Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study

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Summary

Background Non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of congestive heart failure, but little is known about the cardiovascular effects of a newer group of NSAIDs called selective cyclo-oxygenase (COX)-2 inhibitors. We aimed to compare rates of admission for congestive heart failure in elderly patients who were newly dispensed COX-2 inhibitors or non-selective NSAIDs.

Methods In this population-based retrospective cohort study we identified NSAID-naive individuals aged 66 years or older, who were started on rofecoxib (n=18,908), celecoxib (n=18,908), and non-selective NSAIDs (n=5,391), and randomly selected non-NSAID users as controls (n=100,000).

Findings Relative to non-NSAID users, patients on rofecoxib and non-selective NSAIDs had an increased risk of admission for congestive heart failure (adjusted rate ratio 1·8, 95% CI 1·5–2·2, and 1·4, 1·0–1·9, respectively), but not celecoxib (1·0, 0·8–1·3). Compared with celecoxib users, admission was significantly more likely in users of non-selective NSAIDs (1·4, 1·0–1·9) and rofecoxib (1·8, 1·4–2·4). Risk of admission for rofecoxib users was higher than that for non-selective NSAID users (1·5, 1·1–2·1). Of patients with no admission in the past 3 years, only rofecoxib users were at increased risk of subsequent admission relative to controls (1·8, 1·4–2·3).

Interpretation These findings suggest a higher risk of admission for congestive heart failure in users of rofecoxib and non-selective NSAIDs, but not celecoxib, relative to non-NSAID controls.

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Introduction

Rapid adoption of a selective group of non-steroidal anti-inflammatory drugs (COX-2) inhibitors, into clinical practice has been met with both enthusiasm and caution. Although recent evidence suggests that the COX-2 inhibitors celecoxib and rofecoxib are associated with a lower risk of gastrointestinal events than non-selective NSAIDs, the cardiovascular safety of these agents has been challenged. In addition to the debate surrounding their possible association with acute myocardial infarction, selective COX-2 inhibitors might be associated with cardiovascular and renal adverse effects that are similar to those of non-selective NSAIDs, raising systemic vascular resistance and reducing renal perfusion in susceptible individuals.

In non-selective NSAID users, increases in blood pressure and development of peripheral oedema have been consistently associated with the development of congestive heart failure. However, little is known about the association between the use of selective COX-2 inhibitors and this condition. Two small studies separately comparing high doses of celecoxib and rofecoxib to non-selective NSAIDs and placebo reported slight decreases in water, sodium, and potassium excretion, and slight increases in systolic blood pressure in the selective COX-2 inhibitor and non-selective NSAID groups relative to placebo. Published and unpublished secondary analyses from two large randomised trials separately examining celecoxib and rofecoxib suggest differences between various NSAIDs with respect to onset of hypertension and oedema. In the celecoxib trial, the incidence of hypertension and peripheral oedema associated with the drug was significantly lower than that of the non-selective NSAID comparator group. The incidence of congestive heart failure was not reported. In the rofecoxib trial, frequency of hypertension and oedema associated with rofecoxib was significantly greater than that of naproxen. Incidence of congestive heart failure in rofecoxib users was higher than that in naproxen users, although this difference was not statistically significant (0·5% vs 0·2%, respectively, p=0·07). Two small trials directly comparing celecoxib and rofecoxib failed to show significant differences between the two drugs with respect to the effect on blood pressure. However, two large randomised trials in elderly osteoarthritis patients with longstanding hypertension reported significantly greater increases in systolic blood pressure and a higher likelihood of onset, or worsening of, oedema in those receiving rofecoxib than those receiving celecoxib.

In the absence of a large randomised controlled trial comparing the effects of selective COX-2 inhibitors with non-selective NSAIDs and non-NSAID users with respect to admission for congestive heart failure, we examined this association in more than 140 000 NSAID-naïve elderly patients.

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Methods
Patients and procedures
We undertook a population-based retrospective cohort study by linking administrative health-care databases, which covered over 1·3 million individuals aged 65 years and older in Ontario, Canada. These patients had universal access to prescription drug coverage, hospital care, and physician services. This study was approved by the ethics review board of Sunnybrook and Women’s College Health Sciences Centre.

