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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Design Meta-analysis of published and unpublished tabular data from randomised trials, with indirect estimation of the effects of traditional NSAIDs.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) are widely used to treat pain, but their long term use is limited by serious gastrointestinal side effects. Whereas NSAIDs inhibit the two recognised forms of prostaglandin G/H synthase (also referred to as cyclo-oxygenase), selective cyclo-oxygenase-2 (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. However, although some studies have reported a lower incidence of upper gastrointestinal complications with selective COX 2 inhibitors than with traditional NSAIDs,[2 3] recent concerns about the cardiovascular safety of selective COX 2 inhibitors have limited their use.

Although the Vioxx gastrointestinal outcomes research (VIGOR) trial reported a fivefold increase in myocardial infarction among participants allocated to rofecoxib (20 rofecoxib *v* 4 naproxen; P < 0.001),[2] this difference might have occurred, at least in part, because high dose naproxen inhibits platelet aggregation throughout the dosing interval. However, the results of the adenomatous polyp prevention on Vioxx (APPROVe) trial, which was the first relatively large trial comparing a selective COX 2 inhibitor with placebo, indicated that rofecoxib increased the risk of vascular events by about twofold.[4] Soon afterwards, the adenoma prevention with celecoxib (APC) trial, comparing celecoxib with placebo, reported a similar excess.[5]

The accumulating evidence suggests that selective COX 2 inhibitors are associated with an increased risk of vascular events, but several important 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, and is the size of this risk different in people who are also taking aspirin (which chiefly inhibits COX 1 at low doses[6])? 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.

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

Methods

We used three steps to identify prospective randomised controlled trials of a selective COX 2 inhibitor versus placebo, a selective COX 2 inhibitor versus a traditional NSAID, or both. First we approached the manufacturers of each of the selective COX 2 inhibitors—Merck (rofecoxib, etoricoxib), Novartis (lumiracoxib), and Pfizer (celecoxib, valdecoxib). Then we searched the Food and Drug Administration website for data presented at the Cardiorenal Advisory Committee meeting in February 2005. Finally, we used the modified Cochrane strategy[7] combined with the generic names of each of the individual selective COX 2 inhibitors as keywords to search 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 and had recorded serious (that is, admitted to hospital or fatal) cardiovascular events. The pre-specified outcomes were "serious vascular event," as defined by the Antiplatelet Trialists' Collaboration (that is, non-fatal myocardial infarction, non-fatal stroke, or vascular death)[8]; fatal or non-fatal myocardial infarction; fatal or non-fatal stroke; and vascular death (including death from myocardial infarction or stroke). The manufacturers and individual investigators provided summary design details for each trial and information on the process (if any) by which vascular events were adjudicated. All of the manufacturers provided written confirmation that the data provided were complete: Pfizer had locked their data at 31 October 2004, whereas Merck and Novartis had locked their databases at the end of January 2005. We requested numbers of events and person time at risk for each trial, where available, but in a few cases we estimated data from published results or the Food and Drug Administration website.[9]

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 concerning other (non-naproxen) NSAIDs.

We derived rate ratios and their confidence intervals for each of the pre-specified comparisons by using the Peto "one step" approximation (see statistical appendix on bmj.com).[10] In figures and in the text, we have used 99% confidence intervals for individual comparisons to allow for the multiplicity of analyses, reserving 95% confidence intervals for subtotals.

Results

Study population

Tabular data were available from 138 randomised trials involving a comparison of a selective COX 2 inhibitor versus placebo or versus a traditional NSAID (or both), in which there were a total of 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 inhibitor, 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 $\chi^2 = 0.5$, $df = 4$; $P = 1.0$). However, as only two selective COX 2 inhibitors (rofecoxib and celecoxib) had recorded appreciable numbers of such outcomes, the power to identify any real differences that might exist between selective COX 2 inhibitors was limited. In the group of 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 significant 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 (rate ratio 1.02, 0.71 to 1.47; $P = 0.9$), corresponding to an absolute difference of 0 (−2 to 1)/1000/year, and the summary rate ratio for vascular death (1.49, 0.97 to 2.29; $P = 0.07$), 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 these long term trials, allocation to a selective COX 2 inhibitor was associated with a 45% increase in the incidence of vascular events (rate ratio 1.45, 1.12 to 1.89; $P = 0.005$) (fig 2), with no significant heterogeneity between the event rate ratios in the trials (heterogeneity $\chi^2 = 13.4$, $df = 8$; $P = 0.1$).

