An Evidence-Based Approach to Prescribing Nonsteroidal Antiinflammatory Drugs. Third Canadian Consensus Conference

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ABSTRACT. ***Objective.*** To revisit our previous evidence-based recommendations on the appropriate prescription of nonsteroidal antiinflammatory drugs (NSAID) with particular emphasis on cyclooxygenase-2 selective inhibitors (coxibs).

Methods. Needs assessments were conducted among Canadian physicians to determine their educational needs surrounding NSAID/coxibs. A survey of patients with arthritis was also conducted. Consensus participants reviewed articles relating to NSAID/coxibs in peer-reviewed journals between January 2000 and December 2004. At the consensus meeting, held January 21–23, 2005, participants discussed selected topics, after which recommendations were formulated and debated.

Results. At the time of the meeting, it was agreed that emerging cardiovascular data were not clear enough to decide whether unanticipated cardiovascular events associated with coxibs represent a class effect or an effect of an individual drug. However, publications that appeared shortly after the meeting, as well as data presented at both the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the US Food and Drug Administration, February 16-18, 2005, and Health Canada's Expert Advisory Panel on the Safety of Cox-2 Selective NSAID, June 9-10, 2005, clarified that all available coxibs do carry some degree of cardiovascular risk, denoting a class effect. Our consensus group made the following specific recommendations: (1) Patients should be fully informed about treatment options, including the need to balance between cardiovascular risks and gastrointestinal (GI) benefits of NSAID/coxibs. (2) Coxibs are as effective as nonselective NSAID and superior to acetaminophen for the symptoms of arthritis. Topical NSAID may also be beneficial. (3) Coxibs are associated with fewer severe GI complications than nonselective NSAID. A proton pump inhibitor (PPI) should be prescribed if an NSAID must be used in a patient at increased GI risk. (4) The renal/blood pressure (BP) impact of coxibs is similar to that of NSAID. (5) In individuals at risk, creatinine clearance and BP should be determined at baseline and shortly after treatment begins. (6) In the geriatric population, use of nonpharmacological therapies should be maximized, and special caution is required before prescribing oral NSAID/coxibs. (7) Patients taking rofecoxib have been shown to have an increased risk of cardiovascular events. Current data suggest that this increased cardiovascular risk may be an effect of the NSAID/coxib class. (8) Although the data are limited, coxibs may be more cost-effective for patients at high GI risk than nonselective NSAID plus proprietary PPI.

Conclusion. Coxibs continue to be an option in the treatment armamentarium. Given the evolving cardiovascular information, physicians and patients should weigh the benefits and risks of NSAID/coxib treatment. This concern emphasizes the need to routinely reassess patients' risks. These recommendations, which were formulated according to the Appraisal of Guidelines for Research and Evaluation, are intended to be used as guidelines to supplement, but not replace, the physician's judgment in clinical decision-making. (J Rheumatol 2006;33:140-57; First Release Dec 1, 2005)

Key Indexing Terms:
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In 1999, the World Health Organization designated a new subclass of nonsteroidal antiinflammatory drugs (NSAID) termed coxibs[1], developed with a view to reducing serious gastrointestinal (GI) adverse events. Unlike the nonselective NSAID, which inhibit both cyclooxygenase (COX) isoenzymes, the coxibs selectively inhibit the COX-2 isoenzyme, and appear to be associated with fewer serious GI adverse events[2-4].

The Third Canadian Consensus Conference was convened January 21-23, 2005, in Cambridge, Ontario, to revise and update previous evidence-based recommendations for the use of NSAID (including coxibs) among patients with osteoarthritis (OA) and rheumatoid arthritis (RA)[5,6]. The objectives of the conference were to review NSAID-related data published in English between January 2000 and December 2004, to discuss NSAID formulations and molecules for which new drug applications had been submitted to Health Canada's Therapeutic Products Directorate before December 2004, and to develop evidence-based recommendations on the appropriate use of NSAID, including coxibs. Recent events such as the September 2004 voluntary withdrawal of rofecoxib and the December 2004 US Food and Drug Administration (FDA) request to withhold "direct to consumer" advertising of celecoxib in the US have led to confusion among physicians and patients about the cardiovascular safety of coxibs, and made the Consensus Group's deliberations especially timely.

MATERIALS AND METHODS

Needs assessment. To ensure that the content and discussion of the Consensus Conference would meet the informational needs of Canadian physicians, 3 needs assessments were conducted with over 250 physicians using questionnaires and focus groups, one of which has been published in summary form[7]; in addition an Internet based mail-in survey was carried out between December 13, 2004, and January 10, 2005, by a Canadian patient advocacy group, to assess the needs and understanding of arthritis patients following withdrawal of rofecoxib.

Literature search. Medline, OVID, and PubMed searches were conducted by a librarian at the University of British Columbia under the supervision of a rheumatologist to develop a database of articles relating to NSAID (including coxibs) published in English in peer-reviewed journals between January 2000 and December 2004. Using the search terms osteoarthritis, rheumatoid arthritis, guidelines/consensus, acetaminophen, NSAID, celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib, all clinical conferences, clinical trials, evaluation studies, metaanalyses, multicenter studies, randomized controlled trials (RCT), and technical reports were searched. A total of 373 articles were so obtained for consideration. Participants were also free to conduct additional literature searches on their preassigned topics.

Meeting organization. The Consensus organizers (HT, PD, ASR) invited the participation of 28 recognized leaders from across Canada in rheumatology, internal medicine, family medicine, nephrology, cardiology, gastroenterology, geriatrics, pharmacology, pharmacy, orthopedics, and health economics. Representation was also invited from 3 patient advocacy groups (The Arthritis Society, Canadian Arthritis Patient Alliance, and Arthritis Consumer Experts). One nonparticipating observer attended the meeting on behalf of each of the pharmaceutical sponsors (see below for details of funding).

Participants heard and discussed a total of 24 presentations dealing with processes for developing evidence-based guidelines, Appraisal of Guidelines for Research and Evaluation (AGREE, an instrument used worldwide for assessing the adequacy of clinical practice guidelines)[8]; newer NSAID formulations and coxibs; cardiovascular and GI effects of NSAID (including coxibs); and viewpoints of the family physician, geriatrician, orthopedic surgeon, health economist, and patient advocate. All participants debated proposed recommendations to develop a consensus. The strength of each recommendation was graded from A to D based on the level of evidence (Table 1)[9]. New information from articles published after the consensus meeting and from data presented at the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the FDA[10], held February 16–18, 2005, and Health Canada's Expert Advisory Panel on the Safety of COX-2 Selective NSAID[11], held June 9–10, 2005, were subsequently incorporated into the final report after agreement by the consensus participants.

Funding and conflict of interest. The conference was held under the auspices of the Division of Continuing Medical Education of the University of Alberta. Financial support was derived from unrestricted educational grants made to the University of Alberta by Merck Frosst Canada, Ltd., Novartis Pharmaceuticals Canada Inc., Pfizer Canada Inc., Solvay Pharma, and Dimethaid Health Care Ltd. Sponsors had no input into the organization of the meeting, selection of participants, content of presentations, or recommendations. Most of the meeting participants have served as consultants, advisors or speakers, or have received grants, from one or more of the sponsors at some time, but none received financial support directly from any sponsor for their participation at this consensus meeting.

RESULTS

Needs assessment. Although the 3 physician needs assessments differed in format and in specific questions, the responses were thematically similar. Responses from physicians expressed confusion and frustration at mixed messages they were receiving from their colleagues, the pharmaceutical industry, peer-reviewed journals, and the lay press about the comparative benefit to risk ratio of nonselective NSAID versus coxibs. Areas in which physicians cited a particular need for more knowledge included effects of NSAID (especially coxibs) on fluid retention and hypertension; potential cardiovascular safety issues associated with coxibs; and drug interactions and coprescriptions of coxibs with other drugs, particularly angiotensin-converting enzyme (ACE) inhibitors, anticoagulants, angiotensin II receptor blockers (ARB), and proton pump inhibitors (PPI). Finally, respondents wanted more information about the potency of COX-2 selectivity and its relationship with efficacy and toxicity, as well as about the newer coxibs and whether they offer greater benefit or reduced risk compared to the currently available compounds.

Consumer Perspectives

Recommendation:
Patients should be fully informed about the benefit to risk ratios of their treatment options, based on evidence where available. Evolving information should be discussed openly and frankly in order to enhance communication between the patient and the physician. (Level 3, Grade C)

Table 1. Categories of evidence and grades of recommendation.

