RESEARCH ARTICLE

PPI versus Histamine H2 Receptor Antagonists for Prevention of Upper Gastrointestinal Injury Associated with Low-Dose Aspirin: Systematic Review and Meta-analysis

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Abstract

This study compared proton pump inhibitors (PPIs) and histamine H2 receptor antagonists (H2RAs) for prevention of low-dose aspirin (LDA)-related gastrointestinal (GI) erosion, ulcer and bleeding. Electronic databases including PubMed, Embase, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and WanFang Data were searched from the date of their establishment to December 31, 2013. Randomized controlled trials comparing PPIs and H2RAs for prevention of GI injury associated with low-dose aspirin (LDA) were collected. Two reviewers independently abstracted studies and patient characteristics and appraised study quality using the Cochrane risk-of-bias tool. Meta-analysis was performed using RevMan 5.1 software. We included nine RCTs involving 1047 patients. The meta-analysis showed that PPIs were superior to H2RAs for prevention of LDA-associated GI erosion/ulcer (odds ratio (OR=0.28, 95% confidence interval (CI): 0.16–0.50) and bleeding (OR=0.28, 95% CI: 0.14–0.59). In conclusion, PPIs were superior to H2RAs for prevention of LDA-related GI erosion/ulcer and bleeding. Higher quality, large, multicenter RCTs are needed to demonstrate the preventive effect of the two acid-suppressive drugs.

Introduction

Rationale

Low-dose aspirin (LDA) is usually defined as 75–325 mg daily. The mechanism of gastrointestinal (GI) injuries associated with LDA can be subdivided into topical and systemic effects. With the widespread use of LDA in primary and secondary prevention of cardiovascular and cerebrovascular diseases, the incidence of LDA-related upper GI injuries, including gastric...
mucosal erosion, peptic ulcer and bleeding, has increased annually. A retrospective study found that <50% of patients who were long-term LDA users were taking concomitant gastrointestinal protective drugs [1]. Researchers have also found that physicians have poor awareness of LDA-induced GI damage [2], so the prevention of LDA-associated GI injuries has been an important topic for cardiologists and gastroenterologists.

**Objectives**

It is well known that proton pump inhibitors (PPIs) reduce the incidence of LDA-associated GI ulcers and bleeding [3–7]. However, concerns about PPI–clopidogrel interaction, overprescribing of PPIs [8] and side effects of PPIs [9–11] have increased in recent years. Histamine H2 receptor antagonists (H2RAs) are more cost-effective and safer compared with PPIs. Taha et al. confirmed that standard doses of famotidine decrease LDA-associated GI injuries and suggested that high-dose H2RAs are an alternative to PPIs to prevent LDA-associated GI bleeding [12]. Rostom et al. pointed out in their systematic review that PPIs were superior to H2RAs for prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastroduodenal ulcer [13].

Only a few studies have investigated prevention of LDA-associated GI ulcers and bleeding, and it has not been established whether H2RAs are a rational alternative to PPIs. The present meta-analysis compared the effect of PPIs and H2RAs for prevention of LDA-related upper GI injuries, and attempted to provide the best evidence for clinical decision making.

**Methods**

The reporting format of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement revised in 2009 [14].

**Eligibility criteria**

Inclusion criteria. (1) The design of studies was randomized controlled trials. (2) Patients eligible for inclusion were adults (aged ≥18 years) who used LDA for at least two continuous weeks. Studies were included regardless of the patient’s concomitant medication, medical condition and comorbidity. (3) Intervention measures: oral PPIs were used in the experimental group and H2RAs were used as the control drugs. (4) Outcomes of studies: the incidence of LDA-related peptic ulcer and upper GI bleeding in the two groups was observed no matter which was primary endpoint or second endpoint. Exclusion criteria: non-randomized clinical trials, cohort studies, case–control studies, pharmacokinetic experiments, and case reports.

**Search**

We conducted a comprehensive literature search of PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese National Knowledge Infrastructure (CNKI), WanFang Data and Chinese Biomedical Literature Database (CBM) from their inception to December 31, 2013. Only studies published in English and Chinese were included. The search terms included combinations of the following keywords: aspirin, acetylsalicylic, low-dose aspirin, LDA, proton pump inhibitor, PPI, esomeprazole, pantoprazole, omeprazole, rabeprazole, lansoprazole, histamine receptor antagonist, H2RA, famotidine, ranitidine, cimetidine, nizatidine, roxatidine, and randomized controlled trial. The search strategy for PubMed as an example is presented below.

