

Standard triple therapy in *Helicobacter pylori* eradication in Turkey: Systematic evaluation and meta-analysis of 10-year studies

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ABSTRACT

Background/Aims: This study aims at evaluating the mean eradication rate by a systematic compilation of the studies which involved the standard triple therapy (STT) in first-line *Helicobacter pylori* (Hp) eradication in Turkey over a period of 10 years between 2004 and 2013 using the meta-analysis method.

Materials and Methods: The systematic compilation and meta-analysis were carried out according to the PRISMA standards defined in the Cochrane handbook. The results of full-text studies published in national and international journals in English and Turkish languages on Turkish population in a period of 10 years, from 2004 to 2013, are included in this study. The studies include open-label trials, controlled trials, treatment arms, and case series that included a triple therapy regimen consisting of standard doses of a proton pump inhibitor (PPI; omeprazole 20 mg BID, lansoprazole 30 mg BID, pantoprazole 40 mg BID, esomeprazole 40 mg BID, or rabeprazole 20 mg BID) along with clarithromycin 500 mg BID and amoxicillin 1 g BID for 7-14 days. They were scanned electronically via the search engines Google Scholar, PubMed, and the Turkish Medicine Index using specific keywords. The related keywords used were Turkey, *Helicobacter pylori*, infection, standard triple treatment, first-line therapy, eradication, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, clarithromycin, and amoxicillin. Studies carried out with adults were included in the evaluation. The publication year of the studies and the included number of patients, their age, gender, treatment duration (7, 10, and 14 days), and PPIs used were evaluated by two separate gastroenterologists and biostatisticians. Studies that used at least one reliable method (histology, urea breath test (UBT), or *Helicobacter pylori* stool antigen (HpSA) test) four weeks after completing the treatment for the control of Hp eradication were included. Only naive patients were accepted, and patients who had previously received eradication treatment were excluded. The effectiveness of the Hp eradication was analyzed using an intention-to-treat (ITT) or per-protocol (PP) analysis.

Results: The STT regime of 45 studies complying with the inclusion criteria was evaluated. A total of 3715 patients were included in the study. Of the 3010 patients whose gender information was available, 55% were women and 45% were men; the weighted age average given explicitly in the studies was 42.14±0.67. The treatment lasted for 14 days in 42 studies, for 7 days in six studies, and for 10 days in 1 study. The eradication rates evaluated according to the ITT and PP analyses were 60% (95% CI: 56%-63%) and 57% (95% CI: 51%-62%), respectively. The rates for 7 days of treatment were 57% (95% CI: 46%-68%) and 60% (95% CI: 51%-67%) and for 14 days of treatment were 60% (95% CI: 56%-63%) and 56% (95% CI: 50%-62%), respectively. The ITT eradication rate of the only 10-day study was 78% (95% CI: 66%-86%). In the meta-regression analysis, the treatment duration, PPI, age, and gender ratio (women/men) used for the ITT analysis had no effect. The gender ratio and age were not considered in this analysis because they were not clearly stated in studies using the PP analysis. The duration of treatment and the PPI used had no effect.

Conclusion: A systematic meta-analysis of studies conducted during the period 2004-2013 in Turkey revealed that the rate of first-line Hp eradication using STT was unacceptably low, and the duration of treatment and PPI used made no difference.

Keywords: Turkey, *Helicobacter pylori*, infection, first-line therapy, standard triple treatment, eradication

INTRODUCTION

Helicobacter pylori (Hp) infection is the most common bacterial infection in the world. The most recommended treatment for the eradication of Hp is the standard triple therapy (STT) consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin (1-5).

The first handbook for treating Hp infection was published by the National Institutes of Health in 1994. Then, the European *Helicobacter pylori* Study Group recommended STT as the primary treatment during the first Maastricht conference in 1997 (6). Subsequently, this treatment regimen was proposed and implement-

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ed as a general consensus in various countries for 20 years (7-11).

In Turkey, the recommendations of these handbooks were considered for approximately 20 years, and STT was used commonly.

However, the eradication rates using STT have been reported to decrease in studies published in recent years (12). Two previous studies reported an STT eradication rate of 77% (13,14), which was verified by two meta-analysis studies carried out with more than 53,000 patients (15).

As a result of the rising prevalence of antimicrobial resistance of *Hp*, the success rate of eradication with STT has fallen in many countries including Turkey (16-19).

The third Maastricht consensus conference recommended that the eradication rate should be more than 80% for an intention-to-treat (ITT) analysis for an effective treatment of *Hp* infection (5).

Kadayıfçı et al. (20) were the first in Turkey to systematically analyze the efficiency of the triple treatment in first-line *Hp* eradication. In their meta-analysis, the eradication rate of STT regimes in the 10-year period between 1996 and 2005 was found to be 68.8%.

Therefore, the present study aims at evaluating the rate of primary *Hp* eradication in Turkey from 2004 to 2013 as a continuation of the aforementioned studies. The results of research studies published on the standard triple eradication therapy were compiled to estimate the mean eradication rate of STT for the years 2004-2013 using the meta-analysis method.

MATERIALS AND METHODS

The results of full-text studies published in national and international journals in English and Turkish languages on Turkish population in a period of 10 years, from 2004 to 2013, are included in this study.

The studies were scanned electronically via the search engines Google Scholar, PubMed, and the Turkish Medicine Index using specific keywords: Turkey, *Helicobacter pylori*, infection, standard triple treatment, first-line therapy, eradication, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, clarithromycin, and amoxicillin.

The included studies were carried out with adults using a 7-, 10-, or 14-day STT consisting of a PPI (omeprazole

20 mg BID, lansoprazole 30 mg BID, pantoprazole 40 mg BID, esomeprazole 40 mg BID, or rabeprazole 20 mg BID), clarithromycin (500 mg BID), and amoxicillin (1 g BID) for the eradication of *Hp*. The publication year of the studies and the included number of patients, their age, gender, treatment duration (7, 10, and 14 days), and PPIs used were evaluated by two separate gastroenterologists and biostatisticians. Only studies published in a full journal format were accepted. Congress abstracts were not included. Studies that used at least one reliable method (histology, UBT, or HpSA) four weeks after the completion of the treatment for the control of the *Hp* eradication were included in the analysis. Only naive patients were accepted, and patients who had previously received eradication treatment were excluded. The effectiveness of the *Hp* eradication was analyzed using an ITT or PP analysis. The systematic compilation and meta-analysis were carried out according to the PRISMA standards defined in the Cochrane handbook (the full form of PRISMA is presented in the appendices of the manuscript).