Dose

Too few vascular events were available to allow us to assess dose-response in placebo controlled trials of etoricoxib, lumiracoxib, or valdecoxib. For rofecoxib, 85% of vascular events among patients allocated to a selective COX 2 inhibitor occurred at a dose of 25 mg daily, with few events at lower or higher daily doses, so we could not evaluate dose dependence. For celecoxib, we found a significant trend towards an increased incidence of serious vascular events with higher daily doses (trend $P = 0.03$) (fig A on bmj.com).

Aspirin

Among the 84 placebo controlled trials that allowed concomitant use of aspirin for which data were available, we found no significant heterogeneity of the summary rate ratios for vascular events among aspirin users and non-users (heterogeneity $\chi^2 = 0.0$, $df = 1$; $P = 0.9$) (fig B on bmj.com). We found a similar lack of heterogeneity for myocardial infarction, stroke, and vascular death (data not shown).

Comparisons of selective COX 2 inhibitor versus traditional NSAID

Overall, we found no significant difference in the incidence of a serious vascular event between participants allocated to a selective COX 2 inhibitor and those allocated to a traditional NSAID—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 1.38; P = 0.1) (fig 3). However, 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

Overall, compared with naproxen, allocation to a selective COX 2 inhibitor was associated with a highly significant 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 3). We found no significant difference in the incidence of stroke (rate ratio 1.10, 0.73 to 1.65; P = 0.7) or of vascular death (1.47, 0.90 to 2.40; P = 0.1).

Any selective COX 2 inhibitor versus a non-naproxen NSAID

Overall, 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 3). Comparisons of a selective COX 2 inhibitor with ibuprofen (rate ratio 0.85, 99% confidence interval 0.49 to 1.46; P = 0.4), a selective COX 2 inhibitor versus diclofenac (0.85, 0.56

