Coxibs and traditional NSAIDs for pain relief

After doing a meta-analysis of 639 trials that compared non-steroidal anti-inflammatory drugs (NSAIDs) with placebo or another NSAID, the Coxib and traditional NSAID Trialists' (CNT) Collaboration concluded that the vascular risks of high-dose diclofenac were similar to those of coxibs (Aug 31, p 769).[1] We appreciate the effort of analysing this huge amount of data.

For the meta-analysis, all relevant pharmaceutical companies were asked to provide data from published and unpublished trials. Four companies gave information, but some did not provide unpublished data. In their discussion, the CNT Collaboration argue that their method diminished the potential for bias because they obtained individual data from most trials, including some unpublished. However, only some unpublished data were included.

Why did participating companies withhold some unpublished trial data, or not supply data at all? Furthermore, why were these trials unpublished in the first place? Were unfavourable outcomes noted?

Inclusion of only some unpublished data can lead to selection bias because trials with frequent side-effects might be filtered out, and those in which fewer events are reported could be over-represented in the meta-analysis. The relative risk for an event would, in this example, be underestimated. Unbiased selection of trials is a crucial part of a meta-analysis; thus, we need more information about the omitted unpublished data.

We declare that we have no conflicts of interest.

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1 Coxib and traditional NSAID Trialists' (CNT) Collaboration. 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.

The meta-analysis reported by the Coxib and traditional NSAID Trialists' (CNT) Collaboration provides information to guide clinical decision-making for analgesic pharmacotherapy.[1] However, the information used to estimate risks included clinical study data for participants on drug doses that were much higher than those approved for patients with arthritis who seek pain relief.

The risk of major vascular events was about a third higher with coxibs (eg, celecoxib and rofecoxib) than with placebo. However, not all coxib doses were equal. In the appendix (p 18), event rate ratios were provided for different coxibs by dose. Celecoxib showed an increased statistical risk of major vascular events for the 800 mg daily dose but not for the 400 mg or 200 mg doses (800 mg rate ratio 2·96, 99% CI 1·21–7·25; 400 mg 1·29, 0·81–2·04; 200 mg 0·95, 0·30–3·00). The 800 mg supratherapeutic daily dose was investigated in a few clinical trials of novel treatments—eg, for cancer.

The clinical usefulness of the CNT Collaboration findings relates to doses under consideration by prescribers. Doctors and patients should know that the celecoxib 800 mg total daily dose is not an approved therapeutic dose for any medical disorder. Furthermore, for any drug dose, doctors must balance potential risks identified from clinical trials or large meta-analyses with symptomatic benefits for the individual patient.

I am employed by Pfizer (Medical Affairs Product Lead for celecoxib).

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The large meta-analysis[1] by the Coxib and traditional NSAID Trialists' (CNT) Collaboration provides useful data for cardiovascular and upper gastrointestinal risks of NSAIDs. However, it does not answer an important question for rheumatologists and geriatricians: can we prescribe NSAIDs in old and very old patients?

Osteoarthritis typically affects elderly people, and management of this disorder includes prescription of NSAIDs. However, international guidelines are unclear about how to manage pain in elderly patients.[2,3] This patient population is under-represented in randomised controlled trials,[4] in particular those investigating the use of NSAIDs,[5] with a large difference in age between study and clinical populations.

The CNT Collaboration report included individual data for more than 88 000 patients (mean age 61 years). Data were stratified into two age groups: younger than 60 years and 60 years or older. Further division could have been done into narrower age groups (eg, 60–69 years, 70–79 years, and ≥80 years), with the number of patients and major side-effects reported for every age category. Similar proportional effects were recorded for every specific safety outcome, according to age. These data are insufficient to allow us to appreciate fully the respective gastrointestinal, cardiovascular, or renal risks in elderly patients and, thus, to guide the best therapeutic decision in this population.

