CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of *Helicobacter pylori*

Objective: **Proton pump inhibitors, metabolized by the polymorphic enzyme cytochrome P450 (CYP) 2C19, are essential drugs for *Helicobacter pylori* eradication. It was reported that patients with *CYP2C19* wild type in Asia had lower eradication rates. This study tests the hypothesis that *CYP2C19* wild type (*wt/wt*) in white patients is also associated with a higher probability of treatment failure.**

Methods: **This was a cohort study involving 131 *H pylori*–positive white (German) patients treated by quadruple therapy including lansoprazole (30 mg twice daily for 5 days). Eradication success, as well as lansoprazole trough steady-state serum concentrations, was determined according to different *CYP2C19* genotypes.**

Results: **We found 3 homozygous variant patients (2.3%) (*mt/mt*, *CYP2C19*2/*2*), 42 heterozygous patients (32.1%) (*wt/mt*, *CYP2C19*1/*2*), and 86 wild-type individuals (65.6%). Significant differences in eradication success could be found between *wt/wt* patients (80.2%) versus combined *mt/mt* (100%) and *wt/mt* patients (97.8%) ($P < .01$; odds ratio, 10.8 [confidence interval, 1.4-84]), which were associated with corresponding changes in the serum levels of lansoprazole (median, 753 ng/mL for *mt/mt*, 59 ng/mL for *wt/mt*, and 21 ng/mL for *wt/wt*; $P < .001$). Apart from antibiotic resistance, CYP2C19 polymorphism was the most important influencing factor for eradication success on multivariate analysis ($P < .0001$).**

Conclusion: **Eradication rates of *H pylori* highly depend on *CYP2C19* in white patients if standard doses of lansoprazole (30 mg twice daily) are administered within a quadruple regimen. Because *wt/wt* individuals have lower eradication rates and lower serum concentrations of lansoprazole, these patients might benefit from a higher proton pump inhibitor dosage. (Clin Pharmacol Ther 2004;76:201-9.)**

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Helicobacter pylori infection is accepted as a main causal factor in the pathogenesis of chronic gastritis and peptic ulcer disease. Many different *H pylori* eradication regimens have been used for successful ulcer healing and prevention of recurrence.[1,2] However, a large variability in clinical outcome has been observed. Apart from the well-established influence of antibiotic resistance, an impact on eradication was seen to some degree with age, bacterial virulence factors, compliance, and the selected regimen of drugs and their disposition.[3-9]

Actual guidelines recommend triple therapy for eradication of *H pylori* that includes a combination of an antisecretory drug and 2 antibiotics (clarithromycin/amoxicillin or clarithromycin/metronidazole).[10-12] The rationale for this combination is that acid suppression not only contributes to accelerated ulcer healing and improvement in symptoms but also increases the anti-

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Supported by the Robert Bosch Foundation, Stuttgart, Germany.
Received for publication Feb 6, 2004; accepted May 3, 2004.
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0009-9236/$30.00

doi:10.1016/j.clpt.2004.05.002

biotic effectiveness of clarithromycin and, to a lesser extent, that of amoxicillin.[5] Because of their potent and long-lasting acid-inhibitory potential, proton pump inhibitors (PPIs) such as omeprazole, lansoprazole, pantoprazole, and rabeprazole are usually preferred over H_2-receptor antagonists.

The PPI-induced increase in the intragastric pH value depends on the achieved plasma concentrations over time (area under the plasma level–time profile [AUC]), and the AUC itself depends on the applied dosage, bioavailability, and elimination rate of the selected PPI.[5] The elimination of PPIs is accomplished by the hepatic route, and the polymorphically expressed cytochrome P450 (CYP) 2C19 enzyme is mainly involved in the metabolism of omeprazole, lansoprazole, rabeprazole, and pantoprazole.[13] Thus different genotypes of *CYP2C19* will affect the AUC of these PPIs, and as a consequence, it was anticipated that the antisecretory action and the *H pylori* eradication potential might be influenced by enzyme activity of CYP2C19.

