SYSTEMATIC REVIEW AND META-ANALYSIS

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PPIs Prevent Aspirin-Induced Gastrointestinal Bleeding Better than H2RAs. A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: Aspirin is one of the most widely used medication for its analgesic and anti-platelet properties and thus a major cause for gastrointestinal (GI) bleeding. This study compared the preventive effect of histamine-2 receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs) against chronic low-dose aspirin (LDA)-related GI bleeding and ulcer formation.

Methods: Electronic databases of Pubmed, Embase and Cochrane Central Register of Controlled Trials were searched for human observations (randomised controlled trials and observational studies) comparing the long term effects of PPIs and H2RAs treatment in the prevention of GI bleeding or ulcer formation in patients on chronic LDA treatment listed up till September 30, 2016. Two independent authors searched databases using PICO questions (aspirin, H2RA, PPI, GI bleeding or ulcer), and reviewed abstracts and articles for comprehensive studies keeping adequate study quality. Data of weighted odds ratios were statistically evaluated using Comprehensive Metaanalysis (Biostat, Inc., Engelwood, MJ, USA), potential bias was checked.

Results: Nine studies for GI bleeding and eight studies for ulcer formation were found meeting inclusion criteria, altogether 1,879 patients were included into review. The H2RAs prevented less effectively LDA-related GI bleeding (OR= 2.102, 95% CI: 1.008-4.385, p<0.048) and ulcer formation (OR= 2.257, 95% CI: 1.277-3.989, p<0.005) than PPIs.

Conclusion: The meta-analysis showed that H2RAs were less effective in the prevention of LDA-related GI bleeding and ulcer formation suggesting the preferable usage of PPIs in case of tolerance.

Key words: Low-dose aspirin treatment – Proton pump inhibitors – Histamine receptor antagonists – Gastrointestinal bleeding – Ulcer – Aspirin-induced gastroenteropathy.

Abbreviations: COX -1: cyclooxygenase-I enzyme; COX-2: cyclooxygenase-II enzyme; GI: gastrointestinal; H2RA(s): histamine-2 receptor antagonist(s); *H. pylori: Helicobacter pylori*; LDA: low dose aspirin; NSAID(s): non-steroid anti-inflammatory drug(s); OR: Odds ratio; PPI(s): proton-pump inhibitor(s); RCT: randomized controlled trial; RR: relative risk; UGIB: upper gastrointestinal bleeding.

INTRODUCTION

Aspirin has been known for more than a hundred years for its antiphlogistic and pain killer effects. Since its anti-platelet activity was recognized in the late 1960s [1], aspirin has become one of the most used medication mainly for primary or secondary prevention of cardiovascular events and for its classical anti-analgesic properties against migraine, acute pain, osteoarthritis or postoperative pain [2-6]. However, administration of aspirin increases the risk for gastrointestinal (GI) bleeding and ulcer formation [7, 8]. The dose of aspirin influences the occurrence of GI side effects, as well as the advanced age, a history of prior GI events, *Helicobacter pylori* (*H. pylori*) infection, concomitant clopidogrel, anti-coagulant, steroid or non-steroid anti-inflammatory drugs (NSAIDs) use, which further increase the bleeding risk [9-10]. Fortunately, aspirin used in low dose (LDA) (75-325 mg) still has beneficial effects in the prevention of vascular events with lesser frequency of aspirin-related GI side effects [11]. Aspirin induces mostly upper GI injury via inhibition of cyclooxygenase (COX) and cellular effects, acting by topical and systemic effects on epithelial and endothelial cells of mucosa resulting in lower rate of cell proliferation and migration [12-14]. Although aspirin inhibits cyclooxygenase-I

(COX-1) more potently than cyclooxygenase-II (COX-2), interestingly enteropathy occurs less frequently than in case of many other NSAIDs, which can be explained by the concept of Takeuchi et al. [15, 16]. According to their explanation, the inhibition of COX-1 will upregulate COX-2, and the produced prostaglandin E2 derived from COX-2 prevents the adverse effects mediated by COX-1 inhibition in the intestine resulting in less frequent enteropathy than in the case of both isoform inhibition [16].

