The COX-2 inhibitors:
a reasoned review of the data

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Summary

The recent press coverage of the issues surrounding non steroidal anti-inflammatory drugs and the selective COX-2 inhibitors has not allowed for an informed debate to take place regarding the therapeutic risk to benefit ratio of these drugs. The overall discussions that have taken place within the context of the regulatory decision process has been mostly proprietary and thus not made public and the resultant decisions have not been prominantly featured in the popular press so have not gotten the attention of the practicing clinician or the patients who use these drugs. This paper will review the evidence that has been accumulated and highlight the decisions that have been made by some of the regulatory groups to address the issues surrounding overall benefit to risk of the NSAIDs inclusive the COX-2 selective inhibitors.

Key words: non steroidal anti-inflammatory drugs; COX-2 selective inhibitors; hypertension; cardiovascular effects

Until recently the nonsteroidal antiinflammatory drugs (NSAIDs) included some of the most commonly used drugs throughout the world. Each year, in the US, health care providers wrote approximately 60 million prescriptions for various forms of NSAIDs with those written for the elderly approximately 3.6 times those that are written for the younger population. These drugs have been proven to be effective in the treatment of acute and chronic painful and inflammatory musculoskeletal conditions. At least 20 non selective NSAIDs (NS-NSAIDs) are available including aspirin and the various formulations of the non-acetylated salicylates and the non-salicylate NSAIDs as well as COX-2 selective inhibitors [1–4]. Currently, there are NS-NSAIDs as well as aspirin available as over the counter products. Due to the widespread use of NSAIDs, the inherently low incidence of both NS-NSAID-induced adverse effects involving the gastrointestinal (GI) tract and the cardiovascular system risk noted with both the NS-NSAIDs and the COX-2 selective inhibitors, these safety issues become a significantly larger problem for consideration. Increased use of NS-NSAIDs in an aging population in the developed world will increase the number of potential adverse events putatively ascribed to NSAID use. It has been estimated that from 5 to 7 percent of hospital admissions are related to adverse effects of drugs, and of these hospitalizations, those that result from gastrointestinal, nervous system, renal, or allergic effects of aspirin or non-aspirin NS-NSAIDs are responsible for approximately 30 percent [5].

Most of the presently available NS-NSAIDs were approved many years ago by regulatory authorities and as a result their referenced data bases reflected in their approval are paltry in comparison to the accumulated evidence regarding efficacy and safety of the COX-2 selective drugs especially prior to registration. Thus it is not surprising that when studied with more contemporary approaches more issues of safety arise with the NS-NSAIDs. We may never know the full extent of problems with the NSAIDs unless there is a concerted effort by regulatory groups around the world to coordinate activities so that both the older drugs as well as the new selective COX-2 inhibitors can be studied in similar fashion.

The questions regarding clinically important risk for thromboembolic events began early in the study of the COX-2 selective agents. With non clinical (preclinical) observations that COX-2 activity had important roles in regulating kidney blood flow, salt and water handling in the kidney, as well as the possibility that the majority of systemic prostacyclins are a product of COX-2 action led to the incorporation of secondary outcomes into clinical efficacy and safety trials which would investigate presence of cardiovascular effects within longer term trials [1–4].

One trial that began the serious debate was the

Vioxx Gastrointestinal Outcomes Research (VIGOR) trial [6] which was designed to investigate the GI safety of rofecoxib in patients with rheumatoid arthritis. Patients taking low-dose aspirin were excluded. The total exposure to rofecoxib at 2–4 times the treating dose for OA and RA was about 3,947 patient-years vs 3,078 patient-years of exposure to the comparator naproxen at 500 mgs BID. The mean patient exposure was 9 months. After about 80 days of drug exposure and then continuing throughout the trial, statistically more thromboembolic cardiovascular events, as a secondary outcome, occurred in those receiving rofecoxib 50 mg daily compared with naproxen 500 mg twice a day; the incidence of non lethal myocardial infarction was 0.5% vs 0.1% respectively [6].