Impaired metabolism of PPIs results from allelic variants for *CYP2C19*. The *CYP2C19*2* and **3* alleles are associated with non-CYP2C19 enzyme activity compared with the *CYP2C19* wild-type allele (*CYP2C19*1*), because both variants result in a truncated and inactive enzyme or a truncated protein unable to bind to the heme moiety. Individuals who are carriers of 2 nonfunctional *CYP2C19* alleles are so-called poor metabolizers (PMs). It was calculated that the PM phenotype of CYP2C19 leads to a decline in oral clearance by 85% with lansoprazole, by 86% with omeprazole, and by 84% with pantoprazole.[14,15] The frequency of PMs varies among different racial groups[14]: Lower frequencies were found in white subjects (1.8%-2.8%) and black subjects (3.8%) than in Asian subjects (14.0%-14.3%), especially Japanese populations (21%).[15] Therefore it was not surprising that the first investigations addressing the issue of a CYP2C19-dependent eradication of *H pylori* were performed in Japan.[16] Several studies demonstrated that cure rates of *H pylori* infection were lower in wild-type individuals for *CYP2C19* (*wt/wt*) compared with homozygous variant (*mt/mt*) or heterozygous patients (*mt/wt*).[17-32] However, it is unclear whether these findings are relevant only for Asian patients or for eradication regimens of limited efficacy such as dual therapy (PPI/amoxicillin). Moreover, because in white patients heterozygosity (*mt/wt*) for *CYP2C19* is much more frequent (about 30%) than the homozygous variant (*mt/mt*) genotype (up to 3%), this genotype constellation appears to be clinically very relevant.

Thus far, a CYP2C19-dependent *H pylori* eradication has not yet been adequately addressed in white populations. The aim of this study was to test the hypothesis that CYP2C19 status in white patients is associated with differences in clinical outcome (eradication success) by use of a highly effective quadruple regimen for *H pylori* eradication. In addition, we wanted to clarify whether the genotypic differences of a lansoprazole-based regimen (including the antibiotic combination of amoxicillin, clarithromycin, and metronidazole) are responsible for the weak correlation seen previously between trough steady-state serum concentrations of lansoprazole and eradication success.[33] Furthermore, for the first time, other confounding factors for *H pylori* eradication such as age, smoking, bacterial strain factors, and gastrin and pepsinogen levels were taken into consideration for final analyses.

METHODS

Patients. The cohort study of patients was derived from ambulatory or hospitalized care within the MACLOR study project.[33] The project had been set up to investigate 3 different aspects, as follows: eradication success with different treatment regimens,[33] pharmacokinetics of the drugs used,[9] and evaluation of dyspeptic symptoms and corresponding influencing factors.[34] The general inclusion and exclusion criteria, as well as the results according to different treatment regimens, have been reported previously in detail.[33] Patients infected with *H pylori* and untreated before were randomized according to age, smoking status, and diagnosis to 3 different eradication regimens consisting of a 5-day treatment with 3 antibiotics (1 g amoxicillin twice daily, 250 mg clarithromycin twice daily, and 400 mg metronidazole twice daily) and lansoprazole (30 mg twice daily) or ranitidine (300 mg twice daily) or to the same 3-day antibiotic-lansoprazole combination with a 2-day pretreatment with lansoprazole. Combining the 2 lansoprazole treatment arms together appears to be justified because patients did not differ with regard to all baseline characteristics or final outcome according to the randomized treatment[33] and patients in both treatment arms received lansoprazole for 5 days, irrespective of antibiotics. One hundred thirty-one patients could be included in this analysis, and their clinical characteristics are summarized in Table I.

Ethics. The study protocol was conducted according to the Declaration of Helsinki, approved by the local ethics committee and regulating government authorities, and performed according to Good Clinical Practice guidelines, and all patients gave written informed consent before study entry.

