

# Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs

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## Abstract

**Aims**—To determine risk factors for peptic ulcer bleeding other than non-steroidal anti-inflammatory drugs (NSAIDs).

**Methods**—Data on possible antecedent risk factors obtained in a large case control study of 1121 patients admitted to hospitals in Glasgow, Newcastle, Nottingham, Oxford, and Portsmouth with bleeding peptic ulcers were compared with the same information obtained in 989 population controls. Data were analysed by logistic regression with the calculation of odds ratios (OR) and 95% confidence intervals (CI).

**Results**—From a logistic regression model, oral anticoagulants (OR 7.8; 95% CI 2.8–21.5), previous peptic ulcer (3.8; 2.6–4.9), treatment for heart failure (5.9; 2.3–13.1), oral corticosteroid use (2.7; 1.3–4.5), treatment for diabetes (3.1; 1.2–4.3), and current smoking (1.6; 1.2–2.0) were all independent risk factors. No association was found with use of calcium channel antagonists. Odds ratios for concomitant NSAID usage were multiplicative with the exception of current smoking.

**Conclusions**—Some 45% of admissions for peptic ulcer bleeding in England and Wales in those aged 60 or more are calculated to be attributable to, or associated with, these accessory risk factors, which, together with those associated with aspirin or other NSAID use will account for over 80% of predisposing factors to ulcer bleeding.

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Keywords: peptic ulcer; risk factors; anti-inflammatory drugs

There have been many reports on the risks of hospitalisation for peptic ulcer disease or its complications associated with the use of different non-steroidal anti-inflammatory drugs (NSAIDs).<sup>1–12</sup> However, less is known about other factors and how they interact with NSAIDs in altering the chances of ulcer complications; and this predominantly stems from a paucity of studies with population controls, hospital controls being obviously inappropriate. We have previously reported on overall odds ratios of 3.8 (3.1–4.5) for non-aspirin NSAID use in the three months prior to admission<sup>6</sup> and 3.2 (2.3–4.4) for daily aspirin usage of at least one month's duration.<sup>12</sup>

These studies included large numbers of population controls, and we have now undertaken detailed analyses of our data with regard to concurrent illness and medication, previous peptic ulcer or dyspepsia, as well as smoking habits and alcohol consumption.

## Patients and methods

These have been fully described elsewhere.<sup>6</sup> Briefly, 1121 patients aged 60 and over, admitted to hospitals in Glasgow, Newcastle, Nottingham, Oxford, and Portsmouth between April 1986 and January 1991, with haematemesis or melaena due to gastric or duodenal ulceration, were studied. Each patient was matched for age and sex with a hospital control taken from the acute medical intake, and a community control taken from the same general practice as the patient. Patients and controls were only included once. In each centre patients and controls were interviewed by the same research assistant using a structured questionnaire. This included detailed information on previous NSAID and analgesic intake. Current smoking habits and alcohol intake were also included in the inquiry. In addition information was included on the use of other medications in the week prior to admission. These were initially classified into 27 distinct categories using groupings employed by the *British National Formulary*. Reported drug intake was checked against general practitioner (GP) records.

Odds ratios (OR), 95% confidence intervals (CI), and interactions of specific factors with NSAIDs (both aspirin and non-aspirin), were calculated using logistic regression with SAS software. The following were included as independent variables: a previous history of peptic ulcer disease; a history of dyspepsia lasting longer than one week in the past year; NSAID use; current smoking; and alcohol intake. Other risk factors were also included as necessary, and to correct for the greater comorbidity in the patients, a variable for two or more associated illnesses (other than peptic ulcer) was included. Underlying illness was defined both as self reported and by prescribed medication. Thus heart failure was considered both as self reported, and when both digoxin and diuretics were taken; and diabetes was considered as self reported, and again when oral hypoglycaemics or insulin were in use. Statistical significance

**Abbreviations used in this paper:** NSAID, non-steroidal anti-inflammatory drug.

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Table 1 Comparison of patients and controls

