Treatment of Rheumatoid Arthritis and Osteoarthritis With COX-2–Selective Inhibitors: A Managed Care Perspective

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Abstract

The development of cyclooxygenase (COX)-2–selective inhibitors represents a major advance in the management of chronic pain and inflammation that may satisfy an unmet medical need for agents with improved gastrointestinal (GI) safety. This article is a review of the pharmacology, clinical efficacy, and safety of COX-2–selective inhibitors in the managed healthcare setting. The efficacy of COX-2–selective inhibitors in relieving chronic pain from osteoarthritis and rheumatoid arthritis is comparable to that of traditional nonsteroidal anti-inflammatory drugs (NSAIDs). However, the occurrence of GI complications may be less frequent in patients who receive COX-2–selective inhibitors than in patients receiving traditional NSAIDs. Thus, the use of COX-2–selective inhibitors for the management of chronic pain may reduce overall costs and provide an alternative with an improved safety profile compared with traditional NSAIDs.

(Am J Manag Care. 2002;8:S502-S517)

Arthritis and associated chronic inflammatory conditions, which are among the most common causes of disability in the United States, affect ~16% of Americans.[1] In the United States, 17.5% and 16.5%, respectively, of all disabilities are a result of arthritis and back problems.[1] Up to 60 million Americans will be affected by arthritis by 2020.[2]

The enormous economic and social burden of osteoarthritis (OA) and rheumatoid arthritis (RA) includes increased costs of healthcare, lost productivity, and a decreased quality of life. This burden can only be expected to increase as the population ages and more individuals are affected.[3] An economic analysis of the burden of RA and OA in the United States estimated the total cost of arthritis to be $64.8 billion yearly. Of these total costs, about half were the direct costs of medical care expenditures and about half were indirect costs attributable to lost wages and reduced productivity in the workplace.[4]

In a managed care setting, total charges per patient-year adjusted to 1993 dollars for patients with OA were $5294 for patients younger than 65 years and $5704 for patients age 65 years and older compared with charges in control subjects of $2467 and $3741, respectively. Thus, excess charges due to OA were $2827 and $1963, respectively, representing a 2-fold increase in medical care charges for plan enrollees with symptomatic OA compared with enrollees without OA claims.[5] Improved disease management approaches that relieve the pain and disability associated with OA and reduce the incidence of iatrogenic complications and adverse events can potentially alleviate this economic burden.

This article reviews the efficacy and safety of the cyclooxygenase (COX)-2–selective inhibitors, focusing on these drugs in the management of OA and RA in the setting of managed healthcare. Accordingly, the cost-effectiveness of the use of these agents compared with traditional approaches will also be considered.

Pharmacologic Approaches to Chronic Pain Management

Analgesics are widely used for treating chronic OA and RA. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit both isoforms of the COX enzyme, COX-1 and COX-2, are effective in managing pain from both OA and RA. However, these agents are associated with an increased risk of upper gastrointestinal (GI) side effects.[6] The benefits derived from NSAIDs are attributable to suppression of COX-2, while the complications and harmful side effects are attributed to suppression of COX-1.

In contrast, drugs that selectively inhibit only the inducible isoform of prostaglandin G/H synthase (COX-2) produce fewer GI side effects and complications. COX-2–selective inhibitors that spare COX-1 at therapeutic doses may provide patients with arthritis a therapeutic class of agents that is safe, convenient, and as effective as conventional NSAIDs.

The COX-2 Inhibitor Hypothesis

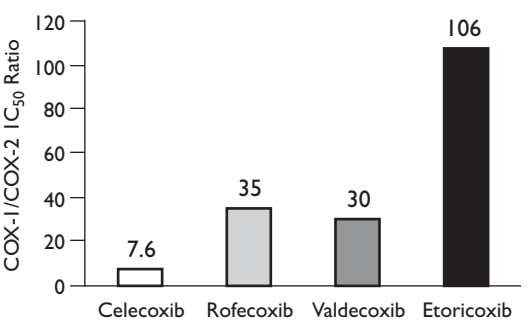
The proven clinical benefits of NSAIDs in pain management are well known but are offset by a high incidence of GI adverse effects.[6] Although NSAIDs are generally inexpensive, the aggregate cost of the use of NSAIDs for managing chronic pain in RA and OA includes the cost of gastroprotective medications taken concomitantly,[7] as well as the medical and pharmacy costs associated with treating these GI complications (perforations, ulcers, bleeds [PUBs]) when they do occur. Selective COX-2 inhibitors were developed on the premise that, compared with nonselective NSAIDs, significantly fewer serious GI adverse effects would occur with specific inhibition of the inducible isoform of the COX enzyme, while yielding comparable efficacy. Accordingly, the implication of this hypothesis is that the COX-2–selective inhibitors would reduce the morbidity and associated healthcare costs of preventing and treating adverse effects caused by nonselective NSAID therapy.

The biochemical specificity of the COX-2–selective inhibitors has been demonstrated. Whole blood assays show no inhibition of COX-1 activity in target organs such as platelets at therapeutic plasma concentrations.[8,9] The biochemical selectivity of coxibs approved in either the United States or Europe is shown in **Figure 1.**[10] In addition to demonstrating that COX-2–selective inhibitors do not produce COX-1 inhibition, confirmation of the COX-2–inhibitor hypothesis requires that fewer clinical manifestations of COX-1–dependent upper GI toxicity must be produced by coxibs[8] while providing relief from pain and inflammation comparable with traditional nonselective NSAID therapy.

