

Minimizing Complications From Nonsteroidal Antiinflammatory Drugs: Cost-Effectiveness of Competing Strategies in Varying Risk Groups

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Objective. To appraise the cost-effectiveness of competing therapeutic strategies in patient cohorts eligible for aspirin prophylaxis with varying degrees of gastrointestinal (GI) and cardiovascular risk.

Methods. Cost-effectiveness and cost-utility analyses were performed to evaluate 3 competing strategies for the management of chronic arthritis: 1) a generic nonselective nonsteroidal antiinflammatory drug (NSAID_{NS}) alone; 2) NSAID_{NS} plus a proton pump inhibitor (PPI); and 3) a cyclooxygenase 2-selective inhibitor (coxib) alone. Cost estimates were from a third-party payer perspective. The outcomes were incremental cost per ulcer complication avoided and incremental cost per quality-adjusted life year (QALY) gained. Sensitivity analysis was performed to evaluate the impact of varying patient GI risks and aspirin use.

Results. In average-risk patients, the NSAID_{NS} + PPI strategy costs an incremental \$45,350 per additional ulcer complication avoided and \$309,666 per QALY gained compared with the NSAID_{NS} strategy. The coxib strategy was less effective and more expensive than the NSAID_{NS} + PPI strategy. Sensitivity analysis revealed that the NSAID_{NS} + PPI strategy became the dominant approach in patients at high risk for an NSAID adverse event (i.e., patients taking aspirin with ≥ 1 risk factor for a GI complication).

Conclusion. Generic nonselective NSAIDs are most cost-effective in patients at low risk for an adverse event. However, the addition of a PPI to a nonselective NSAID may be the preferred strategy in patients taking aspirin or otherwise at high risk for a GI or cardiovascular adverse event.

KEY WORDS. Cost-effectiveness; Nonsteroidal antiinflammatory drugs; Cox-2 inhibitors; Proton pump inhibitors.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are the most commonly used medications for chronic arthritis, accounting for 111 million prescriptions annually and 3% of the American prescription drug market (1,2). These

agents continue to serve as the mainstay of treatment despite their association with clinically significant gastrointestinal (GI) complications, including nonulcer dyspepsia, symptomatic ulcers, ulcer hemorrhages, and ulcer perforations (3). The economic impact of these adverse events is significant: they result in >100,000 hospitalizations annually at a cost of \$1.6 billion (1,4). Moreover, each year there are 17,000 deaths in the United States as a result of NSAID-related GI complications (1). In light of the substantial human and economic costs of NSAID-related adverse events, the decision to use NSAIDs requires a delicate balance between effective pain relief on the one hand and GI complications on the other.

However, the optimal therapeutic strategy is not dictated by generic decision rules, but rather is guided by consideration of individual risk factors (5). In particular, the risk of developing NSAID-related GI complications is highest among patients taking concurrent aspirin, coumadin, or steroids; patients with a previous history of an ulcer hemorrhage; and patients >65 years of age (5,6). Moreover, the prevalence of these risk groups has increased significantly in lockstep with the aging of the

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American population and the increasing use of aspirin for cardioprophylaxis. In light of these clinical data and epidemiologic trends, there is an increasing need to develop strategies that minimize adverse events while effectively treating the burgeoning population of high-risk patients with chronic arthritis.

Cyclooxygenase 2-selective inhibitors, including rofecoxib and celecoxib (coxibs), have been developed to fill the need for a safer alternative to the traditional nonselective NSAID (NSAID_{NS}). When compared with NSAID_{NS} agents, including naproxen and ibuprofen, coxibs achieve equal arthritis pain relief while reducing clinically significant ulcer complications by 50% (7–10). For these reasons, coxibs are now widely used in clinical practice, and at least one professional society has endorsed coxibs as the drug class of choice for the initial management of moderate-to-severe arthritis pain (11).

Despite the enthusiasm for coxibs, emerging data suggest that alternative therapies may be equally or more preferable, including the use of an NSAID_{NS} alone or in combination with a proton pump inhibitor (PPI). In particular, 5 findings cast uncertainty regarding the endorsement of coxibs in lieu of these alternative therapies: 1) despite the significant relative risk reduction in GI complications afforded by coxibs, their absolute risk reduction compared with NSAID_{NS} is <1% for significant ulcer complications (7–10); 2) recent economic models reveal that the small degree of risk reduction is insufficient to offset the increased cost of coxibs versus generic NSAIDs for average-risk patients (12,13); 3) prospective studies in high-risk patients indicate that coxibs do not provide an additional risk reduction when compared with the NSAID_{NS} + PPI combination (14,15); 4) data reveal that the use of concurrent aspirin attenuates the relative GI protective effects of coxibs versus NSAID_{NS} (9); and 5) 1 randomized controlled trial (Vioxx gastrointestinal outcomes research [VIGOR] trial) revealed a significantly increased risk for cardiovascular events with rofecoxib versus naproxen (7).

These circumstances raise questions regarding the cost-effective use of coxibs in patient populations eligible for aspirin prophylaxis with various degrees of GI and cardiovascular risk. Previous decision analyses have demonstrated that coxibs may be cost-effective in patients at high risk for GI complications (12,13,16–19). However, these models generally have focused on a limited number of competing strategies, have not allowed for the use of concurrent aspirin, have not evaluated varying combinations of GI and cardiovascular risks simultaneously, and have not incorporated model flexibility to account for varying management decisions as a function of individual risk.

In light of these new data and uncertainties, we sought to reappraise the initial treatment of choice for arthritis patients with varying risk factors. We therefore performed a comprehensive economic model to estimate the cost-effectiveness of 3 competing strategies: 1) NSAID_{NS} alone, 2) NSAID_{NS} + PPI, and 3) coxib alone. We designed our analysis to account for both GI and cardiovascular risk factors in a cohort of patients eligible for aspirin prophylaxis, and structured the model to reflect the clinical reality that management decisions are conditional upon individual risk profiles.

