

# Incremental Cost-Effectiveness Analysis Comparing Rofecoxib with Nonselective NSAIDs in Osteoarthritis

## Ontario Ministry of Health Perspective

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### Abstract

**Background:** Clinical trials have shown rofecoxib, a selective inhibitor of cyclooxygenase-2, to be associated with fewer gastrointestinal complications than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs).

**Objective:** To evaluate the potential clinical and economic consequences of rofecoxib prescription in Ontario, Canada, for patients with osteoarthritis (OA) aged >65 years who did not respond to paracetamol (acetaminophen) therapy.

**Design:** Decision analytic modelling study.

**Methods:** A model was constructed to compare rofecoxib and nonselective NSAIDs with respect to their gastrointestinal complications in patients with OA. The model had a 1-year horizon and considered direct medical costs from the perspective of the Ontario Ministry of Health. Event rates were estimated from a pooled analysis of 8 phase IIb/III clinical trials. The number of perforations, ulcers and bleeds (PUBs) with each strategy was used as the primary measure of effectiveness.

**Results:** In the base-case scenario, the expected total cost per patient-day on nonselective NSAIDs was 1.60 Canadian dollars (\$Can) versus \$Can1.67 on rofecoxib (1999 values). Rofecoxib was associated with 0.0109 fewer PUBs per patient per year. The incremental cost to avoid 1 additional PUB by substituting rofecoxib for nonselective NSAIDs was \$Can2247. The rofecoxib strategy became dominant if a gastroprotective agent was prescribed to more than 27.5% of the patients receiving nonselective NSAIDs.

**Conclusion:** For patients with OA aged >65 years in whom paracetamol therapy has failed, rofecoxib may represent a cost-effective alternative to nonselective NSAIDs. Increased costs for drug acquisition are offset, in part, by avoidance of gastrointestinal complications and reduced use of gastroprotective agents. Rofecoxib may offer increased benefit among patients at a higher risk of serious gastrointestinal events.

The American College of Rheumatology practice guidelines<sup>[1]</sup> recommend that nonsteroidal anti-inflammatory drugs (NSAIDs) be prescribed for patients with osteoarthritis (OA) who do not experience adequate pain relief with at least 4 g/day of paracetamol (acetaminophen). However, the long term use of NSAIDs is limited by their gastrointestinal adverse effects. Common symptoms associated with NSAIDs include dyspepsia, nausea, epigastric burning, vomiting, diarrhoea and constipation.<sup>[2,3]</sup> Moreover, 2 to 4% of NSAID users per year experience a serious complication such as symptomatic ulcer disease, perforation or haemorrhage.<sup>[4]</sup> The risk of gastrointestinal complications appears to vary among individual NSAIDs<sup>[5]</sup> and with patient demographics such as age, previous gastrointestinal history, concomitant corticosteroid use, disability and cardiovascular disease.<sup>[6,7]</sup>

NSAIDs reduce prostaglandin synthesis through reversible inhibition of both isoforms of cyclooxygenase (COX). COX-1, expressed constitutively, is important in maintaining mucosal homeostasis, whereas COX-2 is the inducible isoform which is responsible for much of the systemic inflammatory response. Rofecoxib is one of a new class of NSAIDs that selectively inhibit COX-2. Rofecoxib appears to have the same anti-inflammatory, analgesic and antipyretic properties as nonselective NSAIDs, with less gastrointestinal toxicity.<sup>[8,9]</sup> Phase IIb/III clinical trials have suggested that patients who receive rofecoxib experience fewer clinically significant gastrointestinal adverse events than those who receive nonselective NSAIDs. We used decision analysis to estimate the economic and clinical implications of substituting rofecoxib for nonselective NSAIDs in Ontario, Canada, for the treatment of patients with OA over the age of 65 years who failed to respond to full-dosage paracetamol.