Efficacy

Osteoarthritis. *First-Generation COX-2–Selective Inhibitors.* Launched in 1999, celecoxib was the first marketed COX-2–selective inhibitor to be approved by the US Food and Drug Administration (FDA). At dosages of 100 to 200 mg bid, celecoxib was shown to be similar in efficacy to naproxen (500 mg bid) and significantly more effective than placebo at alleviating OA pain, while producing fewer endoscopically detectable ulcers.[11,12] Celecoxib 50 mg bid provided less effective pain relief than both the 100- and 200-mg-bid dosages.[12] As shown by McKenna et al,[13] similar improvements in pain and symptoms of OA of the knee were seen with celecoxib 200 mg qd and

Figure 1. COX-1/COX-2 IC_{50} Values for COX Enzyme Inhibition by COX-2 Inhibitors in Human Whole Blood Assays



COX indicates cyclooxygenase; IC_{50}, median inhibitory dose.
Reprinted with permission from Riendeau et al.[10]

diclofenac 150 mg qd, whereas celecoxib had significantly better safety and tolerability compared with diclofenac. No significant difference was noted in OA pain reduction with celecoxib 100 mg bid or 200 mg qd.[14] In a 12-week multicenter trial of 13 274 patients with OA of the hip, knee, or hand that was designed to approximate clinical practice conditions, Singh and coworkers[15] demonstrated that celecoxib 200 or 400 mg qd provided similar pain relief compared with naproxen 1000 mg qd and diclofenac 100 mg qd. Compared with the pooled NSAID-treated patients (2.1%), the celecoxib group (1.0%) had a significantly lower rate of symptomatic ulcers or complications.[15]

The second COX-2–selective inhibitor to receive FDA approval was rofecoxib. Rofecoxib exhibits greater COX-2 selectivity than celecoxib, as shown in Figure 1.[10] The therapeutic efficacy of rofecoxib in patients with OA was confirmed in 4 pivotal studies: two 6-week studies comparing rofecoxib with ibuprofen 800 mg tid and placebo, and two 1-year studies comparing rofecoxib with diclofenac 50 mg tid.[16-18] Randomized, double-blind trials in patients with OA of the knee or hip demonstrated that over 6 weeks of treatment, rofecoxib 12.5 and 25 mg qd and ibuprofen 800 mg tid produced comparable improvements, and over 1 year of treatment, rofecoxib 12.5 or 25 mg qd and diclofenac 50 mg tid provided similar pain relief.[16–18]

Compared with placebo, rofecoxib at both 12.5 and 25 mg qd produced significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and patient and physician global assessments.[19] Several other secondary efficacy variables improved: less use of rescue acetaminophen; fewer premature study withdrawals due to lack of efficacy; and better quality of life as assessed with the 36-item short-form health survey questionnaire. A consistent treatment effect across subgroups, defined by age, sex, race, baseline severity of OA, prestudy medication groups, and affected joint (hip or knee) was demonstrated by subgroup analyses.[20] Roughly equivalent efficacy in OA is seen with the 12.5- and 25-mg-qd dosages. Data from randomized dose-escalation studies, however, suggest that additional relief may be obtained from the 25-mg-qd dosage in some patients.[21]

Second-Generation COX-2–Selective Inhibitors. Valdecoxib 10 mg qd was approved by the FDA in 2001 for the treatment of OA in adults. Clinical trials demonstrated greater efficacy in patients with OA with valdecoxib 5 mg and 10 mg bid than with placebo, and comparable efficacy to that of naproxen 500 mg bid.[22] Valdecoxib produced significantly fewer endoscopically observed gastroduodenal ulcers and GI adverse events compared with the active comparators.[22] Greater improvement in overall patient assessment of pain, the patient global assessment, and the WOMAC score have been demonstrated in two 3-month, double-blind, randomized, controlled trials in patients with OA.[23] No additional benefit of valdecoxib 10 mg bid or 20 mg qd above the pain relief produced by 10 mg qd was observed.[23] In a multicenter, randomized, double-blind, placebo-controlled, 12-week study of valdecoxib 5, 10, or 20 mg qd; placebo; or naproxen 500 mg bid in patients with OA of the knee, the changes from baseline in patient and physician global assessments of arthritis were significantly greater for valdecoxib 10 mg and 20 mg than for placebo but were not significantly different from those for naproxen 500 mg bid. Gastroduodenal ulcers were significantly more frequent in naproxen-treated patients (10%) compared with the valdecoxib groups (3% to 5%) and placebo (4%).[24] It is noteworthy that the decreased incidence of gastroduodenal ulcers in valdecoxib-treated patients compared to naproxen-treated patients was attenuated in the subgroup that also received concomitant low-dose aspirin.[25] However, these data should be regarded as hypothesis generating rather than hypothesis testing, and should not be used to conclude that low-dose aspirin completely abrogates the beneficial effects of COX-2–

selective inhibitors on the risk of gastroduodenal ulcers associated with nonselective NSAID therapy. Indeed, further studies are needed to compare the combination of COX-2–selective inhibitor plus low-dose aspirin versus a nonselective NSAID plus low-dose aspirin.

Another COX-2–selective inhibitor, etoricoxib, which is approved for use in Mexico and the United Kingdom, has been shown to inhibit COX-2 with 106-fold selectivity in human whole blood assays in vitro.[10,26] Curtis et al[27] reported that patients with OA treated with etoricoxib 60 mg qd for 12 weeks in 2 double-blind, randomized, placebo-controlled studies with naproxen 500 mg bid as an active comparator experienced pain relief as early as 4 hours post-dose, and the therapeutic effects of etoricoxib were sustained over the 24-hour dosing interval. In a 12-week study of patients with knee or hip OA, etoricoxib 60 mg qd produced improvement in pain that was significantly greater than that of placebo but comparable to that of naproxen 500 mg bid.[28] No additional efficacy was noted from using 90 or 120 mg qd compared with 60 mg qd. In addition, etoricoxib was well tolerated by patients with OA, and the treatment efficacy was fully sustained for more than 1 year.[28] The efficacy of 12 weeks of treatment with etoricoxib 60 mg qd (n = 224) was compared with naproxen 500 mg bid (n = 221), or placebo (n = 56) in patients with OA of the knee or hip.[29] Etoricoxib 60 mg produced significantly greater improvements in the WOMAC pain and physical function subscales and patient global assessment of disease status (primary efficacy end point) compared with placebo ($P < .005$) and comparable efficacy to naproxen 500 mg bid. Key secondary end points, which included patient and investigator global assessment of response to therapy, WOMAC stiffness subscale, investigator global assessment of disease status, rescue paracetamol use, proportion of patients discontinuing due to lack of efficacy, and study joint tenderness confirmed these results.[29] The treatment effects were evident by day 2, maximal by week 2, and sustained over the entire 12 weeks of the study.