Statistical analysis

The meta-analysis weights of the studies are shown in Table 1. Gender rates were calculated for use in the meta-regression analysis because treatments according to sex were not given separately. These rates were obtained as a ratio of the number of women/the number of men (F/M).

The meta-regression analysis was applied according to the ITT and PP analyses (Table 9). As the age and sex ratios were precisely given in ITT studies, PP was not added to the meta-regression model. Age, sex ratios, treatment days, and PPI varieties were not found as heterogeneity sources for both analyses. However, subgroups were formed for PPIs and treatment days.

The fixed- or random-effects models were used for combining the calculated eradication rate values according to heterogeneity in the meta-analysis. For model selection, the random-effects model was used when the I^2 value was significant or bigger than 25%, and the fixed-effects model was used when it was smaller than 25% and/or insignificant (21). Heterogeneity was not significant in the 7-day PPI, amoxicillin, and clarithromycin (PAC) treatment results using PPI. While the fixed-effects model results were found to be significant, the random-effects model results were found to be insignificant and are added to the table.

In the meta-analysis of the studies, the risk ratio was calculated as eradication rate/noneradication rate. Accord-

Table 1. Meta-analysis weights of the studies and general information

Author (year)	Eradication rate (ITT)	Eradication rate (PP)	Mean age	Type PPI	Treatment duration (days)	F/M
Guliter S (2004)	1.66			LAC	14	0.79
Horoz M (2004)	1.58		43.00	LAC	14	1.14
Horoz M (2004)	1.54		44.00	LAC	7	1.00
Altintas E (2004)	1.80	4.97	45.70	LAC	14	1.00
Altintas E (2004)	1.82		47.50	OAC	14	1.13
Altintas E (2004)	1.80		44.50	PAC	14	1.20
Sivri B (2004)	1.91	5.09	42.40	PAC	7	0.54
Uygun A (2004)	1.77	4.47	45.10	PAC	14	0.90
Uygun A (2004)	1.78	4.47	48.30	LAC	14	1.29
Gumurdulu Y (2004)	1.69		49.00	OAC	7	1.30
Gumurdulu Y (2004)	1.62		48.00	OAC	14	1.46
Guliter S (2005)	1.98			LAC	14	
Erzin Y (2005)	1.71		37.33	LAC	7	2.00
Ozer B (2005)	1.92		41.00	LAC	14	2.04
Goral V (2005)	1.21		34.36	LAC	14	1.20
Duman D.G (2005)		5.71		OAC	14	1.10
Koksal A.S (2006)	1.71		42.00	OAC	10	2.94
Sancar M (2006)	1.03		44.00	LAC	14	0.83
Sancar M (2006)	1.03		42.00	OAC	7	1.33
Uygun A (2007)	2.01	5.45	40.70	LAC	14	0.64
Aydin A (2007)	1.73	4.63		PAC	7	
Aydin A (2007)	1.66	4.13		PAC	14	
Cindoruk M (2007)	1.87		47.56	LAC	14	2.44
Uygun A (2008)	2.04	5.56	41.20	PAC	14	0.74
Oztas E (2008)	1.80	4.85		PAC	7	
Oztas E (2008)	1.71	4.37		PAC	14	
Mesut Z (2008)	1.61			ES-OM	14	
Bektas M (2008)	1.16			LAC	14	
Bektas M (2009)	1.42		44.60	LAC	14	3.00
Songur Y (2009)	1.97	5.40	46.22	LAC	14	1.94
Kebapcilar L (2009)	1.90		32.50	LAC	14	0.74
Soylu A (2009)	2.06		43.30	LAC	14	

Table 1. Meta-analysis weights of the studies and general information (Continue)

Author (year)	Eradication rate (ITT)	Eradication rate (PP)	Mean age	Type PPI	Treatment duration (days)	F/M
Demir M (2009)	1.65		49.17	PAC	14	2.63
Aydemir S (2010)	1.48			LAC	14	
Yasar B (2010)	1.75		36.95	PAC	14	1.71
Abut E (2010)	1.76		36.90	PAC	14	1.60
Ozdil B (2010)	1.87		46.00	LAC	14	1.50
Nadir I (2011)	2.03	5.55	40.16	LAC	14	2.07
Erdogan AF (2011)	2.01		44.50	LAC	14	2.00
Ermis F (2011)	1.96	5.57		LAC	14	
Alkim H (2011)	1.87		39.60	OAC	14	0.83
Alkim H (2011)	1.85		38.90	LAC	14	0.74
Alkim H (2011)	1.64		35.30	RAC	14	0.73
Alkim H (2011)	1.87		37.60	PAC	14	0.94
Alkim H (2011)	1.89		36.40	ES-OM	14	0.70
Çetinkaya ZA (2011)	1.64		37.90	OAC	14	1.31
Çetinkaya ZA (2011)	1.66		39.23	PAC	14	1.00
Çetinkaya ZA (2011)	1.61		40.60	RAC	14	1.31
Demir M (2011)	1.63	4.40	38.90	PAC	14	1.07
Sezikli M (2011)	1.75	4.73	43.00	LAC	14	1.67
Gokturk HS (2011)	1.94	5.29		LAC	14	1.03
Sezikli M (2012)	1.76	4.75	42.70	LAC	14	2.08
Polat Z (2012)	1.93	5.23	41.00	ES-OM	14	0.92
Balcilar E (2012)	1.69			LAC	14	0.74
Uyanikoglu A (2012)	0.95		39.98	LAC	14	1.04
Onal IK (2013)	1.88			PAC	14	3.00
Avsar E (2013)	2.00	5.39	42.60	LAC	14	1.36
Ulasoglu C (2013)	1.79		38.20	LAC	14	1.19
Ustundag Y (2013)	1.65			LAC	14	

PPI: proton pump inhibitor

ing to this, if the risk ratio was greater than 1, the treatment was considered to be successful.

When applying meta-analysis, the NCSS 11 trial package program was used for calculating the risk ratio and forest plot. The Egger test was used as a significance test for

the funnel plot. The study was completed using the PRIS-MA 2009 check list.

For the calculation of eradication rate, meta-regression results, and funnel plots, the Comprehensive Meta-Analysis V3 trial package program was used.

