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Meta-Analysis of Bismuth Quadruple Therapy versus Clarithromycin Triple Therapy for Empiric Primary Treatment of *Helicobacter pylori* Infection

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Key Words

Helicobacter pylori · Quadruple therapy · Triple therapy · Antibiotic resistance

Abstract

Background: In areas with high clarithromycin resistance, bismuth quadruple therapy (BQT) is recommended instead of clarithromycin triple therapy (CTT) as the first-line treatment for *Helicobacter pylori* eradication. ***Methods:*** Randomized clinical trials (RCTs) comparing BQT to CTT were identified through electronic and manual searches. A meta-analysis was performed to compare the efficacy and tolerability of these two regimens as first-line treatments for *H. pylori* infection. The effect of antibiotic resistance on treatment efficacy was also analyzed. ***Results:*** Twelve RCTs were included. BQT achieved eradication in 77.6% of patients, whereas CTT achieved an eradication rate of 68.9% [risk difference (RD) = 0.06, 95% CI: –0.01/0.13]. A high heterogeneity among the trials was found ($\chi^2 = 50.16$, $p < 0.00001$; $I^2 = 78\%$). In the subgroup analysis for treatment duration, the 10-day BQT was more effective than the 7-day CTT (RD = 0.25, 95% CI: 0.18/0.32), whereas no differences were observed between CTT and BQT given for 7 or 10 days. There were no statistical differences in side effects and compliance between both therapies (RD = 0.92, 95% CI: 0.76/1.12, and RD = –0.03, 95% CI: –0.05/0.00, respectively). The effect of antibiotic resistance on eradication rates was reported in 4 of the 12 RCTs. Clarithromycin resistance significantly affected the efficacy of CTT (RD = 0.75, 95% CI: 0.63/0.87), whereas BQT efficacy was not affected by metronidazole resistance (RD = 0.09, 95% CI: –0.06/0.25). ***Conclusions:*** The 10-day BQT was more effective than the 7-day CTT as a first-line therapy for *H. pylori* infection, whereas BQT and CTT for 7 or 10 days yielded similar eradication rates. Compliance and side effect rates were similar for both therapies. BQT overcomes clarithromycin resistance and its efficacy is not affected by metronidazole resistance.

Introduction

Helicobacter pylori infection is still one of the world's most frequent infections and accounts for high morbidity and mortality. About 20% of subjects infected with the bacterium will develop complications of the infection including peptic ulcer disease and gastric cancer, which ac-

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counts for at least 738,000 deaths annually [1]. Given the high prevalence and serious health burden of *H. pylori* infection, it is crucial to use a highly effective and well-tolerated eradication regimen.

The recent Maastricht IV consensus conference recommends for first-line empirical treatment of *H. pylori* infection a combination of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole [clarithromycin triple therapy (CTT)] for 7–14 days in areas of low clarithromycin resistance and a combination of a PPI, bismuth, metronidazole, and tetracycline [bismuth quadruple therapy (BQT)] for 10–14 days in areas of clarithromycin resistance >15–20% [2]. The rationale for these recommendations is the increasing clarithromycin resistance rate in Europe and other geographical regions [3, 4]. Two previous meta-analyses on the effect of CTT and BQT found similar eradication rates for both regimens when used as first-line therapies for *H. pylori* infection. Compliance and side effects were similar for both therapy regimens as well [5, 6]. In the present meta-analysis, we further evaluated and compared the efficacy and tolerability of BQT and CTT by including recent trials. We included the analysis on the effect of resistance to clarithromycin and metronidazole on the efficacy of treatments.

Methods

Data Sources and Search Strategy

To find relevant articles for this review, a search of MEDLINE, EMBASE, and the Cochrane Library for randomized clinical trials (RCTs) published between 1995 and November 2011 was carried out. Only the following search terms were used: '*Helicobacter pylori*', 'triple therapy', 'quadruple therapy', 'amoxicillin', 'clarithromycin', 'bismuth', 'metronidazole', 'tetracycline', and 'eradication'. No limits for language were entered for the search. Boolean operators ('AND', 'OR', 'NOT') were used to narrow and widen the search results. The titles from the search results were examined closely and determined to be suitable for potential inclusion into the study. In addition, the references from selected articles were examined as a further search tool.

Study Selection

For inclusion in the meta-analysis, a study had to meet the following criteria: (1) randomized clinical trial; (2) treatment with BQT (metronidazole, bismuth-containing compound, tetracycline, and PPI) versus CTT (amoxicillin, clarithromycin, and PPI) as the first-line therapy for eradication of *H. pylori* infection; (3) method of *H. pylori* diagnosis by urea breath test, rapid urease test, histology, and/or fecal antigen testing; (4) main outcome measure as an intention-to-treat (ITT) eradication rate, and (5) eradication testing with urea breath test and/or histology at least 4 weeks after completion of therapy.

Data Extraction

Only RCTs were included in our analysis. Using a predefined meta-analysis form, two independent reviewers (M.V. and T.K.) extracted data from each study. This process resulted in high interobserver agreement ($\kappa = 0.91$). Information contained the names of the authors, title of the study, journal in which the study was published, country and year of the study, treatment regimen, dosage, length of the therapy, method by which *H. pylori* infection was diagnosed and method of eradication, testing sample size (with sex differentiation if applicable), the number of patients receiving each regimen and within the group the number of patients who succeeded and the number of patients who failed to eradicate the *H. pylori* infection, the number of patients who were compliant and the number of patients who were not compliant in each group, and the number of patients reporting side effects and the number of patients with no side effects in each arm. In studies where susceptibility tests for clarithromycin and metronidazole in *H. pylori* strains were performed, the number of eradicated subjects with resistant and sensitive strains was collected. After completing the data extraction, the two independent reviewers discussed the results and, if discrepancies were present, a consensus was reached.

Data Synthesis and Analysis

Study outcomes for the meta-analysis included the following: (1) eradication rate of BQT compared with CTT reported as ITT, (2) compliance rate of BQT versus CTT, (3) incidence of side effects associated with BQT versus CTT, and (4) the effect of resistance to clarithromycin and metronidazole on the efficacy of treatments. Risk difference (RD), which represents the difference between the frequency of the events in the two groups (quadruple therapy and triple therapy), was used to calculate the pooled effect of BQT versus CTT. A 95% confidence interval (95% CI) was calculated using both a fixed-effects model and a random-effects model. The test for funnel plot asymmetry was carried out. To assess whether the variation in the effects of treatment across trials was greater than might be expected, a statistical evaluation of heterogeneity by χ^2 test was used. Heterogeneity was considered to be present if the χ^2 test delivered a $p < 0.05$. An I^2 statistic was used to quantify the proportion of total variation in the study estimate due to heterogeneity. Any heterogeneity identified would prompt subgroup analysis on the basis of random-effects models in attempt to explain these findings. For subgroups with considerable heterogeneity, meta-regression for the year of publication was performed. The regression coefficients (r) for the meta-regression analysis were reported. An r value >0.7 was considered relevant. Furthermore, the cumulative effect over time was analyzed using statistical software [7]. This same method was applied to assess compliance rates and the incidence of adverse events between the two study groups. All computations and plots were carried out with meta-analysis software [7].

