

More Evidence Supporting a Link Between Mortality and Use of NSAIDs in Heart Failure Patients

Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med* 2009;169:141–9.

Study Overview

Objective. To determine whether patients with congestive heart failure (CHF) taking nonsteroidal anti-inflammatory drugs (NSAIDs) are at increased risk for cardiovascular morbidity and mortality.

Design. Observational study.

Setting and participants. Patients hospitalized for CHF between January 1995 and December 2004 in Denmark were identified using a national patient registry, and data from the Danish Registry of Medicinal Product Statistics were used to determine posthospitalization prescriptions for selective cyclooxygenase-2 (COX-2) inhibitors (ie, rofecoxib, celecoxib) or nonselective NSAIDs (ie, ibuprofen, diclofenac, naproxen).

Main outcome measures. Mortality and hospitalization for CHF and acute myocardial infarction (MI).

Main results. 107,092 patients were hospitalized with a primary CHF diagnosis between January 1995 and December 2004. 36,354 (33.9%) patients had received a prescription for an NSAID after discharge. 60,974 patients (56.9%) died during the course of the study. NSAIDs were associated with a higher risk of mortality, ranging from a hazard ratio of 1.22 (95% confidence interval [CI], 1.07–1.39) for naproxen to 2.08 (95% CI, 1.95–2.21) for diclofenac. The increased risk in mortality appeared to be dose-dependent. There was also a consistent relationship between NSAID use and higher rates of subsequent hospitalization for CHF and acute MI patients, with the highest increases associated with the use of rofecoxib (CHF and acute MI) and diclofenac (acute MI).

Conclusion. In a sample of patients with CHF, use of NSAIDs appeared to be correlated with increased morbidity and mortality.

Commentary

CHF is the most common cause of hospitalizations in elderly Americans and a major cause of morbidity and mortality. With the increasing age of the population and improved

treatments for CHF, the number of Americans living with CHF is likely to grow rapidly. Understanding how to manage these patients in the ambulatory care setting and how to avoid untoward events is critically important, both for clinicians and for policy makers.

Since the emergence of data showing cardiac toxicity associated with selective COX-2 inhibitors such as rofecoxib [1], there has been increasing concern about the entire class of NSAIDs. Several studies have suggested that even nonselective NSAIDs such as ibuprofen and naproxen may be harmful to the heart [2,3]. Because patients with CHF often have underlying ischemic heart disease and some level of renal impairment, they may be particularly vulnerable to the toxic effects of NSAIDs.

The study by Gislason and colleagues is compelling. Using a national database that could track most medicines used by patients with CHF, a consistent and troubling association was found between the use of any NSAID and both mortality and hospitalizations for cardiac conditions. The increased risk was sizable, suggesting that some medications, such as the selective COX-2 inhibitors, may double patients' risk of death. The sample size was large, and the risk remained high even up to a year after NSAIDs were first used; the risk was greater for patients who used higher doses.

The main weakness of the study is its design. Observational studies can help find correlations but cannot prove causality. Although the authors attempted to statistically adjust for baseline differences, limitations of the data do not allow for full accounting of the potential confounders that affect this relationship. For example, it is likely that sicker patients have more chronic pain and may be more likely to take NSAIDs. Sicker patients are also at higher risk of death. The risk-adjustment scheme used by Gislason and colleagues was not able to fully account for this clinical relationship.

Applications for Clinical Practice

Although the study did not prove a causal link between NSAID use and mortality in patients with CHF, clinicians should use caution before prescribing NSAIDs to these patients given the underlying biologic plausibility of this link and the strength of the association found. While more definitive

evidence is needed (likely from a randomized controlled trial), clinicians should follow the fundamental principle, “first, do no harm.”

—Review by Ashish K. Jha, MD, MPH

References

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