NSAIDs and Cardiovascular Disease

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NSAIDs have long been considered first-line treatments for a variety of pain conditions—most notably, musculoskeletal pain. Many NSAIDs are available in over-the-counter preparations, so they are inexpensive and, for better or worse, can be obtained without consulting physicians or health care professionals. For most patients, these drugs were considered safe, except in those who are at risk for GI bleeding or who have renal dysfunction. The most common adverse effect associated with NSAID use is GI distress.

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Beginning in the late 1990s when the selective cyclooxygenase-2 (COX-2) inhibitors—first celecoxib (Celebrex) and then rofecoxib (Vioxx) and valdecoxib (Bextra)—were introduced, they were initially considered a marked improvement over the older nonselective NSAIDs. This was primarily because they appeared less likely to cause GI bleeding, although this was only demonstrated in rofecoxib to a degree sufficient to allow its manufacturer to state it on its package insert. Unfortunately, many patients viewed the newness of these drugs as an indicator that they were more effective than the already existing NSAIDs; however, there has never been any evidence to support this.

As the selective COX-2 inhibitors entered widespread use, serious adverse effects were noted. Of most concern was an apparent increase in the risk of myocardial infarction and stroke associated with the use of rofecoxib, which was subsequently withdrawn from the market. Valdecoxib was also withdrawn for the primary reason that its use could cause Stevens-Johnson syndrome. Celecoxib remains on the market, but the FDA has required that it add a black box warning stating that it, too, "may cause an increased risk of serious cardiovascular [CV] thrombotic events, myocardial infarction, and stroke."[1]

The nonselective NSAIDs were often considered to have relatively low risk of CV toxicity, with the exception of increasing the risk of hemorrhagic strokes because of their effect on platelet functioning. In fact, these medications were thought to overall have a beneficial effect on the CV system. However, the problems encountered with the selective COX-2 inhibitors resulted in a reexamination of this belief, and all NSAIDs are now required to include black box statements with warnings similar to the one for celecoxib. The FDA's continuing concerns about this class of drugs are indicated by its rejection of the new drug application for etoricoxib (Arcoxia).

The NSAID black box warnings do not specifically mention hypertension; however, a recent paper indicates that this may be an additional problem. Forman and associates[2] performed a prospective study with over 16,000 men without a history of hypertension and found that at 4-year follow-up, those who used NSAIDs (including aspirin) or acetaminophen 6 or 7 days per week were at increased risk for hypertension. American Heart Association statement

Clinicians are left with the question of which analgesics are safest for use in patients with musculoskeletal symptoms who have or are at risk for CV disease. The American Heart Association (AHA) has sought to provide guidance by issuing a scientific statement on this subject.[3] The AHA statement appropriately suggests that nonpharmacological approaches, such as physical therapy, be considered first. With regard to medications, the AHA recommends that aspirin, acetaminophen, narcotic analgesics, and tramadol (Ultram, Ultracet) be considered first, followed by the nonacetylated salicylates, considering factors such as a history or risk of GI bleeding. If these medications are ineffective, not tolerated, or contraindicated, NSAIDs should be tried, progressing from those that are the least COX-2-selective, such as naproxen (Aleve, Anaprox, others) and ibuprofen (Advil, Motrin, others), to those that are the most selective, which is now celecoxib in the United States.
The statement notes that when the pain is chronic, decisions may become difficult, because extended use of aspirin in analgesic dosages carries a high risk of GI bleeding and chronic use of acetaminophen can result in hepatic damage. (It should be noted that the AHA statement was written before the publication of the article by Forman and associates, so it is impossible to know whether its findings would affect the AHA recommendations.) Extended use of narcotics or tramadol can result in substance abuse and dependence.

Although more COX-2-selective NSAIDs appear to be associated with a higher risk of CV problems, the report recommends that patients taking any NSAID be monitored for hypertension in addition to edema, declining renal function, and GI bleeding. It also recommends that in patients who are at increased risk for a thrombotic event, low-dose aspirin (ie, 81 mg/d) be considered, although it notes that this may not provide "sufficient protection" against these adverse events. The statement discusses whether NSAIDs can counteract the cardiac protective actions of aspirin and reports that at present, ibuprofen is the only NSAID that has been found to do so; however, there is limited information on other NSAIDs with regard to this. It also notes that the addition of aspirin while the patient is taking an NSAID can increase the risk of GI distress and bleeding. **Critiques of the AHA statement**

While reading the AHA statement, I experienced déjà vu. With the exception of recommending the use of narcotics before NSAIDs and the addition of the COX-2-selective agents at the bottom of the list, the guidelines are very similar to standard clinical practice up until the introduction of the latter drugs during the late 1990s. Before that, in patients for whom an NSAID was indicated but who were at risk for GI bleeding, a nonacetylated salicylate such as choline and magnesium salicylate (Trilisate) was recommended.

I do have several concerns about the AHA statement. It recommends dividing musculoskeletal problems into "those that result from tendonitis/bursitis, those that result from degenerative joint problems (eg, osteoarthritis), or those that result from inflammatory joint problems (eg, rheumatoid arthritis)," but it fails to note that there are many cases of pain, most notably low back pain, where it is less clear to what extent musculoskeletal problems are the cause.

It also does not discuss the use of topical agents. There is literature supporting the use of topical NSAIDs, capsaicin, and lidocaine transdermal 5% patch (Lidoderm) for musculoskeletal pain. All have the added benefit of being relatively unlikely to cause systemic adverse effects or to interact with other medications.

Finally, in supporting the use of tramadol, it does not note that the drug's analgesic effects appear primarily related to its inhibition of serotonin and norepinephrine reuptake. The tricyclic antidepressants (TCAs) also have been found to be beneficial in pain related to both osteoarthritis and rheumatoid arthritis, although their cardiac effects generally contraindicate their use in patients who have cardiac disease, especially conduction defects. Tramadol may be safer than TCAs for these patients, but it is a very weak serotonin-norepinephrine reuptake inhibitor (SNRI). Although there are limited reports on the use of the SNRIs venlafaxine (Effexor XR) and duloxetine (Cymbalta) in musculoskeletal pain, their effectiveness in other types of pain suggest that they may be beneficial and thus worthy of consideration.

**References:**


**Links:**
[1] [http://www.diagnosticimaging.com/authors/steven-king-md-ms](http://www.diagnosticimaging.com/authors/steven-king-md-ms)