



Systematic review: *Helicobacter pylori* and upper gastrointestinal bleeding risk in patients taking aspirin

Emma H Fletcher, Donna E Johnston, Catherine R Fisher, Roland J Koerner, Julia L Newton, Christopher S Gray

► To cite this version:

Emma H Fletcher, Donna E Johnston, Catherine R Fisher, Roland J Koerner, Julia L Newton, et al.. Systematic review: *Helicobacter pylori* and upper gastrointestinal bleeding risk in patients taking aspirin. *Alimentary Pharmacology and Therapeutics*, 2010, 32 (7), pp.831. 10.1111/j.1365-2036.2010.04415.x . hal-00559605

HAL Id: hal-00559605

<https://hal.science/hal-00559605>

Submitted on 26 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Systematic review: Helicobacter pylori and upper gastrointestinal bleeding risk in patients taking aspirin

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0374-2010.R1
Wiley - Manuscript type:	Systematic Review
Date Submitted by the Author:	24-Jun-2010
Complete List of Authors:	Fletcher, Emma; City Hospitals Sunderland NHS Foundation Trust, Stroke Research Department; Institute for Ageing and Health Johnston, Donna; City Hospitals Sunderland NHS Foundation Trust Fisher, Catherine; City Hospitals Sunderland NHS Foundation Trust Koerner, Roland; City Hospitals Sunderland NHS Foundation Trust; Newcastle Medical School, Newcastle University Newton, Julia; NIHR Biomedical Research Centre in Ageing, Newcastle University; Institute for Ageing and Health, Newcastle University Gray, Christopher; Institute for Ageing and Health, Newcastle University; City Hospitals Sunderland NHS Foundation Trust; Northern Deanery, North East Strategic Health Authority
Keywords:	H. pylori < Topics, Non-variceal bleeding < Topics, X keyword = no topic , Y keyword = no topic

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Systematic review: *Helicobacter pylori* and upper gastrointestinal bleeding risk in patients taking aspirin

EH Fletcher^{1,2}, Clinical Research Fellow. Corresponding author, e.h.fletcher@ncl.ac.uk

DE Johnston², Clinical Trials Manager

CR Fisher², Trust Librarian

RJ Koerner^{2,3}, Consultant Microbiologist, Honorary Clinical Lecturer

JL Newton^{1,4}, Clinical Professor of Ageing and Medicine

CS Gray^{1,2,5}, Postgraduate Dean and Director for Medicine and Dentistry

¹ Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne NE4 5PL, UK

² City Hospitals Sunderland NHS Foundation Trust, Kayll Road, Sunderland SR4 7TP, UK

³ Newcastle Medical School, Newcastle University, Newcastle Upon Tyne NE1 7RU, UK

⁴ NIHR Biomedical Research Centre in Ageing, Newcastle University, Newcastle upon Tyne NE1 7RU, UK

⁵ Northern Deanery, North East Strategic Health Authority, Newburn Riverside, Newcastle upon Tyne NE15 8NY, UK

Keywords: *helicobacter pylori*, aspirin, gastrointestinal haemorrhage

Running title: *H. pylori*, aspirin and upper GI bleeding risk

Systematic review: *Helicobacter pylori* and upper gastrointestinal bleeding risk in patients taking aspirin

Background Aspirin is widely used to modify the risk of recurrent vascular events. It is, however, associated with increased upper gastrointestinal bleeding (UGIB) risk. The influence of *Helicobacter pylori* on this risk is uncertain.

Aim To determine the influence of *H. pylori* on UGIB risk in patients taking aspirin.

Methods MEDLINE and EMBASE databases were searched. All studies providing data regarding *H. pylori* infection in adults taking aspirin and presenting with UGIB were included.

Results 13 studies: 1 case-control, 10 cohort studies and 2 randomised-controlled trials (RCTs). The case-control study (n=245) determined *H. pylori* to be a significant independent risk factor for UGIB. The cohort studies were heterogeneous, varying in inclusion criteria, doses and duration of aspirin used, mode of *H. pylori* testing and causative GI pathology considered. Comprising 5465 patients, *H. pylori* infection was tested for in 163 (0.03%) aspirin users with UGIB. The RCTs yielded no significant results.

