

Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries

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METHODS: We searched MEDLINE, EMBASE and the Cochrane Controlled Trials Register from inception to December 2013, and checked conference abstracts of randomized controlled trials (RCTs) on the effect of PPIs in reducing adverse GI events (hemorrhage, ulcer, perforation, or obstruction) in patients taking LDA. The preventive effects of PPIs were compared with the control group [taking placebo, a cytoprotective agent, or an H₂ receptor antagonist (H₂RA)] in LDA-associated upper GI injuries. The meta-analysis was performed using RevMan 5.1 software.

RESULTS: We evaluated 8780 participants in 10 RCTs. The meta-analysis showed that PPIs decreased the risk of LDA-associated upper GI ulcers (OR = 0.16; 95%CI: 0.12-0.23) and bleeding (OR = 0.27; 95%CI: 0.16-0.43) compared with control. For patients treated with dual anti-platelet therapy of LDA and clopidogrel, PPIs were able to prevent the LDA-associated GI bleeding (OR = 0.36; 95%CI: 0.15-0.87) without increasing the risk of major adverse cardiovascular events (MACE) (OR = 1.00; 95%CI: 0.76-1.31). PPIs were superior to H₂RA in prevention of LDA-associated GI ulcers (OR = 0.12; 95%CI: 0.02-0.65) and bleeding (OR = 0.32; 95%CI: 0.13-0.79).

CONCLUSION: PPIs are effective in preventing LDA-associated upper GI ulcers and bleeding. Concomitant use of PPI, LDA and clopidogrel did not increase the risk of MACE.

Key words: Proton pump inhibitor; Low dose aspirin; Peptic ulcer; Gastrointestinal bleeding; Meta-analyses; Randomized controlled trial

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Core tip: Ten randomized controlled trials on the preventive effect and safety of proton pump inhibitors (PPIs) in

Abstract

AIM: To determine the preventive effect and safety of proton pump inhibitors (PPIs) in low-dose aspirin (LDA)-associated gastrointestinal (GI) ulcers and bleeding.

low-dose aspirin (LDA)-associated gastrointestinal tract injuries were included in this meta-analysis. Based on the data collected and presented, the authors conclude that PPIs are effective in preventing LDA-associated upper gastrointestinal tract ulcers and bleeding, without increasing the risk of major adverse cardiovascular events. The findings further confirm and extend the observations already published.

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INTRODUCTION

With the wide use of low-dose acetylsalicylic acid (LDA) for the primary and secondary prevention of cardiovascular and cerebrovascular diseases, the incidence of LDA-associated upper gastrointestinal (GI) injuries, including gastric mucosal erosions, peptic ulcers, and bleeding has been increasing. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and American Heart Association (AHA) established an expert consensus document on reducing the GI risks of anti-platelet therapy and NSAID use in 2008, and indicated that proton pump inhibitors (PPIs) were the preferred agents for the treatment and prophylaxis of NSAID- and LDA-associated GI injuries^[1].

There have been several randomized controlled trials (RCTs) and observational studies to verify the effect of PPIs on the prevention of LDA-associated GI injuries, but there has been no meta-analysis on this subject to date. This meta-analysis aims to determine the preventive effect and safety of PPIs against LDA-associated GI ulcers and bleeding, and to provide the best evidence for clinical practice.

MATERIALS AND METHODS

Methods

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement revised in 2009^[2].

Eligibility criteria

Patients eligible for inclusion were adults (aged ≥ 18 years) who used LDA for at least 2 continuous weeks. RCTs were included regardless of the combined medication used, medical condition, and comorbidities in the patients. Oral PPIs were used in the experimental group and placebo, cytoprotective agents or histamine 2 receptor antagonists (H_2RA) were used as the controls. The incidences of LDA-related peptic ulcer

and upper gastrointestinal bleeding, and the incidences of the major adverse cardiovascular events (MACE) and diarrhea in the 2 groups were observed. Only studies published in English were included.

Exclusion criteria

Non-RCTs, cohort studies, case-control studies, pharmacokinetic experiments and case reports were excluded from this study.

Search strategy

We conducted a comprehensive literature search of MEDLINE and EMBASE databases, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to December 31, 2013. The following keywords were used: aspirin, acetylsalicylic, low-dose aspirin, LDA, proton pump inhibitor, PPI, esomeprazole, pantoprazole, omeprazole, rabeprazole, lansoprazole, and randomized controlled trial. The search strategy for MEDLINE was as follows: (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; and (3) controlled trial; and (4) #1 AND #2 AND #3.

Study selection

In this meta-analysis, we aimed to evaluate the preventive effect of PPIs against GI injuries in long-term LDA users, therefore, we did not include pharmacokinetic studies, and studies with short-term or intermittent use of LDA. Two independent reviewers (Mo C and Lu ML) used a predefined relevance criteria form to screen the studies. After scrutinized the title and abstract, papers not meeting the inclusion criteria and duplicate papers were eliminated. The remaining full-text papers were screened for inclusion. Discrepancies were resolved through discussion with a third reviewer (SG).

Data extraction

Data were extracted after reading the full-text. Two independent reviewers (Mo C and Lu ML) extracted the data. A third independent reviewer (Sur G) reviewed the data abstraction and resolved any discrepancies. When multiple publications reported the data from the same population, the trial reporting the primary outcome of interest was considered the major publication.

Data items

The extracted data included the following items: authors and publication year, the country or region of the study, medical condition or risk factor, sample size, intervention measures, GI ulcer or bleeding events, adverse events including cardiovascular events and diarrhea, and statistical methods.