Results

Description of Included Studies

The initial search strategy identified a total of 89 potential articles for inclusion. After detailed review of selected articles, 12 RCTs [8–19] with 2,753 patients ful-

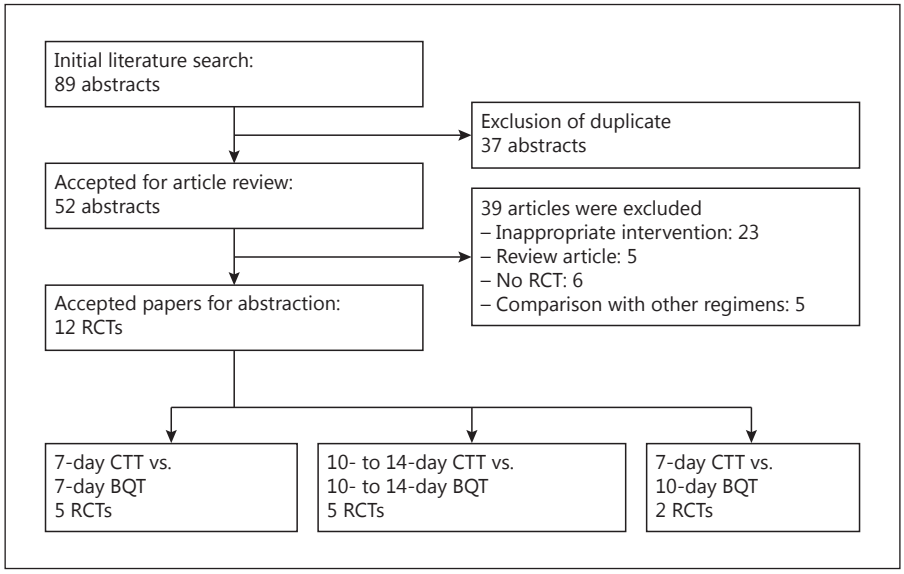


Fig. 1. Flow diagram of studies identified in the systematic review and meta-analysis.

filled the inclusion criteria of the meta-analysis (fig. 1). The most common reasons for exclusion from the meta-analysis included treatment regimens offered as second-line treatment and regimens composed of medications inconsistent with traditional CTT or BQT. Tables 1, 2 and Appendix table 1 summarize the characteristics of the included studies. Antibiotic dosing regimens for triple therapy were quite consistent among trials (clarithromycin 1,000 mg/day, amoxicillin 2,000 mg/day), but varied considerably for quadruple therapy (bismuth 240–1,680 mg/day, metronidazole 400–1,500 mg/day, tetracycline 1,500–2,000 mg/day).

Meta-Analysis of ITT Eradication Rates

In the meta-analysis of ITT eradication rates of the 12 included studies (Appendix fig. 1) the quadruple therapy achieved an eradication rate of 77.6%, whereas the eradication rate with triple therapy was 68.9% (RD = 0.06, 95% CI: –0.01/0.13). There was no evidence to suggest significant publication bias according to the test for asymmetry of the funnel plot (Appendix fig. 2). Our analysis did have high heterogeneity ($\chi^2 = 50.16$, $p < 0.00001$; $I^2 = 78\%$). In an attempt to explain heterogeneity, we conducted subgroup analyses (table 3).

Subgroup Analysis for Duration of Treatment Regimens

The different durations of the treatment regimens (7, 10, or 14 days for each regimen in different combinations) best explains the high heterogeneity among the studies. Therefore, we stratified trials in 3 subgroups according to the duration of treatment regimens (A = 7 days for both groups; B = 10–14 days for both groups; C = 7 days for triple therapy and 10 days for quadruple therapy; fig. 1, 2). No differences were observed between the two therapy regimens in subgroup A. Heterogeneity within group B was still high. When only trials with 10 days of treatment for both regimens were considered [11–13], summation of individual studies was possible. There were also no significant differences observed between the two therapy regimens in this subanalysis. In the sensitivity analysis of group C, BQT achieved eradication in 82.5% of patients, whereas triple therapy achieved an eradication rate of 57.7% (RD = 0.25, 95% CI: 0.18/0.32).

Subgroup Analysis for Year of Publication

The year of publication of the single studies may also represent a source of heterogeneity. The meta-regression analysis for year of publication showed a significant relationship between year of publication and efficacy of therapy regimen (r = 0.88, data not shown). In the subanalysis per year of publication comparing studies published between 2000 and 2005 versus studies published between 2006 and 2011, BQT was more effective than CTT within studies conducted in the period 2006–2011, but comparable to CTT within studies conducted in 2000–2005 (table 3). Heterogeneity was negligible within the group of studies published between 2000 and 2005, and moderate within the groups with a more recent year of publication (2006–2011).

