Ibuprofen Plus Aspirin Might Pose Risks for Some

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Ibuprofen may increase the risk of heart attack, stroke, and congestive heart failure in osteoarthritis patients who also take low-dose aspirin because of a high risk of cardiovascular disease, according to the findings of a post hoc analysis.

Although the absolute number of events was small, these patients were nine times more likely to experience a heart attack or stroke than were those who took lumiracoxib with the preventive aspirin therapy, Dr. Michael E. Farkouh and colleagues have reported (Ann. Rheum. Dis. 2007 [Epub doi:10.1136/and.2006.066001]).

The post hoc analysis findings of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) are strong enough to warrant vigilance when prescribing pain relievers for this group of arthritis patients, wrote Dr. Farkouh and his coauthors. "Owing to the over-the-counter availability of ibuprofen and naproxen, coupled with the scarcity of long-term NSAID clinical trials in high-risk patients, the findings of this study have immediate relevance to patients with arthritis at increased cardiovascular risk. ... Caution is advised for high-risk patients prescribed COX-2 inhibitors and nonselective NSAIDs, particularly ibuprofen."

TARGET, a Novartis-funded study, tested the cardiovascular and gastrointestinal safety of the firm's investigational drug, lumiracoxib. More than 18,000 osteoarthritis patients were enrolled and randomized to high doses of lumiracoxib (400 mg/day), naproxen (1,000 mg/day), or ibuprofen (2,400 mg/day) for 52 weeks. The study drug was found to be as safe as the comparators in the incidence of nonfatal and silent myocardial infarction, stroke, or cardiovascular death (Lancet 2004;364:675-84).

However, critics pointed out that the TARGET population "purposefully excluded patients with known and significant preexisting coronary artery disease" and was not adequately powered to detect significant differences in rates of myocardial infarction (Lancet 2004;364:639-40).

In the new post hoc analysis, the TARGET population was stratified into low- and high-risk groups according to use of low-dose aspirin, said Dr. Farkouh of the Mt. Sinai Cardiovascular Institute in New York.

TARGET involved 3,042 patients who were considered at high risk of cardiovascular disease, based on prior events including silent MI, a high Framingham risk profile, or the presence of diabetes and more than one cardiovascular risk factor. Of this group, 60% were taking low-dose aspirin.

High-risk patients who took naproxen and aspirin were not at increased risk of adverse cardiovascular outcomes, compared with those taking lumiracoxib and aspirin. But those who took ibuprofen and aspirin were nine times more likely to experience a heart attack or stroke than were those who took the lumiracoxib/aspirin combination (8 vs. 1, or 2% vs. 0.25%).

Among high-risk patients who were not taking aspirin, naproxen was the safest choice, with no events occurring in the naproxen group compared with five events (1.57%) in the lumiracoxib group.

The ibuprofen/aspirin combination was also associated with a trend toward more congestive heart failure, compared with the lumiracoxib/aspirin combination (6 vs. 1, or 1.6% vs. 0.25%). This difference was not statistically significant, but was the primary driver of a 10-fold increase in the risk of heart failure in all the patients taking ibuprofen, compared with all of those taking lumiracoxib (8 vs. 1, or 1.28% vs. 0.14%).

Among low-risk patients, there were no significant associations between increased cardiovascular events or heart failure and any of the regimens.

The findings of increased heart attack and stroke seem to support the theory that ibuprofen might block aspirin's beneficial effect on platelet aggregation, the authors said. The drug might also negatively affect fluid balance and blood pressure, leading to the increased incidence of congestive heart failure in aspirin/ibuprofen users.

The hazard ratios may seem large, but it's important to keep the overall numbers in mind before drawing any firm conclusions, said Dr. Roy Altman, professor of medicine in the division of rheumatology at the University of California, Los Angeles. "Cardiovascular events were not the primary objective of the TARGET study. The total number of events was relatively small, and TARGET was smaller than a cardiovascular event study, which usually contains about 30,000 patients. These factors make this a hypothesis-generating study." ■