Categories of Evidence	Level	Grade of Recommendation	Grade
Meta-analysis of RCT	1A	Category 1 evidence	A
At least one RCT	1B		
At least one controlled study without randomization	2A	Category 2 evidence or extrapolated recommendation from Category 1 evidence	B
At least one quasi-experimental study	2B		
Descriptive studies, such as comparative, correlation or case-control studies	3	Category 3 evidence or extrapolated recommendation from Category 1 or 2 evidence	C
Expert committee reports or opinions and/or clinical experience of respected authorities	4	Category 4 evidence or extrapolated recommendation from Category 2 or 3 evidence	D

RCT: randomized controlled trials.

An Internet- and mail-based survey carried out between December 13, 2004, and January 10, 2005, yielded responses from 109 individuals, 84% of whom were currently taking NSAID/coxibs. Overall, 78% of patients felt that their current NSAID was effective in controlling their arthritis, and 87% were very satisfied or satisfied with the information they had received about their NSAID. However, 20% reported that they had had no say in the choice of medication. It was recommended that physicians foster and improve patient-centered communication, transfer of knowledge, and shared decision-making; inadequate reimbursement for drug therapies was identified as another barrier to the appropriate use of these medications.

Medications

Recommendation:
NSAID, including coxibs, are generally more effective and preferred by patients over acetaminophen for pain control in OA and RA. The lowest effective oral dose should be used; topical therapy with an NSAID preparation may be appropriate. Depending on the individual patient, an initial clinical trial of acetaminophen may be warranted. (Level 1, Grade A)

Acetaminophen. RCT and metaanalyses have demonstrated the efficacy of acetaminophen 4 g daily, usually in 20%–30% of patients (range 14%–52%) with knee or hip OA[12-16]. However, nonselective NSAID and coxibs were more effective than acetaminophen 4 g daily[12-15], and patient preference studies have found that over twice as many patients preferred NSAID or coxibs to acetaminophen[14-16]. Acetaminophen has been associated with less frequent GI discomfort than nonselective NSAID[12], but no clinically or statistically significant differences in adverse events have been found between acetaminophen and the coxibs[13,14]. Given its safety profile, acetaminophen could still be considered the first-line drug for patients with OA, as currently recommended by ACR[17] and EULAR[18] guidelines. Lower or intermittent doses may be effective for some patients; on the other hand, many patients who report that they tried acetaminophen and obtained an inadequate response have not taken a dose of 4 g daily.

Topical NSAID. There is evidence that topical NSAID are safe and effective in the treatment of knee OA. Current American College of Rheumatology (ACR)[17] and European League Against Rheumatism (EULAR)[18] guidelines recommend topical NSAID as an effective alternative in the treatment of OA. Since the time of the Second Canadian Consensus Conference[5], a new topical agent, diclofenac 1.5% in dimethylsulfoxide, has become available in Canada[19]. Results from 3 RCT suggest that this formulation of diclofenac is more effective than placebo and as effective as oral diclofenac, but with a lower rate of adverse events[20-23]. However, in a 12-week equivalence study of 622 patients with knee OA, the topical diclofenac solution was shown to be as effective as oral diclofenac 150 mg daily. Improvements were seen in pain scores, physical function, and patient global assessment. The response rates [according to OMERACT-OARSI criteria (Outcome Measures in Rheumatology Clinical Trials–OsteoArthritis Research Society International)] were 66% and 70% for the topical and the oral treatments, respectively. Skin reactions were more common with topical therapy, while total and severe GI events were more common with oral therapy[20]. This treatment is a reasonable alternative or addition to therapy for patients who prefer a topical treatment, are intolerant to oral medications, are insufficiently improved by acetaminophen, or fall into high-risk groups for the use of oral NSAID. Longer-term studies beyond 12 weeks are still needed.

Coxibs. The potency of a coxib (as indicated by its IC_{50}) must be distinguished from its selectivity (the ratio of COX-2 to COX-1 inhibition at any given drug concentration). Moreover, the choice of assay may affect the measured selectivity of a coxib. While the whole-blood assay is probably the most meaningful *in vitro*[24], it is the clinical effects on the gastric mucosa and platelet function that are clinically relevant. The newer coxibs (valdecoxib, etoricoxib, lumiracoxib) inhibit COX-2 more selectively than do cele-

coxib or rofecoxib, but the clinical relevance of this increased selectivity (if any) is still unclear. These 3 coxibs are discussed below.

Valdecoxib. Like celecoxib, valdecoxib has a sulfonamide side chain; it is an active metabolite of the prodrug parecoxib. RCT have demonstrated its efficacy in OA and RA[25-27]; in these trials, the incidence of endoscopically confirmed gastric and duodenal ulcers in patients taking valdecoxib was significantly lower than in patients receiving nonselective NSAID. A metaanalysis of 8 RCT found that the ulcer complication rate (perforation, bleeding, and obstruction) associated with valdecoxib was 3-fold lower than with nonselective NSAID (0.68% vs 1.96%; $p < 0.05$) and similar to that with placebo[28]. Valdecoxib has recently been voluntarily withdrawn from several major markets due to concerns that serious skin reactions (which have been associated with at least 7 deaths reported to the FDA) may occur among patients with or without a known history of sulfonamide allergy[29].

Etoricoxib. Like rofecoxib, etoricoxib has a sulfone side chain and a relatively long half-life of 22 hours. RCT have demonstrated that its efficacy is similar to that of diclofenac 50 mg tid or naproxen 500 mg bid for OA or RA, and comparable to or superior to naproxen 1000 mg daily in RA[30–33]. Etoricoxib has been associated with a lower rate of endoscopic gastric and duodenal lesions than naproxen or ibuprofen[34], and a lower risk of serious GI events [perforations, ulcers, and bleeds (PUB)] than nonselective NSAID[35]. In the Etoricoxib, Diclofenac, Gastrointestinal Evaluation (EDGE) trial[36], which enrolled 7111 OA patients, etoricoxib demonstrated significantly better GI tolerability than diclofenac over a mean treatment duration of 9 months. This drug is presently under review in Canada.

Lumiracoxib. Unlike the other coxibs, lumiracoxib is a weakly acidic structural analog of phenylacetic acid and bears similarity to diclofenac. Of the coxibs developed to date, this compound is the most highly selective for COX-2 inhibition (COX-2/COX-1 inhibition ratio of 500), and has a very short elimination half-life (3–6 hours)[37].

RCT have shown lumiracoxib 100–400 mg daily to be effective in OA and RA[37-39], with a significantly lower risk of serious GI complications than nonselective NSAID comparators. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[2] was the largest GI outcome safety study performed to date, enrolling 18,325 OA patients in two 52-week substudies to receive lumiracoxib 400 mg daily versus naproxen 500 mg bid (Study 0117) or ibuprofen 800 mg tid (Study 2332). The primary outcome variable was the difference between treatment groups in time-to-event distribution of definite or probable upper GI ulcer complications. Compared to the nonselective NSAID groups, there was a 79% reduction in the lumiracoxib group among the study population that was not receiving aspirin (acetylsalicylic acid, ASA). In the total population, lumiracoxib treatment was associated with a dramatically reduced rate of definite or probable upper GI ulcer complications (the primary endpoint) by 66%. Importantly, however, taking ASA largely negated the GI benefits of lumiracoxib, with reduction in complications to only 21%. Lumiracoxib is presently under review by Health Canada.

Gastrointestinal Considerations

Recommendation:
In patients with risk factors for PUB, a coxib is still the NSAID of choice, depending on the patient's cardiovascular risks. If NSAID must be used in high-risk patients (e.g., those with a history of GI bleeding), prescribe a PPI as well (Level 1, Grade A). NSAID can adversely affect the entire GI tract; however, the prevalence of clinically relevant NSAID-associated lower GI disease is unclear.

Coxibs were designed with the goal of producing effective compounds with lower rates of serious GI complications than had been associated with nonselective NSAID. A variety of risk factors for NSAID-associated ulcer complications are shown in Table 2[40-42]. A recent systematic review of 43 trials, involving over 1.3 million patients taking nonselective NSAID for at least 2 months, found that 1 in 5 developed endoscopically visible ulcers, 1 in 70 were symptomatic, 1 in 150 had a bleed or perforation, and 1 in 1200 died[43]. Most patients who develop a serious GI adverse event while taking nonselective NSAID are asymptomatic prior to the event.

