

Risk of Hospitalization for Myocardial Infarction Among Users of Rofecoxib, Celecoxib, and Other NSAIDs

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A Population-Based Case-Control Study

Søren P. Johnsen, MD, PhD; Heidi Larsson, MSc; Robert E. Tarone, PhD; Joseph K. McLaughlin, PhD; Bente Nørgård, MD, PhD; Søren Friis, MD; Henrik T. Sørensen, DMSc

Background: It remains uncertain if the excess cardiovascular risk of rofecoxib and celecoxib reported in clinical trials is present in routine practice and whether the use of other nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) also carries an increased cardiovascular risk. We performed a population-based case-control study to examine the risk of myocardial infarction (MI) among users of various categories of nonaspirin NSAIDs.

Methods: Using data from hospital discharge registries in the counties of North Jutland, Viborg, and Aarhus, Denmark, and the Danish Civil Registration System, we identified 10 280 cases of first-time hospitalization for MI and 102 797 sex- and age-matched non-MI population controls. All prescriptions for nonaspirin NSAIDs filled before the date of admission for MI were identified using population-based prescription databases. Relative risk estimates for MI were adjusted for a history of cardiovascular disease, hypertension, diabetes mellitus, chronic bronchitis or emphysema, alcoholism, liver cirrhosis, upper gastrointestinal bleeding, rheumatoid arthritis, systemic lupus erythematosus and the use of high-dose aspirin, platelet inhibitors, insulin or oral hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, oral anticoagulants, nitrates, penicillamine, gold, oral gluco-

corticoids, and hormone therapy before the date of admission for MI.

Results: Current users of rofecoxib had an elevated risk estimate for hospitalization for MI compared with nonusers of any category of nonaspirin NSAIDs (adjusted relative risk [ARR], 1.80; 95% confidence interval [CI], 1.47-2.21). Increased risk estimates were also found among current users of celecoxib (ARR, 1.25; 95% CI, 0.97-1.62), other cyclooxygenase-2 selective inhibitors (ARR, 1.45; 95% CI, 1.09-1.93), naproxen (ARR, 1.50; 95% CI, 0.99-2.29), and other conventional nonaspirin NSAIDs (ARR, 1.68; 95% CI, 1.52-1.85). The highest ARRs were found among new users of all examined drug categories.

Conclusions: Current and new users of all classes of nonaspirin NSAIDs had elevated relative risk estimates for MI. Although the increased risk estimates may partly reflect unmeasured bias, they indicate the need for further examination of the cardiovascular safety of all nonaspirin NSAIDs.

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THE WITHDRAWAL OF ROFECOXIB based on an increased risk of myocardial infarction (MI) and stroke among patients treated for longer than 18 months in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial marks a dramatic event in the history of the cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs).¹ This has further been underscored by the decision by the US National Cancer Institute to halt the ongoing Adenoma Prevention with Celecoxib (APC) trial owing to increased

cardiovascular risk among patients receiving celecoxib.²

Concerns about the cardiovascular safety of these drugs, however, have been raised for years.³⁻⁶ It became clear in the mid-1990s that COX-2 selective inhibition might

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affect the hemostatic balance and favor thrombosis by selectively inhibiting the generation of COX-2-derived vascular prostacyclin while not affecting the COX-1-mediated generation of thromboxane A₂.^{3,4} The concerns were further stimulated by

Author Affiliations are listed at the end of this article.

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data from the Vioxx Gastrointestinal Outcomes Research (VIGOR)^{7,8} trial, in which rofecoxib was associated with a 5-fold increase in the risk of MI compared with naproxen. However, the lack of a placebo arm and the possible antithrombotic effects of naproxen⁹⁻¹¹ made it difficult to interpret the results.^{12,13} Several questions remain unanswered. First, data on the risk associated with COX-2 selective inhibitors from well-designed observational studies may provide more relevant information on the safety of these drugs in clinical practice than the data from clinical trials,¹⁴⁻¹⁹ since the number of high-risk patients (eg, patients with a history of cardiovascular disease) was small in most trials.^{6,14-19} Second, the association between length of COX-2 selective inhibitor use and cardiovascular risk needs to be further examined because a recent meta-analysis found no association between duration of treatment and cardiovascular risk.⁶ Third, it is unclear whether the cardiovascular risk found for rofecoxib and celecoxib is specific or reflects a broader class effect.¹⁴⁻²¹ Fourth, the unexpected cardiovascular risk associated with naproxen in an ongoing clinical trial on prevention of Alzheimer disease has extended concerns about safety to conventional nonaspirin NSAIDs.²² We therefore examined the risk of MI among users of COX-2 selective inhibitors and other nonaspirin NSAIDs in a Danish case-control study.

