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REVIEW

Cardiovascular safety of NSAIDs: Additional insights after PRECISION and point of view

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Increasing numbers of patients with arthritis use nonsteroidal anti-inflammatory drugs (NSAIDs), some for long periods. The relative cardiovascular safety of NSAID use is of considerable concern, particularly among patients with or at risk of cardiovascular disease. Until recently, the evidence base was limited to older trials with small sample sizes. The large-scale Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) trial and a recent Bayesian meta-analysis of individual patient data in nearly a half-million patients were undertaken to address some of the existing gaps in knowledge relative to the cardiovascular safety of NSAID use. We reviewed the results, strengths, and limitations of PRECISION. We believe that the results of the meta-analysis will further assist clinicians in decision-making for management of patients with osteoarthritis. The totality of evidence would support avoidance of NSAID use, if possible, in patients with or at high risk for cardiovascular disease. If used, the shortest-duration and lowest effective NSAID doses should be chosen, given the evidence that risk is duration- and dose-dependent. We also provide a brief discussion of the mechanism of action of NSAIDs, along with discussion of existing guidelines and the recent meta-analysis.

KEYWORDS

Adverse Events, Cardiovascular Disease, Clinical Pharmacology, Nonsteroidal Anti-Inflammatory Drugs, Pain Relief, Safety

1 | INTRODUCTION

The aging of our population, coupled with continuing declines in cardiovascular (CV) disease (CVD) mortality in Western countries, has resulted in increasing numbers of patients with, or at high risk for, CVD who also have arthritis and related painful musculoskeletal conditions and seek to improve their quality of life. This often prompts use of nonsteroidal anti-inflammatory drugs (NSAIDs), many times for long periods. But the relative CV safety of NSAIDs, particularly among patients with CVD or at higher CV risk, has generated considerable concern among both patients and their physicians because of knowledge gaps in the evidence relative to comparative safety.

Until recently, the evidence base was limited to multiple older trials with relatively small sample sizes. Management of acute and chronic CVD has evolved considerably, raising additional questions about the relevance of this information. A recent meta-analysis of individual patient data involving almost a half-million individuals found that all NSAIDs were associated with an increased risk of myocardial infarction (MI).[1] However, the primary mechanisms for increased CV risk with NSAIDs remain controversial. At present, despite evidence from multiple small studies, there remains an important knowledge gap related to which, if any, NSAID should be prescribed for CVD patients. Moreover, the dose- and duration-related safety profiles of various NSAIDs remain unknown. The pathways influenced by NSAIDS and prior data have raised serious safety concerns. Thus, it was hoped that the results of Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION),[2] a large-scale, prospective, randomized trial, would help to address some of these knowledge gaps to provide guidance for the use of 2 widely used, over-the-counter, nonselective NSAIDs (ibuprofen and naproxen) and a selective prescription cyclooxygenase-2 (COX-2) inhibitor (celecoxib) for patients with, or at risk for, CVD.

2 | PROSTANOID SYNTHESIS AND MECHANISM OF ACTION OF NSAIDS

To better understand the issue, we believe that a brief review of the mechanism of action of NSAIDs is helpful for clinicians. The NSAIDs impart analgesic and anti-inflammatory effects by blockade of COX. COX exists in 2 isoforms: COX-1, which is constitutively expressed in most cells; and COX-2, which is induced by proinflammatory stimuli (cytokines, growth factor, shear) in endothelial cells, monocytes/macrophages, tumor cells, and plaque-associated cells. In general, COX-2 expression is minimal under basal conditions. COX mediates the production of eicosanoids that serve multiple roles in normal homeostasis and disease. Prostanoid biosynthesis is initiated via release of arachidonic acid (AA) from the cell membrane by lipases, primarily phospholipase A2, and subsequent conversion by prostaglandin (PG) H-synthase to PGH2. PGH synthase has both COX activity that converts AA to PGG2 and peroxidase activity that converts PGG2 to PGH2. The role of AA metabolites generated by COX in homeostasis of vascular tone and thrombosis has been well described. PGH2 is metabolized by tissue-specific isomerases such as thromboxane synthase in platelets to thromboxane (TX) A2; PGI synthase in endothelium, vascular smooth-muscle cells, and renal cells to PGI2; and PGE synthase in gastric mucosa and renal cells to PGE2. In addition, leukocytes, vascular smooth-muscle cells, endothelial cells, and platelets express PGE synthase and, as a result, are all capable of generating the inflammatory prostanoid PGE2.[3–6]

