

Relationship Between Selective Cyclooxygenase-2 Inhibitors and Acute Myocardial Infarction in Older Adults

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Background—Although cyclooxygenase-2 inhibitors (coxibs) were developed to cause less gastrointestinal hemorrhage than nonselective nonsteroidal antiinflammatory drugs (NSAIDs), there has been concern about their cardiovascular safety. We studied the relative risk of acute myocardial infarction (AMI) among users of celecoxib, rofecoxib, and NSAIDs in Medicare beneficiaries with a comprehensive drug benefit.

Methods and Results—We conducted a matched case-control study of 54 475 patients 65 years of age or older who received their medications through 2 state-sponsored pharmaceutical benefits programs in the United States. All healthcare use encounters were examined to identify hospitalizations for AMI. Each of the 10 895 cases of AMI was matched to 4 controls on the basis of age, gender, and the month of index date. We constructed matched logistic regression models including indicators for patient demographics, healthcare use, medication use, and cardiovascular risk factors to assess the relative risk of AMI in patients who used rofecoxib compared with persons taking no NSAID, taking celecoxib, or taking NSAIDs. Current use of rofecoxib was associated with an elevated relative risk of AMI compared with celecoxib (odds ratio [OR], 1.24; 95% CI, 1.05 to 1.46; $P=0.011$) and with no NSAID (OR, 1.14; 95% CI, 1.00 to 1.31; $P=0.054$). The adjusted relative risk of AMI was also elevated in dose-specific comparisons: rofecoxib ≤ 25 mg versus celecoxib ≤ 200 mg (OR, 1.21; 95% CI, 1.01 to 1.44; $P=0.036$) and rofecoxib >25 mg versus celecoxib >200 mg (OR, 1.70; 95% CI, 1.07 to 2.71; $P=0.026$). The adjusted relative risks of AMI associated with rofecoxib use of 1 to 30 days (OR, 1.40; 95% CI, 1.12 to 1.75; $P=0.005$) and 31 to 90 days (OR, 1.38; 95% CI, 1.11 to 1.72; $P=0.003$) were higher than >90 days (OR, 0.96; 95% CI, 0.72 to 1.25; $P=0.8$) compared with celecoxib use of similar duration. Celecoxib was not associated with an increased relative risk of AMI in these comparisons.

Conclusions—In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with celecoxib use and no NSAID use. Dosages of rofecoxib >25 mg were associated with a higher risk than dosages ≤ 25 mg. The risk was elevated in the first 90 days of use but not thereafter. (*Circulation*. 2004;109:2068-2073.)

Key Words: cyclooxygenase inhibitors ■ myocardial infarction ■ aging

The Vioxx and Gastrointestinal Outcomes (VIGOR) trial compared the gastrointestinal safety of rofecoxib 50 mg/d with naproxen 1000 mg/d in patients with rheumatoid arthritis who did not take aspirin regularly.¹ Although the trial found that patients taking rofecoxib had fewer serious gastrointestinal outcomes, there were more acute myocardial infarctions (AMIs) with rofecoxib than naproxen. This study could not discern the extent to which the difference in AMI could be explained by a protective effect of naproxen²⁻⁴ and/or an increased risk associated with the selective cyclooxygenase (COX)-2 inhibitor (coxib).

Previous studies on the association between coxibs and AMI have provided conflicting results. In an analysis comparing the rates of AMI in phase III trials of rofecoxib and

celecoxib with the rates in the placebo arms of several trials of aspirin, the coxibs were associated with an elevated risk.⁵ Pooled analyses of rofecoxib randomized clinical trials, including VIGOR, suggested that there may be a statistically significantly increased risk of cardiovascular events in patients taking rofecoxib compared with naproxen, but this risk was not seen when rofecoxib was compared with other nonsteroidal antiinflammatory drugs (NSAIDs) or with placebo.^{6,7} A reanalysis of the Celecoxib Long-term Arthritis Safety Study (CLASS), which compared celecoxib with ibuprofen or diclofenac, found no increase in the risk of AMI associated with celecoxib.⁸ A large observational study suggested that rofecoxib at dosages >25 mg was associated with an approximately 2-fold increased risk of AMI compared

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with celecoxib or no NSAID, whereas rofecoxib ≤ 25 mg was not associated with an elevated risk.⁹ A smaller observational study found no increased risk of AMI with either coxib, but dosage was not addressed.¹⁰

In 2002, more than 41 million prescriptions were filled in the United States for coxibs,¹¹ making any potential relationship between coxibs and AMI a substantial clinical and public health issue. We undertook an observational study examining the association between rofecoxib, celecoxib, NSAIDs, and AMI in a large population of older adults for whom complete information was available on prescription medication use and clinical encounters.

