Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs

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Abstract

Objective To compare rates of upper gastrointestinal haemorrhage among elderly patients given selective cyclo-oxygenase-2 (COX 2) inhibitors and non-selective non-steroidal anti-inflammatory drugs (NSAIDs).

Design Observational cohort study.

Setting Administrative data from Ontario, Canada, used from 17 April 2000 to 31 March 2001 to identify population based, NSAID-naïve cohorts of patients.

Patients Subjects aged ≥ 66 years who started taking non-selective NSAIDs (n=5391), diclofenac plus misoprostol (n=5087), rofecoxib (n=14 583), or celecoxib (n=18 908) and a randomly selected control cohort not exposed to NSAIDs (n=100 000).

Main outcome measures Rate ratios of hospital admission for upper gastrointestinal haemorrhage in each drug cohort with adjustment for potential confounders.

Results Relative to controls, the multivariate model revealed an increased short term risk of upper gastrointestinal haemorrhage for users of non-selective NSAIDs (adjusted rate ratio 4.0 (95% confidence intervals 2.3 to 6.9)), diclofenac plus misoprostol (3.0 (1.7 to 5.6)), and rofecoxib (1.9 (1.3 to 2.8)) but not celecoxib (1.0 (0.7 to 1.6)). Relative to celecoxib, significantly higher risks of upper gastrointestinal haemorrhage were observed for non-selective NSAIDs (4.4 (2.3 to 8.5)), diclofenac plus misoprostol (3.2 (1.6 to 6.5)), and rofecoxib (1.9 (1.2 to 2.8)). Relative to rofecoxib, non-selective NSAID users were at significantly higher risk of upper gastrointestinal haemorrhage (1.9 (1.0 to 3.5)).

Conclusions This population based observational study found a lower short term risk of upper gastrointestinal haemorrhage for selective COX-2 inhibitors compared with non-selective NSAIDs.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world¹ and are consumed by about 20-30% of elderly people

in developed countries.²⁻³ Selective cyclo-oxygenase-2 (COX 2) inhibitors are a new group of NSAIDs that have rapidly gained acceptance in clinical practice.⁴ Within the first three months of its availability, celecoxib became the fastest selling drug in history.⁵

The adoption of selective COX 2 inhibitors has primarily been driven by the assertion that these drugs cause fewer gastrointestinal events than do conventional, non-selective NSAIDs.⁶ Use of conventional NSAIDs is estimated to increase the risk of gastrointestinal complications about fourfold among elderly people,⁷⁻¹⁰ although some drugs may have less gastrototoxic potential than others.¹¹ Two large randomised controlled trials that separately evaluated rofecoxib and celecoxib showed that they significantly reduced the number of clinical upper gastrointestinal events compared with conventional NSAIDs.¹²⁻¹³ Given major differences in study design between these two trials, valid comparisons of the gastrointestinal safety of celecoxib, rofecoxib, and conventional NSAIDs cannot be made from these data alone.

Several important clinical questions remain about the gastrointestinal effects of selective COX 2 inhibitors. It is unclear to what degree they increase gastrointestinal risk relative to not using NSAIDs, and the relative gastrointestinal safety of the different COX 2 inhibitors is uncertain since they have not been directly compared in a single large study. Accordingly, we conducted a population based cohort study to compare the rate of upper gastrointestinal haemorrhage in over 40 000 NSAID-naïve elderly users of rofecoxib, celecoxib, non-selective NSAIDs, and diclofenac plus misoprostol with that in 100 000 non-NSAID users.

Methods

Study design

We conducted a population based retrospective cohort study by linking administrative healthcare databases covering over 1.3 million patients aged 66 years or more in Ontario, Canada, from 17 April 2000 through to 31 March 2001. Ontario's elderly population has universal access to prescription drugs, hospital care,

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and doctor services. This study was approved by the Ethics Review Board of Sunnybrook and Women's College Health Sciences Centre.

