

Editorial

Coxibs and NSAIDs – Is the air any clearer? Perspectives from the OARSI/International COX-2 Study Group Workshop 2007

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In 2005, several of the authors wrote an editorial entitled “Clearing the Air” on coxibs and NSAIDs¹. Of particular import was a concern regarding cardiovascular (CV) risk of these agents. At that time, in 2005, it was already noted that the potential CV risks attributed to the coxibs might be shared by other NSAIDs. In the United States, all marketed prescription NSAIDs, both nonselective and COX-2 selective were required to revise their labeling by the Food and Drug Administration (FDA) to include a boxed warning highlighting the potential for increased CV events and gastrointestinal (GI) bleeding. In addition, the FDA requested manufacturers of nonprescription, over-the-counter NSAIDs to include more specific information on potential CV and GI risks. Given that, in the US, an estimated 17 million individuals are using NSAIDs daily, and that 60 million prescriptions for various forms of NSAIDs are written each year, the status of these agents in the management of pain and inflammation is of particular interest. In the European Union, the European Agency for the Evaluation of Medicinal Products (EMA) released a Public Statement summarizing its review of the COX-2 inhibitor class and noted that they were “contraindicated in patients with ischemic heart disease or stroke” and that “prescribers [should] exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidemia, diabetes and smoking, as well as for patients with peripheral arterial disease” (EMA Public Statement: London, 17 February 2005).

The importance of osteoarthritis (OA) as an international clinical problem prompted a workshop organized by the Osteoarthritis Research Society International (OARSI) and the International COX-2 Study Group that was held on March 24–25, 2007. Meeting of the International COX-2

Study Group with investigators from OARSI provided input from individuals with multiple perspectives enriching the base of information. Of particular interest for review was the confusion regarding utility of NSAIDs and coxibs in the treatment of chronic painful and inflammatory conditions. In that there are no therapies without inherent risk to some patients, it is critical to understand the impact of that potential risk in the context of what clinical improvements can be expected by exposure to the therapy. The difficulty in measuring competing risks vs benefit continues to be challenging. The availability of a large amount of additional information related to NSAIDs and coxibs, both as to efficacy and adverse events, suggested that it might be worthwhile reviewing the current status of these agents and their use, particularly as they apply to OA management. This editorial reviews “what we knew then” and, more importantly, “what we know now”.

Efficacy comparisons

A systematic review of randomized controlled trials of non-opioid analgesics, nonselective NSAIDs (NS NSAIDs) and/or coxibs in the treatment of OA published up to July 2005 was released by the US Agency for Healthcare Research and Quality (AHRQ) in 2006². This review concluded that NSAIDs, including coxibs, were superior to acetaminophen for reducing pain and improving function in patients with OA, and that there were no clinically significant differences in efficacy between the various non-aspirin NS NSAIDs and coxibs when used in comparable doses. Several additional studies and a review published after July 2005 have demonstrated that the COX-2 selective NSAIDs etoricoxib and lumiracoxib have similar efficacy to NS NSAIDs and to celecoxib for the treatment of OA^{3–5}. Choice of a NS NSAID or a coxib in the individual patient with OA is predicated more on differences in safety and cost rather than efficacy. Given the lack of controversy as to any clinically important differences in efficacy between these types of NSAIDs, this discussion will concentrate on issues of adverse event comparisons.

