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Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection

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SUMMARY

Background
The decreasing efficacy of *H. pylori* eradication treatments over time makes the search for better regimens and adjuvant medications a priority.

Aim
To conduct a meta-analysis of studies comparing rabeprazole or esomeprazole with other proton pump inhibitors (PPI) or with each other in *H. pylori* eradication treatment.

Methods
Selection of Studies: Randomised clinical trials comparing esomeprazole or rabeprazole with first-generation PPIs (omeprazole-lansoprazole-pantoprazole) or with each other.

Results
The meta-analysis (35 studies, 5998 patients) showed higher eradication rates for esomeprazole than for first-generation PPIs: 82.3% vs. 77.6%; OR = 1.32 (1.01–1.73); NNT = 21. Rabeprazole also showed better results than first-generation PPIs: 80.5% vs. 76.2%; OR = 1.21(1.02–1.42); NNT = 23. PPI dosage sub-analysis: only esomeprazole 40 mg b.d. improved results [83.5% esomeprazole vs. 72.4% first generation; OR = 2.27(1.07–4.82); NNT = 9]. Whereas rabeprazole 10 and 20 mg b.d. maintained results, esomeprazole 20 mg b.d. obtained lower efficacy. Esomeprazole vs. rabeprazole sub-analysis (five studies): no significant differences were found: 78.7% vs. 76.7%; OR = 0.90(0.70–1.17). CYP2C19 sub-analysis: Genotype did not significantly affect eradication either in first [OR = 1.76(0.99–3.12)] or new generation [OR = 1.19(0.73–1.95)] PPIs. However, sub-analysis considering only extensive metaboliser patients showed higher eradication with new-generation PPIs [OR = 1.37(1.02–1.84)].

Conclusions
Esomeprazole and rabeprazole show better overall *H. pylori* eradication rates than first-generation PPIs. This clinical benefit is more pronounced in esomeprazole 40 mg b.d. regimens. In CYP2C19 extensive metabolisers, new-generation PPIs are more effective than first-generation PPIs for *H. pylori* eradication. However, a general recommendation of using new-generation PPIs in all scenarios remains unclear.

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INTRODUCTION

Helicobacter pylori infection has been associated to the development of gastric lesions, such as chronic gastritis, gastroduodenal ulcer, preneoplastic lesions, MALT lymphoma and gastric cancer.[1] As an infection affecting over half of the world's population and as the major cause of upper gastrointestinal tract disorders, its eradication has been indicated whenever the infection is present.[2–4] But the decreasing efficacy of *H. pylori* eradication treatments over time due to acquired antibiotic resistance by the bacterial strains makes the search for better regimens and adjuvant medications a priority for the management of gastric diseases.[5]

Proton pump inhibitors (PPI) are prodrugs derived from timoprazole, a pyridylmethylsulfinyl benzimidazole compound able to irreversibly block the proton pump (H^+/K^+ ATPase) of gastric parietal cells.[6] As proton pump is the last step on acid secretion in the stomach, it is an ideal target for acid inhibition.

The use of PPIs combined with antibiotics in the eradication of *H. pylori* has demonstrated not only to protect the stomach but also to increase the eradication rate itself.[6, 7] Acid inhibition increases eradication efficacy as antibiotics are more stable in less acidic gastric environments and induces a higher antibiotic sensitivity in the bacteria.[8] Furthermore, many studies in humans have shown that differences on acid control account for differences in eradication rates and that strong acid inhibition increases the efficacy of *H. pylori* treatments[7]

Since the discovery of omeprazole several analogues have been developed and commercialised. First omeprazole, lansoprazole and pantoprazole (first-generation PPIs) were developed and several studies demonstrated their antiacid properties and their role in *H. pylori* eradication. Later, a second generation of PPIs (rabeprazole and esomeprazole) was presented demonstrating even higher acid inhibition.[9–11] But its correlation with higher *H. pylori* eradication rates is still unclear.[12, 13]

For this reason, it seems necessary to review the literature of controlled trials comparing the efficacy of *H. pylori* eradication treatments differing only on the PPI used.

Therefore, the aim of the present meta-analysis was to evaluate the eradication rates of the different PPI when used in association to antibiotic treatment for the eradication of *H. pylori*.

METHODS

Search strategy

A systematic computerised literature search was conducted in Medline, PubMed ISI Web of Knowledge, Cochrane Central Register of Controlled Trials and EMBase online databases up to October 2011. Manual search of evidence from congress abstracts was performed for 'Digestive Disease Week', 'United European Gastroenterology Week' and the 'International Workshop on Helicobacter and Related Bacteria' from 1995 to 2011. Search and Review were conducted independently by two reviewers (AGM and PML) and discordances were resolved by a third investigator (JPG).

Boolean search was performed using MESH categories [Helicobacter OR Pylori] AND [Eradication OR Treatment] AND [PPI OR Rabeprazole OR Esomeprazole OR 'Proton Pump Inhibitor']. Search was limited to only human subjects' studies. Outcome data review followed a three-step exclusion process: Title Exclusion Step, Abstract Exclusion Step and Full Text Review.

