Consensus Conference Report

Controversies in COX-2 Selective Inhibition

The field of rheumatology has undergone significant change as a result of the expansion of knowledge of the pathogenesis of the different types of arthritis, together with the consequent development of new therapeutic agents. One of these advances was the determination that there are 2 isoforms of cyclooxygenase (COX) and the subsequent introduction of drugs that inhibit the COX-2 isoenzyme without affecting COX-1 and its related homeostatic functions, at any therapeutically efficacious dose[1]. Two COX-2 selective (COX-1 sparing) inhibitors — celecoxib and rofecoxib — are currently available for clinical use in the United States, and a third (valdecoxib) has just been approved by the Food and Drug Administration (FDA).

In the development of celecoxib and rofecoxib, a large number of patients were studied, which produced a substantial amount of data. Assessments of the efficacy, tolerability, and safety of celecoxib and rofecoxib versus nonselective nonsteroidal antiinflammatory drugs (NSAID) in a wide range of patient populations have been performed. With this database and the recent publication of the results of 2 large-scale gastrointestinal (GI) outcomes trials, known as the Vioxx® Gastrointestinal Outcomes Research (VIGOR) trial[2] and the Celecoxib Long-term Arthritis Safety Study (CLASS)[3], it seemed appropriate to establish recommendations, as determined by the consensus of a group of experts, for the use of COX-2 selective inhibitors in clinical practice. To that end, a panel was convened under the auspices of the International COX-2 Study Group. This panel comprised rheumatologists, gastroenterologists, nephrologists, cardiologists, epidemiologists, and pharmacologists from North America and Europe (Appendix). The group met in Washington, DC, January 12 and 13, 2001, to explore current and emerging data related to COX-2 selective inhibitors. This report summarizes the discussions of controversial issues concerning the use of these drugs and presents several consensus statements that reflect this group's interpretation of available data. The report has been updated to take into account data that were made available since the meeting was held, especially analyses presented at 2 FDA Arthritis Advisory Committee meetings (US Food and Drug Administration), held in Gaithersburg, Maryland, February 7 and 8, 2001; this additional information has been reviewed by all panel members. Data related only to celecoxib and rofecoxib were considered during this conference.

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CONSIDERATIONS OF UPPER GI SAFETY AND TOLERABILITY

Do COX-2 selective inhibitors have improved GI safety compared with nonselective NSAID?

Symptomatic upper GI ulcers and ulcer complications (i.e., perforation, gastric outlet obstruction, and bleeding) occur annually in 2–4% of patients treated with nonselective NSAID[4,5], with 1–2% of NSAID treated patients experiencing a serious GI complication related to NSAID use[6,7]. The mechanisms by which nonselective NSAID relieve pain and inflammation and produce GI toxicity are largely related to the inhibition of COX-2 and COX-1, respectively. The constitutively expressed COX-1 isoenzyme primarily performs a "housekeeping" function by synthesizing prostanoids that regulate normal cell activity, notably in the GI mucosa and platelets[1,8]. Constitutive expression of COX-2 also occurs in certain tissues, notably brain and kidney, as well as during embryonic development[1,9–12]. Although COX-2 expression is primarily regulated by cytokines, at sites of inflammation (and in other pathologic conditions), physiologic stimuli also play a role in many organ systems[1,8,13].

The COX-2 selective inhibitors celecoxib and rofecoxib were developed to relieve pain and inflammation without affecting COX-1 mediated homeostatic mechanisms (e.g., GI mucosal protection and platelet function) at therapeutic dosages. Randomized controlled trials (RCT) have shown that the incidence of endoscopically confirmed upper GI ulcers is significantly decreased during treatment with COX-2 selective inhibitors compared with nonselective NSAID[14,15]. Clinically, however, upper GI ulcer complications (i.e., perforations, obstructions, and bleeding) and symptomatic ulcers, rather than endoscopic ulcers, are much more relevant events[7]. The effects of COX-2 selective inhibitors on serious ulcer complications have been assessed retrospectively through analysis of data from RCT and open label clinical trials and prospectively from the results of 2 landmark GI outcomes trials.

Goldstein, *et al* recently reported the annualized incidence of upper GI ulcer complications (prospectively defined as ulcer bleeding, perforation, or gastric outlet obstruction) in a combined population of patients with osteoarthritis (OA) and rheumatoid arthritis (RA) treated with celecoxib versus nonselective NSAID by pooling data

from 14 RCT as well as from one longterm open label study[16]. In the RCT, upper GI complications occurred in significantly ($p < 0.05$) fewer celecoxib treated patients compared with those randomized to nonselective NSAID, and in the open label trial, the annualized incidence of upper GI complications associated with celecoxib was similar to that reported with celecoxib in the RCT. In a similar large pooled analysis of the effects of rofecoxib compared with nonselective NSAID, Langman, *et al* determined the incidence of upper GI perforations, ulcers, and bleeding (PUB) in 8 trials involving more than 5000 patients with OA[17]. The cumulative incidence of PUB over 12 months was significantly ($p < 0.05$) lower with rofecoxib compared with nonselective NSAID.

