Selective COX-2 inhibitors, NSAIDs and cardiovascular events – is celecoxib the safest choice?

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Abstract: Inhibitors of cyclo-oxogenase (COX) are widely used anti-inflammatory drugs. In recent years concerns have arisen about the cardiovascular safety of these drugs, initially because of reported associations between therapy with the COX-2 selective inhibitor rofecoxib and myocardial infarction. However, subsequent data have suggested an association between therapy with non-selective COX inhibitors (NSAIDs) and serious cardiovascular events. This article reviews the clinical trial and population data linking COX inhibition to cardiovascular events. The data currently available suggests that both specific and non-specific COX inhibitors may increase the risk of serious cardiovascular events, but that the effect varies between the individual drugs. The strongest evidence for an increased risk of serious cardiovascular events is with rofecoxib therapy. Celecoxib therapy may be associated with an increased risk of cardiovascular events, but only when used at doses substantially higher than those recommended for the treatment of arthritis. There is a greater body of evidence supporting the relative cardiovascular safety of celecoxib when used at the doses recommended for the treatment of arthritis than for any of the other selective COX-2 inhibitors or NSAIDs.

Keywords: COX-2 inhibitors, NSAIDs, myocardial infarction, cardiovascular disease

Introduction

During the last few years there has been considerable concern about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors. This arose initially because of reports of adverse effects of rofecoxib, but the concern spread to include other selective COX-2 inhibitors as it was thought that the problem may have been a class effect related to a potential pro-thrombotic state induced by unopposed COX-2 inhibition. However, closer scrutiny of the relationship between therapy with traditional non-selective COX inhibitors (NSAIDs) and cardiovascular events has suggested that an increased risk of cardiovascular events may occur with a number of members of the class and that this risk may not be related to degree of COX selectivity. This paper reviews the information available from clinical trials and population studies concerning the relationship between selective COX-2 inhibitor or NSAID therapy and cardiovascular events, and focuses on the question of whether or not celecoxib – the most widely prescribed remaining member of the selective COX-2 inhibitors has the greatest evidence for cardiovascular safety.

Methods

A comprehensive database search was performed on Medline and PubMed using the search terms COX-2, celecoxib, rofecoxib, lumiracoxib, etoricoxib, non-steroidal anti-inflammatory and myocardial infarction, stroke or cardiovascular events from 1965 to August 2006. The search was limited to human studies. References from each publication were checked for additional publications. All randomized, controlled

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studies and population studies were included. Beyond this, no attempt to judge the quality of the individual studies was made as it was felt that this may introduce an unwarranted potential for subjectivity. In addition, the US FDA website was accessed to obtain reports concerning the cardiovascular adverse event assessments of rofecoxib, etoricoxib and celecoxib.

A separate search of Medline was performed for both clinical and pre-clinical studies which have investigated possible mechanisms for an increase in cardiovascular events with these drugs, as well as for reviews on the topic.

Long-term placebo controlled trials

There has been one long term placebo controlled trial involving rofecoxib, studying the prevention of intestinal polyps (Bresalier et al 2005), three involving celecoxib (Arber et al 2005; Solomon et al 2005; TMT review 2005), and one involving naproxen (TMT review 2005). Two of the celecoxib studies were on the prevention of intestinal polyps (APC and pre-SAP) and one placebo controlled study of both celecoxib and naproxen examined the prevention of Alzheimers disease progression (ADAPT). An assessment of cardiovascular endpoints in these trials was made from the reporting of adverse events. With the exception of the ADAPT trial, there are no long term placebo controlled studies from which the cardiovascular safety of NSAIDS can be assessed. It is therefore possible that any adverse findings detected in any of the long term placebo controlled trials with celecoxib or rofecoxib may also occur with NSAIDS.

The APPROVe study

The APPROVe study was a 3-year, placebo-controlled study of rofecoxib 25 mg daily in the prevention of adenomatous colonic polyps (Bresalier et al 2005). The study enrolled 2586 patients with a history of colorectal adenoma, 1287 of whom received rofecoxib 25 mg daily and 1299 of whom received placebo. Patients with a history of ischemic heart disease or cerebrovascular disease were excluded. Monitoring of cardiovascular events was a planned component of the trial. Potential cardiovascular endpoints were adjudicated in a blinded manner. Serious adverse cardiovascular events were defined as fatal and non-fatal myocardial infarction, unstable angina, sudden death from cardiac causes, fatal and non-fatal ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism. The patients were followed for approximately three years (3059 patient-years). After about 18 months of therapy a statistically significant difference in cardiovascular events was found between the patients receiving rofecoxib and those receiving placebo (Figure 1). Forty five patients receiving rofecoxib experienced a serious cardiovascular thromboembolic event compared to 25 of the patients receiving placebo (relative risk 1.92, 95% confidence intervals 1.19 to 3.11, P = 0.008). Major contributors to the excess number of cardiovascular events in patients receiving rofecoxib were myocardial infarction (21 on rofecoxib verses 9 on placebo) and ischemic stroke (11 verses 6). These findings led the manufacturer Merck Pty Ltd to voluntarily withdraw the drug from marketing at the beginning of October 2004. A significantly greater number of patients developed hypertension on rofecoxib therapy than on placebo (14.3% verses 7.3%), a factor which could have contributed to the higher incidence of cardiovascular events on rofecoxib therapy.

The APC and pre-SAP studies

The APC and pre-SAP studies were both double blind, randomized, placebo controlled trials studying the use of celecoxib for the prevention of new adenomatous colonic polyps. The APC study was a three-arm study comparing celecoxib 200 mg bd, 400 mg bd and placebo. The pre-SAP study was a two-arm study comparing celecoxib 400 mg once daily with placebo. It was planned to follow up patients in each study after one and three years. The APC study enrolled a total of 2035 patients who were equally divided into the 3 groups. The pre-SAP study enrolled 1561 patients, ~900 in the celecoxib arm and ~600 in the placebo arm (Arber et al 2005; Bertagnolli et al 2006; Solomon et al 2005; TMT review 2005).

After the withdrawal from marketing of rofecoxib, an independent panel of cardiovascular experts was formed who adjudicated all reported serious adverse events for celecoxib from the APC and pre-SAP trials in a blinded manner. Adverse events that were considered to be of a cardiovascular nature were selected for analysis and further categorized into groups reflecting the probable type of cardiovascular event which had occurred. The data were subsequently unblinded and analysed. The principle group of endpoints that were of primary interest was the combination of cardiovascular death (or resuscitated cardiac arrest), fatal or non-fatal myocardial infarction, and fatal or non fatal stroke (CV death/MI/stroke), as these had been the events which had been found to be elevated during rofecoxib therapy compared to placebo in the APPROVe study.

