Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 49, No. 3, June 15, 2003, pp 283–292
DOI 10.1002/art.11121

ORIGINAL ARTICLE

The Cost Effectiveness of Rofecoxib and Celecoxib in Patients With Osteoarthritis or Rheumatoid Arthritis

ANDREAS MAETZEL,[1] MURRAY KRAHN,[1] AND GARY NAGLIE[2]

Objective. **To evaluate the cost effectiveness of the cyclooxygenase 2 (COX-2) selective nonsteroidal antiinflammatory drug (NSAID) rofecoxib compared with naproxen and the COX-2 NSAID celecoxib compared with ibuprofen and diclofenac.**

Methods. **Cost-effectiveness analysis based on a 5-year Markov model. Probability estimates were derived from detailed data of 2 randomized trials and a systematic search of the medical literature. Utility estimates were obtained from 60 randomly selected members of the general public. Cost estimates were obtained from Canadian provincial databases. Incremental cost-effectiveness ratios were calculated for patients at average risk of upper gastrointestinal (UGI) events and for high-risk patients with a prior history of a UGI event. Subjects were patients with osteoarthritis or rheumatoid arthritis (RA) where a decision has been made to treat with NSAIDs but who do not require low-dose aspirin. Main outcome measures were proportion of patients with clinical or complicated UGI events, quality-adjusted life expectancy, and life expectancy.**

Results. **Evaluation of rofecoxib versus naproxen in patients with RA at average risk resulted in costs per quality-adjusted life year (QALY) gained of $Can271,188. Celecoxib was dominated by diclofenac in average-risk patients. Both rofecoxib and celecoxib are cost-effective in high-risk patients. Analyses by age groups and assuming a threshold of Can$50,000 per QALY gained, suggest that rofecoxib or celecoxib would be cost-effective in patients aged over 76 and 81, respectively, without additional risk factors.**

Conclusion. **Both rofecoxib and celecoxib are economically attractive in high risk and elderly patients. They are not economically attractive in patients at average risk. Coprescription of proton-pump inhibitors with COX-2 NSAIDs is not economically attractive for patients at high risk.**

KEY WORDS. Cost effectiveness; Cyclooxygenase 2 inhibitors; Nonsteroidal antiinflammatory drugs.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely prescribed to patients with conditions as diverse as dysmenorrhoea, acute pain episodes, lower back pain, rheumatoid arthritis (RA), and osteoarthritis (OA). Individuals with inflammatory musculoskeletal conditions often need NSAIDs because of the limited activity of non-NSAID analgesics (e.g., acetaminophen) and the unacceptable side effect profiles of corticosteroids. NSAIDs are usually prescribed on a long-term basis for patients with RA, and are recommended in therapeutic guidelines as an option for individuals with OA (1,2).

NSAIDs are generally prescribed with some hesitation, due to the possibility of rare but serious upper gastrointestinal (UGI) events (3). Endoscopic studies have demonstrated the presence of gastric and duodenal ulcers in approximately 21% of users of standard NSAIDs (4). Many such ulcers are subclinical and only 15% of them precipitate a clinical (symptomatic) UGI event (5); however, approximately half of that 15% show signs of active bleeding and are, therefore, defined as complicated. NSAID users are at almost 4 times greater risk than nonusers of developing a clinical UGI event (6).

Two recently approved NSAIDs, rofecoxib and celecoxib, are believed to interact with only 1 of the 2 isoforms of the cyclooxygenase (COX) enzyme (7,8). Inhibition of

Supported by the Canadian Coordinating Office for Health Technology Assessment. Dr. Maetzel's work was supported by a PhD fellowship from the Canadian Institutes of Health Research. Dr. Krahn was the recipient of an investigator award from the Canadian Institutes of Health Research. Dr. Naglie is the Chairman of the Drug Quality and Therapeutics Committee of the Ontario Ministry of Health and Long-Term Care.

[1]Andreas Maetzel, MD, MSc, PhD, Murray Krahn, MD, MSc: University Health Network and University of Toronto, Toronto, Ontario, Canada; [2]Gary Naglie, MD: University Health Network, University of Toronto, and Toronto Rehabilitation Institute, Toronto, Ontario, Canada.

Address correspondence to Andreas Maetzel, MD, MSc, PhD, Division of Clinical Decision Making, University Health Network, Toronto, Ontario, M5G 2C4, Canada. E-mail: maetzel@uhnres.utoronto.ca.

Submitted for publication March 20, 2002; accepted in revised form June 25, 2002.

COX-1 is associated with UGI events and inhibition of platelet aggregation. Inhibition of COX-2 has beneficial analgesic and antiinflammatory effects but might also lead to an increase in cardiovascular thrombotic events by inhibiting prostacyclin, an inhibitor of platelet aggregation. Rofecoxib and celecoxib have been demonstrated to have similar analgesic activity to standard NSAIDs (9,10), while being somewhat less likely to precipitate a UGI event (11–13). However, the reduction in UGI events is not seen in comparison to all standard NSAIDs, and is questionable in patients given low-dose aspirin (12).

The high acquisition cost of COX-2 NSAIDs has led to concern among insurers and payers about their cost effectiveness compared with standard NSAIDs. The objective of the present study is to assess the clinical benefits, costs, and cost effectiveness of the COX-2 NSAIDs rofecoxib and celecoxib compared with the standard NSAIDs naproxen, ibuprofen, and diclofenac in patients with OA or RA (in whom a decision has been made to treat with NSAIDs and who do not require low-dose aspirin). The analysis was funded by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and followed the Canadian Guidelines for Economic Evaluation of Pharmaceuticals (14). A more detailed report of this evaluation can be obtained directly through the CCOHTA website at http://www.ccohta.ca.

METHODS

Strategies. Prescribing strategies for standard and COX-2 NSAIDs were compared in patients similar to those in the 2 randomized trials of COX-2 NSAIDs: RA and OA patients with an average age of 58 years who do not require aspirin therapy for cardiovascular disease (12,13). Our primary estimates of efficacy and side effects were also drawn from these 2 trials, the Celecoxib Long-Term Arthritis Safety Study (CLASS) (12), and the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (13). Detailed data describing these trials can be obtained at http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Arthritis.

