Speculation regarding Vioxx, Celebrex, and Naprosyn, including the recent sequence of events

The following represents an informal review of these issues. An initial discussion of COX-2 inhibitors is followed by a discussion of issues relating to naproxen (Naprosyn).

There has been considerable interest in the unfolding of the events and the knowledge base regarding selective COX-2 inhibitors and cardiovascular risk. The following is an impression on how these events have developed and the status of the current situation.

There were some very early publications raising the possibility of increased cardiovascular risk with selective COX-2 inhibition on the basis of some basic science mechanistic issues. (Vioxx, Celebrex, and Bextra are all in the class of drugs called selective COX-2 inhibitors.) At the time of those early publications, there was not much emphasis on this viewpoint in the medical community. There were a significant number of academic physicians at that time who though that there might be a *decrease* in cardiovascular risk with selective COX-2 inhibition. This was on the basis that selective COX-2 inhibition can decrease inflammation (including lower CRP levels) which could conceivably overpower over any theoretical negative effects of increased clotting resulting in a net reduction in cardiovascular risk. In retrospect, this appears incorrect. **Unfortunately, considerations of basic science mechanisms, until supported by at least some trends in patient data, are not extremely reliable.**

As an example of the lack of surety of considerations simply based solely on a theoretical viewpoint, consider the following. When the clot dissolving medicine called tPA (which is used for treating heart attacks) came out, it was thought mechanistically to have the potential for less bleeding complications than prior medications. This was because tPA was thought to be more selectively directed towards the fresh clot present in patients with a heart attack. As it turned out, this was incorrect. Studies later showed that while tPA was slightly more efficacious than the prior medication, tPA was also was actually associated with an *increased* risk of bleeding complications, rather than a decreased risk.

A very major event regarding the issue of an increase in cardiovascular risk

with COX-2 inhibitors was the publication of the VIGOR[1] trial in 2000. The VIGOR trial was a randomized trial comparing Vioxx (rofecoxib) to naproxen (a generic version of Naprosyn) in 8000 patients with rheumatoid arthritis to assess for the occurrence of gastrointestinal toxicity. **The VIGOR trial unexpectedly showed a higher event rate of adverse cardiovascular events such as heart attacks in the group treated with Vioxx.** Patients requiring aspirin for cardiac events were excluded. Aspirin use was avoided in either treatment arm of the trial as per trial protocol. The VIGOR trial results were a major finding and of considerable concern.

Some very astute clinicians and researchers recognized this significant potential for harm and published their concerns in a JAMA article[2] in 2001. The issue was quite pertinent because the use of Vioxx and Celebrex had rapidly become quite widespread. There were even cardiovascular programs at the time using COX-2 inhibitors for routine post operative care in an attempt to decrease the gastrointestinal problems that occur in some patients with standard nonsteroidal inflammatory medications (NSAID- such as Naprosyn-naproxen, Motrin-ibuprofen, etc.) Perhaps, observant clinicians even directly recognized problems with fluid retention and suggestions of an increased cardiovascular complication rate in this clinical setting.

The VIGOR trial[1] as previously mentioned showed an increase in adverse cardiac events with Vioxx. Nevertheless, the issue remained quite unclear on the basis of the information available at the time because of the nature of the VIGOR study. **The VIGOR study was not a simple randomization of Vioxx vs. placebo. The VIGOR trial compared Vioxx to naproxen (Naprosyn) and naproxen has significant antiplatelet effects.** One consideration at the time was whether the antiplatelet effects of naproxen led to an improved outcome with naproxen, rather than there being an adverse effect with Vioxx to explain the findings of the VIGOR trial. **As it later turned out, Nissen, Topol, et al[2] were insightful and correct that Vioxx did have a significant increase in adverse cardiovascular events including heart attacks.** This web site looks at a separate statistical issue in that report regarding Celebrex that is dwarfed in importance by the positive contribution this article made to the medical community. (The type of statistical analysis used by the authors in the JAMA 2001 article in an attempt to implicate Celebrex on the basis of the CLASS trial[3] was not reliable. The most direct concern at the time (2001) in regards to Celebrex was that Celebrex is in the same class of drugs as Vioxx and if Vioxx truly did have adverse effects, Celebrex might have them as well.)

As a clinician practicing at the time, the issue was unclear. Vioxx seemed to behave differently from Celebrex. Vioxx caused considerable fluid retention in a number of patients and was associated with a 5mm increase in blood pressure. (A 5mm increase in BP alone can increase the cardiovascular event

rate, though there are other important potential adverse mechanisms present such as a decrease in the amount of the beneficial prostacyclin in the walls of the blood vessels.) Vioxx also appeared to quite efficacious for arthritic pain. Celebrex, on the other hand, was a weak COX-2 inhibitor and that seemed to behave differently than Vioxx. Though, it was not going to be any surprise if subsequent studies found a higher cardiovascular event rate with Vioxx, it seemed very uncertain whether Celebrex would ultimately be found to have a problem.

