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Naproxen Best NSAID for Heart-Disease Patients CME

News Author: Sue Hughes

CME Author: Charles P. Vega, MD, FAAFP

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June 8, 2009 — One of the first large studies to look at the safety of different nonsteroidal anti-inflammatory drugs (NSAIDs) specifically in patients with heart disease has found that **naproxen** appears to have better cardiovascular safety than **diclofenac**, **ibuprofen**, and higher doses of **rofecoxib** (Vioxx, Merck) and **celecoxib** (Celebrex, Pfizer) [1].

The study, published in the May 2009 issue of *Circulation: Cardiovascular Quality and Outcomes*, was conducted by a group led by **Dr Wayne Ray** (Vanderbilt University School of Medicine, Nashville, TN).

They explain that the cardiovascular safety of NSAIDs is highly controversial, with several studies suggesting increased cardiovascular risk associated with the new COX-2 inhibitors and also some older traditional NSAIDs, and that this issue is particularly important for patients with existing serious coronary heart disease, whose baseline risk of adverse cardiovascular events is increased. In addition, many of these patients take low-dose aspirin, which may interact with the NSAID.

But they note that data on the cardiovascular safety of these drugs in heart-disease patients is limited. They therefore conducted the current retrospective cohort study in which they examined the cardiovascular safety of individual NSAIDs in 48,566 patients with a hospitalization for myocardial infarction (MI), revascularization, or unstable angina that had been recorded in one of three large databases--Tennessee's expanded Medicaid program, Saskatchewan Health databases in Canada, and the United Kingdom's General Practice Research Database--between 1999 and 2004. Medications given outside the hospital were identified from pharmacy and physician records. The primary study end point was serious coronary heart disease, defined as MI or out-of-hospital death from CHD [coronary heart disease]. A secondary end point was the composite of serious cardiovascular disease (MI or stroke) and death from any cause. Preplanned analyses were conducted for the most frequently prescribed NSAIDs, which were naproxen, ibuprofen diclofenac, celecoxib, and rofecoxib.

Results showed that cardiovascular safety was best for naproxen, which had a lower incidence rate ratio (IRR) for serious cardiovascular disease than non-NSAID users. In contrast, there was evidence that cardiovascular risk was increased for users of the other study NSAIDs.

Incidence Rate Ratios (IRRs) for Serious CV Disease or Serious CV Disease and Death for Users of Various NSAIDs vs Non-NSAID Users

Drug	IRR (serious CV disease)	IRR (serious CV disease/death)
Naproxen	0.88	0.91
Ibuprofen	1.18	1.14
Diclofenac	1.27	1.38
Celecoxib	1.03	0.99
Rofecoxib	1.19	1.07

Other results showed that individuals who took diclofenac had a 50% increased risk of MI, stroke, or death from any cause compared with naproxen users. The authors point out that diclofenac is widely used outside the US and has been the reference drug in several COX-2-inhibitor outcome trials, and this excess risk was present for low and moderate doses (< 150 mg/day) as well as higher doses. Ibuprofen users had a 25% increased risk for the MI, stroke, or death end point compared with naproxen users. In a comparison with high-dose naproxen use, users of higher doses of celecoxib (> 200 mg/day) and rofecoxib (> 25 mg/day) had increased risk of serious coronary heart disease.

Relative to NSAID nonusers, serious coronary heart disease risk increased with short-term (less than 90 days) use for ibuprofen, diclofenac, celecoxib, and rofecoxib, but not for naproxen. The authors note that this is in contrast to a widely publicized post hoc analysis of the **APPROVE** trial data, interpreted by some as suggesting no risk for use of less than 18 months. But they point out that observational studies of rofecoxib have reported increased risk within the first month of therapy, and in the **VICTOR** trial, rofecoxib patients had increased risk after a mean duration of 7.4 months. "Thus, our findings add to the evidence that at least one of the mechanisms for increased cardiovascular risk is acute," they say.