Table I. Prestudy characteristics of patients according to *CYP2C19* genotype distribution

Characteristic	*Wild type*	*Homozygous variant and heterozygous genotype*
No. of patients	86	45
Treatment arm L5 (missing n = 17)	39	28
Treatment arm L3 (missing n = 16)	47	17
Age (y)	56 ± 13	57 ± 19
Sex ratio (M/F) (%)	57	67
BMI (kg/m^2)	26 ± 5	27 ± 4
Creatinine clearance (mL/min)	90 ± 26	89 ± 29
Active peptic ulcer disease (No.)	36	18
Functional dyspepsia (No.)	50	27
History of peptic ulcer disease (%)	50	69
Smoking (%)	32.6	24.4
Alcohol intake (%)	8.1	8.9
Aspirin use (%)	31.4	24.4
NSAID use (%)	14.0	8.9
Gastrin (pg/mL)	121 ± 184	90 ± 84
Pepsinogen I (ng/mL)	151 ± 94	169 ± 105
Anti–*H pylori* titer: IgA	480 ± 411	604 ± 583
Anti–*H pylori* titer: IgG	1862 ± 3076	2486 ± 3591
119-kd Band (Cag-A) (%)	76.7	68.9
35-kd Band (putative Oip-A) (%)	46.5	31.1
Metronidazole resistance (%)	38.5 (n = 26)	20.0 (n = 5)
Clarithromycin resistance (%)	7.7 (n = 26)	0.0 (n = 5)
Amoxicillin trough steady-state serum concentration (μg/mL)	0.51 ± 1.0	0.49 ± 1.0
Clarithromycin trough steady-state serum concentration (μg/mL)	0.60 ± 0.5	0.61 ± 0.4
Metronidazole trough steady-state serum concentration (μg/mL)	6.9 ± 3.4	7.5 ± 4.2

Data are given as mean ± SD unless otherwise stated. Differences between the 2 groups are not significant for all comparisons.
NSAID, Nonsteroidal anti-inflammatory drug; Ig, immunoglobulin.

Variables. Eradication success was determined by the carbon 13 urea breath test performed 1 and 3 months after the end of treatment. Patients were classified as *H pylori*–negative only if the results of these 2 tests were negative. Trough steady-state serum levels of lansoprazole were measured by a specific HPLC assay.[9]

Genomic deoxyribonucleic acid (DNA) was isolated from human serum with the Qiagen MiniKit (Qiagen, Hilden, Germany). Genotyping for *CYP2C19* was performed by use of the predeveloped *Taq*Man Assay-Reagents Allelic Discrimination Kit CYP2C19*2 (Applied Biosystems, Foster City, Calif). The PM phenotype comprises the 2 null alleles *CYP2C19*2* and *3. In several white or European populations (n = 635) the compound heterozygous variant genotype *2/*3* and the homozygous variant genotype *3/*3* have never been found.[15] Only in 1 study investigating omeprazole as a probe drug for CYP2C19 phenotype in Swedish patients was 1 of 22 PM individuals identified to be compound heterozygous for the *CYP2C19*3* allele (*2/*3).[35] Nevertheless, an extremely low frequency for the *CYP2C19*3* allele appears to occur in white patients, because a comprehensive analysis of pooled data in 2712 white patients estimated a *CYP2C19*3* allele frequency of only 0.0004.[14] Therefore in the current study all individuals were genotyped only for the *CYP2C19*2* allele.

