Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Peter Jüni, Linda Nartey, Stephan Reichenbach, Rebekka Sterchi, Paul A Dieppe, Matthias Egger

Summary

Background The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint.

Findings We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20742 patients) the relative risk from randomised controlled trials was 2·30 (95% CI 1·22–4·33, p=0·010), and 1 year later (64 events, 21432 patients) it was 2·24 (1·24–4·02, p=0·007). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; p=0·41) or trial duration (p=0·82). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0·86 [95% CI 0·75–0·99]) and could not have explained the findings of the VIGOR trial.

Interpretation Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

Introduction

On Sept 30, 2004, a press release from Merck announced the withdrawal of rofecoxib (Vioxx) because of an increased cardiovascular risk in patients taking the drug for more than 18 months.1 The decision was based on the 3-year results of the unpublished Adenomatous Polyp Prevention on Vioxx (APPROVe) study, a placebo-controlled trial of rofecoxib for the prevention of recurrence of colorectal polyps in patients with a history of colorectal adenomas. By the time it was withdrawn, rofecoxib had been taken by an estimated 80 million people and sales had reached US$2·5 billion in 2003.2

Rofecoxib is a non-steroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclo-oxygenase 2 (COX2). The COX enzyme is crucial to the formation of prostaglandins and exists in two isoforms, a constitutive isoform (COX1) and an inducible isoform that is expressed at sites of inflammation (COX2). The idea that anti-inflammatory effects are mediated through inhibition of COX2, whereas adverse gastrointestinal effects are attributable to inhibition of COX1, whose prostaglandins protect the gastric mucosa, led to the development of selective COX2 inhibitors.3 Approved by the US Food and Drug Administration (FDA) in 1999, COX2 inhibitors soon dominated the prescription-drug market for NSAIDs.

The safety profile of rofecoxib has been questioned since the Vioxx Gastrointestinal Outcomes Research trial (VIGOR),4 which noted a five-fold higher incidence of myocardial infarction in the rofecoxib group compared with the naproxen group.5-8 Naproxen inhibits the production of thromboxane and platelet aggregation, and the difference in cardiovascular risk was attributed to a cardioprotective effect of naproxen, rather than a cardiotoxic effect of rofecoxib.4 This interpretation was reiterated in a 2001 meta-analysis of randomised trials of rofecoxib7 and three case-control studies of naproxen and myocardial infarction published in 2002.9-11 We report the results of a cumulative meta-analysis to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods

Literature search and inclusion criteria

We aimed to identify all randomised clinical trials that compared rofecoxib with another NSAID or placebo. We searched the Cochrane Controlled Trials Register (issue 3, 2004), and MEDLINE, EMBASE, and CINAHL (from inception to September, 2004). We combined a search for articles relating to rofecoxib with the Cochrane search strategy for randomised trials. We examined citations of key papers in the Science Citation Index, searched conference proceedings, screened...
reference lists of relevant papers, contacted experts, and scrutinised the proceedings of the relevant FDA advisory panels. No large placebo-controlled randomised trials addressing the cardioprotective potential of naproxen are available.11 We therefore identified observational studies combining drug-specific search terms with terms related to cardiovascular disease.

We included all randomised controlled trials in adult patients with chronic musculoskeletal disorders that compared rofecoxib 12.5–50 mg daily with other NSAIDs or placebo. Data for trial arms using other doses of rofecoxib were excluded. We included cohort and case-control studies that examined the association between naproxen use and cardiovascular risk. Two reviewers (PJ, SR) independently evaluated studies for eligibility.

Data collection and outcome measures
Two reviewers (LN, RS) extracted data for publication status, trial design, patients' characteristics, treatment regimens, outcomes, funding, year of publication, year of first presentation at a major conference, and year of submission of data to the FDA, using a standardised form. Completed data forms were checked by two different reviewers (PJ, SR). We assessed two components of trial quality: concealment of allocation of patients to treatment groups, and external review of serious cardiovascular events.

For rofecoxib trials, fatal or non-fatal acute myocardial infarction was the primary endpoint. The following cardiovascular outcomes were regarded as secondary endpoints: fatal or non-fatal strokes (thrombotic or haemorrhagic); cardiovascular mortality (including deaths of unknown cause); and the composite outcome of serious cardiovascular events. For trials with more than two arms, and for extensions of trials, we used appropriate weighting to avoid duplication of data. Comparisons with no events in either group were excluded; comparisons with events only in one group were analysed by adding 0·5 to all cells.