Data sources

The administrative healthcare databases in Ontario allowed for cohort identification, comorbidity assessment, and endpoint ascertainment. The linked databases included computerised pharmacy records of the Ontario Drug Benefit Program, which records prescription drugs dispensed to all Ontario residents aged 65 years or older. Both rofecoxib and celecoxib were first listed on the Ontario Drug Benefit formulary on 17 April 2000 on a limited use basis for patients who did not respond to or were intolerant of traditional NSAIDs or patients with a history of upper gastrointestinal haemorrhage or ulcer. The approved indications for celecoxib included osteoarthritis and rheumatoid arthritis, whereas rofecoxib was approved only for use in osteoarthritis. No such restrictions governed the prescribing of conventional NSAIDs or diclofenac plus misoprostol. We were unable to examine meloxicam use as it was not available on the Ontario Drug Benefit formulary during the study period.

We obtained hospitalisation records from the Canadian Institute for Health Information Discharge Abstract Database, which contains a detailed record of all hospital admissions, including diagnostic and procedural information. The Ontario Health Insurance Plan provided physician billing information for inpatient and outpatient services, and the Ontario Registered Persons Database contained basic demographic information and vital statistics, including death date, for each Ontario resident. These databases were linked anonymously using encrypted individual health card numbers.

Cohort definition

We compared users of rofecoxib, celecoxib, non-selective NSAIDs, or the combination of diclofenac plus misoprostol with a random sample of 100 000 controls dispensed none of these drugs. Despite the potential differences in morbidity between users of NSAIDs and non-users, we chose patients not using NSAIDs as the control group for two reasons: firstly, such a control group provides useful baseline risk estimates of upper gastrointestinal haemorrhage not related to NSAID use, and, secondly, most previous studies of the association between NSAID use and upper gastrointestinal haemorrhage have non-users of NSAIDs as controls. Thus, choosing non-users of NSAIDs as our control group allowed comparison of our incidence and relative risk estimates with such studies. We also conducted pairwise comparisons of the different NSAID study groups in relation to each other.

For the four drug cohorts, the first NSAID prescription during the study period after a patient's 66th birthday served as the index date. To create a cohort of NSAID-naïve subjects within these four drug groups, we excluded individuals who were dispensed an NSAID in the year preceding the index date. We also excluded subjects given NSAIDs from more than one of the study's four groups of drug on the same day. To exclude sporadic users of NSAIDs, we included only those individuals who were given at least two successive

prescriptions of NSAID and who received enough drug for at least 30 days of observation. Events occurring during this initial 30 day period were included in the analysis.

To create the control cohort, all Ontario residents not included in any of the above cohorts were randomly assigned index dates from 17 April 2000 to 15 March 2001, as in the drug cohorts. Individuals aged 66 years and older who were alive on the assigned index date were screened for NSAID use. From those without a prescription for any NSAID in the year before the index date or during the observation period, we randomly selected 100 000 individuals to form the control cohort. This group was not matched for age or sex to any of the drug cohorts, but represented the general elderly population of Ontario not prescribed NSAIDs.

We repeated the analyses using controls matched by age (within one year of the birth date) and sex to all patients in the four drug cohorts as a sensitivity analysis. Because women are more likely than men to receive NSAIDs¹⁴ and may have a lower risk for upper gastrointestinal haemorrhage,⁷ we repeated the analyses separately for men and women. Finally, we repeated the upper gastrointestinal haemorrhage analysis after excluding subjects with a history of such bleeds.

Duration of exposure

For each of the four drug cohorts, we defined the duration of exposure as the period of continuous, exclusive use of one of the study drug groups starting from the index date. In the non-selective NSAID group, subjects were allowed to switch between different non-selective NSAIDs during the observation period. The "days supply" recorded in the pharmacy claims database allowed us to estimate the intended duration of each prescription. If subjects were given another prescription of the drug before the end of this period, the excess drug supply was carried over to the next prescription's estimated duration. Subjects were allowed a period of grace, 20% of the period covered by the previous prescription, to obtain another prescription of the drug. If they failed to obtain a repeat prescription within this time, they were deemed to have discontinued the study drug.

Follow up of subjects ended on their admission to hospital for upper gastrointestinal haemorrhage, exposure to an NSAID from another study group, discontinuation of the study drug, death, or the end of the observation period (31 March 2001). We identified hospital admissions for upper gastrointestinal haemorrhage using diagnosis codes ICD-9 (international classification of diseases, ninth revision) 531, 532, 534, 578.0, 578.1, and 578.9. Such codes have been shown to yield a positive predictive value of 86% for upper gastrointestinal haemorrhage.¹⁵

For the control cohort, each individual was allowed at least 15 days of follow up from the index date, and the end of the observation period was randomly assigned unless a subject was admitted for upper gastrointestinal haemorrhage or died beforehand.

