Speed of Healing and Symptom Relief in Grade II to IV Gastroesophageal Reflux Disease: A Meta-analysis

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Background & Aims: **Esophagitis healing proportions are often incorrectly called the healing rate. The aim of this study was to compare different drug classes by expressing the speed of healing and symptom relief through a new approach.** ***Methods:*** **A fully recursive literature search to July 1996 identified 43 articles on gastroesophageal reflux disease (GERD) (7635 patients) meeting strict inclusion criteria: single- or double-blind randomized studies in adults with endoscopically proven erosive or ulcerative esophagitis. For each drug class, linear regression analysis estimated the average percentage of patients who were healed and heartburn free per week.** ***Results:*** **Mean overall healing proportion irrespective of drug dose or treatment duration (≤12 weeks) was highest with proton pump inhibitors (PPIs; 83.6% ± 11.4%) vs. H_2-receptor antagonists (H_2RAs; 51.9% ± 17.1%), sucralfate (39.2% ± 22.4%), or placebo (28.2% ± 15.6%). Correcting for patients without baseline heartburn, the mean heartburn-free proportion was highest with PPIs (77.4% ± 10.4%) vs. H_2RAs (47.6% ± 15.5%). PPIs showed a significantly faster healing rate (11.7%/wk) vs. H_2RAs (5.9%/wk) and placebo (2.9%/wk). PPIs provided faster, more complete heartburn relief (11.5%/wk) vs. H_2RAs (6.4%/wk).** ***Conclusions:*** **More complete esophagitis healing and heartburn relief is observed with PPIs vs. H_2RAs and occurs nearly twice as fast. This semiquantitative expression of speed of healing and symptom relief permits comparisons for future economic evaluation and quality-of-life assessments.**

Gastroesophageal reflux disease (GERD) is a common condition affecting 7% of the population on a daily basis. A further 29% experiences heartburn weekly to monthly, with 36% of the normal population, both male and female, experiencing symptomatic heartburn at least monthly.[1] Twenty-seven percent of American adults treat themselves with antacids more than twice each month, and 84% of heavy antacid users in one study had an objective diagnosis of reflux esophagitis.[2] Only a small proportion of patients with GERD seek help from their physician, who has a wide choice of therapies available.[3] Furthermore, symptoms of GERD do not necesarily imply mucosal damage because the prevalence of esophagitis is estimated to be only 2%.[4]

The relative efficacy of the various treatment choices have been assessed in numerous clinical trials by a comparison of healing rates at specific but arbitrary time intervals (usually 4, 8, and 12 weeks). Results of healing do not reflect a true rate but rather represent a proportion of those healed vs. those treated at the given time point. For example, two medications may both heal completely, thus achieving the same healing proportion of 100%, but one medication may heal in 4 weeks and the other may take 12 weeks or longer. The true rate or speed (i.e., how quickly) at which the healing occurs is clearly very different. Studies have shown that esophagitis of greater severity (i.e., those with mucosal damage; erosive or ulcerative) is more difficult to heal with H_2-receptor antagonists (H_2RAs) than lesser grades of esophagitis.[5] Furthermore, meta-analysis of acid suppression data correlates with the healing of erosive GERD, and the healing proportion is directly related to the degree and duration of acid suppression.[6,7] Thus, the proton pump inhibitors (PPIs; i.e., omeprazole, lansoprazole, and pantoprazole), which suppress acid secretion to a greater degree and for a longer duration of 24 hours than does H_2RA, show higher and more effective healing.[8,9]

What is clinically more important, especially to the patient, than the simple proportion healed is the speed of healing, which is described as the percentage of erosive esophagitis healed per unit time. This represents the healing rate and can be determined by the slope of a healing-time curve. This applies equally well to symptoms, with respect to rate vs. proportion of patients with symptom relief. From these data, the speed of healing and speed of symptom relief can be calculated; these conceptual data are considered to be important for further economic evaluation such as cost-effectiveness studies and for quality-of-life assessments.

Abbreviations used in this paper: CI, confidence interval; GERD, gastroesophageal reflux disease; H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor.

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We conducted a meta-analysis of GERD trials restricted to patients with endoscopically proven moderate to severe erosive esophagitis. Our main objective was to determine the healing proportions and healing rates of grades II to IV esophagitis, and secondarily, from this healing database, to determine the completeness of symptom relief as determined by the relief of heartburn and the shift toward symptom improvement.

Methods

Study Identification

Relevant articles published to July 1996 were identified through MEDLINE using the Medical Subject Heading terms gastroesophageal reflux and randomized controlled studies, as well as individual searches of explode esophagitis with the names of each respective drug. Articles not in the MEDLINE database, such as earlier issues of the *European Journal of Gastroenterology and Hepatology,* were searched manually. All abstracts, non-English language articles, and dual publications were excluded to yield articles for critical review. Fully recursive searches were performed from the reference lists of all retrieved articles to ensure a complete and comprehensive search of the published literature.

Study Selection

Meta-analysis inclusion criteria included English language and randomized single- or double-blind studies (unblinded studies were excluded) and GERD treatment studies in adults 16 years of age or older with endoscopically proven grade II to IV erosive or ulcerative esophagitis treated by single-drug therapy (combination treatments such as an antisecretory agent and a prokinetic were excluded) with endoscopic healing of all erosions. Studies with fewer than 20 patients per treatment arm were excluded. At baseline, all grades of esophagitis were often lumped together; this was a common reason for exclusion.

Studies that included patients with all grades of esophagitis were included only if it was possible to determine clearly the healing proportions for those with grade II–IV esophagitis. Because these studies often applied different grading systems, only those that explicitly defined and identified the grade of esophagitis in their text were included in the analysis. Although grade I esophagitis in the modified Savary–Miller classification includes erosive changes, it is generally agreed that this represents mild esophagitis, and because the intent was to study healing and symptom relief in those with moderate to severe esophagitis, these patients were not included in this analysis. Recognizing the heterogeneity of the numerous different grading systems used by the various studies, the criteria used to define grade II to IV esophagitis in this analysis are shown in Table 1. In studies classifying esophagitis as mild, moderate, or severe, moderate was considered grade II and severe considered grade III. Grade IV included deep esophageal ulceration and/or strictures or stenosis, and many studies systematically excluded these patients.