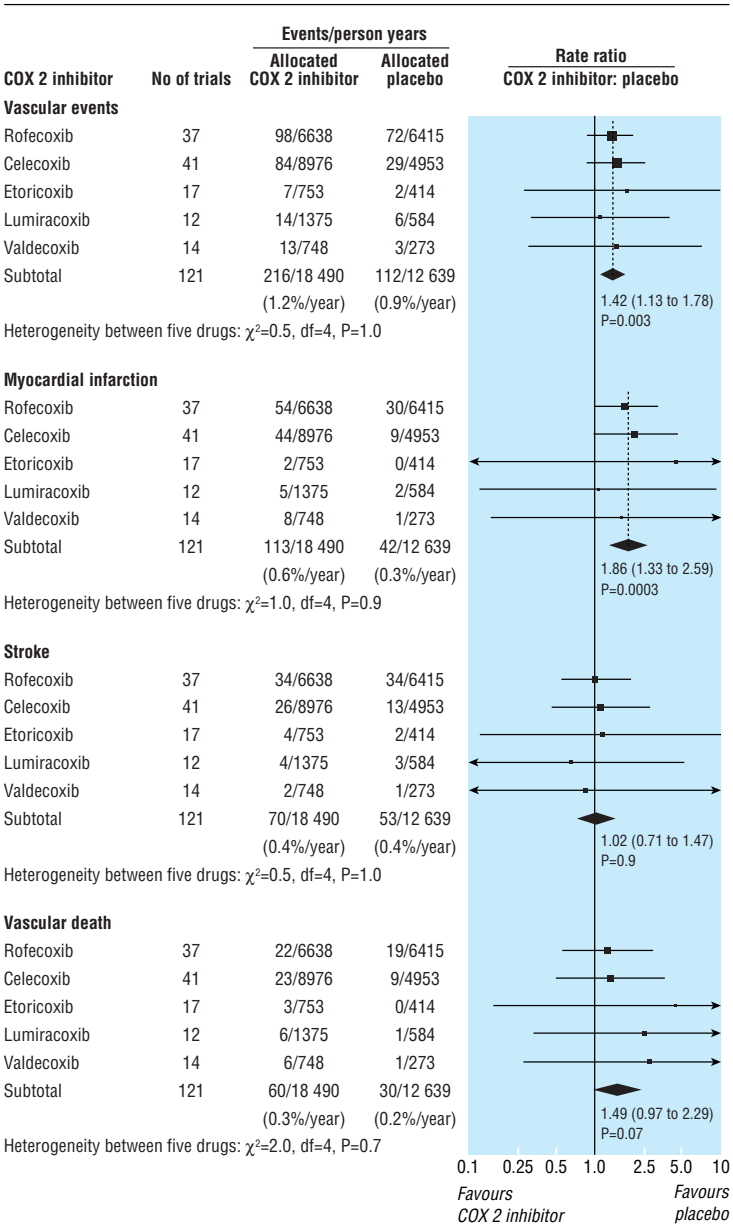

Fig 1 Comparison of effects of different selective COX 2 inhibitors versus placebo on vascular events, myocardial infarction, stroke, and vascular death. Event numbers and person years of exposure, with corresponding mean annual event rates in parenthesis, are presented for patients allocated to selective 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

to 1.27; P = 0.3), and a selective COX 2 inhibitor versus any other non-naproxen NSAID (2.21, 0.49 to 10.03; P = 0.2) yielded similar rate ratios for vascular events (test for heterogeneity $\chi^2 = 2.6$, df = 2; P = 0.3) (fig 3).

Comparisons of traditional NSAID versus placebo

We combined direct estimates of treatment effect (from trials involving a comparison of an NSAID versus placebo) with indirect information (from a comparison of trials of a selective COX 2 inhibitor versus placebo and a selective COX 2 inhibitor versus NSAID) (see statistical appendix on bmj.com). 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 highly significant 1.4-fold increased risk of serious vascular events, largely due to a twofold increased risk of myocardial infarction. Although we found no significant excesses in the incidence of stroke or vascular death, the confidence intervals for each were wide, so we could not exclude a clinically important excess. 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. We were not able to assess time dependent variation in the rate ratio because we sought numbers of events and person time only for the whole period of follow-up in each trial. However, as figure 2 clearly shows, 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 somewhat smaller than the twofold to threefold excess suggested by the combined results of the APC and APPROVe studies.[4 5]

Not all of the trials had independent adjudication of vascular events, so a bias towards the null is possible owing to non-differential misclassification of vascular outcomes in those trials without independent adjudication. As more than 70% of the vascular events occurred in trials that were adjudicated, the potential for misclassification is limited. Indeed, the summary rate ratio for a selective COX 2 inhibitor versus placebo among adjudicated trials was 1.45 (95% confidence interval 1.12 to 1.89), which is very similar to the estimate among all trials of 1.42 (1.13 to 1.78). A further potential source of bias was our prospective decision to limit eligibility to trials of at least four weeks' duration, because this resulted in the exclusion of two small short term randomised trials of parecoxib (the intravenously administered pro-drug of valdecoxib) and valdecoxib versus placebo among patients having coronary artery bypass grafting,[11 12] in which the risk of vascular events was increased threefold.[13] If these two trials had been included, the summary rate ratio for a selective COX 2 inhibitor versus placebo would have been 1.49 (1.20 to 1.85). Hence, although we cannot exclude the possibility that, at least in the context of vascular surgery, the proportional increase in risk of a vascular event is higher with parecoxib or valdecoxib than with other selective COX 2 inhibitors, the exclusion of these trials had a small effect on the overall summary rate ratio for a selective COX 2 inhibitor versus placebo.