Further upper GI safety data related to celecoxib and rofecoxib have been provided by the 2 outcomes trials, the VIGOR trial[2] and CLASS[3]. The VIGOR trial compared rofecoxib with naproxen, and CLASS compared celecoxib with ibuprofen and diclofenac. While both these studies had a median duration of 9 months, with a maximum duration of 13 months, they differed in several significant ways (Table 1). The VIGOR trial involved RA patients only, whereas CLASS included patients with OA (72%) or RA (28%). Low dose aspirin (≤ 325 mg/day) was not permitted in the VIGOR trial but was allowed in CLASS (about 22% of patients took low dose aspirin). Conversely, the VIGOR trial permitted the use of antacids and over-the-counter H_2-receptor antagonists, whereas CLASS allowed 2 days' use of antacids only. The primary endpoints of the trials also differed: "confirmed clinical upper GI events" (i.e., gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic gastroduodenal ulcers) in the VIGOR trial versus ulcer complications (perforations, obstructions, or bleeding ulcers) in CLASS. The intent-to-treat cohort in CLASS comprised 7968 patients [3987 received celecoxib (2320 patient-years), 1996 received diclofenac (1081 patient-years), and 1985 received ibuprofen (1123 patient-years)]. The intent-to-treat cohort in the VIGOR trial comprised 8076 patients [4047 received rofecoxib (2697 patient-years) and 4029 received naproxen (2698 patient-years)]. The patient cohorts in both studies were similar with regard to age (mean age roughly 58 years in the VIGOR trial and 60 years in CLASS), race (predominantly white), sex (predominantly female), and history of upper GI events (7.8% in the VIGOR trial, 9.7% in CLASS).

In the VIGOR trial, the incidence of "confirmed clinical upper GI events" (including perforations, obstructions, bleeding, and ulcers) during a median followup of 9 months was significantly lower with rofecoxib 50 mg QD (2 to 4 times the recommended OA dose) than with naproxen 500 mg BID (1.4% vs 3.0%, respectively; $p < 0.001$)[2]. These percentages equated with 2.1 events per 100 patient-years with rofecoxib versus 4.5 events per 100 patient-years with naproxen, for a relative risk of 0.5 with rofecoxib. The rates of complicated confirmed events (perforation, obstruction, and severe upper GI bleeding) were 0.6 per 100 patient-years for rofecoxib and 1.4 per 100 patient-years for naproxen ($p = 0.005$).

In CLASS, 6 months of treatment with celecoxib 400 mg BID (2 and 4 times the maximal RA and OA dosages, respectively) did not result in a significantly different annualized incidence of upper GI ulcer complications compared with treatment with the comparator nonselective NSAID: 0.76% among patients treated with celecoxib versus 1.45% among patients treated with ibuprofen 800 mg TID or diclofenac 75 mg BID[3]. Thus, the trial did not achieve its primary endpoint.

However, at the FDA Arthritis Advisory Committee meeting (held in Gaithersburg, Maryland, February 7,

Table 1. Comparison of design, study population, and study endpoints of the VIGOR[2] and CLASS[3] trials.

Variable	VIGOR, (N = 8076)	CLASS, (N = 7968)
Drug/dosage	Rofecoxib 50 mg QD (2 × maximum OA chronic dose)	Celecoxib 400 mg BID (4 × OA dose; 2 × maximum RA dose)
Patients	RA*	OA 72%, RA 28%
Comparator NSAID	Naproxen 500 mg BID	Ibuprofen 800 mg TID Diclofenac 75 mg BID
Low dose aspirin allowed?	No	Yes, 22%
Antiulcerant allowed	Antacids and OTC H_2-receptor antagonists allowed	Only antacids (≤ 2/day) allowed
Duration	Median 9 mo Maximum 13 mo	Median 9 mo Maximum 13 mo
Analysis	Intent-to-treat	Intent-to-treat; excludes events at 0–2 days
Primary endpoint	Clinical upper GI events	Complicated ulcers
Secondary endpoint	Complicated upper GI events	Symptomatic ulcers

* Rofecoxib is not approved in the United States for the treatment of RA. OTC: over-the-counter, GI: gastrointestinal.

