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

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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.

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Since their recent introduction, the selective cyclooxygenase (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 subanalysis 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 between 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 relative to NSAID-naive control subjects.

METHODS

STUDY OBJECTIVE, HYPOTHESIS, AND DESIGN

The primary objective of this study was to compare the incidence of hospitalization for AMI among NSAID-naive elderly subjects dispensed celecoxib, rofecoxib, naproxen, or nonnaproxen 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 million residents aged 66 years and older in Ontario, Canada, from April 1, 1998, through March 31, 2001. Ontario's elderly residents have universal access to prescription drug coverage, hospital care, and physician services. This research study was approved 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 end point 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 ulcer. The approved indications for celecoxib included osteoarthritis and rheumatoid arthritis, whereas rofecoxib was approved only for use in osteoarthritis. No such restrictions governed the prescribing of nonselective NSAIDs. We were unable to examine meloxicam because it was not available on the Ontario Drug Benefit Program formulary during the study period.

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

COHORT DEFINITION

We compared users of celecoxib, rofecoxib, naproxen, and nonnaproxen nonselective NSAIDs with a random sample of 100,000 controls dispensed none of these medications. Although we acknowledge 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 association between NSAID use and AMI are largely limited to those with non-NSAID-using controls; a non-NSAID-using control group in this study would allow comparison of our incidence and relative risk estimates with such studies. Pairwise comparisons of the different NSAID study groups in relation to one another instead of the non-NSAID control group were also conducted.

For the 4 drug cohorts, the initial prescription during the study period following a patient's 66th birthday served as the index date. To create a cohort of NSAID-naive subjects within these 4 drug groups, we excluded individuals who were dispensed a medication from any of the 4 study groups in the year preceding the index date. Subjects dispensed prescriptions for drugs from more than 1 study drug group on the same day were excluded. To exclude sporadic users of NSAID therapy, we included only individuals who were dispensed at least 2 successive prescriptions and who received enough drug for at least 30 days of observation. Events occurring during this initial 30-day period were included in the analysis.

To create the control cohort, all Ontario residents not included in any of the previously described cohorts were randomly assigned index dates within the observation period. Individuals 66 years and older who were alive on the assigned index date were screened for NSAID use 1 year before the index date. From those without a prescription for any NSAID in the year before the index date or during the observation period, we randomly selected 100,000 individuals to form the control 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 follow-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 observation 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 allowed a 20% grace period on the previous days supply to refill the next prescription. If subjects failed to refill their prescription 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 hospital for AMI. Occurrence of AMI was defined as a hospital admission with a primary International Classification of Diseases, Ninth Revision diagnosis code of 410, which has a positive predictive value and sensitivity of approximately 89% and a specificity of approximately 93%. Subjects were censored if they were exposed to a medication from another study group, discontinued 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 individual was allowed at least 30 days of follow-up from the index date, and the end of the observation period was randomly assigned up to a maximum of 1 year after the index date to correspond to the follow-up period for the other study groups, unless 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</td>
<td>No. of different drugs in preceding year</td>
<td>Age</td>
</tr>
<tr>
<td>Malignancy in preceding 5 y</td>
<td>preceding 5 y</td>
<td>120 d Before index date until end of follow-up</td>
<td>Sex</td>
</tr>
<tr>
<td>Acute myocardial infarction, stroke,</td>
<td></td>
<td>ACE inhibitors</td>
<td>Long-term care</td>
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<tr>
<td>congestive heart failure, or</td>
<td></td>
<td>Aspirin</td>
<td>Low-income status†</td>
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<td>noninfarct coronary disease in</td>
<td></td>
<td>Antiarhythmics</td>
<td></td>
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<tr>
<td>preceding 5 y</td>
<td></td>
<td>Anticoagulants</td>
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<td></td>
<td></td>
<td>Antiplatelets</td>
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<td></td>
<td>Antidiabetic agents</td>
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<td></td>
<td></td>
<td>Antihyperthetics†</td>
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<td></td>
<td></td>
<td>Nitrates</td>
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<tr>
<td></td>
<td></td>
<td>Other antihypertensives†</td>
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</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 non-naproxen nonselective NSAID group relative to the celecoxib and rofecoxib groups to maximize sample size in all study groups (i.e., naproxen and non-naproxen nonselective NSAIDs were available throughout the study period, whereas celecoxib and rofecoxib were available only after April 17, 2000). We limited this analysis to the naproxen, nonnaproxen nonselective NSAID, and control groups throughout the study period and repeated the analyses with the addition of an interaction term indicating whether the naproxen and nonnaproxen nonselective NSAIDs users entered the cohort before or after the introduction of celecoxib and rofecoxib. The interaction terms were then examined for significant differences in AMI rates between these periods among the 2 study drug groups.

All analyses were performed with SAS for UNIX, Version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Of approximately 1.44 million potential subjects 65 years and older, 593,808 (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 non-naproxen nonselective NSAIDs, and 100,000 controls (Table 2) 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 (Table 2).

During more than 75,000 person-years of follow-up, we observed 701 hospitalizations for AMI (Table 3). 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 exclud-
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 ce-

### Table 2. Characteristics of Cohort Groups

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Community Control Group</th>
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<th>Naproxen Sodium</th>
<th>Nonnaproxen Nonselective NSAIDs</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>
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<tr>
<td>Residence in long-term care facility, No. (%)</td>
<td>4197 (4)</td>
<td>665 (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>
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<td>Hospitalization in past year, No. (%)</td>
<td>11 878 (12)</td>
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<td>6292 (19)</td>
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<td>No. of prescription drugs in past year, mean ± SD</td>
<td>5.3 ± 5.5</td>
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### Table 3. Primary Analysis: AMI Outcomes

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<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>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>
</tr>
<tr>
<td>Adjusted rate ratio (95% CI)</td>
<td>1.0 (Reference)</td>
<td>0.9 (0.7-1.2)</td>
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<td>1.0 (0.6-1.7)</td>
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</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 ce-
lecoxib 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-
coxib 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. Naproxen has been reported to inhibit the
production of thromboxane and reduce platelet aggre-
gation to a much greater extent than other nonselective
NSAIDs. However, the clinical implications of these ef-
fects are also uncertain. Three case-control studies have
recently demonstrated cardioprotective benefits for naproxen in contrast to another case-control study
that failed to find such an association. 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 al that fol-
lowed up NSAID-naïve 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
celecoxib 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.

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. 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 aspirin and therefore may alter its cardioprotective
effects. Furthermore, Ray et al have recently demonstrat-
der 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. 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.

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