

Meta-analysis: Duration of First-Line Proton-Pump Inhibitor–Based Triple Therapy for *Helicobacter pylori* Eradication

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Background: Proton-pump inhibitor (PPI)–based triple therapy is the recommended first-line treatment for *Helicobacter pylori* infection. A consensus on treatment duration is lacking.

Purpose: To summarize the benefits and harms of different durations of PPI-based triple therapy.

Data Sources: PubMed, EMBASE, the Cochrane Library, and proceedings of major meetings through May 2007.

Study Selection: English-language reports of randomized, controlled trials that compared duration (7, 10, or 14 days) of triple therapy and in which adequate testing confirmed the initial *H. pylori* infection and its eradication.

Data Extraction: Two authors independently extracted data on study design, treatment, number of patients enrolled and number of patients with successful eradication, disease at enrollment, testing, adverse effects, year of publication, publication format, and country.

Data Synthesis: Of 21 included studies, 11 compared 7-day therapy with 10-day therapy, and 13 compared 7-day therapy with 14-day therapy. Meta-analysis yielded relative risks (RRs) for eradication of 1.05 (95% CI, 1.01 to 1.10) for 7-day compared with

10-day amoxicillin-containing triple therapy (10 studies) and 1.07 (CI, 1.02 to 1.12) for 7-day compared with 14-day therapy (11 studies). Meta-analysis of the 3 studies that compared 7-day with 14-day metronidazole-containing therapy yielded an RR of 1.08 (CI, 0.96 to 1.22). The 7-day versus 10-day comparisons yielded RRs of 1.03 (CI, 0.97 to 1.10) for peptic ulcer disease and 1.10 (CI, 1.02 to 1.20) for nonulcer dyspepsia. For the 7-day versus 14-day comparisons, the RRs were 1.04 (CI, 0.99 to 1.09) and 1.03 (CI, 0.88 to 1.20), respectively. The RRs for frequency of adverse events were 0.98 (CI, 0.85 to 1.14) and 1.08 (CI, 0.84 to 1.40) for 7-day therapy compared with 10- and 14-day therapy, respectively. Diarrhea and taste disturbance were the most frequently reported adverse events (5%).

Limitations: Subgroup analyses were limited by the few studies evaluating different drug regimens and disease at enrollment. Seventeen of the included studies had poor methodological quality or inadequate reporting.

Conclusion: Available data suggest that extending triple therapy beyond 7 days is unlikely to be a clinically useful strategy.

Ann Intern Med. 2007;147:553-562.

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H*elicobacter pylori* infection causes chronic gastritis and is associated with increased risk for major upper gastrointestinal diseases, such as peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (1). Proton-pump inhibitor (PPI)–based triple therapy, composed of a PPI, clarithromycin, and either amoxicillin or metronidazole, is a widely recommended eradication therapy. However, there is still no consensus on the optimal duration of treatment (7, 10, or 14 days). Two meta-analyses (2, 3) have examined comparative randomized, controlled trials (RCTs) investigating the efficacy of different durations of triple therapy. They have given similar results, showing that 14 days of therapy provides a moderate eradication rate that is significantly higher than that provided by 7-day therapy. The results of these meta-analyses led to the recently published European guideline (4) recommending 14 days as the duration of choice for *H. pylori* infection eradication therapy, in contrast to previous suggestions (5).

Since the last published meta-analysis, 9 comparative studies about this issue have been published, 8 as full articles (6–13) and 1 in abstract form (14). Furthermore, previous meta-analyses presented several methodological weaknesses, such as absence of searching and selection criteria (3) and no evaluation of publication bias or study quality.

We performed an updated meta-analysis of RCTs comparing the efficacy of different durations of triple therapy to verify whether current recommendations reflect the available data and to determine the optimum duration for PPI-based triple therapy for *H. pylori* eradication.

METHODS

Study Sources and Searches

We developed a protocol for the review and followed standard reporting guidelines (15). We identified relevant trials by using separate computer-assisted bibliographic searches of PubMed, EMBASE, and the Cochrane Library. Searches of the literature through 31 May 2007 used combinations of the following terms: *Helicobacter pylori* or *H. pylori* and 7, seven, one-week, 10, ten, 14, fourteen, two-weeks, clarithromycin, amoxicillin, metronidazole, proton

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pump inhibitor, omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, triple, or duration. Abstracts and full articles from relevant studies were independently reviewed by 2 investigators, and those meeting the inclusion criteria were considered for further evaluation. In addition, we identified relevant trials from the reference list of each selected article. We also hand-searched abstracts presented from 1995 to 2006 at the United European Gastroenterology Week meeting and the International Workshop of the European *Helicobacter* Study Group and of abstracts presented at the Digestive Disease Week through 2007. We analyzed only articles published in English.