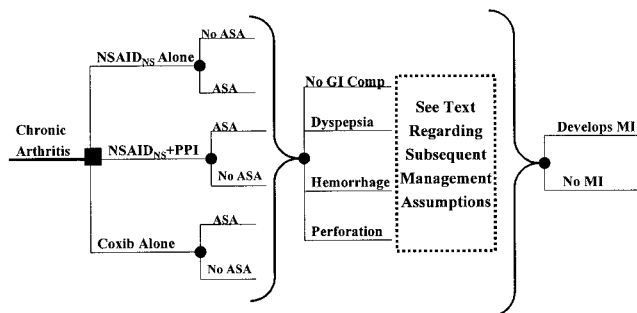


Figure 1. Truncated decision model. The base-case patient has chronic arthritis and is at average risk for gastrointestinal and cardiovascular complications. The clinician may either treat with a generic nonselective nonsteroidal antiinflammatory drug (NSAID_{NS}), an NSAID_{NS} combined with a proton pump inhibitor (NSAID_{NS} + PPI), or a cyclooxygenase 2-selective inhibitor (coxib). Within each strategy, patients are stratified according to whether they receive concurrent aspirin (ASA) for cardiovascular prophylaxis. In each strategy, the patients either develop a gastrointestinal (GI) complication (dyspepsia, ulcer hemorrhage, ulcer perforation) or remain free of GI adverse events. Similarly in each strategy, patients are eligible to develop an acute myocardial infarction (MI) over the course of the 1-year time horizon. See text for details regarding specific assumptions governing patient management and probability estimates for individual branch points.

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 (20). Using decision-analysis software (DATA 4.0, TreeAge Software Inc., Williamstown, MA), we evaluated a hypothetical cohort of 60-year-old patients with chronic arthritis who require long-term NSAID therapy for moderate-to-severe arthritis pain (Figure 1). Patients entered the hypothetical model without GI symptoms and were initially treated with 1 of 3 competing strategies: 1) NSAID_{NS} alone (modeled after naproxen 500 mg twice daily); 2) NSAID_{NS} combined with a PPI (modeled after lansoprazole 15 mg once daily); or 3) coxib alone (either celecoxib 200 mg once daily or rofecoxib 25 mg once daily). To reflect clinical reality, we assumed that a subset of the cohort required daily aspirin for cardiovascular prophylaxis, and therefore stratified the model by both the strategy employed and the aspirin status of the patient, as demonstrated in Figure 1.

Over the course of a 1-year time horizon, the patients either developed a GI complication or remained free of GI adverse events. Patients without complications continued taking their prescribed medication and those with complications required additional evaluation, as described below. Patients in all strategies were also eligible to develop a myocardial infarction during the 1-year time horizon.

Model assumptions. Figure 1 demonstrates the major branch points governing patient flow through the decision tree. To closely emulate clinical practice, we incorporated the following assumptions regarding patient and physician behavior under varying circumstances.

Table 1. Base-case clinical probability estimates for clinically significant ulcer complications among competing strategies*

Therapeutic strategy	Relative risk versus NSAID _{NS} alone (from literature)	Relative risk versus NSAID _{NS} alone (from expert panel)	Base-case estimate (% per year)	References
NSAID _{NS} alone (no ASA)	1.0	NA	3	7–10,24
NSAID _{NS} alone (with ASA)	2.5	NA	7.5	9,25–29
NSAID _{NS} + PPI (no ASA)	0.2–0.54	NA	1.5	14,28–31
NSAID _{NS} + PPI (with ASA)	No literature identified	0.8	2.45	NA
Coxib alone (no ASA)	0.5	NA	1.5	7–10
Coxib alone (with ASA)	2.5	NA	7.5	13

* Each strategy is stratified by subgroups based upon aspirin cotherapy status. Estimates apply to patients at average risk for a gastrointestinal event. NSAID_{NS} = generic nonselective nonsteroidal antiinflammatory drug; ASA = aspirin; NA = not available; PPI = proton pump inhibitor; coxib = cyclooxygenase 2-selective inhibitor.

- 1) Patients were required to develop symptoms or clinically significant complications to prompt further evaluation. We therefore based our model upon patient-reported outcomes rather than surrogate endpoints, such as endoscopic lesions or ulcer-healing rates.
- 2) All patients developing upper GI dyspeptic symptoms were required to visit their primary care provider. Patients not receiving a PPI from the outset were then coprescribed an 8-week trial of PPI therapy to empirically treat a presumed underlying ulcer, and were subsequently referred to a gastroenterologist only if their symptoms persisted despite the PPI trial. In contrast, patients in the NSAID_{NS} + PPI strategy were referred directly to a gastroenterologist for endoscopic evaluation of dyspepsia because these patients had already developed symptoms despite PPI therapy.
- 3) Because management decisions are different for high-risk patients, we designed our model to behave differ-

- ently as a function of individual risk. For example, current guidelines suggest that patients at high risk for a GI event (i.e., elderly patient with previous ulcer bleed) who develop NSAID-related dyspepsia should be referred directly for endoscopy in lieu of empiric PPI cotherapy (21). This type of conditional behavior may be incorporated into a decision model through the use of “logic nodes,” which are branch points governed by conditional statements. Using this technique, we programmed our model to bypass empiric PPI cotherapy and primary care followup in favor of direct endoscopic referral for all patients at high risk for a GI event (defined as relative risk >3.0 versus baseline risk).
- 4) All patients referred to the gastroenterologist for dyspepsia were required to undergo endoscopic evaluation as recommended by current guidelines for the management of recurrent dyspepsia (21). Patients found to have an ulcer by upper endoscopy received rapid ure-

Table 2. Base-case clinical probability estimates for dyspeptic symptoms among competing strategies*

Therapeutic strategy	Relative risk versus NSAID _{NS} alone (from literature)	Relative risk versus NSAID _{NS} alone (from expert panel)	Base-case estimate (% per year)	References
NSAID _{NS} alone (no ASA)	1.0	NA	11	32
NSAID _{NS} alone (with ASA)	No literature identified	1.4	15.5	NA
NSAID _{NS} + PPI (no ASA)	0.29–0.84 (see Figure 2)	NA	9	28–30,33
NSAID _{NS} + PPI (with ASA)	No literature identified	1.0	11	NA
Coxib alone (no ASA)	0.77	NA	8	10,35–44
Coxib alone (with ASA)	No literature identified	1.0	11	NA

* Each strategy is stratified by subgroups based upon aspirin cotherapy status. See text for details regarding relative-risk estimates. See Table 1 for definitions.