Table 1. Grade II to IV Esophagitis

Grade of esophagitis	Defining parameters accepted
II	Isolated round and linear erosions, in some called superficial mucosal ulceration, confluent erosions
III	Confluent erosions extending around the entire circumference or superficial ulcerations, erosions or superficial ulcerations extending >2–3 cm above lower esophageal sphincter
IV	Deep ulceration or strictures/stenosis

Each article was reviewed by two independent reviewers (N.C. and C.de.G.), and one arbitrator (R.H.H.) reviewed discrepancies. All disagreements were easily resolved by discussion and consensus.

Study Evaluation (Validity Criteria)

Study quality was assessed by a series of validity criteria, with blinding of the study being considered most important and whether the randomization was performed strictly being considered the second most important criteria. Other criteria were assessed to evaluate study validity, including patient selection, baseline characteristics, compliance, and definition of healing. These criteria were not usable for subgroup analysis because data within each drug class were heterogeneous for specific drug, dose, and duration, and in the final data set, too few directly comparable studies could be analyzed according to study quality. Observer agreement for an arbitrarily chosen sample of 10 articles was high using weighted κ[10] (range, 0.55–1.0; median, 1.0). Any discrepancies were resolved by consensus and usually reflected an oversight in the initial assessment rather than frank disagreement.

Data Extraction

Data for endoscopic healing were required to be given explicitly to provide the number of patients treated and the number healed at predetermined time points. Per protocol, healing data to 12 weeks of treatment were included. In studies that included patients with lesser grades of esophagitis, only healing data for those with grade II to IV esophagitis were extracted by each of two independent reviewers (N.C. and C.de G.).

Healing Analysis

The data were grouped by drug class, which was decided a priori as placebo, PPIs (included omeprazole, lansoprazole, and pantoprazole), H_2RAs (included cimetidine, nizatidine, ranitidine, and famotidine), sucralfate, prokinetics (included cisapride only because no metoclopramide or domperidone data met the required entry criteria), and other (none). For a given study arm the overall healing proportion (number

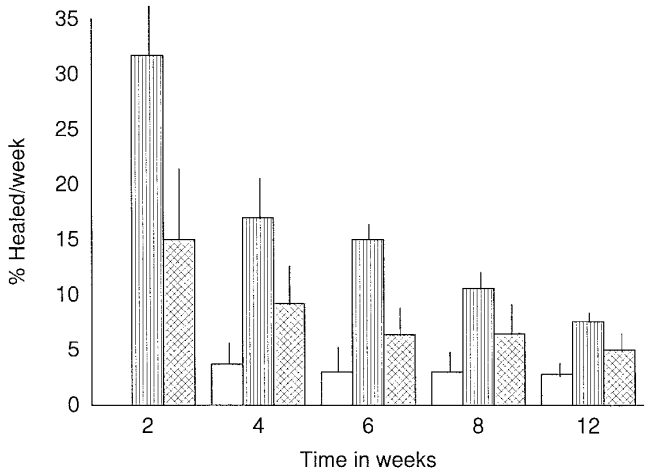

Figure 1. Speed of healing GERD expressed as the mean percentage of healing per week for each drug class ± SD at evaluation time points. With longer treatment, PPIs continue to heal faster than the other drug classes, but the speed of healing falls off as fewer patients are left to be healed. □, Placebo; ▥, PPI; ▩, H_2RA.

healed per number treated expressed as percentage) reported at the final evaluation time point was used to calculate the overall healing proportion to 12 weeks, pooling data within each drug class irrespective of dose, duration of treatment, or specific drug (applies to H_2RAs and PPIs). Groups were compared using analysis of variance.

From the healing proportion at each time point within each drug class, a healing rate (i.e., the percentage healed per week) was calculated (Figure 1). This permitted comparison of the speed of healing between drug classes at each time point. From this was generated a healing-time curve that plotted the percentage of esophagitis patients healed vs. the end point in weeks (Figure 2). From the healing proportions at each evaluation time point within each drug class, the raw data were used to apply linear regression to calculate a slope (with 95% confidence intervals [CIs]) that expressed the overall estimate of the rate of healing per week of treatment. Statistical evaluations were performed using the Statistix V4.1 software package (Analytical Software, Tallahassee, FL).

Symptom Analysis

From the healing studies identified above, two symptom assessments restricted to heartburn were performed on two subgroups of the data. Heartburn was chosen as the representative symptom because it was the most commonly and consistently reported symptom of GERD in these studies compared with other symptoms such as regurgitation. The first assessment identified 16 studies that provided data regarding the total number of patients who obtained complete relief of heartburn symptoms. The second identified 7 studies that used a common symptom scoring system of none, mild, moderate, and severe heartburn and provided data regarding the change or improvement in heartburn symptoms over time. Both symptom analyses were based on patients with grade II to IV esophagitis to ensure comparable baseline severity. Studies that included patients with lesser grades of esophagitis at baseline, with data that did not permit extraction of heartburn severity for patients with the higher grades (II to IV) of esophagitis, were excluded.

In the first subgroup analysis, the overall proportion of patients free of heartburn was calculated, correcting for the numbers of patients without heartburn at the beginning of the study. A particular treatment arm could provide heartburn relief data at not only the baseline but at several other subsequent evaluation time points. The data given for the proportions of patients who were symptom free at the later time points were adjusted by the proportion of patients that were free of heartburn at the beginning of the study to provide a best estimate of the patients that became heartburn free with treatment. This provided the raw data that formed the basis of this part of the analysis. From the corrected symptom-free proportion at each time point within each drug class, a heartburn-free rate (i.e., percentage heartburn free per week) was calculated (Figure 3). This permitted comparison of the rate of symptom relief between drug classes at each time point. From this was generated a symptom relief–time curve that graphically expressed the percentage of patients who were symptom free vs. the end point in weeks (Figure 4). From the heartburn-free proportions at each evaluation time point within each drug class, the raw data were used to apply linear regression to calculate a slope that expressed for heartburn, the overall estimate of the rate of symptom relief per week of treatment. Drug classes could be compared based on estimates of the 95% CIs around the slopes. For the second data set, limited data permitted only descriptive reporting of findings without formal statistical analysis (Figures 5 and 6).