Commonly used medication for reducing GI toxicity associated with prolonged use of aspirin includes prostaglandins, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs) [17]. The prostaglandin E1 analogue misoprostol, the first agent approved for the prevention of NSAID-related ulceration, protects from ulcer formation and stimulates ulcer healing quite significantly. However, it has several side effects and disadvantages, most notably diarrhoea, dyspepsia and compliance problems related to q.i.d. dosage, all limiting its use [18, 19].

The H2RAs effectively prevent the development of gastric and duodenal ulcers as well as erosive esophagitis in patients chronically taking LDA, according to the FAMOUS (Famotidine for the Prevention of Peptic Ulcers in Users of Low-dose Aspirin) trial (OR: 0.2; 0.05; 0.20, respectively) [20]. Since PPIs inhibit acid secretion to a higher extent and result in faster ulcer healing, their prominent role in the prevention of aspirin or other NSAID-induced GI toxicity were concluded and resulted in their dominant use with such indications. However, the past two-decade long dominant use of PPIs has demonstrated certain disadvantages, namely side effects, such as a higher rate of infections, bone fractures, food allergy, development of fundic polyposis as well as an elevated risk of severe thromboembolism [21, 22]. The H2RAs are more cost-effective and safer compared with PPIs. All these have led us to consider the use of H2RA again in certain anti-secretory indications, especially in the prevention of aspirin-induced GI bleeding in which the slightly lesser extent of acid inhibition might not result in its deficiency during long term use. Taha et al. confirmed that standard doses of famotidine decrease LDA-associated GI injuries and suggested that high-dose H2RAs are alternatives to PPIs in preventing LDA-associated GI bleeding [20]. It is still unclear if chronic H2RA intake is capable of preventing GI damage among patients taking aspirin for a longer period of time comparable to PPIs.

This present study was aimed to evaluate whether H2RAs are being equal to PPIs in the prevention of LDA-related GI bleeding or ulcer formation.

METHODS

A systematic review of the studies was performed by the guidance of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [23]. Inclusion criteria were the following: (1) Randomized controlled trials, case-control and observational studies were included; (2) LDA-taking, adult patients (≥18 years) were eligible for enrolment, if they had taken LDA for minimum of 2 weeks; (3) both H2RA takers and PPI takers should have been present as comparable experimental groups in the included studies; (4) the outcome of case numbers with bleeding and/or ulcer formation were mandatorily registered. According to the exclusion criteria, non-human studies, pharmacological experiments and case reports were foreclosed. Studies measuring Rockall scores for bleeding evaluation or Lanza scores for GI injury were not considered to be adequate for inclusion.

The literature search of PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) from their interception till September 30, 2016 were conducted. The filter of human studies was used. Studies published in the English language were selected. The combinations of the following terms were used for the literature search: aspirin, acetylsalicylic, proton pump inhibitor, PPI, esomeprazole, pantoprazole, omeprazole, rabeprazole, lansoprazole, histamine receptor antagonist, H2RA, famotidine, ranitidine, cimetidine, nizatidine, roxatidine, GI bleeding and ulcer (see Supplementary Table I).

Two reviewers (I. S. and R. M.) screened the titles and abstracts of the studies for inclusion criteria. Studies not meeting the inclusion criteria or published in duplicate were eliminated from the analysis. Remaining studies were further analysed in full text. If differences were found in the reviewers' judgement then a committee of five other researchers was invited to draw a conclusion. Data of articles enrolled were extracted by two independent researchers, and the number of patients in studied groups, number of patients with GI bleeding and ulcers, diagnostic method for bleeding and ulcer detection were summarized.