Lumiracoxib, COX-189, is in the final stages of clinical development. A 4-week dose-finding trial showed that COX-189 at 50, 100, 200, and 400 mg bid produced improvements in OA pain, WOMAC index, and patient or physician global assessments that were superior to placebo but comparable to diclofenac slow release 75 mg bid.[30] The 18 000-person Therapeutic Arthritis Research and Gastrointestinal Event Trial is currently under way to compare the safety and efficacy of COX-189 400 mg qd with ibuprofen 800 mg tid and naproxen 500 mg tid.[31]

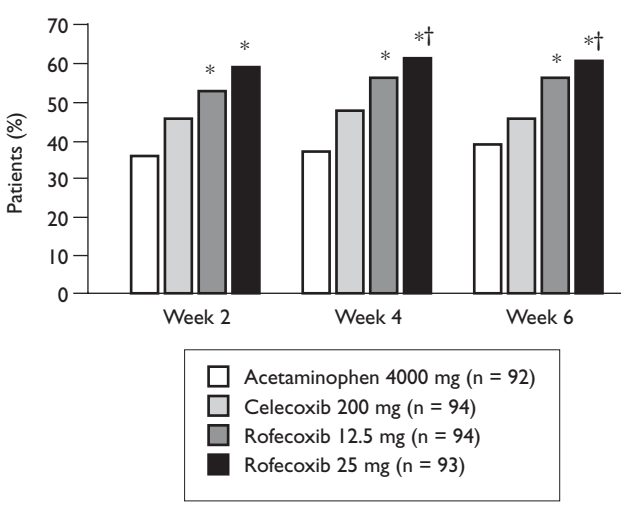
Comparison of COX-2–Selective Inhibitors With Nonsteroidal Anti-inflammatory Drugs. The vast majority of clinical trials have demonstrated that the therapeutic efficacy of COX-2–selective inhibitors is roughly equivalent to that of NSAIDs in patients with OA. These trials also demonstrated that nonselective NSAID therapy was associated with a significantly greater frequency of clinically important upper GI adverse events compared with patients receiving COX-2–selective inhibitor therapy.[15,32,33]

Comparative Efficacy of Celecoxib and Rofecoxib in Osteoarthritis. The efficacy of celecoxib and rofecoxib was compared in 2 head-to-head studies. McKenna et al[34] found no significant difference in the therapeutic efficacy of celecoxib 200 mg qd compared with rofecoxib 25 mg qd in the first of these trials. Significantly greater improvements in arthritis pain were produced by both drugs compared with placebo, as measured on a visual analog scale and the WOMAC score. The celecoxib-treated patients experienced a lower incidence of GI adverse events compared with the rofecoxib group, although both groups had a similar incidence of adverse-event–related study withdrawals.[34]

Results of a 4-arm study comparing rofecoxib 12.5 mg qd, rofecoxib 25 mg qd, celecoxib 200 mg qd, and acetaminophen 1000 mg qid (4 times a day) in 400 patients with symptomatic OA of the knee were published recently.[35] Efficacy measures included ratings of pain on walk-

ing, night pain, pain at rest, and morning stiffness as measured with use of the WOMAC OA index and were obtained during the first 6 days of treatment and over 6 weeks. The acetaminophen group had significantly more frequent premature study withdrawals due to lack of efficacy compared with the groups treated with COX-2 inhibitors (31% versus 18% to 19%). The rofecoxib 25-mg group had significantly greater improvement in all outcome variables compared with the acetaminophen group. Greater relief of pain on walking was seen in the groups treated with either COX-2 inhibitor compared with acetaminophen in the first 6 days of treatment. Rest pain and night pain improved more in the rofecoxib 25-mg group compared with both acetaminophen and celecoxib, whereas the improvement in morning stiffness differed significantly only between the rofecoxib-treated and acetaminophen-treated groups. A similar pattern of responses was noted at 6 weeks: greater improvement with rofecoxib 25 mg in the WOMAC pain and stiffness subscales compared with celecoxib 200 mg qd.

Figure 2. Percentage of Patients With a Good or Excellent Response on Patient Global Assessment of Response to Therapy by Study Week



*$P \leq .05$ vs acetaminophen
†$P \leq .05$ vs celecoxib

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Furthermore, compared with the celecoxib group, a significantly higher percentage of patients in the rofecoxib 25-mg group experienced good to excellent improvement on the patient global assessment of therapy (**Figure 2**).[35] However, no significant differences were noted between celecoxib and the lower dose of rofecoxib.[35]

Geba et al[35] demonstrated greater therapeutic efficacy of rofecoxib 25 mg qd compared with celecoxib 200 mg qd, whereas McKenna et al[34] were unable to identify any significant differences in efficacy. Methodologic differences such as the timing of the dosing of medications relative to assessments, the circadian rhythm of COX-2 expression, and diurnal variation in pain profiles may be partly the cause of these inconsistent outcomes across efficacy studies. Other trials comparing celecoxib with rofecoxib, and rofecoxib with valdecoxib are under way.