Risk ratios and odds ratios from observational studies were pooled using random-effects meta-analyses. For the primary analysis we followed the authors’ choice of reference group. Comparison of naproxen users with users of other NSAIDs, rather than with non-users, might reduce possible confounding by indication. We therefore also analysed the results from comparisons with non-naproxen NSAIDs. We used meta-regression to establish the effect of study design (case-control or cohort), source of funding (Merck vs other), and whether or not analyses had been adjusted for aspirin use.

For all meta-analyses, we calculated the I² statistic,12 which describes the percentage of total variation across studies that is attributable to heterogeneity rather than chance, and did standard tests of heterogeneity. All analyses were undertaken in STATA 8.2 (Stata, College Station, TX, USA).

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Figure 1 summarises the process of identifying eligible clinical trials. 18 randomised controlled trials met inclusion criteria.13–20 We also identified 126 reports of observational studies on naproxen and cardiovascular risk. We excluded 62 articles on the basis of their...
abstracts and obtained the full-text articles for the remaining 64 reports. 11 observational studies met inclusion criteria.8–10,29–36

Characteristics of trials, patients, and interventions

Table 1 shows the characteristics of trials. The 18 trials included a total of 25,273 patients. 12 trials were done in patients with osteoarthritis,13–23 five in individuals with rheumatoid arthritis,4,24–27 and one in people with low back pain.28 Three trials had two arms,4,13,23 seven had three arms,14,18,20,22,24,27,28 and eight had four arms.15–19,21,25,26 Most trials with more than two arms included several rofecoxib arms of different doses.14 trials included a placebo arm.13,15–22,24–28 Trial duration ranged from 4 weeks to more than 1 year. The median incidence of myocardial infarction in control groups was 1.45 per 1000 patient-years (IQR 0–5.2)

Five trials18,21,24–26 were extended after the original protocol had ended, and patients initially allocated to placebo or low doses of rofecoxib were randomly allocated to different groups. For example, patients from placebo and low doses of rofecoxib groups of protocol 02919 were allocated to diclofenac, rofecoxib 12.5 mg, or rofecoxib 25 mg in an extension phase. One extension was excluded because no cardiovascular safety data were reported.21 Therefore, a total of 22 comparisons contributed to analyses. All randomised controlled trials were sponsored by Merck. Four trials described adequate concealment of allocation.13,17,21,28 Cardiovascular events were externally reviewed in eight trials.4,20,22,23,25–28

Cardiovascular risk from randomised controlled trials

The analysis of the primary endpoint—myocardial infarction—was based on 64 events from
Articles

For personal use. Only reproduce with permission from Elsevier Ltd

2004 www.thelancet.com

Figure 2: Meta-analysis of randomised trials comparing rofecoxib with control

16 comparisons between rofecoxib and control, with 52 events in rofecoxib groups and 12 in control groups. As figure 2 shows, the combined relative risk was 2.24 (95% CI 1.24–4.02), with little evidence of between-trial heterogeneity (I²=0%, p for heterogeneity=0.82). Table 2 presents results from stratified analyses. Estimates of relative risk varied depending on whether rofecoxib had been compared with placebo, an NSAID other than naproxen, or naproxen, but 95% CIs were wide and a test of interaction was not significant (p=0.41). Similarly, there was little evidence that relative risks differed depending on the dose of rofecoxib or the duration of trials. The estimated relative risk of myocardial infarction was greater in trials with an external endpoint committee compared with trials without such a committee (p=0.011).

Cumulative meta-analysis (figure 3) showed that an increased risk of myocardial infarction became evident in 2000, when 14,247 patients had been randomised and 44 events had occurred. At the end of 2000 (52 myocardial infarctions, 20,742 patients) the relative risk was 2.30 (95% CI 1.22–4.33, p=0.010). Subsequent trials brought the number of patients to 21,432 and the number of events to 64. Although this resulted in a narrowing of the CI, point estimates remained similar. The most recent data became available in October, 2001; later trials did not report on cardiovascular outcomes.

