

**Dr. Little is a member of a team of researchers from the University of Texas Southwestern Medical School, the Dallas Veterans Affairs Medical Center, and the Texas Data Mining Institute at Tarleton.**

The team's study published in September 2008 compared the risk of a heart attack in patients taking one of two medications: naproxen (marketed as Aleve® and other brands), which had demonstrated a relatively low level of cardiovascular risk compared to Vioxx®, and the less well-known etodolac (LodineSR®, Eccoxolac®). Previous studies had shown that etodolac presented less cardiovascular risk than Vioxx®, but only limited research had been done comparing etodolac to naproxen.

All three medications are nonsteroidal anti-inflammatory drugs (NSAIDs) and "COX-2 inhibitors," which means they are similar but not identical chemical formulations. A slight difference in formulation can translate into an important difference in risk. Knowing whether etodolac presents more cardiovascular risk, less risk or the same risk as naproxen will help doctors decide which medication to prescribe in specific situations.

The study used data from 38,258 male patients (26,376 patient-years) at the Dallas VA Medical Center to measure the adjusted odds ratios of acute myocardial infarction (heart attack) during exposure to one or more medications. The participants in the sample had received outpatient prescriptions for etodolac (25,656 patients), naproxen (16,276 patients), celecoxib (Celebrex®; 2,997 patients) or rofecoxib (Vioxx®; 2,828 patients) between October 1, 1998 and September 30, 2004. (During the study, 8,423 patients changed from one study medication to another.) Patients' medical histories were tracked from their records. Patients were eliminated from the study if they had a heart attack, discontinued use of the drug, or died.

**RESULTS:** diagnosis of acute myocardial infarction was confirmed in 100 patients who were prescribed etodolac, naproxen, celecoxib, or rofecoxib during the study. Compared to naproxen, the increased risk of acute myocardial infarction was not significant for etodolac (OR = 1.32, P = .27), whereas celecoxib (OR = 2.18, 95% ci 1.09-4.35, p = .03) and rofecoxib (OR = 2.16, 95 CI 1.04-4.46, P = .04) were significant. A *post hoc* analysis indicated that patients with a prior history of acute myocardial infarction had a significant, 4.26-fold risk for another myocardial infarction if taking celecoxib or rofecoxib.

**A DOCTOR'S DILEMMA:** of the medications tested, those that present the greatest risk of a heart attack also present the lowest risk of stomach and intestinal bleeding and ulcers. Naproxen's comparatively low risk for heart attacks is offset by its comparatively high risk of stomach and intestinal bleeding and ulcers. In this context, etodolac may be a good compromise because, compared to naproxen, it presents only slightly higher risk for heart attacks and a lower risk for intestinal bleeding.

**The Veterans Administration welcomed these findings because etodolac is considerably less expensive than the other drugs tested. By specifying etodolac as the prescription of choice, the VA estimates it will save hundreds of millions of dollars each year.**

**METHODOLOGY:** Probabilities were calculated using Chi-square tests, unpaired *t* tests, and logistic regression analysis. Logistic regression (Type III sums of squares, direct and stepwise) analysis found that significant independent predictors of acute myocardial infarction (AMI; heart attack) were: previous AMI (P<.01), age equal to or greater than 50 (P<.01), coronary artery disease (P<.01), and rofecoxib (P=.04) and celecoxib (P=.03) use. Etodolac use was not associated with a significantly increased AMI risk (P=.27), compared to naproxen.

**INCIDENTAL FINDINGS:** Tobacco use and family history of coronary artery disease could not be directly assessed because they were not electronically available. Logistic regression analysis of information provided by a random sample of patients divided equally among those who had a heart attack and those who did not revealed that smoking and family history differences were not associated with heart attack risk in the sample. However, the high prevalence of tobacco use and family history of coronary artery disease indicated that the sample was biased toward high-risk patients in the VA population.

Study results were published as "The Risk of Acute Myocardial Infarction With Etodolac is Not Increased Compared to Naproxen: A Historical Cohort Analysis of a Generic COX-2 Selective Inhibitor" in the *Journal of Cardiovascular Pharmacology and Therapeutics*.