The administrative health-care databases in Ontario allowed for cohort identification, comorbidity assessment, and endpoint ascertainment. These linked databases included computerised pharmacy records of the Ontario Drug Benefit Program (ODB), which records prescription drugs dispensed to all Ontario residents 65 years of age and older. An overall error rate of less than 1% in this drug database has been reported. Both rofecoxib and celecoxib were first listed on the ODB formulary on April 17, 2000, on a limited-use basis for patients who failed on, or were intolerant of, non-selective NSAIDs, or for those with a history of gastrointestinal haemorrhage or ulcers. Rofecoxib was approved for use only in osteoarthritis, whereas celecoxib was approved for both osteoarthritis and rheumatoid arthritis. Prescription of non-selective NSAIDs had no such restrictions. We did not examine meloxicam use because the drug was not available on the ODB formulary during the study period.

We obtained admission records from the Canadian Institute for Health information discharge abstract database, which contains a detailed record of all admissions. 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 Ontario resident. We linked these databases anonymously by using encrypted health-card numbers for individuals.

We assembled three separate study drug cohorts, consisting of new users of rofecoxib, celecoxib, or non-selective NSAIDs, as well as a random sample of non-NSAID users selected from community controls who were not given any study drugs. This group provided an estimate of baseline risk of congestive heart failure admissions in the general population that were unrelated to NSAID use. This was a useful reference group, since all individuals in a population are at risk for disorders that are characterised by pain and inflammation, and non-drug management could represent a viable treatment option. In addition to comparisons with the non-NSAID control group, we did pairwise comparisons of the different NSAID study groups in relation to one another.

For these cohorts, we identified individuals aged 66 years and older who were prescribed study drugs from April 17, 2000, to March 31, 2001. We restricted our study to individuals aged 66 years and older to examine their drug use in the previous year, since we had information on drug use for all Ontario residents aged 65 years and older. We defined the index study date as when a study drug was first prescribed during this timeframe. To identify NSAID-naive patients for these three drug groups, we excluded individuals who were given any NSAID medication in the year preceding the index date, or given more than one type of study drug on the same day. To exclude sporadic users of NSAIDs, we included only individuals who received at least two successive prescriptions of the same drug group, and those who received enough medication for at least 30 days of observation. We also repeated analyses to include patients with only one prescription and fewer than 30 days of observation.

To assemble the non-NSAID community control cohort, we began by randomly assigning index dates between April 17, 2000, and March 31, 2001, from a uniform distribution to all Ontario residents aged 66 years and older who were not included in any of the NSAID cohorts. Individuals who were alive on the assigned index date were screened for NSAID use within the preceding year. From those with no NSAID prescription during that time, we randomly selected 100 000 individuals for our non-NSAID control cohort, which represented the general non-NSAID-exposed elderly population of Ontario. As a sensitivity analysis, we repeated analyses with controls matched on sex and by age (born within 1 year) to all patients in the three study drug groups.

For all the three study drug cohorts, we defined the duration of exposure as the period of continuous, exclusive enrolment in the study medication group after the index date. The non-selective NSAID cohort could

Covariates controlled for in analysis

Admissions
- Any admission in past year
- Malignant disease in past 5 years
- Acute myocardial infarction, stroke, congestive heart failure, non-infarct coronary disease, or renal disease in past 5 years
- Congestive heart failure in past 6 months

Procedures
- Echocardiography or revascularisation procedure in past 5 years
- Heart-valve surgery procedure in past 5 years

Drug use during year before index date
- Number of different drugs
- ACE inhibitors or ARBs
- α blockers
- Aspirin
- Antiarrhythmics
- Anticoagulants
- Antiplatelets
- Antihyperglycaemic agents
- Antiarrhythmics
- β blockers
- Calcium-channel antagonists
- Digoxin
- Diuretics:
  - Loop diuretics
  - Non-loop diuretics
- Spironolactone
- Hydralazine
- Lipid-lowering drugs
- Nitrates
- Respiratory inhalers:
  - Inhaled β agonists or anticholinergics
- Other antihypertensives

Other
- Age
- Sex
- Long-term care
- Low income status†

ACE=angiotensin converting enzyme. ARB=angiotensin receptor blockers. *Includes clonidine, guanethidine, methyldopa, minoxidil (oral), and reserpine. †Defined as annual income of less than CAN$16 018 (for singles) and less than $24 175 (for couples), confirmed through personal tax statements on voluntary application for reductions in copayments and deductibles.
switch to different non-selective NSAIDs during the study period. The “days supply” variable of the pharmacy database allowed us to estimate the intended duration of every prescription. If patients were dispensed a drug before the end of this period, the excess drug supply was carried over to the next prescription’s day supply estimation. Individuals were allowed a 20% grace period on the previous day’s supply to refill the next prescription. If they did not refill their prescription for the study drug within these successive time windows, they were deemed to have discontinued the study drug.