Table 3. Additional probability estimates

Variable	Base-case estimate	Range in literature	Range tested in sensitivity analysis	References
Probability that endoscopy for ulcer hemorrhage reveals				
Low-risk ulcer stigmata, %	66	50–90	50–100	62
High-risk ulcer stigmata, %	34	20–70	10–80	62
Probability of recurrent hemorrhage for untreated low-risk ulcer stigmata				
Clean-based ulcer, %	2	0–5	0–10	62
Ulcer with overlying clot, %	10	2–15	2–20	62
Probability of recurrent hemorrhage for high-risk ulcer stigmata following endoscopic hemostasis, %	20	4–40	5–40	62
Probability of successful repeat hemostasis in patients with recurrent hemorrhage treated with second round of endoscopic therapy, %	70	0.5–1.0	50–100	62,63
Probability of endoscopically induced perforation or uncontrollable bleeding, %	0.02	0–3	0–5	64–66
Probability of perioperative death for surgical ulcer repair, %	10	0–20	0–30	66
Average inpatient length of stay for an ulcer hemorrhage, days	7	1–20	1–20	57
Average inpatient length of stay for an ulcer perforation, days	10	1–20	1–20	57
Probability of developing moderate side effect from antibiotics for <i>H. pylori</i> eradication, %*	0.05	0–3	0–5	67–73
Probability of developing severe side effect from antibiotics for <i>H. pylori</i> eradication, %*	0.001	0.001	0–0.01	67–73

* *H. pylori* = *Helicobacter pylori*.

ase testing for *Helicobacter pylori*, and subsequently received a 14-day course of eradication therapy if *H. pylori* positive. Those patients without an ulcer remained on once-daily PPI therapy for an additional 8 weeks for treatment of nonulcer dyspepsia.

- 5) All patients with an ulcer hemorrhage were admitted to the hospital and received endoscopic evaluation. Patients with persistent or recurrent hemorrhage despite endoscopic therapy received surgical intervention. Following successful management, all survivors were tested for *H. pylori* and treated if positive. In addition, all patients received an 8-week course of PPI therapy to heal their ulcer and were placed on acetaminophen for the remainder of the time horizon.

Clinical probability estimates. Our base-case model incorporated 31 probability estimates derived from a systematic review of the medical literature (Tables 1–3). We performed a structured search of published reports from the Medline bibliographic database to identify English-language publications pertaining to our 31 clinical inputs from January 1990 to January 2004. 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, England) to establish point estimates for use in the decision tree. Because our base-case estimates are unlikely to be precisely reproduced in varying populations, we varied each estimate over a wide range in sensitivity analysis, as described below.

Where data were not available for base-case point estimates, we elicited ratings from a multidisciplinary expert panel. The panel was comprised of 9 experienced physicians of various specialties and from mixed practice settings (4 universities and 5 communities) throughout the United States. We used a modified Delphi technique to elicit estimates regarding areas of uncertainty (22), and adopted the median response as our base-case estimate. Each estimate was then subjected to sensitivity analysis over a wide range.

Use of concurrent aspirin. The most recent guidelines for the use of aspirin prophylaxis are more inclusive than ever before, and up to two-thirds of patients with chronic

arthritis now meet criteria for cardiovascular prophylaxis (23). The exact prevalence of aspirin use in patients receiving NSAIDs for chronic arthritis is unknown, but is likely to be lower than that recommended by the current guidelines. Based upon data from the Celecoxib Long-term Arthritis Safety Study (CLASS), which prospectively evaluated over 3,000 patients with osteoarthritis and allowed for the use of concurrent aspirin, we assumed that 20% of our cohort received aspirin in addition to their prescribed NSAID (9). We therefore stratified each therapeutic strategy by aspirin use, and ascribed differential complication rates within each strategy as a function of aspirin status (see below for estimates). Because the prevalence of aspirin use varies between populations, we varied our base-case assumption between 0% and 100% in the sensitivity analysis.

Clinically significant ulcer complications in patients receiving nonselective NSAIDs (Table 1). Clinically significant ulcer complications include symptomatic ulcers, ulcer hemorrhages, and ulcer perforations (5). We identified 5 trials reporting these complications in patients receiving NSAID_{NS} agents (7–10,24). The mean annualized rate of ulcer complications is 3.0% per year, and we adopted this as our base-case estimate for average-risk patients in the NSAID_{NS} strategy. The addition of low-dose aspirin (ASA) to an NSAID_{NS} increases the risk of GI complications by 2.5 times baseline, on average (9,25–29). We therefore assumed that the annualized rate of ulcer complications was 7.5% in the subset of patients receiving an NSAID_{NS} + ASA combination (3.0% base-case rate × 2.5), and we varied this estimate between 5% and 10% in our sensitivity analysis.