Study Selection

Selection criteria were established a priori to minimize bias (16). The abstract or full manuscript of all studies identified by the literature searches were reviewed and selected according to the following criteria for inclusion in the meta-analysis: 1) RCTs with at least 2 parallel groups that compared different durations (7, 10, or 14 days) of identical PPI-based triple therapy (a PPI with clarithromycin and amoxicillin or a PPI with clarithromycin and metronidazole), all given twice daily and at the recommended doses (4); 2) first-line eradication therapy; 3) *H. pylori* infection demonstrated by at least 1 high-accuracy diagnostic test (urea breath test, stool antigen test, gastric mucosal biopsy for histology, rapid urease test, or culture) (4); 4) eradication of infection confirmed at least 4 weeks after completion of treatment, based on an appropriate diagnostic test (4); and 5) report of intention-to-treat results.

Data Extraction and Quality Assessment

Two investigators independently extracted data on the following items from the selected articles: 1) study design; 2) drug regimen, doses, and treatment duration; 3) number of patients enrolled in the study and in each treatment group; 4) enrollment period; 5) diagnosis of peptic ulcer disease or nonulcer dyspepsia at enrollment; 6) testing used to diagnose the infection and to evaluate the eradication (including the timing of testing); 7) number of patients in whom *H. pylori* infection was successfully eradicated (either provided directly or calculated from the intention-to-treat values); 8) number of patients with adverse effects, type and severity of adverse effects, and number of patients who discontinued treatment because of adverse effects; and 9) year of publication, format (abstract or journal article), and country where the trial was performed.

The quality of each study was assessed by using the Jadad composite scale based on 3 items: randomization, double-blinding, and follow-up (17). Points were awarded on the basis of the quality of randomization (2 points: computer-generated random numbers or similar; 1 point: not described; 0 points: quasi-randomized or not randomized [we excluded such studies]), double-blinding (2 points: identical placebo tablets or similar; 1 point: not described; 0 points: no blinding or inadequate method), and follow-up (1 point: number or reasons for dropouts

and withdrawals described; 0 points: number or reasons for dropouts and withdrawals not described). The total score ranged from 1 to 5. To supplement data from the published studies and to complete the Jadad composite score, we sent an e-mail message to the first author or, when clearly expressed, the corresponding author, of all included studies. The e-mail was organized as a simple questionnaire covering randomization, generation of allocation sequence, double-blinding, and description of dropouts and withdrawals.

Two investigators independently assessed study quality, and discrepancies were resolved by the consensus of all investigators. We used the κ coefficient to measure the strength of agreement between the 2 investigators (18).

Data Synthesis and Analysis

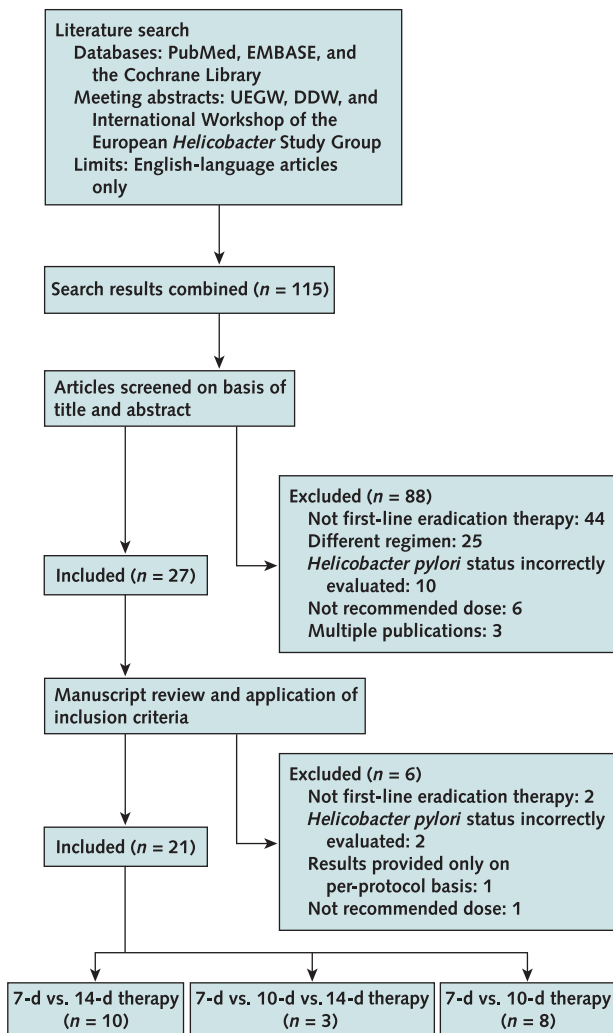
The outcome of the meta-analysis was *H. pylori* eradication, analyzed on an intention-to-treat basis. The meta-analysis assessed *H. pylori* eradication, considering 7-day versus 10-day and 7-day versus 14-day PPI-based triple therapy. Subgroup analyses considered the type of triple therapy (a PPI with clarithromycin and amoxicillin or a PPI with clarithromycin and metronidazole), disease at enrollment (peptic ulcer disease or nonulcer dyspepsia), and study quality. For study quality, analysis was restricted to trials with the highest quality score (4 or 5) on the Jadad composite scale (19). Because different PPIs (omeprazole, lansoprazole, esomeprazole, pantoprazole, and rabeprazole) have been shown to be equivalent when used in triple therapy, we did not consider them separately (20).