The risks of selection, detection, performance, attrition and reporting bias in the enrolled studies were also assessed by the two reviewers independently using the Cochrane Risk of Bias tool [24]. Low risk, high risk or unclear risk was determined in individual studies for (1) sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding outcome assessment, (5) incompleteness outcome data, and (6) selective outcome reporting domains. Since not all domains in Cochrane Risk of Bias tool are relevant for non-RCT studies, we further examined the bias of observational studies for selection and information bias: (a) population selection, (b) assessment of exposure, (c) outcome interest, (d) case selection, (e) control selection, (f) matching and adjustment, (g) assessment of prognostic factors, (h) assessment of outcome, and (i) follow-up were judged [25-27]. In case of disagreement in the reviewers' assessment, a committee comprising five other researchers was invited to draw a conclusion.

The summarized data of bleeding and ulcer detected were expressed as odds ratio (OR) with 95% confidence interval (CI) for comparison. Between-study heterogeneity was tested with: (1) Q homogeneity test statistic (p values of less than 0.05 were considered as indicators of significant heterogeneity) and (2) I^2 statistics, where I^2 is the proportion of total variation attributable to between-study variability (an I^2 value of more than 50 was considered as indicating considerable heterogeneity). These two values were used to model selection purposes too (fixed vs. random). The publication bias was tested by inspecting the Funnel plot. All analyses were performed using the software Comprehensive Metaanalysis (Biostat, Inc., Engelwood, MJ, USA).

RESULTS

The preliminary literature search identified 254 articles with available abstracts (Fig. 1). After subtracting duplications/triplications (18/8), 214 articles were excluded after reading their title and abstract (174) or full text (46), due to exclusion criteria or to missing inclusion criteria. Six articles fulfilled all criteria [28-33]. One systematic review [34] checked during the assessment cited six additional Chinese papers fulfilling inclusion criteria and showed data suitable for comparison. The committee of reviewers accepted the inclusion of data derived from these Chinese written articles [35-40]. Altogether, nine articles reported bleeding, eight papers reported ulcer as an outcome, and five manuscripts investigated both bleeding and ulcer formation. All studies included were published between 2007 and 2016. The characteristics of the studies included in this meta-analysis are summarized in Table I. The number of patients included in comparison groups ranged from 22 to 163 (combined 962 in PPI treated group, 917 in H2RA treated group, altogether 1879 patients). One article did not state the anti-secretory medication doses. In the rest of the studies, the PPIs compared in the articles were pantoprazole, rabeprazole, esomeprazole, omeprazole and lansoprazole at doses from 10 to 40 mg/day; and the H2RAs examined were famotidine and ranitidine 20-80 mg/day and 300 mg/day, respectively. The patients using concomitant medications or having other risk factors were not evaluated to represent mixed general population.

Five RCT studies reported random sequence generation [30, 31, 33, 38, 39]. Three articles stated allocation concealment; eight were unclear for this aspect of selection bias. Three blinded the participants and personnel, as well as the outcome assessment