In VIGOR, rofecoxib (50 mg once per day; 2 times the maximum recommended dose) was compared with naproxen (500 mg twice per day) in 8,076 patients (100% with RA, none receiving low-dose aspirin, 80% female, 56% taking corticosteroids) over a period of 12 months (13,15). In CLASS, celecoxib (400 mg twice per day; 2–4 times the maximum recommended dose) was compared with diclofenac (75 mg twice per day) or ibuprofen (800 mg three times per day) in 7,982 patients (28% with RA, 72% with OA, 22% receiving aspirin, average age 60 years, 70% female, 30% taking corticosteroids) over a period of 12 months (16). We also performed separate analyses for a high-risk scenario where it was assumed that all patients have a positive history of a clinical UGI event. High-risk patients in the standard NSAID strategy were given a proton pump inhibitor (PPI) and patients in the COX-2 strategy were evaluated with and without PPIs.

Model structure. A Markov model (17) was developed in which each 3-month Markov cycle was a period during which a patient might experience gastrointestinal (GI) or cardiovascular events (Figure 1). GI events were classified as follows: dyspeptic symptoms (symptoms severe enough to require a medical consultation, with or without prescription of antacids); clinical UGI events (symptomatic ulcers); and complicated UGI events (symptomatic ulcers with bleeding). Some complicated UGI events may require hospitalization or even surgery, whereas others can be managed on an outpatient basis. Recurrent bleeding was modeled in a separate cycle, because patients who bleed are at higher risk of recurrent GI bleeding, the management of which is identical to that of first bleeds. A small fraction of patients with a bleed but no recurrence was modeled to receive NSAIDs with coprescription of PPI. The remaining patients and all those who experienced a second bleed were switched to non-NSAID analgesics. Exact rates of myocardial infarctions (MIs) observed under treatment with COX-2 NSAIDs in the CLASS and VIGOR study were modeled as well as the respective increase in mortality post MI. At each cycle, patients are subject to age-specific mortality.

Once started on a treatment, the events experienced by a patient determined the Markov state she moves to subsequently. Patients who started out as average-risk individuals and did not experience a clinical UGI event in any 1 cycle remained average risk in the next. Patients who experienced a symptomatic ulcer, i.e., a clinical but not complicated UGI event, were considered high risk from then on and received PPIs while on NSAIDs, whereas those with a complicated UGI event entered the "post-bleed" state and were taken off NSAIDs (except for the few that continue NSAIDs because of their particular clinical circumstances). Patients who experienced an MI were modeled to continue their respective NSAID with coprescription of low-dose aspirin.

Clinical data. Key estimates of event rates and the relative effectiveness of COX-2 NSAIDs in reducing these were derived from VIGOR and CLASS documents submitted to the Food and Drug Administration Arthritis Advisory Panel (Table 1) (15,16). Remaining probability estimates were obtained through a comprehensive literature search of Medline, supplemented by bibliographies of relevant articles (Table 2). Estimates were selected from studies that included patients with arthritis (OA or RA) who receive long-term NSAIDs. The study providing evidence for this target population in a North American setting was used to support the baseline estimate. Confidence intervals (95%) or estimates from other studies were used to support the lower and upper plausible range for each variable for the purposes of sensitivity analysis.

A survey of long-term NSAID patients recruited from the registries of 8 rural practices in the UK was available to provide a probability of dyspepsia requiring medical consultation (18). There are also very few data on the use of antacids among NSAID users (16,19). In VIGOR, 584 (14.5%) of 4,029 patients randomized to the naproxen group used antacids (PPIs and misoprostol were not permitted). Both rofecoxib and celecoxib were credited with a 22.8% reduction in the use of antacids, based on evidence from the VIGOR study. PPIs are preferably used in the