	Patients (n = 1121)	Community controls (n = 989)
<i>Current illnesses</i>		
Heart failure	65	9
Ischaemic heart disease	116	107
Other cardiovascular	221	197
Respiratory disease	183	130
Diabetes	69	27
Other endocrine	46	33
Previous peptic ulcer	290	89
Other gastrointestinal	98	106
Neurological disease	114	76
Haematological disease	36	27
Other diseases	188	161
Two or more illnesses*	438	256
Nursing home	37	3
<i>Drug use in the previous week</i>		
Antacids	252	109
Antiulcer	167	54
Antibiotics	66	29
Digoxin	81	38
Diuretics	379	237
Potassium supplements	90	42
Antianginals/antiarrhythmics	257	218
Oral corticosteroids	64	20
Bronchodilators	117	94
Warfarin	39	7
Psychotropics	176	111
Three or more drugs	451	237
<i>Other</i>		
Alcohol consumption >7 units/week	197	145
Current smokers†	324	220
Dyspepsia in the past year >1 week	588	259

\*Excluding peptic ulcer disease.

†As defined by at least one cigarette a day, one cigar a week, or 1 ounce of pipe tobacco a month.

tests for comparison of logistic regression models were based on the difference between  $-2 \log$  likelihood scores. The referent groups chosen were patients and community controls not exposed to each risk factor. The hospital controls, being inappropriate, were excluded from consideration.

## Results

Table 1 shows the number of patients and community controls with recorded current illnesses or medical treatments, these being grouped in broad systematic categories. Patients were generally more likely to suffer from a wide variety of current illnesses than randomly chosen community controls. As might be expected, there was broad congruence between self reported patterns of illness and drug treatments in use.

Table 2 presents the odds ratios with 95% of confidence intervals for significant associations detected. All of these were independent. The raised odds ratios associated with oral corticosteroid use did not differ materially for gastric (OR 2.73; 95% CI 1.34–5.53) and duodenal ulcer (2.11; 1.02–4.35). Addition of rheumatoid arthritis to the logistic regression as a separate factor did not alter odds ratios obtained here or elsewhere.

Odds ratios were also raised significantly in association with warfarin treatment, and independently with heart failure as categorised by concurrent treatment with digoxin and diuretics. Separate examination of possible associations with antianginal and antiarrhythmic treatments showed no significant differences, and examination of risks associated with calcium channel antagonist use gave an odds ratio of 0.96 (95% CI 0.62–1.48) with 6.0% of patients and 6.1% of controls reporting use in

Table 2 Odds ratios (OR) for significant accessory risk factors compared with community controls

Category	OR	95% CI
Oral corticosteroids	2.7	1.3–4.5
Warfarin	7.8	2.8–21.5
Previous peptic ulcer	3.8	2.6–4.9
Dyspepsia in past year	4.0	3.1–4.8
Heart failure	5.9	2.3–13.1
Diabetes	3.1	1.2–4.3
Current smoking	1.6	1.2–2.0

Odds ratios determined by unconditional logistic regression model.

CI, confidence interval.

Table 3 Interaction between oral corticosteroid and non-steroidal anti-inflammatory drug (NSAID) use

NSAID	Corticosteroid	Patients (n = 1121)	Community controls (n = 989)	Odds ratio
–	–	431	643	1.0*
+	–	626	326	3.8
–	+	26	14	2.6
+	+	38	6	9.0

\*Referent.

Table 4 Non-steroidal anti-inflammatory drug (NSAID) use stratified by current smoking status

NSAID	Current smoker	Patients (n = 1111)*	Community controls (n = 989)	OR (95% CI)
–	–	312	541	1.0†
+	–	477	228	3.6 (2.9–4.5)
–	+	159	149	1.9 (1.4–2.4)
+	+	163	71	4.0 (2.9–5.5)

\*Smoking status unknown for 10 patients.

†Referent.

OR, odds ratio; CI, confidence interval.

the previous week. Risks associated with diabetes did not appear to differ for those receiving oral treatments, insulin, or dietary advice alone. Other categories of drugs, such as antiepileptics or bronchodilators, showed no significant associations (defined as odds ratios of more than 2.0 with probability values greater than 0.02).

Current smoking, a history of prior diagnosed peptic ulcer, and a history of dyspepsia in the past year were associated with significantly raised risk (table 2), but alcohol consumption was not, the odds ratio being 1.20 (95% CI 0.88–1.79).

Table 3 shows the joint effect of NSAIDs and oral corticosteroids using non-takers of either drug as the referent. Odds ratios were approximately tripled for corticosteroid or NSAID use alone, and increased by 10-fold when both were taken together. Logistic regression analysis showed similar multiplicative effects with NSAIDs for the other accessory risk factors, with the exception of current smoking.

