The Cost-Effectiveness of Cyclooxygenase-2 Selective Inhibitors in the Management of Chronic Arthritis

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Background: **Rofecoxib and celecoxib (coxibs) effectively treat chronic arthritis pain and reduce ulcer complications by 50% compared with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). However, their absolute risk reduction is small and the cost-effectiveness of treatment is uncertain.**

Objective: **To determine whether the degree of risk reduction in gastrointestinal complications by coxibs offsets their increased cost compared with a generic nonselective NSAID.**

Design: **Cost-utility analysis.**

Data Sources: **Systematic review of MEDLINE and published abstracts.**

Target Population: **Patients with osteoarthritis or rheumatoid arthritis who are not taking aspirin and who require long-term NSAID therapy for moderate to severe arthritis pain.**

Perspective: **Third-party payer.**

Interventions: **Naproxen, 500 mg twice daily, and coxib, once daily. Patients intolerant of naproxen were switched to a coxib.**

Time Horizon: **Lifetime.**

Outcome Measures: **Incremental cost per quality-adjusted life-year (QALY) gained.**

Results of Base-Case Analysis: **Using a coxib instead of a nonselective NSAID in average-risk patients cost an incremental $275 809 per year to gain 1 additional QALY.**

Results of Sensitivity Analysis: **The incremental cost per QALY gained decreased to $55 803 when the analysis was limited to the subset of patients with a history of bleeding ulcers. The coxib strategy became dominant when the cost of coxibs was reduced by 90% of the current average wholesale price. In probabilistic sensitivity analysis, if a third-party payer was willing to pay $150 000 per QALY gained, then 4.3% of average-risk patients would fall within the budget.**

Conclusions: **The risk reduction seen with coxibs does not offset their increased costs compared with nonselective NSAIDs in the management of average-risk patients with chronic arthritis. However, coxibs may provide an acceptable incremental cost-effectiveness ratio in the subgroup of patients with a history of bleeding ulcers.**

Ann Intern Med. 2003;138:795-806. www.annals.org

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Osteoarthritis and rheumatoid arthritis are prevalent and clinically significant health care problems in the United States today, affecting 15% of the population (1), resulting in more than 100 000 hospitalizations per year (2), and consuming nearly 2.5% of the annual gross domestic product when both direct and indirect costs are considered (3). Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat chronic arthritis pain, and they account for 3% of the U.S. prescription drug market (4). These agents are a mainstay of treatment despite their association with clinically significant peptic ulcer complications, including symptomatic ulcers, ulcer hemorrhages, and ulcer perforations (5). Moreover, NSAIDs may induce upper-gastrointestinal (GI) dyspeptic symptoms (6, 7), including epigastric pain, bloating, nausea, and heartburn, even in the absence of endoscopic lesions (8). The decision to use NSAIDs to treat patients with chronic arthritis requires a delicate balance between effective pain relief and potential GI complications.

Cyclooxygenase-2 selective inhibitors, including rofecoxib and celecoxib (coxibs), have been developed as safer alternatives to nonselective NSAIDs and are widely used in clinical practice. When compared with nonselective NSAIDs, including naproxen and ibuprofen, coxibs achieve equal pain relief while reducing upper GI dyspeptic symptoms by 15% (9) and clinically significant ulcer complications by 50% (10–13). For these reasons, the American Pain Society has recently endorsed coxibs as the drug class of choice for the initial management of moderate to severe arthritis pain, although they cost more than nonselective NSAIDs (14).

Despite the significant relative risk reduction in GI complications afforded by coxibs, their absolute risk reduction compared with nonselective NSAIDs is only 1% to 2% for overall ulcer complications and less than 1% for significant ulcer complications (ulcer hemorrhages or perforations) (10–13). In addition, although coxibs reduce GI-related utilization of health care resources compared with nonselective NSAIDs in controlled trials, recent data from clinical practice indicate that patients switching from nonselective NSAIDs to coxibs do not have a concurrent decrease in overall GI-related resource utilization (15, 16).

The enthusiasm for coxibs may be further tempered by data suggesting that coxibs are associated with a higher rate of cardiovascular events than nonselective NSAIDs (17). For example, one randomized, controlled trial revealed that for every 333 patients treated with rofecoxib instead of naproxen, there was one additional cardiovascular event, including stroke, unstable angina, or acute myocardial infarction (9). Although the reasoning behind this finding is uncertain and controversial (18), the clinical disparity in significant events was highlighted in a systematic review of coxib trials reporting cardiovascular end points (17). Several U.S. Food and Drug Administration (FDA) reports

Context

Relative to nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors have fewer gastrointestinal complications but cost more. The exact tradeoff between cost and effectiveness is unknown.

Contribution

This analysis suggests that using rofecoxib and celecoxib rather than naproxen to treat chronic arthritis is cost-effective only for patients with a previous bleeding ulcer or if the cost of COX-2 inhibitors were 10% of its current average wholesale price.

Implications

At current prices, COX-2 inhibitors offer a cost-effective therapeutic option for treating chronic arthritis only for patients with a previous bleeding ulcer.

–The Editors

have also raised this concern (19–21). In light of these data, we sought to determine whether the degree of risk reduction in GI complications seen with coxibs offsets their increased cost compared with generic nonselective NSAIDs in the management of chronic arthritis. We performed an economic analysis to estimate the cost-effectiveness of coxibs versus nonselective NSAIDs in the management of chronic arthritis pain.

