Effects of CYP2C19 Loss-of-Function Variants on the Eradication of H. pylori Infection in Patients Treated with Proton Pump Inhibitor-Based Triple Therapy Regimens: A Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: There are inconsistent conclusions about whether CYP2C19 variants could affect H. pylori eradication rate in patients treated with the proton pump inhibitor (PPI)-based therapy. We therefore performed a meta-analysis of randomized clinical trials (RCTs) to re-evaluate the impact of CYP2C19 variants on PPI-based triple therapy for the above indication.

Methods: All relevant RCTs in the PubMed, Cochrane Library, EMBASE, Web of Science and two Chinese databases (up to February 2013) were systematically searched, and a pooled analysis was performed with the odds ratio (OR) and 95% confidence interval (CI) by the STATA software.

Results: Sixteen RCT datasets derived from 3680 patients were included. There was no significant heterogeneity across the data available in this meta-analysis. There were significant differences in that rate between homozygous (HomEMs) and heterozygous (HetEMs) extensive metabolizers (OR 0.724; 95% CI 0.594–0.881), between HomEMs and poor metabolizers (PM) (OR 0.507; 95%CI 0.379–0.679), or between HetEMs and PMs (OR 0.688; 95%CI 0.515–0.920), regardless of the PPI being taken. Furthermore, sub-analysis of individual PPIs was carried out to explore the difference across all the PPIs used. A significantly low rate was seen in HomEMs vs. HetEMs taking either omeprazole (OR 0.329; 95%CI 0.195–0.553) or lansoprazole (OR 0.692; 95%CI 0.485–0.988), and also in HomEMs vs. PMs for omeprazole (OR 0.232; 95%CI 0.105–0.515) or lansoprazole (OR 0.441; 95%CI 0.252–0.771). However, there was no significant difference between HetEMs and PMs taking either one. No significant differences were observed for rabeprazole or esomeprazole across the CYP2C19 genotypes of interest.

Conclusions: Carriage of CYP2C19 loss-of-function variants is associated with increased H. pylori eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen. However, there is no a class effect after use of rabeprazole or esomeprazole.

Introduction

It has been well indicated that Helicobacter pylori (also known as H. pylori) infection is the major risk factor for developing chronic gastritis and peptic ulcer, and is also associated with gastric mucosa-associated lymphoid tissue lymphoma and gastric cancer [1–5]. Eradication of H. pylori infection is recommended to reduce the recurrence of such diseases [6–7]. Current therapy regimens used for the eradication of H. pylori are concomitant use of a proton pump inhibitor (PPI) and two antibacterial agents, leading to an eradication rate of 80–90% [8–9]. Except for the antisecretory property, PPI can also enhance the efficacy of the antibiotics through decreased antibiotic decay within the gastric juice and increased sensitivity of H. pylori to antibiotics [10–11]. At present, several PPIs are mainly marketed for patient care, such as omeprazole, esomeprazole (i.e., the pure S-isomer of omeprazole), lansoprazole, pantoprazole, and rabeprazole. Accumulating evidence has shown that PPIs are mainly metabolized by the cytochrome P450 (CYP) enzymes [in particular CYP2C19] [12–13], and that the phenotype of CYP2C19 is categorized into three groups: extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM). Furthermore, the homozygous EM (HomEM) harbors 2 wild-type alleles (or *1/*1), heterozygous EM (HetEM) carries 1 loss-of-function (LOF) variant allele.
(frequently *2 or *3), and PM has 2 LOF variant alleles (*2/*2, or *2/*3) [14–15]. Because most PPIs are the substrates for CYP2C19, and thus carriers of the CYP2C19 LOF variants would have increased plasma drug concentrations due to impaired drug metabolism in the liver [15], with an exception of rabeprazole whose metabolism is partly CYP2C19-mediated [13,16]. Many clinical trials have been published concerning effect of the CYP2C19 genotypes on the eradication of *H. pylori* by PPI-based triple therapies [17–32]. However, there were conflicting conclusions obtained from the currently available randomized clinical trial (RCT) datasets. Moreover, three meta-analysis studies derived from the RCTs or cohort studies were conducted to evaluate the impact of CYP2C19 variants on the eradication of *H. pylori* in patients treated with PPI-based therapy, but there was less consistency across them [33–35]. In addition, few data were available about pantoprazole and esomeprazole in these meta-analysis studies [33–35]. Although several trials have determined the effect of CYP2C19 genotypes on the efficacy of esomeprazole-based therapy [26,29,31], effect of CYP2C19 genotypes in most RCTs was not observed. In line of the fact that there may be a class effect in CYP2C19-dependent PPI metabolism and that RCTs are the gold standard to determine the clinical efficacy and outcomes of a drug that goes to the market, it is necessary to systematically summarize and evaluate the influence of CYP2C19 variants on all PPI-based triple therapy regimens for *H. pylori* eradication, based on the results from RCTs.