Risk of bias in individual studies

Risks of bias in individual studies were assessed using

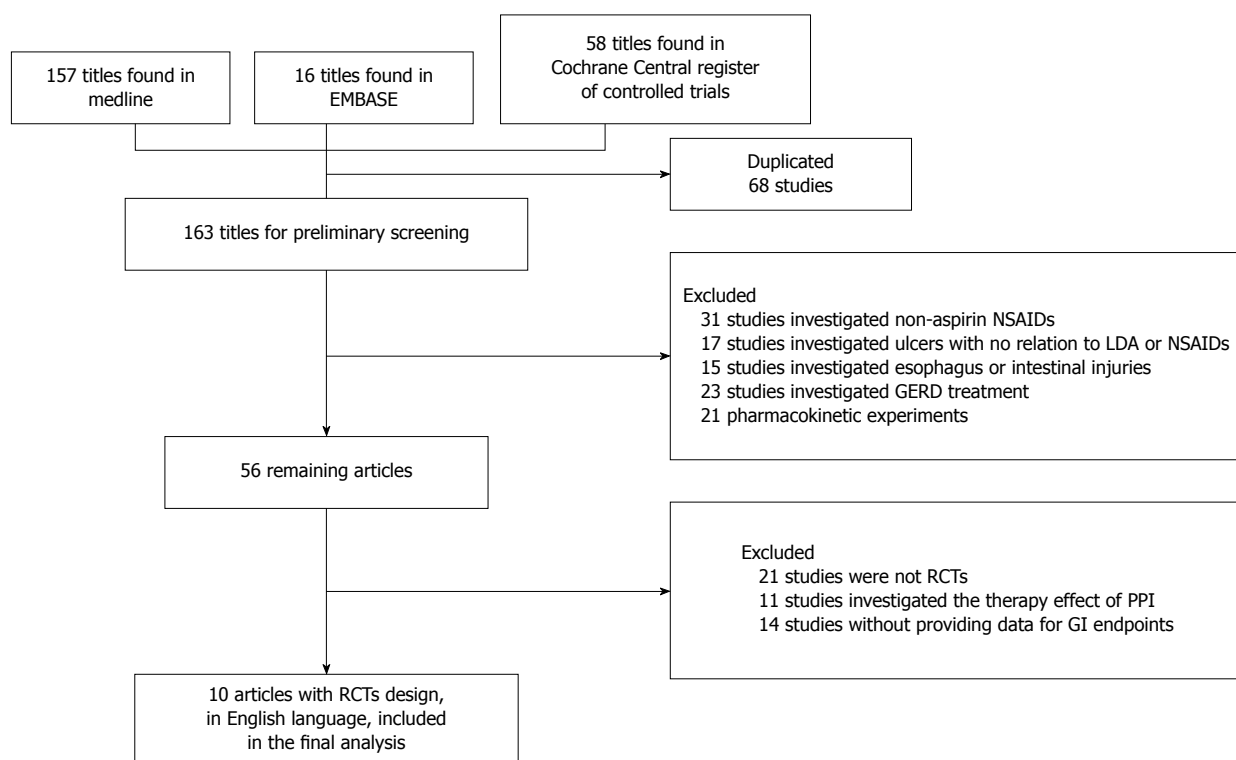


Figure 1 Flow chart of the meta-analysis, summarizing retrieved, included and excluded studies. LDA: Low-dose aspirin; NSAID: Nonsteroidal anti-inflammatory drug; RCT: Randomized controlled trials; GI: Gastrointestinal.

the Cochrane Risk of Bias tool. This tool assesses six domains of bias: sequence generation (low risk, high risk, and unclear risk of bias), allocation concealment (low risk, high risk, and unclear risk of bias), blinding of outcome assessment (low risk, high risk, and unclear risk of bias), incomplete outcome data (low risk, high risk, and unclear risk of bias), selective outcome reporting (low risk, high risk, and unclear risk of bias), and other sources of bias (low risk, high risk, and unclear risk of bias). The two reviewers (Mo C and Lu ML) assessed study quality independently and the assessments were verified by the third reviewer (SG).

Statistical analysis

For dichotomous data, summary statistics are expressed as an odds ratio (OR) with 95%CI. A statistically significant level was considered as $\alpha = 0.05$. Statistical heterogeneity in the included studies was examined using I^2 statistics. If $P \geq 0.10$ in the heterogeneity test, a fixed effects model was used for the meta-analysis; if $P < 0.10$, the sources of heterogeneity were further investigated. If no obvious clinical heterogeneity and no clear statistical heterogeneity occurred, a random effects model was used for the meta-analysis. If the clinical heterogeneity was too large, data synthesis was abandoned and a single analysis used instead. All analyses were conducted using Review Manager Version 5.1.

Assessment of publication bias

Publication bias was determined by the funnel plot.

RESULTS

Study selection

The literature search identified 58 articles in the Cochrane Controlled Trial Register, 16 articles in EMBASE and 157 articles in MEDLINE that met the search criteria. Figure 1 shows the flow chart of the retrieved studies and studies excluded, with the reasons for exclusion. Finally, 10 RCTs published in English were included^[3-12]. Of these, 5 RCTs compared the preventive effect of PPIs with placebo^[3-6,8]; 2 compared PPIs with gefarnate^[7,9], and 3 compared PPIs with famotidine^[10-12].

