

# Primary care

## Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis

Julia Hippisley-Cox, Carol Coupland

Editorial by Jüni et al and p 1370

Institution 13th floor, Tower Building, University Park, Nottingham NG2 7RD

Julia Hippisley-Cox professor of clinical epidemiology and general practice  
Carol Coupland senior lecturer in medical statistics

Correspondence to: J Hippisley-Cox  
julia.hippisley-cox@nottingham.ac.uk

BMJ 2005;330:1366-9

### Abstract

**Aims** To determine the comparative risk of myocardial infarction in patients taking cyclo-oxygenase-2 and other non-steroidal anti-inflammatory drugs (NSAIDs) in primary care between 2000 and 2004; to determine these risks in patients with and without pre-existing coronary heart disease and in those taking and not taking aspirin.

**Design** Nested case-control study.

**Setting** 367 general practices contributing to the UK QRESEARCH database and spread throughout every strategic health authority and health board in England, Wales, and Scotland.

**Subjects** 9218 cases with a first ever diagnosis of myocardial infarction during the four year study period; 86 349 controls matched for age, calendar year, sex, and practice.

**Outcome measures** Unadjusted and adjusted odds ratios with 95% confidence intervals for myocardial infarction associated with rofecoxib, celecoxib, naproxen, ibuprofen, diclofenac, and other selective and non-selective NSAIDs. Odds ratios were adjusted for smoking status, comorbidity, deprivation, and use of statins, aspirin, and antidepressants.

**Results** A significantly increased risk of myocardial infarction was associated with current use of rofecoxib (adjusted odds ratio 1.32, 95% confidence interval 1.09 to 1.61) compared with no use within the previous three years; with current use of diclofenac (1.55, 1.39 to 1.72); and with current use of ibuprofen (1.24, 1.11 to 1.39). Increased risks were associated with the other selective NSAIDs, with naproxen, and with non-selective NSAIDs; these risks were significant at  $<0.05$  rather than  $<0.01$  for current use but significant at  $<0.01$  in the tests for trend. No significant interactions occurred between any of the NSAIDs and either aspirin or coronary heart disease.

**Conclusion** These results suggest an increased risk of myocardial infarction associated with current use of rofecoxib, diclofenac, and ibuprofen despite adjustment for many potential confounders. No evidence was found to support a reduction in risk of myocardial infarction associated with current use of naproxen. This is an observational study and may be

subject to residual confounding that cannot be fully corrected for. However, enough concerns may exist to warrant a reconsideration of the cardiovascular safety of all NSAIDs.

### Introduction

Although evidence shows that cyclo-oxygenase-2 (COX 2) inhibitors are as effective as traditional non-steroidal anti-inflammatory drugs (NSAIDs) in relieving pain, serious concerns about their cardiovascular safety have arisen and rofecoxib has now been withdrawn worldwide. Important questions remain about the safety of other COX 2 inhibitors. The major trials have excluded patients with coronary heart disease,<sup>1</sup> with only one,<sup>2</sup> designed to measure coronary end points. This has left a serious lack of evidence on the safety of COX 2 inhibitors in high risk patients with coronary heart disease, including those on aspirin. This is particularly important, as COX 2 inhibitors are recommended in guidelines for elderly patients.<sup>3</sup>

We did a population based nested case-control study using the QRESEARCH database<sup>4</sup> to determine the comparative risk of myocardial infarction in patients taking COX 2 inhibitors and other NSAIDs in primary care. We investigated the risk of myocardial infarction associated with these drugs in patients with and without pre-existing coronary heart disease and in those taking and not taking aspirin. This analysis was completed before the withdrawal of rofecoxib and now valdecoxib. It sheds light on the risk profile of other NSAIDs, the use of which is likely to increase following the withdrawal of rofecoxib.

### Method

#### Study population and data source

We used data from UK general practices contributing to the QRESEARCH database, which contains the clinical records of more than 7 million patients ever registered with 468 practices over the past 16 years.



This is the abridged version; the full version is on [bmj.com](http://bmj.com)

The information recorded includes patient demographics, characteristics, symptoms, clinical diagnosis, consultations, referrals, prescribed drugs, and results of investigations. The database has been validated against other data sources (see [bmj.com](http://bmj.com)). The study period ran between 1 August 2000 and 31 July 2004, during which time rofecoxib and celecoxib were both available on prescription in the United Kingdom.

### Cohort definition

We identified a cohort of patients registered on 1 August 2000 who had been registered for the whole of the preceding 12 months. Patients entered the study period on 1 August 2000 and left the risk period when they developed a myocardial infarction, died, or left the practice or when the study period ended, whichever was earlier.