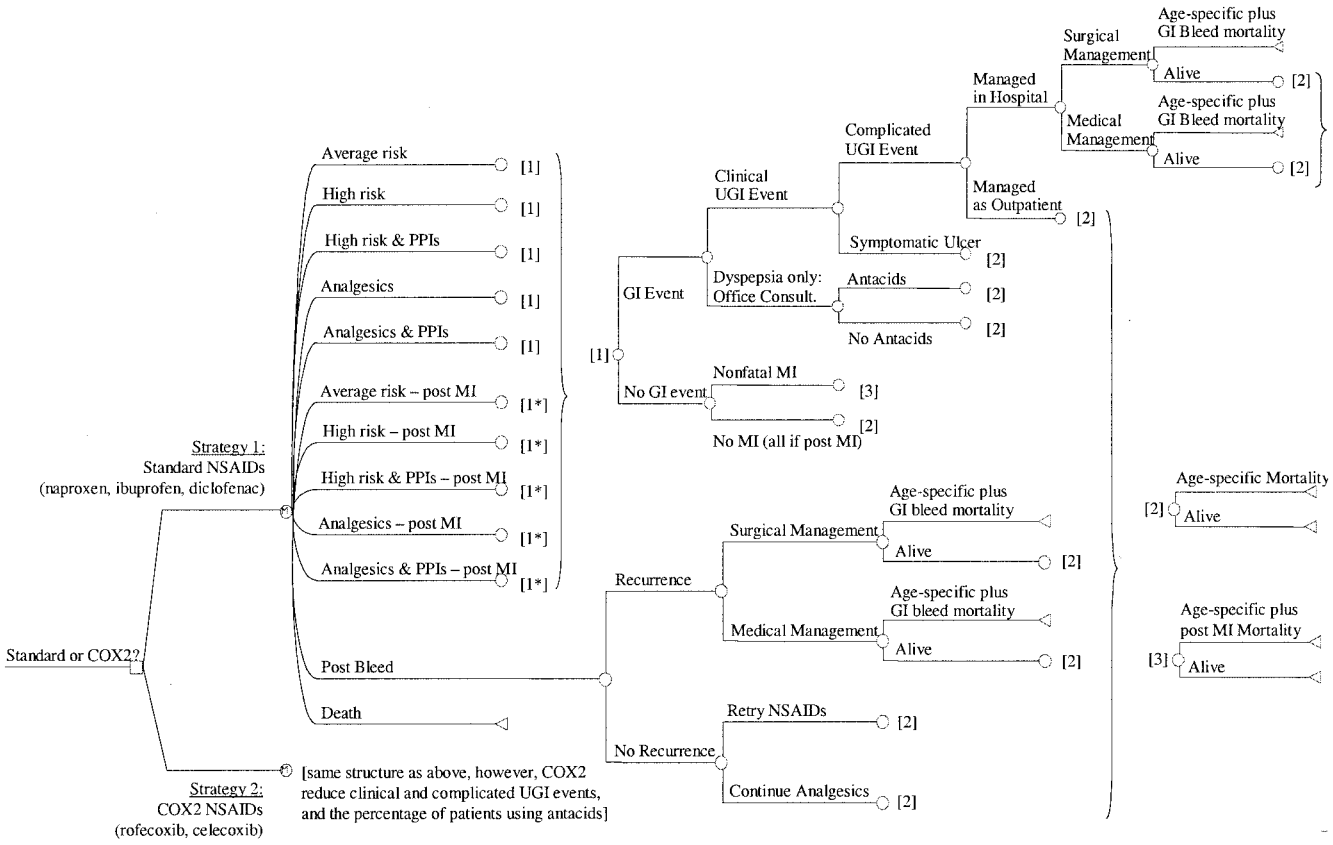

Figure 1. Decision tree used for the cost-effectiveness and cost-utility evaluation. Two strategies are modeled (see text for explanation of flow of events). Subtrees 1 and 2 are repetitive, and are only represented once. GI = gastrointestinal; UGI = upper gastrointestinal; PPI = proton pump inhibitors; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug; COX2 = cyclooxygenase 2. *Represents patients in post-MI states who will go through subtree 1 without further MIs.

prevention and treatment of NSAID-induced GI events. Therefore, the relative effectiveness of PPIs in preventing UGI events was modeled based on the evidence available for misoprostol, the closest comparator, which was shown to reduce UGI events by 40.0% (5). If the comparative efficacy of PPIs in treating clinical UGI events is indicative of its potential to prevent clinical UGI events, then this value may underestimate the actual benefit of PPIs (20).

A history of a clinical UGI event has been estimated to increase risk of future UGI events by up to 5.9 times (6).

Table 1. Incidences (per 100 patient-years) for clinical and complicated UGI events and for myocardial infarctions*

	VIGOR		CLASS		
	Rofecoxib	**Naproxen**	**Celecoxib**	**Diclofenac**	**Ibuprofen**
Total patient years	2,697	2,694	1,804	841	874
Clinical UGI events					
Number	56	121	22	10	29
Events per 100 patient-years	2.08	4.49	1.16	1.19	3.20
RRR COX-2 versus regular NSAID, %		53.7†		2.5	63.8†
Complicated UGI events					
Number	16	37	9	4	11
Events per 100 patient-years	0.59	1.37	0.44	0.48	1.14
RRR COX-2 versus regular NSAID, %		56.9†		8.3	61.4†
MI					
Number	20	4	6	2	2
Events per 100 patient-years	0.74	0.15	0.33	0.24	0.23
Relative risk COX-2 versus regular NSAID		4.93†		1.39	1.44

* Adverse effects as observed in patients recruited into the Vioxx Gastrointestinal Outcomes Research (VIGOR) study and the Celecoxib Long-Term Arthritis Safety Study (CLASS). CLASS study patients are limited to those not taking low-dose aspirin (15,16). UGI = upper gastrointestinal; RRR = relative risk reduction; COX-2 = cyclooxygenase 2; NSAID = nonsteroidal antiinflammatory drug; MI = myocardial infarction.
† $P < 0.05$.

Table 2. Estimates used in the decision analysis model*

Model events	Base case values (range)	Reference
Clinical data		
Dyspepsia requiring consultation, % per 3 months	10.7 (7.7–13.8)	18
RRR: clinical/complicated UGI due to PPIs, %	40.0 (37.5–42.5)	5
RRR: antacid use due to COX-2, %	22.8 (19.3–26.1)	13
Hospitalized if complicated UGI event, %	62.7 (51.1–74.3)	5,13
Surgery if hospitalized, %	8.5 (4.0–35.7)	23,25,30
Mortality in patient with first GI bleed, %	4.3 (1.9–5.13)	32,33
Recurrence of bleed, %	11.5 (10.1–12.8)	32,33
Surgery in patient with second GI bleed, %	71.1 (62.1–80.2)	27
Mortality in patient with a second GI bleed, %	38.7 (12.4–44.8)	27,32
Retrying NSAIDs after GI bleed, %	5.0 (0.0–100.0)	
RR increase due to prior UGI event	4.0 (2.9–5.7)	13
Mortality after experiencing nonfatal MI	0	35
3-month QALY values: range 0 to 0.25†		
Arthritis, no GI events	0.172 (0.159–0.185)	—
Dyspepsia	0.126 (0.108–0.145)	—
Symptomatic ulcer	0.095 (0.080–0.112)	—
Complicated UGI event, medical management	0.078 (0.062–0.096)	—
Complicated UGI event, surgical management	0.000	—
Nonfatal MI	0.000	—
Life post-MI (utility as QALY modifier)	0.97	36
Costs of managing clinical events, $Can (±25%)		
Consultation for dyspepsia	$32	–
Symptomatic ulcer, outpatient management	$471	–
Complicated UGI event, outpatient management	$502	–
Complicated UGI event, medical management	$3,327	–
Complicated UGI event, surgical management	$7,840	–
Costs of managing MI	$13,556	–
Managing patients with prior MI (per 3 months)	$485	–
Costs of drugs per day, $Can		
Ibuprofen (800 mg tid)	$0.22	–
Naproxen (500 mg bid)	$0.42	–
Diclofenac (75 mg bid)	$1.18	–
Rofecoxib (12.5 mg qd/25 mg qd/50 mg qd)	$1.25/$1.25/$2.50	–
Celecoxib (100 mg bid/200 mg bid/400 mg bid)	$1.25/$2.50/$5.00	–
Acetaminophen (1 gm qid)	$0.37	–
Cimetidine (400 mg bid)	$0.27	–
Pantoprazole (40 mg qd)	$1.90	–

* RRR = relative risk reduction; UGI = upper gastrointestinal event; PPIs = proton pump inhibitors; COX-2 = cyclooxygenase 2 inhibitors; GI = gastrointestinal; NSAIDs = nonsteroidal antiinflammatory drugs; MI = myocardial infarction; QALY = quality-adjusted life year; $Can = Canadian dollars; tid = three times per day; bid = twice per day; qd = once per day; qid = four times per day.
† QALY for 3 months in full health = 0.25.

