

Non-steroidal Anti-inflammatory Drugs and Risk of Cardiovascular Events

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis by inhibiting cyclooxygenase, which exists in two isoforms. The cyclooxygenase 1 (COX-1) isoform is constitutively (constantly) expressed in most cells and maintains gastrointestinal mucosal integrity and renal blood flow. The COX-1 isoform is also the only isoform that is expressed in platelets and mediates the production of thromboxane A₂ (TXA₂), a potent platelet activator and aggregator. TXA₂ also mediates vasoconstriction. The COX-2 isoform is induced during periods of inflammation and through the production of prostaglandin, leads to local pain and swelling. The COX-2 isoform also mediates the synthesis of vascular prostacyclin (PGI-2), which is a vasodilator and inhibits platelet aggregation. Non-selective NSAIDs inhibit the production of both thromboxane and PGI-2. Selective COX-2 inhibitors have no effect on thromboxane A₂ production, but by decreasing PGI-2 (vasodilatation and platelet inhibitory prostaglandin) production may potentially lead to an increase in pro-thrombotic and cardiovascular (CV) events. Thus, although the synthesis of COX-2 inhibitors initially was designed to protect the gastric mucosa - which could be affected by non-selective NSAIDs - a decrease of PGI-2 production may also affect the balance between pro-thrombotic and anti-thrombotic eicosanoids. In addition, various agents in each of these classes seem to have variable effect on the relevant enzyme. For example, Naprosyn has significant antiplatelet effects that leads to mean platelet inhibition of 93% compared with 92% for those taking 81 mg of aspirin

daily. Ibuprofen affects platelet aggregation by approximately 80% and diclofenac platelet aggregation by approximately 40%. Similarly, rofecoxib (Vioxx, withdrawn from market in September of 2004) has a much higher relative COX-2 inhibition than valdecoxib (Bextra, withdrawn from the market in 4/05), which is higher than celecoxib (Celebrex). The issue of COX-2 inhibitors in increasing cardiovascular event rates was suggested in two major trials.¹ The VIGOR trial enrolled 8,076 patients. The trial demonstrated a significant increased risk of CV event rates in patients with rheumatoid arthritis randomized to Vioxx 50 mg a day versus Naprosyn 1000 mg per day. The increase in myocardial infarction was increased by a factor of five in this study. Aspirin use, however, was not allowed in this study. The CLASS study enrolled 8,059 patients with osteoarthritis. Patients in the CLASS study received either 400 mg of celecoxib twice daily, 800 mg of Ibuprofen three times daily, or 75 mg of Diclofenac twice daily. Aspirin (less than 325 mg a day) was allowed in this study. In this trial, celecoxib did not demonstrate a significant difference in CV events compared with the use of NSAIDs. In contrast, the placebo controlled Adenoma Prevention with Celecoxib (APC) trial did demonstrate an increased risk of CV events in celecoxib users. Similarly, in the APPROVe study comparing rofecoxib 25 mg a day with placebo in patients with a history of colorectal adenomas, an excess risk of thrombotic cardiovascular events was seen in the rofecoxib group. In one recent study,² women who used non-aspirin NSAIDs or Acetaminophen at high frequency (greater than 22 days a month) or higher doses had a significantly increased risk of major CV events. Of interest is the fact that even Acetaminophen, while weakly inhibiting COX-1 and COX 2, inhibits prostaglandin production and may impair endothelial function. Further concern has been raised in the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT), which was designed to evaluate the potential benefit of long-term Naprosyn use (220 mg twice daily or

celecoxib (200 mg twice daily) versus placebo in reducing the risk of developing Alzheimer's disease in subjects over 70 years of age. There was an increase in CV and cerebral vascular events in the Naprosyn group compared with placebo in the trial suggesting a possible increase in thrombotic events not only with COX-2, but NSAIDs in general. Although no study has prospectively been designed to assess the risk of CV events with selective COX-2 inhibitors, this risk may also extend to non-aspirin NSAIDs and perhaps even other analgesic agents as well. However, these trials were not designed or powered to prove CV safety as a primary end point.

What conclusions can be drawn from the currently available data regarding Cyclooxygenase inhibition and CV risk?

1. Musculoskeletal symptoms should be defined according to the cause (degenerative versus inflammatory) and initial treatment should focus on physical therapy and non-pharmacological approaches.
2. Specific historical patient characteristics should also be considered, such as the risk for GI bleeding where one might choose a proton pump inhibitor in addition to a specific COX inhibitor. Also, the use of Naprosyn appears to be "CV risk neutral". This approach may be safer than low dose celecoxib.
3. Minimizing the duration of NSAID treatment may also decrease the period of risk.
4. It would appear that in patients with an established CV history, such as bypass surgery, unstable angina pectoris or myocardial infarction or cerebral vascular disease, such patients have an increased absolute risk of adverse CV effects when given a COX-2 inhibitor. These agents should, therefore, only be used in the lowest dose for the shortest period of time.

5. The use of low dose aspirin may possibly offer cardioprotective effects when using NSAIDs or selective COX-2 inhibitors, but evidence suggests that Ibuprofen, for example, interferes with aspirin's ability to irreversibly acetylate the platelet COX-1 enzyme and, according to an FDA advisory, patients taking immediate release low dose aspirin and Ibuprofen should take Ibuprofen at least 30 minutes after aspirin ingestion or at least eight hours before aspirin ingestion to avoid any potential interaction. In addition, the anti-thrombotic effects of low dose aspirin may be helpful, but may not necessarily completely ameliorate, the risk of other NSAIDs.
6. Finally, during the treatment with NSAID usage, monitoring the patient for secondary side effects of these agents, such as increasing blood pressure, deterioration of renal function, or GI side effects, must be carefully monitored.³⁻⁸

REFERENCES

1. Mukherjee D, Nissen S, Topol E. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*.2001;286:954-9591.
2. Chan A, Manson J, Albert C, Chae C, Rexrode K, Curhan G, Rimm E, Willett W, Fuchs C. Nonsteroidal anti-inflammatory drugs, Acetaminophen, and the risk of cardiovascular events. *Circulation*.2006;113:1578-1587.
3. Bennett J, Daugherty A, Herrington D, Greenland P, Roberts H, Taubert K. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) A science advisory from the American Heart Association. *Circulation*.2005;111:1713-1716.
4. Antman E, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation*.2005;112;759-770.
5. Andersohn F, Suissa S, Garbe E. Use of first and second generation Cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs and risk of acute myocardial infarction. *Circulation*.2006;113;1950-1957.
6. Graham D. COX-2 inhibitors, other NSAIDs, and cardiovascular Risk. *JAMA*. 2006;296:1653-1656.
7. Finckh A, Aronson M. Cardiovascular risks of cyclooxygenase-2 inhibitors: Where we stand now. *Annals of Internal Medicine*.2007;142:212-214
8. Antman E., Bennett J, Daugherty A, Furberg C, Roberts H, Taubert K. Use of non-steroidal anti-inflammatory drugs. *Circulation*.2007;115:1634-1642.