When this analysis was completed, no economic evaluations comparing COX-2 selective inhibitors with nonselective NSAIDs had been published. Since then, other analyses have suggested COX-2 selective inhibitors to be cost-effective alternatives to nonselective NSAIDs.<sup>[10-16]</sup>

## Methods

A decision analytic model was constructed to reflect practice in the Canadian healthcare setting. Model inputs were obtained from a combined analysis of the phase IIb/III clinical trials of rofecoxib,<sup>[17]</sup> literature review, provincial database access, and a series of expert panel meetings with rheumatologists, gastroenterologists, general practitioners and health economists. Because some elements of usual care were not captured in clinical trials, results of observational studies were used to supplement the clinical data in the analyses.

The model evaluated alternative management strategies in a hypothetical cohort of patients aged >65 years with an established diagnosis of OA who had failed to respond to treatment with full-dosage paracetamol. In the base-case scenario, the cohort was assumed to be otherwise healthy and at average risk of NSAID-related gastrointestinal complications.

Two alternative strategies were evaluated: prescription of rofecoxib and prescription of a nonselective NSAID. The average daily dosage of rofecoxib was assumed to be 24.7mg, to reflect the dosage mix used across phase IIb/III clinical trials of rofecoxib. The recommended daily dose of rofecoxib for the treatment of OA is 12.5 to 25mg.<sup>[17]</sup> Clinical data for the comparator nonselective NSAIDs were obtained from a weighted mix of ibuprofen 2400mg (54%), diclofenac 150mg (38%) and nabumetone 1500mg (8%) daily,<sup>[17]</sup> which reflected the mix of nonselective NSAIDs used as comparators in the clinical trials of rofecoxib used to inform the decision model.

A 1-year incremental cost-effectiveness analysis was performed. Direct medical costs were considered from the perspective of the Ontario Ministry of Health. Effectiveness was defined as the number of perforations, ulcers or bleeds (PUBs) averted.

### Model Structure

The decision analysis modelled the incidence, treatment and outcomes of the major and minor adverse gastrointestinal symptoms associated with

each strategy. Because high dosage nonselective NSAIDs and rofecoxib are considered to have equal analgesic and anti-inflammatory effects, the costs and consequences of treating OA were assumed to occur equally with both strategies and were not modelled. The model decision tree is depicted in figure 1. Gastrointestinal symptoms were defined as ‘minor’ if managed empirically (e.g. mild dyspepsia) or ‘major’ if investigated. Major gastrointestinal symptoms were subclassified as an ‘investigated PUB’ or a ‘confirmed PUB’, depending on whether a true event had occurred. Asymptomatic ulcers that were detected via scheduled study endoscopies (i.e. ‘silent’ or ‘subclinical’ ulcers) were not considered in the model, as they would have no resource consequences.<sup>[8,17]</sup>

Resource utilisation for each event state was profiled separately. Either inpatient or outpatient management of most major gastrointestinal symptoms was permitted. However, all perforations were assumed to require hospital admission.

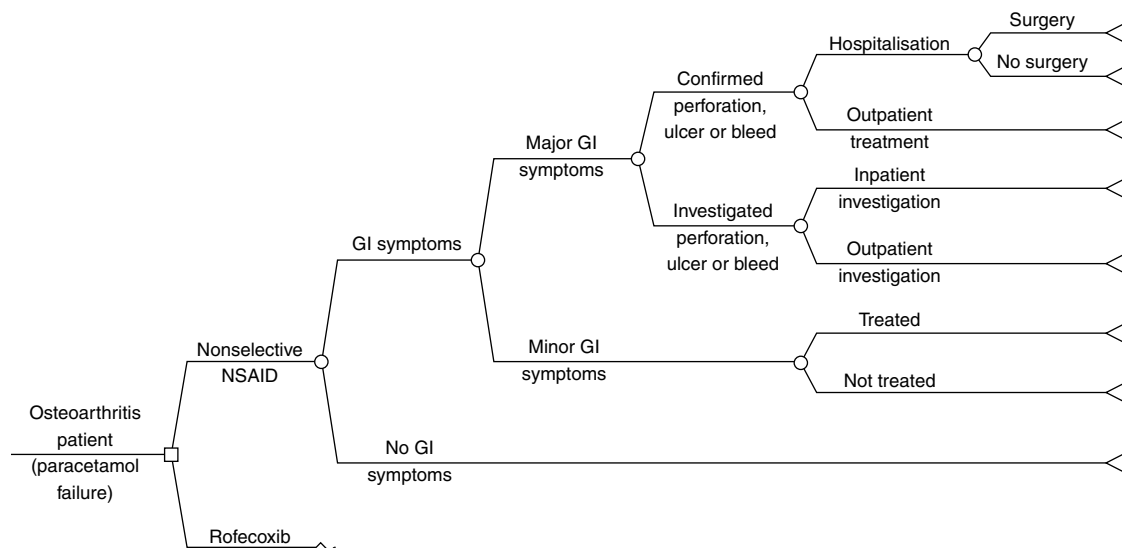
### Gastrointestinal Event Probabilities