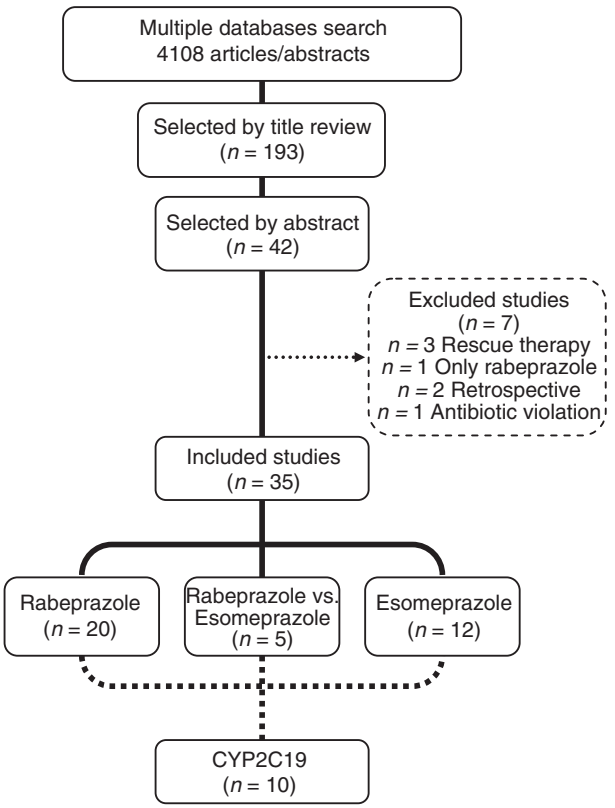


Figure 1 | Meta-analysis flow chart.

Inclusion criteria

Inclusion criteria for articles in the meta-analysis were: (i) Reporting *H. pylori* eradication results of comparative, randomised trials, (ii) The eradication regimens had to be PPI plus two antibiotics, (iii) Including at least two arms of treatment differing only on the PPI used,

Table 1 | Included studies

Reference	Antibiotics (mg)	Length of treatment	Number of patients	Eradication (%)
Adachi (2003)[27]	C 400 b.d. + A 500 t.d.s.	5 days	80	R20 (90.0%) – O20 (75.0%)
Anagnostopoulos (2004)[45]	C 500 b.d. + A 1000 b.d.	7 days	156	E40od (81.0%) – E40 (96.0%) – O20 (71.0%)
Catalano (2002)[26]	C 500 b.d. + A 1000 b.d.	5 days + 5 extra days PPI	127	R40od (90.0%) – R20od (80.9%) – O40od (93.3%)
Chen (2005)[37]	C 500 b.d. + A 1000 b.d.	7 days	104	E20 (88.5%) – O20 (82.7%)
Choi (2007)[34]	C 500 b.d. + A 1000 b.d.	7 days	576	E40 (70.3%) – R20 (69.3%) – P40 (69.3%) – O20 (64.9%)
De los Rios (2009)[44]	C 500 b.d. + A 1000 b.d.	10 days	83	E20 (63.4%) – O20 (59.5%)
Dojo (2001)[28]	C 400 b.d. + A 750 b.d.	7 days	170	R20 (80.2%) – O20 (78.7%)
Fernandez-Bermejo (2001)[25]	C 500 b.d. + A 1000 b.d.	7 days	30	R20 (84.6%) – O20 (82.4%)
Hawkey (2003)[24]	C 500 b.d. + A 1000 b.d.	7 days	174	R20 (80.5%) – O20 (70.1%)
	C 500 b.d. + M 400 b.d.	7 days	174	R20 (64.4%) – O20 (77.0%)
Hsu (2005)[43]	C 500 b.d. + A 1000 b.d.	7 days	200	E40 (94.0%) – P40 (82.0%)
Huh (2004)[42]	C 500 b.d. + A 1000 b.d.	7 days	112	E20 (77.1%) – O20 (74.5%)
Inaba (2002)[30]	C 200 t.d.s. + A 500 t.d.s.	7 days	183	R10 (76.6%) – L30 (86.7%) – O20 (83.1%)
Kang (2008)[47]	C 500 b.d. + A 1000 b.d.	7 days	327	E20 (88.3%) – P40 (82.6%)
Kawabata (2003)[31]	C 400 b.d. + A 750 b.d.	7 days	187	R10 (75.0%) – L30 (69.0%)
Kawai (2007)[32]	C 200 t.d.s. + A 500 t.d.s.	7 days	135	R10od (71.1%) – L30od (62.2%) – O20od (69.9%)
Kim (2003)[50]	C 500 b.d. + A 1000 b.d.	7 days	426	E40 (78.1%) – R40 (75.3%)
Kositchaiwat (2003)[23]	C 500 b.d. + A 1000 b.d.	7 days	162	R10 (84.9%) – R20 (96.3%) – O20 (83.3%)
Kumar (2007)[22]	A 750 b.d. + T 500 b.d.	14 days	92	R20 (86.7%) – P40 (78.1%) – O20 (83.3%)
Kuwayama (2001)[21]	C 200 b.d. + A 500 t.d.s.	7 days	92	R10 (66.7%) – O20 (60.0%)
Lee (2010)[48]	C 500 b.d. + A 1000 b.d.	7 days	256	E20 (67.7%) – R20 (61.1%)
Maev (2003)[41]	C 500 b.d. + A 1000 b.d.	7 days	80	E20 (91.3%) – E40od(89.3%) – O20 + 3W (89.6%)
Miehlke (2003)[40]	C 250 b.d. + M 400 b.d.	7 days	80	E20 (90.4%) – O20 (81.6%)
Miki (2003)[29]	C 400 b.d. + A 1000 b.d.	7 days	145	R10 (85.4%) – R20 (83.3%) – L30 (79.6%)
Miwa (1999)[19]	C 200 b.d. + A 500 t.d.s.	7 days	221	R20 (87.5%) – L30 (83.8%) – O20 (85.3%)
Miwa (2000)[20]	C 200 b.d. + A 500 t.d.s.	7 days	308	R10 (87.0%) – R20 (85.6%) – L30 (82.7%)
Murakami (2002)[18]	C 200 b.d. + A 750 b.d.	7 days	245	R10 (93.9%) – R20 (81.8%) – L30 (78.0%)
Pan (2010)[49]	Lev 500od + A 1000 b.d.	7 days	184	E20 (85.2%) – E40 (87.1%) – R10 (75.4%)
Sheu (2005)[46]	C 500 b.d. + A 1000 b.d.	7 days	200	E40 (86.0%) – O20 (79.0%)
Subei (2007)[39]	C 500 b.d. + A 1000 b.d.	7 days	374	E20 (74.7%) – O20 + 3W (78.7%)
Tulassay (2001)[38]	C 500 b.d. + A 1000 b.d.	7 days	446	E20 (82.9%) – O20 + 3W (85.7%)
Vakil (2004)[17]	C 500 b.d. + A 1000 b.d.	10 days	409	R20 (78.0%) – O20 (73.0%)
Wong (2001)[16]	C 500 b.d. + A 1000 b.d.	7 days	115	R10 (88.0%) – O20 (82.0%)
Wu (2007)[51]	C 500 b.d. + A 1000 b.d.	7 days	420	E40od (89.4%) – R20 (90.5%)
Yang (2003)[15]	C 500 b.d. + A 1000 b.d.	7 days	47	R20 (82.6%) – O20 (87.5%)
Zhang (2010)[33]	C 500 b.d. + A 1000 b.d.	7 days	240	R10 (85.8%) – O20 (79.2%)

