**Helicobacter pylori** infection and the risk of upper gastrointestinal bleeding in low dose aspirin users: systematic review and meta-analysis

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**Abstract**

**Objective:** To determine whether the risk of upper gastrointestinal bleeding in patients taking low dose aspirin (≤325 mg/day) is increased in people with *Helicobacter pylori* infections.

**Study design:** A systematic search for all publications since 1989 (when *H. pylori* was named) using search term equivalents for “upper gastrointestinal haemorrhage” and “aspirin”. Articles were assessed individually for inclusion of data on *H. pylori* infection, as not all relevant papers were indexed with this term. Data that could be pooled were then subjected to meta-analysis, using a random effects model.

**Data sources:** MEDLINE, Embase, Scopus, the Cochrane Library.

**Data synthesis:** Of 7599 retrieved publications, reports for seven case–control studies contained data suitable for meta-analysis; four were deemed high quality on the Newcastle–Ottawa scale. Upper gastrointestinal haemorrhage was more frequent in aspirin users infected with *H. pylori* than in those who were not (odds ratio [OR], 2.32; 95% CI, 1.25–4.33; P = 0.008). The heterogeneity of the studies was significant (Q = 19.3, P = 0.004; I² = 68.9%, 95% CI, 31.5–85.9%), but the pooled odds ratio was similar after removing the two studies that contributed most to heterogeneity (OR, 2.34; 95% CI, 1.56–3.53; P < 0.001). The number needed to treat to prevent one bleeding event annually was estimated to be between 100 and more than 1000.

**Conclusions:** The odds of upper gastrointestinal bleeding in patients taking low dose aspirin is about twice as great in those infected with *H. pylori*. Testing for and treating the infection should be considered in such patients, especially if their underlying risk of peptic ulcer bleeding is already high.

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**Methods**

**Search strategy**

We searched MEDLINE, PubMed, Embase, Scopus, and the Cochrane Library databases for relevant articles published to October 2017. In MEDLINE, PubMed, and the Cochrane Library, we searched for the MeSH heading “peptic ulcer hemorrhage” or the text words “peptic ulcer hemorrhage”, “peptic ulcer bleed**”, “upper gastrointestinal hemorrhage”, “upper gastrointestinal bleed*”, “stomach hemorrhage”, “stomach bleed*”, “small intestine hemorrhage”, “small intestine bleed*”, “duodenum hemorrhage”, or “duodenum bleed**”. The search results were filtered for articles indexed with the MeSH heading “aspirin” or including the text words “aspirin” or “acetylsalicylic acid”. The search was restricted to studies in humans, without language restrictions. The

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search strategy for the Scopus database and Embase (with Emtree phrases) was similar. Embase includes abstracts from major conferences as well as full articles. \textit{H. pylori} was not used as a search term because we were aware that at least one article with data suitable for meta-analysis was not indexed with this term in the databases. Consequently, a large number of articles needed to be searched individually.

Selection criteria

Articles included in the meta-analysis described original studies that reported the frequency of UGI haemorrhage separately for aspirin users who were \textit{H. pylori}-positive or -negative. Endoscopic documentation of UGI bleeding was preferred but not essential. We excluded articles without original data (reviews, editorials, guidelines); articles describing bleeding from sources other than peptic ulcers, such as gastric tumours or haemorrhagic gastritis, or concomitant treatment with NSAIDs; articles without an abstract; articles published before 1989 (when \textit{H. pylori} was named);\textsuperscript{13} and studies for which the full article was not available online.

Data extraction

The title and abstract of an article were screened for relevance before retrieving the article; its full text was then analysed to determine whether it contained data that could be pooled for meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,\textsuperscript{14} including the number of aspirin users with known \textit{H. pylori} status who had or had not experienced a UGI haemorrhage, allowing the odds ratio (OR) for the risk of UGI haemorrhage in aspirin users who were \textit{H. pylori}-positive or -negative to be calculated.

