Randomized controlled trials are viewed as providing gold standard evidence, and the declaratively named PRECISION trial (Prospective Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen)\(^1\) implies the final word on the comparative cardiovascular safety of nonsteroidal anti-inflammatory drugs (NSAIDs).

The analgesic efficacy of NSAIDs derives largely from suppressing cyclooxygenase 2 (COX-2)–derived prostaglandins E\(_2\) and I\(_2\) (prostacyclin), whereas their gastrointestinal adverse effects result from the inhibition of cyclooxygenase 1 (COX-1)–derived gastroduodenal prostaglandins E\(_2\) and I\(_2\) and COX-1–derived thromboxane A\(_2\) in platelets. This prompted the development of NSAIDs engineered to inhibit COX-2 specifically, such as rofecoxib, celecoxib, and valdecoxib. Randomized comparisons, such as VIGOR (Vioxx Gastrointestinal Outcomes Research), comparing rofecoxib and naproxen, showed fewer complicated gastrointestinal events with the COX-2 inhibitors.\(^2\)

The value of randomized trials was also evident when evidence, first from clinical pharmacology and then from experiments in model systems, predicted that cardiovascular events would complicate COX-2 inhibition of prostaglandin I\(_2\) in the vasculature. Evidence consistent with this hypothesis emerged from VIGOR with more serious thromboembolic events with rofecoxib. Definitive evidence of cardiovascular hazard subsequently emerged from 10 placebo-controlled trials of structurally distinct COX-2 inhibitors.\(^2\) Last, overview analysis of individual data derived from \(\approx750\) randomized trials\(^1\) provided a risk estimate of the magnitude of this hazard from COX-2 inhibitors with a rate ratio (RR) for serious vascular events of 1.37 (95% confidence interval, 1.14–1.66). As mechanistically predicted,\(^2\) the RRs for celecoxib (average daily dose, 400 mg) and rofecoxib (average daily dose, 25 mg) were superimposable. By contrast, information on older NSAIDs was fragmentary or nonexistent.

Coincident with the emergence of evidence that valdecoxib conferred a cardiovascular hazard (a finding delayed for months as the rofecoxib story unfolded), Pfizer announced in October 2004 plans to sponsor a placebo-controlled study of celecoxib in 4000 patients at high cardiovascular risk. Almost a year later, Pfizer announced that they would spend “at least $100 million” to conduct what became PRECISION, a comparison of celecoxib, ibuprofen, and naproxen in high-risk cardiovascular patients. The principal investigator predicted completion within 4 years.\(^4\) At the outset, the ethics and the interpretability of the trial prompted controversy. European Union countries declined to participate because of concerns about the safety of celecoxib. It was suggested that such concerns, together with the event-driven nature of the trial, would delay completion, perhaps until expiration of the patent on celecoxib.\(^4\) Furthermore, such high-risk patients would likely be taking low-dose aspirin, which targets platelet COX-1–derived thromboxane A\(_2\). Both ibuprofen and naproxen interact to undermine sustained cardioprotection by aspirin; however, COX-2 is not extant in platelets, risking an intrinsic bias in favor of celecoxib.\(^2\)
A third major constraint to the interpretation of PRECISION is that, of ≈8000 patients randomly assigned to each treatment, ≈5000 had stopped taking their assigned therapy by the end of the study. Approximately 30% were lost to follow-up, and, of those who ceased taking their allocated treatment, a fraction recommenced taking some NSAIDs. All these observations intersect with the comments above to question the validity of the conclusions around noninferiority.

This trial was not designed to address differences in the likelihood of an NSAID interaction with low-dose aspirin as a source of bias in favor of celecoxib. The patients were not randomly assigned as to aspirin use, and there was no objective measurement of aspirin action. We do not know whether aspirin was taken as prescribed (in ≈45%) at outset and whether it was discontinued or started during the study, either by prescription or by patient access to this over-the-counter drug. Thus, it is unknown who took aspirin throughout the study and whether, if they did, cardiovascular events might have ensued in the ibuprofen and naproxen groups because of an interaction undermining the antiplatelet effects of the drug.

Similarly, the trial was not powered or designed to address the reported comparative cardiovascular safety of high-dose naproxen. Naproxen pharmacokinetics are highly variable, and an ill-defined proportion of patients have an extended half-life. Naproxen would be expected to confer cardioprotection comparable to the irreversible platelet inhibitor aspirin only in those individuals who take high doses or have a long naproxen half-life and are not already taking aspirin. As with the aspirin interaction, the absence of evidence is not evidence of absence.

In summary, there are so many problems with the interpretation of PRECISION that it fails to inform clinical practice. Thus, despite the enrollment of >24,000 patients and more than a decade of study, we are no closer to being able to advise the millions of patients with chronic arthritic pain regarding relative efficacy and safety of the treatments available to them. Such a disappointment indicates a need to move away from such blunt instruments as poorly designed trials to deep phenotyping studies that identify factors that predispose to benefit and risk at an individual level, thereby bring more precision to the use of NSAIDs.

DISCLOSURES
Dr FitzGerald has served as a consultant for Pfizer.

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FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

REFERENCES