METHODS

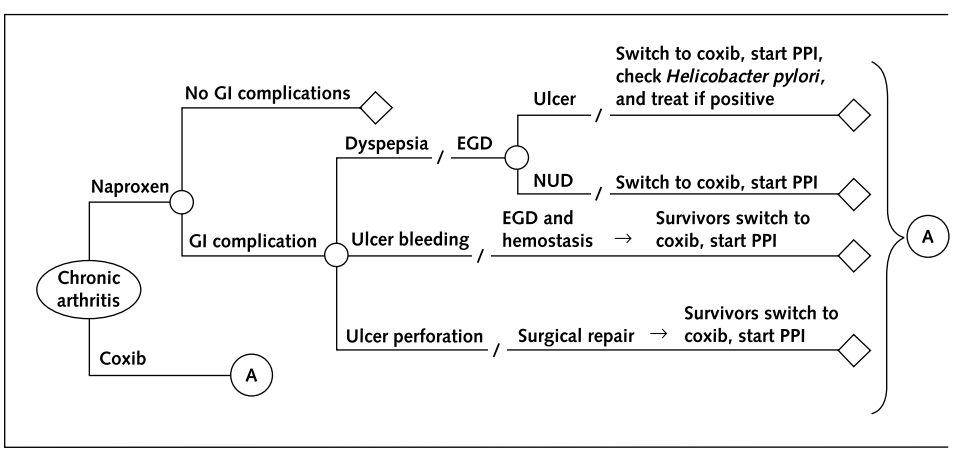
Decision Model Framework

Decision analysis is a quantitative method for estimating the financial costs and clinical outcomes of alternative strategies under conditions of uncertainty (22). By using decision-analysis software (DATA 4.0, TreeAge Software, Inc., Williamstown, Massachusetts), we evaluated two strategies for managing a hypothetical cohort of 60-year-old patients with osteoarthritis or rheumatoid arthritis who were not taking concurrent aspirin and required long-term NSAID therapy for moderate to severe arthritis pain (**Figure 1**). Patients with a history of ulcer complications were not included in our base-case analysis but were evaluated in a sensitivity analysis. Patients who entered the hypothetical model did not have GI symptoms and were initially treated with either a coxib (celecoxib, 200 mg once daily, or rofecoxib, 25 mg once daily) or a nonselective NSAID at the maximum FDA-approved dose (modeled after naproxen, 500 mg twice daily). Over the course of a lifetime horizon, the patients either developed a GI complication (nonulcer dyspepsia, symptomatic ulcer, ulcer hemorrhage, or ulcer perforation) or remained free of GI adverse events. Patients without complications continued taking their prescribed therapy, and those with complications required further evaluation. To make our model clinically realistic, we required patients to develop symptoms or clinically significant adverse outcomes to prompt further evaluation. We based our assumptions about patient and physician behavior on patient-centered outcomes rather than surrogate end points, such as endoscopic lesions or ulcer healing rates. To capture the full range of downstream costs generated by each strategy, we included the ongoing cost of care associated with GI events and the probability of developing recurrent events over the course of a lifetime in the model.

Model Assumptions

To systematically bias our analysis in favor of the coxib strategy, we designed our model to explicitly support a study hypothesis that coxibs are more cost-effective than nonselective NSAIDs. This "best case" model for coxibs was based on four assumptions (**Figure 1**). First, all patients developing upper-GI dyspeptic symptoms, including

Figure 1. **Truncated decision model.**



The base-case patient has chronic arthritis, is at average risk for ulcer complications, and is not taking concurrent aspirin. The clinician may either treat with naproxen, 500 mg twice daily, or with a coxib, once daily. The extended tree (*A*) is shared by the coxib arm, with the exception of switching to coxibs if ulcer complications develop. See text for details about individual strategies and for assumptions about downstream costs and effects (not represented in the figure). EGD = esophagogastroduodenoscopy; GI = gastrointestinal; NUD = nonulcer dyspepsia; PPI = proton-pump inhibitor.

Table 1. **Base-Case Clinical Probability Estimates***

Variable	Base-Case Estimate	Range in Literature	Range Tested in Sensitivity Analysis	Reference
Probability of upper-GI dyspeptic symptom in patients receiving naproxen, %	10.9		5–25	7
Probability of upper-GI dyspeptic symptom in patients receiving coxib, %	8	5–20	3–15	10–12, 24
Probability that nonulcer dyspepsia symptoms improve with trial of PPI therapy, %	45	36–65	25–75	25–28
Probability that ulcer symptoms improve with trial of PPI therapy, %	80	55–98	50–100	29–32
Rate of clinically significant ulcer complications with naproxen during first year of therapy, %	2.6	1.46–4.5	1–5	9–13, 33
Rate of clinically significant ulcer complications with naproxen over lifetime horizon, %	7.2	No range	5–12	See Appendix
Rate of clinically significant ulcer complications with coxibs during first year of therapy, %	1.04	1–2.5	0.05–4	10–13
Rate of clinically significant ulcer complications with coxibs over lifetime horizon, %	4.9	No range	3–10	See Appendix
Probability that a clinically significant ulcer complication is a symptomatic ulcer, %	74	70–80	50–90	10–12, 24
Probability that a clinically significant ulcer complication is an ulcer hemorrhage, %	25	20–30	10–50	10–12, 24
Probability that a clinically significant ulcer complication is an ulcer perforation, %	1	0–1	0–5	10–12, 24
Probability that endoscopy for ulcer hemorrhage reveals low-risk ulcer stigmata, %	66	50–90	50–100	34
Probability that endoscopy for ulcer hemorrhage reveals high-risk ulcer stigmata, %	34	20–70	10–80	34
Probability of recurrent hemorrhage for untreated low-risk ulcer stigmata (clean-based ulcer), %	2	0–5	0–10	34
Probability of recurrent hemorrhage for untreated low-risk ulcer stigmata (ulcer with overlying clot), %	10	2–15	2–20	34
Probability of recurrent hemorrhage for high-risk ulcer stigmata following endoscopic hemostasis, %	20	4–40	5–40	34
Probability of successful repeated hemostasis in patients with recurrent hemorrhage treated with second round of endoscopic therapy, %	70	0.5–1.0	50–100	34, 35
Probability of endoscopically induced perforation or uncontrollable bleeding, %	0.02	0–3	0–5	35–38
Probability of perioperative death for surgical ulcer repair, %	10	0–20	0–30	34
Average inpatient length of stay for an ulcer hemorrhage, *d*	7	1–20	1–20	39
Average inpatient length of stay for an ulcer perforation, *d*	10	1–20	1–20	39
Probability of developing moderate side effect from antibiotics for *Helicobacter pylori* eradication, %	0.05	0–3	0–5	40–43
Probability of developing severe side effect from antibiotics for *H. pylori* eradication, %	0.001	0.001	0–0.01	44–45

