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New British Medical Journal (BMJ) Study on the Cardiovascular Risk of NSAIDs

Although recent clinical trials have questioned the cardiovascular (CV) safety of the non-steroidal anti-inflammatory drug class (NSAIDs), they remain the mainstay therapy for millions of Americans with a broad range of acute and chronic pain conditions. In fact, an estimated 5% of all visits to U.S. physicians are related to prescribing NSAIDs. In reviewing generic pharmacy claims data by volume for 2009 ibuprofen ranked #21, meloxicam #44, and naproxen #48 (1), while CELEBREX ranked #24 of all branded products (2). Unfortunately, these drugs have common and potentially severe adverse effects including renal impairment, gastrointestinal complications, and cardiotoxicity. CV risks associated with NSAIDs, and particularly selective COX-2 inhibitors, have mainly focused on increased risk for thrombotic events due to the relative increases in thromboxane. However, NSAIDs and selective COX-2 inhibitors exert therapeutic and adverse effects by inhibiting prostaglandin synthesis, resulting in decreased renal blood flow; compensatory retention of sodium and water; and increased vascular resistance. These antinatriuretic and vasoconstrictive properties of NSAIDs can destabilize BP control; mitigate the effectiveness of antihypertensive agents; and exacerbate heart failure (HF). Additional risk factors (i.e., diabetes, advanced age, hypertension and renal insufficiency, etc.) can further predispose patients to the detrimental effects of NSAIDs.

Several epidemiological and observational studies have attempted to determine the relative safety and/or CV risk of the various NSAIDs agents available. In the past decade, much attention has been paid to the possible increased CV risk seen in cyclo-oxygenase-2 inhibitors (COX-2). Since the much publicized withdrawal of the COX-2 inhibitor rofecoxib (VIOXX, Merck) in 2004, questions have been raised about the CV safety of not only that class of drugs, but also for other conventional anti-inflammatory medications. The results of a meta-analysis recently published in the British Medical Journal (3) provide some additional insight into the relative risks of seven nonsteroidal agents.

Utilizing a potentially powerful technique known as *network meta-analysis*, researchers at the University of Bern in Switzerland attempted to resolve the issue of relative CV risks among non-steroidal agents by including all available evidence. Included in this comprehensive evaluation were all available randomized clinical trials (31) with a total of 116,429 patients taking naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, lumiracoxib, rofecoxib, and placebo. Of the COX-2 inhibitors examined in this study only celecoxib (CELEBREX, Pfizer) is available for sale in the U.S. The primary outcome measure was myocardial infarction (MI). Secondary outcome measures included risk of stroke, death from CV disease, and death from any cause.

Investigators saw an increase in MI, stroke and CV deaths in patients taking all of these NSAIDs. Not surprisingly, rofecoxib was associated with the highest risk for MI [rate ratio (RR) = 2.12, 95% Credibility Intervals (CI)], followed by lumiracoxib which has also been removed from most markets worldwide. In addition, ibuprofen was found to have the highest risk of stroke (RR = 3.36, 95%CI), followed by diclofenac (RR = 2.86, 95%CI). Lastly, etoricoxib was found to have the highest rate of CV death (RR = 4.07, 95%CI) followed by diclofenac (RR = 3.98, 95%CI).

Rate Ratio (95% Credibility Intervals of NSAID on outcomes)

NSAID	MI	Stroke	CV death
Naproxen	0.82 (0.37-1.67)	1.76 (0.91- 3.33)	0.98 (0.41-2.37)
Ibuprofen	1.61 (0.50-5.77)	3.36 (1.00-11.60)	2.39 (0.69-8.64)
Diclofenac	0.82 (0.29-2.20)	2.86 (1.09-8.36)	3.98 (1.48-12.70)
Celecoxib	1.35 (0.71-2.72)	1.12 (0.60-2.06)	2.07 (0.98-4.55)
Etoricoxib	0.75 (0.23-2.39)	2.67 (0.82-8.72)	4.07 (1.23-15.70)
Rofecoxib	2.12 (1.26-3.56)	1.07 (0.60-1.82)	1.58 (0.88-2.84)
Lumiracoxib	2.00 (0.71-6.21)	2.81 (1.05-7.48)	1.89 (0.64-7.09)

Other study highlights included (4):

- **Network meta-analysis** allows researchers to use comparisons from different studies to identify and compare results from different NSAIDs as long as certain assumptions are met. The methodological quality of the research included in the study was generally high in spite of the fact that the analysis was limited due to the lack of randomized clinical trials of some older NSAIDs.
- Naproxen, diclofenac, and etoricoxib did not appear to significantly increase the **risk for MI**.
- ALL NSAIDs were associated with some increase in the **risk for stroke** with a significantly increased risk seen with ibuprofen, diclofenac, and lumiracoxib.
- ALL NSAIDs (except naproxen) demonstrated some increase in the **risk for cardiovascular death** with statistically increased RR seen with both diclofenac and etoricoxib.
- ALL NSAIDs were associated with some increase in the **risk for all-cause mortality** with rofecoxib showing the most significant increased risk versus placebo.
- Investigators were not able to find a clear **relationship between the specificity of COX-2 inhibition and the risk for CV events**. This finding contradicts previous claims that the increased selectivity of COX-2 inhibitors was associated with increased CV risk (e.g. rofecoxib).
- Overall, **naproxen appears to be associated with a relative low risk for CV events** compared to other NSAIDs.

Conclusion:

So what are the salient points to remember when prescribing NSAIDs for patients at high risk of cardiovascular disease? Overall, current data would suggest that selective COX-2 inhibitors, especially in higher doses, should be avoided. In the recently released study from BMJ, rofecoxib and diclofenac appear to have the highest CV risk while naproxen has the best CV safety profile. In addition, patients with known heart disease should be cautioned to avoid all NSAIDs (both over-the-counter and prescription) without first consulting with their physician. Patients should also inform their provider of certain medical conditions (e.g. impaired renal or hepatic function, recent or chronic bleeding disorders, concomitant use of anti-coagulants, corticosteroids, excessive alcohol use, etc.) before starting on NSAIDs. The authors of this meta-analysis recommend that physicians take special care in evaluating patients prone to CV events. Those who require treatment should take the lowest dose for the shortest period of time (5). Lastly, acetaminophen should still be considered a potential alternative to NSAIDs for mild to moderate pain symptoms when utilized in appropriate doses.

References:

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