A, amoxicillin; b.d., twice daily; C, clarithromycin; E, esomeprazole; ITT, Intention to treat; L, lansoprazole; Lev, levofloxacin; M, metronidazole; O, omeprazole; od, once daily; P, pantoprazole; R, rabeprazole; T, tinidazole; t.d.s., thrice daily.

+3W refers to studies in which one arm of treatment includes 3 weeks of omeprazole after eradication treatment.

* Number by the letter indicates mg per dose. Treatment given twice daily unless mentioned otherwise.

Table 2 | Included studies describing eradication stratified by CYP2C19 polymorphisms

Reference	Antibiotics (mg)	Length	Arm*	Extensive metabolisers % (e/N)	Poor metabolisers % (e/N)
Dojo (2001)[28]	C 400 b.d. + A 750 b.d.	7 days	R20	82.3% (51/62)	87.5% (14/16)
			O20	80.3% (53/66)	85.0% (17/20)
Inaba (2002)[30]	C 200 t.d.s. + A 500 t.d.s.	7 days	R10	76.4% (42/55)	87.5% (7/8)
			L30	89.8% (44/49)	88.9% (8/9)
			O20	83.3% (40/48)	90.0% (9/10)
Kang (2008)[47]	C 500 b.d. + A 1000 b.d.	7 days	E20	86.8% (105/121)	100% (16/16)
			P40	80.8% (135/167)	95.7% (22/23)
Kawabata (2003)[31]	C 400 b.d. + A 750 b.d.	7 days	R10	83.1% (69/83)	60.0% (6/10)
			L30	73.5% (50/68)	83.0% (10/12)
Kawai (2007)[32]	C 200 t.d.s. + A 500 t.d.s.	7 days	R10od	76.5% (26/34)	85.7% (6/7)
			L30od	69.4% (25/36)	100% (3/3)
			O20od	75.8% (25/33)	71.4% (5/7)
Lee (2010)[48]	C 500 b.d. + A 1000 b.d.	7 days	R20	76.2% (64/84)	81.3 (13/16)
			E20	83.6% (77/92)	91.7% (11/12)
Miki (2003)[29]	C 400 b.d. + A 1000 b.d.	7 days	R10	92.3% (36/39)	71.4% (5/7)
			R20	89.7% (35/39)	83.3% (5/6)
			L30	84.2% (32/38)	77.8% (7/9)
Pan (2010)[49]	Lev 500od + A 1000 b.d.	7 days	E20	89.2% (33/37)	90.0% (9/10)
			E40	85.3% (29/34)	100% (12/12)
			R10	72.5% (29/40)	78.6% (11/14)
Sheu (2005)[46]	C 500 b.d. + A 1000 b.d.	7 days	E40	84.8% (67/79)	90.5% (19/21)
			O20	75.3% (58/77)	91.3% (21/23)
Zhang (2010)[33]	C 500 b.d. + A 1000 b.d.	7 days	R10	84.7% (83/98)	90.9% (20/22)
			O20	77.0% (77/100)	90.0% (18/20)

A, amoxicillin; b.d., twice daily; C, clarithromycin; E, esomeprazole; e/N, number of eradications/total number of patients; L, lansoprazole; Lev, levofloxacin; M, metronidazole; O, omeprazole; od, once daily; P, pantoprazole; R, rabeprazole; T, tinidazole; t.d.s., thrice daily.

* Number by the letter indicates mg per dose. Treatment given twice daily unless mentioned otherwise.

(iv) Comparing new-generation PPI (esomeprazole or rabeprazole) between themselves or with old-generation PPI (omeprazole, lansoprazole or pantoprazole), (v) Patients had to be naïve to therapy, (vi) *H. pylori* infection had to be determined by positive histology, culture, rapid urease test and/or urea breath tests prior to treatment, (vii) Eradication had to be evaluated by histology and/or urea breath test at least 4 weeks after the end of treatment.

