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• CLINICAL RESEARCH •

# Head-to-head comparison of H<sub>2</sub>-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: A meta-analysis

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the recommended dose are equally effective for healing esophagitis.

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**Key words:** Erosive esophagitis; H<sub>2</sub>-receptor antagonists; Proton pump inhibitors; Meta-analysis

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## Abstract

**AIM:** To systematically evaluate the efficacy of H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) and proton pump inhibitors in healing erosive esophagitis (EE).

**METHODS:** A meta-analysis was performed. A literature search was conducted in PubMed, Medline, Embase, and Cochrane databases to include randomized controlled head-to-head comparative trials evaluating the efficacy of H<sub>2</sub>RAs or proton pump inhibitors in healing EE. Relative risk (RR) and 95% confidence interval (CI) were calculated under a random-effects model.

**RESULTS:** RRs of cumulative healing rates for each comparison at 8 wk were: high dose vs standard dose H<sub>2</sub>RAs, 1.17 (95%CI, 1.02-1.33); standard dose proton pump inhibitors vs standard dose H<sub>2</sub>RAs, 1.59 (95%CI, 1.44-1.75); standard dose other proton pump inhibitors vs standard dose omeprazole, 1.06 (95%CI, 0.98-1.06). Proton pump inhibitors produced consistently greater healing rates than H<sub>2</sub>RAs of all doses across all grades of esophagitis, including patients refractory to H<sub>2</sub>RAs. Healing rates achieved with standard dose omeprazole were similar to those with other proton pump inhibitors in all grades of esophagitis.

**CONCLUSION:** H<sub>2</sub>RAs are less effective for treating patients with erosive esophagitis, especially in those with severe forms of esophagitis. Standard dose proton pump inhibitors are significantly more effective than H<sub>2</sub>RAs in healing esophagitis of all grades. Proton pump inhibitors given at

## INTRODUCTION

Gastro-esophageal reflux disease (GERD) is one of the most common chronic conditions affecting 20-40% of adult populations and has a major adverse impact on the quality of life<sup>[1-3]</sup>. About 40-60% of patients with symptoms of GERD may have substantial injury of esophageal mucosa ranging from mild inflammation and erythema to various grades of erosions. The major complications of GERD are esophageal ulcer and bleeding, esophageal stricture, and Barrett's esophagus<sup>[1-4]</sup>.

Reflux esophagitis is generally considered to be the result of prolonged and repeated exposure of the distal esophageal mucosa to acidic gastric contents<sup>[5,6]</sup>. It is increasingly clear that the key to reducing symptoms and to healing erosive esophagitis is to decrease the duration of exposure to the acidic refluxate. Acid-suppressing drugs that have been used to treat GERD include H<sub>2</sub>-receptor antagonist (H<sub>2</sub>RAs) and proton pump inhibitors. The efficacy of medical treatment depends on the ability to increase and maintain the intragastric and intra-esophageal pH above 4.0 over the 24-h period<sup>[7,8]</sup>. H<sub>2</sub>RAs are limited in their ability to inhibit postprandial gastric acid secretion and are ineffective in controlling reflux symptoms and healing esophagitis<sup>[9,10]</sup>. In contrast to H<sub>2</sub>RA, proton pump inhibitors block the final step of acid secretion, resulting in a profound and long-lasting acid suppression regardless of the stimulus<sup>[11,12]</sup>. Results from 33 randomized clinical trials with over 3 000 patients showed that symptomatic relief could be anticipated in 83% of proton pump inhibitors-treated patients compared with 60% of patients receiving H<sub>2</sub>RAs. Similarly, esophagitis was healed in 78% and 50%

of patients treated with proton pump inhibitors and H<sub>2</sub>RAs, respectively<sup>[13]</sup>. Previously there have been several systematic reviews and meta-analyses of clinical trials assessing the effects of medical treatments for erosive esophagitis<sup>[14-17]</sup>. Chiba and colleagues<sup>[14]</sup>, and Caro and colleagues<sup>[15]</sup> compared the effectiveness of proton pump inhibitors and H<sub>2</sub>RAs in the healing of esophagitis, whereas the comparative efficacy among proton pump inhibitors was analyzed by Sharma *et al.*<sup>[16]</sup>, and Edwards *et al.*<sup>[17]</sup>. However, comparison of the effects between treatments with proton pump inhibitors and H<sub>2</sub>RAs in patients with esophagitis has been difficult because of the difference in the study design. For example, studies included in the previous meta-analyses were not all head-to-head comparative trials<sup>[14,15]</sup>. The overall estimates of healing rate calculated by one-step pooling from different pairs of comparatives, may produce bias due to the ignorance of study differences such as sample size and differential difference in effect sizes. In addition, healing of esophagitis is significantly influenced by the initial grade of esophagitis, with healing rate being lower for the severe form of esophagitis than for the mild form of esophagitis<sup>[18,20]</sup>. However, no meta-analysis has been published to systematically evaluate the impact of the initial grading of esophagitis on esophagitis healing rates in head-to-head comparative trials. Therefore, the objectives of the current study were firstly to evaluate any difference in healing erosive esophagitis between proton pump inhibitors and H<sub>2</sub>RAs in head-to-head comparative trials, and secondly to estimate the impact of baseline grade of esophagitis on esophagitis healing rates.