Table 2. Mean rate of eradication using the ITT analysis

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio, 7-day treatment		1.34	0.87	2.07	
Event rate, 7-day treatment (random-effects model)	68.95 (p=0.004)	0.57	0.46	0.68	0.202
Average risk ratio, 10-day treatment		3.41	2.13	5.47	
Event rate, 10-day treatment (fixed-effects model)	0.00 (p=1.00)	0.78	0.66	0.86	<0.001
Average risk ratio, 14-day treatment		1.46	1.27	1.68	
Event rate, 14-day treatment (random-effects model)	75.14 (p<0.001)	0.60	0.56	0.63	<0.001
Total average risk ratio		1.47	1.29	1.68	
Event rate (random-effects model)	74.73 (p<0.001)	0.60	0.56	0.63	<0.001

Table 2 shows the results of the meta-analysis in regard to the studies that applied the ITT analysis. According to this, the mean eradication rate of all studies was 0.60 (95% CI: 56%-63%) and the risk ratio was 1.47. Moreover, according to the P value, it was not necessary to add new studies. When subgroups were evaluated according to days, the eradication rate for the 7-day treatment was 0.57 (95% CI: 46%-68%). However, it was not statistically significant. The eradication rate was 0.78 for the 10-day treatment (95% CI: 66%-86%) and 0.60 for the 14-day treatment (95% CI: 56%-63%), and the effects were statistically significant.

Table 3. Mean rate of eradication using the PP analysis

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio, 7-day treatment		1.35	0.82	2.23	
Event rate, 7-day treatment (fixed-effects model)	55.97 (p=0.103)	0.60	0.51	0.67	0.024
Average risk ratio, 14-day treatment		1.30	1.03	1.63	
Event rate, 14-day treatment (random-effects model)	77.80 (p<0.001)	0.56	0.50	0.62	0.037
Total average risk ratio		1.30	1.06	1.61	
Event rate (random-effects model)	75.56 (p<0.001)	0.57	0.51	0.62	0.018

Table 3 shows the results of the meta-analysis in regard to the studies that applied the PP analysis. According to this, the total eradication rate was 0.57 (95% CI: 51%-62%) and the risk ratio was 1.30. This result was found to be statistically significant.

RESULTS

A total of 45 studies, published between the years 2004 and 2013 in the national and international journals, involving the STT application, were evaluated (Table 1) (22-65). A total of 3715 patients were included in the study. Of the 3010 patients whose gender information was available, 55% were women and 45% were men; the weighted age average given explicitly in the studies was 42.14±0.67. The treatment lasted for 14 days in 42 studies, for 7 days in six studies, and for 10 days in 1 study.

The distribution of the studies by years was as follows: six studies were published in 2004, five in 2005, two in 2006, three in 2007, four in 2008, five in 2009, four in 2010, eight in 2011, four in 2012, and four in 2013. The ITT re-

sults were given in 44 of these studies, and 17 studies provided PP results. Table 1 provides the details of these studies.

The mean rate of eradication according to the ITT and PP analyses was 60% (95% CI: 56%-63%) and 57% (95% CI: 51%-62%), respectively. The rate for 7 days of treatment was 57% (95% CI: 46%-68%) and 60% (95% CI: 51%-67%) and for 14 days of treatment was 60% (95% CI: 56%-63%) and 56% (95% CI: 50%-62%), respectively (Tables 2 and 3). The ITT eradication rate of the only 10-day study was 78% (95% CI: 66%-86%) (Figure 1, 2). The eradication results according to the PPI used in the 14-day treatment were as follows: based on ITT and PP, respectively, for esomeprazole combination, 54% (95% CI: 46%-