### Methods

#### Search Strategy

All relevant information was retrieved up to February 2013 by search of the PubMed, EMBASE, the Cochrane Register of Controlled Trials (CENTRAL), ISI Web of Science, and two Chinese databases (CNKI, and Wanfang) for English and Chinese studies that evaluated the effects of CYP2C19 polymorphism on the eradication of *H. pylori* based on PPI-based triple therapy. The search strategy – ‘[(Helicobacter OR Helicobacter pylori OR Helicobacter infection) AND (proton pump inhibitor OR PPI OR omeprazole OR lansoprazole OR rabeprazole OR esomeprazole OR pantoprazole) AND (CYP2C19 OR cytochrome P450)]’ – was used [33]. The search was conducted without language restriction. In addition, the references listed in the retrieved articles and reviews were searched manually. For the missing data, the authors were contacted for detailed information. This meta-analysis was conducted and reported according to the checklists of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [36].

#### Study Selection

For the meta-analysis, all articles had to meet the following inclusion criteria: (1) at least one arm of triple PPI-based therapy for 7–14 days; (2) patients positive for *H. pylori* infection prior to treatment; (3) patients naive to therapy and genotyped for CYP2C19, such as PM, HomEM, and HetEM; and (4) RCTs. Duplicate publications or studies published only in abstract were excluded. Risk of bias of the RCTs was assessed as “low”, “unclear” or “high” according to the Cochrane risk of bias tool by the following dominions: randomization method, allocation concealment, blinding, incomplete outcome data addressed and selective reporting [37]. According to the above criteria, two reviewers (H-LT and YL) evaluated the article eligibility independently. The final inclusion decision was made based on the pre-specified consensus among the reviewers or consultation with a third reviewer (S-DZ).

### Data Management

Data from all eligible articles were extracted independently by the two reviews (H-LT and YL), and discrepancy in data extraction was solved through the consensus or consulted with a third reviewer (S-DZ). A standardized data extraction form was designed to extract the major items of information, including author (year), basic characteristics of patients, treatment regimen and the eradication rate of *H. pylori* for PM, HetEM, and HomEM, respectively. In addition, clinical efficacy from the different treatment regimens was also presented in that form.

#### Statistical Analysis

Meta-analysis was performed for each PPI regimen alone or in combination according to the genotype. A sub-analysis for individual PPIs associated with the genotype was undertaken to calculate odds ratio (OR) and 95% confidence intervals (CIs). Heterogeneity test was carried out for each combined analysis, where *p*<0.1 indicated significant heterogeneity across the studies. If heterogeneity was insignificant, data from individual studies were pooled using the fixed-effects model. However, data were also combined by using a random-effects model as a sensitivity analysis to confirm the estimated effect due to the therapies given and the difference in populations across the studies. Funnel plot was used to evaluate publication bias if there were more than ten studies included [38], and bias of each group for the endpoints was not found. All statistics was performed with STATA 10.0 (Lakeway Drive College Station, Texas, USA).

### Results

#### Characteristics of the Articles Included in the Meta-analysis

Overall, 16 RCTs of 1279 citations were considered to meet the inclusion criteria, and included in the meta-analysis (Figure 1). Of them, the number of esomeprazole arm, lansoprazole arm, omeprazole arm, rabeprazole arm was 4, 9, 6 and 13, respectively, totaling 3636 patients. Characteristics and the risk of bias of all included studies are summarized in Table 1. One lansoprazole arm was derived from Isomoto et al [19], which compared lansoprazole-based triple therapy with lutfidine-based triple therapy. Various doses of esomeprazole evaluated in the trial by Pan et al [31] were included in the sub-analysis of combined data on esomeprazole. The study by Furuta et al [27] (which evaluated doses of lansoprazole based on the CYP2C19 genotype) was also included in our meta-analysis. As shown in each trial, no significant difference in the eradication rate was observed among these PPIs.