METHODS

This study was conducted within North Jutland, Viborg, and Aarhus counties, Denmark (approximately 1.4 million persons) from January 1, 2000, to December 31, 2003. The National Health Service provides tax-supported health care for all inhabitants including costs of prescribed drugs. Unambiguous linkage between various registers can be performed using the civil registry number.

IDENTIFICATION OF CASES AND CONTROLS

Hospital discharge registries in the counties retain data on all discharges from all nonpsychiatric hospitals since 1972 (Viborg County) or 1977 (North Jutland and Aarhus counties). The files include information on the civil registry

Table 1. Descriptive Characteristics of 10 280 Cases With Acute MI and 102 797 Controls (Matched on Age and Sex) From North Jutland, Viborg, and Aarhus Counties, Denmark, 2000-2003*

Characteristic	Cases (n = 10 280)	Controls (n = 102 797)
Age, mean (range), y	69.6 (20-100)	69.6 (19-101)
Sex		
Men	6209 (60.4)	62 087 (60.4)
Women	4071 (39.6)	40 710 (39.6)
Discharge diagnosis† of		
Cardiovascular disease‡	2741 (26.7)	12 779 (12.4)
Hypertension	1483 (14.4)	7681 (7.5)
Diabetes mellitus	980 (9.5)	3883 (3.8)
Chronic bronchitis and emphysema	901 (8.8)	5048 (4.9)
Alcoholism	180 (1.8)	1389 (1.4)
Liver cirrhosis	29 (0.3)	217 (0.2)
Upper gastrointestinal bleeding	359 (3.5)	2514 (2.5)
Rheumatoid arthritis	260 (2.5)	1632 (1.6)
Systemic lupus erythematosus	3 (0.0)	7 (0.0)
Prescription§ for		
Rofecoxib	119 (1.2)	611 (0.6)
Celecoxib	71 (0.7)	521 (0.5)
Other COX-2 selective inhibitors	57 (0.6)	396 (0.4)
Naproxen	26 (0.3)	175 (0.2)
Other nonaspirin NSAIDs	532 (5.2)	3105 (3.2)
High-dose aspirin	1137 (11.1)	6697 (6.5)
Platelet inhibitors	1308 (12.7)	7982 (7.8)
Antihypertensive drugs	5716 (55.6)	41 459 (40.3)
Insulin or oral hypoglycemic drugs	1241 (12.1)	5590 (5.4)
Lipid-lowering drugs	902 (8.8)	4281 (4.2)
Oral anticoagulants	278 (2.7)	2177 (2.1)
Nitrates	1831 (17.8)	7267 (7.1)
Penicillamine and/or gold	34 (0.3)	173 (0.2)
Oral glucocorticocoids	397 (3.9)	1849 (1.80)
Postmenopausal hormone therapy	1078 (10.5)	11 094 (10.8)

Abbreviations: COX-2, cyclooxygenase-2; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Data are given as number (percentage) of patients unless otherwise specified.

†A discharge diagnosis or performed procedure before the admission for MI.

‡A discharge diagnosis of coronary heart disease (not MI), stroke, or peripheral arterial disease or a coronary revascularization before the admission for MI.

§Received a prescription within 30 days (rofecoxib, celecoxib, other COX-2 selective inhibitors, naproxen, other nonaspirin NSAIDs, or oral glucocorticocoids), 90 days (high-dose aspirin, platelet inhibitors, lipid-lowering agents, and oral anticoagulants), or ever (antihypertensive drugs, insulin and oral hypoglycemic drugs, nitrates, penicillamine, gold, and postmenopausal hormone therapy for women) before the date of admission for MI.

number, date of discharge, and up to 20 discharge diagnoses and procedures,²³ coded according to the *International Classification of Diseases, Eighth Revision (ICD-8)*, until the end of 1993, and 10th revision (*ICD-10*) thereafter.²³

Based on the discharge history, we identified patients with a first diagnosis of MI between *ICD-10* codes: I21.0-I21.9 (n=10 343). We excluded patients who had an address outside the counties, had been living within the counties for less than 1 year, or were younger than 20 years (n=63). In total, 10 280 cases were available for analyses (**Table 1**).

Using the Civil Registration System, which retains data on vital status, address, and emigration for the Danish population since 1968, we aimed to se-

lect 10 controls for each case matched by age and sex (n=102 797) using the risk set sampling²⁴ (ie, the controls had to be alive and at risk of a first hospitalization for MI according to their discharge history at the time the corresponding case was diagnosed [index date]).