Statistical analysis

We conducted time-to-event analyses for upper gastrointestinal haemorrhage using Cox proportional hazard models with the control group as the reference. The box lists the covariates used in the model. We

Covariates assessed in analysis**Hospitalisations**

Any hospitalisation in preceding year
 Malignancy in preceding 5 years
 Upper gastrointestinal haemorrhage in preceding 5 years

Procedures

Gastrointestinal endoscopy or radiological series in preceding 5 years

Drug use

Number of different drugs in preceding year
 Narcotic analgesics or gastroprotective agents in preceding 180 days
 In the 120 days before index date until end of follow up:

Aspirin
 Anticoagulants
 Antiplatelets
 Antidiabetic agents
 Antirheumatics
 Glucocorticoids
 Gastroprotective agents

Other

Age
 Sex
 Long term care
 Low income status (annual income of <\$C16 018 (singles) and <\$C24 175 (couples), confirmed through personal tax statements on voluntarily application for reductions in copayments and deductibles)

examined the number of distinct drugs dispensed in the year before the index date as an overall measure of comorbidity,¹⁶ a measure comparable to the Charlson comorbidity index.¹⁷ We compared all pairwise combinations of hazard ratios for the different drug groups. In each analysis we assessed the proportional hazards assumption for each exposure variable for any violations. All analyses were performed with SAS for UNIX, version 8.2 (SAS Institute, Cary, NC).

Results**Cohort description**

Of about 1.3 million potential subjects aged 65 years and older, 364 686 (28%) were dispensed a prescription NSAID during the study period. From the total elderly population, we identified 5391 users of non-selective NSAIDs, 5087 users of diclofenac plus misoprostol, 14 583 users of rofecoxib, 18 908 users of celecoxib, and 100 000 controls (table 1) who met our inclusion criteria. Among the users of non-selective NSAIDs, most started with naproxen (32%), ibuprofen (23%), or diclofenac (20%). A greater proportion of rofecoxib and celecoxib users were women than in the other groups. The control group generally used less healthcare resources than the other study groups. More rofecoxib and celecoxib users had previously undergone upper gastrointestinal diagnostic procedures or received gastroprotective agents than the other groups (table 1). They were also more likely to receive anticoagulants, antirheumatics, and glucocorticoids. The characteristics of the rofecoxib and celecoxib groups, however, were virtually identical.

During over 55 000 person years of follow up, we observed 187 hospitalisations for upper gastrointestinal haemorrhage (table 2). Relative to the control group, model based estimates adjusted for the covariates in the box revealed significantly higher risk ratios for users of non-selective NSAIDs (adjusted rate ratio 4.0; 95% confidence interval 2.3 to 6.9), diclofenac plus misoprostol (3.0; 1.7 to 5.6), and rofecoxib (1.9; 1.3 to 2.8), but not celecoxib (1.0; 0.7 to 1.6) (see figure). Analyses with age and sex matched controls, separate analyses for men and women, and analyses excluding subjects with a history of upper gastrointestinal haemorrhage all yielded similar findings.

Pairwise comparisons revealed significant differences in risk of upper gastrointestinal haemorrhage among the different drug groups. Relative to celecoxib users, a higher risk of hospitalisation for upper gastrointestinal haemorrhage was seen among users of non-selective NSAIDs (adjusted rate ratio 4.4; 2.3 to 8.5), diclofenac plus misoprostol (3.2; 1.6 to 6.5), and rofecoxib (1.9; 1.2 to 2.8). Relative to rofecoxib, a significantly higher risk of upper gastrointestinal haemorrhage was observed for non-selective NSAIDs (1.9; 1.0 to 3.5) but not diclofenac plus misoprostol (1.4; 0.7 to 2.7).