Rheumatoid Arthritis. *First-Generation COX-2–Selective Inhibitors.* The therapeutic efficacy of celecoxib at dosages of 100 to 400 mg bid has been demonstrated in patients with RA. Celecoxib had greater efficacy than placebo and was comparable with naproxen 500 mg bid.[11,36] In 1 study,[36] 1149 adults with symptomatic RA were randomized to receive celecoxib 100, 200, or 400 mg bid; naproxen 500 mg bid; or placebo. Significantly greater improvement in signs and symptoms of RA was noted in the celecoxib and naproxen groups compared with placebo within 2 weeks of initiating treatment, and the improvement was sustained throughout the 12 weeks of the study. The incidence of endoscopically determined gastroduodenal ulcers was similar in the placebo-treated patients (4%) and the celecoxib groups (6%, 4%, and 8% in the 100-, 200-, and 400-mg-bid groups, respectively), which was significantly lower than the 26% incidence observed in the naproxen-treated group. Overall incidences of GI adverse effects were 19% for placebo; 28%, 25%, and 26% for the celecoxib 100-, 200-, and 400-mg-bid groups, respectively; and 31% for naproxen.[36]

Another group found comparable improvements in RA pain after 24 weeks of treatment with celecoxib 200 mg bid and diclofenac slow release 75 mg bid, as measured by changes in the mean number of painful and swollen joints.[37] Endoscopically detected gastroduodenal ulcers were observed in 15% of the patients treated with diclofenac compared with only 4% in the celecoxib group ($P < .001$), and the rate of withdrawal due to any GI-related adverse event, most commonly abdominal pain, diarrhea, and dyspepsia, was 16% in the diclofenac-treated group compared with 6% in the celecoxib group ($P < .001$).[37]

A Phase II study demonstrated that, compared with placebo, greater improvement was seen with rofecoxib 25 and 50 mg qd in patients with RA.[38] In a clinical trial designed to compare GI side effects, the efficacy of rofecoxib 50 mg was similar to that of naproxen 500 mg bid.[39] A significantly lower incidence of upper GI PUBs and complicated PUBs was associated with rofecoxib treatment compared with naproxen.[39] In a Phase III, multicenter clinical trial, 1058 patients with RA were randomized to 12 weeks of treatment with placebo (n = 299), rofecoxib 25 mg (n = 315) or 50 mg (n = 297), or naproxen 500 mg bid (n = 147).[40] The rofecoxib 25- and 50-mg and naproxen groups had comparable outcomes for all 4 primary efficacy variables (patient and investigator global assessments of disease activity and counts of tender and swollen joints), and all improvements (with the exception of the swollen joint count in the naproxen group) were significantly greater in the active treatment groups compared with placebo.[40] No statistically significant differences were noted between rofecoxib 25 and 50 mg or between naproxen and either rofecoxib group for any efficacy measurement. The rofecoxib 25-mg group (3.8%) had fewer premature discontinuations due to adverse events compared with the other active treatment groups (~8%) and placebo (4.7%).[40] In another Phase III study, patients received 12.5 or 25 mg rofecoxib qd, naproxen 500 mg bid, or placebo for 12 weeks. Rofecoxib 25 mg qd was comparable to naproxen and significantly superior to placebo.[41] The recommended dosage of rofecoxib for treatment of RA is 25 mg qd. There is no evidence of clinically important or statistically significant increased efficacy of giving rofecoxib 50 mg qd,[40] whereas evidence does exist of dose-related adverse events at the higher dosage.[39] To date, no clinical trials have compared the efficacy of celecoxib and rofecoxib in patients with RA.

Second-Generation COX-2–Selective Inhibitors. In a 12-week trial of 1089 patients with RA that compared valdecoxib 10, 20, and 40 mg qd with placebo and naproxen 500 mg bid,[42] the primary efficacy variable, the American College of Rheumatology (ACR) 20% responder rate (ACR-20), showed significant separation of all active treatments from placebo as early as 2 weeks, a difference that was fully sustained throughout the trial.[42] Although the therapeutic efficacy of valdecoxib was comparable to that of naproxen, the incidence of abdominal pain, dyspepsia, and constipation was higher in the naproxen group compared with valdecoxib 10 and 20 mg.[43]

When compared with placebo and naproxen 500 mg bid in 819 patients with RA treated for 12 weeks, etoricoxib 90 mg qd was shown to produce significantly greater improvement in swollen joint count; tender joint count; patient and investigator global assessment of disease activity (primary efficacy variables); the ACR-20 responders and completers index; patient global assessment of pain; health assessment questionnaire (a disability scale); and patient and investigator global assessment of response to therapy (secondary efficacy variables).[43] The percentage of patients who achieved a composite ACR-20 response over 12 weeks was 21%, 53%, and 39% in the placebo, etoricoxib, and naproxen groups, respectively ($P < .001$ for etoricoxib and naproxen versus placebo; $P = .005$ for etoricoxib versus naproxen). Compared with the naproxen and placebo groups, fewer patients in the etoricoxib group discontinued prematurely because of lack of efficacy ($P < .001$). All

groups had similar overall incidence of clinical adverse events. Thus, etoricoxib 90 mg qd demonstrated greater therapeutic efficacy in RA compared with naproxen 500 mg bid.[43] In another multinational, double-blind, placebo- and active-comparator–controlled, 12-week study, 891 patients with RA were randomized to treatment with placebo, etoricoxib 90 mg qd, or naproxen 500 mg bid.[44] Primary efficacy measures included direct assessment of arthritis by counts of tender and swollen joints, and patient and investigator global assessments of disease activity. Key secondary measures included the Stanford Health Assessment Questionnaire, patient global assessment of pain, and the percentage of patients who achieved ACR-20 responder criteria response (a composite of pain, inflammation, function, and global assessments). Patients receiving etoricoxib and naproxen had significant improvements in all efficacy end points compared with patients receiving placebo ($P < .05$). Treatment responses were similar between the etoricoxib and naproxen groups for all end points. The ACR-20 responder criteria response was achieved by 41% of the patients in the placebo group, 59% in the etoricoxib group, and 58% in the naproxen group. Thus, etoricoxib 90 mg qd was more effective than placebo and similar in efficacy to naproxen 500 mg bid for treating patients with RA over 12 weeks.[44] Etoricoxib and naproxen were both generally well tolerated.