TXA2 induces platelet aggregation and vasoconstriction (prothrombotic effects), and PGI2 induces vasodilation and nitric oxide generation and inhibits platelet aggregation (antithrombotic effects). Controversy exists regarding the source of PGI2. Some have opined that COX-2 activity in vascular smooth-muscle cells and endothelial cells is the dominant contributor to PGI2 biosynthesis, and that inhibition of PGI2 synthesis, accompanied via decreased synthesis and release of nitric oxide, by coxibs can promote hypertension (HTN) and thrombosis. However, others have reasoned that endothelial COX-1 activity was mainly responsible for PGI2 synthesis in healthy blood vessels. To add further controversy, recent results show that celecoxib can inhibit COX-1–mediated PGI2 synthesis and can reduce endothelium-dependent contraction in mouse arteries. Also, prostanoids have important roles in modulating renal blood flow, glomerular filtration rate, and salt and water excretion. PGE2 induces mucus secretion, bicarbonate release, and mucosal blood flow, thus providing gastric-protective effects.[6,7]

Although NSAIDs are frequently used, safe use of these drugs, particularly among older patients who may have or be at high risk for CVD and/or adverse gastrointestinal (GI) events, is an ongoing challenge for the clinician. The NSAIDs are classified based on their relative selectivity in inhibiting COX-1 and COX-2. Nonselective NSAIDs inhibit both COX-1 and COX-2. These agents include diclofenac, naproxen, ibuprofen, indomethacin, and aspirin. Coxibs are NSAIDs that are COX-2 specific and include rofecoxib and celecoxib. NSAIDs reversibly inhibit the COX enzyme and have a longer half-life compared with aspirin. In contrast, aspirin is only transiently exposed in the circulation and irreversibly acetylates serine 530 of COX-1. Aspirin prevents generation of TXA2 and TXA2-induced platelet aggregation for the life of the platelet. Aspirin also irreversibly acetylates serine 516 of COX-2 and is 166× more potent in inhibiting COX-1 than COX-2. COX-1 inhibition serves as the basis of the cardioprotective effects of aspirin and other NSAIDs. A pharmacodynamic interaction in the inhibition of the platelet has been suggested in patients co-administered aspirin and certain NSAIDS, but the clinical significance of this interaction is unknown.[7,8]

On the other hand, COX-1 inhibition in gastric cells also prevents synthesis of prostaglandins that are protective for gastric mucosa, leading to aspirin-induced GI bleeding. The anti-inflammatory and analgesic properties of NSAIDs are conferred by COX-2 inhibition. In inflammatory conditions, COX-2 expression is induced, and proinflammatory prostanoid production produces pain. The goal of the development of selective COX-2 inhibitors was pain relief without GI concerns. However, increased risk of CV events among patients receiving NSAIDs has been reported. Most mechanisms of enhanced CV event occurrence have been related to untoward effects of COX inhibition; for example, (1) resultant inhibition of renal PGE2 production, leading to fluid retention, renal insufficiency, and HTN; and (2) inhibition of PGI2 production, leading to prothrombosis.[9] Based on a nested case–control study with 8852 nonfatal MI cases, a 35% excess risk of MI in patients treated with NSAIDs was reported that was more pronounced during the first month of treatment and increased slightly thereafter. In this study, increasing the daily dose of NSAIDs, rather than COX-2 selectivity, appeared to determine the extent of in vivo COX-1 and COX-2 inhibition and was the major predictor of the increased risk of MI.[10]

Recent observations indicate that NSAIDs are potent inducers of reactive oxygen species (ROS) generation in cardiac cells and induce cardiotoxicity by a ROS-dependent mechanism involving mitochondrial and proteasome dysfunction.[11] The association of prolonged NSAID use with the development of CVD may be explained, at least in part, by the latter mechanism.