However, in CLASS the relative risk was 2.6, after adjusting for history of NSAID intolerance, global disease status, history of cardiovascular disease, and aspirin use (15). Similarly, in VIGOR the average rate of clinical UGI events increased by less than 2 in patients with a prior history (16). We used the higher estimate from the CLASS study as our baseline estimate, because choice of the higher estimate would favor cost-effectiveness ratios in favor of COX-2 NSAIDs.

Age is an additional risk factor for UGI events, but the risks for specific age groups were not analyzed in either VIGOR or CLASS. We performed supplementary analyses in which estimates of risk for UGI events were estimated for specific age groups. These age-related risks were obtained from a recent metaanalysis in which the risk associated with specific age groups, compared with the reference group of 25–49 year olds, was summarized to be 1.8 (age 50–59 years), 2.4 (60–69 years), 4.5 (70–79 years), and 9.2 (80+ years) (6). We fitted a regression line to the log-transformed risks to determine a risk function based on age: risk = $\exp(-2.18 + 0.05 \times \text{age})$. According to this function, risk increased by ~5% per year. We used this relationship to explore the effects of age in secondary analyses only, as there are no data to substantiate a constant relative risk reduction of COX-2 NSAIDs across different age groups.

Although many other risk factors are reported to play a role in increasing the risk of UGI events (21) only history of a clinical UGI event, age, and aspirin use were found to be significant in multivariable comparison of the CLASS study patients (16). Other studies found male sex, global disease status, and prednisone use to be significant risk

factors, although this relative risk never exceeded a factor of 2 (6,21).

Data on the percentage of patients with a complicated UGI event who require inpatient management are available only from 1 large randomized controlled comparison of misoprostol and placebo in patients with RA taking NSAIDs (5), where 62.7% were managed in the hospital. The proportion of patients with a serious GI event who require surgery varies from 3.3% to 35.7% in cohort studies of patients hospitalized with a GI bleed (5,22–29). Our baseline estimate (8.5%) was taken from a prospective study of 218 Atlanta patients receiving NSAIDs who had a proven ulcer responsible for upper GI bleeding (23). Estimates of the lower range were provided by a study of 1,026 patients in the US, Sweden, and Hungary who were hospitalized for a first episode of major UGI bleeding caused by gastric or duodenal ulcer (25); the upper range was provided by the Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) study (5,30).

Numerous case series describe mortality among patients admitted to hospital with a serious GI bleed (23,24,26–29,31–33). Only 3 distinguish first-time bleeders from recurrent bleeders (27,32,33). We used a large (n = 2,217) study from Nottingham to describe mortality rates in first-time bleeders (4.3%), recurrence (11.5%), and mortality in recurrent bleeders (38.7%) (32). Annual mortality rates for women and men, starting at age 50, were used to model the percentage of patients dying of natural causes as a function of age (34). An excess mortality among patients who had experienced an MI (3.5 deaths per 100 person-years) was determined from the 10-year survival of patients from the Framingham Heart Study who had experienced a Q-wave MI (35).

Health-related quality of life. Utilities for the model health states described in the model were elicited from the general public by surveying 60 randomly selected residents of the city of Sudbury, Ontario. First, rating scale and standard gamble methods were used to elicit utilities for short-term health states compared with the best health state (arthritis without UGI events) and the worst short-term health state (a complicated UGI event requiring surgical management). The short-term health states were 1) dyspepsia, 2) symptomatic ulcer, and 3) complicated UGI event requiring medical management. Rating scale and standard gamble methods were also used to elicit a long-term utility for moderate arthritis with reference to perfect health and immediate death. Short-term utilities were translated into quality-adjusted life year (QALY) values for a 3-month cycle by assuming a utility of 0 for the worst short-term health state of a complicated UGI event requiring surgical management. The utility values for other short-term health states were scaled between this value and the utility for arthritis with no UGI events (0.69). A utility of 0.97 for being a patient with chronic coronary artery disease (CAD) after experiencing an MI was obtained from the published median standard gamble utility of 106 patients in Canadian Cardiovascular Society Class II Angina (36). Utilities for UGI and arthritis health states were multiplied by this utility for patients who have experienced an MI in the model.

Costs. Costs were determined, where possible, from the Ontario Ministry of Health perspective and according to recommendations set out in the National List of Provincial Costs for Health Care (37) (Table 2). Resource intensity weights for the relevant Case Mix Groups associated with GI-related hospitalizations were multiplied by the published cost per weighted case for Ontario (37) to obtain a cost per hospitalization episode. Ambulatory care costs for general GI diagnostic investigation in patients aged over 45 years were derived from the 1999 Annual Report of Ambulatory Care Costing Results for the province of Alberta (38). Costs for all physician billings were derived from the 1999 Ontario Ministry of Health Schedule of Benefits (39). Drug costs were those allowed under the Ontario Drug Benefit Olan, including a maximum allowable markup of 10% and a prescription fee of Can$6.47. Costs of celecoxib are different for OA and RA dosages and were thus weighted based on the percentage of patients with OA and RA recruited into CLASS. The costs for acute CAD were derived from published cost estimates measured in 1,259 Canadian patients enrolled in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events trial, which used the Ontario Case Costing Project as a costing resource (40). The average annual costs for patients with chronic CAD were determined through physicians' focus group assessments of 3 typical scenarios of patients with chronic CAD (41).

Economic assumptions. We adopted the perspective of a third party payer, the Ontario Ministry of Health.

Costs were calculated and are presented in 1999 Canadian dollars.

Future costs and QALYs were discounted at an annual rate of 5%, as recommended in Canadian guidelines (42).

We adopted a 5-year time horizon that allows COX-2 NSAIDs to accumulate additional life years gained, which works in their favor because deaths from MIs or GI bleeds have long-term consequences.