Table 1. Year, location, therapy regimens, and treatment duration of the studies

Author	Year	Location	Triple therapy	Quadruple therapy	Treatment duration, days	
					triple therapy	quadruple therapy
Gomollon et al. [8]	2000	Spain	omeprazole 20 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	omeprazole 20 mg, b.i.d. tetracycline 500 mg, t.i.d. metronidazole 250 mg, t.i.d. bismuth subcitrate 120 mg, t.i.d.	7	7
Calvet et al. [9]	2002	Spain	omeprazole 20 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	omeprazole 20 mg, b.i.d. tetracycline 500 mg, t.i.d. metronidazole 500 mg, t.i.d. bismuth subcitrate 120 mg, t.i.d.	7	7
Katelaris et al. [10]	2002	Australia/ New Zeeland	pantoprazole 40 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	pantoprazole 40 mg, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 200 mg, t.i.d./400 mg q.h.s. bismuth subcitrate 108 mg, q.i.d.	7	7
Mantzaris et al. [11]	2002	Greece	omeprazole 20 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	omeprazole 20 mg, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 500 mg, t.i.d. bismuth subcitrate 120 mg, q.i.d.	10	10
Laine et al. [12]	2003	United States/ Canada	omeprazole 20 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	omeprazole 20 mg, b.i.d. tetracycline 375 mg, q.i.d.[1] metronidazole 375 mg, q.i.d.[1] bismuth biskalcitrate 420 mg, q.i.d.[1]	10	10
Pai et al. [13]	2003	India	lansoprazole 30 mg, b.i.d. amoxicillin 500 mg, q.i.d. clarithromycin 500 mg, b.i.d.	lansoprazole 30 mg, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 400 mg, t.i.d. tripotassium dicitrato bismuthate 120 mg, q.i.d.	10	10
Jang et al. [14]	2005	Korea	PPI, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	PPI, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 500 mg, t.i.d. bismuth subcitrate 300 mg, q.i.d.	7	7
Uygun et al. [15]	2007	Turkey	lansoprazole 30 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	lansoprazole 30 mg, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 500 mg, t.i.d. bismuth subsalicylate 300 mg, q.i.d.	14	14
Ching et al. [16]	2008	UK	lansoprazole 30 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	lansoprazole 30 mg, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 500 mg, t.i.d. bismuth subcitrate 240 mg, b.i.d.	7	7
Songür et al. [17]	2009	Turkey	lansoprazole 30 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	lansoprazole 30 mg, b.i.d. tetracycline 500 mg, q.i.d. metronidazole 500 mg, t.i.d. bismuth subcitrate 300 mg, q.i.d.	14	10
Zheng et al. [18]	2010	China	pantoprazole 40 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	pantoprazole 40 mg, b.i.d. tetracycline 750 mg, b.i.d. metronidazole 400 mg, t.i.d. bismuth subcitrate 220 mg, b.i.d.	7	10
Malfertheiner et al. [19]	2011	France, Germany, Ireland, Italy, Poland, Spain, UK	omeprazole 20 mg, b.i.d. amoxicillin 1 g, b.i.d. clarithromycin 500 mg, b.i.d.	omeprazole 20 mg, b.i.d. tetracycline 375 mg, q.i.d.[1] metronidazole 375 mg, q.i.d.[1] bismuth subcitrate potassium 420 mg, q.i.d.[1]	7	10

b.i.d. = Twice a day; t.i.d. = three times a day; q.i.d. = four times a day; q.h.s. = nightly. [1] The quadruple therapy consisted of three single-triple capsules, each containing 140 mg of the reported bismuth salt, metronidazole 125 mg, and tetracycline 125 mg, given q.i.d. plus one omeprazole 20-mg capsule b.i.d.

Table 2. Study results

Author	Therapy	Patients, n	Patients, n	ITT, %	Compliance, %	Side effects, %
Gomollon et al. [8]	triple	49	40	81.6	98	40
	quadruple	48	33	68.8	100	42
Calvet et al. [9]	triple	171	132	77.0	94	59
	quadruple	168	139	83.0	91	59
Katelaris et al. [10]	triple	134	104	78.0	97	NR
	quadruple	134	110	82.0	94	NR
Mantzaris et al. [11]	triple	78	61	78.2	96	75
	quadruple	71	46	64.8	93	78
Laine et al. [12]	triple	137	114	83.2	94	59
	quadruple	138	121	87.7	91	59
Pai et al. [13]	triple	35	29	82.9	100	11
	quadruple	33	24	72.7	94	15
Jang et al. [14]	triple	75	59	78.7	NR	7
	quadruple	74	53	71.6	NR	10
Uygun et al. [15]	triple	120	69	57.5	96	11
	quadruple	120	84	70.0	91	13
Ching et al. [16]	triple	50	46	92.0	100	90
	quadruple	44	40	91.0	86	95
Songür et al. [17]	triple	113	37	32.7	91	NR[1]
	quadruple	119	56	47.1	87	NR[1]
Zheng et al. [18]	triple	85	54	63.5	100	60
	quadruple	85	76	89.4	100	42.3
Malfertheiner et al. [19]	triple	222	123	55	>95	51
	quadruple	218	174	80	>95	47

NR = Not reported. [1] Frequency of single side effects was reported, but the percentage of patients presenting side effects was not.

Table 3. Subgroup analyses

	Participants n	Studies n	Eradication rate with CTT, %	Eradication rate with BQT, %	RD (95% CI)	p	I^2 statistic[2], %
All included studies [8–19]	2,753	12	68.9	77.6	0.06 (–0.01/0.13)	<0.00001	78
Duration: 7 days for both arms [8–10, 14, 16]	798	4	79.3	80.6	0.01 (–0.05/0.08)	0.2	–
Duration: 10 days for both arms [11–13]	492	3	81.6	78.9	–0.048 (0.08/–0.18)	0.069	–
Duration: 7 days for CTT and 10 days for BQT [18, 19]	610	2	57.6	82.5	0.25 (0.18/0.32)	0.84	–
Studies published 2000–2005 [8–14]	1,345	7	79.4	79	–0.02 (0.05/–0.08)	0.08	–
Studies published 2006–2011 [15–19]	1,408	5	61.5	80.7	0.17 (0.10/0.25)	0.03	61
Location: Eastern hemisphere [10, 11, 13–15, 17, 18][1]	1,296	7	65.6	72.5	0.05 (0.16/–0.06)	<0.00001	82.2
Location Western hemisphere [8, 9, 12, 16][1]	804	4	81.3	84.2	0.03 (0.09/–0.03)	0.245	49.6
Dyspeptic symptoms [16, 17, 19]	766	3	54.5	74.7	0.16 (0.29/0.04)	0.02	87.3
Nonulcer dyspepsia [10, 15, 18]	678	3	67.4	80.0	0.14 (0.26/0.01)	0.025	86.4
Active peptic ulcer [8, 9, 11, 13, 14]	721	5	78.7	78.9	–0.06 (0.03/–0.15)	1.00	61.6

Eradication rate reported as ITT. [1] Spain and UK were considered as part of the Western hemisphere because the largest part of these countries is in the Western hemisphere. [2] I^2 statistic is reported only in the presence of heterogeneity (i.e. χ^2 delivered a $p < 0.05$).

