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Uptake and outcomes associated with cyclooxygenase (COX-2) inhibitors in Ontario's elderly

ICES Investigative Report

July 2005

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Ontario's resource for informed health care decision-making

ICES is an independent, non-profit organization that conducts health services evaluations on a broad range of topical issues to enhance the effectiveness of health care for Ontarians. Internationally recognized for its innovative use of population-based health information, ICES knowledge provides evidence to support health policy development and changes to the organization and delivery of health care services.

Unbiased ICES evidence offers fact-based measures of health system performance; a clearer understanding of the shifting health care needs of Ontarians; and a stimulus for discussion of practical solutions to optimize scarce resources.

Key to ICES' work is our ability to link anonymous population-based health information on an individual patient basis, using unique encrypted identifiers that ensure privacy and confidentiality. This allows scientists to obtain a more comprehensive view of specific health care issues than would otherwise be possible. Linked databases reflecting 12 million of 30 million Canadians allow researchers to follow patient populations through diagnosis and treatment, and to evaluate outcomes.

ICES brings together the best and the brightest talent under one roof. Many of our faculty are not only internationally recognized leaders in their fields, but are also practising clinicians who understand the grassroots of health care delivery, making ICES knowledge clinically-focused and useful in changing practice. Other team members have statistical training, epidemiological backgrounds, project management or communications expertise. The variety of skill sets and educational backgrounds ensures a multi-disciplinary approach to issues management and creates a real-world mosaic of perspectives that is vital to shaping Ontario's future health care.

ICES collaborates with experts from a diverse network of institutions, government agencies, professional organizations and patient groups to ensure that its findings are relevant.

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Foreword

The changing landscape of COX-2 inhibitors: a summary of recent events

The announcement on September 30, 2004 to withdraw Merck & Co.'s Vioxx® (rofecoxib) from the international market sent shockwaves throughout the medical community and instigated a public outcry over the current regulatory approach to monitoring drug safety.[1] The events leading up to the largest drug withdrawal in history certainly warrant discussion.

Vioxx belongs to a relatively new type of nonsteroidal anti-inflammatory drugs (NSAIDs) known as cyclooxygenase (COX)-2 inhibitors. NSAIDs are commonly used to manage pain and inflammation associated with acute conditions, such as sports injuries, and chronic conditions, such as arthritis. Approximately one in four elderly people use these drugs. While COX-2 inhibitors offer levels of pain relief similar to traditional NSAIDs, they are marketed as possessing lower rates of adverse gastrointestinal effects.

The publication of a large randomized controlled trial in November 2000, convincingly demonstrated a favourable gastrointestinal adverse event profile associated with Vioxx compared to a commonly used traditional NSAID, Naprosyn® (naproxen). A 50% relative risk reduction in serious gastrointestinal outcomes was observed among Vioxx users relative to Naprosyn.[2] However, in a secondary analysis of general safety, the same clinical trial also suggested a five-fold increased risk of heart attack associated with rofecoxib relative to naproxen. Consequently, this prompted numerous systematic reviews and observational studies, the results of which further supported a possible adverse cardiovascular effect of Vioxx, and were published long before the Vioxx withdrawal from the market.

Despite this mounting evidence, the decision to withdraw Vioxx from the market was not made until the interim results of a large randomized controlled trial demonstrated an increased cardiovascular risk associated with the drug—about four years after the first clinical trial suggested cardiovascular risk. Allegations that the cardiovascular risks associated with Vioxx were suspected by Merck scientists well before the launch of Vioxx—as early as 1996[3]—have cast serious doubts on the ethical conduct of the pharmaceutical industry and its relationship with the United States' (US) Food and Drug Administration (FDA), its federal drug regulatory body.

The Vioxx withdrawal created a common state of confusion about alternative treatments for frustrated patients and prescribing physicians. At that point, evidence supporting the use of alternative treatments to Vioxx varied significantly. Alternatives included: treatment with other drugs marketed as COX-2 inhibitors in Canada, such as Celebrex® (celecoxib), Bextra™ (valdecoxib), and Mobic® (meloxicam); traditional NSAIDs, such as Naprosyn and Advil® (ibuprofen); topical NSAIDs, such as Pennsaid® (topical diclofenac), for limited joint pain; alternative therapies, such as Lakota®; and non-drug therapies, such as weight-bearing exercise, knee taping, and acupuncture. An obvious first choice for many physicians was to switch patients to Celebrex, as the overwhelming majority of evidence from large comparative studies suggested no excess cardiovascular risk with exposure to commonly used doses.

In December 2004, however, three large randomized clinical trials examining Celebrex were halted due to concerns from interim analyses that indicated cardiovascular risks associated not only with Celebrex, but also with traditional NSAIDs. Two large clinical trials compared Celebrex at varying doses to placebo for the prevention of pre-malignant tumours in more than 3,000 patients. The first of these trials was the Adenoma Prevention with Celebrex (APC) trial, funded by the US National Institutes of Health (NIH). Among users of Celebrex at doses of 400 mg daily, the trial found a greater than two-fold risk of cardiovascular events (though not statistically significant). Among those using 800 mg of Celebrex daily, the trial found a statistically significant three-fold higher risk of such events.[4] The second of these clinical trials, the Prevention of Spontaneous Adenomatous Polyps (PreSAP), funded by the pharmaceutical company Pfizer, did not find any excess cardiovascular risk associated with Celebrex at doses of 400 mg daily relative to placebo.

The third trial, the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT), funded by the NIH, compared Naprosyn at doses of 220 mg twice daily to Celebrex at doses of 200 mg twice daily in roughly 2,400 patients. An

approximately 50% greater risk of cardiovascular events among users of Naprosyn, but not Celebrex, was demonstrated. Still more research suggests that all NSAIDs may possess increased risks of cardiovascular events and this risk may not be limited to the COX-2 inhibitors. With all this confusing and conflicting information, in February 2005, the FDA convened an expert group to review available data and provide recommendations. In June 2005, Health Canada convened a similar panel to review the available evidence and provide recommendations for Canada.

This report presents several large Institute for Clinical Evaluative Sciences (ICES) studies that examine utilization and clinical outcomes of NSAIDs among the elderly population of Ontario, with particular focus on COX-2 inhibitors. Recent events have cast considerable suspicion over the cardiovascular safety of not just COX-2 inhibitors as a drug class, but the entire NSAID category. Thus, the future role of COX-2 inhibitors in managing patients with pain and inflammation continues to evolve. The findings in this report will contribute to a better understanding of the utilization and clinical outcomes associated with this class of drugs.

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Executive Summary

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the world. The introduction of a relatively new group of NSAIDs, the selective cyclooxygenase (COX-2) inhibitors, has been met with widespread acceptance among the medical community. The adoption of selective COX-2 inhibitors has been primarily driven by the assertion that these agents cause fewer gastrointestinal events compared to conventional nonselective NSAIDs, supported by several large randomized trials that separately assessed celecoxib and rofecoxib relative to nonselective NSAID control groups.

Many clinical and policy questions related to outcomes and costs have arisen following the recent introduction of these drugs to formularies. A series of ICES studies were recently conducted to examine the uptake of COX-2 inhibitors from clinical and policy perspectives.

From a clinical perspective, some evidence suggests that rofecoxib may be associated with an increased risk of acute myocardial infarction relative to naproxen. Other data suggest differential effects between rofecoxib and celecoxib with respect to blood pressure elevation and edema. While clinical studies examine relevant outcomes at the patient level, they are often conducted in environments with questionable generalizability. For example, many clinical studies possess artificially high drug adherence rates that would not normally be observed in the real world.

The purpose of this report is to:

1. Examine clinically relevant outcomes associated with COX-2 inhibitors relative to nonselective NSAIDs among an elderly population.
2. Examine changes in population costs to the health care system and clinical outcome rates following the introduction of the COX-2 inhibitors on to the Ontario Drug Benefit formulary.
3. Examine basic adherence rates associated with COX-2 inhibitors and nonselective NSAIDs among an elderly population.

Population-level analysis of drug policy implications and clinical outcomes may help address some of the limitations and help mitigate some of the potentially adverse financial and clinical effects. Clinical studies are crucial to understanding what could be done, while policy studies are crucial in understanding what is being done.

Key messages

Clinical trial data suggest a reduced risk of adverse gastrointestinal events associated with selective COX-2 inhibitors relative to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). High quality data from randomized controlled trials (RCTs) on acute myocardial infarction (AMI) and congestive heart failure (CHF) outcomes are lacking. Observational data from Ontario confirm the relatively lower risk of hospitalization for upper gastrointestinal hemorrhage (UGIH) among continuous users of celecoxib and rofecoxib, (not meloxicam as it was not on the Ontario Drug Benefit [ODB] formulary at the time of the analyses), relative to nonselective NSAIDs.

Among the COX-2 inhibitors, celecoxib is associated with the lowest risk of hospitalization with UGIH. No association between COX-2 inhibitors, naproxen, and nonselective NSAIDs, as they are currently used, and AMI were observed. Rofecoxib and nonselective NSAIDs were observed to significantly increase the risk of hospitalization for CHF, but not celecoxib. However, rofecoxib, celecoxib, and nonselective NSAIDs were observed to significantly increase the risk of being initiated on medications for hypertension or CHF among those previously not on such medications.

The population effects of the introduction of the COX-2 inhibitors on the ODB formulary suggest a somewhat paradoxical outcome. Overall, the number of any NSAID (i.e. nonselective or COX-2 inhibitors) prescription more

than doubled following COX-2 inhibitor introduction, increasing annual drug expenditures from approximately $28 million to more than $75 million. Meloxicam is the most widely dispensed COX-2 inhibitor in Ontario. Nearly 20% of elderly individuals is dispensed an NSAID every six months, up from 14% before the introduction of the COX-2 inhibitors. This translates to at least 90,000 additional users of NSAIDs. New use of COX-2 inhibitors, rather than a switch from nonselective NSAIDs, fuels this observation.

Approximately half of COX-2 inhibitor users only fill one prescription for any NSAID in a year's time and more than three-quarters of these users receive less than 3 months supply of drugs in a year, implying significant short-term use. Further, individuals initiated on COX-2 inhibitors appear, over time, resemble those initiated on nonselective NSAIDs with respect to risk factor profiles. Along with the increase in the number of people exposed to NSAIDs after the introduction of COX-2 inhibitors, a 10% increase in the rate of hospitalizations for UGIH among the Ontario's entire elderly population was observed, translating to more than 650 additional hospitalizations each year. The benefits associated with pain relief, however, could not be assessed.

While the findings of this report support the notion that selective COX-2 inhibitors possess gastrointestinal safety advantages over nonselective NSAIDs at the individual level, the population effects warrant some concern. Given the sporadic nature of use and the changing demographic profile among the COX-2 inhibitor users, there may be concerns about suboptimal utilization of these drugs. A policy review for management of COX-2 inhibitors in Ontario is needed.

Study overview

Clinical outcomes: cohort analyses

Three large cohort studies examining ODB data were conducted using a random sample of approximately 100,000 non-NSAID users from the community as a reference. The first study examined hospitalization rates for UGIH among patients newly initiated on rofecoxib, celecoxib, diclofenac plus misoprostol (Arthrotec®) and nonselective NSAIDs, relative to non-NSAID using control subjects. The second study examined the risk of hospitalization for AMI associated with rofecoxib, celecoxib, naproxen, and non-naproxen nonselective NSAIDs relative to non-NSAID use. The third study examined the risk of hospitalization for CHF among users of celecoxib, rofecoxib, and nonselective NSAIDs relative to non-NSAID users. An additional analysis examined initiation of medication used for management of hypertension and CHF among patients not previously receiving these medications to assess more subtle outcomes that may be associated with these drugs. The crude event rates and adjusted relative risk estimates are outlined in Exhibit 1.

Exhibit 1. Summary of ICES studies examining gastrointestinal and cardiovascular outcomes associated with nonsteroidal anti-inflammatory drug (NSAID) therapies in Ontario

	Community Control	Nonselective NSAIDs	Diclofenac+ Misoprostol	Naproxen	Rofecoxib	Celecoxib
	N = 100,000	N > 5,000	N > 5,000	N > 5,000	N > 14,000	N > 18,000
Crude event rates per 1,000 population						
UGIH	2.2	12.6	9.6	N/A	7.3	3.6
AMI	8.2	12.1	N/A	9.6	12.1	10.7
CHF	9.1	15.7	N/A	N/A	24.5	13.2
Initiation of antihypertensives /CHF medications*	112	286	N/A	N/A	284	218
Adjusted relative risk estimates						
UGIH	1.0	4.0 (2.3–6.9)	3.0 (1.7–5.5)	N/A	1.91.3–2.8)	1.0 (0.7–1.6)
AMI	1.0	1.2 (0.9–1.4)	N/A	1.0 (0.6–1.7)	1.0 (0.8–1.4)	0.9 (0.7–1.2)
CHF	1.0	1.4 (1.0–1.9)	N/A	N/A	1.8 (1.5–2.2)	1.0 (0.8–1.3)
Initiation of antihypertensives /CHF medications	1.0	1.9 (1.7–2.2)	N/A	N/A	1.9 (1.7–2.1)	1.5 (1.4–1.7)

*Sample size estimates for initiation of antihypertensives/CHF medications were smaller (this was a sub-study of the larger study)

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

These findings suggest differences among COX-2 inhibitors in terms of associated risk of hospitalizations for UGIH and CHF, with celecoxib demonstrating lower risk relative to rofecoxib for both outcomes. However, celecoxib and rofecoxib are both associated with an increased risk of initiation of medications to treat hypertension or CHF, implying that exposure to either may result in clinically significant elevations in blood pressure.

The study examining UGIH was repeated to examine patients on meloxicam relative to nonselective NSAIDs and non-NSAID using community controls. Celecoxib and rofecoxib users could not be included in this analysis given small numbers of newly initiated individuals and low event rates following the introduction of meloxicam. The findings are summarized in Exhibit 2.

Exhibit 2. Gastrointestinal outcomes associated with meloxicam compared to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs): cohort study in Ontario, 2001–2002

	Nonselective NSAIDs	Meloxicam
	(N = 4,161)	(N = 10,491)
Number of admissions	14	35
Days of follow-up (mean ± SD)	91.0 (68.0)	119.3 (83.0)
Total follow-up (person-years)	1,037	3,426
UGIH per 1,000 person-years	1.3	1.0
Model-based risk ratios unadjusted rate ratio (95% CI)	1.0 (reference)	0.8 (0.4–1.4)
Adjusted rate ratio (95% CI)	1.0 (reference)	0.9 (0.5–1.8)

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

The risk of hospitalization for UGIH was similar between meloxicam and nonselective NSAID users, raising questions about appropriateness of the policy to approve meloxicam as a General Benefit product relative to celecoxib and rofecoxib, which are Limited Use products.