2001), there were extensive discussions concerning the utility of combining the incidence of symptomatic ulcers (the secondary outcome) with ulcer complications (the primary outcome) and applying this composite outcome, which was not predetermined, as an important outcome of CLASS. For the entire cohort over the entire study period (median exposure 6–9 months), celecoxib was associated with a significantly lower incidence of ulcer complications (perforations, obstructions, and bleeding ulcers) plus symptomatic ulcers versus ibuprofen (1.85% with celecoxib vs 4.31% with ibuprofen; $p = 0.005$). For the non-aspirin–using cohort, celecoxib was associated with significantly fewer ulcer complications compared with ibuprofen (0.44% vs 1.85%; $p = 0.005$) and significantly fewer symptomatic ulcers/ulcer complications combined versus ibuprofen (1.16% vs 4.25%; $p < 0.001$).

The absence of significant differences between celecoxib and diclofenac for both endpoints was possibly a function of the high withdrawal rate for GI events, including issues regarding GI tolerability. The withdrawal rate for moderate to severe GI symptoms (e.g., abdominal pain, diarrhea, dyspepsia, nausea, and vomiting) was significantly higher in the diclofenac group versus the other treatment arms (9.5% for diclofenac vs 7.5% for both celecoxib and ibuprofen; $p < 0.05$ for diclofenac versus celecoxib) (FDA Arthritis Advisory Committee meeting: summary new drug applications review of celecoxib; Gaithersburg, MD, February 7, 2001). In addition, the study was substantially underpowered because of an underrepresentation of patients with known risk factors for GI complications (e.g., history of upper GI bleeding and cardiovascular disease) as well as the recruitment of roughly twice as many patients taking low dose aspirin as was anticipated (see below).

To date, no published studies have directly compared celecoxib and rofecoxib in terms of upper GI safety. Comparisons of these drugs with regard to upper GI effects are partly dependent on whether the doses of rofecoxib and celecoxib are equally effective and clinically comparable.

In summary, the incidence of upper GI ulcer complications over the entire period of the trials was similar for patients treated with rofecoxib and for non-aspirin–using patients treated with celecoxib; these rates equated with a reduction in ulcer complications of roughly 50% versus comparator nonselective NSAID.

At present, the following conclusion can therefore be drawn regarding the upper GI safety of COX-2 selective inhibitors.

> **Current data indicate** that the 2 available COX-2 selective inhibitors are associated with a lower incidence of clinically important upper GI events compared with that attributable to antiinflammatory doses of naproxen (VIGOR trial) and to antiinflammatory doses of ibuprofen (CLASS).

Is there a need for prophylactic antiulcer medications in patients treated with COX-2 selective inhibitors?

Currently, no randomized trials that assess the utility of gastroprotective medications with COX-2 selective inhibitors have been published. Analyses of data from the FDA summary basis of approval from the new drug applications (NDA) for rofecoxib and celecoxib indicate that these drugs induce ulcers at a rate that is similar to that of placebo and significantly less than that of active NSAID comparators at 12 and 24 weeks[18]. This conclusion is supported by clinical trial results involving rofecoxib[15,19] and celecoxib[14]. Thus, the use of gastroprotective medications for ulcer prevention is likely to be unnecessary with COX-2 selective inhibitor treatment in most patients. However, prophylactic cotherapy probably should be used in patients at high risk for ulcer complications (e.g., patients with prior GI complications).

In addition to upper GI ulcers and ulcer complications, nonselective NSAID therapy is often associated with the development of dyspeptic symptoms, which may include acid reflux, epigastric pain and discomfort, nausea, vomiting, bloating, and heartburn. Depending on how dyspepsia is defined, treatment with nonselective NSAID causes dyspeptic symptoms in up to 46% of patients[20]. In clinical trials, the COX-2 selective inhibitors have exhibited somewhat higher rates of nonulcer upper GI adverse events, such as dyspepsia, nausea, vomiting, and abdominal pain, compared with placebo, but lower rates compared with nonselective NSAID[18].

Although the routine use of GI mucosal-protective drugs (e.g., proton pump inhibitors and H_2-receptor antagonists) with COX-2 selective inhibitors does not appear to be warranted for GI mucosal prophylaxis, certain patients may require these drugs for other reasons (e.g., gastroesophageal reflux disease or hiatal hernia).

The following conclusions may be drawn from current data regarding the need for upper GI ulcer prophylaxis in patients taking COX-2 selective inhibitors.

> **Patients who are treated** with COX-2 selective inhibitors do not routinely need cotherapy for upper GI ulcer prophylaxis. However, patients may exhibit symptomatic complaints not associated with upper GI ulcers when using these agents, albeit at a lower frequency than is associated with nonselective NSAID.