Other assumptions. We assumed that the rate of UGI events remains constant over time, irrespective of how long patients take the NSAID. If the rate of UGI events declined in both groups and to the same degree, the absolute difference between COX-2 and standard NSAIDs in the denominator of the cost-effectiveness ratio would decline as well. This, in turn, would increase the cost-effectiveness ratios. This assumption, therefore, favors COX-2 NSAIDs.

We assumed that patients take NSAIDs for the full 5-year period, unless they develop complications of therapy.

We assumed that COX-2 NSAIDs would have no GI benefit in patients who receive low-dose aspirin after experiencing an MI. In the CLASS study, absence of a GI protective effect of COX-2 NSAIDs was observed in the subgroup analysis of patients who took low-dose aspirin (12). However, limited data support this assumption, and

Table 3. Baseline cost-effectiveness and cost-utility ratios*

	Costs, $Can	Clinical UGI events, %	Complicated UGI events, %	QALYs	Life years	Cost/clinical UGI event,† $Can	Cost/compl. UGI event, $Can	Cost/QALY gained, $Can	Cost/life year gained, $Can
Average-risk patients									
VIGOR									
Naproxen (500 mg bid)	1,576	25.10	7.70	2.8938	4.3580				
Rofecoxib (25 mg qd)	3,173	12.10	3.39	2.8997	4.3615	12,287	37,060	271,188	455,071
CLASS									
Ibuprofen (800 mg tid)	1,141	17.80	6.36	2.8990	4.3596				
Diclofenac (75 mg bid)	2,570	6.64	2.68	2.9104	4.3654	12,805	38,811	125,276	248,160
Celecoxib (100/200 mg bid)	3,371	6.50	2.48	2.9095	4.3651	584,453	406,447	Dominated by diclofenac†	
High-risk patients									
VIGOR									
Rofecoxib (25 mg qd)	4,090	26.50	7.45	2.8851	4.3545				
Naproxen (500 mg bid) + PPI	4,766	36.80	11.31	2.8816	4.3519		Dominated by rofecoxib‡		
Rofecoxib (25 mg qd) + PPI	6,486	18.20	5.13	2.8936	4.3587	28,870	103,284	281,244	567,820
CLASS									
Celecoxib (100/200 mg bid)	4,327	14.60	5.54	2.9003	4.3599				
Ibuprofen (800 mg tid) + PPI	4,414	26.60	9.49	2.8894	4.3544		Dominated by celecoxib‡		
Diclofenac (75 mg bid) + PPI	5,980	10.18	4.11	2.9064	4.3631	37,393	115,307	271,066	518,339
Celecoxib (100/200 mg bid) + PPI	6,746	9.93	3.81	2.9057	4.3630	306,440	258,818	Dominated by diclofenac†	

* Ratios are for the 5-year comparison of rofecoxib to naproxen in patients with rheumatoid arthritis and the comparison of celecoxib to diclofenac and ibuprofen in patients with osteoarthritis (72%) or rheumatoid arthritis (28%). Strategies are ordered by increasing cost. The more expensive strategy is compared to the less expensive, nondominated strategy. Future quality-adjusted life years (QALYs) and life years are discounted by 5%. $Can = Canadian dollars; UGI = upper gastrointestinal; compl. = complicated; VIGOR = Vioxx Gastrointestinal Outcomes Research study; bid = twice per day; qd = once per day; CLASS = Celecoxib Long-Term Arthritis Safety Study; tid = three times per day; PPI = proton pump inhibitor (lansoprazole).
† Ratios may not be exactly reproducible with number shown, due to rounding.
‡ i.e., is a more costly and less efficacious strategy.

it is premature to draw definite conclusions about the effects of COX-2s in the presence of aspirin.

We assumed that the relative reduction in UGI events due to prescription of PPIs would be identical in users of standard or COX-2 NSAIDs.

Doses of COX-2 NSAIDS were 2–4 times higher than current recommended doses. We assumed that the efficacy and GI safety profile of COX-2 NSAIDs is identical at the lower recommended doses that were used in this analysis. Analyses were also performed for the higher doses of COX-2 NSAIDs, as used in the VIGOR and CLASS studies.

This research was commissioned and funded by the Canadian Coordinating Office of Health Technology Assessment. The office was not involved in the design or conduct of the study, although we gratefully acknowledge the support and scientific advice given by the office's clinical and scientific advisory panel during the preparation of the report. No limitations on publication were imposed, and review before publication was not required. Dr. Maetzel was supported by a PhD fellowship (health research) from the Canadian Institutes of Health Research. Dr. Naglie was chair of the Drug Quality and Therapeutics Committee of the Ontario Ministry of Health and Long-Term Care and is presently the Mary Trimmer Chair in Geriatric Medicine Research at the University of Toronto. Dr. Murray Krahn is presently holding an investigator award from the Canadian Institutes of Health Research. Dr. Maetzel has a longstanding working relationship with Dr. Claire Bombardier who consulted for Merck & Co. as the chair of the steering committee of the VIGOR study.

RESULTS

Trial-based comparisons: average-risk patients. For patients at average risk, rofecoxib increased costs relative to naproxen ($3,173 versus $1,576), but also decreased clinical GI events by 13% and complicated GI events by 4.3%. The marginal cost for each QALY gained was high, at $271,188 (Table 3).

Use of the CLASS data generated similar results. Celecoxib increased costs relative to diclofenac and ibuprofen ($3,371 versus $1,570 versus $1,141), but reduced the absolute risk of GI events. However, in the CLASS study, celecoxib reduced GI events by a very modest amount in comparison with diclofenac. In addition, cardiovascular events were slightly more common in the celecoxib group, albeit not statistically significantly. Thus, neither of the more effective strategies (celecoxib and diclofenac) appear to be economically attractive compared with the least costly strategy (ibuprofen). The incremental cost-effectiveness ratio for diclofenac in comparison with ibuprofen is

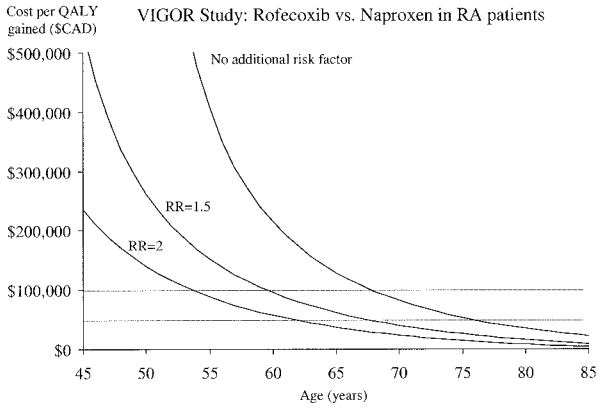

Figure 2. Sensitivity analysis on age and the influence of a potential additional risk factor that confers a relative risk (RR) of 1.5 or 2 times the baseline rate in average-risk patients with rheumatoid arthritis (RA). Cost-effectiveness (cost per quality-adjusted life year [QALY]) ratios were calculated for rofecoxib compared with naproxen based on Vioxx Gastrointestinal Outcomes Research (VIGOR) data in Canadian dollars ($CAD).

unattractive (> $100,000/QALY), and celecoxib is even less attractive (dominated by) than diclofenac, because of its similar efficacy and worse cardiovascular profile.

