Effect of Selective Cyclooxygenase 2 Inhibitors and Naproxen on Short-term Risk of Acute Myocardial Infarction in the Elderly

Muhammad Mamdani, PharmD, MA, MPH; Paula Rochon, MD, MPH; David N. Juurlink, MD; Geoffrey M. Anderson, MD, PhD; Alex Kopp, BA; Gary Naglie, MD; Peter C. Austin, PhD; Andreas Laupacis, MD, MSc

Background: Recent debate has emerged regarding the cardiovascular safety of selective cyclooxygenase 2 inhibitors and the possible cardioprotective effect of naproxen sodium. We compared the rates of acute myocardial infarction (AMI) among elderly patients dispensed selective cyclooxygenase 2 inhibitors, naproxen, and nonselective nonnaproxen nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods: We conducted a population-based retrospective cohort study using administrative health care data from Ontario, Canada, from April 1, 1998, to March 31, 2001. We identified NSAID-naive cohorts of subjects aged 66 years and older in whom treatment was initiated with celecoxib (n=15271), rofecoxib (n=12156), naproxen (n=5669), and nonnaproxen nonselective NSAIDs (n=33868), along with a randomly selected control cohort not exposed to NSAIDs (n=100000). Multivariate Cox proportional hazards models were used to compare AMI rates between study drug groups while controlling for potential confounders.

Results: Relative to control subjects, the multivariate model showed no significant differences in AMI risk for new users of celecoxib (adjusted rate ratio [aRR], 0.9; 95% confidence interval [CI], 0.7-1.2), rofecoxib (aRR, 1.0; 95% CI, 0.8-1.4), naproxen (aRR, 1.0; 95% CI, 0.6-1.7), or nonnaproxen nonselective NSAIDs (aRR, 1.2; 95% CI, 0.9-1.4).

Conclusions: The findings of this observational study suggest no increase in the short-term risk of AMI among users of selective cyclooxygenase 2 inhibitors as commonly used in clinical practice. Furthermore, the findings do not support a short-term reduced risk of AMI with naproxen.

Arch Intern Med. 2003;163:481-486

Since their recent introduction, the selective cyclo-oxygenase (COX) 2 inhibitors have become one of the most widely prescribed groups of drugs in the elderly. However, the cardiovascular safety of these agents has recently been questioned. A sub-analysis of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial demonstrated a significant increase in the risk of acute myocardial infarction (AMI) for rofecoxib users relative to naproxen users. The absence of a placebo group in this trial and the low event rate in this subgroup analysis make interpretation of these findings difficult. Possible explanations for these observations include an increased risk of AMI for rofecoxib, a cardioprotective effect of naproxen, or both. Alternatively, the findings of the VIGOR trial with respect to AMI may have simply occurred by chance and neither rofecoxib nor naproxen truly affects the risk of AMI.

Subsequent to the publication of the VIGOR trial, a study by Mukherjee et al extended the cardiovascular safety concern to celecoxib and potentially all selective COX-2 inhibitors. However, a systematic review of 23 randomized controlled trials examining rofecoxib in relation to nonnaproxen nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) or placebo demonstrated no increased risk of cardiovascular thrombotic events for rofecoxib when compared with nonnaproxen nonselective NSAIDs, but it did observe a significant increased risk for rofecoxib when compared with naproxen. A reanalysis of a large randomized controlled trial of celecoxib failed to find an association between celecoxib and nonnaproxen nonselective NSAIDs and subsequent AMI. Five observational studies examining the potential cardioprotective effects of naproxen have arrived at conflicting conclusions. A recent large observational study comparing individual COX-2 in-
hibitors with naproxen failed to find any association be-
tween these drugs and AMI in the more commonly used
doses. The findings of this study, however, have not been verified.

We examined the incidence of AMI in more than 70'000 elderly new users of selective COX-2 inhibitors,
naproxen, and nonnaproxen nonselective NSAIDs rela-
tive to NSAID-naive control subjects.