Infection with *Helicobacter pylori* (HP) is a predisposing factor for ulcers even without the use of NSAID, but NSAID appear to increase HP-associated risks. In a metaanalysis of 5 controlled studies involving 661 patients, the endoscopic ulcer rate was 5.5% among HP-negative and 26% among HP-positive patients who were not using NSAID; these figures rose to 25% and 49.2%, respectively, among NSAID users[44]. Both HP eradication and the concomitant use of a PPI decrease the incidence of ulcers among NSAID users[45,46]. With regard to GI bleeding, there is evidence that an increased NSAID dose is associated with higher bleeding rates[47]. In a Danish epidemiologic study, the standardized incidence ratio for bleeding in a cohort of 27,694 people was

Table 2. Risk factors for NSAID-associated ulcer complications.

Factor	RR
History of complicated ulcer	13.5
Use of multiple NSAID (including ASA)	9.0
Use of high-dose NSAID	7.0
Use of anticoagulant	6.4
Age > 70 years	5.6
Use of steroids	2.2

RR: relative risk.

2.6 with ASA alone, but 5.6 when ASA and NSAID were taken together[48]. In addition, there is no evidence to suggest that different formulations of ASA (e.g., enteric-coated or buffered tablets) have differing effects on GI bleeding risk[45].

Coxibs and the GI tract. In marked contrast to their nonselective NSAID comparators, several coxibs have been shown in short-term trials (e.g., 3 months) to be associated with a reduced risk of developing an endoscopically confirmed gastric or duodenal ulcer; rates are generally similar to those of placebo[34,35,49,50]. Studies of chromium-labeled fecal red cell loss, measuring blood loss from both upper and lower GI tract, have also shown that neither rofecoxib nor etoricoxib increased fecal red cell loss above placebo levels (up to 1.7 ml daily); on the other hand, ibuprofen has been observed to increase fecal red cell loss by up to 65 ml daily[51]. Lesions distal to the duodenum (e.g., ulcers and strictures of the small or large bowel) may be responsible for this blood loss in up to 40% of cases[50]; such lesions are well recognized, but their baseline prevalence is uncertain. A PPI given with a nonselective NSAID will not protect the lower GI tract.

The VIGOR trial[3], involving 8076 RA patients not taking ASA, showed that the low rate of endoscopic ulcers previously seen with rofecoxib did in fact translate into a significantly lower incidence of clinically relevant upper GI events over 9 months in the rofecoxib 50 mg daily group compared with the naproxen 500 mg twice-daily group. Rofecoxib was also associated with a 54% decrease in the incidence of lower GI events compared to naproxen[50]. In CLASS[4], a trial involving 8059 patients, celecoxib 400 mg twice daily — a higher dose than currently recommended — was compared to ibuprofen 800 mg 3 times daily or diclofenac 75 mg twice daily. An interim analysis conducted at 6 months found a trend to fewer upper GI complications with celecoxib than with the nonselective NSAID. Among the celecoxib patients, the subgroup taking ASA had a risk of upper GI complications comparable to the risk among those taking nonselective NSAID. Analysis of the final CLASS dataset at Day 300 showed that the initial benefit seen with celecoxib was no longer evident: celecoxib did not clearly differ from the nonselective NSAID with regard to protection against ulcers[52]. There are several potential explanations for this, including an overall dropout rate of 57%.

In the recent Therapeutic Arthritis Research Gastrointestinal Event Trial (TARGET[2]), among the 76% of the study population who were not taking ASA the one-year incidence of ulcer complications was significantly greater with the nonselective NSAID than with lumiracoxib. Lumiracoxib treatment also conferred a significant risk reduction in the entire study cohort, but not in the subgroup taking ASA.

Finally, pooled RCT of valdecoxib, with durations of 12–26 weeks, have also found that this agent is associated with a lower rate of ulcer complications than a variety of nonselective NSAID comparators, but no large GI outcome studies of valdecoxib have been undertaken.

Studies of etoricoxib have similarly shown both a lower risk of endoscopic lesions than naproxen or ibuprofen and a decreased risk of clinically serious upper GI adverse events[34-36]. To date, no large outcome studies of etoricoxib are available.

GI Safety Issues

The absolute rates of ulcer complications seen in the comparator groups of the coxib studies are usually lower than those that were seen one to 2 decades ago, probably reflecting a more highly selected study population, changing patient demographics, and a lower prevalence of HP infection. Since HP is a known risk factor for peptic ulcer even without concomitant NSAID therapy, it is important to detect and eradicate HP in such at-risk individuals[43,53,54].

Emerging concerns about the cardiovascular safety of coxibs have modified recommendations that would otherwise be based on their GI safety alone[55]. Nonselective NSAID are appropriate for patients at low risk for GI complications (i.e., under age 65 years, with no other risk factors for upper GI complications). Patients over 65 years old (or any patient with a suspected history of ulcer) should be tested for HP and undergo eradication therapy if they are positive before embarking on a longterm course of NSAID therapy. In the elderly, unless cardiovascular risk factors are present, coxibs are preferred to nonselective NSAID because they are less frequently associated with either upper or lower GI bleeding or interactions with anticoagulants, selective serotonin reuptake inhibitors (SSRI), clopidogrel, or corticosteroids. Patients at risk who are also taking low-dose ASA and who require an NSAID should also receive a PPI for gastroprotection[56].

To date, no adequately powered RCT has been carried out to compare the GI or cardiovascular complication rates of ASA plus coxib versus ASA plus NSAID. Subanalyses of data from patients taking ASA in the CLASS and TARGET trials found no significant differences in GI complication rates. However, subgroup analysis of data from a review of studies comparing celecoxib with NSAID or placebo found that among ASA users, the incidence of endoscopic ulcers was reduced by 53% with celecoxib compared with NSAID[57]. Subsequent to our consensus meeting, further data have appeared on this topic. A retrospective cohort study of patients 65 years of age or older from the Quebec medicare administrative databases analyzed the risk of hospitalization due to an adverse GI event. Compared to NSAID alone, the hazard ratios of GI hospitalization were 0.86 for ASA plus coxib (95% CI 0.63–1.17) and 1.61 for ASA plus NSAID (95% CI 1.02–2.56). Moreover, the hazard ratio of GI hospitalization for ASA plus coxib compared to ASA plus NSAID was 0.53 (95% CI 0.34–0.83)[58]. A metaanalysis of endoscopic ulcer rates among patients with

OA or RA in 5 celecoxib trials lasting 12–24 weeks found that the relative risk of endoscopic ulcers associated with ASA plus celecoxib 200/400 mg was 0.47 (95% CI 0.27–0.83) compared to that associated with ASA plus NSAID[59]. Intuitively, one might expect that ASA plus coxib would be superior to ASA plus NSAID with regard to GI complications, and the weight of the evidence appears to be consistent with this. However, a properly designed prospective RCT would be required to conclude definitively that ASA plus coxib is associated with a lower rate of GI complications than ASA plus NSAID. It should be noted that the combination of ASA plus coxib carries a risk of GI complications that is similar to that of a nonselective NSAID alone.

Renal Considerations

Recommendations:

1. Before starting a nonselective NSAID or coxib, determine creatinine clearance in patients over age 65 or in those with comorbid conditions that may affect renal function. (Level 3, Grade C)
2. Coxibs, like nonselective NSAID, should be used with caution, in any patient with significant renal disease (proteinuria or GFR < 60 ml/min). (Level 4, Grade D)
3. Volume depletion is a risk factor for NSAID-induced acute renal failure. Consider recommending that patients hold their NSAID if they cannot eat or drink that day. (Level 4, Grade D)

Elderly patients, who have declining renal function and often comorbid illnesses, are at a particular risk for renal toxicity. Physicians often underestimate renal dysfunction because they rely erroneously on serum creatinine concentration (a relatively insensitive marker of renal function) and neglect to consider the effects of the patient's age, sex, and weight. For example, an elderly malnourished individual may be at elevated renal risk, even with a serum creatinine value that falls within the normal reference range of the laboratory. It is important for physicians to check the creatinine clearance both before and after initiating NSAID/coxibs, especially in individuals at high risk of renal failure. Since measurements from 24-hour urine collections are unreliable, creatinine clearance can be estimated using the Cockcroft-Gault formula[60] (for male patients multiply × 1.2):

$$\text{Creatinine clearance} = \frac{[140 - \text{age (yrs)}] \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l})}$$

Participants at the Second Canadian Consensus Conference on NSAID developed a creatinine clearance slide rule based on the Cockcroft-Gault formula (Figure 1). The physician need only align the patient's serum creatinine level against weight and read the calculated creatinine clearance according to the patient's age and sex. Using this simple device may alert physicians to impending renal problems and prevent drug-induced complications. Individuals may obtain a ruler upon request from: creatinineclearance@aol.com.

