Seven NSAIDs Linked To Cardiovascular Risk

BY SHERRY BOSCHERT

FROM BMJ

Each of seven NSAIDs was associated with significantly increased risk for MI, stroke, or death from cardiovascular disease, compared with placebo, in the most comprehensive meta-analysis of the subject so far.

The relative risks with any individual NSAID, compared with placebo, often were double, triple, or quadruple the risk with placebo, the study found.

The absolute numbers of MIs and other cardiovascular outcomes were small, but the network meta-analysis design of the study "provides the best available evidence on the safety of this class of drugs," Dr. Sven Trelle and his associates reported.

VITALS

Major Finding: Each of seven NSAIDs was associated with significantly increased risk for MI, stroke, or death from cardiovascular disease, compared with placebo.

Data Source: Network meta-analysis of 31 large, randomized controlled trials comparing any NSAID with other NSAIDs or placebo in 116,429 patients with 117,218 patient-years of follow-up.

Disclosures: The Swiss National Science Foundation funded the study. The investigators reported having no conflicts of interest.

Contrary to some previous reports, the current study also found no suggestion that this increased cardiovascular risk is specific to cyclo-oxygenase-2 (COX-2) inhibitors.

Therefore the use of all NSAIDs – and the over-the-counter availability of some of them – should be reconsidered, Dr. Trelle stated in a report published online by BMJ (Jan. 11, 2011;342:c7086 [doi/10.1136/bmj.c7086]).

Dr. Trelle of the University of Bern, Switzerland, acknowledged that therapeutic options for chronic musculoskeletal pain are limited, but cautioned that "cardiovascular risk needs to be taken into account when prescribing" any NSAID.

The meta-analysis included any large, randomized controlled trials comparing any NSAID with other NSAIDs or placebo. Data were available for naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, and lumiracoxib. The risk for a cardiovascular event had to increase by more than 30% to be considered significant.

Overall, naproxen appeared to be the least harmful NSAID in terms of cardiovascular outcomes. Risks were greatest with ibuprofen, diclofenac, etoricoxib, and lumiracoxib.

Four NSAIDs were associated with significantly increased risk for myocardial infarction (the primary outcome in the current analysis) in 29 of the trials that reported 554 MIs.

The relative risk for MI doubled with rofecoxib or lumiracoxib, was 35% higher with celecoxib, and was 61% higher with ibuprofen, compared with placebo. Evidence was lacking for increased MI risk with the other three NSAIDs.

Among secondary outcomes, stroke risk increased with all NSAIDs in 26 trials that reported 377 strokes. The increased risk was significant with four of the drugs, roughly doubling with naproxen and tripling with ibuprofen, diclofenac, etoricoxib, or lumiracoxib, compared with placebo.

Twenty-six trials reported 312 deaths from cardiovascular disease, accounting for 46% of all deaths in the trials. All NSAIDs except naproxen were associated with higher risk for cardiovascular death, which increased by 58% with rofecoxib, roughly doubled with ibuprofen, celecoxib, or lumiracoxib, and increased approximately fourfold with diclofenac or etoricoxib, compared with placebo.

All the NSAIDs were associated with increased risk for death from any cause, compared with placebo, and the increase was significant for all except naproxen. There were 676 deaths from any cause in 28 trials, and the risk of death roughly doubled with any of the other six NSAIDs.

Looking at a composite of nonfatal MI, nonfatal stroke, or cardiovascular death in 30 trials that reported 1,091 composite events, the risk increased with all the NSAIDs and increased significantly with all but naproxen.

The odds for the composite outcome increased 43% with celecoxib, 44% with rofecoxib, 53% with etoricoxib, 60% with diclofenac, and more than doubled with lumiracoxib or ibuprofen.

An estimated 5% of all visits to U.S. physicians are related to prescribing NSAIDs, which are considered the cornerstone for managing the pain of osteoarthritis and other painful conditions.

Rofecoxib, a COX-2 inhibitor, was withdrawn from the market in 2004 after a randomized, placebo-controlled trial found its use was associated with increased cardiovascular risk.

The Food and Drug Administration has since denied approval of etoricoxib because of an inadequate risk-benefit profile.

Debate about the safety of NSAIDs has continued despite several conventional meta-analyses that could not integrate all available randomized evidence. That's the strength of the network meta-analysis, which allowed a unified analysis of all the large trials while respecting randomization, according to Dr. Trelle.

Because of the low absolute numbers of events, more than 100,000 patients would need to be followed in a trial for at least a year to evaluate the cardiovascular safety of an NSAID, which is unlikely to happen, he added. ■

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POSTMASTER Send changes of address (with old mailing label) to FAMILY PRACTICE NEWS Circulation, 60 Columbia Rd., Bldg. B, 2nd flr., Morristown, NJ 07960.

FAMILY PRACTICE NEWS (ISSN 0300-7073) *is published semimonthly by Elsevier Inc., 60 Columbia Rd., Bldg. B, 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250. Subscription price is $146.00 per year. Periodicals postage paid at Morristown, NJ, and additional offices.*

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