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Patients Exposed to Rofecoxib and Celecoxib Have Different Odds of Nonfatal Myocardial Infarction

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Background: **Studies have postulated that cyclooxygenase-2 (COX-2) selective inhibitors affect cardiovascular risk through various mechanisms. Some of these mechanisms could increase risk (for example, inhibition of prostacyclin production), and some could decrease risk (for example, inhibition of inflammation).**

Objective: **To determine the effect of COX-2 inhibitors on risk for nonfatal myocardial infarction (MI).**

Design: **Case–control study.**

Setting: **36 hospitals in a 5-county area.**

Participants: **1718 case-patients with a first, nonfatal MI admitted to these hospitals and 6800 controls randomly selected from the same counties.**

Measurements: **Self-reported medication use assessed through telephone interviews.**

Results: **The adjusted odds ratio for MI among celecoxib users, relative to persons who did not use nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), was 0.43 (95% CI, 0.23 to 0.79) compared with 1.16 (CI, 0.70 to 1.93) among rofecoxib users. The use of rofecoxib was associated with a statistically significant higher odds of MI compared with the use of celecoxib (adjusted odds ratio for rofecoxib vs. celecoxib, 2.72 [CI, 1.24 to 5.95]; $P = 0.01$). Nonselective NSAIDs were associated with a reduced odds of nonfatal MI relative to nonusers. Comparisons of COX-2 inhibitors with nonselective NSAIDs were the following: rofecoxib versus naproxen (odds ratio, 3.39 [CI, 1.37 to 8.40]) and celecoxib versus ibuprofen or diclofenac (odds ratio, 0.77 [CI, 0.40 to 1.48]).**

Limitations: **The possibility of recall bias and uncontrolled confounding in this observational study limit the ability to make definitive conclusions. The association of celecoxib with a lower odds of MI could have occurred by chance. Only about 50% of eligible participants completed telephone interviews.**

Conclusion: **Celecoxib and rofecoxib were associated with different odds of MI. Cardiovascular effects among the COX-2 inhibitors seem different, but further studies, preferably randomized trials, are needed to fully understand the spectrum of effects of COX-2 inhibitors and potential differences among them.**

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Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) include those that inhibit both the cyclooxygenase-1 (COX-1) isoenzyme and the COX-2 isoenzyme (nonselective NSAIDs) and those that are more selective for the COX-2 isoenzyme (COX-2 selective inhibitors, herein called COX-2 inhibitors). Nonselective NSAIDs may reduce the risk for myocardial infarction (MI) by inhibiting platelet aggregation (1–3). On the other hand, studies have postulated that COX-2 inhibitors increase the risk for atherothrombotic events because they inhibit prostacyclin, which may increase thrombotic tendencies and vascular injury without the beneficial effect of platelet inhibition derived from COX-1 inhibition (4). However, COX-2 inhibitors may also reduce cardiovascular risk by inhibiting vascular inflammation, improving endothelial dysfunction, and enhancing coronary plaque stability (5–8). These effects may differ among COX-2 inhibitors. Along with potential differences in blood pressure effects (9), recent evidence suggests that celecoxib and rofecoxib may differ in their effects on endothelial dysfunction and oxidative stress (8).

Two randomized trials, designed to examine risk for gastrointestinal bleeding, found different cardiovascular results with rofecoxib and celecoxib compared with their respective NSAID comparator. In the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (10), users of 50 mg of rofecoxib per day had a higher rate of nonfatal MI (11) than users of naproxen. In the primary analysis of the Celecoxib Long-term Arthritis Safety Study (CLASS) (12), the rate of cardiovascular events did not differ between celecoxib users and ibuprofen or diclofenac users. Because these studies did not include placebo control groups, we could not determine whether these differences were due to an increased risk from rofecoxib, a decreased risk from naproxen, a combination of both, or a reduction in risk from celecoxib but not rofecoxib that balanced the potential reduction in risk from nonselective NSAIDs.

Three published observational studies (13–15) and 2 meta-analyses (16, 17) have assessed the risk for cardiovascular events from rofecoxib or celecoxib. The former were limited in their ability to adjust for factors that are likely to put COX-2 users at higher cardiovascular risk (18) (for example, higher body mass index [BMI] and lower levels of

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Context

Various cyclooxygenase-2 (COX-2) selective inhibitors may affect cardiovascular risk differently.