Table I. Summary of studies included in meta-analysis

Bleeding								
Studies	Study type	Course	Drug (dose)	n	Bleeding (%)	Drug (dose)	n	Bleeding (%)
Lanas A et al. 2007 [28]	Case-control	4y	PPI*	133	41 (31)	Ranitidine or Famotidine**	55	20 (36)
Hakimoto S et al. 2009 [29]	Cohort	8-20m	PPI** – no details	150	2 (1.3)	H2R antagonists**	212	10 (4.7)
Ng FH et al. 2010 [30]	RCT	48w	Pantoprazole (20 mg bid)	65	0 (0)	Famotidine (40 mg bid)	65	5 (7.7)
Ng FH et al. 2012 [31]	RCT	4-52w	Esomeprazole (20 mg qd)	163	3 (1.8)	Famotidine (40 mg qd)	148	12 (8.1)
Yano et al. 2012 [32]	RCT	12m	Omeprazole (10 mg qd)	65	3 (4.6)	Famotidine (20 mg qd)	65	1 (1.5)
Sun EE et al. 2012 [35]	RCT	90d	Rabeprazole (20 mg qd)	40	0 (0)	Ranitidine (150 mg bid)	40	1 (2.5)
Wang YP et al. 2012 [36]	RCT	90d	Lansoprazole (30 mg qd)	23	0 (0)	Famotidine (20 mg qd)	22	1 (4.5)
Lu BJ et al. 2013 [37]	RCT	30d	Omeprazole (40 mg qd)	50	2 (4)	Ranitidine (150mg dq)	50	9 (18)
Chan et al. 2016 [33]	RCT	12m	Rabeprazole (20mg qd)	138	1 (0.7)	Famotidine (40 mg qd)	132	4 (3.1)
Ulcer formation								
Studies	Study type	Course	Drug (dose)	n	Bleeding (%)	Drug	n	Bleeding (%)
Guo M et al. 2009 [38]	RCT	90d	Omeprazole or Esomeprazole (20 mg qd)	42	6 (14.3)	Famotidine (20 mg bid)	22	5 (22.7)
Ng FH et al. 2010 [30]	RCT	48w	Pantoprazole (20 mg bid)	65	0 (0)	Famotidine (40 mg bid)	65	8 (12.3)
Ng FH et al. 2012 [31]	RCT	4-52w	Esomeprazole (20 mg qd)	163	1 (0.6)	Famotidine (40 mg qd)	148	6 (4.1)
Sun EE et al. 2012 [35]	RCT	90d	Rabeprazole (20 mg qd)	40	3 (7.5)	Ranitidine (150 mg bid)	40	11 (27.5)
Wang YP et al. 2012 [36]	RCT	90d	Lansoprazole (30 mg qd)	23	2 (8.7)	Famotidine (20 mg bid)	22	6 (27.3)
Wang J et al. 2012 [39]	RCT	90d	Esomeprazole (20 mg bid)	43	3 (7.0)	Famotidine (20 mg bid)	46	5 (10.9)
Hu L et al. 2013 [40]	RCT	90d	Rabeprazole (10 mg qd)	50	5 (10)	Famotidine (20mg bid)	50	9 (18)
Chan et al. 2016 [33]	RCT	12m	Rabeprazole (20mg qd)	138	8 (0.5)	Famotidine (40 mg qd)	132	9 (0.1)

* All PPs (omeprazole, pantoprazole, esomeprazole, rabeprazole, lansoprazole) in all doses; ** No dosage given; *** No details given on types or doses.

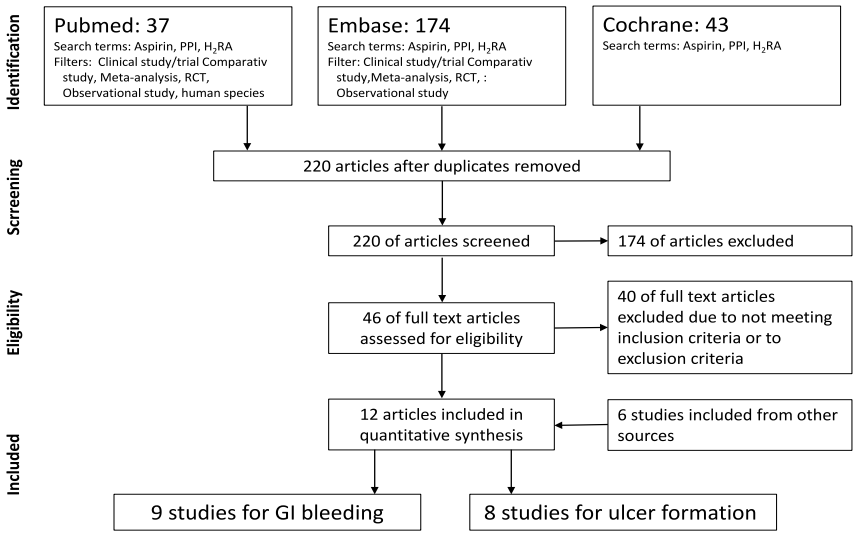

Fig. 1. Flow-chart of study selection and inclusion

process [30, 31, 33]. Seven studies did not perform or state the performance of blinding on either side. Six studies were unclear for incomplete outcome data, while six studies were low risk for this aspect of attrition bias. All studies were judged low risk for reporting bias. The risk of bias within the twelve studies included in the meta-analysis is summarized in Fig. 2.