Incidences of gastrointestinal symptoms and PUBs were obtained from a pooled analysis of 8

double-blind, randomised, controlled clinical trials including 5435 participants.<sup>[17]</sup> One-year cumulative incidence rates of gastrointestinal events as determined by Kaplan-Meier estimation in the pooled analysis of the rofecoxib clinical programme were used in the model. Two of the 8 clinical trial protocols incorporated mandated endoscopies. The pooled analysis reported only ulcers that were adjudicated as clinically meaningful PUB events, and not asymptomatic endoscopically detected ulcers. The probability of healthcare contact for minor gastrointestinal problems was based on the rate of gastrointestinal comedications observed in the clinical trials. The gastrointestinal event probabilities used in the model are summarised in table I.

### Use of Gastroprotective Agents

Published reviews of claims databases suggest that 18 to 28% of nonselective NSAIDs are prescribed with a gastroprotective agent (GPA).<sup>[6,18-22]</sup> The mid-point of the literature-based estimates of GPA use of 23% was used in the base case. The effects of this assumption were tested in the sensitivity analysis.



**Fig. 1.** Decision tree for patients with osteoarthritis not responding to paracetamol (acetaminophen). GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

**Table I.** Gastrointestinal (GI) event probabilities by comparator<sup>[16]</sup>

GI event	Rofecoxib	Nonselective NSAID
NSAID-related GI adverse event	0.299	0.295
PUB, given GI adverse event	0.050	0.091
Investigated PUB, given GI adverse event	0.028	0.072
Treatment, given minor GI adverse event	0.241	0.370
Cumulative annual incidence of PUB	0.0149	0.0268

**NSAID** = nonsteroidal anti-inflammatory drug; **PUB** = perforations, ulcers and bleeds.

Although there is little clinical rationale to coprescribe a GPA with rofecoxib, the model recognised that a low rate of GPA cotherapy would probably persist in real-world practice. In the base case, the rate of coprescription was assumed to be 10% of the rate with nonselective NSAIDs (i.e. the rate of GPA prescription was reduced by 90% relative to nonselective NSAIDs). The effects of this assumption were tested in the sensitivity analysis.

Ontario public drug claims data for 1998 were analysed to determine the type of GPAs used by NSAID patients in Ontario.<sup>[23]</sup> Drug mix data from 1998 were used to calculate GPA costs for Ontario, because omeprazole was restricted in Ontario in the first 6 months of 1999. This restriction was lifted as of 15 September 1999 for NSAID-induced ulcers. An average daily cost of a GPA was calculated for the model based on the GPA mix found in the Ontario market analysis. Prophylactic medications can be divided into 4 primary classes: H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs), surface-active antiulcer drugs, prostaglandin analogues and proton pump inhibitors (PPIs). In 1998, the GPA mix in Ontario consisted of 57.2% H<sub>2</sub>RAs, 22.4% prostaglandin analogues, 17.6% PPIs and 2.8% surface-active antiulcer drugs. In the base case, both the prostaglandin analogue and PPI were assumed to reduce the risk of PUB by 40%.<sup>[20,24]</sup> In the absence of published evidence, and on the recommendation of the expert panel, both standard dose H<sub>2</sub>RA and sucralfate were assumed to confer no benefit. The effects of both of these assumptions were tested in the sensitivity analysis. As GPA coprescription

rates were varied in the sensitivity analysis, this relative risk reduction was applied to the population receiving a GPA. Thus, PUB rates varied proportionately with the rate of GPA coprescription.