Conclusions The current data is not sufficient to allow meta-analyses. The widely held belief that *H. pylori* is a risk factor for UGIB in regular aspirin users is not supported by the very limited evidence available.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Systematic review: *Helicobacter pylori* and upper gastrointestinal bleeding risk in patients taking aspirin

Introduction

Aspirin is used for a wide range of medical conditions including stroke, myocardial infarction and peripheral vascular disease. When used for the secondary prevention of occlusive vascular events it reduces the relative risk by one quarter in high risk patients¹. Aspirin, however, is not without risk. It is associated with increased intra- and extra-cranial bleeding, with gastrointestinal (GI) haemorrhage the most common life-threatening extracranial site for bleeding. Long-term maintenance doses of aspirin increases this risk by over two-fold^{2,3}.

There are other factors contributing to the risk of gastrointestinal haemorrhage in patients taking aspirin. Concurrent medications such as non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs), corticosteroids or anticoagulants increase bleeding risk⁴. In addition, advanced age is a major risk factor for complicated peptic ulcer disease. Ageing is associated with diminished epithelial cell turnover and reduced capacity to repair the gastric mucosa⁵. Prostaglandin levels in the gastric mucosa also decrease⁶. As a consequence, the integrity of the gastric mucosal surface becomes impaired and progressively susceptible to damage by factors that can overwhelm the stomach's protective barriers. Older people are therefore at higher risk of upper gastrointestinal bleeding (UGIB).

Infection with *Helicobacter pylori* is an independent risk factor for peptic ulcer disease. Although it is commonly asserted that *H. pylori* infection will increase the risk of aspirin-associated GI side effects, the current evidence for this has not been formally reviewed.

Furthermore, the impact and influence of *H. pylori* infection on the incidence of UGIB in patients taking aspirin is uncertain.

The mechanisms through which aspirin and *H. pylori* exert their gastric damage differ. Aspirin causes ulceration through both local toxic effects exposing luminal acid to the epithelial cells and, following absorption, the systemic depletion of prostaglandins which are key to promoting the stomach's defence mechanisms. In contrast, *H. pylori* survives in grooves between epithelial cells under the stomach's protective gastric mucosal layer and causes local damage by inducing inflammatory infiltration. *H. pylori* may promote gastric mucosal prostaglandin secretion by up to 50% in order to maintain its preferred environmental conditions⁷⁻⁹. Given these differences in ulcer genesis and antagonistic effects on prostaglandin synthesis, *H. pylori* and aspirin may not have a synergistic effect on ulcer formation.

Studies examining the effect of *H. pylori* infection on UGIB risk in patients taking NANSaIDs yield conflicting results. Even if *H. pylori* is contributory to the development of peptic ulcer disease in users of NANSaIDs it has been suggested that it may be protective against complications of peptic ulcer disease¹⁰.

Aspirin, through its preference for inhibiting the cyclo-oxygenase (COX)-1 enzyme, differs in its actions from other NANSaIDs. Thus, results from NANSaID studies cannot be reliably extrapolated to guide aspirin prescribing. Hence it would be valuable to ascertain the effect of *H. pylori* in this defined patient group. Identifying whether *H. pylori* is a contributory risk factor to UGIB in patients taking aspirin is therefore key to potentially minimising side-effects and improving the delivery of aspirin, and possibly other antiplatelet therapies, in future.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

A broad and inclusive literature search was undertaken for all antiplatelet therapies. Given that, however, only one study described antiplatelet therapy use other than aspirin¹¹ this systematic review focuses on determining the influence of *H. pylori* on the UGIB risk in patients taking aspirin.

