Cost-effectiveness of Strategies for Primary Prevention of Nonsteroidal Anti-inflammatory Drug-induced Peptic Ulcer Disease

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OBJECTIVE: Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of peptic ulcer disease by 5- to 7-fold in the first 3 months of treatment. This study examined the relative cost-effectiveness of different strategies for the primary prevention of NSAID-induced ulcers in patients that are starting NSAID treatment.

MEASUREMENTS AND MAIN RESULTS: A decision analysis model was developed to compare the cost-effectiveness of 6 prophylactic strategies relative to no prophylaxis for patients 65 years of age starting a 3-month course of NSAIDs: (1) testing for *Helicobacter pylori* infection and treating those with positive tests; (2) empiric treatment of all patients for *Helicobacter pylori*; (3) conventional-dose histamine₂ receptor antagonists; (4) high-dose histamine₂ receptor antagonists; (5) misoprostol; and (6) omeprazole. Costs were estimated from 1997 Medicare reimbursement schedules and the *Drug Topics Red Book*. Empiric treatment of *Helicobacter pylori* with bismuth, metronidazole, and tetracycline was cost-saving in the baseline analysis. Selective treatment of *Helicobacter pylori*, misoprostol, omeprazole, and conventional-dose or high-dose histamine₂ receptor antagonists cost \$23,800, \$46,100, \$34,400, and \$15,600 or \$21,500 per year of life saved, respectively, relative to prophylaxis. The results were sensitive to the probability of an ulcer, the probability and mortality of ulcer complications, and the cost of, efficacy of, and compliance with prophylaxis. The cost-effectiveness estimates did not change substantially when costs associated with antibiotic resistance of *Helicobacter pylori* were incorporated.

CONCLUSIONS: Several strategies for primary prevention of NSAID-induced ulcers in patients starting NSAIDs were estimated to have acceptable cost-effectiveness relative to prophylaxis. Empirically treating all patients for *Helicobacter pylori* with bismuth, metronidazole, and tetracycline was projected to be cost-saving in older patients.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs, being prescribed to about 1% of the population daily.^{1,2} Approximately 70 to 100 million prescriptions per year are written for NSAIDs in the United States, and about 15 million people are estimated to be long-term users.³ The extent of use of over-the-counter NSAIDs is not well documented, but most likely several times greater than that of prescription medications. However, it is estimated that 8% to 30% of people using NSAIDs have gastrointestinal symptoms.⁴ In addition, NSAIDs increase the risk of peptic ulcer disease by 5- to 7-fold in the first 3 months of treatment.^{5,6} Endoscopically, 10% to 25% of people will have an ulcer on endoscopy within 3 months of beginning NSAIDs.^{7,8} Risk factors for development of peptic ulcers include increasing age, history of peptic ulcer disease, and concomitant use of corticosteroids.⁹ Unfortunately, gastrointestinal symptoms and the presence of peptic ulcers are not strongly associated, and complications of peptic ulcer disease often occur without antecedent gastrointestinal symptoms.

Because of the widespread use and side effects of NSAIDs, there has been interest in strategies to prevent associated peptic ulcers. Previous studies have demonstrated the efficacy of some agents, such as misoprostol,¹⁰⁻¹⁴ histamine₂ receptor antagonists,¹⁵⁻²⁰ and proton pump inhibitors,^{21,22} in preventing development of endoscopic ulcers. In addition, there is some evidence that treatment of *Helicobacter pylori* infection may decrease the incidence of endoscopic ulcers.^{23,24} However, previous studies of the cost-effectiveness of misoprostol prophylaxis have given differing results,²⁵⁻³¹ and the cost-effectiveness of other strategies has not been extensively analyzed. This study was undertaken to compare the relative cost-effectiveness of several strategies for the primary prevention of NSAID-induced peptic ulcer disease and its complications in patients that are starting NSAID treatment. This study does not address the cost-effectiveness of methods to treat ulcers or dyspepsia that develop in patients already on NSAIDs. The analysis was performed from the perspective of a third party payer.

METHODS

Decision Analysis Model

A decision analysis model was developed to represent the outcomes of a hypothetical cohort of 65-year-old patients beginning a 3-month course of NSAIDs for inflam-

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FIGURE 1. Decision analysis model of strategies for primary prevention of NSAID-induced ulcers. All branches of the tree have the potential outcomes depicted in the outcomes tree in Figure 2. NSAIDs indicates nonsteroidal anti-inflammatory drugs; HP, *Helicobacter pylori*; H2RAs, histamine₂ receptor antagonists.

