

Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials

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Abstract

Objective To assess the effects of selective cyclo-oxygenase-2 (COX 2) inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs) on the risk of vascular events.

Design Meta-analysis of published and unpublished tabular data from randomised trials, with indirect estimation of the effects of traditional NSAIDs.

Data sources Medline and Embase (January 1966 to April 2005); Food and Drug Administration records; and data on file from Novartis, Pfizer, and Merck.

Review methods Eligible studies were randomised trials that included a comparison of a selective COX 2 inhibitor versus placebo or a selective COX 2 inhibitor versus a traditional NSAID, of at least four weeks' duration, with information on serious vascular events (defined as myocardial infarction, stroke, or vascular death). Individual investigators and manufacturers provided information on the number of patients randomised, numbers of vascular events, and the person time of follow-up for each randomised group.

Results In placebo comparisons, allocation to a selective COX 2 inhibitor was associated with a 42% relative increase in the incidence of serious vascular events (1.2%/year *v* 0.9%/year; rate ratio 1.42, 95% confidence interval 1.13 to 1.78; *P* = 0.003), with no significant heterogeneity among the different selective COX 2 inhibitors. This was chiefly attributable to an increased risk of myocardial infarction (0.6%/year *v* 0.3%/year; 1.86, 1.33 to 2.59; *P* = 0.0003), with little apparent difference in other vascular outcomes.

Among trials of at least one year's duration (mean 2.7 years), the rate ratio for vascular events was 1.45 (1.12 to 1.89; *P* = 0.005). Overall, the incidence of serious vascular events was similar between a selective COX 2 inhibitor and any traditional NSAID (1.0%/year *v* 0.9%/year; 1.16, 0.97 to 1.38; *P* = 0.1). However, statistical heterogeneity (*P* = 0.001) was found between trials of a selective COX 2 inhibitor versus naproxen (1.57, 1.21 to 2.03) and of a selective COX 2 inhibitor versus non-naproxen NSAIDs (0.88, 0.69 to 1.12). The summary rate ratio for vascular events, compared with placebo, was 0.92 (0.67 to 1.26) for naproxen, 1.51 (0.96 to 2.37) for ibuprofen, and 1.63 (1.12 to 2.37) for diclofenac.

Conclusions Selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but high dose naproxen is not associated with such an excess.

Introduction

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the two recognised forms of

prostaglandin G/H synthase, which is also referred to as cyclo-oxygenase (COX), whereas selective COX 2 inhibitors are selective inhibitors of the COX 2 isozyme.¹ As the anti-inflammatory effects of NSAIDs were believed to be mediated by inhibition of COX 2, and their gastrointestinal side effects by inhibition of COX 1, people hypothesised that selective COX 2 inhibitors would provide a safer alternative to traditional NSAIDs. Studies have reported a lower incidence of upper gastrointestinal complications with selective COX 2 inhibitors than with traditional NSAIDs,^{2,3} but recent concerns about the cardiovascular safety of selective COX 2 inhibitors have limited their use.

The Vioxx gastrointestinal outcomes research (VIGOR) trial reported a fivefold increase in myocardial infarction among participants allocated to rofecoxib (versus naproxen),² but this difference might have occurred because high dose naproxen inhibits platelet aggregation throughout the dosing interval. However, the APPROVe trial, which compared a selective COX 2 inhibitor with placebo, indicated that rofecoxib increased the risk of vascular events by twofold,⁴ and the APC trial comparing celecoxib with placebo reported a similar excess.⁵

The evidence suggests that selective COX 2 inhibitors are associated with an increased risk of vascular events, but several questions remain unanswered. Firstly, what is the magnitude of any excess risk of myocardial infarction, stroke, and vascular mortality? Secondly, is the excess risk of vascular events dose related? Thirdly, are traditional NSAIDs, which also inhibit COX 2, associated with an increased risk of vascular events? We did a meta-analysis of randomised trials that compared a selective COX 2 inhibitor with placebo or a selective COX 2 inhibitor with a traditional NSAID in an attempt to answer these questions.

