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# NSAID Use in Patients with or at Risk for CVD

The class of drugs known as the non-steroidal anti-inflammatory drugs (NSAIDs) is among the most commonly prescribed in the U.S. With an aging population, both the incidence of cardiovascular disease (CVD) and the use of the NSAIDs will certainly increase.

However, the safety of these drugs for patients with risk factors for CVD has been an issue since 2000, when a study comparing the effects of the popular cycloxygenase-2 (COX-2) inhibitor rofecoxib (Vioxx) to those of naproxen on the gastrointestinal (GI) system pointed to a 5-fold increase in the risk of acute myocardial infarction (AMI), along with the anticipated decrease in GI side effects.[1] In 2004, Merck withdrew Vioxx because of this increased risk.

Additional data collected from randomized controlled studies and meta-analysis of both selective and nonselective NSAIDs raised further concern,[2] and in 2005, the FDA deemed the increased risk of CV events as a class effect for both the non-selective NSAIDs and the COX-2 inhibitors. All products containing either NSAIDs or COX-2 inhibitors now have a black box warning to patients about this possibility, but our patients still suffer from pain and often are dependent on them to stay active.

This issue of *Heartbeat* will focus on the recently released "American Heart Association Scientific Statement: Use of Nonsteroidal Anti-inflammatory Drugs," which reviewed some of the major studies on NSAIDs/COX-2 safety and recommended a stepped care approach to the CV patient with musculoskeletal pain.

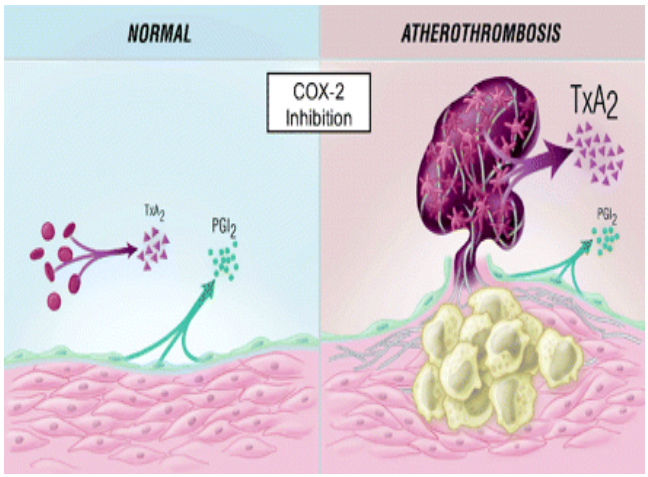
## Overview: COX Inhibitors and NSAIDs

In order to fully understand the risks of these drugs, we must understand how each class functions on a pharmacologic level. The NSAIDs exert their harm (and benefit) from inhibition of cycloxygenase (COX).

There are 2 major COX isoenzymes: COX–1 is expressed constantly in most tissues throughout our body, while the other isoenzyme COX-2 is induced in inflammation. Both COX-1 and COX-2 rely on arachidonic acid in order to generate prostaglandin H2. Animal models have indicated that COX-2 expression is up-regulated in response to stress in normal endothelium cells[3]. The inhibition of COX-2 with drugs such as rofecoxib is associated with suppression of prostacyclin synthesis —a platelet inhibitor.

The cumulative effect of this inhibition of COX-2 was summarized in the following statement from the AHA, "It has been proposed that major CV consequences of COX-2 inhibition include a shift in the prothrombotic/antithrombotic balance on endothelial surfaces toward thrombosis; an increase in sodium and water retention, leading to edema, as well as exacerbations of heart failure and hypertension; and loss of the protective effects of COX-2 up regulation in the setting of myocardial ischemia and infarction, which leads to a larger infarct size, greater thinning of the left ventricular wall in the infarct zone, and an increased tendency to myocardial rupture." [2] (Figure 1)

Figure 1. Consequences of COX inhibition for prostacyclin and $TXA_2$ production in normal & atherosclerotic arteries. (Antman)




We know that prostacyclin is the main prostanoid produced by endothelial cells. It produces local smooth muscle cell relaxation and vasodilatation and also antagonizes platelet aggregation. Platelets contain only COX-1 isoenzyme, which converts arachidonic acid to thromboxane A2 (TXA2)—a platelet activator. TXA2 has potent proaggregatory and vasoconstrictive properties on the endothelium and platelets. Aspirin is effective for preventing arterial thrombi because it inhibits COX-1 production of TXA2.