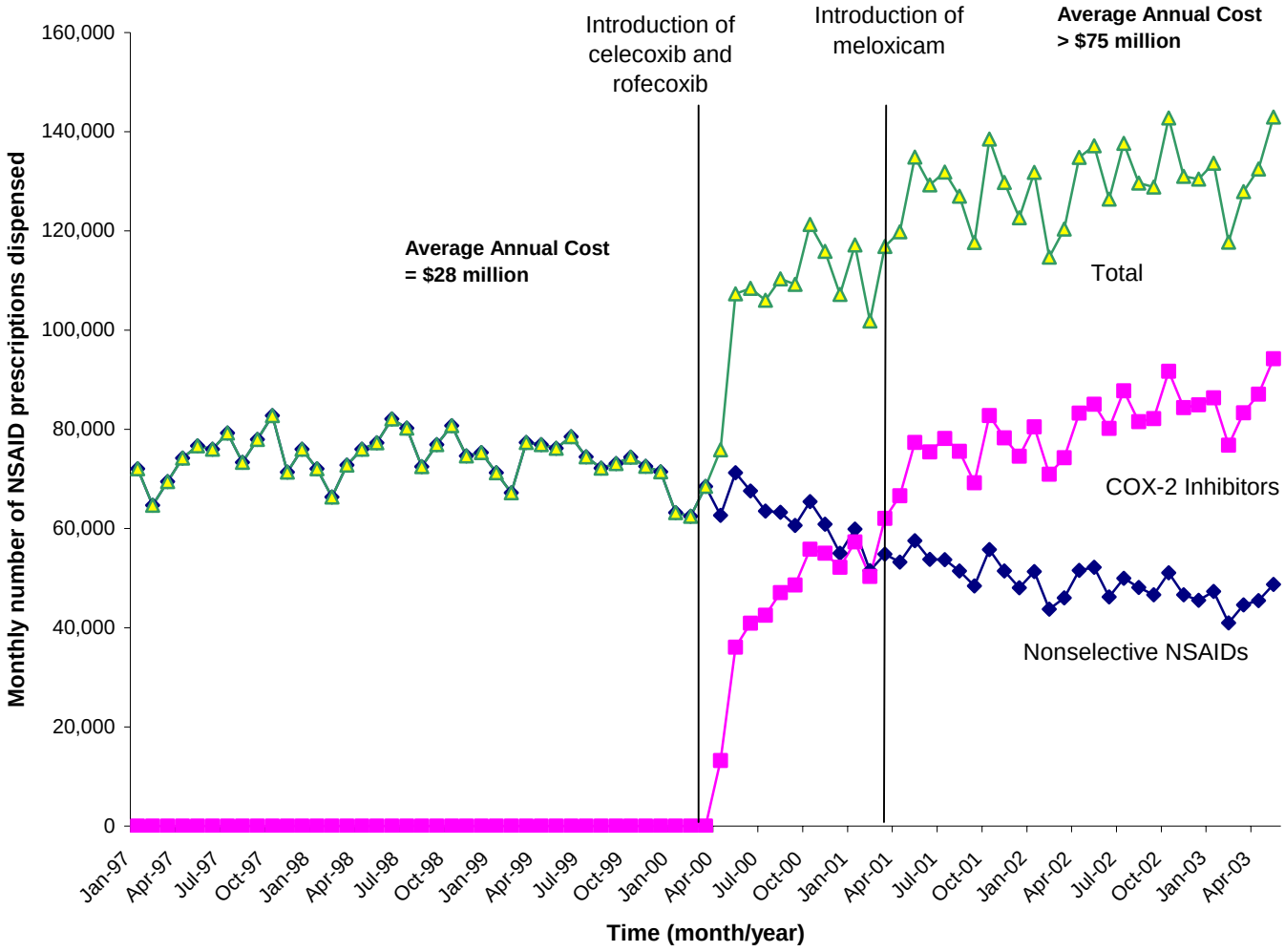
Policy-level utilization analyses

The ODB experienced a dramatic increase in the number of NSAID prescriptions dispensed following the introduction of COX-2 inhibitors. Overall, the number of NSAID prescriptions more than doubled following COX-2 inhibitor introduction, increasing annual drug expenditures from approximately $28 million to more than $75 million (see Exhibit 3). This observation has significant financial and population-based outcomes implications since this increase is largely driven by new use of COX-2 inhibitors rather than switching from nonselective NSAIDs to COX-2 inhibitors. Following the introduction of COX-2 inhibitors, it is estimated that at least 90,000 additional individuals were exposed to NSAIDs each year, raising the population prevalence from 14% to nearly 20%.

Approval of COX-2 inhibitors was intended for arthritic patients at high risk of adverse gastrointestinal outcomes. It would, therefore, be expected that these patients would need chronic NSAID therapy. A cohort study examining 1-year refill rates among NSAID-naïve individuals initiated on COX-2 inhibitor therapy observed that approximately half did not fill another prescription for any NSAID in the following one year, and more than 75% received less than 3 months drug supply in the year of follow-up. These findings suggest acute and sporadic use and that a more comprehensive approach to ensuring optimal use of these drugs may be needed. Further, the risk profiles of individuals initiated on COX-2 inhibitors appeared to be improving over time, implying that patients of lower risk are being initiated in COX-2 inhibitors as physicians become more comfortable prescribing these drugs. For example, prevalence of previous UGIH endoscopy or UGIH radiologic series among those initiated on COX-2 inhibitors decreased from 54% in 2000 to 42% in 2002. This observation further supports a need to better examine which types of patients are receiving COX-2 inhibitors.

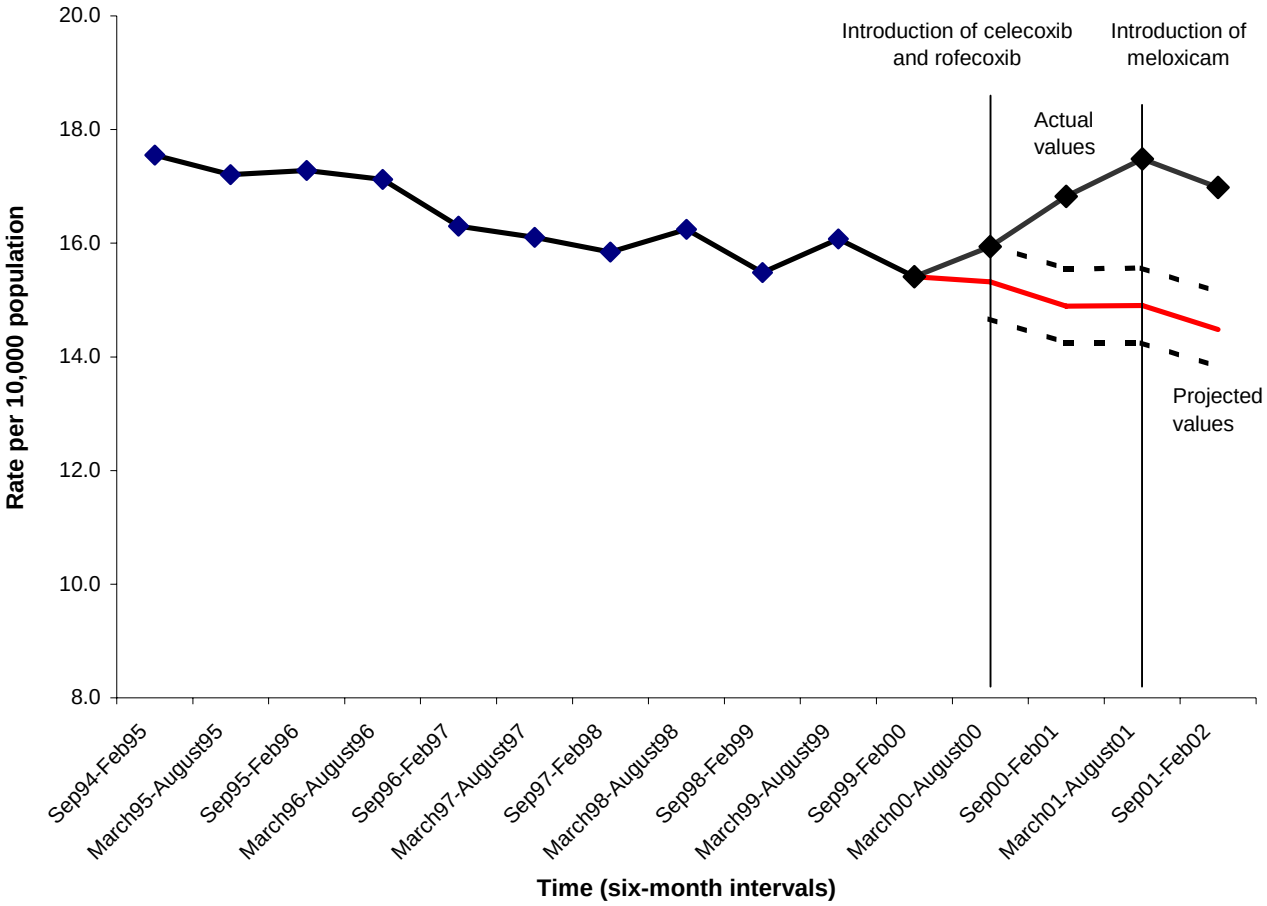
Rates of hospitalization for UGIH among the entire elderly population, irrespective of NSAID, was observed to increase by 10%, translating to at least 650 additional admissions for UGIH since the approval of COX-2 inhibitors in Ontario (see Exhibit 4). This observation was independent of other potentially confounding factors such as the use of gastroprotective medications. A major limitation of this study was the inability to capture the benefits of reduced pain and inflammation.

Exhibit 3. Monthly number of nonsteroidal anti-inflammatory drug (NSAID) prescriptions, in Ontario, January 1997–May 2003



Data source: Ontario Drug Benefit Program

Exhibit 4. Rate of hospital admission for upper gastrointestinal hemorrhage (UGIH) among the elderly population in Ontario, September 1994–February 2002



Data source: Canadian Institute for Health Information

Discussion

The findings of this evaluation suggest potentially reduced risks of hospitalization for UGIH among users of celecoxib and rofecoxib relative to nonselective NSAID users and an increased risk of hospitalization for CHF among users of rofecoxib and nonselective NSAIDs, but not celecoxib. All NSAIDs, however, appear to be associated with clinically meaningful elevations in blood pressure requiring medical management. Given the significant increase in the number of patients dispensed NSAIDs following the introduction of the COX-2 inhibitors, a population-based increase in the rate of hospitalization for UGIH followed, translating to over 650 additional admissions for UGIH that otherwise may not have occurred.

This observation, along with other data presented in this report, raises concerns about the rapid adoption of COX-2 inhibitors, appropriateness of utilization, extent of compliance with the approved conditions for use, and the nature of the policy. For example, meloxicam is approved as a General Benefit product despite the lack of high-quality evidence examining clinically meaningful gastrointestinal outcomes, whereas celecoxib and rofecoxib are approved as Limited Use products with imposed conditions for use. Unpublished observational data from ICES suggest that the risk for hospitalization for UGIHH among meloxicam users is no different from nonselective NSAIDs and meloxicam has become the most widely dispensed COX-2 inhibitor on the ODB. Beyond this issue, and perhaps more important, is the general nature of utilization of these drugs, for which information is lacking. While costs must be balanced with clinical outcomes, this report suggests a re-evaluation of the utilization and outcomes associated with this group of drugs.

Chapter 1. Selective COX-2 Inhibitors and Nonselective NSAIDs: Upper Gastrointestinal Hemorrhage in an Elderly Cohort

Authors

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Abstract

Objective

To compare rates of upper gastrointestinal hemorrhage (UGIH) among elderly patients dispensed selective cyclooxygenase (COX-2) inhibitors and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs).

Design

Observational cohort study.

Setting and patients

Administrative data from April 17, 2000 to March 31, 2001 was used to identify population-based NSAID-naïve cohorts of Ontario subjects aged 66 years and older initiated on nonselective NSAIDs (n=5,391), diclofenac plus misoprostol (n=5,087), rofecoxib (n=14,583), or celecoxib (n=18,908), as well as a randomly selected control cohort not exposed to NSAIDs (n=100,000). Multivariate Cox proportional hazard models were used for analysis.

Main outcome measures

Rate ratios of hospital admission for UGIH in each drug cohort with adjustment for potential confounders.

Results

Relative to control subjects, the multivariate model revealed an increased short-term risk of UGIH for users of nonselective NSAIDs (adjusted rate ratio [aRR]=4.0; 95% CI=2.3 to 6.9), diclofenac plus misoprostol (aRR=3.0; 95% CI=1.7 to 5.6), and rofecoxib (aRR=1.9; 95% CI=1.3 to 2.8) but not celecoxib (aRR=1.0; 95% CI=0.7 to 1.6). Relative to celecoxib, significantly higher risks for UGIHH were observed for nonselective NSAIDs (aRR=4.4; 95% CI= 2.3-8.5), diclofenac plus misoprostol (aRR=3.2; 95% CI=1.6-6.5), and rofecoxib (aRR=1.9; 95% CI=1.2-2.8). Relative to rofecoxib, nonselective NSAID users were at significantly higher risk for UGIH (aRR=1.9; 95% CI=1.0-3.5).

Conclusions

This population-based observational study found a lower short-term risk of UGIH for selective COX-2 inhibitors relative to nonselective NSAIDs. The differences observed between rofecoxib and celecoxib warrant further investigation.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the world[1] and are consumed by approximately 20-30% of elderly people.[2,3] Selective cyclooxygenase (COX-2) inhibitors are a new group of NSAIDs that have rapidly gained acceptance in clinical practice.[4] Within the first three months of its availability, celecoxib became the fastest selling drug in Canadian history.[5]

The adoption of selective COX-2 inhibitors has primarily been driven by the assertion that these agents cause fewer gastrointestinal events in comparison to conventional nonselective NSAIDs.[6] Relative to non-NSAID users, nonselective NSAIDs are estimated to increase the risk of gastrointestinal complications by approximately four-fold among elderly persons,[7-10] although some nonselective NSAIDs may have less gastrotoxic potential than others.[11] Two large randomized controlled trials that separately evaluated rofecoxib[12] and celecoxib[13] in comparison to nonselective NSAIDs demonstrated a significant reduction in clinical upper gastrointestinal events. Given major differences in study design between these two trials, valid comparisons of the gastrointestinal safety of celecoxib, rofecoxib, and nonselective NSAIDs cannot be made from these data alone.

Several important clinical questions remain regarding the gastrointestinal effects of these agents. It is unclear to what degree COX-2 inhibitors increase gastrointestinal risk relative to no use of NSAIDs. The relative gastrointestinal safety of the selective COX-2 inhibitors is also uncertain, as they have not been directly compared in a single large study. Accordingly, a population-based cohort study was conducted to compare the incidence of UGIH in over 40,000 elderly NSAID-naïve users of rofecoxib, celecoxib, nonselective NSAIDs, and diclofenac plus misoprostol to incidence of UGIH in 100,000 non-NSAID users.

Findings

Cohort description

Of approximately 1.3 million potential subjects aged 65 years and older, 364,686 (28%) were dispensed a prescription NSAID during the study period. From these individuals, 5,391 users of nonselective NSAIDs, 5,087 users of diclofenac plus misoprostol, 14,583 users of rofecoxib, 18,908 users of celecoxib, and 100,000 control subjects (Exhibit 1.1) that met the inclusion criteria were identified. Among nonselective NSAID users, the majority of subjects were initiated on naproxen (32%), ibuprofen (23%), or diclofenac (20%). In the rofecoxib and celecoxib cohorts, a greater proportion of users were women. The control group generally used less health care resources than the other study groups. More rofecoxib and celecoxib users had previously undergone upper gastrointestinal diagnostic procedures or received gastroprotective agents compared with the other groups (Exhibit 1.1). They were also more likely to receive anticoagulants, antirheumatics, and glucocorticoids. The characteristics of the rofecoxib and celecoxib groups, however, were virtually identical.

In more than 55,000 person-years of follow-up, 187 hospitalizations for UGIH (Exhibit 1.2) were observed. Relative to the control group, model-based estimates adjusted for the covariates in Table 1.1 revealed significantly higher risk ratios for users of nonselective NSAIDs (adjusted rate ratio [aRR]=4.0; 95% CI=2.3-6.9), diclofenac plus misoprostol (aRR=3.0; 95% CI=1.7-5.6), and rofecoxib (aRR=1.9; 95% CI=1.3-2.8), but not celecoxib (aRR=1.0; 95% CI=0.7-1.6; Exhibit 1.3). Analyses using age- and gender- matched control subjects, separate analyses for men and women, and analyses excluding subjects with a history of UGIH all yielded similar findings.

Pairwise comparisons revealed significant differences in risk of UGIH among the drug groups. Relative to celecoxib users, a higher risk of hospitalization for UGIH was seen among users of nonselective NSAIDs (aRR=4.4; 95% CI= 2.3-8.5), diclofenac plus misoprostol (aRR=3.2; 95% CI=1.6-6.5), and rofecoxib (aRR=1.9; 95% CI=1.2-2.8). Relative to rofecoxib, a significantly higher risk of UGIH was observed for nonselective NSAID (aRR=1.9; 95% CI=1.0-3.5) but not diclofenac plus misoprostol (aRR=1.4; 95% CI=0.7-2.7) users.

Several sensitivity analyses were conducted.

1. The analysis was repeated to examine all individuals who were dispensed a NSAID irrespective of the number of prescriptions dispensed or the quantity of drug supplied. The findings were similar to those of the primary analysis.
2. The analysis was limited to those not residing in a long-term care institution and found results similar to the primary analysis.
3. The analysis was repeated among users of gastroprotective agents and non-users given the substantial discrepancy in use of gastroprotective agents observed in the various cohorts. Subjects dispensed gastroprotective agents had a higher incidence of UGIH relative to subjects in their respective groups not dispensed gastroprotective agents during the follow-up period, implying that these agents are selectively prescribed to those at higher risk for UGIH. Differences in the risk of UGIH between nonselective NSAIDs and the COX-2 inhibitors were present regardless of whether or not patients received gastroprotective agents.
4. The doses used in the celecoxib and rofecoxib groups at the time of the last observed prescription were examined, as some evidence indicates that other COX-2 selective agents may lose their selectivity at higher doses.[19]

Both rofecoxib and celecoxib are approved for osteoarthritis, presumably the most prevalent indication in this cohort, for which 25 mg of rofecoxib and 200 mg of celecoxib are considered to be at the upper end of the

respective dose ranges.[20] A significantly greater proportion of patients dispensed celecoxib (19%) were given high doses (i.e. > 200 mg daily) compared to patients dispensed rofecoxib (8%) (i.e. > 25 mg daily).