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Adverse events

GI ADVERSE EVENTS

The FDA has estimated a general risk of 2–4% per year for NS NSAID-induced symptomatic gastroduodenal ulcer and/or its complications, which corresponds to the combined endpoint of perforations, symptomatic ulcers and bleeds (PUBs) in outcome studies. Several meta-analyses showed a relative risk (RR) of serious adverse GI effects in persons who were current users of NS NSAIDs to be three-to-four times that of non-users in the general population^{2,6–11}. The COX-2 selective (COX-1 sparing) inhibitors are associated with a reduced incidence of symptomatic and complicated ulcers as demonstrated in several large outcome trials. In the Celecoxib Long-term Arthritis Safety Study (CLASS) trial, the incidence of symptomatic and complicated ulcers was statistically significantly lower in the celecoxib-treated group compared with the combined ibuprofen and diclofenac group at 6 months (www.fda.gov/ohrms/dockets/ac/01/transcripts/367711_01.pdf)¹². In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, significantly fewer symptomatic and complicated ulcers occurred in rheumatoid arthritis (RA) patients randomized to rofecoxib as compared to naproxen¹³. In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), OA patients randomized to lumiracoxib, a COX-2 selective inhibitor approved in Europe, Canada, Latin American and Asian countries, but not yet available in the US, had a significantly lower incidence of symptomatic and complicated ulcers compared to patients randomized to either naproxen 500 mg twice daily or ibuprofen 2400 mg daily¹⁴. In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, patients randomized to etoricoxib, another coxib approved in Europe, Latin American and Asian countries but not available in the US, had a significantly lower incidence of symptomatic but not complicated upper GI events compared to patients randomized to diclofenac¹⁵. In this latter study, there was no evidence of effect modification by concomitant use of either low-dose aspirin or proton pump inhibitors (PPIs); indeed, the benefits of etoricoxib were preserved in pre-specified subgroup analyses.

Of particular interest is the issue of GI risks associated with combining aspirin with selective or NS NSAIDs. Endoscopic studies in patients taking aspirin at a dose of 325 mg/day demonstrated an increased risk for gastric ulcers and erosions (27.3%) when naproxen was added, with significantly fewer ulcers/erosions associated with a celecoxib/aspirin combination (18.7%)¹⁶. In patients taking 81 mg of aspirin per day, endoscopic pathologic findings with celecoxib/aspirin (7%) were diminished as compared to the higher dose aspirin findings but remained high (25.3%) with naproxen¹⁷. It is unclear, however, how these endoscopic results translate into clinically relevant outcomes. In the CLASS trial, there was no evidence of a statistically significant reduction in clinical or complicated ulcers in the celecoxib-treated patients in the subgroup that received low-dose aspirin; however, there were relatively few patients on concomitant aspirin in the various arms of the trial (21% of the patient population)¹². In TARGET, while the incidence of complicated upper GI events was numerically reduced by 29% among patients randomized to lumiracoxib in the subgroup that received low-dose aspirin, this did not reach statistical significance¹⁴. However, since neither the CLASS nor the TARGET study was powered to detect the beneficial upper GI effects of celecoxib and lumiracoxib,

respectively, in the subgroup receiving aspirin co-administration, a GI protective effect in the presence of aspirin of coxibs cannot be excluded. Indeed, Laine and colleagues¹⁵ reported that the rate of uncomplicated upper GI clinical events was significantly lower with etoricoxib than with diclofenac even in the presence of aspirin in the MEDAL trial that enrolled approximately 34,000 patients (hazard ratio = 0.67 [95% confidence intervals (CIs): 0.47, 0.96]). The lack of a significant reduction in the incidence of complicated events, primarily upper GI bleeding, may be due to the antiplatelet effects of low-dose aspirin.

Most physicians agree that coxibs are indicated in patients who have a high risk GI history, including a past history of upper GI bleeding related to ulcers, past history of ulcers with recurrent ulcer symptoms, those receiving concomitant anticoagulant and/or glucocorticoid therapy, and in those with other risk factors including aging and presence of comorbid conditions, and that their use in low-risk patients or for acute pain is less likely indicated except for peri-operative administration. It should be noted that even in low-risk patients, the upper GI toxicity of coxibs is lower than that of NS NSAIDs. Since there are considerably more people in the low-risk category, the use of coxibs with their superior GI toxicity profile likely would result in diminished overall adverse events. Cost-effectiveness analyses support their use in the patient group at high risk for serious upper GI complications where the use of coxibs is cost effective, balancing their use vs NS NSAIDs in combination with either misoprostol or a PPI^{18,19}.