However, in another long term GI outcome trial, CLASS [7], no similar differences in cardiovascular or cerebrovascular event rates were observed between the celecoxib at 2–4 times the approved treatment dose for RA and OA compared with the effects of two NS-NSAID treatment groups (diclofenac 75 mg twice a day with 1,081 patient-years of exposure; and ibuprofen 800 mg three times a day with 1,123 years of patient exposure), regardless of aspirin use. Why was celecoxib, with similar level of inhibition of COX-2 activity within the therapeutic window as rofecoxib, not associated with more events, even at the higher dosage (400 mg twice a day)? A suggested explanation was there were fewer patient-years of exposure in CLASS than in VIGOR; another was that the CLASS population had lower risk for thromboembolic cardiovascular events overall, as most patients had osteoarthritis, although in that they were older they were at a reasonable CV risk. Possibly, this difference in observed effects was related to other physiologic effects of rofeccoxib such as those changes which lead to increased risk of hypertension and edema which might have increased the CV thromboembolic risk in patients treated with this COX-2 inhibitor.

Why did more patients have a myocardial infarction with rofecoxib than with naproxen? A possible explanation is that rofecoxib induced a prothrombotic state by inhibiting the vasodilating effects of endothelial prostaglandin I_2 without affecting thromboxane A_2 (a product of platelet COX-1 activity), resulting in an unbalanced prothrombotic state in patients at risk. An alternative hypothesis is that naproxen, which has a long half-life, inhibited platelet thromboxane A_2 synthesis by COX-1 sufficiently to be cardioprotective. A third possibility is that bad luck accounted for these findings, particularly in view of the low overall risk in the study population. Or a combination of these factors may have been responsible [8–17].

These observations prompted the developers of both celecoxib and rofecoxib to support multiple epidemiologic studies and meta-analyses of the data which encompassed the new drug applications and post marketing studies for evidence of increased cardiovascular risk with COX-2 selective agents. Meta-analyses of the new drug application databases for rofecoxib, celecoxib and valdecoxib did not reveal increased risk, although the trials included were by design of short duration, had multiple comparator NSAIDs (also short exposure), had very short term placebo exposure if present at all, were conducted in more patients with osteoarthritis than rheumatoid arthritis, and used COX-2 agents at recommended doses rather than those used in CLASS and VIGOR, 2–4 times the treatment dose [18–24]

During the early period of availability of these drugs, celecoxib was approved for use in the treatment of familial adenomatous polyposis at a dose of 400 mg twice a day. Thus, long-term studies designed to compare either rofecoxib 25 mg daily (APPROVe trial) or celecoxib 200 or 400 mg BID (APC trial) or 400 mg daily (preSAP) vs placebo for prevention of subsequent spontaneous polyp formation were begun which would lead hopefully to a new indication for these drugs. These studies were designed to look at polyp outcomes but because they were prevention trials true placebo was allowed. The trials were all designed to be long term, for at least 3 years and both sponsors agreed to study cardiovascular events as secondary outcomes and outcome adjudication committees were established. The APPROVe trial demonstrated as a secondary outcome an increased risk for sudden cardiac death, stroke and acute myocardial infarction induced by rofecoxib 25 mgs per day compared with the effects of placebo. These differences in the data became evident at 18 months of therapy [25–28]. Announcements have described variable results with celecoxib in long term outcome trials studying the effects of these drugs in either Alzheimer patients or in patients studied for recurrent colonic polyp formation. These data in higher risk patients in the Alzheimer's studies showed no risk for celecoxib but in two studies in the colonic polyp studies (APC, preSAP) there was demonstrated a relative risk increase of 3.4 fold with celecoxib compared to the effects of placebo for cardiovascular thromboembolic events and congestive heart failure at a 400 mgs BID dosing schedule, but a 200 mgs BID arm was not statistically associated with more similar cardiac events although there was a clear numerical trend, while another colonic polyp prevention study (preSAP) demonstrated no risk with a 400 mgs q day dosing schedule compared with placebo. These data revealed a composite cardiovascular end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure in the APC trial in 7 of 679 patients in the placebo group (1.0 percent), as compared with 16 of 685 patients receiving 200 mg of celecoxib twice daily (2.3 percent; hazard ratio, 2.3; 95 percent confidence interval, 0.9 to 5.5) and with 23 of 671 patients receiving 400 mg of celecoxib twice daily (3.4 percent; hazard ratio, 3.4; 95 percent confidence interval, 1.4 to 7.8) [29].