Contribution

This case–control study from 36 hospitals in a 5-county area found that reported recent use of a COX-2 selective inhibitor was similar among adults with a first, nonfatal myocardial infarction (MI) and randomly selected community controls with no history of MI. However, reported use of rofecoxib was associated with a 2.72 (95% CI, 1.24 to 5.95) higher odds of MI than was use of celecoxib.

Cautions

About 50% of eligible participants completed interviews. Although analyses controlled for potential confounders, recall bias and unmeasured factors related to MI risk could have affected results.

–The Editors

physical activity), and the latter had relatively small numbers of MIs. Nonetheless, none of these studies showed an increased risk from celecoxib, whereas some, but not all, studies identified an increased risk from rofecoxib. A recent randomized trial of meloxicam (a relatively COX-2 selective NSAID) compared with placebo suggested a reduction in cardiovascular outcomes with meloxicam (19), and another trial of the COX-2 inhibitor lumiracoxib did not detect a statistically significant increase in the risk for MI (20). Against this backdrop, a recent randomized trial of rofecoxib, the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, was stopped early because of an increase in cardiovascular outcomes among rofecoxib users (relative to placebo) after 18 months of use, and Merck & Co., Inc., voluntarily withdrew rofecoxib from the worldwide market.

Thus, the current data provide conflicting evidence of the potential risks and benefits of different COX-2 inhibitors, but, overall, they suggest that there may be differences between them. We sought to determine the association between COX-2 inhibitors (specifically rofecoxib and celecoxib) and risk for nonfatal MI.

METHODS

Study Site and Participants

The methods of our case–control design have been described in detail previously (21). We designed and powered the current study a priori to address the effects of celecoxib and rofecoxib on MI risk. We prospectively identified case-patients as persons 40 to 75 years of age hospitalized in a 5-county region for first, nonfatal MI between May 1998 and December 2002. Previous research has shown that almost 90% of all case-patients identified by using these methods had verified MIs (21). The participation rate among eligible case-patients was 55%.

We use random-digit dialing to select approximately 4 community controls with no history of MI from the same geographic region and during the same time period as case-patients. We chose community controls because they represent the same source population from which the cases arose and thus are the most appropriate comparison group with which to minimize the possibility of selection bias. The participation rate among known eligible controls was 50%.

We excluded the 13 valdecoxib users because no case-patients were exposed to valdecoxib and the 40 participants who used both COX-2 inhibitors and nonselective NSAIDs at the same time. The institutional review boards of the University of Pennsylvania, Philadelphia, Pennsylvania, and all participating hospitals approved the study.

Data Collection and Exposure Definition

We collected exposure and covariate data for all case-patients and controls by using the same structured telephone interview. Trained telephone interviewers who were not informed of the study hypothesis interviewed the patients. Case-patients were interviewed after returning home from the hospital. To maximize the validity of drug exposure information, case-patients were interviewed only if they could be reached within 4 months of their MI. Controls were interviewed within 4 months of their initial identification to prevent selection bias. To further maximize recall of use of NSAIDs (22), case-patients and controls were prompted with indication-specific questions and examination of photographs of medications. All participants were also instructed to have all of the containers for the medications that they took during the index week (defined later in this article) available during the interview. We have previously shown that these methods enhanced recall of nonselective NSAID use (22). Our previous study also suggested that case-patients recalled more than 80% of nonselective NSAID use (21).

The a priori definition of exposure was any nonselective NSAID, COX-2 inhibitor, or aspirin use within 1 week before the index date (the date of first onset of symptoms of MI for case-patients and the date of the telephone interview for controls). Participants were asked to specify the current dose of these medications. In addition, interviewers asked participants who used these medications in the index week when they began their medication in order to determine duration of use.

Statistical Analysis

The primary analysis focused a priori on the association of and between the 2 COX-2 inhibitors and the odds of nonfatal MI relative to no other NSAID use. We estimated differences in the odds of MI between rofecoxib and celecoxib by comparing these 2 drugs in cross-tabulations and by comparing rofecoxib with celecoxib in logistic regression that used celecoxib as the reference group. Because the effect of aspirin on platelets and MI risk (23) could modify the effects of COX-2 inhibitors, we also performed

