STATE-OF-THE-ART REVIEW

Coxibs, traditional NSAIDs and cardiovascular safety post PRECISION: what we thought we knew then and what we think we know now

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Word count: 4571

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/cpt.696

Abstract

The aim of the present review is to analyze how thinking about the cardiovascular safety of NSAIDs has evolved during the past two decades, and discuss to what extent the additional information from PRECISION may alter our current mechanistic understanding and/or clinical practice.

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most widely prescribed drugs in the world, with more than 100 million prescriptions issued annually in the United States alone.[1] Although chemically heterogeneous, NSAIDs share a common mechanism of action, i.e., the inhibition of the cyclooxygenase (COX) activity of the prostaglandin (PG)G/H-synthase isozymes (also referred to as COX-1 and COX-2), that catalyzes the first committed step in prostanoid biosynthesis.[2] While COX-2 inhibition is necessary and sufficient to explain the analgesic, antipyretic, and antiinflammatory effects of NSAIDs, variable degrees of inhibition of both COX-1 and COX-2 contribute to mechanism-based toxicities affecting the gastrointestinal (GI) tract, the cardiovascular (CV) system and the kidneys. [2-4] Up until the end of the past century, safety concerns were mainly focused on the COX-1-dependent GI toxicity of NSAIDs [5] that led to the successful clinical development of the coxibs, selective inhibitors of COX-2, to reduce its burden.[3] However, the large sample size of GI outcome trials of coxibs versus traditional NSAIDs (tNSAIDs), and the three-year duration of chemoprevention trials of coxibs versus placebo revealed a previously uncharacterized CV toxicity associated with COX-2 inhibition that led to the voluntary decision of Merck & Co. to withdraw rofecoxib from the market on September 30th, 2004.[6,7] Shortly after, quite similar findings were reported from chemoprevention trials of celecoxib, and the Food and Drug Administration (FDA) allowed continued marketing of the sole remaining coxib, but mandated a CV safety trial, the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION).[1] The results of this expensive, 10-year exercise involving the recruitment of a total of 24,222 patients at 926 centers in 13 countries were recently published [1] and generated a hot debate on their interpretation.[8] The aim of the present review is to analyze how thinking about the CV safety of NSAIDs has evolved during the past two decades, and discuss to what extent the additional information from PRECISION may alter our current mechanistic understanding and/or clinical practice. In

doing so, we shall preferably refer to the whole class of NSAIDs as "COX-2 inhibitors", a term which includes both tNSAIDs and coxibs, inasmuch as their COX-isozyme selectivity represents a continuous variable with substantial overlap between the older and newer drugs (e.g., diclofenac and celecoxib: see Figure 1) [3], and does not appear to represent an important determinant of their CV safety profile.[4,7]

The Age of Innocence

Given that aspirin, the first marketed NSAID, reduces the risk of atherothrombotic events over a wide range of doses (from 30 to 1,500 mg daily), including three times daily (tid) and four times daily (qid) analgesic regimens,[9,10] it was widely assumed that non-aspirin NSAIDs would be associated with a similar cardioprotective phenotype, in the absence of any observational or randomized data to support this assumption.[11,12] It should be emphasized that the largest placebo-controlled trials of the most popular tNSAIDs (e.g., diclofenac) typically involved a few hundred patients treated for 3 to 4 months. Moreover, the only reversible COX inhibitors that had been tested for their antithrombotic efficacy were sulfinpyrazone, indobufen, and triflusal, with conflicting results in trials of limited sample size.[11]

tNSAIDs (with the exception of aspirin) and sulfinpyrazone compete dose dependently with arachidonate for binding to a common docking site within platelet COX-1. Such a process closely follows systemic plasma drug concentrations and is reversible as a function of drug elimination.[13] Moreover, at variance with the cumulative inactivation of platelet COX-1 activity following repeated daily dosing with low-dose aspirin,[14] no evidence of cumulative inhibition of platelet COX-1 activity was found with ibuprofen or sulindac in healthy subjects or patients with chronic glomerular disease.[15] Thus, 85% reduction of platelet TXA_2 production was measured after 1 week of treatment with a full analgesic dose (200 mg twice

daily [bid]) of sulindac.[15] With the notable exception of high-dose indomethacin[13] or naproxen,[16] it appears that none of these reversible inhibitors can achieve and sustain greater than 95% inhibition of platelet COX-1 activity throughout the dosing interval. Inasmuch as virtually complete and long-lasting suppression of TXA_2 production is required for maximal inhibition of platelet activation *in vivo*,[17,18] it appeared unlikely -at least to platelet experts- that incomplete and reversible inhibition of platelet COX-1 by most non-aspirin NSAIDs would be sufficient to produce clinically detectable CV protection comparable with that achieved by low-dose aspirin through profound and persistent inactivation of the same drug target.[11]