Discussion

The findings of this study suggest a lower risk of UGIH for selective COX-2 inhibitors relative to conventional nonselective NSAIDs. The UGIH rate for celecoxib was similar to that of the non-NSAID control group. While the risk of UGIH for rofecoxib was significantly lower than nonselective NSAIDs, it was significantly higher than that of celecoxib.

Limitations

Several limitations of this study deserve mention. First, though attempts were made to control for many important confounders, some potentially important factors, such as smoking and alcohol consumption, were not accounted for. The distribution of such factors among the different groups studied and the consequent influences on the findings is unknown. However, despite a potentially heavier disease burden among the rofecoxib and celecoxib groups relative to the other study groups, likely resulting from the limited use policy for the use of selective COX-2 inhibitors in Ontario, lower risk ratios were still observed for these drug groups relative to the nonselective NSAID group. The population-based incidence estimates for UGIH (Exhibit 1.3) among the control[21] and nonselective NSAID[8] groups are also consistent with previous studies, as are the relative risks.[7-10] Users of gastroprotective agents had a higher incidence of UGIH relative to subjects in their respective groups not dispensed gastroprotective agents during the follow-up period. This implies that these agents are selectively prescribed to those at higher risk for UGIH and act as a marker of underlying gastrointestinal disease that is associated with a higher rather than lower risk of UGIH. Lower adjusted relative risks for UGIH were observed for selective COX-2 inhibitor users relative to nonselective NSAID users among both users and non-users of gastroprotective agents.

Second, administrative databases were used to identify and define exposure to study drugs and clinical outcomes, and there was no direct measure of adherence or appropriateness of use. Since NSAIDs may be used in varying doses over time for symptom control, dose equivalence of the various drugs could not be adequately examined with these data. Instead, the NSAIDs were examined as they are commonly used in this population. Use of nonprescription NSAIDs could not be identified. However, ibuprofen is the only nonprescription non-aspirin nonselective NSAID available in Canada and subjects in this study have a strong financial incentive to obtain these drugs by prescription, especially with regular use. Over one-quarter of elderly subjects were dispensed a NSAID during the observation period, consistent with previous studies examining use of prescription or nonprescription NSAIDs among the elderly.[2,3] This implies that the vast majority of NSAID use in this study's population is likely captured by the databases.

Perhaps more problematic is the use of nonprescription aspirin. Given the similar distribution of prescription aspirin use between the study drug groups, however, the utilization of nonprescription aspirin is also likely to be equally distributed. Outcomes were identified using previously validated diagnostic codes but other important information, such as the severity of the gastrointestinal hemorrhage, and more subtle outcomes, such as non-bleeding ulcers, could not be captured. Also, it is possible that upper gastrointestinal hemorrhage is more readily diagnosed or reported among users of traditional NSAIDs as compared to specific COX-2 inhibitors. However, the diagnosis is not generally a difficult one to make, its coding has been validated, and the impact of this potential bias is likely minimal.

Third, the low absolute number of events in the study groups precluded reliable subgroup analyses such as comparisons among users of anticoagulants or individual NSAIDs.

Fourth, the generalizability of these findings to younger patients or settings with different drug policies over longer durations of follow-up is uncertain.

Relative gastrointestinal safety of rofecoxib and celecoxib

Currently, comparisons between rofecoxib and celecoxib are based largely on data from clinical trials and whole blood assay studies. Two large randomized trials separately comparing rofecoxib[12] and celecoxib[13] with nonselective NSAIDs provided similar relative risk reductions of 40–60% in the incidence of clinical UGIH events (i.e. UGIH ulcer complications plus symptomatic ulcers). However, valid comparisons of UGIH event rates between rofecoxib and celecoxib cannot be made from such data for several reasons.

1. In the absence of a direct head-to-head evaluation, conclusions about the relative gastrointestinal safety of these agents are largely speculative.
2. Primary endpoints of the two trials were somewhat different.
3. The nonselective NSAID comparator groups in the two trials were different. The nonselective NSAID comparison group was either ibuprofen or diclofenac in the celecoxib trial and naproxen in the rofecoxib study. Since naproxen is likely more gastrotoxic than either ibuprofen or diclofenac,[11] it is difficult to assess the relative gastrointestinal safety of rofecoxib and celecoxib from these two trials.
4. The interpretation of the celecoxib trial is complicated by the nature of its reporting.[22] The findings were based on a combined analysis of the first six months of two separate and longer trials whose protocols differed significantly from the published paper in design, outcomes, duration of follow-up, and analysis. While 12-month data revealed no significant differences between celecoxib and its nonselective NSAID comparators with respect to complicated ulcer outcomes (the primary endpoint of the trials), the incidence of clinical UGIH events remained significantly different.[23]

Understanding of the cellular effects of the COX-2 inhibitors is also evolving, and conclusions about the relative safety of these agents based on in vitro data may be premature. For example, although whole blood assay studies[24] suggest that rofecoxib is more COX-2 selective than celecoxib, such assays have been criticized for having limited clinical relevance.[25] Furthermore, recent studies of cancer cell lines have demonstrated potentially COX-independent differences in antiproliferative activity between celecoxib and rofecoxib.[26-28] The clinical implications of such differences on the gastrointestinal safety of these two agents are not known.

This evaluation represents the first direct comparison of rofecoxib and celecoxib for a clinically meaningful gastrointestinal outcome using common comparator groups over the same period, with data reflecting actual clinical practice. The demographic characteristics of rofecoxib and celecoxib users were strikingly similar in this study, implying that selection of one COX-2 inhibitor over another is likely arbitrary in clinical practice. Therefore, the differences in unobserved covariates between the rofecoxib and celecoxib groups are probably minimal and would not explain the difference in UGIH observed between the two drugs.

In summary, this study found lower rates of UGIH with selective COX-2 inhibitors relative to nonselective NSAIDs. The significantly higher rate of UGIH among users of rofecoxib compared to celecoxib was unexpected. Although the absolute difference in rates of UGIH were small, these differences, if true, are clinically important given the large numbers of patients prescribed selective COX-2 inhibitors. Large randomized head-to-head controlled trials are urgently needed to better examine these differences.

Exhibits

Exhibit 1.1 Covariates assessed in analysis of gastrointestinal outcomes associated with nonsteroidal anti-inflammatory drugs (NSAIDs), in Ontario

Hospitalizations	Procedures	Drug Utilization	Other
• Any hospitalization in preceding year • Malignancy in preceding 5 years • Upper gastrointestinal hemorrhage in preceding 5 years	• Gastrointestinal endoscopy or radiologic series in preceding 5 years	• Number of different drugs in preceding year • Narcotic analgesics or gastroprotective agents in preceding 180 days • 120 days before index date until end of follow-up: ➢ Aspirin ➢ Anticoagulants ➢ Antiplatelets ➢ Antidiabetic agents ➢ Antirheumatics ➢ Glucocorticoids ➢ Gastroprotective agents	• Age • Gender • Long-term care • Low income status*

*Defined as annual income of less than $16,018 (single) and less than $24,175 (couple), confirmed through personal tax statements upon voluntary application for reductions in co-payments and deductibles

Exhibit 1.2 Characteristics of cohort groups examining gastrointestinal outcomes associated with nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, 2000–2001

	Study Cohort				
	Community Controls	**Nonselective NSAIDs**	**Diclofenac + Misoprostol**	**Rofecoxib**	**Celecoxib**
Number of patients (% women)	100,000 (55%)	5,391 (59%)	5,087 (62%)	14,583 (72%)	18,908 (70%)
Age (mean ± SD)	75.4 ± 7.3	75.5 ± 7.0	76.6 ± 7.1	76.5 ± 6.9	76.5 ± 6.8
Residence in long-term care facility (number, %)	4,074 (4%)	398 (7%)	503 (10%)	652 (4%)	810 (4%)
Low income status (number, %)	21,073 (21%)	1,831 (34%)	1,725 (34%)	4,445 (30%)	5,673 (30%)
Hospitalization in past year (number, %)	11,513 (12%)	1,023 (19%)	925 (18%)	2,900 (20%)	3,651 (19%)
Number of prescription drugs in past year (mean ± SD)	5.4 (5.4)	8.3 (6.4)	8.3 (6.4)	9.9 (6.5)	9.5 (6.4)
Use of gastroprotective agents within 180 days before cohort entry number, %)	17,279 (17%)	1,329 (25%)	1,265 (25%)	6,140 (42%)	7,738 (41%)
Use of narcotic analgesics within 180 days before cohort entry (number, %)	10,623 (11%)	1,419 (26%)	1,321 (26%)	4,511 (31%)	5,587 (30%)
Hospitalizations/procedures in past 5 years:					
Malignancy	4,785 (5%)	371 (7%)	294 (6%)	760 (5%)	1,004 (5%)
Prior UGIH	1,440 (1%)	64 (1%)	66 (1%)	369 (3%)	476 (3%)
Prior GI radiologic procedure	17,839 (18%)	1,090 (20%)	1,043 (21%)	4,731 (32%)	5,855 (31%)
Drug utilization in 120 days before index date to end of follow-up:					
ASA	11,564 (12%)	1,014 (19%)	945 (19%)	2,629 (18%)	3,311 (18%)
Anticoagulants	6,716 (7%)	244 (5%)	266 (5%)	1,515 (10%)	1,929 (10%)
Antihyperglycemics	9,256 (9%)	756 (14%)	706 (14%)	1,819 (12%)	2,344 (12%)
Antirheumatics	0 (0%)	66 (1%)	71 (1%)	401 (3%)	865 (5%)
Glucocorticoids	3,789 (4%)	458 (9%)	384 (8%)	1,928 (13%)	2,471 (13%)
Gastroprotective agents	16,394 (16%)	1,699 (32%)	1,277 (25%)	6,213 (43%)	7,793 (41%)
Proton pump inhibitors	6,139 (6%)	432 (8%)	405 (8%)	3,156 (22%)	3,868 (20%)
Other*	11,615 (12%)	1,407 (26%)	983 (19%)	3,754 (26%)	4,778 (25%)

* Includes histamine-H2 receptor antagonists, misoprostol, and sucralfate

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

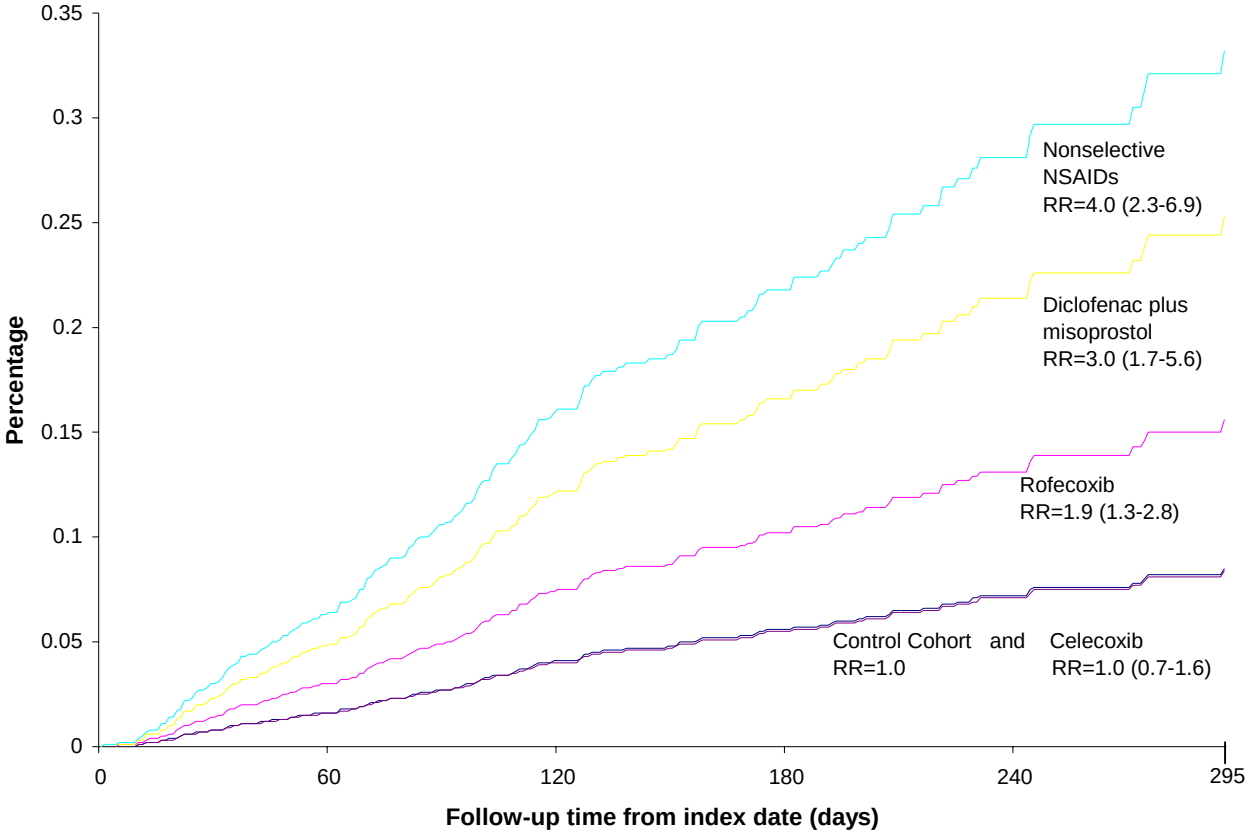
Exhibit 1.3 Upper gastrointestinal hemorrhage outcomes associated with nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, 2000–2001

Study Cohort					
	Community Controls	**Nonselective NSAIDs**	**Diclofenac + Misoprostol**	**Rofecoxib**	**Celecoxib**
	(N = 100,000)	(N = 5,391)	(N = 5,087)	(N = 14,583)	(N = 18,908)
Number of admissions for UGIH	82	17	13	43	32
Days of follow-up (mean ± SD)	138.7 (77.4)	91.7 (68.3)	97.8 (71.2)	146.9 (89.6)	170.3 (97.0)
Total follow-up (person-years)	37,981	1,353	1,361	5,865	8,818
UGIHs per 1,000 person-years	2.2	12.6	9.6	7.3	3.6
Model-based risk ratios **Unadjusted rate ratio (95% CI)**	1.0 (reference)	6.1 (3.6–0.2)	4.6 (2.5–8.2)	3.5 (2.4–5.0)	1.7 (1.1–2.6)
Adjusted rate ratio (95% CI)	1.0 (reference)	4.0 (2.3–6.9)	3.0 (1.7–5.5)	1.9 (1.3–2.8)	1.0 (0.7–1.6)
Numbers needed to treat to harm (NNT [H])*	N/A	403	592	1,389	N/A

*NNT (H) calculations are based on a 295-day follow-up period from the Cox proportional hazard model estimates.

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Exhibit 1.4 Adjusted Cox proportional hazard estimates for hospitalization for upper gastrointestinal hemorrhage (UGIH) in Ontario, 2000–2001



Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Appendix 1.A How the Research was Done

Study design

A population-based retrospective cohort study was conducted by linking administrative health care databases covering over 1.3 million Ontarians aged 66 years and older from April 17, 2000 to March 31, 2001. Ontario's elderly population has 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.

Data sources

The administrative health care databases allowed for cohort identification, comorbidity assessment, and endpoint ascertainment. The linked databases included computerized pharmacy records of the Ontario Drug Benefit program (ODB), which records prescription drugs dispensed to all Ontario residents 65 years of age and older. Both rofecoxib and celecoxib were first listed on the ODB formulary on April 17, 2000 on a limited use basis for patients who failed to respond to, or were intolerant of, traditional NSAIDs, or for patients with a history of UGIH or ulcer. The approved indications for celecoxib included osteoarthritis (OA) and rheumatoid arthritis (RA), whereas rofecoxib was approved only for use in OA. No such restrictions governed the prescribing of nonselective NSAIDs or diclofenac plus misoprostol. Meloxicam use could not be examined, as it was not available on the ODB formulary during the study period.

Hospitalization records were obtained from the Canadian Institute for Heath Information (CIHI) 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 each deceased Ontario resident. These databases were linked anonymously using encrypted individual health card numbers.

Cohort definition

Users of rofecoxib, celecoxib, nonselective NSAIDs, or the combination of diclofenac plus misoprostol were compared to a random sample of 100,000 control subjects dispensed none of these medications. A non-NSAID using control group was chosen as a base reference for two reasons. First, a basic assessment of risks in the overall population provides useful baseline risk estimates of non-NSAID related UGIH. Second, it allowed for comparison of this study's incidence and relative risk estimates with previously published studies that examined the association between NSAID use and UGIH using non-NSAID using control subjects. 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 four drug cohorts, the first prescription during the study period following a patient's 66th birthday served as the index date. To create a cohort of NSAID-naïve subjects within these four drug groups, individuals who were dispensed any of the 4 study drugs in the year preceding the index date were excluded. Subjects that were dispensed prescriptions for drugs from more than one study drug group on the same day were excluded. To exclude sporadic users of NSAID therapy, only individuals who were dispensed at least two successive prescriptions and who received enough drugs for at least 30 days of observation were included. 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 from April 17, 2000 to March 15, 2001 as in the study drug groups. Individuals 66 years of age and older who were alive on the assigned index date were screened for NSAID use one 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, 100,000 individuals were randomly selected to form the control cohort. This group was not age- or gender-matched to any one particular group, but rather represented the general non-NSAID-dispensed elderly population of Ontario.