Clinically significant ulcer complications in patients receiving NSAID_{NS} + PPI (Table 1). Clinical data indicate that PPIs reduce the risk of GI events by 60–80% in patients receiving long-term NSAID_{NS} versus the baseline NSAID_{NS} risk (14,28–31). However, to explicitly bias the model against the NSAID_{NS} + PPI strategy, we assumed that the degree of risk reduction offered by PPIs was only 50%, and therefore set the annualized rate of ulcer complications for the NSAID_{NS} + PPI strategy at 1.5% (3.0% base-case rate × 0.5). Our review did not identify trials reporting complication rates for patients receiving an NSAID_{NS} + PPI + ASA combination. We therefore elicited judgment from the expert panel, which provided a median risk reduction estimate of 20% for the NSAID_{NS} + PPI + ASA combination versus NSAID_{NS} alone. We therefore assumed that the annualized rate of ulcer complications was 2.45% in the subset of patients receiving the NSAID_{NS} + PPI + ASA combination (3.0% base-case rate × 0.8). We varied this estimate from 1% to 10% in the sensitivity analysis.

Clinically significant ulcer complications in patients receiving coxibs (Table 1). Prospective randomized trials indicate that coxibs reduce clinically significant ulcer complications by 50% versus nonselective NSAIDs (7–10). We therefore set the annualized rate of ulcer complications for the coxib strategy at 1.5% (3.0% base-case rate × 0.5). In addition, a recent prospective trial in high-risk patients found equal rates of ulcer complications between patients receiving the NSAID_{NS} + PPI combination versus a coxib alone (14). This observation cross validates our calculated

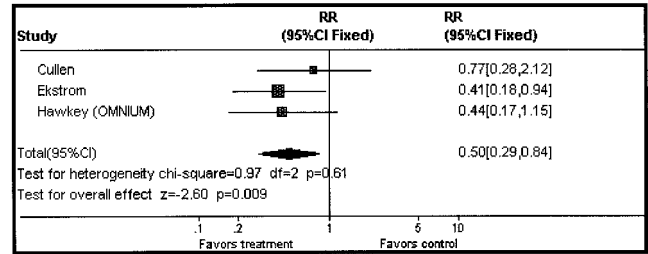


Figure 2. Meta-analysis using the fixed effects model of randomized controlled trials that report upper gastrointestinal dyspeptic symptoms in patients receiving a generic nonselective nonsteroidal antiinflammatory drug (NSAID_{NS}) plus a proton pump inhibitor versus an NSAID_{NS} alone. The summary estimate is the relative risk (RR). 95% CI = 95% confidence interval; OMNIUM = Omeprazole versus misoprostal for NSAID-induced ulcer management; df = degrees of freedom.

estimates for these strategies, because we set the complication rates for the NSAID_{NS} + PPI and coxib strategies to be equivalent (both 1.5% per year). As with NSAID_{NS} agents, concomitant ASA augments the GI toxicity of coxibs (9). Moreover, in the only published randomized trial reporting clinically significant ulcer complications in patients receiving coxib + ASA versus NSAID_{NS} + ASA (CLASS study), there was no significant difference in complicated GI events between interventions (9). Therefore, these data suggest that concurrent aspirin appears to attenuate the relative GI protective effects of coxibs versus NSAID_{NS}. Based on this study, we set the annualized rate of complicated GI events for the coxib + ASA and NSAID_{NS} + ASA subgroups to be equivalent. Because these estimates are potentially controversial, we performed a sensitivity analysis assuming that aspirin does not mitigate the effect of coxib therapy.

Upper GI dyspeptic symptoms in patients receiving NSAID_{NS} (Table 2). 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 annual prevalence of 11%, and we adopted this as our base-case value (32). Because the precision of this estimate is unlikely to be reproduced between different populations, we varied it from 5% to 25% in our sensitivity analysis.

Upper GI dyspeptic symptoms in patients receiving NSAID_{NS} + PPI (Table 2). We identified 4 studies reporting dyspeptic symptoms in patients receiving an NSAID_{NS} + PPI versus NSAID_{NS} alone (28–30,33). These trials are both clinically and statistically homogeneous, with a *P* value of 0.59 for the test of heterogeneity. We performed a meta-analysis of these trials using a fixed-effects model (Figure 2) (34). The pooled relative risk reduction for developing an upper GI dyspeptic symptom is 50% (95% confidence interval [95% CI] 29–84%). However, to explicitly bias the model against the NSAID_{NS} + PPI strategy, we set the risk reduction at only 18%, representing the lower 95% CI from meta-analysis. To derive the probability of dyspeptic symptoms for the NSAID_{NS} + PPI arm, we multiplied this risk reduction by the probability of dyspeptic symptoms for NSAID_{NS} arm, yielding a probability of 9% (11% for NSAID_{NS} × 0.82 relative risk).

Table 4. Utilities, duration, and disutility for modeled health states*

Clinical event	Utility of health state, 0–1	Duration of health state, days	Disutility of health state, QALYs†	Range used in sensitivity analysis
Dyspepsia (resolved)			–0.01	0.00 to –0.15
Severe dyspepsia	0.87‡	12§	–0.0043	
Moderate dyspepsia	0.91‡	23§	–0.0057	
Resolved dyspepsia	1.0	330	–0.0	
Dyspepsia (unresolved)	0.87‡	365	–0.13	–0.01 to –0.25
Ulcer hemorrhage without surgery (survive)			–0.022	0.00 to –0.20
Inpatient treatment for ulcer hemorrhage	0.49‡	4¶	–0.01	
Severe dyspepsia	0.87‡	35¶	–0.012	
Ulcer hemorrhage with surgery (survive)			–0.033	0.00 to –0.30
Inpatient treatment for ulcer hemorrhage and surgery	0.46‡	10¶	–0.021	
Severe dyspepsia	0.87‡	35¶	–0.012	
Myocardial infarction (survive)			–0.12	0.0 to –0.5
Acute event	0.0	4¶	–0.12	
Postmyocardial health state	0.88	364		
Death from ulcer complication or myocardial infarction	0.0	NA	–1.0	NA

* NA = not available.
† QALYs = quality-adjusted life years.
‡ Utilities derived from Groeneveld et al (56) and Ebell et al (58) (see Appendix A for details).
§ Duration of dyspeptic states as reported by Sonnenberg et al (61) (see Appendix A for details).
¶ Average length of stay in as reported by the Center for Medicare and Medicaid Services (59).