High-risk strategies. In patients with a history of a clinical UGI event, rofecoxib alone is both less costly and more effective than naproxen coprescribed with a PPI (Table 3). Adding a PPI to rofecoxib is not an economically attractive strategy in comparison with rofecoxib alone, in view of the high cost-utility ratios of $281,244 per QALY gained. Similarly, celecoxib alone is less costly and more effective compared with ibuprofen (Table 3). Celecoxib alone is the most economically attractive strategy, because the strategies that are marginally more effective (celecoxib + PPI, diclofenac + PPI) are not economically attractive.

Effect of age and other risk factors in average-risk patients. The influence of age and a potential additional risk factor was examined in a sensitivity analysis of average-risk patients (Figure 2 and Figure 3). The results showed that rofecoxib became reasonably cost-effective compared with naproxen below thresholds of $100,000 and $50,000 per QALY gained in patients aged greater than 68 and 76, respectively. Further increasing risk by a factor of 2 would reduce the age thresholds to 54 and 62, respectively (Figure 2). Analysis of age without an additional risk factor for celecoxib compared with ibuprofen in patients with RA or OA led to age thresholds of 70 and 81 for cost-effectiveness ratios of $100,000 and $50,000 per QALY gained. Analysis of age and an additional risk factor of 2 reduced the age thresholds to 56 and 67, respectively (Figure 3).

Sensitivity analyses. Single variable sensitivity analysis was performed for the comparison of rofecoxib and naproxen in RA patients at average risk and showed only a minor impact on the cost-effectiveness ratios (Table 4). Sensitivity analysis results limited to high-risk patients revealed that cost-effectiveness ratios were sensitive to the price of omeprazole and the percentage of patients receiving rofecoxib plus a concomitant PPI. Specifically, prescription of rofecoxib to RA patients is more expensive than naproxen plus a PPI if the daily price of PPIs (before mark-up and prescription fee) drops below $1.35. Prescribing rofecoxib would also become more expensive than prescribing naproxen if more than 28% of RA patients on rofecoxib were coprescribed PPIs. Furthermore, cost-effectiveness ratios would be higher if COX-2 NSAIDs were costed according to dosages used in the clinical trials (Table 4). Sensitivity analysis was also conducted by varying the price for rofecoxib at 12.5 or 25 mg once per day and celecoxib at 100 mg twice per day in patients at average risk, and with naproxen and ibuprofen as the respective standard NSAID comparators. The calculations showed that rofecoxib would be cost saving at a price of approximately $0.33 per dose (12.5 or 25 mg once per day), and have cost-effectiveness thresholds below $50,000 at $0.50/dose, and below $100,000 at $0.67/dose. Celecoxib would be cost saving compared with ibuprofen at a price of $0.25 per 100 mg twice per day, and below thresholds of $50,000 and $100,000 per QALY at a price of $0.50 and $0.70 per 100 mg twice per day, respectively.

DISCUSSION

The results of this analysis show that prescribing either celecoxib or rofecoxib to patients without a prior clinical UGI event and who do not receive low-dose aspirin is associated with costs per QALY gained that exceed thresholds of $100,000 per QALY gained. Both rofecoxib and celecoxib are the most economically attractive strategies in high-risk patients. Analysis by age groups and assuming a cost-effectiveness threshold of $50,000 per QALY gained showed that rofecoxib or celecoxib would be cost-effective in patients aged over 76 and 81 years, respectively.

The findings of the cost-effectiveness and cost-utility analyses are closely influenced by the rates of clinical and complicated UGI events reported in 2 major trials of rofecoxib and celecoxib (12,13). The rates observed in the

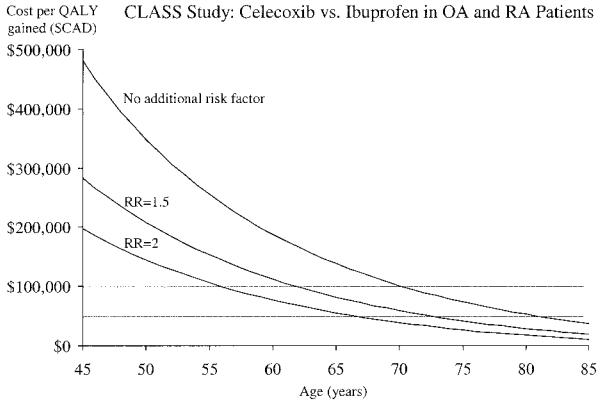

Figure 3. Sensitivity analysis on age and the influence of a potential additional risk factor conferring a relative risk (RR) of 1.5 or 2 times the baseline rate in average-risk patients with osteoarthritis (OA) or rheumatoid arthritis (RA). Cost-effectiveness ratios (cost per quality-adjusted life year [QALY]) were calculated for celecoxib compared with ibuprofen based on Celecoxib Long-Term Arthritis Safety Study (CLASS) data in Canadian dollars ($CAD).