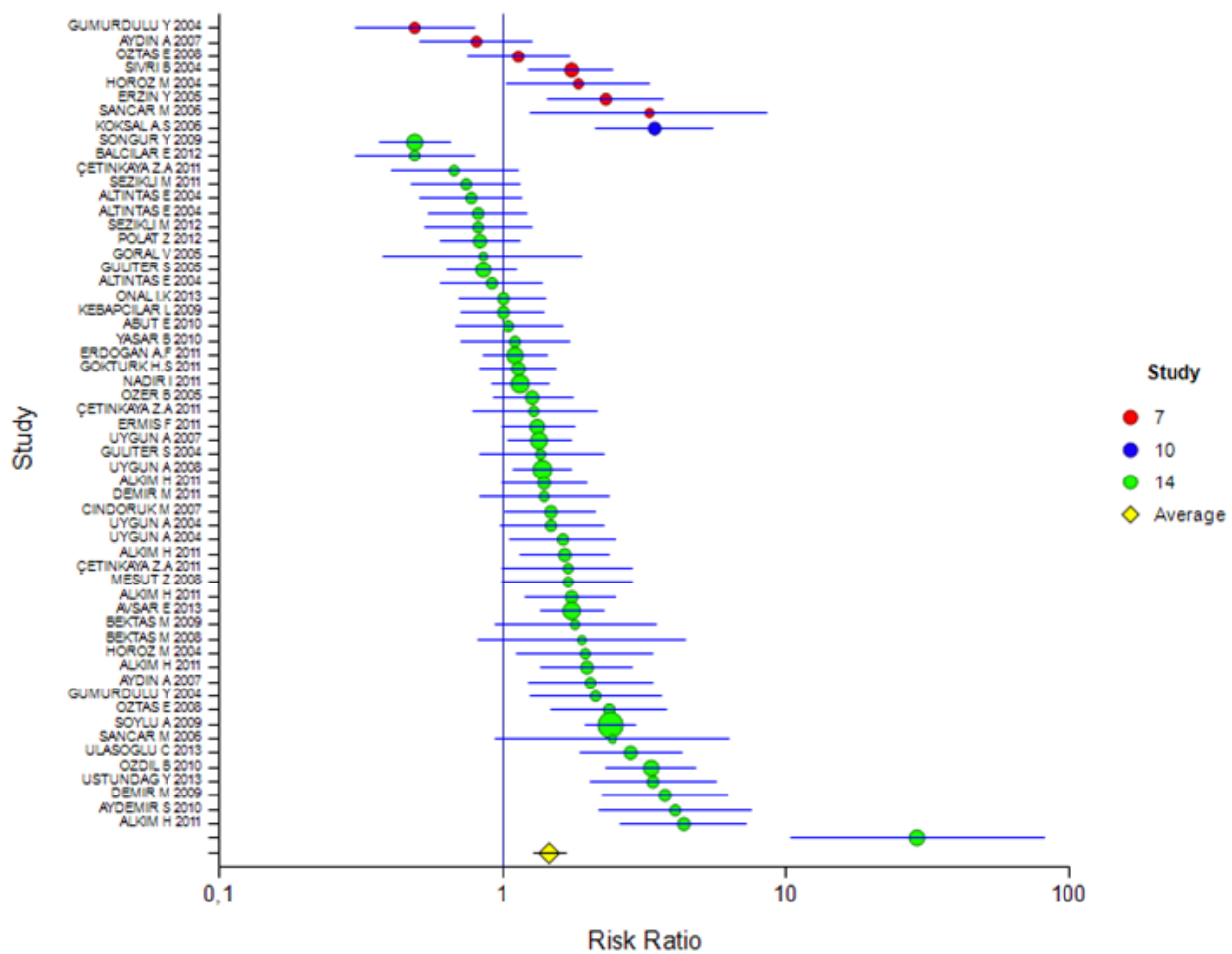


Figure 1. ITT forest plot for all studies

61%) and 51% (95% CI: 39%-63%); for lansoprazole, 60% (95% CI: 54%-65%) and 53% (95% CI: 44%-62%); for omeprazole, 55% (95% CI: 41%-68%) and 55% (95% CI: 47%-62%); and for pantoprazole, 60% (95% CI: 56%-63%) and 64% (95% CI: 55%-72%). For rabeprazole, the ITT eradication rate was 75% (95% CI: 65%-83%), and the PP result was not stated (Table 4, 5; Figure 3, 4). The ITT eradication rate of the only 10-day study, in which omeprazole was used, was 78% (95% CI: 66%-86%) (Table 6; Figure 5). The PP eradication rate was not stated. For pantoprazole, the ITT eradication rate for the 7-day treatment was 50% (95% CI: 48%-64%); it was 60% (95% CI: 51%-67%) for the fixed-effects model and 58% (95% CI: 46%-70%) for the random-effects model. The ITT eradication rate was 68% (95% CI: 50%-78%) for lansoprazole and 55% (95% CI: 15%-90%) for omeprazole. No PP results were stated (Tables 7 and 8; Figure 6, 7).

In the meta-regression analysis, the treatment duration, PPI, age, and gender ratio (women/men) used for the ITT analysis had no effect. The gender ratio and age were not considered in this analysis because they were not clearly stated in studies using the PP analysis. The duration of treatment and the PPI used had no effect (Tables 9 and 10). The I^2 for ITT was 74.73 ($p < 0.001$) and the I^2 for PP was 75.56 ($p < 0.001$). As the I^2 values were more than 25% and were found to be significant, the meta-analysis was applied to subgroups according to the day and PPIs, assuming heterogeneity (21).

The eradication rates of the first 5 and the last 5 years were compared to determine if there was a change in the eradication rates during the 10-year period. There was no difference in terms of ITT (59% vs. 61% $p: 0.650$, respectively), while there was a significant difference in PP results (62% vs. 50%, $p: 0.013$).

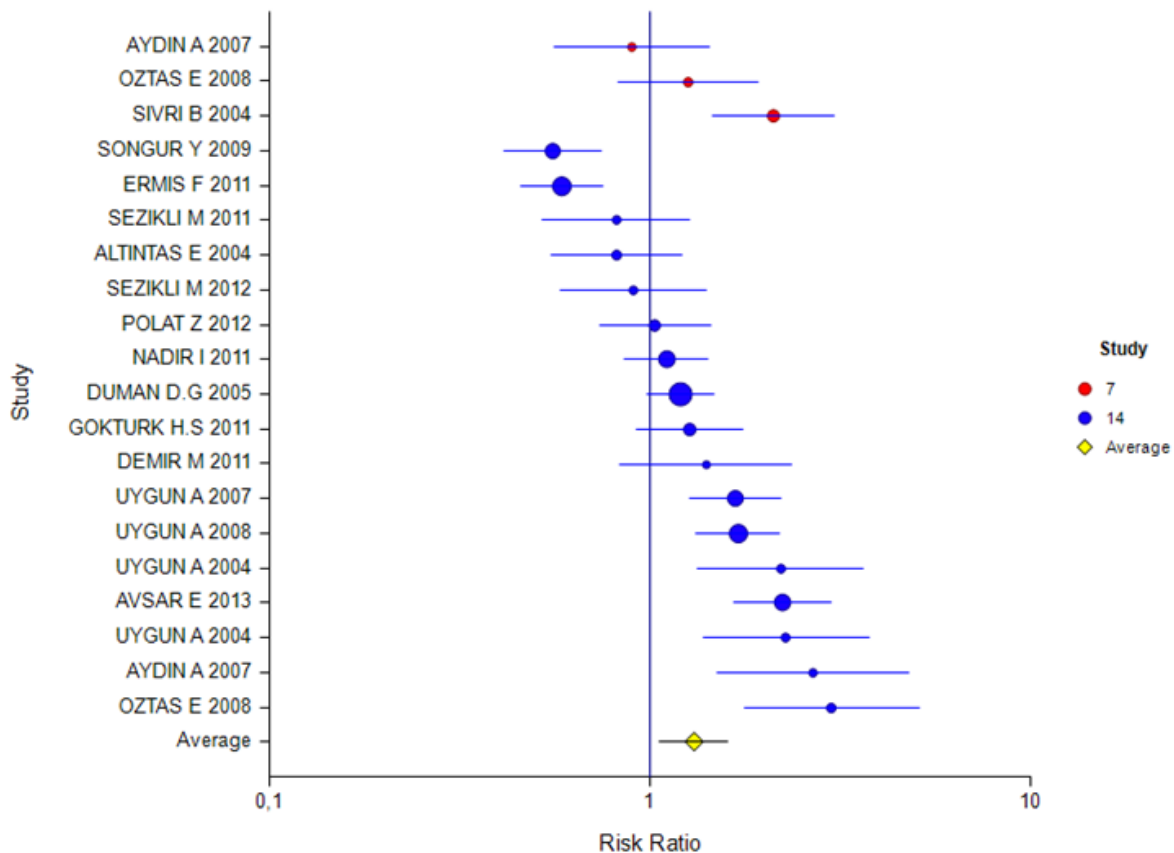


Figure 2. PP forest plot for all studies

Table 4. ITT eradication result for the 14-day treatment

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio [ES-OM]		1.22	0.79	1.86	
Event rate (ES-OM) (fixed-effects model)	47.14 (p=0.151)	0.54	0.46	0.61	0.373
Average risk ratio [LAC]		1.47	1.20	1.80	
Event rate (LAC) (random-effects model)	79.85 (p<0.001)	0.60	0.54	0.65	<0.001
Average risk ratio (OAC)		1.20	0.71	2.02	
Event rate (OAC) (random-effects model)	81.86 (p<0.001)	0.55	0.41	0.68	0.487
Average risk ratio (PAC)		1.47	1.20	1.81	
Event rate (PAC) (fixed-effects model)	43.29 (p=0.054)	0.60	0.56	0.63	<0.001
Average risk ratio (RAC)		2.73	1.08	6.88	
Event rate (RAC) (fixed-effects model)	73.24 (p=0.053)	0.75	0.65	0.83	<0.001

Table 4 shows that studies carried out with ITT were divided into subgroups according to PPIs with a treatment duration of 14 days. Although the effect magnitudes of studies using the ES-OM and OAC combinations were found to be insignificant, the effect of the LAC, PAC, and RAC inhibitors was found to be significant. The highest effect was monitored in the LAC combination.