Data extraction

Data extraction was conducted independently by two reviewers (AGM and PML), discordances were resolved by a third investigator (JPG). Data extraction was standardised using a data extraction form. When any standardised data could not be extracted from the published text, communication with the corresponding author was done to solve queries. Data for genotype analysis were based on intention to treat when possible, if not, analysis used per protocol data.

Statistical Analysis

The primary outcome was 'intention to treat' eradication rate. For each comparison eradication rates, number needed to treat (NNT) and odds ratio (OR) with their corresponding 95% CI were calculated. As the treatments given in the studies and the populations differ between studies we assumed that individual studies estimated different treatment effects and therefore a Random Effects Model was used for the analysis. Cochrane's Q-test and I^2 test were performed to evaluate heterogeneity. If the Cochran's Q-test probability is lower than 0.05 the studies will be considered heterogeneous. I^2 test will classify heterogeneity as low ($\leq 25\%$), medium ($\approx 50\%$) or high ($\geq 75\%$).

Publication bias was evaluated for all comparisons using funnel plots. If publication bias was identified it was be mentioned in the results section. As methods for publication bias correction are not widely accepted, no correction was performed, but bias was discussed in the appropriate section.

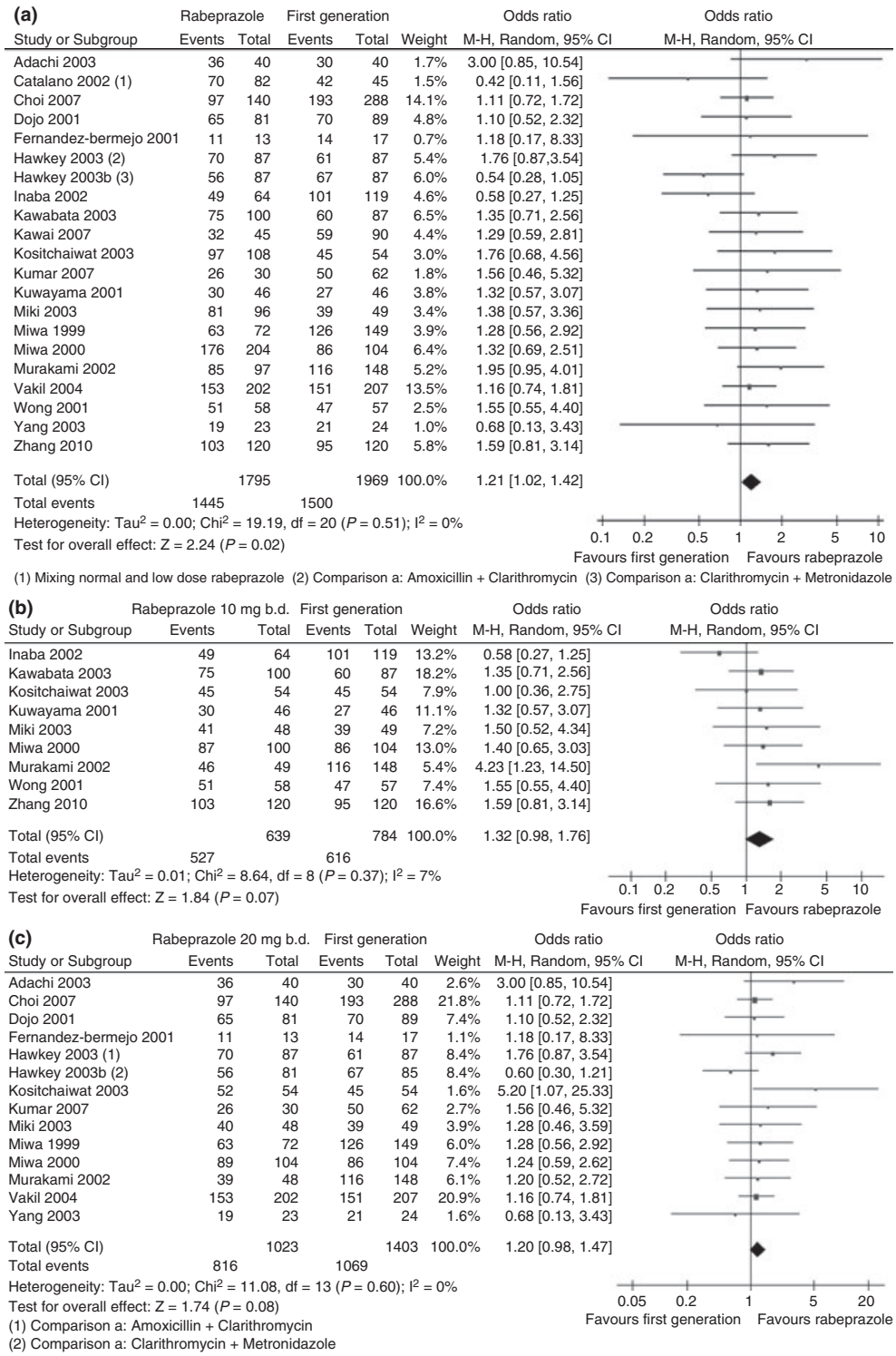


Figure 2 | (a) Overall rabeprazole vs. first-generation PPIs, (b) rabeprazole 10 mg b.d. and (c) rabeprazole 20 mg b.d.

Analysis was performed using the freeware program Review Manager (RevMan; The Cochrane Colaboration, Copenhagen, Denmark) version 5.1. RevMan statistical tests and formulae are detailed in RevMan User Guide.