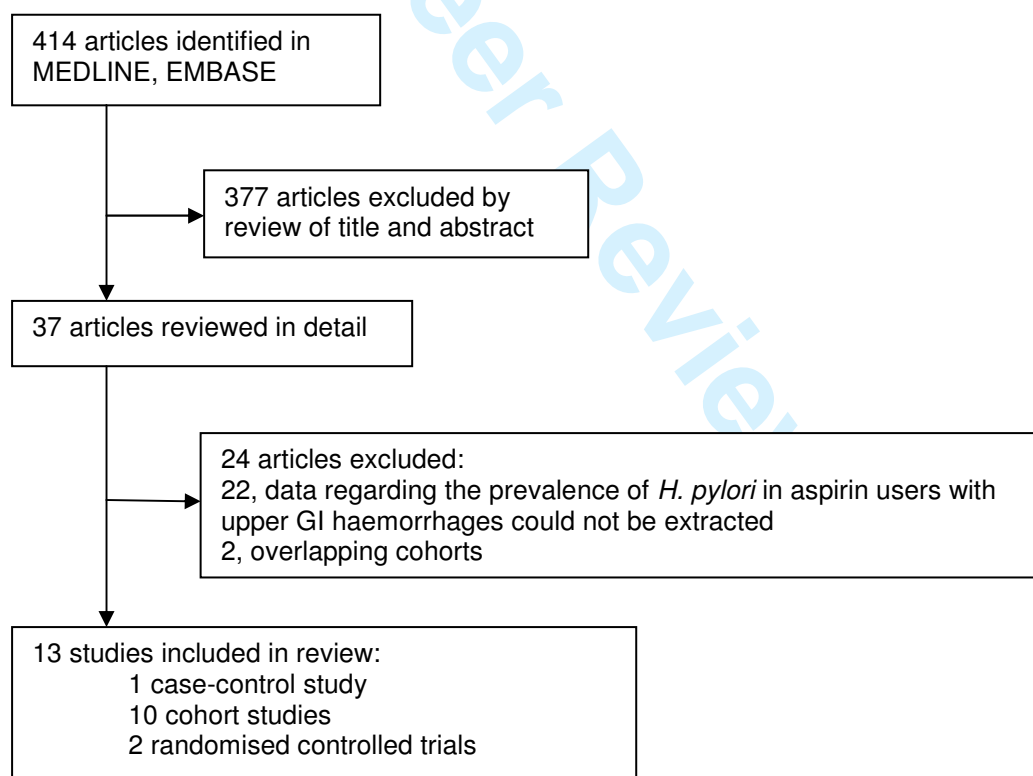
Methods

MEDLINE and EMBASE databases were searched by exploding the MESH headings ‘platelet aggregation inhibitors’, ‘aspirin’ and ‘dipyridamole’ and combining with OR. The search was performed on the 29th January 2010 and included all studies in the MEDLINE and EMBASE databases at that time. Studies with ‘clopidogrel’ were identified using this as the keyword in the title or abstract and merged with the initial search term, again using OR. For bleeding, the MESH headings ‘hemorrhage’ and ‘gastrointestinal hemorrhage’ were exploded and combined with OR. The results for bleeding and antiplatelet use were combined with AND and further combined with the results of an exploded ‘*Helicobacter pylori*’ search. The results from the two databases were merged and the duplicates filtered, leaving 414 studies for review.

At this point EF and CG independently screened the titles and abstracts for eligibility using a structured checklist with audit trail for included/excluded articles. Articles which published data referring to the routine clinical use of aspirin, the occurrence of upper GI bleeding and the testing of *H. pylori* in adult humans were sought for inclusion in the review. Articles that were not clinical trials and those not written in English were excluded. Full articles were retrieved and reviewed for all titles where abstracts were not available and for all abstracts that potentially appeared to fulfil the inclusion criteria.

37 studies were examined in detail. Of these 22 were excluded as no direct data regarding the prevalence of *H. pylori* in patients using solely aspirin (with no other NSAIDs) and the incidence of bleeding could not be extracted (Figure 1). 2 case-control studies were found to describe the same population of participants^{12,13}, with the second examining genetic factors in a smaller subcohort and therefore only the first paper is considered. 2 papers were also published on subjects recruited from overlapping cohorts^{14,15}. The more recent paper reporting the overall cohort was included in the review. Core data from eligible studies were recorded on a standard proforma for subsequent analysis.

Figure 1. Selection process for inclusion of articles in review



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Results

Our searches identified 13 studies from which the prevalence of *H. pylori* in users of aspirin presenting with UGIB could be examined. These 13 studies comprised 1 case-control study, 10 cohort studies and 2 randomised controlled trials (RCTs). In this review we describe these studies; the dose, frequency and duration of aspirin used, antisecretory therapy use and determination of *H. pylori* status across the trials.

Case control study¹²

Consecutive, current users of low-dose aspirin (LDA) admitted with UGIB were prospectively recruited from two hospital sites in North East Spain over a two year period. Inclusion criteria were: witnessed malaena/haematemesis with evidence of peptic ulceration on oesophagoduodenoscopy (OGD); and the use of LDA i.e. ≤325 mg/day, taken daily (≥5 days/wk) for at least 15 days prior to admission. Patients who were taking both LDA and NANSaIDs were excluded. Controls were LDA users, with no UGIB, matched for similar age, sex and extent of aspirin use as the cases, and were recruited from out-patient cardiology and neurology clinics.

Patients were deemed *H. pylori* positive if either the serology or urea breath test was positive. Although both tests were done in the majority of patients, 30.2% had only one test done and this was predominantly serological testing (95% of single tests). The concordance of both tests, however, was high (Table 1). The prevalence of *H. pylori* infection, according to the authors' criteria, was 89.8% in cases and 68.7%, (p=0.0001) in controls. Despite matching for age and gender, controls used anti-secretory treatment more frequently than cases. Past histories of UGIB, alcohol use and lung disease were

more common in cases (Table 2). Following logistic regression, the authors determined that *H. pylori* infection was a risk factor for ulcer bleeding in low-dose aspirin users.