Table 1. **Characteristics of Nonsteroidal Drug Use among Controls***

Characteristic	No NSAID Use (n = 4491)	Celecoxib Use (n = 87)	Rofecoxib Use (n = 78)	Nonselective NSAID Use (n = 2144)
Sociodemographic				
Age, *y*	53.70 ± 9.61	58.61 ± 8.78†	58.06 ± 10.16‡	51.60 ± 8.86§
Insurance, *n (%)*		–†	–‡	–§
Medicare	462 (10.5)	17 (20.0)	16 (20.8)	188 (8.9)
Medicaid or Veterans Affairs	70 (1.6)	0 (0.0)	1 (1.3)	24 (1.1)
Private	3657 (83.6)	68 (80.0)	60 (77.9)	1827 (86.7)
None	187 (4.3)	0 (0.0)	0 (0.0)	69 (3.3)
Race, *n (%)*			–‡	–§
White	3583 (80.2)	68 (80.0)	71 (91.0)	1812 (84.8)
Black	699 (15.7)	12 (14.1)	7 (9.0)	266 (12.4)
Other	182 (4.1)	5 (5.9)	0 (0.0)	59 (2.8)
Duration of education, *y*	14.17 ± 2.45	13.59 ± 2.67†	14.29 ± 2.65	14.38 ± 2.40§
Clinical				
Physical activity score‖	7.42 ± 1.25	6.98 ± 1.31†	7.24 ± 1.24	7.43 ± 1.26
BMI, kg/m^2	27.20 ± 5.52	29.71 ± 6.28†	28.04 ± 5.81	27.70 ± 6.02§
Cigarette smoking, *n (%)*			–‡	
Past	1476 (33.0)	38 (43.7)	33 (42.9)	680 (31.8)
Current	949 (21.2)	15 (17.2)	5 (6.5)	426 (19.9)
Diabetes mellitus, *n (%)*	360 (8.0)	12 (13.8)	10 (12.8)	142 (6.6)§
Family history of coronary disease, *n (%)*	1559 (34.7)	28 (32.2)	29 (37.2)	783 (36.6)
Women, *n (%)*	2462 (54.8)	60 (69.0)	51 (65.4)	1418 (66.1)§
History of congestive heart failure, *n (%)*	49 (1.1)	5 (5.7)†	1 (1.3)	14 (0.7)
Hypercholesterolemia, *n (%)*	1295 (28.9)	37 (42.5)†	26 (33.3)	562 (26.2)§
Hypertension, *n (%)*	1420 (31.6)	44 (50.6)†	33 (42.3)‡	632 (29.5)
Previous angina or coronary disease, *n (%)*	197 (4.4)	10 (11.5)†	5 (6.4)	94 (4.4)
Self-reported osteoarthritis, *n (%)*	304 (6.8)	40 (46.0)†	31 (39.7)‡	207 (9.7)§
Self-reported rheumatoid arthritis, *n (%)*	126 (2.8)	13 (14.9)†	10 (12.8)‡	86 (4.0)§
Self-reported renal disease, *n (%)*	18 (0.4)	0 (0.0)	0 (0.0)	5 (0.2)
History of gastrointestinal ulcer disease, *n (%)*	280 (6.2)	7 (8.0)	4 (5.2)	112 (5.2)
Medication use, *n (%)*				
ACE inhibitors	454 (10.1)	10 (11.5)	12 (15.4)	167 (7.8)
Aspirin	1295 (28.8)	24 (27.6)	25 (32.1)	465 (21.7)§
β-Blockers	392 (8.7)	14 (16.1)†	8 (10.3)	141 (6.6)§
Calcium-channel blockers	427 (9.5)	17 (19.5)	11 (14.1)	150 (7.0)§
Diuretics	409 (9.1)	17 (19.5)†	11 (14.1)	204 (9.4)
HMG-CoA reductase inhibitors	551 (12.3)	27 (31.0)†	18 (23.1)‡	196 (9.1)§
Physician visits per y, *n*	4.76 ± 9.24	9.63 ± 12.76†	10.73 ± 14.31‡	4.83 ± 9.94

* Values expressed with a plus/minus sign are means ± SD. ACE = angiotensin-converting enzyme; BMI = body mass index; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; NSAID = nonsteroidal anti-inflammatory drug.
† $P < 0.05$ comparing celecoxib with no NSAIDs.
‡ $P < 0.05$ comparing rofecoxib with no NSAIDs.
§ $P < 0.05$ comparing nonselective NSAIDs with no NSAIDs.
‖ Validated physical activity score (25). Higher score represents greater physical activity.

analyses separately for users and nonusers of concurrent aspirin.

