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Evaluation of the effectiveness of esomeprazole treatment strategies in the management of patients with gastroesophageal reflux disease symptoms: a meta-analysis

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Here we aimed to evaluate the effectiveness of esomeprazole treatment strategies comparing with other proton pump inhibitors (PPI) in clinical practice for six months in the management of patients with symptomatic gastroesophageal reflux disease (GERD). An extensive search of the literature focusing on PPI therapeutic evaluation was performed up to December 2014. Risk ratio (RR) with its corresponding 95% confidence intervals (CIs) in each study was chosen as the effect size. Cochrane's Q statistic and I^2 test were both conducted to evaluate heterogeneity across individual studies. Meta-regression was conducted to explore the source of heterogeneity and sensitive analysis was performed to assess the risk bias for the meta-analysis. Totally, eleven trials with high quality enrolled in the meta-analysis. Esomeprazole therapy (20 mg daily) had lower relapse rates than other drugs during six months maintenance treatment (RR = 0.67; 95% CI: 0.55-0.83). Heartburn (RR = 0.72; 95% CI: 0.57-0.92) and epigastric pain (RR = 0.82, 95% CI: 0.70-0.96) were less likely to happen after esomeprazole treatment, and no significant advantage was found on acid regurgitation and dysphagia. Moreover, lower risk for serious adverse events was observed after esomeprazole therapy (RR = 1.40, 95% CI: 1.04-1.88). Blind method or difference controlled drugs did not influence heterogeneity across studies. Moreover, the conclusion on acid regurgitation, abdominal pain and dysphagia might be unstable. In GERD patients, esomeprazole 20 mg daily is more effective than other PPIs regarding relapse rates, symptoms of epigastric pain and heartburn, and serious adverse events.

1. Introduction

Gastroesophageal reflux disease (GERD) is defined by esophageal and extraesophageal syndromes caused by the reflux of gastric contents (Vakil et al. 2006). It is acceptable that symptoms induced by GERD seem to be more common now than 25 years ago. GERD is prevalent worldwide with prevalence estimates showing greatest prevalence in North America (19.8%) and lowest in East Asia (5.2%) (El-Serag et al. 2014).

Acid suppression is recognized as the mainstay of treatment for GERD, and proton pump inhibitors (PPIs) therapy traditionally served as the most rapid symptomatic relief in majority of patients (DeVault and Castell 2005). Recently, five PPIs are available for treating GERD, including omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole. Esomeprazole, as the isomer of omeprazole, has been developed and marketed with less adverse events compared with omeprazole (Kendall 2003). All the PPIs are racemates, which leads to pharmacologically differences caused by their spatial disposition. Several previous studies were designed and suggested modest benefits of one drug over another (Goh et al. 2007; Hansen et al. 2005). While the efficacy of esomeprazole in patients with GERD symptoms control, including heartburn, acid regurgitation, dysphagia, and epigastric pain, remains controversial compared with other acid suppression drugs. Previous meta-analysis has been designed and suggests similar healing rates and relapse rates of omeprazole treatment compared with three other developed PPI drugs (pantoprazole, lansoprazole, rabeprazole) (Caro et al. 2001) however not included esomeprazole.

To systematically evaluate the efficacy of these drugs, data from previous randomized control trials (RCTs) were exacted to compare esomeprazole treatment with other PPI drugs treatment. Relapse rates during six months treatment, four main GERD symptoms and adverse events were all evaluated in this meta-analysis.

2. Investigations and results

2.1. Literature selection

A summary of literature selection is shown in Fig. 1. Totally, 277 articles were originally enrolled in the meta-analysis. After eliminating duplicate documents, 213 articles remained. Then title and abstract of the rest of articles were reviewed, and the 193 articles were excluded, including non-original articles (report, review, meeting; 67), articles unrelated with esomeprazole treatment (93), articles unrelated with GERD (21), non-human clinical studies (8), and articles not published in English (4). The full-texts of the remaining 20 articles were retrieved, and 9 articles were excluded (2 articles investigated on patient's quality of life after treatment, 2 articles reported economic evaluation, 2 articles lacked sufficient data, 1 article did not study, 1 article was based on data from previous research esomeprazole treatment, and 1 article was not a RCT). Finally, data from 11 trials (Devault et al. 2006; Goh et al. 2007; Hansen et al. 2005; Johnson et al. 2001; Labenz et al. 2005; Lauritsen et al. 2003; Sjöstedt et al. 2005; Talley et al. 2001; Talley et al. 2002; Tsai et al. 2004; Vakil et al. 2001) were meta-analyzed.