FIGURE 2. Potential outcomes after beginning NSAID therapy, with or without prophylaxis. NSAIDs indicates nonsteroidal anti-inflammatory drugs; H2RAs, histamine₂ receptor antagonists; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; GOO, gastric outlet obstruction.

matory and noninflammatory musculoskeletal conditions (DATA 3.0; TreeAge Software, Inc; Williamstown, Mass). This model does not apply to those taking lower doses of NSAIDs for cardiovascular prophylaxis or to patients who have developed ulcers while already taking NSAIDs. The analytic time horizon was 3 months because many studies of the efficacy of preventive strategies have followed patients for this time period. We chose to use years of life saved rather than quality-adjusted life years saved as the outcome measure because of the lack of published patient utility scores in this area.³² The decision tree compared 7 alternative strategies: (1) no prophylaxis; (2) testing all patients for *Helicobacter pylori* infection by serology and selectively treating those with positive tests; (3) treating all patients empirically for *Helicobacter pylori* infection; (4) conventional-dose histamine₂ receptor antagonists (famotidine, 20 mg, twice daily); (5) high-dose histamine₂ receptor antagonists (famotidine, 40 mg, twice daily); (6) misoprostol (200 µg, 4 times daily); and (7) proton pump inhibitors (omeprazole, 20 mg daily). The model assumed a combined outcome of gastric and duodenal ulcers. We did not model methods of diagnosing *Helicobacter pylori* other than serology, such as the urea breath test or endoscopic biopsies with histology. Although these methods may be more specific, they are also more costly, require more specialized equipment, and are less available in a primary care setting.

The main decision tree is shown in Figure 1. All branches of the tree have the same potential outcomes, depicted in Figure 2. Patients who are not compliant with prophylaxis, defined as taking less than 70% of prescribed doses, are assumed to have the same risk of developing peptic ulcers and complications as patients who do not receive any prophylaxis. In each arm of the tree, patients may develop peptic ulcers, and patients either with or without an ulcer may have symptoms. Patients (with or without an ulcer) who have gastrointestinal symptoms but no other complications were assumed to discontinue NSAID therapy. In addition, 30% of these patients were assumed to receive empiric therapy with histamine₂ receptor antagonists.³³ Symptoms resolve in the majority of patients who receive empiric therapy. Patients whose symptoms persist despite these measures were assumed to undergo further evaluation with upper endoscopy and treatment with omeprazole. Patients in the arm receiving prophylaxis with omeprazole were assumed to receive misoprostol if upper gastrointestinal symptoms persisted despite discontinuing NSAIDs.

The patients who develop peptic ulcer disease may be asymptomatic, develop gastrointestinal symptoms without further complications, or develop complications including gastrointestinal bleeding, ulcer perforation, or gastric outlet obstruction. Patients with gastrointestinal

symptoms but no other complications followed a decision arm initially identical to that followed by patients with symptoms but no ulcer. However, if these patients underwent upper endoscopy, they would be found to have an ulcer, tested for *Helicobacter pylori*, and treated if infected. In addition, to heal the ulcer, they would be treated with omeprazole or with misoprostol (if the initial prophylactic strategy were omeprazole). Patients with gastric ulcers were assumed to undergo a follow-up upper endoscopy and biopsy to exclude malignancy. For patients who developed complications, 90% with clinically significant gastrointestinal bleeding and all patients with an ulcer perforation were assumed to be hospitalized and undergo surgery. It was estimated that 25% of patients with gastric outlet obstruction would undergo surgery, with the remainder being managed with medical therapy, endoscopic therapy, or both. We assumed that prophylaxis would prevent ulcer complications, so that the reduction in risk of ulcer complications would be equivalent to the reduction in the risk of endoscopic ulcers published in the literature. We also assumed that treatment with either dose of histamine₂ receptor antagonists or with omeprazole would reduce the prevalence of dyspeptic symptoms.^{20,22}

For the strategies involving *Helicobacter pylori* treatment, the primary analysis used a 2-week course of bismuth subsalicylate, metronidazole, and tetracycline as the antibiotic therapy. The analysis was repeated using a 10-day course of metronidazole, omeprazole, and clarithromycin as an alternative antibiotic therapy. We assumed that antibiotic therapy does not alter the risk of ulcers unless *Helicobacter pylori* is eradicated. Therefore, patients who are not infected with *Helicobacter pylori* but receive antibiotic therapy and patients whose *Helicobacter pylori* is not eradicated with antibiotic treatment do not receive any benefit of these prophylactic strategies. We assumed that 5% of patients treated with antibiotics for *Helicobacter pylori* develop antibiotic side effects, most notably diarrhea. Twenty percent of patients with diarrhea were assumed to see a physician and be tested with a stool culture and *Clostridium difficile* toxin assay. Patients infected with *Clostridium difficile* were treated with a 10-day course of oral vancomycin.

Costs

Costs for physician visits and procedures were estimated from 1997 Medicare fee schedules (Table 1).^{34,35} Costs for inpatient hospitalizations were estimated from 1997 reimbursements specific to diagnosis-related groups for Medicare.³⁶ Wholesale costs for medications were estimated from the 1997 *Drug Topics Red Book*.³⁷ Costs for laboratory tests were determined from the 1997 American Medical Association *Current Procedural Terminology 1997* code book and the 1997 Medicare fee schedule for clinical laboratories.^{35,39} Indirect costs, such as lost productivity or wages, and nonmedical direct costs were not included.

Costs were calculated as if complications would occur

at the midpoint of the 3-month course of NSAID treatment. Thus, patients who developed complications would receive only 1.5 months of prophylactic treatment with histamine₂ receptor antagonists, misoprostol, or omeprazole. The costs of the entire course of *Helicobacter pylori* therapy were attributed to these patients, as this treatment lasts only 10 to 14 days. Costs were not discounted because they would be incurred within the "up-front" 3-month course of NSAID treatment. All costs are presented as 1997 U.S. dollars.