The composite outcome used in the celecoxib trials was different from that used in the Merck sponsored APPROVe trial [26–29]. Adding in CHF to the CV thromboembolic events in the celecoxib trials changes the hypothetical explanation from a prothrombotic state to a clinical situation in which there is also the potential for increased left ventricular strain in the correct patient [32–38]. This is likely due to the complex physiological effects including fluid and salt retention, evolving increases in systolic hypertension, as well as some effects on the endothelium accrued over time. The possibility arises that these events are also observed with the non selective NSAIDs as demonstrated in the CV outcomes noted in the CLASS trial described previously [7,18]. Furthermore, the number of events is small, the outcomes are secondary outcomes and the trials were not powered to look at cardiovascular events in a rigorous way. We are still awaiting final analysis to determine whether there was also important efficacy with inhibition of recurrent colonic polyps with the COX-2 selective drugs.

To further complicate matters, the studies of paracoxib, an IV form of valdecoxib in patients at extremely high risk for CV events, those patients treated almost immediately post coronary artery bypass graft surgery revealed that this COX-2 selective inhibitor at high dose was associated with an increased risk for myocardial infarction, stroke and sudden death [39, 40] despite the concomitant use of low dose prophylactic doses of aspirin. Unfortunately, due to the unique designs of the trials and the variable use of the cardiac bypass pump in the first of two trials, the different dosage schedules in each of the two trials, variability in the background standard of care, and other issues, it is hard to interpret these data other than to suggest that in such high risk patients it would not be prudent to use this IV COX-2 inhibitor in those types of patients. Whether it is appropriate to extrapolate the effects of this COX-2 inhibitor in these specific patients to the use of valdecoxib chronically at much lower doses in diseases such as osteoarthritis and rheumatoid arthritis is unknown.

These above noted experiments are powerful studies in that they are randomized and placebo controlled; however, they are in different patient populations than those patients who are clinically chronically using these drugs. Thus pharmacoepidemiologic trials become important to evaluate the possible outcomes in more traditional patients and at doses that are typically prescribed, such as those that are both lower and more intermittent. Initial studies by Rahme et al. [41] and Solomon et al. [42] and others [43] failed to show differences in risk for cardiovascular events with rofecoxib and suggested that this was possibly due to the protective effects of naproxen. However, other epidemiologic studies failed to show a protective effect for naproxen or other NS-NSAIDs.

Two subsequent large observational cohort studies found doses of rofecoxib higher than 25 mg daily to be associated with increased risk for cardiovascular events. Ray et al. [44] studied the Tennessee Medicaid database and found an odds ratio of 1.7 for acute myocardial infarction with doses of rofecoxib larger than 25 mg daily compared with ibuprofen. This risk was observed specifically in new users, ie, patients taking rofecoxib for less than 90 days – a predetermined outcome. Solomon et al. [45] analyzed a Medicare database from New Jersey and Pennsylvania and identified an increased relative risk for acute myocardial infarction with rofecoxib doses greater than 25 mg daily compared with celecoxib and traditional NSAIDs, again over the first 90 days of use, but not thereafter. Other studies showed variable results but mostly agreed with the observations that high dose rofecoxib was associated with an increased risk for CV outcomes [46–50]. Yet a third cohort study, a collaborative study by the US Food and Drug Administration and Kaiser Permanente, examined cardiovascular outcomes in approximately 1.4 million patients receiving nonselective NSAIDs or selective COX-2 inhibitors [51]. Doses of rofecoxib higher than 25 mg/day were associated with a more than threefold higher incidence of acute myocardial infarction and sudden cardiac death compared with nonselective NSAIDs or other selective COX-2 inhibitors. There was again no risk observed with celecoxib. Of interest, in the Medicaid, medicare and Kaiser Permanente databases the incidence of acute myocardial infarction with celecoxib treatment was lower than with the other agents [44, 45, 51] And in the Kaiser Permanente analysis, naproxen was associated with an increased risk of thromboembolic cardiovascular events (relative risk [RR] 1.18, 95% confidence interval [CI] 1.04–1.35; P = 0.01), as was indomethacin (RR 1.33, 95% CI 1.09–1.63; P = 0.005) two well understood NS-NSAIDs with functionally long effects on inhibition of both COX-1 and COX-2.

