CLINICAL RESEARCH STUDY

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The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial

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ABSTRACT

BACKGROUND: The relative safety of long-term use of nonsteroidal anti-inflammatory drugs is unclear. Patients and providers are interested in an integrated view of risk . We examined the risk of major nonsteroidal anti-inflammatory drug toxicity in the PRECISION trial.

METHODS: We conducted a post hoc analysis of a double-blind, randomized, controlled, multicenter trial enrolling 24,081 patients with osteoarthritis or rheumatoid arthritis at moderate or high cardiovascular risk. Patients were randomized to receive celecoxib 100 to 200 mg twice daily, ibuprofen 600 to 800 mg thrice daily, or naproxen 375 to 500 mg twice daily. All patients were provided with a proton pump inhibitor. The outcome was major nonsteroidal anti-inflammatory drug toxicity, including time to first occurrence of major adverse cardiovascular events, important gastrointestinal events, renal events, and all-cause mortality.

RESULTS: During follow-up, 4.1% of subjects sustained any major toxicity in the celecoxib arm, 4.8% in the naproxen arm, and 5.3% in the ibuprofen arm. Analyses adjusted for aspirin use and geographic region found that subjects in the naproxen arm had a 20% (95% CI 4-39) higher risk of major toxicity than celecoxib users and that 38% (95% CI 19-59) higher risk. These risks translate into numbers needed to harm of 135 (95% CI, 72-971) for naproxen and 82 (95% CI, 53-173) for ibuprofen, both compared with celecoxib.

CONCLUSIONS: Among patients with symptomatic arthritis who had moderate to high risk of cardiovascular events, approximately 1 in 20 experienced a major toxicity over 1 to 2 years. Patients using naproxen or ibuprofen experienced significantly higher risk of major toxicity than those using celecoxib.

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KEYWORDS: Cox-2 selective inhibitor; Drug toxicity; Nonsteroidal anti-inflammatory drug; NSAID; Randomized controlled trial

INTRODUCTION

Ischemic cardiovascular adverse events associated with nonsteroidal anti-inflammatory drugs have received considerable attention.[1-3] However, nonsteroidal anti-inflammatory drug (NSAID) use also can be tied to a spectrum of clinically important toxicities. These include gastrointestinal bleeding, acute and chronic kidney injury, heart failure, hypertension, and death.[4-8] Patients' and their care teams' concerns about analgesic toxicities reach beyond a single organ system; rather, they want to know the overall safety of a given drug. Thus,

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Conflict of Interest: See last page of article.

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an integrated examination of the relative safety of these commonly used analgesics would provide useful information for healthcare providers and patients alike. Moreover, many patients who might receive chronic NSAID have advanced age and multiple comorbidities—both risk factors for common toxicities. These considerations highlight the importance of precise information regarding the relative safety of NSAID among common subgroups, such as those defined by age, sex, underlying arthritis, NSAID dosage, known cardiovascular disease, diabetes, aspirin use, or tobacco use.

The PRECISION trial examined the relative cardiovascular safety of celecoxib, naproxen, and ibuprofen among patients with osteoarthritis or rheumatoid arthritis who required chronic NSAID.[9] The primary trial results demonstrated that celecoxib was not inferior to the nonselective NSAID with respect to cardiovascular safety.[10] Other end points also were adjudicated in a blinded fashion, allowing for examination of the risk of major NSAID toxicities across the treatment arms.

The current analyses were secondary post hoc assessments of data acquired prospectively from the PRECISION trial. The goal was to examine the comparative risk of major NSAID toxicity related to celecoxib, naproxen, or ibuprofen. We hypothesized that the selective COX-2 inhibitor celecoxib would have a lower risk compared with the nonselective NSAID. This analysis also examined whether various patient subgroups had differential risk of any major NSAID toxicity based on treatment assignment.

CLINICAL SIGNIFICANCE

- Naproxen and ibuprofen at moderate dosages were associated with significantly more major nonsteroidal anti-inflammatory drug toxicity events than celecoxib among older adults with arthritis and established coronary artery disease or risk factors.
- These risks translate into numbers needed to harm of 135 (95% CI, 72-971) for naproxen and 82 (95% CI, 53-173) for ibuprofen, both compared with celecoxib.

METHODS

Study Design and Population

The PRECISION trial was a large phase IV study, testing whether celecoxib was noninferior to naproxen and ibuprofen with respect to cardiovascular toxicity. The design of PRECISION and the main results have been published.[9,10] In brief, PRECISION was an event-driven randomized controlled trial conducted at 923 centers in North America, Central America, South America, Asia, and Eastern Europe between October 2006 and April 2016. The trial could not be performed in Western Europe because of restrictions placed on prescribing of coxibs by the European Medicines Agency.

Eligible patients were those ≥18 years of age with a clinical diagnosis of osteoarthritis or rheumatoid arthritis[11-13] for at least 6 months who required chronic daily NSAID therapy. Participants could be included if they had known cardiovascular disease or cardiovascular risk factors. These entry criteria included any of the following: a known history of major adverse cardiovascular events; occlusive disease of coronary and noncoronary arteries; a clinical diagnosis of diabetes; or evidence of cardiovascular risk based on concomitant risk factors, including age ≥65 years in women and >55 years in men, hypertension, dyslipidemia, left ventricular hypertrophy, microalbuminuria, urine protein/creatinine ratio >2, Ankle Brachial Index <0.9, cigarette smoking, waist-hip ratio ≥0.90, and family history of premature cardiovascular disease. Patients with any of the following were excluded: any cardiovascular event within 3 months, such as major adverse cardiovascular event, unstable angina, evidence of cardiac rhythm instability, or any major cardiovascular surgery; a planned coronary, cerebrovascular, or peripheral revascularization; New York Heart Association (NYHA) Class III or IV heart failure or known left ventricular dysfunction with ejection fraction ≤35%; active, important gastrointestinal, hepatic, renovascular or coagulation disorders; history of acute joint trauma; allergy or hypersensitivity to celecoxib, ibuprofen, naproxen, or aspirin; poor responders to disease-modifying antirheumatic drugs or oral corticosteroid treatments; and required treatment with medications excluded during the course of the study. Women were excluded if they were pregnant, might have become pregnant, or were lactating. Supplemental Table 1 (available online) shows additional selection criteria.

Patient Involvement

Patients were not involved in designing the PRECISION trial or the current set of analyses. The patient burden from the trial was not formally assessed.

Study Protocol

Patients meeting selection criteria who signed informed consent were randomized 1:1:1 to celecoxib 100 mg twice per day for osteoarthritis and up to 200 mg twice per day for rheumatoid arthritis, ibuprofen 600 to 800 mg 3 times per day, or naproxen 375 to 500 mg twice per day with administration of double dummy tablets so that all subjects received the study drug thrice daily. Treatment was double-blinded with matching placebos. Randomization was stratified by geographic region, low-dose aspirin use (yes or no), and arthritis type (osteoarthritis or rheumatoid arthritis) and implemented using an interactive voice response system to ensure masking of allocation. All enrolled patients were provided open-label esomeprazole at 20 to 40 mg per day and allowed low-dose aspirin (≤325 mg/d) for cardiovascular event prevention. Patients had visits at baseline; at months 1, 2, 4, 8, and 12; and then every 6 months through month 42. Partici-