STUDY OBJECTIVE, HYPOTHESIS, AND DESIGN

The primary objective of this study was to compare the inci-
dence of hospitalization for AMI among NSAID-naive elderly
subjects dispensed celecoxib, rofecoxib, naproxen, or non-
naproxen nonselective NSAIDs as commonly used in clinical
practice with a NSAID-naive community control group.

We conducted a population-based retrospective cohort
study by linking the health care records of more than 1.44 mil-
ion residents aged 66 years and older in Ontario, Canada, from
April 1, 1998, through March 31, 2001. Ontario’s elderly resi-
dents have universal access to prescription drug coverage, hos-
pital care, and physician services. This research study was ap-
proved by the Ethics Review Board of Sunnybrook and Women’s
College Health Sciences Centre, Toronto.

DATA SOURCES

The administrative health care databases in Ontario allowed for
cohort identification, comorbidity assessment, and endpoint
ascertainment. The linked databases included computerized
pharmacy records of the Ontario Drug Benefit Program, which
records prescription drugs dispensed to all Ontario residents
65 years and older. Both celecoxib and rofecoxib were first listed
on the Ontario Drug Benefit Program formulary on April 17,
2000, on a limited-use basis for patients in whom traditional
NSAIDs failed or who were intolerant of them, or for patients
with a history of upper gastrointestinal tract hemorrhage or ul-
cer. The approved indications for celecoxib included osteoar-
thritis and rheumatoid arthritis, whereas rofecoxib was ap-
proved only for use in osteoarthritis. No such restrictions
governed the prescribing of nonselective NSAIDs. We were un-
able to examine meloxicam because it was not available on the
Ontario Drug Benefit Program formulary during the study pe-
riod.

We obtained hospitalization records from the Canadian
Institute for Health Information Discharge Abstract Database,
which contains a detailed record of all hospital admissions, in-
cluding diagnostic and procedural information. The Ontario
Health Insurance Plan provided physician billing information
for inpatient and outpatient services, and the Ontario Regis-
tered Persons Database contained basic demographic and vital
statistics information, including death date, for every regis-
tered Ontario resident. These databases were linked anonym-
ously at the individual patient level by means of encrypted
unique health card numbers.

COHORT DEFINITION

We compared users of celecoxib, rofecoxib, naproxen, and non-
naproxen nonselective NSAIDs with a random sample of 100'000
controls dispensed none of these medications. Although we ac-
knowledge potential differences in morbidity between users and
nonusers of NSAIDs, we chose an NSAID-naive control group
as a base reference for 2 reasons. First, the overall population
provides a useful baseline risk estimate of non–NSAID-related
AMI. Second, previously published studies examining the as-
ociation between NSAID use and AMI are largely limited to
those with non–NSAID-using controls; a non–NSAID-using con-
trol group in this study would allow comparison of our inci-
dence and relative risk estimates with such studies. Pairwise
comparisons of the different NSAID study groups in relation

METHODS

To create the control cohort, all Ontario residents not in-
cluded in any of the previously described cohorts were ran-
domly assigned index dates within the observation period. In-
dividuals 66 years and older who were alive on the assigned
index date were screened for NSAID use 1 year before the in-
dex date. From those without a prescription for any NSAID in
the year before the index date or during the observation pe-
riod, we randomly selected 100'000 individuals to form the con-
trol cohort. This group was not age and sex matched to any
one particular group, but rather represented the general non–
NSAID-dispensed elderly population of Ontario.

DURATION OF EXPOSURE

For each of the 4 study drug groups, we defined the duration
of exposure as the period of continuous, exclusive enrollment
in any of the study medication groups starting from the index
date. A maximum follow-up of 1 year was allowed for subjects
in each study drug group to correspond to the maximum fol-
low-up data available for users of celecoxib and rofecoxib. In
the nonselective NSAID group, subjects were allowed to switch
between different nonselective NSAIDs during the observa-
tion period. The “days supply” variable of the pharmacy claims
database allowed us to estimate the intended duration of each
prescription. If subjects were dispensed a drug before the end
of this period, the excess drug supply was carried over to the
next prescription’s days supply estimation. Subjects were al-
lowed a 20% grace period on the previous days supply to refill
the next prescription. If subjects failed to refill their prescrip-
tion for the study drug within these successive time windows,
they were deemed to have discontinued the study drug.