Input Values

Estimates of the probability of developing peptic ulcers and their complications and mortality rates from complications were derived from epidemiological studies of NSAID users (Table 2). Estimates of the efficacy of each prophylactic therapy were derived from published randomized controlled clinical trials. These studies were identified by a MEDLINE search of English-language articles from 1966 through 1998, searching the terms *nonsteroidal anti-inflammatory drugs*, *peptic ulcer*, and *gastrointestinal hemorrhage*. A 3% discount rate for future benefits was used.⁵⁹

Sensitivity Analysis

The analysis was repeated to simulate cohorts of patients aged 55 years or 45 years by adjusting the baseline estimates of the probability of developing an ulcer on NSAID therapy, the prevalence of *Helicobacter pylori*, the mortality rate for ulcer perforations and gastrointestinal bleeding, and life expectancy. For the 65-year-old cohort only, selected variables were examined in 1-way sensitivity analysis: the probability of developing an ulcer on NSAID therapy; the probability of developing symptoms; the probability of developing ulcer complications; mortality rates from complications; costs for physician visits, hospitalization, and endoscopy; the prevalence of *Helicobacter pylori*; and eradication rates with *Helicobacter pylori* therapy. The estimates of costs, effectiveness, and compliance with the various prophylactic regimens were also subjected to 1-way sensitivity analysis. The rate of discounting for life years saved was varied from 0% to 5%.⁵⁹ We did not explicitly model differences in the probability of developing ulcers associated with the known risk factors such as previous peptic ulcer disease or corticosteroid use. However, these risk factors were implicitly modeled in the 1-way and 2-way sensitivity analyses by varying the baseline probability of an ulcer. Two-way sensitivity analysis was performed using combinations of 2 of the following 3 variables: the estimates of the probability of developing an ulcer on NSAIDs; the cost of each prophylactic strategy; and the efficacy of each prophylactic strategy.

For the *Helicobacter pylori* treatment strategies, we were concerned about the possible effects of widespread antibiotic usage on development of antibiotic resistance. Patients

Table 1. Cost Estimates

Parameter*	Base Case Value \$	Range \$	Reference Number
Outpatient visit for new patients (CPT 99203)	161	80–300	34, 35
Outpatient physician visit for established patients (CPT 99213)	102	50–210	34, 35
Esophagogastroduodenoscopy, diagnosis (CPT 43235)	507	400–700	34, 35
Esophagogastroduodenoscopy with biopsy (CPT 43239)	611	500–800	34, 35
Hospitalization for gastrointestinal bleeding with complication (DRG 174)	21,200	15,000–25,000	36
Hospitalization for gastrointestinal bleeding without complication (DRG 176)	5,200	4,000–8,000	36
Hospitalization with death from gastrointestinal bleeding (DRG 174)	25,000	20,000–30,000	36
Hospitalization for ulcer perforation (DRG 170)	14,900	10,000–20,000	36
Hospitalization for surgery for gastric outlet obstruction (DRG 180)	4,500	3,000–6,000	36
Omeprazole 20 mg daily × 90 d	340	250–400	37
Famotidine 20 mg twice daily × 90 d	300	200–400	37
Famotidine 40 mg twice daily × 90 d	540	400–700	37
Ranitidine 150 mg twice daily × 90 d	120	75–180	37
Ranitidine 300 mg twice daily × 90 d	240	150–400	37
Misoprostol 200 µg 4 times daily × 90 d	252	200–300	37
Antibiotic therapy for <i>Helicobacter pylori</i> : bismuth subsalicylate, metronidazole, and tetracycline	15	10–30	37
Antibiotic therapy for <i>Helicobacter pylori</i> : metronidazole, omeprazole, and clarithromycin	120	100–180	37
<i>Helicobacter pylori</i> serology (laboratory-based)	65	50–100	38
Stool culture	12		34, 35
<i>Clostridium difficile</i> toxin assay	27	20–35	34, 35
Vancomycin 125 mg 4 times daily × 10 d	125	100–125	37

*CPT indicates current procedural terminology; DRG, diagnosis-related group.

who are noncompliant with therapy are likely to develop antibiotic-resistant *Helicobacter pylori*.^{52,60} Treatment for these patients may be more expensive should they develop ulcers or complications. For these reasons, increases in costs of treating ulcers in patients with antibiotic-resistant *Helicobacter pylori* were modeled in a secondary analysis. We initially assumed that 50% of patients whose *Helicobacter pylori* was not eradicated with primary treatment would develop antibiotic resistance and that the costs of treating ulcers and their complications would increase by 50% for these patients. In sensitivity analyses, the proportion of patients who developed antibiotic-resistant *Helicobacter pylori* after failed primary treatment varied from 20% to 80%, and the proportional increase in costs of treating ulcers and their complications varied from 20% to 100%.