Methods

We identified trials by approaching the manufacturers of each of the selective COX 2 inhibitors, searching the Food and Drug Administration website, and searching Medline and Embase from January 1966 to April 2005. Randomised trials involving at least four weeks' scheduled treatment were eligible if they included at least one comparison of a selective COX 2 inhibitor versus placebo or a selective COX 2 inhibitor versus a traditional NSAID. The pre-specified outcomes were serious vascular event, fatal or non-fatal myocardial



A table, two extra figures, a statistical appendix, and extra references are on bmj.com



This is an abridged version; the full version of the paper is on bmj.com

infarction, fatal or non-fatal stroke, and vascular death. On the basis of the known pharmacokinetic and pharmacodynamic properties of the NSAIDs studied (which raised the hypothesis that naproxen might have aspirin-like antiplatelet effects), we prospectively specified that analyses of a selective COX 2 inhibitor versus NSAID were to be subdivided into those involving naproxen and those involving other (non-naproxen) NSAIDs. We derived rate ratios for each of the pre-specified comparisons (see statistical appendix on bmj.com).

Results

Study population

Tabular data were available from 138 randomised trials involving 145 373 participants (see table on bmj.com).^{w1-w90}

Comparisons of selective COX 2 inhibitor versus placebo

Figure 1 shows meta-analyses of a selective COX 2 inhibitor versus placebo, subdivided by individual selective COX 2 inhibitors, for each of the primary outcomes. Overall, among 121 placebo controlled trials, 216 vascular events occurred during 18 490 person years of exposure to a selective COX 2 inhibitor (1.2%/year) compared with 112 during 12 639 person years of placebo (0.9%/year), corresponding to a 42% proportional increase in the incidence of a first serious vascular event (rate ratio 1.42, 95% confidence interval 1.13 to 1.78; $P=0.003$). We found no evidence that the proportional excess incidence of vascular events varied among the different selective COX 2 inhibitors (heterogeneity $\chi^2=0.5$, $df=4$; $P=1.0$), although insufficient data limited the power to identify any real differences between selective COX 2 inhibitors. In the trials analysed, this proportional difference corresponded to an excess of 3 (95% confidence interval 1 to 5) people with a vascular event per 1000 allocated to a selective COX 2 inhibitor per year.

We found an almost twofold proportional increase in myocardial infarction (rate ratio 1.86, 1.33 to 2.59; $P=0.0003$) (fig 1), corresponding to an excess of 3 (1 to 4) people with myocardial infarction per 1000 allocated to a selective COX 2 inhibitor per year. We found no heterogeneity in the rate ratios for myocardial infarction among individual selective COX 2 inhibitors (heterogeneity $\chi^2=1.0$, $df=4$; $P=0.9$). We found no difference in the incidence of stroke, corresponding to an absolute difference of 0 (-2 to 1)/1000/year, and the summary rate ratio for vascular death, although it did not reach statistical significance, corresponded to an absolute excess of 1 (0 to 2)/1000/year.

Duration—Of the 121 placebo controlled trials, nine were long term trials with one year or longer of scheduled treatment (mean 139 weeks) and 112 were shorter trials (mean 11 weeks). Around two thirds of the vascular events had occurred in the nine long term trials, in which allocation to a selective COX 2 inhibitor was associated with a 45% increase in vascular events (rate ratio 1.45, 1.12 to 1.89; $P=0.005$), with no heterogeneity between the event rate ratios in the trials (heterogeneity $\chi^2=13.4$, $df=8$; $P=0.1$) (see bmj.com).