They comment that their current findings are generally consistent with previous studies, most of which were not restricted to patients with serious coronary heart disease. They caution that the follow-up in this study began 45 days after the qualifying hospitalization admission for coronary heart disease, so these



results do not apply to the early postdischarge period, during which NSAID use may be particularly hazardous.

Breaking New Ground

In an accompanying editorial [2], **Dr Daniel Solomon** (Brigham and Women's Hospital, Boston, MA) says that this study breaks new ground in focusing on patients with known cardiovascular disease. As arthritis and cardiovascular disease commonly coexist, studying the cardiovascular safety of NSAIDs in this subgroup is of great public-health value, he comments.

Noting that the relative risks for rofecoxib were consistently lower when death from any cause was also included in the end point, Solomon suggests that this raises the possibility that death from gastrointestinal bleeds may have been reduced in persons using rofecoxib. He says this leads to questions about how to measure the overall safety of a drug. "Cardiovascular safety in patients with known cardiovascular disease is tremendously important, but clinicians and patients should focus on 'net' safety," he writes. But he adds that this is difficult concept to understand and even harder to measure.

Solomon continues that the use of NSAIDs in patients with cardiovascular disease is concerning because of the cardiovascular and gastrointestinal toxicities associated with these agents, but until newer analgesics are developed, these agents will continue to be used in this patient group.

While more information will come from the **PRECISION** trial, a large randomized comparison of celecoxib, naproxen, and ibuprofen in patients at moderate cardiovascular risk, these results will not be available until 2011 or later, and thus, until then, doctors will continue to rely on well-done pharmacoepidemiology to help answer questions about the relative safety of various analgesic strategies in important subgroups of patients, Solomon says.

He concludes that the current study "gives us new and useful information from an observational study focusing on an important subgroup with known cardiovascular disease" and that "diclofenac use should be limited in this group and naproxen appears relatively safe, but non-NSAID analgesic strategies might also be considered."

This study was funded by an unrestricted grant from Pfizer. Ray has consulted with plaintiff's attorneys and insurance companies regarding rofecoxib. Two other authors were employees of Pfizer when this research began, and other authors have received research support from Merck, AstraZeneca, Novartis, and Pfizer. Solomon receives salary support for research from Amgen and Abbott. He serves as an unpaid member of the executive committee of the Pfizer-sponsored PRECISION trial, and he serves as an unpaid member of the data safety monitoring board of a Pfizer-sponsored trial investigating a non-NSAID analgesic for osteoarthritis.

References

1. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2009; 2:155-163.
2. Solomon D H. Searching for a safe analgesic in patients with cardiovascular disease. *Circ Cardiovasc Qual Outcomes* 2009; 2:146-147.

Clinical Context

There has been significant attention to the cardiovascular risks associated with NSAIDs and particularly the risk associated with COX-2 inhibitors. In a previous systematic review and meta-analysis by McGettigan and Henry, which was published in the October 4, 2006, issue of the *Journal of the American Medical Association*, the researchers found that rofecoxib significantly increased the risk for cardiovascular events, and this risk increased with higher doses of rofecoxib. Moreover, the risk for cardiovascular events with rofecoxib was evident in the first month of treatment. However, the researchers also found no significant association between celecoxib and the risk for cardiovascular events.

This systematic review also noted a higher risk for cardiovascular events in patients who received older, nonselective NSAIDs, particularly diclofenac. The current study examines this issue in patients at a high risk for events because of preexisting coronary heart disease.

Study Highlights

- Researchers used 3 large patient databases in Canada, the United States, and the United Kingdom to examine disease and prescription data in adults between the ages of 40 and 89 years who had been hospitalized for acute MI, coronary heart revascularization, or unstable angina pectoris.
- All participants were enrolled in a health plan, which provided full medication information to the study database, and all subjects had at least 1 prescription or outpatient visit record. Patients with a history of other potentially life-threatening illness were excluded from study analysis.
- The primary outcome of the study was the relationship between the use of NSAIDs and incident MI or cardiac death. Participants were analyzed from day 45 after their initial cardiovascular event for this outcome, and researchers accounted for participants' comorbid conditions in the study analysis.
- 48,566 adults had data for analysis. The mean age was 65 years, and 58% of the cohort consisted of men. The qualifying hospitalization was for acute MI in 40% of subjects, and coronary revascularization and unstable angina pectoris accounted as reasons for the qualifying hospitalization in another 40% and 20% of subjects, respectively.
- The baseline cardiovascular risk score was similar in adults who did and did not use NSAIDs.