The risk of NSAID-associated renal dysfunction is low in most people; only 5% of nonselective NSAID users have mild fluid retention[61] and renal complications are generally reversible on timely withdrawal of the NSAID. However, in the presence of preexisting renal disease, renal hypoperfusion, or concomitant therapy with drugs including diuretics, ACE inhibitors, other antihypertensive agents, aminoglycosides, or cyclosporin A, the risks of NSAID-induced renal toxicity may be much higher[62].

It is important to recognize that coxibs do not offer greater renal safety than the nonselective NSAID[63,64].

Hypertension

Recommendations:

1. In patients receiving antihypertensive drugs, remeasure blood pressure within a few weeks after initiating NSAID or coxib therapy and monitor appropriately. (Level 1, Grade A)
2. If the introduction of the drug is associated with a rise in blood pressure, the dose of the NSAID/coxib and/or the antihypertensive drug must be modified. (Level 1, Grade A)

NSAID and coxibs antagonize the antihypertensive effects of agents blocking the renin-angiotensin-aldosterone system, such as ACE inhibitors, ARB, and (to a lesser degree) ß-adrenergic blockers. The antihypertensive effects of calcium channel blocker drugs appear to be least influenced by NSAID/coxibs, since they act on peripheral arterioles[65].

Metaanalyses[66], RCT[67-69], and case control studies[70] have shown that NSAID/coxibs can raise blood pressure in both normotensive[71] and hypertensive individuals[67-69]. The effect on systolic blood pressure (generally averaging 3–7 mm Hg[66,72]) is more pronounced than on diastolic blood pressure (1–3 mm Hg); it occurs in 7–16% of patients exposed to coxibs in RCT[68]. Increases in blood pressure are seen more frequently with rofecoxib than celecoxib[67,68,73].

Blood pressure should be obtained regularly because patients over age 55 years, who constitute a large proportion of persons seen by rheumatologists, have a 90% lifetime risk of developing hypertension[74]. To avoid destabilizing blood pressure, the lowest feasible dose of NSAID/coxib should be used for the shortest time necessary to achieve the desired therapeutic effect.

Cardiovascular Safety

Recommendations:

1. Patients taking rofecoxib have been shown to have an

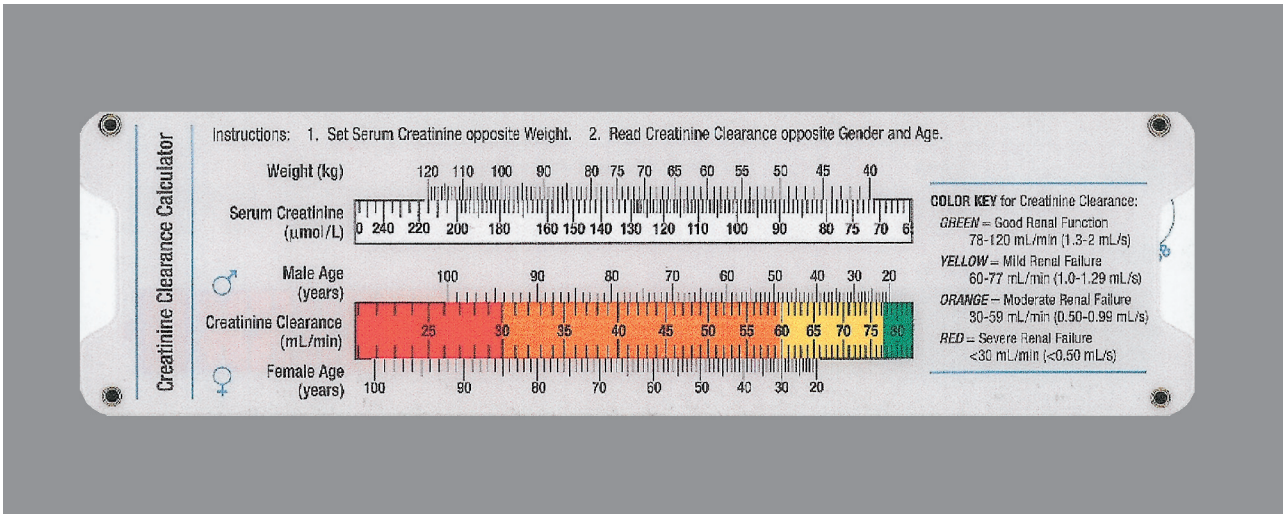


Figure 1. An easy-to-use device for calculating creatinine clearance.

increased risk of cardiovascular events. (Level 1A, Grade A)
2. Current data suggest that this increased cardiovascular risk is a class effect of the NSAID coxibs. (Level 1A, Grade 1)
3. Given the evolving cardiovascular information, physicians and patients should weigh the benefits and risks of NSAID/coxib therapy. (Grade D, Level 4)
4. This concern emphasizes the need to routinely assess patients' cardiovascular risks. (Grade D, Level 4)

The hypothesis that selective inhibition of COX-2 might increase the risk of thrombosis in predisposed individuals was first suggested in 1999[75]. The proposed mechanism was that selective inhibition of prostacyclin (an inhibitor of platelet aggregation) without concomitant inhibition of thromboxane (a promoter of platelet aggregation) could create an imbalance in favor of thrombosis and thus increase the risk of a cardiovascular event. Shortly thereafter, the Vioxx Gastrointestinal Outcomes Research (VIGOR)[3] trial was the first study to show an increase in overall cardiovascular events with a coxib: in this study rofecoxib 50 mg daily was associated with a significantly greater event rate than naproxen 500 mg bid (1.7 vs 0.7 events per 100 patient-years; RR 2.38, 95% CI 1.39–4.00) (Figure 2A[76]). This difference was driven by a significant 5-fold increase in the incidence of myocardial infarctions. The VIGOR study used twice the maximum recommended dose of rofecoxib and included patients with RA, which is known to be associated with increased cardiovascular risk[77,78]. Subsequent meta-analyses of cardiovascular events in all rofecoxib trials showed that rofecoxib was associated with more cardiovascular events than naproxen, but not with other nonselective NSAID or placebo[79,80].

These results suggested 3 hypotheses: (1) Naproxen has an ASA-like cardioprotective effect; (2) rofecoxib increases risk of thrombosis; and (3) a combination of the two. Short-term epidemiologic studies were initiated to investigate these hypotheses: Studies exploring a possible cardioprotective effect of naproxen[81-90] were initially conflicting, but a metaanalysis of available observational studies found a small cardioprotective effect of naproxen[91]. Epidemiologic studies exploring a possible prothrombotic effect of rofecoxib compared events associated with rofecoxib versus other NSAID/coxibs or placebo. Of 7 studies[83,88,90,92-95], 4 indicated that rofecoxib — particularly at a dose of 50 mg daily — might increase cardiovascular risk. However, these observational studies were limited because they used secondary databases, lacked information on patients' characteristics, and did not record actual drug consumption or the use of over-the-counter medications such as NSAID and ASA.

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial[96] provided clear evidence for an increased risk of cardiovascular events with rofecoxib over placebo. This trial, designed to study the possible benefits of rofecoxib to prevent recurrence of colon polyps, was terminated early when the data showed a significant 2-fold increase in the incidence of thromboembolic adverse events in the rofecoxib 25 mg daily group over the placebo group (1.5 vs 0.78 events per 100 patient-years; RR 1.92, 95% CI 1.19–3.11) (Figure 2B[96]). These results prompted the drug company to withdraw rofecoxib from the market on September 30, 2004. Of note, the increased relative risk became apparent after 18 months of treatment; during the first 18 months, the event rates were similar in the 2 groups, highlighting the need for longterm studies to detect cardiovascular outcomes in populations with low cardiac risk.