Does concomitant aspirin therapy increase the risk for ulcer complications in patients treated with COX-2 selective inhibitors?

Considering the large numbers of patients taking low dose aspirin for cardiovascular prophylaxis, it is important to establish whether use of COX-2 selective inhibitors increases the risk of ulcer bleeding. In a case-control study

of hospitalized patients with hematemesis and melena secondary to upper GI ulcers, prophylactic low dose aspirin prescribed at 75, 100, and 300 mg/day was associated with increased risk of development of a bleeding peptic ulcer compared with combined hospital and community controls[21]. The odds ratios for the 3 aspirin regimens (taken for 1 month or longer) were as follows: 2.3 for 75 mg/day, 3.2 for 150 mg/day, and 3.9 for 300 mg/day. Other case-control studies have also shown an increased risk of bleeding associated with upper GI ulcers in patients taking low dose aspirin[22,23]. A recent metaanalysis of 24 randomized, controlled trials has confirmed that longterm low dose aspirin therapy is associated with a significant increase in the incidence of upper GI hemorrhage[24]. Upper GI bleeding occurred in 2.3% of patients taking aspirin at dosages < 163 mg/day compared with 1.45% taking placebo, for an odds ratio of 1.59. Further, evidence indicates that the risk of recurrent bleeding ulcers in patients taking low dose aspirin alone is decreased with proton pump inhibitor therapy.[25]

The VIGOR trial did not allow patients to take aspirin, and so the effects of low dose aspirin on the ulcer complication incidence in rofecoxib users are not known. In CLASS, low dose aspirin (≤ 325 mg/day), used by about 22% of patients, was shown to have a significant effect on the incidence of upper GI ulcer complications in celecoxib treated patients[3]. The relative risk of an upper GI ulcer complication in celecoxib treated patients receiving concomitant low dose aspirin was 4.5 ($p = 0.01$). Low dose aspirin use, however, did not have a significant effect on the rate of upper GI ulcer complications among patients given the nonselective NSAID (relative risk 1.7; $p = 0.29$). In patients taking aspirin, the annualized incidence rates of upper GI ulcer complications were 2.01% for celecoxib versus 2.12% for the nonselective NSAID comparators ($p = 0.92$). In contrast, the corresponding annualized incidence rates among aspirin nonusers were 0.44% and 1.27% ($p = 0.04$). Since CLASS was not powered to determine the effects of aspirin, the only observation that can be made regarding aspirin is that it is an independent risk factor for the development of an upper GI complication or a complication along with a symptomatic ulcer in users of celecoxib. Further, it is premature to conclude that a combination of a COX-2 selective inhibitor with aspirin has the same risk for GI events as that of aspirin with a nonselective NSAID.

These findings allow the following conclusions regarding the need for GI mucosal protective agents in patients at risk of upper GI events who take both COX-2 selective inhibitors and low dose aspirin for cardiovascular prophylaxis.

> **Patients taking low dose aspirin** for cardiovascular prophylaxis and who are at risk for upper GI ulcer complications should also receive GI mucosal protective therapy, irrespective of whether they are receiving COX-2 selective inhibitors. The evidence from CLASS suggests that aspirin use, even in low doses, is a more important risk factor for the occurrence of upper GI events than was anticipated.

RENAL CONSIDERATIONS

Do COX-2 selective inhibitors offer improved renal safety compared with nonselective NSAID?

Normal renal function and development are critically dependent on COX mediated production of prostaglandins. Nonselective NSAID can negatively influence an array of prostaglandin mediated renal homeostatic mechanisms. Potential adverse effects of nonselective NSAID on renal function include fluid and electrolyte disturbances, acute deterioration of renal function, nephrotic syndrome with interstitial nephritis, and renal papillary necrosis[26]. As discussed in detail in the following section, edema and interference with the effectiveness of antihypertensive medications are common NSAID associated adverse effects involving the kidney. In some studies, users of nonselective NSAID have shown a 2-fold increase in the risk of acute and/or chronic renal dysfunction[27,28]. This risk increases with age and is related to the NSAID dose and duration of use[28–31]. Adverse renal effects associated with nonselective NSAID use occur more frequently in volume-depleted patients; in those with hypertension, congestive heart failure, or diabetes; and in the elderly with intrinsic kidney disease.