It is important to remember that the COX-2 inhibitors as well as NSAIDs vary in their ability to inhibit COX-2 versus COX-1 (Figure 2). Interestingly, rofecoxib (Vioxx) was the most selective for COX-2, while celecoxib (Celebrex) was the least selective among the COX-2 inhibitors.

The Multinational Etoricoxib versus Diclofenac Arthritis Long Term (MEDAL) Study Program looked at the COX-2 inhibitor etoricoxib versus the commonly prescribed NSAID diclofenac, which is relatively more selective for COX-2 than COX-1 (Figure 2) in patients with rheumatoid arthritis (RA) and osteoarthritis (OA).[3] The composite end point of vascular death, myocardial infarction (MI) or stroke in the MEDAL study was 1.02. Although the MEDAL study indicated noninferiority between these two medications, we need to look further at each drugs' affinity for COX-2 inhibition before prescribing them to our cardiovascular patients.

In Figure 2, you can see that both etoricoxib and diclofenac have a tendency to inhibit COX-2 more than COX-1. It would then be reasonable to assume that each medication would have the same effect on cardiovascular mortality, MI and stroke. It would also be dangerous for us to base a treatment plan on evidence from studies without fully understanding the COX selectivity of the drugs involved, especially the traditional NSAIDs.

**Figure 2. Implication of the relative degrees of selectivity. (Antman et al.)**

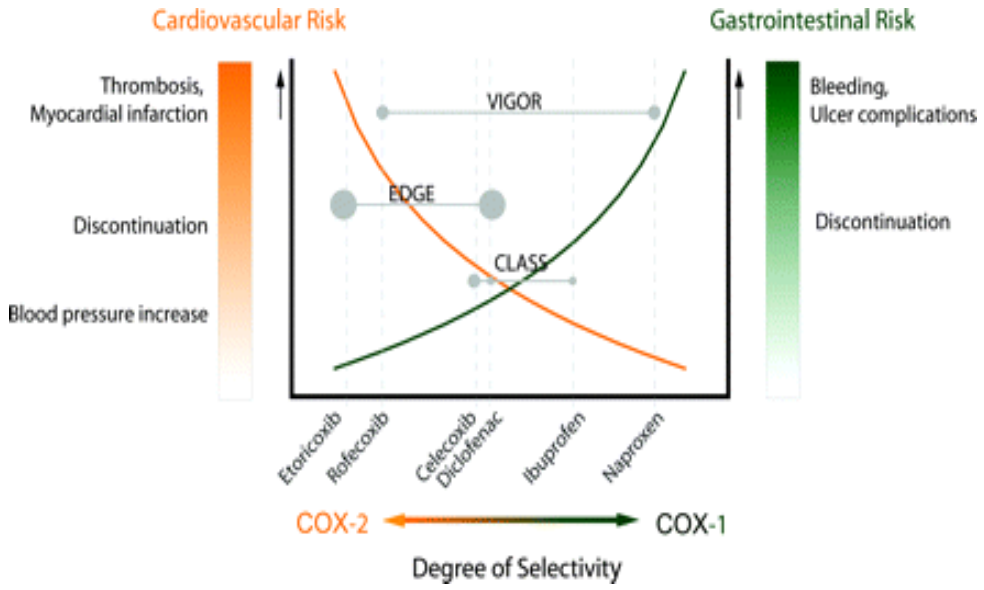
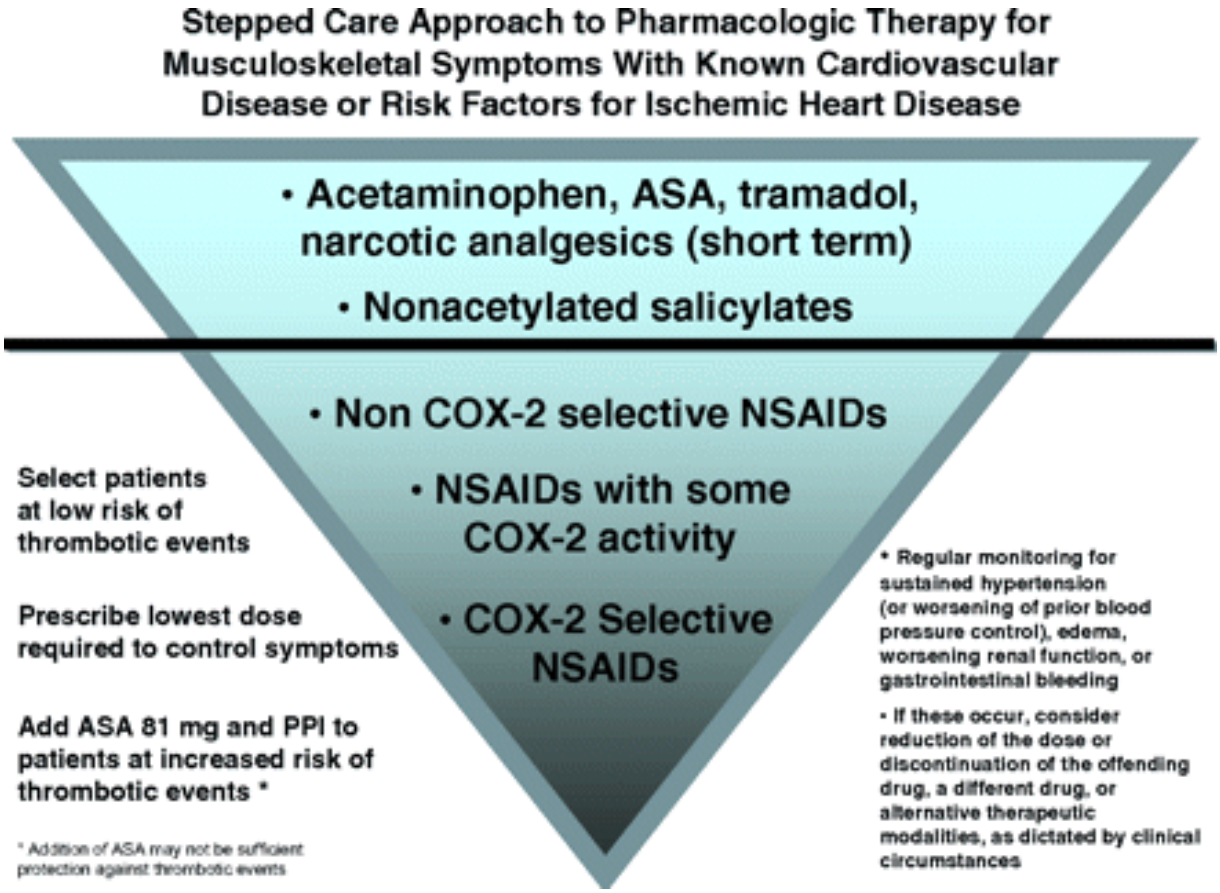


**Figure 3. Stepped care approach to management of musculoskeletal symptoms. (Antman et al.)**




## Pain Management for CVD Patients

When selecting a treatment plan, we must weigh the risks and benefits. The AHA has put forth a stepwise approach to the patient with musculoskeletal symptoms who has risk factors for or known CVD. (Figure 3) Four questions must be considered:

1. **What are the treatment considerations?** Is the patient a candidate for nonpharmacological therapy with physical therapy, heat/cold or orthotics? In those who do not respond or are not candidates for nonpharmacological options, the least dangerous medication should be initiated first at the lowest doses for the shortest amount of time. In clinical practice, this would mean utilizing aspirin and Tylenol as first line therapy. The AHA guidelines also do include a place for narcotics for short term control of pain, despite the potential for abuse (Figure 3).