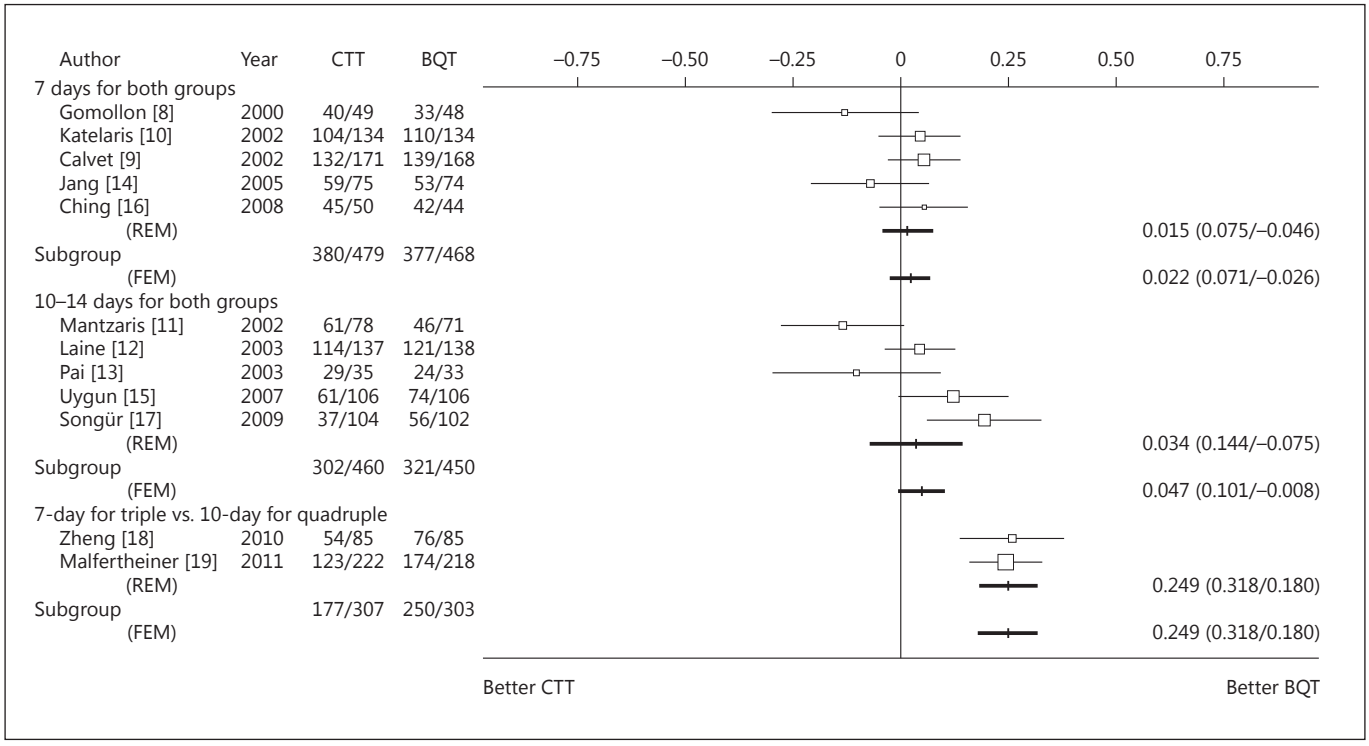


Fig. 2. Forest plot of BQT vs. CTT: subgroup analysis according to the duration of treatment regimens. RD with 95% CI is shown on the right side of the figure. REM = Random-effects model; FEM = fixed-effects model.

Subgroup Analysis for Study Location

Study location may also represent a source of heterogeneity and different antimicrobial resistance rates between the Western and Eastern hemispheres may have an impact on treatment outcomes. Our analysis showed no significant differences in eradication rates between BQT and CTT in studies conducted in the Western hemisphere (Appendix fig. 3, table 3). In the subanalysis of ITT eradication rates of the 7 studies conducted in the Eastern hemisphere, the BQT achieved an eradication rate of 72.5%, whereas the eradication rate with CTT was 65.6% (RD = 0.052, 95% CI: –0.06/0.16). Heterogeneity within the Eastern hemisphere group exceeded our baseline results. In an attempt to explain heterogeneity within this subgroup, a meta-regression analysis for year of publication and frequency of eradication was performed, and showed a significant correlation for both variables (r = 0.88 and –0.75, respectively, data not shown). Thus, again the heterogeneity in this subgroup can be partially explained by the decreasing efficacy of CTT over the years. In studies conducted in 2006–2011 in the Eastern hemisphere, CTT achieved an eradication rate of 51.5% compared with 78.6% in studies conducted in 2000–2005 (data not shown). Furthermore, in the Eastern hemisphere, BQT achieved an ITT eradication rate of 70.3% in studies conducted in 2006–2011, whereas in studies conducted in 2000–2005, an ITT eradication rate of 74.7% was achieved (data not shown).

Influence of Local Clarithromycin Resistance on Efficacy of Therapy Regimens

Local clarithromycin resistance rates may influence the efficacy of both therapy regimens. Therefore, available data on local clarithromycin resistance in the countries of the included trials were collected and a meta-regression analysis for local clarithromycin resistance was performed. The available data on local clarithromycin resistance are as follows: Spain 14% [4], Australia/New Zealand 8% [10], Greece 24.7% [4], India 4.7% [20], United States/Canada 11% [13], Korea 10.8% [21], Turkey 48.2% [22], United Kingdom 9% [4], and China 20.8% [18]. The meta-regression analysis for local clarithromycin resistance showed no influence of local clarithromycin resistance rates on the efficacy of either therapy regimen (r = 0.17).

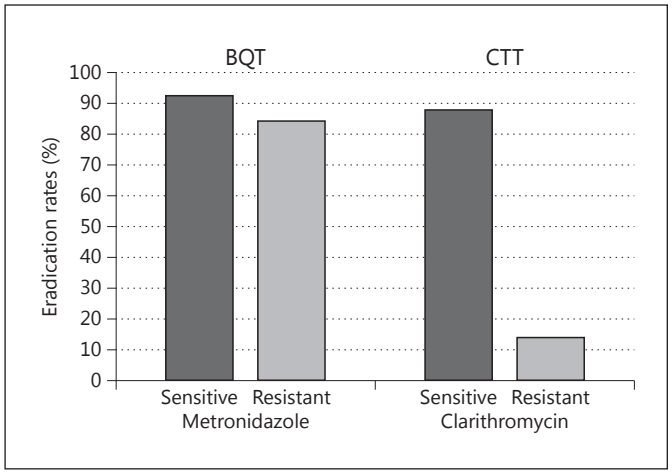


Fig. 3. ITT eradication rates achieved by BQT and CTT based on metronidazole and clarithromycin resistance, respectively (data derived from Katelaris et al. [9], Laine et al. [13], Zheng et al. [18], and Malfertheiner et al. [19]).