The incidence of cardiovascular (CV) death/MI/stroke in APC was 0.8% for placebo, 2.1% for celecoxib 200 mg bd

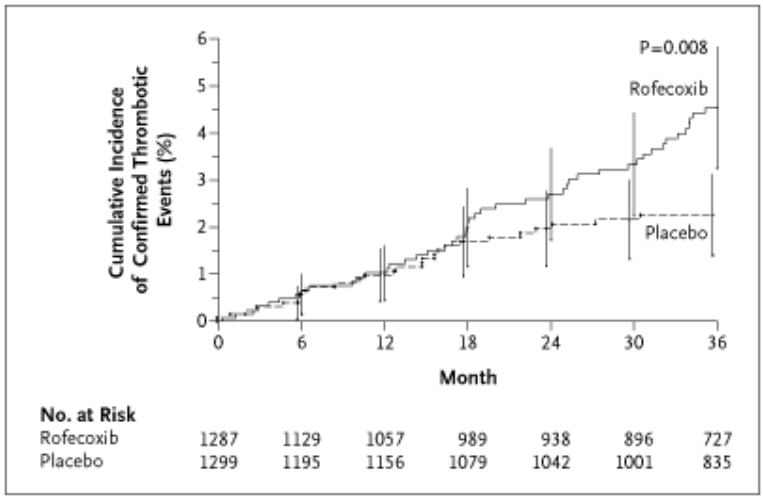

Figure 1 Cumulative incidence of cardiovascular events on rofecoxib and placebo therapy in the APPROVe Study.

and 2.8% for celecoxib 400 mg bd. In pre-SAP the incidences were originally reported to be 1.9% for placebo and 2.2% for celecoxib 400 mg daily (TMT review, 2005) but a subsequent report of the results by the investigators altered this slightly to 1.9% and 2.2% respectively (Arber et al 2005). It is unclear whether the slightly higher number of events represented more reported cases of CV death/MI/stroke or the inclusion of heart failure as an endpoint (Arber et al 2005). In the APC study, the difference between celecoxib 200 mg bd and placebo was of marginal statistical significance (odds ratio 2.8, 95% confidence interval 1.0 to 7.7) while the difference between celecoxib 400 mg bd and placebo was statistically significant (odds ratio 3.2, 95% confidence intervals 1.2 to 8.8; P = 0.01). It was the findings of the APC study that raised safety concerns within regulatory bodies. However, in the pre-SAP study the incidence of CV death/MI/stroke was similar for placebo and celecoxib 400 mg once daily irrespective of whether or not heart failure was included (hazard ratio 1.2, 95% confidence interval 0.6 to 2.5) (Arber et al 2005). This result was difficult to reconcile with the results of the APC study considering the similar study design.

The incidence of the CV death/MI/stroke endpoint was similar for celecoxib at a total daily dose 400 mg in each study (2.1% and 2.2%). The incidence of this endpoint for placebo in the pre-SAP study (1.9%) was similar to that of the 400 mg doses in both studies but the incidence of the endpoint appeared lower for placebo in the APC study (0.8%). Thus the incidence of CV death/MI/stroke for placebo in the APC study may have been spuriously low, particularly considering the small number of endpoints that the conclusions from the APC study have been drawn from.

A further issue is the use of myocardial infarction as an endpoint in clinical trials without other indicators of myocardial ischemia. This has been debated frequently in recent times due to the changing classification, diagnosis and management of ischemic heart disease. The distinction between a diagnosis of myocardial infarction and admission to hospital with unstable angina (acute coronary syndrome) has become less clear. Most importantly, early interventions with procedures such as angioplasty have undoubtedly prevented many myocardial infarctions. When evaluating myocardial ischemic events it is therefore more relevant to use a combination of myocardial infarction, hospital admission for unstable angina and unplanned coronary revascularization. This was done in the evaluation of the APPROVe study but not in the published cardiovascular events of the APC and pre-SAP studies.

The data from the APC and pre-SAP studies using a combined endpoint of CV (sudden) death, stroke, myocardial infarction, hospitalization for unstable angina and cardiovascular procedures are presented in Table 1. It should be noted that these data are complete only up until about February 2005 and the final publication of the APC and pre-SAP studies included a small number of events that were reported subsequent to this date (Bertagnolli et al 2006) (complete data including unstable angina have not been reported).

It can be seen from the result of this analysis of all ischemic cardiac events and stroke that there is relative consistency in the percentage of events occurring on celecoxib therapy and on placebo therapy between the APC and pre-SAP studies; there are no statistically significant

Table 1 Serious cardiovascular events in the APC and pre-SAP studies including unstable angina and emergency (unplanned) revascularizations

	APC			pre-SAP	
	Placebo (n = 679)	**200 mg bd (n = 685)**	**400 mg bd (n = 671)**	**Placebo (n = 628)**	**400 mg od (n = 933)**
Number of events	18	28	27	19	38
Percent	2.6	4.0	4.0	3.0	4.0
Odds ratio		1.56 (0.85–2.85)	1.53 (0.83–2.82)		1.36 (0.77–2.38)
p vs placebo		0.14	0.16		0.27

differences between celecoxib and placebo and there is no evidence of an increase in the number of events at the higher dose of 800 mg/day of celecoxib in the APC study.

Nonetheless, the publicized results of the APC and pre-SAP studies have raised the suspicion that high doses of celecoxib (two to four times the usual dose used for the treatment of arthritis) may be associated with an increased risk of cardiovascular events, but this is not as convincing as for the effects of rofecoxib at a dose routinely used for the management of arthritis.

The ADAPT study

The ADAPT study was a long-term, randomized, double blinded, placebo controlled investigation of the effects of celecoxib 200 mg bd or naproxen 220 mg bd on the development of dementia in elderly subjects who had a history of dementia in a first degree relative (TMT review, 2005). The intention was to study approximately 2500 patients equally divided into the three groups for a period of 7 years. The Treatment Effects Monitoring Committee (TEMC) met every 6 months and at its 10 December meeting considered data available up to the 1 October 2004, which included 750 patients who had been exposed to celecoxib for greater than 1.5 years. They concluded there was no reason to cease the trial. However, on 17 of December in response to the suspension of celebrex administration in the APC and pre-SAP trials, the executive board of the ADAPT trial suspended enrolment and study drug administration to ADAPT patients. The TEMC for the ADAPT study released the principle results of the safety analysis that had been prepared for their 10th of December meeting. These results indicated significantly higher risks of gastrointestinal bleeding, cardiovascular and cerebrovascular events in patients taking naproxen compared to placebo but no increase in these risks for celecoxib compared to placebo. The TEMC subsequently supplemented these data with safety reports of adverse events that had not previously been captured.

