Cite this article as: BMJ, doi:10.1136/bmj.38947.697558.AE (published 19 September 2006)

Research

BMJ

Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study

Jesper Hallas, Michael Dall, Alin Andries, Birthe Søgaard Andersen, Claus Aalykke, Jane Møller Hansen, Morten Andersen, Annmarie Touborg Lassen

Abstract

Objectives To assess the risk of serious upper gastrointestinal bleeding associated with the newer antithrombotic agents used alone or in combination with other antithrombotic drugs; to describe the trends in use of antithrombotic drugs in the background population.
Design Population based case-control study.
Setting Funen County, Denmark (population 470 000).
Subjects 1443 cases of serious upper gastrointestinal bleeding identified during 2000-4; 57 720 age and sex matched controls.
Main outcome measure Exposure to low dose aspirin, clopidogrel, dipyridamole, vitamin K antagonists, and combined antithrombotic treatment.
Results Adjusted odds ratios associating drug use with upper gastrointestinal bleeding were 1.8 (95% confidence interval 1.5 to 2.1) for low dose aspirin, 1.1 (0.6 to 2.1) for clopidogrel, 1.9 (1.3 to 2.8) for dipyridamole, and 1.8 (1.3 to 2.4) for vitamin K antagonists. Corresponding figures for combined use were 7.4 (3.5 to 15) for clopidogrel and aspirin, 5.3 (2.9 to 9.5) for vitamin K antagonists and aspirin, and 2.3 (1.7 to 3.3) for dipyridamole and aspirin. Other combinations were used too infrequently to allow estimation. The number of treatment years needed to produce one excess case varied from 124 for the clopidogrel-aspirin combination to 8800 for clopidogrel alone. During the study period, exposure to combined antithrombotic regimens increased by 425% in the background population.
Conclusion Antithrombotic treatment is becoming increasingly aggressive. Combined antithrombotic treatment confers particular risk and is associated with high incidence of gastrointestinal bleeding.

Introduction

Aspirin (acetylsalicylic acid) is the mainstay of prophylactic antiplatelet treatment in patients with atherosclerotic disease.[1 2] After the results of several large intervention trials during the past decade,[3–10] other antiplatelet drugs have come into clinical practice. The two most important are clopidogrel and dipyridamole. With few notable exceptions,[11] clinical trials have established the superiority of combined antiplatelet treatment over aspirin alone in preventing thrombotic outcomes.[4–10] Furthermore, antiplatelet treatment is increasingly used in combination with vitamin K antagonists in patients who have dual indications for treatment, such as those with ischaemic heart disease and atrial fibrillation. Antithrombotic treatment has thus shifted towards more aggressive regimens, often involving more than one drug. Unfortunately, safety data on the use of combined regimens are relatively scarce.

We did this population based case-control study to assess the risk of serious upper gastrointestinal bleeding associated with the newer antithrombotic agents used alone or in combination with other antithrombotic drugs. We also aimed to describe the trends in use of antithrombotic drugs in the background population.

Methods

Setting

The data for this study came from three different sources—Odense University pharmacoepidemiological database, the Funen County patient administrative system, and the Danish central person register.

In brief, information on reimbursed drug dispensing in Funen County (population 470 000) has been recorded in the pharmacoepidemiological database since 1990. Each prescription record includes a person identifier; the date of dispensing; and the brand, quantity, and form of the drug. The substances and quantities are registered according to the World Health Organization's anatomical-therapeutic-chemical system and defined daily doses methods.[12] The indication for treatment and the dosing instruction are not recorded. Drugs not reimbursed, and therefore not recorded in the database, are over the counter drugs and some non-reimbursed prescription drugs, mainly oral contraceptives, sedatives, hypnotics, and some antibiotics.[13]

Data on patient contacts came from the Funen County patient administrative system. All Funen County residents have had their secondary care contacts registered since 1977. As inpatient care is provided almost exclusively by the national health services, this data source in effect allows true population based epidemiological studies. Inpatient data are available from 1977 and outpatient data from 1989. Diagnoses are encoded by the ICD-8 (international classification of diseases, 8th revision) until January 1994 and ICD-10 thereafter.

