NSAIDs Associated With 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. ■

VIEW ON THE NEWS

Time to Reevaluate NSAIDs

The cardiotoxicity of NSAIDs is particularly worrisome because many patients have both cardiovascular disease and musculoskeletal disease, Wayne A. Ray, Ph.D., noted in an editorial accompanying Dr. Trelle's study (BMJ Jan. 11, 2011;342:c6618 [doi:10.1136/bmj.c6618]).

What Dr. Trelle's study adds to the existing literature on NSAIDs is the potentially powerful technique known as network meta-analysis, which can extract more information from the data when certain assumptions are met, compared with traditional analyses, he wrote. The strength of the technique is that it uses all of the data, but it has some inherent weaknesses that should inspire caution when interpreting estimates based on indirect comparisons, explained Dr. Ray.

For example, no large, placebo-controlled trials compared etoricoxib vs. placebo. Risks of etoricoxib vs. placebo were estimated based on a chain of direct comparisons in separate trials – etoricoxib vs. diclofenac; diclofenac vs. rofecoxib or celecoxib, and finally rofecoxib or celecoxib vs. placebo.

Based on all the studies, what are the best strategies for clinicians who are considering NSAIDs for patients at high risk of cardiovascular disease? Avoid COX-2 inhibitors, especially in higher doses, Dr. Ray advised. Avoid diclofenac. Remember that ibuprofen may attenuate the antiplatelet effects of aspirin.

For now, naproxen seems to be the safest NSAID in terms of cardiovascular risk.

With any NSAID, consider also prescribing gastroprotective drugs.

NSAIDs are not the only option for treatment of musculoskeletal symptoms. Clinicians also prescribe paracetamol, low-dose opioid analgesics, and newer drugs, but without large-scale comparison studies, it's impossible to tell which is best for both efficacy and safety, Dr. Ray wrote. "Perhaps it is time for a larger, more systematic evaluation of a broader range of alternatives," he suggested.

DR. WAYNE A. RAY is a professor and director of pharmacoepidemiology at Vanderbilt University, Nashville, Tenn. Dr. Ray has received financial support from Pfizer, was a paid expert witness in a lawsuit by the state of Texas against Merck, and is a paid expert in an insurance company action against the maker of Prempro.

RA Duration Affects Structural Damage, Inflammation

BY SHARON WORCESTER

FROM THE ANNUAL SCIENTIFIC MEETING OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

ATLANTA – Physical functioning in rheumatoid arthritis patients is affected more by inflammation early in the disease process, and more by structural damage as the disease progresses, according to an analysis of pooled data from two large clinical trials.

"We feel that this study confirms that deterioration of physical functioning as a result of RA may be driven predominantly by inflammation earlier in the course of disease, but over time it is driven more by structural damage than it is by inflammation. It also suggests that earlier treatment of these patients with appropriate therapy prior to development of significant structural damage should dramatically improve the long-term physical function and disability outcomes of our patients with rheumatoid arthritis," reported Dr. Martin J. Bergman.

Dr. Bergman and his colleagues studied 1,415 patients from the two trials, each of which assessed the effects of adalimumab in RA: The PREMIER (Prospective Registry Evaluating Outcomes After Myocardial Infarction: Events and Recovery) trial was a double-blind, placebo-controlled phase III trial in patients with early RA, and the DE019 trial was a randomized, placebo-controlled trial of patients with established RA. A total of 908 patients from these trials had a disease duration of 3 years or less, and 507 had a disease duration of greater than 3 years.

VITALS

Major Finding: After investigators controlled for age and sex, Spearman's correlation coefficients showed a significant relationship between all measures of physical functioning and CRP level in early RA, but no correlation between those measures and modified Total Sharp Score (mTSS). In longstanding RA, the measures of physical functioning were significantly correlated with mTSS and with CRP.

Data Source: From a pooled analysis of data from two trials of RA patients.

Disclosures: Dr. Bergman disclosed that he has received research grants and consulting fees or other remuneration, and/or served on the speakers bureau for Abbott Laboratories, Bristol-Meyers Squibb, Roche, and UCB.

"We pooled data to assess the relationship between structural damage as measured by the modified Total Sharp Score, joint space narrowing, and joint erosions. We also looked at inflammation as measured by C-reactive protein," said Dr. Bergman, who is both on the staff of the division of rheumatology at Drexel University in Philadelphia, and chief of the division of rheumatology at Taylor Hospital of Arthritis and Rheumatology in Ridley Park, Pa.

Physical functioning was assessed using the Health Assessment Questionnaire (HAQ), and the Physical Component Score and Physical Functioning domain of the Short Form (SF)-36 Questionnaire, which assesses quality of life, he said.

Spearman's correlation coefficients showed a significant relationship between all three measures of physical function and C-reactive protein in early RA, but no correlation between those measures and a modified Total Sharp Score (mTSS).

In patients with longstanding RA, the measures of function were significantly correlated with mTSS and with CRP – although the latter associations were weaker than those seen in early disease, Dr. Bergman concluded. ■