All adverse event forms and death reports were reviewed by a committee of three physicians involved with the study but who were unaware of the associated study drug treatment to ensure consistency of the event categorization. The main outcome measure was that used by the Anti-Platelet Trialists Collaboration, which is CV (sudden death)/MI/stroke. The potential limitations of this endpoint have been discussed above. A further limitation is that it does not include cerebral transient ischemic attacks (TIA's). However, TIA's were adjudicated and included in the presentation of the data. The results of the cardiovascular adverse events reported in the ADAPT Study are presented in Table 2. The odds ratios with 95% confidence limits and P values for comparisons between celecoxib or naproxen and placebo corresponding to Table 5 are presented in Table 3.

It is of interest that the only result of statistical significance was a higher risk of CV death/AMI/stroke/TIA for the non-specific NSAID naproxen compared to placebo. This appeared to be largely due to an increased incidence of stroke. Naproxen inhibits both COX-1 and COX-2 and does not disturb the balance between prostacyclin and thromboxane production.

After at least 1.5 years of therapy with celecoxib 400 mg in elderly patients there were no significant differences between celecoxib and placebo for any of the cardiovascular endpoints retrospectively assessed from reported adverse events. In contrast, the reported incidence for the composite cardiovascular endpoint was significantly higher in the subjects who received naproxen compared to those that received placebo.

Conclusions from long-term placebo-controlled clinical trials

The placebo controlled trials of selective COX-2 inhibitors and the NSAID naproxen suggest an increased risk of serious

Table 2 Incidence of serious cardiovascular events in the ADAPT study

Event	**Celecoxib (n = 704)**	**Naproxen (n = 702)**	**Placebo (n = 1057)**
Myocardial infarct	10 (1.42%)	9 (1.28%)	10 (0.95%)
Stroke	10 (1.42%)	12 (1.70%)	8 (0.76%)
CV death/AMI/stroke	17 (2.41%)	21 (2.99%)	20 (1.89%)
CV death/AMI/stroke/TIA	22 (3.13%)	30 (4.27%)	25 (2.37%)

Table 3 Odds ratios and statistical significance of differences in serious adverse events between naproxen or celecoxib and placebo in the ADAPT study

Event	Celecoxib vs placebo	Naproxen vs placebo
Myocardial infarct	1.50 (0.62–3.64) P = 0.35	1.36 (0.55–3.37) p = 0.50
Stroke	1.88 (0.74–4.81) P = 0.18	2.28 (0.92–5.6) p = 0.06
CV death/AMI/stroke	1.28 (0.66–2.46) P = 0.45	1.59 (0.86–2.97) p = 0.13
CV death/AMI/Stroke/TIA	1.33 (0.74–2.38) P = 0.33	*1.84 (1.07–3.61)* p = 0.02

adverse cardiovascular events of about 2-fold in patients receiving rofecoxib 25 mg daily. Naproxen therapy may be associated with an increased risk of stroke. The studies do not provide convincing evidence of an increase in the risk of cardiovascular events during celecoxib therapy, although is possible that higher doses of celecoxib (800 mg per day) may be associated with an increased cardiovascular risk based on the results of the APC study. It should be emphasized that similar long term, placebo controlled studies have not been performed with NSAIDs other than naproxen, so it is unknown whether they may be associated with similar indications of an increased cardiovascular risk.

Comparative trials between COX-2 specific inhibitors and NSAIDS

The VIGOR Study (Bombardier et al 2000) was designed to compare the gastrointestinal safety of rofecoxib with naproxen in patients with rheumatoid arthritis; 8076 patients were randomized to receive rofecoxib 50 mg per day or naproxen 500 mg daily and followed for a mean duration of 9 months. The incidence of serious cardiovascular thrombotic events was significantly higher in patients who received rofecoxib than in those that received placebo (Figure 2) principally due to a higher incidence of myocardial infarction (0.4 percent verses 0.1 percent). A subsequent analysis by the US FDA, which included additional adverse cardiovascular events to those available when the CLASS study was published, produced similar findings. The results of this study generated a lot of discussion, including the proposal that the results were evidence that the imbalance on prostacyclin and thromboxane formation that resulted from COX-2 specific inhibition, predisposed patients to adverse cardiovascular events.

Although numerous comparative studies between celecoxib and NSAIDS have been performed, most have been of short duration. The longest and largest comparative study between celecoxib and NSAIDS was the CLASS Study (Silverstein et al 2000; White et al 2002). This was a comparison of an average of 9 months of therapy with either celecoxib or one of the NSAIDS, ibuprofen or diclofenac. The aim of the study was to compare the incidence of gastro-intestinal ulceration between the therapies. Celecoxib was given at a dose of 400 mg twice daily, while the NSAIDS were administered at their usual recommended therapeutic doses (ibuprofen 800 mg three times a day and diclofenac 75 mg twice daily). Approximately 22% of the population studied also took low dose aspirin (which also inhibits both COX-1 and COX-2) as prophylaxis against cardiovascular disease. Patients were enrolled into the study if they suffered from either rheumatoid arthritis or osteoarthritis; 3987 patients were randomized to receive celecoxib and 3981 patients received either ibuprofen or diclofenac in approximately equal numbers.

Adverse events were classified retrospectively by the investigators (White et al 2002) into three cardiovascular groups: cardiac (myocardial infarction, myocardial ischemia, unstable angina, cardiac arrest or sudden death, other cardiac death); cerebrovascular (stroke, TIA); and peripheral vascular events.

There were no significant differences between any of the single or composite outcomes between celecoxib and NSAIDS except for stroke (which presumably also included TIA). The incidence of stroke was significantly lower in patients receiving celecoxib than in the combined NSAID groups. The odds ratio for patients receiving NSAIDS having a higher risk of stroke was 2.98 (95% confidence intervals 0.96–9.25; P = 0.047). A selection of the same cardiac endpoints that used in the analysis of the placebo controlled trials which reflect ischemia – CV (sudden) death, stroke, myocardial infarction, myocardial ischemia and unstable angina (information was not provided concerning coronary revascularizations) produced an odds ratio for this group of endpoints of 1.19 (95% confidence intervals 0.70–2.04; P = 0.50).

A separate analysis of the 78% of patients who were not taking aspirin was also performed by the investigators. Overall the results were similar to those obtained in the whole study population. For the combined endpoint of CV (sudden) death, stroke, myocardial infarction, myocardial ischemia and unstable angina the odds ratio was 0.75 (95% confidence intervals 0.35–1.59; p = 0.45).