It was in this climate of presumed CV safety of tNSAIDs that two unexpected findings were reported.[19,20] The first came from a study of the clinical pharmacology of celecoxib in healthy subjects, in which 37 young volunteers of both sexes were randomized under double blind conditions to receive a single dose of celecoxib (100, 400, or 800 mg), 800 mg of ibuprofen, or placebo.[19] Repeated measurements of pharmacokinetic (PK) and pharmacodynamic (PD) parameters were performed up to 24 hours after dosing. The study demonstrated that the COX-2 selectivity of celecoxib is relative, rather than absolute, but also provided indirect evidence to imply a major role for COX-2 in the biosynthesis of both systemic and renal prostacyclin (PGI_2), under physiological conditions in healthy humans. Thus, the urinary excretion of both a major enzymatic metabolite (PGI-M, largely reflecting systemic biosynthesis) and the non-enzymatic hydrolysis product (6-keto-$PGF_{1\alpha}$, predominantly reflecting renal synthesis) of PGI_2 was similarly reduced following celecoxib 400 and 800 mg and ibuprofen 800 mg. Celecoxib depressed PGI-M excretion to a comparable degree at doses that inhibited blood monocyte COX-2 activity to the same extent as ibuprofen.[19] This unexpected finding was reinforced by similar effects on both urinary 6-keto-$PGF_{1\alpha}$ and PGI-M of a structurally distinct COX-2 inhibitor -rofecoxib- under chronic

dosing conditions in elderly humans.[21] Although Topper et al. [22] had previously shown that laminar, but not turbulent, shear may up-regulate COX-2 in endothelial cells *in vitro*, the findings of FitzGerald's group represented the first demonstration that the low baseline rate of PGI_2 biosynthesis is largely driven by the inducible COX-isozyme thought -at the time- to be involved primarily in pathophysiologic processes. PGI_2 is a potent platelet inhibitor and vasodilator. However, its pathophysiologic role *in vivo* had remained largely speculative in the absence of a selective antagonist of the PGI_2 receptor (IP), up until 1997 when Murata et al succeeded in generating mice deficient in the IP receptor whose phenotype suggested an important role for PGI_2 in mediating inflammation and in protecting against thrombosis.[23]

The second unexpected finding came from a large GI outcome trial, VIGOR, a prospective, randomized, double-blind comparison of rofecoxib (50 mg once daily) and naproxen (500 mg bid) in 8076 patients with rheumatoid arthritis (RA). [20] Although its results provided the first convincing validation of the COX-1-dependence of GI toxicity, by demonstrating a highly significant 50% reduction in confirmed clinical upper GI events associated with selective COX-2 inhibition during a median follow-up of 9.0 months, it also reported that "myocardial infarctions were less common in the naproxen group than in the rofecoxib group" (0.1% vs. 0.4%), a finding interpreted by the authors as reflecting an aspirin-like "coronary protective effect" of naproxen due to its PK/PD properties, i.e., a relatively long half-life and 95% inhibition of platelet TXB_2 production throughout the dosing interval.[20] In light of what was known at the time of publication of the VIGOR study,[19,21-23] an equally biologically plausible explanation was that its vascular results reflected a mechanism-based thrombogenic effect of rofecoxib, the size of which was likely inflated by the small number of events recorded in the whole trial, due to the relatively low CV risk of the exposed patients and short duration of follow-up.[3] However, the lack of a placebo arm in the trial precluded unequivocal interpretation of its findings.

The Coxib Enlightenment

The publication of the VIGOR study [20] represented a turning point in the public awareness of a potential CV hazard of COX-2 inhibitors, and prompted ongoing and planned clinical trials of these agents to prospectively collect and adjudicate CV events during follow-up. Because 5 different coxibs (celecoxib, rofecoxib, valdecoxib, etoricoxib and lumiracoxib) underwent clinical development and regulatory approval -in at least some countries- with phase 3/4 trials involving over 100,000 osteoarthritis (OA)/RA patients, this allowed the cumulative accrual of substantial new information on their CV effects, with the main limitation being that most long-term efficacy and safety trials compared a coxib to one or two tNSAIDs (mostly, ibuprofen, naproxen and diclofenac). However, the emergence of an important role for COX-2 in colorectal cancer [24] induced both Merck and Pfizer to initiate placebo-controlled, long-term chemoprevention studies of rofecoxib and celecoxib in relatively younger subjects with sporadic colorectal adenomas.[25,26] The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial was designed to evaluate the hypothesis that three years of treatment with rofecoxib (25 mg daily) would reduce the risk of recurrent adenomatous polyps among patients with a history of colorectal adenomas.[25] In APPROVe, a total of 46 patients in the rofecoxib group had a confirmed thrombotic event during 3059 patient-years of follow-up (1.50 events per 100 patient-years), as compared with 26 patients in the placebo group during 3327 patient-years of follow-up (0.78 event per 100 patient-years); the corresponding relative risk (RR) was 1.92 (95% confidence interval [CI], 1.19 to 3.11; P=0.008).[25] These findings led Merck to halting the trial and announcing the voluntary withdrawal of rofecoxib from the market on September 30th, 2004. These events prompted the data and safety monitoring board (DSMB) and steering committee of a similar ongoing trial of celecoxib (the Adenoma Prevention with Celecoxib [APC]) to request a focused