## MATERIALS AND METHODS

### Literature search

A computerized literature search was performed in the PubMed, Medline, Embase and Cochrane databases for clinical trials published in English up to May 2004 with the following MeSH terms and/or text words in various combinations: gastroesophageal reflux, GERD, GORD, esophagitis, and healing, as well as the name of each respective drug (H<sub>2</sub>-receptor antagonists: cimetidine, ranitidine, famotidine, nizatidine, roxatidine; proton pump inhibitors: omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole). The title and abstract of all potentially relevant studies were screened for their relevance before retrieval of full articles. Full articles were also scrutinized for relevance if the title and abstract were ambiguous. Fully recursive searches were performed from the reference list of all retrieved articles to ensure a complete and comprehensive search of the published literature. All searches were conducted independently by at least two reviewers.

### Study selection

The inclusion criteria were as follows: (1) Randomized, controlled clinical trials in adults with an endoscopically confirmed diagnosis of GERD. (2) Two or more treatment arms: high dose *vs* standard dose H<sub>2</sub>RA, or an H<sub>2</sub>RA *vs* a proton pump inhibitor, or a proton pump inhibitor *vs* a proton pump inhibitor. (3) Healing of esophagitis was documented by endoscopy. (4) Studies with explicit information about the number of patients treated in each group, drug

dosage and schedule, and healing rate of esophagitis.

We excluded studies that only assessed symptom relief without endoscopic documentation of esophagitis healing. Also excluded were studies dealing only with relapsed or recurrent esophagitis, studies of pediatric patients, duplicate publications or studies published only in abstract form, or those focusing on pharmacokinetics and pharmacodynamics. Combination treatments such as an anti-secretory agent and a prokinetic drug were also excluded.

### Data extraction

Data was extracted from each study independently and entered into a computerized database. Differences were resolved by discussion to reach consensus between the reviewers. The information retrieved covered country of study, study design, characteristics of population, grading of esophagitis, treatment regimen, number of patients treated, evaluated and healed, and confounding variables such as alcohol use, cigarette smoking, and caffeine use, where applicable. Healing data, up to 12 wk were extracted for both intention-to-treat (ITT) and per-protocol (PP) analyses. Data on healing based on the initial grade of esophagitis were also extracted, if applicable. In studies where only per-protocol healing rates were reported, we calculated the ITT healing rates based on the initial randomized number of patients. Articles that did not specify the type of analysis were assumed to report per-protocol data.

### Quality assessment

Study quality was assessed by a series of validity criteria, including study design, level of blinding, method of randomization, patient selection, baseline characteristics, severity of esophagitis, definition of healing, compliance, and analysis by intention to treat criteria. Discrepancies in quality assessment were resolved by consensus among the authors. No quality score was assigned to any study to avoid possible introduction of subjectivity by the authors.

### Statistical analysis

The data were grouped as follows: high dose *vs* standard dose H<sub>2</sub>RAs; proton pump inhibitors *vs* H<sub>2</sub>RAs, or one proton pump inhibitor *vs* another proton pump inhibitor. We defined standard dose of each drug as: ranitidine 300 mg/d, famotidine 40 mg/d, nizatidine 300 mg/d, cimetidine 800 mg/d, omeprazole 20 mg/d, lansoprazole 30 mg/d, pantoprazole 40 mg/d, rabeprazole 20 mg/d, esomeprazole 40 mg/d. The newer proton pump inhibitors include lansoprazole, pantoprazole, rabeprazole and esomeprazole.

The outcomes considered were healing rates of esophagitis for each group at different time points (2, 4, 6, 8, and 12 wk), based on initial grade of esophagitis, if applicable. Healing rate was calculated by pooling raw data from qualified studies within each group. These data were then expressed as a healing-time curve that plotted the cumulative percentage of patients healed *vs* the end point in weeks.

Relative risk (RR) and 95% confidence interval (CI), under a random-effects model<sup>[21]</sup>, were calculated using raw data of the selected studies at specified time points (2, 4, 6, 8, and 12 wk). The potential effect of publication bias was assessed using a funnel plot suggested by Egger *et al.*<sup>[22]</sup>.

Statistical heterogeneity between studies was assessed using the  $Q$  value calculated from the Mantel-Haenszel method. In the presence of statistical heterogeneity, we searched for the sources of any possible clinically important heterogeneity, i.e., methodological or biological heterogeneity. We did not simply exclude outliers on the basis of statistical test of heterogeneity. Furthermore, to test the robustness of the analysis, we performed sensitivity analyses to evaluate whether exclusion of a single study substantially altered the result of the summary estimate.

All analyses were carried out using EasyMa software for meta-analysis written by M Cucherat, Lyon, France (EasyMa, 2001).