#### Resource Utilisation and Costs

All costs are reported in 1999 Canadian dollars (\$Can). Unit costs from years other than 1999 were converted to 1999 dollars using the health and personal care component of the Consumer Price Index.<sup>[25]</sup> Costs were not discounted, as the time horizon of the study was 1 year. The direct medical unit cost inputs used in the model are summarised in table II. Because the model was analysed from the perspective of the provincial Ministry of Health, direct nonmedical and indirect costs were not addressed.

The number, size and costs of nonselective NSAID and GPA prescriptions in Ontario for 1999 were used to inform the NSAID and GPA drug cost components of the model.<sup>[23]</sup>

On the basis of these data, it was determined that, for Ontario, the average daily GPA cost for patients over the age of 65 years taking these drugs was \$Can1.57 per day. A dispensing fee of \$Can6.47 was assumed for each prescription, minus a \$Can2.00 copayment. After the dispensing fees and copayment have been taken into account, the average daily cost to the Ontario government increases to \$Can1.67 (table II).

Similarly, it was determined that the average daily cost of nonselective NSAIDs for patients over the age of 65 years is \$Can0.86 per day. After the dispensing fees and copayment have been taken into account, the average daily cost to the Ontario government increases to \$Can1.00 (table II).

All other prescription drugs were priced according to the Ontario Drug Benefit Formulary,<sup>[29]</sup> using the best available price.

The costs for inpatient medical and surgical management of a PUB were obtained through the Ontario Case Costing Project (OCCP)<sup>[26]</sup> from indexed admissions with one of the following International Classification of Diseases, 9th Edition (ICD-9) codes as the primary discharge diagno-

**Table II.** Costs of medical resources in Ontario, Canada

Component	Estimate (1999 \$Can)	Source
<b>Daily medication costs covered by the provincial government<sup>a</sup></b>		
Nonselective NSAIDs (per day) [see text for description]	1.00	Ontario Public Claims Data, 1999 <sup>[23]</sup>
Rofecoxib (per day) [see text for description]	1.51	Merck Frosst Canada Ltd
Prophylactic GPA (per day) [see text for description]	1.67	Ontario Public Claims Data, 1999 <sup>[23]</sup>
Omeprazole (per day) [average of all dosages used in Ontario]	2.88	Ontario Public Claims Data, 1999 <sup>[23]</sup>
PPIs/H <sub>2</sub> RAs (per day) [average of all PPIs and H <sub>2</sub> RAs used in Ontario]	1.03	Ontario Public Claims Data, 1999 <sup>[23]</sup>
<b>Costs for patients treated in hospital</b>		
Cost of surgical PUB inpatient treatment	8808.60	OCCP <sup>[26]</sup> b
Cost of medical PUB inpatient treatment	2670.44	OCCP <sup>[26]</sup> b
Physician fees: surgical PUB patient	240.03	Profile <sup>c</sup> + Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Physician fees: medical PUB patient	198.35	Profile <sup>d</sup> + Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
<b>Costs for patients treated as outpatients</b>		
Outpatient clinic visit	18.00	Hamilton Health Sciences Corporation, Chedoke McMaster Hospitals, 1995/96
Complete blood count	5.71	Ontario Schedule of Benefits, 1992 <sup>[28]</sup>
Crossmatch (2 units)	10.34	Ontario Schedule of Benefits, 1992 <sup>[28]</sup>
Routine chemistry	54.29	Ontario Schedule of Benefits, 1992 <sup>[28]</sup>
Radiology (2 views of the abdomen)	30.44	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Day surgery	606.88	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Endoscope with biopsy	128.86	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Repeat endoscopy	106.56	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Clinic physician (consult)	69.30	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Gastroenterologist (consult)	105.40	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>
Pathologist ( <i>Helicobacter pylori</i> testing)	18.20	Ontario Schedule of Benefits, 1998 <sup>[27]</sup>

a Dispensing fees, mark-up and patient copayments have been incorporated into these calculations.