To adjust for confounding, we performed multiple logistic regression analyses that a priori included risk factors plus any variable that changed the odds ratio of interest by 10% or more, with adjustment for that specific variable (24). We considered all variables in **Table 1** as potential confounders (25). (Adjustment for the following variables did not alter the results; therefore, we did not include them in the multivariable models: years of education, history of renal dysfunction, rheumatoid arthritis, or osteoarthritis, income, and use of hormone replacement therapy (among women). We tested interactions with COX-2 inhibitors for all variables in **Table 1** by using the product term of nonsteroidal drug type by each risk factor in multivariable regression. We also examined the association of increasing frequency of COX-2 use with nonfatal MI by using the appropriate linear term for frequency in the models with nonusers included.

Analysis of COX-2 inhibitors by dosage or duration was not possible because of small numbers. Only 2 case-patients used rofecoxib, 50 mg/d; 4 used rofecoxib, less than 25 mg/d; 1 used celecoxib, greater than 200 mg/d; and 3 used celecoxib, less than 200 mg/d. Thus, to examine whether differences between rofecoxib and celecoxib were due to the effects of higher dose of rofecoxib, we performed analyses after excluding patients using 50 mg of rofecoxib per day. Similarly, few case-patients used COX-2 inhibitors for less than 3 months or more than 12 months. No rofecoxib users and 2 celecoxib users reported less than 3 months of use, and only 3 rofecoxib users and 7 celecoxib users reported more than 12 months of use. Thus, to determine whether shorter (<3 months) or longer (>12 months) durations of medication affected the comparison

Table 2. **Characteristics of Nonsteroidal Use among Case-Patients***

Characteristic	No NSAID Use (n = 1354)	Celecoxib Use (n = 18)	Rofecoxib Use (n = 27)	Nonselective NSAID Use (n = 319)
Sociodemographic				
Age, *y*	58.67 ± 9.10	60.50 ± 9.28	60.52 ± 8.82	57.46 ± 9.13†
Insurance, *n (%)*				
Medicare	246 (18.8)	5 (31.3)	9 (36.0)	57 (18.1)
Medicaid/Veterans	44 (3.4)	0 (0.0)	0 (0.0)	16 (5.1)
Private	963 (73.6)	11 (68.8)	16 (64.0)	232 (73.7)
None	55 (4.2)	0 (0.0)	0 (0.0)	10 (3.2)
Race, *n (%)*				
White	974 (72.8)	11 (61.1)	17 (65.4)	233 (73.5)
Black	320 (23.9)	6 (33.3)	9 (34.6)	76 (24.0)
Other	44 (3.3)	1 (5.6)	0 (0.0)	8 (2.5)
Duration of education, *y*	13.24 ± 2.71	13.53 ± 2.27	13.12 ± 2.18	13.12 ± 2.65
Clinical				
Physical activity score‡	7.01 ± 1.28	6.90 ± 1.06	7.14 ± 0.97	7.14 ± 1.33
BMI, kg/m^2	29.16 ± 6.01	28.38 ± 5.18	29.42 ± 6.77	30.17 ± 6.38†
Cigarette smoking, *n (%)*				
Past	472 (35.1)	4 (22.2)	8 (29.6)	112 (35.2)
Current	448 (33.3)	7 (38.9)	10 (37.0)	115 (36.2)
Diabetes mellitus, *n (%)*	324 (23.9)	3 (16.7)	2 (7.4)	51 (16.0)†
Family history of coronary disease, *n (%)*	563 (41.6)	7 (38.9)	4 (14.8)§	150 (47.2)
Women, *n (%)*	470 (34.8)	10 (55.6)	17 (63.0)§	131 (41.1)†
History of congestive heart failure, *n (%)*	58 (4.3)	2 (11.1)	1 (3.7)	11 (3.4)
Hypercholesterolemia, *n (%)*	626 (46.2)	11 (61.1)	18 (66.7)§	172 (53.9)†
Hypertension, *n (%)*	744 (54.9)	13 (72.2)	12 (44.4)	179 (56.1)
Previous angina or coronary disease, *n (%)*	246 (18.2)	3 (16.7)	6 (22.2)	46 (14.4)
Self-reported osteoarthritis, *n (%)*	80 (5.9)	2 (11.1)	7 (25.9)§	49 (15.4)†
Self-reported rheumatoid arthritis, *n (%)*	55 (4.1)	5 (27.8)‖	3 (11.1)	25 (7.9)†
Self-reported renal disease, *n (%)*	29 (2.1)	1 (5.6)	0 (0.0)	1 (0.3)†
History of gastrointestinal ulcer disease, *n (%)*	109 (8.1)	4 (22.1)	1 (3.7)	21 (6.6)
Medication use, *n (%)*				
ACE inhibitors	234 (17.3)	5 (27.8)	2 (7.4)	46 (14.4)
Aspirin	447 (33.0)	8 (44.4)	10 (37.0)	113 (35.4)
β-Blockers	212 (15.7)	3 (16.7)	5 (18.5)	52 (16.3)
Calcium-channel blockers	241 (17.8)	3 (16.7)	5 (18.5)	57 (17.9)
Diuretics	188 (13.9)	7 (38.9)‖	5 (18.5)	55 (17.2)
HMG-CoA reductase inhibitors	298 (22.0)	7 (38.9)	10 (37.0)	66 (20.7)
Physician visits per y, *n*	6.77 ± 19.28	16.47 ± 42.30	11.89 ± 25.08	6.42 ± 10.71

