide evidence against a broad class effect for COX-2–mediated cardiotoxicity when used at usual doses. Nevertheless, given the widespread use of these agents and the increased risk seen in a recent cancer trial of high-dose celecoxib, further research should be undertaken. Until evidence to the contrary is available, new agents with COX-2 inhibitory potency similar to or greater than that of rofecoxib should be used only with extreme caution, even in populations at relatively low risk for cardiovascular events.

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Disclaimer: This study is based on nonidentifiable data provided by several Québec Government agencies. The interpretation and conclusions contained herein do not necessarily represent those of the government of Québec or these agencies.

Grant Support: By a grant from the Canadian Institutes of Health Research (CIHR grant MOP62871). Dr. Brophy is a Physician-Scientist of the Fonds de la recherche en santé du Québec.

Potential Financial Conflicts of Interest: None disclosed.

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