### Case-control analysis

Cases were all patients aged 25 to 100 with a first ever myocardial infarction recorded during the study period, including those who had a diagnosis of myocardial infarction recorded as the cause of death. We matched up to 10 controls by age, calendar time, sex, and practice by using incidence density sampling. All controls were alive and registered with the practice at the time their matched case had the myocardial infarction. The index date for each control was the date of myocardial infarction of their matched case. We excluded cases and controls who had less than three years of computerised prescribing data available before their index date to ensure that the prescribing data were complete.

### Assessment of exposure

We extracted and coded data on the medical history and use of prescribed drugs before the index date for each set of cases and controls. We identified all prescriptions for selective and non-selective NSAIDs in the three years before their index date. Twenty seven different NSAIDs were in use during the study period. We grouped the drugs as follows: celecoxib, rofecoxib, ibuprofen, diclofenac (including combination preparations), naproxen, other selective NSAIDs (meloxicam, etoricoxib, etodolac, valdecoxib), and other non-selective NSAIDs.

For each drug group we identified the first and last prescription date and the total number of prescriptions issued in the three years before the index date. We categorised the total number of prescriptions for each drug group as zero, one to three, and more than three prescriptions. We tested for trend by using the actual number of prescriptions issued within the three year period.

### Statistical analysis

We used conditional logistic regression to derive odds ratios with 95% confidence intervals for myocardial infarction associated with each of our drug groups. We made adjustments for possible confounding effects of comorbidity, smoking, deprivation, or use of aspirin, antidepressants, and statins and for the other NSAID groups. (See [bmj.com](http://bmj.com) for details of analysis.)

## Results

We identified 9218 cases with a first ever myocardial infarction between the ages of 25 and 100 (63.1% men)

Odds ratios for use of non-steroidal anti-inflammatory drug (NSAID) within previous three years for cases and controls

Drug and time of last prescription	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	P value
<b>Celecoxib</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.37 (1.13 to 1.64)	1.14 (0.93 to 1.40)	0.22
Within 3 months of index date	1.39 (1.11 to 1.73)	1.21 (0.96 to 1.54)	0.11
<b>Rofecoxib</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.43 (1.23 to 1.66)	1.05 (0.89 to 1.24)	0.54
Within 3 months of index date	1.67 (1.40 to 2.00)	1.32 (1.09 to 1.61)	0.005
<b>Other selective NSAIDs</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.26 (1.08 to 1.47)	0.93 (0.79 to 1.10)	0.41
Within 3 months of index date	1.55 (1.25 to 1.92)	1.27 (1.00 to 1.61)	0.046
<b>Ibuprofen</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.20 (1.13 to 1.28)	1.05 (0.98 to 1.12)	0.16
Within 3 months of index date	1.40 (1.27 to 1.55)	1.24 (1.11 to 1.39)	<0.001
<b>Diclofenac</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.29 (1.21 to 1.37)	1.13 (1.05 to 1.21)	0.001
Within 3 months of index date	1.69 (1.53 to 1.86)	1.55 (1.39 to 1.72)	<0.001
<b>Naproxen</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.28 (1.13 to 1.44)	1.09 (0.96 to 1.24)	0.16
Within 3 months of index date	1.38 (1.11 to 1.72)	1.27 (1.01 to 1.60)	0.04
<b>Other non-selective NSAIDs</b>			
No use of drug in past three years	1.00	1.00	
>3 months before index date	1.40 (1.28 to 1.54)	1.18 (1.06 to 1.30)	0.002
Within 3 months of index date	1.40 (1.20 to 1.64)	1.21 (1.02 to 1.44)	0.03

\*Adjusted simultaneously for each NSAID, use of aspirin, statin, tricyclic antidepressant, selective serotonin reuptake inhibitor, ischaemic heart disease, diabetes, hypertension, osteoarthritis, rheumatoid arthritis, smoking, obesity, deprivation.

and 86 349 controls, which gave an average of 9.4 controls for each case. The median number of months of prior data available was 86 (interquartile range 63-117). The crude incidence of myocardial infarction was 1.71 per 1000 person years for patients aged 25 years and over, rising to 4.57 per 1000 person years for patients aged 65 years and over.

Cases and controls were well matched for age, sex, and the number of months of previous data available. (See [bmj.com](http://bmj.com) for baseline characteristics.) As expected, a higher proportion of cases were smokers, were obese, and had comorbidities. Cases also tended to be from slightly more deprived areas than controls.

The table shows the odds ratios for myocardial infarction associated with current use of each type of NSAID. The unadjusted analysis showed that each drug group was associated with a significantly increased risk of myocardial infarction. In the multivariate analysis, we adjusted for potential confounders. The use of rofecoxib within the previous three months was associated with a significantly increased risk of myocardial infarction, as was use of ibuprofen and diclofenac.