Dose—Data were sufficient to assess dose-response for celecoxib only. We found a significant trend towards

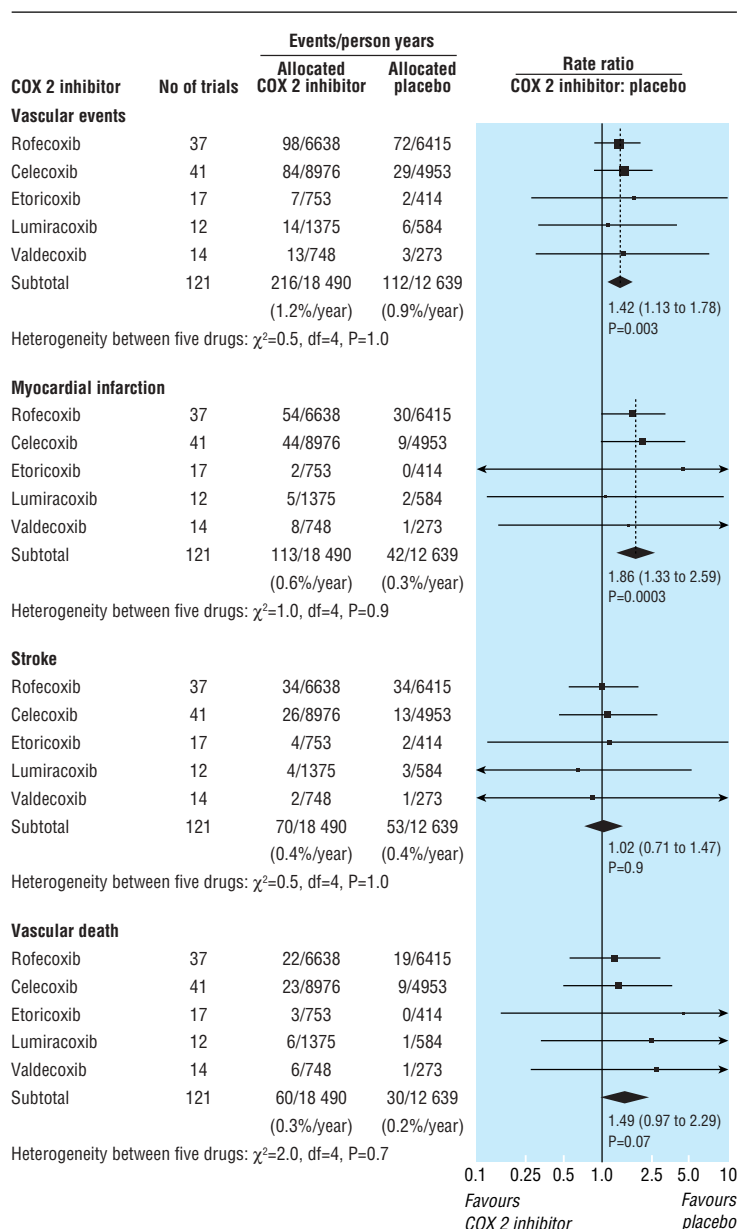


Fig 1 Comparison of effects of different selective COX 2 inhibitors versus placebo on vascular events, myocardial infarction, stroke, and vascular death. Event numbers and person years of exposure, with corresponding mean annual event rates in parenthesis, are presented for patients allocated to selective COX 2 inhibitor and placebo. Event rate ratios for subtotals, with 95% confidence intervals, are indicated by a diamond; rate ratios for individual selective COX 2 inhibitors, with 99% confidence intervals, are indicated by a square and horizontal line. Diamonds to the right of the solid line indicate hazard with a selective COX 2 inhibitor compared with placebo, but this is conventionally significant only if the diamond does not overlap the solid line

an increased incidence of serious vascular events with higher daily doses (trend $P=0.03$) (fig A on bmj.com).