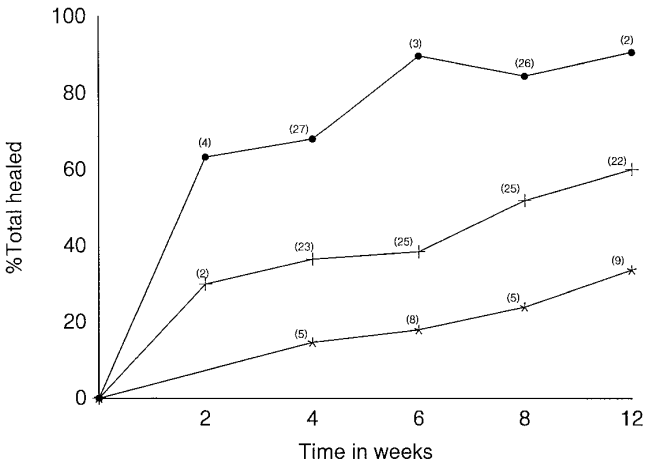

Figure 2. Healing-time curve expressed as the mean total healing for each drug class per evaluation time in weeks. By week 4, PPIs heal more patients than any other drug class, even after a much longer duration of treatment (12 weeks), implying a substantial therapeutic gain despite the fact that all drug classes achieve higher healing with longer durations of therapy. The number of studies is shown in parentheses. ●, PPI; +, H_2RA; *, placebo.

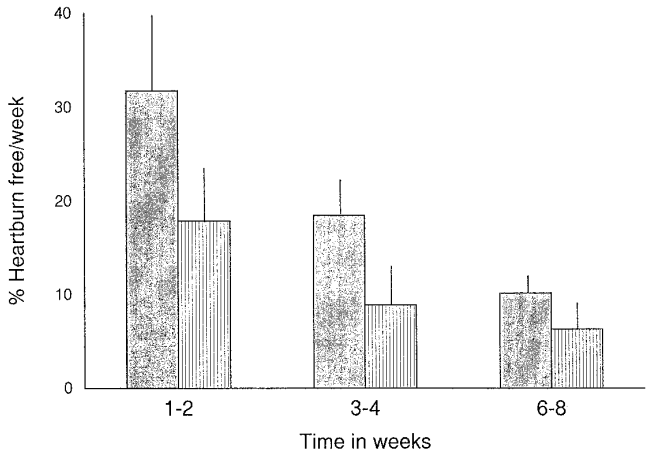

Figure 3. Speed of heartburn relief expressed as the mean percentage of patients symptom free per week for each drug class ± SD corrected for patients free of heartburn at baseline. With longer therapy, PPIs continue to relieve heartburn faster than the H_2RA, but the speed of symptom relief falls off as fewer patients remain symptomatic. ■, PPI; ▥, H_2RA.

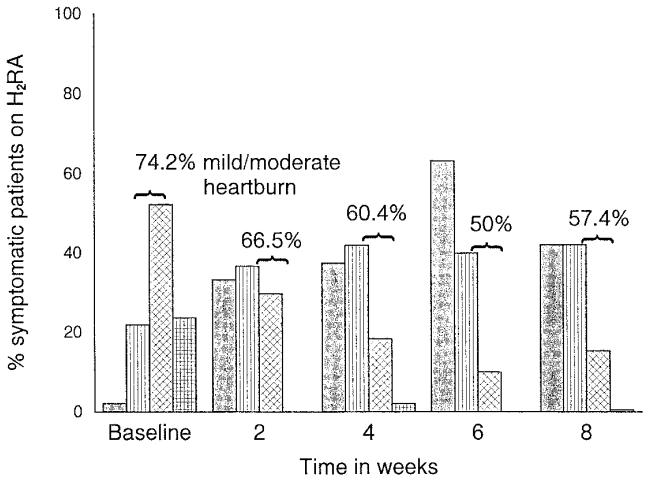

Figure 5. Shift in heartburn relief with H_2RAs. From studies using a symptom scale of none, mild, moderate, or severe, the shift in symptom severity with duration of treatment can be observed. With H_2RAs, although there is an increase in the number of patients completely heartburn free, at the end of the study, more than half of the patients still have mild to moderate symptoms. ■, None; ▥, mild; ▩, moderate; ▦, severe.

Results

Esophagitis Healing

Our search yielded a total of 43 articles[5,11–52] meeting strict inclusion criteria in which healing data for patients with grade II to IV erosive or ulcerative esophagitis were presented clearly. Tables 2–4 list the healing data for each of the drug classes. The majority were double-blind studies (40 of 43; 93%). Only 12 of 43 (27.9%) had nonmanipulable randomization methods, whereas the rest had potentially manipulable methods. These studies provided data from 95 study arms (placebo, n = 14; H_2RA, n = 48; PPI, n = 27; sucralfate, n = 4; prokinetic, n = 2), yielding 196 assessable study time points in 7635 patients. Study patients (includes all patients at baseline) were predominantly male (65%) with a mean age of 51 years

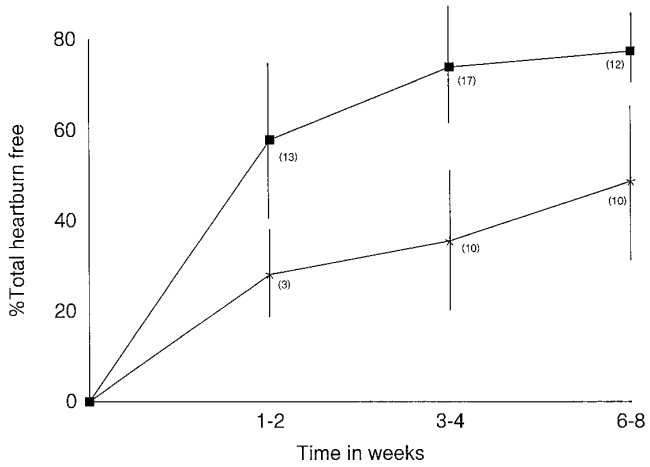

Figure 4. Symptom relief–time curve expressed as the mean total heartburn relief for each drug class corrected for patients free of heartburn at baseline at 1–2, 3–4, and 6–8 weeks. By week 2, more patients treated with PPIs are asymptomatic compared with H_2RA, even after a much longer duration of treatment (8 weeks), implying a substantial therapeutic gain despite the fact that both drug classes achieve greater symptom relief with longer durations of treatment. The number of studies is shown in parentheses. ■, PPI; *, H_2RA.

