

# Histamine H<sub>2</sub> receptor antagonists for decreasing gastrointestinal harms in adults using acetylsalicylic acid: systematic review and meta-analysis

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## ABSTRACT

**Background:** It is unclear if histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers) prevent a variety of gastrointestinal harms among patients taking acetylsalicylic acid (ASA) over long periods.

**Methods:** Electronic databases (e.g., MEDLINE, Embase and Cochrane Central Register of Controlled Trials; from inception to November 2010) and reference lists of retrieved articles were searched. Randomized placebo-controlled trials (RCTs) assessing the efficacy of H<sub>2</sub> blockers in reducing gastrointestinal harms (bleeding, ulcers) among adults taking ASA for 2 weeks or longer were included. Two reviewers independently abstracted study and patient characteristics and appraised study quality using the Cochrane risk-of-bias tool. Peto odds ratio (OR) meta-analysis was performed, 95% confidence intervals (CIs) were calculated, and statistical heterogeneity was assessed using the  $I^2$  and  $\chi^2$  statistics.

**Results:** Six RCTs (4 major publications and 2 companion reports) with a total of 498 participants (healthy volunteers or patients with arthritis, cardiovascular or cerebrovascular disease, or diabetes mellitus) were included. One trial adequately reported allocation concealment and sequence generation, with the other 3 trials being judged as unclear for both aspects. In one RCT, no statistically significant differences for gastrointestinal hemorrhage requiring admission to hospital ( $p = 0.14$ ) or blood transfusion ( $p = 0.29$ ) were observed between the group receiving concomitant famotidine and ASA and the group receiving concomitant placebo and ASA. After a median of 8 weeks' follow-up, H<sub>2</sub> blockers were more effective than placebo in reducing gastrointestinal hemorrhage (2 RCTs, total of 447 patients, OR 0.07, 95% CI 0.02–0.23) and peptic ulcers (3 RCTs, total of 465 patients, OR 0.21, 95% CI 0.12–0.36) among patients taking ASA for 2 weeks or longer. Despite substantial clinical heterogeneity across the studies, including types of H<sub>2</sub> blockers, dosing of ASA and underlying conditions, no statistical heterogeneity was observed.

**Interpretation:** H<sub>2</sub> blockers reduced gastrointestinal harm among patients taking ASA for 2 weeks or longer. These results should be interpreted with caution, because of the small number of studies identified for inclusion.

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➤ **ACETYLSALICYLIC ACID (ASA) IS ONE OF THE MOST** widely used medications in the world.<sup>1</sup> It is recommended for use by patients with high-risk vascular conditions because of its antiplatelet effects.<sup>2–8</sup> According to surveys, more than 85% of physicians prescribe ASA after myocardial infarction.<sup>9,10</sup> ASA also has analgesic, antipyretic and anti-inflammatory properties. It is often prescribed for patients with migraine,<sup>11</sup> acute pain,<sup>12</sup> osteoarthritis<sup>13</sup> or postoperative pain.<sup>14</sup>

Prolonged use of ASA is associated with various harms, including dyspepsia, gastrointestinal mucosal injury and bleeding, especially among elderly patients.<sup>15</sup> Commonly used medications for reducing the gastrointestinal harms associated with prolonged use of ASA include prostaglandin analogues, histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers) and proton pump inhibitors. H<sub>2</sub> blockers were chosen as the focus of this systematic review because adverse events have been reported for other agents, including prostaglandin analogues<sup>16</sup> and proton pump inhibitors.<sup>17–19</sup> Furthermore, H<sub>2</sub> blockers have been found to be more cost-effective than other agents (e.g., proton pump inhibitors)<sup>20</sup> and, although their use has decreased over time, they are still widely used to provide gastroprotection in drug utilization studies.<sup>21,22</sup>

It is unclear if H<sub>2</sub> blockers prevent various gastrointestinal harms among patients taking ASA over long periods of time. Given that H<sub>2</sub> blockers are used for treating acid-related gastrointestinal conditions, including dyspepsia, peptic ulcer disease and gastroesophageal reflux, they might also be useful for preventing ASA-induced gastrointestinal adverse events. We aimed to evaluate the role of H<sub>2</sub> blockers administered concomitantly with ASA in decreasing gastrointestinal harm.