It can be concluded from the CLASS study that over a period of approximately 9 months the risk of adverse cardiovascular events on celecoxib therapy appears to be similar to

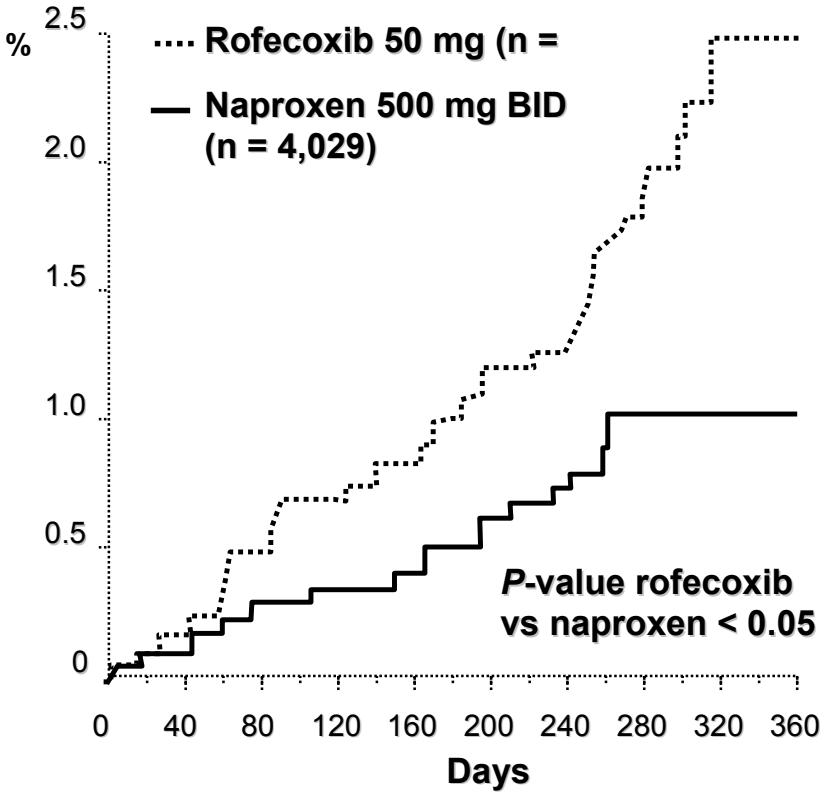

Figure 2 Cumulative incidence of serious cardiovascular events on rofecoxib and naproxen in the VIGOR study.

that which occurs during therapy with two commonly used NSAIDS, with the exception of stroke which appeared to be more common in patients receiving NSAIDs. As there was no placebo group, the study was unable to determine whether both groups of drugs have no effect on cardiovascular events or they have similar adverse effects. It should be noted that the average duration of the CLASS study was 9 months. It is possible that longer comparative studies may produce different results.

It is of interest to examine the cardiovascular events that occurred on celecoxib therapy compared to the individual NSAIDS studied, ibuprofen and diclofenac. The rate of accumulation of adverse cardiovascular events during the CLASS study for each of the drugs used is presented in Figure 3. In the top part of the Figure (A), the celecoxib group and both NSAIDS combined data are compared, while in the bottom part of the Figure (B) celecoxib and the individual NSAIDS are compared.

While there was no difference in the rate of cardiovascular events when celecoxib was compared to the combination of the two NSAIDS, the lower part of the Figure gives the impression that there may have been differences between the rates of cardiovascular events between the two NSAIDS, with diclofenac having a higher rate than ibuprofen and celecoxib lying somewhere in the middle. While these differences were not statistically significant, they are of interest considering the epidemiology data suggesting differences in the risk of myocardial infarction between NSAIDS which is discussed below. Some of these data suggest that ibuprofen may have a relatively lower risk of thromboembolic events while diclofenac may have a relatively higher risk (Johnsen et al 2005; Hippisley-Cox et al 2005; Andersohn et al 2006).

A pooled analysis of cardiovascular adverse events from 15 studies that compared celecoxib with NSAIDS or placebo was published by White et al in 2003 (White et al 2003). (This analysis did not include the APC study or the pre-SAP study which were completed after this time). With the exception of the CLASS study, most of the studies were either of short duration or involved relatively small numbers of patients. The CLASS study therefore contributed most of the data to the pooled analysis and the results not surprisingly were similar to those reported for the CLASS Study. Adverse events were adjudicated in a blinded manner by the investigators and the endpoint used for comparison between therapies was a combination of myocardial infarction, myocardial ischemia, unstable angina, cardiac revascularizations, death (including cardiac and sudden or unexplained deaths), stroke and TIA.

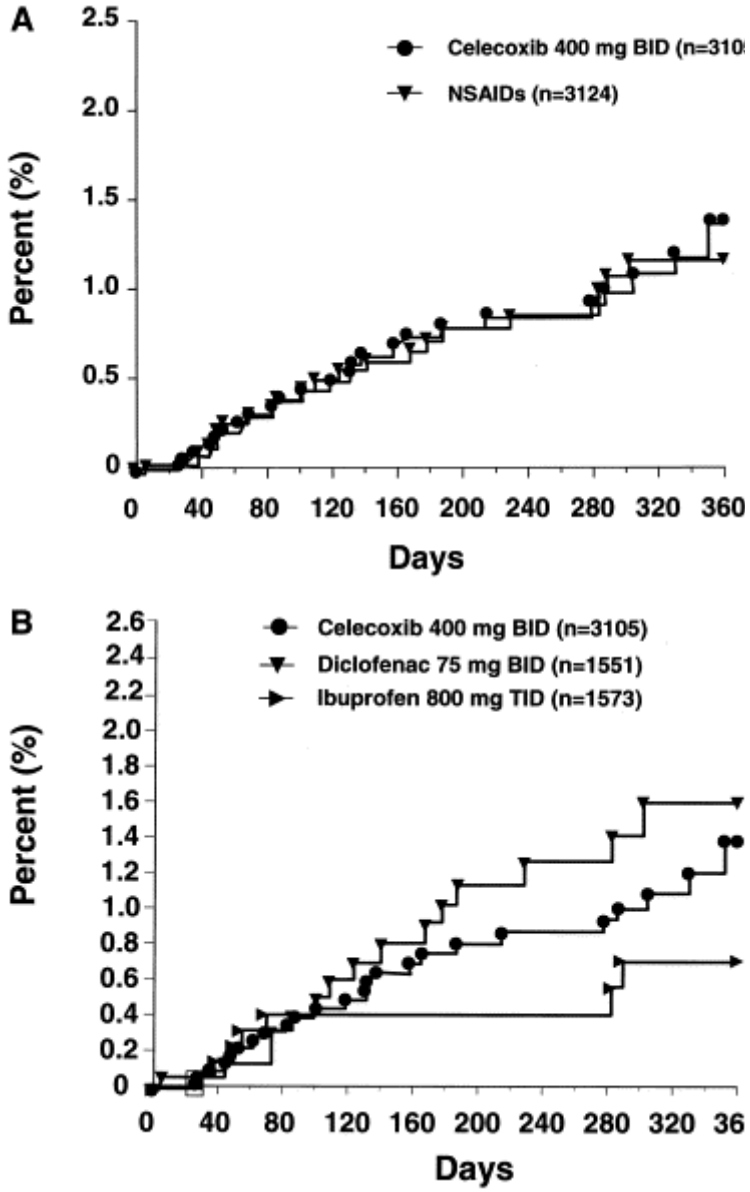

Figure 3 Cumulative incidence of serious cardiovascular events on celecoxib compared to the combined NSAID group (Upper Panel **A**) and compared to the individual results for ibuprofen and diclofenac (Lower Panel **B**).