Methods

Study Participants

All persons studied were Medicare beneficiaries who received prescription medications through the Pennsylvania Pharmaceutical Assistance Contract for the Elderly or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled during 1998, 1999, and 2000. These 2 programs cover medication expenses for low-income elderly with annual household incomes between \$10 000 and \$17 000. To be included, participants had to be enrolled and active users of Medicare and the respective prescription drug benefit program from 1998 through their index date (defined below), as demonstrated by presence in the program eligibility files and filling at least 1 prescription as well as having at least 1 healthcare encounter in each 6-month period.

From this pool of eligible persons ($n=310\,229$), we excluded patients who had illnesses that might have obscured any potential relationship between coxibs and AMI. These included persons with a serious life-threatening illness, including HIV/AIDS ($n=114$) or malignancy ($n=50\,973$), and persons with a coagulopathy ($n=5403$). We also excluded persons with a hospitalization during 1998 who received a diagnosis of AMI that was not the principal discharge diagnosis ($n=2441$).

All patient identifiers and all traceable information were deleted from the case-control study database to protect patients' privacy. The Human Subjects Committee of Brigham and Women's Hospital and the Centers for Medicare and Medicaid Services approved this study.

Acute Myocardial Infarction

The case-defining event was a hospitalization in 1999 or 2000 with a discharge diagnosis code of AMI (ICD-9-CM 410) in the first or second position. The length of hospitalization must have been at least 3 days and no more than 180 days, unless the patient died. This was found to be an accurate algorithm for defining AMI in another study population.¹² To assess the accuracy of this algorithm in our study population, we identified a subset of patients with Medicare diagnosis codes for AMI and had their primary hospital records reviewed. We chose all patients from Pennsylvania taking a coxib or an NSAID who had a Medicare diagnosis code for AMI in 1998 ($n=1525$), as well as a random subset of those not taking these agents ($n=675$). Trained chart abstractors blinded to the study question reviewed the charts using a review form developed as part of the Cardiovascular Coordinating Project.¹³ On the basis of the primary medical records, we determined whether each admission met criteria for an AMI established by the World Health Organization.¹⁴ The Medicare ICD-9-CM diagnosis plus the length-of-stay requirements had a positive predictive value of 93% (95% CI, 92% to 94%). We identified 10 895 hospitalizations for AMI in the eligible study population on the basis of this algorithm.

Four control subjects (controls) who did not sustain an AMI during the study period were identified for each case. The date of hospitalization for AMI was the index date for cases. A randomly selected date was the index date for controls. Controls were matched to cases on the basis of age (± 1 year), gender, and the month of index date.

Coxib and Nonselective NSAID Use

The study database contained information on all prescription drugs filled by eligible beneficiaries, including drug name, dosage, frequency, and days of supply. The exposures of interest were the use of celecoxib or rofecoxib on the index date. During the study period, both drugs were covered by the prescription benefit programs without restriction, and copayments were less than \$10. The risk of AMI associated with these agents was compared with several reference groups: use of the other coxib, no NSAID or coxib, ibuprofen, naproxen, or other NSAIDs. Prescriptions filled on the index date were excluded in the primary analyses. Persons with prescriptions for more than one of the drug categories on the index date were included in both categories.

Two dosage and 3 duration categories were defined a priori for all relevant exposures. Dosage categories for the coxibs and NSAIDs were split at the modal daily dosage. For example, the modal dosage of celecoxib was 200 mg, so current use was categorized as ≤ 200 mg or >200 mg. For rofecoxib, the modal dosage was 25 mg; current use was dichotomized as ≤ 25 mg or >25 mg. Dosage categories were created for the NSAIDs on the basis of the same methodology. For each individual study drug, 3 duration categories were created: 1 to 30 days, 31 to 90 days, and >90 days.