These data were surprising and confounded the "imbalance hypothesis" that COX-2 inhibition without concomitant inhibition of COX-1 activity in the right patient might lead to an imbalance and as risk for thrombosis thrombosis. These data suggested that even with inhibition of COX-1 activity, COX-2 inhibition in some fashion led to an increased risk for thromboembolic complications. This latter hypothesis was first considered after a report by Crofford and others suggested a clinically observed increased risk for thrombosis [52, 53]. Yet other studies demonstrated that COX-1 inhibition as observed with NS-NSAIDs did not lead to cardioprotection. This last observation was supported by the FDA Kaiser Permanente data [51]. It still remains accepted that low dose aspirin is useful to prevent secondary and perhaps primary CV outcomes but may not prevent those events when associated with the use of the COX-2 selective inhibitor [54–56].

In addition to these epidemiologic analyses, more robust data sets from clinical trials and new drug application summaries of both celecoxib and

rofecoxib demonstrate a dose-related effect of rofecoxib on raising blood pressure and causing edema, not apparent with celecoxib at any dose. Therapeutic doses of both celecoxib and rofecoxib are associated with approximately a 2% incidence of hypertension and edema, not different from that observed with the NS-NSAIDs. However, a dose response for increased hypertension and edema is particularly evident with rofecoxib at 50 mg daily [30, 57, 58].

Patients with treated hypertension may have elevated levels of angiotensin II and norepinephrine. These vasoconstrictors increase the release of vasodilator prostaglandins from the kidney, which act locally to minimize the degree of renal ischemia [35, 60]. When this compensatory response is inhibited by an NSAID, the increase in renal and systemic vascular resistance can cause an elevation in blood pressure. This effect can generally be induced by any NS-NSAID (including over-the-counter ibuprofen). Typically, the NS-NSAID-induced or COX-2 selective induced blood pressure changes are small; in one meta-analysis the mean rise in supine blood pressure was 5.0 mm Hg [22]. NSAIDs antagonized the antihypertensive effect of beta blockers (blood pressure elevation 6.2 mm Hg) more than vasodilators and diuretics in this report. Piroxicam produced the most marked elevation in blood pressure (6.2 mm Hg), while sulindac and aspirin had the least hypertensive effect. The consequences of these modest increases in blood pressure in patients taking NSAIDs have not been specifically studied. However, a 5 to 6 mm Hg elevation in blood pressure over several years may be associated with a 67 percent increase in total stroke occurrence and a 15 percent increase in coronary heart disease [35].

Two studies comparing these effects of rofecoxib and celecoxib [32, 60] have recently been confirmed in a randomized controlled trial using continuous ambulatory blood pressure monitoring [36]. In hypertensive patients (treated with various antihypertensive drugs including angiotensin-converting enzyme inhibitors) who have osteoarthritis, both agents cause an increase in systolic and diastolic blood pressure, which is more pronounced with rofecoxib. The subsequent ambulatory blood pressure monitoring trial was a trial that compared the effects of celecoxib 200 mg, rofecoxib 25 mg, and naproxen 500 mg twice a day in hypertensive diabetic patients with osteoarthritis on treatment for high blood pressure [36]. At 6 weeks, there was a sustained increase in systolic blood pressure of about 4.2 mm Hg with rofecoxib, but no rise with naproxen or celecoxib. Although there is no evidence that these increases in blood pressure are associated with short-term increases in risk for acute myocardial infarctions, there is clear evidence that sustained increases in blood pressure are associated with ischemic cardiac events and stroke [35].