#### Effects of CYP2C19 Genotypes on the Overall Efficacy of All PPI-based Triple Therapies

All PPI-based triple therapies, regardless of the doses and antibiotics used, were combined in our initial analysis, and a significant difference in *H. pylori* eradication rates was found between the HomEM and HetEM genotype groups as shown in Figure 2 (OR 0.724, 95%CI 0.594–0.881; *p*=0.001), between the HomEM and PM genotype groups (Figure 3, OR 0.507, 95%CI 0.379–0.679; *p*<0.001), or between the HetEM and PM genotype groups (Figure 4, OR 0.688, 95%CI 0.515–0.920; *p*=0.012) with the fixed-effects model, due to no significant heterogeneity across all the studies (all *p*>0.1). In addition, by using a random effects model, a sensitivity analysis showed that results were robust as showed in Figures 2–4.
Effects of CYP2C19 Genotypes on the Efficacy of Individual PPI-based Triple Therapies

Because there was no significant heterogeneity across all the studies (all \( p > 0.1 \)), a fixed effects model was used firstly. Results of the meta-analysis showed that a significant difference existed in the \( H. pylori \) eradication rates with omeprazole-based triple therapy between the HomEM and PM genotypes (OR 0.232, 95% CI 0.105–0.515; \( p < 0.0001 \)), between HomEM and HetEM genotypes (OR 0.329, 95% CI 0.195–0.533; \( p < 0.001 \)), but not between the HetEM and PM genotypes (OR 0.694, 95% CI 0.299–1.608, \( p = 0.394 \)). Similarly, lansoprazole-based triple therapy exhibited a significant difference in the \( H. pylori \) eradication rates between HomEM and PM genotypes (OR 0.441, 95% CI 0.252–0.771; \( p = 0.004 \)), between HomEM and HetEM genotypes (OR 0.692, 95% CI 0.485–0.988, \( p = 0.043 \), but not between HetEM and PM genotypes (OR 0.584, 95% CI 0.333–1.024, \( p = 0.778 \)). Contrary to the above, rabeprazole- or esomeprazole-based triple therapies did not show any significant difference in \( H. pylori \) eradication rates among all three genotypes (Table 2). Furthermore, results of the sub-analysis by a random effects model were in consistency with above results.

Discussion

The results about the effects of CYP2C19 variants on the \( H. pylori \) eradication rate in patients treated with PPI-based triple therapies were controversial across all relevant clinical trials and three published meta-analyses [33–35]. Our findings clearly confirmed that clinical efficacy of PPI-based triple therapies on the eradication rate was influenced by \( CYP2C19 \) genotype status. There was a significant difference in the eradication rate among the three genotypes for some but not all PPI-based triple therapy regimens, such as omeprazole, and lansoprazole. As expected, a higher eradication rate in PMs than in HomEM, in PMs than in HetEM, and in HetEM than in HomEM were observed, suggesting a gene dosage effect on the metabolism of PPIs and also on the eradication of \( H. pylori \), consistent with the conclusions reported by a previously published meta-analysis [34].

Considering the difference among individual PPI-based triple therapies influenced by the \( CYP2C19 \) genotype, sub-analysis of individual PPIs was conducted to explore the effects of \( CYP2C19 \) genotypes on each PPI. Significant differences were observed on the \( H. pylori \) eradication between HomEM and HetEM, between HomEM and PM, but not between HetEM and PM genotypes in patients taking lansoprazole- or omeprazole-based triple therapies. This result may be explained, at least in part, by the observation that omeprazole is a mechanism-based inhibitor of CYP2C19 [39]. The antisecretory activity of omeprazole or lansoprazole is expected to be different between the genotypes of \( CYP2C19 \), and thus, the cure rate of \( H. pylori \) of omeprazole- or lansoprazole-based regimens should be influenced by the \( CYP2C19 \) genotype. Our study showed that patients with PM genotype had a higher cure rate of \( H. pylori \) than those with HomEM genotype by about 80% and 60% in those taking omeprazole and lansoprazole, respectively, suggesting that patients with HomEM genotype may need to take a higher-than-standard dose of omeprazole or lansoprazole. The meta-analysis by McNicholl et al. showed that non-CYP2C19 metabolized PPIs (such as rabeprazole or esomeprazole) could achieve a higher cure rate of \( H. pylori \) in patients with EMs than CYP2C19 metabolized PPIs (such as omeprazole or lansoprazole) [35]. Therefore, it is necessary to use higher dose of omeprazole or lansoprazole or non-CYP2C19-metabolized PPIs such as rabeprazole, in order to minimize or even avoid the effect of \( CYP2C19 \) genotypes.