Evidence suggests that COX-2 has a homeostatic role in renal function, predominantly at 2 sites. In the thick ascending limb of the loop of Henle and the macula densa, COX-2 is associated with maintenance of salt and water homeostasis and, via its effect on tubular glomerular feedback, with glomerular filtration[26]. In the distal nephron, COX-2 has a role in protecting against hypertonic insult. As more has been learned about the physiologic role of COX-2, the role that COX-1 plays in maintaining renal function has become less clear[26]. Nevertheless, it is likely that the 2 isoenzymes have overlapping functional roles in the kidney. Since it is now evident that COX-2 is not only constitutively expressed in the kidney but also can be upregulated[32–34], understanding renal effects following administration of COX-2 selective inhibitors has become important.

In a study of normotensive salt depleted young subjects, COX-2 selective inhibition with celecoxib resulted in sodium and potassium retention, suggesting that COX-2 selective inhibition may not spare renal function during salt depletion.[35] Whelton, *et al* recently compared the renal effects of celecoxib (200 mg BID and 400 mg BID) and naproxen (500 mg BID) in 29 healthy elderly subjects (ages 65–85 years)[36]. Apart from a statistically significantly smaller reduction in glomerular filtration rate (GFR) compared with baseline values in celecoxib treated subjects

compared with naproxen treated subjects, other renal variables were similar in both groups. Catella-Lawson and colleagues reported similar effects on GFR in healthy older subjects (ages 59–80 years) treated with rofecoxib 50 mg QD, indomethacin 50 mg TID, or placebo for 2 weeks[37]. GFR was decreased following administration of indomethacin but was not significantly altered by rofecoxib; other renal measures (e.g., sodium excretion) were affected similarly by both active drugs. However, a report by Swan, *et al* showed that in elderly subjects receiving a low salt diet, rofecoxib and indomethacin similarly and significantly decreased GFR compared with placebo[38].

Analysis of data from the North American arthritis trials involving celecoxib (at dosages of 100 mg BID, 200 mg QD, or 200 mg BID) showed that the incidence of renal adverse events was low; the incidence of "any renal event" was 4.3% in celecoxib treated patients and 2.5% in those randomized to placebo (FDA summary basis of approval from NDA for celecoxib, 1998). In CLASS, analysis of data from the entire study period showed that the incidence of serum creatinine levels > 2 mg/dl and/or blood urea nitrogen (BUN) > 40 mg/dl was statistically significantly ($p < 0.05$) higher in patients receiving diclofenac versus those receiving celecoxib (2.1% vs 1.3%), but there was no statistically significant difference between ibuprofen (1.4%) and celecoxib (FDA Arthritis Advisory Committee meeting: summary NDA review of celecoxib; Gaithersburg, MD, February 7, 2001).

In the controlled clinical trials of rofecoxib 12.5 mg QD and 25 mg QD in OA, no significant differences were noted in the incidence of renal adverse events between rofecoxib and nonselective NSAID comparators (FDA summary basis for approval from the NDA for rofecoxib, 1999). In the VIGOR trial, no statistically significant difference was observed between rofecoxib and naproxen in the incidence of reported renal adverse events (FDA Arthritis Advisory Committee meeting: summary NDA review of rofecoxib; Gaithersburg, MD, February 8, 2001).

Therefore, precautions that are advised for the use of nonselective NSAID in patients with impaired renal function or at risk for renal adverse effects should also be applied when considering the use of COX-2 selective inhibitors.

Based on available evidence, the following conclusions may be drawn with regard to the renal safety profile of COX-2 selective inhibitors.

> **COX-2 selective inhibitors** have similar effects on renal function as nonselective NSAID. Thus, in patients with potential renal failure, COX-2 selective inhibitors should be used cautiously, and the patients followed carefully. At-risk patients (such as those with preexisting cardiac, renal, or hepatic disease) who receive these drugs must be monitored in the same fashion as those taking nonselective NSAID.

CARDIORENAL CONSIDERATIONS: HYPERTENSION AND EDEMA

Do COX-2 selective inhibitors differ from nonselective NSAID with regard to their effects on blood pressure or edema development?

Two large metaanalyses have shown that nonselective NSAID may increase blood pressure (BP) in both normotensive and hypertensive individuals and may antagonize the BP-lowering effects of antihypertensive agents[39,40], although the severity of these effects varies considerably among NSAID. In an analysis by Pope, *et al*[39], for example, indomethacin and naproxen increased mean arterial BP by 3.59 and 3.74 mm Hg, respectively, whereas piroxicam had a negligible effect (an increase of 0.49 mm Hg) and sulindac actually decreased mean arterial BP. The use of nonselective NSAID has also been shown to increase the risk of initiation of antihypertensive therapy in older individuals (aged ≥ 65 years)[41]. The precise mechanisms by which nonselective NSAID increase BP remain unclear but may include, in addition to prostaglandin inhibition, such diverse factors as decreased plasma renin activity, changes in vascular resistance, and effects on cardiac function[40].

