Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 56, No. 2, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2009.12.071

Cardiovascular Risk in Clopidogrel-Treated Patients According to Cytochrome P450 2C19*2 Loss-of-Function Allele or Proton Pump Inhibitor Coadministration

A Systematic Meta-Analysis

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Objectives The aim of this study was to assess the association between the loss-of-function cytochrome P450 2C19 (CYP2C19)*2 variant (10 studies, 11,959 patients) or the use of proton pump inhibitors (PPIs) (13 studies, 48,674 patients) and ischemic outcomes (major adverse cardiovascular events [MACE]) in patients treated with clopidogrel.

Background In clopidogrel-treated patients, increased cardiovascular risk has been identified with the loss-of-function CYP2C19*2 allele or the use of PPIs, some of them CYP2C19 inhibitors. To further estimate the effect of a reduction in activity of this enzyme, the authors performed a meta-analysis of the studies available.

Methods The meta-analysis was performed on 23 studies using the odds ratio (OR) as the parameter of efficacy, with a fixed-effect model. The end points were MACE, mortality, or stent thrombosis.

Results Of the 11,959 patients, carriers of the loss-of-function CYP2C19*2 allele (28% [n = 3,418]) displayed a 30% increase in the risk for MACE compared with noncarriers (9.7% vs. 7.8%; OR: 1.29; 95% confidence interval [CI]: 1.12 to 1.49; $p < 0.001$). This single gene variant (CYP2C19*2) was also associated with an excess of mortality (1.8% vs. 1.0%; OR: 1.79; 95% CI: 1.10 to 2.91; $p = 0.019$; n = 6,225) and of stent thrombosis (2.9% vs. 0.9%; OR: 3.45; 95% CI: 2.14 to 5.57; $p < 0.001$; n = 4,905). This increased risk was apparent in both heterozygotes and homozygotes and was independent of the baseline cardiovascular risk. PPI users (42% [n = 19,614]) displayed increased risk for MACE (21.8% vs. 16.7%; OR: 1.41; 95% CI: 1.34 to 1.48; $p < 0.001$) and mortality (12.7% vs. 7.4%; OR: 1.18; 95% CI: 1.07 to 1.30; $p < 0.001$; n = 23,977) compared with nonusers. The impact of PPI use was, however, significantly influenced by baseline cardiovascular risk, being significant only in high-risk patients.

Conclusions In this global meta-analysis, reduced CYP2C19 function appears to expose clopidogrel-treated patients to excess cardiovascular risk and mortality. Conflicting results among studies may be explained by differences in types and/or levels of risk of patients. (J Am Coll Cardiol 2010;56:134–43) © 2010 by the American College of Cardiology Foundation

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Manuscript received October 29, 2009; revised manuscript received December 1, 2009, accepted December 17, 2009.

Clopidogrel, with or without aspirin, reduces cardiovascular events in symptomatic vascular patients (1–3). However, there is wide interindividual variability of response to clopidogrel, with poor inhibition of platelet aggregation in some patients (4).

Metabolic activation by cytochrome P450 2C19 (CYP2C19) has emerged as a crucial determinant of clopidogrel pharmacodynamic response and clinical efficacy (5). CYP2C19 is a liver enzyme involved in the metabolic transformation of the prodrug clopidogrel into its active metabolite, which irreversibly binds to the platelet adenosine diphosphate receptor. CYP2C19 metabolic activity is highly variable among patients because of genetic variation. Several gene variants associated with reduced or absent CYP2C19 activity exist, although the CYP2C19*2 allele (or G681A polymorphism) accounts for more than 90% of cases of poor metabolism (6–8). Carriers (approximately 30% of the Caucasian population) of the loss-of-function CYP2C19*2 allele display a reduced pharmacodynamic response to clopidogrel and a higher rate of recurrent cardiovascular events compared with noncarriers (9–16).