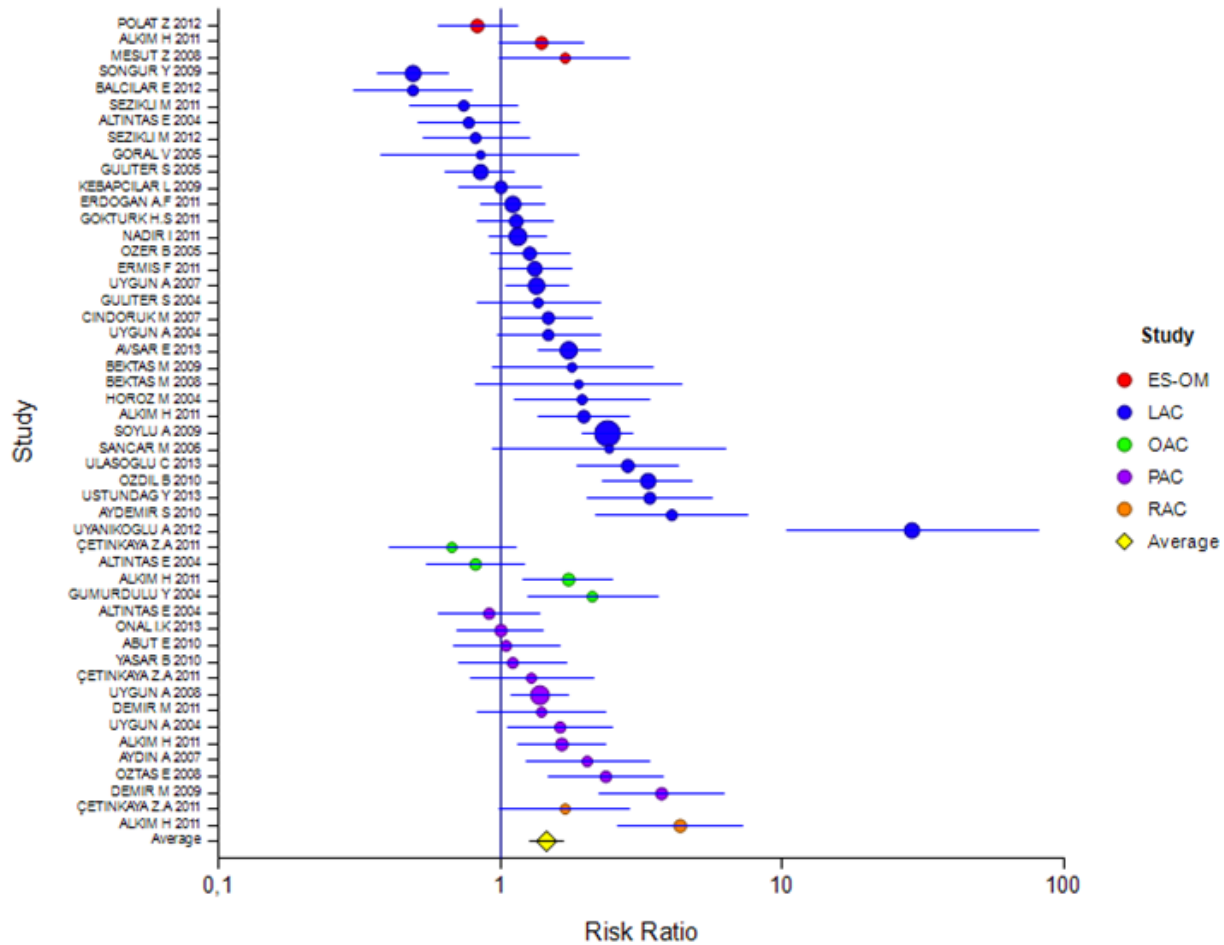


Figure 3. Forest plot for different inhibitors in the ITT analysis for the 14-day treatment

Table 5. PP eradication result for the 14-day treatment

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio (ES-OM)		1.03	0.74	1.44	
Event rate (ES-OM) (fixed-effects model)	0.00 (P=1.00)	0.51	0.39	0.63	0.903
Average risk ratio (LAC)		1.11	0.78	1.58	
Event rate (LAC) (random-effects model)	83.22 (p<0.001)	0.53	0.44	0.62	0.566
Average risk ratio (OAC)		1.20	0.98	1.47	
Event rate (OAC) (fixed-effects model)	0.00 (p=1.00)	0.55	0.47	0.62	0.212
Average risk ratio (PAC)		1.77	1.22	2.57	
Event rate (PAC) (random-effects model)	58.99 (p=0.032)	0.64	0.55	0.72	0.003

Table 5 shows that studies carried out with PP were divided into subgroups according to PPIs with a treatment duration of 14 days. Although the effect magnitudes of studies using the ES-OM, LAC, and OAC combinations were found to be insignificant, the effect of the PAC inhibitors was 0.64 and was found to be significant.