When long term pain relief is required, and or aspirin and Tylenol are not adequate, then thought must be given to beginning a traditional NSAID, while being aware that we may be placing our patients at a "small but real increase risk for cardiovascular or cerebrovascular complications." [2] As shown in Figure 2, naproxen is the most nonselective COX-2 inhibitor and therefore is believed to be the preferred choice when prescribing traditional NSAIDs. I use the word believe, because even the low risk NSAIDs have not been subjected to randomized control trials to demonstrate their increased safety. In fact, the ADAPT study which looked at naproxen or celecoxib versus

placebo did raise some concern regarding the use of naproxen in cardiovascular patients.

Nonpharmacological intervention may not always be indicated as first line therapy in all patients. For example, Rheumatologist Dr Michael Weinblatt (Brigham and Women's Hospital) recently said, "It should also be noted that multiple different diseases are grouped in the musculoskeletal family, including rheumatoid arthritis, which is a systemic inflammatory disease with increased morbidity and mortality. I would not agree with the recommendations that initial therapy of that disease focus on nonpharmacologic approaches. In fact, the initial approach of RA is institution of therapeutic doses of anti-inflammatory drugs and disease-modifying therapies. The use of narcotics as an initial therapy for rheumatoid arthritis is not supported by the extensive rheumatology literature."

**2. What patient characteristics should be considered?** Patients at an increased risk for GI bleed may benefit from a trial of Tylenol initially or may need concomitant proton-pump inhibitors when taking aspirin.[4] An important note should be made that the deleterious effects of COX-2 inhibitors and NSAIDs are believed to be amplified in patients experiencing active cardiovascular events and are considered contraindicated by the European Medicine Agency in patients with ischemic heart disease and stroke. The FDA seems slightly behind the times in their recommendations which only state that all NSAIDs may have "similar risk."

**3. If a patient requires a COX-2 inhibitor, does selectivity matter?** It is important to remember that even a lack of COX-2 selectivity still confers some magnitude of risk, and the risk/benefits should be strongly weighed. The COX-2 inhibitors seem to pose the most risk. In the opinion of the European Medicine Agency they should be avoided in patients with known CAD and used sparingly in the lowest doses for the shortest amount of time in patients with risk factors for CVD only in those patients for whom other treatment plans have failed.

4. **Can patients on aspirin for cardio protection also use NSAIDs or COX-2 inhibitors for pain relief?** The newly published results of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) published in the Annals of the Rheumatic Diseases randomized 18,325 osteoarthritis patients 50 years or older to receive lumiracoxib 400mg daily (4X recommended dose), naproxen 500mg twice daily (high dose), or ibuprofen 800 mg three times daily (high-dose).[5] A subset analysis performed on patients considered high CV risk (previous MI, high CV risk based on the Framingham risk equation, or diabetes with 1 or more CV risk factors) who had been taking low-dose aspirin had more primary events (MI, stroke) when taking aspirin along with ibuprofen as compared to lumiracoxib (Table 1 and 2).[6] The primary event rates were similar among patients taking lumiracoxib and ibuprofen who had not been taking a low-dose aspirin.

**Table 1. Composite cardiovascular outcomes in the ibuprofen sub study of high-risk patients.**

| Composite cardiovascular outcomes* | Lumiracoxib (%) | Ibuprofen (%) | p |
|---|---|---|---|
| No aspirin | 0.92 | 0.80 | NS |
| Low-dose aspirin | 0.25 | 2.14 | 0.03 |
| Overall | 0.56 | 1.61 | 0.05 |

**Table 2. Composite cardiovascular outcomes in the naproxen sub study of high-risk patients.**

| Composite cardiovascular outcomes* | Lumiracoxib (%) | Naproxen (%) | p |
|---|---|---|---|
| No aspirin | 1.57 | 0 | 0.02 |
| Low-dose aspirin | 1.48 | 1.58 | NS |
| Overall | 1.51 | 0.95 | NS |