2.2. Characteristics of study

As shown in Table 1, all the 11 enrolled trials, including 4 996 cases and 4 953 controls, were performed in a multi-centers pattern. All

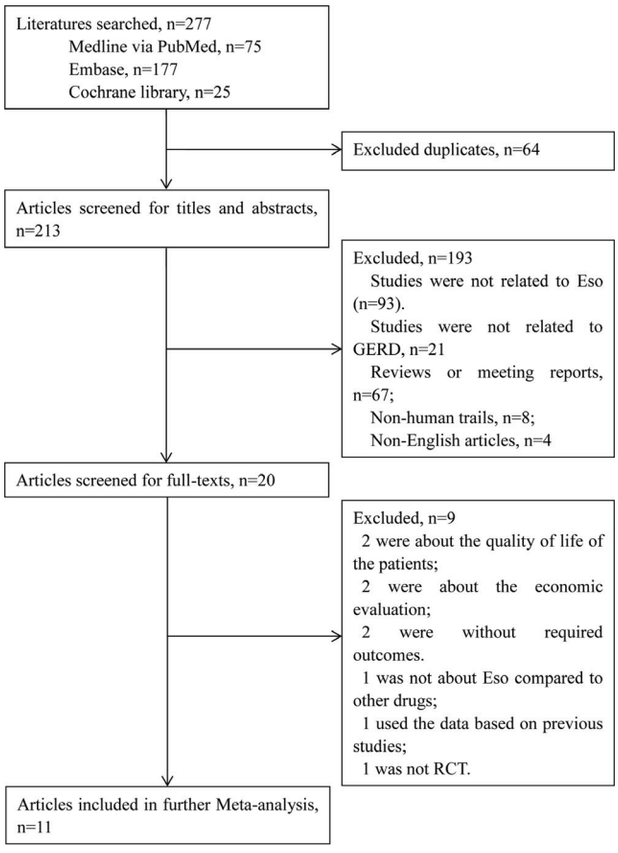

Fig. 1: Flow of literature search and study selection;

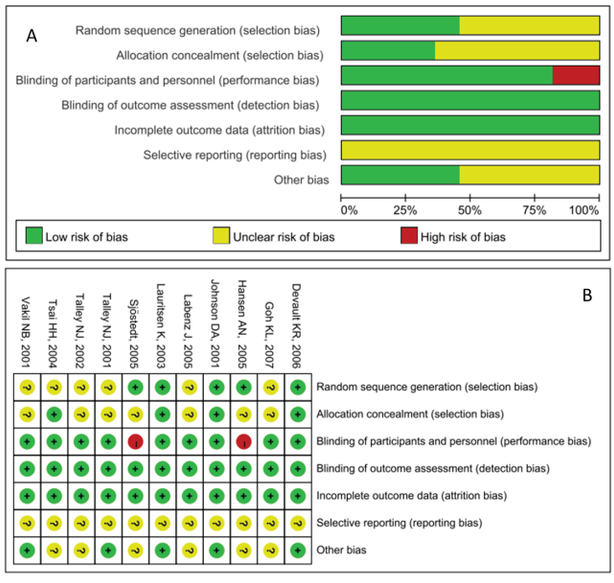

Fig. 2: Risk of bias across individual studies. A: Risk of bias graph; B: Risk of bias summary.

the patients firstly underwent four to eight weeks' acute treatment, and maintenance therapy for at least six months. All studies were double-blind RCTs except three studies conducted by Hansen et al. (2005), Sjostedt et al. (Sjöstedt et al. 2005), and Tsai et al. (Tsai et al. 2004). Diagnosis methods for GERD were esophagogastroduodenoscopy (Devault et al. 2006; Johnson et al. 2001), endoscopy (Goh et al. 2007; Labenz et al. 2005; Lauritsen et al. 2003; Sjöstedt et al. 2005; Talley et al. 2001; Talley et al. 2002; Tsai et al. 2004; Vakil et al. 2001) and symptom assessment (Hansen et al. 2005). All patients in the esomeprazole group accepted esomeprazole 20 mg daily administration and were compared with other PPIs (Devault et al. 2006; Goh et al. 2007; Labenz et al. 2005; Lauritsen et al. 2003; Talley et al. 2001; Tsai et al. 2004) or oral esomeprazole with other doses (Hansen et al. 2005; Johnson et al. 2001; Sjöstedt et al. 2005; Talley et al. 2002; Vakil et al. 2001).