b ICD-9 codes used for OCCP access: perforations – 531.[1,5], 532.[1,5], 533.[1,5], 534.[1,5]; ulcers – 531.[3,7], 532.[3,7], 533.[3,7], 534.[3,7]; bleeds – 531.[0,2,4,6], 532.[0,2,4,6], 533.[0,2,4,6], 534.[0,2,4,6], 578.

c Physician treatment for surgically treated inpatients includes: gastroenterologist, 1 consultation + 1 visit; primary care physician, 1 visit; general surgeon, 1 consultation + 1 visit.

d Physician treatment for medically treated inpatients includes: gastroenterologist, 1 consultation + 1 visit; primary care physician, 1 visit; general surgeon, 1 consultation.

**GPA** = gastroprotective agent; **H<sub>2</sub>RA** = H<sub>2</sub> receptor antagonist; **ICD-9** = International Classification of Diseases, 9th Edition; **NSAID** = nonsteroidal anti-inflammatory drug; **OCCP** = Ontario Case Costing Project; **PPI** = proton pump inhibitor; **PUB** = perforations, ulcers and bleeds; **\$Can** = Canadian dollars.

sis: 531.[1,5], 532.[1,5], 533.[1,5], 534.[1,5], 531.[3,7], 532.[3,7], 533.[3,7], 534.[3,7], 531.[0,2,4,6], 532.[0,2,4,6], 533.[0,2,4,6], 534.[0,2,4,6], 578. The OCCP is a joint initiative of the Ontario Ministry of Health and the Ontario Hospital Association, which generates direct medical costs for inpatient care at a network of academic and community hospitals in Ontario. Costs are indexed by individual patient encounters and fully allocated to include ward care, pharmacy costs, overhead and the capital depreciation of equipment and infrastructure. Physician fees for

inpatient care are not tabulated by OCCP and were obtained from the Ontario Ministry of Health Schedule of Benefits.<sup>[27]</sup>

Standard profiles of resource utilisation for outpatient investigation and/or treatment of minor and major gastrointestinal symptoms were developed in consultation with the Ontario expert panel.

#### Sensitivity Analyses

One-way and 2-way sensitivity analyses were performed to assess the stability of the model con-

clusions to changes in key assumptions about: (i) the rate of GPA coprescription in both strategies; (ii) the relative baseline risk of PUB in the study population; (iii) drug costs; and (iv) the effectiveness of GPAs in preventing complications.

## Results

### Base-Case Scenario

The costs and outcomes of each strategy are summarised in table III. The average annual direct medical cost per patient was \$Can584.91 in the nonselective NSAID strategy versus \$Can609.36 in the rofecoxib strategy. Thus, the incremental cost of substituting rofecoxib for nonselective NSAIDs was \$Can24.45 per patient per year, or approximately \$Can0.07 per day.

The results of the incremental cost-effectiveness analysis are also summarised in table III. If rofecoxib replaced nonselective NSAIDs for management of OA in the study cohort, the incremental cost to avoid 1 additional PUB per year would be \$Can2246.56 (\$Can24.45/0.0109).

### Sensitivity Analyses

The results of the sensitivity analyses are summarised in table IV. In the first such analysis, the rate of prophylactic GPA prescription with nonselective NSAIDs was varied from 0 to 100% (base-case estimate 23%). A threshold rate of 27.5% was identified, above which the rofecoxib arm became dominant (i.e. less costly and more effective). This threshold fell within the range of coprescription rates identified from the literature.<sup>[6,18-22]</sup>

In the second sensitivity analysis, the relative rate of GPA prescription with rofecoxib was varied between 0 and 100% of the rate with nonselective