Upper GI dyspeptic symptoms in patients receiving coxibs (Table 2). We identified 11 trials reporting dyspeptic symptoms in patients receiving coxibs versus NSAID_{NS} (10,35–44). A previous meta-analysis of these trials calculated a pooled risk reduction of 23% for coxibs versus NSAID_{NS} (12). To derive the probability of dyspeptic symptoms for the coxib arm, we multiplied this risk reduction by the rate of dyspeptic symptoms for the NSAID_{NS} arm, yielding a rate of 8% (11% for NSAID_{NS} × 0.77 relative risk).

Cardiovascular event rates. A large randomized controlled trial of rofecoxib versus naproxen (the VIGOR trial) revealed a significantly increased rate of cardiovascular events with rofecoxib, with a relative risk of 1.89 (95% CI 1.03–3.45) in the subgroup of patients without an indication for aspirin (7,45). Although the reasoning behind this finding is uncertain and controversial (46), the clinical disparity in significant events was highlighted in a systematic review of coxib trials reporting cardiovascular endpoints (45) and has been a point of concern raised by several US Food and Drug Administration (FDA) reports (47–49). Based upon the relative risk and the annualized rates reported in the major coxib trials (0.74% for rofecoxib, 0.80% for celecoxib), we set the annualized rates of significant cardiovascular events in the subgroups not receiving aspirin to be 0.77% for the coxib arms and 0.4% for the NSAID_{NS} arms (7,9,45). We further assumed that cardiovascular events were equal across strategies for the subgroups receiving aspirin prophylaxis. Because these estimates are controversial and uncertain, we performed an additional analysis

assuming equal rates of cardiovascular events across all strategies.

Additional probability estimates. Our model included probability estimates regarding the management and consequences of peptic ulcer hemorrhage and perforation, along with estimates regarding the complications of endoscopy, surgery, and antibiotic therapy for *H. pylori*. Table 3 displays these base-case probabilities, the ranges used in sensitivity analyses, and the references from which the estimates were derived.

Outcomes. Although 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 analyses (50), previous economic models for NSAID therapy have used ulcer complications as the main outcome measure (12,15–19). We therefore evaluated 2 outcomes: the incremental cost per ulcer complication avoided and the incremental cost per QALY gained.

Utilities. To calculate QALYs for our decision model, we incorporated validated utilities for 7 discrete health states: 1) moderate dyspepsia; 2) severe dyspepsia; 3) ulcer hemorrhage without surgery; 4) ulcer hemorrhage or perforation with surgery; 5) myocardial infarction; 6) postmyocardial infarction state for survivors; and 7) death from an ulcer complication or myocardial infarction. Refer to Appendix A and Table 4 for the specific utility values employed and for the extended rationale supporting these estimates and their use in calculating QALYs for the model.

Table 5. Cost estimates*

Variable	Base-case cost estimate, \$	Range tested, \$
Cost of general medicine office visit	99	25–150
Cost of diagnostic upper endoscopy for dyspeptic symptoms		
Endoscopist's consultation fee	160	
Endoscopist's procedure fee	231	
Facility fee	433	
Biopsy and rapid urease test for <i>H. pylori</i>	150	
Total	974	400–1,500
Cost of inpatient admission for ulcer hemorrhage		
Medicare DRG for upper gastrointestinal hemorrhage	4,072	
Cost of emergency room fee	168	
Cost of inpatient gastroenterologist consultation	160	
Cost of endoscopist's fee	299	
Cost of 3 followup visits by gastroenterologist	159	
Total	4,858	2,000–10,000
Cost of inpatient admission of ulcer perforation		
Medicare DRG for bowel perforation	13,531	
Cost of emergency room fee	168	
Initial surgical consultation	97	
Surgeon's fee	710	
Anesthesiologist's fee	299	
Cost of 6 followup visits by surgeon	318	
Total	15,123	5,000–20,000
Cost of inpatient care for an acute MI		
Medicare DRG for uncomplicated MI	10,558	
Cost of emergency room fee	168	
Cost of initial cardiology consultation	160	
Cost of interpretation fee for ECHO	100	
Cost of angiographer's fee for PTCA	299	
Cost of 3 followup visits by cardiology	159	
Total	11,444	5,000–20,000
Monthly cost of outpatient care following acute MI		
Monthly cost of generic ACE inhibitor	120	
Monthly cost of generic selective beta-blocker	75	
Monthly cost of generic aspirin	3	
Monthly cost of cardiac rehabilitation, 3/month	360	
Cost of cardiologist office visit	53	
Total	611	100–1,000
Cost per tablet of naproxen	0.15	0.04–0.50
Cost per tablet of coxib	2.43	1.00–3.00
Cost per tablet of PPI (lansoprazole 15 mg tablet)	3.37	0.3–4.00
Cost of PPI + naproxen per day	3.52	0.3–4.00
Cost per tablet of aspirin	0.03	0.0–0.20

* *H. pylori* = *Helicobacter pylori*; DRG = diagnostic related group; MI = myocardial infarction; ECHO = echocardiogram; PTCA = percutaneous transluminal coronary angiogram; ACE = angiotensin-converting enzyme; coxib = cyclooxygenase 2-selective inhibitor; PPI = proton pump inhibitor.

Cost estimates. We estimated costs from the perspective of a third-party payer, considering only direct health care costs (Table 5). We obtained costs for diagnostic procedures, physician services, and inpatient hospitalizations (including length of stay) from the 2002 American Medical Association Current Procedural Terminology codebook, 2002 Medicare Diagnosis Related Group listings, and the 2002 Medicare Fee Schedule. Drug costs were derived by subtracting 10% from the average wholesale prices listed in the Red Book.