Comparisons of selective COX 2 inhibitor versus traditional NSAID

Overall, we found no significant difference in the incidence of a serious vascular event between selective COX 2 inhibitors and traditional NSAIDs—340 vascular events during 33 260 person years of exposure to a selective COX 2 inhibitor (1.0%/year) versus 211 vascular events during 23 325 person years with a traditional NSAID (0.9%/year) (rate ratio 1.16, 0.97 to

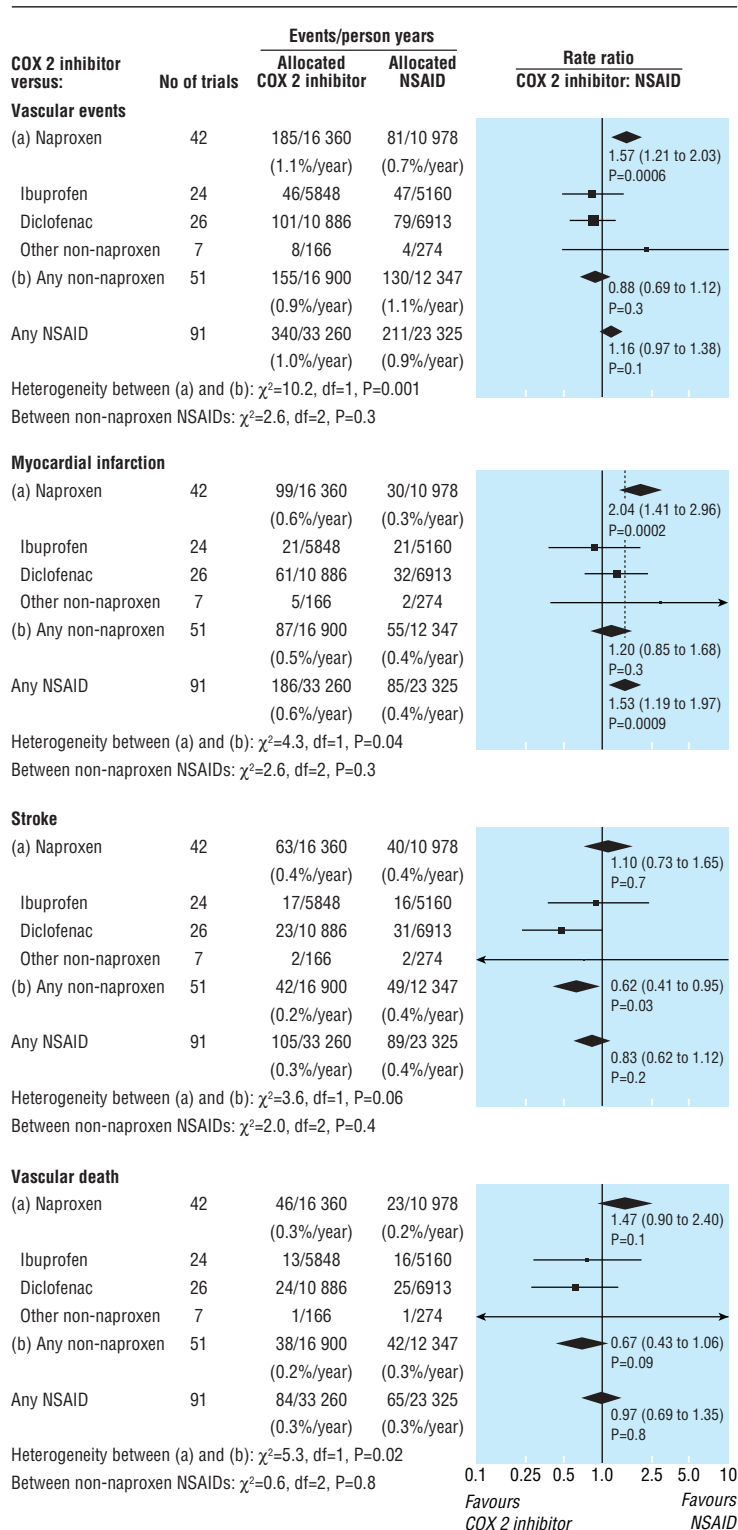


Fig 2 Comparison of effects of selective COX 2 inhibitors versus traditional NSAIDs on vascular events, myocardial infarction, stroke, and vascular death. Symbols and conventions are as in fig 1. Some trials involved more than one NSAID comparator, so numbers of trials in subtotals are not a strict sum of numbers for each NSAID