Study characteristics

All the included studies were published in the United States or Japan between 2002 and 2012. 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 62 to 1876, and the duration of follow-up from 4 to 52 wk. The PPIs used were esomeprazole, pantoprazole, omeprazole, rabeprazole and lansoprazole, at doses ranging from 10 to 40 mg/d. The number of participants in the control group ranged from 61 to 1885 and the duration of follow-up from 4 to 52 wk. The drugs used in the control group included placebo, cytoprotective agents (gefarnate 100 mg/d) and H₂RA (famotidine 20-80 mg/d). The populations varied across the included RCTs, but all had a high risk of gastrointestinal bleeding. Of these studies, 4 RCTs^[3,7,9,12] included

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

Ref.	Country/ region	Risk factors	Ppis			Control			Peptic ulcer		UGIB		MACE		Diarrhea	
			Drug	<i>n</i>	Dose (mg/d)	Drug	<i>n</i>	Dose (mg/d)	PPI	Control	PPI	Control	PPI	Control	PPI	Control
Lai <i>et al</i> ^[3]	Hong Kong	ADA-induced ulcers <i>H. pylori</i> eradicated	Lansoprazole	62	30	Placebo	61	-	1	9	0	8	-	-	-	-
Yeomans <i>et al</i> ^[4]	10 countries	Aged ≥ 60, without ulcer	Esomeprazole	493	20	Placebo	498	-	8	27	2	4	8	14	-	-
Bhatt <i>et al</i> ^[5]	15 countries	Combined with clopidogrel	Omeprazole	1876	20	Placebo	1885	-	2	6	8	26	55	54	56	34
Ren <i>et al</i> ^[6]	China	Combined with clopidogrel	Omeprazole	86	20	Placebo	86	-	-	-	0	2	22	22	-	-
Scheiman <i>et al</i> ^[8]	20 countries	<i>H. pylori</i> -negative, high risk	Esomeprazole	1623	20-40	Placebo	804	-	19	53	1	3	1	1	48	18
Sugano <i>et al</i> ^[9]	Japan	With a history of ulcer	Lansoprazole	226	15	Gefarnate	235	100	6	53	2	9	-	-	19	2
Sanuki <i>et al</i> ^[7]	Japan	With a history of ulcer	Rabeprazole	176	10-20	Gefarnate	85	100	9	20	0	1	-	-	-	-
Ng <i>et al</i> ^[12]	Hong Kong	Aspirin-related ulcers/erosions	Pantoprazole	65	20	Famotidine	65	80	0	6	0	5	-	-	-	-
Ng <i>et al</i> ^[11]	Hong Kong	Combined with clopidogrel	Esomeprazole	163	20	Famotidine	148	40	1	5	3	12	7	5	-	-
Yano <i>et al</i> ^[10]	Japan	Combined with clopidogrel	Omeprazole	65	10	Famotidine	65	20	-	-	3	1	8	11	-	-

PPIs: Proton pump inhibitors; UGIB: Upper gastrointestinal bleeding; MACE: Major adverse cardiovascular events; *H. pylori*: *Helicobacter pylori*.

patients who suffered from ulcer/erosion or with a history of peptic ulcer, 3 RCTs^[3,8,12] included *Helicobacter pylori* (*H. pylori*)-negative patients or patients whose infection had been eradicated, 4 RCTs^[4,5,7,9] performed hierarchical analysis according to the infection status of *H. pylori*, 4 RCTs^[5,6,10,11] included patients with acute coronary syndrome and myocardial infarction who were treated with dual anti-platelet therapy of PPIs and clopidogrel, 4 RCTs^[3,4,7,12] performed endoscopy in the patients before and after treatment, and 4 RCTs^[5,8,9,11] only conducted endoscopy after treatment.

Risk of bias within studies

The risks of bias within the 10 studies included in this meta-analysis are summarized in Table 2 and Figures 2 and 3.

RESULTS

Comparison of preventive effect of PPIs with control in LDA-associated ulcer

Eight of the 10 included studies reported the incidence of LDA-associated peptic ulcer in the PPI group and

the control group (taking placebo, gefarnate and H₂RA). There was no statistical heterogeneity among the research results ($I^2 = 0$; $P = 0.67$), and the fixed effects model was used for the meta-analysis. The result showed that PPIs were superior to the control drugs (OR = 0.16; 95%CI: 0.12-0.23) in prevention of LDA-associated peptic ulcer (Figure 4).

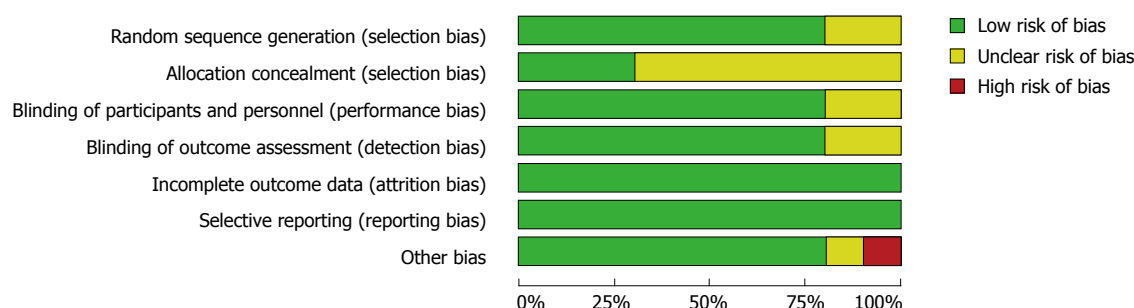
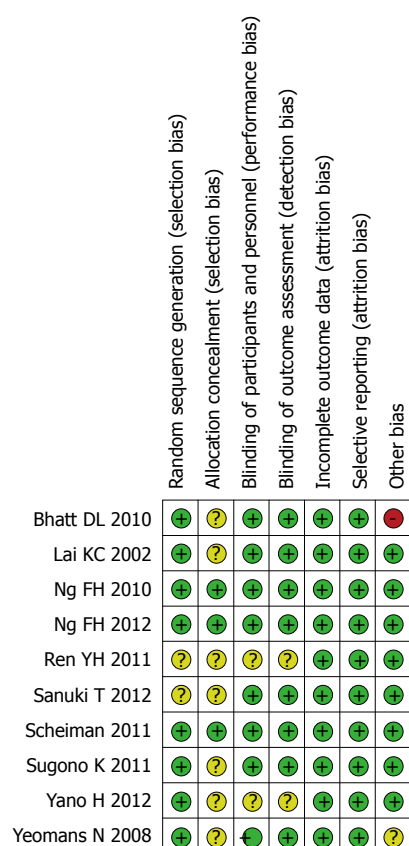
Subgroup analysis was used in different control groups. Four RCTs compared the incidence of LDA-associated ulcer after a PPI and placebo, 2 after a PPI and gefarnate, and 2 after a PPI and famotidine. The results showed that PPIs were superior to placebo (OR = 0.20; 95%CI: 0.13-0.30), gefarnate (OR = 0.12; 95%CI: 0.07-0.22), and famotidine (OR = 0.12; 95%CI: 0.02-0.65) in prevention of LDA-associated peptic ulcer (Figure 5).