Observation ended when patients were admitted to the hos-
pital for AMI. Occurrence of AMI was defined as a hospital ad-
mission with a primary International Classification of Diseases,
Ninth Revision diagnosis code of 410, which has a positive pre-
dictive value and sensitivity of approximately 89% and a speci-
licity of approximately 93%. Subjects were censored if they
were exposed to a medication from another study group, dis-
continued their study medication, died, reached the end of the
1-year follow-up limit, or reached the end of the observation
period (March 31, 2001).

For the non-NSAID random control cohort, each indi-
vidual was allowed at least 30 days of follow-up from the in-
dex date, and the end of the observation period was randomly
assigned up to a maximum of 1 year after the index date to cor-
respond to the follow-up period for the other study groups, un-
less the control subject experienced the outcome of interest or
died beforehand.
**Table 1. Covariates Assessed in Analysis**

<table>
<thead>
<tr>
<th>Hospitalizations</th>
<th>Procedures</th>
<th>Drug Use</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hospitalization in preceding year</td>
<td>Coronary angiography or revascularization procedure in preceding 5 y</td>
<td>No. of different drugs in preceding year</td>
<td>Age</td>
</tr>
<tr>
<td>Malignancy in preceding 5 y</td>
<td></td>
<td>120 d before index date until end of follow-up</td>
<td>Sex</td>
</tr>
<tr>
<td>Acute myocardial infarction, stroke, congestive heart failure, or noninfarct coronary disease in preceding 5 y</td>
<td></td>
<td>ACE inhibitors</td>
<td>Long-term care</td>
</tr>
</tbody>
</table>

Abbreviation: ACE, angiotensin-converting enzyme.

*Defined as annual income of less than Can $16 018 (singles) and less than Can $24 175 (couples), confirmed through personal tax statements on voluntary application for reductions in copayments and deductibles.

†Includes clonidine, doxazosin, guanethidine, hydralazine, methyldopa, minoxidil (oral), prazosin, reserpine, and terazosin.

**STATISTICAL ANALYSIS**

Time-to-event analyses were conducted for AMI by means of Cox proportional hazards models with the control group as the reference. Covariates in the model are outlined in Table 1. As an overall measure of comorbidity, we examined the number of distinct drugs dispensed in the 1 year before the index date, a measure comparable to the Charlson Comorbidity Index. All pairwise combinations of hazard ratios for different exposure groups were compared. The proportional hazards assumption for each exposure variable was assessed in each analysis for any violations.

Several sensitivity analyses were conducted to examine the impact of the study design features on our findings. First, the analyses were repeated with the use of controls matched by age (within 1 year of the birth date) and sex to all patients in the 4 study drug groups as a sensitivity analysis. Second, because women are more likely than men to receive NSAIDs and may have a relatively lower risk of AMI, we repeated analyses separately for men and women. Third, we repeated the AMI analysis excluding those with a previous history of AMI. Fourth, a sensitivity analysis was conducted to address differences between study groups in periods for subject accrual. More time was allowed for patient accrual in the naproxen and nonnaproxen nonselective NSAID group relative to the celecoxib and rofecoxib groups to maximize sample size in all study groups.

**RESULTS**

Of approximately 1.44 million potential subjects 65 years and older, 593808 (41%) were dispensed a prescription NSAID during the study period. From these individuals, we identified 15 271 users of celecoxib, 12 156 users of rofecoxib, 3 669 users of naproxen, 33 868 users of nonnaproxen nonselective NSAIDs, and 100 000 controls who met our inclusion criteria. Among nonselective NSAID users, most subjects initiated treatment with the combination of diclofenac and misoprostol (58%), ibuprofen (14%), or diclofenac (13%). A greater proportion of rofecoxib and celecoxib users were women compared with the other groups. The control group generally used fewer health care resources than the other study groups. More rofecoxib and celecoxib users had cardiovascular-related hospitalizations before cohort entry and were dispensed cardiovascular medications compared with the other groups.