## RESULTS

### Study characteristics

We identified a total of 485 citations with the computerized search. Screening of the title and abstract of the citations identified 72 potentially relevant studies for full article retrieval. Of these, 52 studies met the inclusion criteria<sup>[19,20,23-72]</sup>, and 20 studies were subsequently excluded for the following reasons: 17 were not head-to-head comparative studies<sup>[73-89]</sup>, 1 duplicate publication<sup>[90]</sup>, 1 without raw data<sup>[91]</sup>, and 1 with a confusing treatment allocation<sup>[92]</sup>. The manual search of the reference list of the retrieved articles did not yield any additional studies. Of the 52 studies, the majority were double blind studies (51/52, 98.1%). Ten (19.2%) compared high dose H<sub>2</sub>RA with standard dose H<sub>2</sub>RA<sup>[23-32]</sup>, 26 (50.0%) compared a proton pump inhibitor with an H<sub>2</sub>RA<sup>[33-57,71]</sup>, and 16 (30.8%) compared a proton pump inhibitor with another proton pump inhibitor<sup>[19,20,58-70,72]</sup>. Only 25 (48.1%) reported raw healing data by the initial grade of esophagitis<sup>[19,20,23,24,30,32,35,38,43-47,49,52,53,55-58,60,61,69-71]</sup>.

The proportion of patients with a smoking history was reported in 61.5% of studies, alcohol consumption was reported in 48.1% of studies. The initial grade of esophagitis was reported in 58% studies. However, only 48.1% studies provided raw data on healing by the initial grade of esophagitis.

### Healing of esophagitis

**High dose H<sub>2</sub>RAs vs standard dose H<sub>2</sub>RAs** Ten studies involving 27 treatment arms compared high dose ( $n = 2041$  patients) with standard dose H<sub>2</sub>RAs ( $n = 1967$  patients)<sup>[23-32]</sup>. Table 1 summarizes the pooled healing rates of esophagitis in patients treated with high dose H<sub>2</sub>RAs *vs* standard dose H<sub>2</sub>RAs. Statistical significance was achieved at 4, 8 and 12 wk,

indicating that high dose H<sub>2</sub>RAs healed significantly more esophagitis than did standard dose H<sub>2</sub>RAs (Table 1).

No comparative study reported data on the healing of esophagitis at 2 wk. Only one study<sup>[29]</sup> reported healing rates at 3 wk, of 17.2% (29/169) for high dose H<sub>2</sub>RAs and 19.6% (33/168) for standard dose H<sub>2</sub>RAs (RR 0.87, 95%CI 0.56-1.37) (Table 1).

**Proton pump inhibitors vs H<sub>2</sub>RAs** There were 14 studies with 28 treatment arms comparing standard dose proton pump inhibitors ( $n = 861$  patients) with standard dose H<sub>2</sub>RAs ( $n = 752$  patients)<sup>[33-45,71]</sup>. The pooled healing rates achieved with the standard dose proton pump inhibitors were superior to that of H<sub>2</sub>RAs at all given time points (Table 2). Similar findings were observed when the comparison was made between high dose H<sub>2</sub>RAs ( $n = 234$  patients) and the standard dose proton pump inhibitors ( $n = 237$  patients)<sup>[50,51]</sup> (Table 2).

Three studies compared low dose proton pump inhibitors ( $n = 279$  patients) with standard dose H<sub>2</sub>RAs ( $n = 276$  patients) for healing esophagitis<sup>[52,53,71]</sup>. The pooled healing rates of the low dose proton pump inhibitors were higher than that of the standard dose H<sub>2</sub>RAs at both 4 and 8 wk (Table 2).

**Omeprazole 20 mg daily vs other proton pump inhibitors** Eleven studies with 23 treatment arms reported comparative results on the healing of esophagitis between omeprazole 20 mg daily ( $n = 3137$  patients) and other proton pump inhibitors at standard doses ( $n = 3397$  patients)<sup>[20,59-68]</sup>. No significant difference in the healing rate was observed between omeprazole 20 mg daily and other proton pump inhibitors at 2-8 wk (Table 3).

The esophagitis healing time curves are depicted in Figures 1-3. As shown in Figure 1, high dose H<sub>2</sub>RA achieved higher healing rates than standard dose H<sub>2</sub>RA. However, the healing rate achieved with standard dose proton pump inhibitors at 2 wk was even higher than that of H<sub>2</sub>RAs at wk 8 (63.4% *vs* 52.0%), suggesting that proton pump inhibitors healed esophagitis significantly faster than did H<sub>2</sub>RAs (Figure 2). Similar healing rates were also observed when the newer proton pump inhibitors were compared with omeprazole 20 mg daily (Figure 3).