**Tables 1 and 2 excerpted from www.theheart.org. "High-risk patients taking aspirin at greater risk of cardiovascular events with ibuprofen: TARGET analysis." April 5, 2007.**

The authors of the TARGET study call it a "hypothesis generating study" which is "subject to its inherited limitations." The results reinforce the belief that NSAID therapy should be used with the minimal doses and length of treatment in high risk patients. Also, per an FDA advisory, **"Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400 mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion to avoid any potential interaction."**[7] The FDA did not see enough evidence to make as strong a recommendation with enteric coated aspirin. "One study showed that the antiplatelet effect of enteric-coated low dose aspirin is attenuated when ibuprofen 400 mg is dosed 2, 7, and 12 hours after aspirin."[5]

## Summary

As more evidence emerges, it is becoming clearer that the increased risks of CV complications are not confined to rofecoxib (Vioxx) or other COX-2 inhibitors. The safety of the non-selective NSAIDs has also been brought into question, although observational studies have yielded conflicting conclusions. No long term randomized control trial has evaluated the safety of NSAIDs in high risk CV patients but the ongoing PRECISION study is attempting to do so. **Therefore, the clinician needs to evaluate each patient on an individual basis and weigh the risks versus the benefits of this class of medications for that person.**

Treatment of musculoskeletal pain should be limited to the safest agents, beginning first with aspirin and Tylenol, with a stepwise progression to the NSAIDS with the least COX-2 selectivity (naproxen), with or without short term narcotics for appropriate patients. When NSAIDS are needed, the shortest length of treatment with the smallest dosage should be used. Non pharmacologic treatments like splints, physical therapy and RICE (Rest, Ice, Compress, and Elevate) should be used where appropriate.

## Strategy for CV Risk Reduction

While some physicians feel that celecoxib poses no cardiovascular risk at doses less than 200 mg BID, strategies to minimize risk with COX-2 inhibitors have been evaluated and are used in clinical practice. It is important to note that even with CV risk concerns, COX-2 inhibitors are necessary to the treatment of patients with OA and RA. Not all NSAIDs may impose similar CV risks; some agents—for example, naproxen 500 mg twice daily and celecoxib 200 mg once daily—appear to be safer than others agents, such as rofecoxib, valdecoxib, diclofenac, and ibuprofen. It is generally felt that the CV risks of the COX-2 inhibitors may increase with higher doses, greater than QD dosing, and longer durations of therapy. The risk of NSAID treatment is obviously of more concern to high-risk individuals, but of limited consequence to low-risk individuals.

One strategy that has been explored for reducing CV risk in patients taking COX-2 inhibitors is the addition of low-dose aspirin but the evidence for the effectiveness of this approach is limited. Additionally, data suggest that the benefits of reduction in GI toxicity with COX-2 inhibitors may be attenuated with the addition of low-dose aspirin.

All of the NSAIDs are also not without CV concerns. They can elevate and destabilize blood pressure, interfere with the cardio protective effect of aspirin and worsen renal function.

Let's not overlook the obvious here while living with some degree of uncertainty about the CV safety profile of all the NSAIDs. Recognizing and aggressively treating patients with increased CV risk with cardio protective medications (statins, ACE- inhibitors etc.) is more important to the health of the patient than the choice of NSAIDs.

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[4] Lai KC et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med.* 2002; 346: 2033–2038.

5 Farkouh ME, et al. Cardiovascular outcomes in high-risk patients with osteoarthritis treated with ibuprofen, naproxen, or lumiracoxib. *Ann Rheum Dis* 2007: DOI:10.1136/ard.2006.066001. Available at: http://ard.bmj.com.

6 www.theheart.org: High-risk patients taking aspirin at greater risk of cardiovascular events with ibuprofen: TARGET analysis. April 5, 2007.

7 US Food and Drug Administration Web site. Food and Drug Administration Science Paper. *Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin.* http://www.fda.gov/cder/drug/infopage/ibuprofen/science_paper.htm. Accessed January 29, 2007.