1.38; P = 0.1) (fig 2). We found marked heterogeneity between the rate ratios for vascular events in trials comparing a selective COX 2 inhibitor with naproxen and those comparing a selective COX 2 inhibitor with a non-naproxen NSAID ($\chi^2 = 10.2$, df = 1; P = 0.001).

We found similar heterogeneity for myocardial infarction ($\chi^2 = 4.3$, df = 1; P = 0.04), stroke ($\chi^2 = 3.6$, df = 1; P = 0.06), and vascular death ($\chi^2 = 5.3$, df = 1; P = 0.02).

Any selective COX 2 inhibitor versus naproxen—Compared with naproxen, allocation to a selective COX 2 inhibitor was associated with an increase in the incidence of a vascular event (rate ratio 1.57, 1.21 to 2.03; P = 0.0006) and a twofold increased risk of a myocardial infarction (2.04, 1.41 to 2.96; P = 0.0002) (fig 2). We found no significant difference in the incidence of stroke (rate ratio 1.10, 0.73 to 1.65; P = 0.7) or vascular death (1.47, 0.90 to 2.40; P = 0.1).

Any selective COX 2 inhibitor versus a non-naproxen NSAID—We found no significant difference in the incidence of a vascular event (rate ratio 0.88, 0.69 to 1.12; P = 0.3), myocardial infarction (1.20, 0.85 to 1.68; P = 0.3), or vascular death (0.67, 0.43 to 1.06; P = 0.09), but a selective COX 2 inhibitor was associated with a significantly lower incidence of stroke than any non-naproxen traditional NSAID (rate ratio 0.62, 0.41 to 0.95; P = 0.03) (fig 2).

Comparisons of a traditional NSAID versus placebo

The summary rate ratio for vascular events, in comparison with placebo, was 0.92 (95% confidence interval 0.67 to 1.26) for naproxen, 1.51 (0.96 to 2.37) for ibuprofen, and 1.63 (1.12 to 2.37) for diclofenac.

Discussion

When we considered all the randomised trial data, selective COX 2 inhibitors were associated with a 1.4-fold increased risk of serious vascular events, largely due to a twofold increased risk of myocardial infarction. If, as some people have suggested (on the basis of the delayed divergence of survival curves), the hazard emerges only after a year or 18 months,^{4,5} then combining short term and long term trials might underestimate the effects of long term exposure to a selective COX 2 inhibitor. However when all the long term trials are considered, the summary rate ratio is similar to that from short term and long-term trials combined, and is somewhat smaller than the twofold to threefold excess suggested by the results of the APC and APPROVe studies.

The available data from placebo controlled trials were inadequate to allow assessment of whether the cardiovascular risks of selective COX 2 inhibitors are dose dependent (fig A on bmj.com). Although we found a weak trend towards larger risks with higher daily doses of celecoxib, this result was driven by the results of one trial.⁴

Cardiovascular effects of traditional NSAIDs

As traditional NSAIDs inhibit the COX 2 enzyme, these drugs might also be associated with an increased risk of vascular events,⁶ but long term placebo controlled trials have not been done. As the plasma half life of naproxen is around 14 hours, a regimen of 500 mg twice daily results in sustained inhibition of COX 1 dependent thromboxane biosynthesis, whereas both ibuprofen and diclofenac have much shorter half lives and standard twice or three times daily regimens have only transient effects. Our results indicated that high dose ibuprofen (800 mg three times daily) and high dose diclofenac (75 mg twice daily) were each

associated with an increased risk of vascular events, but that the risks of high dose naproxen (500 mg twice daily) were substantially smaller. Uncertainty remains as to whether the cardiovascular effects of standard (that is, lower) daily doses of these drugs would differ from those identified in this meta-analysis, and this is an important topic for future research.