The analyses were repeated using control subjects matched by age (within one year of the birth date) and gender to all patients in the four study drug groups as a sensitivity analysis. Because women are more likely than men to receive NSAIDs[14] and may have a relatively lower risk for UGIH,[7] analyses were repeated separately for men and women. Finally, the UGIH analysis was repeated excluding subjects with a history of UGIH.

Duration of exposure

For each of the four study drug groups, the duration of exposure was defined as the period of continuous, exclusive enrolment in any of the study medication groups starting from the index date. 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 researchers 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 day supply estimation. Subjects were allowed a 20% grace period on the previous day supply to refill the next prescription. If subjects did not refill their prescription for the study drug within these successive time windows, they were deemed to have discontinued the study drug.

Subject follow-up ended upon admission to hospital for UGIH, exposure to a medication from another study group, discontinuation of the study medication, death, or the end of the observation period (March 31, 2001). Hospital admission with a most responsible diagnosis of UGIH was identified using strict diagnosis codes (International Classification of Diseases, revision 9 – ICD9) 531, 532, 534, 578.0, 578.1, and 578.9. Such codes have been demonstrated to yield a positive predictive value of 86% for UGIH.[15]

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 unless the control subject experienced the outcome of interest or died beforehand.

Statistical analysis

Time-to-event analyses were conducted for UGIH using Cox proportional hazard models with the control group as the reference. Covariates in the model are outlined in Exhibit 1.1. As an overall measure of comorbidity, the number of distinct drugs dispensed in the one year before the index date was examined,[16] a measure comparable to the Charlson comorbidity index.[17] 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. All analyses were performed using SAS for UNIX, Version 8.2 (SAS Institute, Cary, NC).

Appendix 1.B Detailed Analytic Methods

Supplementary analyses of the COX-2 inhibitor and UGIH outcomes study

These findings should be interpreted with caution given the potentially suboptimal study design for assessment and relatively small sample sizes upon which inferences are based.

Figure 1.1 Subanalysis 1—Upper gastrointestinal outcomes stratified by gastroprotective agent use in Ontario, 2000–2001

Study Cohort					
Users of Gastroprotective Agents					
	Community Controls	**Nonselective NSAIDs**	**Diclofenac + Misoprostol**	**Rofecoxib**	**Celecoxib**
Sample size	16,394	1,699	1,277	6,213	7,793
Number of admissions for UGIH	61	13	5	31	26
Days of follow-up (mean ± SD)	143.9 79.0)	98.4 (70.9)	107.3 (77.9)	155.2 (91.4)	178.0 (97.9)
Total follow-up (person-years)	6,457	458	375	2,640	3,798
UGIHs per 1,000 person-years	9.4	28.4	13.3	11.7	6.8
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	3.1 (1.7–5.6)	1.5 (0.6–3.6)	1.3 (0.8–2.0)	0.8 (0.5–1.2)
Adjusted rate ratio (95% CI)	1.0 (reference)	2.0 (1.1–3.8)	1.2 (0.5–3.0)	1.4 (0.9–2.2)	0.9 (0.5–1.4)
Non-users of gastroprotective agents					
Sample size	83,606	3,692	3,810	8,370	11,115
Number of admissions for UGIH	21	4	8	12	6
Days of follow-up (mean ± SD)	138.3 (77.1)	88.7 (66.8)	94.6 (68.5)	140.8 (87.7)	165.0 (96.0)
Total follow-up (person-years)	31,661	896	987	3,226	5,020
UGIHs per 1,000 person-years	0.7	4.5	8.1	3.7	1.2
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	7.0 (2.4–20.4)	12.6 (5.6–28.6)	5.7 (2.8–11.6)	1.8 (0.7–4.6)
Adjusted rate ratio (95% CI)	1.0 (reference)	5.8 (1.9–17.3)	9.8 (4.2–22.8)	4.2 (2.0–9.0)	1.4 (0.6–3.6)

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Figure 1.2 Subanalysis 2—Upper gastrointestinal hemorrhage (UGIH) outcomes stratified by ASA use in Ontario, 2000–2001

Study Cohort					
Users of Prescription ASA					
	Community Controls	**Nonselective NSAIDs**	**Diclofenac + Misoprostol**	**Rofecoxib**	**Celecoxib**
Sample size	11,564	1,014	945	2,629	3,311
Number of admissions for UGIH	12	3	5	7	11
Days of follow-up (mean ± SD)	144.2 (78.4)	94.2 (68.7)	106.1 (74.8)	150.3 (89.9)	171.8 (97.1)
Total follow-up (person-years)	4,565	261	275	1,082	1,558
UGIHs per 1,000 person-years	2.6	11.5	18.2	6.5	7.1
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	4.6 (1.3–16.5)	7.2 (2.5–20.5)	2.5 (1.0–6.4)	2.8 (1.2–6.3)
Adjusted rate ratio (95% CI)	1.0 (reference)	5.1 (1.3–19.1)	7.1 (2.4–21.5)	1.6 (0.6–4.3)	1.8 (0.8–4.4)
Non-users of prescription ASA					
Sample size	88,436	4,377	4,142	11,954	15,597
Number of admissions for UGIH	70	14	8	36	21
Days of follow-up (mean ± SD)	138.6 (77.2)	91.2 (68.2)	95.9 (70.2)	146.2 (89.5)	170.0 (97.0)
Total follow-up (person-years)	33,553	1,092	1,087	4,784	7,261
UGIHs per 1,000 person-years	2.1	12.8	7.4	7.5	2.9
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	6.4 (3.6–11.3)	3.6 (1.7–7.6)	3.7 (2.5–5.5)	1.4 (0.9–2.3)
Adjusted rate ratio (95% CI)	1.0 (reference)	4.0 (2.2–7.3)	2.2 (1.0–4.6)	1.9 (1.2–2.9)	0.8 (0.5–1.3)

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

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Chapter 2. Effect of Selective Cyclooxygenase (COX-2) Inhibitors and Naproxen on Short-Term Risk of Acute Myocardial Infarction in the Elderly

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Abstract

Background

Recent debate has emerged regarding the cardiovascular safety of selective cyclooxygenase (COX-2) inhibitors and the possible cardioprotective effect of naproxen. The rate of acute myocardial infarction (AMI) was compared among elderly patients dispensed selective COX-2 inhibitors, naproxen, and nonselective non-naproxen non-steroidal anti-inflammatory drugs (NSAIDs).

Methods

A population-based retrospective cohort study was conducted using administrative health care data from Ontario, Canada from April 1, 1998 to March 31, 2001. NSAID-naïve cohorts of subjects age 66 years and older initiated on celecoxib (n=15,271), rofecoxib (n=12,156), naproxen (n=5,669), and non-naproxen nonselective NSAIDs (n=33,868) were identified along with a randomly selected control cohort not exposed to NSAIDs (n=100,000). Multivariate Cox proportional hazards models were used to compare AMI rates between study drug groups while controlling for potential confounders.

Results

Relative to controls, the multivariate model revealed no significant differences in AMI risk for new users of celecoxib (adjusted rate ratio [aRR]=0.9; 95% C.I.=0.7 to 1.2), rofecoxib (aRR=1.0; 95% CI=0.8 to 1.4), naproxen (aRR=1.0; 95% CI=0.6 to 1.7), or non-naproxen nonselective NSAIDs (aRR=1.2; 95% CI=0.9 to 1.4).

Conclusions

The findings of this observational study suggest no increase in the short-term risk of AMI among users of selective COX-2 inhibitors. Furthermore, the findings do not support a short-term reduced risk of AMI with naproxen.

Introduction

Since their recent introduction, the selective cyclooxygenase (COX-2) inhibitors have become some of the most widely prescribed group of drugs in the elderly.[1] However, the cardiovascular safety of these agents has recently been questioned. A subanalysis of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial[2] 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 the 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 affect the risk of AMI.

Subsequent to the publication of the VIGOR trial, a separate study by Mukherjee et al[3] extended the cardiovascular safety concern to celecoxib and potentially all selective COX-2 inhibitors. However, a systematic review of 23 random control trials (RCTs) examining rofecoxib in relation to non-naproxen nonselective NSAIDs (nonsteroidal non-inflammatory drugs) or placebo, demonstrated no increased risk of cardiovascular thrombotic events for rofecoxib when compared with non-naproxen nonselective NSAIDs, but did observe a significant increased risk for rofecoxib when compared with naproxen.[4] A re-analysis of a large celecoxib RCT failed to find an association between celecoxib and non-naproxen nonselective NSAIDs and subsequent AM.I[5] Five observational studies examining the potential cardioprotective effects of naproxen have arrived at conflicting conclusions.[6-10]

In the absence of a direct comparison between selective COX-2 inhibitors, naproxen, non-naproxen nonselective NSAIDs and NSAID-naïve control subjects, the incidence of AMI in over 70,000 elderly new users of these medications was examined.

Findings

Cohort description

Of approximately 1.4 million potential subjects aged 65 years and older, 593,808 (40%) were dispensed a prescription NSAID during the study period from April 17, 2000 to March 31, 2001. From these individuals, 15,271 users of celecoxib, 12,156 users of rofcoxib, 5,669 users of naproxen, 33,868 users of non-naproxen nonselective NSAIDs, and 100,000 control subjects (Exhibit 2.1) meeting the inclusion criteria were identified. Among nonselective NSAID users, the majority of subjects were initiated on the combination of diclofenac and misoprostol (58%), ibuprofen (14%), or diclofenac (13%). A greater proportion of rofecoxib and celecoxib users were women compared to the other groups. The control group generally used less 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 (Exhibit 2.1).

During over 75,000 person-years of follow-up, 701 hospitalizations for AMI (Exhibit 2.2) were observed. Relative to the control group, model-based estimates adjusted for the covariates in Table 2.1 did not reveal any statistically significant association with AMI for users of celecoxib (adjusted rate ratio [aRR]=0.9; 95% 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 non-naproxen nonselective NSAIDs (aRR=1.2; 95% CI=0.9-1.4). When the drug groups were compared to 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 gender- matched control subjects, separate analyses for men and women, and analyses excluding subjects with a history of AMI yielded similar findings. No significant differences in AMI rates between the two subject accrual periods were observed for the naproxen and non-naproxen nonselective NSAID groups.

Discussion

This study has two 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 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 inaccurate.

Although selective COX-2 inhibitors interfere with the synthesis of vascular prostacyclin and do not block the synthesis of thromboxane A2, in contrast to nonselective NSAIDs,[17] the clinical implications of such activity is largely unknown. These neutral findings for celecoxib and rofecoxib are consistent with previously published reviews of RCTs 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 aggregation to a much greater extent than other nonselective NSAIDs.[18] However, the clinical implications of these effects are also uncertain. Three case-control studies have recently demonstrated cardioprotective benefits for naproxen[7,9,10] in contrast to another case-control study, [which] 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 the findings. Such relationships have been examined in a large cohort study by Ray et al[6] that followed NSAID-naïve subjects from the time of nonselective NSAID initiation onward. This study failed to demonstrate cardioprotective benefits for naproxen relative to non-use, even when stratifying by dose.

Limitations

Several limitations of this study deserve mention. First, although many important confounders were controlled for, some potentially important factors, such as smoking, obesity, and alcohol consumption, could not be accounted

for. However, this is believed to be an unlikely explanation for the findings. Despite a potentially 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 the use of selective COX-2 inhibitors in Ontario, neutral risk ratios were still observed for these drug groups relative to the other study groups following adjustment for available confounders. The population-based incidence estimate for AMI (Exhibit 2.3) among the control group is also consistent with those of previous studies.[19]

Second, administrative databases were used to identify and define exposure to study drugs and clinical outcomes. There is no direct measure of indication, adherence, or appropriateness of use, and use of nonprescription NSAIDs could not be identified. However, ibuprofen is the only non-prescription non-aspirin nonselective NSAID available in Canada and subjects in this study have a strong financial incentive to obtain these drugs by prescription. Nearly half of elderly residents of Ontario were dispensed a NSAID during the observation period, which is higher than previous studies examining consumption of either prescription or nonprescription NSAIDs among the elderly[2,3] and implies that the vast majority of NSAID use in this population is captured by the databases.

Similarly, 342,050 subjects, or 23% of the elderly population of Ontario, were dispensed aspirin during the study period. Although these figures suggest minimal over-the-counter use of these drugs, the actual magnitude of such activity is unknown. Outcomes were identified using previously validated diagnostic codes, but AMI that resulted in death before reaching the hospital could not be captured.

Third, the low absolute number of events in the study groups precluded reliable subgroup analyses to examine the outcomes of those using specific NSAIDs and aspirin concomitantly. This issue is important to examine as recent evidence suggests that concomitant administration of ibuprofen, but not rofecoxib, acetaminophen, or diclofenac, antagonizes the irreversible platelet inhibition induced by aspirin,[20] and therefore may alter its cardioprotective effects. Fourth, the generalizability of these findings to younger patients or settings with less restrictive access to these drugs over longer durations of follow-up is uncertain.

In summary, no significant increased risk of AMI among users of celecoxib or rofecoxib nor a significant protective effect for naproxen, was observed. While these findings allay concerns about increased risks of AMI associated with celecoxib and rofecoxib, they call into question the cardioprotective benefits of naproxen observed in previous studies.

Exhibits

Exhibit 2.1 Covariates assessed in examining myocardial infarction outcomes associated with NSAIDs in Ontario

Hospitalizations	Procedures	Drug Utilization	Other
• Any hospitalization in preceding year • Malignancy in preceding 5 years • Acute myocardial infarction, stroke, congestive heart failure, or non-infarct coronary disease in preceding 5 years	• Coronary angiography or revascularization in preceding 5 years	• Number of different drugs in preceding year • 120 days before index date until end of follow-up: ➢ ACE inhibitors ➢ Aspirin ➢ Antiarrhythmics ➢ Anticoagulants ➢ Antiplatelets ➢ Antidiabetic agents ➢ Antirheumatics ➢ Beta-blockers ➢ Calcium channel • Antagonists ➢ Digoxin ➢ Loop diuretics ➢ Non-loop diuretics ➢ Estrogen ➢ Lipid-lowering drugs ➢ Nitrates ➢ Other • Antihypertensives**	• Age • Gender • Long-term care • Low income status*

*Defined as annual income of less than $16,018 (single) and less than $24,175 (couple), confirmed through personal tax statements upon voluntary application for reductions in co-payments and deductibles

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

Exhibit 2.2 Characteristics of cohort groups examining myocardial infarction outcomes in Ontario, 2000–2001

