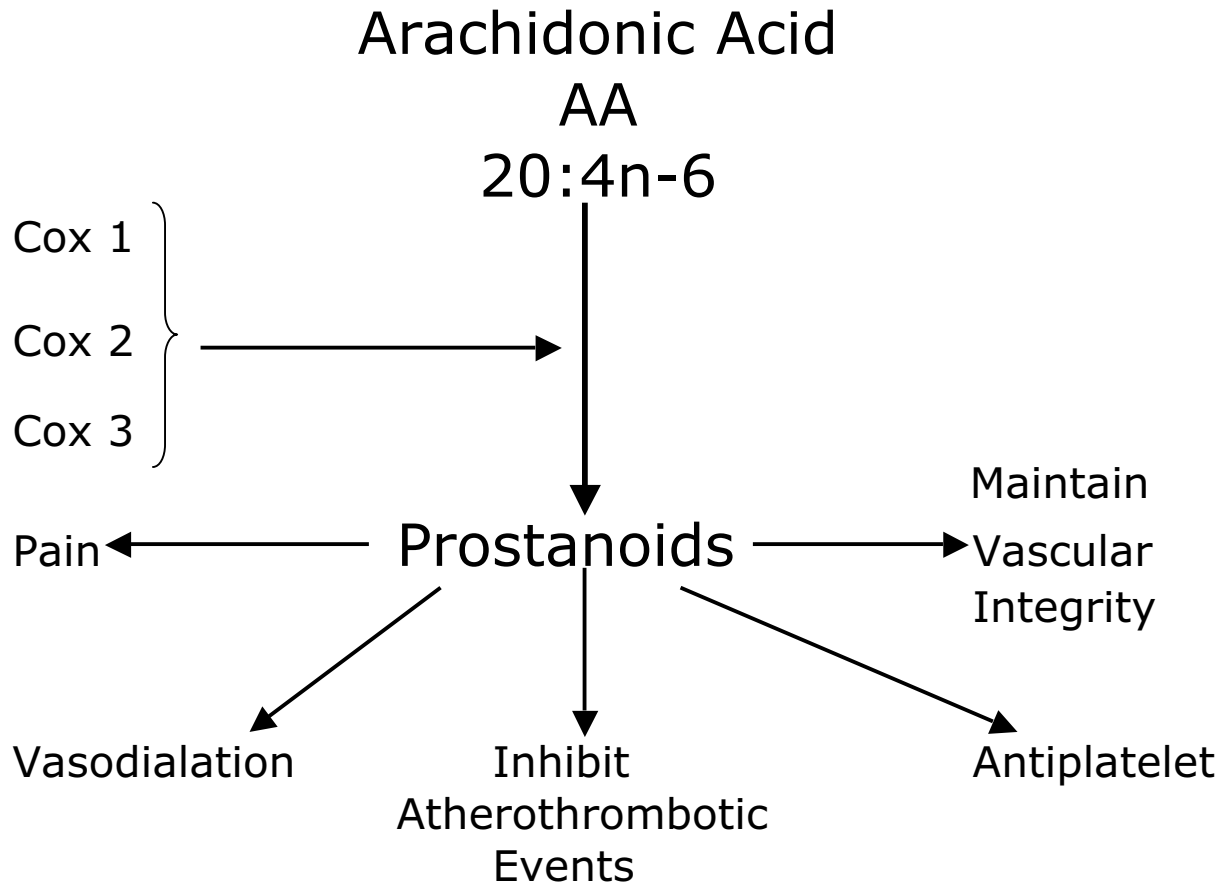


## Selective COX-2 Inhibitors and Risk of Myocardial Infarction

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### SUMMARY FROM DAN MURPHY:

Drugs that inhibit COX enzymes reduce pain, but also cause vasoconstriction (bad), reduce vascular integrity (bad), increase platelet adhesiveness and cause thrombotic events (very bad).

### FROM ABSTRACT:

Selective inhibitors of cyclooxygenase-2 (COX-2, 'coxibs') are highly effective anti-inflammatory and analgesic drugs that exert their action by preventing the formation of prostanoids.

Recently some coxibs, which were designed to exploit the advantageous effects of non-steroidal anti-inflammatory drugs while evading their side effects, have been reported to increase the risk of myocardial infarction and atherothrombotic events.

This has led to the withdrawal of rofecoxib [Vioxx] from global markets, and warnings have been issued by drug authorities about similar events during the use

of celecoxib [Celebrex] or valdecoxib/parecoxib, bringing about questions of an inherent atherothrombotic risk of all coxibs and consequences that should be drawn by health care professionals.

COX-2 is expressed in tissues like the kidney and vascular endothelium, where it executes important physiological functions.

Prostanoids that exert vasodilatory and antiplatelet properties are formed to a significant extent by COX-2, and their levels are reduced to less than half of normal when COX-2 is inhibited. **[Important]**

THESE AUTHORS ALSO NOTE:

“The spectacular, worldwide withdrawal of Vioxx (rofecoxib) from the market, followed by a similar warning about Celebrex (celecoxib), has initiated legal and commercial sequelae and has also induced great uncertainty among patients and physicians.”

Patients lost confidence in medical professionals and in the pharmaceutical industry because there was speculation that the atherothrombotic risk of these drugs was known.

The enzyme cyclooxygenase (COX) uses arachidonic acid as a substrate to generate prostaglandins.