Estimating absolute risk

In this particular group of trials, allocation to a selective COX 2 inhibitor was associated with around three extra people having a vascular event per 1000 per year. The annual excess incidence associated with full compliance with a selective COX 2 inhibitor would be expected to be larger than this, however. In the APPROVe study approximately one third of randomised patients discontinued treatment before the end of the study.⁴ If this discontinuation rate was typical, the absolute excess incidence of vascular events produced by full compliance with a selective COX 2 inhibitor might be four or five additional patients having a vascular event per 1000 treated per year.

Study limitations

The chief limitation is the relatively small number of events available for analysis, which limits assessment of the different selective COX 2 inhibitors and traditional NSAIDs in particular clinical circumstances. We were also unable to assess the timing of the hazard or variation among subgroups of patients. Moreover, we limited attention to cardiovascular hazards, whereas the choice between different anti-inflammatory regimens also needs to take account of differences in gastrointestinal effects.

Conclusions

This meta-analysis has shown that selective COX 2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high dose regimens of ibuprofen and diclofenac, but that high dose naproxen is not associated with such an excess.

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Competing interests: CTSU has a staff policy of not accepting honorariums or other payments from the drug industry, except for the reimbursement of costs to participate in scientific or advisory committee meetings. CB has had such costs reimbursed for attending meetings arranged by Bayer, Merck, Novartis, GlaxoSmithKline, and Astra-Zeneca. He is the lead investigator of the study of heart and renal protection, a study of cholesterol lowering in chronic kidney disease, which is sponsored by the University of Oxford and supported by an unrestricted grant from Merck. CP has received grant support

What is already known on this topic

Some selective cyclo-oxygenase-2 (COX 2) inhibitors have been shown to increase the risk of occlusive vascular events, but important details remain unclear

Traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX 2 enzyme, but their effects on vascular events are unknown

What this study adds

Selective COX 2 inhibitors are associated with a moderately increased risk of vascular events, largely attributable to a twofold increased risk of myocardial infarction

High dose regimens of some traditional NSAIDs, such as diclofenac and ibuprofen, but not high dose naproxen, are associated with a similar excess risk of vascular events

The choice between different anti-inflammatory regimens requires assessment of the individual expected absolute attributable risks of cardiovascular and serious gastrointestinal events

from Bayer, Merck, and Pfizer. In addition, he has received honorariums for lecturing and consulting from Bayer and NiCox. PMK, JG, HH, and JRE have no competing interests. No funding was provided by any drug company for this project. None of the authors has any stockholdings in pharmaceutical companies, and none is involved in advising any organisation or individual on issues related to litigation.

- 1 FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42.
- 2 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
- 3 Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the therapeutic arthritis research and gastrointestinal event trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004;364:665-74.
- 4 Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.
- 5 Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.
- 6 Baigent C, Patrono C. Selective cyclooxygenase 2 inhibitors, aspirin, and cardiovascular disease: a reappraisal. *Arthritis Rheum* 2003;48:12-20. (Accepted 19 April 2006)

Endpiece

A warning to scholars

Dr Wedderburne gave mee this Medicall Counsayle. That I should not be sicke before I was sicke, Noteing the puling spirits of some, & generally of Scholars, who doe allwayes phantsy themselves to be sicke, or sickly, & by phantsye & frequent medicines doe make themselves sick indeede.

John Beale writing to Robert Boyle in 1663, quoted in: Jardine L. *The Curious Life of Robert Hooke*. London: Harper Perennial, 2003

Submitted by Elizabeth Wager, publications consultant, Princes Risborough