Table 4 shows the separate and joint effects associated with current smoking and with NSAID use. The calculated risk for smokers who take NSAIDs is little different from the figure for NSAID takers who are non-smokers.

## Discussion

We have analysed the data from our study population to determine risk factors other than NSAIDs for peptic ulcer bleeding. The data for hospital controls are not included as hospital controls came from the acute medical intake and form an inherently sick population. Including them in the analysis of second diseases or their treatments as risk factors would have been illogical. By the same token, the use of hospital controls, whether inpatient or outpatient, is subject to unquantifiable biases which make judgement of the true weight of observed differences impossible. Although comparisons between patients with ulcer complications and population controls are clearly preferable, the operation of Berkson's bias in the patient group with a second disease being intrinsically more likely to be reported in hospital attendees<sup>13</sup> than non-attendees could still pose problems. Given the serious nature of bleeding from peptic ulcer, and the lack of any reason to suspect that such patients with associated illnesses are more likely to be admitted on clinical grounds, we think that bias through the preferential admission of patients with two diseases is unlikely.

Our data suggest that apart from a previous history of ulcer or dyspepsia, the occurrence of heart failure or diabetes as well as smoking and oral anticoagulant intake are significant accessory risk factors. We think it unlikely that information bias could account for these results. Interview times and subjects' cooperation were recorded and were not significantly different between the two groups. Recall bias is possible because current illness was self reported. For patients hospital notes were also available as potential interviewer prompts. However, for medication taken in the previous week bias is less likely as the medicines would be to hand in the home. Drug histories were also checked against GP records and found to be in substantial agreement.<sup>6</sup> Bias due to non-response in sick controls seems unlikely because control responses were high (86%), and associations detected with disease outside the gut were selective.

Diabetes and heart failure remained significant risk factors for peptic ulcer bleeding after adjustment for other underlying illnesses and other known risk factors. We know of no comparable data for diabetes. Silverstein and colleagues<sup>14</sup> found a weakly significant association between a history of heart disease and serious NSAID related upper gastrointestinal complications, a result consonant with data indicating that patients with coronary artery stents who receive both prophylactic aspirin and warfarin are at high risk of gastrointestinal bleeding compared with those receiving aspirin alone.<sup>15</sup> This appears to be the only dataset which bears on the plausible hypothesis that anticoagulant use poses material risks. One previous claim<sup>16</sup> has been of an association with calcium channel antagonist use, albeit of modest degree, with a second result showing a non-significantly

raised odds ratio of 1.2.<sup>17</sup> Our data, in agreement with others,<sup>18</sup> do not confirm this. Taken overall it seems unlikely that calcium channel antagonists pose risks. The associations we have detected with heart failure and diabetes could have arisen by chance in multiple comparative analyses, but this is unlikely because the odds ratios are reasonably substantial, and because the numbers on which estimates are based are large. Possible mechanisms include mucosal congestion or slowed hepatic drug metabolism in heart failure, and vascular disease impairing mucosal integrity in diabetes.

The association between corticosteroid treatment and ulcer disease has been variously described as a myth,<sup>19</sup> associated with a twofold increase in risk,<sup>20</sup> and most recently as only present when steroids are prescribed together with NSAIDs.<sup>9</sup> In a meta-analysis of 42 randomised studies of non-complicated ulcer, Conn and Blitzer<sup>19</sup> found no increase in risk and concluded that the association dated from anecdotal reports during the early use of ACTH and adrenocorticosteroids. In a larger meta-analysis of 71 randomised studies, Messer and colleagues<sup>20</sup> showed a relative risk for peptic ulcer haemorrhage of 2.1 (1.1–4.0) and concluded that the earlier study had failed to show an association because of small numbers, and differences in datasets included and excluded. A case control study of computerised Medicaid files<sup>9</sup> later gave a relative risk for hospitalisation for peptic ulcer of 2.0 (1.3–3.0). The risk was increased only in those who concurrently received NSAIDs. It was concluded that steroids may be more important in delaying healing of lesions caused by NSAIDs than in causing *de novo* ulceration. It is unclear why steroids should only delay the healing of NSAID induced ulcers and we believe our finding of an increased overall risk with multiplicative effects for concomitant NSAID administration is more plausible.