A total of 44 strokes were recorded in 11 comparisons, with 25 events in rofecoxib groups and 19 in control groups. The combined relative risk was 1.02 (95% CI 0.54–1.93). Nine comparisons contributed to the analysis of cardiovascular death, with 18 deaths in rofecoxib groups and 11 in control groups and a pooled relative risk of 0.79 (0.29–2.19). Finally, 17 comparisons contributed to the analysis of serious cardiovascular events, with 85 events in rofecoxib groups and 38 in control groups (combined relative risk 1.55 [95% CI 1.05–2.29]). Again, there was little evidence of between-trial heterogeneity for these outcomes (I² 0%, 27%, and 0%, respectively).

Cardioprotective effect of naproxen

For the analysis of naproxen there were eight case-control studies and three retrospective cohort studies (table 3). All studies except one used data from large administrative or clinical databases. Four studies were based on the UK General Practice Research Database. Figure 4 shows the meta-analysis of results from primary analyses. The combined estimate was 0.86 (95% CI 0.75–0.99). Almost identical results were obtained when analyses were based on comparisons with non-naproxen NSAIDs (0.86 [0.75–0.99]). In both analyses, there was considerable between-study heterogeneity (I² 68% and 43%, respectively). Meta-regression analysis indicated that the funding source largely explained between-study heterogeneity, with studies funded by Merck indicating larger cardioprotective effects of naproxen (p=0.001 and p=0.056, respectively, by test of interaction). There was little evidence for an association with study design or adjustment for aspirin use (p=0.30).

Discussion

The voluntary withdrawal of rofecoxib by its manufacturer, Merck, on the basis of a fairly small trial that was designed for a different purpose raises several questions. In particular, we must establish whether the drug should have been withdrawn earlier. Our cumulative meta-analysis of randomised controlled trials indicates

<table>
<thead>
<tr>
<th>Relative risk (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All comparisons</td>
<td>2.24 (1.24–4.02)</td>
</tr>
<tr>
<td>Type of control</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.04 (0.34–3.12)</td>
</tr>
<tr>
<td>Non-naproxen NSAIDs</td>
<td>1.35 (0.55–4.36)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.93 (1.36–2.73)</td>
</tr>
<tr>
<td>Daily dose</td>
<td></td>
</tr>
<tr>
<td>12.5 mg</td>
<td>2.71 (0.99–7.44)</td>
</tr>
<tr>
<td>25 mg</td>
<td>1.37 (0.52–3.61)</td>
</tr>
<tr>
<td>50 mg</td>
<td>2.83 (1.24–6.43)</td>
</tr>
<tr>
<td>Trial duration</td>
<td></td>
</tr>
<tr>
<td>≥6 months</td>
<td>2.17 (1.03–4.59)</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>2.13 (0.90–4.93)</td>
</tr>
<tr>
<td>Concealment of allocation</td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>2.04 (0.32–12.93)</td>
</tr>
<tr>
<td>Unclear</td>
<td>2.16 (1.02–4.19)</td>
</tr>
<tr>
<td>External endpoint committee</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.88 (1.88–8.02)</td>
</tr>
<tr>
<td>No or unclear</td>
<td>0.79 (0.29–2.13)</td>
</tr>
</tbody>
</table>

Table 2: Relative risk of myocardial infarction comparing rofecoxib with control, from stratified meta-analyses

Figure 2: Meta-analysis of randomised trials comparing rofecoxib with control
that an increased risk of myocardial infarction was evident from 2000 onwards. At the end of 2000, the effect was both substantial and unlikely to be a chance finding.

We found an increased risk of myocardial infarction in trials of both short and long duration, which is in contrast to the unpublished results from the APPROVe trial.1 Our findings thus indicate that patients are at risk even if rofecoxib is taken for a few months only. Therefore, the reassuring statement by Merck, that there is no excess risk in the first 18 months,1 is not supported by our data. Similarly, we recorded no evidence to support the notion that rofecoxib’s cardiovascular toxicity is dose-dependent.35,38 The reported increase in risk was greater in trials with an external endpoints committee (relative risk 3·9), suggesting that misclassification of coronary events could have biased results in trials that did not include external appraisal of safety outcomes. The inclusion of an independent endpoints committee should be the rule, and exceptions to this rule should be justified. The difference in coronary risk in the VIGOR trial has been widely interpreted as being due to a cardioprotective effect of naproxen, rather than an adverse effect of rofecoxib.5,9,40 We examined this hypothesis by stratifying results from randomised trials according to the control intervention and found that the increase in risk was indeed greater in trials comparing rofecoxib with naproxen, but that this finding was probably attributable to chance (p=0·41). The possible cardioprotective effect of naproxen has also been examined in several observational, pharmacoepidemiological studies. Taken together, the data from these studies indicate that if a protective effect of naproxen exists, it is probably small, and, as pointed out earlier,6,29 not large enough to explain the findings of VIGOR.4