Subgroup Analysis according to Treatment Populations

The failure rate of *H. pylori* eradication has been reported to be significantly lower in patients with duodenal ulcer than in patients with nonulcer dyspepsia [18]. Therefore, we further stratified studies according to treatment populations, i.e. studies investigating *H. pylori* eradication rates in patients with dyspeptic symptoms, nonulcer dyspepsia, and active peptic ulcer (table 3, Appendix figure 4). BQT was more effective than CTT for *H. pylori* eradication in patients with dyspeptic symptoms and nonulcer dyspepsia, yet within both groups we found significant heterogeneity. Our analysis did not find any significant difference between BQT and CTT in patients with peptic ulcer disease, yet within this group no heterogeneity was found.

Meta-Analysis of Compliance and Side Effects

Eleven out of the 12 studies [8–13, 15–19] included data on compliance rates (table 2). Acceptable compliance was differently defined and varied from 75 to 100% of completed therapy. Overall, the compliance rate was 92 and 96% with BQT and CTT, respectively. There was a statistically significant difference between the two groups (RD = –0.03, 95% CI: –0.05/0.00). Heterogeneity was not present.

All but two of the included studies [10, 17] describe the incidence of side effects within each group. The overall incidence of side effects in patients receiving BQT and CTT was 46 and 46.3%, respectively (table 2). There were no statistically significant differences in side effects yielded by each group. Heterogeneity was not present.

Role of Antibiotic Resistance

Four out of 12 studies [10, 12, 18, 19] also assessed the effect of antimicrobial susceptibility on eradication rates. ITT eradication rates achieved by quadruple and triple therapies based on metronidazole and clarithromycin resistance are shown in figure 3. Clarithromycin resistance significantly affected the efficacy of triple therapy (RD = 0.75, 95% CI: 0.63/0.87). Indeed, CTT achieved eradication in 88% of clarithromycin-sensitive strains and in 14.3% of clarithromycin-resistant strains. However, metronidazole resistance did not affect the efficacy of quadruple therapy. Indeed, BQT achieved eradication in 92% of metronidazole-sensitive strains and 84.2% of metronidazole-resistant strains. The role of simultaneous susceptibility for metronidazole and clarithromycin was tested in 2 of the 12 studies [18, 19]. In the presence of simultaneous metronidazole and clarithromycin resistance, BQT was superior to CTT for eradication of *H. pylori* infection (RD = 26.52, 95% CI: 3.43/205.06, data not shown). Given the small number of patients with simultaneous metronidazole and clarithromycin resistance (14 in the group receiving BQT and 17 in the group receiving CTT) included, these results should be interpreted cautiously.

Discussion

In our meta-analysis, CTT and BQT given both for 7 or 10 days yielded similar eradication rates when used as a first-line therapy for eradication of *H. pylori* infection. Furthermore, no difference in compliance rate or incidence of treatment-associated side effects between BQT and CTT was found. The results of our updated meta-analysis at first glance are consistent with those from two previous meta-analyses that compared these treatment regimens [5, 6]. However, in the subgroup analysis of treatment duration, the 10-day BQT was shown to be more effective than the 7-day CTT. The comparison of two different treatment durations may raise criticism of our analysis. To rebut this point, a recent meta-analysis reported that a treatment with CTT beyond 7 days would confer only a slight benefit of about 5% in eradication efficacy if the treatment is extended to 14 days [23]. Furthermore, if this analysis is restricted to the four highest-quality trials as assessed by the Jadad scale [24], prolongation of CTT beyond 7 days (with extension up to 10 days) was not associated with an additional benefit. This has

been confirmed in a recent randomized trial in patients infected with *H. pylori* without an increase in eradication efficacy if CTT was extended up to 14 days [25]. Clarithromycin resistance obviously cannot be overcome by increasing the dose or duration of therapy [26]. Regarding BQT, a 10- to 14-day treatment is recommended by international guidelines [27–29]. A recent survey in Europe reported that the *H. pylori* resistance rate for metronidazole is as high as 34.9% [4]. Unlike clarithromycin, metronidazole resistance can to a great extent be overcome by increasing the duration of therapy and the dose of metronidazole, which should not be lower than 1,500 mg [30]. Indeed, a meta-analysis of 91 treatment arms concluded that 'if nitroimidazole resistance is present, a nitroimidazole-containing regimen should be avoided or a quadruple regimen should be given for >1 week' [31]. On the basis of these data, a first-line empirical *H. pylori* treatment with BQT given for 10 days or longer is expected to work.

The strongest predictor of *H. pylori* treatment failure appears to be antimicrobial resistance [32]. Clarithromycin resistance is the most important clinically because resistance cannot be overcome by increasing the dose or duration of therapy. Amoxicillin and tetracycline resistance instead is negligible as resistance for these two antibiotics is reported to be very low (<1%) in most countries [4, 32]. In our analysis CTT achieved eradication in 88% of clarithromycin-sensitive strains but only in 14.3% of clarithromycin-resistant strains. Furthermore, the meta-regression analysis for year of publication showed a decreasing efficacy of triple therapy over years, mostly due to increasing clarithromycin resistance. With few exceptions worldwide, the prevalence of clarithromycin resistance has increased to a level where CTT is no longer effective [4, 32]. Thus, in the future, a clinical trial comparing a candidate effective first-line *H. pylori* therapy with CTT can no longer be considered ethical in countries with a high rate of clarithromycin resistance. On the contrary, BQT achieved an ITT-eradication rate as high as 92% in metronidazole-sensitive strains and 84.2% in metronidazole-resistant strains. Thus, BQT is effective even in cases with proven metronidazole resistance in vitro and represents a good treatment option for empirical first- and second-line *H. pylori* eradication therapy.

In patients with dyspeptic symptoms and nonulcer dyspepsia, BQT was more effective than CTT for *H. pylori* eradication. A higher resistance rate to clarithromycin reported in nonulcer dyspeptic patients in comparison to duodenal ulcer patients is likely to account for this [33].

In patients with peptic ulcer disease, BQT and CTT yielded similar eradication rates as a first-line treatment for *H. pylori* infection. The lower prevalence of *H. pylori* strains with clarithromycin resistance among patients with peptic ulcer disease accounts for the similar eradication rates between the CTT and the BQT in this specific group of patients. A lower prevalence of clarithromycin resistance among patients with peptic ulcer disease was described previously [4], but remains unexplained.