Few studies have compared the GI safety of coxibs to the combination of a NS NSAID plus a PPI. A randomized trial in a very specific population (RA patients with a recent history of upper GI bleeding) failed to demonstrate a statistically significant difference between treatment with celecoxib plus placebo vs 150 mg of diclofenac plus 20 mg omeprazole daily for 6 months, with a re-bleed rate over 6 months of approximately 6%²⁰. However, two recent trials have suggested that a coxib plus a PPI may provide greater gastroprotection than a traditional NSAID plus a PPI. For example, a subsequent study by Chan *et al.*²¹ demonstrated that in a high risk population, celecoxib plus esomeprazole was more effective than celecoxib alone in preventing recurrent ulcer bleeding: the 13-month cumulative incidence was 0% in the celecoxib + esomeprazole group vs 8.9% in the celecoxib alone controls (95% CI difference: 4.1–13.7; $P=0.0004$). In the MEDAL program, described above, the reduction in uncomplicated events with etoricoxib vs diclofenac was maintained in the subgroup of patients treated with PPIs¹⁵.

CV ADVERSE EVENTS

As noted in our previous editorial, the incidence of myocardial infarction (MI) in RA patients enrolled in the VIGOR trial was significantly higher with rofecoxib 50 mg/day than that seen with patients receiving naproxen 500 mg twice daily¹³. Explanations for the observation of the increased rate of non-fatal acute MIs with rofecoxib as compared to naproxen included, for example, (1) all patients in the study group had RA, a disease known to be associated with a higher CV risk; (2) low-dose aspirin was not allowed; and (3) a possible CV prophylactic effect of naproxen similar to that seen with aspirin because of an antiplatelet effect due to inhibition of platelet-derived thromboxane during the dosing interval. Alternatively, it was suggested that rofecoxib might induce a prothrombotic state related to an

imbalance of inhibition of thromboxane and prostacyclin^{22,23}. Inhibiting prostacyclin could result in lessening of vasodilatation as well as diminished inhibition of platelet aggregation without a counterbalanced inhibition of thromboxane A2 in the at-risk patient. Other important issues may contribute to the increased CV risk including varying drug effects on nitric oxide (NO), effects on mean blood pressure, salt and water balance, and differential membrane effects of various therapies.

A meta-analysis of the celecoxib database did not demonstrate an increased CV risk²⁴; however, the trials were usually 6 months or less in duration and the number of events was low. The relationship of rofecoxib and celecoxib use to increased CV events was observed in placebo-controlled trials for polyp prevention in patients with colonic polyps, and, in the case of celecoxib was observed at higher than clinically recommended therapeutic doses for OA^{25–27}. An increased frequency of cardiac events was also noted in patients undergoing coronary bypass surgery receiving perioperative administration of valdecoxib and parecoxib²⁸. In TARGET¹⁴, no statistically significant increased risk for CV events was noted when lumiracoxib was compared to ibuprofen and naproxen; however, there was a numerically higher incidence of CV events in the lumiracoxib group compared to naproxen, although the overall incidence of events was low. A recent *post hoc* analysis of patients at high risk for CV events studied in TARGET showed that participants who were randomized to ibuprofen and took concomitant low-dose acetylsalicylic acid (ASA) had significantly more CV primary events and congestive heart failure than those randomized to lumiracoxib (2.14% vs 0.25%, $P = 0.038$), suggesting that ibuprofen may interfere with the cardioprotective effects of low-dose aspirin²⁹. Indeed, this result is consistent with experimental data showing a pharmacodynamic interaction between low-dose aspirin and ibuprofen and epidemiologic data showing an increase in mortality in persons with MIs taking ibuprofen^{29–31}. Based on these latter data, the FDA issued a warning against the use of ibuprofen in patients taking low-dose aspirin for secondary prophylaxis after a CV thrombotic event.

In the MEDAL program, there was no difference in the rate of CV thrombotic events between patients randomized to etoricoxib or diclofenac; patients were stratified on the use of low-dose aspirin and participating investigators were encouraged to administer aspirin prophylaxis as indicated for secondary prevention³². There was, however, a significant increase in the number of etoricoxib-treated patients who withdrew from the trial due to congestive heart failure and increased hypertension.