3 | PRECISION TRIAL DESIGN AND STUDY OUTCOMES

PRECISION was a multicenter, multinational, noninferiority study conducted by Pfizer to address these gaps.[2] It used a randomized, double-blind, triple-dummy, 3-arm (celecoxib, ibuprofen, or naproxen) parallel-group design in arthritis patients at increased CVD risk. Randomization was stratified according to arthritis diagnosis (either osteoarthritis or rheumatoid arthritis), aspirin use, and geographic region. At randomization, patients received either celecoxib 100 mg b.i.d., ibuprofen 600 mg t.i.d., or naproxen 375 mg b.i.d. Subsequently, patients with rheumatoid arthritis could have their dose increased to the maximum (celecoxib, 200 mg b.i.d.; ibuprofen, 800 mg t.i.d.; or naproxen, 500 mg b.i.d). For patients with osteoarthritis, ibuprofen and naproxen dose increases were allowed, but celecoxib upward titration was limited based on regulatory restrictions on a per-country basis (eg, US Food and Drug Administration [FDA]- or European Medicines Agency–approved labeling). Increased CV risk was defined as presence of, or high risk for, CVD. In addition, diabetes mellitus

was considered a "CV disease equivalent." Inclusion under the category of high risk for CVD required subjects to have ≥3 atherosclerosis risk criteria.

Subjects were excluded for uncontrolled HTN, severe heart failure (New York Heart Association class ≥III), or left ventricular ejection fraction ≤35%, atrial fibrillation or other serious arrhythmia within the past 3 months, treatment with >325 mg/d of aspirin or anticoagulation, moderately severe liver or kidney disease, or current major GI hemorrhage or high bleeding risk.

The primary outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. Secondary outcomes included first occurrence of a major adverse CV event among CV death (including hemorrhagic death), nonfatal MI, nonfatal stroke, hospitalization for unstable angina or transient ischemic attack, or revascularization. Arthritis pain (using a visual analog scale) and clinically significant GI events (defined as symptomatic gastric or duodenal ulcer; gastroduodenal, small-bowel, or large-bowel perforation or hemorrhage; gastric outlet obstruction; or acute GI hemorrhage of unknown origin) were evaluated as secondary endpoints. Other clinically significant renal or vascular events also were evaluated, including initiation of dialysis or hospitalization for acute renal failure, congestive heart failure, or uncontrolled HTN.

3.1 | Findings from PRECISION

A total of 24 222 patients were randomized between 2006 and 2014. The mean daily doses of study drug received were 209 mg in those assigned celecoxib, 852 mg in those assigned naproxen, and 2045 mg in those assigned ibuprofen. Unfortunately, nearly 70% of patients discontinued study drug during the trial, and 27% were lost to follow-up. The mean durations of treatment and follow-up were approximately 20 months and 34 months, respectively, across all patients.

The primary finding was that celecoxib was noninferior for the primary CV outcome to prescription-level dosing of both naproxen and ibuprofen, both in the intent-to-treat (ITT) analysis (celecoxib vs naproxen, hazard ratio [HR]: 0.93, 95% confidence interval [CI]: 0.76-1.13; celecoxib vs ibuprofen, HR: 0.85, 95% CI: 0.70-1.04; $P < 0.001$ for noninferiority in both comparisons) and the "on-treatment" analysis representing CV events occurring during or within 30 days of treatment discontinuation (celecoxib vs naproxen, HR: 0.90, 95% CI: 0.71-1.15; celecoxib vs ibuprofen, HR: 0.81, 95% CI: 0.65-1.02; $P < 0.001$ for noninferiority in both comparisons). The overall event rate was low in the ITT analysis: 2.3% in the celecoxib group, 2.5% in the naproxen group, and 2.7% in the ibuprofen group. The secondary outcome of major adverse CV events also showed no significant difference between celecoxib and naproxen (HR: 0.97, 95% CI: 0.83-1.12, $P = 0.64$) and celecoxib and ibuprofen (HR: 0.87, 95% CI: 0.75-1.01, $P = 0.06$).

"Serious" GI events were significantly lower overall in the celecoxib group than with either naproxen (HR: 0.71, 95% CI: 0.54-0.93, $P = 0.01$) or ibuprofen (HR: 0.65, 95% CI: 0.50-0.85, $P = 0.002$). No differences were observed for "clinically significant" GI events. Serious renal events were significantly lower among those assigned celecoxib compared with those assigned ibuprofen (HR: 0.61, 95% CI: 0.44-0.85, $P = 0.004$), but there was no significant difference between celecoxib and naproxen (HR: 0.79, 95% CI: 0.56-1.12, $P = 0.19$).