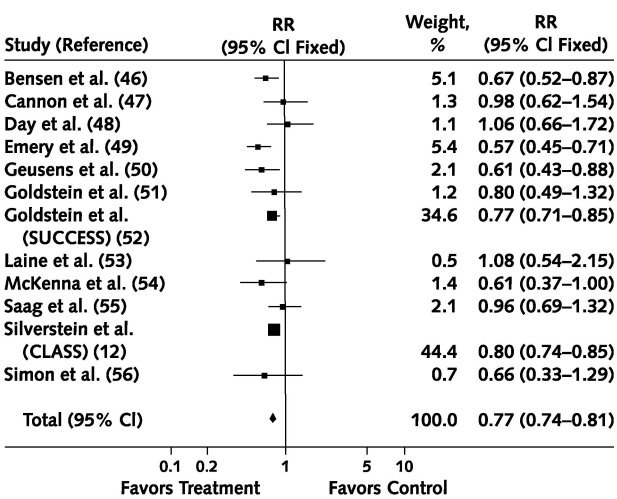
* GI = gastrointestinal; PPI = proton-pump inhibitor.

epigastric pain, bloating, nausea, or heartburn, were required to undergo upper endoscopy and were prescribed once-daily proton-pump inhibitor (PPI) therapy for the remainder of their lifetimes, regardless of whether an ulcer was identified. Although many patients who develop GI symptoms while taking NSAIDs do not receive endoscopy or long-term PPI therapy, our exaggerated assumption was designed to impart a significant economic penalty for the presence of upper GI symptoms. This assumption economically favors coxibs because they are associated with substantially fewer dyspeptic symptoms than nonselective NSAIDs (9). Second, all patients receiving a nonselective NSAID who developed an upper-GI dyspeptic symptom were also required to discontinue their therapy and switch to a coxib for the remainder of their lifetimes, regardless of whether an ulcer was found on endoscopy. Third, all symptomatic patients found to have an ulcer by upper endoscopy were required to undergo endoscopic biopsy and rapid urease testing for *Helicobacter pylori* and subsequently received a 14-day course of eradication therapy if positive for *H. pylori*. Although the role of *H. pylori* in the pathogenesis of NSAID-related ulcers is controversial (23), we purposely required all patients to be tested and treated for *H. pylori* to incur an additional economic penalty for the presence of ulcers, therefore biasing the model in favor of coxibs. Finally, although data indicate that nonselective NSAIDs are associated with more GI adverse events than coxibs, a recent FDA review indicates that the incidence of overall serious adverse events is lower with nonselective NSAIDs than with coxibs (7.8% vs. 9.3%) (20). However, to bias our model in favor of coxibs, our base-case analysis included only GI-related adverse events and did not model the observed disparity in adverse events for other organ systems (20).

Clinical Data

Our base-case model incorporated 23 probability estimates derived from a systematic review of the medical literature (**Table 1**). We performed a structured search of published reports from the MEDLINE bibliographic databases and hand-searched published abstracts from two major subspecialty journals (*Arthritis & Rheumatism* and *Gastroenterology*) to identify English-language publications from January 1985 to December 2002 that pertained to our 23 clinical inputs. We targeted randomized, controlled trials with one or more arms that investigated the use of either nonselective NSAIDs or coxibs in managing chronic arthritis pain and selected trials that reported clinically significant GI complications. Where available, we used summary estimates derived from published systematic reviews and meta-analyses. Where there was a range of data without previous meta-analysis, we used meta-analysis software (RevMan 4.1, Cochrane Collaboration, Oxford, United

Figure 2. **Meta-analysis using the fixed-effects model of randomized, controlled trials that report upper gastrointestinal dyspeptic symptoms in patients receiving a coxib versus a nonselective nonsteroidal anti-inflammatory drug.**



The summary estimate is the relative risk (*RR*). CLASS = Celecoxib Long-term Arthritis Safety Study; SUCCESS = Successive Celecoxib Efficacy and Safety Study.

Kingdom) to establish point estimates for use in the decision tree.

Clinical Probability Estimates

Upper Gastrointestinal Dyspeptic Symptoms

Patients Receiving Nonselective NSAID. Upper-GI dyspeptic symptoms include epigastric pain, bloating, nausea, and heartburn. A recent meta-analysis of randomized, controlled NSAID trials reporting upper-GI dyspeptic symptoms as an outcome derived a pooled prevalence of dyspeptic symptoms of 10.9% in the large exposure studies (sample size > 1000 patients); we adopted this as our base-case value (7). Because the precision of this estimate is unlikely to be reproduced among different populations and may vary with duration of therapy, we varied it from 5% to 25% in our sensitivity analysis.