Table 4. Sensitivity analysis of model estimates in the comparison of rofecoxib and naproxen*

Variables changed in sensitivity analysis	Cost per QALY gained	
	Low range, $Can	High range, $Can
Average risk: rofecoxib 25 mg qd versus naproxen 500 mg bid		
RRR clinical UGI events (36.0–67.0%)	536,852	188,538
RRR complicated UGI events (22.0–76.0%)	560,091	212,400
Hospitalization if complicated UGI event (51.1–74.3%)	292,606	251,864
Surgery if hospitalized (4.0–35.7%)	275,522	245,632
Mortality in patients with first bleed (1.9–5.3%)	315,289	258,272
RRR UGI events due to PPI (37.5–42.5%)	267,341	274,536
Discount rate (0% and 3%)	267,431	269,507
Relative risk if positive history of UGI bleed (2.0–5.9)	292,547	194,694
All resource utilization costs, ±25%	278,024	262,993
Daily cost of omeprazol (less markup, fee) ($0.10–$2.00)	289,475	269,854
Percent with UGI event retrying NSAIDs (0–100)	272,561	241,323
QALY for arthritis (0.159–0.185)	330,986	229,259
QALY for dyspepsia (0.108–0.145)	285,365	257,118
QALY for symptomatic ulcer (0.080–0.112)	226,397	348,503
QALY for compl. UGI event with medical management (0.062–0.096)	256,026	289,811
High risk: rofecoxib 25 mg qd versus naproxen 500 mg bid		
Price of PPIs ($0.10–$2.00)	438,161	Dominance†
Relative risk if positive history of UGI bleed (2.0–5.9)	Dominance†	Dominance†
Trial dosages of COX-2 NSAIDs		
Average risk: rofecoxib 50 mg qd versus naproxen 500 mg bid	638,240	
High risk: rofecoxib 50 mg qd versus naproxen 500 mg bid	420,112	
Average risk: celecoxib 400 mg bid versus ibuprofen 800 mg tid	774,929	
High risk: celecoxib 400 mg bid versus ibuprofen 800 mg tid	526,236	

* Future quality-adjusted life years (QALYs) are discounted by 5%. $Can = Canadian dollars; qd = once per day; bid = twice per day; RRR = relative risk reduction; UGI = upper gastrointestinal; PPI = proton pump inhibitor; NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase 2; tid = three times per day.
† The COX-2 is less costly and more efficacious than regular NSAIDs.

VIGOR study are higher than those observed in the CLASS study, which may be due to the inclusion of only RA patients in VIGOR, whereas 72% of the patients in CLASS had OA. The CLASS study found no difference in rates between OA and RA patients (43), in contrast to other evidence suggesting that GI events are more common in RA patients (21). However, OA and RA patients have never been observed in a prospective study with the same drug regimens, which raises the possibility that differences in rates between the 2 diseases are entirely due to NSAID dosages and regimens. In view of the fact that the cost of both drugs is similar at OA doses, and that the absolute risk reduction in GI events was similar in both CLASS and VIGOR, we believe that the qualitative results observed in this analysis (economically attractive in high-risk patients, not so in average-risk patients) most likely apply to both rofecoxib and celecoxib for OA patients. We also believe that the qualitative results of this analysis also apply to RA patients, although celecoxib appears somewhat less attractive at the higher dosages (200 mg twice per day) suggested for RA patients, mainly because, in Ontario, it is twice as expensive as the recommended dose of rofecoxib (25 mg once per day).

One large, randomized controlled trial of COX-2 NSAIDs has been published in abstract form since publication of VIGOR and CLASS. The SUCCESS-1 study was a multinational, randomized controlled trial that compared celecoxib (100–200 mg/day) to naproxen (1,000 mg/day) or diclofenac (100 mg/day) in 13,274 patients with OA during a 12-week period (44). Incidence of complicated UGI events per 100 person-years were reported to be 0.8 in the NSAIDs group and 0.1 in the celecoxib group, while incidence of clinical UGI events was reported to be 2.1 in the NSAID group and 1.0 in the celecoxib group. All event rates were lower than reported in the CLASS study and their use would lead to higher cost-effectiveness ratios for celecoxib.

We are less confident about the extrapolation of the rate of UGI events observed in the study populations to specific age strata. Estimates for the relationship between age and UGI event rates were not available from the VIGOR and CLASS studies. Hence, conclusions about precise age thresholds should be viewed with caution. Similarly, extrapolation to patients taking aspirin is uncertain. Our baseline analysis assumes that the gastroprotective effect of COX-2 NSAIDs does not extend to aspirin users, because aspirin increases bleeding risk and because clinical UGI events in the CLASS study were not different, in fact slightly higher, in aspirin users who took celecoxib versus those who took ibuprofen or diclofenac (16). However, this conclusion must be regarded as uncertain, as this interpretation is based on results from a small subgroup of the CLASS study.

The results here are comparable to those observed in other cost-effectiveness analyses. A previous analysis comparing standard NSAIDs with and without coprescrip-

tion of misoprostol conducted by the present authors showed that misoprostol was not cost-effective in patients at low risk, but was cost-effective among high-risk individuals (30). The results were somewhat similar to the present findings, because both economic evaluations were based on clinical UGI events observed in large, randomized controlled trials. Many other economic evaluations comparing standard NSAIDs to coprescription with gastroprotective agents had overstated the economic attractiveness of gastroprotective agents because of their reliance on extrapolated endoscopic evidence, rather than clinically important GI events. A similar overestimation would have occurred here, had the analysis been based on the very positive endoscopic findings among patients taking COX-2 NSAIDs.

The present cost-effectiveness and cost-utility analyses show that the COX-2 NSAIDs rofecoxib and celecoxib are a cost-effective treatment option for RA and OA patients considered to be at high risk due to a history of clinical UGI events. COX-2 NSAIDs are not a cost-effective treatment option in all patients at average risk, but may reach reasonable thresholds in certain age and risk groups.