Covariates

Covariates were defined on the basis of data from the year before the study period. Although information for most of these patients and covariates was available for longer than 12 months, we restricted the ascertainment to this period to reduce potential bias that might arise because of varying lengths of covariate assessment. The covariates assessed include age, gender, race, previous MI, angina, coronary artery revascularization, congestive heart failure, ischemic cerebrovascular accident, diabetes, hypertension, use of a lipid-lowering drug (statin), use of hormone replacement therapy, use of an anticoagulant (clopidogrel, dipyridamole, ticlopidine, and warfarin), use of an NSAID in 1998, rheumatoid arthritis, osteoarthritis, presence of a hospitalization, number of visits for ambulatory care, number of comorbid medical conditions,¹⁵ and number of different medications used.

Several variables of interest were not available within the study database, including body mass index, tobacco use, aspirin use, and socioeconomic status. In theory, these variables could be differentially related to use of a coxib, use of an NSAID, and AMI.¹⁶⁻¹⁸ We therefore analyzed data from the Medicare Current Beneficiary Survey,¹⁹ a nationwide in-home survey conducted among 8785 beneficiaries ≥ 65 years old in 1999 with a 97% response rate. We compared patients' body mass index, tobacco use, aspirin use, annual household income, and educational attainment between patients reporting use of celecoxib ($n=562$), rofecoxib ($n=244$), and an NSAID ($n=1302$). In these analyses, body mass index was comparable in both groups of coxib users (celecoxib, 27.5 kg/m² versus rofecoxib, 27.2 kg/m², $P=0.2$) and similar to that of NSAID users (27.7 kg/m², $P=0.5$ versus coxib users). Current tobacco use was equally common in both groups of coxib users (celecoxib, 8.7% versus rofecoxib, 7.0%, $P=0.5$) and was more common among NSAID users (9.8%, $P=0.005$). Aspirin use was similar in both coxib groups (celecoxib, 8.2% versus rofecoxib, 11.5%, $P=0.2$) and among NSAID users (10.2%, $P=0.4$). The proportion of persons with an educational level of college or higher was not statistically different between coxibs (celecoxib, 29.6% versus rofecoxib, 31.8%, $P=0.11$) or between coxibs and NSAIDs (26.5%, $P=0.2$). The mean annual household income of both coxib groups was similar ($P=0.7$) and higher than that for NSAID users ($P=0.0001$).

Analyses

The distribution of covariates was assessed in each exposure category. The unadjusted odds ratio (OR) between each covariate and AMI was then examined separately for New Jersey and Pennsylvania. The CIs for the crude ORs for each state overlapped for every covariate; data from both states were combined for the multivariable analyses. All covariates were tested in multivariable conditional