Patients Receiving Coxibs. Our review identified 12 trials of coxibs versus nonselective NSAIDs that reported upper-GI dyspeptic symptoms as an outcome (11, 46–56). These trials are both clinically and statistically homogeneous ($P = 0.11$ for heterogeneity). We performed a meta-analysis of these trials by using a fixed-effects model (**Figure 2**) (57). The pooled relative risk for developing an upper-GI dyspeptic symptom is 0.77 (95% CI, 0.74 to 0.81). However, to bias the model in favor of the coxib strategy, we set the risk reduction at 0.74, representing the lower boundary of the CI from meta-analysis. The probability of dyspeptic symptoms for the coxib arm was derived by multiplying this relative risk by the probability of dyspeptic symptoms for the nonselective NSAID arm, which yielded a probability of 8% (10.9% for nonselective NSAIDs × 0.74 relative risk).

Adverse Ulcer Complications

Patients Receiving Nonselective NSAIDs. Up to 30% of patients receiving nonselective NSAIDs develop endoscopic ulcers within 1 year of starting therapy (5). However, endoscopic ulcers are a surrogate end point of unclear clinical significance because only a fraction of these lesions are accompanied by concurrent symptoms. Our review identified five trials that reported clinically significant ulcer complications, including symptomatic ulcers, ulcer hemorrhages, and ulcer perforations (**Table 2**) (9–12, 24). The rates of ulcer complications range from 1.8% to 4.5% per year in patients receiving nonselective NSAIDs. The mean rate of ulcer complications weighted by sample size is 2.6% per year, and we adopted this as our base-case estimate for the first year of NSAID use. After the first year, however, data suggest that the incidence of ulcer complications decreases over time (33). We therefore assumed that 7.2% of the cohort developed an ulcer complication over the course of the lifetime horizon and varied this estimate between 4% and 14% in sensitivity analysis. See the Appendix (available at www.annals.org) for the extended rationale supporting this estimate.

Patients Receiving Coxibs. We identified four trials that reported clinically significant ulcer complications for patients receiving coxibs versus nonselective NSAIDs (**Table 2**) (9–12). These trials are both clinically and statistically ho-

Table 2. **Ulcer Complication Rates (Including Symptomatic Ulcers, Ulcer Hemorrhages, and Ulcer Perforations) for Nonselective Nonsteroidal Anti-Inflammatory Drugs versus Coxibs as Reported in Published Randomized, Controlled Trials***

Study (Reference)	Nonselective NSAID Complication Rate (NSAIDs Evaluated)†	Coxib Complication Rate (Coxib Evaluated)
	%	
Bombardier et al. (VIGOR) (10)	4.5/y (naproxen)	2.1/y (rofecoxib)
Langman et al. (11) (8 studies combined)	1.8/y (ibuprofen and diclofenac)	1.3/y (rofecoxib)
Silverstein et al. (CLASS) (12)	2.91/y (ibuprofen and diclofenac)	2.08/y (celecoxib)
Goldstein et al. (SUCCESS I) (13)	2.0/3 mo (naproxen and diclofenac)	0.9 (celecoxib)
Silverstein et al. (MUCOSA) (24)	1.46/6 mo (various NSAIDs)	–

* CLASS = Celecoxib Long-term Arthritis Safety Study; MUCOSA = Misoprostol Ulcer Complications Outcomes Safety Assessment; NSAID = nonsteroidal anti-inflammatory drug; SUCCESS = Successive Celecoxib Efficacy and Safety Study; VIGOR = Vioxx Gastrointestinal Outcomes Research.
† Data for subgroup not taking aspirin (consistent with base-case model cohort).

mogeneous ($P > 0.2$ for heterogeneity). We performed a meta-analysis of these trials by using a fixed-effects model (**Figure 3**). The pooled relative risk for developing a clinically significant ulcer complication is 0.50 (CI, 0.4 to 0.63). However, to bias the model in favor of the coxib strategy, we set the risk reduction at 0.40, representing the lower boundary of the CI from meta-analysis. The probability of ulcer complications for the coxib arm was derived by multiplying this relative risk by the annualized rate of ulcer complications for the nonselective NSAID arm, which yielded a rate of 1.04% per year (2.6% rate for nonselective NSAIDs × 0.4 relative risk). We adopted this as our base-case estimate for the first year of coxib use. However, data indicate that the relative risk reduction by coxibs versus nonselective NSAIDs may decrease with time. We therefore assumed that 4.9% of the coxib cohort developed an ulcer complication over the lifetime horizon. See the Appendix for the extended rationale supporting this estimate.

Additional Probability Estimates

Our model included probability estimates on the management and consequences of peptic ulcer hemorrhage and perforation, as well as estimates on the complications of endoscopy, surgery, and antibiotic therapy for *H. pylori* infection (**Table 1**). See the Appendix (available at www.annals.org) for the rationale supporting these base-case estimates.