* Values expressed with a plus/minus sign are means ± SD. ACE = angiotensin-converting enzyme; BMI = body mass index; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; NSAID = nonsteroidal anti-inflammatory drug.
† $P < 0.05$ comparing nonselective NSAIDs with no NSAIDs.
‡ Validated physical activity score (25). Higher score represents greater physical activity.
§ $P < 0.05$ comparing rofecoxib with no NSAIDs.
‖ $P < 0.05$ comparing celecoxib with no NSAIDs.

between rofecoxib and celecoxib, we performed analyses after excluding those with short or long durations of use.

To determine the potential effects of recall bias, we determined the odds ratio of MI for patient-reported use of other prescription analgesics in the index week (mostly those containing acetaminophen plus opioids, and none with known effects on MI risk). We also compared reported COX-2 use with reported prescription analgesic use in the index week. If the results of the latter comparisons were similar to that of the primary study comparison, that would argue against recall bias as an explanation for the study findings.

We chose the sample size to have an 80% power to detect an odds ratio of 0.6 or less or 1.5 or greater for COX-2 use versus no use in those not using aspirin or nonselective NSAIDs. We performed all analyses by using SPSS, version 10.0.5 (SPSS, Inc., Chicago, Illinois).

Role of the Funding Sources

The National Institutes of Health (R01HL57312), Searle Pharmaceuticals, Inc. (now Pfizer, Inc.), and Merck & Co., Inc., supported this work. The funding organizations were not involved in the conduct of the study or in the collection, analysis, or interpretation of the data. The sponsors did not have editorial authority or rights to decisions about publication.

RESULTS

Risk Factors by NSAID Use

Tables 1 and **2** show differences in risk factors by drug use for controls and case-patients, respectively. In general, COX-2 users were more likely than nonusers of NSAIDs to have cardiovascular risk factors, including higher BMI and lower levels of physical activity. This was particularly

Table 3. **Association of Cyclooxygenase-2 Inhibitor and Nonselective Nonsteroidal Anti-Inflammatory Drug Use within the Index Week with the Odds of Nonfatal Myocardial Infarction***