Use of other selective NSAIDs within the previous three months was also associated with a significantly increased risk of myocardial infarction in the unadjusted analysis, but the magnitude was reduced after adjustment for potential confounders. Similarly, we found a tendency to increased risks for use of naproxen and other non-selective NSAIDs within the previous three months. The numbers needed to harm for use of each drug within the previous three months

for patients aged 65 years and over were 521 (95% confidence interval 355 to 866) for diclofenac, 1005 (569 to 3089) for ibuprofen, and 695 (344 to 3841) for rofecoxib. The adjusted odds ratios for patients whose last prescription was more than three months before the index date were all above one, apart from for the other selective NSAIDs.

We repeated the analyses, restricting them to cases and controls with complete data for smoking and body mass index and obtained similar odds ratios for all the drugs except for naproxen, for which the adjusted odds ratio for use within the previous three months was 1.42 (1.09 to 1.85), and the group of other non-selective NSAIDs, for which the adjusted odds ratio for use within the previous three months was 1.11 (0.90 to 1.37). We also restricted the analysis to patients aged 65 and over; the odds ratios were similar for all the drugs except the group of other non-selective NSAIDs, for which the adjusted odds ratio for use within the previous three months was 1.14 (0.93 to 1.24).

We repeated the analysis again, restricting it to patients without either coronary heart disease or diabetes. This did not affect the odds ratios substantially, apart from use of celecoxib within the previous three months (adjusted odds ratio 1.02, 0.74 to 1.39).

We found highly significant tests for trend, with increased risk of myocardial infarction associated with increasing number of prescriptions for diclofenac, ibuprofen, naproxen, and other NSAIDs. The adjusted odds ratio for more than three prescriptions compared with no prescriptions were 1.46 (1.33 to 1.60) for diclofenac, 1.14 (1.03 to 1.27) for ibuprofen, 1.27 (1.06 to 1.53) for naproxen, and 1.28 (1.12 to 1.47) for other non-selective NSAIDs. We found no clear pattern for rofecoxib (test for trend = 0.13). We found no significant interactions between any NSAID and aspirin, nor between any NSAID and coronary heart disease.

## Discussion

We found a significantly increased risk of myocardial infarction in patients taking three specific drugs—rofecoxib, diclofenac, and ibuprofen. Current use of these drugs was associated with a 24-55% increase in risk of myocardial infarction after adjustment for potential confounders. Stratification by the number of prescriptions did not yield materially different results from the analysis based on current use. No significant interactions occurred between any NSAID and either aspirin or pre-existing coronary heart disease. Given the high prevalence of the use of these drugs in elderly people and the increased risk of myocardial infarction with age, the relatively large number of patients needed to harm could have considerable implications for public health.

We also found a similar increase in risk with other selective NSAIDs, with naproxen, and with other non-selective NSAIDs, although the results reached only the 0.05 significance level on multivariate analysis. This probably reflects the relatively small number in each of the subgroups. We found no significant increase in cardiovascular risk associated with use of celecoxib, although the odds ratios were of similar magnitude to those observed with other drugs.

The lack of a cardioprotective effect for naproxen in our study is consistent with other studies,<sup>5 6</sup> but we

found one study that suggested a weak protective effect of naproxen for acute myocardial infarction.<sup>7</sup> All these studies, however, were done before data on COX 2 inhibitors were available.

## Comparison with other studies

Another report found a similar increased risk to ours of acute myocardial infarction associated with use of ibuprofen in a high risk population over the age of 50.<sup>5</sup> Patients taking diclofenac had a similar risk of myocardial infarction to that reported in a much smaller study of non-selective NSAIDs in patients with rheumatoid arthritis.<sup>8</sup> Other observational studies conducted before data on COX 2 inhibitors were available reported increased risks of first time myocardial infarction associated with non-selective NSAIDs similar to the risks reported in our study.

Our study included younger patients and longer follow-up than has been possible before.<sup>9</sup> We also had information on a range of comorbidities and sufficient information on rates of prescription of aspirin to adjust for its potential confounding effect.

## Discussion of methods

This is an observational study and therefore at risk of bias and confounding. Confounding by indication could be present if patients were prescribed NSAIDs for chest pain that was actually angina. This would apply equally to all drug groups. Similarly, we have minimised the impact of any channelling,<sup>10</sup> by adjusting for many potential confounders. Our cases and controls were well matched. Our outcome is likely to be well recorded on the general practice clinical databases.

No recall bias occurred, as the exposure data were recorded before the date of myocardial infarction. We included only patients who had been registered with the practice for the entire observation period, so prescribing data were complete. Misclassification of exposure status (use of drugs) is unlikely, as more than 99% of all repeat prescriptions by general practitioners are recorded on computer. Ibuprofen is the only NSAID available without prescription, so some patients might have been misclassified as not being on ibuprofen. This is likely to be a small proportion in patients over 65 years, as they are entitled to free prescriptions in the United Kingdom. Our results for ibuprofen were similar in an analysis restricted to patients aged 65 and over. Also, such misclassification would bias the odds ratio towards one, making the exposure seem less harmful than it really is. Some residual confounding may result from misclassification of variables and confounding by unmeasured variables.