2.3. Quality evaluation

As shown in Fig. 2, quality of the overall enrolled studies was relatively high. However, two open trials (Hansen et al. 2005; Sjöstedt et al. 2005) caused high performance bias. In addition, some trials did not clarify the methods for random allocation or/and hidden distribution that caused unknown risks in the meta-analysis. Reporting biases in all studies were unable to be determined, thus they were all defined as unclear risk.

2.4. Effectiveness of esomeprazole treatment strategies compared with other PPIs

The outcomes of the meta-analysiswere mainly divided into three parts, including relapse rates during six months treatment for GERD, four main symptoms of gastroesophageal reflux recurrence, and side events occurrence.

2.4.1. Relapse rates comparison during six months treatment for GERD

Five studies reported the relapse rates for PPI treatment during six months, including 3 403 cases and 3 368 controls. Heterogeneity test results showed that there was significant heterogeneity across individual studies ($p< 0.01$, $I^2 = 77\%$). Therefore, the random effects model was selected to pool RR from individual studies. Fig. 3 shows that esomeprazole treatment had better curative effects than treatment with other drugs (risk ratio (RR) = 0.67; 95% confidence interval (CI): 0.55-0.83; $p< 0.01$).

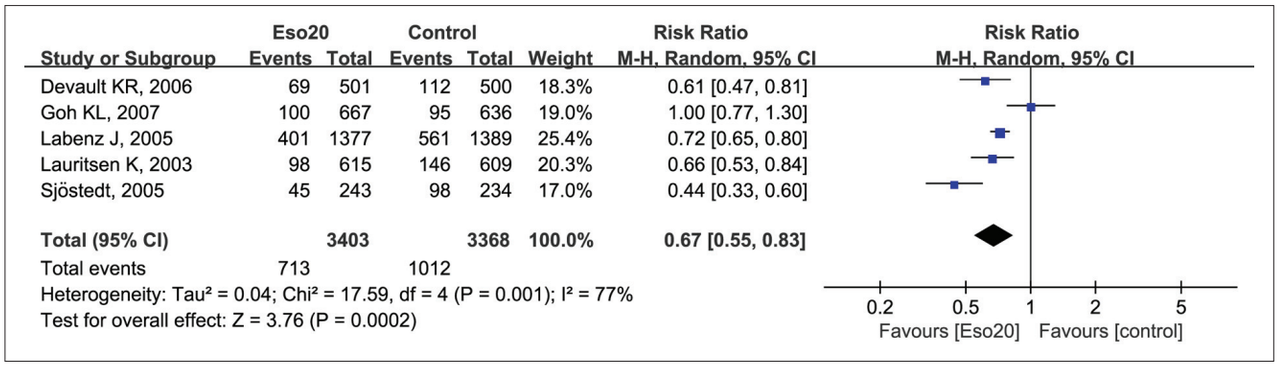

Fig. 3: Forest plot of gastroesophageal reflux disease relapse rates during 6 month maintenance treatment.