We used the central person register to extract the controls and to ensure that all cases and controls were Funen County residents on their index dates and during the previous 365 days.

Sample size calculation

By using our prescription database, we estimated the cumulative exposure to the aspirin-clopidogrel regimen throughout the study period at 700 person years with an average age of 70 years.

With an age specific bleeding incidence of 4 per 1000 person years and an odds ratio of 5, this would yield about 14 exposed cases. This would allow us to estimate the odds ratio with a confidence interval of −45% to 70% around the point estimate.

Cases and controls

We defined cases by fulfilment of three criteria: admission with peptic ulcer or gastritis as the main diagnosis to one of the county's hospitals during 1 January 2000 to 31 December 2004; significant bleeding defined by melaena, a subnormal haemoglobin, or the need for transfusions; and a potential bleeding source in the stomach or duodenum identified by endoscopy or surgery. We excluded gastric varices.

To retrieve all relevant cases, we manually reviewed discharge summaries of all 4449 admissions with a main diagnosis of peptic ulcer (complicated or not) or gastritis (ICD-10 code K25-9) within the study period. We were blinded to the exposure status of the subjects. For each case, we considered only the first episode within the study period. Eventually, 1443 validated cases could be included.

We sampled controls, 40 for each case, by using a risk set sample technique.[14] In brief, we selected 40 random controls from among people who, on the admission date of the corresponding case, had one year's residency within the county and who matched the case with respect to sex and age (within 10 years). We assigned the controls an index date identical to the admission date of the corresponding case. Cases were eligible to be selected as control subjects until their first admission with upper gastrointestinal bleeding. The odds ratios derived by such sampling are unbiased estimates of the incidence rate ratio.[14]

Analysis

The antithrombotic drugs included in this study were aspirin, clopidogrel, dipyridamole, and vitamin K antagonists. We defined current use as the redeeming of a prescription within the previous 90 days. We classified people whose latest prescription was redeemed 91-180 days before the index date as recent users and those whose latest prescription was redeemed more than 180 days before the index date as past users. We used the same exposure criteria for all drugs in the analysis. Unless otherwise stated, we based analyses on current exposure, and the reference was person time currently non-exposed to all four classes of antithrombotic drugs. When analysing for recent use we excluded current users of any antithrombotic drugs, and when analysing for past use we excluded both current and recent users.

As potential confounders we included current use of non-steroidal anti-inflammatory drugs (including selective cyclo-oxygenase-2 inhibitors), selective serotonin reuptake inhibitors, antiulcer drugs, systemic corticosteroids, or nitrate vasodilators and a past diagnosis of peptic ulcer or upper gastrointestinal bleeding (more than one month before the index date), diabetes, ischaemic heart disease, or alcohol related diagnoses or use of disulfiram. Each of these showed a statistically significant association with upper gastrointestinal bleeding in univariate analyses of people non-exposed to antithrombotic drugs. We controlled for confounders by conditional logistic regression modelling. Results are presented with 95% confidence intervals, whenever relevant.

In order to express the risk caused by use of antithrombotic treatment in absolute terms, we used the "the number of patients needed to be treated for one additional patient to be harmed" (NNTH) principle.[15] We used the adjusted odds ratios (OR) and the incidence of upper gastrointestinal bleeding in the background population unexposed to any antithrombotic drug and aged 50 or above. For the period 2000 to 2004, the cumulative person time unexposed to antithrombotic drugs for people aged 50 or more was 762 000 person years. We found 960 cases aged 50 or above who were unexposed to all four antithrombotic drugs, yielding an unexposed event rate ER_{unexp} of 1.26 per 1000 person years in this age group. NNTH is then calculated simply as $NNTH = 1/(ER_{unexp} \times (OR - 1))$.[15]