Do the results of the rofecoxib studies apply to other available coxibs or even nonselective NSAID? The data on the risks associated with celecoxib are conflicting. There was no evidence for an increased risk of cardiothrombotic events with celecoxib compared to nonselective NSAID in the Celecoxib Long-term Arthritis Safety Study (CLASS)[4]

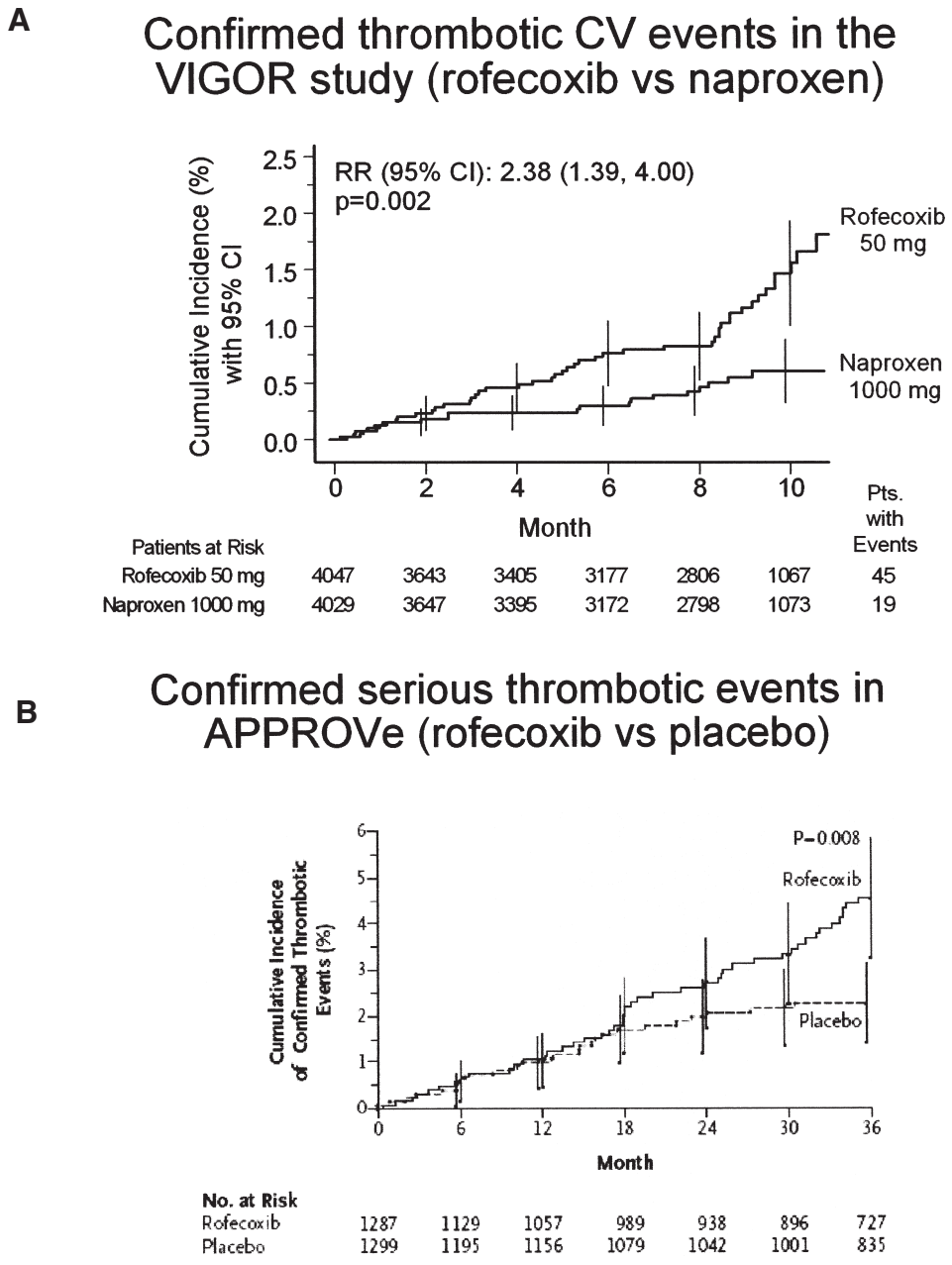
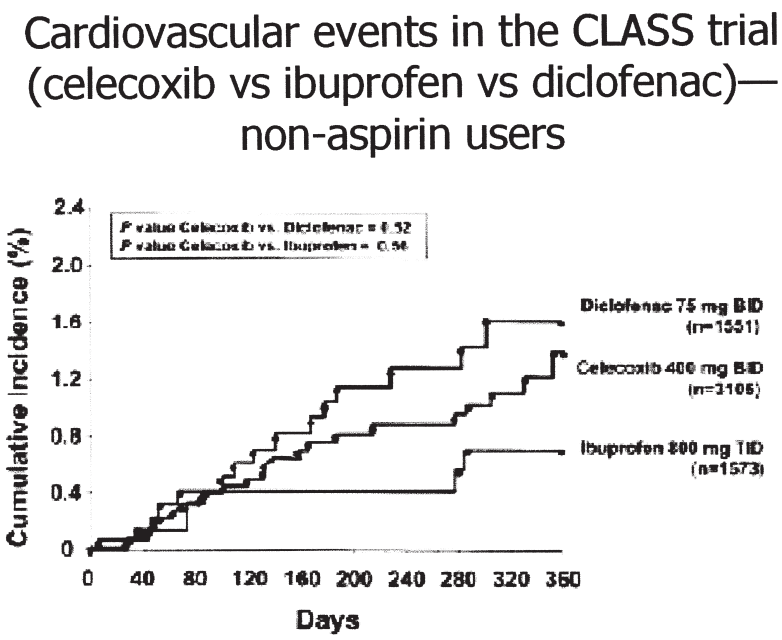


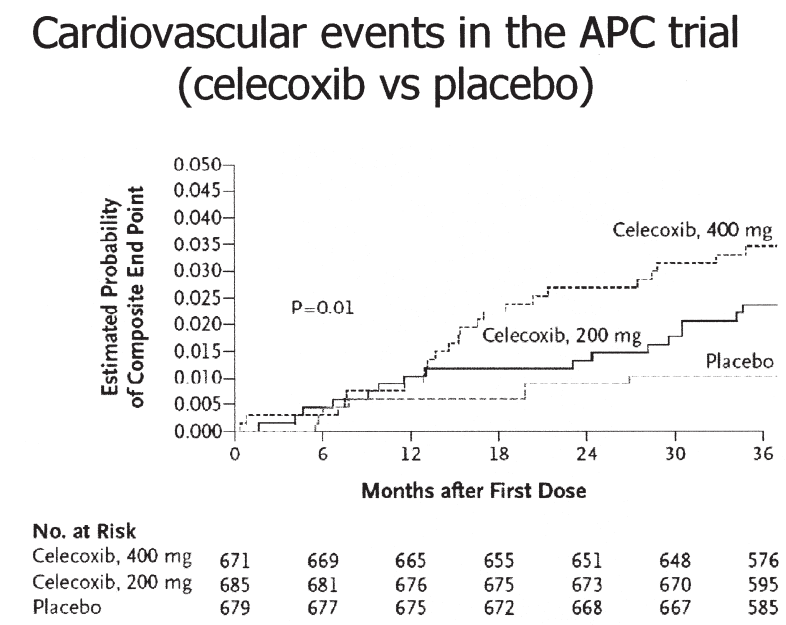
Figure 2. Key studies, presented February 16-18, 2005, at the COX-2 FDA Advisory Committee, that reported cardiovascular outcomes with rofecoxib: A. The VIGOR study[3] (from briefing documentation[76]); and (B) the APPROVe study (from Bresalier, *et al.* N Engl J Med 2005;352:1092-102[96]; with permission).

(Figure 3A[97]) or in a review of the entire dataset from all RCT of celecoxib in arthritis[98]. However, these were generally short-term studies designed to assess arthritis pain relief, and may not have been adequately powered to examine relatively rare outcomes. More recently, 2 trials of celecoxib have been undertaken for the prevention of adenomatous polyps. In the Adenoma Prevention with Celecoxib (APC) study, there was a significant increase in cardiovascular events among patients receiving celecoxib 400 mg bid (3.4% vs 1.0%; HR 3.4; 95% CI 1.4–7.8), but not celecoxib 200 mg bid (2.3% vs 1%; HR 2.3; 95% CI 0.9–5.5) (Figure 3B)[99]. In contrast, preliminary analysis of data from the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial showed no increase in cardiovascular risk with celecoxib 400 mg once daily (RR 1.1; 95% CI 0.6–2.3)[100], nor did an early analysis of data from the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which evaluated celecoxib 200 mg bid[101].

