

# Nonsteroidal antiinflammatory drugs did not increase risk for all-cause mortality in osteoarthritis

Lee TA, Bartle B, Weiss KB. Impact of NSAIDs on mortality and the effect of preexisting coronary artery disease in US veterans. *Am J Med.* 2007;120:98.e9-16.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★☆☆ Rheumatology ★★★★★☆☆

## QUESTION

In patients with osteoarthritis, what are the mortality and cardiovascular (CV) and cerebrovascular (CBV) risks associated with long-term nonsteroidal antiinflammatory drug (NSAID) use?

## METHODS

**Design:** Nested case-control study of a cohort of veterans from the Veterans Health Administration (VHA) health care system with 3-year follow-up.

**Setting:** U.S. VHA health care system.

**Patients:** 354 456 patients with osteoarthritis who had  $\geq 2$  prescriptions from a VHA pharmacy. Patients were divided into those with coronary artery disease (CAD) at baseline (11 912 cases, 135 379 controls, mean age 72 y, 98% men) and those without CAD (16 869 cases, 190 296 controls, mean age 70 y, 97% men). Exclusion criteria included receipt of  $> 1$  type of NSAID during follow-up; history of myocardial infarction, stroke, or cancer; NSAID prescription filled or outcome event within the first 90 days of follow-up; and  $> 90$  inpatient days. Patients with  $\geq 1$  NSAID dispensed during follow-up were defined as exposed.

**Risk factors:** Baseline CAD, receipt of any NSAID, cyclooxygenase-2 (COX-2)-selective NSAID, and nonselective NSAID.

**Outcomes:** All-cause mortality, and CV or CBV events.

## MAIN RESULTS

Exposure to any NSAID or nonselective NSAID was associated with decreased risk for death and increased risks for CV or CBV events in patients both with and without CAD (Table). Exposure to a COX-2 NSAID was not associated with any effect on mortality or CV or CBV events, except for a decrease in mortality in the no-CAD group (Table). In the no-CAD group, exposure to rofecoxib (OR 1.32, CI 1.04 to 1.67), naproxen (OR 1.18, CI 1.07 to 1.30), ibuprofen (OR 1.11, CI 1.02 to 1.22), diclofenac (OR 1.32, CI 1.08 to 1.62), or etodolac (OR 1.33, CI 1.10 to 1.62) was

associated with increased risk for CV or CBV events. In the CAD group, exposure to ibuprofen increased risk for CV or CBV events (OR 1.27, CI 1.15 to 1.42).

## CONCLUSION

In patients with osteoarthritis, nonsteroidal antiinflammatory drugs were associated with decreased risk for all-cause mortality and increased risk for cardiovascular or cerebrovascular events.

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## Association between use of nonsteroidal anti-inflammatory drugs (NSAIDs) and risk for all-cause mortality and cardiovascular (CV) or cerebrovascular (CBV) events\*

Risk factors	Type of NSAID use	Adjusted odds ratio (95% CI)†	
		All-cause mortality	CV or CBV event
Patients with CAD	Any NSAID	0.79 (0.73 to 0.86)	1.18 (1.11 to 1.27)
	Nonselective NSAID	0.77 (0.71 to 0.85)	1.20 (1.12 to 1.29)
	COX-2-selective NSAID	0.93 (0.76 to 1.13)‡	1.08 (0.89 to 1.30)‡
Patients without CAD	Any NSAID	0.72 (0.68 to 0.77)	1.14 (1.08 to 1.21)
	Nonselective NSAID	0.71 (0.67 to 0.76)	1.14 (1.08 to 1.21)
	COX-2-selective NSAID	0.81 (0.68 to 0.97)	1.12 (0.94 to 1.35)‡

\*CAD = coronary artery disease; COX-2 = cyclooxygenase-2. CI defined in Glossary.

†Odds ratio adjusted for age, sex, anticoagulant, antiplatelet, aspirin, digoxin,  $\beta$ -blocker, calcium-channel blocker, nitrates, antiarrhythmics, statins, diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, hypoglycemics, angina, chronic heart failure, peripheral vascular disease, obesity, and tobacco or alcohol dependence.

‡Not significant.

## COMMENTARY

The study by Lee and colleagues adds fuel to the fire that selective and nonselective NSAIDs are associated with increased CV events. Do they cause these events? This is a much harder question to answer. Association does not necessarily mean causality. This study used a nested case-control design. Patient selection may have been biased, and issues with compliance in taking the medication are difficult to ascertain. The exclusion of patients who switched NSAIDs raises concerns about generalizability because switching among NSAIDs, including COX-2 NSAIDs, is common in clinical practice.

Despite the association of all NSAIDs with CV and CBV events in Lee and colleagues' study, overall mortality was not increased. This finding begs the still-unanswered question—what benefit might NSAIDs have that could decrease mortality?

At present, COX-2 NSAIDs are thought to carry a higher risk for CV and CBV events than older NSAIDs, and naproxen to carry a lower risk for CV and CBV events than other older NSAIDs (although this remains controversial) (1). A recent randomized trial (2) concluded

that etoricoxib, a new unapproved COX-2 NSAID, did not differ in efficacy or in CV harm from diclofenac. However, perhaps naproxen would have been a better comparator. A randomized controlled trial is needed to compare naproxen, celecoxib, and a control group (i.e., patients who would receive only acetaminophen perhaps with an added narcotic if necessary to control breakthrough arthritis pain).

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## References

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