## Methods

A systematic review protocol was used to guide our review and is available upon request. Reporting of the systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.<sup>23</sup>

**Eligibility criteria.** Patients eligible for inclusion were adults (aged ≥ 18 years) who used H<sub>2</sub> blockers concurrently with ASA for at least 2 continuous weeks. We included randomized placebo-controlled trials (RCTs) and quasi-RCTs reporting the incidence of gastrointestinal hemorrhage requiring transfusion or admission to hospital, hemorrhage identified by endoscopy, ulcers or dyspepsia. Studies were included regardless of the patient's medical condition and comorbidities. Only studies published in English were included.

**Information sources.** Medical Subject Headings and text words related to use of H<sub>2</sub> blockers (e.g., ranitidine, cimetidine, famotidine) by adults taking ASA were used to search MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials. All databases were searched from inception until November 2010. The database search was supplemented by searching a clinical trial registry (MetaRegister),<sup>24</sup> the reference lists of included studies and the authors' personal files, and by contacting experts in H<sub>2</sub> blockers. In addition, studies included in the review were entered into the "related citations" function of PubMed to identify additional studies. Search strategy. The search strategy for the main electronic search (MEDLINE) is presented in Appendix A; details for the other searches are available from the authors on request.

**Study selection.** Two independent reviewers (AA, MT) used a predefined relevance criteria form to screen the studies identified by the search and then obtained the full text of potentially relevant articles and screened them for inclusion. Discrepancies at any stage were resolved by discussion or the involvement of a third reviewer (ACT). The level of agreement during screening was assessed using a kappa statistic.<sup>25</sup> We determined a priori that an acceptable level of agreement would be at least 0.60.

**Data collection.** A draft data extraction form was developed, piloted and modified as necessary. The 2 reviewers (AA, MT) independently extracted all of the data using the standardized data extraction form, and data extraction was verified by the third reviewer (ACT). When multiple study publications reported data from the same population (i.e., companion reports), the trial reporting the primary outcome of interest was considered the major publication, and the other report or reports were used for supplementary data. Companion reports were identified by examining the date when the study was conducted, the list of study authors and the number of patients. When it was unclear whether studies were companion reports, the corresponding author was contacted by email for clarification. If the included study was a crossover RCT, only data for the first period (before the crossover) were abstracted.

**Data items.** The extracted data included study characteristics (e.g., study period, sample size, trial arms, setting), participant characteristics (e.g., population, medical condition, mean age, sex) and results for the primary and secondary outcomes.

The primary outcome of interest was the incidence of clinically relevant bleeding, defined as major hemorrhage requiring transfusion or admission to hospital. Secondary outcomes were the incidence of gastrointestinal hemorrhage (defined as bleeding observed on endoscopy), fecal blood loss, ulcers (categorized as peptic ulcers overall and subdivided by duodenal and gastric ulcers), dyspepsia and H<sub>2</sub>-blocker-related harms.

**Risk of bias.** The risk of bias in individual studies was assessed using the Cochrane Risk of Bias tool.<sup>26</sup> This tool consists of 7 items pertaining to selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other sources of bias. Although source of funding is not considered in the current Cochrane guidance on assessing risk of bias,<sup>26</sup> there is some evidence to suggest that this factor may be a potential “other” source of bias.<sup>27</sup> As such, this item was also assessed. The 2 reviewers (AA, MT) assessed study quality independently, and the assessments were verified by the third reviewer (ACT).