This estimate can be construed as the number of person years' treatment needed to produce one excess case, if the drug is given to "average" citizens aged over 50 years. We introduced the 50 year limit because otherwise the low risk of bleeding and low rate of use of antithrombotic drugs among young people would dilute the NNTH towards unrealistically high values. Confidence intervals for NNTH are presented as suggested by Altman.[16]

To describe the shift in use of antithrombotic drugs, we extracted all 830 000 prescriptions for antithrombotic drugs for the entire background population for the period 1995 to 2004. We used the same exposure criteria as when we assigned exposure status to cases and controls. That is, we assigned each prescription a 90 day exposure window and charted all users with respect to periods of single and combined use within each calendar year. Finally, we summed the periods of exposure for each antithrombotic regimen within each year during the period.

Table 1 Characteristics of cases of serious upper gastrointestinal bleeding and of controls. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=1443)	Controls (n=57 720)
Mean (SD) age (years)	72.4 (14.3)	71.8 (14.3)
Male	710 (49.2)	28 400 (49.2)
Bleeding source:		
Gastric ulcer	606 (42.0)	NA
Duodenal ulcer	645 (44.7)	NA
Other erosive lesions	192 (13.3)	NA
Current drug use:		
Low dose aspirin	275 (19.1)	5 032 (8.7)
Clopidogrel	30 (2.1)	269 (0.5)
Dipyridamole	83 (5.8)	1 494 (2.6)
Oral anticoagulants	78 (5.4)	1 367 (2.4)
Acid suppressing drugs	309 (21.4)	4 802 (8.3)
NSAID	523 (36.2)	6 200 (10.7)
SSRI	191 (13.2)	3 430 (5.9)
History of:		
Upper gastrointestinal bleeding	53 (3.7)	497 (0.9)
Uncomplicated peptic ulcer	187 (13.0)	2 279 (3.9)
Helicobacter pylori eradication	96 (6.7)	1 123 (1.9)
Chronic obstructive lung disease	184 (12.8)	2 565 (4.4)
Ischaemic heart disease	374 (25.9)	6 294 (10.9)
Alcohol related diagnosis or drug use	149 (10.3)	1 157 (2.0)
Diabetes	157 (10.9)	3 047 (5.3)
Liver cirrhosis	29 (2.0)	195 (0.3)
Renal failure	56 (3.9)	325 (0.6)

NA=not applicable; NSAID=non-steroidal anti-inflammatory drug; SSRI=selective serotonin reuptake inhibitor.

Results

In all, 380 (26.3%) of the 1443 cases were exposed to at least one of the four categories of antithrombotic drugs. Table 1 shows the clinical characteristics of cases and controls. Cases had more chronic disease and were more likely to use ulcerogenic drugs such as non-steroidal anti-inflammatory drugs, as well as antithrombotic drugs, gastroprotective drugs, and selective serotonin reuptake inhibitors. In all, 127 (8.8%) cases died within 30 days of their index date.

Table 2 Crude and adjusted odds ratios for association between use of antithrombotic drug and serious upper gastrointestinal bleeding