Strengths and Limitations

To minimize bias, two authors selected the studies and extracted the data; this process resulted in high interobserver agreement ($\kappa = 0.91$). The presence of publication bias was excluded by both graphical and statistical evaluation. All studies included in the analysis were RCTs. Our literature research was not restricted to English-language reports. We were able to extract data from each study, regardless of the language, with the exception of the exclusion criteria from the article by Jang et al. [14], which was published in Korean.

When considering the results of this meta-analysis, potential limitations should be considered. Heterogeneity was present and could not be accounted for by multiple subgroup analyses. Further, individual studies included in our analysis differed in several respects. Indeed, studies defined varying inclusion and exclusion criteria and used different PPIs. Relevant to BQT, antibiotic dosing regimens and bismuth formulations varied considerably among trials. The heterogeneity in the regimens included in this analysis could have affected eradication rates, as increasing dose and duration can improve efficacy [26]. Many efforts have been made to optimize the BQT. Possibly, the most effective BQT is the one employing the highest practical doses of the single drugs for the longest reasonable duration, such as 14 days. A one-arm, open-label pilot study of 47 *H. pylori*-infected, asymptomatic/mildly dyspeptic adult Hispanic residents of El Paso, Texas showed a per-protocol effectiveness of 97.7% for BQT given for 14 days [34]. In this study the combination capsule of bismuth, metronidazole, and tetracycline (daily doses: 1,680, 1,500, and 1,500 mg, respectively) plus omeprazole (daily dose: 40 mg) was used. Unfortunately, only one of the trials included in our meta-analysis evaluated the BQT for 14 days, without employing the highest practical doses of the single drugs. Thus, the heterogeneity in the treatment regimens included in the present analysis does not allow for the recommendation of an 'optimal' BQT. Only 2 RCTs were available for the subgroup

analysis comparing the 10-day BQT versus the 7-day CTT.

In conclusion, on the basis of our analysis, the 10-day BQT is more effective than the 7-day CTT as a first-line therapy for *H. pylori* infection, whereas BQT and CTT, both taken for 7 or 10 days, yielded similar eradication rates. BQT is independent of clarithromycin resistance and is at all only minimally affected by metronidazole resistance. Compliance rates and side effects were comparable for both treatment regimens.

Disclosure Statement

Peter Malfertheiner, MD is the guarantor of the article. No funding was received for the preparation of this manuscript. Marino Venerito has no conflicts of interest relevant to this study. Tina Krieger received honoraria from Aptalis Pharma. Thomas Ecker received honoraria from Aptalis Pharma. Gioacchino Leandro has no conflicts of interest relevant to this study. Peter Malfertheiner received honoraria from Aptalis Pharma, Abbott, AstraZeneca, and Takeda.