**Statistical analysis.** The studies were presented in forest plots to examine heterogeneity visually. Statistical heterogeneity was examined using the  $I_2$  and  $\chi^2$  statistics.<sup>28</sup> Peto odds ratios (ORs) were calculated, as few patients and events were included in the studies.<sup>26</sup> Ninety-five percent confidence intervals (CIs) were derived on the basis of a normal distribution. All analyses were conducted in Review Manager Version 5.<sup>26</sup>

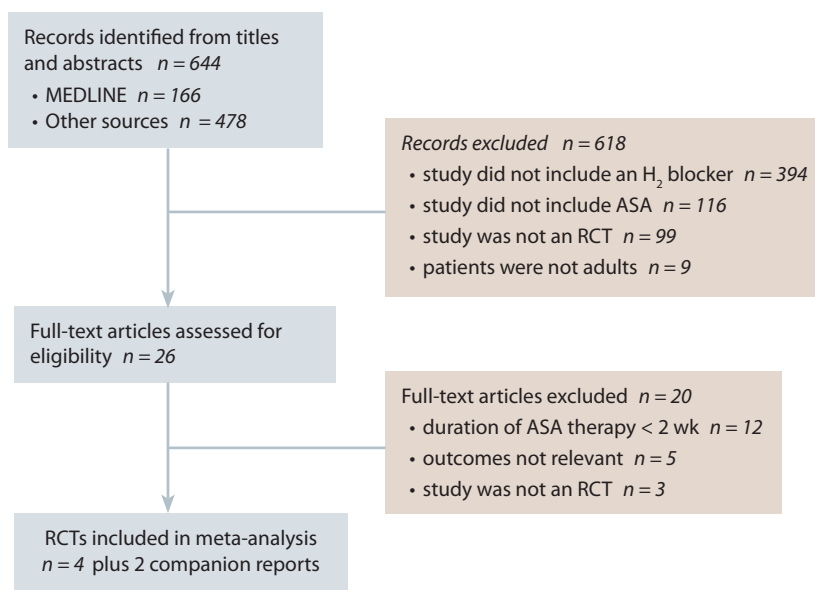
## Results

**Study selection.** The literature search yielded 644 citations (i.e., titles and abstracts; Figure 1). Of these, 394 citations were excluded because they did not examine H<sub>2</sub> blockers, 116 because ASA was not the comparator, 99 because they were not RCTs and 9 because study participants were not adults. Twenty-six full-text articles were retrieved and examined for relevance. Of these, 12 articles were excluded because they examined ASA use for less than 2 weeks, 5 because they did not examine relevant outcomes and 3 because they were not RCTs. Four RCTs fulfilled the inclusion criteria.<sup>29–32</sup> One of the RCTs<sup>32</sup> had

2 companion reports,<sup>33,34</sup> which were used for supplemental data only. At level 1 screening, the level of agreement between the 2 reviewers was acceptable (kappa = 0.60, 95% CI 0.41–0.72).

**Study and patient characteristics.** All of the included studies were RCTs published between 1978 and 2009 in the United States or the United Kingdom (Table 1). The number of participants ranged from 18 to 404 and the duration of follow-up from 4 weeks to 12 weeks. The H<sub>2</sub> blockers examined were ranitidine, cimetidine and famotidine, at doses ranging from 40 to 1200 mg/day. The ASA dosage ranged from low (75 mg/day) to high (3900 mg/day).

The patient populations varied across the included RCTs (Table 2). One RCT included only healthy adults,<sup>31</sup> 2 RCTs included patients with rheumatic diseases,<sup>29,30</sup> and 1 RCT included patients with cardiovascular disease, cerebrovascular disease or diabetes mellitus.<sup>32</sup> In all of the studies, endoscopy was performed before and after ASA use. The results of pre-ASA endoscopy were used to determine participants' eligibility for inclusion in several studies: more specifically, 1 RCT included only patients without mucosal injury,<sup>31</sup> 2 RCTs included patients with ulcers or sores,<sup>30,32</sup> and 2 RCTs excluded patients with ulcers or bleeds.<sup>31,32</sup> Only one of the included studies reported the time for which patients had been taking ASA, which had to be at least 1 month before entry into the trial.<sup>30</sup>



**Figure 1** Identification of randomized controlled trials (RCTs) for inclusion in a meta-analysis of histamine H<sub>2</sub> receptor antagonists to reduce the gastrointestinal adverse effects of acetylsalicylic acid (ASA) therapy.