TABLE 1. Baseline Characteristics of Study Population by Exposure Category

	Celecoxib (n=2140)	Rofecoxib (n=941)	Naproxen (n=331)	Ibuprofen (n=263)	Other NSAID (n=1874)	No Current Exposure (n=49 044)
Gender, female	1814 (84.8)	813 (86.4)	272 (82.2)	207 (78.7)	1531 (81.7)	37 690 (76.9)
Age, y, mean±SD	81.4±6.7	81.7±6.5	80.8±6.7	80.8±6.8	80.7±6.4	81.7±7.0
Race						
White	1967 (91.9)	877 (93.2)	288 (87.0)	227 (86.3)	1686 (90.0)	44 628 (91.0)
Black	132 (6.2)	45 (4.8)	35 (10.6)	30 (11.4)	151 (8.1)	3478 (7.1)
Other	41 (1.9)	19 (2.0)	8 (2.4)	6 (2.3)	37 (2.0)	938 (1.9)
Nursing home resident in previous year	135 (6.3)	56 (6.0)	8 (2.4)	16 (6.1)	82 (4.4)	3393 (6.9)
No. of physician visits, mean±SD	9.8±7.7	9.6±7.1	7.9±5.6	7.8±6.1	8.5±6.3	7.5±6.2
Hospitalized in previous year	617 (28.8)	266 (28.3)	70 (21.2)	72 (27.4)	429 (22.9)	13 519 (27.6)
Comorbid conditions, mean±SD	0.9±1.1	0.9±1.1	0.7±0.9	0.9±1.1	0.8±1.0	0.9±1.2
Diabetes	674 (31.5)	273 (29.0)	92 (27.8)	77 (29.3)	549 (29.3)	14 185 (28.9)
Hypertension	1367 (63.9)	609 (64.7)	202 (61.0)	156 (59.3)	1178 (62.9)	27 829 (56.7)
No. of different prescription drugs, mean±SD	7.6±5.2	7.3±5.3	6.4±4.8	6.1±4.5	7.3±4.9	5.4±4.4
History of previous myocardial infarction	170 (7.9)	84 (8.9)	19 (5.7)	17 (6.5)	132 (7.0)	4293 (8.8)
History of angina	323 (15.1)	160 (17.0)	44 (13.3)	34 (12.9)	265 (14.1)	6985 (14.2)
History of coronary revascularization	22 (1.0)	14 (1.5)	5 (1.5)	7 (2.7)	18 (1.0)	728 (1.5)
History of congestive heart failure	321 (15.0)	128 (13.6)	38 (11.5)	33 (12.6)	266 (14.2)	7166 (14.6)
History of a cerebrovascular accident	273 (12.8)	141 (15.0)	30 (9.1)	24 (9.1)	219 (11.7)	6800 (13.9)
Use of a statin	431 (20.1)	196 (20.8)	52 (15.7)	39 (14.8)	360 (19.2)	7624 (15.6)
Use of hormone replacement therapy	139 (6.5)	69 (7.3)	18 (5.4)	14 (5.3)	97 (5.2)	1756 (3.6)
Use of any anticoagulant*	311 (14.5)	145 (15.4)	25 (7.6)	19 (7.2)	189 (10.1)	7047 (14.4)
Rheumatoid arthritis	126 (5.9)	33 (3.5)	20 (6.0)	8 (3.0)	86 (4.6)	823 (1.7)
Osteoarthritis	783 (36.6)	328 (34.9)	94 (28.4)	66 (25.1)	661 (35.3)	8368 (17.1)
Previous nonselective NSAID use	319 (14.9)	105 (11.2)	238 (71.9)	187 (71.1)	190 (10.1)	3451 (7.0)

Values are n (%) unless noted. Current use refers to use on the index date. Persons who were current users of multiple agents (n=117) are counted in the appropriate column for each drug used.

*Anticoagulants include clopidogrel, dipyridamole, ticlopidine, and warfarin.

logistic regression models conditioning on all matching factors. On the basis of a backward selection routine with a threshold of $P < 0.2$, anticoagulant use, previous hospitalization, osteoarthritis, and nursing home residence were dropped from all versions of the adjusted model. The remaining covariates were included in all multivariable conditional logistic regression models. The model was rerun for each reference group (the alternative coxib, no NSAID, ibuprofen, naproxen, and other NSAIDs). A secondary analysis excluded persons exposed to multiple agents on the index date (n=117). The results were virtually identical to the main analyses and are not shown.

We assessed the relationship between dosage categories and AMI for the coxibs and NSAIDs using similar multivariable regression models in which the dosage was classified as less than or equal to the modal dosage or greater than the modal dosage. For example, in analyses comparing the coxibs, the most commonly used dosages of rofecoxib (≤ 25 mg) were compared with the most commonly used dosages of celecoxib (≤ 200 mg). Users of rofecoxib > 25 mg were then compared with users of celecoxib > 200 mg.

Several sensitivity analyses were undertaken. On the basis of previous findings that first-time users may be at the highest risk for cardiovascular events associated with coxibs,⁹ we constructed conditional regression models that considered persons exposed only if their use on the index date was their first time using a coxib. We examined the relationship between AMI and the duration of exposure to coxibs in this group of users. Assessing the effect of duration among first-time users provides a more precise estimate of the actual period of exposure, because persons with intermittent prescriptions

were not considered exposed. Another set of sensitivity analyses redefined the no NSAID use reference group to only persons who had never been exposed to an NSAID during the study period. Finally, we assessed the relationship between coxibs and AMI in subgroups of persons with rheumatoid arthritis, a history of MI, or NSAID use during the baseline period.