reassessment of data on CV safety by an independent committee, with the results presented at their scheduled meeting on December 10th, 2004. In the APC trial, a composite CV end-point of death from CV causes, myocardial infarction, stroke, or heart failure was reached in 7 of 679 patients allocated to the placebo group (1.0%), as compared with 16 of 685 patients allocated to 200 mg of celecoxib bid (2.3%; hazard ratio [HR], 2.3; 95% CI, 0.9 to 5.5) and with 23 of 671 patients receiving 400 mg of celecoxib bid (3.4%; HR, 3.4; 95% CI, 1.4 to 7.8).[26] On the basis of these findings, the DSMB recommended early discontinuation of the study drug. These placebo-controlled trials showed unequivocally that two structurally unrelated coxibs were associated with an increased risk of atherothrombotic vascular events, and suggested that this was a dose-dependent class effect. However, the size of the increased risk was substantially uncertain, potentially ranging from a modest 20% to an implausible 8-fold increase.[25,26] Soon after the APPROVe and APC studies were reported, a meta-analysis of randomized trials comparing a coxib versus placebo or a coxib versus tNSAID indicated that some tNSAIDs (notably, diclofenac and ibuprofen) might also enhance atherothrombotic events, but that these hazards might depend on the degree and duration of suppression of platelet COX-1.[27] In these analyses, high-dose naproxen (generally, 500 mg bid), which stands alone among current tNSAID regimens in being able to induce near complete suppression of platelet TXA_2 biosynthesis *in vivo* throughout the 12-hour dosing interval,[16] did not seem to increase the risk of atherothrombosis, but other high-dose tNSAID regimens with only transient effects on platelet COX-1 were associated with a small, but definite, vascular hazard.[27] Interestingly, and perhaps surprisingly, given that this evidence was available to both regulatory authorities at the beginning of 2005, the FDA required that the summaries of product characteristics of all NSAIDs (with the exception of aspirin) carry a black-boxed warning about the risks of CV disease, whereas the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) decided that coxibs (but

not tNSAIDs) should be contraindicated in patients with coronary heart disease (CHD) or stroke, and used with caution in patients with risk factors for CHD.[7] Only during the last few years, has the CHMP extended similar restrictive labeling to diclofenac and high-dose ibuprofen.

Because randomized trials avoid selection bias, they could provide more reliable estimates of the size, timing, and severity of any moderate CV hazards of NSAID regimens than observational studies. Accordingly, we initiated a collaborative meta-analysis of individual participant data (IPD) (or, if not available, tabular data) from all the available randomized trials of NSAIDs (the Coxib and traditional NSAID Trialists' [CNT] Collaboration).(4) The main objective was to characterize and quantify the CV and GI risks of particular NSAID regimens among different types of patients, particularly those at increased risk of vascular disease. This meta-analysis had access to IPD from trials comparing a coxib vs placebo, and a coxib vs tNSAID, and the ratio of the estimated rate ratios (RRs) in these two comparisons was used to calculate RRs corresponding to a tNSAID vs placebo. This method was justified since the average dose of a coxib in the two types of comparison was similar, with only a few exceptions the tNSAID regimens studied in these trials were similar (naproxen 500 mg bid, diclofenac 75 mg bid, ibuprofen 800 mg tid), and there was no evidence of heterogeneity in RRs among different types of patients studied in the trials. The RRs thus estimated for different dose regimens of celecoxib (200, 400 and 800 mg daily), ibuprofen (2400 mg daily), and naproxen (1000 mg daily) are illustrated in Figure 2a. In the CNT meta-analysis, the RR for comparisons of any coxib vs ibuprofen (2400 mg daily) was 0.95 (0.58-1.46), which may be seen as the ratio of the RRs for a coxib vs placebo (1.37; 95% CI, 1.14-1.66) and ibuprofen (2400 mg daily) vs placebo (1.44; 95% CI, 0.89-2.33). Similarly, the comparison of any coxib vs naproxen (1000 mg daily) was 1.49 (1.16-1.92), the ratio of RRs of 1.37 (coxib vs placebo) and 0.93 (naproxen 1000 mg vs placebo) (Figure 2a).[4] This representation serves to highlight

the difference between the neutral effect of naproxen 1000 mg daily (probably resulting from a COX-2 mediated hazard masked or mitigated by a protective antiplatelet effect) and the cardiotoxic effect of ibuprofen 2400 mg daily. The method of indirect comparisons produced internally consistent results in the CNT analyses where the doses studied were similar, but this meta-analysis also demonstrated that the CV hazards of COX-2 inhibitors were dose-dependent, reflecting the adverse impact of more intensive COX-2 inhibition (at least when not opposed by sustained COX-1 inhibition).[4] Although dose comparisons were not possible for ibuprofen and diclofenac, the meta-analysis highlighted the potential importance of the dose of naproxen. In particular, the results of the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) trial,[28] which compared celecoxib (200 mg bid) vs ibuprofen (800 mg tid) vs naproxen (220 mg bid), suggested that, when used at such a lower dose, naproxen may be associated with CV hazards. The CNT Collaboration's overview indicated that the RR for celecoxib 400 mg daily vs placebo was 1.29 (95% CI, 0.81-2.05), and the RR for the comparison of celecoxib 400 mg vs naproxen 440 mg (most of which was from ADAPT) was 1.00 (0.38-2.48), implying that the RR for naproxen 440 mg daily vs placebo was 1.29 (95% CI, 0.69-2.71) – a hazard as compared to the estimated neutral effect of a daily dose of 1000 mg (Figure 2a). These findings are mechanistically consistent with the dose-dependent inhibition of platelet COX-1 activity by naproxen, whereby -in contrast to the 1000 mg dose- the 440 mg dose is associated with lower than 95% inhibition of serum TXB_2 for most of the 12-hour dosing interval.[29] Given the strikingly non-linear relationship between inhibition of platelet COX-1 activity measured *ex vivo* and indices of *in vivo* platelet activation,[30,31] with suppression of the latter increasing exponentially above 95% inhibition of the former,[31] low-dose naproxen is expected to produce similar deleterious CV effects as other COX-2 inhibitors because of its failure to produce an aspirin-like antiplatelet effect throughout the dosing interval.[32]

The Post-Factual Era

Following publication of the CNT meta-analysis (4) two CV safety trials have been reported, the Standard care vs. Celecoxib Outcome Trial (SCOT) (33) and PRECISION.(1) Both were mandated by regulatory authorities (EMA and FDA, respectively), and funded by Pfizer. The SCOT trial used a Prospective, Randomized, Open label, Blinded Endpoint evaluation (PROBE) design to compare the CV and GI safety of continuing prescribed tNSAID therapy vs. switching to prescribed celecoxib in individuals with OA (94% of the study population) or RA free from significant CV disease (only 12% were reported taking aspirin at baseline). The original power calculation was for 13,682 patients to be followed up to two years to generate 611 primary endpoints (the composite of hospitalization for non-fatal MI or other biomarker-positive acute coronary syndrome, non-fatal stroke or CV death) with an anticipated event rate of about 2% per year. Fewer subjects than expected agreed to take part in the study, so the participating academic centers and primary care practices had to follow up those randomized for longer. In fact, 7297 subjects were followed for an average of 3.2 years yielding 87% of the planned drug exposure. However, the adjudicated primary CV event rate was substantially lower than expected: observed 0.9% vs expected >2%.(33) The main non-inferiority analysis for the primary outcome used on-treatment comparisons. The final study design had a non-inferiority limit HR of 1.4 for the primary CV endpoint requiring 277 first primary endpoints for 80% power. In the prescribed celecoxib group, 51% withdrew from the randomized therapy compared with 30% not continuing with any prescribed tNSAID therapy ($P<0.0001$). The prevailing reason recorded for the higher withdrawal of those allocated to switch to celecoxib was lack of efficacy, with other reasons being represented by poor tolerability and adverse effects of celecoxib.(33) The mean doses of NSAIDs taken per day in Scotland -where full data were available- were 170 mg for celecoxib, 79 mg for diclofenac, 676

mg for ibuprofen, and 581 mg for naproxen.(33) In the on-treatment analysis, 65 participants (0.95 per 100 patient-years) in the celecoxib group had a primary outcome compared with 81 (0.86 per 100 patient-years) in the tNSAID group (HR 1.12; 95% CI, 0.81–1.55; P.0.50). Therefore, the pre-specified on-treatment noninferiority of celecoxib vs tNSAIDs was not demonstrated. According to the authors of the SCOT trial, this study excluded an increased risk of the primary endpoint of more than two events per 1000 patient-years associated with switching to prescribed celecoxib.(33) However, the limited statistical power of this trial, as well as differential withdrawal rates in the two treatment arms, make unequivocal interpretation of its findings problematic at best.

PRECISION was a randomized, multicenter, double-blind, noninferiority trial involving over 24,000 OA (90% of the study population) and RA patients who had established CVD or an increased CVD risk.(1) Among the randomized patients, 77% were categorized as being in primary prevention and 23% in secondary prevention. However, only about half were reported as being aspirin or statin users at study entry, with no information on CV drug use during the trial. Naproxen was designated as the primary comparator for the assessment of the CV noninferiority of celecoxib. Noninferiority required four criteria to be met; in the original design, a HR not exceeding 1.12 was required, with an upper limit of the one-sided 97.5% CI of less than 1.33 in both the intention-to-treat population (ITT) and the on-treatment population. The trial was event-driven, requiring 762 events of the primary end-point (a composite of death from CV causes, including hemorrhagic death, nonfatal MI, or nonfatal stroke) to provide 90% power to demonstrate noninferiority. Under the assumption of an annual event rate of 2% and a treatment discontinuation rate of 40%, the required sample size was estimated to be 20,000 patients. However, the observed event rate was lower, the discontinuation rate higher, and the enrollment rate slower than expected. Therefore, the protocol was amended to have the study provide 80% power, and the upper

97.5% confidence limit for noninferiority in the on-treatment population was modified to 1.40, which required 580 events in the ITT and 420 events in the on-treatment population.(1) A total of 24,222 patients were randomized, of whom 8072 patients assigned to the celecoxib group (mean daily dose, 209 mg), 7969 assigned to the naproxen group (852 mg), and 8040 assigned to the ibuprofen group (2045 mg). In assessing the comparability of these mean daily doses, it is important to emphasize that patients were randomly assigned to receive fixed regimens of celecoxib (100 mg bid), ibuprofen (600 mg tid), or naproxen (375 mg bid) with matching placebo. At subsequent visits, investigators could increase the dose of celecoxib to 200 mg bid, the dose of ibuprofen to 800 mg tid, or the dose of naproxen to 500 mg bid for the treatment of symptoms of RA patients. For OA patients increases in the doses of ibuprofen and naproxen were allowed; however, regulatory restrictions precluded dose escalation for celecoxib in these patients.(1) The mean durations of treatment and follow-up were 20.3 and 34.1 months, respectively. During the 10-year duration of the trial, 69% of patients stopped taking the study drug, and 27% discontinued follow-up. These low levels of adherence and retention make interpretation of "noninferiority" problematic.(8) In the ITT population, the primary outcome occurred in 188 patients in the celecoxib group (2.3%), 201 in the naproxen group (2.5%), and 218 in the ibuprofen group (2.7%). The HR for this outcome in the celecoxib group, as compared with the naproxen group, was 0.93 (95% CI, 0.76 to 1.13; P<0.001 for noninferiority). The HR for celecoxib versus ibuprofen was 0.85 (95% CI, 0.70 to 1.04; P<0.001 for noninferiority). In the on-treatment population, the primary outcome occurred in 134 patients in the celecoxib group (1.7%), 144 in the naproxen group (1.8%), and 155 in the ibuprofen group (1.9%). The HR in the celecoxib group, as compared with the naproxen group, was 0.90 (95% CI, 0.71 to 1.15; P<0.001 for noninferiority); for celecoxib versus ibuprofen, the HR was 0.81 (95% CI, 0.65 to 1.02; P<0.001 for noninferiority). Nissen et al argue that these results do not support the "widely advocated belief that naproxen

treatment, as compared with treatment with other NSAIDs, results in better cardiovascular outcomes".(1) However, they fail to acknowledge that any potential CV safety advantage of naproxen, as demonstrated by the CNT Collaboration's meta-analysis in a largely non-aspirin-treated population receiving naproxen 1000 mg daily, was masked by at least two features of the PRECISION population, i.e., the lower naproxen dose used and the concomitant administration of aspirin in 60% and 46% of the patients, respectively.(1) In both subgroups, naproxen would be expected to produce the same untoward CV effects as any other COX-2 inhibitor, as predicated on the basis of the mechanistic considerations discussed in the previous section.(7) Moreover, PRECISION was not designed to assess the potential clinical consequences of a differential impairment of aspirin-dependent platelet COX-1 acetylation by naproxen and ibuprofen versus celecoxib, previously demonstrated in healthy subjects (34,35) as well as in OA patients with stable ischemic heart disease.(36) According to the authors, the PRECISION trial "provides statistically strong evidence that the cardiovascular risk associated with moderate doses of celecoxib is not greater than that associated with tNSAIDs".(1) However, as acknowledged by the authors, the dose of celecoxib was limited by regulatory constraints to 200 mg daily for most patients, which clearly provided a potential safety advantage for celecoxib.(1)

A network meta-analysis of da Costa et al (37) assessing the effectiveness of COX-2 inhibitors for the treatment of pain in knee and hip OA provided evidence for a linear dose-effect of both celecoxib (P=0.030) and naproxen (P=0.026). In PRECISION, only about 5% of the celecoxib-treated patients (about half of those with RA) were allowed to switch from the moderate 200-mg dose to the maximum 400-mg dose, while approximately 40% of the naproxen-treated patients (with either RA or OA) were allowed to switch from the moderate dose of 750 mg to the maximum 1000-mg dose.(1) Not surprisingly, naproxen-treated patients had a significantly greater reduction in pain, as assessed with the use of VAS scores,

than did patients treated with celecoxib (P<0.001).(1) This finding is consistent with the PK/PD analyses of McAdam et al (19) showing the requirement for high plasma levels of celecoxib in order to achieve >80% inhibition of monocyte COX-2 activity in healthy subjects. Additional evidence for dose-dependent, COX-2-mediated effects of celecoxib is provided by placebo-controlled studies of its chemopreventive properties against familial (38) and sporadic (39) colorectal adenomas at daily doses ranging between 200 and 800 mg. Thus, in patients with familial adenomatous polyposis, celecoxib 800 mg -but not 200 mg- daily was effective in reducing the polyp burden.(38) Moreover, celecoxib 400 or 800 mg daily was associated with dose-dependent reduction in sporadic adenoma recurrence and increase in CV events in the APC trial discussed above.(39)

In our view, PRECISION failed to answer the key question of the relative CV safety of different COX-2 inhibitors in a high CV risk setting. First of all, the patients recruited in PRECISION were not at high CV risk, as reflected by an annual rate of serious vascular events of about 1%. Secondly, it did not compare daily doses of the three COX-2 inhibitors achieving equivalent levels of COX-2 inhibition, as indicated by significantly lower analgesic effects, renal adverse events and blood pressure changes in celecoxib-treated patients than in naproxen- or ibuprofen-treated patients.(1) It is unfortunate that such a large trial will not be useful in informing guideline committees, regulatory authorities or practicing physicians on how to manage OA or RA patients at truly high CV risk when they need NSAID therapy.

Conclusions

Within the limits to interpretation outlined in this review, the results of PRECISION (Figure 2b) are not incompatible with previous knowledge on the CV hazard of COX-2 inhibitors, as summarized by the CNT Collaboration's meta-analyses.(4) Moreover, these results do not alter our mechanistic understanding of the COX-2-dependent CV effects of these

agents (Figure 3),(7,32) and are unlikely to change current medical practice. Rather than mandating this kind of very expensive, but poorly informative study, regulatory authorities should perhaps rely on overviews of the totality of the randomized evidence, as summarized by tabular data (27) and eventually IPD (4) meta-analyses that are feasible through international collaboration of independent trialists and drug companies. In fact, given the moderate size of the increased risk in serious vascular events in a comparison of any high-dose coxib regimen versus placebo (RR=1.42; 95% CI, 1.13-1.78, P=0.003),(27) that was known at the time of initiation of PRECISION, it could have been anticipated that any difference among lower dose regimens of different COX-2 inhibitors would be too small to be measurable even in a 24,000 patient trial.

What is needed to really advance the safe use of COX-2 inhibitors for chronic pain relief is greater understanding of the major determinants of the interindividual variability in drug response. With a small fraction of the money spent by Pfizer to fund the PRECISION trial, the National Heart Lung and Blood Institute is funding an international group of scientists, the Personalized NSAID Therapeutics Consortium (PENTACON, www.pentaconhq.org), who are exploring what factors might contribute to variability in drug response and how that might be reflected by quantitative assays that might predict efficacy or hazard.

Finally, to put a discussion on the CV safety of COX-2 inhibitors in the appropriate context, we should not forget that pain symptoms associated with OA result in physical and walking disabilities,which are associated with an increased risk of death.(40) Although these drugs increase CV and GI risks to a varying extent, the CNT collaboration's analyses indicate that the effects of different COX-2-inhibitor regimens in particular patients can be predicted, which could help in guiding decisions about the clinical management of chronic inflammatory disorders.(4)

ACKNOWLEDGMENTS

This work was supported by grants from the UK Medical Research Council and the British Heart Foundation.

CONFLICT OF INTEREST

C.P. is Professor of Pharmacology at the Catholic University School of Medicine and a member of the Scientific Advisory Boards of the International Aspirin Foundation, the Dutch Heart Foundation and the William Harvey Research Institute. C.B. is Professor of Epidemiology, Director of the MRC Population Health Research Unit and Deputy Director of the Clinical Trial Service Unit and Epidemiological Studies Unit at the University of Oxford.

FINANCIAL DISCLOSURES

Dr. Patrono has received consulting and lecture fees from Amgen, AstraZeneca, and Bayer AG and an institutional grant from Bayer AG for investigator-initiated research on platelet activation and inhibition in diabetes mellitus. Dr. Baigent has received research grants from Merck & Co., Pfizer, and Novartis awarded to the University of Oxford for randomized trials in which the University is the trial sponsor.

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FIGURE LEGENDS

Figure 1. Concentrations of various drugs required to inhibit the activity of cyclooxygenase (COX)-1 and COX-2 by 50 percent (IC50) in human whole blood assays. Each point is the mean of three or four determinations. Drugs plotted below the diagonal line indicating equivalence are more potent inhibitors of COX-2 than COX-1.

6-MNA denotes 6-methoxy-2-naphthylacetic acid, the active metabolite of nabumetone.

Modified and updated from FitzGerald and Patrono, N Engl J Med 2001; 345,433-442.(3)

Figure 2. Effects of different COX-2 inhibitor regimens on major vascular events.

Rate ratios (RRs) are indicated by squares and their 99% CIs by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Squares or diamonds to the right of the solid line indicate hazard.

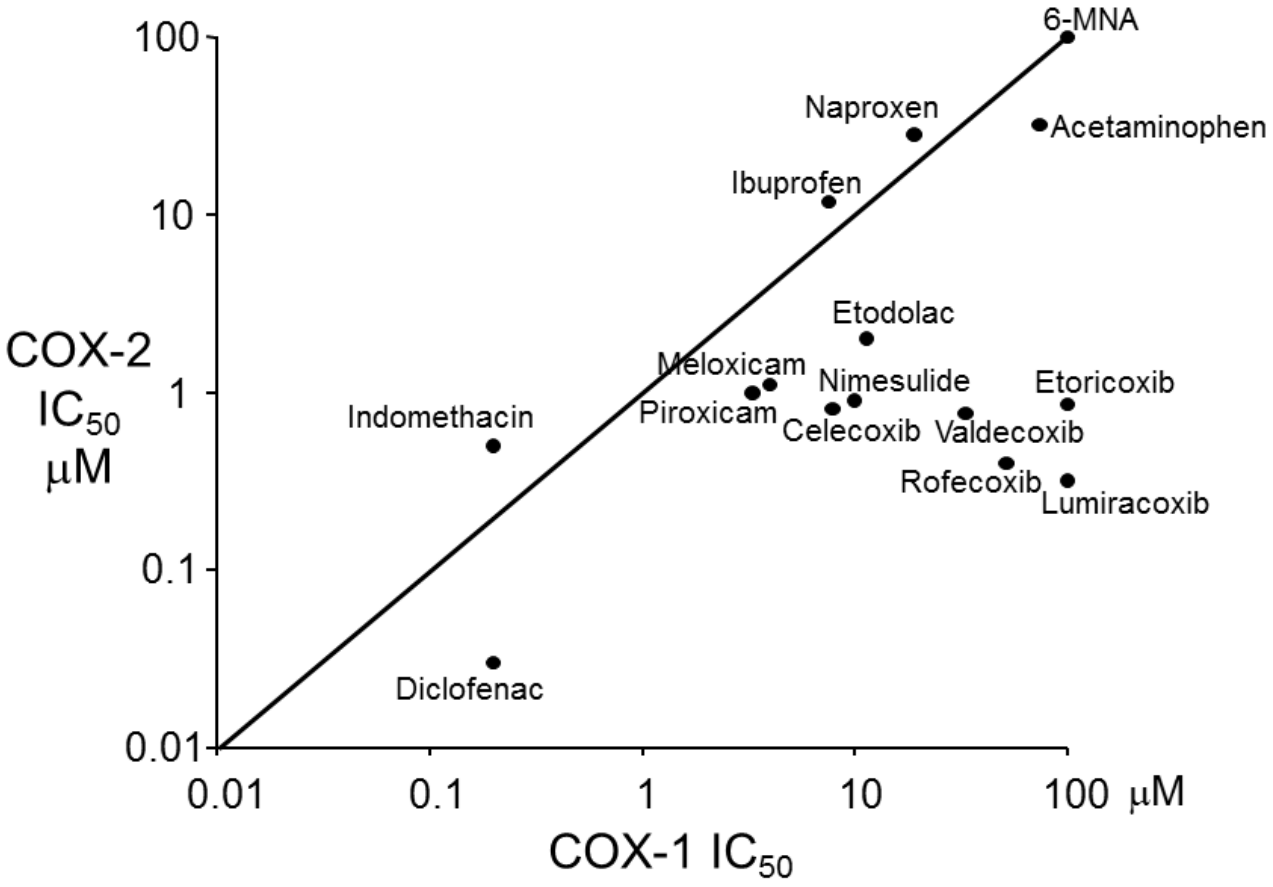
Panel a) reproduces both direct (celecoxib) and indirect (ibuprofen and naproxen) estimates from the CNT meta-analyses.(4) Panel b) is based on the assumption that the RR for ibuprofen vs placebo in the PRECISION trial (mean daily dose 2045 mg) was the same as in the CNT analyses (mean daily dose 2400 mg), and depicts estimates for naproxen and celecoxib relative to ibuprofen as derived from the direct comparisons in PRECISION.(1)

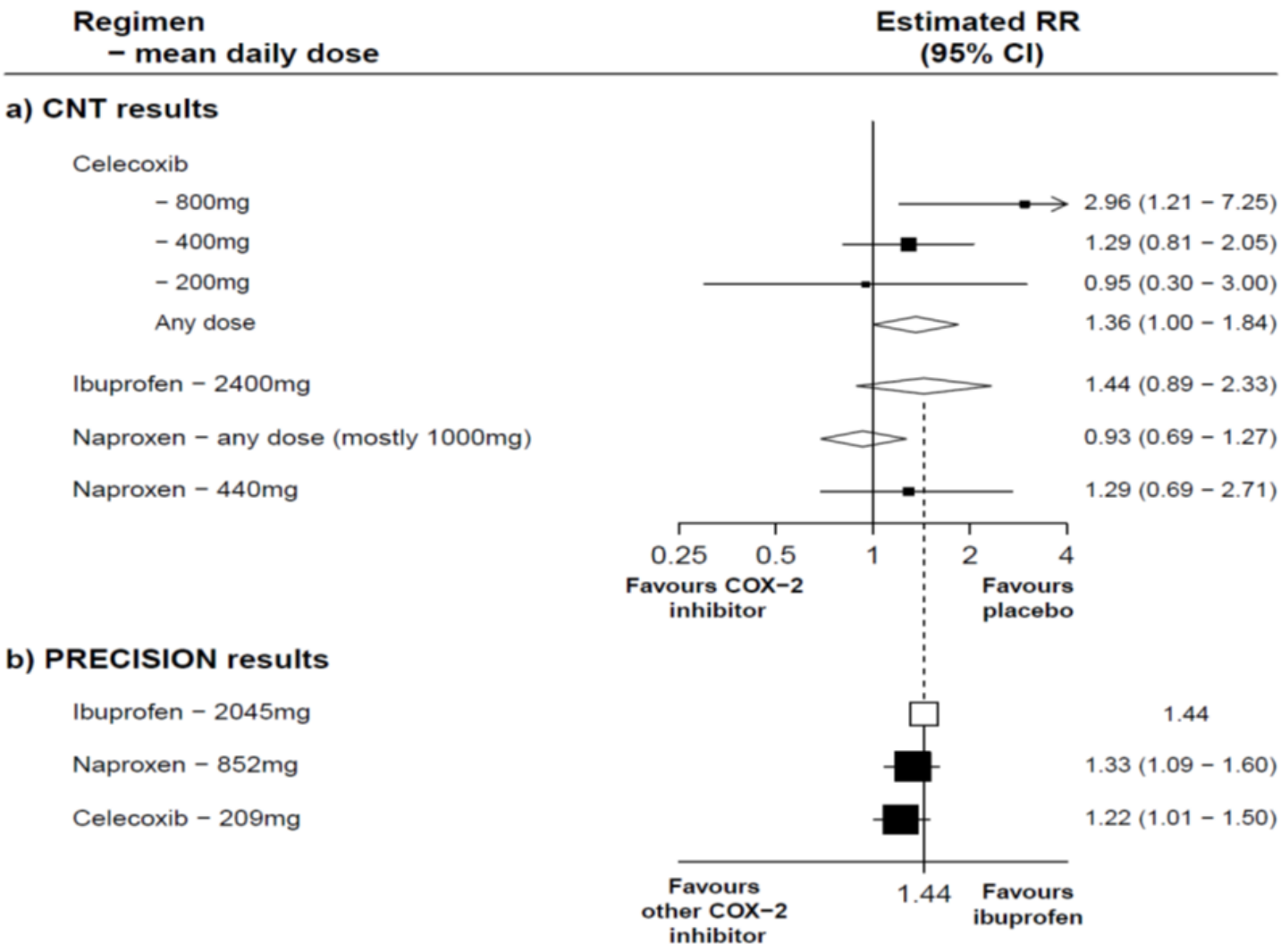
Major vascular event=myocardial infarction, stroke, or vascular death.

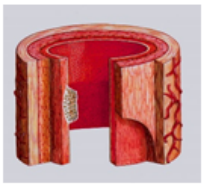
Figure 3. Mechanisms contributing to the cardiovascular effects of COX-2 inhibitors. The figure depicts the consequences of COX-2 inhibition in the vasculature, the heart, and the kidney, and its short-term and long-term clinical read-outs.

COX, cyclooxygenase; CV, cardiovascular; GFR, glomerular filtration rate; NO, nitric oxide; PG, prostaglandin; RBF, renal blood flow

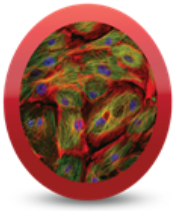
Reproduced from Patrono, Br J Clin Pharmacol 2016; 82:957-964.(32)



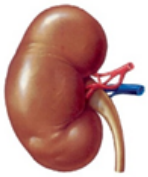




Vascular Endothelial & Smooth Muscle Cells



Cardiomyocytes



Renal

COX-2

≈

↓PGI_2

Unrestrained platelet activation onto eroded/ruptured coronary plaques

↓NO

Endothelial dysfunction

Enhanced probability of coronary atherothrombosis

COX-2

≈

↓PGI_2, PGE_2

Decreased protection against arrhythmias & oxidative injury

Increased risk of heart failure

Cortical COX-2

≈

↓PGI_2

↓RBF ↓GFR

Medullary COX-2

≈

↓PGE_2

↓ Na^+, H_2O excretion

↑ Blood Pressure

Increased long-term CV risk