Comparison of preventive effect of PPI and control in LDA-associated GI bleeding

All 10 included studies reported the incidence of LDA-associated GI bleeding in a PPI group and a control group. There was no statistical heterogeneity among the research results ($I^2 = 0$; $P = 0.60$), and the fixed

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

Ref.	Random sequence generation	Allocation blinding	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lai <i>et al</i> ^[3]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yeomans <i>et al</i> ^[4]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bhatt <i>et al</i> ^[5]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	high risk
Ren <i>et al</i> ^[6]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Scheiman <i>et al</i> ^[8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sugano <i>et al</i> ^[9]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sanuki <i>et al</i> ^[7]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ng <i>et al</i> ^[12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ng <i>et al</i> ^[11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yano <i>et al</i> ^[10]	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk

**Figure 2** Risks of bias graph.**Figure 3** Risks of bias summary.

effects model was used for the meta-analysis. The result showed that PPIs were superior to the control drugs (OR = 0.27; 95%CI: 0.16-0.43) in prevention of LDA-associated GI bleeding (Figure 6).

Subgroup analysis was also used according to the different control groups. Five RCTs compared the incidence of LDA-associated GI bleeding after PPI and placebo, 2 after PPI and gefarnate, and 3 after PPI and famotidine. The results showed that PPIs were superior to placebo (OR = 0.26; 95%CI: 0.14-0.49), gefarnate (OR = 0.21; 95%CI: 0.05-0.86), and famotidine (OR = 0.32; 95%CI: -0.13-0.79) in prevention of LDA-associated GI bleeding (Figure 7).

Comparison of the incidence of GI bleeding and cardiovascular adverse events in patients treated with dual anti-platelet therapy with PPI and with control

Four RCTs reporting dual anti-platelet therapy with LDA and clopidogrel were included in this meta-analysis^[5,6,10,11]. There were 2190 patients in the PPI group treated with omeprazole or esomeprazole and 2184 patients in the control group. There was no statistical heterogeneity between the groups ($I^2 = 30\%$; $P = 0.23$) and the fixed effects model was used for the meta-analysis. The results showed that PPIs were superior to control drugs (OR = 0.36; 95%CI: 0.15-0.87) in prevention of dual anti-platelet drug-associated GI bleeding (Figure 8). At the same

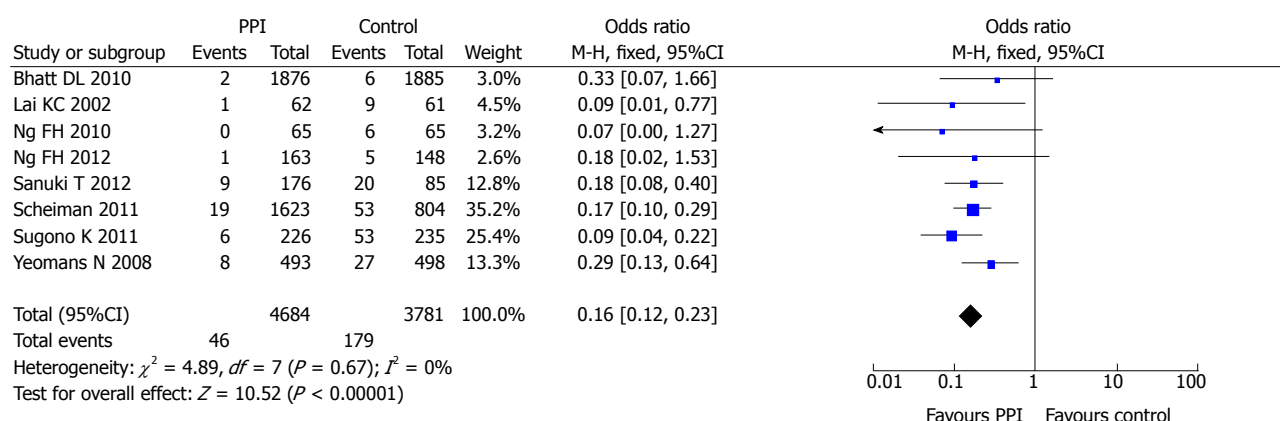


Figure 4 Comparison of the effects of proton pump inhibitors and control drugs in prevention of low-dose aspirin-associated upper gastrointestinal ulcer. LDA: Low-dose aspirin; PPIs: Proton pump inhibitors.