Safety and Tolerability

Gastrointestinal Effects. The COX-2 hypothesis predicts that GI safety and tolerability will be better with coxibs than with nonselective NSAIDs (**Table 1**).[45] GI complications and adverse events in OA and RA are discussed in detail elsewhere in this supplement; however, a brief consideration of the healthcare cost implications of GI adverse effects is relevant to the managed healthcare outlook on arthritis pain management. Peloso and

Table 1. Selected Gastrointestinal Symptoms in Pooled Celecoxib and Rofecoxib Trials

Drug/Symptom	Persons Receiving Placebo	Persons Receiving COX-2 Inhibitors	Persons Receiving Ibuprofen, 2400 mg/d	Persons Receiving Diclofenac, 150 mg/d	Persons Receiving Naproxen, 1000 mg/d
Celecoxib, 200 to 400 mg/d*					
Abdominal pain	2.8 (2.0 to 3.5)	4.1 (3.5 to 4.7)	9.0 (6.2 to 11.9)	9.0 (6.0 to 12.0)	7.7 (6.3 to 9.1)
Dyspepsia	6.2 (5.1 to 7.3)	8.8 (7.9 to 9.7)	10.9 (7.8 to 14.0)	12.8 (9.2 to 16.3)	12.2 (10.5 to 14.0)
Nausea	4.2 (3.3 to 5.1)	3.5 (2.9 to 4.1)	3.4 (1.6 to 5.2)	6.7 (4.0 to 9.3)	6.0 (4.7 to 7.3)
Diarrhea	3.8 (2.9 to 4.7)	5.6 (4.9 to 6.3)	9.3 (6.4 to 12.2)	5.8 (3.3 to 8.3)	5.3 (4.1 to 6.5)
Rofecoxib, 12 to 25 mg/d†					
Abdominal pain	4.1 (2.7 to 5.5)	3.4 (2.7 to 4.1)	4.6 (3.2 to 6.0)	5.8 (5.8 to 7.9)	—
Dyspepsia	2.7 (1.6 to 3.8)	3.5 (2.8 to 4.2)	4.7 (3.3 to 6.2)	4.0 (2.3 to 5.7)	—
Nausea	4.7 (3.2 to 6.2)	5.2 (4.4 to 6.0)	7.1 (5.4 to 8.8)	7.4 (5.1 to 9.7)	—
Diarrhea	6.8 (5 to 8.5)	6.5 (5.6 to 7.4)	7.1 (5.4 to 8.8)	10.6 (7.9 to 13.4)	—

Values are percentage (SD).
*Trials involved a total of 8108 patients. Withdrawals due to adverse events occurred in 7.1% of celecoxib-treated patients in controlled celecoxib trials and in 6.1% of placebo recipients. Withdrawal due to abdominal pain or dyspepsia occurred in 0.7% and 0.8% of celecoxib-treated patients and in 0.6% and 0.6% of placebo patients, respectively.
†Trials involved a total of 4957 patients. No published information is available on withdrawal rates.
COX-2 indicates cyclooxygenase-2.
Source: Reference 45.

Scheiman[46] estimated the healthcare costs for prevention and treatment of GI adverse effects of traditional approaches to OA and RA pain management. COX-2–selective therapy was considered cost-saving because treatment with coxibs mitigates the need for medical therapy to offset iatrogenic GI complications. NSAID therapy is estimated to cause dyspepsia in roughly 25% of users and to increase the risk of GI bleeding in ~4% of users.[47,48] As many as 1.4% of patients with arthritis are estimated to be hospitalized for GI bleeding annually. This hospitalization rate represents 37.5% of the direct cost of arthritis care.[49] Estimates of costs for NSAID-associated GI bleeding range from $1050 for medically managed outpatients to $20 649 for surgically managed inpatients, respectively (1992 US dollars).[46]

Two Canadian studies[50,51] noted that 25% of patients filling NSAID prescriptions also filled a co-prescription for a proton-pump inhibitor, an H_2 receptor blocker, sucralfate, or misoprostol to reduce NSAID-related dyspepsia. Economic models suggest that in high-risk patients, the use of more costly pain medications with greater GI safety is associated with better outcomes at lower incremental costs compared with initial use of a low-cost, generic NSAID followed by acid suppression and other GI therapies.[50,51] However, these models underestimate the overall value of COX-2–selective therapy because they do not include impaired quality of life or indirect costs related to lost productivity. An economic model based on the Swiss healthcare system predicted that a policy of switching patients from NSAIDs to COX-2–selective inhibitor therapy would result in cost savings for health insurers, with greater cost savings when patients are switched from NSAIDs plus concomitant gastroprotective agents.[52] This useful model requires validation in clinical practice.