**Risk of bias.** One of the included RCTs<sup>32</sup> adequately generated the random sequence and adequately concealed the allocation sequence (Table 3); the other 3 studies were judged unclear on these items. Blinding of participants and personnel was deemed adequate in all 4 RCTs, but blinding of outcome assessment was adequate in only 2 RCTs<sup>29,32</sup> (judged as unclear in the other 2 RCTs<sup>30,31</sup>). Two RCTs adequately addressed incomplete outcome

data,<sup>30,32</sup> whereas the other 2 RCTs were judged as having high risk of bias for this item.<sup>29,31</sup> Selective outcome reporting was deemed unclear in 3 of the RCTs,<sup>29,31,32</sup> with 1 trial being judged as having high risk of bias for this item.<sup>30</sup> Only 1 RCT was free of other types of bias,<sup>30</sup> with the other 3 being judged unclear because of funding from private industry.<sup>29,31,32</sup>

**Table 1**  
**Study characteristics**

| Reference  | Type of trial  | Total no. of patients | Setting  | Duration of trial, wk* | Trial arms (daily dose, mg)  |
|--|----------------|-----------------------|--|------------------------|--|
| Welch et al. <sup>29</sup> (1978)  | Crossover RCT† | 26                    | Rheumatology clinics, University of Texas Health Science Center at San Antonio, USA  | 8                      | Cimetidine (1200) + ASA (2600–3900); placebo + ASA (2600–3900)   |
| O’Laughlin et al. <sup>30</sup> (1982)                                   | RCT            | 18                    | Rheumatology clinics and general medicine wards at the Harry S. Truman Memorial Veterans Hospital and the University of Missouri Medical Center, USA | 8                      | Cimetidine (1200) + antacids (Maalox 300 mL, prn) + ASA (2600); placebo + antacids (Maalox 300 mL, prn) + ASA (2600) |
| Berkowitz et al. <sup>31</sup> (1987)                                    | RCT            | 50                    | Unspecified hospital, USA  | 4                      | Ranitidine (300) + ASA (2600); placebo + ASA (2600)  |
| Taha et al. <sup>32</sup> (2009) plus companion reports <sup>33,34</sup> | RCT            |                       | Gastroenterology Unit, Crosshouse Hospital, University of Glasgow, Kilmarnock, UK  | 12                     | Famotidine (40) + ASA (75–325); placebo + ASA (75–325)   |

ASA = aspirin, prn = *pro re nata* (as required), RCT = randomized controlled trial.

\*In all studies, the longest duration of follow-up was the same as the overall duration of the trial.

†Data from this crossover RCT were abstracted before the crossover stage, to make the data consistent with data from the other RCTs.

**Table 2**  
**Patient characteristics**

| Reference   | No. of patients              | Medical reason for ASA                                       | Sex, % male | Age, yr  | Endoscopy before and after ASA | Mucosal inclusion criteria                                   | Exclusion of patients with ulcers or bleeds    |
|---|------------------------------|--|-------------|--|--------------------------------|--|--|
| Welch et al. <sup>29</sup>  | 26 (22 included in analysis) | RA or degenerative joint disease                             | NR          | NR   | Yes                            | NR   | No   |
| O’Laughlin et al. <sup>30</sup>                                   | 18 (ITT analysis)            | Rheumatic disease  | NR          | NR   | Yes                            | Patients with confirmed gastric ulcer included               | No   |
| Berkowitz et al. <sup>31</sup>                                    | 50 (43 included in analysis) | None   | 100         | Ranitidine mean 28.5 (SE 2.2), placebo mean 26.2 (SE 2.0), overall range 18–57 | Yes                            | Patients with no abnormality included                        | Yes  |
| Taha et al. <sup>32</sup> plus companion reports <sup>33,34</sup> | 404 (ITT analysis)           | Diabetes mellitus, cardiovascular or cerebrovascular disease | 68.6        | Famotidine median 63 (range 36–86), placebo median 63 (range 37–86)            | Yes                            | Patients with gastric or duodenal scars or erosions included | Yes (patients with scars or erosions included) |

ASA = acetylsalicylic acid, ITT = intention-to-treat, NR = not reported, RA = rheumatoid arthritis, SE = standard error.