Cohort studies^{11,15-23}

Ten cohort studies were examined in detail. Five recruited patients who had clinical or endoscopic evidence of UGIB. Four studies included patients who had been investigated for upper GI symptoms but one of these reported only the results of patients found to have gastric ulcers on investigation. The tenth study was a prospective cohort study of patients taking LDA for ischaemic heart disease.

H. pylori prevalence

The five cohort studies^{11,15-18} where UGIB was the inclusion criterion comprised 1353 patients in total (Table 3). The prevalence of *H. pylori* was not specified in one study and only determined in 190/238 (79.8%) patients in another. Therefore, in total, 975 patients presenting with UGIB in these studies were tested for *H. pylori*. Of these, 626 (64.2%) were positive. The number of patients using aspirin, as the only non-steroidal anti-inflammatory drug, was 230 (17.0%). However, in only 133 patients with UGIB who were taking aspirin could the prevalence of *H. pylori* be determined - 68.4% of aspirin users who presented with bleeding were *H. pylori* positive.

3209 patients were recruited to cohort studies where the inclusion criterion was upper GI symptoms¹⁹⁻²². 627 had clinical or endoscopic evidence of UGIB. 106 of these were tested for *H. pylori*, of whom 90 (84.9%) were positive. The prevalence of *H. pylori* in aspirin users, who presented with bleeding, however, could only be determined from one study. In this study, of the 6 patients with bleeding seen on endoscopy, all were taking LDA and all were *H. pylori* positive.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For the tenth study²³, where LDA use was the inclusion criterion, during the mean 45 month follow-up, 41 patients developed UGIB. 24 of these 41 (58.5%) were tested for *H. pylori* and all 24 were positive. However, 19 of the total 903 patients included in this study were taking NANSaIDs in addition to LDA, and whether the 41 patients with bleeding complications included anyone on dual therapy was not specified.

Across all the cohort studies only five provided sufficient data to determine the prevalence of *H. pylori* infection in aspirin users with UGIB. The studies have different inclusion criteria and given that only 163 aspirin users with UGIB were tested for *H. pylori* a meta-analysis is not appropriate. Furthermore it is impossible to determine bleeding risk in *H. pylori* positive patients versus *H. pylori* negative patients in those taking regular aspirin.

Aspirin dose used

For studies where the inclusion criteria were clinical or endoscopic evidence of UGIB two did not specify the dose of aspirin patients were taking (Table 4). The other three included patients taking LDA; the definition of LDA, however, was not specified in one study, was 100mg/day in a second, and less than or equal to 300mg/day in the third. Where upper GI symptoms were the principal inclusion criterion, two studies did not specify the dose of aspirin used, one used 75-300mg daily and the fourth used a range of doses which was dichotomised at the 300mg dose. In this study 9/106 (8.5%) users of aspirin <300mg/day had UGIB compared with 9/42 (21.4%) users >300mg/day had UGIB. For the LDA study, again a range of aspirin doses were used, with the majority either taking 125mg or 200mg daily. The dose of aspirin used by those patients who experienced complications with bleeding, however, was not specified.

Frequency of aspirin use

For the bleeding inclusion studies, two included patients who were taking daily aspirin, two did not specify the frequency of aspirin use and the fifth categorised aspirin use as occasional, acute or chronic (with most of these patients being only occasional users). In the GI symptom studies two did not specify the frequency of aspirin use, one stated daily aspirin use and the other divided use into acute (including as required use), and chronic. Most of the participants who had bleeding in this study were acute users of aspirin. In the LDA study all were daily users.

Duration of aspirin use

The majority of studies did not report the duration of prior aspirin use. As outlined previously, there was some indication in two studies, where use was defined as acute or chronic. In one other study the inclusion criteria specified that aspirin use had to be greater than 3 months.

Antisecretory therapy use

Concomitant antisecretory therapy use cannot be easily extracted from the published data. In the majority of studies it is not reported and where it has been, the use by patients with UGIB and those taking aspirin cannot be specifically determined.

*Determination of *H. pylori* status*

All studies used several modes of testing, either individually or in combination, to determine the *H. pylori* status of individuals and deemed the patient to be positive for the infection if any one of the tests were positive (Table 5). Five included the use of serological testing. None specified the concordance of the *H. pylori* test results but two^{11,15} did state that if the rapid urease test, culture or breath tests were negative, serological

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

testing was then performed. The number of additional patients considered to be *H. pylori* positive as a result of serological testing was not detailed.