In addition to decreased costs associated with improved GI safety observed with COX-2–selective therapy compared with traditional NSAIDs, differences in GI safety between COX-2–selective therapies should also be considered. In this regard, treatment of patients with RA with rofecoxib 50 mg qd resulted in a 54% reduction in GI side effects compared with naproxen 1000 mg, suggesting that costs associated with the various COX-2–selective therapies may differ.[39]

Nongastrointestinal Effects. Nongastrointestinal side effects and safety issues are also an important consideration in the therapeutic management of chronic OA and RA pain, particularly in light of the overall evaluation of the cost-effectiveness of treatment. Clear evidence suggests that COX-2–selective inhibitors share the same effects of nonselective NSAIDs on blood pressure and kidney function when given in similar efficacious doses.[53] The possibility of an increased risk for cardiovascular (CV) events associated with COX-2–selective inhibitors compared with traditional NSAID therapy has been suggested, although the results remain controversial.[54]

Renal Effects, Including Hypertension. The fact that both nonselective NSAIDs and the COX-2–selective inhibitors have an unfavorable effect on renal function in high-risk patients suggests that COX-2–derived products support normal renal function.[8] The negative effects of these drugs on renal function are thought to be related to their suppressive effect on prostaglandin synthesis. NSAIDs have been shown to decrease sodium excretion, potassium excretion, and renal perfusion and impair renal function sufficiently to cause acute renal failure. While fluid reten-

Table 2. Risk Factors for Renal Adverse Events

- Age >70 years
- Hypertension
- Diabetes mellitus
- Cirrhosis
- Congestive heart failure
- History of renal disease
- Electrolyte imbalance

tion causing edema and exacerbation of hypertension can occur in anyone, patients at increased risk for these renal adverse effects (**Table 2**) can be readily identified and appropriate precautionary measures instituted.[55]

COX-2–selective inhibitors can exert a deleterious effect on renal function (**Table 3**).[56] Whelton et al[57] evaluated the renal safety of celecoxib 200 mg qd and rofecoxib 25 mg qd in a 6-week, randomized, parallel-group, double-blind study in patients with OA older than 65 years who were taking antihypertensive agents. The primary end points were the development of edema, changes in systolic blood pressure, and changes in diastolic blood pressure at any time in the study. Of the 810 patients who received study medication (celecoxib, n = 411; rofecoxib, n = 399), systolic blood pressure increased significantly in 17% of rofecoxib-treated and 11% of celecoxib-treated patients, and diastolic blood pressure increased in 2.3% of the rofecoxib group and 1.5% of the celecoxib group.[57]

Dose-related renal adverse events (eg, increases in blood pressure, edema) have been documented with all FDA-approved coxibs (celecoxib, rofecoxib, and valdecoxib) as well as with nonselective NSAIDs. In high-risk patients, both coxibs and NSAIDs should either be avoided or used in the lowest possible dose with careful monitoring of blood pressure and renal function.

A recent retrospective analysis of patients in a large managed care population evaluated the clinical impact of COX-2–selective inhibitors on new-onset hypertension in patients who received at least 1 prescription for rofecoxib or celecoxib, but no concurrent therapy with any

Table 3. Renal Effects of COX-2–Selective Inhibitors

Drug	Patients	End Points	Results
Celecoxib	Salt-depleted healthy subjects (n = 40)	BP, weight, RBF, GFR, urinary Na^+ & K^+ excretion, plasma renin activity	Transient decline in RBF & GFR, decreased Na^+ & K^+ excretion, decreased plasma renin activity*
	Healthy elderly (n = 24)	GFR, urinary PG & Na^+ excretion	No change in GFR, decrease in PG,* transient decrease in Na^+ excretion
	Chronic renal failure with GFR = 31 to 36 mL/min (n = 75) activity	GFR, urinary PG & Na^+ excretion, plasma renin activity or Na^+ excretion*	No change in GFR,* decrease in PG,* no change in plasma renin
	2 cases with chronic renal failure	Case reports	Acute renal failure, hyperkalemia, and volume overload
Rofecoxib	Healthy elderly subjects (n = 36)	BP, weight, GFR, PG, urinary Na^+ & K^+ excretion	No change in weight, BP, GFR,† or K^+ excretion, transient decrease in Na^+ excretion, decrease in PG‡
	Elderly with GFR = 30 to 80 mL/min (n = 60)	GFR, BP, weight, urinary Na^+ & K^+ excretion	Decrease in GFR,‡ no change in BP, weight, or Na^+ & K^+ excretion
	1 case with chronic renal failure	Case reports	Acute renal failure and hyperkalemia, 1 hemodialysis treatment for hyperkalemia

*Similar between celecoxib and naproxen groups.
†Decrease in GFR in indomethacin group only.
‡Similar between rofecoxib and indomethacin groups.
BP indicates blood pressure; COX-2, cyclooxygenase-2; GFR, glomerular filtration rate; PG, prostaglandin; RBF, renal blood flow.
Source: Reference 56.

other NSAID during an 18-month period. The rates of new-onset hypertension were similar for patients who received rofecoxib (3.83%) and celecoxib (3.43%) and included the incidence of hypertension not attributable to COX-2–selective inhibitor use.[58] Furthermore, these incidence rates are similar to that of ~4% for white men and women reported in the Atherosclerosis Risk in Communities study.[59]

Curtis et al[60] evaluated the renovascular safety profile of etoricoxib from 8 pooled Phase III studies in patients with OA, RA, and chronic low back pain treated with placebo; etoricoxib 60, 90, or 120 mg/d; naproxen 1000 mg/d; or ibuprofen 2400 mg/d. They found no episodes of acute renal failure in any treatment group. The incidences of lower extremity edema and hypertension adverse events with etoricoxib therapy were generally low, similar to comparator NSAIDs, and provided no compelling evidence of dose-related deleterious renal effects.[60]

Other studies have noted that the COX-2 inhibitors rofecoxib and celecoxib altered urinary prostaglandin excretion, glomerular filtration rate, and sodium retention, similar to nonselective NSAIDs.[61] These results suggest that similar precautions should be exercised with the use of COX-2 selective inhibitors as with traditional NSAIDs in patients at greater risk for impaired renal function, such as the elderly and those receiving antihypertensive therapy.[57]

