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

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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

Cyclo-oxygenase-2 (COX 2) inhibitors are a selective type of non-steroidal anti-inflammatory drug (NSAID) developed for the treatment of acute inflammation in joints caused by arthritis without the gastrointestinal side effects associated with traditional NSAIDs.[1] Although evidence shows that COX 2 inhibitors are as effective as traditional NSAIDs in relieving pain,[2 3] serious concerns about their cardiovascular safety have arisen. In the Vioxx gastrointestinal outcomes research (VIGOR) study, patients taking rofecoxib had a much higher risk of myocardial infarction than did patients taking the comparator drug (naproxen). Initially, suggestions were made that the difference was due to a cardioprotective effect of naproxen rather than a deleterious effect of rofecoxib.[3] However, this is now known not to be the case, and Merck has very recently ordered an immediate worldwide withdrawal of rofecoxib because of its adverse cardiovascular profile.

Despite this, important questions remain about the safety of other COX 2 inhibitors. The major trials have excluded patients with coronary heart disease,[4] and none (with the exception of the recently reported therapeutic arthritis research and gastrointestinal event trial[5]) has been 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,[4 6–9] including those on aspirin. This is particularly important given the extent to which COX 2 inhibitors are now being used and that they are still recommended in guidelines for elderly patients.[10]

We did a population based nested case-control study using the new QRESEARCH database[11] to determine the comparative risk of myocardial infarction in patients taking COX 2 inhibitors and other NSAIDs in primary care between 2000 and 2004. 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. Although this analysis was completed before the announcement of the withdrawal of rofecoxib and now valdecoxib, we think 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 new QRESEARCH database (www.qresearch.org). This is a new clinical database containing the clinical records of more than 7 million patients ever registered with 468 practices over the past 16 years. The information recorded on the database includes demographics (year of birth, sex, socioeconomic data associated with postcode area), characteristics (height, weight, smoking status),

symptoms, clinical diagnosis, consultations, referrals, prescribed drugs, and results of investigations. The database has been validated by comparing birth rates, death rates, consultation rates, prevalence, and mortality with other data sources including the general household survey and the general practice research database.[12] The age-sex structure of the population has been compared with that reported in the 2001 census. We found a good correspondence for all of these measures (results available on request), although in some instances our prevalence figures were marginally higher than less recent data.[13] We have also compared practices taking part in regional research networks on these and other measures and found a good correspondence.[14] Detailed analyses have shown good levels of completeness and consistency.[15] Similar databases have been used for studies investigating risk factors for coronary heart disease or effects of conventional NSAIDs.[16–19] In previous studies, the diagnosis of acute myocardial infarction has been confirmed by reviewing hospital discharge notes or comparison with the paper based records and found to be correct in more than 90% of cases.[18–20]

The study period ran between 1 August 2000 and 31 July 2004 (the date of the most recent download of QRESEARCH data at the time of the analysis). We used this period as rofecoxib and celecoxib were both available on prescription in the United Kingdom.

Cohort definition

We selected practices that had their current Egton Medical Information Services (EMIS) computer system installed before 1 August 1999. 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.

We identified potential cases of acute myocardial infarction on the basis of a first time diagnosis of acute myocardial infarction recorded with appropriate Read codes during the four year study period. We excluded patients with a myocardial infarction before the start of the study period. We included in the cohort other patients with a diagnosis of coronary heart disease (but without mention of a myocardial infarction). We used this cohort to determine the incidence of myocardial infarction by age and sex.

Case-control analysis

Cases were all patients aged 25 to 100 with a first ever myocardial infarction identified in the cohort analysis. We included patients who had a diagnosis of myocardial infarction recorded as the cause of death. We matched up to 10 controls to each case 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. We derived an index date for each control, which 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 used standardised computerised routines to extract and code 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. We compared the prescribing rates for each drug per 1000 population with data from the prescribing cost analysis tool (PACT) for 2002 for drugs prescribed by general practice and dispensed in the community and found similar rates and rank order for the preparations.

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 coded the time since last prescription as not prescribed within the past three years, prescribed within 90 days (defined as current use), or prescribed more than 90 days ago. 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. General practitioners in the United Kingdom issue patients with sufficient drugs to last one calendar month, so one prescription is approximately equivalent to one month of treatment.