Similar to most studies, no significant association was observed between \( CYP2C19 \) genotypes and \( H. pylori \) eradication rates in patients taking rabeprazole- or esomeprazole-based triple therapies [29,40]. Previous studies have confirmed that esomeprazole is metabolized, to a less content, by CYP2C19 than omeprazole [41], because esomeprazole is a pure 5S-isomer of omeprazole, which is different from omeprazole composed of the equal amount of R- and S-isomer. The proportion of the S-isomer metabolized via CYP2C19 is less than that of the R-isomer, resulting in less interindividual variation in plasma drug concentrations than omeprazole [42]. Our meta-analysis results suggest that esomeprazole is not significantly affected by the \( CYP2C19 \) genotype, and that influence of small sample sizes in individual studies seems to be less important as expected. Similarly, rabeprazole is metabolized to thioether-rabeprazole mainly via a non-enzymatic pathway, with minor involvement of CYP2C19 [43], consistent with the results derived from our meta-analysis. Thus, esomeprazole- or rabeprazole-based triple therapies with the standard dose can be used to eradicate \( H. pylori \) infection for all patients, without need in considering the status of \( CYP2C19 \) polymorphisms. However, in terms of the fact that the sample size of most clinical investigations was small, it was not observed that carriage of different \( CYP2C19 \) genotypes is not associated with the eradication rate of the \( H. pylori \) infection in patients treated with PPI-based triple therapies. Our meta-analysis overcame the limitation of power by pooling such studies. Except for the \( CYP2C19 \) genotype, antibiotic resistance, and interleukin (IL)-1B genotype may play an important role in affecting the eradication rates. For example, when nitroimidazole/clarithromycin resistance was
Table 1. Characteristics of the included studies and summary of the eradication rates.