There was subsequently the publication in 2003 of a very troubling study[4] where a group of patients following coronary bypass surgery were randomized to a placebo compared to an intravenous COX-2 inhibitor (parecoxib) followed by an oral COX-2 inhibitor (valdecoxib). In this study, there were multiple adverse trends in the patients who received the selective COX-2 inhibitors (parecoxib and valdecoxib). Neither of these agents was released by the FDA in the United States.

In September 2004, there was the very major announcement that a randomized trial examining whether Vioxx compared to placebo was beneficial for gastrointestinal pathology was halted after finding a doubling of confirmed thrombotic events (3.5% with Vioxx vs. 1.9% with placebo) including stroke and heart attack. Vioxx was shortly thereafter pulled from the market. The concerns about Vioxx had been well placed.

In October 2004, Pfizer, the drug manufacturer of Bextra warned physicians that valdecoxib (Bextra) increases the risk of death in heart patients who receive the drug for the management of postoperative pain following cardiac surgery. This documented for the second time an increased cardiovascular adverse event rate with the use of a COX-2 inhibitor in the treatment of patients immediately following cardiac bypass surgery, but this time with Bextra. Clearly, there was an adverse class effect for the COX-2 inhibitors apparent in this clinical situation.

However, at this point it was still unknown whether Celebrex was going to be associated with an increase in adverse cardiovascular events. Prior to the study that led to Vioxx being withdrawn, there had been a number of studies accumulating patients from multiple prior studies that suggested Vioxx was associated with an increase in cardiovascular events, but not implicating Celebrex in the same fashion. Given that Celebrex was a weak COX-2 inhibitor, even if there was an adverse effect, it was possible that only a very large study involving patients at high risk for cardiac events would be sensitive enough to make this determination. (Dr. Topol has been a strong advocate for the need of this type of study to be instituted beginning when the issue arose with the VIGOR study.) There were numerous randomized trials in progress at that time,

but it was not clear whether they had sufficient power and adequate design to detect a problem.

In 2004, the results of a study comparing high dosages of Celebrex (400mg and 800mg) to placebo in a cancer prevention trial revealed a significant increase in adverse cardiovascular rate with Celebrex. (One wonders if the higher dose of this relatively weak selective COX-2 inhibitor, Celebrex, magnifies the potential for adverse effects with Celebrex.)

Now, there was evidence that both Vioxx and Celebrex were found to have a higher risk of heart attacks and other adverse cardiovascular events than placebo. Though the weight of the evidence suggests that this problem is more prominent with Vioxx the more powerful selective COX-2 inhibitor, Celebrex was also found to have a problem in this one randomized study.

In summary, in regards to COX-2 inhibitors, the issue until publication of recent trials did not seem as clear as it does now in retrospect. The saga has been slow to unfold with the type studies that have been previously designed and carried out. Of note, there is an additional randomized trial testing lower doses of Celebrex in patients with prior myocardial infarctions planned that will add further information regarding these issues.

And now, Naprosyn?

Given the events with Vioxx and Celebrex, there is a heightened awareness in the press for any similar event occurring in a medical study. Naproxen, the generic version of Naprosyn, has recently fallen under adverse publicity.

There was an ongoing NIH study involving naproxen (Naprosyn) for the prevention of Alzheimer's disease which was halted in December 2004 which was prior to planned completion. Given the lack of formal published data, the study is difficult to assess, but it was said to have shown a 50% increase in cardiovascular events. Full formal data end point review and data analysis have not yet been completed and fully reported.

Regardless, the preponderance of the prior information on naproxen suggests that an incidental observation that naproxen increases the risk of adverse cardiovascular events will not be accurate for the general population for the following reasons.

Naproxen (Naprosyn) inhibits platelets. Platelet inhibition tends to decrease the rate of heart attacks in patient populations at risk. This is thought to be

the primary basis for the beneficial and protective effect of aspirin.

What can be said about the potential benefits or risks of naproxen at the present time?
Naproxen is a nonsteroidal anti-inflammatory drug (NSAID). It tends to inhibits platelets more than a number of other NSAID drugs.

The platelet inhibition effect of naproxen would actually be expected to decrease the cardiovascular event rate for large segments of the population. For patients not taking aspirin, who do not have problems with congestive failure or a cardiomyopathy (weak heart muscle), naproxen, on a mechanistic basis, would be expected to decrease the adverse cardiovascular events such as heart attacks. (The summation of the prior clinical trials using naproxen is suggestive of a trend for benefit with naproxen as well.)