We measured *H. pylori* eradication by using relative risk (RR) to compare the frequency of eradication in the treatment group (patients receiving 10 or 14 days of therapy) with that in the control group (patients treated for 7 days). The disadvantage of using RR is its susceptibility to alteration by the prevalence rate in the control group. This is particularly emphasized by large variations in baseline events; thus, in such circumstances, the odds ratio may be more appropriate. However, RR remains preferable to the odds ratio for most investigators because of its more intuitive interpretation (21). We pooled the RRs for all studies into a summary RR, using both a fixed-effects model and a random-effects model (22). We provided *P* values and 95% CIs for the summary RRs.

We constructed funnel plots of RR versus the reciprocal of the SE, and we used the Begg and Egger tests to assess publication bias. To assess the presence of heterogeneity, we used graphical methods (Galbraith plot) and formal tests of heterogeneity (Cochran *Q* test and Higgins test). In the presence of heterogeneity, potential sources were investigated by subgroup analyses and meta-regression analysis. The influence plot was also analyzed to investigate the influence of each study and the presence of excessively influential studies.

All calculations were performed with the freeware program Review Manager 4.2.5 (The Cochrane Collabora-

Figure 1. Flow diagram of trials identified and selected.



DDW = Digestive Disease Week; UEGW = United European Gastroenterology Week.

tion, Oxford, United Kingdom) and Stata statistical software (Stata, College Station, Texas).

Role of the Funding Source

No funding was received for the preparation of this manuscript.

RESULTS

Search Results

The abstracts of 115 relevant articles were reviewed, and 27 full papers were retrieved. After imposing exclusion criteria, we included 21 trials in the analysis (Figure 1). Four of these were published in abstract form (14, 23–25). Of the 21 included studies, 13 compared 7-day and 14-day treatments (a total of 2849 patients) and 11 trials compared 7-day and 10-day treatments (1982 patients). There was strong agreement between the 2 investigators ($\kappa =$

0.91). The analysis of the funnel plot and results of the Begg and Egger tests indicated that publication bias was not present.

We excluded Kiyota and colleagues' study (26) because posttreatment *H. pylori* status was evaluated soon after a ranitidine treatment period. Similarly, we excluded the study by de Silva and colleagues (27) because it assessed eradication 2 weeks after completion of therapy. The studies by Paoluzi and colleagues (28) and Gumurdulu and colleagues (29) were excluded because the study samples included patients who had already received *H. pylori* eradication treatment that had failed. We excluded Lamouliatte and colleagues' study (30) because it reported results only on a per-protocol basis. The study by Bhasin and coworkers (31) was excluded because the drug doses administered were not the recommended doses. We did include Dammann and associates' study (32) in the final analysis. However, for labeling reasons, metronidazole was given for only 10 days in the 14-day treatment group; thus, we performed each analysis twice, once including this study and once excluding it. Although the study by Dal Bò and colleagues (33) administered metronidazole 4 times daily, we included it because the overall daily dosage remained at the recommended level (1000 mg/d). We included Ching and associates' study (34) but considered only the subgroup of patients with nonulcer dyspepsia because the investigators assessed *H. pylori* status in patients with peptic ulcer 1 week after the completion of PPI therapy.

All but 5 included studies were performed in Europe. Of the non-European studies, 2 were from the United States, 2 were from Asia, and 1 was from South Africa. All studies were randomized, but information about generation of allocation sequence was available for only 8 studies (6–9, 12, 13, 33, 35) and was judged adequate for only 7 (6–9, 12, 13, 35). Of these 7 trials, 3 (6, 9, 13) concealed allocation sequences. For all other studies, generation and concealment of allocation sequence remained unclear. Only 4 studies were designed as double-blind and double-dummy (6, 13, 32, 36); all of the others were open studies.