| Study    | N    | Basic character of patients                                                                 | Treatment regimen                  | Eradication Rate (n/N) | CYP2C19 | Efficacy | Risk of bias |
|----------|------|---------------------------------------------------------------------------------------------|-----------------------------------|------------------------|---------|---------|--------------|
|          |      |                                                                                             | HomEM | HetEM | PM |       |                 |
| Dojo 2001| 170  | Japanese H. pylori-positive chronic gastritis; M/F:87/83; age: 43 ± 0.6 yr                   | OAC (20 mg bid);                  | 22/30                  | 31/36   | 17/20   | n/a           | No           | Unclear      |
|          |      |                                                                                             | RAC (20 mg bid)                   | 17/21                  | 34/41   | 14/16   | n/a           |              |              |
| Inaba 2002| 183  | Japanese H. pylori-positive peptic ulcer disease; M/F:142/41; age: 20–83 yr                  | OAC (20 mg bid);                  | 16/21                  | 24/27   | 9/10    | n/a           | No           | Low          |
|          |      |                                                                                             | RAC (20 mg bid)                   | 18/20                  | 26/29   | 8/9     | Yes           |              |              |
|          |      |                                                                                             | LAC (30 mg bid)                   | 15/24                  | 27/31   | 7/8     | n/a           |              |              |
| Isomoto 2003| 122 | Japanese H. pylori-positive peptic ulcer or nonulcer dyspepsia; M/F:90/32; age: 52.1 (21–79) yr | LAC (30 mg bid)                   | 16/21                  | 22/28   | 11/12   | n/a           | No           | Unclear      |
|          |      |                                                                                             | Lafutidine-AC                     | 18/21                  | 27/34   | 7/9     | n/a           |              |              |
| Kawabata 2003| 187 | Japanese H. pylori-positive peptic ulcer disease; M/F:138/49; age: 52 (20–78) yr            | RAC (20 mg bid)                   | 26/30                  | 45/53   | 6/10    | Yes           | No           | Unclear      |
|          |      |                                                                                             | LAC (30 mg bid)                   | 24/33                  | 26/35   | 10/12   | Yes           |              |              |
| Miki 2003 | 145  | Japanese H. pylori-positive gastritis or peptic ulcers; M/F:113/32; age: 48.9 ± 17.3 yr       | RAC (20 mg bid)                   | 11/13                  | 23/26   | 5/6     | n/a           | No           | High         |
|          |      |                                                                                             | RAC (10 mg bid)                   | 18/19                  | 18/20   | 5/7     | n/a           |              |              |
|          |      |                                                                                             | LAC (30 mg bid)                   | 10/12                  | 22/26   | 7/9     | n/a           |              |              |
| Take 2003| 249  | Japanese H. pylori-positive peptic ulcer disease; M/F: 219/30; age: 48.7 ± 7.2 yr            | OAC (20 mg bid);                  | 56/72                  | 93/119  | 36/40   | n/a           | No           | High         |
|          |      |                                                                                             | RAC (20 mg bid)                   |                         |         |         |               |              |              |
|          |      |                                                                                             | LAC (30 mg bid)                   |                         |         |         |               |              |              |
| Okudaira 2005| 177 | Japanese H. pylori-positive gastritis or peptic ulcers; age: 44 yr                           | LACFa (30 mg bid)                 | 29/34                  | 35/41   | 11/11   | n/a           | Yes          | High         |
|          |      |                                                                                             | LAC (30 mg bid)                   | 22/35                  | 40/46   | 6/6     | Yes           |              |              |
| Furuta 2007| 300 | Japanese H. pylori-positive gastritis or peptic ulcers; M/F:192/108; age: 60 (17–69) yr     | LAC (CYP2C19- based)              | 54/54                  | 69/73   | 21/23   | n/a           | Yes          | Low          |
|          |      |                                                                                             | LAC (30 mg bid)                   | 30/52                  | 53/74   | 22/24   | Yes           |              |              |
| Kuwayama 2007| 479 | Japanese H. pylori-positive gastritis or peptic ulcers; M/F:331/128; age: 50 yr              | RAC (10 mg bid)                   | 33/39                  | 53/63   | 16/17   | n/a           | No           | Unclear      |
|          |      |                                                                                             | RAC (10 mg bid)                   | 28/32                  | 51/58   | 18/19   |               |              |              |
|          |      |                                                                                             | RAC (20 mg bid)                   | 30/36                  | 56/60   | 20/20   |               |              |              |
|          |      |                                                                                             | RAC (20 mg bid)                   | 37/42                  | 44/49   | 23/24   |               |              |              |
| He 2004 | 128  | Chinese H. pylori-positive gastritis or peptic ulcers; M/F:68/60; age: 48.3 ± 15.6 yr        | RAC (10 mg bid)                   | 28/35                  | 45/57   | 19/23   | n/a           | Yes          | High         |
|          |      |                                                                                             | RAM (10 mg bid)                   | 19/23                  | 38/45   | 10/10   | n/a           | No           | High         |
| Jiang 2004| 169  | Chinese H. pylori-positive gastritis; M/F:101/68; age: 41 yr                                 | RAC (10 mg bid)                   | 19/23                  | 38/45   | 10/10   | n/a           | No           | High         |
| Study | N | Basic character of patients | Treatment regimen | Eradication Rate (n/N) | Risk of bias |
|-------|---|-----------------------------|-------------------|-----------------------|-------------|
|       |   |                             |                   | HomEM | HetEM | PM | CYP2C19<sup>a</sup> | Efficacy<sup>b</sup> |
|       |   |                             | OAC (20 mg bid)   |       |       |    |                     |                        |
| Sheu 2005 | 200 | Chinese H. pylori-positive gastritis or peptic ulcers; M/F:101/99; age: 41 yr | 17/30 | 35/40 | 11/12 | Yes |                      |                        |
|         |   |                             | EAC (40 mg bid)   |       |       |    |                     |                        |
| Zhang 2009 | 240 | Chinese H. pylori-positive gastritis or peptic ulcers; M/F:181/59; age: 18–70 yr | 32/36 | 27/30 | 21/22 | Yes | No               | Unclear               |
| Pan 2010    | 184 | Chinese H. pylori-positive gastritis or peptic ulcers; M/F:85/99; age: 44 yr | 16/19 | 27/21 | 11/14 | n/a | No               | Unclear               |
| Zhang 2010 | 240 | Chinese H. pylori-positive peptic ulcer disease; M/F:194/46; age: 45.2±14.2 yr | 33/34 | 50/59 | 20/22 | n/a | No               | High                  |
| Lee 2010 | 463 | Korean H. pylori-positive peptic ulcer disease, post-endoscopic mucosal resection of gastric cancer or adenoma, not ulcer dyspepsia; M/F:276/187; age: 54 yr | 59/86 | 81/111 | 23/32 | n/a | No               | High                  |