NONASPIRIN NSAIDs USE

Data on prescriptions for nonaspirin NSAIDs were obtained from prescription databases maintained in the counties, which retain information on refundable drugs, including type of drug and date of prescription (date of dispensing of the drug). Data were available from 1991 (North Jutland County), 1996 (Aarhus County), and 1998 (Viborg County), respectively. Thus, complete

Table 2. Crude and Adjusted Relative Risk Estimates for MI According to Prescription for Celecoxib, Rofecoxib, Other COX-2 Selective Inhibitors, Naproxen, and Other Nonaspirin NSAIDs

Category of Use*	Cases (n = 9287)	Controls (n = 93 270)	Crude RR (95% CI)	Adjusted RR (95% CI)†
Nonuser	4178	47 122	1.00 (Reference)	1.00 (Reference)
Rofecoxib				
Current user	119	611	2.23 (1.82-2.72)	1.80 (1.47-2.21)
New user	39	149	2.97 (2.08-4.24)	2.52 (1.74-3.64)
Recent user	68	520	1.50 (1.12-1.93)	1.07 (0.82-1.39)
Former user	49	420	1.35 (1.00-1.82)	1.13 (0.83-1.53)
Celecoxib				
Current user	71	521	1.56 (1.21-2.00)	1.25 (0.97-1.62)
New user	35	148	2.67 (1.85-3.87)	2.13 (1.45-3.13)
Recent user	60	454	1.51 (1.15-1.98)	1.18 (0.89-1.55)
Former user	45	344	1.50 (1.10-2.05)	1.24 (0.90-1.72)
Other COX-2 selective inhibitor				
Current user	57	396	1.63 (1.24-2.16)	1.45 (1.09-1.93)
New user	22	68	3.64 (2.25-5.90)	3.37 (2.05-5.53)
Recent user	33	319	1.17 (0.82-1.68)	0.97 (0.67-1.41)
Former user	189	1680	1.27 (1.09-1.48)	1.19 (1.01-1.39)
Naproxen				
Current user	26	175	1.68 (1.11-2.53)	1.50 (0.99-2.29)
New user	4	25	1.82 (0.63-5.23)	1.65 (0.57-4.83)
Recent user	25	199	1.41 (0.93-2.14)	1.27 (0.83-1.94)
Former user	213	2059	1.17 (1.01-1.35)	1.13 (0.97-1.31)
Other nonaspirin NSAID				
Current user	532	3105	1.94 (1.76-2.14)	1.68 (1.52-1.85)
New user	65	278	2.65 (2.02-3.48)	2.65 (2.00-3.50)
Recent user	421	3512	1.36 (1.22-1.51)	1.20 (1.07-1.33)
Former user	3201	31 833	1.14 (1.08-1.19)	1.04 (0.99-1.09)

Abbreviations: See Table 1; CI, confidence interval; RR, relative risk.

*Category of use was defined as the following: nonusers (no recorded prescriptions for any nonaspirin NSAID before index date), current users (having filled a prescription within 0-30 days), new users (a subset of current users, defined as having filled their first prescription within 0-30 days), recent users (having filled a prescription within 31-90 days), and former users (having filled a prescription >90 days before index date). Persons using more than 1 category of nonaspirin NSAID in the most recent period were excluded (993 cases and 9527 controls).

†Adjusted for discharge diagnoses of cardiovascular disease, hypertension, diabetes mellitus, chronic bronchitis or emphysema, alcoholism, liver cirrhosis, upper gastrointestinal bleeding, rheumatoid arthritis, systemic lupus erythematosus and prescriptions for high-dose aspirin, platelet inhibitors, insulin or oral hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, oral anticoagulants, hormone therapy, nitrates, penicillamine, gold, and glucocorticoids before the date of admission for MI.

coverage was ensured from 2000 through 2003.

All types of nonaspirin NSAIDs, except low-dose ibuprofen (200 mg per tablet), were available only by prescription. Although low-dose ibuprofen was available without prescription, pensioners and regular users of this drug are typically all registered in the databases because the cost is partly refunded when ibuprofen is prescribed by a physician.

Use of rofecoxib, celecoxib, other COX-2 selective inhibitors (ie, the COX-2 selective conventional NSAIDs etodolac, meloxicam, and nabumetone), naproxen, and other nonaspirin NSAIDs was assessed. We classified individuals according to their most recent use: current users (having filled a prescription within 0-30 days), new users (a subset of current users, who were defined as having filled their first prescription within 0-30 days), recent users (having filled a pre-

scription within 31-90 days), former users (having filled a prescription >90 days before index date), or nonusers (no recorded prescriptions for any nonaspirin NSAID before index date). The minimum length of prescription history was 1 year. Persons with prescriptions for more than 1 of the drug categories within the most recent period of use were grouped in a separate category (data not presented). Users were also categorized according to the total number of filled prescriptions for each type of NSAID (ie, no prescriptions, 1-3 prescriptions, 4-9 prescriptions, and ≥10 prescriptions).