During more than 75 000 person-years of follow-up, we observed 701 hospitalizations for AMI (Table 2). Relative to the control group, model-based estimates adjusted for the covariates in Table 1 did not disclose any statistically significant association with AMI for users of celecoxib (adjusted rate ratio [aRR], 0.9; 95% confidence interval [CI], 0.7-1.2), rofecoxib (aRR, 1.0; 95% CI, 0.8-1.4), naproxen (aRR, 1.0; 95% CI, 0.6-1.7), or nonnaproxen nonselective NSAIDs (aRR, 1.2; 95% CI, 0.9-1.4). When the drug groups were compared with each other through pairwise comparisons, no significant differences in AMI rates were observed between the drug groups after controlling for possible confounders.

Analyses using age- and sex-matched controls, separate analyses for men and women, and analyses excluding...
ing subjects with a previous history of AMI yielded similar findings. No significant differences in AMI rates between the 2 subject accrual periods were observed for the naproxen and nonnaproxen nonselective NSAID groups.

This study has 2 primary findings of importance to clinicians and patients. First, there does not appear to be an increased short-term risk of AMI among users of celecoxib or rofecoxib. Second, the addition of celecoxib or rofecoxib to naproxen did not further increase the risk of AMI compared to naproxen alone.

Table 2. Characteristics of Cohort Groups

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Community Control Group</th>
<th>Celecoxib (n = 15 271)</th>
<th>Rofecoxib (n = 12 156)</th>
<th>Naproxen Sodium (n = 5669)</th>
<th>Nonnaproxen Nonselective NSAIDs (n = 33 868)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (% female)</td>
<td>100 000 (56)</td>
<td>15 271 (70)</td>
<td>12 156 (71)</td>
<td>5669 (59)</td>
<td>33 868 (62)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>75.2 ± 7.2</td>
<td>76.5 ± 6.9</td>
<td>76.6 ± 7.0</td>
<td>75.0 ± 6.5</td>
<td>76.4 ± 7.0</td>
</tr>
<tr>
<td>Residence in long-term care facility, No. (%)</td>
<td>4197 (4)</td>
<td>466 (4)</td>
<td>548 (5)</td>
<td>291 (5)</td>
<td>2550 (8)</td>
</tr>
<tr>
<td>Low-income status, No. (%)</td>
<td>21 666 (22)</td>
<td>4517 (30)</td>
<td>3625 (30)</td>
<td>1742 (31)</td>
<td>11 602 (34)</td>
</tr>
<tr>
<td>Hospitalization in past year, No. (%)</td>
<td>11 878 (12)</td>
<td>2934 (19)</td>
<td>2363 (19)</td>
<td>1100 (19)</td>
<td>6292 (19)</td>
</tr>
<tr>
<td>No. of prescription drugs in past year, mean ± SD</td>
<td>5.3 ± 5.5</td>
<td>9.3 ± 6.4</td>
<td>9.7 ± 6.5</td>
<td>7.8 ± 6.2</td>
<td>8.3 ± 6.3</td>
</tr>
<tr>
<td>Hospitalizations/procedures in past 5 y, No. (%)</td>
<td>3.0 (3)</td>
<td>7.2 (5)</td>
<td>7.4 (5)</td>
<td>6.3 (4)</td>
<td>7.6 (4)</td>
</tr>
</tbody>
</table>