RESULTS

Studies Included

Overall 35 (18.1%) studies[14–48] of the 193 relevant references initially selected were included (4108 results on first

step of the search). A flow chart of the multi-step exclusion process is presented in Figure 1. The studies, published between 1999 and 2011, presented the overall data of 7360 infected adult patients (Table 1). Twenty studies compared rabeprazole with first-generation PPIs (1795 patients in the rabeprazole arm vs. 1969 patients with the other PPIs),[14–33] and 12 studies compared esomeprazole with first-generation PPIs (1240 vs. 1358 patients respectively).[33–44] Five studies compared rabeprazole with esomeprazole (772 vs. 802 patients respectively).[33, 45–48]

Most studies[32] were based on clarithromicyn plus amoxicillin regimens. Although the dosage, number of intakes per day and length of treatment varied among studies, the most used regimen (18 studies, 3850 patients) was amoxicillin 1 g plus clarithromicyn 500 mg both taken twice daily for 7 days. Data on CYP2C19 genotype was presented in 10 studies (Table 2)[27–32, 43–46]; therefore sub-analyses were performed to evaluate the effect of this polymorphism on eradication rates among the different PPIs studied.

Six studies were excluded in the full text review step. Both Van Zanten *et al.* studies[50, 59] (827 patients) were excluded as the presented data did not differentiate between first line and rescue treatments. The trial by Kuwayama *et al.*[51] (479 patients) was excluded as it only compared different rabeprazole doses. Hong's study[52] (2297 patients) was a retrospective protocol comparing all different PPIs. The article by Kuo *et al.*[53] presented the data on 190 patients randomised for rescue therapy and for this reason was also excluded. Another excluded trial[54] compared rabeprazole and omeprazole in 199 patients, but on a dual therapy with amoxicillin.

Rabeprazole vs. first-generation PPIs

Twenty studies (Figure 2a) compared rabeprazole (any dose) with first-generation PPIs showing better eradication rates for the rabeprazole arm (80.5%) than for the first-generation arm (76.2%). The OR was 1.21 (95% CI = 1.02–1.42, *Q*-test $P = 0.51$, $I^2 = 0\%$) with a calculated NNT of 23. A small improvement was found when excluding Catalano *et al.* (2002) that used a once daily rabeprazole for 5 days in normal and low doses (40 and 20 mg od) (OR = 1.22). Sub-analyses were performed for rabeprazole 10 mg b.d. (Figure 2b) and 20 mg b.d. (Figure 2c), with an OR of 1.32 (95% CI = 0.98–1.76) and 1.20 (95% CI = 0.98–1.47) respectively. No heterogeneity was found in the sub-analyses.

Esomeprazole vs. first-Generation PPIs

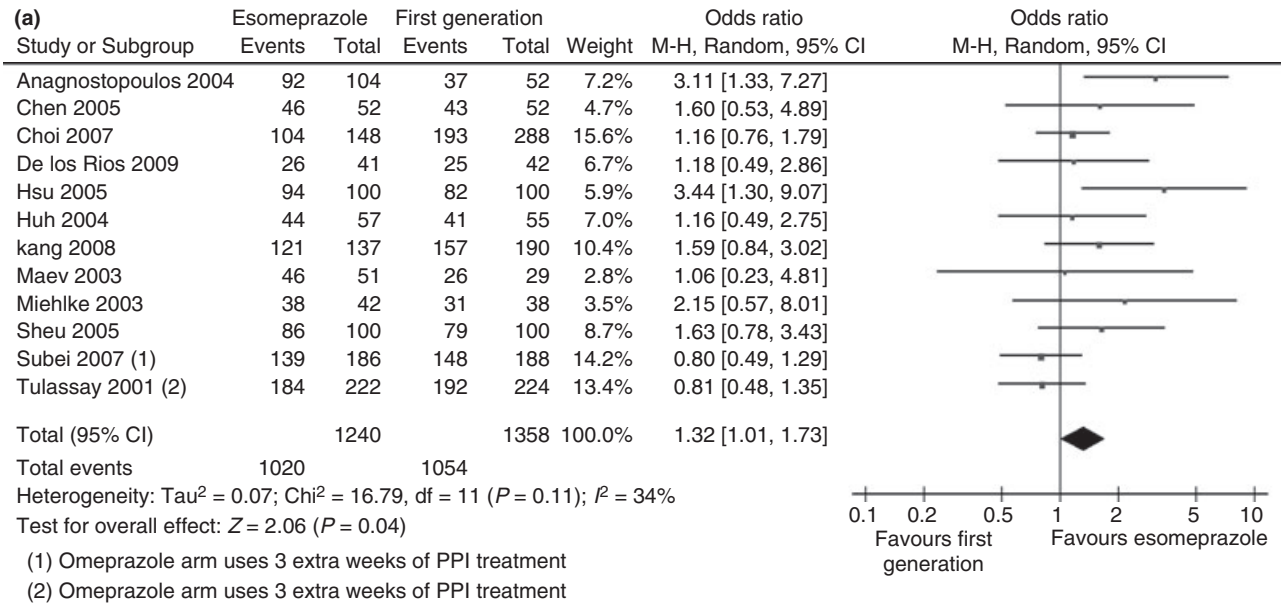
Twelve studies presented data comparing esomeprazole (any dose) to first-generation PPIs showing eradication rates 82.3% and 77.6% respectively. OR was 1.32 (95% CI = 1.01–1.73), with mild heterogeneity (*Q*-test $P = 0.11$ and $I^2 = 34\%$) and a NNT of 21 (Figure 3a). This heterogeneity disappeared (*Q*-test $P = 0.72$, $I^2 = 0\%$) after excluding two included studies, Subei *et al.*[36] and Tulassay *et al.*[35] that used a 3 week omeprazole (20 mg b.d.) course after eradication treatment in the omeprazole arm. The funnel plot analysis presented asymmetry caused by these two studies. After excluding those studies, due to methodical differences, the OR was 1.52 (95% CI = 1.19–1.95). Sub-analyses by Esomeprazole dose (40 mg b.d. and 20 mg b.d.) were also performed (Figures 3b and c). Better OR were found for esomeprazole 40 mg b.d. OR = 2.27 (95% CI = 1.07–4.82, NNT = 9) than for esomeprazole 20 mg b.d. OR = 1.04 (95% CI = 0.80–1.1.35), but the esomeprazole high-dose analysis (including only four studies) was highly heterogeneous (*Q*-test $P = 0.02$, $I^2 = 71\%$). Heterogeneity was not found in the esomeprazole 20 mg b.d. analysis (*Q*-test $P = 0.58$, $I^2 = 0\%$).