The primary outcome was admission with a primary diagnosis of congestive heart failure (International Classification of Diseases, revision 9 [ICD9], code 428). A recent records-abstraction study validating the accuracy of coding for such admission in our databases showed positive predictive values of 90–96%, dependent on the criteria used to define the disease.21 We censored follow-up for every patient on admission for congestive heart failure, exposure to a medication from another study group, discontinuation of the study drug, death, or the end of the study period.

Statistical analysis
We did time-to-event analyses for congestive heart failure admission with Cox proportional hazards models using the community control group as the reference and controlling for all covariates outlined in the panel. As an overall measure of comorbidity, we controlled for the number of distinct drugs dispensed in the year before the index date,21 a measure comparable to the Charlson comorbidity index.22 We undertook separate subgroup analyses for patients with, and without, a history of congestive heart failure. Individuals with a history were defined as having a heart-failure-related admission within 3 years before the index date. We investigated disease history because some evidence has suggested that non-selective NSAID use might be associated with exacerbation of existing congestive heart failure rather than development of de-novo heart failure.23

Admission for congestive heart failure represents a severe outcome that is often preceded by more subtle, although clinically important, events. To capture these effects we also examined new initiation of treatment for hypertension (α blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β blockers, calcium-channel blockers, thiazide diuretics, nitrates, and other antihypertensive medications) or for congestive heart failure (digoxin, hydralazine, loop diuretics, or spironolactone) in patients who were not prescribed these medications in the year before cohort entry. Such new treatment would be a marker of clinically significant rises in blood pressure or onset of heart failure-related symptoms. Finally, we undertook pairwise comparisons of the study groups with specific NSAID groups as the reference, rather than the community control group. The proportional hazards assumption for all exposure variables was assessed in every analysis. All analyses were done with

### Table 1: Characteristics of cohort groups

<table>
<thead>
<tr>
<th>Drug use &amp; year before index date</th>
<th>Non-NSAID users</th>
<th>Celecoxib users</th>
<th>Rofecoxib users</th>
<th>Non-selective NSAIDs users</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>23 712 (24%)</td>
<td>6319 (33%)</td>
<td>4993 (34%)</td>
<td>3611 (31%)</td>
</tr>
<tr>
<td>α blockers</td>
<td>3312 (3%)</td>
<td>794 (4%)</td>
<td>660 (5%)</td>
<td>575 (5%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>12 475 (12%)</td>
<td>3616 (19%)</td>
<td>2886 (20%)</td>
<td>2411 (21%)</td>
</tr>
<tr>
<td>Antiarhythmics</td>
<td>2461 (2%)</td>
<td>594 (3%)</td>
<td>469 (3%)</td>
<td>258 (2%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>5816 (6%)</td>
<td>1631 (9%)</td>
<td>1262 (9%)</td>
<td>491 (4%)</td>
</tr>
<tr>
<td>Antihyperglycaemics</td>
<td>9456 (9%)</td>
<td>2302 (12%)</td>
<td>1809 (12%)</td>
<td>1607 (14%)</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>1014 (1%)</td>
<td>302 (2%)</td>
<td>271 (2%)</td>
<td>122 (1%)</td>
</tr>
<tr>
<td>Antineumatics</td>
<td>0</td>
<td>852 (5%)</td>
<td>399 (3%)</td>
<td>123 (1%)</td>
</tr>
<tr>
<td>β blockers</td>
<td>15 870 (16%)</td>
<td>4126 (22%)</td>
<td>3116 (21%)</td>
<td>2163 (19%)</td>
</tr>
<tr>
<td>Calcium-channel antagonists</td>
<td>17 404 (17%)</td>
<td>5163 (27%)</td>
<td>4265 (29%)</td>
<td>2631 (23%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5987 (6%)</td>
<td>1464 (8%)</td>
<td>1079 (7%)</td>
<td>666 (6%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>8693 (9%)</td>
<td>3091 (16%)</td>
<td>2327 (16%)</td>
<td>1528 (15%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1677 (2%)</td>
<td>580 (3%)</td>
<td>465 (3%)</td>
<td>272 (2%)</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>14 543 (15%)</td>
<td>4554 (24%)</td>
<td>3411 (23%)</td>
<td>2399 (21%)</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>199 (1%)</td>
<td>57 (1%)</td>
<td>32 (&lt;1%)</td>
<td>30 (&lt;1%)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>17 386 (17%)</td>
<td>4433 (23%)</td>
<td>3558 (24%)</td>
<td>2630 (23%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10 072 (10%)</td>
<td>3255 (17%)</td>
<td>2522 (17%)</td>
<td>1625 (14%)</td>
</tr>
<tr>
<td>Other antihypertensives</td>
<td>465 (&lt;1%)</td>
<td>169 (&lt;1%)</td>
<td>111 (&lt;1%)</td>
<td>98 (&lt;1%)</td>
</tr>
<tr>
<td>Respiratory inhalers</td>
<td>9 941 (10%)</td>
<td>2997 (17%)</td>
<td>2107 (15%)</td>
<td>1703 (15%)</td>
</tr>
</tbody>
</table>