Statistical analysis. Data are expressed as originals, median, mean and SD, or 95% confidence interval (CI) if not stated otherwise. For multiple regression analysis, all baseline characteristics were encoded into binary variables; analysis was performed at an entry *P* level of .05 by use of the forward step method. Parametric (*t*) and nonparametric (*U*) tests were used for comparisons of 2 groups (*wt/wt* versus combined *wt/mt* and *mt/mt*) where appropriate. The Fisher exact test was applied for comparison of proportions of patients; the significance between trough steady-state serum concentration values in the 3 groups was tested by use of 1-way ANOVA with Bonferroni correction. Correlations were calculated by use of a nonparametric test; in addition,

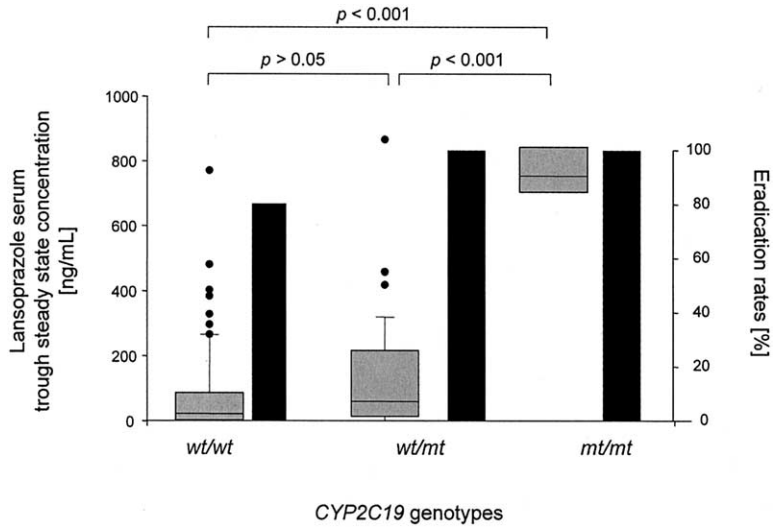

Fig 1. Association of trough steady-state serum concentrations of lansoprazole given as *box-and-whisker plot* and *H pylori* eradication success rates according to 3 different *CYP2C19* genotypes. The eradication rate of the combined genotypes *mt/mt* and *wt/mt* was significantly better (97.8%; odds ratio, 10.8 [95% confidence interval (CI), 1.4-84]; $P < .01$) than in *wt/wt* individuals (80.2%). The *boxes* extend from the 25th to the 75th percentile, with a *line* at the median. *Whiskers above and below the box* indicate the 90th and 10th percentiles. In addition, all outlying points are illustrated.

these correlations were corrected for confounding factors (partial correlations). A statistical P value $< .05$ (2-sided) was considered as significant for all comparisons.

Sample size calculations were performed by use of the data from Furuta et al.[17] At least 126 patients had to be enrolled to detect a 25% or greater difference in eradication success rates (estimated probability, 70% for *wt/wt* and 95% for *mt/mt* and *wt/mt*) based on a power of 90% and a 5% α level of incorrectly rejecting the null hypothesis. Assuming that the genotype distribution between *wt/wt* ("controls") and *mt/mt*/*wt/mt* ("cases") would be based on a 2:1 ratio, we calculated that 42 *mt/mt*/*wt/mt* and 84 *wt/wt* patients would need to be included (corrected chi square and Fisher exact test method for independent cohort). The statistical programs used were Prism 3.0 (GraphPad Software, Inc, San Diego, Calif), SPSS 11.0 (SPSS Inc, Chicago, Ill), and StatsDirect 2.2.10 (StatsDirect Ltd, Cheshire, United Kingdom).

RESULTS

Of 243 patients, 234 had completed the MACLOR eradication trial without protocol violations.[33] Either sera were no longer available or DNA content was insufficient in 41 patients. As a result, in the remaining 193 patients, we found 6 homozygous variant individuals (3.1%) (**2/*2*), 62 heterozygous patients (32.1%) (**1/*2*), and 125 wild-type individuals (64.8%) (**1/*1*). Sixty-two subjects received ranitidine for acid inhibition. From 131 patients, complete data sets consisting of *H pylori* eradication and *CYP2C19* genotype were analyzed and other potential confounding factors were also considered. These had a comparable genotype distribution: 3 patients (2.3%) showed the *CYP2C19*2/*2* genotype, 42 (32.1%) were heterozygous subjects (**1/*2*), and 86 (65.6%) were wild-type individuals (**1/*1*). Consequently, analyzed patients were representative for the entire population initially studied.