No significant differences in serious cardiovascular events were found between celecoxib and NSAIDS (including naproxen alone) or between celecoxib and placebo. The relative risk for the combined endpoint was 0.85 (95% confidence intervals 0.23–3.15, p = 0.81) for the comparison between celecoxib and placebo and 1.06 (95% confidence intervals 0.70 –1.61, P = 0.79). However the limited extent of exposure in the studies comparing celecoxib with placebo should be noted. Hence this study was principally one comparing celecoxib with other NSAIDS.

A meta-analysis was provided by Pfizer Pty Ltd in response to requests by the European Medicines Evaluation Agency (EMEA) which included 41 randomized, controlled clinical trials involving 44,308 patients studied for between 2 weeks and 12 months (Pfizer- data on file, 2005). The APC, pre-SAP and ADAPT trials were not included in this analysis. The data included 1268 patient-years of exposure to celecoxib in trials compared with 585 patient years of exposure to placebo. The relative risk for any serious cardiovascular thromboembolic event was 1.02 (95% confidence intervals 0.49–2.13; P = 0.957).The relative risk for the same endpoint compared to all NSAIDs (5651 patient-years of exposure for celecoxib and 4386 patient years of exposure for NSAIDs)

was 0.88 (0.65–1.19; P = 0.403). No significant differences in the results were observed between aspirin users and non-aspirin users. However, of interest was a statistically significantly lower incidence of stroke in celecoxib users compared to NSAID users. These results are in keeping with those of the CLASS and ADAPT studies, which found a lower incidence of stroke in celecoxib users than in the patients receiving NSAIDs.

It has been suggested the apparent adverse cardiovascular effects of rofecoxib in the VIGOR study may have been due to the fact that rofecoxib was a more specific inhibitor of COX-2 than celecoxib. This proposition may be supported by the findings of pooled analysis of randomized controlled trials of etoricoxib, another highly selective COX-2 inhibitor, which suggest an increased risk of cardiac ischemic events for etoricoxib compared to either placebo or NSAIDs – although the number of events that this analysis is based on is relatively small (Food and Drug Administration 2005). However, a subsequent 12-month study comparing another COX-2 specific inhibitor, lumiracoxib – which is more COX-2 selective than rofecoxib (Farouk et al 2004) – with two NSAIDS (naproxen or ibuprofen) found no significant differences in cardiovascular events between the groups. This study had over 9000 patients with osteoarthritis in each of the lumiracoxib and combined NSAID arms, and cardiovascular events (myocardial infarction, unstable angina, cardiovascular death, cardiac arrest, stroke (ischemic and haemorrhagic), transient ischemic attack, deep vein thrombosis, and pulmonary embolism) were pre-specified study endpoints. The hazard ratio for cardiovascular events between the lumiracoxib and NSAID arm was 1.14 (95% confidence intervals 0.78–1.66; P = 0.50). Similar results were obtained in patients receiving low dose aspirin as cardiovascular prophylaxis and those not receiving low dose aspirin. The study has been criticized because the number of cardiovascular events was low and patients with a significant risk of cardiovascular events were excluded. However, the number of myocardial infarctions (21 in the lumiracoxib group and 17 in the NSAID group) was similar to that which occurred in the rofecoxib group in the VIGOR study and the study had greater statistical power. Nonetheless, the criticism that patients with an increased risk of cardiovascular events were excluded may be valid.

The results of the TARGET study argue that the differences in cardiovascular outcomes between the CLASS and VIGOR studies were principally because of differences in selectivity for COX-2 inhibition. The results also argue against the hypothesis that an imbalance between thromboxane and prostacyclin production results in a risk of thrombotic and other cardiovascular events and that this is a class effect of COX-2 specific inhibitors. However, others remain unconvinced that the results of the TARGET study provide evidence against the thromboxane/prostacyclin imbalance hypothesis, although these commentaries have often adopted the premise that the hypothesis is true without a discussion of all the epidemiological and mechanistic data (Clark et al 2004; Vonkeman et al 2006).

Epidemiological studies

Numerous epidemiological studies have been performed comparing the risk of cardiovascular events (almost exclusively myocardial infarction) between users of COX-2 specific inhibitors, NSAIDS and non-users of anti-inflammatory drugs. These studies have the inherent problem that the results may be biased because of differences in the populations using different drugs that may affect their risk of having a myocardial infarct. Correction for potential bias is generally made in the statistical analysis, but it always remains possible that unrecognized bias persists.

The studies have varied widely in their scientific quality. In general, studies involving large numbers of subjects are likely to be more reliable than those with smaller numbers, and studies in which the data have been collected prospectively are more reliable than those in which retrospective collection of data have been used.

A tabular summary of all of the studies that have compared COX-2 specific inhibitors and/or NSAIDS with non-users of these drugs is presented in Table 4.

A positive association between NSAID use and myocardial infarction was first described by Garcia-Rodriguez in 2000 (Garcia-Rodriguez et al 2000). The risk of myocardial infarction appeared to be greatest in those who had recently commenced taking the drugs, an observation that has also been made in a number of other studies. Overall, the studies presented in Table 4 provide evidence that a number of NSAIDS may be associated with an increased risk of myocardial infarction, and that the risk varies between different drugs. Rofecoxib has been associated with an increased risk of myocardial infarction in 12 out of 14 studies which have evaluated its use. Celecoxib has been associated with a statistically significant risk of myocardial infarction in four out of 15 studies (Johnsen et al 2005; Singh and Mithal, 2005; Andersohn et al 2006; Motsko et al 2006). In the first study the increase in risk only occurred in patients who had recently commenced taking the drug. There was no significant difference between celecoxib use and remote use of anti-inflammatory drugs for the primary endpoint, which was long term use of the

Table 4 Summary of population studies that have assessed the relationship between NSAID or selective COX-2 inhibitor therapy and cardiovascular events. Studies in which the number of events are not provided for each drug on which the relative risks were based have a ? after the name of the drug. Statistically significant results are highlighted in italics