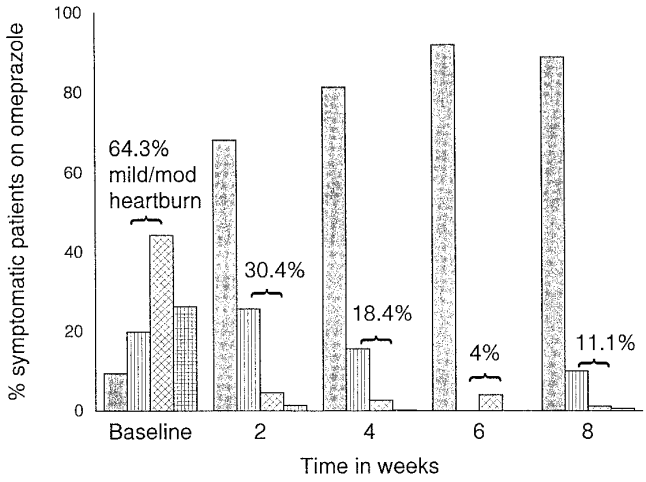

Figure 6. Shift in heartburn relief with PPIs. PPIs (omeprazole)-treated patients have a dramatic shift in the number of patients completely symptom free, particularly early in treatment, and at the end of the study, very few patients have any residual heartburn in contrast to patients treated with H_2RAs. ■, None; ▥, mild; ▩, moderate; ▦, severe.

Table 2. Healing of Grade II to IV Esophagitis With H_2RAs

First author, year	Drug dose (*mg*)	Healing data (*wk*) (no. healed/no. treated)					Randomization[a]
		2	4	6	8	12	
Elsborg, 1991[11]	C400 bid	—	7/27	—	—	16/27	0
Galmiche, 1988[12]	C1000/day	—	—	8/24	—	11/24	0
Palmer, 1990[13]	C800 bid	—	—	47/93	—	62/93	0
Dehn, 1990[14]	C400 qid	—	9/31	—	7/31	—	0
Bate, 1990[5]	C400 qid	—	25/116	—	36/116	—	0
Ross, 1991[15,b]	C400 qid	—	—	—	11/20	—	0
Sherbaniuk, 1984[16]	R150 bid	—	—	6/36	—	—	+
Havelund, 1988[19]	R150 bid	—	11/42	—	17/39	19/35	+
Sandmark, 1988[20]	R150 bid	—	23/75	—	33/66	—	+
Blanchi Porro, 1992[25]	R150 bid	—	6/29	—	10/29	—	+
Londong, 1992[26]	R150 bid	—	18/49	—	26/46	—	+
Bardhan, 1995[29]	R150 bid	—	21/57	—	26/54	—	+
Klinkenberg-Knol, 1987[17]	R150 bid	—	7/25	—	10/25	—	0
Sontag, 1987[18]	R150 bid	—	—	41/73	—	—	0
Vantrappen, 1988[21]	R150 bid	—	10/25	—	13/25	—	0
Johnson, 1989[22]	R150 bid	—	17/59	—	30/56	—	0
Bremner, 1991[23]	R150 bid	—	—	—	6/25	—	0
Frame, 1991[24]	R150 bid	—	31/68	—	42/70	—	0
Feldman, 1993[27]	R150 bid	7/33	11/33	14/32	12/32	—	0
Simon, 1993[28]	R150 bid	—	—	76/172	—	107/172	0
Koop, 1995[30]	R150 bid	—	39/83	—	46/83	—	0
McKenna, 1995[31]	R150 bid	—	—	—	94/158	112/158	0
Robinson, 1995[32]	R150 bid	48/124	64/123	80/118	86/123	—	0
Lundell, 1990[33]	R300 bid	—	8/47	—	18/47	22/47	+
Silver, 1996[34]	R300 bid	—	72/248	—	118/230	148/225	0
Roufail, 1992[35]	R150 qid	—	47/104	—	68/100	78/94	0
Euler, 1993[36]	R150 qid	—	48/105	—	73/105	83/105	0
Silver, 1996[34]	R150 qid	—	93/250	—	145/235	172/223	0
Johnson, 1989[22]	R300 qid	—	40/63	—	46/61	—	0
Roufail, 1992[35]	R300 qid	—	50/109	—	73/105	83/102	0
Euler, 1993[36]	R300 qid	—	49/105	—	65/105	77/105	0
Sabesin, 1991[37]	F20 bid	—	—	33/96	—	48/90	0
Simon, 1993[28]	F20 bid	—	—	48/93	—	63/93	0
Wesdorp, 1993[38]	F20 bid	—	—	51/144	—	—	0
Simon, 1994[39]	F20 bid	—	—	37/110	—	61/110	0
Sabesin, 1991[37]	F40 qhs	—	—	28/98	—	42/98	0
Simon, 1993[28]	F40 bid	—	—	81/175	—	122/175	0
Wesdorp, 1993[38]	F40 bid	—	—	73/143	—	—	0
Simon, 1994[39]	F40 bid	—	—	52/106	—	72/106	0
Cloud, 1991[40]	N150 bid	—	—	21/99	—	29/99	+
Cloud, 1992[41]	N150 bid	—	14/88[c]	28/88	—	—	+
Cloud, 1991[40]	N300 qhs	—	—	10/95	—	20/95	+
Quik, 1990[42]	N300 qhs	—	—	19/83	—	30/83	0
Baldi, 1993[43]	N150 tid	—	—	37/74	—	—	0
Baldi, 1993[43]	N150×2/300	—	—	31/72	—	—	0
Cloud, 1992[41]	N300 bid	—	12/92[c]	28/92	—	—	+
Quik, 1990[42]	N300 bid	—	—	29/85	—	38/85	0
Baldi, 1993[43]	N300 bid	—	—	37/80	—	—	0

bid, twice daily; qid, four times daily; qhs, each night; tid, three times daily; C, cimetidine; R, ranitidine; F, famotidine; N, nizatidine;
[a]Method of randomization: +, nonmanipulable; 0, potentially manipulable; —, quasirandomized.
[b]Single blind studies; all others are double blind.
[c]Three weeks.