CONFOUNDING FACTORS

Data were obtained from the discharge and prescription registries based on the available history for each case and control. The discharge diagnoses included coronary heart disease (other than MI), stroke, pe-

ripheral arterial disease and coronary revascularization procedures (percutaneous coronary intervention or coronary by-pass operation), hypertension, diabetes mellitus, chronic bronchitis or emphysema (a proxy measure of smoking), alcoholism, liver cirrhosis, upper gastrointestinal track bleeding, rheumatoid arthritis, and systemic lupus erythematosus registered before the index date.

The prescription data included prescriptions for high-dose aspirin (200-500 mg), low-dose aspirin, dipyridamole, clopidogrel bisulfate, angiotensin-converting enzyme inhibitors, β-blockers, calcium antagonists, diuretics and angiotensin II receptor antagonists, insulin and oral hypoglycemic drugs, lipid-lowering drugs, warfarin, phenprocoumon, nitrates, penicillamine, gold, oral glucocorticoids, and postmenopausal hormone therapy (women) filled before the index date.

STATISTICAL ANALYSIS

We used conditional logistic regression to compute relative risk estimates with 95% confidence intervals (CIs) for MI among each drug exposure category (see table footnotes for possible confounding factors included in the analyses). Nonusers were used as the reference group in all analyses.

For comparison, the risk of hospitalization for MI was also estimated among users of high-dose aspirin. The likelihood ratio test was used to compare the adjusted risk estimates. Furthermore, separate analyses were performed among new users and among persons at low and high risk of MI. Low risk was defined as no previous hospitalizations for cardiovascular disease, hypertension, diabetes mellitus or coronary revascularization, and no previous prescriptions for cardiovascular drugs, insulin, or oral hypoglycemic drugs. High risk was defined as at least 1 previous hospitalization for cardiovascular disease, hypertension, diabetes mellitus, or coronary revascularization or at least 1 previous prescription for cardiovascular drugs, insulin, or oral hypoglycemic drugs.

Finally, the association between length of use of the nonaspirin NSAIDs and risk of MI was examined by comparing the risk of MI according to the total number of filled prescriptions (ie, no prescriptions, 1-3 prescriptions, 4-9 prescriptions, and ≥10 prescriptions) separately for persons who had filled prescriptions for 1 (exclusive users) or more than 1 category (combined users) of nonaspirin NSAIDs. All analyses were conducted using SAS version 8.00 (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 gives the characteristics of the cases and controls. As expected, cases were characterized by a more adverse cardiovascular risk profile compared with controls. **Table 2** presents risk estimates for MI among users of rofecoxib, celecoxib, other COX-2 selective inhibitors, naproxen, and other nonaspirin NSAIDs. Current and new use of rofecoxib was associated with an increased risk estimate of MI compared with the nonuse of any category of nonaspirin NSAIDs with adjusted relative risks (ARRs) of 1.80 (95% CI, 1.47-2.21) and 2.52 (95% CI, 1.74-3.64), respectively. No increased risk estimates were apparent among recent or former rofecoxib users.

Similar patterns were seen for celecoxib, other COX-2 selective inhibitors, naproxen, and other nonaspirin NSAIDs. Adjusted relative risks estimates ranged from 1.25 for celecoxib to 1.80 for rofecoxib among current users ($P=.03$) and from 1.65 for naproxen to 3.37 for other COX-2 selective inhibitors among new users ($P=.25$) (Table 2). For new users, the risk estimates were similarly elevated for all nonaspirin NSAID categories except naproxen. Although not statistically significant, the risk appeared lower for recent and former users in all drug categories except celecoxib.

For comparison, elevated risk estimates were found among both current (ARR, 1.34; 95% CI, 1.18-1.52), recent (ARR, 1.26; 95% CI: 1.13-1.40), and former users (ARR, 1.29; 95% CI, 1.13-1.48) of high-dose aspirin (data not shown).

The highest ARRs in both the low- and high-risk MI groups were found among current users of rofecoxib (2.77 and 1.58, respectively), whereas the lowest ARRs were found among current users of celecoxib (1.68 and 1.15, respectively) and other COX-2 selective inhibitors (1.80 and 1.13, respectively) (**Table 3**). We found no association between the number of filled prescriptions and risk of MI for any of the examined drug categories (**Table 4**).