In 2006, Kearney and colleagues³³ published a systematic review and meta-analysis of 138 randomized placebo or active-comparator controlled trials of coxibs to estimate the increased risk for CV thrombotic events among patients treated with coxibs. This study found a 42% increased risk (95% CI: 1.18, 1.78) for the combined Anti-Platelet Trialist Collaboration (APTCL) endpoint among patients randomized to a coxib as compared to placebo: absolute rates were 1.2 per 100 person-years as compared to 0.9 per 100 person-years corresponding to an excess rate of 0.3 events per 100 person-years and a number needed to harm of 333. The increased risk was primarily attributed to an approximate twofold increase in the rate of non-fatal MI and a 50% increase in the risk of vascular death; there was no significant difference in the risk of stroke. Among studies that compared coxibs to NSAIDs, there was no evidence of a difference in the risk for APTC events among patients

randomized to a coxib as compared to non-naproxen NS NSAIDs, primarily ibuprofen and diclofenac, while there was a significantly increased risk for APTC events among patients randomized to a coxib as compared to naproxen. Again, this increased risk was primarily attributed to an increase in the risk of non-fatal MI and, less so, vascular death, without a significant excess in risk of stroke. While the authors failed to demonstrate heterogeneity in risk among the different coxibs, there was evidence of a dose-response relationship for celecoxib with increased risk for APTC events associated with higher doses (e.g., 200 mg and 400 mg twice daily as compared to 200 mg once daily).

In addition to randomized clinical trials, epidemiologic studies have evaluated the RR for CV events with coxibs and NS NSAIDs. Two large observational cohort studies demonstrated increased risk for CV events with rofecoxib used in doses greater than 25 mg daily^{34,35}. In a third cohort study³⁶, doses of rofecoxib greater than 25 mg/day were associated with more than a threefold higher incidence of acute MI and sudden cardiac death compared with NS NSAIDs. In this analysis of Kaiser Permanente patients, naproxen was associated with an increased risk of thromboembolic CV events (RR = 1.18; 95% CI: 1.04–1.35; $P = 0.01$), as was indomethacin (RR = 1.33; 95% CI: 1.09–1.63; $P = .005$). In another study, Singh and colleagues demonstrated increased CV risk in patients being treated with diclofenac, indomethacin, sulindac and meloxicam, with decreasing rates of CV risk for other selective and NS NSAIDs³⁷. Since the publication of the previous editorial in 2005¹, two systematic reviews of observational studies of the relationship of NSAIDs and coxibs with CV thrombotic events have been published^{38,39}. The former included 16 studies that examined the association of coxib or NSAID use and MI; the latter included 23 studies that examined the association of coxib or NSAID use and CV events, primarily MI and vascular death. In both analyses, rofecoxib use was associated with a statistically significant increased risk of a CV event in a dose-response relationship (i.e., the risk was greater for users of doses greater than 25 mg/day than for those using doses of 25 mg or less per day) while celecoxib use was not associated with a statistically significant increased risk of a CV event. The latter finding is consistent with that from the meta-analysis of Kearney and colleagues (*vide supra*) in suggesting that celecoxib at a dose of 200 mg/day is not associated with a significant increase in risk for MI or other CV thrombotic event. Both meta-analyses of observational studies found no evidence of increased risk for MI or other CV events among users of naproxen, and evidence of a significant increased risk for MI or other CV events among users of diclofenac; there were, however, conflicting results for ibuprofen. The former analysis reported an increased risk associated with the use of ibuprofen (summary RR = 1.07, 95% CI: 1.02, 1.12), while the latter failed to find a significant increased risk associated with the use of ibuprofen (summary RR = 1.07, 95% CI: 0.97, 1.18); note that the point estimates in the two studies were identical.