Alcohol consumption has long been believed to increase the chances of peptic ulcer bleeding but there is little evidence from the endoscopic era when duodenal as well as gastric ulcer could be confidently recognised. Henry *et al* found an odds ratio of 6.0 for alcohol consumption, but the comparator group appears to have been a predominantly hospital control group,<sup>4</sup> and so the conclusion is questionable. One much smaller study of ours in the past suggested no interaction with alcohol consumption,<sup>21</sup> while a second more recent study suggested that risk was raised by threefold with heavy alcohol consumption (over 80 g per day in men and 60 g per day in women).<sup>22</sup> Our questionnaire was only able to distinguish unsafe levels (>21 units a week) of beer consumption, and grouped together all subjects drinking seven units a week or more of wine or spirits. Neither high levels of beer consumption nor drinking seven units of alcohol a week or more were significant risk factors. It may be argued that if a population of heavy alcohol consumers could be identified then a raised risk might be demonstrable;

Table 5 Attributable risk associated with individual risk factors

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Aspirin or non-aspirin NSAID use	3300
Smoking	1000
Oral anticoagulants	300
Treated heart failure	475
Treated diabetes	425
Oral corticosteroids	325
Prior peptic ulcer	1900
Total*	7725

\*77% of the total 10 000 cases estimated to occur each year in those aged 60 years and over.  
NSAID, non-steroidal anti-inflammatory drug.

however, it appears that heavy alcohol consumption was not characteristic of the relatively elderly group we studied, who, in general terms, form two thirds of those admitted to hospital with ulcer bleeding in the United Kingdom.

Evidence conflicts as to whether smoking is,<sup>22</sup> or is not<sup>21</sup> an accessory factor. Previous studies have been small, and are therefore likely to be unreliable. We have, however, shown here that smoking is a weak risk factor for peptic ulcer bleeding. The lack of an apparent interaction with NSAID intake may reflect the comparative weakness of the smoking association, but raised fibrinogen levels associated with smoking<sup>23</sup> could tend to protect against an interaction increasing the risk of bleeding. Our comparator group seems likely to be representative because their level of smoking was equivalent to the 21% found in a similar age group as part of The Health Survey for England.<sup>24</sup>

Previous data, based on smaller numbers of patients, again conflict in suggesting that a history of ulcer does,<sup>22</sup> or does not<sup>21</sup> increase the risk of ulcer bleeding. Both these series were much smaller than ours. A further study is unreliable because the comparator was a hospital control.<sup>7</sup> Our results suggest that risks may be substantial, whether measured as prior history of ulcer, or as recent dyspeptic symptoms. Our data give information about the likely influence of *Helicobacter pylori* infection through any association with previous ulcer disease, but do not help directly to determine the role of *H pylori* without ulcer.

The population attributable risk (PAR) of disease depends not only on the relative risk (for which the odds ratios in these studies are close approximations), but also on the extent of exposure in the population, and from a public health perspective is at least as important as the relative risk. We have previously calculated<sup>6</sup> that about a third of an estimated 10 000 annual hospitalisations in England and Wales for peptic ulcer bleeding in those aged 60 and over are attributable to NSAID or aspirin use. Assuming that our patient and community control populations are representative we can use the data on potential risk factors in table 1 and the odds ratios in table 2 (these being adjusted for the simultaneous operation of other factors) to estimate the numbers of cases of ulcer bleeding associated with accessory risk factors.

Thus 25.9% (290) of patients had a history of previous peptic ulcer compared with 9.0% (91) of 989 community controls with an odds ratio adjusted for the operation of other factors of 3.8. Episodes associated with prior ulcer would therefore have been expected in 6.9% of patients, giving an aetiological fraction of 0.19. In the same way, the aetiological fractions associated with smoking, heart failure, diabetes, use of oral corticosteroids, and of anticoagulants can be calculated as 0.1, 0.05, 0.04, 0.03, and 0.03 respectively to give a total of 0.44. To these can be added 0.22 for prior NSAID use<sup>6</sup> and 0.11 for prophylactic aspirin use,<sup>12</sup> to give an overall total of 0.77. The remaining 20–25% has to accommodate all other known and unknown risk factors, including short term aspirin use and *H pylori* infection without ulcer. This gives some support to the contested claim that *H pylori* infection does not adversely affect the course of NSAID associated ulcer<sup>25–27</sup> because the amount of potentially unexplained disease appears limited (table 5).

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