RESULTS

Baseline Analyses

With the baseline estimates of probabilities and costs, the strategy of treating all patients empirically for *Helicobacter pylori* with bismuth subsalicylate, metronidazole, and tetracycline was cost-saving, even though compliance was assumed to be only 65% (Table 3). The cost-effectiveness of the remaining strategies varied from \$23,800 per year of life saved for *Helicobacter pylori* testing and selective treatment with bismuth subsalicylate, metronidazole, and tetracycline to \$78,800 per year of life saved for con-

ventional-dose histamine₂ receptor antagonists. The combination of bismuth subsalicylate, metronidazole, and tetracycline was used as the antibiotic regimen in the original study,²³ but it is not necessarily the optimal regimen for *Helicobacter pylori* treatment. A popular alternative treatment regimen is metronidazole, omeprazole, and clarithromycin. If this treatment regimen were used, the empiric *Helicobacter pylori* treatment strategy and the *Helicobacter pylori* testing and selective treatment strategy would cost \$30,000 and \$47,400 per year of life saved, respectively.

The primary analysis was done using proprietary prices for famotidine because this was the histamine₂ receptor antagonist studied at high doses for prophylaxis. However, generic histamine₂ receptor antagonists at equivalent doses are likely to have fairly similar effects when used for ulcer prophylaxis. If the costs of the histamine₂ receptor antagonist prophylaxis strategies were adjusted to generic drug prices, the conventional-dose strategy would cost \$15,600 per year of life saved, and the high-dose strategy would cost \$21,500 per year of life saved.

In the 55-year-old and 45-year-old cohorts, all prophylactic strategies were less cost-effective, owing to this lower probability of developing an ulcer and lower mortality rates associated with ulcer complications (Table 3). However, in these cohorts, the empiric *Helicobacter pylori* treatment with bismuth subsalicylate strategy was still very cost-effective, costing \$600 to \$10,000 per year of life saved. No other strategy cost less than \$50,000 per year of life saved in 45-year-old patients. In 55-year-old patients,

Table 2. Input Values

Parameter*	Reference Value	Range	Reference Number
Ulcer while on NSAID therapy with no prophylaxis	0.15	0.10–0.35	7, 8
Relative risk of ulcers if			
<i>Helicobacter pylori</i> positive	1.8	1.0–2.0	23, 40
<i>Helicobacter pylori</i> eradicated	0.3	0.18–1.0	23, 40
<i>Helicobacter pylori</i> negative	0.8	0.6–1.0	23, 46
Low-dose histamine ₂ receptor antagonists	0.7	0.4–1.0	15, 16, 20
High-dose histamine ₂ receptor antagonists	0.4	0.24–1.0	20
Misoprostol	0.48	0.28–1.0	11–13, 41
Omeprazole	0.28	0.16–1.0	21, 22
Presence of symptoms if			
No ulcer present	0.20	0.10–0.30	4
Ulcer present	0.40	0.20–0.70	23, 42
Complication rate if			
Asymptomatic ulcer	0.04	0.01–0.10	43
Symptomatic ulcer	0.06	0.01–0.10	43
Compliance with prophylaxis			
BMT	0.65	0.25–0.90	44
MOC	0.85	0.25–0.90	45–47
Low-dose histamine ₂ receptor antagonists	0.90	0.25–0.95	37
High-dose histamine ₂ receptor antagonists	0.85	0.25–0.90	37
Misoprostol	0.75	0.25–0.90	37
Omeprazole	0.90	0.25–0.95	37
Prevalence of <i>Helicobacter pylori</i>			
At age 65 y	0.60	0.30–0.75	48, 49
At age 55 y	0.50		
At age 45 y	0.40		
<i>Helicobacter pylori</i> serology test characteristics			
Sensitivity	0.90	0.80–0.96	38, 50
Specificity	0.90	0.80–0.99	38, 50
<i>Helicobacter pylori</i> eradication if			
Compliant with BMT	0.85	0.75–0.95	44, 51
Not compliant with BMT	0.69	0.50–0.75	44, 52
Compliant with MOC	0.85	0.75–0.95	51
Not compliant with MOC	0.70	0.50–0.75	44, 53
Mortality after ulcer perforation			54–56
At age 65 y	0.10	0.05–0.26	
At age 55 y	0.09		
At age 45 y	0.08		
Mortality after ulcer hemorrhage			57
At age 65 y	0.10	0.05–0.15	
At age 55 y	0.08		
At age 45 y	0.07		
Life expectancy, y (prior to discounting)			58
At age 65 y	17.5		
At age 55 y	25.1		
At age 45 y	33.8		

*NSAID indicates nonsteroidal anti-inflammatory drug; BMT, bismuth, metronidazole, and tetracycline; MOC, metronidazole, omeprazole, and clarithromycin.

the conventional-dose and high-dose histamine₂ receptor antagonist strategies were cost-effective, at \$35,300 and \$45,000 per year of life saved, respectively.