The mechanisms whereby both selective and NS NSAIDs may contribute to adverse CV events may be multiple in origin. The hypothesis whereby there is an imbalance of prostacyclin and thromboxane inhibition may play a significant role in part in the etiology of these findings²². Of import in this regard is the demonstration that the maximal biosynthetic capacity of human platelet production of thromboxane A2 when challenged *in vitro* by thrombin exceeds the actual rate of thromboxane A2 synthesis *in vivo* by several 1000-folds⁴⁰. This impressive ability of the

platelet to increase production of Thromboxane A2 (TBXA2) may explain, at least in part, the unusual requirement for virtually complete suppression of platelet COX-1 activity in order for pharmacologic inhibition to translate into functional platelet impairment. In addition, TBXA2 inhibition at a level of 95% or more is required before a demonstrable effect on platelet aggregation can be seen. Of interest is the finding that, however, a protective role for aspirin administered at the same time as coxibs has not appeared to consistently diminish CV risk^{26,28,33,36,38,39,41}. Accordingly, other causes to explain increased CV risk have been considered. Both nonselective and selective NSAIDs may be associated with increased blood pressure in individuals receiving anti-hypertensive therapy, particularly diuretics and angiotensin converting enzyme inhibitors^{42,43}. This effect may at times be dramatically obvious with raises of 20 mm or more associated with NSAID administration. Studies have demonstrated mean increases in systolic blood pressure of 4–6 mm, an elevation sufficient to result in a clinically important increase in total stroke occurrence and coronary heart disease⁴⁴. Differences amongst the nonselective and selective NSAIDs in their propensity to induce hypertensive changes may account for some of the differences seen clinically in the CV event profile. Differences in risk may be related to drug half-life, as well as the level of protein binding. Agents with a long half-life will have a more pronounced, prolonged effect on blood pressure; similarly, agents which are less tightly protein bound may exert free drug activity at a greater level and for longer periods of time than those which have almost complete protein binding.

Other factors such as NO production by endothelial cells may play a role in the CV event profile^{45–47}. NO reduces proliferation and leukocyte migration with an effect on vessel inflammation. Decreased NO production has been implicated in the pathogenesis of CV disease. NO effects may potentially outweigh the effects of prostacyclin and thromboxane. The pro-oxidant effects as well as effects on vasoconstriction and blood pressure increase have been studied⁴⁸. There are differential effects of these drugs on membranes and on NO. In addition to the factors noted above, the effect of pain as an important CV risk factor is not often appreciated. Pain increases stress and sympathetic nerve responses with increased heart rate and elevated blood pressure, aggravating any CV risk resulting from other mechanisms.

Acetaminophen has been recommended as an initial pharmacologic therapy for OA patients with mild to moderate pain by the American College of Rheumatology, the American Pain Society and the European League of Associations of Rheumatology^{49–51}. Of concern in this regard are recent studies demonstrating that acetaminophen, when administered more than 15 days a month in women increases the RR of acute MI, sudden cardiac death and stroke by approximately 50%, especially in the individuals who are smokers, similar to the effects of the NS NSAIDs within the same database⁵². This increased CV risk may be associated with increased hypertension reported in chronic users of acetaminophen in observational studies^{53,54}. Even at low doses, acetaminophen was shown capable of inhibiting prostacyclin without affecting thromboxane⁵⁵, the imbalance paradigm seen with coxibs and NSAIDs. Given the greater efficacy of NSAIDs and coxibs as compared to acetaminophen (*vide supra*) and the apparent similarity in CV risk in observational studies, the benefits of acetaminophen use may require renewed scrutiny.