Outcomes

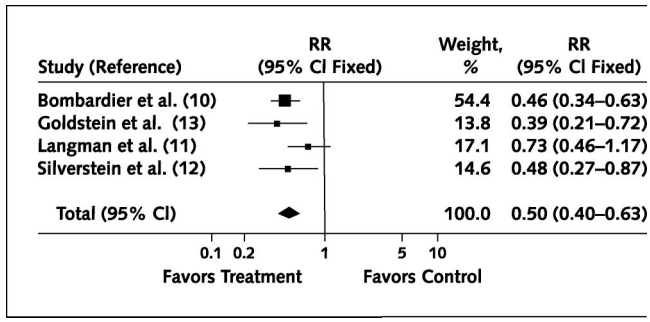
Although previous economic models for NSAID therapy have used ulcer complications as the main outcome measure (58–62), the National Panel on Cost-Effectiveness in Health and Medicine suggests that quality-adjusted life-years (QALYs) are the most appropriate unit for cost-effectiveness analysis (63). Because the main objective of cost-effectiveness analysis is to compare different interventions in medicine and because QALYs are the exchange currency to allow these comparisons to be made, we adopted QALYs as our main outcome. Our analysis reports the incremental cost per QALY gained between the competing strategies.

Utilities

Our analysis was designed to evaluate GI outcomes, rather than the disutility associated with chronic arthritis. Because coxibs are as effective as nonselective NSAIDs in treating arthritis pain (9–12, 24), we assumed that the baseline disutility of arthritis was equal between the two groups.

However, because the probability of GI complications is different between the two groups, incorporating utilities for GI outcomes may have significant cost-effectiveness implications. Using validated utilities developed by previous investigators, we assigned a utility of 0.87 for severe dyspepsia, 0.91 for moderate dyspepsia, 0.49 for an ulcer hemorrhage, and 0.46 for a complicated ulcer requiring surgery (64). All utilities were discounted at a rate of 3%, as recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine (63). See the Appendix (available at www.annals.org) for the extended rationale supporting these estimates and their use in calculating QALYs for the model.

Figure 3. **Meta-analysis using the fixed-effects model of randomized, controlled trials that report clinically significant ulcer complications (symptomatic ulcer, ulcer hemorrhage, or ulcer perforation) in patients receiving a coxib versus a nonselective nonsteroidal anti-inflammatory drug.**



The summary estimate is the relative risk (*RR*).

Cost Estimates

We conducted our analysis from the perspective of a third-party payer, considering only direct health care costs (**Table 3**). We obtained costs for endoscopic and surgical procedures and physician services from the 2002 American Medical Association *Current Procedural Terminology* codebook and the 2002 Medicare Fee Schedule and derived our base-case pharmaceutical costs from the average wholesale prices listed in the *Red Book* (65). Because large buying consortiums are often capable of obtaining prices lower than the *Red Book* average wholesale prices, we performed a sensitivity analysis using the acquisition costs of the Veterans Administration (VA) as a proxy for the discounts achieved by large third-party payers. Our base-case analysis discounted costs at 3%, and we performed an additional analysis discounted at 5%, as recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine (63).

Sensitivity Analyses

Base-Case Sensitivity Analysis

Table 1 lists our base-case probability estimates with the plausible range of values for each estimate. To test the influence of all variables on the model results, we performed a multivariable sensitivity ("tornado analysis") to rank-order the most influential variables (66). We then performed one-way sensitivity analyses on the most influential variables and reported the threshold values at which the coxib strategy became dominant (that is, values at which the coxib strategy became more effective and less expensive than the naproxen strategy).

Although one-way sensitivity analyses provide information about the robustness of a model, they are inade-

Table 3. **Cost Estimates***

Variable	Base-Case Cost Estimate, $	Range Tested
General medicine office visit	99	25–150
Diagnostic upper endoscopy for dyspeptic symptoms		
Endoscopist's consultation fee	160	
Endoscopist's procedure fee	231	
Facility fee	433	400–1500
Biopsy and rapid urease test for *Helicobacter pylori*	150	
Total cost	974	
Inpatient admission for ulcer hemorrhage		
Medicare DRG for upper gastrointestinal hemorrhage	4072	
Emergency department fee	168	
Inpatient gastroenterologist consultation	160	2000–10 000
Endoscopist's fee	299	
Follow-up visit by gastroenterologist	53/d × 7-d follow-up	
Total cost	4918	
Inpatient admission for ulcer perforation		
Medicare DRG for bowel perforation	13 531	
Emergency department fee	168	
Initial surgical consultation	97	
Surgeon's fee	710	5000–20 000
Anesthesiologist's fee	299	
Follow-up visit by surgeon	53/d × 10-d follow-up	
Total cost	15 335	
Inpatient care for an acute MI		
Medicare DRG for uncomplicated MI	10 558	
Emergency department fee	168	
Initial cardiology consultation	160	
Interpretation fee for echocardiography	100	5000–20 000
Angiographer's fee for PTCA	299	
Follow-up visit by cardiologist	53/d × 5-d follow-up	
Total cost	11 550	
Outpatient care per month after acute MI		
Generic ACE inhibitor	120	
Generic selective β-blocker	75	
Generic aspirin	3	100–1000
Cardiac rehabilitation	120 × 3 sessions/mo	
Cardiologist office visit	53	
Total monthly cost	611	
Naproxen tablet	0.18 (AWP)	
	0.04 (VA price)	0.04–0.50
Coxib tablet	2.66 (AWP)	
	1.35 (VA Price)	1.00–3.00
PPI tablet	3.10 (AWP)	
	0.30 (VA price)	0.30–4.00

* Costs obtained from the 2002 American Medical Association *Current Procedural Terminology* codebook, the 2002 Medicare Fee Schedule, and the 2002 *Red Book* of average wholesale drug prices (65). ACE = angiotensin-converting enzyme; AWP = average wholesale price (as listed in the *Red Book* [65]); DRG = diagnosis-related group; MI = myocardial infarction; PPI = proton-pump inhibitor; PTCA = percutaneous transluminal coronary angioplasty; VA = Veterans Administration.

quate to simulate real-world conditions. To acknowledge the reality that each individual carries a unique composition of clinical probabilities, we conducted a probabilistic (Monte Carlo) simulation under the assumption that all variables were triangular in distribution (66). The triangular distribution assumes that a parameter's base-case value is most likely to occur and that the minimum and maximum values are least likely to occur. The probability of observing a value between the base-case and extreme value is linearly interpolated. We evaluated 1000 trials through this simulation and report the median and 2.5th and 97.5th percentile values of the incremental cost-effectiveness ratio between the competing strategies. Because different third-party payers have different willingness-to-pay thresholds, we also report the percentage of trials falling below four incremental cost-effectiveness ratio thresholds: $200 000, $150 000, $100 000, and $50 000 per QALY gained.