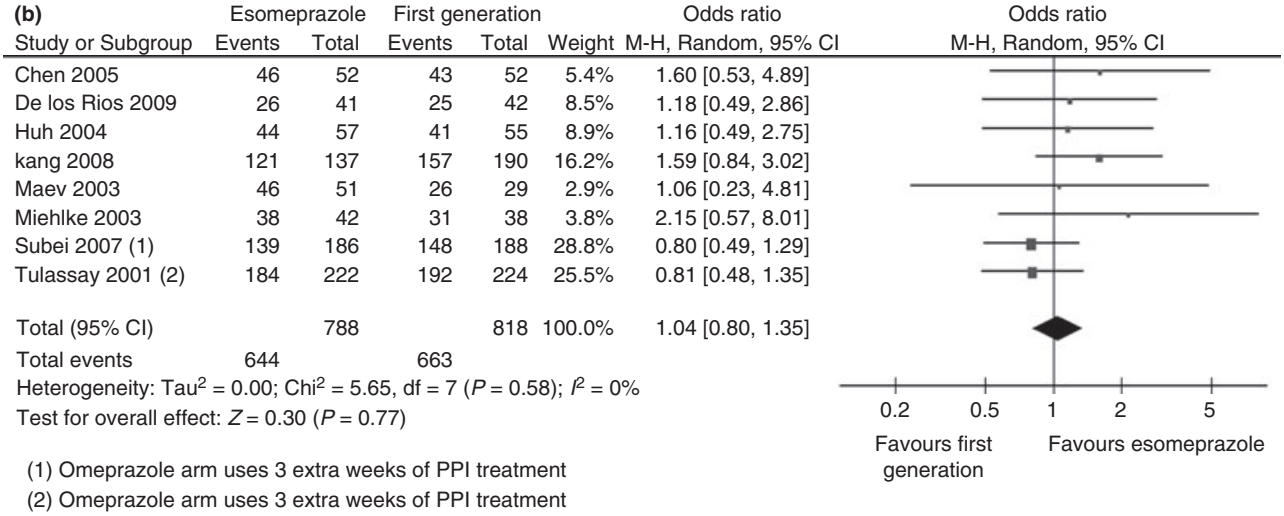
Rabeprazole vs. esomeprazole

Five studies compared the eradication rates of rabeprazole vs. esomeprazole containing therapies (772 and 802 patients respectively) (Figure 4). The comparison was not heterogeneous (*Q*-test $P = 0.35$, $I^2 = 11\%$) and found no statistically significant differences (OR = 0.90, 95% CI = 0.70–1.17). Eradication rates were 76.7% for rabeprazole and 78.7% for esomeprazole (NNT = 50).

CYP2C19 effect

The effect of CYP2C19 genotype on eradication rates was evaluated in four different sub-analyses: Differences between PM and EM in new-generation PPIs (Figure 5a), differences between PM and EM in first-generation PPIs (Figure 5b), differences between new- and first-generation PPIs in PM patients (Figure 5c) and differences between new- and first-generation PPIs in EM patients (Figure 5d). In the sub-analysis considering only patients treated with first-generation PPIs, a strong tendency towards better eradication rates were found for PM than for EM patients (OR = 1.76, 95% CI = 0.99–3.12). This tendency was not as marked in the sub-analysis of patients treated with new-generation PPIs (OR = 1.19, 95% CI = 0.73–1.95). In the sub-analysis evaluating only PM patients, no differences were found between first- and new-generation PPI treatments (OR = 0.91, 95% CI = 0.41–1.98). In EM patients, the eradication rates were





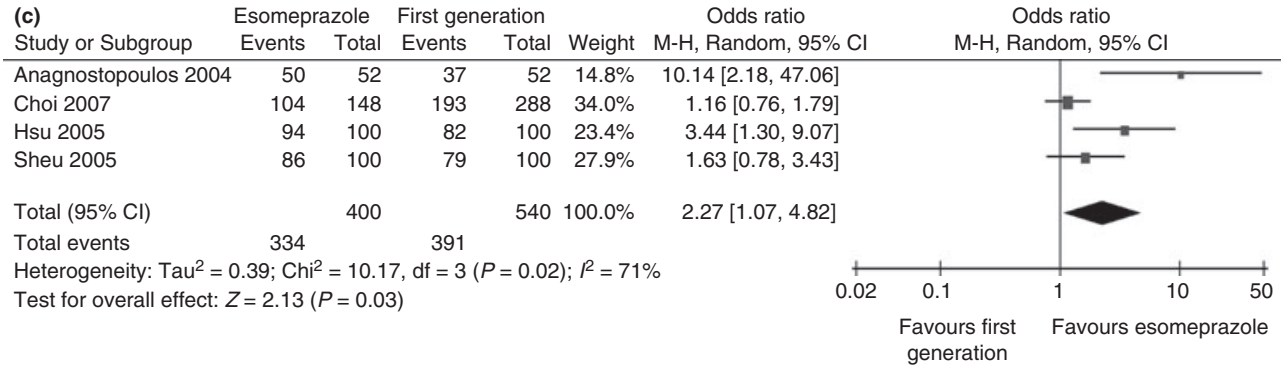


Figure 3 | (a) Overall esomeprazole vs. first-generation PPIs, (b) esomeprazole 20 mg b.d. and (c) esomeprazole 40 mg b.d.

