Clinical Practice Committee
COX-2 Inhibitors (Coxibs)

Sources [Methodology for choosing sources]
(See References)

Clinical Question
In patients requiring anti-inflammatory therapy, should COX-2 inhibitors be used?

Bottom Line
Although there is fair to good evidence to suggest that coxib therapy results in fewer symptomatic ulcers and serious ulcer complications than therapy with nonselective NSAIDs, there is fair to good evidence of a cardiotoxic class effect from coxib therapy leading to an increased risk of myocardial infarction. The current, available evidence does not clearly demonstrate a safe dose or duration of dosing for coxibs free of excess cardiotoxicity. Because of this, the EBM Working Group does not recommend the routine use of coxibs in patients requiring anti-inflammatory therapy (B Level Recommendation). For high-risk patients, the EBM Working Group recommends the use of low-dose nonselective NSAIDs or the use of nonselective NSAIDs with GI protective agents (e.g. PPI’s). Patients and physicians may choose to use coxibs in selected patients after full education of the benefits and harms.

Setting
Outpatient

Synopsis
COX-2 inhibitors (coxibs) have appeal since they hold the promise of a lower incidence of gastrointestinal side effects than traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin. Recently, however, this class of drugs has come under increased scrutiny because of evidence suggesting an increased risk of cardiovascular events. To date, no RCT has been designed and completed to specifically study the cardiovascular risks and benefits of coxibs. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial first suggested a problem when it found a statistically significant number of myocardial infarctions associated with rofecoxib. More recently, the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial was stopped early because rofecoxib nearly doubled the risk of major cardiovascular events. This prompted the reevaluation of the Adenoma Prevention with Celecoxib (APC) Study, which found that the risk of cardiovascular events almost tripled with the use of celecoxib. With the use of coxibs, the estimated number needed to harm (NNH) for 1 year to cause one myocardial infarction is 70 patients whereas the number needed to treat (NNT) to avoid one hospitalization for peptic ulcer disease is 157. Collectively, these findings prompt real concern for the potential cardiovascular risks associated with the use of coxibs.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
<th>Study Quality</th>
<th>Full Name of Study</th>
<th>Designed To Evaluate CV Risk?</th>
<th>n</th>
<th>Experimental Drug vs (Control Drug)</th>
<th>GI Events</th>
<th>ARI/ (NNH) (CV)</th>
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| APC (2005)  | Pfizer and National Cancer Institute                                     | Level 2       | CV Risk with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention        | Not originally, but independent CV committee asked to reassess data.     | 2035 | Celecoxib 200 mg BID               |           | 1.3/(77)         | 2.4/(42) | - No other RCTs have shown increased CV risk with celecoxib.  
|             |                                                                         |               |                                                                                     |                              |     | 400 mg BID (Placebo)            |           | NNH= CV Death    | 2.8 to 3.1 yrs | - People with known CV disease were excluded.  
|             |                                                                         |               |                                                                                     |                              |     |                                    |           |                 |           | - During the first 18 months of f/u, the CV event rates were similar in the two groups.                                                                                                          |
| APPROVe (2005) | Merck                                                                  | Level 2       | Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial | Not originally, but independent CV committee asked to reassess data.     | 2586 | Rofecoxib 25 mg QD                |           | 1.6/(63)         | 3 yr      | - At 0-8 months, no sig difference in CV events.  
|             |                                                                         |               |                                                                                     |                              |     | (Placebo) Only 50 mg QD has been shown to prevent GI adverse events. |           | NNH= CV Event   |           | - But 8-12 months, CV events spiked to a five-fold increase in MI risk in high risk patients.                                                                                                          |
| Nussmeier (2005) | Pharmacia and Pfizer                                                  | Level 2       | Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib after Cardiac Surgery | Yes                          | 1671 | IV Parecoxib x 3 days, then Valdecoxib for 10 days (Placebo)     | 0.7/(143) | 1.5/(67)         | 30 days   | - Not designed to capture CV events.  
|             |                                                                         |               |                                                                                     |                              |     |                                    |           | NNH= CV Event   |           | - Very short F/U time.  
|             |                                                                         |               |                                                                                     |                              |     |                                    |           |                 |           | - Enrolled only low CV risk patients.                                                                                               |
| VIGOR (2000) | Merck                                                                  | Level 2       | Comparison of Upper GI Toxicity of Rofecoxib and Naproxen in Patients with RA       | No                           | 8076 | Rofecoxib 50 mg QD                | 1.6/(62)  | 0.3/(333)        | 0.5 - 13 months | - Not found.  
|             |                                                                         |               |                                                                                     |                              |     | (Naproxen) 500 mg BID             |           | NNH= MI Rate    |           | - Wide range of f/u times.  
|             |                                                                         |               |                                                                                     |                              |     |                                    |           |                 |           | - Found increased risk in MI with rofecoxib short- and long-term use.  
|             |                                                                         |               |                                                                                     |                              |     |                                    |           |                 |           | - Found that trials that did not find increased CV risk tended not to have external endpoint committees.                                                                                                                 |
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**Major Trials**


Celecoxib. PhRMA IQ5-97-02-001 at [http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf](http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf). [An RCT of celecoxib in patients with Alzheimer's disease, reported to the FDA, showed an increase in CV events among patients receiving celecoxib.] [Level 2 study]


**Other References**


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Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-3. [Observational data that shows that patients who are prescribed rofecoxib are more likely to have a history of major cardiovascular disease than a history of major GI bleeding.]


Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. Am J Epidemiol 1995;141:539-45. [Observational data that shows that patients who are prescribed rofecoxib are more likely to have a history of major cardiovascular disease than a history of major GI bleeding.]


Villalba ML. FDA medical officer review of VIOXX (rofecoxib), NDA 21-042 (capsules) and NDA 21-052 (oral solution). At [http://www.fda.gov/cder/foi/nda/index.htm](http://www.fda.gov/cder/foi/nda/index.htm). [Before rofecoxib was approved, this FDA reviewer stated, “that in 6-week studies, thromboembolic events are more frequent in patients receiving rofecoxib (0.67%) than placebo (0.24%).”]


Zhao SZ, Burke TA, Whelton A, von Allmen H, Henderson SC. Comparison of the baseline cardiovascular risk profile among hypertensive patients prescribed COX-2-specific inhibitors or nonspecific NSAIDs: data from real-life practice. Am J Manag Care 2002;8:Suppl:S392-S400. [Observational data that shows that many of the patients prescribed coxibs have a high cardiovascular risk profile.]