	Study Cohort				
	Community Controls	**Celecoxib**	**Rofecoxib**	**Naproxen**	**Non-naproxen nonselective NSAIDs**
Number of patients (% women)	100,000 (56%)	15,271 (70%)	12,156 (71%)	5,669 (59%)	33,868 (62%)
Age (mean ± SD)	75.2 ± 7.2	76.5 ± 6.9	76.6 ± 7.0	75.0 ± 6.5	76.4 ± 7.0
Residence in long-term care facility (number, %)	4,197 (4%)	665 (4%)	548 (5%)	291 (5%)	2,550 (8%)
Low income status (number, %)	21,666 (22%)	4,517 (30%)	3,625 (30%)	1,742 (31%)	11,602 (34%)
Hospitalization in past year (number, %)	11,878 (12%)	2,934 (19%)	2,363 (19%)	1,100 (19%)	6,292 (19%)
Number of prescription drugs in past year (mean ± SD)	5.3 (5.5)	9.3 (6.4)	9.7 (6.5)	7.8 (6.2)	8.3 (6.3)
Hospitalizations/procedures in past 5 years					
AMI	4,533 (5%)	909 (6%)	716 (6%)	277 (5%)	1,739 (5%)
CHF	4,507 (5%)	960 (6%)	702 (6%)	248 (4%)	1,725 (5%)
IHD	8,649 (9%)	2,040 (13%)	1,679 (14%)	614 (11%)	3,793 (11%)
Stroke	3,298 (3%)	605 (4%)	498 (4%)	215 (4%)	1,388 (4%)
Non-AMI coronary disease*	3,314 (3%)	752 (5%)	608 (5%)	208 (4%)	1,209 (4%)
Malignancy	4,758 (5%)	836 (5%)	634 (5%)	492 (9%)	1,968 (6%)
Drug utilization in 120 days before index date to end of follow-up					
ACEIs	21,915 (22%)	5,308 (35%)	4,4404 36%)	1,429 (25%)	9,333 (28%)
Aspirin	12,236 (12%)	2,670 (17%)	2,148 (18%)	1,028 (18%)	6,550 (19%)
Antiarrhythmics	2,317 (2%)	473 (3%)	378 (3%)	138 (2%)	750 (2%)
Anticoagulants	5,645 (6%)	1,339 (8%)	1,028 (8%)	217 (4%)	1,426 (4%)
Antihyperglycemics	9,155 (9%)	1,872 (12%)	1,518 (12%)	762 (13%)	4,589 (14%)
Antiplatelet drugs	976 (1%)	288 (2%)	248 (2%)	43 (1%)	368 (1%)
Antirheumatics	0 (0%)	639 (4%)	313 (3%)	77 (1%)	619 (2%)
Beta-blockers	14,869 (15%)	3,335 (22%)	2,644 (22%)	943 (17%)	5,772 (17%)
Calcium channel antagonists	17,002 (17%)	4,121 (27%)	3,488 (29%)	1,167 (21%)	7,822 (23%)
Digoxin	6,424 (6%)	1,210 (8%)	908 (7%)	351 (6%)	2,355 (7%)
Diuretics					
Loop diuretics	9,097 (9%)	2,527 (17%)	1,988 (16%)	727(13%)	4,970 (15%)
Other diuretics	14,790 (15%)	4,041 (26%)	3,166 (26%)	1,147 (20%)	6,975 (21%)
Estrogen	5,506 (6%)	1,871 (12%)	1,456 (12%)	484 (9%)	2,698 (8%)
Lipid-lowering drugs	15,540 (16%)	3,668 (24%)	3,020 (25%)	1,055 (19%)	6,360 (19%)
Nitrates	9,746 (10%)	2,478 (16%)	1,927 (16%)	670 (12%)	4,389 (13%)
Other antihypertensives	3,710 (4%)	772 (5%)	655 (5%)	308 (5%)	1,796 (5%)

*Defined as previous coronary angiography or revascularization procedure

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Exhibit 2.3 Primary analysis: acute myocardial infarction outcomes associated with nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, 2000–2001

Study Cohort					
	Community Controls	**Celecoxib**	**Rofecoxib**	**Naproxen**	**Non-naproxen nonselective NSAIDs**
	(N = 100,000)	(N = 15,271)	(N = 12,156)	(N = 5,669)	(N = 33,868)
Number of admissions	419	75	58	15	134
Days of follow-up (mean ± SD)	187 (101)	168 (97)	144 (89)	100 (88)	120 (101)
Total follow-up (person-years)	51,194	7,004	4,806	1,559	11,085
Crude AMI rate per 1,000 person-years	8.2	10.7	12.1	9.6	12.1
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	1.3 (1.0–1.7)	1.5 (1.1–1.9)	1.2 (0.7–2.0)	1.5 (1.2–1.8)
Adjusted rate ratio (95% CI)	1.0 (reference)	0.9 (0.7–1.2)	1.0 (0.8–1.4)	1.0 (0.6–1.7)	1.2 (0.9–1.4)

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Appendix 2.A How the Research was Done

Objective

The primary objective of this study was to compare the incidence of hospitalization for AMI among NSAID-naïve elderly subjects dispensed celecoxib, rofecoxib, naproxen, or non-naproxen nonselective NSAIDs (nonsteroidal anti-inflammatory drugs) as compared to a NSAID-naïve community control group

A population-based retrospective cohort study was conducted by linking the health care records of more than 1.4 million Ontario residents aged 66 years and older from April 1, 1998 to March 31, 2001. Ontario's elderly 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.

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 (ODB), which records prescription drugs dispensed to all Ontario residents 65 years of age and older. Both celecoxib and rofecoxib were first listed on the ODB formulary on April 17, 2000 on a limited use basis for patients who failed to respond to, or were intolerant of, traditional NSAIDs, or for patients with a history of upper gastrointestinal hemorrhage or ulcer. The approved indications for celecoxib included osteoarthritis (OA) and rheumatoid arthritis (RA), whereas rofecoxib was approved only for use in OA. No such restrictions governed the prescribing of nonselective NSAIDs. Meloxicam could not be examined as it was not available on the ODB formulary during the study period.

Hospitalization records were obtained from the Canadian Institute for Heath Information (CIHI) 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 using encrypted unique health card numbers.

Cohort definition

Users of celecoxib, rofecoxib, naproxen, and non-naproxen nonselective NSAIDs were compared to a random sample of 100,000 control subjects dispensed none of these medications. An NSAID-naïve control group was chosen as a base reference for two reasons. First, the overall population provides a useful baseline risk estimate of non-NSAID related AMI (acute myocardial infarction). Second, it allows comparison of this study's incidence and relative risk estimates to previously published studies that examined the association between NSAID use and AMI utilizing non-NSAID user controls. 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 four 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-naïve subjects within these four drug groups, individuals who were dispensed any of the 4 study drugs in the year preceding the index date were excluded. Subjects that were dispensed prescriptions for drugs from more than one study drug group on the same day were excluded. To exclude sporadic users of NSAID therapy, only individuals who were dispensed at least two successive prescriptions and who received enough drugs for at least 30 days of observation were included. 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 of age and older who were alive on the assigned index date were screened for NSAID use one 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, 100,000 individuals were randomly selected to form the control cohort. This group was not age and gender-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 four study drug groups, the duration of exposure was defined as the period of continuous, exclusive enrolment 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 researchers 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 day supply estimation. Subjects were allowed a 20% grace period on the previous day 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 hospital for AMI. Occurrence of AMI was defined as a hospital admission with a primary diagnosis code of 410, which has a positive predictive value and sensitivity of approximately 89% and a specificity of approximately 93%.[13,14] 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 following 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.

Statistical analysis

Time-to-event analyses were conducted for AMI using Cox proportional hazard models with the control group as the reference. Covariates in the model are outlined in Exhibit 2.1. As an overall measure of comorbidity, the number of distinct drugs dispensed in the one year before the index date, was examined,[15] a measure comparable to the Charlson comorbidity index.[16] 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 the findings. First, the analyses were repeated using control subjects matched by age (within one year of the birth date) and gender to all patients in the four study drug groups. Second, because women are more likely than men to receive NSAIDs[11] and may have a relatively lower risk for AMI,[12] the analyses were repeated separately for men and women. Third, the AMI analysis was repeated excluding those with a history of AMI. Fourth, a sensitivity analysis was conducted to address differences among study groups in terms of time required 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 only available after April 17, 2000). The analysis was limited to the naproxen, non-naproxen, nonselective NSAID, and control groups throughout the study period. The analyses were repeated with the addition of an interaction term indicating whether the naproxen and non-naproxen nonselective NSAID 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 among the two study drug groups.

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

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Chapter 3. COX-2 Inhibitors Versus Nonselective NSAIDs: Congestive Heart Failure Outcomes Among an Elderly Cohort

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Abstract

Background

While nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of congestive heart failure (CHF), little is known about the cardiovascular effects of selective cyclooxygenase (COX-2) inhibitors. The primary objective of this study was to compare rates of hospitalization for CHF among elderly patients newly dispensed selective COX-2 inhibitors or nonselective NSAIDs. Subgroup analyses examined 1) the risk of CHF hospitalization among patients with and without established disease and 2) new use of medications for hypertension or CHF among those with no prior use, as markers of elevations in blood pressure or onset of CHF symptoms.

Methods

Population-based retrospective cohort study using administrative data from April 17, 2000 to March 31, 2001 to identify NSAID-naïve cohorts in Ontario aged 66 years or older initiated on rofecoxib (n=14,583), celecoxib (n=18,908), nonselective NSAIDs (n=5,391), and a randomly selected non-NSAID using control cohort with none of these exposures (n=100,000). Multivariate Cox proportional hazard models were used to analyze rates of hospitalization for CHF in the year after drug use began, adjusting for previous comorbidities, hospitalizations, procedures, and drug use.

Findings

Relative to non-NSAID users, the multivariate model revealed an increased short-term risk of CHF hospitalization for users of rofecoxib (adjusted rate ratio [aRR]=1·8; 95% CI=1·5 to 2·2) and nonselective NSAIDs (aRR=1.4; 95% C.I.=1.0 to 1.9) but not celecoxib (aRR=1.0; 95% CI=0.8 to 1.3). Relative to celecoxib users, hospital admission for CHF was significantly more likely among users of nonselective NSAIDs (aRR=1.4; 95% CI= 1.0-1.9) and rofecoxib (aRR=1.8; 95% CI=1.4-2.4). Relative to nonselective NSAID users, rofecoxib users were at a higher risk of CHF hospital admission (aRR=1.5; 95% CI=1.1-2.1). Among those without a CHF admission in the previous 3 years, only rofecoxib users (aRR=1.8; 95% CI=1.4–2.3) were at increased risk of subsequent CHF hospitalization relative to control subjects. Among those with such a history, both rofecoxib (aRR=1.8; 95% CI=1.2-2.7) and nonselective NSAID (aRR=2.2; 95% CI=1·3-3·7) users were at significantly increased risk of readmission for CHF relative to non-NSAID users. New use of medications for hypertension or CHF was significantly more likely among patients newly treated with rofecoxib (aRR=1.9; 95% CI=1.7-2.1), celecoxib (aRR=1.5; 95% CI=1.4-1.7), or nonselective NSAID (aRR=1.9; 95% CI=1.7-2.2) users compared to control subjects.

Interpretation

These findings suggest a higher short-term risk of hospital admission for CHF among users of rofecoxib and nonselective NSAIDs but not celecoxib relative to non-NSAID using community controls. Commencing any study drug was associated with a high rate of initiation of drug therapies for hypertension or CHF, suggesting a need for careful monitoring of the cardiovascular effects.

Introduction

The rapid adoption of the selective cyclooxygenase (COX-2) inhibitors into clinical practice[1] has been met with both enthusiasm and caution. While recent evidence suggests that the COX-2 inhibitors celecoxib and rofecoxib are associated with a significantly lower risk of gastrointestinal events than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs),[2-4] the cardiovascular safety of these agents has been challenged.[5,6] Aside from the debate surrounding their possible association with acute myocardial infarction, selective COX-2 inhibitors may be associated with similar cardiovascular and renal adverse effects as nonselective NSAIDs, raising systemic vascular resistance and reducing renal perfusion in susceptible individuals.[7]

Among nonselective NSAID users, increases in blood pressure and development of peripheral edema have been consistently associated with the development of congestive heart failure (CHF).[8-10] However, little is known about the association between use of the selective COX-2 inhibitors and CHF. Two small studies separately comparing high doses of celecoxib[11] and rofecoxib[12] to a nonselective NSAID comparator 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 nonselective NSAID groups relative to placebo.

Published and unpublished secondary analyses from two large randomized trials separately examining celecoxib[2,13] and rofecoxib[3,14] suggest differences between various NSAIDs with respect to onset of hypertension and edema. In the celecoxib trial, the incidence of hypertension and peripheral edema associated with celecoxib was significantly lower than that of the NSAID comparator group[2]. The incidence of congestive heart failure was not reported. In the rofecoxib trial the incidence of hypertension and edema associated with rofecoxib was significantly greater than that of naproxen.[14] The incidence of congestive heart failure among rofecoxib users was higher than that among naproxen users although this difference was not statistically significant (0.5% vs. 0.2%, respectively, p=0.07).

While two small trials directly comparing celecoxib and rofecoxib failed to find significant differences between the two drugs with respect to the effect on blood pressure,[15,16] two large randomized trials among elderly osteoarthritis patients with long-standing hypertension reported significantly greater increases in systolic blood pressure and higher likelihood of onset or worsening of edema among those receiving rofecoxib relative to those receiving celecoxib.[17,18] In the absence of a large randomized controlled trial comparing the effects of selective COX-2 inhibitors to nonselective NSAIDs and non-NSAID users with respect to hospitalization for CHF, a population-based cohort study was conducted to examine this association in more than 140,000 NSAID-naïve elderly subjects.

Findings

Of approximately 1.3 million potential subjects aged 65 years and older, 364,686 (28%) were dispensed a NSAID during the study period. From these individuals, 11,606 new users of nonselective NSAIDs, 18,908 users of celecoxib, 14,583 users of rofecoxib, and 100,000 non-NSAID users (Exhibit 3.1) meeting the inclusion criteria. Among nonselective NSAID users, the majority of subjects were started on the combination of diclofenac plus misoprostol (49%), naproxen (17%), ibuprofen (12%), or diclofenac alone (10%). The characteristics of the rofecoxib and celecoxib cohorts were virtually identical (Exhibit 3.1). However, compared with other groups, rofecoxib and celecoxib users were more likely to be women, to have previously undergone echocardiography, or to have received loop diuretics or digoxin compared with the other groups (Exhibit 3.1). They were also more likely to have received angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel antagonists. The control group tended to have fewer antecedent hospital admissions and receive fewer prescription drugs than the other study groups.

In more than 55,000 person-years of follow-up, including the control group, 654 hospitalizations for CHF (Exhibit 3.2) were observed. Relative to non-NSAID users, the rate of hospitalization for CHF was significantly higher for users of rofecoxib (adjusted rate ratio [aRR]=1.8; 95% CI=1.5–2.2) and nonselective NSAIDs (aRR=1.4; 95% CI=1.0–1.9), but not celecoxib (aRR=1.0; 95% CI=0.8–1.3). Additional analyses using age- and gender- matched control subjects and allowing for sporadic NSAID use yielded similar findings.

Pairwise comparisons revealed significant differences in risk of CHF among the drug groups. Relative to celecoxib users, a significantly higher risk of hospitalization for CHF was observed among users of rofecoxib (aRR=1.8; 95% CI=1.4–2.4) and nonselective NSAIDs (aRR=1.4; 95% CI= 1.0–1.9). Relative to nonselective NSAID users, the risk of hospitalization for CHF was higher among rofecoxib users (aRR=1.5; 95% CI=1.1–2.1).

Subgroup analyses revealed a 15 to 30-fold higher risk of subsequent CHF hospitalization among those with, compared to those without, a recent history of CHF hospitalization (Exhibit 3.3). Among those with no history of CHF hospitalization in the preceding 3 years, rofecoxib users (aRR=1.8; 95% CI=1.4–2.3) were at a significantly increased risk of subsequent hospital admission for CHF, whereas nonselective NSAID (aRR=1.1; 95% CI=0.7–1.6)

and celecoxib (aRR=0.9; 95% CI=0.7–1.2) users were not. Among those with such a history, rofecoxib (aRR=1.8; 95% CI=1.2–2.7) and nonselective NSAID (aRR=2.2; 95% CI=1.3–3.7) users were at significantly increased risk of readmission for CHF relative to non-NSAID users, whereas celecoxib users were not (aRR=1.2; 95% CI=0.8–1.7). The estimated needed to harm among subjects with a history of recent hospital admission for CHF were significantly lower than those of subjects without such a history (Exhibit 3.3).

Restricting analysis to those with no prior use of antihypertensive agents or medications for CHF, users of rofecoxib (aRR=1.9, 95% CI=1.7–2.1), celecoxib (aRR=1.5, 95% CI=1.4–1.7), and nonselective NSAIDs (aRR=1.9, 95% CI=1.7–2.2) were all more likely to be initiated on antihypertensive medications relative to non-NSAID users (Exhibit 3.3). Relative to celecoxib, users of rofecoxib (aRR=1.3, 95% CI=1.1–1.5) and nonselective NSAIDs (aRR=1.2, 95% CI=1.0–1.4) were significantly more likely to be started on antihypertensive drugs. The estimated numbers needed to treat to harm were low at 24 for celecoxib, 14 for rofecoxib, and 14 for nonselective NSAIDs.

Discussion

It is the authors' understanding that this study represents the largest and perhaps most comprehensive evaluation to date of the association between new NSAID use and hospitalization for CHF among the elderly using high quality administrative databases. The rofecoxib and celecoxib cohorts were virtually identical in their comorbidity profiles, allowing more confidence in the comparative analyses between these two drugs. Statistically significant differences between the study drug groups were observed with respect to hospitalization for CHF. Relative to non-NSAID users, celecoxib users were at similar risk, nonselective NSAID users were at increased risk, and rofecoxib users were at even greater risk than nonselective NSAID users. These findings for nonselective NSAID users are consistent with previous studies that report an approximately two-fold increased risk of hospitalization with CHF relative to non-NSAID users.[8,9,23] All drug groups were found to be associated with a significantly increased risk of new initiation of therapies for hypertension or CHF.