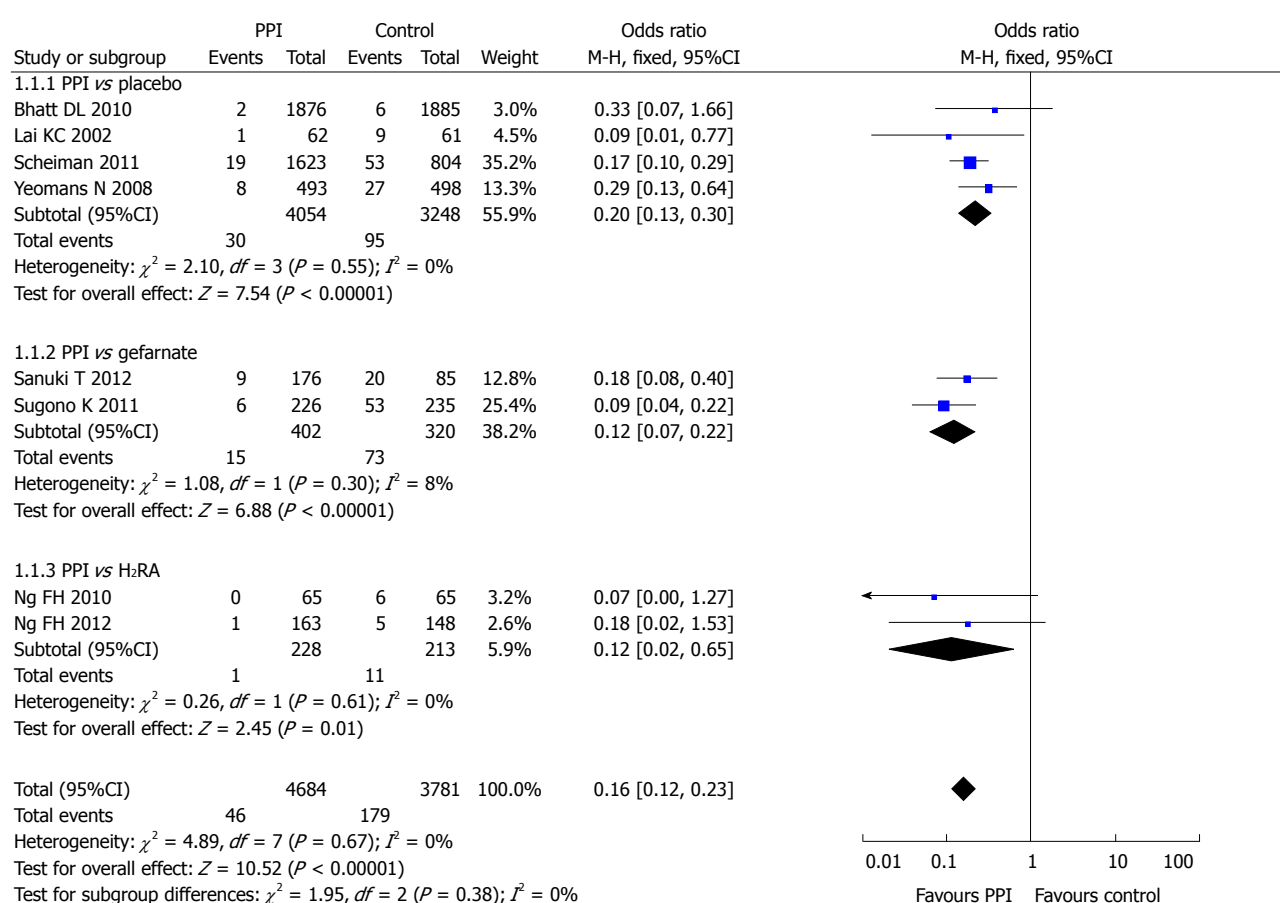


Figure 5 Comparison of the effects of proton pump inhibitors and 3 different control drugs in prevention of low-dose aspirin-associated upper gastrointestinal ulcer. LDA: Low-dose aspirin; PPIs: Proton pump inhibitors.

time, no significant difference (OR = 1.00; 95%CI: 0.76-1.31) in cardiovascular adverse events in the 4 RCTs was found between PPI and control drugs (Figure 9).

Publication bias

Funnel plot analysis of the 10 RCTs of PPIs and controls drugs in the prevention of LDA-associated GI bleeding indicated an asymmetric distribution that suggested the presence of publication bias (Figure 10).

DISCUSSION

It has been confirmed that long-term LDA use increases the risk of GI injury and bleeding^[13]. The mechanism of LDA-associated GI injuries involves both topical and systemic effects, and the latter is the main cause^[1]. Aspirin is a relatively soluble, weak acid which is deionized and becomes fat-soluble, diffusing back into the mucosal cells when pH < 3.5. On the other hand, LDA blocks production of prostaglandins *via* the COX-1

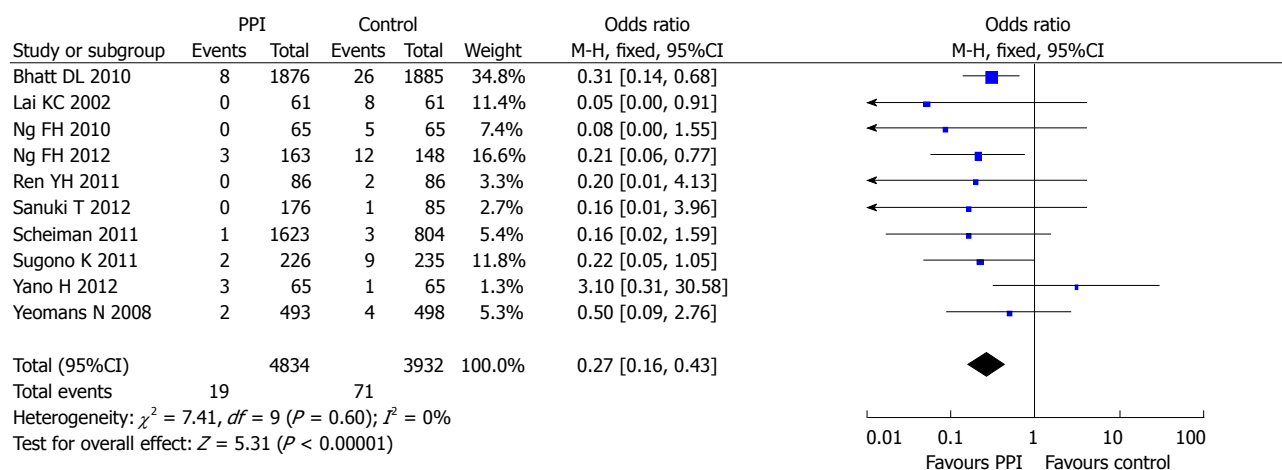


Figure 6 Comparison of the effects of proton pump inhibitors and control drugs in prevention of low-dose aspirin-associated upper gastrointestinal bleeding. LDA: Low-dose aspirin; PPIs: Proton pump inhibitors.

