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CLINICAL RESEARCH STUDY

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Impact of NSAIDS on Mortality and the Effect of Preexisting Coronary Artery Disease in US Veterans

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ABSTRACT

BACKGROUND: Evidence indicates increased risk of cardiovascular events with certain nonsteroidal anti-inflammatory drug (NSAID) use; however, less is known about NSAID use and mortality. In addition, it is unclear whether risks observed with NSAIDs are modified by coronary artery disease (CAD). The association between NSAID exposure and mortality, cardiovascular, and cerebrovascular events was examined.

METHODS: A nested case-control study in a cohort of 565,451 US veterans with a diagnosis of osteoarthritis was conducted. The cohort was divided into those with preexisting CAD (16,869 cases) and those without (11,912 cases). Up to 20 controls were selected for each case.

RESULTS: The average age of participants was 69.8 years (non-CAD) and 71.8 years (CAD). Relative to no exposure, adjusted odds ratios for cardiovascular or cerebrovascular events for any NSAID were 1.14 (95% confidence interval [CI], 1.08-1.21) in the non-CAD group and 1.18 (95% CI, 1.11-1.27) in the CAD group. Exposure to NSAIDs was associated with a decreased risk of all-cause mortality in both the non-CAD (0.72, 95% CI, 0.68-0.77) and CAD (0.79, 95% CI, 0.73-0.86) groups.

CONCLUSIONS: As in previous reports, there was an increased risk of cardiovascular and cerebrovascular events for NSAIDs. However, NSAID exposure was associated with a reduced risk of death. This study raises important questions about NSAIDs in patients with osteoarthritis given that they seem to increase the risk of cardiovascular events but decrease overall mortality.

KEYWORDS: Osteoarthritis; Nonsteroidal anti-inflammatory agent; Mortality; Coronary artery disease; Pharmacoepidemiology

Cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs) have received significant attention because of evidence suggesting untoward cardiovascular and cerebrovascular effects.[1-12] The nonselective NSAIDs also have received increased scrutiny in part because initial claims indicated the increased risk with rofecoxib was the result of cardioprotective effects from naproxen.[13,14] Subsequently, several studies have shown there may not be a cardioprotective association with nonselective NSAIDs and conversely have raised concerns about the cardiovascular safety of the NSAID class.[4-6,15-18] The evidence to date has led to a call for an examination of the safety of the entire class of medications.[19]

Two important aspects about risks with both COX-2 and nonselective NSAIDs that have not been closely examined are: whether observed adverse effects are modified by baseline cardiovascular risk and the impact on overall risk of mortality. Only the study of parecoxib and valdecoxib focused specifi-

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cally on patients with clear cardiovascular risk.[8] Although observational studies included high-risk patients, it is not clear whether COX-2 or nonselective NSAIDS are associated with differential risk based on patients' underlying cardiovascular risk. The purpose of this study is to examine the effect of both COX-2 and nonselective NSAID exposure on mortality and the effect of preexisting coronary artery disease (CAD). We also examined the risk of cardiovascular and cerebrovascular events to confirm previous findings in the data used for this analysis.

CLINICAL SIGNIFICANCE

- Both COX-2 and nonselective NSAIDs are associated with an increased risk of cardiovascular and cerebrovascular events.
- Baseline cardiovascular risk seems to modify the risk associated with rofecoxib; therefore, it may be important to consider the baseline risk of cardiovascular events when making COX-2 treatment decisions with patients.
- In this study, all NSAIDs were associated with a decreased risk of mortality.

METHODS

To examine the risk of exposure to NSAIDs in a cohort at risk for long-term NSAID use, we conducted this nested case-control study in patients with osteoarthritis.

The study population was US veterans using the Veterans Health Administration health care system. As of April 2000, there were more than 26.5 million veterans.[20] Of the 26.5 million veterans, approximately 4.4 million were enrolled and receiving health care services through the Veterans Health Administration.[20]

Patients with a diagnosis for osteoarthritis (International Classification of Diseases, Ninth Revision, 715) between October 1, 2000, and September 30, 2001, were identified. Patients were followed for events from October 1, 2001, to September 30, 2004. Patients were required to have received at least two medication dispensings from a Veterans Health Administration pharmacy to ensure use of pharmacy services. To attribute risk to specific NSAIDs, patients receiving more than one NSAID during follow-up were excluded. To ensure that events identified during follow-up were new events and not diagnoses from previous events listed as a comorbidity at an encounter, patients were excluded if they had any diagnosis for a myocardial infarction (ICD-9 410, 411.0, 412) or stroke (ICD-9 431, 433, 434) before October 1, 2001.

Patients meeting all criteria were divided into 2 cohorts according to the presence of preexisting CAD. We included patients in the CAD cohort if they had a diagnosis for angina (413) or ischemic heart disease (414.0) between October 1, 1999, and September 30, 2001. All other patients were included in the non-CAD group. After identification, the groups were further restricted by additional exclusion criteria. Because prescriptions filled at Veterans Health Administration pharmacies are frequently 90-day supplies, we excluded those who filled an NSAID prescription within the first 90 days of follow-up to avoid misclassifying exposure status and to identify an inception cohort to limit the impact of survivorship bias in patients previously using NSAIDs. Thus, to avoid immortal time bias, those with an event in the first 90 days of follow-up also were excluded. Finally, those with more than 90 inpatient days before their index date and those with cancer were excluded.

Cases were identified on the basis of occurrence of a cardiovascular or cerebrovascular event or death. Patients were identified as having a cardiovascular event if there was a diagnosis of acute myocardial infarction (410), old myocardial infarction (412) (to capture out-of-system events that occurred during follow-up), postmyocardial infarction syndrome (411), acute or subacute ischemic heart disease (411.1, 411.8), or an inpatient event with a primary diagnosis of angina (413). The angina diagnosis was only included in the non-CAD group as a cardiovascular event (0.55% of cases had angina as qualifying event). Patients were identified as having a cerebrovascular event with codes 433, 434, or 435. Validation studies for cardiovascular and cerebrovascular events in these data have shown that diagnosis codes are valid compared with medical records.[21] Both inpatient and outpatient records were used to identify events, because acute events may not have occurred at a Veterans Health Administration facility. Rather, they may occur at the nearest health care facility, and thus, outpatient diagnoses were also used to identify events. Deaths were identified in the beneficiary database, which captures between 90% and 95% of veterans who die.[22,23] Deaths identified represent all-cause mortality rather than cause-specific mortality. For the composite end point, the first occurring event was identified. In separate analyses of mortality, all deaths during follow-up were included as cases.

An incidence density sampling approach was used, and a maximum of 20 controls were randomly selected for each case from eligible patients at risk at the time of the case event.[24,25] Controls were individually matched on age ($\pm$2 years) and sex, and given the same index date as cases. There was an average of 11.3 controls per case, with 24 cases having fewer than 5 controls (1 case 3 controls, 23 cases 4 controls).

NSAID exposure was determined from pharmacy-dispensing records. Patients with at least one dispensing during follow-up were defined as exposed. Specific drugs examined were celecoxib, rofecoxib, naproxen, ibuprofen, diclofenac, etodolac, and indomethacin. These represented the most frequently used NSAIDs during follow-up. All other