A major issue regarding CV thrombotic events relates to the administration of aspirin concomitantly with NSAIDs. Evidence has shown that administration of NSAIDs such as ibuprofen, naproxen and indomethacin may be associated with attenuation of aspirin prophylaxis of CV events^{29,30,56–58}. Aspirin irreversibly acetylates the serine 530 site on the COX-1 enzyme in the platelet. In the presence of ibuprofen which blocks the binding site, the aspirin effect on the platelet at this same site will be abrogated, putting the patient at increased risk associated with loss of aspirin protection. Blockage of the aspirin-binding site is not seen with simultaneous administration of aspirin and coxibs or with diclofenac, due to differences in binding to COX-1 by these agents. It has been suggested that if the aspirin is taken several hours before the NS NSAIDs, that the aspirin effect will not be diluted. This may be true for single or occasional multiple doses of NSAIDs but, in the presence of continued therapy steady state leading to a constant low level of NSAID, inhibition of the aspirin effect is likely. Although *in vitro* data demonstrate this interaction in definitive fashion, clinical studies demonstrating increased CV event risk in patients receiving a combination of aspirin and ibuprofen have been inconsistent (*vide supra*). Nevertheless, the risk that a patient receiving ibuprofen will have effective aspirin prophylaxis inhibited is of significant concern; indeed, ibuprofen has been relabeled by the FDA to reflect this caution. It is possible that different NSAIDs will have different effects in this regard. For example, naproxen, given at a dose of 500 mg every 12 h may be an effective inhibitor of platelet aggregation *per se* in some patients due to its long half-life; recent data suggest that the vast majority of subjects maintains inhibition of thromboxane production at greater than 95% even at the end of a 12-h dosing interval. Nonetheless, as long-term clinical studies demonstrating prophylaxis equal to that of aspirin have not been performed, naproxen cannot be recommended as an antiplatelet agent in clinical practice. In addition, there may be differences in the ability of various NSAIDs to bind to the aspirin-binding site leading to clinical differences in NSAID and aspirin interaction. Paradoxically, individuals taking low, over-the-counter doses of NSAIDs may be at higher risk of inhibiting the aspirin platelet protective effect than NSAIDs given at full doses since, at low doses, effective inhibition of thromboxane might be less likely than that seen with higher doses.

So where do we stand

We have a great deal more information than 2 years ago but, paradoxically, this new information has made our life as physicians treating OA more complex. It seems that “the more we know, the more we realize we need to know more”. There are some areas in which there is general agreement. Coxibs appear to be safer with respect to GI toxicity and tolerance than nonselective NSAIDs. Studies have demonstrated that up to 40% of GI bleeds associated with the use of NSAIDs are of lower intestinal origin, occurring in sites distal to the Ligament of Treitz⁵⁹. The use of PPIs will decrease upper but not lower GI events. Misoprostol is prophylactic with respect to upper, but not necessarily lower GI bleeding, but has its own GI adverse intolerance profile. A large outcome study comparing a coxib to the combination of a NS NSAID plus a PPI would provide important information of the contribution of lower GI bleeding to the total adverse GI outcomes.

With respect to CV risk, there appears to be concern with respect to all NSAIDs, both selective and nonselective. This concern, however, does not appear to be equal for all NSAIDs. For example, rofecoxib, at least in higher doses, appeared to have a consistently higher CV risk profile than other coxibs or NS NSAIDs. Naproxen appears to have a somewhat safer CV profile, possibly related to a more effective inhibition of platelets, perhaps related to its long half-life. Celecoxib in a dose of 200 mg once daily appears to be similarly safer although long-term studies exceeding 12 months would be reassuring (as supported by Prevention of Sporadic Adenomatous Polyps (preSAP) at 400 mg/day)²⁷. In patients receiving low-dose aspirin, the addition of a NS NSAID agent with its potential to inhibit aspirin prophylaxis may be more harmful to the patient than the CV risk associated with the NSAID alone. In patients receiving aspirin prophylaxis in the presence of high CV risk factors, coxib therapy has an advantage of not interfering with aspirin prophylaxis. The authors note, however, that use of coxibs is proscribed in patients with high CV risk factors in countries under EMEA jurisdiction. Moreover, although more definitive studies are necessary, the data do suggest that ibuprofen may interfere with the ASA cardioprotective effect. Indeed, in the patient with both high CV and GI risk, the "best" option might be to combine low-dose aspirin with a coxib and a PPI.