Table 1: Characteristics of the selected studies

Author, year	Study type	Country	Follow up	Population	Identification	Esomeprazole			Control			Outcomes
						N (M/F)	Age, years	Administration	N (M/F)	Age, years	Administration	
Devault et al. 2006	Double-blind, double-dummy, parallel-group, multicenter, RCT	US, 143 centers	6 months	Patients healing of EE at 4 or 8 weeks	EGD	501 (297/204)	47.5 (18-75)	20 mg, once daily	500 (293/207)	47.9 (18-78)	Lan: 15 mg, once daily	Remission rate, four symptoms, AE, SAE, drug -related AE
Goh et al. 2007	Double-blind, parallel-group RCT	133 centers in 16 countries	6 months	Patients with healing GERD	Endoscopy	667 (396/271)	48.8±14.5	20 mg, once daily	636 (373/263)	49.0±14.1	Pan: 20 mg, once daily	Remission rate, AE, SAE, drug -related AE
Hansen et al. 2005	Prospective, open, parallel-group, RCT	281 centers in Norway	6 months	Patients who were symptom-free	Symptomas-sessment	658 (375/283)	50.5 (20-87)	20 mg, once daily	634 (349/285)	51.4 (18-85)	Eso: 20 mg on-demand	Heartburn, AE
Johnson et al. 2001	Multicenter, double-blind, parallel-group RCT	US, 47 centers	6 months	Patients who were *Helicobacter pylori* negative	endoscopy	82 (51/31)	46.3 (21-81)	20 mg, once daily	82 (48/34)	46.9 (19-73)	Eso: 40 mg, once daily	Remission rate, heartburn, AE
Labenz et al. 2005	Double-blind, multicenter, RCT	263 centers in 14 countries	6 months	Patients with no confirmed EE	Endoscopy	1377 (888/489)	50.2±14.1	20 mg, once daily	1389 (856/533)	50.7±13.8	Pan: 20 mg, once daily	Remission rate, SAE
Lauritsen et al. 2003	Double-blind, double-dummy, RCT	148 centers in Europe and South Africa	6 months	Patients with healed oesophagitis	Endoscopy	615 (388/227)	49.3	20 mg, once daily	609 (356/253)	49.2	Lan: 15 mg, once daily	Remission rate, heartburn, dysphagia, epigastric pain, SAE
Sjöstedt et al. 2005	Multicenter, open, parallel-group, RCT	Sweden, 38 centers	6 months	Patients with healing erosive reflux oesophagitis	Endoscopy, symptomas-sessment	241 (157/84)	55 (22-87)	20 mg, once daily	229 (128/101)	54 (20-82)	Eso: 20 mg, on demand	Remission rate, heartburn, dysphagia, epigastric pain, SAE
Talley et al. 2001	Multicenter, double-blind, parallel-group, RCT	65 centres in Denmark, Fenland, Norway and Sweden	6 months	Patients with complete resolution of heartburn	Endoscopy	170 (94/76)	49 (19-78)	20 mg, once daily	172 (98/74)	49 (21-79)	placebo	Heartburn, SAE
Talley et al. 2002	Multimetre, double-blind, parallel-group, RCT	116 centres in UK, Ireland and Canada	6 months	Patients with complete resolution of heartburn	Endoscopy	282 (135/147)	48.4	20 mg, once daily	293 (135/158)	48	Eso: 40, mg, on demand	AE, SAE
Tsai et al. 2004	Multicentre, single-blind, parallel group, RCT	28 hospitals in UK	6 months	Patients with complete resolution of heartburn	Endoscopy and physical examination	311 (143/168)	51±13.8	20 mg, once daily	311 (130/181)	51±13.8	Lan: 15 mg, once daily	Heartburn, SAE
Vakil et al. 2001	Multicentre, double-blind, parallel-group, RCT	51 centers in US	6 months	Patients healing of erosive oesophagitis	Endoscopy	92 (51/41)	47.1 (18-84)	20 mg, once daily	98 (58/40)	45.2 (19-76)	Eso: 40 mg, once day	Remission rate, heartburn, AE

RCT: randomized controlled trial; EE: erosive esophagitis;GERD: gastroesophageal reflux disease; EGD: esophagogastroduodenoscopy;M: male; F: female; Eso: esomeprazole; Lan: lansoprazole; Pan: pantoprazole.