North American phase II and III clinical trials involving more than 4000 patients with OA showed no significant increases in the incidence of investigator reported hypertension with celecoxib at dosages of 100, 200, 400, and 800 mg/day versus nonselective NSAID (FDA summary basis of approval from the NDA for celecoxib, 1998)[42]. In CLASS, the incidence of hypertension over the entire study period was significantly lower with celecoxib compared with ibuprofen (2.0% vs 3.1%, respectively; $p < 0.05$) (FDA Arthritis Advisory Committee meeting: summary NDA review of celecoxib; Gaithersburg, MD, February 7, 2001). Additional data related to the effects of celecoxib on BP were provided in a 4 week trial involving 178 hypertensive patients whose ambulatory BP was controlled by the angiotensin-converting enzyme (ACE) inhibitor lisinopril[43]. In this short term trial, administration of celecoxib did not have a significant effect on the 24 hour, daytime, or nighttime antihypertensive effects of lisinopril.

Trials conducted during the clinical development of rofecoxib showed that, at doses recommended for treatment of OA (12.5 and 25 mg QD) there was not an increased incidence of hypertension or edema. However, in patients with OA receiving doses of 50 mg/day, generally higher rates of hypertension were observed compared with those receiving ibuprofen or diclofenac, and these hypertension rates appeared to be dose related (FDA summary basis of approval from the NDA for rofecoxib, 1999). Further, data from the VIGOR trial indicate that rofecoxib 50 mg/day was associated with a higher rate of hypertension compared with

naproxen in patients with RA (8.5% vs 5.0%, respectively) (FDA Arthritis Advisory Committee meeting: summary NDA review of rofecoxib; Gaithersburg, MD, February 8, 2001). However, at doses used to treat OA, there appears to be little difference between the hypertensive effects of rofecoxib and those of ibuprofen, naproxen, and diclofenac.

In addition to potential effects on hypertension, chronic therapy with nonselective NSAID has been associated with the development of generalized peripheral edema or lower extremity edema. In the celecoxib trials, data are reported as generalized edema or as peripheral edema, which relates to upper and lower limbs. In contrast, in the rofecoxib trials, data are reported as lower extremity edema, which relates to the legs only.

In the North American randomized controlled trials in OA, rates of peripheral edema in patients receiving celecoxib (dosages of 100, 200, 400, or 800 mg/day) or nonselective NSAID (naproxen, ibuprofen, and diclofenac) were similar (2.1% vs 2.4%, respectively) and significantly greater than in the placebo treated patients (1.1%; $p < 0.05$) (FDA summary basis of approval from NDA for celecoxib, 1998)[42]. Reported rates of peripheral edema over the entire study period in CLASS were statistically higher in ibuprofen treated patients compared with celecoxib treated patients (5.2% vs 3.7%, respectively; $p < 0.05$), but there were no statistically significant differences between diclofenac (3.5%) and celecoxib (FDA Arthritis Advisory Committee meeting: summary NDA review of celecoxib; Gaithersburg, MD, February 7, 2001).

Reported rates of lower extremity edema with rofecoxib 12.5 and 25 mg QD (recommended dosages for OA) were 3.6% and 3.8% versus 3.8% with ibuprofen (2400 mg/day) and 3.4% with diclofenac (150 mg/day) (FDA summary basis of approval from NDA for rofecoxib, 1999). Administration of rofecoxib 50 mg QD (a dosage that is not recommended for > 5 days) was associated with a higher incidence of lower extremity edema (6.3%). In the VIGOR trial, lower extremity edema was reported in 4.0% and 2.6% of patients randomized to receive rofecoxib 50 mg QD and naproxen 500 mg BID, respectively (FDA Arthritis Advisory Committee meeting: review of summary NDA for rofecoxib; Gaithersburg, MD, February 8, 2001).