Therapeutic judgment requires balancing any increased CV risk with the not inconsequential risk of NS NSAIDs associated with GI bleeding. Balancing these various risks is not easy and requires individualization from patient to patient. Human nature being what it is, the thought of having a heart attack is more frightening to most individuals than is having a GI bleed; they consider that blood can be replaced and the bleeding stopped with resolution of findings to the pre-morbid status without necessarily having permanent organ damage. With respect to heart attacks, however, patients see this in a more threatening light with the potential for irreversible cardiac damage leading to the development of congestive heart failure, an understandable concern.

Treatment guidelines for the use of analgesic and anti-inflammatory agents in OA have been published by many organizations including but not limited to the American College of Rheumatology, American Pain Society and European League of Associations of Rheumatology⁴⁸⁻⁵¹; most have not been updated except for the recent Seventh Canadian Consensus statement⁶⁰. These guidelines are meant to provide evidence-based recommendations that will allow the physician, in concert with the patient, to select the most appropriate treatment for each patient, balancing safety and efficacy. There is no one single pathway that is correct for all patients in all situations! The statement was made several years ago that there would be no use for traditional NS NSAIDs given the advantages of coxibs with respect to their advantageous GI adverse event profile. The new findings related to CV events, however, have led to a re-evaluation of therapeutic approaches. Given the finding that there appears to be a level playing field with respect to CV events for both coxibs and NS NSAIDs except naproxen and perhaps low-dose celecoxib, coxibs with their combined higher GI safety profile and lack of aspirin-platelet interaction (not shared by naproxen), may be an advantageous therapeutic approach in many patients.

A recent scientific statement from the American Heart Association (AHA) on the treatment of OA is of interest⁶¹. This directive, authored by highly respected cardiologists, presented an inverted pyramid describing a stepped care

approach to pharmacologic therapy for musculoskeletal symptoms in patient with known CV disease or with CV risk factors. These authors suggested acetaminophen, full doses of aspirin, non-acetylated salicylates or short-term narcotic analgesics as an initial therapy. Although full doses of aspirin up to 4 gm or more a day was not uncommon 30 or 40 years ago, the use of aspirin at such dosage levels is almost nonexistent in today's practices. The risk of high-dose aspirin, not only with respect to GI bleeding but also with respect to the potential for increased hemorrhagic stroke makes its use untenable. Non-acetylated salicylates may be a consideration but these tend to be less effective than commonly used NSAIDs and may take a longer time to begin to benefit the patient. Historically, the non-acetylated salicylates, which unlike aspirin do not acetylate the COXs, have been considered to be safer with respect to bleeding and peptic ulcer disease due to their lack of COX-1 inhibition. However, there are no data which suggest that non-acetylated salicylates are safer than other NSAIDs with respect to CV adverse events. It is of concern that the AHA guidelines, presented as evidence-based scientific recommendations, promote these agents as preferred to NSAIDs and coxibs in patients with CV risk as there is no evidence to support their long-term safety. It is important to note that non-acetylated salicylates are COX-1 sparing, and, in principle, at therapeutic doses should have the same potential to impart CV complications as other NSAIDs. We strongly recommend to the AHA that this non-evidence-based recommendation, together with the recommendation that high-dose aspirin be administered alone, be withdrawn as recommendations for first line therapy for patients with chronic pain and arthritis.

In the AHA document, coxibs are recommended as a last therapeutic approach. The authors also suggest that NS NSAIDs can be differentiated as to CV toxicity on the basis of *in vitro* COX-2 to COX-1 inhibition ratios. Data do not exist at this time that would allow transposition of these ratios to clinically observed CV events. Indeed, the weight of the clinical evidence indicates that we cannot differentiate CV risk among the currently available NSAIDs, except possibly high-dose naproxen and lower dose celecoxib. Accordingly, recommendation of the use of NS NSAIDs prior to the use of COX-2 selective agents lacks clinical support, particularly in the patient at increased risk for a serious upper GI adverse event. As these authors note, even a relative lack of COX selectivity does not completely eliminate the risk of CV events, and, accordingly, all drugs in the NSAID spectrum require prescription only after thorough consideration of the risk/benefit balance.