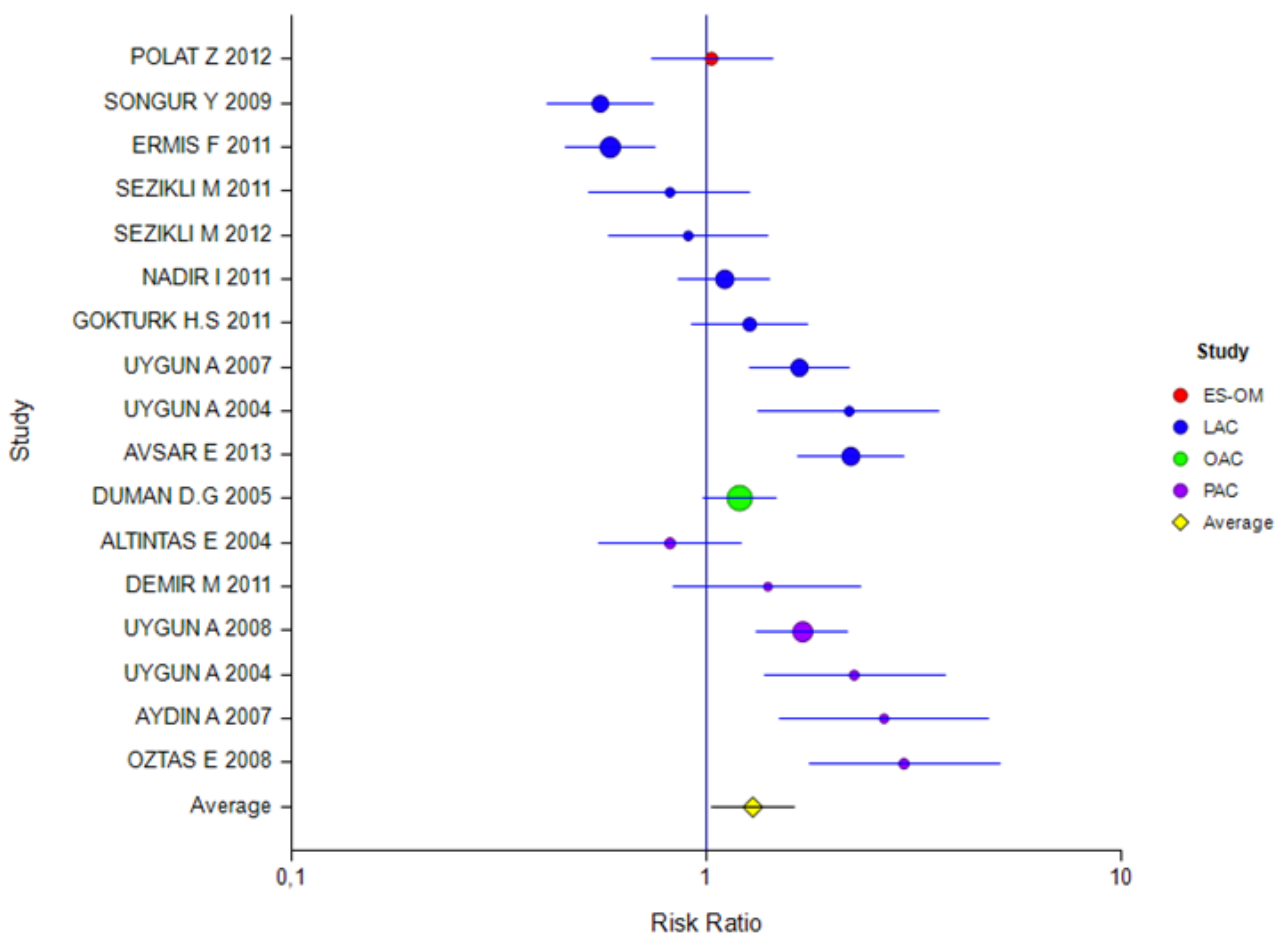


Figure 4. Forest plot for different inhibitors in the PP analysis for the 14-day treatment

Table 6. ITT eradication result for the 10-day treatment

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio (OAC)		3.41	2.13	5.47	
Event rate (OAC) (fixed-effects model)	0.00 (p=1.00)	0.78	0.66	0.86	<0.001

Table 6 shows the results of a study using OAC combination with a treatment duration of 10 days with ITT. For this PPI, the effect was 0.78 (95% CI: 66%-86%) and was found to be significant.

DISCUSSION

STT has been proposed by all authorities in the last two decades as the first option for first-line *Hp* eradication treatment. However, its effectiveness is gradually diminishing. Studies from different geographical regions of the world have shown a decrease in the success of STT.

In a study published by our group in 2004, the mean eradication rate with a 14-day STT treatment with different PPIs was found to be 45% (18). The type of PPI used did not change the result. Unfortunately, the eradication rates, in studies carried out by us after 2004, with different combinations to increase the eradication success were always less than the optimal limits (50,66-71).

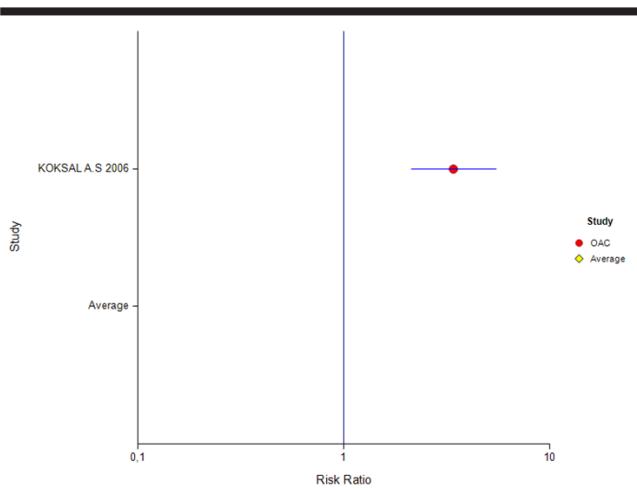


Figure 5. Forest plot for different inhibitors in the ITT analysis for the 10-day treatment

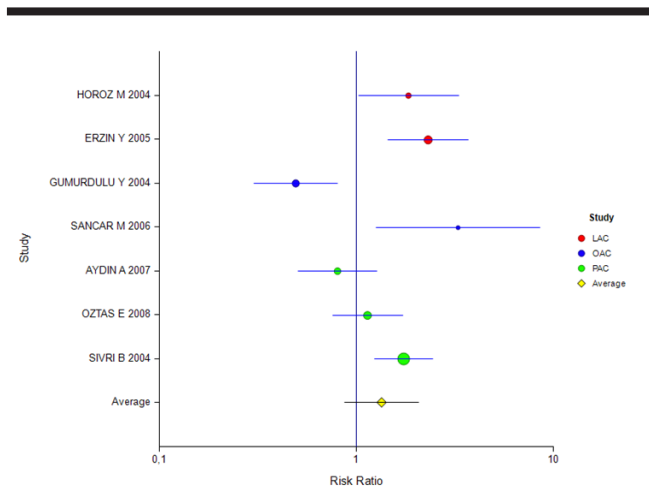


Figure 6. Forest plot for different inhibitors in the ITT analysis for the 7-day treatment

Table 7. ITT eradication rate for the 7-day treatment

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio (LAC)		2.11	1.47	3.05	
Event rate (LAC) (fixed-effects model)	0.00 (p=0.671)	0.68	0.50	0.78	0.002
Average risk ratio (OAC)		1.21	0.19	7.79	
Event rate (OAC) (random-effects model)	86.94 (p=0.006)	0.55	0.15	0.90	0.837
Average risk ratio (PAC)		1.19	0.77	1.86	
Event rate (PAC) (fixed-effects model)	48.05 (p=0.146)	0.50	0.48	0.64	0.123

Table 7 shows that studies carried out using the ITT analysis were divided into subgroups according to PPIs with a treatment duration of 7 days. According to this, although the effect magnitudes of studies using the PAC and OAC combinations were found to be insignificant, the effect for the LAC combination was significant.