Two non-RCT studies were further examined for bias relevant in cohort and case-control studies [25-27]. Both studies achieved mostly low risk for selection bias aspects. Study of Lanas et al. was judged low risk for matching and adjustment as well as assessment for prognostic factors and outcome. Risk of bias within two observational studies included in the meta-analysis is summarized in a combined table (Fig. 3).

We found the combined OR of 2.102 (95% CI: 1.008-4.385) for bleeding in H2RA treated group compared to PPI treated (Fig. 3). The OR for upper GI ulcer formation was 2.257 (95% CI: 1.277-3.989) in H2RA treatment compared to PPI treatment (Fig. 4). The difference of risk for both GI bleeding and ulcer formation was significant ($p<0.048$; $p<0.005$, respectively). The visual analysis of Funnel plots did not reflect worthwhile publication bias.

To further analyse the data quality, we compared the results of the RCT studies with the exclusion of non-RCT studies. The OR of RCT studies for upper GI bleeding was 2.553 (95% CI: 1.187-5.489) in H2RA treatment compared to PPI treatment ($p<0.016$). Since the studies used for the analysis of ulcer formation included only RCTs no further analyses were performed for the investigation of ulcer formation from this aspect. Visual observation of Funnel plot of RCT studies for ulcer bleeding showed acceptable spread of data.

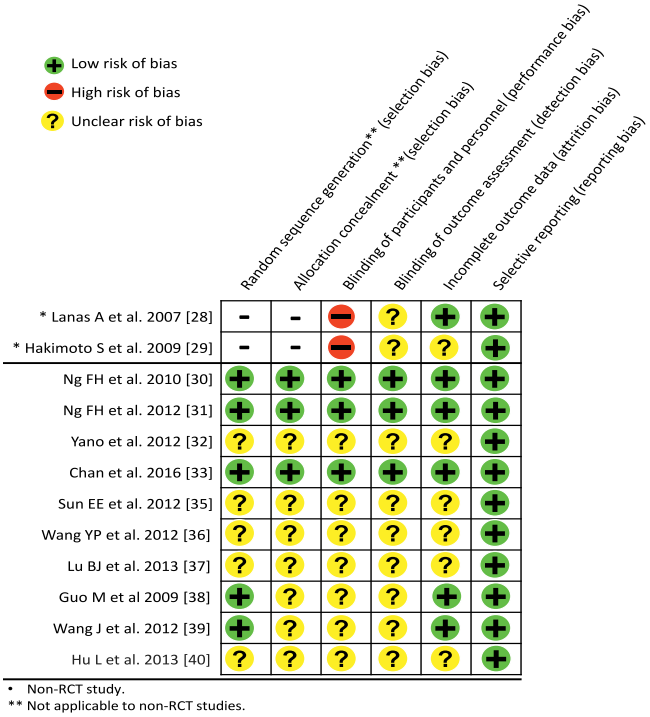

Fig. 2. Summary of risk of bias of studies included in meta-analysis

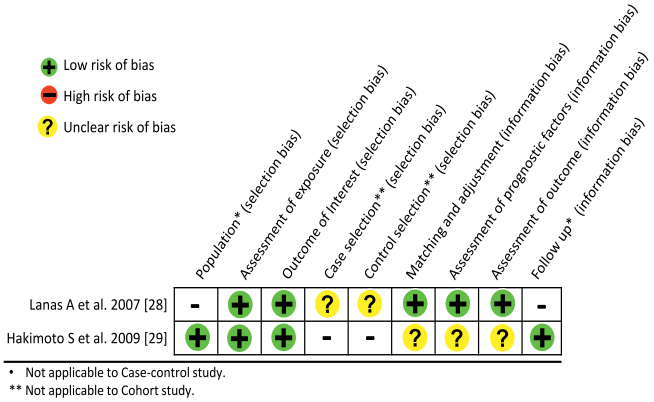

Fig. 3. Summary of risk of bias of non-RCT studies included in meta-analysis

DISCUSSION

It is well known that aspirin treatment causes GI side effects, such as dyspepsia, GI damage and bleeding [7, 8]. A recent meta-analysis of the RCT data showed that LDA use was associated with a 50% increase in UGIB risk (OR 1.5 [95% CI 1.2 to 1.8]). Upper GI bleeding risk was most pronounced in observational studies (OR 3.1, 95% CI 2.5 to 3.7) [41]. Very