(range, 18–89). Many studies did not specify the mean duration of symptoms, but in those that provided this data (15 of 43), most patients had experienced symptoms for a long duration (mean, 65 months; maximum, 228 months). Baseline severity of esophagitis was grade II in 61.8%, grade III in 31.7%, and grade IV in 6.5% of patients. Therefore, although the intent was to concentrate our analysis on more severe disease,

Table 3. Healing of Grade II to IV Esophagitis With PPIs

First author, year	PPI dose (*mg*)	Healing data (*wk*) (no. healed/no. treated) 2	4	6	8	12	Randomization[a]
Hetzel, 1988[44]	O20 od	—	57/82	—	65/82	—	+
Sandmark, 1988[20]	O20 od	—	46/69	—	56/66	—	+
Blanchi Porro, 1992[25]	O20 od	—	15/30	—	23/29	—	+
Sontag, 1992[45]	O20 od	—	32/83	—	61/83	—	+
Mossner, 1995[46]	O20 od	—	67/86	—	81/86	—	+
Bate, 1990[5]	O20 od	—	68/122	—	85/122	—	0
Frame, 1991[24]	O20 od	—	38/61	—	52/70	—	0
Bate, 1993[47,b]	O20 od	—	80/151	—	103/147	—	0
Bate, 1993,[47,b]	O20 od	—	74/152	—	—	—	0
Robinson, 1993[48,b]	O20 od	—	63/92	—	75/92	—	0
Corinaldesi, 1995[49]	O20 od	—	83/105	—	96/105	—	0
Hetzel, 1988[44]	O40 od	—	67/82	—	70/82	—	+
Havelund, 1988[19]	O40 od	—	32/46	—	39/46	42/46	+
Lundell, 1990[33]	O40 od	—	32/51	—	44/51	46/51	+
Sontag, 1992[45]	O40 od	—	39/87	—	65/87	—	+
Vantrappen, 1988[21]	O40 od	—	22/26	—	24/25	—	0
Dehn, 1990[14]	O40 od	—	16/28	—	20/28	—	0
Klinkenberg-Knol, 1987[17]	O80 od	—	19/24	—	22/24	—	0
Bardhan, 1995[29]	L30 od	—	45/56	—	51/57	—	+
Feldman, 1993[27]	L30 od	44/62	50/62	—	53/55	—	0
Robinson, 1995[32]	L30 od	76/114	94/114	106/114	105/114	—	0
Robinson, 1995[50]	L30 od	13/23	20/23	21/23	22/23	—	0
Bardhan, 1995[29]	L60 od	—	35/51	—	42/48	—	+
Robinson, 1995[50]	L60 od	16/27	20/27	23/27	24/27	—	0
Corinaldesi, 1995[49]	P40 od	—	81/103	—	97/103	—	0
Koop, 1995[30]	P40 od	—	103/149	—	122/149	—	0
Mossner, 1995[46]	P40 od	—	126/170	—	153/170	—	+

O, omeprazole; L, lansoprazole; P, pantoprazole; od, once daily.
[a]Method of randomization: +, nonmanipulable; 0, potentially manipulable; —, quasirandomized.
[b]Single-blind studies; all others are double blind.

the reality was that most patients entered into esophagitis healing trials had only moderate mucosal damage with a predominance of grade II esophagitis.

Overall Pooled Healing Proportions

The PPIs (omeprazole, lansoprazole, and pantoprazole) healed esophagitis in the most patients when compared with all other drug classes, irrespective of the dose of medication and duration of treatment (2–12 weeks). PPIs' overall healing proportion was 83.6% ± 11.4% (95% CI, 79.1–88.1) and significantly better than 51.9% ± 17.1% (95% CI, 46.9–56.9) by H_2RAs and 28.2% ± 15.6% (95% CI, 19.2–37.2) by placebo ($P < 0.0005$ between groups). The healing proportion with sucralfate (39.2% ± 22.4%), in particular, had a very broad 95% CI (3.6–74.8), which indicated inconsistent results with this therapy; however, the data were limited by small sample size, with only four assessable treatment arms. Prokinetics healed a mean of 37.9% ± 4.5% in only two study arms (cisapride).

Speed of Healing Esophagitis

Within each drug class, the healing proportion at each evaluation time interval was used to calculate an average rate of healing, i.e., percentage of patients healed per week (Figure 1). This gave a useful, comparative measure of the speed of healing, representing how fast healing of esophagitis was achieved by each drug class. At week 2, PPIs healed at a rate of 31.7% ± 3.3% per week, approximately double the rate of the next fastest group (H_2RAs at 15.0% ± 6.2% per week). For PPIs, the speed of healing slowed to 17.0% ± 3.3% per week by week 4, 15.0% ± 0.7% per week by week 6, 10.6% ± 1.1% per week at week 8, and 7.6% ± 0.1% per week at week 12; and for H_2RAs, 9.2% ± 3.0% per week at week 4, 6.4% ± 2.2% per week at week 6, 6.5% ± 1.9% per week at week 8, and 5.0% ± 1.3% per week at week 12. At these later time points, the speed of PPI healing declined but maintained a significant therapeutic advantage over all other treatments, because patients are healed earlier on in their treatment, and with longer duration of treatment, an increasingly

Table 4. Healing of Grade II–IV Esophagitis With Placebo, Sucralfate, and Prokinetics