The findings are consistent with previous research.[2,13,14,17,18] The population-based CHF hospitalization rates among the community control group are similar to those reported elsewhere.[24] Further, the use of nonselective NSAIDs was found to be associated with worsening CHF among patients with a history of the disease but not with new-onset CHF, similar to Feenstra et al.[10] Although the estimated absolute risks of CHF hospitalization among those without a recent previous history of CHF were small, the low estimated number needed to treat to harm among those with a recent history of CHF hospitalization makes these findings very clinically relevant. Further, the high rate of initiating antihypertensive or CHF medications in those previously not receiving such therapies suggests a need for careful monitoring of cardiovascular effects for patients receiving celecoxib, rofecoxib, or nonselective NSAIDs.

It is unlikely that selection bias explains the differences in outcomes between the rofecoxib and celecoxib groups. The demographic and clinical characteristics of rofecoxib and celecoxib users were remarkably similar, implying that selection of one COX-2 inhibitor over another is likely arbitrary in clinical practice. Therefore, the differences in unobserved risk factors for cardiac outcomes between the rofecoxib and celecoxib groups are probably minimal so that selection bias could not likely explain the difference in CHF hospitalization observed between the two drugs. A previous study using the same databases and similar study design failed to observe any significant differences between rofecoxib and celecoxib with respect to hospitalization for AMI,[25] implying that cardiovascular risks are similar for these groups. If the rofecoxib group was 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 AMI in this group.

The differences in outcomes between rofecoxib and celecoxib are intriguing. The findings are consistent with two large randomized trials of osteoarthritis patients with long-standing hypertension that reported significantly greater increases in systolic blood pressure and higher likelihood of onset or worsening of edema among those receiving rofecoxib relative to those receiving celecoxib.[17,18] Possible explanations include the pharmacokinetic properties of the drugs themselves. Rofecoxib has a significantly longer elimination half-life than celecoxib. While this longer half-life allows for once-daily dosing, rofecoxib remains in the body for a relatively longer period. Further,

celecoxib has linear pharmacokinetics with no evidence of accumulation whereas rofecoxib has non-linear saturable pharmacokinetics, and with repetitive dosing accumulation of the drug occurs until steady state is reached.[25] These factors could contribute to a more pronounced hypertensive effect for rofecoxib relative to celecoxib. However, the increased incidence of initiation of medications used to treat hypertension or CHF with celecoxib among subjects not previously on these medications, although lower than that of rofecoxib or nonselective NSAIDs, suggest that celecoxib may not be entirely devoid of clinically meaningful cardiovascular effects.

Limitations

Several limitations of this study deserve mention. First, although attempts were made to control for important confounders, some potentially important cardiac risk factors, such as weight, dietary salt intake, smoking, alcohol intake, and over-the-counter medications such as aspirin, could not be accounted for. Despite a potentially heavier disease burden among the rofecoxib and celecoxib groups relative to the nonselective NSAID group, lower risks of CHF were still observed for celecoxib relative to the nonselective NSAID group, implying that these unmeasured factors are unlikely to explain these findings. Nearly half of the nonselective NSAID group used diclofenac plus misoprostol (i.e. 49%). Misoprostol is a prostaglandin E1 analogue and although some evidence indicates that intravenous prostaglandin therapy may improve the hemodynamic status of patients with congestive heart failure,[27] the implications of low doses of oral misoprostol on the study findings are unknown.

Second, the low absolute number of events in the study groups precluded reliable subgroup analyses, such as comparisons among users of high-dose and low-dose drugs. For example, less than 10% of rofecoxib users in this study were estimated to be using more than 25 mg daily, leaving very few events for analyses among this group. Third, use of administrative databases to define exposure to study drugs provides no direct measure of adherence or appropriateness of use. Since NSAIDs may be used in varying doses over time for symptom control, dose equivalence of the various drugs could not be examined with these data and use of nonprescription NSAIDs could not be identified. However, ibuprofen is the only non-aspirin nonselective NSAID available in Canada without a prescription, so that elderly Ontario residents have a strong financial incentive to obtain these drugs by prescription, especially for regular use. Notably, over one-quarter of elderly subjects were dispensed a NSAID during the observation period, consistent with previous studies examining use of prescription or nonprescription NSAIDs among the elderly,[2,3] implying that the majority of NSAID use in this study's population is likely captured by the databases.

In summary, higher rates of hospital admission for CHF among elderly patients initiated on treatment with rofecoxib and nonselective NSAIDs, but not celecoxib, were found. These differences are clinically important given the large numbers of patients treated with NSAIDs of any type. In particular, there were large increases in risk of readmission among patients previously hospitalized for CHF that received rofecoxib or nonselective NSAIDs. Further, all drug groups were found to be associated with a significantly increased risk of initiation of medications used to treat hypertension or CHF among those not previously on such therapy. Large head-to-head randomized controlled trials are needed to better examine these outcomes.

Exhibits

Exhibit 3.1 Characteristics of cohort groups examining heart failure outcomes associated with nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, 2000–2001

	Study Cohort			
	Non-NSAID Users	**Celecoxib**	**Rofecoxib**	**Nonselective NSAIDs**
Number of patients (% women)	100,000 (55%)	18,908 (70%)	14,583 (72%)	11,606 (61%)
Age (mean ± SD)	75.4 ± 7·3	76.5 ± 6.8	76.5 ± 6.9	75.9 ± 7.0
Residence in long-term care facility (number, %)	4,060 (4%)	810 (4%)	652 (4%)	930 (8%)
Low income status (number, %)	21,065 (21%)	5,673 (30%)	4,445 (30%)	3,943 (34%)
Hospitalization in past year (number, %)	11,589 (12%)	3,651 (19%)	2,900 (20%)	2,091 (18%)
Number of prescription drugs in past year (mean ± SD)	5.4 (5.5)	9.5 (6.4)	9.9 (6.6)	8.3 (6.4)
Hospitalizations/procedures in past 5 years				
CHF	4,475 (4%)	1,170 (6%)	857 (6%)	542 (5%)
CHF in past 6 months	405 (<1%)	99 (<1%)	69 (<1%)	48 (<1%)
AMI	4,658 (5%)	1,111 (6%)	865 (6%)	544 (5%)
IHD	8,760 (9%)	2,524 (13%)	2,034 (14%)	1,180 (10%)
Stroke	3,147 (3%)	734 (4%)	589 (4%)	446 (4%)
Heart valve surgery	305 (<1%)	61 (<1%)	44 (<1%)	27 (<1%)
Echocardiography	20,579 (21%)	5,243 (28%)	4,265 (29%)	2,631 (23%)
Non-AMI coronary disease*	3,680 (4%)	931 (5%)	729 (5%)	445 (4%)
Malignancy	4,647 (5%)	1,004 (5%)	760 (5%)	725 (6%)
Drug utilization one year before index date				
ACEIs	23,712 (24%)	6,319 (33%)	4,993 (34%)	3,611 (31%)
Alpha-blockers	3,312 (3%)	794 (4%)	660 (5%)	575 (5%)
Aspirin	12,475 (12%)	3,616 (19%)	2,886 (20%)	2,411 (21%)
Antiarrhythmics	2,461 (2%)	594 (3%)	469 (3%)	258 (2%)
Anticoagulants	5,816 (6%)	1,631 (9%)	1,262 (9%)	491 (4%)
Antihyperglycemics	9,456 (9%)	2,302 (12%)	1,809 (12%)	1,607 (14%)
Antiplatelet drugs	1,014 (1%)	302 (2%)	271 (2%)	122 (1%)
Antirheumatics	0 (0%)	852 (5%)	399 (3%)	123 (1%)
Beta-blockers	15,870 (16%)	4,126 (22%)	3,116 (21%)	2,163 (19%)
Calcium channel antagonists	17,404 (17%)	5,163 (27%)	4,132 (28%)	2,783 (24%)
Digoxin	5,987 (6%)	1,464 (8%)	1,079 (7%)	666 (6%)
Diuretics: Loop diuretics	8,693 (9%)	3,091 (16%)	2,327 (16%)	1,528 (13%)
Spironolactone	1,677 (2%)	580 (3%)	465 (3%)	272 (2%)
Other diuretics	14,543 (15%)	4,554 (24%)	3,411 (23%)	2,399 (21%)
Hydralazine	199 (<1%)	57 (<1%)	32 (<1%)	30 (<1%)
Lipid-lowering drugs	17,386 (17%)	4,433 (23%)	3,558 (24%)	2,630 (23%)
Nitrates	10,072 (10%)	3,255 (17%)	2,522 (17%)	1,325 (14%)
Other antihypertensives	465 (<1%)	169 (<1%)	111 (<1%)	98 (<1%)
Respiratory inhalers	9,941 (10%)	2,997 (16%)	2,464 (17%)	1,703 (15%)

*Defined as previous coronary angiography or revascularization procedure

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Exhibit 3.2 Primary analysis: congestive heart failure (CHF) outcomes in Ontario, 2000–2001

Study Cohort				
	Non-NSAID Users	**Celecoxib**	**Rofecoxib**	**Nonselective NSAIDs**
	(N = 100,000)	(N = 18,908)	(N = 14,583)	(N = 11,606)
Number of admissions	348	116	143	47
Days of follow-up (mean ± SD)	139 (77)	170 (97)	146 (90)	94 (70)
Total follow-up (person-years)	38,099	8,801	5,846	2,993
Crude CHF rate per 1,000 person-years	9.1	13.2	24.5	15.7
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	1.5 (1.2–1.8)	2.7 (2.2–3.3)	1.7 (1.2–2.3)
Adjusted rate ratio (95% CI)	1.0 (reference)	1.0 (0.8–1.3)	1.8 (1.5–2.2)	1.4 (1.0–1.9)
Numbers needed to treat to harm (NNT (H))*	N/A	N/A	402	882

*NNT (H) calculations are based on a 319-day follow-up period from the Cox proportional hazard model estimates.

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Exhibit 3.3 Subgroup analyses: congestive heart failure (CHF) outcomes stratified by CHF history and new onset of antihypertensive or CHF medications in Ontario, 2000–2001

Study Cohort				
	Non-NSAID Users	**Celecoxib**	**Rofecoxib**	**Nonselective NSAIDs**
Stratified CHF Analysis				
Subjects without a recent history of CHF hospitalization				
Sample Size	98,409	18,517	14,317	11,424
Number of admissions	248	84	111	30
Days of follow-up (mean ± SD)	139 (77)	170 (97)	147 (90)	94 (69)
Total follow-up (person-years)	37,507	8,642	5,749	2,944
Crude CHF rate per 1,000 person-years	6.6	9.7	19.3	10.2
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	1.5 (1.2 – 1.9)	3.0 (2.4 – 3.7)	1.5 (1.1 – 2.3)
Adjusted rate ratio (95% CI)	1.0 (reference)	0.9 (0.7–1.2)	1.8 (1.4–2.3)	1.1 (0.7–1.6)
Numbers needed to treat to harm (NNT (H))	N/A	N/A	434	N/A
Subjects with a recent history of CHF hospitalization				
Sample Size	1,591	391	266	182
Number of admissions	100	32	32	17
Days of follow-up (mean ± SD)	136 (78)	148 (96)	133 (86)	97 (77)
Total follow-up (person-years)	593	159	97	49
Crude CHF rate per 1,000 person-years	169	202	330	350
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	1.2 (0.8–1.8)	2.0 (1.3–2.9)	2.0 (1.2–3.3)
Adjusted rate ratio (95% CI)	1.0 (reference)	1.2 (0.8–1.7)	1.8 (1.2–2.7)	2.2 (1.3–3.7)
Numbers needed to treat to harm (NNT (H))	N/A	N/A	19	12
New onset of antihypertensive or CHF medications				
Sample size	51,527	5,632	4,632	4,100
Number of subjects initiated on therapy	2,148	521	456	273
Days of follow-up (mean ± SD)	136 (77)	155 (96)	134 (87)	85 (64)
Total follow-up (person-years)	19,196	2,392	1,605	956
Crude therapy initiation rate per 1,000 person-years	112	218	284	286
Model-based risk ratios Unadjusted rate ratio (95% CI)	1.0 (reference)	2.0 (1.8–2.2)	2.5 (2.3–2.8)	2.5 (2.2–2.8)
Adjusted rate ratio (95% CI)	1.0 (reference)	1.5 (1.4–1.7)	1.9 (1.7–2.1)	1.9 (1.7–2.2)
Numbers needed to treat to harm (NNT (H))	N/A	24	14	14

Data sources: Ontario Drug Benefit Program; Canadian Institute of Health Information; Ontario Hospital Insurance Plan; Registered Persons Database

Appendix 3.A How the Research was Done

Study design

A population-based retrospective cohort study was conducted by linking administrative health care databases covering over 1.3 million individuals 65 years of age and older in Ontario, Canada from April 17, 2000 through March 31, 2001. These patients have 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.

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 (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.[19] Both rofecoxib and celecoxib were first listed on the ODB formulary on April 17, 2000 on a limited use basis for patients who failed to respond to, or were intolerant of, traditional nonsteroidal anti-inflammatory drugs (NSAIDs), or for patients with a history of gastrointestinal hemorrhage or ulcer. Rofecoxib was approved only for use in OA, whereas the approved indications for celecoxib included osteoarthritis (OA) and rheumatoid arthritis (RA). No such restrictions governed the prescribing of nonselective NSAIDs. Meloxicam use was not examined as it was not available on the ODB formulary during the study period.

Hospitalization records were obtained from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which contains a detailed record of all hospital 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 each Ontario resident. These databases were linked anonymously using encrypted individual health card numbers.

Cohort definitions

Three separate study drug cohorts were assembled consisting of new users of rofecoxib, celecoxib, or nonselective NSAIDs, as well as a random sample of 100,000 non-NSAID-using individuals selected from community controls dispensed none of these medications. The community control group provided an estimate of baseline risk of congestive heart failure (CHF) admissions in the general population unrelated to NSAID use. This is a useful reference group since all individuals in a population are at risk for disorders characterized by pain and inflammation, and non-drug management may represent a viable treatment option. Pairwise comparisons of the different NSAID study groups in relation to one another rather than the non-NSAID control group were also conducted.

For the three drug cohorts, all individuals 66 years of age and older who were dispensed a prescription for rofecoxib, celecoxib, or nonselective NSAIDs from April 17, 2000 to March 31, 2001 were identified. The index study date was defined as the date of initial study drug prescription during this timeframe. To create a cohort of NSAID-naïve subjects within these three drug groups, individuals who were dispensed any NSAID medication in the year preceding the index date, as well as those dispensed study drugs from more than one group on the same day, were excluded. To exclude sporadic users of NSAIDs, only individuals who received at least two successive prescriptions of the same drug group and who received enough drugs for at least 30 days of observation were included. The analyses were also repeated to include patients with only one prescription and fewer than 30 days of observation.

The non-NSAID community control cohort was created by randomly assigning index dates between April 17, 2000 to March 31, 2001 from a uniform distribution to all Ontario residents age 66 years and older 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, 100,000 individuals were randomly selected to serve as the non-NSAID control cohort, representing the general non-NSAID-dispensed elderly population of Ontario. The analyses were repeated using control subjects matched by age (born within one year) and gender to all patients in the three study drug groups as a sensitivity analysis.

Duration of exposure

For each of the three study drug cohorts, the duration of exposure was defined as the period of continuous, exclusive enrolment in the study medication group after the index date. The nonselective NSAID cohort was allowed to switch among different nonselective NSAIDs during the observation period. The "days supply" variable of the pharmacy claims database allowed researchers 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 day supply estimation. Subjects were allowed a 20% grace period on the previous day 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 of the study was admission to hospital for CHF. Admission to hospital for CHF was defined using admission with a primary diagnosis of CHF (International Classification of Diseases, revision 9 [ICD9] code 428). A recent chart abstraction study validating the accuracy of coding for CHF admission in the databases revealed positive predictive values of 90–96% depending on the criteria used to define CHF.[20] Follow-up for each subject was censored (stopped) upon admission to hospital for CHF, exposure to a medication from another study group, discontinuation of the study medication, death, or the end of the observation period (March 31, 2001).

