Do cyclooxygenase inhibitors increase risk of cardiovascular thrombotic events?

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Mukherjee D, Steven NE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA **2001;286:954-8.**

Research question

Do patients who take anti-inflammatory medications from the cyclooxygenase (COX) inhibitor class have more cardiovascular thrombotic events than patients who do not?

Type of article and design

Systematic review and descriptive subgroup analysis.

Relevance to family physicians

Cyclooxygenase (COX) inhibitors (celecoxib marketed as Celebrix by Pfizer and rofecoxib marketed as Vioxx by Merck) are thought to be safer analgesic or anti-inflammatory drugs because patients taking them have fewer gastric mucosa complications. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2, but COX inhibitors selectively inhibit COX-2 receptors. The introduction of these drugs resulted in many new prescriptions for them.

Cyclooxygenase-2 inhibition is associated with ameliorating inflammation; COX-1 inhibition is associated with adverse effects in the gastrointestinal tract.[1] Although endoscopically viewed lesions in the gastrointestinal tract depend on COX-1 inhibition, it is uncertain whether finding these lesions by endoscopy actually predicts serious gastrointestinal complications, such as perforation, obstruction, and bleeding. The hemorrhagic nature of most serious gastrointestinal adverse events experienced by patients taking NSAIDs seems to reflect inhibition of COX-1 in platelets rather than in gastric mucosa.

Thus, drugs that inhibit COX-1, such as NSAIDS, not only increase risk of hemorrhagic events but might have a protective antiplatelet effect against cardiovascular thrombotic events. Some researchers also speculate that COX inhibition lead to increased cardiovascular thrombotic events. Cyclooxygenase-2 has an important role in increasing prostacyclin formation. Prostacyclin is thought to be part of a homeostatic defence mechanism that limits the consequences of platelet activation in vivo. Theoretically, lower prostacyclin levels could lead to increased platelet activation. The decrease of prostacyclin through COX-2 inhibition, however, has never been shown to increase risk of spontaneous thrombosis in mice.

Could family physicians be lowering one risk (gastrointestinal bleeding) while raising another (thrombotic cardiovascular events)?

Overview of study and outcomes

Randomized controlled trials (RCTs) performed on COX inhibitors were analyzed to determine whether these medications are associated with a higher rate of cardiovascular events. MEDLINE was searched from January 1998 to February 2001 for English-language, double-blind RCTs (COX inhibitors were approved in 1998). The Internet was also searched, and two unpublished studies submitted to the United States Federal Drug Administration were considered.

The authors do not list specific inclusion criteria and then determine whether the studies meet the criteria. They excluded studies that did not report cardiovascular adverse effects. Articles in languages other than English were not searched or evaluated. Importantly, no studies that looked directly at cardiovascular risk were included. All the studies asked broader questions and used subgroup analyses.

It is unlikely that important relevant studies were missed because this class of medications is very

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new, and trials should have been easy to find. Including submissions to the Federal Drug Administration strengthens the authors' claim that all important studies were considered. Apparently, cardiovascular event data from the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial, although not published, were also obtained from the Federal Drug Administration and analyzed. Studies included were described, but no attempt was made to measure them against criteria to determine their worthiness and validity. All the studies were double-blind RCTs.

Myocardial infarction (MI) rates were determined from the placebo group of a recent meta-analysis of four acetylsalicylic acid primary prevention trials.[2] These rates were compared with MI rates in the two largest studies included.

The main information given from the original studies is a brief summary of how the primary end points were reported and data on each study's cardiovascular events. Because some studies have not been published, it would be very difficult for other authors to summarize these studies.

Results

Results of the studies examined were listed separately. It is important to understand who was studied and why, as the authors try to draw some broad conclusions from the various trials.

VIGOR trial. The VIGOR trial,[3] a double-blind RCT, compared 50 mg/d of rofecoxib with 500 mg twice a day (bid) of naproxen in 8076 patients with rheumatoid arthritis. Patients were treated for a median of 9 months; 80% were women. No ASA was allowed. Cardiovascular events were experienced by 65 of 4047 in the rofecoxib arm and 33 of 4029 in the naproxen arm (adjusted relative risk [ARR] 0.016 - 0.008 = 0.008; number needed to treat [NNT] 125, or one cardiovascular event for every 125 people treated with rofecoxib compared with naproxen; relative risk [RR] 2.0).

In all, 46 of 4047 in the rofecoxib arm and 20 of 4029 in the naproxen arm were judged to have had serious cardiovascular events. A serious cardiovascular event is defined as MI, unstable angina, resuscitated cardiac arrest, sudden or unexpected death, ischemic cardiovascular accident, or transient ischemic attack (ARR 0.011 – 0.005 = 0.006; NNT 167, or one serious cardiovascular event for every 167 people treated with rofecoxib compared with naproxen; RR 2.2).

These are statistically significant differences between treatment and control groups.

CLASS trial. The Celecoxib Long-Term Arthritis Safety Study (CLASS)[4] is two separate studies. In one, celecoxib (400 mg bid) was compared with diclofenac (75 mg bid); in the other, celecoxib (400 mg bid) was compared with ibuprofen (800 mg three times daily). A total of 8059 patients with osteoarthritis, 68.5% of whom were women, were enrolled in the two studies. Acetylsalicylic acid was allowed, and 21% of the patients were taking it. The study lasted 13 months, but only the first 6 months of follow-up data were published.

