# ‘COX-2 Safety’
# Many Questions-Some Answers

Number 71 September, 2002

Given the prevalence of arthritic/musculoskeletal and cardiovascular disease (CVD) and use of NSAIDS or COX-2 inhibitors for treatment, a large, event-driven, properly powered trial of COX-2 inhibitors is needed to prove their CV and GI safety compared to NSAIDS. This *Heartbeat* will discuss the recent COX-2 controversy, including mechanism of action, and provide a plan of action until many questions are resolved and further study is completed.

## Background

Complications, mostly gastrointestinal (GI), associated with the long-term use of non-steroidal anti-inflammatory drugs (NSAIDS)—cyclooxygenase (COX) inhibitors—are common and have a major impact on patient care because of the large numbers of patients who take them. The GI toxicity appears to be related to COX-I inhibition, which predominates in the gastric mucosa and yields protective prostaglandin. COX-2 is induced by inflammation and leads to pain, swelling, and discomfort. The discovery that inhibition of COX-2 has little impact on GI mucosal integrity has made it possible to treat patients who require anti-inflammatory medication without precipitating the same degree of GI toxicity associated with COX-1 inhibition.

## Caution

Recently, a “cautionary flag” has been raised, regarding an association between COX-2 inhibition and a higher risk of cardiovascular disease (CVD) events than that seen with traditional NSAIDS. This has caused many to speculate as to how COX-2 inhibition might increase CVD risk and whether there is any difference among the available COX-2 inhibitors (coxibs) in this regard.

Results from a retrospective review of the **V**ioxx (rofecoxib - Merck) **G**astrointestinal **O**utcomes **R**esearch Study **(VIGOR**; 8076 patients) and the **C**elecoxib (Celebrex – Pfizer) **L**ong –term **A**rthritis **S**afety **S**tudy (**CLASS**; 8059 patients) found that the predicted annual myocardial infarction (MI) rates, 0.74% (VIGOR) and 0.80% (CLASS), were higher than the 0.52% MI rate in a large cohort of placebo patients included in a meta-analysis of primary CV prevention trials.[1] In VIGOR, the relative risk of a CV thrombotic event was significantly higher with rofecoxib (2.38) compared with naproxen (Naprosyn), while in CLASS there was no significant difference in CV event rate between celecoxib and NSAIDS. Two other smaller studies of rofecoxib, which allowed the use of low dose aspirin (ASA), also were reviewed and did not demonstrate the increase in CV event rate noted in VIGOR.

## Theoretical Arguments

Traditional NSAIDS inhibit both COX-1 and COX-2 isoforms and have no effect on the “thrombotic balance.” They inhibit thromboxane, a platelet activator whose action is controlled by COX-1, and prostacylin, a platelet inhibitor whose action is controlled by COX-2. The coxibs only inhibit COX-2, thereby suppressing prostacyclin but not thromboxane formation. This possibly shifts the thrombotic balance

toward the pro-thrombotic state, which may lead to increased CV thrombotic events. Assuming this hypothesis is correct, the effect of COX-2 therapy would be similar to an at-risk population not taking aspirin.

In contrast, atherothrombotic CVD is thought to be a disease that is triggered—and probably exacerbated—by inflammation. The anti-inflammatory effects of coxibs could prove anti-atherogenic over time, resulting in decreased CV events.

## Questions

If the anti-inflammatory hypothesis is correct, how can we explain the increased CVD events in VIGOR and CLASS compared to primary prevention trials and the reported excess of CVD events with rofecoxib compared with naproxen in the VIGOR trial?

The small number of events, which occurred in both trials, as well as heterogeneous patient populations and methodological issues, result in a degree of uncertainty over whether the results reflect actual risk. Considerable uncertainty always remains in any post-hoc analysis. All the patients in VIGOR had rheumatoid arthritis (RA), and it has been established that RA patients have a higher risk of MI.[2] CV events were significantly higher in VIGOR patients who would have been on ASA had it been allowed. By contrast ~25% of CLASS patients took ASA, probably reducing any potential prothrombotic risk associated with celecoxib.

The reported excess of MI associated with rofecoxib compared to naproxen in VIGOR could have been the result of the anti-platelet effect of naproxen decreasing CV risk rather than the prothrombotic effect of rofecoxib increasing risk. This increased anti-platelet effect of naproxen compared to the NSAIDS used in CLASS (diclofenac and ibuprofen), along with ASA usage, could also explain the lack of a significant increase in CV event rates when NSAIDS were compared to celecoxib.