Drug Use	Case-Patients, *n (%)*	Controls, *n (%)*	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
Overall	1718 (100)	6800 (100)		
No NSAID use	1354 (78.8)	4491 (66.0)	1.0	1.0
Nonselective NSAID use	319 (18.6)	2144 (31.5)	0.49 (0.43–0.56)	0.61 (0.52–0.71)
All COX-2 inhibitors	45 (2.6)	165 (2.4)	0.90 (0.65–1.26)	0.73 (0.49–1.07)
Rofecoxib use only	27 (1.6)	78 (1.2)	1.15 (0.74–1.79)	1.16 (0.70–1.93)
Celecoxib use only	18 (1.0)	87 (1.3)	0.69 (0.41–1.14)	0.43 (0.23–0.79)
Stratified by aspirin use				
Non–aspirin users‡	1140 (100)	4991 (100)		
No NSAID use	907 (79.5)	3196 (64.0)	1.0	1.0
Nonselective NSAID use	206 (18.1)	1679 (33.6)	0.43 (0.37–0.51)	0.55 (0.46–0.66)
All COX-2 inhibitors	27 (2.4)	116 (2.3)	0.82 (0.54–1.25)	0.68 (0.41–1.11)
Rofecoxib use only	17 (1.5)	53 (1.1)	1.13 (0.65–1.96)	1.19 (0.64–2.22)
Celecoxib use only	10 (0.9)	63 (1.3)	0.56 (0.29–1.09)	0.35 (0.16–0.76)
Aspirin users‡	578 (100)	1809 (100)		
No NSAID use	447 (77.3)	1295 (71.6)	1.0	1.0
Nonselective NSAID use	113 (19.6)	465 (25.7)	0.70 (0.56–0.89)	0.77 (0.59–1.00)
All COX-2 inhibitors	18 (3.1)	49 (2.7)	1.06 (0.61–1.84)	0.88 (0.45–1.72)
Rofecoxib use only	10 (1.7)	25 (1.4)	1.16 (0.55–2.43)	1.14 (0.47–2.77)
Celecoxib use only	8 (1.4)	24 (1.3)	0.97 (0.43–2.16)	0.67 (0.25–1.80)

* COX-2 = cyclooxygenase-2; NSAID = nonsteroidal anti-inflammatory drug.
† Adjusted for age; sex; race; smoking; insurance; number of physician visits in the previous year; family history of coronary disease; body mass index; activity score; year; previous angina or coronary disease; history of diabetes, hypertension, heart failure, and hypercholesterolemia; and use of statins, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and diuretics.
‡ Adjusted for all variables above, except aspirin use.

true for celecoxib users, who tended to have more risk factors for MI than rofecoxib users. Results within the case-patients yielded similar findings.

Odds of Nonfatal MI by COX-2 Use

Overall, we did not detect an association between COX-2 inhibitor use and nonfatal MI (adjusted odds ratio, 0.73 [95% CI, 0.49 to 1.07]) (**Table 3**).

There were, however, statistically significant differences between COX-2 inhibitors. Rofecoxib was not associated with an altered odds of MI, relative to nonusers, even after adjustment for confounding (**Table 3**). Celecoxib, however, was associated with a statistically significantly lower odds of MI in adjusted analyses (**Table 3**). Adjustment for BMI and activity level was responsible for a large reduction in the celecoxib–MI odds ratio (adjusted odds ratio for only these 2 variables, 0.53 [CI, 0.30 to 0.91]; this represents a 23% reduction from the unadjusted odds ratio).

The use of rofecoxib was associated with a significantly higher odds of MI when compared with the use of celecoxib (adjusted odds ratio for rofecoxib vs. celecoxib, 2.72 [CI, 1.24 to 5.95]; $P = 0.01$). After exclusion of the 7 total participants reporting use of 50 mg of rofecoxib per day (the highest dosage), the results of the comparison between celecoxib and rofecoxib were unchanged ($P = 0.008$). Similarly, the difference between celecoxib and rofecoxib was unchanged in analyses that excluded participants with less than 3 months of use ($P = 0.006$) and participants with more than 12 months of use ($P = 0.010$).

The odds ratio for the celecoxib–MI association was much lower (odds ratio, 0.35) among nonaspirin users than among aspirin users (odds ratio, 0.67) (**Table 3**), while the odds ratios for the rofecoxib–MI association did not differ by the presence or absence of aspirin use (**Table 2**). Celecoxib and rofecoxib use statistically significantly differed among nonaspirin users ($P = 0.015$) but not among aspirin users ($P > 0.2$). However, the P values for interaction with aspirin use were all greater than 0.2 in these comparisons.

The odds ratio for those using celecoxib at least every other day in the index week was 0.39 (CI, 0.20 to 0.75), while the odds ratio for those using celecoxib less frequently was 0.82 (CI, 0.16 to 4.37; test for trend, $P = 0.005$). The odds ratios for those using rofecoxib at least every other day in the index week or less frequently were 1.11 (CI, 0.64 to 1.93) and 1.43 (CI, 0.40 to 5.19), respectively (test for trend, $P > 0.2$).

No result was altered when we removed variables that may be caused by COX-2 inhibitors (hypertension and antihypertensive medication use) from the model (data not shown).