Table 3. Crude and Adjusted RR Estimates for MI According to Current Use of Celecoxib, Rofecoxib, Other COX-2 Selective Inhibitors, Naproxen, and Other Nonaspirin NSAIDs Among Low- and High-Risk Persons

Low-Risk/High-Risk Persons*	Cases	Controls	Crude RR (95% CI)	Adjusted RR (95% CI)†
Low-risk persons				
Nonuser	1533	10 641	1.00 (Reference)	1.00 (Reference)
Rofecoxib	26	49	2.99 (1.83-4.89)	2.77 (1.69-4.54)
Celecoxib	15	44	1.84 (1.01-3.36)	1.68 (0.92-3.10)
Other COX-2 selective inhibitor	15	47	1.84 (1.01-3.35)	1.80 (0.98-3.28)
Naproxen	8	29	2.06 (0.93-4.55)	1.97 (0.89-4.35)
Other nonaspirin NSAID	128	434	2.06 (1.67-2.53)	1.99 (1.62-2.46)
High-risk persons				
Nonuser	2585	14 857	1.00 (Reference)	1.00 (Reference)
Rofecoxib	92	362	1.67 (1.32-2.12)	1.58 (1.24-2.00)
Celecoxib	56	299	1.24 (0.93-1.67)	1.15 (0.85-1.54)
Other COX-2 selective inhibitor	41	211	1.18 (0.84-1.66)	1.13 (0.80-1.60)
Naproxen	18	74	1.47 (0.87-2.49)	1.38 (0.82-2.34)
Other nonaspirin NSAID	396	1448	1.59 (1.41-1.79)	1.55 (1.37-1.76)

Abbreviations: See Table 2.

*The number of cases and controls in the different categories does not add up to the total number of cases ($n = 10\,280$) and controls ($n = 102\,797$) in the study because the study population was stratified by variables not used for matching cases and controls.

†Adjusted for discharge diagnoses of chronic bronchitis and emphysema, alcoholism, liver cirrhosis, upper gastrointestinal bleeding, rheumatoid arthritis, systemic lupus erythematosus and prescriptions for high-dose aspirin, penicillamine, gold, and oral glucocorticocoids before the date of admission for MI.

COMMENT

We found elevated risk estimates for MI among current and in particular new users of rofecoxib and celecoxib. Elevated risk estimates were also found among current and new users of other COX-2 selective inhibitors, naproxen, other conventional nonaspirin NSAIDs, and high-dose aspirin. For current users, the lowest risk estimates were found for celecoxib and the highest for rofecoxib and other nonaspirin NSAIDs. For new users, the risk estimates were similarly elevated for all nonaspirin NSAID categories evaluated, except naproxen.

The strengths of our study are its size, the population-based design, and the ability to examine specific types of nonaspirin NSAIDs. Furthermore, the data on exposures and possible confounding factors were prospectively recorded, and extensive efforts were made to adjust the risk estimates for influence from possible confounding factors, in particular underlying inflammatory conditions.

The limitations include the use of discharge diagnoses, since it is well-known that these are not entirely accurate. However, the validity of an

MI discharge diagnosis in Denmark is high because less than 10% of the cases are misclassified.²⁵ Although we adjusted for a wide range of possible confounding factors, our results may still be confounded by diet and lifestyle factors, by channeling bias²⁶ (eg, patients prescribed rofecoxib or celecoxib may have an elevated baseline risk of cardiovascular disease compared with patients being prescribed other categories of nonaspirin NSAIDs),^{27,28} or by the use of proxy measures. However, our findings appeared consistent after stratification according to baseline risk of MI.

The elevated risk estimates for all types of NSAIDs may to some extent reflect the existence of a protopathic bias, which occurs in observational studies when the indication for being prescribed a drug may be an unrecognized clinical manifestation related to the outcome in question (eg, angina pectoris misdiagnosed as chest pain of a musculoskeletal nature). Such a bias may have inflated the association between the studied drugs and the risk of MI and may thus partly underlie the pattern of clearly increased risk estimates found among current and new users of the examined categories

Table 4. Crude and Adjusted RR Estimates for MI According to Total Number of Filled Prescriptions for Celecoxib, Rofecoxib, Other COX-2 Selective Inhibitors, Naproxen, and Other Nonaspirin NSAIDs