A 6 week, double blind study compared celecoxib 200 mg QD and rofecoxib 25 mg QD in 810 patients with OA aged ≥ 65 years with hypertension that was controlled with diuretics and/or antihypertensives[44]. This study has limitations since it utilized cuff BP measures at trough levels of drug response. Also, rofecoxib has a half-life of roughly 17 hours[45], whereas that of celecoxib is about 11 hours[46]. Further, it is unclear whether the dosages that were studied are clinically equivalent. Results of the trial showed that clinically significant edema occurred in both treatment groups, and by the end of the trial 9.5% of rofecoxib treated patients experienced edema compared with 4.9% of those given celecoxib ($p = 0.014$). In addition, at any time point, systolic BP increased significantly in 17% of the rofecoxib treated patients compared with 11% of the celecoxib treated patients ($p = 0.032$). At week 6, the change from baseline in mean systolic BP at trough drug levels was +2.6 mm Hg for rofecoxib and –0.5 mm Hg for celecoxib ($p = 0.007$). This study showed that administration of both COX-2 selective inhibitors, celecoxib and rofecoxib, appears to be associated with an increased incidence of loss of hypertension control and/or an increase in peripheral edema in older OA patients with treated hypertension. A recent trial that involved normotensive elderly subjects that was only 2 weeks in duration showed no significant difference between celecoxib and rofecoxib in mean changes in BP from baseline values when BP was measured at peak blood levels[47].

In view of these clinical findings, the following conclusion may be drawn.

> **Reported rates** of hypertension and edema in patients receiving COX-2 selective inhibitors appear to be similar to those observed with nonselective NSAID. More important, in patients with controlled hypertension receiving COX-2 selective inhibitors, blood pressure and edema should be carefully monitored, as with nonselective NSAID.

CARDIOVASCULAR CONSIDERATIONS

Should arthritis patients at risk for cardiovascular disease be given low dose aspirin in conjunction with a COX-2 selective inhibitor?

Only recently have data from RCT documented that aspirin is an effective antithrombotic agent for primary as well as secondary prevention of thromboembolic cardiovascular events[48–50]. Low dose aspirin (75 to 325 mg/day) has been shown to reduce the recurrence of myocardial infarctions (MI) and cerebrovascular accidents (CVA) by 25 to 30% in several patient populations[51]. This effect is attributed to permanent and irreversible inactivation of COX-1 activity in platelets[48,51].

García Rodríguez and colleagues recently compared aspirin and nonselective NSAID in primary prevention of MI in postmenopausal women in an epidemiologic study[52]. Overall relative risk for MI in patients currently taking aspirin (for > 1 month at a dosage of ≥ 75 mg/day) was 0.56, in contrast to 1.32 in those receiving non-aspirin nonselective NSAID. This study and other epidemiologic data indicate that low dose aspirin prophylaxis offers primary and secondary protection against cardiovascular thromboembolic events, whereas reversible inhibition of COX-1 platelet activity by non-aspirin nonselective NSAID does not.

Nonselective NSAID that have been specifically tested in RCT for potential antithrombotic effects include sulfinpyra-

zone, indobufen, flurbiprofen, and triflusal[53]. The results of these trials are inconclusive and fail to demonstrate sustained improvements in cardiovascular outcome. The Sixth ACCP Consensus Conference on Antithrombotic Therapy concluded: "Because nonaspirin NSAIDs have been investigated inadequately in terms of their potential cardiovascular effects, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin, even though concomitant administration of the two may amplify the risk of upper GI bleeding."[53]

As expected for COX-2 selective inhibitors, neither celecoxib nor rofecoxib has clinically relevant effects on COX-1 mediated platelet function (e.g., platelet aggregation), even at supratherapeutic dosages[54,55]. In a double blind RCT of healthy adults, administration of naproxen (500 mg BID) over 10 days resulted in a significant ($p < 0.05$) mean increase from baseline in bleeding times compared with administration of celecoxib 600 mg BID (3 and 6 times the recommended maximal doses for RA and OA, respectively)[54]. In a double blind, 10 day study of healthy volunteers, administration of rofecoxib 50 mg QD (twice the recommended dose for the treatment of OA) led to no inhibition of platelet aggregation on Day 4; this was equivalent to the effect observed with placebo ($p = 0.35$)[55]. On Days 4–10, subjects received low dose aspirin (81 mg/day). Both aspirin plus placebo and aspirin plus rofecoxib inhibited platelet aggregation by > 93%, indicating that rofecoxib did not alter the antiplatelet effect of aspirin.

Together, these data support the conclusion that aspirin, nonselective NSAID, and COX-2 selective inhibitors exhibit different patterns of inhibition of COX-1 mediated thromboxane. Theoretically, COX-2 selective inhibitors could also increase the risk of thromboembolic events as a result of preferential inhibition of endothelial prostacyclin synthesis without corresponding inhibition of platelet thromboxane synthesis[56]. A temporal association between celecoxib treatment and ischemic complications in 4 patients with connective tissue disease and anticardiolipin antibodies has been reported[57]. Although it is likely that COX-2 selective inhibitors may not increase the risk of thrombi formation in patients without alterations in coagulation balance or other known risk factors, caution is advised when using these agents.