We conducted several sensitivity analyses. Firstly, we repeated the analysis examining all individuals who were given an NSAID irrespective of the number of prescriptions dispensed or the quantity of drug supplied. The findings were similar to those of the primary analysis. Secondly, we limited our analysis to patients not residing in a long term care institution and also found results similar to those of the primary analysis. Thirdly, we repeated the analysis among users of gastroprotective agents and non-users given the substantial discrepancy in use of gastroprotective agents observed in the various cohorts. Subjects given gastroprotective agents had a higher incidence of upper gastrointestinal haemorrhage than subjects in their respective groups not given gastroprotective agents during follow up, implying that these agents are

Adjusted Cox proportional hazard estimates for hospitalisation for upper gastrointestinal haemorrhage among elderly patients using prescribed NSAIDs

Table 1 Characteristics of cohorts in study of elderly patients using different NSAIDs. Values are numbers (percentages) unless stated otherwise

	Study cohort				
	Community controls	Non-selective NSAIDs	Diclofenac + misoprostol	Rofecoxib	Celecoxib
No of patients (% women)	100 000 (55)	5391 (59)	5087 (62)	14 583 (72)	18 908 (70)
Mean (SD) age (years)	75.4 (7.3)	75.5 (7.0)	76.6 (7.1)	76.5 (6.9)	76.5 (6.8)
Residence in long term care facility	4 074 (4)	398 (7)	503 (10)	652 (4)	810 (4)
Low income status	21 073 (21)	1831 (34)	1725 (34)	4 445 (30)	5 673 (30)
Hospitalisation in past year	11 513 (12)	1023 (19)	925 (18)	2 900 (20)	3 651 (19)
Mean (SD) No of prescription drugs in past year	5.4 (5.4)	8.3 (6.4)	8.3 (6.4)	9.9 (6.5)	9.5 (6.4)
Use of gastroprotective agents within 180 days before entry to cohort	17 279 (17)	1329 (25)	1265 (25)	6 140 (42)	7 738 (41)
Use of narcotic analgesics within 180 days before entry to cohort	10 623 (11)	1419 (26)	1321 (26)	4 511 (31)	5 587 (30)
Hospitalisations or procedures in past 5 years:					
Malignancy	4 785 (5)	371 (7)	294 (6)	760 (5)	1 004 (5)
Prior upper gastrointestinal haemorrhage	1 440 (1)	64 (1)	66 (1)	369 (3)	476 (3)
Prior gastrointestinal or radiological procedure	17 839 (18)	1090 (20)	1043 (21)	4 731 (32)	5 855 (31)
Drug use in 120 days before index date to end of follow up:					
Aspirin	11 564 (12)	1014 (19)	945 (19)	2 629 (18)	3 311 (18)
Anticoagulants	6 716 (7)	244 (5)	266 (5)	1 515 (10)	1 929 (10)
Antihyperglycaemics	9 256 (9)	756 (14)	706 (14)	1 819 (12)	2 344 (12)
Antirheumatics	0	66 (1)	71 (1)	401 (3)	865 (5)
Glucocorticoids	3 789 (4)	458 (9)	384 (8)	1 928 (13)	2 471 (13)
Gastroprotective agents:	16 394 (16)	1699 (32)	1277 (25)	6 213 (43)	7 793 (41)
Proton pump inhibitors	6 139 (6)	432 (8)	405 (8)	3 156 (22)	3 868 (20)
Other*	11 615 (12)	1407 (26)	983 (19)	3 754 (26)	4 778 (25)

*Includes histamine-H₂ receptor antagonists, misoprostol, and sucralfate.

selectively prescribed to those at higher risk of upper gastrointestinal haemorrhage. Differences in the risk of upper gastrointestinal haemorrhage between users of non-selective NSAIDs and of the COX 2 inhibitors were present whether or not patients received gastroprotective agents. Fourthly, we examined the doses used in the celecoxib and rofecoxib groups at the time of the last observed prescription, since some evidence indicates that other selective COX 2 drugs may lose their selectivity at higher doses.¹⁸ Both rofecoxib and celecoxib are approved for osteoarthritis, presumably the most prevalent indication in this cohort, for which 25 mg of rofecoxib and 200 mg of celecoxib are considered to be at the upper end of the dose ranges.¹⁹ A significantly greater proportion of patients given celecoxib (19%) were given high doses (>200 mg daily) compared with patients given rofecoxib (8% given >25 mg daily).

Discussion

Our findings suggest a lower risk of upper gastrointestinal haemorrhage associated with use of selective

COX 2 inhibitors than with conventional, non-selective NSAIDs. The rate of haemorrhage with celecoxib was similar to that among the control group not using NSAIDs. While the risk of haemorrhage with rofecoxib was significantly lower than that with non-selective NSAIDs, it was significantly higher than that with celecoxib.