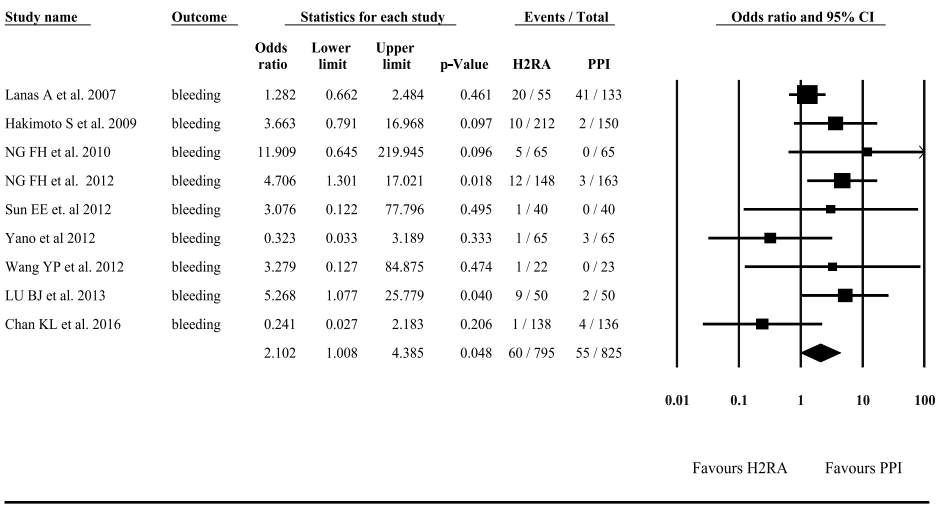

Fig. 4. Forest plot analysis of studies of H2RA and PPI for the prevention of low dose aspirin-induced gastrointestinal bleeding (Q value: 8.585; df(Q): 9; P-value: 0.284; I2:18.46%).

often the absence of aspirin-induced patients' complaints does not reflect GI damage and ongoing bleeding [42]. Which might be the reason why a lot of chronic aspirin takers do not use concomitant GI protective drugs. Observational studies still reflect that less than 50% of the aspirin users take protective maintenance therapy [43]. Since more and more patients take aspirin worldwide for primary and secondary prevention of cardiovascular disease, to promote physicians' poor awareness toward the prevention of GI damage is an important task. Anti-secretory medications are effective in reducing GI complications of aspirin [44]. The PPIs being potent inhibitors of gastric acid secretion have been extensively studied in preventing aspirin-induced GI complications. Recently, we are facing the side effects of long-term PPI therapy, such as *Clostridium difficile* colitis, community-acquired pneumonia, osteoporosis, iron and vitamin deficiencies, as well as the increase of food allergies [45-49]. The interaction caused by PPIs on the cytochrome enzymes hazard appropriate drug actions of clopidogrel, vitamin K antagonists, and benzodiazepines [50, 51]. All these raised the question whether the less expensive H2RAs are suitable to prevent aspirin-induced GI bleeding. The only meta-analysis published so far [34] comparing H2RAs to PPI in the prevention of ASA-related GI harms examined exclusively RCT studies up till 2013. In the present study we extended the review to a wider field including data of appropriate observational studies and more recent findings of literature.