First author, year	Blinding	Dose	Healing data (*wk*) (no. healed/no. treated)				Randomization[a]
			4	6	8	12	
Placebo							
Sherbaniuk, 1984[16]	DB	—	—	3/33	—	—	+
Sontag, 1987[18]	DB	—	—	29/71	—	—	0
Hetzel, 1988[44]	DB	—	2/32	—	3/32	—	+
Palmer, 1990[13]	DB	—	—	17/86	—	31/86	0
Quik, 1990[42]	DB	—	—	16/77	—	21/77	0
Cloud, 1991[40]	DB	—	—	10/94	—	12/94	+
Sabesin, 1991[37]	DB	—	—	3/46	—	12/46	0
Cloud, 1992[41]	DB	—	7/98[b]	16/98	—	—	+
Roufail, 1992[35]	DB	—	21/103	—	30/92	46/80	0
Sontag, 1992[45]	DB	—	3/43	—	6/43	—	+
Euler, 1993[36]	DB	—	21/115	—	32/115	45/115	0
Simon, 1994[39]	DB	—	—	11/56	—	18/56	0
Richter, 1995[51]	DB	—	—	—	—	6/28	0
Silver, 1996[34]	DB	—	51/238	—	79/217	106/203	0
Sucralfate							
Bremner, 1991[23]	DB	3 g bid	—	—	5/20	—	0
Elsborg, 1991[11]	DB	1 g qid	6/30	—	—	20/30	0
Vermeijden, 1992[52]	DB	1 g qid	—	—	4/23	—	0
Ros, 1991[15]	SB	1 g qid	—	—	10/21	—	0
Prokinetic							
Richter, 1995[51]	DB	10 mg qid	—	—	—	11/33	0
Richter, 1995[51]	DB	20 mg qid	—	—	—	17/40	0

DB, double blind; SB, single blind; bid, twice daily; qid, four times daily.
[a]Method or randomization: +, nonmanipulable; 0, potentially manipulable; —, quasirandomized.

smaller increment of patients is available to heal. For placebo, the figures are all much lower than for PPIs or H_2RAs: 2.4% per week at week 3, 3.7% ± 1.9% per week at week 4, and 3.0% ± 1.8% per week at week 6, stabilizing at 3.0% ± 1.5% per week at week 8 and 2.8% ± 1.2% per week at week 12. For prokinetics and sucralfate, there were too few points for analysis.

These data were then expressed as a healing-time curve (Figure 2). By the second week of treatment with PPIs (63.4% ± 6.6%), the same number of patients had healed esophagitis as after 12 weeks of treatment with H_2RAs (60.2% ± 15.9%). The healing-time curves were analyzed by linear regression to yield a slope that represented an overall estimate of the speed of healing. It is important to qualify that the actual speed of healing is more rapid earlier in treatment and the slope represents an overall estimate of healing over the whole time course of a treatment study. The r^2 for the regression slopes (placebo, 0.84; PPIs, 0.91; H_2RAs, 0.89) were all significant at $P < 0.0001$, which indicated appropriate modeling. PPI provided the fastest overall healing rate (slope ± SE) of 11.7% ± 0.5% (95% CI, 10.7–12.6) healed per week, twice as fast as H_2RAs (5.9% ± 0.2%; 95% CI, 5.5–6.3) and four times faster than placebo (2.9% ± 0.2%; 95% CI, 2.4–3.4). There is clear separation of the 95% CIs, indicating that the slopes were distinct and significantly different.

Symptom Relief

Complete heartburn relief. From the above database of esophagitis healing trials, studies that provided explicit symptom data were identified. These studies were required to present the number of patients who started out with grade II to IV esophagitis and reported heartburn and the proportion of patients who obtained complete symptom relief. Sixteen studies[11,14,17,20–22,25,30,33,44–50] with 31 treatment arms, 105 treatment points, and 2198 patients were identified (Table 5). Most study data were available for H_2RAs and PPIs, with only one study each reporting placebo and sucralfate. Many studies were excluded because it was difficult to tell which symptom actually resolved, and investigators often grouped together the whole study population, which could have included those without endoscopic esophagitis, and reported data for the whole group. Other investigators reported symptomatic change using their own summary symptom scores, and some simply did not report symptoms at all.

Table 5. Complete Symptom Relief Database to No Heartburn

Drug	Reference	Baseline	1 wk	2 wk	4 wk	6 wk	8 wk	12 wk	Comments
Placebo	45	0/43		4/43	12/43		15/43		Baseline assumed 0
Cim 400 mg bid	11	0/28			4/28		8/28	13/28	
Cim 400 mg qid	14	1/31		13/31	17/31	19/30	17/29		5/31, nonerosive
Ran 150 mg bid	17	0/26		6/26	8/26				
Ran 150 mg bid	20	3/77	20/75		34/75		28/60		
Ran 150 mg bid	21	0/30			6/25		9/25		
Ran 150 mg bid	30	2/83		30/69	39/69				
Ran 150 mg bid	22	2/59			27/59		38/59		
Ran 150 mg bid	25	0/30			6/29		12/28		
Ran 300 mg bid	33	2/47			15/47		15/47		
Ran 300 mg qid	22	3/63			42/63		53/63		
Sulc 1 g qid	11	0/32			6/32		10/32	15/32	
Ome 20 mg/day	44	15/82		51/82	62/82				
Ome 20 mg/day	20	4/73	35/69		50/69		57/66		
Ome 20 mg/day	25	0/30			18/30		18/28		
Ome 20 mg/day	45	0/83		41/83	52/83		66/83		Baseline assumed 0
Ome 20 mg/day	46	0/86		70/86	81/86				
Ome 20 mg/day	47	14/313			220/303		115/147		2 arms combined
Ome 20 mg/day	48	0/92	25/92	33/92	55/92	61/92	67/92		
Ome 20 mg/day	49	0/101		77/101	83/101				
Ome 40 mg/day	44	10/82		61/82	66/82				
Ome 40 mg/day	33	4/51			44/51		46/51		
Ome 40 mg/day	45	0/87		48/87	62/87		71/87		Baseline assumed 0
Ome 40 mg/day	21	3/31			22/26		22/25		
Ome 40 mg/day	14	3/28		21/28	26/28	24/25	23/25		1/28, nonerosive
Ome 60 mg/day	17	1/25		17/25	23/25				
Lanso 30 mg/day	50	1/23						14/23	Whole study, 5/50 G1
Lanso 60 mg/day	50	4/27						23/27	Whole study, 5/50 G1
Panto 40 mg/day	46	0/170		121/166	148/165				
Panto 40 mg/day	49	0/99		76/99	87/99				
Panto 40 mg/day	30	5/166		100/149	127/149				

NOTE. Data are expressed as number with no heartburn per number evaluated at each time point.
Cim, cimetidine; Ran, ranitidine; Sulc, sucralfate; Ome, omeprazole; Panto, pantoprazole; Lanso, lansoprazole; bid, twice daily; qid, four times daily; G1, grade 1; defined as erosive in text.