Sensitivity analyses. *Base-case sensitivity analysis.* To test the influence of all variables on the model results, we performed a “tornado analysis” to rank order the most influ-

ential variables (51). We performed one-way sensitivity analyses on the most influential variables and report the thresholds in which the relative order between strategies changes.

Incorporating GI and cardiovascular risk. We performed a sensitivity analysis to account for GI risk and ASA use by comparing the results achieved in 4 groups of patients, as demonstrated in Figure 3 (52). This 2 × 2 matrix indicates that patients may be stratified by their degree of GI risk (where high risk is defined by a relative risk of 3.0 for a GI complication versus baseline) and whether ASA cardioprophylaxis is coprescribed. In this manner, “patient group 1” is at the lowest risk for a GI event (low GI risk, no ASA) and “patient group 4” is at the highest risk for a GI event (high GI risk, using ASA).

	Low GI Risk	High GI Risk
No Aspirin	Patient Group 1	Patient Group 2
Aspirin	Patient Group 3	Patient Group 4

Figure 3. Four patient groups stratified by gastrointestinal (GI) risk and aspirin use (based on classification scheme developed by Fendrick and Garabedian-Ruffalo [52]).

RESULTS

Base-case results. The results of our base-case analysis in the average-risk cohort are displayed in Table 6. The NSAID_{NS} strategy cost \$650 per average patient treated and avoided an ulcer complication in 96.1% of the cohort, and was therefore the least expensive yet least effective of the 3 competing approaches. Compared with the NSAID_{NS} strategy, the NSAID_{NS} + PPI strategy cost an incremental \$45,350 per additional ulcer complication avoided, and an incremental \$302,333 per QALY gained. The coxib strategy was less effective yet more expensive than the NSAID_{NS} + PPI strategy and was therefore dominated. The coxib strategy remained dominated despite lifting the assumption that coxibs are associated with more cardiovascular events than nonselective NSAIDs. Similarly, coxibs remained dominated despite assuming that aspirin does not partially mitigate the gastroprotective effects of coxibs (data not shown).

Base-case sensitivity analysis. Sensitivity analysis revealed that the model was sensitive to the following variables, in descending order of influence: cost per pill of coxib, cost per pill of naproxen, cost per pill of PPI, number of coxib pills consumed daily, and the probability of

ulcer complications with naproxen. Table 7 displays the results of one-way sensitivity analyses for each of these parameters, and lists the thresholds at which the relative order between strategies changes. The remaining probability estimates did not alter the order of strategies when varied over a wide range.

Incorporating GI and cardiovascular risk. Table 8 demonstrates the cost-effectiveness and cost-utility results achieved in the 4 patient groups depicted in Figure 3. In patients at lowest risk for an ulcer complication (patient group 1), the use of any gastroprotection (either NSAID_{NS} + PPI or coxib) had an incremental cost of >\$60,000 per ulcer complication avoided and >\$300,000 per QALY gained compared with NSAID_{NS} alone. In contrast, the incremental cost of the NSAID_{NS} + PPI strategy fell to \$4,355 per ulcer complication avoided and \$28,000 per QALY gained in patients at high risk for a GI event who are not receiving ASA (patient group 2). The coxib strategy was dominated in patients receiving ASA prophylaxis (patient groups 3 and 4). The NSAID_{NS} + PPI strategy achieved an incremental cost of \$16,341 per ulcer complication avoided versus NSAID_{NS} in patients at low GI risk using ASA (patient group 3), and became the dominant strategy overall in patients at high GI risk using ASA (patient group 4).

DISCUSSION

This analysis of therapies in the management of chronic arthritis suggests that the optimal strategy is highly dependent upon individual risk factors. For patients at average risk for an NSAID-related GI complication, the analysis supports the finding of previous models that the use of generic nonselective NSAIDs is optimally cost-effective. Specifically, the analysis reveals that the substitution of either a coxib or an NSAID_{NS} + PPI combination in lieu of generic naproxen may cost >\$300,000 more per QALY gained in average-risk patients—a cost that is significantly higher than most accepted interventions in medicine.

Table 6. Base-case cost-effectiveness and cost-utility results in average risk patient population, assuming 20% receiving aspirin cardioprophylaxis*

Analysis	Strategy	Average cost† \$	Average effectiveness‡	Incremental cost-effectiveness§
Cost-effectiveness analysis	NSAID _{NS}	650	96.1	—
	NSAID _{NS} + PPI	1,557	98.1	\$45,350
	Coxib	1,572	97.3	Dominated by NSAID _{NS} + PPI¶
Cost-utility analysis	NSAID _{NS}	650	0.989	—
	NSAID _{NS} + PPI	1,557	0.992	\$302,333
	Coxib	1,572	0.991	Dominated by NSAID _{NS} + PPI¶

* NSAID_{NS} = generic nonselective nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; Coxib = cyclooxygenase 2-selective inhibitor. † Average cost per patient treated for 1 year.

‡ In cost-effectiveness analysis: percentage of patients avoiding an ulcer complication at 1 year (symptomatic ulcer, ulcer hemorrhage, or ulcer perforation); in cost-utility analysis: quality-adjusted life year gained.

§ In cost-effectiveness analysis: incremental cost per additional ulcer complication prevented compared with the NSAID_{NS} strategy; in cost-utility analysis: incremental cost per quality-adjusted life year gained compared with the NSAID_{NS} strategy.

¶ Coxib has higher costs and lower effectiveness than NSAID_{NS} + PPI.