## Conclusions

Since we completed this analysis, rofecoxib has been withdrawn, and adverse cardiovascular effects have been reported with both celecoxib and valdecoxib. We found increased risk of myocardial infarction with two commonly used non-selective NSAIDs (diclofenac and ibuprofen). We saw similar odds ratios for naproxen, other selective NSAIDs, and celecoxib, although the results did not reach the 0.01 significance level. This could be because of the relatively low usage of these drugs, which is likely to increase now that rofecoxib has been withdrawn. We found no evidence to support a reduction in risk of myocardial infarction associated with naproxen.

### What is already known on this topic

The VIGOR study found that rofecoxib was associated with an increased risk of myocardial infarction compared with naproxen

Uncertainty existed as to whether this reflected a true increase or an apparent increase due to a cardioprotective effect of naproxen

Rofecoxib has been withdrawn, but uncertainty persists about the cardiovascular safety of the other selective non-steroidal anti-inflammatory drugs (NSAIDs)

### What this study adds

Rofecoxib, diclofenac, and ibuprofen were associated with a higher risk of myocardial infarction; no evidence of a cardioprotective effect for naproxen was found

The increased risk with rofecoxib in the VIGOR study was genuine; the toxicity of conventional NSAIDs and newer selective NSAIDs is also of concern

No clinically important interactions occurred between any NSAID and either aspirin or coronary heart disease

This is an observational study and may be subject to residual confounding. However, we think that enough concerns exist to warrant a reconsideration of the cardiovascular safety of all NSAIDs.

We thank the EMIS practices contributing to QRESEARCH database and David Stables (EMIS Computing) and Mike Pringle for their help and expertise in establishing QRESEARCH.

Contributors: See [bmj.com](http://bmj.com)

Funding: This study was unfunded. QRESEARCH is a not for profit organisation that has received funding from the Department of Health, Health Protection Agency, National Audit Office, Disability Rights Commission, Medicines Partnership, Royal College of Physicians, and various universities for unrelated analyses and research. QRESEARCH is entirely independent of the pharmaceutical industry.

Competing interests: None declared.

Ethical approval: Trent Multi-Centre Research Ethics Committee.

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(Accepted 13 April 2005)

doi 10.1136/bmj.38456.398507.8F

### Corrections and clarifications

#### *Self harm was misrepresented (again)*

We inadvertently mangled the first name of the first author of this letter by Naveen Kapur and Jayne Cooper (*BMJ* 2000;330:1026, 30 Apr). Our apologies.

#### *Global functions at the World Health Organization*

We slipped up in making some late changes to this editorial by Jennifer Prah Ruger and Derek Yach (*BMJ* 2005;330:1099-100, 14 May). The competing interests for the first author should have read: "Dr Ruger worked previously at the World Bank and served on the health and development satellite of former Director-General Brundtland's transition team."

#### *Obituary: Archibald John Ogg*

When we scanned the original obituary into our system, we failed to notice that the initial O in the name of one of the contributors (J K Oates) got corrupted and appeared as a "D" (*BMJ* 2005;330:968, 23 Apr).

#### *The hazards of good memory*

In this Personal View by Mukaili Raji, an editing error led to the attribution of Alzheimer's disease to the reviewer of a book on the disease rather than to the author of the book (*BMJ* 2005;330:913, 16 Apr). The sentence that began "In a book review Dr Peter Whitehouse, who also happened to have Alzheimer's disease, said" should have read: "In a review of a book by an author with Alzheimer's disease (Thomas DeBaggio's *Losing My Mind: An Intimate Look at Life with Alzheimer's*), Dr Peter Whitehouse said . . ."

#### *Why clinicians are natural bayesians*

It seems that Thomas Bayes was a presbyterian minister—not a vicar, as was stated in this article by Christopher J Gill and colleagues (*BMJ* 2005;330:1080-3, 7 May).

#### *Minerva*

Minerva mixed up her penicillins in her opening sentence of the final item of her 7 May column (*BMJ* 2005;330:1094). She referred to flucloxacillin as a broad spectrum antibiotic; it is in fact a penicillinase-resistant penicillin.

#### *Excess coronary heart disease in South Asians in the United Kingdom*

The authors of this editorial, Velmurugan C Kuppaswamy and Sandeep Gupta, have alerted us to two errors in their article (*BMJ* 2005;330:1223-4). Firstly, the third from last paragraph should have referred to the South Asian Health [not Heart] Foundation. Secondly, three authors were inadvertently omitted from reference 12: the full list of authors is Kuppaswamy V, Jhuree K, Cunliffe E, Sheikh AQ, Feder G, Gupta S.