O, omeprazole; L, lansoprazole; R, rabeprazole; E, esomeprazole; A, amoxicillin; C, clarithromycin; M, metronidazole; Fa, famotidine; Le, levofloxacin; HomEM, homozygous extensive metabolizers; HetEM, heterozygous extensive metabolizers; PM, poor metabolizer; ITT, intent-to-treat; M, male; F, female. Year, yr; n/a, not available. <sup>a</sup> Effect by the CYP2C19 genotype; <sup>b</sup> Effect between randomized groups.

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### Figure 2. Forest plot of RCTs comparing HomEMs vs. HetEM in relation to *H. pylori* eradication rate of all PPI-based triple therapies.

![Forest plot](image1)

**Study** | **OR (95% CI)** | **Events, HomEM** | **Events, HetEM**
--- | --- | --- | ---
Dojo 2001 | 0.60 (0.25, 1.47) | 39/51 | 65/77
Inaba 2002 | 0.40 (0.17, 0.95) | 49/65 | 77/87
Isomoto 2003 | 0.87 (0.23, 3.37) | 16/21 | 22/28
Kawabata 2003 | 1.06 (0.48, 2.34) | 50/63 | 69/88
Miki 2003 | 1.11 (0.35, 3.57) | 39/44 | 63/72
Take 2003 | 0.98 (0.48, 1.98) | 56/72 | 93/119
He 2004 | 1.07 (0.38, 3.03) | 28/35 | 45/57
Jiang 2004 | 0.35 (0.15, 0.81) | 36/53 | 73/85
Okudaia 2005 | 0.45 (0.20, 1.02) | 51/69 | 75/87
Sheu 2005 | 0.49 (0.16, 1.46) | 70/83 | 55/60
Furuta 2007 | 0.78 (0.41, 1.48) | 84/106 | 122/147
Kuwayama 2007 | 0.78 (0.42, 1.44) | 128/149 | 204/230
Zhang 2009 | 0.62 (0.21, 1.83) | 62/71 | 67/73
Lee 2010 | 0.76 (0.48, 1.19) | 122/171 | 168/219
Pan 2010 | 1.00 (0.38, 2.65) | 41/50 | 50/61
Zhang 2010 | 0.96 (0.39, 2.35) | 61/70 | 99/113
I–V Overall (I–squared = 0.0%, p = 0.784) | 0.72 (0.59, 0.88) | 932/1173 | 1347/1603
D+L Overall | 0.72 (0.59, 0.88) | 0.72 (0.59, 0.88) |

Figure 2. Forest plot of RCTs comparing HomEMs vs. HetEM in relation to *H. pylori* eradication rate of all PPI-based triple therapies.
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### Figure 3. Forest plot of RCTs comparing HomEMs vs. PM in relation to *H. pylori* eradication rate of all PPI-based triple therapies.

![Forest plot](image2)

**Study** | **OR (95% CI)** | **Events, HomEM** | **Events, PM**
--- | --- | --- | ---
Dojo 2001 | 0.52 (0.17, 1.65) | 39/51 | 31/36
Inaba 2002 | 0.38 (0.10, 1.44) | 49/65 | 24/27
Isomoto 2003 | 0.29 (0.03, 2.84) | 16/21 | 11/12
Kawabata 2003 | 1.44 (0.47, 4.42) | 50/63 | 16/22
Miki 2003 | 2.29 (0.59, 8.98) | 39/44 | 17/22
Take 2003 | 0.39 (0.12, 1.26) | 56/72 | 36/40
He 2004 | 0.84 (0.22, 3.28) | 28/35 | 19/23
Jiang 2004 | 0.10 (0.01, 0.81) | 36/53 | 21/22
Okudaia 2005 | 0.08 (0.00, 1.39) | 51/69 | 17/17
Sheu 2005 | 0.27 (0.06, 1.25) | 70/83 | 40/42
Furuta 2007 | 0.36 (0.12, 1.10) | 84/106 | 43/47
Kuwayama 2007 | 0.24 (0.07, 0.82) | 128/149 | 77/80
Zhang 2009 | 0.86 (0.32, 2.30) | 62/71 | 72/81
Lee 2010 | 0.64 (0.33, 1.24) | 122/171 | 59/73
Pan 2010 | 0.57 (0.16, 2.02) | 41/50 | 32/36
Zhang 2010 | 0.54 (0.14, 2.10) | 61/70 | 38/41
I–V Overall (I–squared = 10.9%, p = 0.059) | 0.56 (0.41, 0.76) | 932/1173 | 552/621
D+L Overall | 0.55 (0.39, 0.77) | 0.55 (0.39, 0.77) |