The secondary analysis of efficacy found a significant, but small, pain-relief benefit for naproxen compared with either celecoxib or ibuprofen. The change in pain score from baseline was -9.3 ± 0.26 mm for celecoxib, -9.5 ± 0.26 for ibuprofen, and -10.2 ± 0.26 for naproxen ($P < 0.001$ for naproxen vs celecoxib and $P = 0.01$ for naproxen vs ibuprofen).

4 | DISCUSSION AND MESSAGE FOR CARDIOLOGISTS

COX-2–specific inhibitors were developed for their anti-inflammatory properties while minimizing the adverse GI effects associated with COX-1 inhibition. Yet, these drugs have the potential disadvantage of increasing the risk of CV events based on lack of COX-1 inhibition and associated antiplatelet activity and inhibition of production of the endogenous antithrombotic molecule PGI2. Although COX selectivity characteristics of individual NSAIDs may be determined in vitro, it is difficult to know how the COX selectivity profile of an NSAID may translate to risk of side effects for specific patients, clinically.

One of our roles as cardiologists is to provide expert advice to patients and other physicians about balancing CV risks with the proven therapeutic benefits of these medications, particularly when higher doses are required to effectively treat chronic pain. We also have the added challenge of advising patients on analgesic use when low-dose aspirin and other antiplatelet and/or antithrombotic drugs are indicated.

Several guidelines are currently available to assist physicians in the choice of analgesic for management of patients with osteoarthritis, including the Osteoarthritis Research Society International Classification and Guidelines,[12] as well as recommendations from the First International Working Party on Gastrointestinal and Cardiovascular Effects of NSAIDs and Anti-platelet Agents[13] and others. Now that these new data are available from PRECISION, it is critical that cardiologists understand the strengths and limitations of those results.

4.1 | Strengths

PRECISION was a huge undertaking, and the study organizers are commended for enrolling >24 000 patients starting more than a decade ago. The results offer some insights into 3 commonly used NSAIDs and add to our knowledge base about their respective safety profiles. Importantly, we can reassure our patients that the overall CV, GI, and renal event rates are low or very low for each of 3 drugs studied.

4.2 | Limitations

Unfortunately, some important limitations hinder interpretation of the results from PRECISION and emphasize some critical knowledge gaps. More than a quarter of patients were lost to follow-up, and the majority (7 out of 10) discontinued their randomly assigned treatment

during the study. At just 6 months after randomization, a quarter of patients had already discontinued treatment. This finding raises questions about how to best interpret the results of the ITT analysis, given uncertainty over how treatment affected outcomes later in the follow-up period or in patients lost to follow-up. Although death-registry searches would have been most useful, the investigators attempted to deal with this limitation by emphasizing the "on-treatment analysis." But this analysis was not prespecified as the primary endpoint, and this type of analytical approach is limited, as it introduces potential bias. Furthermore, due to challenges associated with recruiting these patients, protocol amendments were made that reduced the power and noninferiority margins of the study, potentially obscuring real differences between the randomized therapies. Furthermore, PRECISION employed an ITT method for risk analysis. This methodology dilutes the risk, because nonusers have no risk and inclusion of these patients dilutes the overall risk associated with the respective therapy. A maximum bias analysis for risk would be a per-treatment analysis along with analysis using time-dependent variables for exposure.

Dosing is another important issue that raises questions about what the study measured. Although dosing, in trials like this one, rarely conforms to normal distributions, only mean doses were reported. Although mean dosing levels for naproxen and ibuprofen were near the upper end of the protocol-specified dose range, dosing of celecoxib was nearer the lower end if its range. This was due, at least in part, to the fact that approximately 90% of patients had osteoarthritis and the protocol restricted dose escalation in osteoarthritis patients. Indeed, the relatively low dose of celecoxib may have driven the comparatively weaker efficacy documented by the pain-score data while also being responsible for lowering the rate of adverse events. The relative safety of higher doses of celecoxib remains an open question. Furthermore, the mean dose is not sufficient for assessing any correlations between lower vs higher doses and the rates or types of adverse events.