#1 aspirin OR acetylsalicylic OR low-dose aspirin OR LDA
#2 proton pump inhibitor OR PPI OR omeprazole OR esomeprazole OR lansoprazole OR pantoprazole OR rabeprazole

#3 histamine receptor antagonist OR H₂RA OR famotidine OR ranitidine OR cimetidine OR nizatidine OR roxatidine

#4 #1 AND #2 AND #3

**Study selection**

Two independent reviewers (C Mo and YZ Wang) used a predefined relevance criteria form to screen the studies. After reading the title and abstract, the documents that did not meet the inclusion criteria and duplicate articles were eliminated. The full text of relevant articles was screened for inclusion. Discrepancies at any stage were resolved by discussion with a third reviewer (G Sun). The level of agreement during screening was evaluated using a $\kappa$ statistic and we determined a priori that an acceptable level of agreement should be at least 0.60.

**Data collection process**

The data were extracted after the full text reading. Two independent reviewers (C Mo and YZ Wang) extracted the data. A third independent reviewer (G Sun) reviewed the data abstraction and resolved any discrepancies. When multiple publications reported data from the same population, the trial reporting the primary outcome of interest was considered the major publication. The extracted data included: authors and publication year, medical condition or risk factor, sample size, intervention measures, drug doses, course of treatment, drug co-administration, GI ulcer/erosion or bleeding events, and statistical methods.

**Risk of bias in individual studies**

Risk of bias in individual studies was assessed using the Cochrane Risk of Bias tool. This tool assesses the following six domains of bias: sequence generation (decided as low risk, high risk and unclear risk), allocation concealment (decided as low risk, high risk and unclear risk), blinding of outcome assessment (decided as low risk, high risk, and unclear risk), completeness of outcome data (decided as low risk, high risk and unclear risk), selective outcome reporting (decided as low risk, high risk and unclear risk), and other types of bias (decided as low risk, high risk and unclear risk). The two reviewers (C Mo and YZ Wang) assessed study quality independently and the assessments were verified by the third reviewer (G Sun).

**Statistical analysis**

All analyses were conducted using Review Manager version 5.1. For dichotomous data, summary statistics were expressed as odds ratio (OR) with 95% confidence interval (CI) for interpretation. Statistical significance level was considered as $\alpha = 0.05$. Statistical heterogeneity in the included studies was examined using $I^2$ statistics. If the result of the heterogeneity test was $P \geq 0.10$, a fixed-effect model was used for the meta-analysis; if $P < 0.10$, the sources of heterogeneity were investigated. If no obvious clinical heterogeneity and no clear statistical heterogeneity occurred, a random-effect model was used for the meta-analysis. If the clinical heterogeneity was too large, data synthesis should be abandoned and a single research analysis should be used instead. Sensitivity analysis was performed on some of the results of aggregate analysis. Potential publication bias was evaluated by funnel plot analysis.
Results

Study selection

The literature search identified 735 articles: 497 published in English and 238 in Chinese. Five hundred and seventy-two articles were excluded because they were duplicate publications or did not meet the inclusion criteria. One hundred and twenty articles were excluded after reading the titles and abstracts. Forty-three full-text articles were retrieved, including 34 articles published in English and nine in Chinese. Twelve articles were excluded because they were not RCTs [15–26]; eight because they compared the therapeutic effects [18,27–33]; seven because they did not investigate upper GI endpoints [34–40]; and seven because they were pharmacokinetic experiments [41–47]. The details of References to Studies Excluded in meta-analysis please see in Supporting Information (S1 File). Nine RCTs fulfilled the inclusion criteria including three in English [48–50] and six in Chinese [51–56]. Fig 1 shows the flow chart of the retrieved articles. The level of agreement between the two reviewers was acceptable ($\kappa = 0.67$).
Study characteristics

All the studies included were published in the US or China between 2009 and 2013. Demographic and clinical characteristics of the studies included in this meta-analysis are summarized in Table 1. The number of participants in the experimental group ranged from 42 to 163 and the duration of follow-up from 4 to 52 weeks. The PPIs examined were pantoprazole, rabeprazole, esomeprazole, omeprazole and lansoprazole, at doses ranging from 10 to 40 mg/day. The number of participants in the control group ranged from 22 to 148 and the duration of follow-up from 4 to 52 weeks. The H2RAs in the control group included famotidine (20–80 mg/day) and ranitidine (300 mg/day). The risk factors of patients differed among the RCTs. One RCT included patients with peptic ulcer or erosions [48]; one RCT included patients who were negative for Helicobacter pylori and without a history of ulcer bleeding or active ulcers [52]; four RCTs included patients with acute coronary syndrome or myocardial infarction [49,50,55,56]; and one RCT included older patients who needed long-term LDA treatment [52]. Three RCTs had endoscopy before and after treatment [48,49,53]. Four RCTs included patients who co-administered clopidogrel and enoxaparin or another anticoagulant [49,50,55,56].