Overall eradication success rates (per protocol basis), as reported previously, averaged 89.7%. When the 2 lansoprazole treatment regimens were combined, 113 of 131 patients (86.3%) were cured of *H pylori* infection, and again, these rates were not different from those in the overall population studied. All patients classified as *H pylori*–positive already had a positive ^{13}C-urea breath test result at 1 month after treatment end.

However, if differentiation was done according to *CYP2C19* genotype, important differences in *H pylori* eradication rate could be observed (Fig 1). The combined genotypes *mt/mt* and *wt/mt* had a significantly better clinical outcome (97.8%; odds ratio, 10.8 [95% CI, 1.4-84]; $P < .01$) than *wt/wt* individuals (80.2%).

The absolute difference of 17.6% translates into a number needed to treat (NNT) of 5 to 6 patients.

The Spearman nonparametric correlation coefficient between eradication success and genotype distribution (*wt/wt* versus *mt/mt* and *wt/mt*) was 0.238 ($P = .001$). This correlation remained significant ($r = 0.226$, $P < .01$) after combined adjustment for other potentially influencing factors (age, body mass index, smoking, diagnosis, history of peptic ulcer disease, bacterial strain factors such as 119-kd [Cag-A] and 35-kd [putative Oip-A] bands on immunoblot, creatinine clearance, gastrin, and pepsinogen).

On forward step multiple logistic regression analysis, treatment success was best described by *CYP2C19* genotypes ($P < .0001$), presence of metronidazole resistance ($P = .008$), 35-kd band on immunoblot ($P < .05$), age ($P < .05$), and presence of gastric atrophy as expressed by serum pepsinogen 1 ($P = .05$). It should be noted that in our study population pepsinogen 1 was used as a surrogate marker for gastric atrophy before *H pylori* eradication was started. Thus it is not surprising that we did not find a significant association between pepsinogen 1 levels and variant *CYP2C19* genotypes as described by Sagar et al,[36] because they determined serum pepsinogen 1 levels in patients treated for more than 1 year with omeprazole.

Five patients in the *wt/wt* group and 4 patients in the *wt/mt* group had missing lansoprazole serum measurements. In the remaining 122 patients, trough steady-state serum levels of lansoprazole, even if corrected for body weight, were significantly higher in *mt/mt* and *wt/mt* patients than in wild-type individuals (Fig 1). The corresponding median values were 753 ng/mL (mean, 766 ng/mL; 95% CI, 591-941 ng/mL) for *mt/mt*, 58.5 ng/mL (mean, 135 ng/mL; 95% CI, 77.7-193 ng/mL) for *wt/mt*, and 20.7 ng/mL (mean, 78.1 ng/mL; 95% CI, 48.4-108 ng/mL) for *wt/wt* ($P < .001$ for *wt/wt* versus *mt/mt* and *wt/mt* versus *mt/mt*). Within the wild-type group, there was no significant difference in mean lansoprazole drug levels between patients with versus those without subsequent treatment failure (56.6 ± 93.2 ng/mL [95% CI, 0-119 ng/mL] versus 74 ± 132 ng/mL [95% CI, 42-106 ng/mL]). As demonstrated by Fig 1, the increase in median serum levels of lansoprazole parallels the increase in eradication rates according to the different *CYP2C19* genotypes. Thus, as could be expected, the higher eradication rates observed in *mt/mt* individuals and heterozygous subjects for *CYP2C19* are associated with elevated serum concentrations of lansoprazole.