	Cases (exposed/ unexposed)	Controls (exposed/ unexposed)	Crude odds ratios (95% CI)	Adjusted odds ratios (95% CI)*
Single drug regimens, current use				
Aspirin alone	196/1063	4123/50 498	2.4 (2.0 to 2.8)	1.8 (1.5 to 2.1)
Clopidogrel alone	12/1063	203/50 498	3.1 (1.7 to 5.6)	1.1 (0.6 to 2.1)
VKA alone	56/1063	1227/50 498	2.2 (1.7 to 3.0)	1.8 (1.3 to 2.4)
Dipyridamole alone	36/1063	738/50 498	2.4 (1.7 to 3.4)	1.9 (1.3 to 2.8)
Two drug regimens, current use				
Aspirin and clopidogrel	13/1063	49/50 498	12.6 (6.6 to 24)	7.4 (3.5 to 15)
Aspirin and VKA	16/1063	114/50 498	6.4 (3.7 to 11)	5.3 (2.9 to 9.5)
Dipyridamole and aspirin	44/1063	737/50 498	3.1 (2.2 to 4.2)	2.3 (1.7 to 3.3)
Past use				
Aspirin	108/886	3990/44 968	1.5 (1.2 to 1.8)	0.9 (0.7 to 1.2)
Clopidogrel	4/990	111/48 847	1.8 (0.7 to 5.1)	0.8 (0.3 to 2.2)
Dipyridamole	2/992	152/48 806	0.8 (0.2 to 2.9)	0.4 (0.1 to 1.6)
VKA	48/946	1028/47 930	2.4 (1.8 to 3.3)	1.8 (1.3 to 2.4)

VKA=vitamin K antagonist.
*Adjusted for previous discharge diagnosis of peptic ulcer, peptic ulcer bleeding, chronic obstructive lung disease, ischaemic heart disease, alcohol related diagnosis or drug use, or liver cirrhosis or renal failure; for past *Helicobacter pylori* eradication; and for concurrent use of non-steroidal anti-inflammatory drugs, antiulcer drugs, nitrate vasodilators, selective serotonin reuptake inhibitors, or systemic corticosteroids.

Table 2 shows the results of the univariate and multivariate analyses. We found consistently higher odds ratios for combinations than for the single drug regimens. Too few cases were exposed to three or more antithrombotic agents to allow a meaningful estimate of the odds ratios. Furthermore, we found only one case using a vitamin K antagonist and clopidogrel and no cases exposed to either clopidogrel and dipyridamole or vitamin K antagonist and dipyridamole.

All estimates for past use were consistently lower than for current use, and confidence intervals crossed the null value, except the estimate for vitamin K antagonists (1.3 to 2.4). Results for recent use showed intermediate values between current use and past use for aspirin and vitamin K antagonists (data not shown).

The estimated NNTHs ranged between one bleeding episode per 124 treatment years for the clopidogrel-aspirin combination to one bleeding episode per 1040 treatment years for vitamin K antagonist monotherapy (table 3). For clopidogrel, the confidence interval of the odds ratio crossed the null value, so the upper limit of the confidence interval for the NNTH was infinite.

The figure shows trends in use of combined antithrombotic drugs. All regimens showed a dramatic increase over the period 1995-2004. The total exposure to combined regimens was 758 person years in 2000 and 3978 person years in 2004, an increase of 425% over four years.

Discussion

The main findings of our study are that combinations of antithrombotic drugs are increasingly prevalent and that they are associated with high rates of bleeding. The apparent effect reflects a true synergism—that is, the effect of combined

Table 3 Number of person years' treatment needed to produce one excess case of serious upper gastrointestinal bleeding. Estimates are based on data for people aged 50 or above

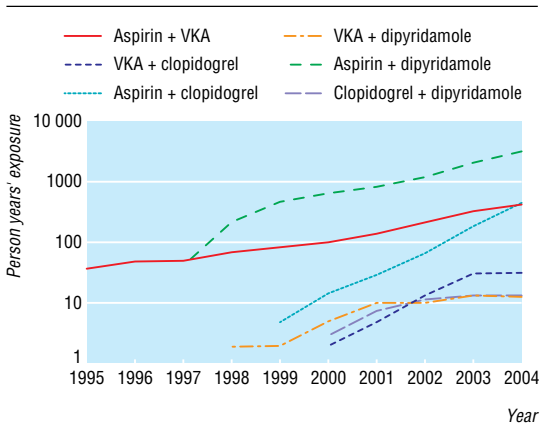
Exposure	Total drug exposure in background population (person years)	NNTH: person years^{-1} (95% CI)
Aspirin alone	40 599	1040 (725 to 1641)
Clopidogrel alone	2 391	8800 (NNTH 723 to ∞; NNTB 1832 to ∞)
VKA alone	13 205	985 (550 to 2372)
Dipyridamole alone	8 007	873 (445 to 2557)
Aspirin and clopidogrel	739	124 (54 to 312)
Aspirin and VKA	1 213	184 (93 to 407)
Dipyridamole and aspirin	7 713	595 (348 to 1201)