Bleeding criteria

The ten cohort studies used a mix of clinical and endoscopic definitions for UGIB (Table 6). The pathologies found on OGD also varied. One study included only gastric ulcers, whereas the majority included both gastric and duodenal ulcers, with two of these additionally including acute gastroduodenal mucosal lesions, gastritis and oesophagitis. Three studies, however, also included bleeding which had occurred as a result of non-peptic ulcer pathologies e.g. Mallory Weiss tears and varices.

Randomised controlled trials^{24,25}

Chan *et al.*²⁴ included data on both aspirin and naproxen use but, for the purposes of this review, only the aspirin data were examined. Both RCTs were of identical design and therefore, the results have been combined. Patients diagnosed with UGIB on endoscopy and who were taking LDA and determined as *H. pylori* positive by rapid urease test or histology testing were included in the studies. 312 patients were recruited in total. At least 8 weeks of proton-pump inhibitor (PPI) treatment was prescribed to heal the ulcers and then the patients were randomly allocation to receive either eradication therapy or long-term maintenance PPI treatment (n=156 in each group). At 6 months the PPI group had 2 recurrent bleeds compared with 4 bleeds in the eradication group. One of the patients in the eradication group did however commence taking a **N**ANSAID in addition to the prescribed aspirin during the course of the study. In the study by Chan *et al.*²⁴ the group allocated to eradication treatment had a higher proportion of patient with previous

1
2
3 symptomatic ulcers (30%) and UGIB (26%) compared to the PPI treatment group, (24%
4
5 and 18% respectively).
6
7

8 9 10 Discussion

11
12 After adjusting for confounding factors such as previous UGIB, smoking and the use of
13 gastroprotective medication, the study by Lanas *et al.*¹² suggests that *H. pylori* is a
14
15 significant risk factor for UGIB in patients taking long term LDA. The prevalence of
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
The prevalence of *H. pylori* infection in the study (controls 69%) was higher than what may
be expected in a developed world sample. Average rates of *H. pylori* infection are
approximately 50% worldwide, varying from 20-40% in the developed world to over 80% in
some developing countries. It may be that higher rates are seen in this study differ from
epidemiological studies as a result of selection bias; both the cases and controls are taking
LDA for vascular disease secondary prevention. The risk factors associated with vascular
disease are more prevalent in populations with poorer socioeconomic factors – a major
risk factor the childhood contraction of *H. pylori*. Thus, participants potentially have a
higher prevalence of *H. pylori* infection compared to the standard population in that area.

With the cohort studies the prevalence of *H. pylori* in users of aspirin presenting with UGIB
varied from 62 to 100% but the total number of patients involved is small. It is also
impossible to interpret this apparently high rate of *H. pylori* infection without reference to a
control group and the data does not allow for comparative testing.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Moreover the variety of inclusion criteria, doses or duration of aspirin taken, and *H. pylori* testing used makes comparisons difficult. The inclusion of serological testing inflates the proportion of participants who are *H. pylori* positive, as seen in the case-control study, since this reflects positive results for both active and previous *H. pylori* infection. Although some studies specified this was only used in cases where *H. pylori* eradication had not previously been prescribed, it does not account for eradication through other antibiotic use or spontaneous clearance of the infection. In fact the prevalence of *H. pylori* in aspirin users with UGIB was less than that in the overall study population in two studies^{14,17} but again this involves only small numbers and is unlikely to be of statistical significance.

The aspirin dose used, varied in the studies and the doses at which bleeding occurred was not reported in all but one of the studies²¹, but this limited data is consistent with previous studies where higher doses of aspirin are associated with an increased bleeding risk²⁶.

The bleeding risk associated with acute versus chronic use is important to address, given that with chronic use the stomach may partially adapt to the local toxic effects of aspirin²⁷, and thus more acute use may be associated with increased bleeding risk. This review demonstrates, however, that current evidence cannot distinguish between the bleeding risk associated with acute or chronic aspirin use.

Although PPI treatment can reduce the incidence of UGIB with aspirin, it is associated with *Clostridium difficile* diarrhoea and more recently has been found to attenuate the antithrombotic effects of clopidogrel in some patients. Its impact on patients taking aspirin who have *H. pylori* and subsequent bleeding risk cannot be determined from this review but would be important to clarify in future.

With the inclusion of non-ulcer pathologies as a cause of UGIB in some studies the incidence of UGIB may be overestimated.