Another question, which remains unanswered, is whether co-administration of low-dose ASA cancels the favorable (less propensity for GI toxicity) or the unfavorable (greater prothrombotic potential) effects of COX-2 inhibitors. Further study is needed.

If the coxibs do have an adverse effect on CV risk as a result of their ability to shift prostacyclin and thromboxane balance towards the prothrombotic state, it should be a class effect because both coxibs inhibit COX-2. However, rofecoxib is a more specific inhibitor of COX-2, possibly accounting for its slightly higher CV risk compared to celecoxib. Rofecoxib's superior specificity is supported by the GI safety profiles. The GI safety profile for rofecoxib over naproxen was incontrovertibly demonstrated in VIGOR. In contrast, in CLASS, the primary endpoint did not reach statistical significance, but the combined GI side effects were lower in celecoxib patients compared with NSAIDS as long as they weren't taking ASA. It is also important to remember that at higher doses coxibs may inhibit COX-1, and this could explain increased GI side effects.

## More Studies

What makes all of this even more relevant is the new or pending release of more coxibs:….

(Arcoxia –Merck)
Valdecoxib (Bextra – Pfizer), released 4-02
Parecoxib (Dynastat – Pfizer)

In a recent study of etoricoxib from Johns Hopkins Medical Institutions, the authors conclude that 90mg once daily was more effective than either placebo or naproxen 500mg daily for treating patients with RA over 12 weeks.[3] In an accompanying editorial, Dr Richard Day (St Vincent's Hospital, Sydney, Australia) describes the findings of VIGOR and

CLASS and the fact that the FDA has required a cautionary statement on the label for rofecoxib with regard to CV safety.[4] He also notes important exclusions in the etoricoxib study. There were 2 confirmed adjudicated CV adverse events—a TIA and a non-Q wave MI—both occurring in the patients taking etoricoxib. The following patients were excluded from the study: those with a history of angina, heart failure, MI or coronary intervention within the past year, or stroke or TIA within the last 2 years.

Day concludes that large, event-driven, properly powered, randomized controlled clinical trials are needed of COX-2 inhibitors versus NSAIDS using maximal clinically relevant doses to prove both GI and CV safety.

## Conclusions/Recommendations

Results from the *JAMA* meta-analysis are thought provoking and hypothesis generating, but really don't supply all the answers. The availability of selective COX-2 inhibitors has raised several important clinical questions. These concern the prothrombotic potential of COX-2 inhibitors, differences in the anti-thrombotic effect of various NSAIDS, the mandatory use of ASA with COX-2 inhibitors—especially in high-risk patients—and whether simultaneous use of ASA negates the GI protective effect of selective COX-2 inhibitors.

Until more data is available, physicians should assess the evidence supporting the various perspectives and balance these perspectives against their own clinical judgment and experience. When a COX-2 inhibitor is needed for symptomatic control of musculoskeletal symptoms, physicians should weigh the GI benefits of using a COX-2 inhibitor against the risk of using an NSAID, particularly in higher risk patients. *Co-administration of baby ASA is strongly recommended for patients who require prophylactic ASA for appropriate cardio protective indications in those in whom a COX-2 is chosen.*

BP control in hypertensive patients may be attenuated by concomitant use of a coxib, but these increases do not seem to be significantly greater than with NSAIDS and probably don't contribute to increased CV events. *Carefully monitoring BP in all hypertensive patients after initiation of either coxibs or NSAIDS is strongly recommended.*

Similarly, close monitoring of renal and hepatic function is recommended for those at risk (elderly, azotemic, heart failure or diabetic patients) after treatment with either NSAIDS or coxibs.

In contrast to NSAIDS, coxibs can be used more safely with warfarin and anti-thrombotic agents, but close monitoring is still warranted.

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[1] Mukherjee D, et al. Risk of cardiovascular events associated with selective COX II inhibitors. *JAMA* 2001; 286: 954-59.

[2] Wallberg-Jonsson S, et al. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis: a retrospective cohort study from disease onset. *J Rheumatol* 1999; 26: 2562-71.

[3] Matsumoto AK, et al. A randomized, controlled trial of etoricoxib in the treatment of rheumatoid arthritis. *J Rheumatol* 2002; 29: 1623-30.

[4] Day R. Another selective COX-2 inhibitor: More questions than answers? *J Rheumatol* 2002; 29: 1581-82.