**Meta-analysis results for primary outcome.** Only one study reported gastrointestinal hemorrhage requiring admission to hospital (relative risk 0.11, 95% CI 0.01–2.01,  $p = 0.14$ ) and gastrointestinal hemorrhage requiring blood transfusion (relative risk 0.20, 95% CI 0.01–4.06,  $p = 0.29$ ).<sup>32</sup> Neither outcome was statistically significant for the comparison between patients receiving famotidine plus ASA and those receiving placebo plus ASA.

**Meta-analysis results for secondary outcomes.** Two studies reported gastrointestinal hemorrhage as confirmed by endoscopy.<sup>31,32</sup> After a median of 8 weeks' follow-up, patients who received an H<sub>2</sub> blocker were significantly less likely to experience gastrointestinal hemorrhage than those who received placebo ( $n = 2$  RCTs, 447 patients, OR 0.07, 95% CI 0.02–0.23; Figure 2).<sup>31,32</sup> This means that patients who took placebo had 14.3 times greater odds of experiencing gastrointestinal hemorrhage observed by endoscopy as patients who took H<sub>2</sub> blockers. Both of these studies examined low doses of H<sub>2</sub> blockers ( $\leq 300$  mg/day), in conjunction with either a low dose of ASA (up to 325 mg/day)<sup>32</sup> or a high dose of ASA (2600 mg/day).<sup>31</sup> Furthermore, one of the studies included healthy adults,<sup>31</sup> whereas the other included patients with cardiovascular disease, cerebrovascular disease or diabetes.<sup>32</sup> One study excluded patients with mucosal inclusion, ulcers or bleeds,<sup>31</sup> and the other study included patients with gastric or duodenal scars or erosions but also excluded patients with ulcers or bleeds.<sup>32</sup> Despite this clinical heterogeneity between the studies, statistical heterogeneity was not observed ( $\chi^2 = 0.47$ ,  $df = 1$ ,  $p = 0.49$ ,  $I^2 = 0\%$ ). The results of these 2 studies were consistent, despite the long interval between them (the first being conducted in the 1980s<sup>31</sup> and the second in the 2000s<sup>32</sup>). We were unable to perform a sensitivity analysis to explore the clinical heterogeneity, as only 2 studies were included in this analysis.

One RCT reported fecal blood loss.<sup>29</sup> In that study, patients receiving cimetidine experienced significantly less blood loss than those receiving placebo (mean  $\pm$  standard deviation 4.1  $\pm$  0.3 mL/day v. 2.2  $\pm$  0.3 mL/day).<sup>29</sup>

After a median of 8 weeks' follow-up, H<sub>2</sub> blockers were effective in reducing the incidence of peptic ulcers ( $n = 3$  RCTs, 465 patients, OR 0.21, 95% CI 0.12–0.36) (Figure 3).<sup>30–32</sup> Two of the RCTs examined low doses of H<sub>2</sub> blockers ( $\leq 300$  mg/day),<sup>31,32</sup> and the third examined a high dose of H<sub>2</sub> blockers (1200 mg/day).<sup>30</sup> One of the RCTs examined low doses of ASA (75–325 mg/day),<sup>32</sup> and the others examined a high dose of ASA (2600 mg/day).<sup>30,31</sup> Furthermore, the patients ranged from healthy adults<sup>31</sup> to patients with rheumatic disease<sup>30</sup> and those with cardiovascular disease, cerebrovascular disease or diabetes.<sup>32</sup> Results were consistent between one of the RCTs conducted in the 1980s<sup>31</sup> and the most recent RCT,<sup>32</sup> but the results of these 2 studies were inconsistent with the results of the other older RCT.<sup>30</sup> No statistical heterogeneity was observed ( $\chi^2 = 1.79$ ,  $df = 2$ ,  $p = 0.41$ ,  $I^2 = 0\%$ ).