Quality assessment

The quality of case–control studies was assessed with the Newcastle–Ottawa Scale.\textsuperscript{15} This tool assesses three components of a case–control study to rank its quality on a nine-point scale: selection criteria for cases and controls; comparability of cases and controls; and methods used to assess exposure to the investigated risk factor. Articles were assessed independently by each investigator, discrepancies in individual scores discussed, and the mean score calculated. Studies scoring seven or more were deemed to be high quality studies.

Statistical analysis

The key outcome was the summary OR (with 95% confidence interval [CI]) for UGI bleeding in \textit{H. pylori}-infected vs uninfected patients, pooled across the included studies. The ORs for individual studies were calculated from the published raw data; when the required raw data were not explicitly reported, the total numbers of cases and controls who were \textit{H. pylori}-positive or -negative were calculated from other reported data for the study.

Meta-analysis summary statistics and forest plots were generated in a random effects model with MIX 2.0 Pro (https://www.meta-analysis-made-easy.com). Heterogeneity was estimated as the Q, I$^2$ and $\tau^2$ statistics. Separate sensitivity analyses excluded studies deemed to be outliers or low quality studies. Publication bias was assessed by generating a trim-and-fill plot. Number needed to treat was calculated as the reciprocal of the absolute odds reduction.

Results

Publications

Our search initially retrieved 7599 records. After excluding duplicates and articles published before 1989, the titles and abstracts of 3932 articles were screened; after excluding articles without original data and those that clearly did not meet our inclusion criteria (eg, single case reports, outcomes other than UGI bleeding, no data on \textit{H. pylori}), 225 articles were reviewed in detail, seven of which were eligible for the meta-analysis (Box 1).\textsuperscript{16,22} The PRISMA flowchart of the selection process is provided in the online Appendix, figure 1.

Study characteristics

The seven included studies were all case–control studies. They included a total of 1172 patients, 1132 of whom took low dose aspirin, defined as $\leq 325$ mg/day; the dosage for 40 patients was not reported. Cases were patients who had presented with UGI bleeding. Five of the seven studies required that UGI bleeding had been endoscopically confirmed; two did not state whether there was endoscopic evidence of UGI haemorrhage, but the context made it highly likely.\textsuperscript{16,21} Controls were age- and sex-matched, with no clinical signs of UGI haemorrhage at the time of interview. The participants were drawn from Spain, Denmark, Finland, the United Kingdom, and Japan.

Infection with \textit{H. pylori} was assessed in cases by a variety of methods (Box 1). In all studies, controls were tested with the $^{13}$C-urea breath test. The pooled prevalence of \textit{H. pylori} infection was 61.1%.

Quality assessment of studies (Newcastle–Ottawa Scale)

Four of the seven studies were of high quality (7 or more points on the Newcastle–Ottawa Scale) (Box 1). The main reasons for three studies rating lower than 7 were limited representativeness of the cases with respect to the overall population and the absence of community-based controls. There was excellent agreement between the scores given to each study by the two investigators (for discrimination of high quality studies: $\kappa = 1.00$; $r = 0.93$, $P = 0.002$).

Meta-analysis

All studies reported sufficient data to allow ORs to be calculated for UGI haemorrhage in aspirin users according to \textit{H. pylori} status. Six of the seven provided raw numbers for each category;\textsuperscript{16,18-22} one reported only the crude OR for association between \textit{H. pylori} infection and bleeding peptic ulcers in aspirin users,\textsuperscript{17} so we calculated numbers of cases and controls from the published OR and the total numbers in each group.

The pooled effect size in the meta-analysis indicated that UGI bleeding was almost two-and-one-half times as frequent in \textit{H. pylori}-positive patients taking aspirin as in \textit{H. pylori}-negative patients (OR, 2.32; 95% CI, 1.25–4.33; $P = 0.008$) (Box 2). The heterogeneity of the included studies was significant ($Q = 19.3$, $P = 0.004$; $I^2 = 68.9\%$ [95% CI, 31.5–85.9%]; $\tau^2 = 0.43$ [95% CI, 0.09–1.19]). Two studies were deemed outliers.\textsuperscript{20,21} (Box 3). A Baujat plot (online Appendix, figure 2) indicated that the Shiotani study\textsuperscript{21} made the greatest contribution to the Q statistic and summary OR.