Treatment with valdecoxib, approved for use at 10 and 20 mg/day, appears to be associated with a higher incidence of hypertension and edema at doses of 40 and 80 mg/day. The new drug application database has not revealed an increased risk for thromboembolic cardiovascular events, although it is smaller and does not include a large outcome trial similar to CLASS or VIGOR [37]

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) [61] demonstrated no statistically significant increased risk for cardiovascular events with the selective COX-2 inhibitor lumiracoxib. Although numerically higher than in the group receiving naproxen, the overall incidence of these events was quite low.

Potential differences in these observed cardiovascular outcomes with the selective COX-2 inhibitors may be due to differences in the drugs' molecular structures, pharmacokinetics, and pharmacodynamics. Celecoxib and valdecoxib are sulfonamides; celecoxib has a halogenated side chain. Rofecoxib is a sulfone with a halogen-containing ring structure. The half-life of rofecoxib is more than 17 hours compared with approximately 11 hours for celecoxib and 8 hours for valdecoxib. Of course, further supportive of half life exposure as important in this regard, is the data from the two colonic polyp outcome trials with celecoxib. These data demonstrate that the trial with BID dosing separated statistically and importantly with at least a 2.5 fold increased relative risk for MI, stroke and CV death from placebo; whereas the trial with only q day celecoxib therapy revealed no increased risk for these events. However, the Alzheimer's trial also used a BID dose of celecoxib and as of yet did not reveal an increased relative risk.

Much has been said about the "differential selectivity" of rofecoxib, celecoxib, and valdecoxib for inhibition of COX-2 vs COX-1 activity, although in vitro and ex vivo assays employing different molecular targets may not accurately reflect in vivo effects. Regardless, each of these agents effectively and selectively inhibits COX-2 activity when used in approved therapeutic doses, and none affects in vivo platelet aggregation at any recommended dose.

Whether these differences in molecular structure and pharmacodynamics can translate into differences in clinical effects such as hypertension and edema is unknown. Furthermore, the exact biology that may explain the observed increased risk for thromboembolic cardiovascular events with at least some COX-2-selective inhibitors is unknown. The data accumulated to date, would suggest that is likely that all non selective NSAIDs and the selective NSAIDs all to variable degrees put the patients who are at risk at potential increased risk for a CV thromboembolic event. The exact cause is unknown but likely due to the interaction with COX-2 activity and may be modified by the half life of the inhibition, the extent of hypertension and or edema that might develop which may alter left ventricular load, as well as other potential changes induced by physicochemical properties of the various drugs. It is likely the pharmaco-epi-

demiology studies did not show much risk is the fact that the events are rare with these drugs yet the cardiovascular events are common in the same population without these therapeutic agents.

In June, 2005, the US FDA published the requirements for the new warnings for all NS-NSAIDs and the available COX-2 selective inhibitors within the US. These required changes include a boxed warning which would highlight the potential for increased risk of cardiovascular events and serious life threatening gastrointestinal bleeding events. In addition, a medication guide describing the risk of all NSAIDs written in lay language would be required for patients. This action further supports the notion that the inhibition of COX-2 activity by NS-NSAIDs and COX-2 selective inhibitors places a patient at increased risk for a CV thromboembolic event, or some other CV event including congestive heart failure. This risk then has to be balanced against the relative decreased GI risk associated with the use of the COX-2 selective inhibitors as compared with the NS-NSAIDs. It is clear that the development of the COX-2 selective inhibitors has been an advance over the NS-NSAIDs in the terms of GI safety [62–64]. Newer trials and review data continue to demonstrate this observation [65–67]. With the clear understanding that all drugs which inhibit COX-2 activity, both COX-2 selective inhibitors and the NS-NSAIDs, may increase the risk for thromboembolic events thru very complex physiologic and pathologic mechanisms, there remains the important clinical decision making process which should reside with the patient and their health care provider in deciding which therapies are most important for their unique problem.

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