Two of the studies excluded patients with ulcers or bleeds,<sup>31,32</sup> and the other 2 studies included such patients.<sup>29,30</sup> A sensitivity analysis was conducted to examine the effects of including patients with ulcers or bleeds on the meta-analysis results. The results were unchanged when the meta-analysis was conducted with only the 2 studies that excluded ulcers (OR 0.19, 95% CI 0.11–0.33,  $I^2 = 0\%$ ).<sup>31,32</sup>

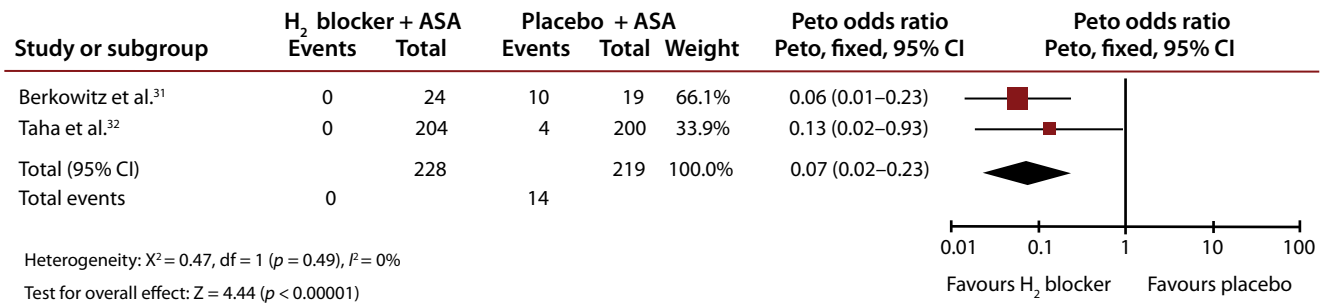
One RCT reported no statistically significant changes observed by endoscopy between the placebo and cimetidine groups ( $p = 0.06$ ).<sup>29</sup> The study did not report the number of ulcers that did (or did not) occur, so it was not included in any of the meta-analyses.<sup>29</sup> Another study reported gastric ulcers, which occurred less frequently in the group receiving famotidine than in the placebo group ( $p = 0.002$ ).<sup>32</sup>

Table 3

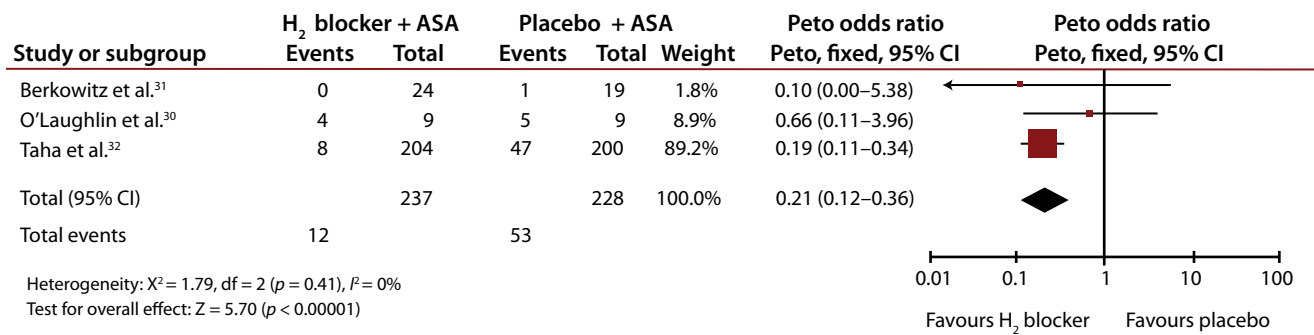
**Results of assessment of risk of bias,\* based on Cochrane risk-of-bias tool<sup>26</sup>**

| Reference                       | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|---------------------------------|----------------------------|------------------------|--|--------------------------------|-----------------------------------|-----------------------------|--------------------|
| Welch et al. <sup>29</sup>      | Unclear                    | Unclear                | Low                                    | Low                            | High                              | Unclear                     | Unclear            |
| O'Laughlin et al. <sup>30</sup> | Unclear                    | Unclear                | Low                                    | Unclear                        | Low                               | High                        | Low                |
| Berkowitz et al. <sup>31</sup>  | Unclear                    | Unclear                | Low                                    | Unclear                        | High                              | Unclear                     | Unclear            |
| Taha et al. <sup>32</sup>       | Low                        | Low                    | Low                                    | Low                            | Low                               | Unclear                     | Unclear            |

\*Assessments are presented in terms of the risk of bias associated with each item.