Additionally, the AHA statement suggested early use of opioids more often and before use of NSAIDs in OA patients. Although short-term use of opioids for severely painful exacerbations is not unreasonable, use of long-term opioids is not recommended for chronic non-cancer pain by either the American Pain Society or the American Academy of Pain Management. Further, the fact that patients with OA tend to be older and, accordingly more predisposed to opioid-related adverse events including constipation, dizziness, confusion and central nervous system toxicity related to dysphoria, risk of falls and, consequently, risk of hip fracture militates against their routine use.

Prospective studies to evaluate CV risk are underway. The Standard Care Celecoxib Outcome Trial (SCOTT) has been designed utilizing the so-called Streamline Safety model study. The trial will identify subjects taken chronic NSAIDs in the setting of primary care practices, and will randomize consenting subjects to continue to receive standard

care or celecoxib. Trial medication will be supplied by prescription; prescribing will be tracked by capturing prescribing data from primary care computer systems. The primary endpoint will be CV events and upper GI hemorrhage. This trial is intended to provide data on CV safety using celecoxib vs standard care NSAIDs in the European Union indicated population. Participants will be free of established CV disease on entry.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen (PRECISION) Trial has been designed to compare CV and GI events related to the use of celecoxib, naproxen and ibuprofen in patients with moderate CV risk. Approximately 20,000 patients will be evaluated in a trial whose outcome includes MI, stroke or death. Up to two-thirds of the individuals will be taking low-dose aspirin prophylaxis; one-third will be non-users of aspirin. The trial, which will extend for 3 years or longer, will not have a placebo—control group given the difficulty of maintaining individuals in a study for this period of time without some form of continuous pharmacologic therapy. Accordingly, it may be difficult to evaluate the results of this investigation in the event that all three agents have equal number of CV events. Should one of the agents appear to be superior, one will still not be able to ascertain whether that agent has more risk than no therapy alone. All patients will receive a PPI as part of baseline therapy. Patients recruited in the study will have to have a history of increased CV risk factors such as hypertension, diabetes, hypercholesterolemia and the like. Daily doses of medication may be varied but should not exceed 400 mg of celecoxib, 1000 mg of naproxen, or 2400 mg of ibuprofen. Patients will be instructed to take their medication 2 h or more after low-dose aspirin. Although, as noted, this study has inherent problems with respect to lack of a placebo—control group, as well as the potential for increased risk of individuals being administered NS NSAIDs which may affect aspirin prophylaxis, the study should provide important information which will help us address important, often controversial issues.

The OARSI has appointed a Guidelines Committee to define recommendations for the treatment of OA that would have international acceptance. These guidelines are based on a systematic review of the literature delineating evidence-based information covering therapeutic modalities, which are used in OA treatment. Publication of these guidelines is anticipated for late summer or autumn 2007. Although the guidelines have not been finalized, there is concurrence that both nonselective and selective NSAIDs have a major role in the management of OA. Use of any therapeutic agent needs to be based on effectiveness, a combination of efficacy and risks, individualized to take into account the needs of each specific patient. “Treatment paralysis” wherein we send the patient out of the office in pain based on risk concerns needs to be avoided to the degree feasible. The importance of evaluation of risk and the concept of “First, do no harm” should always be uppermost in the physician’s mind. Accordingly, any agent, when possible, should be used at the lowest possible dose for the shortest possible time — this is true not only of NSAIDs and coxibs, but for any drug being used for any purpose. Patients in pain experience not only pain but also functional loss and psychologic stress. Although risks, including both GI and CV adverse events are not to be considered lightly, relief of pain with its resultant improved quality of life may outweigh associated therapeutic risk. Only the patient, armed with knowledge of the risk/benefit ratio can make

the final decision—not always an easy one. In medicine, as in life, the wind is not always at one’s back!

Disclosures

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