NNTB=number needed to treat for one patient to benefit; NNTH=number needed to treat for one patient to be harmed; VKA=vitamin K antagonist.

treatment is more than a simple addition of the effects of individual drugs. Some of the combinations involving antiplatelet drugs or vitamin K antagonists have not been assessed formally in randomised trials, and safety data are very scarce.[17 18] With, for example, one excess case per 184 treatment years for the vitamin K antagonist-aspirin regimen, clinicians should consider the expected benefit carefully before prescribing this combination.

The finding of a null value odds ratio for clopidogrel monotherapy is interesting. Evidence on gastrointestinal effects of clopidogrel monotherapy is scarce and mostly indirect. Evidence exists to show that clopidogrel causes little gastric mucosal inflammation,[19] that clopidogrel monotherapy is safer than aspirin monotherapy,[3] and that safety is better with aspirin plus esomeprazole than with clopidogrel monotherapy.[20] In a large case-control study, Lanas et al found an odds ratio of 2.8 after adjustment for use of aspirin.[21] Our own study suggests that clopidogrel by itself carries little if any risk of upper gastrointestinal bleeding, but when it is given with aspirin the risk increases beyond the effect of aspirin given alone. To our knowledge, this is not contradicted by data from the large clinical trials.

Another interesting finding is the moderately elevated odds ratio for dipyridamole monotherapy. Again, safety data from the large clinical trials are scarce, essentially limited to the second European stroke prevention study.[4] The number of serious bleeding events reported for dipyridamole did not differ from placebo, but figures were small and bleeding sources were not stated.



Use of combined antithrombotic regimens in outpatient settings. Data from Funen County, Denmark, 1995-2004. Note logarithmic y axis. VKA=vitamin K antagonist

One of the strengths of our study is a thorough retrieval and ascertainment of cases, all of which we reviewed manually. The validity of the prescription data is also well established.[13] As the data are used for reimbursement between retail pharmacies and the county, pharmacies have a strong economic incentive to be comprehensive and accurate. Low dose and high dose aspirin and 200 mg ibuprofen tablets were available over the counter throughout the study period. By comparing the quantity registered in our database with the gross volume sales,[22] we can estimate that the amount sold without prescription was on average 1.5% for low dose aspirin, 12% for non-aspirin non-steroidal anti-inflammatory drugs, and 93% for high dose aspirin.

One limitation of our study is that we did not have data on certain risk factors for upper gastrointestinal bleeding that might be potential confounders, such as smoking, high alcohol consumption, or use of over the counter non-steroidal anti-inflammatory drugs. Although an alcohol related marker, a diagnosis of chronic obstructive pulmonary disease, and use of non-steroidal anti-inflammatory drugs were risk factors for upper gastrointestinal bleeding by themselves (odds ratios 6.0, 3.2, and 4.9), their inclusion or exclusion in the multivariate models did not change our main estimates (data not shown). We find it unlikely that strong residual confounding by smoking, alcohol use, or over the counter non-steroidal anti-inflammatory drugs would be present.

Finally, we need to consider the possibility of selection bias, mainly that patients taking antithrombotic treatment would be more readily admitted when presenting with symptoms suggestive of upper gastrointestinal bleeding.[23] We have focused only on cases of severe bleeding that would be admitted irrespective of their drug exposure. Both our incidence and our case fatality are within the typical ranges for this patient group.[24]

Our study presents data on only the adverse effects of antithrombotic treatment. The decision to treat a patient with an aggressive antithrombotic regimen ultimately relies on the balancing of benefits and risks. Although we included a sizeable number of cases, we had too few to identify subgroups with particularly high or low risk. Future studies with higher power might aid in individualising treatment.