Risk of bias across studies

The risk of bias within the eight studies included in the meta-analysis is summarized in Table 2. Figs 2 and 3 show the risk of bias graph and the risk of bias summary.

Comparison of incidence of LDA-associated GI ulcers/erosions. Seven of the eight included studies reported the incidence of LDA-associated GI ulcer/erosions in the PPI and H2RA groups. There was no statistical heterogeneity among the results ($I^2 = 0, P = 0.70$), so a

Table 1. Characteristics of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Risk Factor</th>
<th>Co-administration</th>
<th>Course</th>
<th>n</th>
<th>Prevention Group</th>
<th>Control Group</th>
</tr>
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<td></td>
<td>Usage</td>
<td>Usage</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ulcer/ Erosion (%)</td>
<td>Ulcer/ Erosion (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bleeding (%)</td>
<td>Bleeding (%)</td>
</tr>
<tr>
<td>Ng 2010 [48]</td>
<td>Ulcer or erosions</td>
<td>no</td>
<td>48w</td>
<td>65</td>
<td>20 mg bid</td>
<td>65</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ng 2012 [49]</td>
<td>ACS or MI</td>
<td>Clopidogrel and</td>
<td>4-52w</td>
<td>163</td>
<td>20 mg qd</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anticoagulant</td>
<td></td>
<td></td>
<td>1 (0.6)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Yano 2012 [50]</td>
<td>ACS</td>
<td>Clopidogrel</td>
<td>12m</td>
<td>65</td>
<td>10 mg qd</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Guo M 2009 [51]</td>
<td>Not clear</td>
<td>no</td>
<td>90d</td>
<td>42</td>
<td>20 mg qd</td>
<td>22</td>
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<td></td>
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<td></td>
<td></td>
<td>6 (14.3)</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>Sun RR 2012 [52]</td>
<td>Elders</td>
<td>no</td>
<td>90d</td>
<td>40</td>
<td>20 mg qd</td>
<td>40</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (7.5)</td>
<td>150 mg bid</td>
</tr>
<tr>
<td>Wang YP 2012 [53]</td>
<td>HP-, no ulcer</td>
<td>no</td>
<td>90d</td>
<td>23</td>
<td>30 mg qd</td>
<td>22</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>2 (8.7)</td>
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<td>0 (0)</td>
<td>6 (27.3)</td>
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<td></td>
<td></td>
<td>1 (4.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Hu L 2012 [54]</td>
<td>Not clear</td>
<td>no</td>
<td>90d</td>
<td>50</td>
<td>10 mg qd</td>
<td>48</td>
</tr>
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<td>5 (10)</td>
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<td></td>
<td></td>
<td>-</td>
<td>9 (18.8)</td>
</tr>
<tr>
<td>Lu BJ 2013 [55]</td>
<td>ACS</td>
<td>Clopidogrel</td>
<td>30d</td>
<td>50</td>
<td>40 mg qd</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>-</td>
<td>150 mg bid</td>
</tr>
<tr>
<td>Wang J 2012 [56]</td>
<td>ACS</td>
<td>Clopidogrel</td>
<td>90d</td>
<td>43</td>
<td>20 mg bid</td>
<td>46</td>
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<td>3 (7.0)</td>
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<td>-</td>
<td>5 (10.9)</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; MI: myocardial infarction

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A fixed-effect model was used for meta-analysis. The result showed that PPIs were superior to H2RAs (OR = 0.28, 95% CI: 0.16–0.50) for prevention of LDA-associated GI ulcers or erosions (Fig 4).

Comparison of incidence of LDA-associated GI bleeding. Six of the eight included studies reported the incidence of LDA-associated GI bleeding in the PPI and H2RA groups. There was no statistical heterogeneity among the results ($I^2 = 6\%$, $P = 0.38$) and a fixed-effect model

Table 2. Bias risk evaluation of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo M 2009</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Ng 2010</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Yano 2012</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Wang YP 2012</td>
<td>Unclear risk</td>
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<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Sun RR 2012</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
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<tr>
<td>Wang J 2012</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
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<td>Unclear risk</td>
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<tr>
<td>Lu BJ 2013</td>
<td>Unclear risk</td>
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<td>Unclear risk</td>
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<td>Ng 2012</td>
<td>Low risk</td>
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<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
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<tr>
<td>Hu L 2012</td>
<td>Unclear risk</td>
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<td>Low risk</td>
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<td>Wang J 2012</td>
<td>Low risk</td>
<td>Unclear risk</td>
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<td>Unclear risk</td>
<td>Low risk</td>
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</table>

doi:10.1371/journal.pone.0131558.t002

Fig 2. Risk of bias graph.

doi:10.1371/journal.pone.0131558.g002

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### Fig 3. Risk of bias summary.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo M2009</td>
<td>+</td>
<td>?</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
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<tr>
<td>Ng2010</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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</table>

Additional information: doi:10.1371/journal.pone.0131558.g003
was used for meta-analysis. The result showed that PPIs were superior to H2RAs (OR = 0.28, 95%CI: 0.14–0.59) for prevention of LDA-associated GI bleeding (Fig 5).