Statistical analysis

We used conditional logistic regression for individually matched case-control studies 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 smoking (smoker, not smoker, not recorded), comorbidity (diabetes, hypertension, coronary heart disease, osteoarthritis, rheumatoid arthritis, obesity), and deprivation in fifths. We used the Townsend score based on the 2001 census related data associated with the output area of each patient's postcode as a measure of deprivation.[21] We categorised obesity as body mass index (kg/m^2) less than 30, 30 or more, or not recorded. We also adjusted for the use of other drugs known to affect the risk of myocardial infarction or to be commonly associated with use of NSAIDS—namely, antidepressants[16] (selective serotonin uptake inhibitors and tricyclic antidepressants separately) and statins.[22] We also adjusted the results for each drug group for the other NSAID groups.

We calculated the numbers needed to harm by applying the incidence of first myocardial infarction per 1000 using the adjusted odds ratio from current usage of drugs. We calculated this separately for all patients aged 25 and over and for those aged 65 and over. We calculated approximate 95% confidence intervals. We examined two way interactions between different NSAIDs and aspirin and coronary heart disease. We fitted a second model restricted to cases and controls with complete data for smoking status and body mass index. We fitted a third model restricted to patients without either coronary heart disease or diabetes in order to reduce possible effects of residual confounding.[23] We used Stata (version 8.2) for all the analyses. We selected a P value of 0.01 (two tailed) as significant.

Results

We used the fourth version of the QRESEARCH database for this analysis. We identified 9218 cases with a first ever myocardial infarction between the ages of 25 and 100 (63.1% men). We matched these by age, calendar time, sex, and practice to 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

Table 1 Characteristics of cases and matched controls. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=9218)	Controls (n=86 349)
Female	3405 (36.9)	31 718 (36.7)
Male	5813 (63.1)	54 631 (63.3)
Median (interquartile range) Townsend score	–0.88 (–2.90-2.25)	–1.21 (–3.10-1.82)
Median No (interquartile range) of months of prior data	87 (63-117)	86 (63-117)
Age band (years)		
25-34	28 (0.3)	263 (0.3)
35-44	281 (3.0)	2800 (3.2)
45-54	957 (10.4)	9468 (11.0)
55-64	1812 (19.7)	17 900 (20.7)
65-74	2497 (27.1)	24 448 (28.3)
75-84	2525 (27.4)	23 801 (27.6)
≥85	1118 (12.1)	7669 (8.9)
Body mass index (kg/m^2)		
<30	5444 (59.1)	49 593 (57.4)
≥30	1593 (17.3)	11 903 (13.8)
Not recorded	2181 (23.7)	24 853 (28.8)
Smoking status		
Non-smoker	5457 (59.2)	52 983 (61.4)
Smoker	2550 (27.7)	15 709 (18.2)
Not recorded	1211 (13.1)	17 657 (20.4)
Morbidity before index date		
Ischaemic heart disease	2639 (28.6)	8216 (9.5)
Diabetes	1225 (13.3)	6188 (7.2)
Hypertension	3582 (38.9)	25 841 (29.9)
Osteoarthritis	1593 (17.3)	12 168 (14.1)
Rheumatoid arthritis	216 (2.3)	1185 (1.4)
Drugs in three years before index date		
Statin	1787 (19.4)	8098 (9.4)
Tricyclic antidepressant	1263 (13.7)	8570 (9.9)
Selective serotonin reuptake inhibitor	832 (9.0)	5923 (6.9)
Aspirin	3277 (35.6)	17 693 (20.5)

years and over, rising to 4.57 per 1000 person years for patients aged 65 years and over.

Table 1 shows the baseline characteristics of cases and their controls. Cases and controls were well matched for age, sex, and the number of months of previous data available for analysis. 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.

Table 2 shows the pattern of use of the different drug groups in cases and controls. Table 3 shows the unadjusted and adjusted 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 (smoking status, diabetes, hypertension, coronary heart disease, osteoarthritis, rheumatoid arthritis, obesity, deprivation (fifth of Townsend score), and use of selective serotonin uptake inhibitors, tricyclic antidepressants, statins, and aspirin). Table 3 shows that the use of rofecoxib within the previous three months was associated with a significantly increased risk of myocardial infarction (adjusted odds ratio 1.32, 95% confidence interval 1.09 to 1.61), as was use of ibuprofen (1.24, 1.11 to 1.39) and diclofenac (1.55, 1.39 to 1.72).

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 (unadjusted odds ratio 1.55, 1.25 to 1.92). The magnitude of the odds ratio was reduced after adjustment for potential confounders (adjusted odds ratio 1.27, 1.00 to 1.61). Similarly, we found a tendency to increased risks for use of naproxen and other non-selective NSAIDs within the previous three months, as shown in table 3. 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. For patients aged 25 and over the numbers needed to harm were 2444 (1504 to 5332) for ibuprofen, 1066 (815 to 1504) for diclofenac, and 1833 (961 to 6517) for rofecoxib.