Eighteen studies compared the efficacy of different durations of amoxicillin-based triple therapy. Four studies (12, 32, 33, 36) compared the metronidazole-based regimen, but only 1 compared 7-day and 10-day therapy (36). Indications for *H. pylori* eradication therapy were peptic ulcer in 15 studies and nonulcer dyspepsia in 11 studies. However, 3 studies (12, 14, 37) that enrolled both types of patients did not stratify the results according to the disease, and 1 study (35) did not specify disease at enrollment. Therefore, we did not analyze all of these studies.

Table 1 further lists the characteristics of the 21 included studies (6–14, 23–25, 32–41).

Efficacy of *H. pylori* Eradication according to Different Durations of Therapy

Because analysis by the fixed-effects and random-effects models produced identical overall estimates, we

Table 1. Studies Comparing the Duration of Proton-Pump Inhibitor–Based Triple Therapy Included in the Meta-analysis*

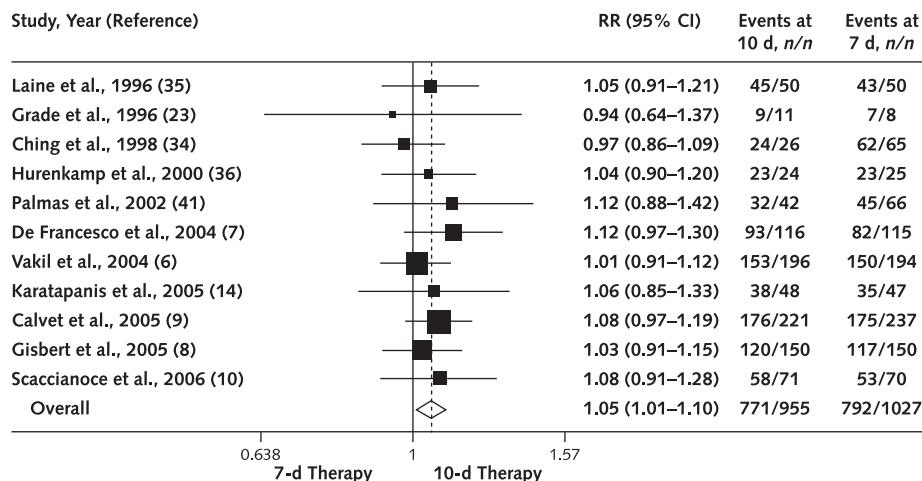
Study, Year (Reference)	Country	Format	Enrollment Period	Duration of Therapy, <i>d</i>	Generation of Allocation Sequence
Katicic et al., 1996 (25)	Croatia	Abstract	NR	7, 14	NS
Moayyedi et al., 1996 (38)	United Kingdom	Journal article	NR	7, 14	NS
Laine et al., 1996 (35)	United States	Journal article	NR	7, 10, 14	Computer-generated
Grade et al., 1996 (23)	United States	Abstract	NR	7, 10	NS
Monès et al., 1997 (24)	Spain	Abstract	May 1995–May 1996	7, 14	NS
Dal Bò et al., 1998 (33)	Italy	Journal article	NR	7, 14	Arbitrarily sorted
Louw et al., 1998 (39)	South Africa	Journal article	NR	7, 14	NS
Ching et al., 1998 (34)	Hong Kong	Journal article	NR	7, 10	NS
Dammann et al., 2000 (32)	Germany	Journal article	NR	7, 14	NS
Hurenkamp et al., 2000 (36)	Netherlands	Journal article	April 1997–October 1999	7, 10	NS
Maconi et al., 2001 (37)	Italy	Journal article	January 1996–December 1997	7, 14	NS
Palmas et al., 2002 (41)	Italy	Journal article	NR	7, 10, 15	NS
Vakil et al., 2004 (6)	United States	Journal article	NR	7, 10	Treatment allocation numbers in a random order
De Francesco et al., 2004 (7)	Italy	Journal article	NR	7, 10	Computer-generated
Gisbert et al., 2005 (8)	Spain	Journal article	NR	7, 10	Table of contingent numbers
Calvet et al., 2005 (9)	Spain	Journal article	September 2002–November 2003	7, 10	Random-number generator
Karatapanis et al., 2005 (14)	Greece	Abstract	NR	7, 10, 14	NS
Scaccianoce et al., 2006 (10)	Italy	Journal article	NR	7, 10	NS
Paoluzi et al., 2006 (12)	Italy	Journal article	NR	7, 14	Computer-generated
Zagari et al., 2007 (13)	Italy	Journal article	May 1996–June 1998	7, 14	Computer-generated
Kim et al., 2007 (11)	Korea	Journal article	December 2002–May 2003	7, 14	NS

* NR = not reported; NS = not specified; PPI = proton-pump inhibitor.