One-way Sensitivity Analyses

Sensitivity analyses were performed only for the cohort of 65-year-old patients because prophylaxis is more

likely to be used and most cost-effective in this age group. With 1-way analysis, the cost-effectiveness ratios were most sensitive to the efficacy of prophylaxis. The results were also sensitive to the probability of an ulcer with NSAID therapy, the probability of symptoms with or without an ulcer, the probability of ulcer complications, the mortality rate from gastrointestinal bleeding or ulcer perforation, the cost of prophylaxis, and the compliance with

Table 3. Cost-effectiveness of Primary Prophylaxis of Ulcers Induced by Nonsteroidal Anti-inflammatory Drugs*

Strategy	65 Years of Age			55 Years of Age			45 Years of Age		
	Cost per 1,000 Patients, \$	Years of Life Saved per 1,000 Patients	Cost per Year of Life Saved, \$	Cost per 1,000 Patients, \$	Years of Life Saved per 1,000 Patients	Cost per Year of Life Saved, \$	Cost per 1,000 Patients, \$	Years of Life Saved per 1,000 Patients	Cost per Year of Life Saved, \$
No prophylaxis	209,000	N/A	N/A	161,000	N/A	N/A	140,000	N/A	N/A
<i>Helicobacter pylori</i> testing and selective treatment									
With BMT	259,000	2.1	23,800	222,000	1.2	50,800	205,000	0.8	81,200
With MOC	318,000	2.3	47,400	274,000	1.3	86,900	249,000	0.8	136,300
Treat all empirically for <i>Helicobacter pylori</i>									
With BMT	194,000	2.6	Cost-saving	162,000	1.6	630	149,000	0.9	10,000
With MOC	296,000	2.9	30,000	265,000	1.6	65,000	252,000	0.9	124,000
Low-dose histamine ₂ receptor antagonists									
Proprietary	406,000	2.5	78,800	373,000	1.5	141,300	359,000	0.9	243,300
Generic	248,000	2.5	15,600	214,000	1.5	35,300	199,000	0.9	65,600
High-dose histamine ₂ receptor antagonists									
Proprietary	571,000	4.6	78,700	551,000	2.8	139,300	543,000	1.7	237,100
Generic	308,000	4.6	21,500	287,000	2.8	45,000	279,000	1.7	81,800
Misoprostol	366,000	3.4	46,100	337,000	2.1	83,800	325,000	1.3	142,300
Omeprazole	388,000	5.2	34,400	372,000	3.2	65,900	365,000	1.9	118,400

*Estimates are shown in cost (\$) per life year saved as compared with no prophylaxis. BMT indicates bismuth subsalicylate, metronidazole, and tetracycline; MOC, metronidazole, omeprazole, clarithromycin; N/A, not applicable.

prophylaxis. The results were not sensitive to the prevalence of *Helicobacter pylori*, other costs (including costs for physician visits, endoscopy, and hospitalization), the probability of symptoms with or without prophylaxis, or the discount rate (data not shown). Results are presented here using the combination of metronidazole, omeprazole, and clarithromycin for *Helicobacter pylori* treatment and generic prices for histamine₂ receptor antagonists because these are probably used more commonly than the combination of bismuth subsalicylate, tetracycline, and metronidazole or proprietary histamine₂ receptor antagonists.

With generic pricing, the histamine₂ receptor antagonist strategies appeared cost-effective, costing less than \$50,000 per year of life saved for most input values tested (Table 4). However, this threshold was exceeded when compliance with prophylaxis was less than 35% or the relative risk of an ulcer with prophylaxis was greater than 0.85. The high-dose histamine₂ receptor antagonist strategy exceeded this cost-effectiveness threshold when compliance with prophylaxis was less than 33%, the cost of prophylaxis was greater than \$390, or the relative risk of an ulcer with prophylaxis was greater than 0.70. The results were most sensitive to the efficacy of prophylaxis (Table 4). However, for all other variables tested, the empiric *Helicobacter pylori* treatment strategy cost less than \$66,000 per year of life saved at all ranges of values tested and was always more cost-effective than the selective *Helicobacter pylori* treatment strategy. Likewise, when variables other than the efficacy of prophylaxis were

tested, the omeprazole strategy never cost more than \$80,000 per year of life saved, and the misoprostol strategy never cost more than \$85,000 per year of life saved.

Two-way Sensitivity Analyses

Two-way sensitivity analyses were performed by simultaneously varying the values of 2 of the following 3 variables: the probability of developing an ulcer on NSAIDs, the cost of the prophylactic strategy, and the efficacy of the prophylactic strategy. Again, results are presented using metronidazole, omeprazole, and clarithromycin as the *Helicobacter pylori* treatment regimen and generic prices for histamine₂ receptor antagonists (Table 5).

The cost-effectiveness ratios of the prophylactic strategies varied widely depending on the inputs used. However, in the best-case scenarios, conventional-dose histamine₂ receptor antagonists were actually cost-saving compared with no prophylaxis. No strategy was cost-effective when the efficacy of prophylaxis was at the low range of the values tested (the worst-case scenarios), and in some cases the prophylaxis strategies were actually dominated by the no prophylaxis option.