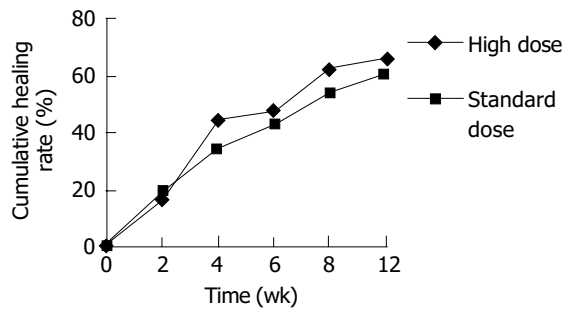
### Refractory esophagitis

Refractory esophagitis was defined as treatment failure with a standard dose of H<sub>2</sub>RAs given for at least 12 wk<sup>[55-57]</sup>. Three studies compared the effectiveness of proton pump inhibitors with ranitidine for the treatment of refractory esophagitis<sup>[55-57]</sup> (Table 4). Two of them reported that lansoprazole 30 mg daily achieved significantly higher healing

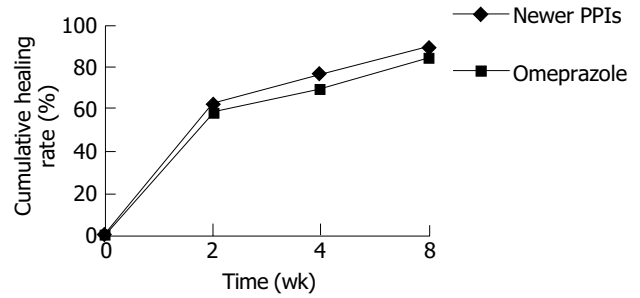
**Table 1** Healing rate of esophagitis by ITT with standard dose vs high dose of H<sub>2</sub>RA at 3, 4, 6, 8, 12 wk

		3-wk	4-wk	6-wk	8-wk	12-wk
Number of comparisons		1	5	9	5	12
High dose	Pooled data	29/169	297/669	607/1294	413/669	1142/1729
	Pooled healing rate (%)	17.2	44.4	46.9	61.7	66.0
Standard dose	Pooled data	33/168	198/573	584/1361	309/573	920/1520
	Pooled healing rate (%)	19.6	34.6	42.9	53.9	60.5
Summary RR		0.874	1.281	1.096	1.165	1.084
95% CI		0.557-1.371	1.036-1.583	0.930-1.293	1.020-1.329	1.019-1.152

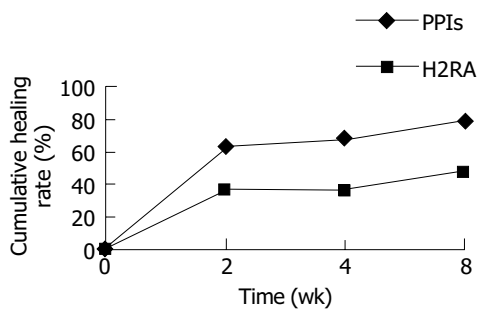
ITT, intention-to-treat analysis; No, number; RR, relative risk; 95%CI.



**Figure 1** Healing-time curve of esophagitis in patients treated with H<sub>2</sub>RA. Statistical significance was achieved at 4, 8, and 12 wk, indicating that high dose H<sub>2</sub>RAs achieved significantly better healing rates for erosive esophagitis than standard dose H<sub>2</sub>RAs.



**Figure 3** Healing-time curve of esophagitis in patients treated with standard dose of the newer proton pump inhibitors vs omeprazole. No significant difference in the pooled healing rates between the newer proton pump inhibitors and omeprazole was observed.



**Figure 2** Healing-time curve of esophagitis in patients treated with standard doses of proton pump inhibitors vs H<sub>2</sub>RAs. At wk 2, 4, 8, proton pump inhibitors significantly healed more patients than did H<sub>2</sub>RAs.

other study indicated that treatment with high dose omeprazole (40 mg/d) in patients refractory to H<sub>2</sub>RAs therapy significantly improved esophagitis healing when compared to high dose ranitidine (600 mg/d) (RR 3.69, 95%CI 2.30-5.90 at 4 wk; and RR2.03, 95%CI 1.54-2.67 at 8 wk)<sup>[57]</sup>.

**Healing by initial grade of esophagitis**

Twenty-five studies<sup>[19,20,23,24,30,32,35,38,43-47,49,52,53,55-58,60,61,69-71]</sup> with 54 treatment arms provided raw data on healing by the initial grade of esophagitis (Tables 5-7). Because data by intention-to-treat analysis were not available from the majority of trials, the healing rate by per-protocol analysis was therefore used.

When the healing rate was adjusted according to the initial severity of esophagitis, no significant differences in the healing rates was observed when patients with the severe

rates than ranitidine 300 mg, daily at 4 wk (RR 1.38; 95%CI 1.31-1.83) and 8 wk (RR 2.54; 95%CI 1.86-3.46)<sup>[55,56]</sup>. The

**Table 2** Healing rate of esophagitis by ITT at 2, 3, 4, 8, 12 wk comparing proton pump inhibitors (PPIs) with H<sub>2</sub>RA