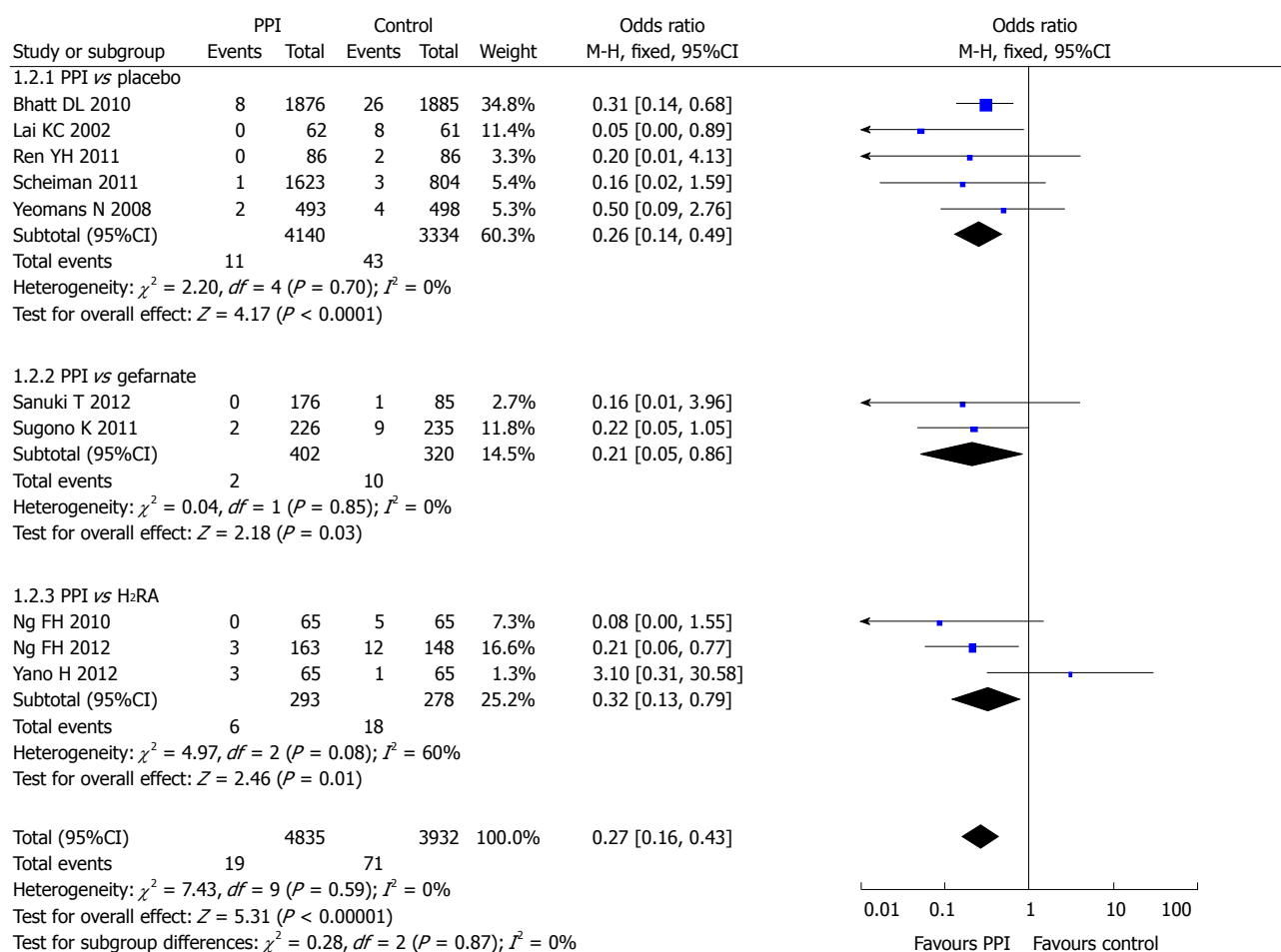


Figure 7 Comparison of the effects of proton pump inhibitors and control drugs in prevention of low-dose aspirin-associated upper gastrointestinal bleeding. LDA: Low-dose aspirin; PPIs: Proton pump inhibitors.

pathway. The inhibition of prostaglandins impairs protective factors such as gastric acid, pepsin, and bile salts, resulting in a gastric environment that is more susceptible to topical attack^[1]. In theory, synthetic prostaglandin replacement therapy can reduce the GI toxicity of LDA. In addition, misoprostol has been shown to be superior to placebo in preventing the recurrence

of gastric ulcers among patients with a history of gastric ulcer who were receiving LDA and NSAID^[14]. However, misoprostol is associated with side effects such as diarrhea and abdominal pain that often restrict its clinical use. Acid suppressors are able to inhibit the acid secretion, and lower the pH in the stomach, thus reducing mucosal injury and bleeding complications.