Table 1—Continued

Double-Blinding?	Description of Follow-up?	Therapy	Method for Assessing Eradication	Indication	Jadad Score
No	No	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Histology	Peptic ulcer disease	1
No	Yes	Lansoprazole, 30 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Nonulcer dyspepsia	2
No	Yes	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	NS	3
No	Yes	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Nonulcer dyspepsia	2
No	No	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease	1
No	Yes	Omeprazole, 20 mg twice daily, + metronidazole, 250 mg 4 times daily, + clarithromycin, 250 mg twice daily	Histology	Nonulcer dyspepsia	2
No	Yes	Lansoprazole, 30 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Histology	Peptic ulcer disease	2
No	Yes	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Nonulcer dyspepsia	2
Yes (double-dummy)	Yes	Pantoprazole, 40 mg twice daily, + clarithromycin, 500 mg twice daily, + metronidazole, 500 mg twice daily (for 10 d)	Histology, urea breath test, culture	Peptic ulcer disease	4
Yes (double-dummy)	Yes	Omeprazole, 20 mg twice daily, + clarithromycin, 250 mg twice daily, + metronidazole, 400 mg twice daily	Histology, culture	Peptic ulcer disease	4
No	Yes	Lansoprazole, 30 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease/ nonulcer dyspepsia	2
No	Yes	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test, histology	Peptic ulcer disease	2
Yes (double-dummy)	Yes	Rabeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease/ nonulcer dyspepsia	5
No	Yes	Rabeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease/ nonulcer dyspepsia	3
No	Yes	Esomeprazole, 40 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease	3
No	Yes	Rabeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease/ nonulcer dyspepsia	3
No	Yes	Rabeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Histology	Peptic ulcer disease/ nonulcer dyspepsia	2
No	Yes	Esomeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Nonulcer dyspepsia	2
No	Yes	Omeprazole, 20 mg twice daily, + clarithromycin, 500 mg twice daily, + amoxicillin, 1 g twice daily, or metronidazole, 400 mg twice daily	Urea breath test, histology	Peptic ulcer disease/ nonulcer dyspepsia	3
Yes (double-dummy)	Yes	Omeprazole, 20 mg twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test, histology	Peptic ulcer disease	5
No	Yes	Omeprazole, 20 mg or equivalent doses of other PPIs twice daily, + amoxicillin, 1 g twice daily, + clarithromycin, 500 mg twice daily	Urea breath test	Peptic ulcer disease	2

Figure 2. Forest plot of the 11 studies comparing 7-day with 10-day proton-pump inhibitor–based triple therapy.



Results of the Cochran *Q* tests for heterogeneity were not statistically significant ($P = 0.93$), and the Higgins test failed to reject the hypothesis of homogeneity between studies ($I^2 = 0\%$). The Galbraith plots confirmed that no studies fell outside the 95% limit area. The area of the boxes corresponds to the weight of each study. RR = relative risk.

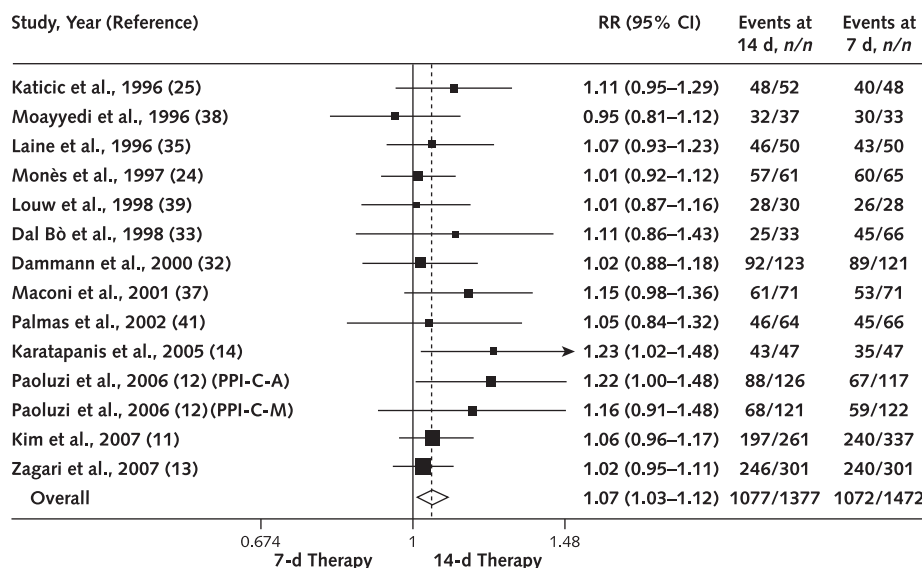
present just the results obtained with the fixed-effects model. The pooled analysis of all the selected studies comparing 7-day and 10-day therapies yielded an RR of 1.05 (95% CI, 1.01 to 1.10) (Figure 2). Overall, eradication rates were 77% for 7-day therapy and 81% for 10-day therapy. Rates for 7-day and 14-day treatments were 73% and 78%, respectively, and the RR was 1.07 (CI, 1.03 to 1.12) (Figure 3).