Table 7. Results of one-way sensitivity analyses on average-risk cohort*

Variable	Base-case estimate	Threshold	Comment
Cost per pill of a coxib, \$	2.43	0.45	If less than threshold, then coxib strategy has lowest average cost-effectiveness ratio
Cost per pill of naproxen, \$	0.15	1.55	If more than threshold, then coxib strategy has lowest average cost-effectiveness ratio
Cost per pill of PPI, \$	3.37	0.40	If less than threshold, then naproxen + PPI strategy has lowest average cost-effectiveness ratio
Annual ulcer complication rate on naproxen, %	3.0	10.0	If greater than threshold, then coxib strategy has lowest average cost-effectiveness ratio

* The listed thresholds are the values at which the relative order between strategies changes. Coxib = cyclooxygenase 2-specific inhibitor; PPI = proton pump inhibitor.

However, in patients with one or more risk factors for a GI event (age >65 years, taking coumadin or steroids, previous ulcer complication), the unprotected use of NSAID_{NS} alone is dominated by the NSAID_{NS} + PPI strategy.

Our analysis indicates that the use of coxibs alone may not be cost-effective compared with the NSAID_{NS} + PPI strategy. These findings emerge despite explicitly biasing the model against the NSAID_{NS} + PPI strategy and in favor of the coxib strategy. Four assumptions, in particular, exemplify this bias: 1) rather than assume that PPIs reduce clinically significant ulcer complications by up to 80%, as suggested by the literature (14,28–31), we instead adopted a 50% risk reduction as our base-case estimate; 2) rather than assume that PPIs reduce nonulcer dyspepsia by 50%, as suggested by meta-analysis (Figure 2), we instead adopted an 18% risk reduction (representing the lower 95% CI from the meta-analysis); 3) rather than assume that up to 50% of the hypothetical 60-year-old cohort was eligible for cardioprophylaxis, as suggested by current guidelines (23), we assumed that only 20% received aspirin cotherapy—an assumption that favors coxibs given their attenuated gastroprotection when used with aspirin (9); and 4) rather than assume that the incidence of overall serious adverse events is lower with nonselective NSAIDs than coxibs, as indicated by an FDA review measuring outcomes across all organ systems (7.8% versus 9.3%) (49), our analysis only included GI adverse events and did not model the observed disparity in adverse events for other organ systems (e.g., renal effects, heart failure, etc.). Despite these assumptions, the coxib strategy was less effective and more expensive than the NSAID_{NS} + PPI combination.

This finding partly results from 2 key assumptions regarding coxibs: 1) the assumption that coxibs may be associated with a higher rate of cardiovascular events than NSAID_{NS} agents such as naproxen (7,45), and 2) the assumption that aspirin cotherapy may partially mitigate the gastroprotective effects of coxibs. In acknowledgement of the controversy and uncertainty surrounding the first assumption, we performed a separate analysis assuming equal rates of cardiovascular events across all strategies. Despite this favorable assumption for coxibs, however, the NSAID_{NS} + PPI combination remains dominant over the coxib strategy. Nonetheless, firm conclusions regarding these exploratory data cannot be drawn until further well-

designed prospective trials are conducted to evaluate the cardiovascular effects of coxibs. In the meantime, decision making should proceed with a keen awareness of the impact that potential variations in cardiovascular safety may have on overall effectiveness and cost-effectiveness.

Our assumption that aspirin partially mitigates the ability of coxibs to reduce ulcer complications versus generic NSAIDs is controversial. Nonetheless, it is based upon the only fully published randomized prospective trial to date reporting clinically significant ulcer complications in patients receiving coxib + ASA versus NSAID_{NS} + ASA (CLASS study) (9). Of note, sensitivity analysis of our model indicates that coxibs gain in cost-effectiveness when the CLASS data are disregarded. However, until prospective data from well-designed trials are collected that contradict the observation in CLASS, there will be insufficient evidence to conclude that coxibs are cost-effective in the increasingly large population of patients who are candidates for aspirin cardioprophylaxis.

Our study has several unique features compared with previous economic analyses for NSAID use in arthritis (12,16–19,53–55). First, whereas previous models focus on the selected subgroup of patients not eligible for aspirin cardioprophylaxis, this analysis allows for the use of concurrent aspirin, and therefore attempts to reflect clinical practice. Second, whereas most analyses compare the use of an NSAID_{NS} versus one “safer” strategy (e.g., coxib, nabumetone, NSAID_{NS} + misoprostal) (53,55), this analysis focuses on the role of PPI coprescription to address a currently debated option available in the primary care setting. Third, whereas previous models are designed as rigid trees that manage patients similarly regardless of individual risk, this model incorporates flexibility through the use of conditional logic nodes to account for varying management decisions as a function of patient risk. Last, whereas previous models handle areas of uncertainty by imputing data based on the authors’ best estimates, this analysis relied upon a multidisciplinary panel of 9 expert physicians to judge uncertain estimates, and elicited these estimates through an explicit and reproducible process (Delphi technique).

There are also several limitations to the present study. As with any decision analysis, the results depend upon the validity of the base-case estimates. Because our base-case point estimates are largely derived from randomized con-

Table 8. Results of cost-effectiveness and cost-utility analyses stratified by 4 patient groups of varying GI risk and aspirin use*

Analysis	Patient risk group	Strategy	Cost†	Effectiveness‡	Incremental cost/ effectiveness§	
Cost-effectiveness analysis	Low GI risk, no ASA (patient group 1)	NSAID _{NS} NSAID _{NS} + PPI Coxib	563 1,492 1,515	97.0 98.5 98.5	— 61,933 62,467	
	High GI risk, no ASA (patient group 2)	NSAID _{NS} NSAID _{NS} + PPI Coxib	1,556 1,752 1,782	91 95.5 95.5	— 4,355 5,022	
	Low GI risk with ASA (patient group 3)	NSAID _{NS} NSAID _{NS} + PPI Coxib	1,000 1,719 1,892	92.5 96.9 92.5	— 16,341 Dominated	
	High GI risk with ASA (patient group 4)	NSAID _{NS} NSAID _{NS} + PPI Coxib	2,382 2,302 3,061	77.5 90.7 77.5	Dominated — Dominated	
	Cost-utility analysis	Low GI risk, no ASA (patient group 1)	NSAID _{NS} NSAID _{NS} + PPI Coxib	563 1,492 1,515	0.990 0.993 0.992	— 309,666 476,000
		High GI risk, no ASA (patient group 2)	NSAID _{NS} NSAID _{NS} + PPI Coxib	1,556 1,752 1,782	0.986 0.993 0.990	— 28,000 56,500
		Low GI risk with ASA (patient group 3)	NSAID _{NS} NSAID _{NS} + PPI Coxib	1,000 1,719 1,892	0.985 0.992 0.987	— 102,714 Dominated
		High GI risk with ASA (patient group 4)	NSAID _{NS} NSAID _{NS} + PPI Coxib	2,382 2,302 3,061	0.973 0.989 0.976	Dominated — Dominated