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2 American Geriatrics Society panel on the pharmacological management of persistent pain in older persons. Pharmacological management of persistent pain in older persons. *Pain Med* 2009; **10:** 1062–83.
3 Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2012; **64:** 465–74.
4 Konrat C, Boutron I, Trinquart L, et al. Underrepresentation of elderly people in randomised controlled trials: the example of trials of 4 widely prescribed drugs. *PLoS One* 2012; **7:** e33559.
5 Rochon PA, Fortin PR, Dear KB, Minaker KL, Chalmers TC. Reporting of age data in clinical trials of arthritis: deficiencies and solutions. *Arch Intern Med* 1993; **153:** 243–48.

Authors' reply

Martina de Ketterij-de Ridder and Maria Hoogerhuis request further information about unpublished data that were not provided to us. Before coxibs were developed, most trials of traditional NSAIDs were small and of short duration, so they provided little information about the risks of major vascular or upper gastrointestinal events. In our meta-analysis,[1] the trials that included a coxib (ie, coxib *vs* placebo or coxib *vs* traditional NSAID) were larger and of longer duration than these earlier trials, so they encompass almost all the presently available information about the hazards of traditional NSAIDs. The companies manufacturing a coxib undertook to provide data from all eligible trials, and no evidence is available to suggest that they concealed the existence of trials that might have been informative. Unless such trials do exist, and they recorded substantial numbers of relevant events, there is little risk of serious publication bias in estimates of the hazards of the three main high-dose traditional NSAID regimens (naproxen 500 mg twice daily, ibuprofen 800 mg three times daily, and diclofenac 75 mg twice daily) studied in those trials.

A limitation of available evidence from randomised trials is that little is known about the effects of different doses of NSAIDs on vascular or gastrointestinal events. Although Peter Park is correct when he points out that the adverse effect of celecoxib 800 mg daily (an unapproved dose) on major vascular events seemed especially large, the estimated effect of the approved daily dose of 400 mg was similar to the estimated effect of all coxib regimens combined.

We agree with Christian Cadet and his colleagues that the management of elderly patients with rheumatological diseases is an important clinical issue. We reanalysed our data with patients subdivided into four categories: younger than 60 years; age 60–69 years; age 70–79 years; and 80 years or older. There was no evidence for a greater relative risk of major vascular events with older age for coxibs (p=0·88 for trend), naproxen (p=0·62), or other traditional NSAIDs (p=0·18), and no trend was noted for symptomatic upper gastrointestinal events (p=0·28, p=0·37, and p=0·30, respectively). These findings reinforce the important message that the proportional increases in the risks of vascular and upper gastrointestinal hazards are predictable in a wide range of people. Whether or not the patient judges the predicted risks to be acceptable in return for relief of their symptoms should be a major consideration when prescribing an NSAID regimen.

We declare that we have no conflicts of interest.

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Analysis of the Born in Bradford birth cohort

Eamonn Sheridan and colleagues on the Born in Bradford study (Oct 19, p 1350)[1] analysed birth cohort data in relation to consanguinity and risk of major congenital anomalies. They concluded that consanguinity is a major risk factor for congenital anomalies, even after adjusting for deprivation. Furthermore, high levels of educational attainment were associated with a reduced risk of congenital anomalies in all ethnic groups. We are concerned about the second conclusion.

The continuing Born in Bradford birth cohort recruits pregnant women at a gestational age of 26–28 weeks, after the first and second trimester prenatal screenings for congenital anomalies have been undertaken. Therefore, all pregnancies with severe congenital anomalies that have ended in a termination are excluded. According to UK data from 2007 to 2011, 21% of all pregnancies with a congenital anomaly result in a termination.[2] In a study of the prevalence at birth of specific anomalies,[3] an association was recorded with social class, but when all diagnoses (births, terminations, and fetal losses) were included, no such association was noted. The association with social class in that study was attributable to differences in the rates of prenatal diagnosis and subsequent terminations. We suggest that the same situation might be occurring in the Born in Bradford dataset, with women who have higher levels of education being more likely to undergo a termination for a fetal anomaly. To relate education to the risk of a congenital anomaly, fetal losses and terminations must be included, which the Born in Bradford study is unable to do.

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