Table 8. PP eradication rate for the 7-day treatment

	I ²	Effectiveness	0, 95% LCL	0, 95% UCL	p
Average risk ratio (PAC)		1.35	0.82	2.23	
Event rate (PAC) (fixed-effects model)	55.97 (p=0.103)	0.60	0.51	0.67	0.024
Event rate (PAC) (random-effects model)		0.58	0.46	0.70	0.204

Table 8 shows that the 7-day treatment duration was evaluated according to PPI using PAC. The I² value was 55.97, but was not found to be significant (P=0.103). The eradication rate in the case of the fixed-effects model was 0.60% (95% CI: 51%-67%) and was found to be statistically significant (0.024). The risk ratio was 1.35; however, it was not statistically significant as the confidence intervals included a value of 1. Although the risk ratio with the random-effects model was 0.58 (95% CI: 46%-70%), the confidence intervals were wider and statistically insignificant (p=0.204).

Kadayıfçı et al. (20) were the first in Turkey to systematically analyze the efficiency of the triple treatment in first-line *Hp* eradication. They evaluated 94 studies involving 3637

patients who underwent an STT regimen during the 10-year period between 1996 and 2005. In the present meta-analysis, the eradication rate was found to be 68.8% (20).

The results of *Hp* eradication with STT during the 10-year period following this study were examined. As a result of the systematic meta-analysis of STT used within 10 years from 2004 to 2013, the effectiveness of STT against *Hp* infection was found to be much lower than

desired. The ITT analysis showed an eradication rate of 60% (95% CI: 56%-63%) while the PP analysis showed an eradication rate of 57% (95% CI: 51%-62%). Unfortunately, these eradication rates were much less than the 80% required for successful eradication. ITT eradication rates did not show a change over a 10-year period, whereas PP eradication rate decreased in the second 5-year period compared to the previous years. However, the rates of eradication in both periods were unacceptably low.

As is known, the intention-to-treat analysis is a comparison of the treatment groups that includes all patients and it ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. On the other hand, per-protocol analysis is a comparison of treatment groups that includes only those patients who have completed the treatment. Therefore, PP eradication rates are usually higher than those of ITT analysis. But in our study, some PP eradication rates are higher than ITT rates (for example: the mean rate of eradication of all studies according to the ITT and PP analyses was 60% and 57%, respectively; also eradication rates for 14 days of treatment were

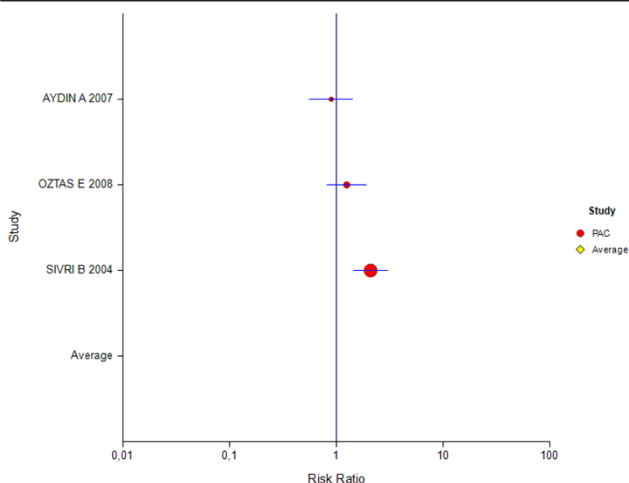


Figure 7. Forest plot for different inhibitors in the PP analysis for the 7-day treatment

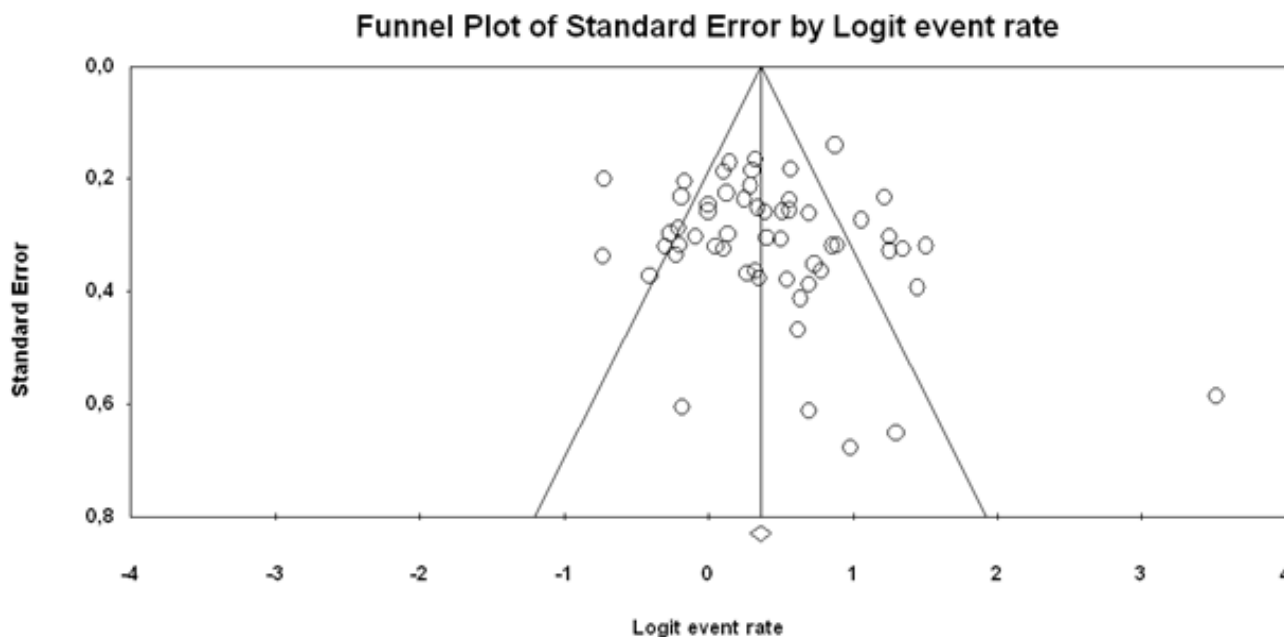


Figure 8. ITT funnel plot

Figure 8 shows the funnel plot of the studies that used the ITT analysis. The studies were distributed homogeneously. However, there were two studies (43 and 61) outside the funnel plot; the rates of eradication were very high in these two studies (100% and 97%, respectively), but the percentages of the contribution to the meta-analysis were quite low. Therefore, the effect of the image on the funnel plot is negligible. As a result of the Egger test, it does not appear to be a publication bias. Therefore, the publication bias was not detected ($p=0.294$).