Some patients did not report heartburn at the beginning of the study, although they may have had some other GERD symptom such as reflux. Only 3.8% (95% CI, 2.1–5.5) of patients enrolled in these studies did not have heartburn, emphasizing the importance of this symptom in those with grade II to IV esophagitis. Data at each evaluation time point were corrected by subtracting the small proportion of patients who were heartburn free at baseline to provide the best estimate of the proportion of patients that became heartburn free with treatment from 1 to 12 weeks. From the total heartburn relief reported per study (from 4 to 12 weeks), we determined that the PPIs, irrespective of dose or duration of treatment, provided the greatest overall symptom relief, with 77.4% ± 10.4% heartburn free, which was significantly better ($P < 0.0001$) than with H_2RAs (47.6% ± 15.5%).

Within each drug class, the symptom-free proportion of patients at each evaluation time point was used to calculate an average speed of symptom relief, i.e., percentage of patients who were heartburn free per week (Figure 3). This provided an analogous comparison to the speed of healing analysis and represented how fast heartburn relief was achieved by each drug class. At week 2, PPI-treated patients became heartburn free at a rate of 31.8% ± 7.9% per week, nearly double (1.8 times) that of H_2RAs at 17.9% ± 5.8% per week. By week 4, PPIs continued to provide rapid, 18.5% ± 2.9% per week heartburn relief that decreased to 10.2% ± 1.5% per week by week 8. Corresponding figures for H_2RAs were 8.9% ± 3.7% per week by week 4 and 6.3% ± 2.4% per week by week 8. Thus, the speed of symptom relief declines as treatment duration lengthens, but the therapeutic gain for the PPIs over other treatments was maintained.

The data were next expressed as a symptom relief–time curve (Figure 4). As many patients became heartburn free by the second week of treatment with PPIs (58.0% ± 16.9%) as after 8 weeks of treatment with H_2RAs (48.8% ± 16.2%). The symptom relief–time

curves were analyzed by linear regression to yield slopes that represented an overall estimate of the speed of symptom relief. The r^2 for the regression slopes (PPI, 0.78; H_2RA, 0.83) were both significant ($P < 0.0001$), indicating appropriate modeling. The data were comparable to those observed with the analysis of the speed of healing. PPIs provided overall heartburn relief (slope ± SE) of 11.5% ± 0.8% (95% CI, 9.9–13.0) per week, which was significant and nearly twice as fast as H_2RAs (6.4% ± 0.5% per week; 95% CI, 5.4–7.4).

Time shift in heartburn relief. From the same data set identified for healing, studies that used a uniform symptom scoring system of none, mild, moderate, or severe in patients with grade II to IV esophagitis were identified. Only 7[14,17,19–21,33,44] such studies were found because the majority did not use this classification system. This analysis involved 14 treatment arms with a total of 730 patients. Six arms with H_2RAs (Figure 5) and eight arms with PPIs (all omeprazole studies; Figure 6) were assessable.

Severe symptoms were recorded at baseline in 25% of all patients, and by the end of treatment almost no patient had severe symptoms. More patients became completely free of heartburn with PPIs at 2 weeks (68.2%) than with longer 8-week treatment with H_2RAs (42%). Even at the end of the study at 8 weeks, 57.4% of patients taking H_2RAs were still symptomatic and experienced mild to moderate heartburn, which was only slightly fewer than at the start (74.2%). In contrast, by week 8, only 11.1% of PPI-treated patients still had mild to moderate heartburn compared with 64.3% at baseline and 18.4% at 4 weeks. This analysis showed that heartburn relief was most complete for patients treated with PPIs.

Discussion

The main objective of this study was to establish a model to analyze the comparative efficacy of treatments for GERD that could be expressed as the rate or speed of healing and symptom relief in patients with erosive or ulcerative esophagitis. To do so, we determined a large number of raw data points that were used to calculate, by linear regression analysis, estimates of the speed of healing and speed of symptom relief in patients with grade II–IV esophagitis. Many studies enrolled patients with all grades of esophagitis but did not report separately the healing data according to baseline grade. For our purposes, these studies could not be included in our analysis. Many studies that did provide these data in their report did not necessarily do so explicitly, making data extraction difficult. Most of the prokinetic studies (such as with cisapride) that were retrieved by our search studied lesser grades of esophagitis, reflecting milder forms of GERD, and were not eligible for this systematic overview. Not surprisingly, most data existed for H_2RAs and PPIs (mostly for omeprazole, but lansoprazole and pantoprazole data were available). The PPI studies were generally consistent in study design, were most comparable to each other, and applied the best study methodology. Consistent with our original protocol, we analyzed data within drug classes and did not perform subgroup analyses of specific drugs within each drug class. In most cases there were too few study arms of individual drugs, doses, and durations of treatment for meaningful comparison.

We presented our data in preliminary form[53,54] and have updated the analysis to keep it current. An important change is that studies with fewer than 20 patients per arm have now been arbitrarily excluded. The more recent articles have tended to be larger, multicenter studies with data more clearly presented. Furthermore, data from earlier studies were mostly per protocol, but more recent studies express intent-to-treat data. As such, these newer, larger studies, if anything, have given us more conservative data.

Our systematic overview has identified the PPI as providing the highest, overall healing proportion (83.6% ± 11.4%) irrespective of drug dose and duration of treatment. Of importance is the observation that this drug class also healed most consistently with the narrowest 95% CI (79.1–88.1). Most studies used either 20 mg or 40 mg of omeprazole as once-daily dosing. Lansoprazole was studied as 30 or 60 mg daily and pantoprazole as 40 mg daily. Unfortunately, it was not possible to perform subgroup analysis of healing in relation to the initial grade of esophagitis because the studies evaluated did not consistently break down the healing by grade. Other drug classes, particularly sucralfate (only four studies) showed inconsistent healing. The mean pooled healing in the placebo group was surprisingly high (28.2% ± 15.6%) but the 95% CI was broad (19.2–37.2).