Table 3. Primary Analysis: AMI Outcomes

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Community Control Group (n = 100 000)</th>
<th>Celecoxib (n = 15 271)</th>
<th>Rofecoxib (n = 12 156)</th>
<th>Naproxen Sodium (n = 5669)</th>
<th>Nonnaproxen Nonselective NSAIDs (n = 33 868)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of admissions</td>
<td>419</td>
<td>75</td>
<td>58</td>
<td>15</td>
<td>134</td>
</tr>
<tr>
<td>Days of follow-up, mean ± SD</td>
<td>187 ± 101</td>
<td>168 ± 97</td>
<td>144 ± 89</td>
<td>100 ± 88</td>
<td>120 ± 101</td>
</tr>
<tr>
<td>Total follow-up, person-years</td>
<td>51 194</td>
<td>7004</td>
<td>4806</td>
<td>1559</td>
<td>11 085</td>
</tr>
<tr>
<td>Crude AMI rate/1000 person-years</td>
<td>8.2</td>
<td>10.7</td>
<td>12.1</td>
<td>9.6</td>
<td>12.1</td>
</tr>
<tr>
<td>Model-based risk ratios</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted rate ratio (95% CI)</td>
<td>1.0 (Reference)</td>
<td>1.3 (1.0-1.7)</td>
<td>1.5 (1.1-1.9)</td>
<td>1.2 (0.7-2.0)</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Adjusted rate ratio (95% CI)</td>
<td>1.0 (Reference)</td>
<td>0.9 (0.7-1.2)</td>
<td>1.0 (0.8-1.4)</td>
<td>1.0 (0.6-1.7)</td>
<td>1.2 (0.9-1.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; CHF, congestive heart failure; IHD, ischemic heart disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Defined as previous coronary angiography or revascularization procedure.

This study has 2 primary findings of importance to clinicians and patients. First, there does not appear to be an increased short-term risk of AMI among users of celecoxib or rofecoxib. Second, the addition of celecoxib or rofecoxib to naproxen did not further increase the risk of AMI compared to naproxen alone.
lecoxb or rofecoxib as commonly used relative to the
general non–NSAID-using population. Second, naproxen
does not appear to significantly decrease the short-term
risk of AMI. These results suggest that the findings from
the subanalysis of the VIGOR trial examining AMI rates
were either spurious or not applicable to the lower
doses of rofecoxib that are more commonly used in
clinical practice.

Although selective COX-2 inhibitors interfere with
the synthesis of vascular prostacyclin and do not block
the synthesis of thromboxane A2, in contrast to nonse-
lective NSAIDs, the clinical implications of such activ-
ity are largely unknown. Our neutral findings for cele-
cobix and rofecoxib are consistent with previously
published reviews of randomized controlled trials that
have failed to demonstrate an increased risk of AMI with
these drugs.4,5 Naproxen has been reported to inhibit the
production of thromboxane and reduce platelet aggrega-
tion to a much greater extent than other nonselective
NSAIDs.6 However, the clinical implications of these ef-
fects are also uncertain. Three case-control studies have
recently demonstrated cardioprotective benefits for
naproxen7,8,9 in contrast to another case-control study
that failed to find such an association.8 These studies have
not demonstrated dose-response, duration-response, or
temporal relationships, making it difficult to assess the
validity of their findings. Such relationships have been
examined in a large cohort study by Ray et al8 that fol-
lowed up NSAID-naive subjects from the time of non-
selective NSAID initiation onward. This study failed to
demonstrate cardioprotective benefits for naproxen rela-
tive to nonuse, even when stratifying by dose.

Several limitations of this study deserve mention.
First, although we controlled for many important con-
founders, we were unable to account for some poten-
tially important factors such as smoking, obesity, and al-
cohol consumption. However, we believe this is an
unlikely explanation for our findings. Despite a poten-
tially heavier disease burden among the rofecoxib and
celcoxib groups relative to the other study groups, which
may have resulted from the limited-use policy for selec-
tive COX-2 inhibitors in Ontario, neutral risk ratios were
still observed for these drug groups relative to the other
study groups after adjustment for available confound-
ers. Our population-based incidence estimates for AMI
(Table 3) among the control group are also consistent
with those of previous studies.20