Prescription	Cases (n = 8265)	Controls (n = 85 332)	Crude RR (95% CI)	Adjusted RR* (95% CI)
Nonuser	4178	47 122	1.00 (Reference)	1.00 (Reference)
Rofecoxib				
Exclusive users				
1-3 Prescriptions	63	456	1.59 (1.22-2.08)	1.35 (1.03-1.78)
4-9 Prescriptions	15	136	1.28 (0.75-2.18)	1.04 (0.60-1.80)
≥10 Prescriptions	3	62	0.56 (0.18-1.78)	0.47 (0.14-1.51)
Combined users				
1-3 Prescriptions	276	1994	1.59 (1.39-1.81)	1.25 (1.09-1.43)
4-9 Prescriptions	98	623	1.81 (1.46-2.25)	1.36 (1.09-1.70)
≥10 Prescriptions	54	340	1.84 (1.38-2.45)	1.38 (1.02-1.86)
Celecoxib				
Exclusive users				
1-3 Prescriptions	62	391	1.81 (1.38-2.38)	1.53 (1.16-2.02)
4-9 Prescriptions	11	107	1.19 (0.64-2.21)	0.98 (0.52-1.85)
≥10 Prescriptions	5	45	1.28 (0.51-3.22)	1.16 (0.45-2.96)
Combined users				
1-3 Prescriptions	193	1701	1.30 (1.11-1.52)	0.99 (0.85-1.16)
4-9 Prescriptions	61	501	1.40 (1.07-1.83)	1.07 (0.81-1.41)
≥10 Prescriptions	25	195	1.47 (0.97-2.24)	1.02 (0.67-1.58)
Other COX-2 selective inhibitor				
Exclusive users				
1-3 Prescriptions	168	1497	1.27 (1.08-1.49)	1.19 (1.01-1.41)
4-9 Prescriptions	30	251	1.35 (0.92-1.98)	1.23 (0.83-1.81)
≥10 Prescriptions	27	187	1.64 (1.10-2.46)	1.42 (0.94-2.15)
Combined users				
1-3 Prescriptions	500	4201	1.35 (1.22-1.49)	1.13 (1.02-1.25)
4-9 Prescriptions	84	890	1.07 (0.85-1.34)	0.85 (0.67-1.07)
≥10 Prescriptions	59	563	1.19 (0.91-1.56)	0.94 (0.72-1.24)
Naproxen				
Exclusive users				
1-3 Prescriptions	183	1749	1.18 (1.01-1.38)	1.15 (0.98-1.35)
4-9 Prescriptions	27	295	1.03 (0.70-1.53)	0.97 (0.65-1.45)
≥10 Prescriptions	32	208	1.74 (1.20-2.53)	1.65 (1.13-2.41)
Combined users				
1-3 Prescriptions	491	4374	1.27 (1.15-1.40)	1.07 (0.97-1.19)
4-9 Prescriptions	93	789	1.34 (1.08-1.66)	1.05 (0.84-1.31)
≥10 Prescriptions	56	436	1.46 (1.10-1.93)	1.01 (0.76-1.35)
Other nonaspirin NSAID				
Exclusive users				
1-3 Prescriptions	2299	23 343	1.11 (1.05-1.17)	1.04 (0.99-1.10)
4-9 Prescriptions	922	7963	1.31 (1.22-1.42)	1.16 (1.07-1.25)
≥10 Prescriptions	707	5707	1.41 (1.30-1.54)	1.17 (1.07-1.28)
Combined users				
1-3 Prescriptions	635	6107	1.18 (1.08-1.29)	1.01 (0.92-1.11)
4-9 Prescriptions	399	3369	1.35 (1.21-1.51)	1.08 (0.97-1.21)
≥10 Prescriptions	435	3195	1.56 (1.40-1.73)	1.18 (1.05-1.31)

Abbreviations: See Table 2.

*Adjusted for discharge diagnoses of cardiovascular disease, hypertension, diabetes mellitus, chronic bronchitis or emphysema, alcoholism, liver cirrhosis, upper gastrointestinal bleeding, rheumatoid arthritis, systemic lupus erythematosus and prescriptions for high-dose aspirin, platelet inhibitors, insulin or oral hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, oral anticoagulants, nitrates, penicillamine, gold, oral glucocorticocoids, hormone therapy, and nitrates before the date of admission for MI.

of nonaspirin NSAIDs, including naproxen, vs a lower risk among recent and former users.

Other limitations included the lack of data on over-the-counter sale of NSAIDs (low-dose ibuprofen and aspirin), compliance, and duration

of actual use of the prescribed drugs. However, the sales of low-dose ibuprofen constituted only approximately 14% of the total nonaspirin NSAID sales during the study period,²⁹ and the fact that part of the costs of the prescribed drugs is paid

by the patients is likely to have improved compliance. Moreover, we had no data on doses and were therefore unable to examine whether high doses of rofecoxib were associated with a particular high risk, as suggested by previous findings.^{7,14,15,19} Finally, the precision of several of our risk estimates was admittedly moderate owing to relatively low proportions of exposed cases and controls, so caution should be taken before drawing conclusions.