The mean pooled overall healing proportion in grade II–IV esophagitis with the H_2RAs was 51.9% ± 17.1%. In this drug class, cimetidine, ranitidine, nizatidine, and famotidine were all represented. The doses of H_2RAs used were, commonly, cimetidine 400 mg daily, ranitidine 150 mg twice daily, and in higher doses, nizatidine 300–600 mg daily and famotidine 20 or 40 mg twice daily. Three studies[22,35,36] used ranitidine at a high dose of 300 mg four times daily to achieve 67.9% healing at 8 weeks and 77.3% by 12 weeks. In two direct comparative studies[35,36] with

ranitidine, 150 mg or 300 mg four times daily with placebo, there was no therapeutic gain obtained with the higher dose of ranitidine, suggesting that the H_2RAs are limited in their ability to suppress acid secretion adequately. Even at this higher dosing with treatment given for 12 weeks, the overall healing proportion achieved was lower than that observed with PPIs after a shorter 6-week duration. Thus, H_2RA efficacy can be improved to a point; however, when one considers that four-times-daily dosing is required, this compromises compliance and significantly raises cost compared with the greater efficacy and once-daily dosing of PPI therapy.

The speed of healing as obtained from the percentage of patients healed per week (Figure 1) best expresses how rapidly healing occurred. PPIs healed at a rate approximately twice as fast as H_2RAs at all time points and the largest gain in efficacy was seen early in treatment. As treatment duration was prolonged, a larger proportion of patients with esophagitis were healed, and the speed of healing decreased as there were fewer patients left to be healed. However, PPIs maintained a significant advantage throughout the treatment period.

The slopes of the healing-time curves provided an overall estimate of the speed of healing of each drug class. PPI patients healed at an average rate of 11.7% ± 0.5% per week, which was nearly twice as fast as H_2RA at 5.9% ± 0.2% per week and four times faster than placebo at 2.9% ± 0.2% per week. The absolute value of each slope is an average and is less meaningful than the relative comparisons between the drug classes. This provides a useful and quantitative means of comparing the relative efficacy of different drug classes in healing erosive GERD. The greater degree and more prolonged acid suppression achieved by PPIs accounts for the greater speed of healing.[7]

It is important to emphasize that the patient population studied comprises those with grade II–IV GERD. Overall, 61.8% of patients had grade II, 31.7% had grade III, and only 6.5% of patients had grade IV esophagitis. Therefore, although these studies were restricted to patients with grade II–IV esophagitis, which represents only 2% of GERD,[4] the majority had moderate disease and only a small proportion had the most severe disease. It is commonly believed that H_2RAs are as useful as PPIs in treating grade II esophagitis. In our analysis, the therapeutic gain of PPIs over H_2RA is clearly evident for grade II disease, and would support a recent editorial that suggested that standard twice-daily dosing with H_2RAs for complicated GERD is inappropriate.[55] It would have been desirable to evaluate healing per grade of esophagitis, but because most studies did not present these data clearly, we were unable to perform this analysis with confidence.

However, in other studies patients with peptic strictures had a reduced need for repeat dilatation and greater relief of dysphagia when treated with PPIs compared with ranitidine.[56,57]

Our study was restricted to evaluation of acute healing of esophagitis. Once healing is achieved and treatment is stopped, recurrence is common, particularly in patients with erosive esophagitis. Thus, maintenance therapy may be necessary in a large number of these patients. This was not systematically reviewed in our analysis, although PPIs have been found consistently superior to H_2RA in maintenance of esophagitis healing.[58–60]

The symptom data were methodologically less robust than the healing data. Not all studies assessed symptom relief, and in those that did, a standardized symptom score was seldom used. Similar to healing data, studies of PPI-treated patients reported a significantly greater overall proportion of patients free of heartburn at the end of the study, nearly twice as many as H_2RAs.

The speed of heartburn relief (percentage of symptom relief per week) in PPI-treated patients was analogous to the healing data, with 30.7% ± 7.5% patients per week becoming asymptomatic by week 2 (Figure 3). This was approximately twice as fast as the H_2RA-treated patients. The rate of symptom relief declined for both drug classes with longer duration of treatment, as the increment of patients who were still symptomatic became smaller. Therefore, symptom relief occurred more rapidly earlier in treatment and by 2 weeks, a mean of 58.0% ± 16.9% of PPI-treated patients became heartburn free, a similar proportion to the 63.4% ± 6.6% of patients healed. Thus, symptom relief tends to occur at a rate correlating with that of healing.

Using data from studies that reported symptom relief, the overall speed of symptom relief was estimated by linear regression, and PPIs provided the fastest overall rate of symptom relief (11.5% ± 0.8% per week), which was nearly twice as fast as noted with H_2RAs. For both PPIs and H_2RAs, the slopes of the symptom relief–time curves were comparable to the slopes of the healing-time curves, implying that symptom relief occurred in parallel to healing.

Only seven studies used a scoring system to grade symptoms as none, mild, moderate, or severe. Although the data are limited, they provide some interesting observations. Patients experienced more complete heartburn relief on treatment with PPIs compared with H_2RAs.

Also, at the end of the studies, more than half of the patients given H_2RA had persistent mild to moderate heartburn even after 8 weeks treatment, whereas after 4 weeks, only 18.4% of patients still had residual mild to moderate heartburn if treated with PPIs. Thus, PPI-treated patients had not only more complete heartburn relief, but this occurred more rapidly with a shift in time required for heartburn relief to occur.

Our overview clearly identified that PPIs provided healing and symptom relief of grade II to IV esophagitis at a rate nearly twice as fast as that observed with H_2RAs. The calculated slopes from regression analysis are not intended to represent the actual rates of healing or symptom relief, but rather to provide a conceptual and quantitative framework that can allow appropriate comparisons of efficacy that will be useful in studies of economic evaluation and assessment of quality of life in the management of patients with GERD.

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