Table 3 also shows the adjusted odds ratios for patients whose last prescription was more than three months before the index date. Apart from one category of drugs (the other selective NSAIDs), the odds ratios were all above one and ranged from 1.05 to 1.18.

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 examined the odds ratios for myocardial infarction associated with increasing numbers of prescriptions for each of the drugs. 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, indicating that the risk of myocardial infarction for each NSAID does not vary according to whether aspirin is prescribed. Similarly, we found no significant interactions between any NSAID and coronary heart disease, although the odds ratios tended to be higher in patients without pre-existing coronary heart disease.

Discussion

We have reported the results of a large population based nested case-control study designed to investigate the risk of myocardial infarction in patients taking COX 2 inhibitors and non-selective NSAIDs. This was an observational study, and we were able to include patients at high risk and substantial numbers of patients taking aspirin. Our most important consistent finding was a significantly increased risk of myocardial infarction in patients taking three specific drugs—rofecoxib, diclofenac, and ibuprofen. This was despite adjustment for potential confounders, including comorbidity (such as pre-existing coronary heart disease) and current use of other drugs. 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.

Our numbers needed to harm show that for every 695 patients aged 65 and over taking rofecoxib, one additional patient would have a first myocardial infarction in a year. For ibuprofen, one additional myocardial infarction would happen for every 1005 patients aged 65 and over, and for diclofenac the figure would be one additional myocardial infarction for every 521 treated patients. Given the high prevalence of the use of these drugs in elderly people and the increased risk of myocardial infarction with age, even 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 rather than our prespecified level of 0.01. 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.

We found no evidence to support the hypothesis, proposed by the authors of the VIGOR trial, that naproxen actually lowers the risk of a myocardial infarction.[3] This lack of a cardioprotective effect for naproxen in our study is consistent with other studies that have failed to find any protective effect for naproxen and a recent meta-analysis.[24 25] We found one study that suggested a weak protective effect of naproxen for acute myocardial infarction, but the detailed analysis failed to show any proximity-response relation between exposure to naproxen and

Table 2 Cases and controls with prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs) within previous three years. Values are numbers (percentages)

Drug and time of last prescription	Cases (n=9218)	Controls (n=86 349)
Celecoxib		
No use of drug in past three years	8988 (97.5)	84 762 (98.2)
>3 months before index date	137 (1.5)	953 (1.1)
Within 3 months of index date	93 (1.0)	634 (0.7)
Rofecoxib		
No use of drug in past three years	8848 (96.0)	83 991 (97.3)
>3 months before index date	219 (2.4)	1488 (1.7)
Within 3 months of index date	151 (1.6)	870 (1.0)
Other selective NSAIDS		
No use of drug in past three years	8917 (96.7)	84 198 (97.5)
>3 months before index date	200 (2.2)	1513 (1.8)
Within 3 months of index date	101 (1.1)	638 (0.7)
Ibuprofen		
No use of drug in past three years	7262 (78.8)	71 073 (82.3)
>3 months before index date	1496 (16.2)	12 086 (14.0)
Within 3 months of index date	460 (5.0)	3190 (3.7)
Diclofenac		
No use of drug in past three years	7365 (79.9)	72 822 (84.3)
>3 months before index date	1311 (14.2)	10 270 (11.9)
Within 3 months of index date	542 (5.9)	3257 (3.8)
Naproxen		
No use of drug in past three years	8790 (95.4)	83 142 (96.3)
>3 months before index date	332 (3.6)	2530 (2.9)
Within 3 months of index date	96 (1.0)	677 (0.8)
Other non-selective NSAIDs		
No use of drug in past three years	8477 (92.0)	81 214 (94.1)
>3 months before index date	560 (6.1)	3869 (4.5)
Within 3 months of index date	181 (2.0)	1266 (1.5)

Table 3 Odds ratios for use of non-steroidal anti-inflammatory drugs (NSAIDs) 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
Celecoxib			
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
Rofecoxib			
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
Other selective NSAIDS			
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
Ibuprofen			
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
Diclofenac			
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
Naproxen			
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
Other non-selective NSAIDs			
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.

acute myocardial infarction.[26] All these studies, however, were done before data on COX 2 inhibitors were available.[17 24 26]