The excess overall risk of MI among users of rofecoxib is in accordance with the data from APPROVE,³ from a meta-analysis of trials of rofecoxib in patients with chronic musculoskeletal disorders,⁶ and from 3 observational studies.^{14,15,19} The particular high-risk estimates found among new users were also in accordance with previous studies and do not support the hypothesis of no excess risk within the first 18 months of use as reported from the APPROVE trial.³ The differences in the risk estimates between new users and all current users could be explained by early events in the patients most susceptible to MI, different induction periods of beneficial and adverse effects of the studied drugs, physiologic adaptation that may occur during prolonged periods of treatment, or selection factors, including adherence bias, which vary according to treatment duration.²⁸

Because rofecoxib has already been withdrawn from the market, the focus should be shifted to the safety of the other nonaspirin NSAIDs, in particular the other COX-2 selective NSAIDs. This interest has been further fueled by the recent publication of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), in which lumiracoxib, the most selective COX-2 inhibitor available, was compared with ibuprofen or naproxen.²¹ A nonsignificant increased MI risk associated with use of lumiracoxib compared with naproxen (relative risk, 1.77; 95% CI, 0.82-3.84) but not ibuprofen (relative risk, 0.66; 95% CI: 0.21-2.09) were seen. Until recently, to our knowledge, no studies had found an increased risk of MI or other cardiovascular events among users of celecoxib compared with users of

placebo, users of other nonaspirin NSAIDs, or nonusers of nonaspirin NSAIDs.^{14-20,29-34} The excess risk among celecoxib users compared with nonusers of nonaspirin NSAIDs in our study is, however, in accordance with the recently halted APC trial, in which a significant increase in the risk of cardiovascular events (a composite end point of cardiovascular death, MI, and stroke) has been found among patients randomized to a daily dose of 400 or 800 mg of celecoxib.² However, it should be noted that the doses in the APC trial are high compared with currently approved dosing regimens for the most common indications (eg, osteoarthritis and rheumatoid arthritis) and that no increased cardiovascular risk so far has appeared in 2 other ongoing trials of celecoxib, similar in size and duration to the APC trial.²

A number of traditional nonaspirin NSAIDs (including etodolac, meloxicam, and nabumetone) also demonstrate a high degree of COX-2 selectivity, and the cardiovascular safety data are sparse. However, the similarities in pharmacology with rofecoxib and the particular high risk of MI among new users of these drugs found in our study raises new concerns.

Until recently, naproxen has not been associated with an elevated cardiovascular risk compared with either no use or the use of other nonaspirin NSAIDs.^{5,8-10,35,36} However, a National Institutes of Health review recently revealed an unexpected increased risk of cardiovascular events among patients randomized to naproxen in the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT).²² Furthermore, an elevated risk of MI (adjusted odds ratio, 1.14; 95% CI, 1.00-1.30) among current users of naproxen was also reported in a recent case-control study.¹⁹ Although our risk estimates for naproxen were not significantly elevated, our estimates were higher than previously reported and thus provide some support for the concerns regarding naproxen.

Aspirin, in particular small doses, is considered a cardioprotective agent. The elevated risk estimates found in our study for use of high-

dose aspirin may therefore reflect uncontrolled confounding because the risk was increased among former users. However, the cardiovascular safety of persistent high-dose aspirin use, which inhibits both COX-1 and COX-2, has not been well examined, and at least 1 study had found that high-dose aspirin use was associated with an increased risk of ischemic heart disease.³⁷ A causal association can therefore not be excluded.

In conclusion, we found that rofecoxib and celecoxib were associated with an excess risk of MI. However, risk estimates were also increased among users of other COX-2 selective inhibitors and other categories of nonaspirin NSAIDs. The risk estimates appeared lower for celecoxib compared with rofecoxib. The overall increased relative risk of MI associated with use of nonaspirin NSAIDs in general may to some extent reflect a protopathic bias; however, continued attention to the cardiovascular safety of all nonaspirin NSAIDs appears warranted.

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Author Affiliations: Department of Clinical Epidemiology, Aarhus Hospital, Aarhus University Hospital, Aarhus, Denmark (Drs Johnsen, Nørgård, and Sørensen and Ms Larsen); Center of Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark (Dr Johnsen); International Epidemiology Institute, Rockville, Md (Drs Tarone and McLaughlin); Department of Medicine, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, Tenn (Drs Tarone and McLaughlin); and Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (Dr Friis).