The analysis-of-influence plot shows that for the stud-

ies comparing 7-day and 14-day therapies, the most influential study was that by Zagari and colleagues (13). For the studies comparing standard therapy with 10-day therapy, the most influential study was that by Ching and associates (34). None of the studies seemed to be excessively influential; accordingly, none was omitted.

Heterogeneity tests excluded the presence of statistical heterogeneity across the studies. Two possible sources of clinical heterogeneity (type of triple therapy and disease at

Figure 3. Forest plot of the 13 studies comparing 7-day with 14-day proton-pump inhibitor (PPI)–based triple therapy.



No statistical evidence of heterogeneity was detected ($I^2 = 0\%$; $P = 0.61$ for Cochran *Q* test; no studies fell outside the 95% limit area in the Galbraith plots). The area of the boxes corresponds to the weight of each study. A = amoxicillin; C = clarithromycin; M = metronidazole; RR = relative risk.

Table 2. Pooled Relative Risks of the Frequency of All Adverse Events, Adverse Events That Caused Discontinuation of Triple Therapy, and Different Types of Adverse Events

Adverse Events	Studies Contributing to Pooled Assessment, <i>n</i>	References	Relative Risk (95% CI)	
			7-Day vs. 10-Day Therapy	7-Day vs. 14-Day Therapy
All adverse events	15	6–13, 24, 32, 33, 35, 37–39	0.98 (0.85–1.14)	1.08 (0.84–1.40)
Discontinuation because of adverse events	8	6, 10, 12–14, 35, 37, 38	1.17 (0.53–2.59)	0.60 (0.32–1.10)
Type of adverse event				
Diarrhea	6	6, 7, 10, 11, 13, 38	0.90 (0.52–1.58)	0.99 (0.61–1.59)
Nausea	6	6, 7, 10, 11, 13, 38	0.62 (0.28–1.33)	3.82 (0.94–15.55)
Taste disturbance or glossitis	5	6, 7, 10, 11, 38	1.90 (0.99–3.63)	1.24 (0.60–2.57)

enrollment) were identified ex ante and were used in the subgroup analysis to investigate whether the effect size (RR) varied among different subgroups.

Subgroup analysis of the 18 trials that compared the efficacy of amoxicillin-based triple therapy confirmed that duration beyond 7 days yielded superior benefit. Analysis of the 10 studies comparing 7-day with 10-day therapy yielded an RR of 1.05 (CI, 1.01 to 1.10). For the 11 studies comparing 7-day and 14-day therapies, the RR was 1.07 (CI, 1.03 to 1.12).

According to the pooled analysis of the 3 trials, which analyzed the effect of metronidazole instead of amoxicillin over 7 days compared with 14 days, the summary RR was 1.08 (CI, 0.96 to 1.22).

Seventeen studies were available for subgroup analysis based on the indication for the eradication therapy (peptic ulcer disease or nonulcer dyspepsia). Thirteen studies enrolled patients with peptic ulcer disease. Six studies compared 7-day with 10-day therapy (6–9, 36, 41), and 7 studies compared 7-day with 14-day therapy (11, 13, 24, 25, 32, 39, 41). For the studies comparing 7- and 10-day treatments, the RR was 1.03 (CI, 0.97 to 1.10). A similar RR was obtained for the studies that compared 7-day with 14-day treatment (RR, 1.04 [CI, 0.99 to 1.09]). Eight studies evaluated patients with nonulcer dyspepsia (6, 7, 9, 10, 23, 33, 34, 38), but only 2 of these (33, 38) compared 7-day and 14-day therapies (RR, 1.03 [CI, 0.88 to 1.20]). For studies comparing 7-day and 10-day treatments, the RR was 1.10 (CI, 1.02 to 1.20).