DISCUSSION

Over the last 10 years, considerable progress has been achieved in the treatment of *H pylori* infection by standard triple therapy for first-line and quadruple therapy for second-line treatment.[11,12] However, even with optimal patient compliance, recommended regimens will usually achieve cure rates in primary care that are well below the satisfactory goal of 90% or greater, and the problem of multiple treatment failures is increasing.[11,12,37,38] For virtually all regimens, acid inhibition is crucial for the enhancement of concomitant antibiotic efficacy,[5] especially in dual therapy. However, even the presence or absence of a PPI in a regimen with bismuth, tetracycline, and metronidazole results in a 10% difference in eradication rates.[6] Therefore PPIs generally represent an essential drug in *H pylori* treatment.

The magnitude of PPI plasma levels achieved (drug exposure) as expressed by the AUC is an important factor in determining the pharmacodynamic action: An increase in the AUC of PPIs is associated with an increase in the intragastric pH value.[5] Because PPIs are mainly eliminated by hepatic metabolism accomplished by the polymorphically expressed CYP2C19, the genotype of this enzyme determines drug exposure and consequently also the achievable increase in intragastric pH.[5,15] Therefore it can be assumed that the *CYP2C19* genotype might affect *H pylori* eradication. Because PMs are much more frequent in Asian populations, this problem has been addressed thus far primarily in Japanese patients. In Fig 2 the relevant studies have been summarized. It is obvious that the more effective the overall regimen, the smaller the difference between homozygous variant or heterozygous patients and wild-type individuals. Therefore marked differences are seen with dual therapy. With the more effective triple therapy, there is approximately a 20% difference in clinical outcome if wild-type and heterozygous patients are compared with subjects who are homozygous variant for *CYP2C19*. However, because the frequency of *mt/mt* and *wt/mt* individuals is much higher in Asian populations, the clinical importance of the CYP2C19 polymorphism for *H pylori* eradication treatment in white populations (North America, Western Europe) has been questioned.

In contrast to a very recent trial from Italy,[18] our study used a highly effective quadruple regimen (overall intention to treat [ITT] eradication rate, 87%). Therefore the observed differences in *H pylori* eradication rates between *wt/wt* and *CYP2C19* variant patients are not due to an insufficient drug combination or to a high impact of antibiotic resistance. Another advantage of our study is that we used only one PPI