significantly better with the new-generation PPI treatments (84.3% vs. 79.0%, OR = 1.37, 95% CI = 1.02–1.84, NNT = 19).

DISCUSSION

The present meta-analysis aimed to pool data from clinical trials comparing the eradication rates of *H. pylori* in studies

comparing therapies differing only on the PPI used. The main finding of the study is that the new-generation PPIs (rabeprazole and esomeprazole) compared with the first-generation PPIs (omeprazole, lansoprazole and pantoprazole) increase cure rates. This small superiority of new-generation PPIs has been previously reported in reviews and retrospective studies and seems to correlate with the higher acid inhibition power of these new PPIs that has been reported to affect eradication rates,[6–8, 12, 13, 55, 56] but the clinical advantage may be limited from a cost-effective perspective due to the higher prices of rabeprazole and esomeprazole when compared with omeprazole.

Rabeprazole obtained, overall, a higher efficacy than first-generation PPIs, but the clinical relevance was small as its NNT was quite high. This higher eradication efficacy but low clinical relevance of rabeprazole was maintained for doses of 10 mg b.d. and 20 mg b.d.. On the other hand, esomeprazole slightly improved the overall result, but this was mainly due to four studies that administered a 40 mg dose twice daily. This probably highlights the dependence of eradication rates on the level of acid inhibition. However, even though the results from the esomeprazole 40 mg b.d. seemed promising and clinically relevant (NNT = 9), only four studies were included and the heterogeneity was high, therefore this results have to be taken cautiously.

The overall results, as well as the separated subanalysis, improved the OR in favour of the new-generation PPIs when three outlier studies were excluded. Two of these studies[35, 36] focused on ulcer healing and compared esomeprazole 20 mg b.d. vs. omeprazole 20 mg b.d. plus amoxicillin and clarithromycin for 7 days. However, the omeprazole arm added a 3 week course of PPI, whereas the esomeprazole arm was followed by placebo. Even though the eradication efficacy of monotherapy with a PPI is probably ineffective,[57] a 3 weeks post treatment, after *H. pylori* has been exposed to antibiotics, might affect the apparent eradication rate. The other outlier study used a once daily dose of PPI, what has been demonstrated to reduce the eradication rate.[6, 58, 59]

It has been reported that CYP2C19 polymorphism can affect PPI's metabolisation and therefore their acid inhibitory capacity and consequently their effect on *H. pylori* eradication.[6, 55, 60] The literature has reported higher eradication success in PM, homozygous for the low activity allele, although these differences were not reported for rabeprazole or esomeprazole.[6] In our meta-analysis, rabeprazole and esomeprazole eradication rates were not affected by the CYP2C19 phenotype, whereas first-generation PPIs showed a clear tendency towards lower eradication rates in EM patients, which is in accordance with previously published data.[6]

When comparing new-generation vs. first-generation PPIs in PM patients, a small tendency towards better eradication rates was found when treatment contained first-generation PPIs. However, when evaluating only EM patients, the analysis demonstrated a significant improvement when the treatment contained new-generation PPIs. This could be explained because standard doses of any PPI achieve near maximal acid inhibition in poor metabolisers, whereas far larger doses of PPI are needed to achieve the same degree of acid inhibition in extensive metabolisers.

The main limitation of the present meta-analysis was the complex diversity of regimens; the antibiotics used, the number of intakes per day, the doses and the length of treatment. This diversity and the impossibility to meta-analyse data from more similar protocols made it hard to assume one unique effect for all studies.

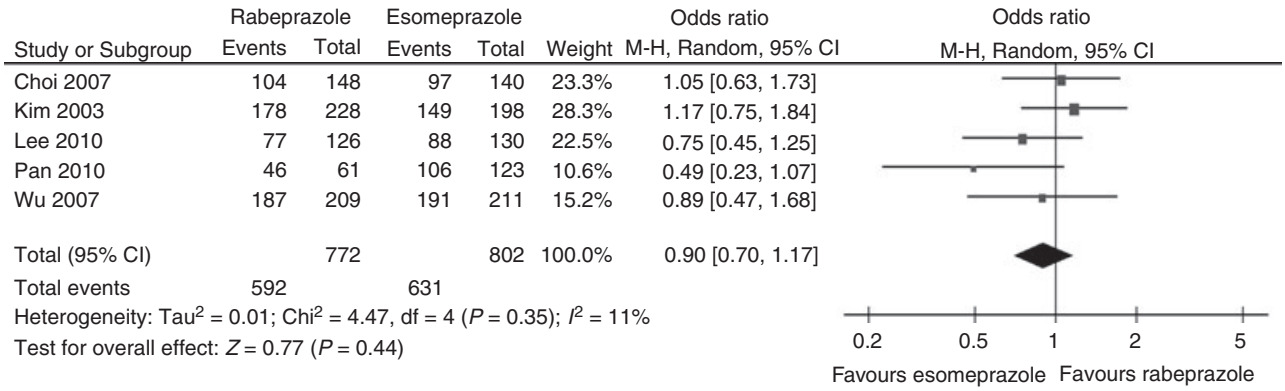


Figure 4 | Rabeprazole vs. esomeprazole.