Author/year	Design	Endpoints	Number of events	Relative risks (adjusted) compared to non-use unless otherwise stated	Comment
Garcia-Rodriguez et al 2000 (July)	Prospective case control study in women 50–74 years	First ever fatal or non-fatal AMI	Current NSAID use 167 Duration of therapy <60 days 70 Duration 61–365 days 40 Duration >365 days 57 Low/medium dose 19 High dose 38 Past user 344	*1.45 (1.18–1.79)* *1.76 (1.31–2.38)* 1.33 (0.91–1.95) 1.25 (0.90–1.72) 1.22 (0.71–2.09) 1.25 (0.85–1.84) 0.89 (0.76–1.05)	Recent initiation of NSAID therapy associated with AMI
Schlienger et al 2002 (September)	Retrospective case control in patients ≤ 75 years free from cardiovascular disease	First ever AMI	All NSAIDS 3319	1.17 (0.99–1.37) 1.20 (0.94–1.55) for long term use	Did not look at individual NSAIDS
Ray et al 2002 (October)	Retrospective cohort	AMI or CHD death	Celecoxib (current) 75 Celecoxib (new) 55 Rofecoxib <25 mg (current) 55 (new) 47 Rofecoxib >25 mg (Current) 13 (new) 12	0.96 (0.76–1.21) 0.88 (0.67–1.16) 1.03 (0.78–1.35) 1.02 (0.76–1.37) 1.70 (0.98–2.75) *1.93 (1.09–3.43)*	
Mamdami et al 2003 (February)	Retrospective cohort	AMI	Celecoxib 75 Rofecoxib 58 Naproxen 15 Other NSAIDS 134	0.9 (0.7–1.2) 1.0 (0.8–1.4) 1.0 (0.6–1.7) 1.2 (0.9–1.4)	
Whelton et al 2003 (February)	Retrospective cohort in hypertensives with OA	AMI or *stroke*	Celecoxib ? Rofecoxib ? Other NSAIDS ?	1.35 (0.98–1.86) *2.45 (1.71–3.51)* 1.11 (0.74–1.67)	Event numbers not given Years of exposure 453 to 3612. Contribution of stroke not given.
Kimmel et al 2004 (March)	Prospective case control	First, non-fatal AMI	NSAIDS ? Ibuprofen ? Naproxen ?	*0.53 (0.42–0.67)* *0.52 (0.39–0.69)* *0.48 (0.28–0.82)*	Claims NSAIDS are cardioprotective and do not interfere with the beneficial effects of aspirin
Kurth et al 2003 (September)	Retrospective subgroup analysis of randomized trial of aspirin verses placebo in US Physicians	First fatal or non-fatal AMI	All NSAIDS < 59 days/yr 26 All NSAIDS > 60 days/yr 6	1.21 (0.78–1.87) *2.86 (1.25–6.56)*	Very small study. All patients on aspirin. No information on individual NSAIDS
Solomon et al 2004 (May)	Retrospective, case-control in adults over 65 years (mean age 81 years)	AMI coded as 1st or 2nd discharge diagnosis	Celecoxib 2140 Rofecoxib 941	0.93 (0.84–1.02) *1.14(1.00–1.31)** *Rofecoxib/celecoxib* *1.24 (1.05–1.46)*	*marginal (P = 0.054) Data for other NSAIDS obtained but not compared with non-use
Garcia-Rodriguz et al 2004 (June)	Prospective case control study in patients aged <70.	Fatal and non-fatal AMI	All NSAIDS 4975 Naproxen 49 Ibuprofen 155	1.07 (0.95–1.20) 0.89 (0.64–1.24) 1.06 (0.87–1.29)	Risk of AMI markedly increased in patients prescribed NSAIDS for

(*Continued*)

Table 4 (*Continued*)

Author/year	Design	Endpoints	Number of events	Relative risks (adjusted) compared to non-use unless otherwise stated	Comment
			Diclofenac 213 Ketoprofen 16 Meloxicam 25 Piroxicam 16 Indomethacin 29	1.18 (0.99–1.40) 1.08 (0.59–1.96) 0.97 (0.60–1.56) 1.25 (0.69–2.25) 0.86 (0.56–1.32)	ill-defined chest pain. Diclofenac almost significant. Unadjusted odds *1.37 (1.17–1.61)*
Shaya et al 2005 (January)	Prospective cohort, Observational	AMI, *stroke*, sudden death, haemorrhagic death (APTC) criteria. Also AMI alone.	Celecoxib plus rofecoxib 66 Other NSAID 60 (No non-user Group comparison)	1.12 (0.67–1.85) for AMI comparing celecoxib and rofecoxib combined with other NSAIDS. For APTC, celecoxib vs NSAIDS 1.19 (0.93–1.51); rofecoxib vs NSAIDS 0.99 (0.76–1.30)	No evidence of differences between celecoxib or rofecoxib and other NSAIDS
Graham et al 2005 (January)	Prospective, case-control, adults 18–84.	AMI,SCD (*Note that non-AMI ACS and revascularization not included)*	Celecoxib 126 Ibuprofen 670 Naproxen 367 Rofecoxib 68 Rof ≤25 mg 58 Rof ≥25 mg 10 Other NSAID 534 All anti-inflam. 1720	0.84 (0.67–1.04) 1.06 (0.96–1.17) *1.14 (1.00–1.30)* 1.34 (0.98–1.82) 1.23 (0.89–1.71) *3.00 (1.09–8.31)* *1.13 (1.01–1.27)* *1.11 (1.03–1.19)*	Significant increase in risk of AMI/SCD for all anti-infl. (11%) driven driven mostly by the effects of NSAIDS (294 vs 1571 events)
Kimmel et al 2005 (February)	Prospective, case control, adults 40–75	Hospitalization for non-fatal AMI only	Celecoxib 18 Rofecoxib 27 NSAIDS 319	*0.43 (0.23–0.79)* 1.16 (0.70–1.93) *0.61 (0.52–0.71)*	Small study, very limited endpoint.
Levesque et al 2005 (April)	Retrospective, case-control adults over 66. (current use)	Hospitalization for >3 days for fatal or non-fatal AMI	Celecoxib 287 Rofecoxib 239 Naproxen 23 Other NSAID 51	0.99 (0.85–1.16) *1.24 (1.05–1.46)* 1.17 (0.75–1.84) 1.00 (0.73–1.37)	
Fischer et al 2005 (April)	Retrospective case control current use of NSAIDS	First time AMI	All NSAIDS 650 Ibuprofen ? Naproxen ? Diclofenac ?	1.07 (0.96–1.19) 1.16 (0.92–1.46) 0.96 (0.66–1.38) *1.34 (1.00–1.51)*	
Johnsen et al 2005 (May)	Retrospective case control study aged 20 or greater.	Hospitalization for AMI coded as their 1st diagnosis. Data included new users (1st Rx within last 30 days.	Celecoxib 71 Cel. (new) 35 Rofecoxib 119 Rof. (new) 39 *Other COX2 57 *Other (new) 22 Naproxen 26 Napr. (new) 4 Other NSAID 532 Other NSAID (new) 65	1.25 (0.97–1.62) *2.13 (1.45–3.13)* *1.80 (1.47–2.21)* *2.52 (1.74–3.64)* *1.45 (1.09–1.930)* *3.37 (2.05–5.53)* 1.50 (0.99–2.29) 1.65 (0.57–4.63) *1.68 (1.52–1.85)* *2.65 (2.00–3.50)*	Numbers for naproxen small. All NSAIDS commenced within previous 30 days associated with ↑ risk of AMI. Long term treatment with traditional NSAIDS or rofecoxib associated with ↑ AMI * included meloxicam
Hippisley-Cox et al 2005 (June)	Retrospective, case control study aged 25–100. Prior AMI excluded but 28% recorded as having prior IHD. Cases and controls classified as no prescription in last year,	First ever AMI (?including fatal)	<u>Remote use</u> Celecoxib 137 Rofecoxib 219 Other COX2* 200 Ibuprofen 1496 Diclofenac 1311 Naproxen 332 Other NSAID 560	 1.14 (0.93–1.40) 1.05 (0.89–1.24) 0.93 (0.79–1.10) 1.05 (0.98–1.12) *1.13 (1.05–1.21)* *1.27 (1.01–1.60)* *1.18 (1.06–1.30)*	Recent use of ALL anti-inflammatories other than celecoxib associated with ↑ risk of AMI. Remote use of some NSAIDS associated with ↑ risk of AMI. Risk increased with increasing

