Celebrex (celecoxib)

An Unreliable Cross Trial Comparison in an Otherwise Commendable Study

How the initial article that beneficially raised public awareness of the potential risks of Vioxx and Celebrex was right about Celebrex for the wrong reason.

The 2001 JAMA article[1] which raised the concern of an increased cardiovascular risk with use of the selective COX-2 inhibitors Vioxx and Celebrex was of great benefit to the medical community. However, this initial 2001 JAMA article[1] that brought widespread commendable attention to the potential risk of COX-2 inhibitors used a statistical analysis which did not reliably link Celebrex to an increased cardiovascular risk.

The initial JAMA article consisted of an analysis of the data and implications of two prior randomized trials, the VIGOR trial[2] and the CLASS trial[3]. The JAMA article did not study any new patients, but was an article evaluating and trying to synthesize data from these two previously published trials and other data available from the FDA and prior studies.

The VIGOR trial[2] was a randomized trial comparing rofecoxib (Vioxx) 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 CLASS trial[3] was a randomized trial comparing Celebrex (celecoxib) to Motrin (ibuprofen) or diclofenac in a different 8000 patients**. The CLASS trial study reported in 2000 showed no significant difference in the cardiovascular event rates for Celebrex and ibuprofen and diclofenac.**

This JAMA article did a service to patients and the medical community by raising the issue of the potential for increased cardiovascular events with the use of COX-2 inhibitors. And, as it now appears, Celebrex use as shown in a single

study using high doses of Celebrex (400mg and 800mg) does appear to be associated with a higher risk of events, at least, at these higher doses.

However, this website will analyze only the portion of the JAMA 2001 article[1] that relates to the reliability of cross trial analyses that the authors used to analyze the Celebrex data in the CLASS trial[3]

Unreliable Cross Trial Analysis of the Celebrex Trial:

The 2001 JAMA analysis[1] purported to show that data that regarding Celebrex in the CLASS[3] trial suggested an increase in the occurrence of heart attacks. This particular portion of the analysis was not reliable.

The CLASS trial[3] which studied Celebrex (celecoxib) was analyzed by the JAMA authors[1] in a fashion that was unreliable because the treatment arm of a randomized clinical trial was compared to the placebo arm of completely different trials. What the JAMA article[1] did was compare the frequency of heart attack with Celebrex use in the CLASS trial with the frequency of heart attack in a combined placebo group from three totally different studies. This type of analysis is quite problematic. **A comparison of a treatment group in a randomized study with a placebo group from a different study in regards to side effect incidence does not give reliable information.**

The frequency of adverse events varies greatly with what patient group is studied.

To demonstrate how dependent the frequency of adverse cardiac events is on the type of patients being studied, a closer look within the CLASS[3] trial is all that is needed. Aspirin use was not randomized, but rather used if clinical situation was thought to make that advisable. Patients in the CLASS trial, who had previously been identified by their personal physicians as being at higher risk and warranting the simultaneous administration of aspirin, had a myocardial infarction (heart attack) rate seven times higher than other patients in the trial (14/1645 vs.7/6323)[3]. This was not because aspirin use was adverse in these patients, but rather that these patients were truly at higher preexisting risk.

The preexisting risk of the patients for developing a heart attack overwhelms other factors. Even when close attention is paid to statistically trying to adjust for those differences in risk, it is extremely difficult to do so reliably.

Randomized trials create groups of equal preexisting risk:

One of the reasons that a comparison within a randomized trial is the gold standard is because the preexisting risk of the patient groups can be made equivalent through randomization. A comparison with a large placebo group from a completely different trial does not increase the precision of determining the expected cardiovascular event rate for the particular randomized group of patients studied within the CLASS trial.

Celebrex was found in late 2004 to be associated with an increased risk of MI in a trial using higher dosages of this medication. **However, the reason for concern in regard to Celebrex in 2001 was not this unreliable cross trial analysis, but rather that Celebrex and Vioxx were in the same class of medications.** The JAMA 2001 paper gives an example of a cross trial analysis which is not reliable.

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

2. 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

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.