Our meta-analysis containing data of 12 studies showed that H2RAs are less effective in preventing upper GI ulcers and bleeding in LDA takers. However, these studies were mainly conducted in far eastern countries (China, Japan), and their sample numbers were also small. The gastric acid secretion of far-east patients, especially in Japan has been shown to be lower than in western developed countries probably due to higher *H. pylori* infection prevalence [52]. Extrapolating from our results, probably the difference in the preventive action of PPIs and H2RAs might be larger in European and American

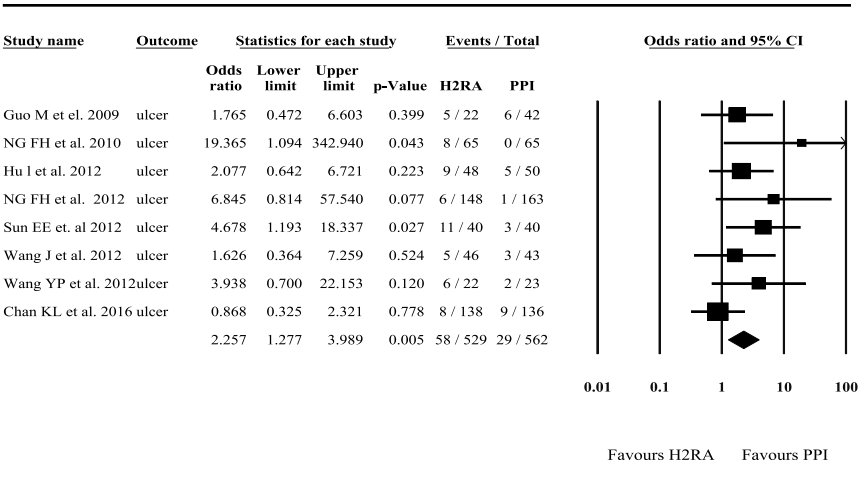

Fig. 5. Forest plot analysis of studies of H2RA and PPI for the prevention of low dose aspirin-induced upper gastrointestinal ulcer formation (Q value: 12.936; df(Q): 8; P-value: 0,114; I2: 38.16%).

population. Analysing the risk of bias within the included studies, we found that uncertain risks of bias were relatively frequent among the examined aspects, suggesting the rather low quality of the included studies. Studies with a lower rate of uncertainty in bias showed a higher difference in GI bleeding and ulcer formation rate between H2RA and PPI groups, also suggesting the relevance of our results.

Beside the small sample number and the relatively high partition of low quality of studies, this study has another limitation. We did not divide the patients into subgroups by their risk factors for GI bleeding such as age, history of previous bleeding, *H. pylori* positivity, and concomitant medications due to lack of data. Our goal was to represent a heterogeneous general population, and to predict whether H2RAs are suitable to substitute PPIs in the prevention of LDA-induced GI bleeding and ulcer formation without further examination of patients. It is still possible that subgroups of patients lacking certain risk factor(s) might qualify for prevention achieved by H2RAs along with long-term aspirin treatment. Since the dose range of LDA is wide (75-325mg), the preventive efficacy against the lower range doses surely differs from the top dose, which may point out the possibility for H2RAs in the protection against low range LDA-caused GI damage. This rationale is supported by the data of Lanas et al. [28] showing the adjusted relative risk (RR) for peptic ulcer bleeding according to aspirin doses. He found that at 100 mg aspirin use, the relative risk (RR) for peptic ulcer bleeding is almost the same in PPI takers and H2RA takers (0.32 and 0.33, respectively), whereas it differs quite a bit in 300 or 500 mg aspirin users (RR: 0,32, 0.44; and 0.19, 0.49, respectively). Genetic differences may also lead to different susceptibility for damage. Possibly, future findings on genetic polymorphisms of cyclooxygenases, factors involved in platelet aggregation or enzymes in aspirin metabolism will further help in the fight against aspirin-induced mucosal damage.

CONCLUSION

The PPIs are superior to the H2RAs in preventing LDA-associated GI ulcer formation and bleeding. Further high quality studies on risk factors-related differences on the efficacy of preventive actions of PPIs and H2RAs might reveal new details and result in rewarding forthcoming therapeutic protocols.

Conflicts of interest: No conflict to declare.