A trim-and-fill plot generated to assess the likelihood of publication bias suggested that three negative studies might be missing, one of lower precision and two studies of higher precision (online Appendix, figure 3).

Sensitivity analyses

In the first sensitivity analysis, we recalculated the pooled effect size for meta-analyses from which the two outliers in the
### 1 Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Cases: inclusion criteria</th>
<th>Controls: matched factors</th>
<th>Aspirin dosage</th>
<th>H. pylori testing</th>
<th>Concomitant medications</th>
<th>Mean NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cullen et al., 1997</strong></td>
<td>16</td>
<td>Peptic ulcer bleeding</td>
<td>Age, sex</td>
<td>Not specified</td>
<td>Serology</td>
<td>Not reported</td>
<td>6</td>
</tr>
<tr>
<td><strong>Aalykke et al., 1999</strong></td>
<td>17</td>
<td>Endoscopy-verified peptic ulcers as source of bleeding</td>
<td>Age (10-year bands), sex; no signs of ulcer bleeding at interview</td>
<td>Cases: ≥ 1 DDD in week prior to UGI bleeding; low dose aspirin: ≤ 7 DDDs/week</td>
<td>Serology or ¹³C-urea breath test</td>
<td>Not reported</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Santolaria et al., 1999</strong></td>
<td>18</td>
<td>Endoscopy-verified peptic ulcer bleeding (gastric or duodenal mucosal break ≥ 5 mm diameter)</td>
<td>Age (5-year bands), sex; no signs of upper gastrointestinal haemorrhage at interview</td>
<td>&lt; 300 mg/day</td>
<td>Cases: histology, urease test; ¹³C-urea breath test if negative. Controls: ¹³C-urea breath test</td>
<td>NSAIDs (some cases and controls)</td>
<td>7.25</td>
</tr>
<tr>
<td><strong>Lanas et al., 2002</strong></td>
<td>19</td>
<td>Endoscopy-verified upper gastrointestinal haemorrhage</td>
<td>Age (5-year bands), sex, aspirin use; no signs of ulcer bleeding at interview</td>
<td>≤ 325 mg/day for at least 15 days prior to bleeding episode (similar for cases and controls)</td>
<td>Serology or ¹³C-urea breath test</td>
<td>Antisecretory drugs, nitrovasodilators, calcium channel blockers (some cases and controls)</td>
<td>8.5</td>
</tr>
<tr>
<td><strong>Udd et al., 2007</strong></td>
<td>20</td>
<td>Endoscopy-verified peptic ulcer bleeding</td>
<td>Age (5-year bands), sex; patients without ulcers having elective endoscopy to investigate dyspepsia</td>
<td>50–250 mg/day</td>
<td>Histology, urease test</td>
<td>Warfarin (some cases and controls)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Shiotani et al., 2014</strong></td>
<td>21</td>
<td>Peptic ulcer bleeding</td>
<td>Not matched</td>
<td>100 mg enteric coated aspirin daily</td>
<td>Serology</td>
<td>NSAIDs, antisecretory drugs, β-blockers, calcium channel blockers, ARBs/ACEIs, statins, nitrates</td>
<td>5.75</td>
</tr>
<tr>
<td><strong>Sostres et al., 2015</strong></td>
<td>22</td>
<td>Endoscopy-verified peptic ulcer bleeding</td>
<td>Age (5-year bands), sex</td>
<td>≤ 300 mg/day</td>
<td>Serology</td>
<td>Proton pump inhibitors, anticoagulants (some cases and controls)</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**Notes:**
- ARBs/ACEIs = angiotensin receptor blockers/angiotensin-converting enzyme inhibitors; DDD = defined daily dose (150 mg); NOS = Newcastle–Ottawa Scale; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation; UGI = upper gastrointestinal.
heterogeneity plot were sequentially removed. Removing the Udd study resulted in a pooled OR of 1.94 (95% CI, 1.13–3.35, \(P = 0.016\)) and less heterogeneity (\(Q = 13.0, P = 0.024; I^2 = 61.4\% [95\% CI, 5.9–84.2\%]; \(r^2 = 0.27 [95\% CI, 0.01–0.89]\)). Removing the Shiotani study resulted in a pooled OR of 2.81 (95% CI, 1.59–4.97; \(P < 0.001\)) and heterogeneity was no longer statistically significant (\(Q = 9.85, P = 0.08; I^2 = 13.6\% [95\% CI, 0–79.8\%]; \(r^2 = 0.23 [95\% CI, 0–0.93]\)). Removing both studies produced a pooled OR of 2.34 (95% CI, 1.56–3.53; \(P < 0.001\)), and heterogeneity was not statistically significant (\(Q = 4.63, P = 0.33; I^2 = 13.6\% [95\% CI, 0–82.0\%]; \(r^2 = 0.03 [95\% CI, 0–0.96]\)).