Publication bias
Funnel plot analysis of the seven RCTs of PPIs and H2RAs for prevention of LDA-associated GI ulcers/erosions indicated an asymmetrical distribution that indicated the presence of publication bias (Fig 6).

Discussion
Summary of evidence
It is well known that long-term use of LDA increases the risk of upper GI injuries and bleeding [57]. The pathogenetic mechanism involves topical effects of acid reverse diffusion and
systemic effects of inhibiting prostaglandin synthesis through the cyclo-oxygenase-1 pathway. Anti-secretory drugs are effective in reducing upper GI mucosal injuries and bleeding complications by inhibiting gastric acid secretion and lowering gastric pH. Studies of prophylaxis for LDA-associated GI injuries have focused on PPIs, but PPIs are expensive and their long-term use has side effects such as *Clostridium difficile*-associated diarrhea, community-acquired pneumonia, osteoporosis and fractures [9–11]. LDA is frequently prescribed concurrently with clopidogrel in dual antiplatelet therapy. However, PPI–clopidogrel interaction increases cardiovascular risks so the use of PPI with LDA is currently restricted. As traditional anti-secretory drugs, H2RAs are cost-effective. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) revised the expert consensus document of 2010 on reducing the GI risks of antiplatelet therapy and NSAID use, which states that H2RAs are a reasonable alternative to PPIs for the prophylaxis and treatment of LDA-associated GI injury [58]. However, the preventive effect of H2RAs is still controversial. The OITA-GF2 study indicated that lansoprazole might be more effective than famotidine in preventing the development of LDA-related gastroduodenal injuries [59]. Ng et al. concluded that H2RAs were inferior to PPIs for preventing LDA-related upper GI injuries in a cohort study and RCTs [48,49,60]. The present meta-analysis compared the preventive effect of PPIs and H2RAs in LDA-associated GI injuries, and explored the advantages of H2RAs, so as to provide more reasonable and cost-effective drugs for clinical practice.

There were nine RCTs included in our meta-analysis. We found that PPIs were superior to H2RAs for prevention of LDA-associated upper GI ulcers/erosions and bleeding. However, among the nine RCTs included, six studies were from mainland China and had small samples and were poorly reported. The bias of random sequence generation, allocation concealment, blinding method, incomplete outcome data, and other bias in most of the studies were not clear, which means that the results of our meta-analysis should be interpreted with caution.
Lanas et al. discovered in a case–control study that *H. pylori* infection increased the risk of GI bleeding (OR, = 4.7; 95% CI: 2.0–10.9) and indicated that *H. pylori* infection was an independent risk factor for LDA-associated GI bleeding [61]. Only one RCT in our analysis included patients who were negative for *H. pylori*, and one RCT showed *H. pylori* eradication. Most of our studies did not determine *H. pylori* infection status, thus, it is not clear whether infection interacted with LDA to increase mucosal injuries. So, selection bias may have been present in our meta-analysis.

**Limitations**

Because meta-analyses are secondary research, their conclusions are influenced by the quality of the included studies. There were some limitations in our meta-analysis that should be mentioned. First, the quality of some studies was low and we need more high-quality, multicenter, high-standard RCTs in the future. Second, we searched the unpublished articles in English and Chinese, but were unable to identify all relevant unpublished data to include. Funnel plot analysis showed that publication bias was also present. Third, we searched articles written in English and Chinese, but only three RCTs in English were included, and they may have had reporting bias. Last, All of the nine trials included Asian patients, one from Japan, two from Hong Kong and the others from mainland China. So the representativeness of patients are not well enough.

**Conclusions**

In conclusion, PPIs were superior to H2RAs in preventing LDA-associated GI ulcers/erosions and bleeding. Some of the RCTs included in our meta-analysis were poorly reported and of low quality, therefore, our meta-analysis should be interpreted with caution. More multicenter, high-quality RCTs are needed to compare two anti-secretory drugs for prevention of LDA-associated GI injuries.

**Supporting Information**

S1 File. References to Studies Excluded in Meta-analysis. (PDF)

S2 File. PRISMA Statement. (PDF)

S1 PRISMA Checklist. PRISMA 2009 Checklist. (DOC)

**Author Contributions**

Conceived and designed the experiments: CM YSY. Performed the experiments: CM MLL YZW. Analyzed the data: CM GS YZW. Contributed reagents/materials/analysis tools: CM GS YZW. Wrote the paper: CM.

**References**