Figure 3. Forest plot of RCTs comparing HomEMs vs. PM in relation to *H. pylori* eradication rate of all PPI-based triple therapies.
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occurred, the *H. pylori* eradication rate dropped significantly in patients treated with most PPI-based triple therapy regimens [44–45]. IL-1ß genotype was considered to influence the cure rate of PPI-based eradication therapy for *H. pylori*, by affecting gastric acid secretion [46–47]. However, effect of IL-1ß genotype on *H. pylori* eradication was still controversial [22,32,48–49]. It is necessary to evaluate the effect of these factors on the *H. pylori* eradication by PPI-based therapy.

Our results were in agreement with that from meta-analysis of the observational trials by Zhao et al [34]. However, effect of the CYP2C19 genotype on pantoprazole is not evaluated in our meta-analysis, due to limited randomized trials available. A non-randomized trial showed that CYP2C19 genotype might affect the efficacy of *H. pylori* eradication in peptic ulcer patients treated with pantoprazole [49]. Different from above-mentioned meta-analysis performed for clinical observational studies [33–34], only RCTs were included in our meta-analysis, because RCTs can minimize the influence of various confounding factors or bias on clinical efficacy of that therapy strategy for that indication. However, in our meta-analysis, individual PPIs were pooled without considering the dose, duration of therapy and the type of antibiotic agents, resulting in some confounders for CYP2C19 phenotypes and the eradication rates of PPI-based therapy. Therefore, it may not be extended well to clinical practice. However, no significant heterogeneity and publication bias were found in our meta-analysis, suggesting that our conclusions seem to be reasonable.

In summary, the CYP2C19 variant carriage is the major determinant of altered *H. pylori* eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen. In contrast, the CYP2C19 polymorphism has less effect on that eradication rate after use of rabeprazole or esomeprazole. Choice of different PPIs and/or doses should be individualized based on the pharmacogenetics background of each patient and pharmacological profile of each drug in the human body.

### Table 2. Effect of CYP2C19 genotypes on the eradication rate of individual PPI-based triple therapies.

| Subgroup   | HomEM vs. HetEM | HomEM vs. PM | HetEM vs. PM |
|------------|-----------------|--------------|--------------|
|            | N    | OR (95% CI) | sig | Het | N    | OR (95% CI) | sig | N    | OR (95% CI) | sig |
| Omeprazole | 435   | 0.329 (0.195–0.553), P = 0.000 | 0.945 | 296   | 0.232 (0.105–0.515), P = 0.001 | 0.890 | 343   | 0.694 (0.299–1.608), P = 0.394 | 0.986 |
| Lansoprazole | 806   | 0.692 (0.485–0.988), P = 0.043 | 0.540 | 493   | 0.441 (0.252–0.771), P = 0.004 | 0.275 | 607   | 0.584 (0.333–1.024), P = 0.060 | 0.778 |
| Esomeprazole | 232   | 1.000 (0.410–2.437), P = 0.999 | 0.185 | 177   | 0.623 (0.200–1.942), P = 0.414 | 0.426 | 193   | 0.642 (0.209–1.975), P = 0.440 | 0.973 |
| Rabeprazole | 1055  | 0.931 (0.669–1.294), P = 0.669 | 0.396 | 623   | 0.769 (0.477–1.238), P = 0.279 | 0.303 | 842   | 0.778 (0.491–1.232), P = 0.264 | 0.716 |

Data were presented with odds ratio (OR) and 95% CI; sig, significance; Het, heterogeneity test.

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Figure 4. Forest plot of RCTs comparing HetEMs vs. PM in relation to *H. pylori* eradication rate of all PPI-based triple therapies.

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