- There were 111,162 person-years of follow-up and 3600 coronary heart disease events during this period.
- Compared with adults who did not use NSAIDs, the use of naproxen was associated with nonsignificant reductions in the rates of serious coronary heart disease events and cardiovascular disease/death.
- Conversely, users of diclofenac experienced significantly higher rates of serious coronary heart disease events (IRR, 1.44) and cardiovascular disease/death (IRR, 1.52) vs adults who received naproxen.
- Compared with the use of naproxen, the use of ibuprofen also increased the risk for cardiovascular disease/death (IRR, 1.25).
- Even high-dose naproxen was not associated with a higher risk for cardiovascular disease. However, users of higher dose of high-dose celecoxib and rofecoxib had a higher risk for serious coronary heart disease vs subjects who received high-dose naproxen (IRR, 1.61 and 2.29, respectively).
- The NSAIDs noted were associated with a higher risk for coronary heart disease events when the duration of use was less than 90 days but not with longer periods of use.
- Subgroup analysis failed to alter the main outcome of the study.

Clinical Implications

- In a previous meta-analysis, rofecoxib was found to increase the risk for cardiovascular events in a dose-dependent fashion, and this risk was apparent within 1 month of the initiation of therapy. However, celecoxib was not associated with a significantly increased risk for cardiovascular events.
- In the current study, the use of naproxen was not associated with a higher risk for coronary heart disease events or cardiac death in patients with a history of coronary heart disease. However, ibuprofen; high-dose celecoxib; high-dose rofecoxib; and, most significantly, diclofenac, did increase this risk.

CME Test

All of the following statements were findings of the previous meta-analysis of NSAIDs and the risk for cardiovascular events by McGettigan and Henry *except*:

- Diclofenac increased the risk for cardiovascular events
- Higher doses of rofecoxib were associated with higher rates of cardiovascular events
- Celecoxib increased the risk for cardiovascular events
- Rofecoxib was associated with a higher rate of cardiovascular events within 1 month of the initiation of therapy

Which of the following NSAIDs was *least* associated with an increased risk for serious cardiovascular events in the current study by Ray and colleagues?

- Naproxen
- Ibuprofen
- Diclofenac
- High-dose celecoxib

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Author(s)

Sue Hughes

Sue Hughes is a journalist for Medscape. She joined theheart.org, part of the WebMD Professional Network, in 2000. She was previously science editor of Scrip World Pharmaceutical News. Graduating in pharmacy from Manchester University, UK, she started her career as a hospital pharmacist before moving

as a journalist to a UK pharmacy trade publication. She can be reached at Shughes@webmd.net.

Disclosure: Sue Hughes has disclosed no relevant financial relationships.

Editor(s)

Brande Nicole Martin

is the News CME editor for Medscape Medical News.

Disclosure: Brande Nicole Martin has disclosed no relevant financial information.

CME Author(s)

Charles P. Vega, MD, FAAFP



Associate Professor; Residency Director, Department of Family Medicine, University of California, Irvine

Disclosure: Charles P. Vega, MD, FAAFP, has disclosed no relevant financial relationships.

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This article is intended for primary care clinicians, cardiologists, rheumatologists, and other specialists who care for patients receiving nonsteroidal anti-inflammatory drugs.

Goal

The goal of this activity is to provide medical news to primary care clinicians and other healthcare professionals in order to enhance patient care.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify the risk for cardiovascular events associated with cyclooxygenase 2 inhibitors in a previous meta-analysis.
2. Specify a nonsteroidal anti-inflammatory drug associated with a lower risk for cardiovascular events in patients with existing coronary heart disease.

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