A



B



No. at Risk

Celecoxib, 400 mg	671	669	665	655	651	648	576
Celecoxib, 200 mg	685	681	676	675	673	670	595
Placebo	679	677	675	672	668	667	585

Figure 3. Key studies that reported cardiovascular outcomes with celecoxib: A. Celecoxib Long-term Arthritis Safety Study (CLASS)[4] (from Strand, *et al.* Arthritis Care Res 2002;47:349-55[97]; with permission). B. Adenoma Prevention with Celecoxib (APC) study (from Solomon, *et al.* N Engl J Med 2005;352:1071-80[99]; with permission).

Cardiovascular and other adverse events were seen in studies in which parecoxib/valdecoxib was given to high-risk patients to treat postoperative pain after coronary artery bypass grafting (CABG). In a multicenter study[102] involving 462 patients (New York Heart Association functional class I–III), parecoxib/valdecoxib was associated with an increased incidence of serious adverse events overall (19.0% vs 9.9%; p = 0.015) and sternal wound infections in particular (3.2% vs 0%; p = 0.035). In a second study of 1671 patients undergoing CABG surgery[103], parecoxib/valdecoxib was also associated with a higher incidence of cardiovascular events than placebo (2.0% vs 0.5%; RR 3.7; p = 0.03). This excess of serious adverse events has prompted an advisory from the manufacturer that valdecoxib has not been approved for use in any peri- or postoperative setting. A metaanalysis of data from these studies found a 3-

fold increased cardiovascular risk with valdecoxib/parecoxib over placebo[104]. In valdecoxib trials involving other populations (a total of 7934 patients, most with OA or RA), no increase in cardiovascular risk was detected, but there are few data assessing longterm cardiovascular safety.

What about the newer coxibs on the horizon? The results of the TARGET study suggested that lumiracoxib is associated with a nonsignificant increase in the risk of cardiovascular events compared with naproxen but not with ibuprofen, and only among patients in the non-ASA group[105] (Figure 4A, 4B[106,107]). Etoricoxib was also associated with a nonsignificant increase in cardiovascular events compared to naproxen (RR 1.70; 95% CI 0.91–3.18) but not compared to non-naproxen nonselective NSAID (RR 0.83; 95% CI 0.26–2.64) or placebo (RR 1.11; 95% CI 0.32–3.81)[108] (Figure 4C[109]). The Multinational Etoricoxib vs Diclofenac in Arthritis Long-term (MEDAL) study, a large prospective trial, is currently evaluating the cardiovascular safety of etoricoxib in about 23,450 patients, and the results (expected in 2006) should provide more robust data on cardiovascular safety.

A joint meeting of the Arthritis Advisory Committee and the Risk Management Advisory Committee of the FDA was held in February 2005 to review the totality of the evidence on cardiovascular risk of coxibs. According to evidence then available, there appeared to be less cardiovascular risk associated with celecoxib than with rofecoxib or valdecoxib. Nonetheless, the panel recognized the cardiovascular effects of all COX-2 inhibitors and recommended that their labels carry "black box" warnings emphasizing both GI and cardiovascular risks. The panel also recommended that celecoxib should continue to be available, valdecoxib should be withdrawn, and the reintroduction of rofecoxib should be considered, pending further discussions with the manufacturer. These recommendations were driven primarily by the philosophy that patients should be informed of the available findings and given a choice of medication. In addition, given the paucity of longterm trials and the cardiovascular signals for some nonselective NSAID, the panel recommended a cardiovascular warning for all NSAID.

The Health Canada Expert Advisory Panel reached very similar conclusions. At these meetings, data were presented from a systematic review of 138 RCT of at least 4 weeks' duration that involved over 144,000 patients. According to this analysis, patients treated with coxibs had significant increases in rates of clinically important cardiovascular events compared to patients treated with placebo or naproxen, and a numerical (but not statistically significant) increase compared to those treated with non-naproxen NSAID. This analysis further reinforces the notion that coxibs and non-naproxen NSAID have similar cardiovascular safety profiles, with an absolute increase in risk of 0.3% per year[11].

Drug to Drug Interactions

When a single dose of ibuprofen 400 mg is administered 2 hours before ASA[110], it negates the antiplatelet effects of ASA. This does not occur with naproxen[111], meloxicam[112], rofecoxib, or diclofenac[110]. However, a retrospective clinical study involving 3859 patients receiving either ASA and ibuprofen simultaneously or ASA alone did not find an increased risk of myocardial infarction among those taking both drugs[113]. Coxibs may be preferred over nonselective NSAID for patients who are also taking anticoagulants, SSRI[114,115], or clopidogrel[116] because these latter drugs are themselves associated with GI bleeds[117]. SSRI increase the risk of GI complications by 3.6-fold; and combining an SSRI with a nonselective NSAID increases the odds ratio to 12.2[114]. Both coxibs and nonselective NSAID should be used with caution in patients receiving diuretics, antihypertensives, or cyclosporin A.

Geriatric Considerations

Recommendation:
The use of nonpharmacologic therapies should be maximized before considering the use of NSAID/coxibs. These drugs should be used with caution in elderly patients, who are at the greatest risk for serious GI, renal, and cardiovascular side effects (Level 3, Grade C). Risks associated with NSAID/coxib combinations are cumulative.

The elderly are especially vulnerable to drug toxicity for many reasons, including difficulties with treatment adherence, nutritional insufficiency, altered pharmacokinetics, and end-organ responsiveness, and the enhanced potential for drug to drug interactions arising from polypharmacy for diverse comorbidities. Moreover, most clinical drug trials exclude the elderly (with or without comorbid disease), and results obtained with younger patients cannot necessarily be extrapolated to the geriatric setting. Clinicians who are treating elderly patients for OA or RA should do so in the context of a multifaceted treatment plan that aims to preserve function and independence and improve quality of life.

Costs

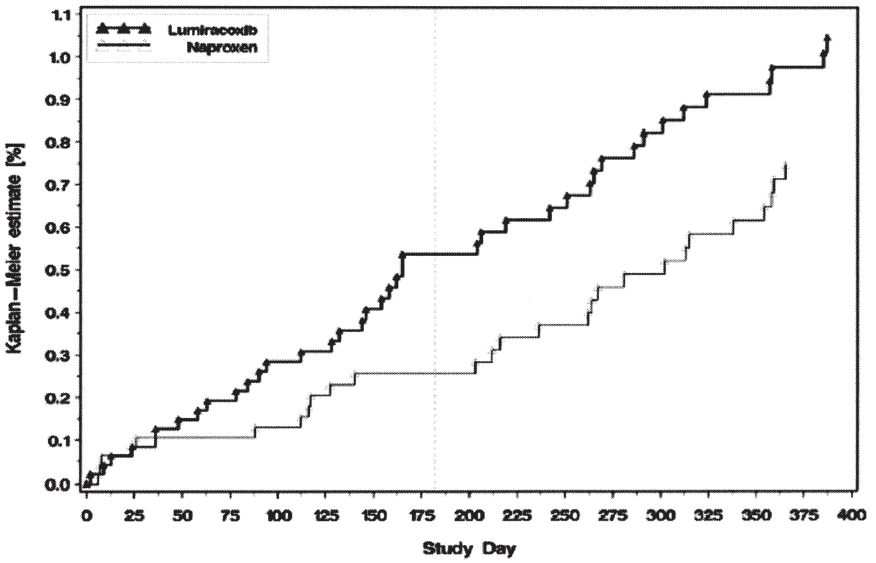
Recommendation:
Although the data from health economic studies are ambiguous, prescription of coxibs in patients at high risk for developing GI events may be a more cost-effective strategy than the use of nonselective NSAID plus a proprietary PPI. (Level 3, Grade C)

NSAID-induced GI adverse events have considerable economic consequences for healthcare budgets where the prevalence of OA and RA is high. A study using the RAMQ (Regie de l'assurance-maladie du Quebec) database in Quebec found

