Trial reveals differences in pain-relieving drugs when combined with aspirin

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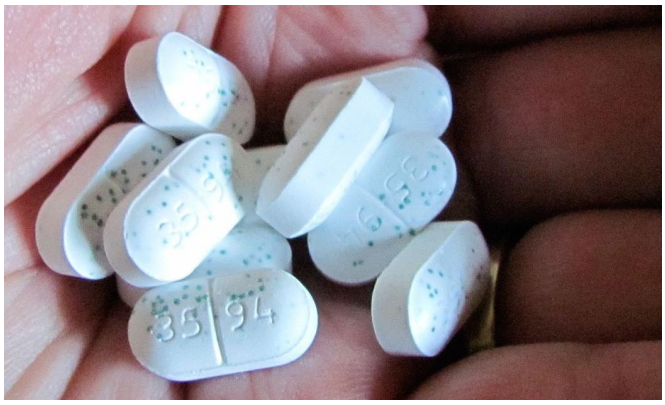

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A landmark 2016 Cleveland Clinic study of widely used pain-relieving drugs showed that celecoxib (Celebrex) was associated with comparable cardiovascular safety and better gastrointestinal (GI) and kidney safety when compared with either naproxen (Naprosyn) and ibuprofen (Motrin).

A new substudy, published today in the *Journal of the American College of Cardiology*, analyzed outcomes in PRECISION based on the presence or absence of aspirin use with specific NSAIDs (nonsteroidal anti-inflammatory drugs). The research shows that taking aspirin with celecoxib lessened its cardiovascular safety advantage, although it was still associated with fewer GI problems than either of the other drugs and fewer kidney issues than ibuprofen.

The decade-long PRECISION trial - Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen - studied osteoarthritis or rheumatoid arthritis patients who required daily prescription use of NSAIDs for pain relief. All participants had pre-existing heart disease or increased risk for developing heart disease.

The researchers reviewed occurrences of major adverse cardiovascular events such as heart attack or stroke, noncardiovascular death, clinically significant GI events, anemia of GI origin or serious renal events. GI problems including ulcers or chronic bleeding are known complications of NSAIDs, and NSAIDs are also known to cause kidney complications.

The substudy followed nearly 24,000 patients with osteoarthritis or rheumatoid arthritis who were taking daily prescription doses of either celecoxib, naproxen or ibuprofen for a minimum of 18 months. Of those patients, 11,000 were also taking aspirin. Adding aspirin diminished some of the safety advantage for celecoxib that was observed in the PRECISION trial - as patients taking both had more of a risk for major adverse events compared to those on just celecoxib alone. However, even with aspirin, celecoxib patients still had slightly less overall adverse outcomes than those taking ibuprofen with aspirin (6 percent vs 7.1 percent). There was not a significant overall difference between celecoxib and naproxen with aspirin. In addition, celecoxib patients had fewer GI problems than ibuprofen (0.9 percent vs. 1.4 percent) or naproxen (1.6 percent) and fewer renal issues than ibuprofen (0.6 percent vs. 1.2 percent).

"NSAIDS are some of the most widely used drugs in the world with more than 100 million prescriptions issued annually in the United States. Past studies have reported conflicting results regarding using NSAIDs together with aspirin, but we know that many patients do combine the medications, so it was vital to understand the risks and differences among the drugs," said Steve Nissen, M.D., chairman of Cardiovascular Medicine at Cleveland Clinic, and the study's principle investigator.

"The outcomes of this study could lead to changes in clinical practice. If a patient is not on aspirin, these results suggest that in many cases, celecoxib

may be the NSAID of choice," said Grant Reed, M.D., an interventional cardiology fellow at Cleveland Clinic, and the study's first author. "Our findings underscore how important it is that physicians counsel their patients when starting them on an NSAID and consider the potential effects of use together with aspirin."

The PRECISION trial was initiated following the withdrawal of rofecoxib (Vioxx) - a drug in the same class as celecoxib that worked similarly - from the market in 2004. The FDA mandated a clinical trial to determine if celecoxib shared a similar increased risk of heart-related complications. PRECISION, known as a non-inferiority trial, demonstrated celecoxib is not more risky than the other two drugs, which are older and work in a different way. The primary outcomes of heart attack, stroke or death occurred in 2.3 percent of patients taking celecoxib, 2.5 percent of patients taking naproxen, and 2.7 percent of patients taking ibuprofen. PRECISION also assessed a broader measure of cardiovascular safety - the primary outcome plus hospitalization for unstable angina or coronary revascularization (stenting or bypass) - and showed a 15 percent higher risk for ibuprofen than celecoxib, but this difference was borderline in statistical significance.

The PRECISION trial also assessed GI and renal complications. GI problems including ulcers or chronic bleeding are known complications of NSAIDs. Celecoxib and rofecoxib were introduced in 1999 as a new type of NSAID designed to reduce the risk of GI complications. In the PRECISION trial, the rate of ulcers or GI bleeding was 54 percent higher for ibuprofen, and 41 percent higher for naproxen than celecoxib.

NSAIDs are also known to cause kidney complications and the trial showed a statistically significant 64 percent higher risk of worsening kidney function for ibuprofen compared with celecoxib. Numerically more kidney complications occurred with naproxen, but the difference was not statistically significant. Death from any cause was approximately 25 percent higher with naproxen than celecoxib, but this difference was borderline in statistical significance.

Osteoarthritis is the most common form of arthritis affecting more than 16 million Americans. Rheumatoid arthritis is a type of chronic arthritis that is an autoimmune disease affecting joints on both sides of the body. Rheumatoid arthritis is 2.5 times more common in women than men and affects more than 1.3 million people in the United States. Patients with rheumatoid arthritis are at an increased risk for heart disease. In the trial, 90 percent of patients had osteoarthritis and 10 percent had rheumatoid arthritis.

Provided by Cleveland Clinic

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