Given the heterogeneous nature of these cohort studies, and the lack of explicit data regarding *H. pylori* prevalence in aspirin users presenting with UGIB in most studies, the current available evidence is not sufficient to support a meta-analysis and thus is inadequate to allow conclusions to be drawn regarding the impact of *H. pylori* on UGIB risk in aspirin users.

The results from the randomised controlled trials are equivocal owing to their small sample size and do not guide our clinical practice further. PPI therapy reduces the risk of bleeding from peptic ulcers caused by aspirin in patients who are *H. pylori* negative²⁸. *H. pylori* is thought to impair the gastric mucosa's adaptation to long-term aspirin use, but it may also potentiate the effects of PPI therapy therefore reducing the overall bleeding risk. Its interaction with aspirin is certainly complex and poorly defined.

Unfortunately occlusive vascular disease is common. With aspirin being key to its secondary prevention, and *H. pylori* potentially one of the few modifiable risk factors for UGIB, it is essential we understand the impact of this organism on upper gastrointestinal bleeding risk in patients taking regular aspirin.

Statement of Interests

Dr Emma Fletcher was awarded the Kuck Clinical Research Training Fellowship by Research into Ageing and the British Geriatrics Society, grant number 313.

References:

- ¹ Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *British Medical Journal*. 2002;324:71-86.
- ² Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *British Medical Journal*. 1995;310(6893):827-30.
- ³ CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-39.
- ⁴ Aalykke C, Lauritsen K. Epidemiology of NSAID-related gastroduodenal mucosal injury. *Best Practice & Research Clinical Gastroenterology*. 2001;15(5):705-22.
- ⁵ Liu L, Turner JR, Yu Y, Khan AJ, Jaszewski R, Fligel SE, Majumdar AP. Differential expression of EGFR during the early reparative phase of the gastric mucosa between young and aged rats. *American Journal of Physiology*. 1998;275:G943-50
- ⁶ Cryer B, Redfern S, Goldschmidt M, Lee E, Feldman M. Effect of aging on gastric and duodenal mucosal prostaglandin concentrations in humans. *Gastroenterology* 1992;102:1118-23
- ⁷ Santolaria S, Lanas A, Benito R, Perez-Aisa MA, Montoro M, Sainz R. *Helicobacter pylori* infection is a protective factor for bleeding gastric ulcers but not for bleeding duodenal ulcers in NSAID users. *Alimentary Pharmacology & Therapeutics*. 1999;13:1511-18.
- ⁸ Hudson N, Balsitis M, Filipowicz F, Hawkey CJ. Effect of *Helicobacter pylori* colonisation on gastric mucosal eicosanoid synthesis in patients taking non-steroidal anti-inflammatory drugs. *Gut*. 1993;34:748-51.
- ⁹ Feldman M, Cryer B, Mallat D, Go MF. Role of *Helicobacter pylori* infection in gastroduodenal injury and gastric prostaglandin synthesis during long term/low dose aspirin

therapy: a prospective placebo-controlled, double-blind randomized trial. American Journal of Gastroenterology. 2001;96(6):1751-7.

¹⁰ Pilotto A, Leandro G, Di Mario F, Franceschi M, et al. Role of helicobacter pylori infection on upper gastrointestinal bleeding in the elderly: a case-control study. Digestive Diseases and Sciences. 1997;42(3):586-91

¹¹ Liu N-J, Lee C-S, Cheng J-H, et al. Outcomes of bleeding peptic ulcer: A prospective study. Journal of Gastroenterology and Hepatology. 2008;23(8):e340-e7.

¹² Lanas A, Fuentes J, Benito R, Serrano P, Bajador E, Sainz R. Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Alimentary, Pharmacology and Therapeutics. 2002;16(4):779-86.

¹³ Piazuolo E, Fuentes J, Garcia-Gonzalez MA, Jimenez P, Lanas A. A case-control study of the association between polymorphisms of the endothelial nitric oxide synthase and glycoprotein IIIa genes and upper gastrointestinal bleeding in users of low-dose aspirin. Clinical Therapeutics. 2008;30(1):121-30.

¹⁴ Ootani H, Iwakiri R, Shimoda R, et al. Role of Helicobacter pylori infection and nonsteroidal anti-inflammatory drug use in bleeding peptic ulcers in Japan. Journal of Gastroenterology. 2006;41(1):41-6.

¹⁵ Nakayama M, Iwakiri R, Hara M, et al. Low-dose aspirin is a prominent cause of bleeding ulcers in patients who underwent emergency endoscopy. Journal of Gastroenterology. 2009;44:912-8.