REFERENCES

1. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. American College of Rheumatology. Arthritis Rheum 1995;38:1535–40.
2. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. Arthritis Rheum 1995;38:1541–6.
3. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs [review]. N Engl J Med 1999;340:1888–99.
4. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991;115:787–96.
5. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241–9.
6. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000;160: 2093–9.
7. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci U S A 1993;90:11693–7.
8. Hawkey CJ. COX-2 inhibitors. Lancet 1999;353:307–14.
9. Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA 1999;282:1921–8.
10. Day R, Morrison B, Luza A, Castaneda O, Strusberg A, Nahir M, et al. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis: Rofecoxib/Ibuprofen Comparator Study Group. Arch Intern Med 2000;160:1781–7.
11. Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
12. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial: Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247–55.
13. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520–8.
14. Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluation of pharmaceuticals: Canada, 2nd ed. Ottawa: CCOHTA; 1997.
15. Goldkind L. Medical officer's advisory committee GI briefing document division of anti-inflammatory, analgesic and ophthalmologic drug products: HFD-550. NDA 21-042; 2001. p. 1–56.
16. Witter J. Medical officer review: sNDA 20 998, 1-100. Rockville (MD): U.S. Food and Drug Administration; 2001.
17. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322–38.
18. Jones RH, Tait CL. Gastrointestinal side-effects of NSAIDs in the community. Br J Clin Pract 1995;49:67–70.
19. Rahme E, Joseph L, Kong SX, Watson DJ, LeLorier J. Gastrointestinal health care resource use and costs associated with nonsteroidal antiinflammatory drugs versus acetaminophen: retrospective cohort study of an elderly population. Arthritis Rheum 2000;43:917–24.
20. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs: omeprazole versus misoprostol for NSAID-induced ulcer management (OMNIUM) study group. N Engl J Med 1998; 338:727–34.
21. Singh G, Rosen RD. NSAID induced gastrointestinal complications: the ARAMIS perspective—1997: arthritis, rheumatism, and aging medical information system. J Rheumatol Suppl 1998;51:8–16.
22. Bakowsky VS, Hanly JG. Complications of nonsteroidal antiinflammatory drug gastropathy and use of gastric cytoprotection: experience at a tertiary care health center. J Rheumatol 1999;26: 1557–63.
23. Wilcox CM, Clark WS. Association of nonsteroidal antiinflammatory drugs with outcome in upper and lower gastrointestinal bleeding. Dig Dis Sci 1997;42:985–9.
24. Holvoet J, Terriere L, Van Hee W, Verbist L, Fierens E, Hautekeete ML. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case-control study. Gut 1991;32:730–4.
25. Laszlo A, Kelly JP, Kaufman DE, Sheehan JE, Retsagi G, Wiholm BE, et al. Clinical aspects of upper gastrointestinal bleeding associated with the use of nonsteroidal antiinflammatory drugs. Am J Gastroenterol 1998;93:721–5.
26. Klein WA, Krevsky B, Klepper L, Ljubich P, Niewiarowski TJ, Rothstein KD, et al. Nonsteroidal antiinflammatory drugs and upper gastrointestinal hemorrhage in an urban hospital. Dig Dis Sci 1993;38:2049–55.
27. Branicki FJ, Coleman SY, Fok PJ, Pritchett CJ, Fan ST, Lai EC, et al. Bleeding peptic ulcer: a prospective evaluation of risk factors for rebleeding and mortality. World J Surg 1990;14: 262–9.
28. Duhamel C, Czernichow P, Dechelotte P, Ducrotte P, Lerebours E, Colin, et al. [Upper gastrointestinal hemorrhage caused by anti-inflammatory agents]. [French]. Gastroenterol Clin Biol 1989;13:239–44.
29. Godil A, DeGuzman L, Schilling RC III, Khan SA, Chen YK. Recent nonsteroidal anti-inflammatory drug use increases the risk of early recurrence of bleeding in patients presenting with bleeding ulcer. Gastrointest Endosc 2000;51:146–51.
30. Maetzel A, Ferraz MB, Bombardier C. The cost-effectiveness of misoprostol in preventing serious gastrointestinal events associated with the use of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1998;41:16–25.
31. Loperfido S, Monica F, Maifreni L, Paccagnella A, Fama R, Dal Pos R, et al. Bleeding peptic ulcer occurring in hospitalized patients: analysis of predictive and risk factors and com-

parison with out-of-hospital onset of hemorrhage. Dig Dis Sci 1994;39:698–705.
32. Katschinski B, Logan R, Davies J, Faulkner G, Pearson J, Langman MJ. Prognostic factors in upper gastrointestinal bleeding. Dig Dis Sci 1994;39:706–12.
33. Zimmerman J, Siguencia J, Tsvang E, Beeri R, Arnon R. Predictors of mortality in patients admitted to hospital for acute upper gastrointestinal hemorrhage. Scand J Gastroenterol 1995;30:327–31.
34. United Nations Statistics Division. United Nations Demographic Yearbook–Historical Supplement. New York: United Nations; 1999.
35. Guidry UC, Evans JC, Larson MG, Wilson PW, Murabito JM, Levy D. Temporal trends in event rates after Q-wave myocardial infarction: the Framingham heart study. Circulation 1999;100:2054–9.
36. Nease RF, Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Shaw L, et al. Variation in patient utilities for outcomes of the management of chronic stable angina: implications for clinical practice guidelines: ischemic heart disease patient outcomes research team. JAMA 1995;273:1185–90.
37. Institute of Health Economics. A national list of provincial costs for health care: Canada 1997/8. 1-125. Edmonton, Alberta: Institute of Health Economics; 2000.
38. Alberta Health and Wellness. Health costing in Alberta—1999 annual report. Edmonton, Alberta: Health and Wellness; 1999.
39. Ontario Ministry of Health. Schedule of benefits: physician services under the health insurance act. Toronto: Ontario Ministry of Health; 1998.
40. O'Brien BJ, Willan A, Blackhouse G, Goeree R, Cohen M, Goodman S. Will the use of low-molecular-weight heparin (enoxaparin) in patients with acute coronary syndrome save costs in Canada? Am Heart J 2000;139:423–9.
41. Nordmann AJ. Cost-effectiveness of routine echocardiography in hypertensive patients requiring antihypertensive drug therapy. Toronto: University of Toronto; 2001.
42. Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. Rheumatology 2000;39:28–33.
43. Sponsor Presentation: FDA Arthritis Advisory Committee. February 7, 2001.
44. Singh G, Goldstein J, Bensen W, Agrawal N, Eisen G, Fort J, et al. SUCCESS-1 in osteoarthritis (OA) trial: celecoxib significantly reduces risk of serious upper GI complications compared to NSAIDs while providing similar efficacy in 13,274 randomized patients [abstract]. European Congress of Rheumatology; Jun 13–16, 2001; Prague. Abstract no OP0053. Available online at URL: http://www.eular.org/eular2001/AbstractsOnline.cfm.