Clearly, COX-2 selective inhibitors as well as nonselective NSAID do not appear to reduce cardiovascular risk and should not be prescribed as a substitute for aspirin for cardiovascular prophylaxis. In CLASS, in all patients, the incidence of MI was 0.2% in the celecoxib group and 0.3% in the combined nonselective NSAID group; the incidence of CVA was 0.1% and 0.3%, respectively[3]. Differences between celecoxib and individual comparator NSAID were not statistically significant in the intent-to-treat or the non-aspirin populations[3]. In the VIGOR trial, rofecoxib and naproxen administration resulted in similar mortality rates associated with thromboembolic cardiovascular events, including CVA[2]. However, significantly different incidences of MI were reported in the naproxen treated group compared with the rofecoxib treated groups (0.1% vs 0.5%, respectively; $p < 0.05$). Although patients requiring low dose aspirin prophylaxis were specifically excluded from enrollment in the VIGOR trial, a retrospective analysis indicated that 4% of patients met established criteria for cardiovascular prophylaxis; 47% of MI occurred in this group. In the remaining 96% of patients, there was no significant difference in the rates of MI between the rofecoxib and naproxen groups.

Three hypotheses offer explanation for differences in MI rates observed in the entire rofecoxib and naproxen treatment groups. Naproxen may have a cardioprotective effect; since naproxen has a long half-life (12–17 hours), it potentially has a sustained effect on COX-1 activity. (A small study suggested that flurbiprofen provided secondary cardiovascular protection in patients' post-bypass surgery, but confidence intervals were large and did not result in differences in mortality and/or post-bypass thromboses[58].) A second explanation could be that rofecoxib at 50 mg QD dosage may have a thrombogenic effect. Data from other RCT do not currently support this hypothesis. Finally, this finding may simply be a result of chance.

Therefore, these cardiovascular findings, as with other comparisons of the CLASS and VIGOR trials, must be viewed with caution, especially considering the short term followup in both studies (median 9 months, range 6–13); the relatively low absolute risk of cardiovascular disease in both patient populations; the small numbers of cardiovascular events reported, particularly in comparison with other RCT powered to reveal cardiovascular events; and the absence of a placebo control arm. It is important to remember that neither CLASS nor the VIGOR trial was specifically designed to ascertain the incidence of cardiovascular effects. It is clear that further data are needed to resolve this issue.

In view of the above discussion, the following conclusions may be drawn.

In patients receiving COX-2 selective inhibitors or nonselective NSAID, prophylaxis with low dose aspirin should be continued or instituted if aspirin prophylaxis is indicated because of prior vascular events or established vascular disease. Similarly, patients for whom aspirin prophylaxis is indicated should not discontinue low dose aspirin when they are prescribed a COX-2 selective inhibitor or a nonselective NSAID.

COMPARATIVE SAFETY OF THE 2 AVAILABLE COX-2 SELECTIVE INHIBITORS

Although differences in reported data from RCT may exist, clinically relevant differences between

the currently available COX-2 selective inhibitors with regard to upper GI toxicity, cardiovascular disease, hypertension, and renal function have not been confirmed and will only be resolved by further appropriate head-to-head trials (i.e., randomized trials with placebo and nonselective NSAID controls). In the interim, when using COX-2 selective inhibitors, careful monitoring for potential hypertension and edema and low dose aspirin prophylaxis in patients at risk for thromboembolic cardiovascular events are required.

CONCLUSION

Considering that the COX-2 selective inhibitors were recently introduced into clinical practice, an unprecedented amount of data exist regarding these agents. Regardless, many questions remain unanswered.

Do COX-2 selective inhibitors result in fewer symptomatic upper GI ulcerations and secondary complications than do nonselective NSAID plus proton pump inhibitors?

Since COX-2 selective inhibitors appear to result in fewer symptomatic upper GI ulcerations and secondary complications, do they delay healing of mucosal damage relative to nonselective NSAID? What are the underlying causes of adverse effects associated with these agents?

What are clinically equivalent doses for celecoxib and rofecoxib?

From a pharmacoeconomic perspective, which patient groups, in addition to those at risk for NSAID induced upper GI ulcers and complications, should be candidates for COX-2 selective inhibitors?

What potential clinical benefits do COX-2 selective inhibitors offer compared with other antiinflammatory agents or with acetaminophen?

What are the potential benefits and risks of administration of COX-2 selective inhibitors on bone resorption and bone formation?

Would direct comparisons with RCT between celecoxib and rofecoxib in selected patient populations help define their preferential use compared with nonselective NSAID?

Would these RCT reveal clinically significant differences between the agents?

These and other clinically important questions can only be resolved through continued investigation and additional well designed RCT.

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APPENDIX

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