**Figure 2**  
**Meta-analysis of 2 randomized controlled trials of histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers) in conjunction with acetylsalicylic acid (ASA) therapy for outcome of gastrointestinal bleeding.** CI = confidence interval, OR = odds ratio.



**Figure 3**  
**Meta-analysis of 3 randomized controlled trials of histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers) in conjunction with acetylsalicylic acid (ASA) therapy for outcome of peptic ulcer.** CI = confidence interval, OR = odds ratio.

One of the included studies reported the proportion of patients experiencing dyspepsia, yet few patients experienced this outcome ( $n = 4$ ), and this result was not reported per treatment group.<sup>29</sup> None of the other included studies reported data on dyspepsia.

**Harms related to H<sub>2</sub> blockers.** One RCT reported adverse events,<sup>31</sup> but no events were observed among patients receiving ASA plus H<sub>2</sub> blockers or among those taking ASA plus placebo. In another RCT, fewer harms occurred in the famotidine group than in the placebo group (9 v. 15); all of these harms were judged as being not related to H<sub>2</sub> blockers.<sup>32</sup>

**Interpretation**

ASA is one of the drugs most commonly prescribed to patients, and the gastrointestinal harm associated with its prolonged use is well known. A recent systematic review found that 109 major cardiovascular events were prevented for every 10 000 patients with diabetes who were treated with ASA, at the expense of 19 major bleeding events.<sup>35</sup> We found that H<sub>2</sub> blockers were effective in

reducing gastrointestinal bleeding and peptic ulcers, which suggests that these agents should be considered for adults who will be taking ASA for 2 weeks or more. Only one of the included studies reported the proportion of patients experiencing dyspepsia, so we were unable to assess this outcome.

Given that ASA is such a common drug and its adverse effects are well known, the dearth of studies identified in the literature search was surprising. The number of studies meeting our inclusion criteria may have been low because most of the research in this area has focused on other agents, such as proton pump inhibitors and misoprostol or on nonsteroidal anti-inflammatory drugs (NSAIDs) other than ASA. Indeed, a recent Cochrane review on a similar topic found double the number of studies comparing misoprostol and H<sub>2</sub> blockers among patients concurrently taking a variety of NSAIDs.<sup>16</sup> However, in the Cochrane review,<sup>16</sup> the differences among the H<sub>2</sub> blockers were unclear. Future reviews should examine these differences to determine if there is a class effect or if one of the agents is superior to the others agents. This question could be addressed through indirect

comparisons meta-analysis (or network meta-analysis), as few head-to-head trials have been performed. Another issue to be taken into consideration in future reviews is the cost of H<sub>2</sub> blockers, given that a recent cost-effectiveness analysis found that starting with antacids and H<sub>2</sub> blockers was more cost-effective than starting with proton pump inhibitors and moving on to H<sub>2</sub> blockers and antacids.<sup>20</sup>

Although our review was more focused, we included other important outcomes, such as gastrointestinal hemorrhage requiring admission to hospital, gastrointestinal hemorrhage requiring blood transfusion and gastrointestinal hemorrhage observed on endoscopy, that were not considered in the Cochrane review. Only one of the RCTs included in the current systematic review<sup>31</sup> overlapped with studies included in the Cochrane review. A companion report to a more recent RCT included in our analysis<sup>32</sup> was also included in the Cochrane review. We identified 2 additional RCTs<sup>29,30</sup> that were not included in the Cochrane review. We were unable to conduct meta-analysis on data for gastric ulcers because only one of the included RCTs examined this outcome;<sup>32</sup> none of the RCTs included in the Cochrane review examined this outcome for patients taking H<sub>2</sub> blockers with ASA versus ASA alone.

Most of the RCTs included in our analysis had small sample sizes and were poorly reported. Furthermore, only one of the included RCTs reported adequately on more than 3 of the 7 risk-of-bias items,<sup>32</sup> which suggests that our meta-analyses results should be interpreted with caution. In addition, all RCTs were funded by private industry except for one.<sup>30</sup> Although statistical heterogeneity was not apparent, there was significant clinical heterogeneity across studies. For example, we combined studies regardless of ASA dose, H<sub>2</sub> blocker dose or patients' medical conditions. We were unable to fully assess these differences via subgroup analysis, as too few studies were included in the meta-analysis. This limitation should be addressed in updates of this systematic review.