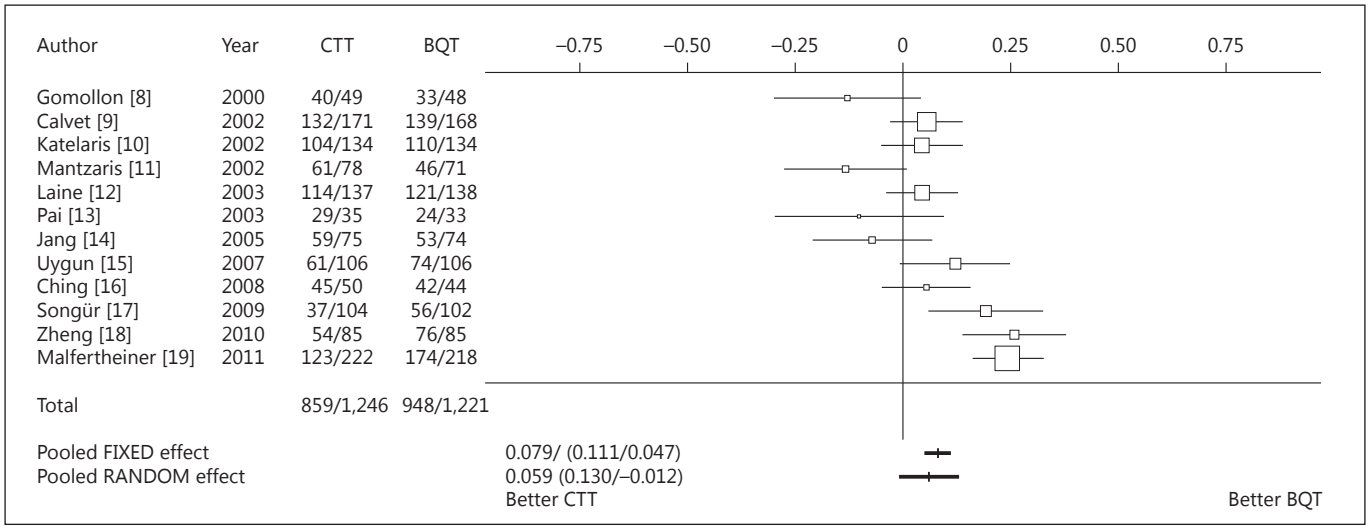
Appendix

Appendix Table 1. Study characteristics

Author	Patient characteristics	Diagnosis of *H. pylori* infection for inclusion in the study	Exclusion criteria	*H. pylori* diagnostic after eradication therapy
Gomollon et al. [8]	*H. pylori*-positive patients with endoscopically proven peptic ulcer disease, age between 18 and 80 years	patients were enrolled if both RUT and histology were positive	pregnancy, allergy to any study medications, chronic ingestion of NSAIDs, severe esophagitis, gastric cancer, severe GI bleeding in the previous 6 months, previous *H. pylori* treatment	^{13}C-UBT or biopsy-based testing at 8 weeks after treatment
Calvet et al. [9]	*H. pylori*-positive patients with endoscopically proven peptic ulcer disease, age 18 years or older	patients were enrolled if ^{13}C-UBT, RUT, or histology was positive	inability to attend follow-up, previously failed eradication therapy, treatment with antibiotics during the 4 weeks prior to the study, and previous ulcer surgery	^{13}C-UBT or biopsy-based testing at least 2 months after treatment
Katelaris et al. [10]	*H. pylori*-positive patients with dyspepsia and no evidence of peptic ulcer disease or esophagitis at endoscopy, age 18 years or older	patients were enrolled if the RUT was positive; confirmatory test: histology and ^{13}C-UBT	previous *H. pylori* treatment or concomitant or recent (within 30 days) use of PPIs, antibiotics, bismuth salts, or NSAIDs	^{13}C-UBT at 8 weeks after treatment
Mantzaris et al. [11]	*H. pylori*-positive patients with endoscopically proven active duodenal ulcer	patients were enrolled if the RUT was positive; confirmatory test: histology	chronic alcoholism, chronic renal or hepatic failure, malignant disease, previous gastric surgery, treatment with anticoagulants, treatment with antibiotics during the month preceding study entry, and allergy to any study medications	HUT, histology and immunohistochemistry performed 10–12 weeks after treatment
Laine et al. [12]	*H. pylori*-positive patients with active duodenal ulcer at baseline endoscopy or a history of duodenal ulcer (within the last 5 years) documented by endoscopy or radiology	patients were enrolled if ^{13}C-UBT plus histology and/or culture were positive	upper GI bleeding within the past month, prior *H. pylori* treatment, use of antibiotics or bismuth in the prior 30 days, regular use of a PPI in the 15 days or of an H_2-receptor antagonist, sucralfate, or misoprostol in the 7 days before baseline, chronic use of NSAIDs (except for aspirin 325 mg/day), contraindication to use of study medications, pregnancy or lactation, other serious medical conditions, or clinically significant laboratory abnormalities at baseline	2 negative ^{13}C-UBTs performed at least 29 and 57 days after treatment
Pai et al. [13]	*H. pylori*-positive patients with endoscopically proven active or healed peptic ulcers	patients were enrolled if both RUT and histology were positive	peptic ulcer complications, recent (within 2 weeks) use of PPIs, antibiotics, or bismuth salts	biopsy-based test performed 30 days after treatment

Author	Patient characteristics	Diagnosis of *H. pylori* infection for inclusion in the study	Exclusion criteria	*H. pylori* diagnostic after eradication therapy
Jang et al. [14]	*H. pylori*-positive patients with peptic ulcer disease	patients were enrolled if both RUT and histology were positive	exclusion criteria not extractable, article in Korean	^{13}C-UBT performed 4–6 weeks after treatment
Uygun et al. [15]	*H. pylori*-positive patients with nonulcer dyspepsia	patients were enrolled if both RUT and histology were positive	pregnancy; lactation; age <18 years; previous *H. pylori* treatment; consumption of PPIs, H_2-receptor blockers, NSAIDs, bismuth salts, or antibiotics in the previous 4 weeks before enrollment; previous gastric surgery; presence of liver dysfunction or renal failure; alcohol abuse, and known allergy to the prescribed antibiotics	^{13}C-UBT performed 6 weeks after treatment
Ching et al. [16]	*H. pylori*-positive patients with dyspeptic symptoms and a recent endoscopy showing peptic ulcers or gastritis	patients were enrolled if histology and culture, RUT or ^{13}C-UBT was positive	age less than 18 or above 75 years, symptomatic gallstones, treated with antibiotic or bismuth-containing drugs during the month prior to inclusion, treated with PPIs during the week prior to inclusion, disturbed GI physiology (gastric surgery, vagotomy, Zollinger-Ellison syndrome, chronic ingestion of NSAIDs), concomitant serious disease, concomitant medications that may adversely interact with the study drugs (e.g. warfarin, antiepileptics), pregnancy and breast-feeding, childbearing age without adequate contraception, allergy to drugs used in the study, mental illness, and heavy drinking or abuse of drugs	^{13}C-UBT performed at 8 weeks after treatment
Songür et al. [17]	*H. pylori*-positive patients with dyspeptic symptoms	patients were enrolled if ^{13}C-UBT or histology was positive	previous *H. pylori* treatment therapy; treatment with NSAIDs, PPIs, H_2-receptor blockers, or antimicrobials within the previous 4 weeks, pregnancy; history of allergy to penicillin or any antibiotic, and previous gastric surgery	^{13}C-UBT performed at 6 weeks after treatment
Zheng et al. [18]	*H. pylori*-positive patients with nonulcer dyspepsia, age between 18 and 70 years	patients were enrolled if both ^{13}C-UBT and histology were positive	previous *H. pylori* treatment therapy, treatment with PPIs, H_2-receptor blockers, bismuth or antimicrobials within the previous 4 weeks, pregnancy or lactating, history of allergy to penicillin or any antibiotic used in the study, duodenal or gastric ulcer, a severe heart condition, hepatic or renal diseases, and previous gastric surgery	^{13}C-UBT performed at least 4 weeks after treatment.
Malfertheiner et al. [19]	*H. pylori*-positive patients with upper GI symptoms, age 18 years or older	*H. pylori* infection confirmed by both ^{13}C-UBT and RUT; confirmatory test: histology, culture, or PCR	previous *H. pylori* treatment therapy, contraindications to study drugs, substantial organ impairment, severe or unstable cardiopulmonary or endocrine disease, history of surgery of the upper GI tract, evidence of bleeding or iron-deficiency anemia, Barrett's esophagus or high-grade dysplasia, dysphagia, history of malignancy, history of drug or alcohol misuse within 1 year of the trial, continuously used antiulcer drugs (including PPIs during the 2 weeks before the ^{13}C-UBT), antibiotics or bismuth compounds (more than 3 times per week, 1 month before screening), systemic glucocorticoids, NSAIDs, or anticoagulation or platelet aggregation inhibitors (except acetylsalicylic acid ≤100 mg per day)	2 negative ^{13}C-UBTs performed at least 28 and 56 days after treatment

UBT = Urea breath test; RUT = rapid urease test; NSAIDs = nonsteroidal anti-inflammatory drugs.



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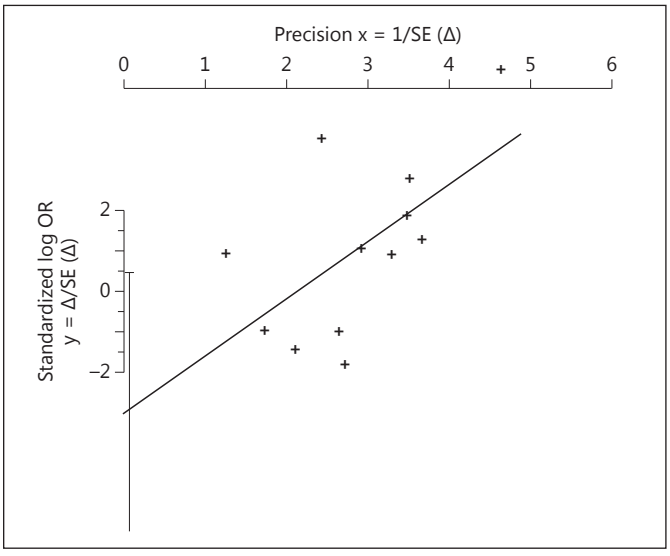

