



Published in final edited form as:

Circulation. 2017 January 10; 135(2): 113–115. doi:10.1161/CIRCULATIONAHA.116.026324.

ImPRECISION: Limitations to Interpretation of a Large Randomized Clinical Trial

Garret A. FitzGerald, MD, FRS

The Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia

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

The analgesic efficacy of NSAIDs derives largely from suppressing cyclooxygenase (COX-2)-derived prostaglandins (PG) E₂ and I₂ (prostacyclin), while their gastrointestinal adverse effects result from inhibition of COX-1-derived gastroduodenal PGE₂ and PGI₂ and COX-1-derived thromboxane (Tx)A₂ in platelets. This prompted 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 GI events with the COX-2 inhibitor (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 PGI₂ in the vasculature. Evidence consistent with this hypothesis emerged from VIGOR with more serious thromboembolic events with rofecoxib. Subsequently, definitive evidence of cardiovascular hazard emerged from 10 placebo-controlled trials of structurally distinct COX-2 inhibitors (2). Finally overview analysis of individual data derived from ~750 randomized trials (3) provided a risk estimate of the magnitude of this hazard from COX-2 inhibitors with 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 non-existent.

Coincident with 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 due to 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 expiry of the patent on celecoxib (4). Furthermore, such high risk patients would likely be taking low dose aspirin which targets platelet COX-1 derived TxA₂. 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).

Eleven years later, just after celecoxib, with sales over \$2B annually, comes off patent, the results of PRECISION have been presented at the Scientific Sessions of the American Heart Association. The headline results are striking; no difference in the cardiovascular hazard from the three NSAIDs; no evidence supportive of an aspirin – NSAID interaction and no evidence to suggest that naproxen is safer than the other two drugs. Fewer serious GI events and renal adverse events were also noted on celecoxib-treated subjects. Given that this was a randomized trial in ~24,000 patients, has PRECISION delivered a precise outcome and should it alter practice? Unfortunately, the answer is no.

PRECISION is not a study of arthritis patients at high cardiovascular risk. It mostly included osteoarthritis patients at low cardiovascular risk – cardiac event rates were roughly 1% per year. Yet the mechanism of cardiovascular hazard from NSAIDs is conditioned by the underlying cardiovascular risk substrate of the patient population (2). Furthermore, this is a non-inferiority trial. Due to the low number of events accruing, the statistical upper bound was relaxed during the trial from 1.3 to 1.4 (with a power of only 80%). How likely would celecoxib be found inferior? The RR for serious vascular events from celecoxib is 1.36 (3).

A second series of concerns relate to whether pharmaco-equivalent levels of drug exposure were attained. Clearly, less drug exposure means less efficacy, but also fewer cardiovascular and GI adverse effects. Practitioners in PRECISION could increase the dose of ibuprofen and naproxen to attain efficacy. However restraint on dose escalation of celecoxib – a regulatory response in many countries to the cardiovascular signal detected in 2 previous randomized controlled trials – limited the average daily dose to just over 209mg. In the overview of RCTs, this dose was indistinguishable from placebo; its RR for serious vascular events was 0.95, in contrast to RRs of 1.29 and 2.96 at total daily doses of 400mg and 800mg. There were no primary analgesic efficacy endpoints in PRECISION. However, visual analog scale reporting of efficacy, reports of arthralgia and of osteoarthritis and the number of patients with “insufficient clinical response” are all significantly worse on celecoxib, consistent with the possibility of reduced comparative efficacy. Indeed, the higher rates of hypertension and renal effects of the other two drugs are also consistent with lower drug exposure in the celecoxib group. Interestingly, Pfizer sponsored a concurrent comparison of switching to prescribed celecoxib or continuing on conventional NSAID therapy in a European population at low cardiovascular risk; here interpretation of the trial was undermined by asymmetric withdrawal from celecoxib (average ~170mg mean daily dose in a limited data set) due to lack of efficacy (5).

A third major constraint to the interpretation of PRECISION is that of ~ 8000 patients randomized to each treatment, ~ 5000 had had stopped taking their assigned therapy by the end of the study. Roughly 30% were lost to follow up, and of those who ceased taking their allocated treatment, a fraction recommenced taking some NSAID. All of these observations intersect with the comments above to question the validity of the conclusions around non-inferiority.

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 randomized as to aspirin use and there was no objective measurement of aspirin action. We do not know if aspirin was taken as prescribed (in ~45%) at outset, 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 due to an interaction undermining the anti-platelet effects of the drug.

Similarly, the trial was not powered or designed to address the reported comparative cardiovascular safety of high dose naproxen (3). 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 and/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.

References

1. Becker MC, Wang TH, Wisniewski L, Wolski K, Libby P, Lüscher TF, Borer JS, Mascette AM, Husni ME, Solomon DH, Graham DY, Yeomans ND, Krum H, Ruschitzka F, Lincoff AM, Nissen SE, PRECISION Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. *Am Heart J.* 2009; 157:606–12. [PubMed: 19332185]
2. Grosser T, Yu Y, FitzGerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annu Rev Med.* 2010; 61:17–33. [PubMed: 20059330]
3. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Bhalra N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanasa A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet.* 2013; 382:769–79. [PubMed: 23726390]

4. Couzin J. Drug testing. Massive trial of Celebrex seeks to settle safety concerns. *Science*. 2005; 310:1890–1.
5. MacDonald TM, Hawkey CJ, Ford I, McMurray JJ, Scheiman JM, Hallas J, Findlay E, Grobbee DE, Hobbs FD, Ralston SH, Reid DM, Walters MR, Webster J, Ruschitzka F, Ritchie LD, Perez-Gutthann S, Connolly E, Greenlaw N, Wilson A, Wei L, Mackenzie IS. Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT). *Eur Heart J*. 2016 Oct 4. pii: ehw387 [Epub ahead of print].

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript