Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committees

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Testimony of Sidney Wolfe MD Public Citizen's Health Research Group

I have no financial conflicts of interest

----------**DOSAGE AND ADMINISTRATION**----------

-- **Use lowest effective dose for the shortest duration consistent with treatment goals for the individual patient. (1, 5.1, 5.4)**

OA: 200 mg once daily or 100 mg twice daily (2.1, 14.1)

RA: 100 to 200 mg twice daily (2.2, 14.2)

JRA: 50 mg twice daily in patients 10-25 kg. 100 mg twice daily in patients more than 25 kg (2.3, 14.3)

AS: 200 mg once daily single dose or 100 mg twice daily. If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit (2.4, 14.4)

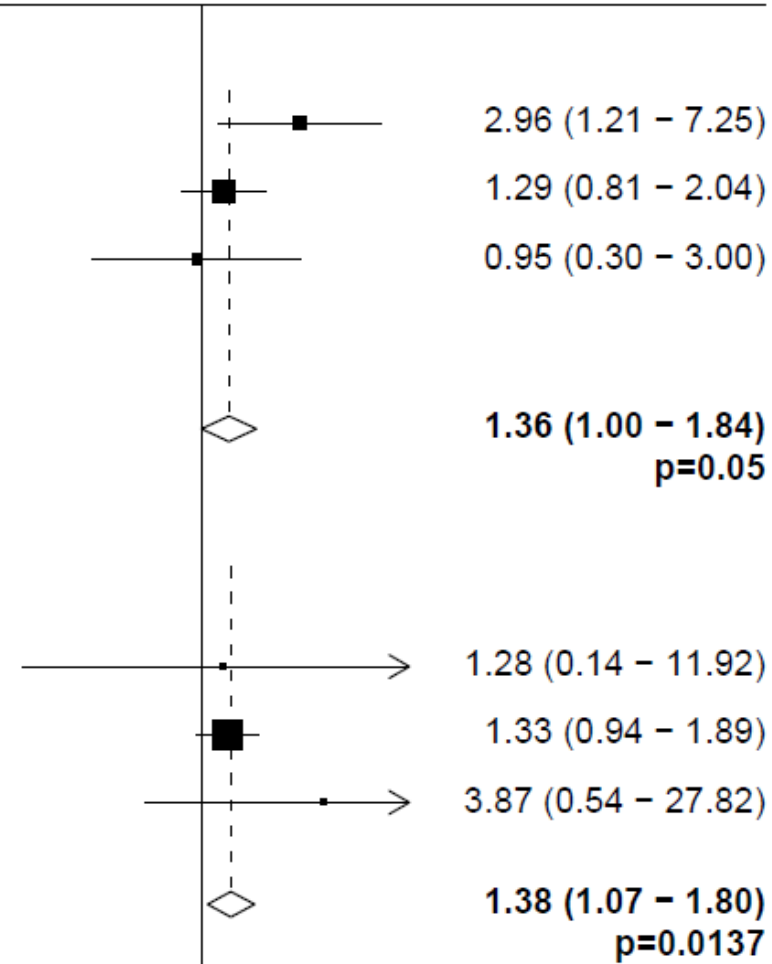
AP and PD: 400 mg initially, followed by 200 mg dose if needed on first day. On subsequent days, 200 mg twice daily as needed (2.5, 14.5)

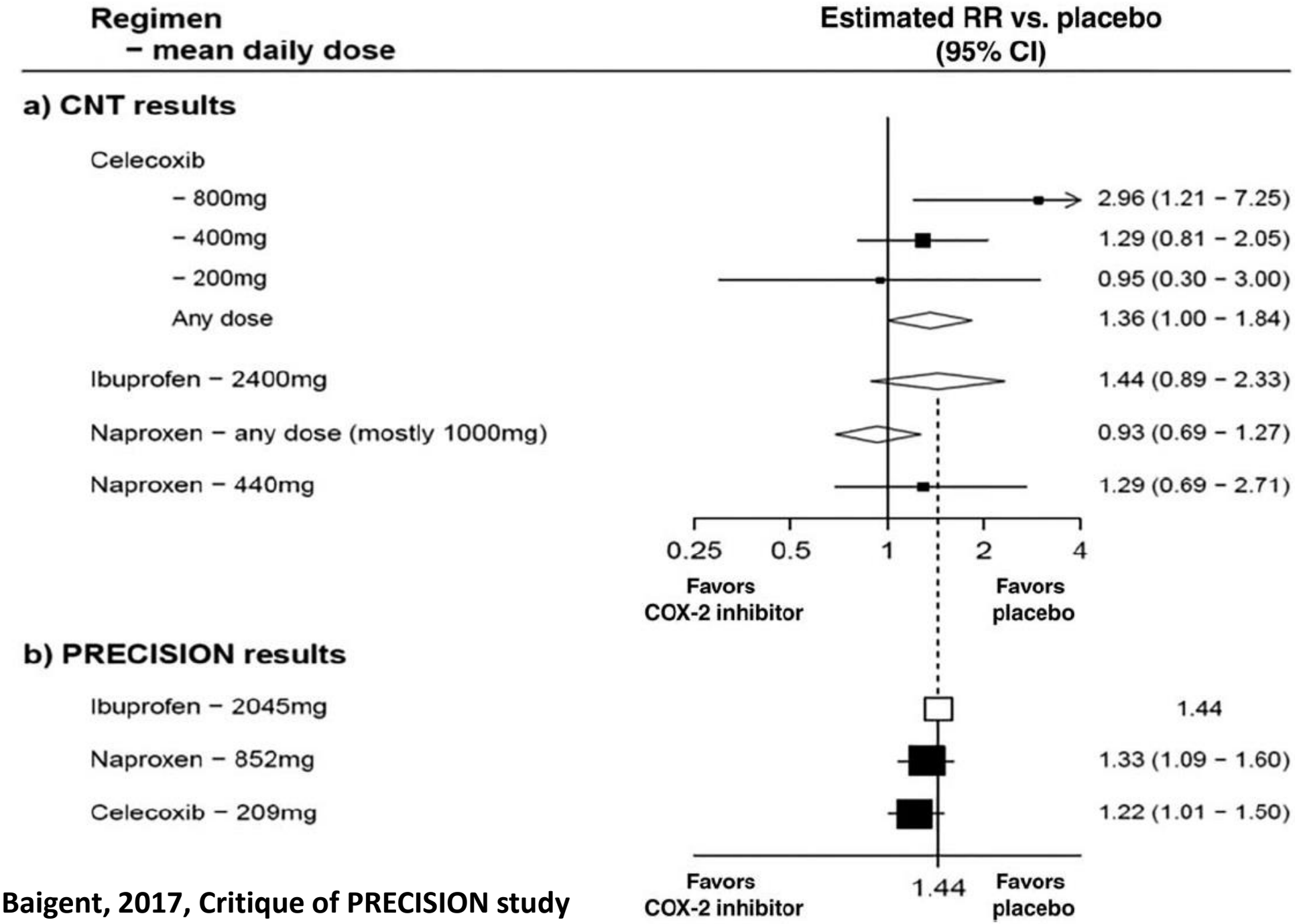
Current labeling for celecoxib

Webfigure 15: Effect of different coxib regimens on major vascular events, by dose: trials of a coxib vs placebo

2013 *Lancet* CNT study
Appendix, page 18

Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated placebo	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 6.4 (p=0.0117)				
800mg daily	5	83	30 (1.65)	8 (0.46)	2.96 (1.21 − 7.25)
400mg daily	22	74	81 (1.01)	56 (0.70)	1.29 (0.81 − 2.04)
200mg daily	17	10	14 (1.26)	11 (1.45)	0.95 (0.30 − 3.00)
100mg daily	2	8	1 (1.63)	1 (1.97)	
Any dose	**41**		**126 (1.13)**	**66 (0.74)**	**1.36 (1.00 − 1.84) p=0.05**
(b) Rofecoxib	χ^2_1 trend = 0.1 (p=0.71)				
125mg daily	1	6	1 (20.35)	0 (0.00)	
50mg daily	4	15	4 (2.29)	3 (2.19)	1.28 (0.14 − 11.92)
25mg daily	18	71	130 (1.16)	102 (0.89)	1.33 (0.94 − 1.89)
12.5mg daily	6	7	9 (4.36)	1 (0.71)	3.87 (0.54 − 27.82)
Any dose	**25**		**144 (1.22)**	**103 (0.89)**	**1.38 (1.07 − 1.80) p=0.0137**





Patrono and Baigent, 2017, Critique of PRECISION study

“ImPRECISION: Limitations to Interpretation of a Large Randomized Clinical Trial” G.A. Fitzgerald, January 2017. *Circulation*

“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%...Yet the mechanism of cardiovascular hazard from NSAIDs is conditioned by the underlying cardiovascular risk substrate of the patient population. Furthermore, this is a noninferiority trial. Because of 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 is it that celecoxib would be found inferior?

Second, 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.

Effect of PRECISION in-study dosage escalation on clinical benefit

Only 5.8% of all celecoxib-treated patients were allowed to switch from the moderate 200-mg dose to the maximum 400-mg dose, while 55% of the naproxen-treated patients were allowed to switch from the moderate dose of 750 mg to the maximum 1,000-mg dose.*

Accordingly, naproxen-treated patients had a significantly greater clinical benefit as evidenced by fewer discontinuations because of “insufficient clinical response” than did patients treated with celecoxib (P <0.004).**

***Pfizer Briefing Materials. PDF page 229**

**** *NEJ*M Supplement to PRECISION, page 30**

Additional Points from “ImPRECISION”

“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. 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. 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.”

Coxibs, Traditional NSAIDs, and Cardiovascular Safety Post-PRECISION: What We Thought We Knew Then and What We Think We Know Now. Patrono and Baigent. *Clin Pharmacol Ther*. August, 2017

The question posed by these researchers, Colin Baigent a principal author of the CNT study, was "to what extent the additional information from the Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen study may alter our current mechanistic understanding and/or clinical practice."

After reviewing many of the PRECISION defects noted previously in the ImPRECISION review, they concluded that:

"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."

Comments about the prospects of PRECISION at the February, 2014 Advisory Committee Meeting

Gareth Fitzgerald:

"So ibuprofen and naproxen, but not celecoxib, may interact to undermine the platelet inhibitory effects of low-dose aspirin. So I would contend, as I suggested in 2005,that the result of this trial will be uninterpretable."

Several advisory committee members, at that meeting, also voiced skepticism about learning anything new from the results of the PRECISION, when it is finished, that would change FDA's regulation of these drugs.