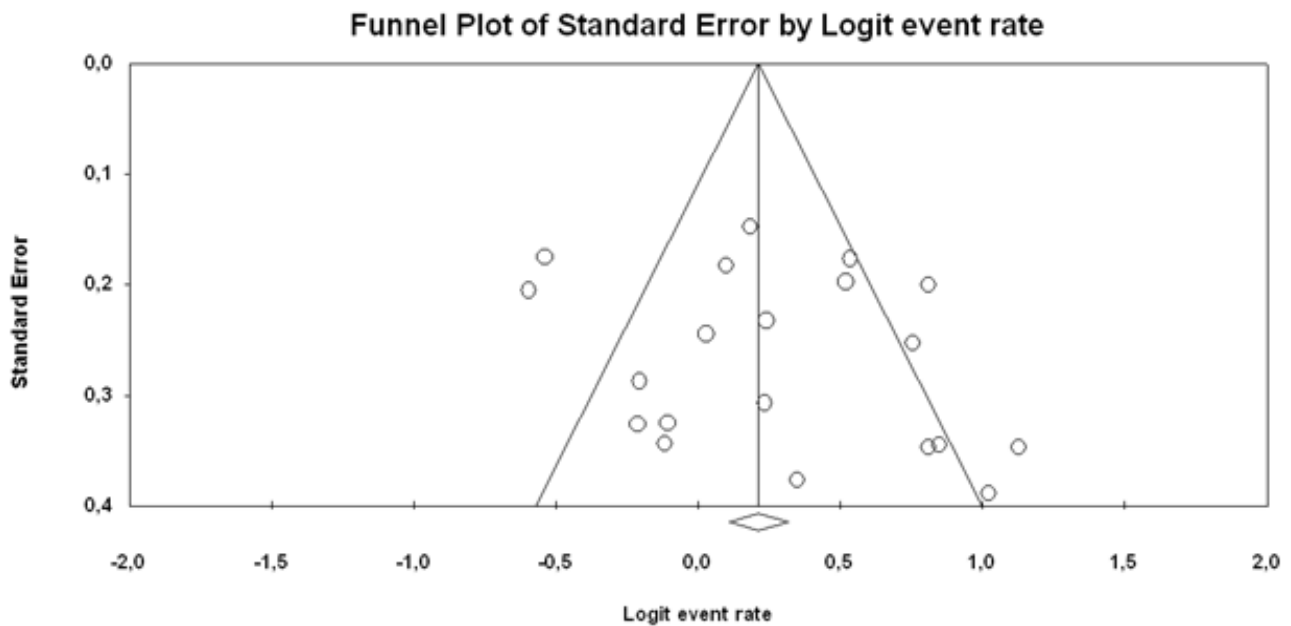


Figure 9. PP funnel plot
 Figure 9 shows the funnel plot of the studies that used the PP analysis. The studies were distributed homogeneously. The publication bias was not detected ($p=0.230$).

Table 9. Meta-regression analysis results using the ITT analysis

		ITT				
		Coefficient	95% lower	95% upper	p	p
Intercept		0.422	-1.663	2.505	0.692	-
Age		-0.003	-0.052	0.046	0.898	-
Sex ratio (F/M)		-0.099	-0.458	0.259	0.588	-
Days	7	Reference				0.169
	10	1.182	-0.306	2.670	0.120	
	14	-0.143	-0.737	0.450	0.636	
PPI	ES-OM	Reference				0.376
	LAC	0.408	-0.430	1.245	0.340	
	OAC	0.076	-0.875	1.027	0.876	
	PAC	0.325	-0.503	1.207	0.420	
	RAC	0.995	-0.137	2.128	0.085	

60% and 56% for ITT and PP analysis, respectively; a similar trend was observed when different PPIs were used). The reason for this is that the PP results were not stated in some studies.

Another important result of this study was that the type of PPI used and the treatment duration did not affect the eradication result. However, at the third Maas-tricht consensus conference, the duration of STT was

Table 10. Meta-regression analysis results using the PP analysis

		PP				
		Coefficient	95% lower	95% upper	p	p
Intercept		-0.241	-1.511	1.029	0.710	-
Days	7	Reference				-
	14	0.271	-0.420	1.034	0.486	
PPI	ES-OM	Reference				0.375
	LAC	0.076	-0.995	1.146	0.890	
	OAC	0.155	-1.230	1.539	0.827	
	PAC	0.559	-0.550	1.668	0.324	

As age and gender information were generally given in all studies for patients participating in the study and because ITT covered all randomized patients, the PP analysis could not be used in the data analysis.

The treatment application time for ITT ($p=0.169$), age ($p=0.898$), gender ratio ($p=0.588$), and application of different PPIs ($p=0.376$) did not affect the success of the treatment.

The treatment application time for PP ($p=0.486$) and the application of different PPIs ($p=0.375$) did not affect the success of the treatment.

extended to 14 days because the success of treatment increased with an increased duration of treatment (5). Accordingly, the treatments were given for at least 14 days for years (72). This meta-analysis showed that a treatment duration of 7 or 14 days did not change the success of STT. Thus, this became a subject that needed attention. A similar result was obtained by Kadayıfçı et al. (20) in their evaluation carried out in 2004 (20). There has been a consensus for years that different PPIs used for treatment show similar effects (18,73-76). The present study also yielded the same result. The type of PPI used in the combination treatment did not lead to any change in the eradication result.

Although the most important cause of eradication failure is accepted as antibiotic resistance, other reported causes include treatment incompatibility, drug-related side effects, bacterial load, smoking and underlying co-morbidities, and genetic differences in PPI metabolism (77-80). Studies in Turkey and our region (Mediterranean area) showed that, especially, the antibiotic resistance against clarithromycin and metronidazole was very high (16,17). The studies included did not analyze antibiotic resistance. Therefore, high antibiotic resistance rates were believed to be an important factor in the failure of STT regimes, although no definite conclusion was reached in this regard. However, further reduction of *Hp* eradication success in the second 5-year period may be related to this issue.

The main limitation of this study was its retrospective design. As a limited number of randomized controlled studies were identified, uncontrolled and open-label studies and case series were included. To increase the number of studies and patients included in this analysis, factors such as study design and minimum number of subjects per treatment arm were not strictly defined. The PP results and gender information were not stated in some studies. Patients who underwent STT were selected and evaluated from different study groups.

This systematic meta-analysis of studies conducted between 2004 and 2013 in Turkey indicated that the rate of first-line *Hp* eradication with STT was unacceptably low. Also, the duration of treatment and PPI used made no difference.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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