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

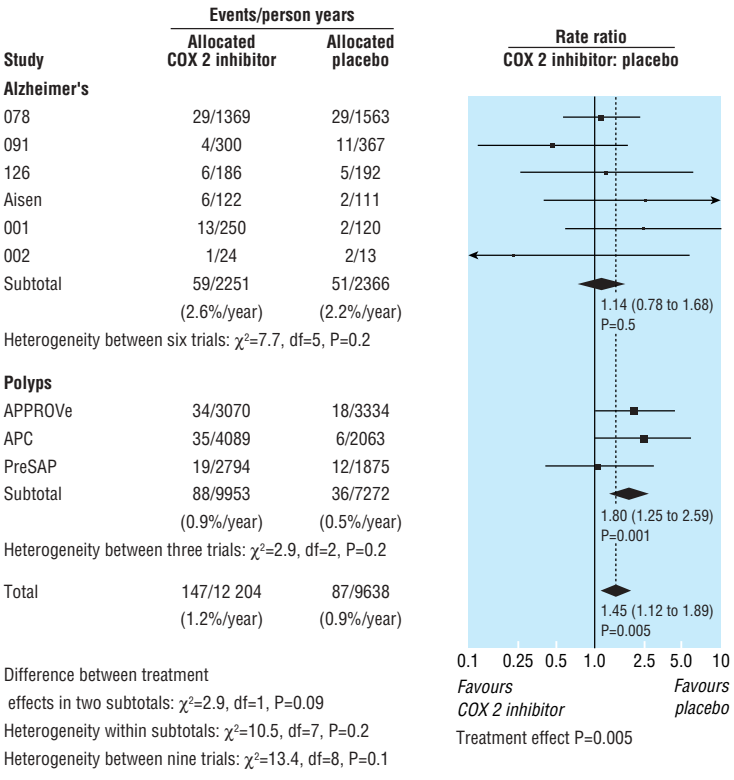

Fig 2 Comparison of effects of selective COX 2 inhibitors versus placebo among trials with scheduled duration of at least one year. Symbols and conventions are as in fig 1

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.[5] We were also unable to determine reliably whether the cardiovascular effects of selective COX 2 inhibitors might differ among aspirin users and non-users (fig B on bmj.com).