Cardiovascular Effects. Data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial indicated an increased risk of confirmed CV thrombotic events in patients taking rofecoxib 50 mg qd for RA (a dose 2 to 4 times greater than that approved for use in patients with OA and 2 times greater than that approved for use in patients with RA) compared with patients taking naproxen 500 mg bid.[39] This excess risk was largely, although not exclusively, limited to nonfatal myocardial infarction (MI). Because the protocol for the VIGOR trial prohibited the use of aspirin, the ability of naproxen but not rofecoxib to inhibit thromboxane production by platelets may have contributed to the difference in serious CV effects observed. This unexpected observation led to a hypothesis-generating analysis by Mukherjee et al[54] that COX-2–selective inhibitors were associated with an increased risk of CV thrombotic events. This claim, however, was based on invalid comparisons of different studies rather than robust scientific observations.[62] Roughly 20% of the patients in the Celecoxib Long-Term Arthritis Safety Study (CLASS) received low-dose aspirin therapy for secondary prevention while, in contrast, none of the patients in the VIGOR trial received low-dose aspirin therapy because of protocol restrictions. Furthermore, the VIGOR trial included only patients with RA, whereas 75% of the patients in CLASS had OA. A number of studies show that patients with RA are at increased risk for CV thrombotic events.[63,64]

FitzGerald and Patrono[8] proposed 3 possible explanations for the observation in VIGOR: 1) prothrombotic tendency with rofecoxib, 2) beneficial antithrombotic tendency with naproxen, or 3) play of chance. Any possible prothrombotic effect of COX-2-selective inhibitors may be due to their ability to inhibit vascular prostacyclin (PGI_2) synthesis in the absence of an inhibitory effect on prothrombotic COX-1–mediated platelet thromboxane production and aggregation.[65] Both selective and nonselective NSAIDs reduce prostacyclin formation, but only nonselective NSAIDs inhibit the formation of thromboxane, a prothrombotic eicosanoid. COX-2 plays a role in PGI_2 production, and PGI_2 is known to promote vasodilation and inhibit platelet aggregation. Thus, selective COX-2 inhibition could facilitate increased prothrombotic activity by decreasing vasodilatory and antiaggregatory PGI_2 production.[65,66] The relative increase in thromboxane due to unopposed COX-1–mediated thromboxane synthesis, coupled with diminished prostacyclin, favors a prothrombotic state, which may increase the risk of thrombotic CV events.[67] A meta-analysis

by Konstam et al[68] and a comparison study by Reicin et al,[69] however, failed to show evidence of a prothrombotic effect of rofecoxib at doses within the therapeutic range of 12.5 to 25 mg qd compared with either placebo or non-naproxen nonselective NSAIDs. Three observational epidemiologic studies showed a lower risk of MI in persons taking naproxen compared with control subjects taking non-naproxen NSAIDs or nothing.[70-73] Hence, the aggregate data show no evidence of a deleterious effect of COX-2–selective inhibitors, when used in approved therapeutic doses. Until further data are available, caution should be exercised when treating patients with known ischemic heart disease, and low-dose aspirin should be used in conjunction with COX-2–selective inhibitors when aspirin is indicated for secondary prevention.[53] It is recommended that low-dose aspirin be used for CV prophylaxis when indicated (in spite of the potential attenuation of the GI-protective effect of COX–selective inhibition). Further-more, COX-2–selective inhibitors should not be taken as a substitute for low-dose aspirin, as they do not inhibit platelet-derived thromboxane synthesis.[53] Additional studies are necessary to evaluate the relative impact of low-dose aspirin when given concomitantly with a coxib.[53]

Implications for Managed Healthcare Organizations

Data from a number of trials have demonstrated that the improved GI safety profile of COX-2-selective inhibitors translates in clinical practice into fewer GI complications, decreased use of concomitant GI protective medications, and a decreased rate of hospitalization, with implications for improvements in cost burden for managed care organizations. In patients with RA in the VIGOR trial, treatment with rofecoxib was associated with significantly fewer clinically important upper GI events than patients given naproxen.[39] In another rofecoxib trial, treatment discontinuations secondary to GI adverse effects were significantly lower with rofecoxib than with NSAIDs.[74] In the ADVANTAGE trial (which included patients treated with low-dose aspirin), patients with OA treated with rofecoxib required significantly less use of concomitant GI protective medications compared with patients given naproxen.[75] Finally, in the SUCCESS trial, upper GI hospitalization rates were 2 to 4 times lower, and less upper GI-related healthcare resources were used for celecoxib- versus NSAID-treated patients.[76]

Several studies have used actual data, simulated analyses, and actual analyses of treatment costs and outcomes, to evaluate the cost-effectiveness of arthritis and chronic pain management regimens. As a result of the enhanced GI safety of COX-2–selective inhibitors compared with nonselective NSAIDs, patients prescribed coxibs use significantly fewer GI-related healthcare resources (eg, medications, procedures) than patients taking nonselective NSAIDs.[77] Sturkenboom et al[78] retrospectively analyzed the iatrogenic costs of NSAID therapy related to medical interventions for upper GI disorders after NSAID treatment (ie, prescriptions for gastroprotective drugs, hospitalizations, and outpatient diagnostic procedures) in 265 114 individuals who received at least 1 prescription for any NSAID. The estimated cost of medical interventions for GI events added 58% to the cost of NSAID therapy, of which 78.6% was for coprescriptions for gastroprotective drugs.[78] Clinical and economic data suggest that the use of coxibs has clinical GI benefits at a potentially acceptable incremental cost for all chronic NSAID users. For individuals who are at an increased risk of developing GI complications attributable to NSAIDs, Fendrick[77] concluded that the coxibs are clearly a cost-effective treatment option.