CHF=congestive heart failure. AMI=acute myocardial infarction. IHD=ischaemic heart disease. ACEI=angiotensin-converting enzyme inhibitor. *Defined as previous coronary angiography or revascularisation procedure.
SAS for UNIX, version 8.2. All statistical tests were done at the 5% level of significance and were two-sided.

Role of the funding source

This study was funded by a national, peer-review health research granting agency, which had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of about 1·3 million potential patients aged 65 years and older, 364 686 (28%) were dispensed an NSAID during the study period. From these individuals, we identified 11 606 new users of non-selective NSAIDs, 18 908 users of celecoxib, 14 583 users of rofecoxib, and 100 000 non-NSAID users (table 1). In non-selective NSAID users, most patients were started on the combination of diclofenac plus misoprostol (5720 individuals, 49%), naproxen (1920, 17%), ibuprofen (1384, 12%), or diclofenac alone (1182, 10%). The characteristics of the rofecoxib and celecoxib cohorts were virtually identical (table 1). However, compared with other groups, rofecoxib and celecoxib users were more likely to be female, to have previously undergone echocardiography, or to have received loop diuretics or digoxin. COX-2 inhibitor users were also more likely to have received angiotensin-converting enzyme inhibitors, β blockers, and calcium-channel antagonists. Patients from the control group tended to have fewer preceding admissions, and were prescribed fewer drugs than the other study groups.

During over 55 000 person-years of follow-up, including the control group, we recorded 654 admissions for congestive heart failure (table 2). Relative to non-NSAID users, the rate of admission was significantly higher for users of rofecoxib and non-selective NSAIDs, but not celecoxib. Additional analyses with age-matched and sex-matched controls and allowing for sporadic NSAID use yielded similar findings.

Pairwise comparisons between the drug groups showed significant differences in admission risk for congestive heart failure. Relative to celecoxib users, a significantly higher risk of admission for congestive heart failure was seen in users of rofecoxib (adjusted rate ratio 1·8, 95% CI 1·5–2·2).
Selection bias might well not explain the difference in rofecoxib and celecoxib groups are probably minimum, so arbitrary in clinical practice. Therefore, the differences in selection of one COX-2 inhibitor over another is probably

The demographic and clinical characteristics of rofecoxib and non-selective NSAIDs were at significantly increased risk of readmission (model-based risk ratios in table 3) compared with non-NSAID users, whereas celecoxib users were not. The estimated numbers needed to treat to harm in patients with a history of recent admission for heart failure were significantly lower than those of individuals with no previous history (table 3). Analysis of individuals with no previous use of antihypertensive agents or medications for congestive heart failure revealed that users of rofecoxib, celecoxib, and non-selective NSAIDs were all more likely to be initiated on such medications than were non-NSAID users (table 3). Relative to users of celecoxib, rofecoxib (adjusted rate ratio 1.3, 95% CI 1.1–1.5) and non-selective NSAID (1.2, 1.0–1.4) users were significantly more likely to be started on hypertensive drugs or medication for congestive heart failure. The estimated numbers needed to treat to harm were low for celecoxib, rofecoxib, and non-selective NSAIDs.

**Discussion**

Compared with non-NSAID users, we have recorded higher rates of admission for congestive heart failure in elderly patients who were initiated on treatment with rofecoxib and non-selective NSAIDs, but not celecoxib. These differences are clinically important, in view of the large numbers of patients given NSAIDs of any type. In particular, there was a greater risk of readmission in individuals previously admitted for heart failure and who received rofecoxib or non-selective NSAIDs. Further, all drug groups were associated with a significantly increased risk of initiation of treatment for hypertension or congestive heart failure in those not previously on such therapy. Our findings are consistent with those of others. Our population-based rates of admissions for congestive heart failure in the community control group are similar to those reported elsewhere.