(*Continued*)

Table 4 (*Continued*)

Author/year	Design	Endpoints	Number of events	Relative risks (adjusted) compared to non-use unless otherwise stated	Comment
	>3 months prior to index event (remote), and <3 months prior to index event (recent).		Recent use		prescription numbers. Risk not affected by prior diagnosis of CHD use of aspirin
			Celecoxib 93	1.21 (0.96–1.54)	
			Rofecoxib 151	*1.32 (1.09–1.61)*	
			Other COX2 101	*1.27 (1.00–1.61)*	
			Ibuprofen 460	*1.24 (1.11–1.39)*	
			Diclofenac 542	*1.55 (1.39–1.72)*	
			Naproxen 96	*1.27 (1.01–1.60)*	*other COX2 presumably mainly meloxiam.
			Other NSAID 181	*1.21 (1.02–1.44*	
Singh and Mithal 2005 (June)	Retrospective case-control. Current exposure compared to remote exposure.	AMI (fatal or non-fatal).	15,343 cases. Distribution between different drugs not available.		Variable increased risk of AMI with recent use of most anti-inflammatories.
			Celecoxib	*1.09 (1.02–1.15) (all doses)*	Dose response relationships found for rofecoxib, diclofenac, naproxen and celecoxib (RR at doses ≤200 mg/day 1.01 >200 mg/day = 1.24.
			Meloxicam	*1.37 (1.05–1.78)*	
			Rofecoxib	*1.32 (1.22–1.42)*	
			Valdecoxib	0.99 (0.72–1.37)	
			Indomethacin	*1.71 (1.35–2.17)*	
			Sulindac	*1.41(1.01–1.96)*	
			Ibuprofen	*1.11(1.01–1.22)*	
			nabumetone	0.83 (0.60–1.14)	
Huang et al 2006	Retrospective, cohort	AMI and stroke	9602 patients who received either therapy for at least 180 days celecoxib, meloxicam rofecoxib	AMI (verses meloxicam) *0.81 (0.70–0.93)* *0.78 (0.63–0.96)*	Stroke also lower for celecoxib Risk of AMI and stroke similar for rofecoxib and meloxicam
Andersohn et al April 2006	Case control	AMI	3643 cases 13918 controls		
			rofecoxib	*1.33 (1.02–1.63)*	
			celecoxib	*1.56 (1.23–1.98)*	
			etoricoxib	*2.09 (1.10–3.97)*	
			valdecoxib	4.60 (0.61–34.51)	
			diclofenac	*1.36 (1.17–1.58)*	
			ibuprofen	1.00 (0.86–1.25)	
			naproxen	1.16 (0.86–1.58)	
			other NSAIDs	*1.19 (1.02–1.39)*	
Solomon et al May 2006	Cohort study	AMI and ischaemic stroke	74838 users of NSAIDs or coxibs, recently commenced therapy (new users). Comparison with non-users.		No altered risk for celecoxib, valdecoxib or other NSAIDs Note reduced risk for naproxen
			rofecoxib	*1.15 (1.06–1.25)*	
			naproxen	*0.75 (0.62–0.92)*	
Motsoko et al 2006	Retrospective cohort study 1999–2001	Cardiovascular events	11930 users of NSAIDs or coxibs, 142 CV events. Comparison of events relative to ibuprofen <180 days or >180 days after starting therapy.		Risk greater in elderly. No difference between ibuprofen, naproxen and etodolac. Other NSAIDs not studied. Risk for celecoxib and rofecoxib increased progressively after 150 days of therapy.

(*Continued*)

Table 4 (*Continued*)

Author/year	Design	Endpoints	Number of events	Relative risks (adjusted) compared to non-use unless otherwise stated	Comment
			>180 days		
			celecoxib (18)	*3.64 (1.36–9.70)*	
			rofecoxib (8)	*6.64 (2.17–20.8)*	
			<180 days		
			celecoxib (21)	0.75 (0.42–1.35)	
			rofecoxib (9)	0.85 (0.39–1.86)	
Helin-Salmivaara et al 2006 June	Nationwide (Finland) case-control study 2000–2003	First-time AMI	33039 cases, 138949 controls		Most NSAIDs had relative risk of of ~ 1.40, including ibuprofen. *(Naproxen risk 1.19 (1.02–1.38).* No evidence of increasing risk with longer duration of therapy. No increased risk for celecoxib.
			Any NSAID	*1.40 (1.33–1.48)*	
			Conventional NSAID	*1.34 (1.26–1.43)*	
			Semi selective	*1.50 (1.32–1.71)*	
			(etodolac,	1.35 (0.44–4.17)	
			nimensuide,	*1.69 (1.43–1.99)*	
			meloxicam)	1.24 (0.99–1.55)	
			Coxibs	*1.31 (1.13–1.50)*	
			(celecoxib,	1.06 (0.83–1.34)	
			rofecoxib,	*1.44 (1.20–1.72)*	
			etoricoxib)	2.21 (1.18–4.14)	

drug (Johnsen et al 2005). It is of interest that one investigator (Garcia-Rodriguez et al 2004) found a markedly increased risk of myocardial infarction in patients who had recently commenced NSAID therapy because of ill-defined chest pain. It is possible that other studies that have found a greater association between NSAID use and myocardial infarction following the recent commencement of therapy may have been partly biased by patients taking NSAIDS for undiagnosed ischemic chest pain. The second study to show an increased risk of myocardial infarction during celecoxib use was very large and had the statistical power to detect small differences in relative risk. The relative risk associated with low doses (≤200 mg) of celecoxib was 1.01 which increased to 1.24 at higher doses (Singh and Mithal 2005). A third study found a significant increased risk of myocardial infarction for celecoxib (relative risk 1.56) and evidence of a greater risk at higher doses than at lower doses (Andersohn et al 2006). A recent study found an elevated relative risk of myocardial infarction of 3.64 for celecoxib compared to ibuprofen. (The relative risk for rofecoxib compared to ibuprofen in this study was 6.64). The increased risk was only apparent during long term administration (>180 days). These data may be consistent with an increased risk of myocardial infarction at higher doses of celecoxib and during prolonged therapy. In all, 10 studies have found no altered risk in myocardial infarction for celecoxib, one has found a significantly reduced risk and four have found an increased risk.