The data and all analyses were under control of the authors. An independent review of the study protocol and statistical programming was performed by an epidemiologist external to the study sponsor and project team. All analyses were conducted using SAS statistical software (version 8.2).

Results

The baseline characteristics of patients are shown in Table 1. The study population was primarily elderly women with a mean age > 80 years in all drug use groups. More than 85% of patients were white. The study population used substantial healthcare resources. Risk factors for AMI, such as diabetes and hypertension, were common, and previous cardiovascular disease was frequent. In the baseline period, more than 5% of the population had sustained a previous MI, more than 13% had angina, more than 12% had congestive heart failure, and more than 9% had a previous ischemic stroke. Statins were used by more than 15% of all patients. As seen in Table 1, patients using celecoxib or rofecoxib were similar with regard

TABLE 2. Adjusted Association Between Coxibs and Acute Myocardial Infarction

	Adjusted Odds Ratio (95% CI)	P
Exposure (reference group)		
Rofecoxib (celecoxib)	1.24 (1.05–1.46)	0.011
Celecoxib (no current use)	0.93 (0.84–1.02)	0.13
Rofecoxib (no current use)	1.14 (1.00–1.31)	0.054
Celecoxib (naproxen)	0.95 (0.74–1.21)	0.7
Rofecoxib (naproxen)	1.17 (0.90–1.52)	0.2
Celecoxib (ibuprofen)	0.98 (0.76–1.26)	0.9
Rofecoxib (ibuprofen)	1.21 (0.92–1.58)	0.2
Celecoxib (other NSAID)	0.95 (0.82–1.10)	0.4
Rofecoxib (other NSAID)	1.17 (0.99–1.38)	0.073
Covariate		
Race, white	1.20 (1.12–1.29)	<0.001
No. of physician visits		
4–6	1.11 (1.05–1.18)	<0.001
7–12	1.11 (1.05–1.17)	<0.001
13+	1.09 (1.02–1.16)	0.011
Comorbid conditions		
1–2	1.25 (1.20–1.31)	<0.001
3+	1.42 (1.33–1.52)	<0.001
No. of different drugs		
6–9	1.14 (1.08–1.19)	<0.001
10+	1.18 (1.12–1.25)	<0.001
Diabetes	1.48 (1.42–1.54)	<0.001
Hypertension	1.15 (1.11–1.20)	<0.001
Previous myocardial infarction	1.56 (1.48–1.66)	<0.001
Angina	1.31 (1.25–1.38)	<0.001
Previous coronary revascularization	0.78 (0.69–0.89)	<0.001
Congestive heart failure	1.37 (1.31–1.44)	<0.001
Cerebrovascular accident	1.07 (1.01–1.27)	0.014
Use of statin	1.00 (0.94–1.04)	0.7
Use of hormone replacement therapy	0.88 (0.79–0.98)	0.02
Rheumatoid arthritis	1.16 (1.02–1.31)	0.02
Previous nonselective NSAID use	0.97 (0.90–1.04)	0.3

Conditional logistic model matched on age, gender, and month of index date. All other variables listed were adjusted for in the multivariable models. The number of AMIs in each exposure group was as follows: celecoxib 425, rofecoxib 225, ibuprofen 49, naproxen 63, other NSAID 371, and no current use 9793.

to baseline characteristics. Compared with NSAID users, coxib users were somewhat less healthy during the baseline period, with more health service use, hypertension, previous MIs, cerebrovascular accidents, angina, and cardiovascular medication use (statins and anticoagulants).

The results of the multivariable conditional logistic regression models are shown in Table 2. After control for all available confounders, rofecoxib was associated with an elevated risk of AMI compared with persons who were taking celecoxib (OR, 1.24; 95% CI, 1.05 to 1.46). The adjusted relative risk of AMI associated with rofecoxib was elevated

but did not reach statistical significance compared with no current NSAID (OR, 1.14; 95% CI, 1.00 to 1.31), naproxen (OR, 1.17; 95% CI, 0.90 to 1.52), and ibuprofen (OR, 1.21; 95% CI, 0.92 to 1.58). Relatively few patients were current users of naproxen (n=331) or ibuprofen (n=263), contributing to the wide CIs. Celecoxib was not associated with an elevated risk of AMI in these analyses.