Study limitations

Although we attempted to control for many important confounders, we were unable to account for some potentially important factors such as smoking and alcohol consumption. The distribution of such factors among the different groups studied and the consequent influences on our findings is unknown. However, despite a potentially heavier disease burden among the patients using rofecoxib and celecoxib (as a result of the limited use of selective COX 2 inhibitors licensed in Ontario), they had lower risk ratios than the patients using non-selective NSAIDs. Our population based incidence estimates for upper gastrointestinal haemorrhage (table 2) among the controls and non-selective NSAID group are also consistent with those of other

Table 2 Upper gastrointestinal haemorrhage among elderly patients using different NSAIDs

	Study cohort				
	Community controls (n=100 000)	Non-selective NSAIDs (n=5391)	Diclofenac + misoprostol (n=5087)	Rofecoxib (n=14 583)	Celecoxib (n=18 908)
No of admissions for upper gastrointestinal haemorrhage	82	17	13	43	32
Mean (SD) days of follow up	138.7 (77.4)	91.7 (68.3)	97.8 (71.2)	146.9 (89.6)	170.3 (97.0)
Total follow up (person years)	37 981	1353	1361	5865	8818
No of upper gastrointestinal haemorrhages per 1000 person years	2.2	12.6	9.6	7.3	3.6
Model based risk ratios (95% CI):					
Unadjusted	1.0 (reference)	6.1 (3.6 to 10.2)	4.6 (2.5 to 8.2)	3.5 (2.4 to 5.0)	1.7 (1.1 to 2.6)
Adjusted	1.0 (reference)	4.0 (2.3 to 6.9)	3.0 (1.7 to 5.5)	1.9 (1.3 to 2.8)	1.0 (0.7 to 1.6)
Number needed to treat to harm (NNT(H))*	N/A	403	592	1389	N/A

*NNT(H) calculations are based on a follow up of 295 days from the Cox proportional hazard model estimates.

studies,^{8, 20} as are our relative risks.⁷⁻¹⁰ In addition, when we analysed results among both users and non-users of gastroprotective agents, we still found lower adjusted relative risks for upper gastrointestinal haemorrhage for users of selective COX 2 inhibitors than among non-selective NSAID users. Users of gastroprotective agents had a higher incidence of upper gastrointestinal haemorrhage than subjects in their respective groups not dispensed gastroprotective agents. This implies that these agents were selectively prescribed to those at higher risk of upper gastrointestinal haemorrhage and were a marker for underlying gastrointestinal disease associated with a higher risk of upper gastrointestinal haemorrhage.

A second limitation is that we used administrative databases to identify and define exposure to study drugs and clinical outcomes. We have no direct measure of adherence or appropriateness of use. Since NSAIDs may be used in varying doses over time for symptom control, dose equivalence of the various drugs could not be adequately examined with these data. Instead, the NSAIDs were examined as they are commonly used in this population.

We were unable to identify use of non-prescription NSAIDs. However, ibuprofen and aspirin are the only non-prescription non-selective NSAIDs available in Canada, and subjects in our study have a strong financial incentive to obtain these drugs by prescription, especially with regular use. Over a quarter of the elderly subjects were given a NSAID during the observation period, consistent with previous studies examining the use of prescription and non-prescription NSAIDs among elderly people.^{2, 3} This implies that the vast majority of NSAID use in our population is probably captured by our databases. The use of non-prescription aspirin is perhaps the biggest problem, but since the distribution of prescription aspirin use was similar in the study drug groups, the use of non-prescription aspirin is also likely to be equally distributed.

We identified outcomes using diagnostic codes that have been validated previously, but we were unable to capture other important information such as the severity of the gastrointestinal haemorrhage and more subtle outcomes such as non-bleeding ulcers. Also, it is possible that upper gastrointestinal haemorrhage is more readily diagnosed or reported among users of traditional NSAIDs than among users of specific COX 2 inhibitors. However, the diagnosis is not generally difficult to make, its coding has been validated, and the impact of this potential bias is likely minimal.

The low absolute number of events in the study groups precluded reliable subgroup analyses such as comparisons among users of anticoagulants or individual NSAIDs, and the generalisability of our findings to younger patients or settings with different drug policies over longer periods of follow up is uncertain.