Further, we noted that use of non-selective NSAIDs was associated with worsening heart failure in patients with a history of the disease, but not with new-onset of disease, as did Feenstra and colleagues. Although the estimated absolute risks of admission were small in those without a recent previous history of congestive heart failure, the low estimated number needed to treat to harm in those with a recent history makes these findings clinically relevant. Moreover, the high rate of initiating antihypertensive or congestive heart failure medications in those not receiving such treatment previously suggests a need for careful monitoring of cardiovascular effects for patients receiving celecoxib, rofecoxib, or non-selective NSAIDs.

Selection bias is unlikely to account for the differences in outcomes between the rofecoxib and celecoxib groups. The demographic and clinical characteristics of rofecoxib and celecoxib users were closely similar, implying that selection of one COX-2 inhibitor over another is probably arbitrary in clinical practice. Therein unobserved risk factors for cardiac outcomes between the rofecoxib and celecoxib groups are probably minimum, so selection bias might well not explain the difference in admission seen between the two drugs. In a previous study using the same databases and similar study design, we failed to record any significant differences between rofecoxib and celecoxib with respect to admission for acute myocardial infarction at commonly used doses, suggesting that cardiovascular risks are similar for these drug groups. If the rofecoxib group were truly at higher risk of cardiac disease than the celecoxib group in some immeasurable way, one would have expected the previous study to find an increase in admission for acute myocardial infarction in this group.

Our findings are consistent with those of two large randomised trials of osteoarthritis patients with longstanding hypertension showing significantly greater increases in systolic blood pressure and higher likelihood of onset or worsening of oedema in those receiving rofecoxib than those receiving celecoxib. Possible explanations include the pharmacokinetic properties of the drugs themselves. Rofecoxib has a substantially longer elimination half-life than celecoxib. Further, celecoxib has linear pharmacokinetics with no evidence of accumulation, whereas rofecoxib has non-linear saturable pharmacokinetics. These factors could contribute to a more pronounced hypertensive effect for rofecoxib than for celecoxib. Further, the increased frequency of initiation of treatment for hypertension or congestive heart failure seen in celecoxib users, although still lower than that of rofecoxib or non-selective NSAIDs, suggests that celecoxib might not be entirely devoid of clinically important cardiovascular effects.

Our study had several limitations. First, although we attempted to control for important confounders, we were unable to account for potentially important cardiac risk factors such as weight, dietary salt intake, smoking, alcohol intake, and medications sold over the counter, such as aspirin. However, despite a potentially heavier disease burden in the rofecoxib and celecoxib groups relative to the non-selective NSAID group, lower risks of congestive heart disease were still seen for celecoxib relative to the non-selective NSAID group. Therefore, these unmeasured factors would probably not explain our findings. Nearly half the non-selective NSAID group used diclofenac plus misoprostol. Misoprostol is a prostaglandin E1 analogue and, although some evidence indicates that intravenous prostaglandin treatment might improve the haemodynamic status of patients with congestive heart failure, the implications of low doses of oral misoprostol are unknown. Second, the low absolute number of events in the study groups precluded reliable subgroup analyses, such as comparisons in users of high-dose and low-dose drugs. For example, less than a tenth of rofecoxib users in our study were estimated to be on more than 25 mg per day, leaving very few events for analyses in this group. Third, use of administrative databases to define exposure to study drugs provided no direct measure of adherence or appropriateness of use. Since NSAIDs could be used in different doses over time for symptom previously described an NSAID during the study period, a proportion that was consistent with previous studies examining use of prescription or non-prescription NSAIDs in elderly patients, implying that...
most NSAID use in our population was probably captured by our databases. Despite these limitations, our findings suggest significant differences between non-selective NSAIDs and individual COX-2 inhibitors with respect to risk of admission for congestive heart failure. The clinical relevance of these findings, in view of the widespread use of the drugs, warrants the implementation of large-scale randomised controlled trials to examine this issue further.

Contributors
M Mamdani, D N Juurlink, D S Lee, P A Rochon, G Naglie, and A Laupacis designed the study; M Mamdani, D N Juurlink, D S Lee, P C Austin, and A Kopp undertook the study. T A Stukel, G Naglie, P C Austin, and A Laupacis advised and supervised. Statistical advice was given by T A Stukel and P C Austin. M Mamdani is the guarantor.

Conflict of interest statement
M Mamdani undertook research in an unrelated content area for an academic institution whose funding was supported by Pharmacia in the past 3 years, but none of the funding for this study was provided by any pharmaceutical company.

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