Modeling of Treatment Costs for Ulcers Associated with Antibiotic-Resistant *Helicobacter pylori*

For this portion of the analysis, we first assumed that antibiotic-resistant *Helicobacter pylori* would develop in

Table 4. Cost-effectiveness Estimates with Selected One-way Sensitivity Analyses*

Parameter Varied (range tested)	<i>Helicobacter pylori</i> Testing and Selective Treatment (MOC)	Treat All Empirically for <i>Helicobacter pylori</i> (MOC)	Low-dose Histamine ₂ Receptor Antagonists (generic)	High-dose Histamine ₂ Receptor Antagonists (generic)	Misoprostol	Omeprazole
Probability ulcer on NSAID (0.10–0.35)	15,700–78,700	7,500–51,600	900–30,600	2,900–38,100	14,900–74,300	8,900–57,700
Probability of complications with symptomatic ulcer (0.01–0.10)	35,900–82,300	21,300–56,500	10,000–40,000	13,400–50,400	33,900–83,500	22,900–76,200
Probability of complications with asymptomatic ulcer (0.01–0.10)	24,600–83,100	13,200–52,800	7,200–28,100	10,700–34,100	23,200–79,000	12,900–53,100
Cost of prophylactic strategy†	37,400–67,400	16,200–57,600	Cost saving–36,800	4,300–52,000	34,100–57,100	19,800–44,200
Efficacy of prophylactic strategy†	38,500–Dominated	23,800–Dominated	2,600–660,000	15,200–352,000	30,200–1,940,000	29,300–311,400
Compliance with prophylactic strategy†	47,000–68,800	29,700–41,700	14,600–70,000	20,000–74,300	40,500–105,000	29,900–93,500
Mortality from gastrointestinal bleeding (0.05–0.15)	40,400–72,700	25,600–45,800	13,400–24,400	17,800–30,300	39,000–68,300	28,900–50,000
Mortality from ulcer perforation (0.05–0.26)	32,100–45,400	20,200–28,100	10,800–18,200	14,200–45,400	35,400–52,000	26,300–38,100

*Results show the cost-effectiveness estimates for each strategy for the range of values tested for each parameter. Estimates are presented as cost (\$) per year of life saved as compared with no prophylaxis. MOC indicates metronidazole, omeprazole, and clarithromycin; NSAID, nonsteroidal anti-inflammatory drug.

†Range tested varies for each strategy. For values tested, see Table 1.

50% of patients who failed primary antibiotic treatment, and that the costs of treating ulcers and their complications would increase by 50% in this subset of patients. Even with this increase in costs, the strategy of treating all patients empirically with bismuth subsalicylate, metronidazole, and tetracycline remained cost-saving in 65-

year-old patients. With the same antibiotic regimen, testing for *Helicobacter pylori* and selective treatment cost \$27,400 per year of life saved. If metronidazole, omeprazole, and clarithromycin were used as the initial antibiotic regimen, the empiric treatment strategy and the selective treatment strategy cost \$39,000 and \$50,200 per year of

Table 5. Cost-effectiveness Estimates with Selected Two-way Sensitivity Analyses*

Strategy	Probability of Ulcer/ Cost of Prophylaxis		Probability of Ulcer/ Efficacy of Prophylaxis		Cost of Prophylaxis Efficacy of Prophylaxis	
	High Probability/ Low Cost (best case)	Low Probability/ High Cost (worst case)	High Probability/ High Efficacy (best case)	Low Probability/ Low Efficacy (worst case)	Low Cost/ High Efficacy (best case)	High Cost/ Low Efficacy (worst case)
<i>Helicobacter pylori</i> testing and selective treatment (MOC)	11,000	109,300	11,200	Dominated	30,000	Dominated
Treat all empirically for <i>Helicobacter pylori</i> (MOC)	1,100	93,700	4,600	Dominated	12,100	Dominated
Low-dose histamine ₂ receptor antagonists (generic)	Cost-saving	63,800	Cost-saving	670,000	Cost-saving	1,180,000
High-dose histamine ₂ receptor antagonists (generic)	Cost-saving	83,500	300	490,000	1,400	352,500
Misoprostol	8,900	90,400	7,300	Dominated	21,500	Dominated
Omeprazole	2,000	72,000	6,500	570,000	16,300	384,300

*Results show the cost-effectiveness estimates for each strategy for the range of values tested for each combination of parameters. Estimates are presented as cost (\$) per year of life saved as compared with no prophylaxis. The range of values tested varies for each strategy. For values tested, see Table 1. MOC indicates metronidazole, omeprazole, and clarithromycin.

life saved, respectively. Empirically treating all patients with bismuth subsalicylate, metronidazole, and tetracycline remained cost-saving even if antibiotic-resistant *Helicobacter pylori* were to develop in 80% of patients who failed initial treatment and the cost of treating ulcers and their complications in this subset were to double (Table 6). The cost-effectiveness for the selective treatment strategies with either antibiotic regimen or for the empiric treatment strategy with metronidazole, omeprazole, and clarithromycin did not change substantially even in this worst-case scenario (Table 6).

DISCUSSION

Several strategies for primary prophylaxis of NSAID-induced ulcers are efficacious, but their relative cost-effectiveness is unknown. In the baseline analysis, the cost-effectiveness of all strategies was less than \$78,800 per year of life saved. In 1-way sensitivity analysis, the cost-effectiveness of the prophylactic strategies varied widely depending on the ranges of inputs tested. However, for most ranges of probability and cost inputs tested, the strategy of empiric *Helicobacter pylori* treatment with bismuth subsalicylate, metronidazole, and tetracycline was actually cost-saving. This strategy became more costly than no prophylaxis only when the drugs cost more than \$30 or the relative risk of an ulcer with prophylaxis was greater than 0.60.