CYP2C19 is also inhibited by some proton pump inhibitors (PPI), notably omeprazole and lansoprazole (17). PPIs are often coadministered with clopidogrel to reduce the risk for gastrointestinal tract bleeding. Ex vivo biological studies have suggested that the coadministration of omeprazole or lansoprazole may decrease the antiplatelet effect of clopidogrel, whereas this interaction was not reported with other PPIs, such as pantoprazole or esomeprazole (18–22). These studies suggest that some PPIs may affect the conversion of clopidogrel to its active metabolite by a possible inhibition of CYP2C19, but the exact mechanism of this drug-drug interaction remains to be determined. There is also controversy as to whether the use of PPIs reduces the clinical efficacy of clopidogrel. Several population studies have reported that the use of PPIs increases the risk for cardiac events in clopidogrel-treated patients. Whether a differential effect exists between individual PPIs was unclear. However, the lack of risk adjustment was a limitation of several of these early studies.

Despite the absence of definitive evidence on the magnitude of risk associated with inherited or acquired reduced-function CYP2C19, the labeling of clopidogrel has been recently updated to highlight the potential impact of CYP2C19 alteration on the pharmacodynamic response to clopidogrel and clinical outcomes of clopidogrel-treated patients. Our objective was to perform a quantitative review of the relationship between the reduced-function CYP2C19*2 allele or the use of PPIs and major adverse cardiovascular events (MACE) and mortality in patients with long-term exposure to clopidogrel.

Methods

Eligibility and search strategy. This meta-analysis was performed according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology group. We conducted a systematic search of Medline (1966 to October 1, 2009) and the Cochrane Library (1980 to October 1, 2009) for studies describing the association between adverse outcomes in patients with long-term exposure to clopidogrel therapy and CYP2C19 genetic variants or concomitant use of PPIs. We considered reports published in any language, and we used a search approach described by Egger and Smith (23) to identify both observational studies and studies of prognosis. The search themes were combined using the Boolean operator AND. The first theme was "clopidogrel" and was combined with the following Medical Subject Headings: "cytochrome P450 2C19," "CYP2C19," "proton pump inhibitors," and "proton pumps." In addition, we searched the reference lists of all identified relevant publications. We finally reviewed the abstracts of selected scientific meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics).

Abbreviations and Acronyms

CI = confidence interval
CYP2C19 = cytochrome P450 2C19
MACE = major adverse cardiovascular event(s)
OR = odds ratio
PPI = proton pump inhibitor

Selection criteria. Our primary objective was to determine the specific contribution of the CYP2C19*2 loss-of-function genetic variant and of the use of PPIs to the occurrence of cardiovascular outcomes in patients with established coronary artery disease who were treated with clopidogrel.

Two authors (J.-S.H. and J.-P.C.) identified reports eligible for further review by performing an initial screen of identified abstracts or titles. Reports were considered for inclusion in the systematic review if they reported data from original studies (i.e., no reviews) and reported on the use of clopidogrel in patients. We used broad inclusion criteria for studies, including all indications for clopidogrel therapy. Both reviewers fully agreed on the eligibility of reports in this first screening. The second screening was based on full-text review. To be included, studies could be randomized or cohort studies (prospective cohort or historical cohort) composed of patients with coronary artery disease who were treated with clopidogrel. Studies were selected if they reported on the incidence of MACE or mortality. Studies were excluded if the primary end point was only biological or gastrointestinal safety driven or if there was inappropriate group comparison. Any disagreement was resolved by consensus.

The quality of the observational and case-control studies was assessed using the Newcastle-Ottawa quality assessment scale (24). Briefly, studies were quoted using prespecified items on patients' selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts, and assessment of outcomes (recording, adequacy of follow-up). Ratings for each item were added to provide a study quality score (maximal score, 10). We also corresponded with study investigators to clarify issues.

Data extraction and clinical end points. We extracted details on study and patient characteristics, treatment information, specific outcomes, methods for outcome assessment, and follow-up from the selected studies. These data were extracted independently by 2 of the authors (J.-S.H. and J.-P.C). Any discrepancies between reviewers were resolved by consensus. When both abstracts and publications were available for a single study, only numbers given in the publications were taken into account.