Second, we used administrative databases to iden-
tify and define exposure to study drugs and clinical out-
comes. We have no direct measure of indication, adher-
ence, or appropriateness of use and were unable to identify
use of nonprescription NSAIDs. However, ibuprofen is
the only nonprescription, nonaspirin nonselective NSAID
available in Canada, and subjects in our study have a
strong financial incentive to obtain these drugs by pre-
scription. Nearly half of elderly residents of Ontario were
dispensed an NSAID during the observation period, which
is higher than in previous studies examining consump-
tion of either prescription or nonprescription NSAIDs
among the elderly population.2,3 This finding implies that
the vast majority of NSAID use in our population is cap-
tured by our databases. Similarly, 342,050 subjects, or 24%
of the elderly population of Ontario, were dispensed as-
pirin during the study period. Although these figures sug-
gest minimal over-the-counter use of these drugs, the ac-
tual magnitude of such activity is unknown. We identified
outcomes by means of diagnostic codes that have been
validated previously, but we were unable to capture AMI
that resulted in death before reaching the hospital. Third,
the low absolute number of events in the study groups
precluded reliable subgroup analyses examining the out-
comes of those using specific NSAIDs and aspirin con-
comitantly or the dose-related effects of these drugs. These
issues would be important to examine, since recent evi-
dence suggests that concomitant administration of ibu-
profen but not rofecoxib, acetaminophen, or diclofenac
antagonizes the irreversible platelet inhibition induced by
aspirin10 and therefore may alter its cardioprotective
effects. Furthermore, Ray et al11 have recently demon-
strated increased risk of AMI among users of high-dose
rofecoxib, which is consistent with the findings of the
rofecoxib trial, but not the more commonly used lower
doses of rofecoxib.11 Fourth, the generalizability of our
findings to younger patients or settings with less restric-
tive access to these drugs over longer durations of fol-
low-up is uncertain.

In summary, we observed no significant increased
risk of AMI among users of celecoxib or rofecoxib, nor
did we observe a significant protective effect for naproxen
as these drugs are commonly used in clinical practice.
While our findings relieve concerns about increased risks
of AMI associated with celecoxib and rofecoxib, they call
into question the cardioprotective benefits of naproxen
observed in previous studies.

Accepted for publication September 30, 2002.

From the Institute for Clinical Evaluative Sciences
(Drs Mamdani, Rochon, Juurlink, Anderson, Naglie, Aus-
tin, and Laupacis and Mr Kopp); Faculty of Pharmacy (Dr
Mamdani) and the Departments of Medicine (Drs Rochon,
Juurlink, Naglie, and Laupacis), Health Policy, Manage-
ment, and Evaluation (Dr Anderson), and Public Health Sci-
ences (Dr Austin), Faculty of Medicine, University of Toronto;
Division of General Internal Medicine, Sunnybrook and
Women’s College Health Sciences Centre (Drs Juurlink and
Laupacis); Department of Geriatric Medicine, University
Health Network and Toronto Rehabilitation Institute (Dr
Naglie); and Department of Geriatric Medicine, Baycrest
Centre for Geriatric Care (Dr Rochon), Toronto, Ontario.
In the past 2 years, Dr Mamdani has conducted research in
an unrelated content area at the request of an academic in-
stitution whose funding was supported by Pharmacia Cor-
poration (Peapack, NJ), but none of the funding for this study
was provided by any pharmaceutical company.

Dr Mamdani is supported by a New Investigator award
from the New Emerging Teams of the Canadian Institutes
of Health Research (CIHR), Ottawa, Ontario. Dr Rochon
is supported by a Career Scientist award from the CIHR.
Dr Juurlink is supported by a fellowship award from the CIHR
and from the Clinician-Scientist Program of the Depart-
ment of Medicine at the University of Toronto, Toronto. Dr
Laupacis is a Senior Scientist of the CIHR. This study was
supported by a CIHR operating grant (MOP-49527) and a
CIHR Chronic Disease New Emerging Team program grant

Downloaded From: https://archinte.jamanetwork.com/ by a Non-Human Traffic (NHT) User on 09/02/2019
The New Emerging Teams program receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the CIHR Institutes of Nutrition, Metabolism & Diabetes and Circulatory & Respiratory Health, Ottawa.

Corresponding author and reprints: Muhammad Mamdani, PharmD, MA, MPH, Institute for Clinical Evaluative Sciences, 2075 Bayview Ave—G215, Toronto, Ontario, Canada M4N 3M5 (e-mail: muhammad.mamdani@ices.on.ca).

REFERENCES