	PPIs				H <sub>2</sub> RA			
	2-wk	4-wk	8-wk	12-wk	2-wk	4-wk	8-wk	12-wk
<b>sd PPIs vs sd H<sub>2</sub>RA</b>								
Number of arms	2	13	12		2	13	12	
Pooled data	116/183	577/824	640/783		60/163	271/713	350/673	
Pooled healing rate (%)	63.4	70.0	81.7		36.8	38.0	52.0	
Summary RR	1.759	1.832	1.586					
95%CI	1.398-2.213	1.622-2.070	1.438-1.749					
<b>hd PPIs vs sd H<sub>2</sub>RA</b>								
Number of arms		4	4	1		4	4	1
Pooled data		150/204	175/201	72/80		79/211	106/207	49/81
Pooled healing rate (%)		73.5	87.1	90.0		37.4	51.2	60.5
Summary RR		1.722	1.623	1.488				
95%CI		1.464-2.027	1.417-1.859	1.230-1.800				
<b>sd PPIs vs hd H<sub>2</sub>RA</b>								
Number of arms		2	2		2	2		
Pooled data		152/235	208/235		87/234	155/234		
Pooled healing rate (%)		64.7	88.5		37.2	66.2		
Summary RR		1.744	1.336					
95%CI		1.442-2.110	1.206-1.481					
<b>ld PPIs vs sd H<sub>2</sub>RA</b>								
Number of arms		3	3		3	3		
Pooled data		187/279	219/279		120/276	161/276		
Pooled healing rate (%)		67.0	78.5		43.5	58.3		
Summary RR		1.605	1.374					
95%CI		1.156-2.229	1.081-1.744					

hd: high dose; sd: standard dose; ld: low dose; ITT, intention-to-treat analysis; No., number; RR, relative risk; 95% CI, 95% CIs.

**Table 3** Healing rate (ITT) of esophagitis at 2, 4, 8 wk comparing PPIs with omeprazole

	Other PPIs			Omeprazole		
	2-wk	4-wk	8-wk	2-wk	4-wk	8-wk
<b>sd PPIs vs sd Omeprazole</b>						
Number of arms	1	12	12	1	12	12
Pooled data	264/421	2 615/3 412	3 050/3 411	257/431	2 229/3 217	2 719/3 216
Pooled healing rate (%)	62.7	76.6	89.4	59.6	69.3	84.5
Summary RR				1.052	1.044	1.061
95%CI				0.945-1.171	0.983-1.109	0.979-1.055
<b>ld PPIs vs sd Omeprazole</b>						
Number of arms		2	2		2	2
Pooled data		590/822	724/822		551/811	707/811
Pooled healing rate (%)		71.8	88.1		67.9	87.2
Summary RR					1.026	0.981
95%CI					0.904-1.164	0.870-1.105
<b>sd PPIs vs hd Omeprazole</b>						
Number of arms		2	1		2	1
Pooled data		310/440	284/337		302/434	282/332
Pooled healing rate (%)		70.5	84.3		69.6	84.9
Summary RR					1.031	0.985
95%CI					0.937-1.015	0.883-1.099

hd: high dose; sd: standard dose; ld: low dose; ITT, intention-to-treat analysis; No., number; RR, relative risk; 95% CI, 95% CIs.

**Table 4** Healing rate of refractory esophagitis at 2, 4, 6, 8, 12 wk comparing PPIs with H<sub>2</sub>RA

Author	PPIs						H <sub>2</sub> RAs					
	Number of			Healing rate (ITT)			Number of			Healing rate (ITT)		
	Drug	Dose	Patient	4 wk	8 wk	12 wk	Drug	Dose	Patient	4 wk	8 wk	12 wk
<b>sd PPIs vs sd H<sub>2</sub>RA</b>												
Feldman <sup>(55)</sup>	Lan	30 o.d.	61		54/61		Ran	150 b.d.	32		12/32	
Sontag <sup>(56)</sup>	Lan	30 o.d.	105	75/105	84/105		Ran	150 b.d.	54	28/54	16/54 <sup>1</sup>	
Pooled data			166	75/105	138/166				86	28/54	28/86	
Pooled rate (%)				71.4	83.1					51.9	32.6	
<b>hd PPIs vs hd H<sub>2</sub>RA</b>												
Lundell <sup>(57)</sup>	Ome	40 o.d.	51	32/51	35/51	46/51	Ran	300 b.d.	47	8/47	18/47	22/47

Ome: omeprazole; Lan: lansoprazole; Ran: ranitidine; o.d.: once daily in the morning; b.d.: twice daily; h.d.: high dose; sd: standard dose. <sup>1</sup>This study did not report cumulative healing rate at 8 wk. All patients' endpoint was at 8 wk. The decreased healing rate at 8 wk for ranitidine group may be due to subsequent relapse of esophagitis.

form of esophagitis ( $\geq$  grade III) were treated with either high dose or standard dose H<sub>2</sub>RAs. However, a significant difference was observed for patients with grade II esophagitis at 4 wk (Table 5). No patients with grade IV esophagitis were included in any of the studies comparing high dose with standard dose H<sub>2</sub>RAs.