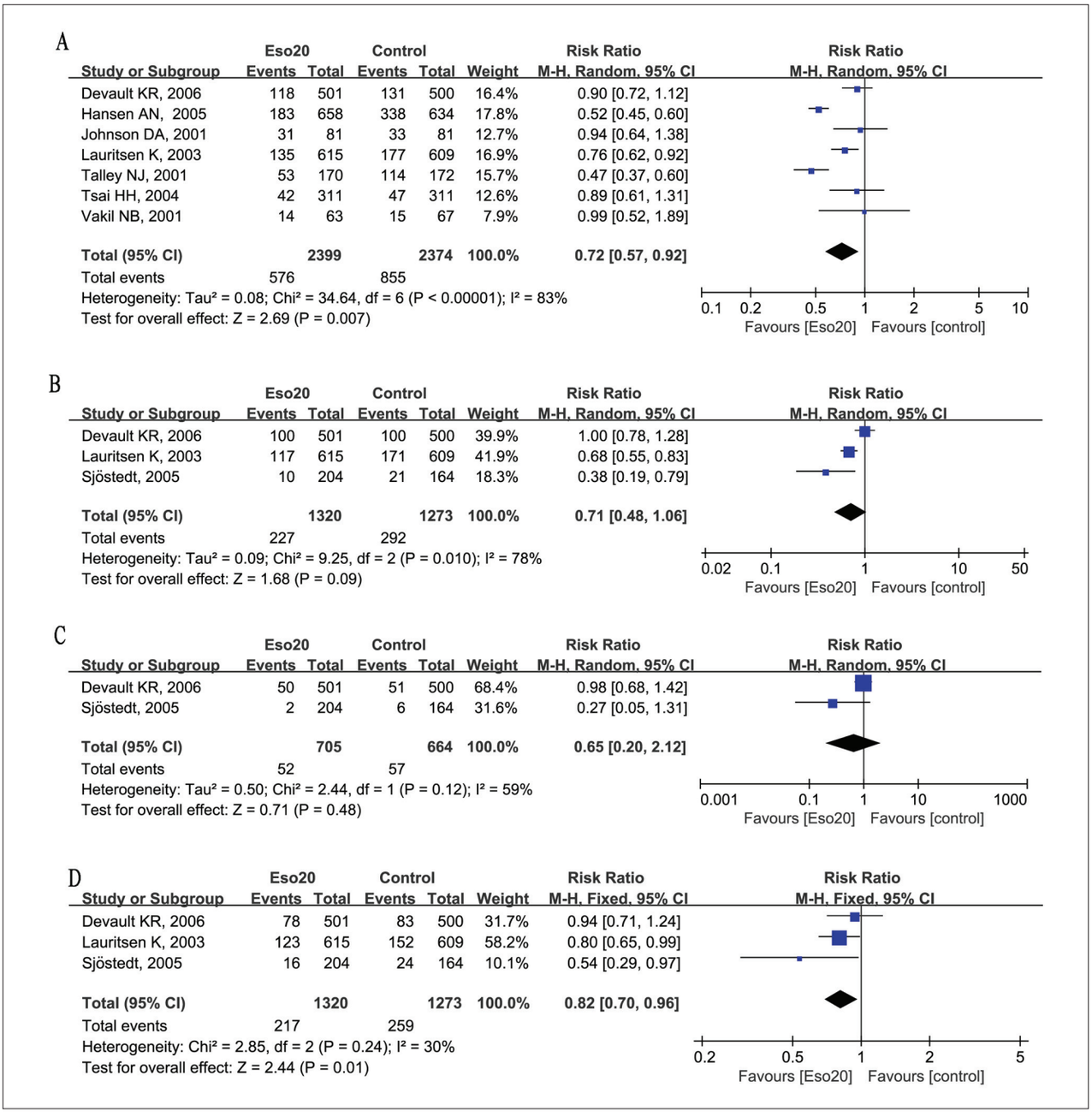

Fig. 4: Forest plot of four main symptoms (heartburn, acid regurgitation, dysphagia, epigastric pain) of gastroesophageal reflux disease recurrence. A: heartburn; B: acid regurgitation; C: dysphagia; D: epigastric pain.

2.4.2. Evaluation for four main symptoms recurrence of GERD

Four main symptoms of GERD recurrence were evaluated such as heartburn, acid regurgitation, dysphagia, epigastric pain.

Seven articles reported heartburn symptoms of GERD reoccurrence after PPI treatment. Significant heterogeneity between the studies ($p< 0.05$, $I^2 = 83\%$) was found. When we pooled data from the seven studies, esomeprazole showed better a curative effect on heartburn compared with other treatments using random effects model (Fig. 4A, RR = 0.72; 95% CI: 0.57-0.92; $p< 0.01$).

Three articles reported acid regurgitation symptom reoccurrence after PPI treatment. According to the results of the heterogeneity test, heterogeneity across individual studies was found with statistical significance ($p< 0.05$, $I^2 = 78\%$). When data from the three studies were pooled using the random effects model, results showed no significant difference on acid regurgitation occurrence between esomeprazole treatment and other drug treatment (Fig. 4B, RR = 0.71, 95% CI: 0.48-1.06; $p> 0.05$).

In addition, dysphagia reoccurrence after PPI treatment was reported in two trials, including 705 cases and 664 controls. As shown in Fig. 4C, significant heterogeneity was found between individual studies ($p> 0.05$, $I^2 = 59\%$), and no significant difference was calculated using the random effects model (RR = 0.65, 95% CI: 0.20- 2.12; $p> 0.05$).

Abdominal pain reoccurrence after PPI treatment was reported in three papers. Totally, 1 320 cases and 1 273 controls enrolled in this comparison (Fig. 4D). Lower abdominal pain occurrence after esomeprazole treatment compared with other PPI treatment was found using the fixed effect model (heterogeneity, $p> 0.05$, $I^2 = 30\%$; RR = 0.82, 95% CI: 0.70-0.96; $p< 0.05$).