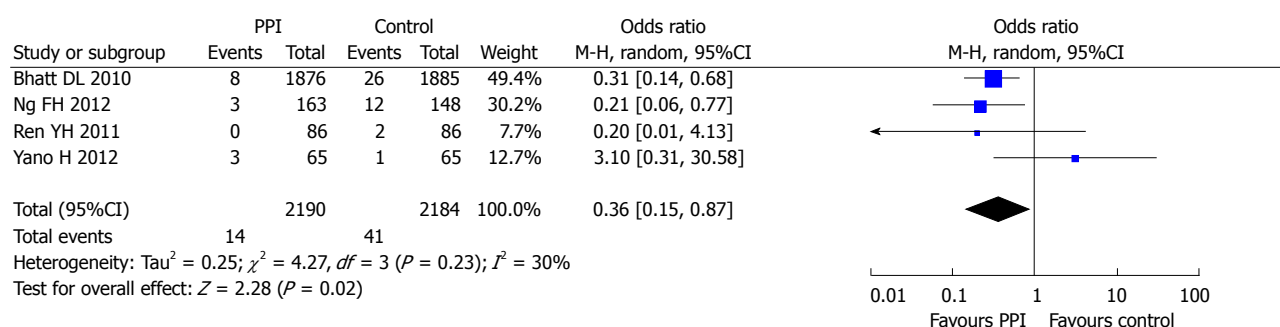


Figure 8 Comparison of the preventive effects of proton pump inhibitors and control drugs in the dual anti-platelet medication-associated upper gastrointestinal ulcer. PPIs: Proton pump inhibitors.

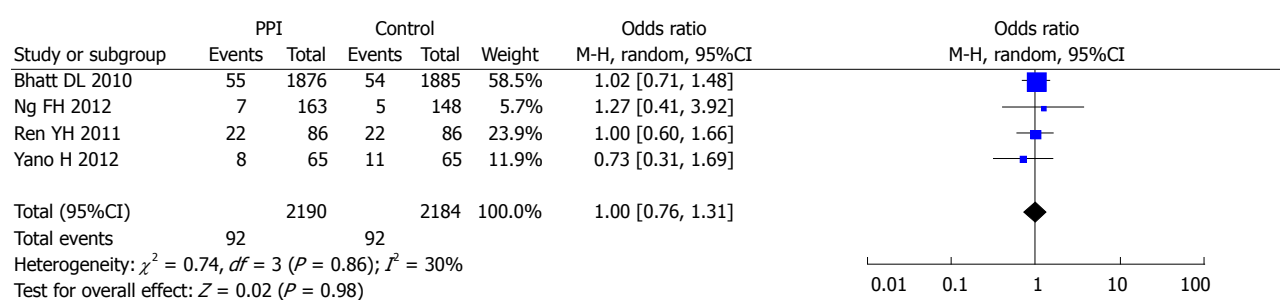


Figure 9 Comparison of proton pump inhibitors and control drugs on major adverse cardiovascular events of dual anti-platelet medication. PPIs: Proton pump inhibitors; MACE: Major adverse cardiovascular events.

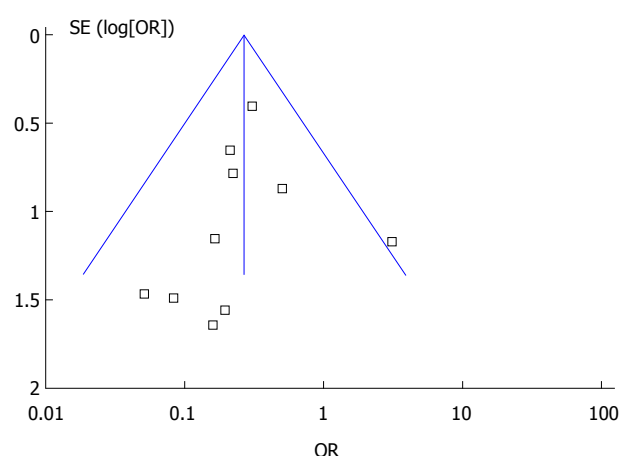


Figure 10 Funnel plot analysis of proton pump inhibitors and control drugs in prevention of upper gastrointestinal bleeding.

H₂RA can prevent LDA-associated GI injuries effectively, although data are limited. Nakashima^[15] indicated in a retrospective study that H₂RA were effective for the prevention of LDA-induced peptic ulcer, similar to the effects of PPIs, compared with cytoprotective anti-ulcer drugs. Lanas^[16] discovered in a case control study that H₂RA reduced the risk of GI bleeding induced by LDA and clopidogrel (relative risk: 0.65; 95%CI: 0.50-0.85). The FAMOUS trial evaluated the effect of a standard dose of famotidine in the prevention of ulcers and esophagitis induced by LDA, and concluded that famotidine was effective in the prevention of gastric and duodenal ulcers, and erosive

esophagitis in patients taking LDA^[17].

The studies in the prevention of LDA-associated GI injuries have focused on PPIs. The OITA-GF study indicated that about one-third of asymptomatic patients taking LDA had been found to have gastric and duodenal ulcers/erosions during the 3-mo follow-up, and PPI use was the only independent factor for gastroduodenal ulcers/erosions (OR = 0.35; 95%CI: 0.14-0.86; $P = 0.02$)^[18]. Chin *et al*^[19], Ng *et al*^[20], and Yasuda *et al*^[21] reported that PPI reduced upper GI bleeding after percutaneous coronary intervention. Lanas *et al*^[13] included 3 RCTs in their meta-analysis evaluating the preventive effect of PPIs in long-time LDA users, and concluded that PPIs reduced the risk of major GI bleeding in patients given LDA (OR = 0.34; 95%CI: 0.21-0.57).

Five RCTs comparing the preventive effect of PPIs with placebo in LDA users were included in this meta-analysis, and the result indicated that PPIs were effective in preventing LDA-associated GI ulcers compared with placebo.