¹⁶ Adamopoulos A, Efsthathiou S, Tsioulos D, Tsami A, Mitromaras A, Mountokalakis T. Acute upper gastrointestinal bleeding: Comparison between recent users and nonusers of nonsteroidal anti-inflammatory drugs. Endoscopy. 2003;35(4):327-32.

- ¹⁷ Nakashima S, Arai S, Mizuno Y, et al. A clinical study of Japanese patients with ulcer induced by low-dose aspirin and other non-steroidal anti-inflammatory drugs. *Alimentary, Pharmacology and Therapeutics*. 2005;21(Suppl 2):60-6.
- ¹⁸ Tsesmeli NE, Kotsaftis PS, Savopoulos CG, et al. Incidence and etiology of acute non-malignant upper gastrointestinal bleeding in northern Greece. *Journal of Gastroenterology and Hepatology*. 2007;22:1009-13.
- ¹⁹ Ng TM, Fock KM, Khor JL, et al. Non-steroidal anti-inflammatory drugs, *Helicobacter pylori* and bleeding gastric ulcer. *Alimentary Pharmacology & Therapeutics*. 2000;14:203-9.
- ²⁰ Akhtar AJ, Shaheen M. Upper gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs in African-American and Hispanic elderly patients. *Ethnicity and Disease*. 2003;13(4):528-33.
- ²¹ Pilotto A, Franceschi M, Leandro G, et al. The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. *Aging clinical and experimental research*. 2003;15(6):494-9.
- ²² Pilotto A, Franceschi M, Leandro G, Longo MG, Perri F, Scarcelli C. *Helicobacter pylori* infection and the risk of gastro-duodenal damage in symptomatic elderly chronic low-dose aspirin users: effect of antisecretory drugs. *Age and Ageing*. 2004;33(4):402-4.
- ²³ Serrano P, Lanás A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. *Alimentary Pharmacology & Therapeutics*. 2002;16:1945-53.
- ²⁴ Chan FKL, Chung SCS, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *New England Journal of Medicine*. 2001;344(13):967-73.

- ²⁵ Dowlatshahi S, Ghofrani H, Togha M, Dowlatshahi S. Secondary prevention of upper gastrointestinal bleeding in low dose aspirin users infected with *Helicobacter pylori*. Medical Journal of the Islamic Republic of Iran. 2005;19:35-6.
- ²⁶ Campbell CL, Smyth S, Montalescot G, Steinhubl S. Aspirin Dose for the Prevention of Cardiovascular disease. JAMA. 2007;297(18):2018-24.
- ²⁷ Kawai T, Yamagishi T, Goto S. Circadian variations of gastrointestinal mucosal damage detected with transnasal endoscopy in apparently healthy subjects treated with low-dose aspirin (ASA) for a short period. Journal of Atherosclerosis and Thrombosis. 2009;16:155-63.
- ²⁸ Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. Current Medical Research and Opinion. 2007;23(1):163-73.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. H. pylori infection in cases and controls

Variable	Cases (n=98) n (%)	Controls (n=147) n (%)
H. pylori infection	88/98 (89.8)	102/147 (69.4)
Positive serology	83/96 (86.5)	93/145 (64.1)
Positive urea breath test	63/78 (80.7)	61/97 (62.9)

Table 2. Clinical characteristics

	Cases (%)	Controls (%)
PPI use	1.0	10.2
H ₂ RA use	7.1	15.6
Previous UGIB	12.2	1.4
Alcohol use	24.5	8.8
History of lung diseases	14.4	6.6
Nitrovasodilator use	19.4	33.3
Ca channel blocker use	408	27.2

PPI – proton pump inhibitor, H₂RA – H₂ receptor antagonist

Table 3. *H. pylori* infection and aspirin use in UGIB

Study n	Inclusion criteria	UGIB n (%)	<i>H. pylori</i> infection in UGIB cases n (%)	Aspirin use in UGIB cases n (%)	<i>H. pylori</i> infection in aspirin users with UGIB n (%)
Adamopoulos <i>et al.</i> ¹⁶ 330	Clinical UGIB	330 (100)	-	103 (31.2)	51/76 tested (67.1)
Nakashima <i>et al.</i> ¹⁷ 238	Bleeding PU on OGD	238 (100)	156/190 tested (82.1)	18 (7.6)	10/16 tested (62.5)
Nakayama <i>et al.</i> ¹⁵ 285	Bleeding PU on OGD	285 (100)	221 (77.5)	41 (14.4)	30 (73.2)
Tsesmeli <i>et al.</i> ¹⁸ 110	Clinical UGIB	110 (100)	32 (29.1)	23 (20.9)	-
Liu <i>et al.</i> ¹¹ 390	Bleeding PU on OGD	390 (100)	217 (55.6)	45 (11.5)	-
Ng <i>et al.</i> ¹⁹ 217	GU on OGD	100 (46.1)	84 (84.0)	21 (21.0)	-
Akhtar <i>et al.</i> ²⁰ 552	Upper GI symptoms	296 (53.6)	-	51 (17.2)	-
Pilotto <i>et al.</i> ²¹ 2251	>65 yrs, OGD*	225 (10.0)	-	8 (8.0)	-
Pilotto <i>et al.</i> ²² 189	>65 yrs, OGD*, LDA users	6 (3.2)	6 (100)	6 (100)	6 (100)
Serrano <i>et al.</i> ²³ 903	LDA use	41 (4.5)	24/24 tested (100)	41 (4.5)	24/24 tested (100)