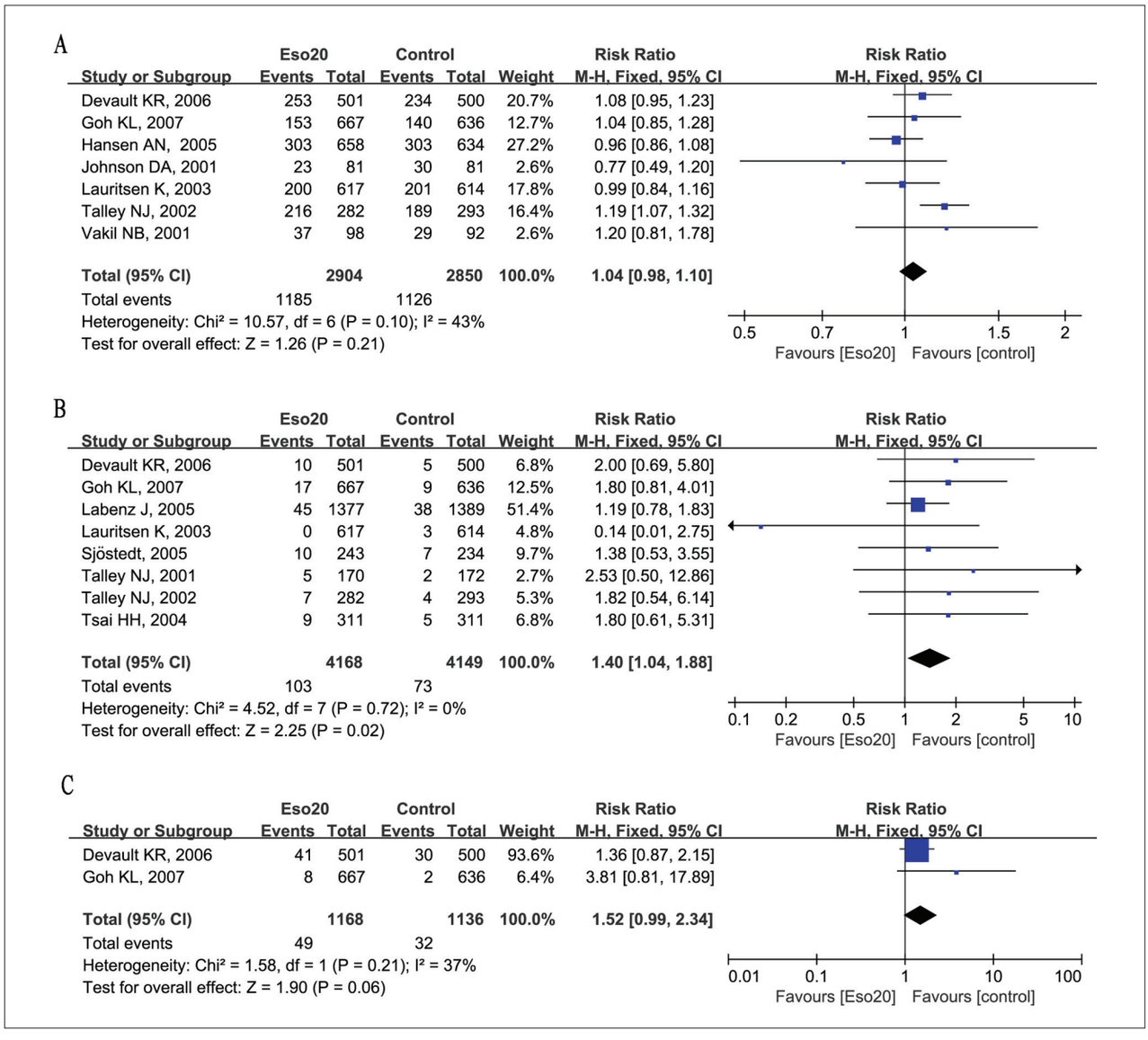

Fig. 5: Forest plot of adverse events occurrence (adverse events, serious adverse events, drug-related adverse events) evaluation comparing esomeprazole treatment with other proton pump inhibitors. A: adverse events; B: serious adverse events; C: drug-related adverse events.

2.4.3. Adverse events evaluation

Adverse events occurrence is a key indicator for evaluating drug treatment. Here, we compared adverse events, serious adverse events, and drug-induced adverse events during six months maintenance treatment between esomeprazole group and control group. Adverse events were reported in seven studies. Fig. 5A shows no significant difference between esomeprazole treatment and other drug treatment on adverse events occurrence (RR = 1.04, 95% CI: 0.98-1.10; $p > 0.05$), and no significant heterogeneity was found across studies ($p = 0.10$, $I^2 = 43\%$).