NSAIDs (base-case estimate 10%). Over this range, the incremental cost per PUB averted with rofecoxib varied from \$Can999 to \$Can12 937 (table IV). The effect of simultaneous variation in the rates of GPA prescription and GPA-associated relative risk reduction with nonselective NSAIDs and rofecoxib is shown in figure 2. This 2-way sensitivity analysis demonstrates that if no GPAs were prescribed with rofecoxib (i.e. 100% reduction), that strategy became less costly (and dominant) when the rate of GPA prescription with nonselective NSAIDs exceeded a threshold of 25%. If the rate of GPA prescription with rofecoxib equalled that with nonselective NSAIDs (i.e. 0% reduction), the rofecoxib strategy remained more costly than the nonselective NSAID strategy by \$Can144 per patient per year.

A third series of sensitivity analyses (table IV) examined the potential cost-effectiveness of rofecoxib substitution in populations with higher baseline risk of a PUB. To simulate variation in baseline risk, the baseline relative risk of a PUB was altered from half baseline risk to 4 times baseline risk to reflect some of the variability within published estimates.<sup>[30]</sup> An increase in PUB risk of 215% was found to be the threshold for cost savings. As high risk patients are more likely to receive a GPA than those at average or low risk, a 2-way sensitivity analysis was also conducted by simultaneously varying the baseline risk of PUB and the rate of GPA coprescription over plausible ranges. When the baseline risk was increased 3-fold and the GPA coprescription rate with nonselective NSAIDs increased to 28%, rofecoxib treatment was less expensive by \$Can43.66 per patient per year, while averting 0.032 PUBs per patient per year.

The fourth series of sensitivity analyses assessed the influence of the costs of GPAs and non-

**Table III.** Incremental cost-effectiveness analysis: base-case scenario

Treatment	Annual cost per patient (\$Can)	Incremental cost per patient per year (\$Can)	No. of PUB per patient per year	Increment in PUB averted per patient per year	Incremental cost-effectiveness ratio (\$Can/PUB averted)
NSAID	584.91		0.0258		
Rofecoxib	609.36	24.45	0.0149	0.0109	2246.56

**NSAID** = nonsteroidal anti-inflammatory drug; **PUB** = perforations, ulcers and bleeds; **\$Can** = Canadian dollars.

**Table IV.** Sensitivity analyses

Variable	Variable estimates		Results per patient		
	sensitivity estimate	base-case estimate	incremental annual costs (\$Can) <sup>a</sup>	annual PUBs averted with rofecoxib	incremental cost-effectiveness ratio (\$Can per PUB averted)
<b>Rate of prophylactic GPA prescribing with nonselective NSAIDs</b>					
Low estimate	0%	23%	144.45	0.0118	12 226.93
High estimate	100%	23%	-380.20	0.0078	Dominant <sup>b</sup>
Threshold value	27.5%	23%	0	0.0107	0
<b>Relative rate of GPA prescribing with rofecoxib compared with nonselective NSAIDs</b>					
Low estimate	0%	10%	10.82	0.0108	998.76
High estimate	100%	10%	147.22	0.0114	12 936.59
<b>Relative rate of GPA prescribing: 2-way sensitivity analyses</b>					
With GPA rate reduction (refer to fig. 2)					
<b>Relative risk of PUB in study population (ratio to baseline)</b>					
Low estimate	0.5	1	35.15	0.0054	6 458.04
Moderate estimate	2	1	3.03	0.0218	139.27
High estimate	3	1	-18.44	0.0327	Dominant
High to very high estimate	4	1	-39.95	0.0435	Dominant
<b>Risk of a PUB: 2-way sensitivity analyses</b>					
High risk population			-43.66	0.0320	Dominant
rate of prophylactic GPA prescribing with NSAID	28%	23%			
relative risk of a PUB	3	1			
<b>Average daily cost of GPA (weighted average)</b>					
Low estimate	\$Can0.72	\$Can1.51	86.52	0.0109	7 948.37
High estimate	\$Can2.11	\$Can1.51	-14.98	0.0109	Dominant
<b>Average daily cost of nonselective NSAIDs (weighted average)</b>					
Low estimate	\$Can0.49	\$Can0.86	155.58	0.0109	14 292.46
High estimate	\$Can1.24	\$Can0.86	-110.21	0.0109	Dominant
<b>Risk reduction in PUB rate with H<sub>2</sub>RA as GPA</b>					
	40%	0%	27.10	0.0096	2 835.18

a Rofecoxib costs – nonselective NSAID costs.

b Less costly, more effective.