Proton pump inhibitors achieved consistently and significantly higher healing rates than H<sub>2</sub>RAs across all grades

of esophagitis, irrespective of the dose and duration of treatment (Table 6). With a wide range of CI, the superiority of proton pump inhibitors over H<sub>2</sub>RAs was even greater when the initial grade of esophagitis was considered in studies of patients with refractory esophagitis (Table 6) despite that one study reported the same effects on grade I esophagitis at 12 wk, when omeprazole 40 mg daily was compared with ranitidine 300 mg daily<sup>[47]</sup>. The healing rates

**Table 5** Healing by grade with standard dose vs high dose of H<sub>2</sub>RA at 4, 6, 8, 12 wk (PP rate)

	4-wk		6-wk			8-wk		12-wk			
	II	III	I	II	III	II	III	I	II	III	
Number of arms	3	3	4	4	4	3	3	4	6	6	
Standard dose	Pooled data	84/190	22/105	86/137	102/266	42/180	126/187	37/105	107/129	264/383	119/256
	Pooled rate (%)	44.2	21.0	62.8	38.3	23.3	67.4	35.2	82.9	69.0	46.5
High dose	Pooled data	177/325	60/198	112/157	120/272	60/214	226/323	92/198	122/153	400/532	190/376
	Pooled rate (%)	54.4	30.3	71.3	44.1	28.0	70.0	46.5	79.7	75.2	50.5
Summary RR											
95% CI	1.231	1.430	1.136	1.150	1.200	1.039	1.316	0.962	1.032	1.059	
	1.020-1.486	0.941-2.202	0.966-1.337	0.939-1.408	0.854-1.686	0.919-1.174	0.977-1.774	0.860-1.076	0.961-1.108	0.913-1.229	

PP, per-protocol analysis; No., number; RR, relative risk; 95%CI.

**Table 6** Healing by grade at 4, 8, 12 wk comparing PPIs with H<sub>2</sub>RAs (PP rate)

		4 wk				8 wk				12 wk	
		I	II	III	IV	I	II	III	IV	I	II
Number of arms		2	4	3		2	5	3	1		
sd PPIs	Pooled data	53/60	128/162	20/54		23/23	166/178	28/47	2/3		
	Pooled rate (%)	88.3	79.0	37.0		100.0	93.3	59.6	66.7		
sd H <sub>2</sub> RAs	Pooled data	27/54	65/172	2/41		16/25	101/182	6/34	0/2		
	Pooled rate (%)	50.0	37.8	4.9		64.0	55.5	17.6	0		
Summary RR		1.760	2.037	5.588		1.502	1.648	2.766	2.525		
95%CI		1.329-2.332	1.631-2.545	1.701-18.363		1.107-2.038	1.440-1.885	1.284-5.916	1.046-6.093		
No. of arms		2	4	2		2	4	2		1	1
hd PPIs	Pooled data	40/46	88/123	21/30		46/46	104/120	24/30		29/29	42/46
	Pooled rate (%)	87.0	71.5	70.0		100.0	86.7	80.0		100.0	91.3
sd H <sub>2</sub> RAs	Pooled data	26/50	49/126	3/28		37/49	62/121	6/28		28/32	19/35
	Pooled rate (%)	52.0	38.9	10.7		75.5	51.2	21.4		87.5	54.3
Summary RR		1.665	1.835	6.110		1.300	1.689	3.626		1.111	1.676
95%CI		1.248-2.222	1.436-2.345	2.138-17.459		1.102-1.534	1.400-2.036	1.772-7.418		0.957-1.291	1.222-2.298
Number of arms		2	1	1		2	1	1			
ld PPIs	Pooled data	144/175	34/42	9/28		162/175	42/44	15/28			
	Pooled rate (%)	82.3	81.0	32.1		92.6	95.5	53.6			
sd H <sub>2</sub> RAs	Pooled data	104/175	15/50	1/22		132/175	27/49	2/21			
	Pooled rate (%)	59.4	30.0	4.5		75.4	55.1	9.5			
Summary RR		1.384	2.698	7.071		1.227	1.732	5.625			
95%CI		1.202-1.592	1.724-4.224	0.967-51.707		1.116-1.349	1.335-2.249	1.440-21.980			
Refractory esophagitis											
Number of arms			1		1		2	1		2	
sd PPIs	Pooled data		62/77		11/22		105/116	13/15		18/29	
	Pooled rate (%)		80.5		50.0		90.5	86.7		62.1	
sd H <sub>2</sub> RAs	Pooled data		20/40		1/11		26/61	2/8		0/14	
	Pooled rate (%)		50.0		9.1		42.6	25.0		0	
Summary RR			1.606		5.500		2.117	3.229		35.881	
95%CI			1.158-2.228		0.835-25.337		1.575-2.845	1.034-10.091		0.728-1767.6	

sd: standard dose; ld: low dose.

were similar between omeprazole and the newer proton pump inhibitors across all grades of esophagitis (Table 7).