Authors' contribution: All the authors were involved in the study design, edited the manuscript, read and approved the final manuscript. During the study, I.L.S. and P.M. performed literature search and collected data of enrolled studies. P.S., B.J., Á.S., D.M. and K.S. rechecked the enrolled studies for inclusion and exclusion criteria, and constituted a committee of five to decide on controversial issues. K.M. and K.C. assessed the risks of bias in the enrolled studies. B.K. and Á.V. outlined the figures of risks. R.M. and A.I. performed the statistical analysis and Forest plot figure assembly. I.L.S., P.H., A.G. and Z.R. drafted the manuscript.

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Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://www.jgld.ro/wp/archive/y2017/n4/a14/ and http://dx.doi.org/10.15403/jgld.2014.1121.264.hra.

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Supplementary Table. Summary of PICO literature search

Electronic Database	Search term used	Number of matching publication
Pubmed	(("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND (("proton pump inhibitors"[Pharmacological Action] OR "proton pump inhibitors"[MeSH Terms] OR ("proton"[All Fields] AND "pump"[All Fields] AND "inhibitors"[All Fields]) OR "proton pump inhibitors"[All Fields] OR ("proton"[All Fields] AND "pump"[All Fields] AND "inhibitor"[All Fields]) OR "proton pump inhibitor"[All Fields]) OR PPI[All Fields] OR ("esomeprazole"[MeSH Terms] OR "esomeprazole"[All Fields]) OR ("lansoprazole"[MeSH Terms] OR "lansoprazole"[All Fields]) OR ("pantoprazole"[Supplementary Concept] OR "pantoprazole"[All Fields]) OR ("rabeprazole"[MeSH Terms] OR "rabeprazole"[All Fields]) OR ("omeprazole"[MeSH Terms] OR "omeprazole"[All Fields]))) AND (("histamine antagonists"[Pharmacological Action] OR "histamine antagonists"[MeSH Terms] OR ("histamine"[All Fields] AND "antagonists"[All Fields]) OR "histamine antagonists"[All Fields] OR ("histamine"[All Fields] AND "receptor"[All Fields] AND "antagonist"[All Fields]) OR "histamine receptor antagonist"[All Fields]) OR H2RA[All Fields] OR ("famotidine"[MeSH Terms] OR "famotidine"[All Fields]) OR ("ranitidine"[MeSH Terms] OR "ranitidine"[All Fields]) OR ("cimetidine"[MeSH Terms] OR "cimetidine"[All Fields]) OR ("roxatidine acetate"[Supplementary Concept] OR "roxatidine acetate"[All Fields] OR "roxatidine"[All Fields])) AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Observational Study[ptyp] OR Comparative Study[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms]) AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Observational Study[ptyp] OR Comparative Study[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms])	37
Embase	'aspirin'/exp AND 'proton pump inhibitor'/exp AND ('h2 blocker'/exp OR 'h 2 receptor blocking agent' OR 'h2 antagonist' OR 'h2 blocker' OR 'h2 blocking agent' OR 'h2 receptor antagonist' OR 'h2 receptor blocker' OR 'h2 receptor blocking agent' OR 'antihistamines, h2' OR 'histamine 2 receptor antagonist' OR 'histamine 2 receptor blocker' OR 'histamine 2 receptor blocking agent' OR 'histamine h 2 receptor antagonist' OR 'histamine h2 antagonist' OR 'histamine h2 antagonists' OR 'histamine h2 blocker' OR 'histamine h2 blocking agent' OR 'histamine h2 receptor antagonist' OR 'histamine h2 receptor blockaders' OR 'histamine h2 receptor blocker' OR 'histamine h2 receptor blocking agent') AND 'gi bleeding' AND 'human'/exp	63
Cochrane	"aspirin" OR "LDA" and "histamine antagonist" OR "H2RA" OR "cimetidine" OR "famotidine" OR "ranitidine" OR "nizatidine" OR "roxatidine" and "proton pump inhibitor" OR "PPI" OR "omeprazole" OR "esomeprazole" OR "pantoprazole" OR "rabeprazole"	43