Contributors: JH wrote the first protocol draft, validated some cases, did the analyses, and wrote the first article draft. BSA, JMH, ATL, MD, CA, and AA provided input to the protocol and article and validated some cases. MA provided input to the article draft and analyses. All authors have approved the current version. JH is the guarantor.

Funding: The University of Southern Denmark and Funen County provided data free of charge.

Competing interests: JH has received fees for teaching from AstraZeneca and the Danish Association of the Pharmaceutical Industry and research grants from Novartis and Nycomed. JMH has received fees for teaching from AstraZeneca. All other authors: none declared.

Ethical approval: The Danish Data Protection Agency approved the study. Approval from an ethics committee was not needed.

What is already known on this topic

Use of antithrombotic drugs is a risk factor for serious upper gastrointestinal bleeding

Some combined drug regimens have better preventive effect than monotherapy against thrombosis

What this study adds

Use of antithrombotic drugs, whether combined or single drug regimens, has increased dramatically

Combined antithrombotic drug treatment confers particular risk and is associated with high incidence of gastrointestinal bleeding

1 Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. *JAMA* 2004;292:1867-74.
2 Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;353:2373-83.
3 CAPRIE Steering Group. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
4 Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
5 Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Clopidogrel for the reduction of events during observation: early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20.
6 Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the clopidogrel in unstable angina to prevent recurrent events (CURE) study. *Circulation* 2003;108:1682-7.
7 Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-33.
8 Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 2005;294:1224-32.
9 Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
10 Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-7.
11 Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
12 WHO Collaborating Centre for Drug Statistics Methodology. *ATC index with DDDs and guidelines for ATC classification and DDD assignment*. Oslo: Norwegian Institute of Public Health, 2006.
13 Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;44:445-8.
14 Rothman K. *Epidemiology: an introduction*. Oxford: Oxford University Press, 2002:78.
15 Bjerre LM, LeLorier J. Expressing the magnitude of adverse effects in case-control studies: "the number of patients needed to be treated for one additional patient to be harmed". *BMJ* 2000;320:503-6.
16 Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.
17 Massel D, Little SH. Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. *J Am Coll Cardiol* 2001;37:569-78.
18 Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* 2005;165:784-9.
19 Fork FT, Lafolie P, Toth E, Lindgarde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers: a gastroscopic study. *Scand J Gastroenterol* 2000;35:464-9.
20 Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238-44.
21 Lanas A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez Perez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective COX-2 inhibitors, traditional non-aspirin NSAIDs, aspirin, and combinations. *Gut* 2006; May 10, Epub ahead of print (doi:10.1136/gut.2005.080754).
22 Danish Medicines Agency. www.medstat.dk/MedStatDataViewer.php (accessed 5 Sept 2006).
23 Collet J-P, Boivin J-F. Bias and confounding in pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. Chichester: Wiley and Sons, 2000:765-84.
24 Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *BMJ* 1995;311:222-6.

(Accepted 14 August 2006)

doi 10.1136/bmj.38947.697558.AE

Department of Clinical Pharmacology, IST, Syddansk Universitet, 5000 Odense, Denmark
Jesper Hallas *professor*

Research Unit of General Practice, Syddansk Universitet
Morten Andersen *senior researcher*

Department of Medical Gastroenterology, Odense University Hospital, Odense
Michael Dall *registrar*
Claus Aalykke *senior registrar*
Jane Møller Hansen *senior physician*

Department of Cardiology, Odense University Hospital

Alin Andries *registrar*
Birthe Søgaard Andersen *senior registrar*
Department of Infectious Medicine, Odense University Hospital

Annmarie Touborg Lassen *senior registrar*
Correspondence to: J Hallas jhallas@health.sdu.dk