In all comparisons related to dose, use of rofecoxib >25 mg/d was associated with a higher adjusted relative risk of AMI than rofecoxib ≤25 mg. The adjusted relative risk of rofecoxib >25 mg (OR, 1.70; 95% CI, 1.07 to 2.71) was higher than that seen for ≤25 mg (OR, 1.21; 95% CI, 1.01 to 1.44) compared with celecoxib >200 mg or ≤200 mg. The magnitude in elevation of relative risk was similar when rofecoxib was compared with no current NSAID, naproxen, ibuprofen, and other NSAIDs. Neither celecoxib dosage was associated with an elevated risk of AMI in any comparison.

Sensitivity analyses that considered only the first-time use of a coxib or NSAID during the study period provided findings very similar to those of the primary analysis. A sensitivity analysis comparing rofecoxib users with patients who had no use of either a coxib or NSAID since January 1, 1999, produced results nearly identical to those of the primary analysis (OR, 1.14; 95% CI, 0.99 to 1.31; P=0.062).

We also examined the relationships between duration of coxib exposure and AMI in first-time users. Compared with celecoxib use of similar duration, rofecoxib use for 1 to 30 days was associated with an elevated risk of AMI (OR, 1.43; 95% CI, 1.12 to 1.83; P=0.005). A similar elevation was associated with 31 to 90 days of rofecoxib use (OR, 1.46; 95% CI, 1.14 to 1.86; P=0.003), but no elevation in AMI risk was observed with >90 days of rofecoxib use (OR, 1.04; 95% CI, 0.77 to 1.38; P=0.8). The elevated relative risk of AMI seen in patients taking rofecoxib for 90 days or less was not restricted to those taking >25 mg. Compared with patients taking celecoxib ≤200 mg for 1 to 90 days, the adjusted relative risk of AMI associated with rofecoxib ≤25 mg (OR, 1.37; 95% CI, 1.15 to 1.63; P=0.0004) was similar to the adjusted relative risk for rofecoxib >25 mg (OR, 1.38; 95% CI, 0.80 to 2.37; P=0.3). No duration category for celecoxib use was associated with an elevated risk.

Subgroup analyses that focused on patients with previous AMI (n=4698) and compared persons taking rofecoxib with those taking celecoxib found no elevation in relative risk associated with rofecoxib (OR, 0.91; 95% CI, 0.60 to 1.38; P=0.6). Analyses restricted to patients with rheumatoid arthritis (n=1088) also found no elevation in AMI risk with either coxib. These subgroup analyses were limited by small numbers of patients.

Discussion

We studied the relationship between coxibs, NSAIDs, and hospitalization for AMI in a large population of older patients. The study database contained information on more than 50 000 older adults in 2 US states with complete prescription drug coverage. The main analyses, as well as dose- and duration-specific analyses, found an elevated risk of AMI associated with rofecoxib but not with celecoxib. The risk was higher in persons taking >25 mg of rofecoxib and

during the first 90 days of use and was observed consistently in relation to several reference groups.

It is important that these findings be considered in light of previous research. In the VIGOR trial, which compared 50 mg of rofecoxib with 1000 mg of naproxen in patients with rheumatoid arthritis, the risk of AMI was elevated in patients treated with rofecoxib.¹ Patients were not allowed to take aspirin during the trial. In an analysis that compared data from phase III randomized clinical trials of celecoxib and rofecoxib with data from the placebo groups of 4 aspirin primary prevention trials, the annualized MI rates for patients randomized to either celecoxib or rofecoxib were higher than rates for the meta-analysis of the placebo groups.⁵ This analysis has been criticized because the coxib trials included osteoarthritis and rheumatoid arthritis patients, and the latter group has been observed to have an elevated baseline risk of AMI.²⁰ The control population was characterized by relatively low rates of AMI. A reanalysis of data from the CLASS trial, in which patients were allowed to take aspirin, found no elevation in risk of AMI associated with celecoxib.⁸ An observational study conducted in the Tennessee Medicaid population found that rofecoxib at dosages >25 mg/d was associated with a nearly 2-fold increased risk of AMI compared with nonuse of any NSAID.⁹ Our findings differ from the pooled analyses of rofecoxib randomized controlled trials, which showed no significant increase in cardiovascular events compared with non-naproxen NSAIDs.^{6,7} In addition, a recently published observational analysis from Ontario also found no increased risk of AMI associated with any dosage of rofecoxib.¹⁰ This analysis excluded persons who were prescribed a coxib for <30 days. The findings of our study suggest that the first 30 days of use may include a period of elevated risk. Finally, rofecoxib dosages >25 mg, which were associated with the highest relative risk of AMI in this study and the study by Ray and colleagues,⁹ were not reported separately in the Ontario study.