Statistical analysis

Time-to-event analyses were conducted for CHF hospitalization using Cox proportional hazards models with the community control group as the reference, controlling for all covariates outlined in Figure 3.1. As an overall measure of comorbidity, the number of distinct drugs dispensed in the year before the index date, was controlled for, [21] a measure comparable to the Charlson comorbidity index.[22] Separate subgroup analyses were performed among those with, and without, a history of CHF. This was defined as CHF-related hospital admission within 3 years before the index date, because some evidence suggests that NSAID use may be associated with exacerbation of existing CHF rather than development of *de novo* CHF.[10]

Figure 3.1 Covariates controlled for in analysis of heart failure outcomes associated with nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario

Hospitalizations	Procedures	Drug utilization	Other
Any hospitalization in preceding year Malignancy in preceding 5 years Acute myocardial infarction, stroke, congestive heart failure, non-infarct coronary disease, or renal disease in preceding 5 years Congestive heart failure in preceding 6 months	Echocardiography or revascularization procedure in preceding 5 years Heart valve surgery procedure in past 5 years	In year preceding index date: ACE inhibitors or ARBs Alpha-blockers Aspirin Antiarrhythmics Anticoagulants Antiplatelets Antihyperglycemic agents Antirheumatics Beta-blockers Calcium channel antagonists Digoxin Diuretics: Loop diuretics Non-loop diuretics Spironolactone Hydralazine Lipid-lowering drugs Nitrates Respiratory inhalers: inhaled β_2 agonists or anticholinergics Other antihypertensives**	Age Gender Long-term care Low income status*

*Defined as annual income of less than $16,018 (single) and less than $24,175 (couple), confirmed through personal tax statements upon voluntarily application for reductions in co-payments and deductibles

**Includes clonidine, guanethidine, methyldopa, minoxidil (oral), and reserpine

Hospitalization for CHF represents a severe outcome that is often preceded by subtle, though clinically important, events. As a marker of clinically significant elevations in blood pressure and onset of CHF-related symptoms, the initiation of medications for hypertension (e.g. alpha-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers, thiazide diuretics, nitrates, and others) and CHF (e.g. digoxin, hydralazine, loop diuretics, or spironolactone) were examined for patients with no prior use in the year before cohort entry. Finally, pairwise comparisons of the study groups were conducted using specific NSAID groups instead of the community control group as the reference. The proportional hazards assumption for each exposure variable was assessed in each analysis. All analyses were performed using SAS for UNIX, Version 8.2 (SAS Institute, Cary, NC). All statistical tests were performed at the 5% level of significance and were two-sided.

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Chapter 4. COX-2 Inhibitors and Nonselective NSAIDs: Adherence to Temporal Trends in Patient Comorbidity

Authors
Muhammad Mamdani, PharmD, MA, MPH, Alex Kopp, BA

Introduction

Medication adherence is influenced by numerous factors, including patient beliefs, nature of the treatment (e.g. symptomatic vs. preventive), nature of the disease (e.g., life-threatening vs. non life-threatening), and adverse effects of the medications. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to manage pain and inflammation associated with a variety of conditions including chronic conditions such as arthritis and acute conditions such as sports injuries. The introduction of the selective cyclooxygenase (COX-2) inhibitors has raised concerns around its utilization given its significantly higher drug cost relative to the older nonselective NSAIDs, although the COX-2 inhibitors may offer a reduced risk of gastrointestinal events relative to the nonselective NSAIDs.

To curtail costs and promote optimal use, the Ontario Drug Benefits program restricts celecoxib and rofecoxib to Limited Use status for patients with arthritis who failed to respond to, or were intolerant of, traditional NSAIDs, or those arthritis patients with a history of gastrointestinal hemorrhage or ulcer. These criteria were applied upon introduction of celecoxib and rofecoxib in April 2000. Meloxicam was introduced in March 2001 without any such restrictions given the relatively lower acquisition cost. The Limited Use status program is based on an honour system and although audits may be performed none have occurred thus far, leading to concern that the conditions for the use of COX-2 inhibitors are being poorly followed.

Related issues that can be assessed through administrative claims data include drug adherence and patient comorbidity. Patients using NSAIDs for arthritis management are likely to receive continual therapy, although symptoms may flare and dissipate over time. Short-term use is expected for treatment of acute conditions. There is concern that as time progresses, less severe patients will receive therapy to a point where users of COX-2 inhibitors will appear similar in their comorbidity to users of nonselective NSAIDs.

To address these issues, three analyses were conducted. First, prescription utilization and costs associated with COX-2 inhibitor uptake before and after their introduction were examined. Second, a cohort study was to crudely examine adherence to COX-2 inhibitors and nonselective NSAIDs (i.e. the refill study) was conducted. Third, the comorbidity prevalence of NSAID-naïve individuals initiated on therapy at different points in time was examined.

Findings and Discussion

COX-2 inhibitor adherence: the refill study

Using the administrative databases in Ontario, as outlined in previous studies in this report, NSAID-naïve individuals (i.e. those without any NSAID therapy, including COX-2 inhibitors in preceding year) aged 66 years and older initiated on nonselective NSAIDs or COX-2 inhibitors from April 1, 2000 through March 31, 2002 were identified. The date of the first prescription during this timeframe was defined as the index date. These patients were followed for one year post-index date for refilling of NSAIDs (i.e. either nonselective NSAIDs or COX-2 inhibitors). As the primary outcome measures, the number of prescriptions for any NSAID following the initial prescription and the days of drug supplied over the one-year follow-up period were estimated using the days supplied field in the ODB database. The findings are outlined in Exhibit 4.1.

The key findings of this study suggest that among NSAID-naïve elderly individuals initiated on COX-2 inhibitors, the initial prescription will be the only NSAID prescription dispensed for over half of these patients over a one-year follow-up. More than three-quarters of individuals receive less than or equal to 3 months of prescription NSAID therapy. As might be expected, the prescription NSAID utilization among individuals initiated on nonselective NSAID therapy appears to be even more short-term. The findings suggest that a substantial proportion of patients initiated on COX-2 inhibitors may be receiving short-term therapy for acute pain that may not be entirely consistent with chronic management of arthritis.

Temporal trends in NSAID prescription utilization

A cross-sectional time series analysis was conducted to examine the monthly numbers of prescriptions dispensed for nonselective NSAIDs and selective COX-2 inhibitors and associated prescription costs from January 1, 1997 to May 31, 2003. Time series analysis using autoregressive integrated moving average models (ARIMA) were used for analysis. Further information on temporal trends in outcomes and drug utilization is provided in the next chapter.

The findings of this analysis suggest significant increases in the utilization of COX-2 inhibitors with a much more modest decline in nonselective NSAID use (Exhibit 4.2). Prescription NSAID (i.e. nonselective NSAIDs or selective COX-2 inhibitors) utilization increased dramatically by nearly 100% over this time period and this increase was solely driven by the introduction of the selective COX-2 inhibitors ($p<0.001$). The implication for this increase in prescription utilization is that significantly more individuals in the population are being newly exposed to NSAIDs rather than switching from nonselective NSAIDs to COX-2 inhibitors.

The public health implications of this phenomenon are explored in the next chapter. The annual prescription costs to the ODB associated with NSAID therapy also increased dramatically from approximately $28 million before the introduction of the COX-2 inhibitors to greater than $75 million following their introduction ($p<0.001$). Exhibit 4.2 outlines the implications of the approval of meloxicam as a General Benefit product. Meloxicam continuously gained market share to become the most commonly prescribed COX-2 inhibitor, despite the lack of high quality outcomes evidence, comparable to that for celecoxib and rofecoxib, regarding its safety. As noted in the Executive Summary, internal analyses at ICES suggest that the risk of hospitalization for upper gastrointestinal hemorrhage is no different between nonselective NSAIDs and meloxicam. The implications of these observations are left to the policymakers.

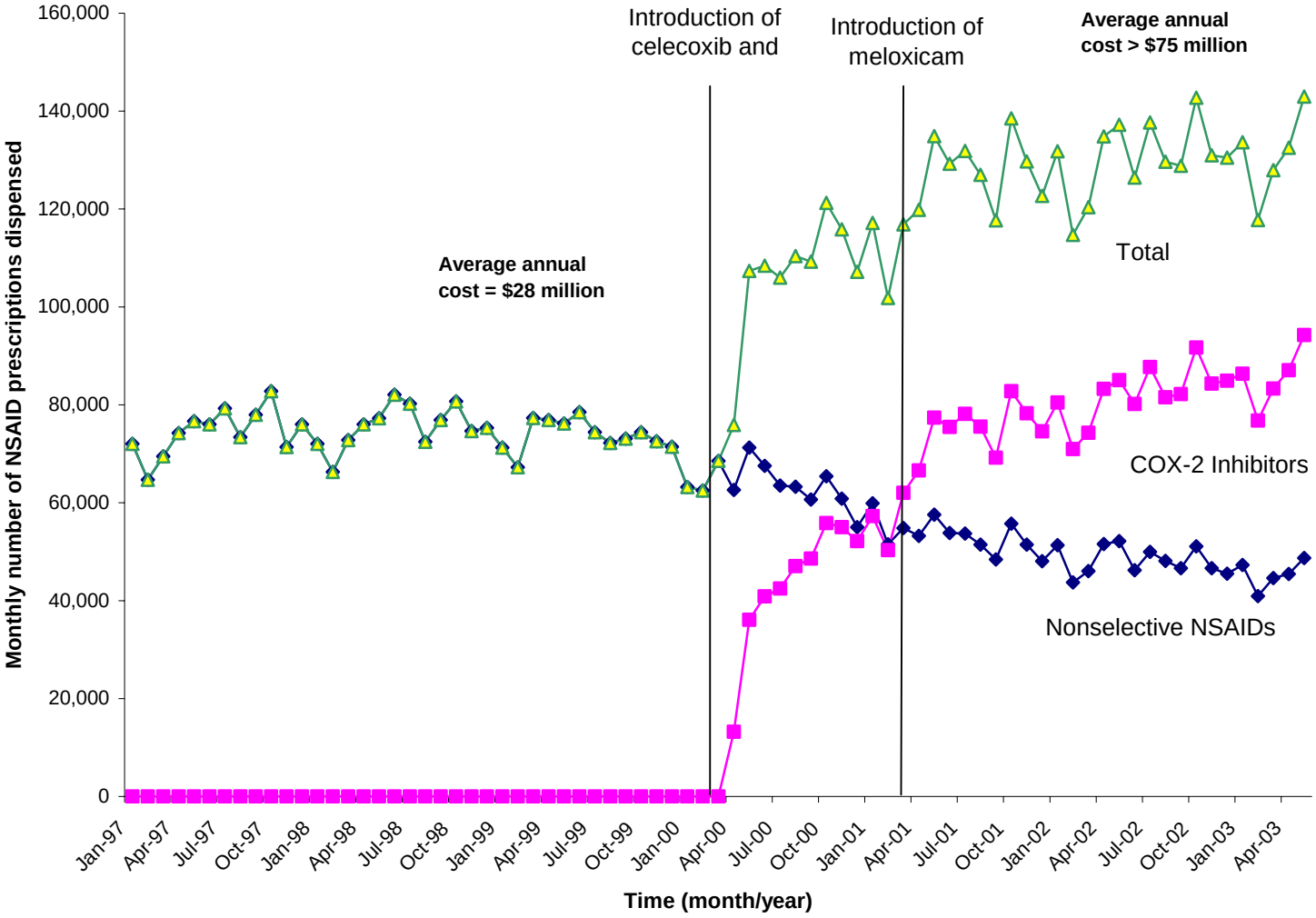
Exhibits

Exhibit 4.1 One-year nonsteroidal anti-inflammatory drug (NSAID) prescription refilling among individuals initiated on NSAIDs in Ontario, April 2000–March 2003

	Initial Drug	
	Nonselective NSAID	**COX-2 Inhibitor**
Sample size	34,649	33,167
Number of NSAID prescriptions during follow-up, mean (SD)	1.9 (2.3)	2.4 (2.6)
Frequency of numbers of prescriptions		
Stratification by # of **any NSAID** prescriptions dispensed		
1 prescription in total (i.e. the initial prescription)	21,247 (61.3%)	16,953 (51.1%)
2 prescriptions	7,081 (20.4%)	7,143 (21.5%)
3 prescriptions	2,927 (8.4%)	3,707 (11.2%)
≥ 4 prescriptions	3,394 (9.8%)	5,370 (16.2%)
Stratification by # of nonselective NSAID prescriptions dispensed		
No nonselective NSAID prescriptions	0 (0%)	30,678 (92.5%)
1 prescription in total (i.e. the initial prescription)	23,346 (67.4%)	1,693 (5.1%)
2 prescriptions	6,561 (18.9%)	446 (1.3%)
3 prescriptions	2,419 (7.0%)	171 (0.5%)
≥ 4 prescriptions	2,323 (6.7%)	179 (0.5%)
Stratification by # of COX-2 inhibitor prescriptions dispensed		
No COX-2 inhibitor prescriptions	31,302 (90.3%)	0 (0%)
1 prescription in total (i.e. the initial prescription)	1,904 (5.5%)	18,273 (55.1%)
2 prescriptions	669 (1.9%)	6,750 (20.4%)
3 prescriptions	357 (1.0%)	3,402 (10.3%)
≥ 4 prescriptions	417 (1.2%)	4,742 (14.3%)
Adherence by days of drug supplied		
Stratification by # of **any NSAID** prescriptions dispensed		
≤ 3 months	31,146 (89.9%)	25,959 (78.3%)
3–6 months	1,689 (4.9%)	2,934 (8.8%)
≥ 6 months	1,814 (5.2%)	4,274 (12.9%)
Stratification by # of nonselective NSAID prescriptions dispensed		
No nonselective NSAID prescriptions	0	30,678 (92.5%)
≤ 3 months	32,140 (92.8%)	2,329 (7.0%)
3–6 months	1,238 (3.6%)	93 (0.3%)
≥ 6 months	1,271 (3.7%)	67 (0.2%)
Stratification by # of COX-2 inhibitor prescriptions dispensed		
No COX-2 inhibitor prescriptions	31,302 (90.3%)	0 (0%)
≤ 3 months	2,794 (8.1%)	26,431 (79.7%)
3–6 months	252 (0.7%)	2,732 (8.2%)
≥ 6 months	301 (0.9%)	4,004 (12.1%)

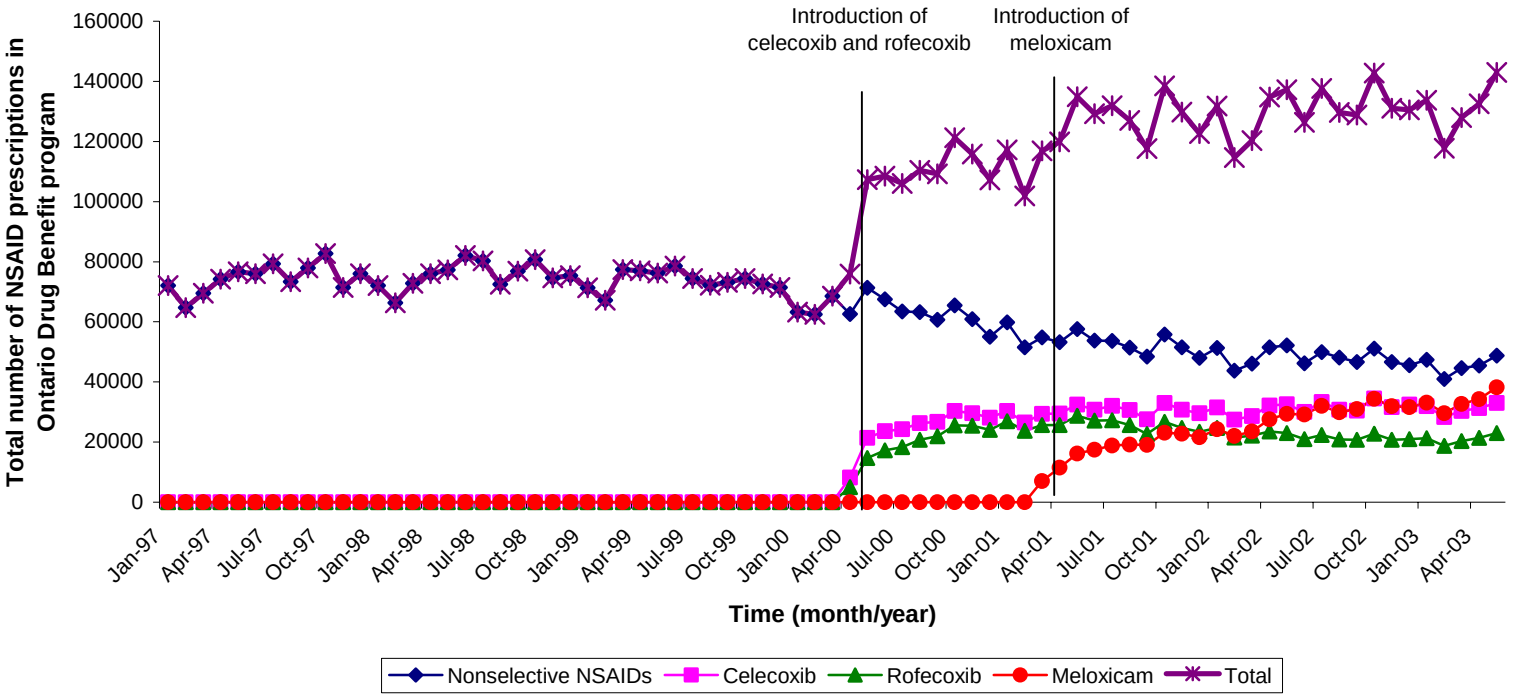
Data source: Ontario Drug Benefit Program

Exhibit 4.2 Temporal patterns in nonsteroidal anti-inflammatory drug (NSAID) prescription utilization and costs in Ontario, 1997–2002



Data source: Ontario Drug Benefit Program

Exhibit 4.3 Temporal patterns in nonsteroidal anti-inflammatory drug (NSAID) prescription utilization by specific COX-2 inhibitors in Ontario, 1997–2002



Data source: Ontario Drug Benefit Program

Appendix 4.A How the Research was Done

Changing comorbidity prevalence among COX-2 inhibitors

NSAID-naïve individuals initiated on NSAID therapy were identified according to data availability during the following time intervals:

- April 1 to June 30, 1999
- April 1 to June 30, 2000
- April 1 to June 30, 2001
- January 1 to March 31, 2002.