**GPA** = gastroprotective agent; **H<sub>2</sub>RA** = H<sub>2</sub> receptor antagonist; **NSAID** = nonsteroidal anti-inflammatory drug; **PUB** = perforations, ulcers and bleeds; **\$Can** = Canadian dollars.

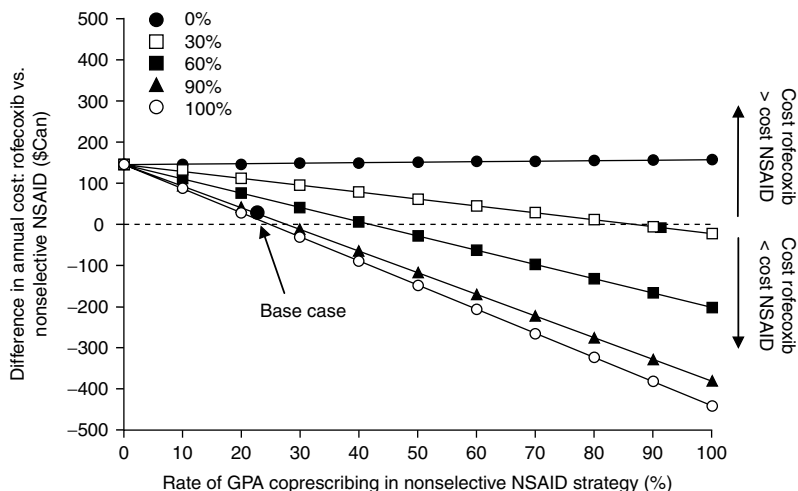
selective NSAIDs, which vary among Canadian provinces because of differences in the base drug costs, dispensing fees and copayment plans. For example, the average daily cost to the Ontario Ministry of Health for the GPA mix assumed in the model was \$Can1.51 per patient per day, versus \$Can0.72 in New Brunswick and \$Can2.11 in Alberta.<sup>[15]</sup> The results presented in table IV indicate that the model is sensitive to alterations in drug prices. High drug prices lead to dominance of the

rofecoxib strategy, whereas low drug prices increase the incremental cost-effectiveness ratio to as high as \$Can14 292 per PUB averted.

Further sensitivity analyses demonstrated that the model was robust to variation in the effectiveness of H<sub>2</sub>RAs as a prophylactic GPA (table IV).

## Discussion

This decision model demonstrates that substituting rofecoxib for nonselective NSAIDs for



**Fig. 2.** Expected annual cost difference [1999 Canadian dollars (\$Can)] between rofecoxib and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), by coprescribing rate of prophylactic gastroprotective agents (GPAs). The lines correspond to different percentage reductions in the rate of GPA coprescribing with the rofecoxib strategy.

the treatment of OA would increase direct medical costs to the Ontario Ministry of Health by \$Can24.45 per patient per year, but reduce the annual risk of a serious gastrointestinal complication (PUB) from 2.6% to 1.5%. The incremental cost to avoid 1 additional PUB would be \$Can2247 given the base-case assumptions. The higher acquisition cost for rofecoxib is partly offset by the cost savings from reduced GPA coprescription, physician visits, tests and hospitalisations.

The results of this model reflect, in part, differences in gastrointestinal toxicity between rofecoxib and nonselective NSAIDs. The nonselective NSAID comparator chosen for the model was a weighted mixture of ibuprofen, diclofenac and nabumetone, with event rates derived empirically from clinical trials. As these nonselective NSAIDs are reported to have relatively low gastrointestinal toxicity,<sup>[31]</sup> this assumption can be considered conservative, and the model may have underestimated any advantage of rofecoxib substitution. The magnitude of the gastroprotective benefit of rofecoxib might be diminished if patients take aspirin (acetylsalicylic acid) concurrently for cardiovascular prophylaxis. This has been observed with the

COX-2-specific inhibitor celecoxib,<sup>[32]</sup> but has not been reported for rofecoxib, as aspirin cotherapy has been prohibited in safety and outcomes studies.