There are important potential limitations to the present study. One is the concern about possible misclassification of end points using Medicare use data. We studied the accuracy of the AMI diagnosis codes and found that they had a positive predictive value of 93% compared with primary hospital records. However, patients who suffered an AMI and were not hospitalized because of sudden death or a silent event would not be counted in these analyses for any exposure group. In addition, it is possible that some cases sustained their AMI during the hospitalization. If so, these patients may not have been exposed to the medications of interest for a period of time before their event. This may have influenced the results if patients taking one particular medication before admission were more likely to suffer an AMI during the course of a hospitalization. However, we have no reason to believe that this was the case. Second, similar to all retrospective observational studies, these results may have been biased because of confounding by factors not observable in Medicare use data. We examined this possibility using data from the in-home Medicare Current Beneficiary Survey and found that people taking rofecoxib or celecoxib were similar with respect to 5 variables known to be independent risk factors for cardiovascular end points, including body mass

index, aspirin use, tobacco use, income status, and educational attainment. A comparison of people taking coxibs with those taking NSAIDs suggests that unmeasured confounding by each of these factors may result in a small degree of bias toward the null. In addition to the potential for bias by unmeasured confounders, these results may be influenced by residual confounding by factors that were incompletely assessed in this administrative database, such as severity of cardiovascular risk factors. However, the relationship between available covariates and AMI is consistent with results from previous observational studies. Third, it is possible that some patients prescribed coxibs and/or NSAIDs used them on an as-needed basis. Thus, patients may not have been exposed to the drug on all days of the calculated prescription period, leading to potential misclassification of exposure status. If the pattern of misclassification was similar across drugs, the bias would be toward the null value. Alternatively, if it varied by drug or dose, as a function of the indication for the medication (such as acute versus chronic pain) or the efficacy of the treatment, the magnitude and direction of bias could be toward or away from the null value. We have no compelling reason to believe that this misclassification of exposure would have differed by drug. Finally, one must consider the generalizability of findings on the basis of data from an older, low-income population in 2 states, whose prescription drug use was slightly higher than the national average. Because the elderly are among the most frequent users of coxibs, the study population examined is relevant.

Several biological pathways could underlie a potential association between selective COX-2 inhibition and coronary events. Although NSAIDs inhibit both COX isoforms, selective inhibition of COX-2 results in decreased prostacyclin, a vasodilator and moderator of platelet activation, without reducing COX-1-dependent thromboxanes, contributors to platelet aggregation and vasoconstriction.^{21,22} Emerging data support a varied role for COX-2 in the vascular bed, with important functions in vascular resistance,²³ late preconditioning,²⁴ endothelial function,^{25,26} and atherogenesis.^{27,28} Data from rat models of hypertension suggest that celecoxib may be associated with improvements in endothelial function and reductions in oxidative stress²⁹; neutral findings have been reported for rofecoxib and diclofenac.³⁰ Although both rofecoxib and celecoxib, like most NSAIDs, have been associated with hypertension, several large head-to-head randomized controlled trials have reported higher rates among patients treated with rofecoxib³¹; other smaller studies in healthy adults suggest similarity between coxibs.

In conclusion, we observed an elevated risk of hospitalization for AMI among elderly Medicare enrollees treated with rofecoxib. This risk was higher in persons taking >25 mg of rofecoxib than in patients taking the most common dosages used of \leq 25 mg. The risk was elevated during the first 90 days of exposure but not thereafter. We did not find an elevated risk of AMI for persons taking celecoxib. Because of the important potential public health implications, our findings should be followed up by additional clinical and mechanistic studies, several of which are ongoing.