Meloxicam, an NSAID which is claimed to be relatively COX-2 specific and which is has a different chemical structure to both rofecoxib and celecoxib, was reported in one study to have no associated increased risk of myocardial infarction (relative risk 0.97) (Garcia-Rodriguez et al 2004). In another large, statistically powerful study (Singh and Mithal 2005) meloxicam was found to be associated with a statistically significant increased risk of myocardial infarction (relative risk 1.37), which was higher than that observed for rofecoxib (relative risk 1.32). However, the relative risk for meloxicam was lower than that reported for the non-selective NSAIDs indomethacin (relative risk 1.71) and sulindac (relative risk 1.41). A population study in Taiwan found that the long term use of meloxicam was associated with a greater risk of myocardial infarction and stroke that celecoxib use. The risk of myocardial infarction and stroke amongst rofecoxib users in this study was similar to that found for meloxicam use (Huang et al 2006). A pooled analysis of randomized, controlled studies of meloxicam therapy of up to 60 days duration found that meloxicam was associated with a statistically significantly lower number of thromboembolic complications than the NSAID diclofenac (0.2% verses 0.8% respectively) but a similar incidence of thromboembolic events to naproxen and piroxicam (Singh and Lanes 2004). A large study of all myocardial infarctions in Finland from 2000 to 2003 found a significantly increased realtive risk for meloxicam of 1.24.

It should be noted that population studies have not yet been able adequately to assess the cardiovascular risk associated

with the newer selective COX-2 inhibitors, lumiracoxib, etoricoxib and valdecoxib. Data for valdecoxib have been included in two studies and was not found to be associated with an increased risk of myocardial infarction (Singh and Mithal 2005; Andersohn et al 2006). Etoricoxib has been evaluated in two studies and found to be associated with a significantly increased relative risk of myocardial infarction of 2.02 in one (Andersohn et al 2006) and 2.21 in the other (Helin-Salmivaara et al 2006).

A large, recent Finnish study of over 33,000 myocardial infarctions found an increased relative risk of 1.34 for all conventional NSAIDs combined and 1.31 for all coxibs combined. The relative risk values for individual NSAIDs were similar over a wide range of drugs, the lowest values being for ketoprofen (1.11) and naproxen (1.19) (Helin-Salmivaara et al 2006). Etoricoxib had the highest value amongst the selective COX-2 inhibitors (2.21) while the relative risk for rofecoxib was 1.6. Of the three selective COX-2 inhibitors studied, only celecoxib therapy was not associated with a significantly increased risk of myocardial infarction (relative risk 1.06).

The interpretation of population studies is hampered by the fact that they are not randomized and are often retrospective, and there is a significant potential for unrecognized selection bias. In addition, comparisons between studies that assess different endpoints in different populations are difficult. Nonetheless, the population studies as a group suggest that COX inhibitors as a class (whether COX-2 selective or not) have the potential to increase the risk of serious cardiovascular events. While there appear to be differences between individual drugs in the risk of producing serious cardiovascular events, this does not appear to be clearly related to the degree of COX-2 selectivity. Rofecoxib has been shown to be associated with increased cardiovascular events fairly consistently, but some commonly used traditional NSAIDs (indomethicin, diclofenac, sulindac) have been reported in some studies to have a higher risk than rofecoxib (Hippisley-Cox et al 2005; Singh and Mithal 2005). Celecoxib has not been associated with an increased risk of serious cardiovascular events in most of the studies which have evaluated its risk.

Mechanisms via which non-selective or selective COX-2 inhibitors may increase the risk of cardiovascular events

While there is evidence that both rofecoxib and celecoxib reduce prostacyclin formation in normal volunteers (Fitzgerald 2003) while leaving thromboxane formation unchanged, it is likely that other mechanisms such as the nitric oxide and endothelium derived hyperpolarization factor (EDHF) pathways compensate to an extent for this effect. Nonetheless, these potential compensatory mechanisms could theoretically fail in patients with vascular disease or cardiovascular risk factors, placing them at greatest risk for cardiovascular complications of selective COX-2 inhibitor therapy. However, measurements of endothelium dependent vasodilator responses (an independent predictor of future cardiovascular events) have been shown to remain unchanged in patients with ischemic heart disease receiving long term rofecoxib therapy (Bogarty et al 2004) and to improve in a similar group of patients receiving celecoxib therapy (Chenevard et al 2003). While COX-2 inhibition has been reported to reduce the late phase of myocardial ischemic preconditioning and increase infarct size in animal models, this effect occurs with both selective and non-selective COX inhibitors (Shinamura et al 2002).

Other potential mechanisms exist via which selective and non-selective COX inhibitors may increase the risk of myocardial infarction and other serious cardiovascular events. Rofecoxib has been described to have pro-oxidant activity and to increase the formation of reactive molecules leading to increased oxidative damage to LDL-cholesterol (Walter et al 2004). Selective and non-selective COX inhibitors may increase blood pressure leading to a short-term and long-term increase in cardiovascular events (Aw et al 2005). In particular, rofecoxib has been demonstrated to have a greater effect on blood pressure than celecoxib and some other non-selective NSAIDs (Sowers et al 2005).

The individual effect that a NSAID or COX-2 inhibitor has in modifying the risk of cardiovascular events may depend upon a complex interaction of pharmacological properties including duration and extent of platelet inhibition, extent of blood pressure rise and properties that appear to be unique to the molecule. Examples of the latter include the pro-oxidant effects of rofecoxib and the ability of celecoxib to improve endothelial function.

Conclusion

The published scientific literature suggests that both specific and non-specific COX inhibitors may increase the risk of myocardial infarction and other serious cardiovascular events, but that the effect varies between the individual drugs. There is little evidence to support the proposition that an imbalance of thromboxane and prostacyclin resulting from COX-2 specific inhibition increases the risk of cardiovascular

events and that this is a class effect. The evidence available so far (which must be accepted as being indirect and incomplete) suggests that a higher cardiovascular risk may be associated with rofecoxib, while a lower cardiovascular risk may be associated with celecoxib. Some NSAIDs, particularly indomethacin, diclofenac and meloxicam may have cardiovascular risks similar to rofecoxib. There is a much greater body of evidence supporting the relative cardiovascular safety of celecoxib when used at the usual doses to treat arthritis than for any of the other selective COX-2 inhibitors or NSAIDs.

It will be important to establish the individual cardiovascular safety of novel COX inhibitors before they are introduced into widespread use. It is important at the present time that some widely used NSAIDs may have a similar cardiovascular risk to rofecoxib, which was removed from the market because of cardiovascular toxicity.

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