Additionally, the fact that naproxen- and ibuprofen-assigned patients received doses at the higher end of the protocol-specified range (852 mg for naproxen and 2045 mg for ibuprofen) may have led to higher rates of adverse events with these drugs. Furthermore, because these drugs were dosed at prescription levels, no extrapolations can be made to the much lower prescription doses patients often take for a brief time to manage occasional pain exacerbations. It is also important to note that clinical trials and meta-analyses continue to suggest that naproxen has no significant increase in cardiac risk compared with no treatment. Thus, the adverse-outcome implications of dosing to equivalent pain suppression represents an important knowledge gap. In this line, a recent individual patient-level meta-analysis of 446 763 individuals, including 61 640 with acute MI, from Canadian and European healthcare databases, explored the potential influence of different NSAIDs and their dosing and duration of therapy on the risk of MI. This analysis found that odds ratios for MI risk were 1.24 for celecoxib, 1.48 for ibuprofen, 1.50 for naproxen, and 1.58 for rofecoxib. Importantly, this increased risk was dose-dependent and time-dependent, with the greatest observed during the initial month of NSAID use.[1]

5 | TAKE-HOME MESSAGE

Although the results from PRECISION offer some general reassurance about the overall safety of these 3 NSAIDs, conclusions about the relative safety of celecoxib, naproxen, and ibuprofen are difficult and represent persisting knowledge gaps. In the low-risk PRECISION population, most of whom were receiving risk-reducing treatment, the data suggested that short-term CV risks associated with all 3 drugs are indeed low and similar. However, this suggestion is weakened by the fact that two-thirds of patients stopped taking their assigned drug and ~30% were lost to follow-up. Furthermore, the dose of celecoxib was limited by FDA labeling and doses of the 2 nonselective NSAIDs were not, likely contributing to their better pain control. So, the question of which NSAID can be safely recommended to CVD patients and the precise dose for use over longer periods, as required by many patients with arthritis, remains largely unanswered.

The 2014 American Heart Association/American College of Cardiology (AHA/ACC) non–ST-segment Elevation Acute Coronary Syndrome (NSTE-ACS) Guideline[14] recommended a stepped-care approach for patients with chronic musculoskeletal pain. Prior to any consideration of therapy with NSAIDs, it is a class 1 recommendation to start with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics if the latter do not adequately control symptoms—although there is a class 2a recommendation for use of nonselective NSAIDs, such as naproxen, if initial therapy with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics is insufficient. However, the low and similar adverse-event rates for ibuprofen and naproxen in PRECISION argue against a single "safe" nonselective NSAID for CVD patients. Finally, when used at the doses used in PRECISION, both agents appear relatively safe. In addition, there remains controversy regarding the influence of duration and dose of NSAID use on CV risk. A meta-analysis found no increased risk of NSAIDs when used for <30 days or at less than full doses. The lack of an early rise in event rates in PRECISION supports the latter observation. There will likely be clinical scenarios where use of NSAIDs will be considered at high doses and for prolonged periods of time to treat severe inflammatory disease. Therapy in this scenario should be individualized. In patients with a prior history of arterial thrombosis, in the opinion of the authors, consideration should be given to non-NSAID analgesic therapy, including possible use of narcotics.

Practitioners should continue to assess their patients' use of NSAIDs based on individual risk factors to optimize the balance between anti-inflammation and potential for adverse events. The totality of evidence would support avoidance of NSAID use, if possible, in patients with CVD or at high risk for CVD. If used, the shortest duration and lowest effective doses should be chosen, given the evidence that risk is duration- and dose-dependent.

Conflicts of interest

Dr. Gurbel reports receiving personal fees from Boehringer Ingelheim, Merck, Janssen Pharmaceuticals, Bayer, Medicure, and Haemonetics; and grants from Haemonetics, Merck, Duke Clinical Research Institute, Harvard Clinical Research Institute, National Institutes of Health,

Amgen, Medicure, Coramed Technologies, and MedImmune. He has a patent for platelet function testing. Dr. Pepine was a PRECISION investigator and principal investigator of a grant from Pfizer to the University of Florida. He also has been a consultant to Amgen, AstraZeneca, Bayer HealthCare, BioCardia, FACT (Foundation for the Accreditation of Cellular Therapy), Gilead, Merck, SLACK Inc., and XyloCor Therapeutics, Inc.

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