Concerning cardiovascular events, all we are told is that there was no significant difference in incidence between the groups.

Study 085. A double-blind RCT of rofecoxib (12.5 mg/d) versus nabumetone (1000 mg/d) or placebo studied 1042 patients; ASA therapy was allowed in the rofecoxib and nabumetone groups.

- One event (0.2%) was recorded in the rofecoxib group, two (0.4%) in the nabumetone group, and none in the placebo group.
- Absolute risk ratio was 0.002 – 0 = 0.002.
- The NNT was 1/0.002 = 500, or one event for every 500 people treated with rofecoxib compared with placebo.

Study 090. A double-blind RCT of rofecoxib (12.5 mg/d) versus nabumetone (1000 mg/d) or placebo included 978 patients; ASA therapy was allowed in the rofecoxib and nabumetone groups.

- Six events (1.5%) were recorded in the rofecoxib group, two (0.5%) in the nabumetone group, and one in the placebo group (0.5%).
- The ARR was 0.015 – 0.005 = 0.01.
- The NNT was 1/0.005 = 200, or one cardiovascular event for every 200 people treated with rofecoxib compared with placebo.

Myocardial infarction rates. From the meta-analysis of the four primary prevention ASA trials that studied a total of 48 540 patients (23 407 patients in the placebo arm), the annualized MI rate of the placebo group was 0.52.

- The annualized MI rate in the VIGOR trial was 0.74.
- The annualized MI rate in the CLASS trial was 0.8.

Analysis of methodology

Baseline characteristics of the populations were not compared between studies, although the size of the populations was. Some studies allowed use of ASA (critical in preventing cardiovascular events) and

some studies did not. Various NSAIDs were compared with various COX inhibitors. Not all studies used placebos. To trust blindly that cardiovascular event rates from one study are comparable to those from another study—especially when this was not the main focus of the study—is foolhardy. Yet important clinical effects could be noted.

Application to clinical practice

The NNT over a defined period to cause one thrombotic event ranged from 125 to 500. In the VIGOR trial, concomitant use of ASA, which can lower the rate of thrombotic events, was not allowed. Naproxen has an anticoagulant effect, apparently greater than both the diclofenac and ibuprofen used in the CLASS trial. Rofecoxib was used at dose of 50 mg daily, which is higher than the 25-mg dose frequently used. Thus the naproxen group theoretically had some antiplatelet benefit and the rofecoxib group used high doses, potentially widening the gap in thrombotic rates. People with rheumatoid arthritis are at greater risk of MI than the general population or those who have osteoarthritis are.

In the CLASS trial, people tended to have osteoarthritis rather than rheumatoid arthritis. There is no significant difference in event rates between the medications, but diclofenac and ibuprofen appear to have less protective anticoagulant effect than naproxen.

Celecoxib (0.8%) and rofecoxib (0.74%) have similar MI rates when compared as annualized percentages. This compares to a baseline rate of 0.52%, but we do not know the characteristics of the populations in the meta-analysis studies.

Bottom line

- This systematic review raises a cautionary flag about the risk of cardiovascular events with use of COX inhibitors. The original studies did not set out specifically to answer the cardiovascular risk question, so subgroup analysis must be approached with caution. Further prospective trials are needed to characterize and determine the magnitude of risk.
- There are rational arguments to explain why rofecoxib seems to lead to higher rates of cardiovascular events than celecoxib when ASA use, naproxen's greater antiplatelet actions than diclofenac or ibuprofen, and underlying pathology of study patients are considered.
- One could trade a reduced risk of gastrointestinal side effects with COX inhibitors for an increased rate of thrombosis.
- If ASA is used with COX inhibitors, does this negate the protective effect of this class of medications? Gastrointestinal bleeding with ASA is not dose related.

Points saillants

- Cette étude méthodique lance une mise en garde concernant le risque d'incidents cardiovasculaires avec l'utilisation des inhibiteurs de la COX. Les études originales n'étaient pas conçues spécifiquement pour évaluer le risque cardiovasculaire; c'est pourquoi l'analyse des sous-groupes doit être envisagée avec circonspection. D'autres essais prospectifs sont nécessaires pour caractériser le risque et en déterminer l'ampleur.
- Il y a des arguments rationnels pour expliquer pourquoi le rofécoxib semble entraîner des taux plus élevés d'incidents cardiovasculaires que le célécoxib quand on prend en considération l'utilisation de l'AAS, l'action antiplaquettaire plus grande du naproxène par comparaison au diclofénac ou à l'ibuprofène ainsi que la pathologie sous-jacente des sujets de l'étude.
- On pourrait troquer un risque réduit d'effets secondaires gastro-intestinaux avec les inhibiteurs de la COX pour un taux accru de thromboses.
- Si l'AAS est utilisée avec les inhibiteurs de la COX, cela élimine-t-il l'effet protecteur de cette classe de médicaments? Les hémorragies gastro-intestinales ne sont pas reliées à la dose d'AAS.

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