Incorporating Patient Risk for Ulcer Complications

We performed further sensitivity analysis by considering an alternative cohort of patients at high risk for ulcer

complications. In this analysis, we assumed that all patients entering the model had a history of an ulcer hemorrhage and were therefore at high risk for recurrent ulcer complications. We set the probability of developing an ulcer complication at 19% for the nonselective NSAID strategy, based on data from randomized, controlled trials of high-risk patients receiving naproxen (67). On the basis of a recent high-quality randomized, controlled trial (68), we set the probability of ulcer complications for the coxib arm at 4.9%.

Incorporating Cardiovascular Events

We constructed an alternative model to account for the potential effect of clinically significant cardiovascular events, including stroke, unstable angina, and acute myocardial infarction. On the basis of cumulative data (16), including an FDA review (20) of a large coxib outcomes study (the Vioxx Gastrointestinal Outcomes Research trial [10]) and ongoing postmarketing surveillance (19), we set the rates of significant cardiovascular events at 0.77% per year for coxibs and 0.4% per year for naproxen. We based our cost estimates for a severe cardiovascular event on the inpatient and follow-up care for a myocardial infarction (**Table 3**) and adopted a utility of 0.88 for the post–myocardial infarction health state (69). See the Appendix (available at www.annals.org) for the rationale supporting these estimates.

Role of the Funding Sources

The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Table 4 displays the results of the analysis under varying conditions. Under base-case conditions (assuming a 3% discount rate), the use of coxibs instead of nonselective NSAIDs cost an incremental $275 809 to gain 1 additional QALY. Accounting for the potential disparity in cardiovascular events increased the incremental cost to $395 324 per QALY gained. When the VA acquisition costs were used as a surrogate for a large third-party buying consortium, the incremental cost decreased to $142 095 per QALY gained.

The inclusion of high-risk patients altered our base-case results. For patients with a history of ulcer hemorrhage, the incremental cost per QALY gained decreased to $55 803 when a coxib was used instead of a nonselective NSAID.

Multivariable sensitivity analysis of all parameters revealed that the model was sensitive to the following variables (in descending order of influence): cost per coxib pill, number of coxib pills consumed daily, cost per pill of naproxen, and probability of ulcer complications with naproxen (**Table 5**). The remaining probability estimates did not affect the model when varied over a wide range.

Figure 4 displays the results of 1000 trials through a probabilistic Monte Carlo simulation. The median incremental cost-effectiveness ratio of these trials was $268 000 per QALY gained (2.5th and 97.5th percentiles, $146 000 and $633 000, respectively). The percentages of trials beneath the $200 000, $150 000, $100 000, and $50 000 willingness-to-pay thresholds were 19.5%, 4.3%, 0.1%, and 0.0%, respectively. For example, if a third-party payer was willing to pay $150 000 per QALY gained for coxib therapy, 4.3% of the patients in this simulation would fall within the budget.

DISCUSSION

Our analysis of competing management strategies for the use of NSAIDs in arthritis suggests that the recent recommendation to adopt coxibs as the first-line agent for moderate to severe arthritis pain (14) may not be cost-

Table 4. **Results of Cost-Utility Analysis under Varying Conditions***

Analysis	Strategy	Cost†	Effectiveness	Incremental Cost-Effectiveness‡
		$	*QALYs gained*	*$*
Base-case analysis (3% discount rate)	Naproxen	4859	15.2613	—
	Coxib	16 443	15.3033	275 809
Base-case analysis (5% discount rate)	Naproxen	4238	12.6933	—
	Coxib	13 820	12.7282	274 555
Including cardiovascular events	Naproxen	5037	15.2539	—
	Coxib	16 620	15.2832	395 324
Using VA prices	Naproxen	1917	15.2613	—
	Coxib	7885	15.3033	142 095
Assuming high-risk cohort (previous ulcer hemorrhage)	Naproxen	14 294	14.7235	—
	Coxib	19 015	14.8081	55 803

* QALY = quality-adjusted life-year; VA = Veterans Administration.
† Average cost per patient.
‡ Cost per additional QALY gained when using a coxib versus naproxen.