A

TARGET- 0117

Confirmed & Probable APTC Events



B

TARGET- 2332

Confirmed & Probable APTC Events

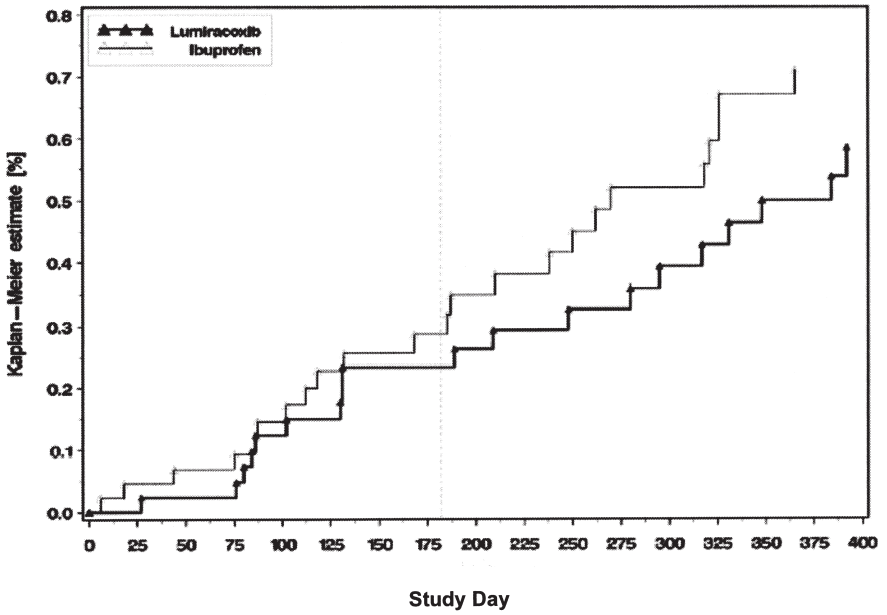
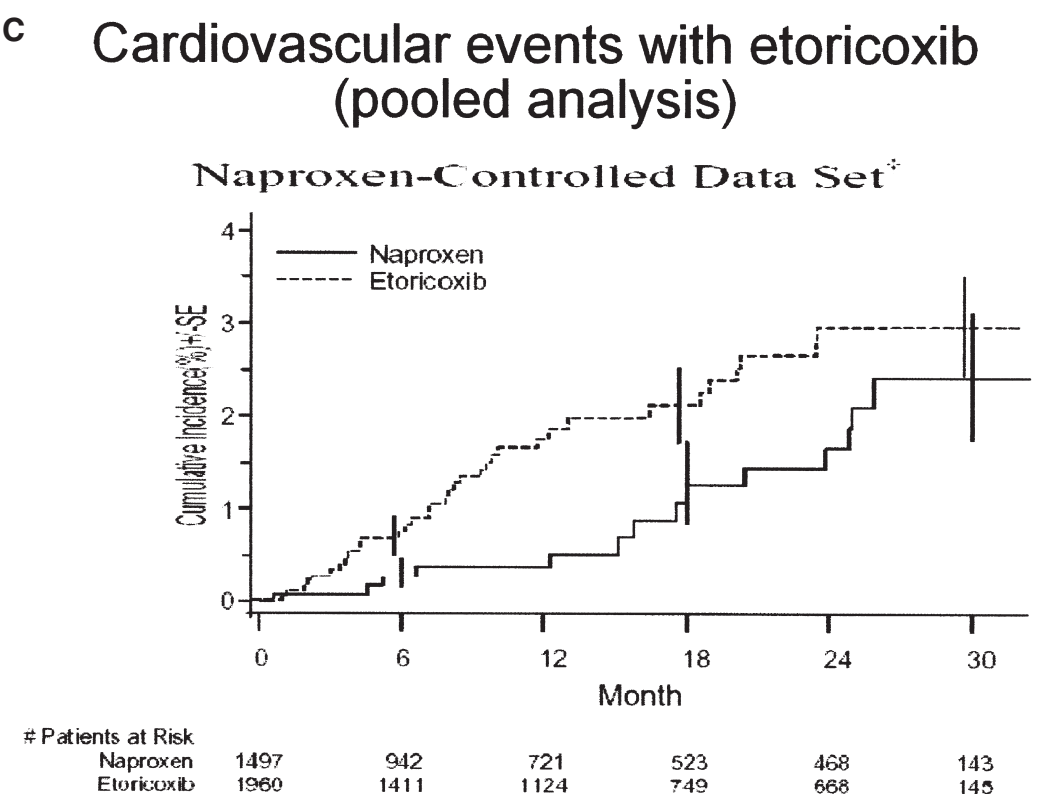


Figure 4. Key studies, presented February 16-18, 2005, at the COX-2 FDA Advisory Committee Meeting, that reported cardiovascular outcomes with (A and B) lumiracoxib (TARGET[105]) (from briefing documentation[106,107]); and (C) etoricoxib (from pooled analysis of the naproxen dataset[108,109]). APTC: Events as defined by the Antiplatelet Trialists' Collaboration.



that for each dollar spent on nonselective NSAID, an additional $0.66 was spent on their side effects[118].

One of the most comprehensive economic analyses[119] compared the costs of celecoxib and rofecoxib to costs of nonselective NSAID among patients in Canada with RA or OA whose average age was 58 years. The model accounted for decreases in quality-adjusted life years (QALY) associated with GI and cardiovascular events. Among high-risk patients, celecoxib and rofecoxib were both less costly and more effective than nonselective NSAID plus PPI. Assuming a threshold of CDN $50,000 per QALY gained, analysis by age groups showed that rofecoxib and celecoxib would be cost-effective in patients aged over 76 and 81 years, respectively, who had no additional risk factors. Doubling the GI risk reduced the age thresholds to 56 and 67 years, respectively. However, the estimated cost for PPI used in this model was higher than the current cost of generic PPI available in Canada, a change that might affect the results. Finally, another study compared the pharmacoeconomic implications of using an NSAID, an NSAID plus PPI, or a coxib among patients at differing risks of developing GI or cardiovascular adverse events. In patients at low risk for adverse events, generic NSAID were the most cost-effective. However, NSAID plus generic PPI appeared to be the preferred strategy for higher-risk patients (e.g., those taking ASA and especially those with more than one risk factor for GI complication)[56]. The pharmacoeconomic benefits of reducing lower GI blood loss with coxibs have not yet been adequately evaluated.

DISCUSSION

The mandate of the Canadian Consensus Group was not to recreate comprehensive guidelines for the management of OA or RA, akin to those of the ACR or EULAR, but to update evidence-based recommendations on the appropriate and safe use of NSAID/coxibs in the treatment of OA and RA. Other important and beneficial treatment modalities, both nonpharmacologic (e.g., education, exercise, physiotherapy, walking aids, orthotic devices, and lifestyle changes) and pharmacologic (e.g., intraarticular steroids, viscosupplementation), were therefore not reviewed.

The process for development of these recommendations was developed in light of the framework for evaluating guidelines established by the Appraisal of Guidelines for Research & Evaluation (AGREE) Collaboration. In the AGREE rubric, guidelines are scored in 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence[8].

Surveys of patient-consumers[120,121] found that patients' drug preferences were most affected by variations in the risks of associated adverse events, and particularly by whether they were bearing the costs of the drug. Patients were more concerned about safety than efficacy. The results of our needs assessments and patient survey strongly indicate that family physicians, rheumatologists, and patients need answers about the use of coxibs. One of the key recommendations of this consensus group was that physicians should enhance their communication with patients by

explaining where the scientific data are still insufficient to provide clear answers.

New GI safety results published since our previous Canadian Consensus Conference[5] have supported the impression that the coxibs are associated with greater GI safety than the nonselective NSAID. Low-dose ASA is clearly associated with serious GI complications such as bleeding, and its use together with coxibs largely negates the upper GI-sparing effects of the coxibs. It has long been known that nonselective NSAID are associated with small bowel lesions (including frank ulceration and strictures) and increased occult fecal blood loss[51]. New data suggest that these complications are much rarer with coxibs. On the whole, it appears that coxibs have a more favorable upper and lower GI safety profile than do nonselective NSAID.