Only 3 (12, 35, 39) of the 21 authors responded to our e-mail survey regarding the Jadad scoring. After compiling the data, we found that only 4 studies achieved a Jadad composite score of 4 or 5: 2 studies (13, 32) compared 7-day with 14-day therapy (RR, 1.02 [CI, 0.95 to 1.10]) and 2 studies (6, 36) compared 7-day with 10-day therapy (RR, 1.01 [CI, 0.92 to 1.11]).

Adverse Events

All but 2 studies (23, 25) reported on the frequency of adverse events. However, only 15 studies stratified the frequency according to the different durations of treatment: 6 comparing 7-day with 10-day treatment (6–10, 35) and 10 comparing 7-day with 14-day therapy (11–13, 24, 32, 33,

35, 37–39). The pooled RRs were 0.98 (CI, 0.85 to 1.14) and 1.08 (CI, 0.84 to 1.40), respectively. Eight studies contributed to the analysis of patients who withdrew because of adverse events: 4 comparing 7-day with 10-day therapy (6, 10, 14, 35) and 6 comparing 7-day with 14-day therapy (12–14, 35, 37, 38). These gave pooled RRs of 1.17 (CI, 0.53 to 2.59) and 0.60 (CI, 0.32 to 1.10), respectively. Most studies did not specify how they assessed severity of adverse events; the few that did specify did not present standard and uniform criteria. It was therefore not possible to perform a subgroup analysis according to the severity of adverse events. Only 6 studies contributed to the analysis of the type of adverse events: 3 compared 7-day with 10-day therapy (6, 7, 10) and 3 evaluated 7-day and 14-day treatments (11, 13, 38). We pooled the data on the frequency of diarrhea, nausea, and taste disturbance (Table 2). Diarrhea and taste disturbance were the most frequently reported adverse events (5%). None of the included studies evaluated the frequency, severity, or type of adverse events by using a validated questionnaire.

DISCUSSION

Our meta-analysis of RCTs comparing different durations of PPI-based triple therapy shows that extension of therapy beyond 7 days provides a slight increase (approximately 5%) in the eradication rate when the longest duration (14 days) is considered. Most studies considered amoxicillin-based triple therapies, and our data suggest that only this regimen has a higher eradication rate when used for more than 7 days. Further data are required to draw similar conclusions for metronidazole-based triple therapy.

Although no physiologic reasons suggest that eradication therapy should work differently in patients with nonulcer dyspepsia compared with those who have peptic ulcer disease, it has been suggested that *H. pylori* eradication is more successful in patients with dyspepsia (42, 43). Indeed, our analysis revealed a slight but statistically significant increase in eradication rate after a 10-day course compared with 7-day therapy in patients with dyspepsia but not in those with peptic ulcer.

When only the 4 well-conducted, high-quality methodological trials (as assessed with the Jadad scale) were considered, prolonging treatment beyond 7 days had no advantage; this effect was seen when each study was individually considered and when all studies were pooled in the meta-analysis. However, the limited number of high-quality studies restricted the pooled analysis.

Incomplete and often inadequate data on the frequency, severity, and type of adverse events that occurred during the various treatment periods prevent any definitive conclusion on the tolerability of the different therapy durations.

Strengths and Limitations

To minimize bias, 2 authors selected the studies, extracted the data, and assessed study quality; this process resulted in high interobserver agreement ($\kappa = 0.91$).

Our meta-analysis evaluated the presence of both statistical and clinical heterogeneity. The latter was investigated by identifying, a priori, potential sources of heterogeneity, such as drug type and disease at enrollment. However, the subgroup analyses were limited by the lack of studies investigating the comparative efficacy of altering treatment durations of metronidazole-containing versus amoxicillin-containing regimens. For the same reason, analysis of patients with nonulcer dyspepsia compared with those who have peptic ulcer disease was restricted.

The presence of publication bias was excluded by both graphical and statistical evaluation. Quality assessment was based on a widely used and validated scale (17, 44). One of the main disadvantages of the Jadad scale is dependence on the completeness of reporting. To complete the Jadad scale, we directly contacted the authors with an e-mail survey. However, only 3 authors (12, 35, 39) of the 21 we contacted responded. The low response rate resulted in a lack of relevant information, such as the adequacy of the generation of allocation sequence for 13 of the studies. Most of the included studies ($n = 17$) had poor methodological quality or inadequate reporting, and only 2 of the 4 double-blind, double-dummy studies with adequate generation of allocation sequence also adequately concealed allocation. The poor quality of the included studies could have affected the results of the meta-analysis. Indeed, when we evaluated only well-performed trials, we found no evidence of better eradication with longer treatment.