Correspondence: Søren P. Johnsen, MD, PhD, Department of Clinical Epidemiology, Aarhus Hospital, Aarhus University Hospital, Ole Worms Allé 150, DK-8000 Aarhus C, Denmark (spj@dce.au.dk).

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REFERENCES

1. Merck announces voluntary worldwide withdrawal of VIOXX. News release. Whitehouse Station, NJ: Merck; 2004. Available at: http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf Accessed September 30, 2004.
2. FDA statement on the halting of a clinical trial of the Cox-2 inhibitor Celebrex. Rockville, Md: US Food and Drug Administration; December 17, 2004. Available at: <http://www.fda.gov/bbs/topics/news/2004/NEW01144.html>.
3. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2001; 345:433-442.
4. Ray WA, MacDonald TM, Solomon DH, Graham DJ, Avorn J. COX-2 selective non-steroidal anti-inflammatory drugs and cardiovascular disease. *Pharmacoepidemiol Drug Saf*. 2003;12:67-70.
5. Topol EJ, Falk GW. A coxib a day won't keep the doctor away. *Lancet*. 2004;364:639-640.
6. Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet*. 2004; 364:2021-2029.
7. Bombardier C, Laine L, Reicin A, et al; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000;343: 1520-1528.
8. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.
9. Solomon DH, Glynn RJ, Levin R, Avorn J. Non-steroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Intern Med*. 2002; 162:1099-1104.
10. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med*. 2002;162:1105-1110.
11. Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. *Arch Intern Med*. 2002; 162:1111-1115.
12. Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled clinical trials of rofecoxib. *Circulation*. 2001;104:2280-2288.
13. Reicin A, Shapiro D, Sperling RS, Barr E, Yu Q. 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.
14. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation*. 2004;109:2068-2073.
15. Ray WA, Stein MC, Daugherty JR, Hall K, Arbo-gast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet*. 2002;360: 1071-1073.
16. 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.

17. Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med.* 2005;142:157-164.
18. Shaya FT, Blume SW, Blanchette CM, Weir MR, Mullins D. Selective cyclooxygenase-2 inhibition and cardiovascular effects. *Arch Intern Med.* 2005;165:181-186.
19. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet.* 2005;365:475-481.
20. Silverstein FE, Faich G, Goldstein JL. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomised controlled trial: Celecoxib Long-term Arthritis Safety Study. *JAMA.* 2000;284:1247-1255.
21. Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomized controlled trial. *Lancet.* 2004;364:675-684.
22. *FDA Statement on Naproxen.* Rockville, Md: US Food and Drug Administration; December 20, 2004. Available at: <http://www.fda.gov/bbs/topics/news/2004/NEW01148.html>.
23. Andersen TF, Madsen M, Jørgensen J, Møllekjær L, Olsen JH. The Danish National Hospital Register. *Dan Med Bull.* 1999;46:263-268.
24. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies, I: principles. *Am J Epidemiol.* 1991;134:433-437.
25. Madsen M, Davidsen M, Rasmussen S, et al. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol.* 2003;56:124-130.
26. Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sørensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther.* 2002;9:199-205.
27. Zhao SZ, Burke TA, Whelton A, von Allmen H, Henderson SC. Comparison of the baseline cardiovascular risk profile among hypertensive patients prescribed COX-2 specific inhibitors or non-specific NSAIDs: data from real-life practice. *Am J Manag Care.* 2002;8(15 suppl):S392-S400.
28. Rahme E, Marentette MA, Kong SX, Leloirier J. Use of NSAIDs, COX-2 inhibitors, and acetaminophen and associated coprescriptions of gastroprotective agents in an elderly population. *Arthritis Rheum.* 2002;47:595-602.
29. Møllekjær L, Blot WJ, Sørensen HT, et al. Upper gastrointestinal bleeding among users of NSAID: a population-based cohort study in Denmark. *Br J Clin Pharmacol.* 2002;53:173-181.
30. Ray W. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol.* 2003;158:915-920.
31. Mamdani M, Juurlink DN, Lee DS, et al. Cyclooxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet.* 2004;363:1751-1756.
32. Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension.* 2004;44:140-145.
33. Whelton A, White WB, Bello AE, Puma JA, Fort JG; SUCCES-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥ 65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol.* 2002;90:959-963.
34. White WB, Faich G, Whelton A. 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.
35. Schlienger RG, Jick H, Meier CR. Use of anti-inflammatory drugs and the risk of first-time acute myocardial infarction. *Br J Clin Pharmacol.* 2002;54:327-332.
36. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and the risk of serious coronary heart disease: an observational study. *Lancet.* 2002;359:118-123.
37. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. *BMJ.* 1989;299:1247-1250.