* GI = gastrointestinal; ASA = aspirin; NSAID_{NS} = nonsteroidal antiinflammatory drug; PPI = proton pump inhibitor; coxib = cyclooxygenase 2-specific inhibitor.

† Average cost per patient in dollars treated for 1 year.

‡ In cost-effectiveness analysis: percentage of patients avoiding an ulcer complication at 1 year (symptomatic ulcer, ulcer hemorrhage, or ulcer perforation); in cost-utility analysis: quality-adjusted life year gained.

§ In cost-effectiveness analysis: incremental cost in dollars per additional ulcer complication prevented compared with the NSAID_{NS} strategy; in cost-utility analysis: incremental cost in dollars per quality-adjusted life year gained compared with the NSAID_{NS} strategy.

trolled trials and expert opinion, our findings may not be generalizable to all relevant arthritis populations. Moreover, several of our estimates are based on studies of varying design, patient population, followup, and quality. However, we 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 precise point estimates. In addition, we relied upon an expert panel of physicians to provide estimates in areas in which data are lacking. In circumstances where clinical data are incomplete, the National Panel for Cost-Effectiveness in Health and Medicine suggests that estimates should be developed on the basis of extrapolation and imputation of the best available evidence and theory (50). In this regard, the National Panel considers this method of estimation to be “a valid form of scientific inquiry.” We therefore believe that our exploratory analysis is based upon the best-available data.

In conclusion, this analysis reveals that the cost-effectiveness of competing NSAID strategies in chronic arthritis is highly dependent on individual risk factors. Our analysis suggests that generic nonselective NSAIDs are most cost-effective in patients at low risk for an adverse event. However, as both the GI and cardiovascular risk increase, the addition of a PPI to a nonselective NSAID may be preferable to coxib-based strategies. We therefore suggest

that the cost-effectiveness of these competing strategies be reappraised with additional prospective trials comparing the accrued cost and effectiveness across a range of risk profiles.

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APPENDIX A: QALY CALCULATIONS

Utility estimates

To calculate quality-adjusted life years (QALYs) for our decision model we incorporated the utilities of 7 discrete health states: 1) moderate dyspepsia; 2) severe dyspepsia; 3) ulcer hemorrhage without surgery; 4) ulcer hemorrhage or perforation with surgery; 5) myocardial infarction; 6) postmyocardial infarction state for survivors; and 7) death from an ulcer complication or myocardial infarction.

A recent study of 73 patients with dyspepsia employed the time tradeoff method to derive mean utilities for moderate and severe dyspepsia, which were 0.87 and 0.91, respectively (62). The same investigators measured the disutility for both ulcer hemorrhage and ulcer perforation, and calculated a median disutility of 0.01 QALY for each. The relationship between the disutility of a health state and the utility of a health state may be described by the following formula (50,51):

$$\text{Disutility in QALYs} = \frac{(1 - \text{utility of health state}) \times (\text{duration of health state in days})}{365 \text{ days}}$$

Therefore, assuming a mean duration of 7 days for a complicated ulcer (based upon Center for Medicare and Medicaid data) (57), and incorporating the reported disutility of 0.01 QALY, the utility for an ulcer bleed or perforation is 0.52. This calculated value is similar to utilities derived by Ebell and colleagues using the Index of Well-Being (IWB) (58), a validated multiattribute scale of general health status. Specifically, the IWB utilities for an uncomplicated ulcer hemorrhage and a complicated ulcer requiring surgery are 0.49 and 0.46, respectively (58). Our group and others have incorporated these utilities into previous economic models of competing strategies for uninvestigated dyspepsia (12,58,59).

We did not identify published utilities for an acute myocardial infarction. In the absence of data, we assigned a utility of 0.0 for the acute event and for deaths attributable to the event. However, survivors of an acute myocardial infarction may achieve partial resolution of their health-related quality of life following recovery from the acute event. Based on a previous report of time tradeoff elicitation in the 64 survivors of a myocardial infarction (obtained during the months following the initial event) (67), we attributed a utility of 0.88 to the postmyocardial infarction patient.

QALY calculations

As patients move between different health states over time, their health-related quality of life varies accordingly. To account for this clinical reality, the QALYs used for a decision analysis must capture the dynamic path of health states experienced by the patient cohort. This requires a 3-step process: 1) identify the relevant health states for the model; 2) estimate the time spent in each health state; and 3) calculate the disutility of each health state using validated utility estimates (51). We assumed that patients with unresolved dyspepsia (i.e., unresponsive to proton pump inhibitor [PPI] therapy) remained in their health state indefinitely, and assigned the utility for severe dyspepsia (0.87) over the remaining time horizon (56). To model the disutility of resolved dyspepsia (i.e., responsive to PPI therapy), we used published data on the impact of symptomatic ulcers in a study of 4,580 patients (61). Specifically, the mean duration of “bed days” (analogous to “severe dyspepsia”) and “restricted days” (analogous to “moderate dyspepsia”) in patients recovering from a symptomatic ulcer were 12 and 23, respectively (61). However, because the utility and duration of these health states vary substantially between individuals, we varied the disutility of each health state over a wide range in the sensitivity analysis.