For patients taking aspirin, the issue is more difficult to predict. Aspirin is a more potent inhibitor of platelets than naproxen. If aspirin and naproxen are both taken chronically, the antiplatelet effects of naproxen are potentially made irrelevant by aspirin.

Up until relatively recently, the literature suggested that the chronic daily intake of low dose aspirin (81 mg) routinely confers the full beneficial effects of aspirin. In contrast, a single dose low dose of aspirin lacks the full antiplatelet effects of aspirin[5]. (The issue of receiving an adequate single dose of aspirin becomes important in emergency cardiac situations. In fact, I have personally made efforts in the literature regarding patients, at the time of a heart attack or an emergency procedure such as balloon angioplasty, receiving an adequate initial dose of aspirin. (See Inadequate dose of aspirin prior to angioplasty and Incorrect article suggesting low dose aspirin is sufficient).

The problem of the whether chronic ingestion of low dose aspirin as well as enteric formulations uniformly gives the full antiplatelet effect of aspirin to all patients has now become apparent. Though small prior studies with healthy controls showed uniform benefit, there has been recent documentation of some patients who do not achieve the full antiplatelet effects possible with low dose aspirin, who then improve with higher doses of aspirin.[6]

For patients at significant risk for heart attacks not taking aspirin, naproxen is likely to be protective. For patients already taking aspirin, it is difficult to predict. Those patients who achieve the full effect of aspirin on platelets are unlikely to benefit from naproxen and it is then possible other less potent adverse effects are dominant.

For the patient group already taking aspirin who achieve only a part of

aspirin's usual inhibitory effect, they could conceivably experience a benefit if naproxen significantly augmented the effect of aspirin on platelets in these patients. However, research is very limited in this area and I am unaware of any definitive studies that speak to this issue.

Finally, there is a group of patients for which naproxen (and other NSAIDs) may potentially worsen cardiovascular outcome. For patients with congestive heart failure (CHF), and possibly other patient subgroups, there has been evidence of some negative mechanistic effects with NSAIDs. There have been no definitive randomized clinical outcome studies specifically addressing this issue that I am aware of, but there is significant reason for concern. It would seem likely from my perspective, particularly for patients with CHF already receiving aspirin, that NSAIDs including naproxen, could be found to have an adverse outcome if a trial is performed with adequate numbers.

Even the net effect of aspirin in patients with congestive heart failure on standard therapy with an ACE inhibitor (a type of medication that can help with congestive heart failure as well as blood pressure) is less clear than desirable. Most likely, there is a significant net positive benefit with aspirin when compared to placebo in these patients. This presumes that the net positive effect of the aspirin's antiplatelet activity outweighs the lessening of the effectiveness of an ACE inhibitor that can occur with aspirin use. However, though probable, this is conjecture because this has not specifically tested by a large randomized clinical trial to my knowledge.

The above review highlights some of the recent events and trial outcome regarding the use of COX-2 inhibitors such as Vioxx and Celebrex and the risk of cardiovascular events. The issues do not always look as straight forward in earlier times, as they do in retrospect, following more definitive studies. The issue of naproxen (Naprosyn) in respect to potential cardiovascular benefit and risk gives a perspective on the complexity of the issues involved. Unfortunately, at this time very preliminary information on topics such as naproxen is making it to the media without the adequate formal reporting of the detailed pertinent trial information. This more detailed information is what allows the medical community the opportunity to effectively evaluate these issues.

In addition, it must be observed, that a number of the viewpoints that have been voiced here are made on a mechanistic basis, which, as noted, is not always a reliable predictor of future outcome.

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1. Bombardier C, Laine L, Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000; 343:1520-1528

2. Risk of cardiovascular events associated with selective COX-2 inhibitors. Mukherjee D, Nissen S, Topol E. JAMA 2001; 286:954-959

3. Silverstein F, Faich G Goldstein J, et al. Gastrointestinal Toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis, the CLASS Study: a randomized controlled trial. JAMA. 2000; 284:1247-1255.

4. Ott E, Nussmeier N, Duke P, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thor CV Surg 2003: 125: 1481-1492

5. Kuster Ll, Frolich JC. Platelet aggregation and thromboxane release induced by arachidonic acid, collagen, ADP, and platelet-activating factor following low dose acetylsalicylic acid in man. Prostaglandins 1986;32:415-423

6. Alberts M, Bergman D, Molner E, et al. Antiplatelet effect of aspirin in patients with cardiovascular disease. Stroke. 2004; 35:175-178