By contrast to our findings, two earlier meta-analyses from Merck Research Laboratories showed no evidence of a rise in cardiovascular risk41 or an increase in risk that was restricted to trials comparing rofecoxib with naproxen.7 Possible explanations for these discrepant results include: confounding by trial, in analyses inadequately pooling individual patients’ data; use of composite cardiovascular endpoints, which will have diluted any increase in risk of myocardial infarction; and inclusion of safety data that had not undergone independent adjudication. Pooled analyses of industry-sponsored drug trials, undertaken by the company manufacturing the drug in question, are becoming increasingly common. To clarify the reasons behind the

![Figure 3: Cumulative meta-analysis of randomised trials comparing rofecoxib with control](See figure 2 for sequence of trials.)
Articles

misleading results of Merck’s meta-analyses of cardiovascular events in clinical trials of rofecoxib will be important. Also, the notion that meta-analyses of individual patients’ data are always superior to meta-analyses of published work might have to be revised.42

We recorded little evidence of an increased risk of stroke, although the number of events was small and 95% CIs wide. The rofecoxib trials were done in patients at low cardiovascular risk and the discrepant results for myocardial infarction and stroke mirror what is noted

Table 3: Characteristics of observational studies of naproxen use and myocardial infarction

Source population (study period) Design Case/outcome definition Definition of exposure to naproxen Reference group in primary analysis Control for confounding Funding source

Jick et al (2000)32 NSAID users attending general practices* (1996–98) Matched case-control study First acute MI Use in previous 3 months based on prescription data Diclofenac users Exclusion of patients with history of CVD Boehringer Ingelheim

Rahme et al (2002)7 Elderly people covered by Quebec Health Care Fund (1988–94) Matched case-control study Acute MI Current and chronic use based on prescription data Users of other NSAIDs Exclusion of patients with recent MI, adjustment for drugs to treat cardiovascular disease, previous cardiovascular diseases, comorbidity Merck

Ray et al (2002)10 Middle-aged and elderly people enrolled in Tennessee Medicaid programme (1987–98) Retrospective cohort study Acute MI or death from CHD Current use based on prescription data People not using NSAIDs Adjustment for risk score based on prescriptions, hospital admissions, emergency room visits AHRQ and FDA

Ray et al (2002 A)10 Middle-aged and elderly people enrolled in Tennessee Medicaid programme (1999–2001) Retrospective cohort study Acute MI or death from CHD Current use based on prescription data People not using NSAIDs Adjustment for risk score based on prescriptions, hospital admissions, emergency room visits AHRQ, US Public Health Service and FDA

Schlienger et al (2002)33 Patients attending general practices* (1992–97) Matched case-control study First acute MI Current use based on prescription data People not using NSAIDs Exclusion of patients with history of CVD; adjustment for smoking status, BMI, hormone replacement therapy, aspirin use No specific funding

Solomon et al (2002)9 New Jersey Medicare, Medicaid or Pharmaceutical Assistance for the Aged and Disabled Program enrollees (1991–95) Matched case-control study Acute MI Use in previous 6 months based on prescription data People not using NSAIDs Exclusion of patients with history of CVD; adjustment for Medicaid enrolment, nursing home residency, diabetes, hypertension, congestive heart failure, comorbidity index, drug prescriptions, hospitalisations Arthritis Foundation and NIA


Kimmel et al (2004)36 Cases from 36 hospitals and community controls resident in five counties surrounding Philadelphia (1998–2000) Unmatched case-control study First non-fatal MI Use within 1 week based on telephone interview People not using NSAIDs Adjustment for smoking, BMI, health services utilisation, diabetes, hypertension, hypercholesterolaemia, education NIH, Pharmacia, Merck


Table 3: Characteristics of observational studies of naproxen use and myocardial infarction

*We recorded little evidence of an increased risk of stroke, although the number of events was small and the 95% CIs wide. The rofecoxib trials were done in patients at low cardiovascular risk and the discrepant results for myocardial infarction and stroke mirror what is noted.
with antiplatelet treatment: risk of myocardial infarction, but not stroke, is reduced in individuals at low risk of cardiovascular disease.44 This situation is consistent with opposite patterns of inhibition of the COX1 selective aspirin and the COX2 selective rofecoxib, with the two drugs inversely affecting the balance between COX1 and COX2 activity.45