Probably NSAIDs are overused in patients with musculoskeletal diseases. For example, many patients with arthritis have substantial pain reduction by treatment with only acetaminophen or exercise programs.^{61,62} This study examined a hypothetical cohort of patients only after the decision has been made to start NSAIDs and did

not consider the cost-effectiveness of interventions designed to decrease the use of these medications. Using less-risky modes of therapy rather than NSAIDs should be considered the primary means to decrease the morbidity and mortality associated with NSAID therapy. However, in older patients who require NSAIDs despite these measures, prevention can be considered to be cost-effective.

The role of *Helicobacter pylori* in NSAID-induced ulcers has been controversial.⁶³ This study used the randomized controlled trial by Chan et al.²³ as the most definitive evidence for a role of *Helicobacter pylori* eradication in preventing ulcers in patients who are just beginning NSAIDs. In contrast, a study by Hawkey et al. did not show a benefit of *Helicobacter pylori* eradication in treating ulcers or dyspepsia that develop in patients already taking NSAIDs.⁶⁴ The effect of any prophylactic strategy, including *Helicobacter pylori* eradication, may differ for prevention as opposed to healing of these ulcers. Therefore, the results of this analysis cannot be generalized to the treatment of ulcers in patients who are already taking NSAIDs.

Although cost-effective, the *Helicobacter pylori* treatment strategies must be carefully considered before they are implemented. Benefits of a strategy involving the potential widespread use of antibiotics need to be weighed against the clinical and economic effects of developing antibiotic resistance. In the secondary analysis in which we modeled increased costs of treating ulcers associated with antibiotic-resistant *Helicobacter pylori*, empiric treatment of all patients starting NSAIDs with bismuth subsalicylate, metronidazole, and tetracycline remained cost-saving even in the worst-case scenario. Nevertheless, an empiric *Helicobacter pylori* treatment strategy would involve treating a large number of patients who are not infected and who may develop antibiotic resistance in other host

Table 6. Cost-effectiveness of *Helicobacter pylori* Treatment Strategies with Increased Costs for Antibiotic-Resistant Organisms*

Increase in Treatment Costs for Patients with Antibiotic-Resistant <i>Helicobacter pylori</i> , %	Patients with Antibiotic-Resistant <i>Helicobacter pylori</i> After Failed Initial Treatment, %	Test for <i>Helicobacter pylori</i> and Selective Treatment		Empirically Treat all for <i>Helicobacter pylori</i>	
		Bismuth Subsalicylate, Metronidazole, and Tetracycline	Metronidazole, Omeprazole, and Clarithromycin	Bismuth Subsalicylate, Metronidazole, and Tetracycline	Metronidazole, Omeprazole, and Clarithromycin
20	20	24,300	48,000	Cost-saving	30,600
	50	25,200	48,800	Cost-saving	30,700
	80	26,100	49,600	Cost-saving	32,100
50	20	25,200	49,100	Cost-saving	31,400
	50	27,400	50,200	Cost-saving	32,500
	80	29,700	53,300	Cost-saving	35,300
80	20	26,100	50,000	Cost-saving	32,100
	50	29,700	52,500	Cost-saving	34,500
	80	33,300	56,700	Cost-saving	38,300
100	20	26,700	50,600	Cost-saving	32,700
	50	31,200	53,900	Cost-saving	35,700
	80	35,600	59,100	Cost-saving	40,300

*Results are shown as cost (\$) per year of life saved as compared with no prophylaxis.

bacteria. Modeling such problems is outside the scope of this analysis, but these factors must be taken into consideration before implementing this strategy.

Our results show better cost-effectiveness than previous studies of the cost-effectiveness of misoprostol.²⁵⁻³⁰ There are several possible explanations for these discrepancies. Previous studies did not include ulcer perforations and gastric outlet obstruction as potential complications, focusing instead on gastrointestinal bleeding. These events comprise over 25% of all ulcer complications,^{6,65,66} and they should be analyzed along with gastrointestinal bleeding. In this study, misoprostol will appear more cost-effective than in previous analyses because it can effectively prevent perforations and gastric outlet obstruction and their associated costs and mortality.¹³ Previous analyses have also not considered the costs associated with evaluating gastrointestinal symptoms when a complication had not occurred. Because gastrointestinal symptoms are far more common than ulcer complications, evaluating symptoms may contribute a large component of the costs of NSAID therapy. Prophylaxis appears to be more cost-effective if these symptom evaluations are considered.

To our knowledge, no studies examining the cost-effectiveness of histamine₂ receptor antagonists or omeprazole in preventing NSAID-induced ulcers have been published. Only 1 study has been done looking at the role of *Helicobacter pylori* eradication.⁶⁷ This study concluded that *Helicobacter pylori* eradication would cost \$16,805 per symptomatic ulcer avoided and \$31,842 per complicated ulcer avoided. However, the impact of this strategy on patient survival was not estimated, making it difficult to compare the results of this study with the results presented here.