Gilard *et al*^[22] first discovered in an *in vitro* experiment that PPI diminished the biological action of clopidogrel in coronary revascularization patients, and confirmed in the subsequent RCT that omeprazole decreased the P2Y₁₂ inhibition of clopidogrel significantly^[23]. Ho *et al*^[24] discovered in an retrospective cohort trial that patients with acute coronary syndromes who used clopidogrel and a PPI concomitantly had an increased risk of adverse cardiovascular outcomes than those who used clopidogrel without a PPI (15.5% vs

11.9%; OR = 1.49; 95%CI: 1.30-1.71), suggesting that use of a PPI may be associated with attenuation of the benefits of clopidogrel with acute coronary syndromes. In view of the results above, the FDA suggested in January 2009 that a combination of a PPI and clopidogrel should be avoided. However, subsequent clinical trials did not support this suggestion. Ray *et al*^[25] found in a retrospective cohort trial of 20596 patients with coronary heart disease that concomitant use of a PPI and clopidogrel decreased the occurrence of GI bleeding (95%CI: 11.7-36.9), and did not increase MACE (95%CI: 0.82-1.19). GHOST and FAST-MI trials also concluded that concomitant use of a PPI and clopidogrel did not increase the risk of MACE^[26,27]. Charlott *et al*^[28] found that PPIs increased the risk of MACE in myocardial infarction patients after discharge whether clopidogrel was used or not, and indicated that a PPI was the independent risk factor of MACE. Kwok included 7 observational studies in his meta-analysis and found that either concomitant use of a PPI and clopidogrel or sole use of a PPI increased the risk of MACE. He concluded that a PPI was an important confounding factor and that the clinical hypothesis of a PPI-clopidogrel interaction remained to be further verified^[29].

Our study included 4 RCTs investigating dual anti-platelet therapy with a PPI and clopidogrel and the preventive effect of PPIs against GI injuries and the incidence of MACE. The results showed that PPIs were able to prevent the dual anti-platelet therapy-associated GI bleeding, and at the same time, PPIs did not increase the risk of MACE. Our study aimed to evaluate the preventive effect of PPIs, so the number of studies we included may be insufficient, selection bias may exist and the interpretation of the results needs further verification.

Considering the debate regarding the PPI-clopidogrel interaction, the ACC/AHA/SCAI consensus indicated that H₂RA may be a reasonable alternative for a lower risk of GI bleeding^[30]. The FAMOUS trial^[17] suggested that high dose H₂RA may be an alternative to PPI to prevent LDA-associated GI bleeding. However, some scholars doubt the effects of H₂RA and believe that H₂RA are inferior to PPIs in the prevention of LDA-associated GI injuries. The OITA-GF2 study indicated that lansoprazole (15 mg/d) was superior to famotidine (40 mg/d) in the prevention of LDA-associated GI injuries^[31]. Our meta-analysis included 3 RCTs to evaluate the preventive effects of PPI and H₂RA in LDA-associated ulcers and bleeding, and the results indicated that PPIs were superior to H₂RA in preventing both ulcers (OR = 0.12; 95%CI: 0.02-0.65) and bleeding (OR = 0.32; 95%CI: 0.13-0.79). Since the studies we included are all published in English, the number of studies is small and selection bias may exist, and better designed RCTs are needed to support our results.

Although this study is the first systematic review regarding the preventive effect of PPIs in LDA-

associated GI injuries, there are some limitations as we did not include studies published in languages other than English. Furthermore, we searched for unpublished material, but were unable to identify any relevant papers. So there may be selection bias. We only included 4 RCTs related to the interactions of PPIs and clopidogrel because we focused on the adverse events but not the therapeutic effects, and studies which did not report GI endpoints events were not included in our meta-analysis. Publication bias was also found from the funnel plot with an asymmetric distribution.

In conclusion, PPIs are able to prevent LDA-associated upper GI ulcers and bleeding effectively. Concomitant use of a PPI, LDA and clopidogrel did not increase the risk of cardiovascular adverse events, so PPIs are safe in the prevention of LDA-associated GI injuries. Given the selection bias and publication bias, our results should be interpreted with caution.

COMMENTS

Background

With the widespread use of low-dose acetylsalicylic acid (LDA) in the primary and secondary prevention of cardiovascular and cerebrovascular diseases, the incidence of LDA-associated upper gastrointestinal injuries, including gastric mucosal erosions, peptic ulcers, and bleeding has been increasing. The aim of this meta-analysis is to verify that proton pump inhibitors (PPIs) are the preferred agents for the prophylaxis of LDA-associated gastrointestinal injuries.

Research frontiers

The FDA suggested in January 2009 that combined use of PPI and clopidogrel should be avoided. However, subsequent clinical trials did not support this suggestion. Several randomized controlled trials concluded that concomitant use of a PPI and clopidogrel decreased the occurrence of GI bleeding, and did not increase the risk of major adverse cardiovascular events.

Innovations and breakthroughs

This meta-analysis aimed to determine the preventive effect and safety of PPIs in the LDA-associated GI ulcer and bleeding and this is the first meta-analysis on this subject.

Applications

This meta-analysis provided the best evidence for clinical practice that PPIs are able to prevent LDA-associated upper GI ulcers and bleeding effectively and safely.

Terminology

LDA-associated upper gastrointestinal injury: Gastroduodenal mucosal erosions, peptic ulcers and upper gastrointestinal bleeding induced by the use of low-dose aspirin.

Peer-review

Based on the data collected and presented, the authors conclude that PPIs are effective in the prevention of LDA-associated upper gastrointestinal tract ulcers and bleeding, without increasing the major adverse cardiovascular events. In general, this is an interesting and well written review on an important topic. The data presented have confirmed and significantly extended the observations already published.

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