There are 3 different forms of cyclooxygenase:

COX-1, COX-2, and COX-3

COX-3 appears to be a variant of COX-1 and “has been discussed to be the target of acetaminophen.” [Tylenol]

COX-2 is expressed in the endothelium and kidney. [Important because COX inhibition is also known to adversely affect the kidneys]

COX-2 expression has important physiological roles in gastric tissue, kidneys, uterine epithelium, in the eyes, in the brain, and “is of special importance with regard to cells of the vascular system.” **[This implies that all of these tissues can be adversely affected by drugs that cause COX inhibition]**

Any drug that targets the cyclooxygenases will alter the balance of platelet-activation and platelet-inhibition, which is of crucial importance in vascular biology and thrombosis.

In 2003, Vioxx and Celebrex accounted for about 75% of sales of the market for NSAIDs in the United States. **[WOW]**

Selective COX-2 inhibitors increase the risk for platelet activation and subsequent thrombosis. **[Important]**

The first evidence for enhanced platelet activation with enhanced thrombotic risk under inhibition of COX-2 was published in Circulation in 2001.

Selective COX-2 inhibitors enhance platelet activation and thus are able to trigger the onset of thrombotic events. **[Important]**

Studies showed an "alarming result of a nearly 5-fold increased risk of myocardial infarction in those patients that received rofecoxib [Vioxx]."

Because of the increased risk of atherothrombotic complications after 18 months of Vioxx intake, Vioxx was withdrawn from global markets.

The manufacturer of Celebrex has "issued a warning of potential cardiovascular atherothrombotic side effects" in December 2004.

Because of the vasoconstrictor effects of COX inhibition, other cardiovascular or related effects may theoretically occur, like disturbance of vision due to altered blood supply. **[Important]**

Like NSAIDs, COX inhibitors "are likely to moderately elevate systemic blood pressure, which is probably due not only to detrimental effects on the endothelial function but also to nephrotoxicity." **[Important]**

"Similar to myocardial infarction, further atherothrombotic effects such as stroke or pulmonary embolism are likely to occur at increased rate, and this has already been observed in some of the clinical studies."

According to the data available on selective COX-2 inhibitors and their known effects on vascular pathophysiology "it is highly likely that the risk for thrombotic events is a class effect inherent in coxibs." **[Important]**

All health professionals should be aware of the fact that there is a risk to receive selective COX-2 inhibitors. **[Important]**

KEY POINTS FROM DAN MURPHY:

- 1) COX-2 inhibitors Vioxx and Celebrex are prescription pain drugs that block the conversion of the omega-6 fatty acid arachidonic acid to pain producing prostaglandins.
- 2) By 2003 Vioxx and Celebrex accounted for about 75% of sales of the market for NSAIDs in the United States. **[WOW]**
- 3) However, COX-2 inhibition also causes vasoconstriction, reduces vascular integrity, increases platelet adhesiveness and thrombotic events, adversely affects vision, the brain, gastrointestinal system, the uterus, and are toxic to the kidney.

- 4) Tylenol (acetaminophen) appears to target the COX-3 enzymes.
- 5) COX-2 inhibition increases vascular thrombosis.
- 6) Vioxx studies show an alarming result of a nearly 5-fold increased risk of myocardial infarction in patients.
- 7) Both NSAIDs and COX inhibitors "are likely to moderately elevate systemic blood pressure, which is probably due not only to detrimental effects on the endothelial function but also to nephrotoxicity." **[Important]**
- 8) COX-2 inhibiting drugs not only cause increase incidences of myocardial infarction, but also increase the incidences of other atherothrombotic effects such as stroke and pulmonary embolism.
- 9) All health professionals should be aware of the fact that there is a risk to receive selective COX-2 inhibitors. **[Important]**

#### COMMENTS FROM DAN MURPHY:

Recall, in 2003, SPINE published a randomized clinical trial study comparing the COX-2 inhibiting drugs reviewed in this article, Celebrex and Vioxx, to specific chiropractic adjustments in the treatment of chronic neck and back pain. In that study, more patients suffered an adverse from Celebrex and Vioxx than were helped by the drugs. Importantly, chiropractic adjustments were better than 5 times more effective than Celebrex and Vioxx in treating chronic spinal pain, and in contrast to the drugs, there were no adverse reactions (1). Also, these same patients were reassessed a year after completion of the study, and the results were published in the Journal of Manipulative and Physiological Therapeutics in 2005. The results showed that the few who obtained short-term (9 weeks) improvement from the drugs did not enjoy any long-term lasting benefit, and their pain had returned. In contrast, those who obtained initial improvement from chiropractic adjusting largely maintained their improvement a year later. These authors concluded "In patients with chronic spinal pain syndromes, spinal manipulation may be the only treatment modality of the assessed regimens that provides broad and significant long-term benefit."

- 1) Lynton GF Giles and Reinhold Muller, Chronic Spinal Pain: A Randomized Clinical Trial Comparing Medication, Acupuncture, and Spinal Manipulation, Spine, July 15, 2003; 28(14): 1490-1502
- 2) Reinhold Muller, PhD, Lynton G.F. Giles, DC, PhD, Long-Term Follow-up of a Randomized Clinical Trial Assessing the Efficacy of Medication, Acupuncture, and Spinal Manipulation for Chronic Mechanical Spinal Pain Syndromes, Journal of Manipulative and Physiological Therapeutics, January 2005, Volume 28, Number 1.