Sensitivity analyses demonstrate that the outcomes of this model are sensitive to the baseline PUB risk of the population, the costs of GPAs and nonselective NSAIDs, and the rates of GPA coprescription in both strategies. The rofecoxib strategy was dominant for patients whose risk of PUB was at least 2.15 times the base-case value. Also of note, the rofecoxib strategy was dominant when the rate of GPA coprescription with nonselective NSAIDs exceeded 27.5%, a value which falls well within the range reported in the literature.<sup>[18-22]</sup>

Variation in the rate of attributable GPA coprescription with rofecoxib caused a shift in the conclusions from the model, ranging from dominance to an incremental cost of \$Can12 227 per PUB averted. In addition, variation in the costs of nonselective NSAIDs and GPAs caused a shift ranging from dominance to an incremental cost of \$Can14 292 per PUB averted. Thus, postmarketing surveillance of GPA use with rofecoxib and of prescription drug costs will be important, in order to

validate the assumptions and conclusions of this model.

Because this analysis was conducted from the perspective of the Ontario Ministry of Health, indirect costs were not considered. However, OA is associated with a high rate of pain, disability and indirect costs. Although this model assumed no difference in efficacy, as demonstrated in the clinical studies,<sup>[8,9]</sup> it has been hypothesised that rofecoxib may prove more effective than nonselective NSAIDs in clinical practice because of improved practice compliance and tolerance of higher drug dosages.<sup>[33]</sup> In principle, this could reduce disability and enhance productivity, and increase the benefit of rofecoxib substitution. However, data do not exist to inform estimates of the cost effectiveness of rofecoxib substitution in settings of occasional NSAID use or to quantify the benefit of improved compliance. Differences in dosages, compliance and related benefits remain highly speculative, and further prospective studies of these outcomes are required.

Most of the previous economic models of nonselective NSAID use have concentrated on assessing the cost effectiveness of misoprostol as a GPA.<sup>[34-40]</sup> However, the majority of these analyses have inferred differences in clinical event rates from observed differences in endoscopic ulceration. A strength of this model was its use of clinical event rates derived empirically from the pooled results of 8 randomised, controlled trials. In each of these trials, clinical complications were reported through unscheduled investigation and adjudicated by an independent blinded case-review committee. Endoscopic lesions detected at scheduled endoscopies were not considered as clinical events; thus, these data did not require correction for 'silent ulceration'.

This analysis focused on the cost effectiveness of substituting rofecoxib for nonselective NSAIDs in patients who are current NSAID users. It does not address the overall economic impact of introducing rofecoxib to the marketplace. Policy-makers are still faced with the unresolved question of whether rofecoxib will be prescribed to people

who would not otherwise have received a nonselective NSAID, thereby expanding the total number of NSAID users. Again, postmarketing data will be important to identify changes in the overall pool of NSAID users.

## Conclusion

Nonselective NSAIDs are a standard and effective therapy for OA pain that does not respond to lifestyle measures or standard dosages of paracetamol. The development and licensing of COX-2-specific inhibitors has focused renewed attention on the role of conventional, nonselective NSAIDs in the management of chronic disorders such as OA. This model demonstrates that the replacement of nonselective NSAIDs with rofecoxib for treatment of OA would reduce the incidence of serious gastrointestinal adverse events at a modest incremental cost to a Canadian provincial government for each additional event averted. Despite higher acquisition costs, the improved safety profile of rofecoxib may make it a cost-effective alternative to nonselective NSAIDs for the long term treatment of patients with OA who have not responded to paracetamol therapy. Rofecoxib may be cost saving and dominant over nonselective NSAIDs among patients at increased baseline risk of a serious gastrointestinal event.

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