Nonselective NSAIDs and Comparisons with COX-2 Inhibitors

In analyses comparing celecoxib with ibuprofen or diclofenac use among both aspirin and nonaspirin users (similar to CLASS [12]), the adjusted odds ratio was 0.77 (CI, 0.40 to 1.48). This is consistent with the negative association both between celecoxib and nonfatal MI (**Table 2**) and between ibuprofen or diclofenac and nonfatal MI (adjusted odds ratio, 0.53 [CI, 0.43 to 0.66]) when compared

with no NSAID use. In analyses comparing rofecoxib with naproxen among nonaspirin users (similar to the VIGOR study [10]), the adjusted odds ratio was 3.39 (CI, 1.37 to 8.40). This is consistent with the odds ratio for rofecoxib of 1.19 (**Table 2**) and the negative association of naproxen (adjusted odds ratio, 0.48 [CI, 0.32 to 0.73]) compared with no NSAID use. The adjusted odds ratio for rofecoxib versus ibuprofen or diclofenac was 2.04 (CI, 1.16 to 3.60), and the adjusted odds ratio for celecoxib versus naproxen was 0.81 (CI, 0.37 to 1.77).

Other Prescription Analgesics

Other prescription analgesics were not associated with nonfatal MI (adjusted odds ratio, 1.16 [CI, 0.71 to 1.89]). When comparing COX-2 inhibitors to other prescription analgesics, the odds ratios for celecoxib and rofecoxib were 0.30 (CI, 0.13 to 0.65) and 0.95 (CI, 0.46 to 1.95), respectively.

DISCUSSION

We show a statistically significant difference in the odds of nonfatal MI between users of rofecoxib and celecoxib. This difference was not due to an increased risk for MI among rofecoxib users but rather an association between celecoxib and lower odds of MI. Perhaps most important, the study supports the hypothesis that different COX-2 inhibitors differ in their cardiovascular effects.

Studies have proposed that COX-2 inhibitors could increase the risk for MI by inhibiting prostacyclin, but not thromboxane, production (4, 26). However, COX-2 inhibitors have several potentially beneficial effects, including reductions in vessel wall inflammation, improvement in endothelium-dependent vasodilation, reduction in C-reactive protein and oxidized low-density lipoprotein cholesterol levels, and inhibition of atherogenesis (5–7, 27). Several pieces of evidence suggest that COX-2 inhibitors may not be equivalent in some of these proposed mechanisms. Rofecoxib has been associated with greater elevations in blood pressure and more peripheral edema than celecoxib, and, in ex vivo assays, rofecoxib is also more selective for the COX-2 isoenzyme, at least at supratherapeutic doses (26, 28). A direct comparison of rofecoxib versus celecoxib in salt-sensitive rats revealed that celecoxib but not rofecoxib improved endothelium-dependent relaxation and decreased 8-isoprostane plasma levels at the doses used (8). Although limitations of these mechanism studies make their applicability to the clinical effects of the drugs unclear, our study results are consistent with the theory that differences within the class of COX-2 inhibitors may exist.

Unlike our study, 3 published studies (13–15) using administrative databases did not detect a statistically significant protective effect of celecoxib (odds ratios, 0.96 [13], 0.9 [14], and 0.93 [15]). However, these studies could not measure actual COX-2 consumption; could not account for nonprescription aspirin or NSAID use; and were limited in their ability to adjust for confounding (29), including important confounders (BMI and physical activity) that we identified in our study. These limitations could explain the differences in findings from our study. For example, without adjustment for BMI or physical activity or accounting for nonprescription NSAID use, our odds ratio for celecoxib would have been 26% higher (that is, closer to 1.0). With respect to rofecoxib, 1 of the 3 studies found no association between rofecoxib and MI (14), 1 reported an increased risk for cardiovascular events among users of more than 25 mg of rofecoxib but no effect of 25 mg or less of rofecoxib (13), and 1 reported an increased risk for rofecoxib relative to no use of prescription NSAIDs (odds ratio, 1.14; $P = 0.054$) (15). The latter study also found that the increased risk for rofecoxib was greatest when compared with celecoxib users and with dosages of rofecoxib more than 25 mg/d or durations of less than 3 months (both compared with celecoxib, which had a non–statistically significantly lower odds of MI [odds ratio, 0.93 (CI, 0.84 to 1.02)]) (15). Our study had too few case-patients who used more than 25 mg of rofecoxib or who used COX-2 inhibitors for less than 3 months to analyze these subsets of users.