Because of restrictive inclusion criteria, most trials included only few individuals with a history of cardiovascular disease. This contrasts with the situation encountered in routine clinical settings. For example, in middle-aged and elderly people from the Tennessee Medicaid programme, Ray and colleagues46 reported that more than 40% of rofecoxib users had a history of cardiovascular disease and that, compared with trial populations, the risk of fatal or non-fatal myocardial infarction was eight times higher (11·6 vs 1·45 per 1000 patient-years). This risk translates into numbers needed to treat for 1 year to cause one myocardial infarction of 556 patients in trial populations, but only 70 patients in routine populations in Tennessee.

Some limitations need to be noted. Our analysis was restricted to trials in patients with chronic musculoskeletal disorders. Safety data were available from FDA files for most of these trials, but this was not the case for more recent trials in Alzheimer's disease and colon adenoma. Only one trial in people with Alzheimer's disease presented results for myocardial infarction (three events in 122 individuals assigned to rofecoxib and one event in 229 individuals assigned to naproxen or placebo).47 The APPROVe trial in patients with a history of colorectal adenomas1 was recently presented at the Annual Scientific Meeting of the American College of Rheumatology, but different cardiovascular outcomes were not reported separately. Furthermore, we were unable to adjust for possible duplication of data between the four case-control studies based on the UK General Practice Research Database. Adjustment would have shifted the pooled estimate towards the null and would have inflated CIs. Therefore, our meta-analysis might overestimate naproxen's cardioprotective potential.

What lessons should be learned for the future? First, we can never be sure that we know all there is to know about mechanisms. The VIGOR study group presented the myocardial infarction data exclusively as “a reduction in the risk of myocardial infarction in the naproxen group”, on the basis of the documented inhibition of platelet aggregation by naproxen, but not rofecoxib.48 That rofecoxib could increase the risk was not discussed, despite the fact that, since the mid 1990s, the drug has been known to reduce production of prostacyclin, a vasodilator and inhibitor of platelet aggregation.49 In the context of hormone replacement therapy and cardiovascular outcomes, Petitti recently pointed out that we should resist being seduced by mechanisms, that we should suspend our beliefs, and allow healthy scepticism when interpreting data.46 Clearly, the same holds true when reporting and interpreting unexpected results of randomised trials, and ultimately when writing prescriptions for patients.

Second, the FDA and other drug licensing authorities should review their procedures, and identify and remove the obstacles to making continuously updated summary information available to decision makers.11 The present analysis would not have been possible without access to the proceedings of the FDA, which underscores the importance of free access to these files. In some instances, important discrepancies were noted between published data and figures in FDA files. For example, the VIGOR Study Group reported a four-fold increased risk of myocardial infarction,7 whereas the figures available from FDA files indicated a five-fold increase in risk.50 Making important safety data accessible to interested researchers and the public at large does, of course, not absolve authorities from their duty to carefully and continuously monitor the evidence on the adverse effects of drugs. Clearly, this has not happened in the case of rofecoxib, the most recent labelling changes were made several years earlier, when the data summarised here first became available. Instead, Merck continued to market the safety of rofecoxib.

![Figure 4: Meta-analysis of observational studies of naproxen and risk of myocardial infarction](image-url)
Contributors
P Jüni had the idea for the study, was responsible for protocol development, study supervision, and statistical analysis, and contributed to data extraction and management, quality assessment, and interpretation of data. M Egger contributed to protocol design, study supervision, data extraction, quality assessment, statistical analysis, and interpretation of data. J Narrey, S Reichenbach, and R Sterchi contributed to protocol design, data extraction and management, and data interpretation. P Dieppe contributed to protocol development, study supervision, and data interpretation. M Egger and P Jüni wrote the first draft of the paper, and all authors contributed to the final draft.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgements
This study was funded by the Swiss National Science Foundation’s National Research Programme 53 (grant numbers 3200–066178.01 and 405340–104762). We thank Bettina Lässer for bibliographic work, Beat Jordi for database development, and Nicola Low for helpful comments on earlier drafts of this paper.

References
11 Dieppe PA, Ebrahim S, Martin RM, Juni P. Lessons from the withdrawal of rofecoxib: patients would be safer if drug companies disclosed adverse events before licensing. BMJ 2004; 328: 867–68.