Eight articles reported serious adverse events, including 4 168 cases and 4 149 cases. As shown in Fig. 5B, we pooled data from the studies and found higher serious adverse events risk after other drug treatment than esomeprazole treatment (RR = 1.40, 95% CI: 1.04-1.88; $p < 0.05$) without significant heterogeneity ($p = 0.72$, $I^2 = 0\%$).

Adverse events induced by drugs were reported in two articles containing 1 168 cases and 1136 controls. As shown in Fig. 5C, no significant heterogeneity was found across individual studies ($p > 0.05$, $I^2 = 37\%$), and pooled data from these studies suggest no significant difference on adverse events occurrence induced by drug between esomeprazole treatment and other PPI treatment (RR = 1.52, 95% CI: 0.99, 2.34; $p > 0.05$).

2.5. Meta-regression analysis

To explore the source of heterogeneity among studies reaching on remission rates of GERD, meta-regression analysis was performed according to blind design and different drugs used in control group. Table 2 shows that difference from blind method or different controlled drugs does not influence heterogeneity across studies ($p > 0.05$).

2.6. Sensitivity analysis

As shown in Table 3, the results were reversed by using using fixed effect model and random effects model to pool the effect sizes of symptoms of acid regurgitation, abdominal pain, and dysphagia, suggesting the results on these three symptoms might be unstable. Similar estimates were observed using both fixed effect model and random effects model with regard to adverse events, indicating the stable results.

Table 2: Meta regression analyses

Log RR	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
Blind	-0.8593045	0.3497507	-2.46	0.133	-2.36416	0.6455514
Control	0.2438739	0.1825803	1.34	0.313	-0.5417056	1.029453
_cons	0.170942	0.2798235	0.61	0.603	-1.033041	1.374925

Table 3: Sensitivity analysis (random effects model *vs.* fixed effect model)

Outcomes	Random effects model		Fixed effect model	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Endoscopic relapse rates	0.67 (0.55, 0.83)	<0.01	0.70 (0.65, 0.76)	<0.01
Heartburn	0.72 (0.57, 0.92)	<0.01	0.66 (0.61, 0.73)	<0.01
Acid regurgitation	0.71 (0.48, 1.06)	0.09	0.76 (0.65, 0.89)	<0.01
Dysphagia	0.65 (0.20, 2.12)	<0.01	0.90 (0.63, 1.28)	0.55
Epigastric pain	0.81 (0.66, 1.00)	0.05	0.82 (0.70, 0.96)	0.01
AE	1.05 (0.97, 1.14)	0.26	1.04 (0.98, 1.10)	0.21
SAE	1.42 (1.05, 1.92)	0.02	1.40 (1.04, 1.88)	0.02
Drug-related AE	1.73 (0.74, 4.09)	0.21	1.52 (0.99, 2.34)	0.06

AE: adverse event; SAE: serious adverse event.

2.7. Publication bias

To explore the publication bias, Egger's regression test was performed among individual studies. No significant publication bias was observed among these studies ($p > 0.05$).

3. Discussion

Currently, five PPIs are approved for treatment of GERD, namely omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole. Mixed results have been provided when esomeprazole, the new developed drug from omeprazole, compared with the other four PPI drugs. The present meta-analysis suggests that esomeprazole treatment has lower relapse rates during six months maintenance therapy than other four PPIs. Esomeprazole treatment showed a better curative effect on heartburn and epigastric pain, while no significant advantage was found on acid regurgitation and dysphagia. As for adverse events, less severe adverse events were observed after esomeprazole treatment than with other drug treatment. Notably, the conclusion on acid regurgitation, abdominal pain, and dysphagia might be unstable.

With regard to relapse rates during PPI maintenance therapy, although significantly lower relapse rates were induced by esomeprazole treatment, significant heterogeneity occurred among the individual studies. Population from five included studies assessed on the remission rate were different from each other. For example, the study by Goh et al. (2007) included patients with GERD (Goh et al. 2007), while the study by Devault et al. (2006) studies patients suffering from erosive esophagitis at 4 or 8 weeks (Devault et al. 2006). Erosive esophagitis is one of the serious complications developed from chronic GERD (Johnson et al. 2001). It is possible that patients' different background might account for the potential bias of the meta-analysis. However, the risk of population backgrounds would not reverse our conclusion since adjustment for the assessment ensured cases from individual studies which were compared with their own control.