Table 5. **Results of One-Way Sensitivity Analyses***

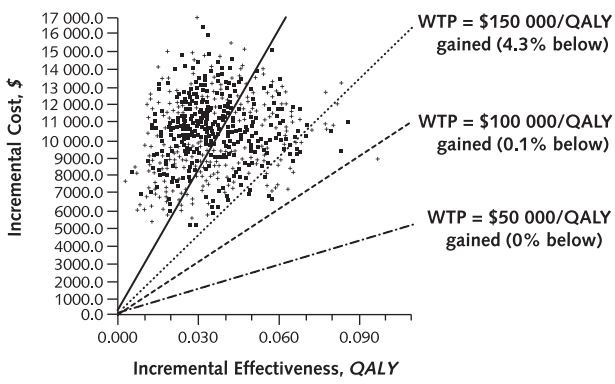
Variable	Base-Case Estimate	Threshold	Comment
Cost per coxib tablet, $	2.66	0.25	If less than threshold, then coxib strategy becomes dominant
Coxib pills consumed daily, *n*	1.0	0.2	If less than threshold, then coxib strategy becomes dominant
Probability of upper-gastrointestinal dyspeptic symptoms in patients receiving naproxen, %	10.9	42	If greater than threshold, then coxib strategy becomes dominant
Rate of clinically significant ulcer complications with naproxen over lifetime horizon, %	7.2	40	If greater than threshold, then coxib strategy becomes dominant
Cost per naproxen tablet, $	0.18	2.17	If greater than threshold, then coxib strategy becomes dominant

* The listed thresholds are the values at which the coxib strategy becomes dominant (that is, becomes more effective and less expensive than the naproxen strategy).

effective in patients at average risk for ulcer complications. Although coxibs significantly decrease both ulcer-related complications (10–13) and nonulcer dyspepsia (9) compared with nonselective NSAIDs, our analysis reveals that the use of coxibs instead of nonselective NSAIDs may cost an additional $275 809 per year to gain 1 additional QALY—a value that is more than twice the cost per QALY associated with initiating dialysis and continuing aggressive care for hospitalized patients who are seriously ill (**Appendix Table 1**, available at www.annals.org) (74). We estimate that the coxib strategy will dominate the nonselective NSAID strategy only if the cost per coxib tablet is decreased by nearly 90%. Our study yielded these findings despite our construction of a model that was explicitly biased in favor of coxibs. If our analysis were not designed to reflect a "best case" scenario for coxibs, the incremental cost-effectiveness of the coxib strategy would be higher.

Our analysis further suggests that the potential disparity in cardiovascular events associated with coxibs may have substantial cost-effectiveness implications. By incorporating data derived from a systematic review of the published coxib trials reporting cardiovascular outcomes (17) and data presented in several FDA reviews (19–21), we estimated that it may cost nearly $400 000 per QALY to use a coxib instead of a nonselective NSAID—a value that is more than 3.5 times the cost per QALY associated with initiating intensive care and mechanical ventilation for patients with respiratory failure and a poor prognosis (**Appendix Table 1**, available at www.annals.org) (73). These data suggest that further trials evaluating the cardiovascular effects of coxibs are necessary and the decision to adopt coxibs as the first-line agent for arthritis should be made with a keen awareness of the potential effect of the added relative risk for cardiovascular events on overall effectiveness and cost-effectiveness.

Figure 4. **Probabilistic sensitivity analysis using 1000 trials.**



This analysis simultaneously varies all parameters over the full range of plausible values. Each point represents the incremental cost-effectiveness ratio generated by one trial through the simulation. The median incremental cost-effectiveness ratio of $268 000 per quality-adjusted life-year (*QALY*) gained is shown (*solid line*), and, by definition, 50% of the trials fall on either side. Points below and to the right of each line represent trials that generated an incremental cost-effectiveness ratio below the specified threshold. For example, if a third-party payer was willing to pay $150 000 per QALY gained for coxib therapy, then only 4.3% of the patients in this simulation would fall within the budget. WTP = willingness-to-pay thresholds.

Patients with a history of ulcer complication are at high risk for developing recurrent complications while receiving NSAIDs (67). The use of coxibs in these high-risk patients is therefore conceptually attractive. Our analysis reveals that the use of coxibs instead of nonselective NSAIDs in high-risk patients decreases the incremental cost-effectiveness ratio from $275 809 to $55 803 per QALY gained. This diminished incremental cost-effectiveness ratio may be acceptable to many third-party payers, suggesting that coxibs may be a more cost-effective option in the management of patients at high risk for developing an ulcer complication from nonselective NSAIDs.

Notably, our findings are not consistent with previous decision models that have evaluated the cost-effectiveness of coxibs. For example, Pellissier and colleagues (61) estimated that rofecoxib is likely to be both more effective and cost-saving when compared with nonselective NSAIDs. Careful evaluation of this analysis, however, revealed that the model may have been biased in favor of rofecoxib. In particular, the analysis set the cost of nonselective NSAIDs at $1.47 per tablet and further assumed that 25.5% of patients receiving nonselective NSAIDs are co-prescribed omeprazole at a cost of $3.77 per tablet. Therefore, on the basis of these assumptions, the initial cost for prescribing a nonselective NSAID was $2.43 per tablet ($1.47 + [$3.77 × 0.255])—a value $0.01 more than the cost of rofecoxib, which was set at $2.42 per tablet. Moreover, while requiring the nonselective NSAID arm to incur the

costs of co-prescribed omeprazole, the authors did not allow for the decreased rate of GI complications afforded by PPIs. Because recent data indicate that the combination of a nonselective NSAID and a PPI is as effective as a coxib alone (68, 75), the model is biased in favor of coxibs by economically penalizing the nonselective NSAID arm without awarding additional effectiveness. Therefore, because coxibs are more effective than nonselective NSAIDs in preventing GI complications, these assumptions ensure that rofecoxib is both more effective and less expensive than nonselective NSAIDs. A recently published critical review of this analysis (76) failed to address these potential shortcomings.