All but 3 of the trials in our meta-analysis were performed in western countries (11, 34, 39). Our literature search was restricted to English-language reports because of translation limitations, which could have introduced some bias. Language-inclusive meta-analyses are theoretically more precise, but it has previously been shown that differences due to language restriction, if present, are negligible (45–47).

Relation to Other Meta-Analyses

Two other meta-analyses (2, 3) have been performed on this specific issue. In 2000, Calvet and colleagues (2)

published a meta-analysis of 10 studies comparing 7-day and 14-day regimens and 4 studies comparing 7-day and 10-day regimens. On the basis of their analysis of the studies reporting intention-to-treat results, they concluded that extending the duration of triple therapy to 14 days increased the eradication rate by 9%. Subsequently, in 2003, Ford and Moayyedi (3) presented the results of a meta-analysis evaluating 10 studies that compared 7-day with 14-day therapy and 6 studies that compared 7-day with 10-day regimens. These findings confirmed that the 14-day regimen increased the eradication rate, with a 12% reduction in RR. In that meta-analysis, the authors did not specify whether the analysis was based only on the intention-to-treat principle or whether they also included per-protocol results. Furthermore, Ford and Moayyedi (3) concluded that longer treatment was still significantly more effective, regardless of whether triple therapies used amoxicillin or metronidazole, although they provided no data for this subgroup analysis. In both meta-analyses, no evidence for a difference in eradication rate for 7- and 10-day therapies was found.

We included 9 additional studies (7–11, 13, 14, 34, 41) in our meta-analysis. It is noteworthy that 2 of these, although available, were not included in the previous meta-analyses: One study (40) was available at that time in abstract form (recently published as a full-length report [13]) and 1 was available as a full article (34). In the present meta-analysis, we excluded 3 trials (26, 28, 30) that were included in the last published meta-analysis (3). However, sensitivity analysis that included these studies shows results similar to those reported in our meta-analysis. The lack of specified inclusion and exclusion criteria by Ford and Moayyedi (3) prevents any comment on the different studies evaluated in our meta-analysis.

In contrast to the meta-analysis performed by Calvet and colleagues (2), we included the study by Monès and associates (24) because it met all of our selection criteria. Moreover, as previously described, we excluded the studies by Lamouliatte (30) and Paoluzi (28) and their colleagues. Again, when the sensitivity analysis was performed with the addition and exclusion of studies previously included and excluded by Calvet and associates, results obtained were similar to those reported in our meta-analysis.

Neither of the previous meta-analyses assessed the presence of publication bias or the quality of the included trials. We evaluated the tolerability of different durations of eradication therapies, considering the frequency, severity, and type of adverse events. In contrast, the meta-analysis by Calvet and colleagues (2) did not present these data, and the meta-analysis by Ford and Moayyedi (3) did not assess tolerability at all.

Implications for Research and Practice

The methodological and reporting quality of most of the included trials was low. In the future, comparative studies should be designed to reduce potential sources of

bias, carefully considering the generation and concealment of allocation sequence and blinding. The quality of reporting could also be improved by adherence to widely accepted standards (48). Because most studies considered the amoxicillin-based triple therapies, more studies should assess therapy with metronidazole. Furthermore, because eradication rates are possibly influenced by disease status at enrollment, future studies need to be stratified according to the presence of peptic ulcer disease or nonulcer dyspepsia. To date, the frequency, severity, and type of adverse events have been poorly investigated and reported. Given the relevance of such factors in the therapeutic outcome, future studies should consider them more thoroughly.

In the developing world, *H. pylori* infection is a public health issue because of its high prevalence and the high level of antibiotic resistance (49). However, clinicians should consider the lack of well-performed comparative RCTs in these countries when recommending treatment for eradication strategies. Further research is needed to determine whether the induction of secondary antibiotic resistance is related to the duration of treatment. In clinical practice, the optimal duration of treatment must also depend on cost. Although we did not perform a cost analysis, our results show that increasing the duration of therapy avoids a second course of therapy in, at best, 5% of individuals treated. Because this does not seem to be a cost-effective strategy, a careful cost analysis should be performed before treatment beyond 7 days can be recommended.

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Acknowledgments: The authors thank Dr. Catherine Henderson for editorial support.

Potential Financial Conflicts of Interest: *Honoraria:* F. Bazzoli (Astra-Zeneca, Takeda, Altana Pharma).

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