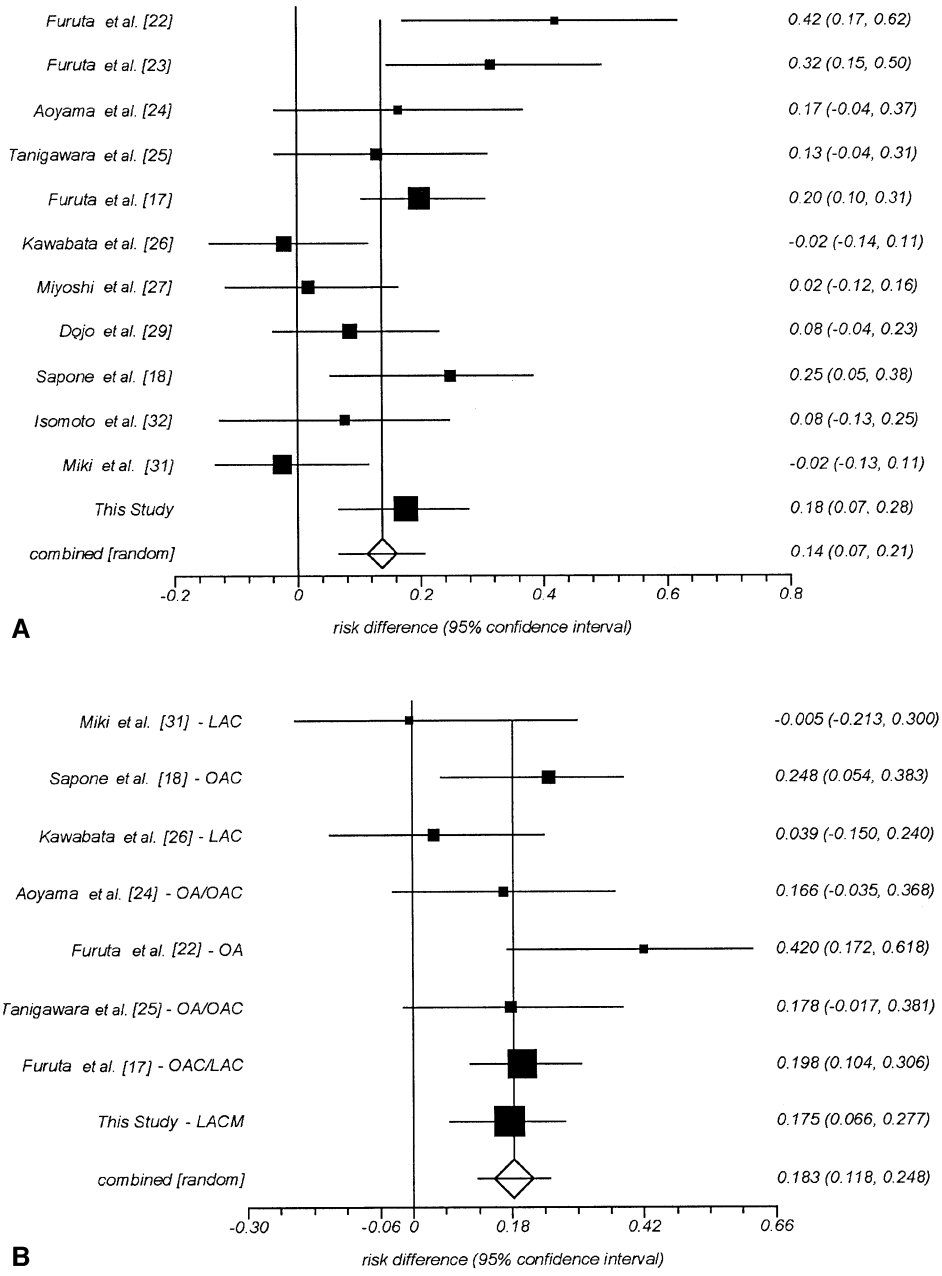

Fig 2. Meta-analysis plot (random effects) of available literature data showing absolute risk differences in eradication outcome between *wt/wt* versus combined *wt/mt* and *mt/mt*. Size of *rectangles* corresponds directly to sample size of study. Significant ($P = .0012$) heterogeneity could be observed by including all studies (**A**). This heterogeneity could be resolved ($P = .227$) by excluding studies with rabeprazole, within either separate or mixed treatment arms. The remaining studies based on omeprazole or lansoprazole are displayed below (**B**). Bias assessment by use of Funnel diagrams was negative for either analysis. In **A**, all studies are shown (including rabeprazole studies): DerSimonian-Laird pooled risk difference, 0.13605; approximate 95% CI, 0.066573 to 0.205526; DerSimonian-Laird $\chi^2 = 14.730435$ ($df = 1$); $P = .0001$. In **B**, omeprazole-lansoprazole studies only are shown: DerSimonian-Laird pooled risk difference, 0.182789; approximate 95% CI, 0.117573 to 0.248004; DerSimonian-Laird $\chi^2 = 30.178348$ ($df = 1$); $P < .0001$. L, Lansoprazole; O, omeprazole; A, amoxicillin; C, clarithromycin; M, metronidazole.

(lansoprazole) and did not include heterogeneous patients from several studies. In addition, all previous studies (Fig 2) did not evaluate other potentially confounding factors, including age, smoking, bacterial strain factors (resistance, toxicity), and gastrin or pepsinogen levels.[33] According to our limited data on antibiotic resistance testing (Table I), this covariable seems to be of similar importance as the *CYP2C19* genotype. On the basis of a variety of data[17-29] that were systematically reviewed[30] and extended by recent publications[31,32] and our current work, it is obvious that the CYP219-dependent eradication rate is of clinical relevance for some PPIs such as omeprazole and lansoprazole. The absolute risk difference between wild-type and homozygous variant patients of around 20% translates into a low NNT of 5 patients (Fig 2).