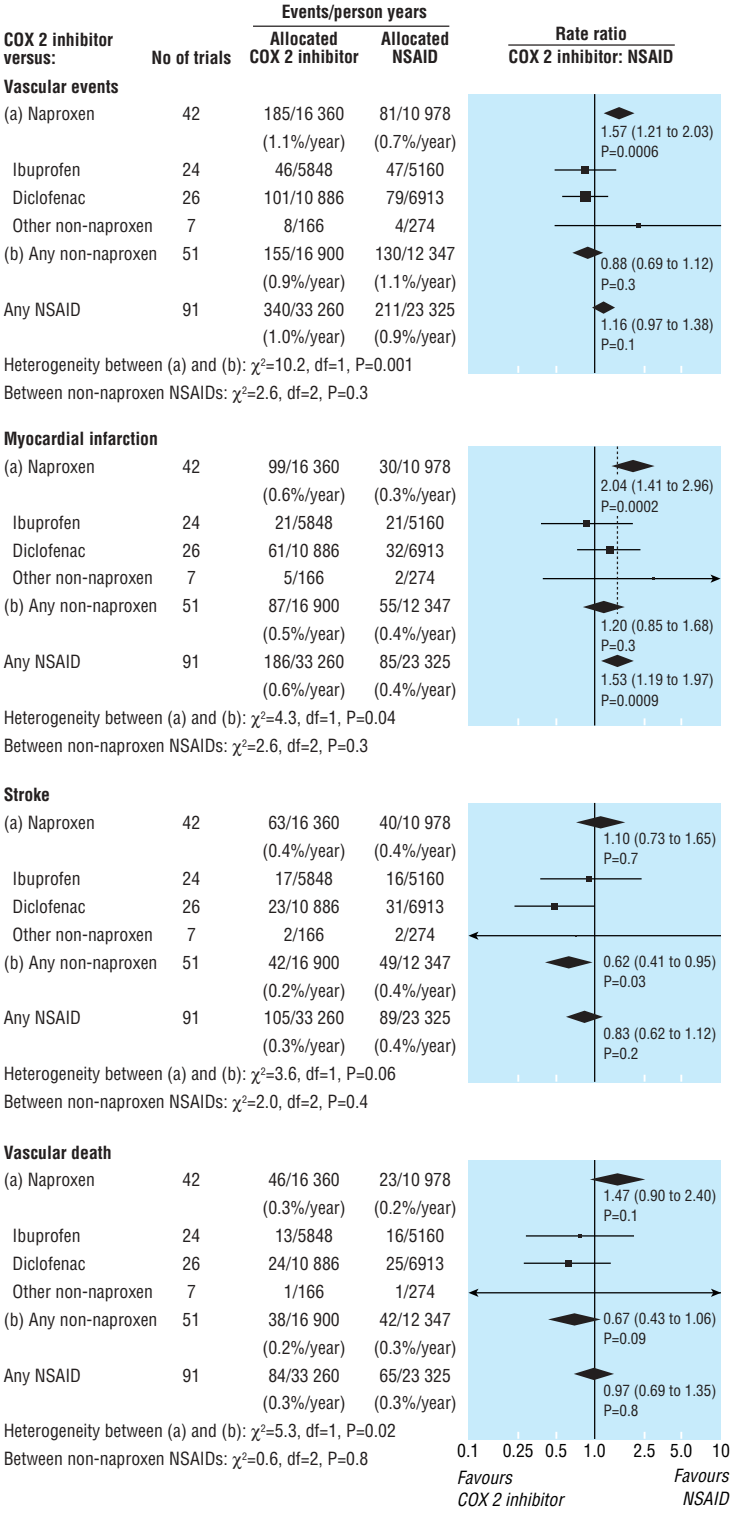

Fig 3 Comparison of effects of selective COX 2 inhibitors versus traditional NSAIDs on vascular events, myocardial infarction, stroke, and vascular death. Symbols and conventions are as in fig 1. Some trials involved more than one NSAID comparator, so numbers of trials in subtotals are not a strict sum of numbers for each NSAID

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.[14] As NSAIDs were originally developed for the relief of pain, long term placebo controlled trials have not been done. A few traditional NSAIDs with prominent effects on the COX 1 isozyme, such as indobufen and flurbiprofen, have been tested as potential antiplatelet agents in small studies,[15 16] but no adequately powered long term randomised trials have assessed drugs without such antiplatelet effects. 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 (one to two hours), and standard twice or three times daily regimens have only transient effects. We therefore hypothesised that the cardiovascular effects of naproxen would differ from those of non-naproxen NSAIDs. 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. We had insufficient information to determine whether naproxen was protective. Uncertainty remains, however, 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, with most of this excess attributable to myocardial infarction. 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, for example, approximately one third of randomised patients discontinued study 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 overall, with a smaller excess among those at lower than average risk (such as young women with rheumatoid arthritis) and a higher excess in those at above average risk (such as older patients with established atherosclerotic disease).

Study limitations

The chief limitation of this study is the relatively small number of events available for analysis, which limits assessment of the hazards of the various different selective COX 2 inhibitors and traditional NSAIDs in particular clinical circumstances. We were also limited to analysing tabular summaries of data, which prevented us from assessing the timing of the hazard or variation in the rate ratio among particular 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 their gastrointestinal effects. Some of these outstanding uncertainties may be resolved by a planned meta-analysis of data on individual patients from these trials.

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. As differences between anti-inflammatory regimens are likely to be small, very large randomised trials will be needed if we are to identify which anti-inflammatory drug regimens minimise the overall burden of adverse gastrointestinal and cardiovascular outcomes.

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

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