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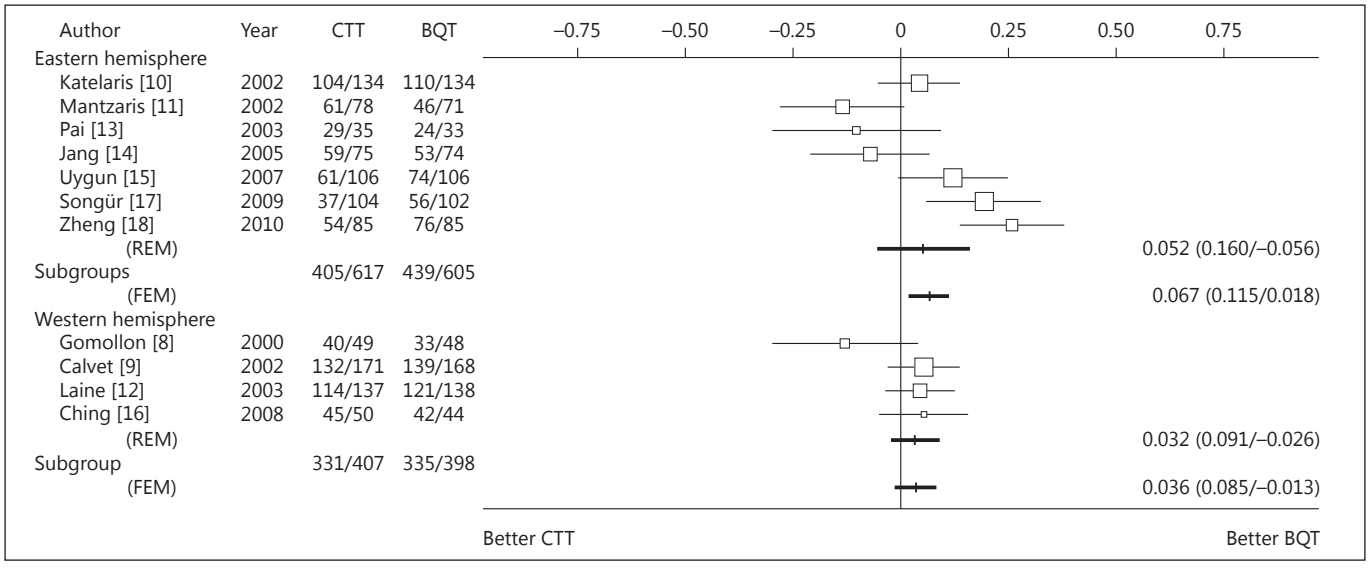
Appendix figure 1. Forest plot of BQT vs. CTT. RD with 95% CI is shown on the right side of the figure.
Appendix figure 2. Test for asymmetry of the funnel plot.
Appendix figure 3. Forest plot of BQT vs. CTT; subgroup analysis according to location: Eastern and Western hemispheres. RD with 95% CI is shown on the right side of the figure. REM = Random-effects model; FEM = fixedeffects model.



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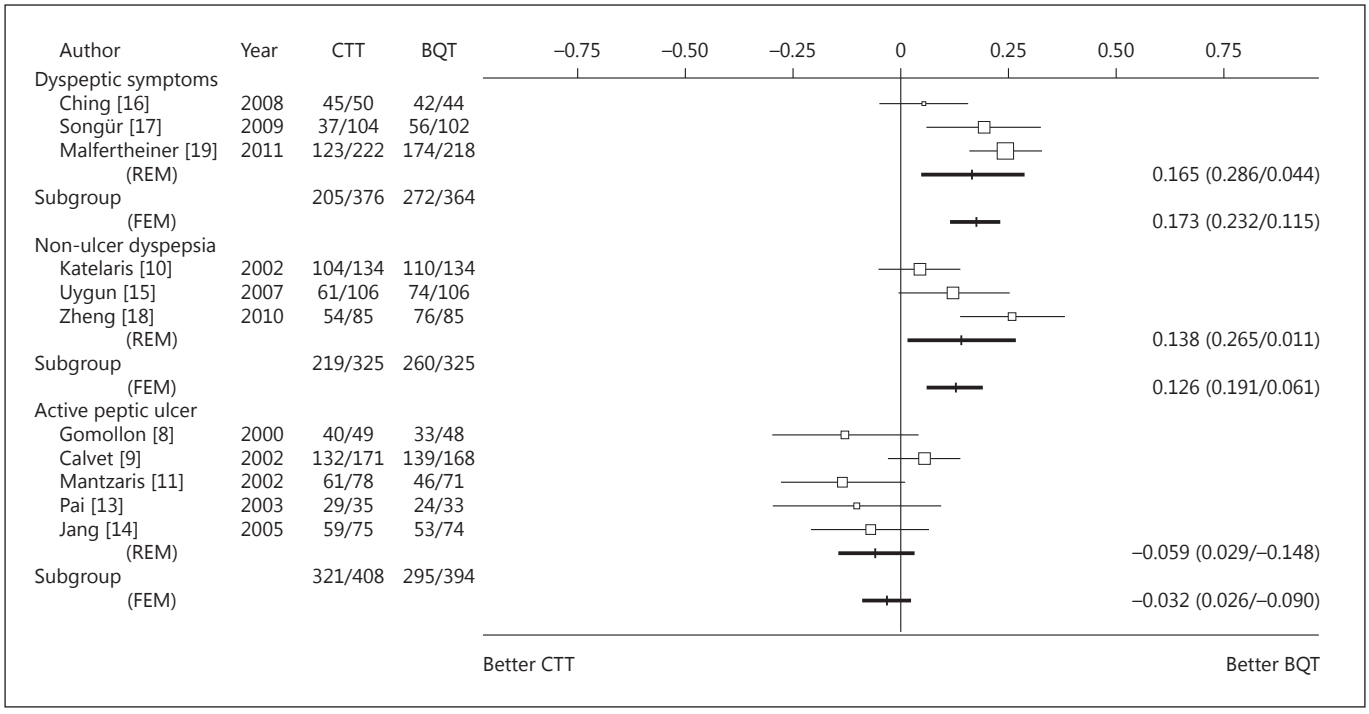

Appendix figure 4. Forest plot of BQT vs. CTT; subgroup analysis according to treatment indication: dyspeptic symptoms, nonulcer dyspepsia and active peptic ulcer. RD with 95% CI is shown on the right side of the figure.

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