Up to three quarters of GERD patients have symptoms, mostly heartburn, epigastric pain, acid regurgitation and dysphagia. Thus, maintaining control of symptoms was recognized as the most important goal of GERD therapies (DeVault and Castell 2005). This meta-analysis suggests th esomeprazole treatment leads to less recurrence rates of heartburn and epigastric pain, while no significant advantage was found regarding acid regurgitation and dysphagia. Heartburn (68%) and acid regurgitation (60%) occurred in most of the adults patients with GERD and in about 2% of 3-9-year-old children and about 5-8% of 10-17-year-old children (Klauser et al. 1990; Nelson et al. 2000). Thus, this meta-analysis supports the esomeprazole application in GERD patients, particularly those with heartburn and epigastric pain.

Another potential source of bias might be included in the meta-analysis. Lifestyle modification was recognized as one of the most important provisions GERD patients can make (DeVault and Castell 2005). Thus, obesity, smoking, and alcohol consumption have been proved as major contributors for GERD (Sise and Friedenberg 2008; Watanabe et al. 2003). Besides, there was no restriction in the methods of GERD diagnosis and endoscopic-negative patients were included in selected studies (Hansen et al. 2005; Talley et al. 2001; Talley et al. 2002; Tsai et al. 2004) in this meta-analysis, which also might induce bias. Finally, it should not be ignored that all of the included studies had been supported by drug manufacturers, and there might be a high possibility of bias. According to sparse data, further systematic review is needed stratified by lifestyle and individual body mass index and the biases should be taken into account.

In conclusion, the present study provided some indirect evidence of the benefits of esomeprazole treatment for GERD patients, especially those with heartburn and epigastric pain symptoms, including lower relapse rates after six months, lower risk of heartburn and epigastric pain recurrence, and lower risk for serious adverse events. However, given the possible biases, further systematic review is needed.

4. Experimental

4.1. Search strategy

The databases PubMed, EMBASE and Cochrane were searched for relevant RCTs up to December 2014. We used "gastroesophageal reflux", "esomeprazole" and "maintenance therapy" as the keywords. A bibliography of reviews and enrolled articles were also searched by hand to obtain sufficient resources.

4.2. Literature screening

YY and JM performed literature screening according to the predesigned inclusion and exclusion criteria independently. Disagreement was resolved through discussing with XY.

The inclusion criteria were as follows: 1) study was designed as RCT; 2) the enrolled subjects were GERD patients; 3) the study compared the role of esomeprazole with any other drug; 4) maintenance therapy lasted for at least six months; 5) at least one of the following outcomes as maintenance treatment evaluation for GERD, such as remission rates of six months (endoscopic relapse rates through six months), four major symptoms (heartburn, acid regurgitation, dysphagia, epigastric pain) of gastric reflux disease recurrence, adverse events, serious adverse event, drug-related adverse event; 6) study was published in English.

The exclusion criteria were as follows: 1) research for short-term treatment (4-8 weeks) of GERD; 2) economic evaluation for esomeprazole treatment of gastroesophageal reflux disease; 3) reviews, meeting summary, and letters.

4.3. Data extraction and quality assessment

Data extraction was carried out by YY and JM independently, and disagreement would be resolved through discussing with XY. A detailed form had been designed to extract data from the enrolled studies, including the first author, year of publication, research types, research areas, follow-up time, reflux disease diagnosis method, the number of cases in the control group and esomeprazole group, the average age, dosing method, and recurrence rate and adverse effects for outcome measurement.
Quality assessment was performed using the Cochrane quality evaluation system for RCTs (Higgins and Green 2008).

4.4. Statistical analysis

The main outcome was GERD relapse after esomeprazole treatment for six months. Secondary outcomes included the relapse symptoms of four main symptoms (heartburn, acid regurgitation, dysphagia, epigastric pain) for GERD and adverse events evaluation (adverse events, serious adverse events, drug-related adverse events). RR with its corresponding 95% CIs in each study was chosen as the principal measure of effect to evaluate the effectiveness of esomeprazole therapy compared with other PPI drugs.
Cochrane Q statistic and I^2 test were both conducted to evaluate research heterogeneity among all the individual studies. Significant heterogeneity occurred if $p< 0.05$ or $I^2> 50\%$, then, a random effects model would be chosen to pool the effect size. Otherwise, a fixed effect model would be used.
To assess the stability of the meta-analysis, we compared the RR value pooled by the random effects model and fixed effect model, respectively. The result was recognized stable if same conclusion was obtained under two kinds of model, otherwise, the result was not stable.
Furthermore, meta-regression analysis was conducted to investigate the source of heterogeneity. Finally, publication bias was evaluated by Egger's linear regression test.
All statistical analyses were conducted by STATA 11.0 (Stata Corporation, College Station, TX, USA) and RevMan 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

Conflict of interest: All authors declare that they have conflict of interests to state.

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