The second sensitivity analysis included only higher quality studies (7 or more points on the Newcastle–Ottawa scale); the summary OR was 2.41 (95% CI, 1.46–3.96; \(P < 0.001\)), similar to the result when all studies were pooled.

**Number needed to treat**

The incidence of UGI bleeding in people taking low dose aspirin is 0.1–1 events per 100 patient-years. Applying our finding that the incidence of bleeding among patients with \(H. pylori\) infections was approximately double that for uninfected people, the number needed to treat to prevent one bleeding event annually ranges between 100 and more than 1000.

**Discussion**

Our meta-analysis indicates that the proportion of \(H. pylori\)-positive patients taking low dose aspirin who have UGI haemorrhages is greater than that for low dose aspirin users who are \(H. pylori\)-negative. For only one of the eligible studies was the OR less than 1, and its 95% CI included unity; the other six studies had ORs between 1.6 and 40. Two sensitivity analyses (omitting two outlier studies in the heterogeneity plot or three studies of lower quality on the Newcastle–Ottawa Scale) each yielded similar estimates of the increased frequency of UGI bleeding associated with \(H. pylori\) infection. The magnitude of the effect is moderate (OR, 2.32), slightly larger than the OR of 1.67 (95% CI, 1.59–4.97).
bleeding in aspirin users. Most of the articles providing relevant data did not pursue this question as their primary aim, and the data often needed to be extracted from their results sections, perhaps explaining why a meta-analysis was not undertaken earlier. However, the most relevant studies were of high quality. A further strength is that the results of our sensitivity analyses increased our confidence in those of the main analysis.

Limitations include the fact that positive *H. pylori* serology results do not necessarily indicate a current infection. The antibody titre falls gradually after successful treatment; about 50% of treated patients will return a negative test result by 12 months, but in 50% the antibody titre falls more slowly. If patients in the included studies had been treated for *H. pylori* infection very recently, they may have been incorrectly assigned to *H. pylori*-positive groups, and we will have underestimated the strength of the association between *H. pylori* infection and UGI bleeding. Another limitation is that the data were derived from observational case–control studies, so that comparability of groups cannot be assured and unrecognised confounders may have influenced outcomes. A controlled trial in which patients infected with *H. pylori* are randomised to treatment or placebo before commencing aspirin would minimise this risk. Trials of this type have not been reported, and may even be unethical, as there is evidence that *H. pylori* is a class I carcinogen and causes non-NSAID-linked peptic ulcers; most practitioners would institute treatment as soon as a patient was known to carry the organism.

**Conclusion**

Despite these limitations, the consistency of our results (after sensitivity analyses) indicates that the likelihood of UGI haemorrhage in patients taking low dose aspirin is more than twice as high for those with *H. pylori* infections. The cost–benefit balance of testing for and treating the bacterium may be insufficient to permit recommending this approach for all patients receiving aspirin on a long term basis. However, the evidence is sufficient to warrant considering eradication of the infection in patients who are at high risk of ulcer complications because of comorbid conditions.

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