Two new pieces of evidence are available; however, neither study has been published. Graham and colleagues (30) recently presented an analysis from a health maintenance organization database. The results showed a higher risk for MI and sudden death from rofecoxib dose greater than 25 mg relative to remote NSAID use. In addition, lower-dose rofecoxib ($\leq$25 mg) was associated with an increased risk when compared with celecoxib. The other study, the APPROVe trial, demonstrated a higher risk for cardiovascular events from 25 mg of rofecoxib relative to placebo, but only after 18 months into treatment. We could not examine sudden death or longer-term use of rofecoxib.

The current literature thus supports an increase in cardiovascular risk from rofecoxib, at least in doses greater than 25 mg, over longer periods of treatment, or relative to celecoxib. No study discussed here has identified an increased risk from celecoxib. In addition, in a recent randomized trial in patients without previous cardiovascular events, another COX-2 inhibitor, lumiracoxib (a highly COX-2 selective drug [31]), was not associated with a statistically significant increase in cardiovascular outcomes relative to nonselective NSAID comparators, albeit with limited power (32).

Several limitations must be considered in interpreting our results. First, although studies have hypothesized a protective effect of COX-2 inhibitors against MI (5, 6), including potentially beneficial effects of celecoxib (6, 8), the association between celecoxib use and lower odds of nonfatal MI may have occurred by chance. Second, recall bias could have created our results if controls had better recall of their COX-2 inhibitor use than case-patients. However, analysis of other prescription analgesics did not demonstrate evidence of recall bias, and the comparisons of

COX-2 inhibitors with these prescription analgesics are not likely to be biased by differential recall. Third, nonparticipation bias could occur if prevalence of analgesic use differed between participants and nonparticipants. However, if the likelihood of nonparticipation was the same for COX-2 users and for other prescription analgesic users, the comparison between COX-2 use and prescription analgesic use (which yielded similar results) should be unbiased by nonparticipation. This is consistent with our previous substudies within this study that demonstrated the same relative differences in analgesic use between participants and nonparticipants for case-patients as for controls (21). Because case-patients and controls did not differ with respect to the effect of nonparticipation, the estimate of nonparticipation on the nonselective NSAID–MI association had no effect (3). Fourth, despite adjustment for many potential confounders, above and beyond that available in administrative database studies, uncontrolled confounding is always possible in observational studies. Fifth, because we included only nonfatal MIs, a harmful effect of COX-2 inhibitors could be masked if the drugs increased the risk for fatal MI. However, the difference between rofecoxib and naproxen in the VIGOR study (10) was due to a difference in nonfatal MIs, with no difference in fatal events (11). Finally, because of limited power, we could not exclude an up to 1.9-fold increase in risk for nonfatal MI with the use of rofecoxib, nor could we directly measure the effect of 50 mg of rofecoxib or short- or long-term rofecoxib use. However, our results suggest that the difference between celecoxib and rofecoxib is not due to an isolated increase in risk from 50 mg of rofecoxib or different durations of use.

Most important, the difference between rofecoxib and celecoxib is less likely to be biased by nonparticipation, uncontrolled confounding, or recall bias. The comparison between the 2 drugs would be biased only if the recall or participation between case-patients and controls differed specifically by which COX-2 inhibitor they used. We believe that this is unlikely because there is no reason to suspect that participants had different recall or participation on the basis of which COX-2 inhibitor they used. With respect to uncontrolled confounding, celecoxib users were at higher risk than rofecoxib users, which should, if anything, have biased against showing the difference demonstrated.

Current data support an increased risk for cardiovascular outcomes from rofecoxib, particularly at higher doses or longer duration of use. Our study of mostly lower-dose and shorter-duration use suggests that rofecoxib may not have an increased risk in this setting, but this remains speculative. The possibility that celecoxib or other relatively COX-2 selective inhibitors (19) could protect against MI should also be considered only a hypothesis that deserves further study. The possibility of recall bias, nonparticipation, and uncontrolled confounding in our observational study precludes definitive conclusions. However, these potential limitations are less likely in the direct comparison of rofecoxib with celecoxib, and our study, as well as other evidence (8, 15), suggests potential differences among COX-2 inhibitors in cardiovascular effects. Further studies, preferably randomized trials, are needed to fully understand the spectrum of effects of COX-2 inhibitors, both with respect to each other and to the various populations of patients that use them.

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