# Largest Study Yet Supports NSAIDs' Effect on MI

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VIENNA — The cyclooxygenase-2 (COX-2)–selective NSAIDs have acted as lightning rods for recent concern regarding cardiovascular risk, but the reality is that many traditional NSAIDs carry as great or even greater associated risks of acute myocardial infarction, Gurkirpal Singh, M.D., reported at the annual European congress of rheumatology.

"All the media attention has focused on the COX-2–selective inhibitors as the drugs that cause heart attacks, but when you look at the coxibs compared to noncoxibs—and this is very important—it turns out the coxibs do not cause heart attacks any more than the non–COX-2 drugs, except for rofecoxib (Vioxx), which has a higher rate than all the other noncoxibs. But both celecoxib (Celebrex) and valdecoxib (Bextra) do not seem to increase the risk compared to traditional NSAID therapies," said Dr. Singh of Stanford (Calif.) University.

This was the key finding of his just-completed nested case-control study examining the link between NSAIDs and acute MI in a cohort of 651,000 adults with physician-diagnosed arthritis featuring nearly 2.4 million patient-years of follow-up within the California Medicaid program.

"This is by far the largest study on this issue. In fact, it's larger than all the other studies done so far combined," he noted at the meeting, which was sponsored by the European League Against Rheumatism.

Although the study was presented for the first time at the Vienna meeting, the results are generally supportive of the Food and Drug Administration's decision months earlier that NSAID-associated MI risk is essentially a drug class effect. The FDA will require all NSAIDs sold in the United States, whether by prescription or over the counter, to include a black box warning that any of these drugs may increase the risk of MI.

Dr. Singh's study, commissioned by the FDA and conducted by the Institute of Clinical Outcomes Research and Education, Palo Alto, Calif., included 15,343 arthritis patients with acute MI, each matched with four controls. The key end point was MI rate in current users of specific NSAIDs compared with MI rate in patients with remote exposure to any NSAID or in those who never used these drugs.

After adjustment for 39 potential confounders, including concurrent aspirin use, the NSAID that emerged as having the greatest MI risk was indomethacin. Current users had an adjusted 71% greater risk of MI than did remote NSAID users.

"There's not an obvious correlation between the risk of MI and selectivity of the NSAID. They're all over the place. One of the least selective NSAIDs, indomethacin, seems to have the highest risk. Some of the most selective drugs, like celecoxib and valdecoxib, are on the lower side," Dr. Singh observed.

As a class, the nonselective NSAIDs increased MI risk by 12%—a modest increase, but clinically relevant given the huge number of patients taking the drugs and the high background MI rate, he continued. The risk of MI was 18% greater in rofecoxib users than in patients on nonselective NSAIDs, but 3% less in current celecoxib users and 12% less in valdecoxib users than in traditional NSAID users.

A strong dose-dependent risk was evident with many NSAIDs. For example, diclofenac at up to 150 mg/day was associated with a nonsignificant 2% increase in MI risk, but with a 37% increase in risk at doses higher than 150 mg.

Observers praised the California study as reflecting real-world clinical experience, in contrast to the FDA-mandated randomized, controlled NSAID safety trials, which have used unrealistically high drug doses.

The California study wasn't the only bad news for NSAIDs to surface during the Vienna meeting. The conference coincided with online publication of a large British study concluding that the current use of diclofenac was associated with an adjusted 55% increased risk of MI compared with no use in the previous 3 years.

The unfunded study, involving 9,218 patients with a first MI and more than 86,000 matched controls in 367 U.K. primary care practices, also found a 32% increased MI risk with current use of rofecoxib and a 24% increase with ibuprofen, reported Julia Hippisley-Cox, M.D., professor of clinical epidemiology and general practice at University of Nottingham (BMJ 2005;330:1366-72). ■