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References

- Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med.* 2000;343:1520–1528.
- Solomon DH, Glynn RJ, Levin R, et al. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Intern Med.* 2002;162:1099–1104.
- Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Arch Intern Med.* 2002;162:1111–1115.
- Watson DJ, Rhodes T, Cai B, et al. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med.* 2002;162:1105–1110.
- Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA.* 2001;286:954–959.
- Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation.* 2001;104:2280–2288.
- Reicin A, Shapiro D, Sperling RS, et al. Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, and nabumetone). *Am J Cardiol.* 2002;89:204–209.
- White WB, Faich G, Whelton A, et al. Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol.* 2002;89:425–430.
- Ray WA, Stein CM, Daugherty JR, et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet.* 2002;360:1071–1073.
- Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med.* 2003;163:481–486.
- DrugTopics.com: The Online Magazine for Pharmacists.* March 17, 2003. Available at: http://www.drugtopics.com/be_core/content/journals/d/data/2003/0317/past_issues_show. Accessed April 17, 2003.
- Petersen LA, Wright S, Normand SLT, et al. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. *J Gen Intern Med.* 1999;14:555–558.
- Ellerbeck EF, Jencks SR, Randford MJ, et al. Quality of care for Medicare patients with acute myocardial infarction: report on a four state pilot of the Cooperative Cardiovascular Project. *JAMA.* 1995;273:1509–1514.
- Myocardial infarction and coronary deaths in the World Health Organization MONICA project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. WHO/MONICA Project. *Circulation.* 1994;90:583–612.
- Romano R, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol.* 1993;46:1075–1079.
- Palmieri V, de Simone G, Arnett DK, et al. Relation of various degrees of body mass index in patients with systemic hypertension to left ventricular mass, cardiac output, and peripheral resistance. *Am J Cardiol.* 2001;88:1163–1168.
- Weir MR, Maibach EW, Bakris GL, et al. Implications of a health lifestyle and medication analysis for improving hypertension control. *Arch Intern Med.* 2000;160:481–490.
- Kington RS, Smith JP. Socioeconomic status and racial and ethnic differences in functional status associated with chronic diseases. *Am J Pub Health.* 1997;87:805–810.
- Adler GS. A profile of the Medicare Current Beneficiary Survey. *Health Care Financing Review.* 1994;15:153–163.
- Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation.* 2003;107:1303–1307.
- Lipsky PE, Brooks P, Crofford LJ, et al. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. *Arch Intern Med.* 2000;160:913–920.
- FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med.* 2001;345:433–442.
- Topper JN, Cai J, Falb D, et al. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. *Proc Natl Acad Sci U S A.* 1996;93:10417–10422.
- Bolli R, Shimamura K, Tang XL, et al. Discovery of a new function of cyclooxygenase (COX)-2: COX-2 is a cardioprotective protein that alleviates ischemia/reperfusion injury and mediates the late phase of preconditioning. *Cardiovasc Res.* 2002;55:506–519.
- Chenevard R, Hurlimann D, Bechir M, et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. *Circulation.* 2003;107:405–409.
- Cheng Y, Austin SC, Rocca B, et al. Role of prostacyclin in the cardiovascular response to thromboxane A₂. *Science.* 2002;296:539–541.
- Burleigh ME, Babaev VR, Oates JA, et al. Cyclooxygenase-2 promotes early atherosclerotic lesion formation in LDL receptor-deficient mice. *Circulation.* 2002;105:1816–1823.
- Cipollone F, Prontera C, Pini B, et al. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E₂-dependent plaque instability. *Circulation.* 2001;104:921–927.
- Hermann M, Camici G, Fratton A, et al. Differential effects of selective cyclooxygenase-2 inhibitors on endothelial dysfunction in salt-induced hypertension. *Circulation.* 2003;108:2308–2311.
- Title LM, Giddens K, McInerney MM, et al. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. *J Am Coll Cardiol.* 2003;42:1747–1753.
- Whelton A, White WB, Bello AE, et al, for the SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol.* 2002;90:959–963.