### Testing for between-study heterogeneity and sensitivity analyses

In the comparison of the healing rates achieved with omeprazole and the newer proton pump inhibitors, a significant heterogeneity was found at 4 and 8 wk ( $P < 0.001$ ). However, no further heterogeneity ( $P = 0.43$  at 4 wk, and  $P = 0.92$  at 8 wk) was found after exclusion of the studies from Kahrilas *et al.*<sup>[67]</sup>, and Richter *et al.*<sup>[68]</sup>, suggesting that the heterogeneity was caused by these two studies. Further scrutiny of these two studies revealed that *Helicobacter pylori* (*H. pylori*) positive patients were excluded in both studies, whereas other studies

did not use *H. pylori* status as an exclusion criterion. No additional confounding factors such as the study design, level of blinding and compliance of patients were identified. Sensitivity analysis showed no difference in the healing rates of erosive esophagitis between omeprazole and the newer proton pump inhibitors (RR 1.00, 95% CI 0.96-1.04 at 4 wk; and RR 0.99, 95% CI 0.97-1.02) when the data from the two studies were excluded. There was no evidence of heterogeneity in any other comparisons.

### Publication bias

Tests for publication bias were assessed with funnel plots using RRs against the sample size of each study. Due to the inadequacy of the number of studies in each comparison,

**Table 7** Healing by grade at 4, 8 wk comparing standard dose of other PPIs vs omeprazole

		4-wk				8-wk			
		I	II	III	IV	I	II	III	IV
Number of arms		3	3	3	1	3	3	3	1
sd PPIs	Pooled data	195/239	302/362	148/210	3/7	214/235	329/360	175/209	2/4
	Pooled rate (%)	81.6	83.4	70.5	42.9	91.1	91.4	83.7	50.0
sd omeprazole	Pooled data	190/238	315/393	132/195	3/5	214/233	345/390	159/188	1/2
	Pooled rate (%)	79.8	80.2	67.8	60.0	91.8	88.5	84.6	50.0
Summary RR		1.022	1.041	1.041	0.733	0.992	1.033	0.990	1.000
95%CI		0.936-1.116	0.973-1.113	0.914-1.186	0.250-2.147	0.938-1.048	0.985-1.084	0.927-1.057	0.213-4.694

sd: standard dose.

funnel plots did not demonstrate strong patterns. Therefore, figures are not shown.

## DISCUSSION

There have been a few systematic reviews and meta-analyses summarizing the effect of medical treatments for reflux esophagitis<sup>[14-17]</sup>. However, most of them suffered from methodological flaws. The current study was the first attempt to systematically evaluate the effects of antisecretory agents in healing esophagitis based on head-to-head comparative trials. We believe that analysis of comparative trials provides more robust results than that obtained from simple pooling of results from non-comparative trials because no stratification was used in the latter form of analysis. We found that high dose H<sub>2</sub>RAs was superior to standard dose H<sub>2</sub>RAs in healing erosive esophagitis at wk 4, 8, and 12, and proton pump inhibitors achieved significantly higher healing rates of esophagitis than did H<sub>2</sub>RAs, irrespective of dose and treatment duration. However, no statistically significant difference in healing rates was observed between standard dose omeprazole and the newer proton pump inhibitors after 4 and 8 wk of treatment.

The difference in the rate of healing esophagitis between proton pump inhibitors and H<sub>2</sub>RAs can also be expressed as a healing-time curve for the ease of comparison<sup>[14]</sup>. Using this method, we have shown that proton pump inhibitors healed esophagitis at a rate approximately twice that of H<sub>2</sub>RAs at all time points and the healing rate achieved at 2 wk with proton pump inhibitors was greater than that obtained with H<sub>2</sub>RAs at 8 wk. This is consistent with the findings from previous meta-analyses using a different study design<sup>[14-17]</sup>.

H<sub>2</sub>RAs are less effective for healing esophagitis because they cannot effectively inhibit meal-stimulated acid secretion<sup>[9,10]</sup>. Moreover, tolerance may occur to H<sub>2</sub>RAs, resulting in a significant decrease in their anti-secretory effect<sup>[93,94]</sup>. Therefore, patients with reflux esophagitis often require high dose H<sub>2</sub>RAs to maintain an intragastric pH above the critical threshold of 4.0 to achieve satisfactory symptom relief and remission of esophagitis<sup>[7,8]</sup>. Proton pump inhibitors have been proved to be effective in suppressing gastric acid secretion throughout the 24-h period, including meal-stimulated acid production<sup>[95,96]</sup>. So far, tolerance to proton pump inhibitors has not been reported in the literature even after long-term treatment.

The severity of esophagitis is a good predictor of a successful treatment<sup>[97]</sup>. In this analysis, we have shown that high dose H<sub>2</sub>RAs achieved a significantly better healing rate of esophagitis than standard dose H<sub>2</sub>RAs. However, this difference disappeared when the results were adjusted by the initial grade of esophagitis except for the comparison at 4 wk when high dose H<sub>2</sub>RAs healed 10% more esophagitis (Table 5). A possible explanation for the rapid loss of superiority of anti-secretory effect of high dose H<sub>2</sub>RAs over standard dose H<sub>2</sub>RAs after 4 wk could be due to the subsequent development of tolerance to the continuous use of H<sub>2</sub>RAs<sup>[93,94]</sup>.