Such a marked difference and low NNT might also have some clinical consequences for daily practice. It would imply that *CYP2C19* genotyping should be performed before *H pylori* eradication therapy. This polymerase chain reaction–based procedure, although rapid and easy to do, is not yet generally available and currently not reimbursed. However, in the near future, genotyping is expected to be performed with next-day-available results by use of high-throughput gene chips. Major interest of the industry has already led to the development of DNA microarrays comprising up to 39 of the most relevant drug-metabolizing enzyme polymorphisms (eg, *CYP2C9*, *CYP2C19*, *CYP2D6*, *NAT2*, *MDR*) to provide a definite screening profile.[39] In addition, the so-called PPI-gastrin test might offer an alternative "phenotyping" approach.[19] However, it is complicated (PPI test dose, blood sampling, gastrin measurement), gain of information is delayed, and there is a considerable overlap of gastrin values between various groups.

What are the consequences of genotype testing? Whereas patients with the homozygous variant or heterozygous *CYP2C19* genotype will achieve high cure rates when undergoing standard triple therapy with recommended doses of omeprazole, lansoprazole, or pantoprazole, there is a necessity for increasing the daily dose of PPIs in wild-type individuals, who represent about two thirds of white populations. It has been calculated that after oral administration of 20 mg omeprazole the AUC in PMs was almost equal to the AUC after 80 mg in wild-type individuals.[20] Nevertheless, it should be noted that in wild-type individuals additional confounding factors such as age, smoking, bacterial strain factors, and so on may contribute more intensively to *H pylori* eradication success than in *CYP2C19* variant patients. This assumption was corroborated very recently by the observation that the interleukin 1β polymorphism −511 has a much more marked effect as a further important determinant of successful eradication of *H pylori*, especially in patients with *CYP2C19* wild type compared with those with a *CYP2C19* variant genotype.[40]

Besides adaptation of the dose according to the *CYP2C19* genotype, it could be anticipated that selection of a PPI that is partly metabolized by non-CYP2C19 pathways (eg, rabeprazole) might offer an alternative.[41] There are some arguments that in rabeprazole-based regimens the difference between the different *CYP2C19* genotypes is less pronounced.[23,27,29,31] Likewise, it has been suggested that esomeprazole has a slightly different metabolism if compared with omeprazole.[21] However, no clinical data in terms of *CYP2C19* genotype and *H pylori* eradication rates are available. Whether the proposal of *CYP2C19* genotype–guided eradication treatment should be generally recommended remains to be clarified by stratified prospective trials.[30]

In conclusion, we have shown that genotypic differences in *CYP2C19* status affect *H pylori* eradication rates in both white patients and Asian patients if the regimen contains lansoprazole (or any other PPI), which is predominantly metabolized by CYP2C19. Moreover, heterozygous individuals are very similar with regard to clinical outcome compared with that in homozygous variant patients. Furthermore, we could demonstrate that the significantly better clinical outcome in *mt/mt* and *wt/mt* patients was associated with higher plasma concentrations of lansoprazole if compared with those in wild-type patients. Testing for *CYP2C19* genotypes in addition to antibiotic resistance appears to be clinically relevant, because about 20% lower eradication rates must be expected in wild-type patients, who represent two thirds of white populations. In some of these patients, standard doses of certain PPIs might achieve an insufficient level of acid inhibition.

In summary, pharmacogenetically determined (CYP2C19) pharmacokinetics (elimination of PPI) and resulting pharmacodynamics (intragastric pH) affect the clinical outcome of *H pylori* eradication in populations with a lower prevalence of CYP2C19 polymorphisms than previously reported.

The secretarial help of Mrs H. Bonilla-Torres is appreciated.

All authors have no conflict of interest related to the content of this manuscript. No pharmaceutical company was involved in the design, analysis, or interpretation of this study.

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