Relative gastrointestinal safety of rofecoxib and celecoxib

Currently, comparisons between rofecoxib and celecoxib are based largely on data from clinical trials and studies of whole blood assays. Two large randomised trials separately comparing rofecoxib¹² and celecoxib¹³ with non-selective NSAIDs provided

similar relative risk reductions of 40-60% in the incidence of clinical upper gastrointestinal haemorrhage events (that is, upper gastrointestinal haemorrhage ulcer complications plus symptomatic ulcers). However, valid comparisons of upper gastrointestinal haemorrhage event rates between rofecoxib and celecoxib cannot be made from such data for several reasons. Firstly, in the absence of a direct comparison, conclusions about the relative gastrointestinal safety of these drugs are largely speculative. Secondly, the primary endpoints of the two trials were slightly different. Thirdly, the comparator groups, using non-selective NSAIDs, in the two trials were different: the non-selective NSAIDs assessed in the celecoxib trial were either ibuprofen or diclofenac, whereas naproxen was assessed in the rofecoxib study. Since naproxen is probably more gastrototoxic than ibuprofen or diclofenac,¹¹ it is difficult to assess the relative gastrointestinal safety of rofecoxib and celecoxib from these two trials. Fourthly, the interpretation of the celecoxib trial is complicated by the nature of its reporting.²¹ The findings were based on a combined analysis of the first six months of two separate and longer trials whose protocols differed substantially from the published paper in design, outcomes, duration of follow up, and analysis. Although 12 month data revealed no significant differences between celecoxib and its non-selective NSAID comparators with respect to complicated ulcer outcomes (the primary endpoint of the trials), the incidence of clinical upper gastrointestinal haemorrhage events remained significantly different.²²

Our understanding of the cellular effects of the COX 2 inhibitors is also evolving, and conclusions about the relative safety of these agents based on in vitro data may be premature. For example, although whole blood assay studies suggest that rofecoxib is more COX 2 selective than celecoxib,²³ such assays have been criticised for having limited clinical relevance.²⁴ Furthermore, recent studies of cancer cell lines have shown what may be COX independent differences in antiproliferative activity between celecoxib and rofecoxib.²⁵⁻²⁷ The clinical implications of such differences for the gastrointestinal safety of these two drugs are not known.

Our evaluation represents the first direct comparison of rofecoxib and celecoxib for a clinically meaningful gastrointestinal outcome using common comparator groups over the same period, with data reflecting clinical practice. The demographic characteristics of rofecoxib and celecoxib users were strikingly similar in our study, implying that selection of one COX 2 inhibitor over another is probably arbitrary in clinical practice. Therefore, the differences in unobserved covariates between the rofecoxib and celecoxib groups are probably minimal and would not explain the difference in upper gastrointestinal haemorrhage observed between the two drugs.

Conclusions

Our study found lower rates of upper gastrointestinal haemorrhage with selective COX 2 inhibitors than with non-selective NSAIDs. The significantly higher rate of upper gastrointestinal haemorrhage among users of rofecoxib than users of celecoxib was unexpected. Although the absolute difference in rates

What is already known on this topic

Long term NSAID use is associated with the development of peptic and duodenal ulcers

Selective COX 2 inhibitors are claimed to cause fewer gastrointestinal problems than conventional, non-selective NSAIDs

It is unclear to what degree COX 2 inhibitors increase gastrointestinal risk relative to not using NSAIDs, and the relative gastrointestinal safety of the different COX 2 inhibitors is uncertain

What this study adds

The risk of upper gastrointestinal haemorrhage with the COX 2 inhibitors rofecoxib and celecoxib was significantly lower than with conventional NSAIDs, but the risk with rofecoxib was significantly higher than that with celecoxib

The risk of gastrointestinal haemorrhage with celecoxib was similar to that in controls not using NSAIDs

of upper gastrointestinal haemorrhage was small, the difference, if true, is clinically important given the large numbers of patients prescribed selective COX 2 inhibitors. Large randomised controlled trials directly comparing the drugs are urgently needed to better examine these differences.

Contributors: MM, PAR, DNJ, GMA, GN, and AL designed the study; MM, DNJ, PCA, and AK performed the study. GN, PCA, and AL advised and supervised. Statistical advice was given by PCA. MM is the guarantor.

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Competing interests: MM has conducted research in an unrelated content area at the request of an academic institution whose funding was supported by Pharmacia in the past two years, but none of the funding for this study was provided by any pharmaceutical company.

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