Our study has several limitations. As with any decision analysis, the results depend on the validity of the base-case estimates. Because our base-case point estimates are unlikely to reflect all populations, our results are unlikely to be precisely reproduced in all populations. Moreover, several of our estimates are based on studies of varying design, patient population, follow-up, and quality. However, we have attempted to guard against inaccurate base-case results by systematically reviewing the literature, relying on preexisting meta-analyses when available, and conducting our own meta-analyses when necessary to develop point estimates. When there was a range of data, we selected conservative estimates that tended to bias the model in favor of the coxib strategy and therefore systematically biased the model against nonselective NSAIDs. In addition, we performed a probabilistic sensitivity analysis to acknowledge that each estimate is likely to vary widely in clinical practice. Despite this conservative approach, our model indicates that the degree of risk reduction seen with coxibs does not offset their increased costs compared with nonselective NSAIDs in the management of average-risk patients with chronic arthritis.

In light of recent data indicating that rofecoxib and celecoxib may have differences in clinical and economic outcomes, our analysis may be criticized for grouping both cyclooxygenase-2 inhibitors into the same strategy. For example, a recent case–control study (77) found a higher short-term incidence of upper-GI hemorrhage with rofecoxib versus celecoxib. Moreover, data indicate that dyspepsia rates between rofecoxib and nonselective NSAIDs converge after 6 months (9), whereas celecoxib maintains its dyspepsia risk reduction without convergence (78). In contrast, a multicenter randomized, controlled trial found that rofecoxib provides an efficacy advantage over celecoxib for osteoarthritis of the knee (79). In addition, analysis of a large pharmacy database revealed that patients require a mean of 1.4 celecoxib pills per day (200 mg) versus 1.1 rofecoxib pills per day (25 mg) (80). An analysis of prescribing patterns in the VA system suggests that this disparity may form the economic basis for preferring rofecoxib over celecoxib (81). However, to explicitly bias our model in favor of coxibs, we designed a hypothetical "best-case" coxib that represents the most favorable hybrid between celecoxib and rofecoxib. Four estimates, in particular, exemplify this bias. First, rather than model a higher rate of ulcer complications for rofecoxib than celecoxib, we assumed a favorable 60% risk reduction in ulcer complications for both coxibs compared with naproxen. Second, rather than assume that rofecoxib provided no risk reduction in dyspepsia after 6 months, we assumed that both coxibs provided a 30% reduction over the course of the entire lifetime horizon. Third, rather than assume that the efficacy of celecoxib was inferior to rofecoxib, we assumed that both coxibs were equally effective in providing symptom relief for arthritis pain. Finally, rather than estimate a daily average consumption of 1.4 celecoxib pills and 1.1 rofecoxib pills, we assumed that only 1 pill was required daily for all coxibs. Therefore, where clinical data tend to disfavor rofecoxib (for example, upper-GI hemorrhage and dyspepsia rates), we used celecoxib data, and where clinical data tend to disfavor celecoxib (for example, arthritis efficacy and daily average consumption), we adopted rofecoxib data. Despite modeling this "best-case" hybrid coxib, our analysis suggests that coxibs may not be cost-effective in our base-case cohort.

Our base-case analysis applies only to a narrow patient population. Specifically, our hypothetical cohort has chronic arthritis and is not taking concurrent aspirin. Therefore, our results may not be applicable to alternative populations, including those using coxibs for other musculoskeletal disorders or those in need of aspirin prophylaxis. However, the FDA currently approves coxibs only for the management of osteoarthritis and rheumatoid arthritis. In addition, although many patients with chronic arthritis require aspirin once daily for cardiovascular prophylaxis, data from the major coxib studies reveal that the use of concurrent aspirin seems to attenuate the relative GI protective effects of coxibs (12). Therefore, there might be no difference in GI complications among the competing strategies if we allowed aspirin use in our model, in which case the incremental cost-effectiveness ratio for coxibs would be infinite (additional cost for no additional benefit). The most recent guidelines for the use of aspirin prophylaxis are more inclusive than before (82). With the probable increase in aspirin prophylaxis in response to these guidelines, a smaller cohort of patients may reap the GI protective benefits of coxibs. Therefore, the increase in aspirin use prompted by these guidelines should be met with a decrease in coxib use, since coxibs have not been shown to be either effective or cost-effective in patients using aspirin.

In conclusion, this analysis reveals that the risk reduction for GI complications seen with coxibs is unlikely to offset their increased cost versus nonselective NSAIDs in the management of average-risk patients with chronic arthritis. Our analysis suggests that the potential disparity in cardiovascular events between nonselective NSAIDs and coxibs may further increase the incremental cost-effectiveness between these strategies. However, this finding will require further confirmation in large clinical trials. For the

subgroup of patients with a history of ulcer complications, our results suggest that coxibs may be associated with an acceptable incremental cost-effectiveness ratio. In light of the pervasive trend of increasing pharmaceutical expenditures in the United States, these findings may have relevance to patients, clinicians, insurers, and policymakers who pay for and benefit from health care.

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Presented in part at the American Gastroenterological Association COX-2 Inhibitor Research Forum at Digestive Disease Week, May 2002, San Francisco, California.

Acknowledgments: The authors thank Emmett Keeler, PhD; Paul G. Shekelle, MD, PhD; Catherine MacLean, MD, PhD; Gerald Kominski, PhD; and A. Mark Fendrick, MD, for their thoughtful reviews of the manuscript.

Grant Support: Dr. Spiegel is supported by National Institutes of Health training grant DK-07180. Dr. Dulai is supported by National Institutes of Health K23 Career Development Award RR-16188. Dr. Gralnek is supported by a VA HSR&D Advanced Research Career Development Award.

Potential Financial Conflicts of Interest: *Consultancies:* I.M. Gralnek (Pharmacia); *Honoraria:* G.S. Dulai (Merck Pharmaceuticals), I.M. Gralnek (Merck Pharmaceuticals and Pharmacia); *Grants received:* I.M. Gralnek (Pharmacia).

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