Pellissier et al[79] used the rofecoxib Phase III clinical trial data to evaluate the economic impact of the use of rofecoxib compared with nonselective NSAIDs for the treatment of OA. Base-case 1-year analyses of GI adverse events, specifically PUBs, indicated a cost savings in GI complications and co-medications averted by use of rofecoxib versus NSAIDs of $0.81 per day, which represented an 85% offset

of the higher cost of rofecoxib.[79] Even when endoscopic data were considered (instead of overt PUBs), rofecoxib was still found to be cost-effective across all assumptions about the incidence rate of silent ulcers. This analysis, based on differences in the occurrence of clinically significant GI events in patients with OA, demonstrated that the cost differences between rofecoxib and NSAIDs were offset by savings in the cost of preventing and treating GI complications. A review of clinical GI toxicity data indicated that use of COX-2–selective inhibitors compared with NSAIDs is associated with an ~1% absolute risk reduction for symptomatic ulcer disease, equivalent to the prevention of 1 symptomatic ulcer in every 100 patients during the first year of exposure.[45]

Recently, one of the most comprehensive economic analyses of RA and OA

Table 4. Baseline Cost-Effectiveness Ratios (Canadian Dollars) for VIGOR and CLASS Trials, According to Patient Risk for Gastrointestinal Events

	Costs* ($ Can)	QALYs*	Life-Years*	Cost/QALY Gained* ($ Can)	Cost/Life-Year Gained* ($ Can)
Average-Risk Patients					
VIGOR					
Naproxen (500 mg bid)	1576	2.894	4.358	—	—
Rofecoxib (25 mg qd)	3173	2.900	4.361	271 188	455 071
CLASS					
Ibuprofen (800 mg tid)	1141	2.899	4.360	—	—
Diclofenac (75 mg bid)	2503	2.910	4.365	119 395	236 510
Celecoxib (100/200 mg bid)	3371	2.909	4.365	Dominated by diclofenac†	
Celecoxib (100/200 mg bid) versus ibuprofen	—	—	—	212 593	402 545
High-Risk Patients					
VIGOR					
Rofecoxib (25 mg qd)	4090	2.885	4.354	—	—
Naproxen (500 mg bid) + PPI	4766	2.882	4.352	Dominated by rofecoxib†	
Rofecoxib (25 mg qd) + PPI	6486	2.894	4.359	281 244	567 820
CLASS					
Celecoxib (100/200 mg bid)	4327	2.900	4.360	—	—
Ibuprofen (800 mg tid) + PPI	4414	2.889	4.354	Dominated by celecoxib†	
Diclofenac (75 mg bid) + PPI	5881	2.906	4.363	254 803	487 241
Celecoxib (100/200 mg bid) + PPI	6746	2.906	4.363	Dominated by diclofenac†	

The VIGOR trial was a 5-year comparison of rofecoxib with naproxen in patients with RA; CLASS was a 5-year comparison of celecoxib with diclofenac and ibuprofen in patients with OA (72%) or RA (28%). Strategies are ordered by increasing cost. The more expensive strategy is compared with the less expensive, nondominated strategy.
*Future QALYs and life-years are discounted by 5%.
†Indicates a more costly and less efficacious strategy.
CLASS indicates Celecoxib Long-Term Arthritis Safety Study; OA, osteoarthritis; PPI, proton pump inhibitor (lansoprazole); QALY, quality-adjusted life year; RA, rheumatoid arthritis; VIGOR, Vioxx Gastrointestinal Outcomes Research trial.
Source: Reference 80.

treatment costs, taking into account medication costs and costs of both GI and CV adverse effects, was performed by Maetzel et al.[80] This economic evaluation determined the cost-effectiveness of celecoxib compared with the NSAIDs diclofenac and ibuprofen, and rofecoxib compared with naproxen, in patients with OA and RA who were not taking concomitant low-dose aspirin for the prevention of CV disease. The findings are based on the clinical outcomes (including upper GI events and MIs) in the CLASS and VIGOR trials. A decision-analysis model was constructed in which GI and CV events were modeled as a consequence of medication usage, and the clinical trial results were extrapolated over a 5-year period.[80]

The analyses concluded that the COX-2–selective inhibitors are cost-effective for patients who are at high risk for GI events (**Table 4**).[80] In addition, rofecoxib and celecoxib become cost-effective treatments for patients older than 75 years who have no additional risk factors. The economic analyses, however, indicated that the COX-2–selective inhibitors are not cost-effective treatments in patients at average risk of upper GI events. Thus, the COX-2–selective inhibitors appear to be the most economically attractive treatment strategy in high-risk and elderly patients. Further studies are necessary, however, to evaluate the pharmacoeconomic benefits of coxibs in these high-risk patient populations that also have an increased risk for CV thrombotic events.

Conclusion

COX-2–selective inhibitors appear to be roughly comparable in therapeutic efficacy with traditional high-dose nonselective NSAIDs in patients with OA and RA, although 1 study[43] has suggested greater efficacy of etoricoxib over naproxen in RA. Given the similar efficacy, the safety profile emerges as a primary factor for discrimination between the COX-2–selective inhibitors and traditional nonselective NSAIDs.[57] In several outcome studies, patients treated with COX-2–selective inhibitors experienced fewer upper GI adverse events and complications than patients treated with active comparators. Because COX-2–selective inhibitors do not inhibit platelet-derived thromboxane synthesis, concomitant low-dose aspirin remains indicated in patients requiring CV prophylaxis. In addition, precautions are necessary with COX-2–selective inhibitors as with traditional NSAIDs in patients at risk for impaired renal function. Following the recommendations by the American Pain Society,[81] the ACR,[82,83] and the International Consensus Conference,[53] the increased use of COX-2–selective inhibitors in appropriate patients should lead to a decrease in the mortality, morbidity, and healthcare utilization and costs associated with serious upper GI complications of nonselective NSAIDs.

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