There are several limitations to this analysis. First, the link between prevention of endoscopic ulcers and the prevention of clinically significant ulcers is not proven for most strategies considered here. Of the strategies modeled, only misoprostol has definitely been shown to reduce ulcer complications, whereas the other strategies have only been shown to reduce endoscopic ulcers.¹³ For the baseline analysis in this study, the other strategies were assumed to reduce ulcer complications to a degree equivalent to the reduction in endoscopic ulcers. Until larger definitive studies are done, the validity of this assumption is unproven. However, it is reasonable to believe that some reduction in ulcer complications would also occur with the nonmisoprostol prophylactic strategies.

The effect of the uncertainty in the actual degree of reduction of ulcer complications was examined with sensitivity analysis. In the 1-way sensitivity analyses, the efficacy of prophylaxis varied across a wide range that included a relative risk of 1, indicating no benefit of prophylaxis. The results were markedly sensitive to this variable, with cost-effectiveness ratios ranging as high as \$1,940,000 per year of life saved for misoprostol at the lowest degree of efficacy. This variable also had a marked effect in the 2-way sensitivity analysis, where prophylaxis was actually dominated by no prophylaxis in certain scenarios. These sensi-

tivity analyses emphasize the importance of obtaining precise estimates of the efficacy of prophylaxis for this analysis. Because our results were markedly sensitive to this variable, it is important not to generalize these results to other clinical situations in which the benefits of ulcer prophylaxis and treatment may be different. Nevertheless, if one believes that the degree of reduction in endoscopic ulcers approximates the reduction in clinical ulcer complications, the strategies tested would be cost-effective, as seen in the baseline analysis.

Another limitation of this study is that the use of the new selective COX-2 inhibitors was not modeled. These new agents have not been extensively used, and duration of follow-up in clinical studies is limited. Initial studies have indicated that these agents reduce the incidence of ulcers by 30% to 70%,⁶⁸⁻⁷⁰ fairly similar to the risk reduction with the prophylactic strategies studied here. These agents are fairly expensive (\$2-\$3 per day), and thus may not be cost-effective compared with other strategies. These agents can be compared with other prophylactic strategies after clinical experience has accumulated.

This study looked at NSAID therapy of fairly short duration and did not model longer or repeated courses of therapy. Most clinical trials of prophylaxis have had short follow-up over only 3 to 6 months, and the benefit of longer-term prophylaxis is not clearly established. As the rate of reinfection with *Helicobacter pylori* is estimated at less than 1% per year,⁴⁸ the preventive benefit of the initial eradication should persist if longer or additional courses of NSAIDs are prescribed. All the other strategies evaluated should require continued administration of the prophylactic agent at additional cost to maintain their benefit. If longer or repeated courses of NSAID therapy were modeled, this "one-time" approach to prophylaxis by treatment of *Helicobacter pylori* would appear to be even more cost-effective than the other strategies considered here.

This study assumed a combined outcome of gastric and duodenal ulcers. Although NSAIDs are more closely associated with gastric than duodenal ulcers, the potential complications of gastric and duodenal ulcers—abdominal pain, bleeding, perforation, and gastric outlet obstruction—are similar. In the model, the estimates of the risk reduction associated with the various prophylactic strategies were derived from the literature on this combined outcome of gastric and duodenal ulcers. Thus, our model should provide valid estimates for the cost-effectiveness of preventing ulcers in both sites.

Current recommendations are that economic analyses use quality-adjusted life years as the preferred effectiveness measure.³² We chose to report our results as cost per life year saved rather than cost per quality-adjusted life year saved owing to the lack of published patient preferences for prophylaxis against NSAID-induced peptic ulcer disease. To our knowledge, only 1 study has tried to assess patient preferences.²⁶ This study only assessed patient preferences for prophylaxis with misoprostol, an agent with prominent side effects. In addition, patient re-

sponses were quite heterogeneous in this study, with some showing a marked preference for prophylaxis and others a marked preference for no prophylaxis. We are not aware of studies of patient preferences with prophylactic medications that may be better tolerated, such as omeprazole.

In summary, several strategies for prevention of NSAID-induced ulcers are cost-effective in patients 65 years of age. The strategy of empirically treating *Helicobacter pylori* with bismuth subsalicylate, metronidazole, and tetracycline was consistently cost-saving in sensitivity analyses, and remained so even when increased costs associated with antibiotic resistance were incorporated into the model. Nevertheless, in addition to cost-effectiveness, decisions about implementing a particular therapy in individual patients must be based on clinical considerations that cannot all be incorporated into economic models, such as concern over growing antibiotic resistance in other host bacteria,⁶⁰ as well as the consequences of antibiotic side effects. In addition, the role of *Helicobacter pylori* in NSAID-induced ulcer disease is not clear-cut and remains controversial. Further studies, especially those clarifying the role of *Helicobacter pylori* in NSAID-related ulcer disease and defining the economic effects of antibiotic resistance, will provide further information to use along with these results in choosing a prophylactic strategy. More documentation that these prophylactic strategies actually reduce ulcer complications as well as reducing endoscopic ulcers will also strengthen the results of this analysis.

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