Our systematic review was also limited because we did not include studies written in languages other than English. Furthermore, although we searched for unpublished material and contacted trial authors to request unpublished material, we were unable to identify any relevant unpublished material to include. Because of the limited number of RCTs included in the analysis, we were unable to perform statistical assessment of publication bias (e.g., through a funnel plot<sup>36</sup>). Furthermore, we did not compare H<sub>2</sub> blockers with more commonly used medications, such as proton pump inhibitors, as we

wanted to get a sense of the efficacy of H<sub>2</sub> blockers in relation to that of placebo.

Across all of the included RCTs, the longest duration of follow-up was 12 weeks.<sup>32</sup> Although the prolonged use (i.e., > 45 weeks) of H<sub>2</sub> blockers has been found to be safe,<sup>37</sup> the long-term safety of concurrent ASA and H<sub>2</sub> blocker intake is unclear. Future RCTs should evaluate the efficacy and safety of using these agents concurrently over time. Furthermore, future RCTs should examine gastrointestinal hemorrhage requiring admission to hospital and gastrointestinal hemorrhage requiring blood transfusion, important outcomes that were examined in only one of the included RCTs.<sup>32</sup>

In conclusion, H<sub>2</sub> blockers reduced gastrointestinal harm among patients taking ASA for 2 weeks or longer. Given the small number of RCTs included, the short duration of follow-up across the included RCTs and the heterogeneous patient populations, our results should be interpreted with caution. Future research is warranted on the long-term efficacy and safety of H<sub>2</sub> blockers for patients who are taking ASA concurrently.

**Contributors:** Andrea C. Tricco, Abdullah Alateeq, Muhammad Mamdani and Sharon E. Straus conceptualized and designed the study. Mohammad Al-Omran provided input into the study design. Abdullah Alateeq, Mariam Tashkandi and Andrea C. Tricco were involved in the acquisition of the data. Andrea C. Tricco analyzed the data. Andrea C. Tricco, Abdullah Alateeq, Muhammad Mamdani and Sharon E. Straus interpreted the data. Andrea C. Tricco and Abdullah Alateeq wrote the first draft, which was revised for intellectual content by all other authors.

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## Appendix A

**MEDLINE search strategy to identify articles assessing the efficacy of histamine H2 receptor antagonists in reducing gastrointestinal harms among adults taking acetylsalicylic acid for  $\geq 2$  weeks**

Database: Ovid MEDLINE® <1950 to November Week 1 2010>,  
Ovid MEDLINE® In-Process & Other Non-Indexed Citations  
<November 16, 2010>

## Search strategy:

- 1 Aspirin/
  - 2 (acetylsalicylic adj acid).tw.
  - 3 ASA.tw.
  - 4 aspirin.tw.
  - 5 or/1-4
  - 6 Histamine H2 Antagonists/
  - 7 (H2 adj blocker?).tw.
  - 8 "Histamine H2 Antagonist?".tw.
  - 9 "histamine H2 receptor antagonist\$.tw.
  - 10 Ranitidine/
  - 11 ranitidin?.tw.
  - 12 Cimetidine/
  - 13 cimetidine.tw.
  - 14 Famotidine/
  - 15 famotidine.tw.
  - 16 Nizatidine/
  - 17 nizatidine.tw.
  - 18 ebrotidine.nm.
  - 19 ebrotidine.tw.
  - 20 or/6-19
  - 21 randomized controlled trial.pt.
  - 22 controlled clinical trial.pt.
  - 23 randomized.ab.
  - 24 placebo.ab.
  - 25 drug therapy.fs.
  - 26 randomly.ab.
  - 27 trial.ab.
  - 28 groups.ab.
  - 29 or/21-28
  - 30 exp Animals/ not (Humans/ and exp Animals/)
  - 31 29 not 30
  - 32 5 and 20 and 31
  - 33 limit 32 to english language
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