The index date was defined as the date of initiation in these time intervals. These individuals were categorized as being initiated on either selective COX-2 inhibitors or nonselective NSAIDs. Utilization of the following parameters were examined using the Discharge Abstract Database (DAD) for hospitalization data, the Ontario Drug Benefits (ODB) database for drug utilization data, the Ontario Health Insurance Program (OHIP) database for physician visits and outpatient procedures. Indicators for gastrointestinal and cardiovascular health at various time points relative to the index date were collected as outlined in Figure 4.1.

Figure 4.1 Collection of parameters for demographics assessment

Hospitalizations	Procedures	Drug Utilization	Other
History of upper gastrointestinal hemorrhage in preceding 5 years History of acute myocardial infarction, stroke, congestive heart failure, ischemic heart disease, or stroke in preceding 5 years	Revascularization procedure in preceding 5 years UGIH endoscopy or radiologic GI series in past 5 years	Use of the following prescription drugs within 120 days following initiation: Aspirin Warfarin Gastroprotective Drugs: Proton pump inhibitors H2RAs Misoprostol Sucralfate	Age Gender

The temporal data are reported in Figures 4.2 to 4.5. The data suggest some temporal changes in the demographics of individuals initiated on selective COX-2 inhibitors. For example, the proportion of COX-2 inhibitor users that are women decreased from 72% in 2000 to 62% in 2002, which is more similar to those initiated on nonselective NSAIDs. Further, prevalence of gastrointestinal comorbidity, as measured by upper gastrointestinal (UGI) endoscopy and radiologic GI series in the past 5 years also decreased amongst those initiated on COX-2 inhibitors from 54% in 2000 to 42% in 2002, again becoming more similar to nonselective NSAID users. Less subtle changes were observed among other covariates, however the general trends suggest that individuals initiated on COX-2 inhibitors may more closely resemble individuals initiated on nonselective NSAIDs over time. Primary data is needed to better characterize this phenomenon.

Figure 4.2 Comorbidity prevalence of people initiated on nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, April 1–June 30, 1999

	COX-2 Inhibitors	Arthrotec®	Nonselective NSAIDs
Sample size	0	15432	24554
Age			
Mean (SD)		74.7 (6.4)	74.0 (6.3)
% Women		9,531 (62%)	13,738 (56%)
GI-related utilization			
Endoscopy/UGI series		6,113 (40%)	9,270 (38%)
GI bleed in last 5 years		175 (1%)	218 (1%)
Cardiovascular-related utilization (past 5 years)			
AMI hospitalization		628 (4%)	1,078 (4%)
CHF hospitalization		527 (3%)	914 (4%)
IHD hospitalization		1,315 (9%)	2,225 (9%)
Stroke hospitalization		379 (2%)	589 (2%)
Revascularization procedures		465 (3%)	862 (4%)
Drug utilization (120 days post-initiation)			
Warfarin		441 (3%)	790 (3%)
ASA		2,322 (15%)	3,604 (15%)
Gastroprotective agents		3,398 (22%)	6,177 (25%)
PPIs		822 (5%)	1,189 (5%)
H2RAs		2,452 (16%)	4,232 (17%)
Misoprostol/Sucralfate		249 (2%)	1,278 (5%)

Data sources: Ontario Drug Benefit Program, Ontario Hospital Insurance Plan; Canadian Institute for Health Information; Registered Persons Database

Figure 4.3 Comorbidity prevalence of people initiated on nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, April 1–June 30, 2000

	COX-2 Inhibitors	Arthrotec®	Nonselective NSAIDs
Sample size	29,777	12,663	19,224
Age			
Mean (SD)	75.8 (6.7)	74.9 (6.5)	74.1 (6.2)
% Women	21,334 (72%)	7,854 (62%)	10,611 (55%)
GI-related utilization			
Endoscopy/UGIH series	16,054 (54%)	5,440 (43%)	8,132 (42%)
GI bleed in last 5 years	691 (2%)	125 (1%)	203 (1%)
Cardiovascular-related utilization (past 5 years)			
AMI hospitalization	1,667 (6%)	578 (5%)	924 (5%)
CHF hospitalization	1,620 (5%)	437 (3%)	800 (4%)
IHD hospitalization	3,849 (13%)	1,139 (9%)	1,882 (10%)
Stroke hospitalization	974 (3%)	327 (3%)	496 (3%)
Revascularization procedures	1,426 (5%)	482 (4%)	871 (5%)
Drug utilization (120 days post-initiation)			
Warfarin	2,051 (7%)	367 (3%)	700 (4%)
ASA	4,019 (14%)	1,882 (15%)	2,738 (14%)
Gastroprotective agents	10,667 (36%)	2,587 (20%)	4,690 (24%)
PPIs	5,406 (18%)	811 (6%)	1181 (6%)
H2RAs	5,588 (19%)	1,822 (14%)	3,178 (17%)
Misoprostol/Sucralfate	441 (1%)	130 (1%)	691 (4%)

Data sources: Ontario Drug Benefit Program, Ontario Hospital Insurance Plan; Canadian Institute for Health Information; Registered Persons Database

Figure 4.4 Comorbidity prevalence of people initiated on nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, April 1–June 30, 2001

	COX-2 Inhibitors	Arthrotec®	Nonselective NSAIDs
Sample size	21,083	6,086	10,910
Age			
Mean (SD)	75.2 (6.7)	74.7 (6.5%)	74.0 (6.4)
% Women	13,541 (64%)	3,700 (61%)	5,659 (52%)
GI-related utilization			
Endoscopy/UGIH series	10,321 (49%)	2,528 (42%)	4,491 (41%)
GI bleed in last 5 years	304 (1%)	50 (1%)	92 (1%)
Cardiovascular-related utilization (past 5 years)			
AMI hospitalization	1,008 (5%)	247 (4%)	476 (4%)
CHF hospitalization	873 (4%)	177 (3%)	432 (4%)
IHD hospitalization	2,224 (11%)	481 (8%)	1,026 (9%)
Stroke hospitalization	596 (3%)	150 (2%)	284 (3%)
Revascularization procedures	1,015 (5%)	232 (4%)	489 (4%)
Drug utilization (120 days post-initiation)			
Warfarin	1,181 (6%)	205 (3%)	448 (4%)
ASA	2,774 (13%)	804 (13%)	1,429 (13%)
Gastroprotective agents	5,839 (28%)	1,191 (20%)	2,421 (22%)
PPIs	2,863 (14%)	439 (7%)	749 (7%)
H2RAs	3,148 (15%)	769 (13%)	1,505 (14%)
Misoprostol/Sucralfate	179 (1%)	50 (1%)	296 (3%)

Data sources: Ontario Drug Benefit Program, Ontario Hospital Insurance Plan; Canadian Institute for Health Information; Registered Persons Database

Figure 4.5 Comorbidity prevalence of people initiated on nonsteroidal anti-inflammatory drugs (NSAIDs) in Ontario, January 1–March 31, 2002

	COX-2 Inhibitors	Arthrotec®	Nonselective NSAIDs
Sample size	12,814	3,576	7,440
Age			
Mean (SD)	75.0 (6.9)	74.6 (6.8)	73.8 (6.6)
% Women	7,970 (62%)	2,133 (60%)	3,835 (52%)
GI-related utilization			
Endoscopy/UGIH series	5,350 (42%)	1,281 (36%)	2,729 (37%)
GI Bleed in last 5 years	141 (1%)	28 (1%)	61 (1%)
Cardiovascular-related utilization (past 5 years)			
AMI hospitalization	508 (4%)	125 (4%)	282 (4%)
CHF hospitalization	416 (3%)	102 (3%)	251 (3%)
IHD hospitalization	1,132 (9%)	262 (7%)	583 (8%)
Stroke hospitalization	284 (2%)	78 (2%)	155 (2%)
Revascularization procedures	497 (4%)	117 (3%)	294 (4%)
Drug utilization (120 days post-initiation)			
Warfarin	734 (6%)	132 (4%)	327 (4%)
ASA	1,618 (13%)	436 (12%)	898 (12%)
Gastroprotective agents	3,543 (28%)	804 (22%)	1,695 (23%)
PPIs	1,877 (15%)	306 (9%)	639 (9%)
H2RAs	1,758 (14%)	484 (14%)	1,008 (14%)
Misoprostol/Sucralfate	99 (1%)	71 (2%)	151 (2%)

Data sources: Ontario Drug Benefit Program, Ontario Hospital Insurance Plan; Canadian Institute for Health Information; Registered Persons Database

Chapter 5. An Observational Time Series Analysis of the COX-2 Inhibitor Paradox: Less Bleeding is More?

Authors
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Introduction

Recent evidence suggests a lower risk of upper gastrointestinal hemorrhage for selective cyclooxygenase (COX-2) inhibitors relative to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) at the patient level,[1-3] although COX-2 inhibitors are likely not devoid of gastrointestinal toxicity. At the population level, however, the widespread proliferation of the COX-2 inhibitors might lead to an increase in the overall numbers of people exposed to these drugs with uncertain implications on population-wide gastrointestinal event rates. An ecological study was conducted to examine temporal changes in NSAID utilization and upper gastrointestinal hemorrhage hospitalization rates among a population of individuals aged 66 years and older following COX-2 inhibitor introduction.

Findings

The prevalence of NSAID use among Ontario's population aged 66 years and older individuals increased from 14.0% just before COX-2 inhibitor introduction to 19.8% by the end of the observation period (Exhibit 5.1; $p<0.01$), representing an absolute increase of > 90,000 additional individuals annually using NSAIDs, entirely attributable to the use of COX-2 inhibitors rather than switching from nonselective NSAIDs to COX-2 inhibitors. The rate of hospitalization for upper gastrointestinal hemorrhage was decreasing before the introduction of the COX-2 inhibitors, but increased from approximately 15.4 to 17.0 per 10,000 population aged 66 years and older after their introduction (Exhibit 5.1; $p<0.01$), representing an absolute increase of more than 650 upper gastrointestinal hemorrhage hospitalizations annually. Besides a small, but statistically significant, increase in the prevalence of gastroprotective agent use, no significant differences in myocardial infarction or heart failure hospitalization rates or the use of medications that might affect upper gastrointestinal risk over expected projections were observed.

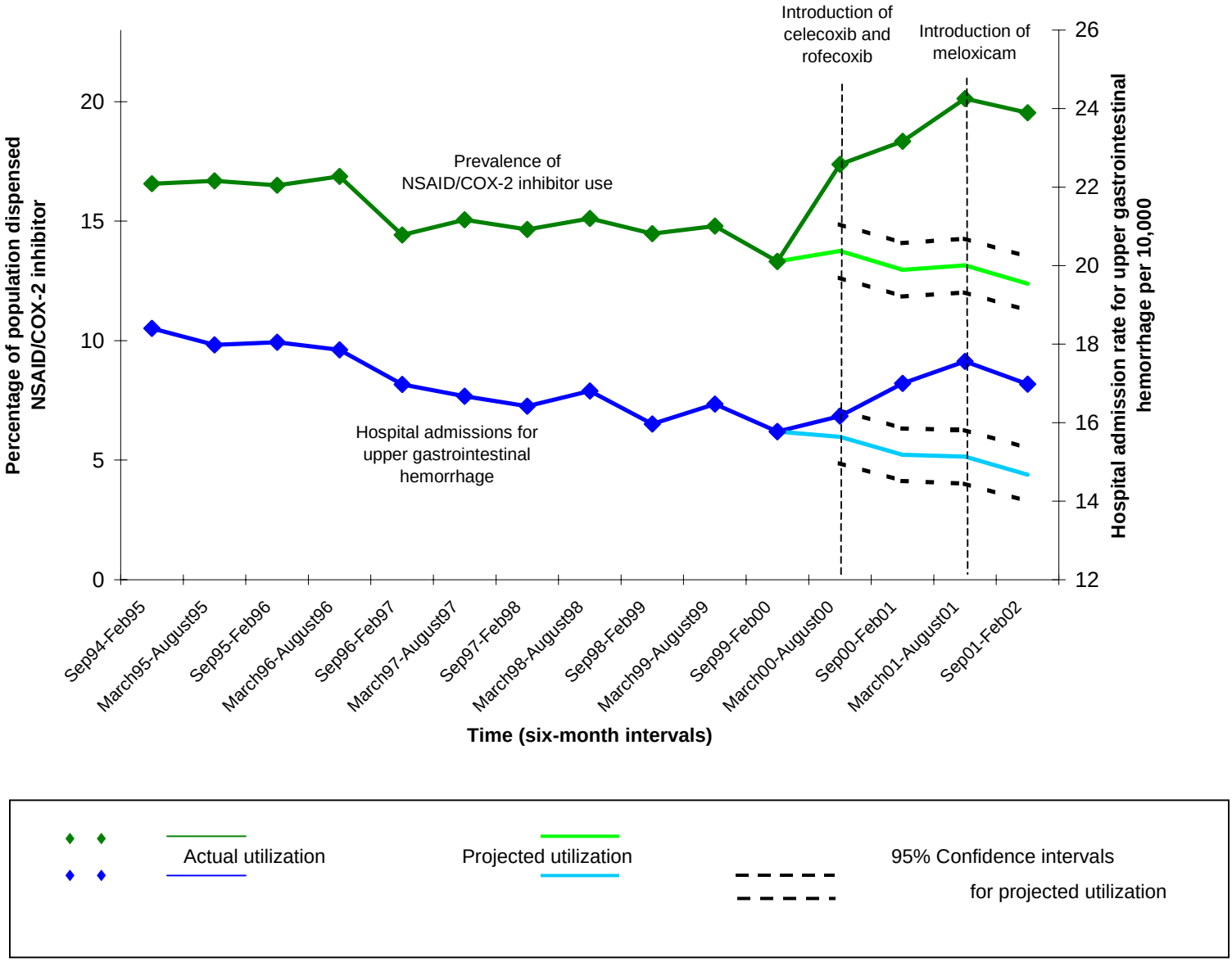
Discussion

In this population-based study, a 41% rise in NSAID use, entirely due to increased use of COX-2 inhibitors, was accompanied by a 10% increase in upper gastrointestinal hemorrhage hospitalization rates. Although the researchers could not prove causation, it is believed that the striking temporal correlation, biological plausibility, and lack of any other trends that would explain the association strongly suggest that the two events are directly related. There were no significant changes in coding practices for hospital admissions for upper gastrointestinal hemorrhage during the study period. However, researchers could not evaluate whether the potential improvement in population-level pain relief offsets the increase in hospitalizations for upper gastrointestinal hemorrhage.

The findings of this study suggest that even if a new drug is associated with lower side effects than previous drugs in its class at the patient level, a marked increase in its use can be associated with an apparently paradoxical adverse impact on the population.

Exhibits

Exhibit 5.1 Age and gender standardized prevalence of nonsteroidal anti-inflammatory drug (NSAID) utilization and hospitalization rates for upper gastrointestinal hemorrhage over time among an elderly population in Ontario, 1995–2002



Appendix 5.A How the Research was Done

A population-based cross-sectional time series analysis was conducted using administrative health care databases[4] covering over 1.3 million residents of Ontario, Canada aged ≥ 66 years. This population has universal access to hospital care, physician services, and prescription drugs. The study's timeframe was divided into fifteen intervals of six months each from September 1, 1994 to February 28, 2002. Rofecoxib and celecoxib were introduced on the provincial drug formulary in April 2000 and meloxicam was introduced in March 2001. The prevalence of nonsteroidal anti-inflammatory drug (NSAID) use in each interval was determined by dividing the unique number of individuals dispensed any NSAID (either nonselective NSAIDs or COX-2 inhibitors) by the total number of individuals alive at the beginning of the interval.

Similarly, hospitalization rates for upper gastrointestinal hemorrhage were examined. As secondary endpoints, hospitalizations for myocardial infarction and heart failure were examined. All rates were age and gender standardized. As supplementary analyses, changes in the use of gastroprotective agents, oral corticosteroids, prescription aspirin, and warfarin were also examined, as these factors may be strongly related to upper gastrointestinal hemorrhage. Time series analyses[5] involving autoregressive integrated moving average models were used to evaluate changes over time. Statistical analyses were conducting using SAS v8.2.

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