*indication for OGD not specified

PU – peptic ulcer, GU – gastric ulcer

Table 4. Profile of aspirin use

Study	Dose of Aspirin	Frequency of Aspirin	Duration of Aspirin
Adamopoulos <i>et al.</i> ¹⁶	-	71/71 occasional (prn in previous week) 24/24 acute (reg, <1 month) 8/8 chronic (reg, >1 month)	acute vs. chronic
Nakashima <i>et al.</i> ¹⁷	LDA (not defined)	-	-
Nakayama <i>et al.</i> ¹⁵	≤300mg/day	daily	-
Tsesmeli <i>et al.</i> ¹⁸	100mg/day	daily	-
Liu <i>et al.</i> ¹¹	-	-	-
Ng <i>et al.</i> ¹⁹	-	-	-
Akhtar <i>et al.</i> ²⁰	-	-	-
Pilotto <i>et al.</i> ²¹	9/106 <300mg/day 9/42 >300mg/day	8/36 acute (prn or reg >5 days, <30 days) 10/112 chronic (reg >1 month)	acute vs. chronic
Pilotto <i>et al.</i> ²²	75-300mg/day*	daily	>3 months
Serrano <i>et al.</i> ²³	3 75mg/day*	daily	chronic
	27 100mg/day		
	341 125mg/day		
	89 150mg/day		
	416 200mg/day		
	8 250mg/day 19 325mg/day		

*doses at which bleeding occurred not specified.
Numbers in bold are those who had UGIB

Table 5. H. pylori testing

Study	Serology	Breath test	Histology	Culture	Rapid Urease Test
Adamopoulos <i>et al.</i> ¹⁶	-	-	√	√	√
Nakashima <i>et al.</i> ¹⁷	√	-	-	√	-
Nakayama <i>et al.</i> ¹⁵	√	√	-	-	√
Tsesmeli <i>et al.</i> ¹⁸	-	√	√	-	√
Liu <i>et al.</i> ¹¹	√	-	-	√	√
Ng <i>et al.</i> ¹⁹	-	-	√	√	-
Akhtar <i>et al.</i> ²⁰	√	-	Biopsies taken, test not specified		
Pilotto <i>et al.</i> ²¹	-	-	√	-	√
Pilotto <i>et al.</i> ²²	-	-	√	-	√
Serrano <i>et al.</i> ²³	√	√	√	-	√

Table 6. Bleeding diagnoses and pathologies

Study	Bleeding Diagnosis	UGI pathology
Adamopoulos <i>et al.</i> ¹⁶	Signs & symptoms of UGIB	All
Nakashima <i>et al.</i> ¹⁷	Bleeding PU on OGD	PU
Nakayama <i>et al.</i> ¹⁵	Bleeding PU on OGD	PU
Tsesmeli <i>et al.</i> ¹⁸	H/M requiring admission	All
Liu <i>et al.</i> ¹¹	Bleeding lesions on OGD	PU
Ng <i>et al.</i> ¹⁹	H/M or drop in Hb >2g/dL with raised urea or bleeding GU on OGD	GU
Akhtar <i>et al.</i> ²⁰	UGIB symptoms	All
Pilotto <i>et al.</i> ²¹	H/M or drop in Hb >3g/dL and/or bleeding lesions on OGD	PU
Pilotto <i>et al.</i> ²²	Bleeding lesions on OGD	PU/inflammation
Serrano <i>et al.</i> ²³	H/M requiring admission	PU/inflammation

H/M - Haematemesis or malaena

All - all upper GI pathologies include, for example varices and Mallory Weiss tears



PRISMA 2009 Checklist

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2,3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a



PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a
----------------------	----	---	-----

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12-14
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

Page 24 of 25



PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

For Peer Review