The consensus of the group at the time of the meeting in January 2005 was that there was insufficient evidence to determine whether the increases in cardiovascular events represented a class effect of the coxibs or whether they reflect the toxicity of an individual drug. More recent publications, combined with evidence reviewed at recent FDA and Health Canada meetings, strongly suggest that increased cardiovascular adverse events are indeed a class effect of the NSAID coxibs. However, it is possible that the degree of risk is correlated with variables such as potency, COX-2 selectivity, dosing, frequency of administration, half-life, duration of treatment, cumulative exposure, or combination of any of these factors or of others yet unknown. For example, coxibs with a long half-life (e.g., rofecoxib) may confer cardiovascular risk. Alternatively, dosing frequency may make a difference: one of the 2 trials of celecoxib in adenomatous polyps, which used celecoxib 200 mg twice daily, found an increased cardiovascular risk, but the other trial, which used celecoxib 400 mg once daily, did not. Similarly, selectivity may make a difference: lumiracoxib, a highly selective coxib, showed a signal of increased cardiovascular risk relative to naproxen but not ibuprofen. The precise correlates of cardiovascular risk with the coxibs thus remain to be elucidated.

Moreover, concern was also expressed at the FDA meetings about the paucity of cardiovascular data on nonselective NSAID, especially data from longterm placebo-controlled trials. The FDA and Health Canada have recommended that the labeling of all prescription nonselective NSAID and coxibs should be revised to include a warning highlighting the potential for serious cardiovascular events and to reemphasize the GI toxicity of these medications. The FDA further recommended that labeling for nonprescription NSAID (naproxen, ibuprofen, ketoprofen in the US) should be changed to include more specific information about cardiovascular and GI risks to assist patients to use these drugs more safely[29]. Health Canada has received a recommendation from its Expert Advisory Panel that ibuprofen, the only NSAID sold over the counter in Canada, should now be sold only after discussion with a pharmacist and must ensure that the risks of cardiovascular events are prominently displayed in material that individuals receive when they purchase the drug, as well as in any package inserts[11]. These concerns emphasize the need for clinicians to assess patients' cardiovascular risks on a routine basis and to implement current recommendations about cardioprotective therapy for appropriate patients[122,123].

It has been stated that just as low-dose ASA affords cardiac protection with a small but absolute risk of GI bleed, so do coxibs afford gastroprotection with a small but absolute risk of cardiovascular events[124]. Clearly, physicians and patients must balance the GI benefits and potential cardiovascular risks of NSAID/coxib therapy. Under what circumstances, then, should patients use coxibs versus nonselective NSAID, with or without PPI? Patients who are not at elevated GI risk and are not taking ASA (and are presumed to be at relatively low cardiovascular risk) are suitable candidates for nonselective NSAID alone. Patients who are taking ASA for cardioprotection should be aware that coxibs alone do not appear to offer GI benefits in the presence of ASA. Although ASA plus coxibs may have a better GI safety profile than ASA plus NSAID, such patients should consider using the more cost-effective combination of a generic nonselective NSAID together with a generic PPI, whether or not they are at elevated GI risk. Finally, patients whose GI risk is elevated (including, by virtue of age alone, all individuals 65 years or over) and who are not taking ASA may be candidates for a coxib or for a nonselective NSAID together with a PPI (Table 3).

There was a clear consensus that coxibs are not different from nonselective NSAID in promoting renal or hypertensive adverse events. Especially in patients who are hypertensive or otherwise at elevated renal risk, it is appropriate to remeasure blood pressure and creatinine clearance within weeks of initiating an NSAID or a coxib.

The use of a nonselective NSAID together with a PPI appears to protect the upper GI tract as well as a coxib[46], but the relative costs of these options differ depending on the cost of the PPI. Available pharmacoeconomic models have considered the relatively benign GI effects of coxibs and their potential for cardiac complications, but not the benefits of decreasing colonic polyps and colon cancer, or avoiding small bowel inflammation.

We have updated the recommendations of the Second Canadian Consensus Conference[5] by extending the systematic literature review to December 2004, and supplementing this with additional publications from early 2005 and updates on the cardiovascular risks of NSAID from the Joint Meeting of the Arthritis Advisory Committee and the Risk Management Advisory Committee of the FDA and the Health Canada Expert Advisory Panel on the Safety of Cox-2 Selective NSAID. We intend to disseminate this new information and to produce up to date tools and other edu-

Table 3. Guidelines for the use of nonsteroidal antiinflammatory drugs (NSAID)/coxibs.

	No Elevated GI Risk	Elevated GI Risk
Not on ASA	Nonselective NSAID alone*	Coxib Nonselective NSAID + PPI
On ASA	Coxib + PPI Nonselective NSAID + PPI**	Coxib + PPI Nonselective NSAID + PPI**

* An individual aged 65 or over would be considered to have an elevated GI risk. ** Generic nonselective NSAID + generic PPI preferred on pharmacoeconomic grounds. GI: gastrointestinal; ASA: acetylsalicylic acid; PPI: proton pump inhibitor.

Table 4. Summary of recommendations.

	Recommendation	Level of Evidence	Grade of Recommendation
1. Patient-physician communication	Patients should be fully informed about evolving information regarding the benefits and risks of their treatment options.	3	C
2. Indications	NSAID and coxibs are generally more effective and preferred by patients over acetaminophen, although a trial of the latter is warranted for some patients. Topical NSAID formulations may confer benefit in knee OA.	1	A
3. GI toxicity	In patients with risk factors for PUB, a coxib is still the antiinflammatory drug of choice, depending on the patient's cardiovascular risks. High-risk patients who must use nonselective NSAIDs should have a PPI.	1	A
4. Renal	Before starting an NSAID or coxib, determine renal status and creatinine clearance in patients over age 65 years or in those with comorbid conditions that may affect renal function.	3	C
	Advise patients that if they cannot eat or drink that day, they should withhold that day's dose of NSAID/coxib.	4	D
5. Hypertension	In patients receiving antihypertensive drugs, measure blood pressure within a few weeks after initiating NSAID/coxib therapy and monitor appropriately; drug doses may need adjustment.	1	A
6. Cardiovascular	Patients taking rofecoxib have been shown to have an increased risk of CV events. Current data suggest that this increased CV risk may be an effect of the NSAID/coxib class. Physicians and patients should weigh the benefits and risks of NSAID/coxib therapy.	1	A
7. Geriatric considerations	NSAIDs/coxibs should be used with caution in elderly patients, who are at the greatest risk for serious GI, renal and CV side effects.	3	C
8. Pharmacoeconomics	Although the data are ambiguous, coxibs may be more cost-effective than traditional NSAID + proprietary PPI among high-risk patients.	3	C

NSAID: nonsteroidal antiinflammatory drugs; GI: gastrointestinal; CV: cardiovascular; PUB: perforations, ulcers and bleeds; PPI: proton pump inhibitor.

cational materials geared to physicians and consumers to better inform them about the benefits and risks of NSAID and coxibs. Three patient advocacy groups, The Arthritis Society, the Canadian Arthritis Patient Alliance, and Arthritis Consumer Experts, have offered to support campaigns in this endeavor.

The recommendations contained in this consensus document are summarized in Table 4. The information supporting these recommendations is current as of July 2005. Meanwhile, jurisdictions around the world are reassessing the safety of coxibs and requiring either new warnings or outright withdrawal of various members of the coxib class. In the light of rapidly emerging new data, we therefore anticipate revising our recommendations in the future.

ACKNOWLEDGMENT

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Presenters at the Consensus Conference: Marty Atkinson, University of Calgary; William Bensen, McMaster University; Louis Bessette, Université Laval; Claire Bombardier, University of Toronto; Simon Carette, University of Toronto; Denis Choquette, Université de Montréal; John Fleming, The Arthritis Society; Nigel Flook, University of Alberta; Hani El-Gabalawy, University of Manitoba; Robert Hollinshead, University of Calgary; Richard Hunt, McMaster University; Angela Juby, University of Alberta; Cheryl Koehn, Arthritis Consumer Experts; Yves Lacourcière, Université Laval; Jacques Lelorier, Université de Montréal; Dianne Mosher, Dalhousie University; Muhammed Mamdani, University of Toronto; Wojciech Olszynski, University of Saskatchewan; Robert Petrella, University of Western Ontario; Janet Pope, University of Western Ontario; Kam Shojania, University of British Columbia; Hyman Tannenbaum, McGill University; Sheldon Tobe, University of Toronto; Subodh Verma, University of Toronto. Other participants: Vivian Bykerk, University of Toronto; Duncan Gordon, University of Toronto; Jean Légaré, Canadian Arthritis Patient Alliance; Beny Masella, Lackman-Masella Pharmacy, Montreal; Pierre Raiche, Université de Montréal.

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