Comparison with other studies

We found evidence to suggest an increased risk of myocardial infarction in patients taking ibuprofen, diclofenac, and rofecoxib and possibly also those taking other selective and non-selective NSAIDs. Patients currently taking ibuprofen had a 24% increased risk of an infarct, and patients who had been on ibuprofen for longer had higher risks. These findings are consistent with those of Ray et al, who reported an increased risk of acute myocardial infarction associated with use of ibuprofen in a high risk population over the age of 50.[24] Patients taking diclofenac had a 55% increased risk of myocardial infarction, which is similar to that reported in a much smaller study of non-selective NSAIDs in patients with rheumatoid arthritis conducted on data from the general practice research database.[27]

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. For example, Schlienger et al reported an adjusted odds ratio of 1.26 (95% confidence interval 1.01 to 1.57) for acute myocardial infarction in patients at low risk taking non-selective NSAIDs.[17] However, the analysis did not adjust for the potential confounding effect of socioeconomic status, as this information was not available.

Our study included younger patients and longer follow-up than has been possible before.[28] In addition, we had information on obesity, smoking, deprivation, and an important range of comorbidities. Rates of prescription of aspirin in the study population were also sufficient for us to adjust for its potential confounding effect and do analyses in patients taking aspirin compared with those not taking aspirin, which has not been possible before.[28] We have reported high levels of comorbidity in both cases and controls, which underlines the need to investigate the risks and benefits of new treatments in elderly populations at high risk, especially given that many trials are not designed to detect adverse effects or exclude high risk patients.[9 29]

Discussion of methods

This is an observational study and therefore at risk of bias and confounding. For example, some confounding by indication could be present, such as if patients have been prescribed NSAIDs for chest pain that was actually angina. If this had been the case, we would have expected the results to apply equally to all drug groups in our analysis. Similarly, we considered whether channelling might be an explanation for our results.[30] Patients who are more at risk of a myocardial infarction may be more likely to be prescribed a COX 2 inhibitor than patients at lower risk. Our analysis included adjustment for many potential confounders, including comorbidity, concurrent drug use, and deprivation, and we expect this to have minimised the impact of any channelling.

Our cases and controls were well matched on age, sex, practice, and calendar time, making this an effective design to assess the effects of different NSAIDs on risk of myocardial infarction. This approach allowed us to examine timing and duration and also to investigate interactions with aspirin and coronary heart disease. Our outcome (whether patients had a myocardial infarction or not) is likely to be well recorded on the general practice clinical databases, especially as the study period coincided with the publication of the *National Service Framework for Coronary Heart Disease*, which prioritises recording of cardiovascular

disease, especially myocardial infarction.[31] Apart from an analysis of the number of prescriptions (which can be used as a proxy for cumulative dose), we did not analyse dose. Although data on prescribed dose are available on the QRESEARCH database, we did not think that this would necessarily correlate well with the number of tablets taken by patients, as this can vary day to day according to levels of pain.

No recall bias occurred, as the exposure data were recorded on computer before the date of myocardial infarction. In addition, we included only patients who had been registered with the practice for the entire observation period in order to ensure that the prescribing data were complete. Misclassification of exposure status (that is, use of drugs) is unlikely, as more than 99% of all repeat prescriptions by general practitioners are recorded on computer because these drugs are not currently available in the UK without prescription. Ibuprofen is the only NSAID available without prescription, so some patients obtaining ibuprofen over the counter 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 and so tend to have drugs prescribed rather than buy them separately. Our results for ibuprofen were similar in an analysis restricted to patients aged 65 and over. Also, such misclassification, if present and if non-differential, would have had the effect of biasing the odds ratio towards one, making the exposure seem less harmful than it really is.[32] Although we have adjusted for several confounding variables, some residual confounding may result from misclassification of those variables and confounding by unmeasured variables.

Conclusions

Since we completed this analysis, Merck has announced the immediate worldwide withdrawal of rofecoxib because of its adverse cardiovascular profile. Since we submitted this manuscript, adverse cardiovascular effects have been reported with both celecoxib and valdecoxib. Our study offers no reassurance that the increased risk of myocardial infarction is specific to rofecoxib alone or specific to COX 2 inhibitors. Indeed, we found similar effects 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. Lastly, we found no evidence to support a reduction in risk of myocardial infarction associated with naproxen.

This is an observational study and may be subject to residual confounding that we cannot fully correct for. However, we think that enough concerns exist to warrant a reconsideration of the cardiovascular safety of all NSAIDs.

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Contributors: JHC initiated and designed the study, got ethical approval, did the data extraction and manipulation, did the analysis, and drafted the paper. CC contributed to the study design, supervised and checked the analysis, advised on interpretation, and contributed to drafting the paper. JHC and CC are both guarantors.

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Competing interests: None declared.

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

Ethical approval: Trent Multi-Centre Research Ethics Committee.

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