Our study has confirmed that proton pump inhibitors were significantly more effective than H<sub>2</sub>RAs in healing erosive esophagitis across all grades. In patients with mild

forms of esophagitis (grades I and II), the healing rate achieved with proton pump inhibitors was significantly higher than that with H<sub>2</sub>RAs (100.0% *vs* 64.0% for grade I, and 93.3% *vs* 55.5% for grade II) at 8 wk (Table 6). This suggested that, even in patients with the mild form of esophagitis, H<sub>2</sub>RAs is a less effective treatment compared to proton pump inhibitors. The difference was even greater in patients with grade III/IV esophagitis. The healing rate achieved with proton pump inhibitors at 8 wk was 59.6%, but only 17.6% with H<sub>2</sub>RAs (Table 6). In patients refractory to H<sub>2</sub>RAs, proton pump inhibitors healed 50.0% and 62.1% of grade IV esophagitis after 4 and 8 wk of treatment, respectively (Table 4). Thus, proton pump inhibitors are significantly more effective than H<sub>2</sub>RAs for treating all grades of esophagitis, including patients refractory to H<sub>2</sub>RAs.

It is known that individual proton pump inhibitors differ with respect to the onset of action and duration of effect because of the variability in their bioavailability. Although omeprazole has a relative lower bioavailability than other proton pump inhibitors<sup>[98-100]</sup>, which may contribute to the late onset of symptom relief, this has not been translated into a disadvantage in healing rate of esophagitis of all grades when compared with the newer proton pump inhibitors according to the results of this analysis.

A statistically significant heterogeneity was found in the overall analysis comparing the efficacy of healing esophagitis among different proton pump inhibitors. Two studies identified to have contributed to the heterogeneity, compared esomeprazole to omeprazole and excluded patients with *H pylori* infection in their analyses<sup>[67,68]</sup>. Although a higher healing rate of reflux esophagitis has been observed in patients with *H pylori* infection compared to uninfected patients when treated with proton pump inhibitors<sup>[101,102]</sup>, there is no evidence that esomeprazole would work better on *H pylori* negative patients. Therefore, there might in fact be real difference in efficacy between esomeprazole and omeprazole, because esomeprazole is the enantiomer of omeprazole and the active compound is the achiral cyclic sulfenamide. Comparing 40 mg of esomeprazole with 20 mg of omeprazole would be more or less the same, as comparing double dose of omeprazole<sup>[103]</sup>. More data are needed to further confirm the presumption.

There are several limitations in this meta-analysis. Firstly, the quality of a meta-analysis, in general is dependent on the quality of original studies, particularly the study design and reporting. To correct reporting bias from original studies is difficult and requires collaboration of investigators involved. Because of the practical difficulties, such as lapse in time between the time of publication and the time of this analysis, we did not contact investigators for raw data or clarification of unclear presentation. Secondly, three different esophagitis grading systems were used in the individual studies, which might have confounded the results of analyses. Huang *et al.*, previously reported that there is a systematic difference in healing rates between studies using Hetzel-Dent scoring system and those using Savary-Miller system<sup>[104]</sup>. Therefore, we considered that the impact of different esophagitis scoring systems on the analysis of esophagitis healing rates deserves a systematic evaluation in its own right. This warrants an immediate consensus of using a



standard esophagitis scoring system among investigators so that a truly meaningful comparison of the efficacy of different drugs can be made. Thirdly, the stratified analysis by the initial grade of esophagitis may also be biased because per-protocol data were used in the analysis. Fourthly, we excluded meeting abstracts and non-English publications for technical reasons such as inadequate reporting of outcomes in meeting abstracts and no resources for translation of non-English articles. This might have introduced selection bias. To estimate the magnitude of possible impact, we searched the literature and identified six articles published in non-English literature, but with an English abstract<sup>[18,105-109]</sup>. Four studies compared a standard dose proton pump inhibitor with an H<sub>2</sub>RA, one between two H<sub>2</sub>RAs and one between two different doses of cimetidine. The conclusions of these trials are consistent with those of this meta-analysis. Therefore, we believe that the inclusion of non-English studies would not change the conclusions of this analysis. Fifthly, relief of reflux symptoms is another important aspect in the management of patients with GERD. However, the large variability in measuring and reporting symptom data in the literature prohibited us from conducting a reliable meta-analysis of the effects of antisecretory agents on relieving reflux symptoms. This requires an urgent attention to establishing a standard instrument for the assessment of symptom response in patients with GERD.

In conclusion, this meta-analysis of comparative trials clearly identifies that H<sub>2</sub>RAs are not effective treatment for patients with esophagitis of all grades irrespective of dose. Proton pump inhibitors are significantly more effective than H<sub>2</sub>RAs for healing esophagitis of all grades including those refractory to H<sub>2</sub>RAs. No significant differences in healing esophagitis exist among standard dose of different proton pump inhibitors. Therefore, proton pump inhibitors should be used for patients with esophagitis of all grades.

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