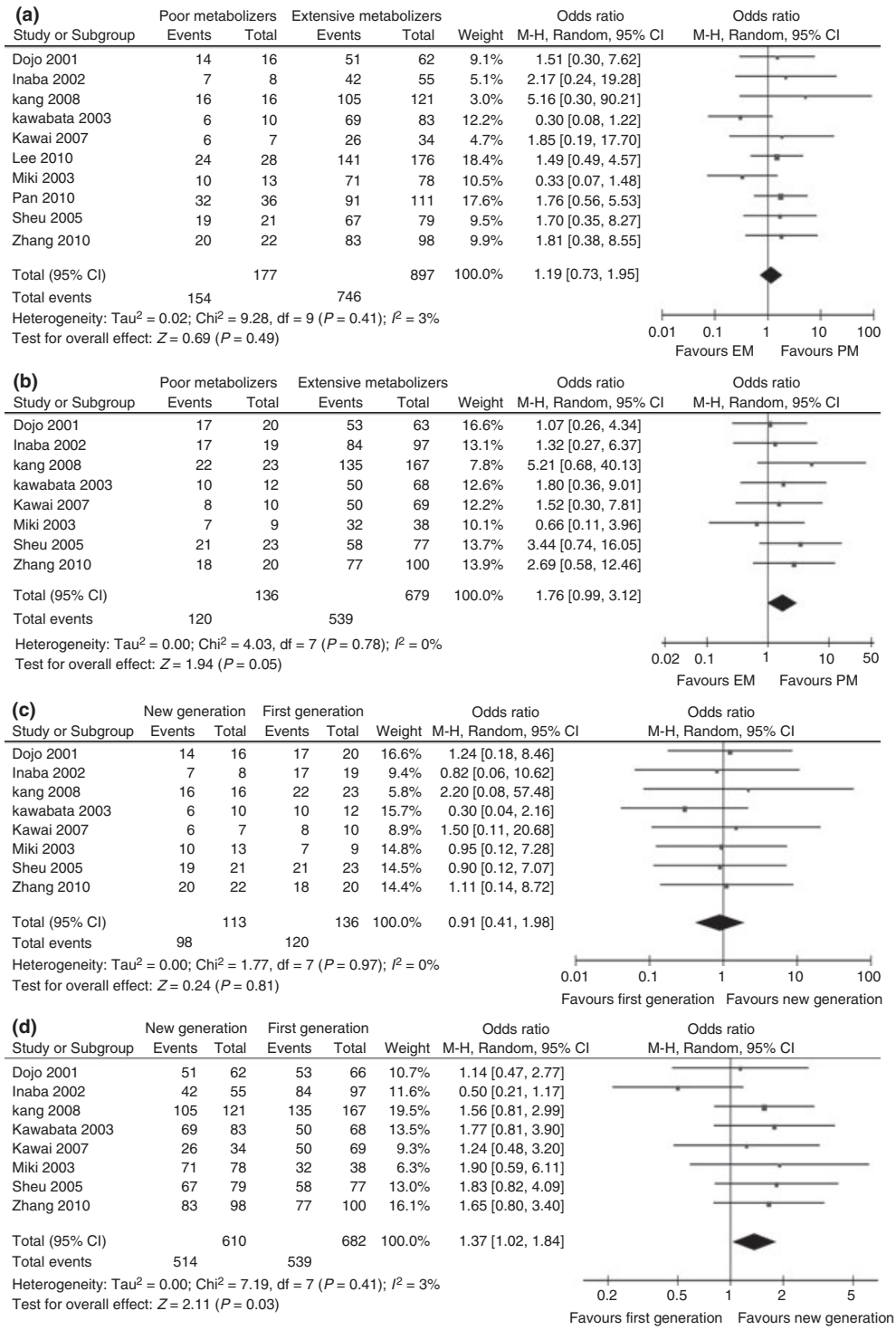


Figure 5 | (a) New generation: CYP2C19 poor metabolisers (PM) vs. extensive metabolisers (EM), (b) first generation: CYP2C19 poor metabolisers (PM) vs. extensive metabolisers (EM), (c) CYP2C19 poor metabolisers: new generation vs. first generation and (d) CYP2C19 extensive metabolisers: new generation vs. first generation.

Therefore, we decided to use a random effects model which allows the estimation of intervention effect without assuming one unique global effect for the intervention.[61] An additional limitation of the study is that in most of the studies antibiotics are given for only 7 days. Current recommendations suggest using triple therapy

for at least 10 days or using quadruple therapies. The usefulness of strong acid inhibition in these new settings has still to be proved.

In conclusion, esomeprazole and rabeprazole obtained an overall higher eradication rate than omeprazole, lansoprazole and pantoprazole, although this difference was more marked in esomeprazole, especially when given in double doses. Moreover, new-generation PPIs' efficacy was not affected by CYP2C19 polymorphisms, and they obtained higher eradication rates that first-generation PPIs in EM patients. Therefore, new-generation PPIs might be an interesting option in countries with high proportion of EM patients. However, the cost effectiveness of a general recommendation of using new-generation PPIs has to be confirmed by pharmacoeconomic analysis.

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