The primary end point was the occurrence of MACE, as defined in each study by the occurrence of death, nonfatal myocardial infarction, stroke, or urgent revascularization. A secondary analysis was performed on mortality, which was defined either as cardiovascular or overall mortality. End points were evaluated at the longest follow-up available. The definition of reinfarction was different in each trial, and we thus decided to use the trial-specific definitions of reinfarction. Definite or definite or probable stent thrombosis according to the definition of the Academic Research Consortium was also evaluated in studies that included patients undergoing percutaneous coronary intervention.

Statistical analysis. The results of each trial were those obtained on an intention-to-treat basis. The meta-analysis was performed using the odds ratio (OR) as the parameter of efficacy with a fixed-effect model (Mantel-Haenszel), with appropriate tests for association and heterogeneity. The p value for significance of association and heterogeneity tests was set at 0.10, as previously suggested (25). Meta-analysis calculation (association test) and heterogeneity were performed using EasyMA software (26). Sensitivity analyses were performed according to the type of publication (abstracts only vs. full-length reports), population size, and study quality (higher than median and median vs. lower than median) (23). The p value for significance was set at 0.05. Potential small study bias and/or publication bias (i.e., the likelihood of small yet nominally significant studies being selectively published) was examined by visual inspection of constructed "funnel plot" and analytically with Egger's test (27). Egger's method plots linearly the standard normal deviate (natural logarithm of the relative risk/SE of the relative risk) and precision (1/SE of the relative risk) as independent variable, with test results based on the p value of the regression constant. We also investigated relationships according to the effect model analysis described by Walter. Briefly, the annual MACE rates in PPI users and nonusers were plotted for each study. A weighted regression analysis was then performed providing estimates of the regression line slope and the intercept.

This meta-analysis was performed according to the Quality of Reporting of Meta-Analyses guidelines (28).

Results

Search results. Our search yielded a total of 100 potentially relevant studies (Fig. 1). No previous meta-analyses were identified. A total of 23 studies, 10 on the impact of the reduced-function CYP2C19*2 genetic variant for a total of 11,959 participants (9–11,13–16,29–31) and 13 on the impact of PPI coadministration for a total of 48,674 participants (9,15,32–42), were selected. Eighteen studies were observational studies from prospective or retrospective registries, and 5 provided reanalyzed data from randomized clinical trials (Table 1). A total of 21 studies (10 of the CYP2C19*2 genetic variant and 11 of PPIs) provided data for the occurrence of MACE, and 12 provided specific data on mortality (9–11,13–16,29,30). Stent thrombosis was reported in 4 studies (10,11,14,15).

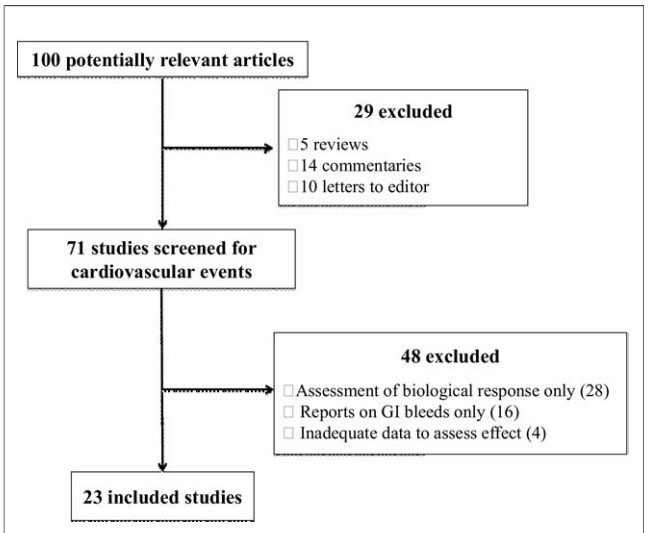

Figure 1 Flow Diagram of the Systematic Overview Process

GI = gastrointestinal.

MACE and stent thrombosis. Our pooled data from the 10 studies investigating the influence of CYP2C19 genetic variants (n = 11,959) showed that carriers of the CYP2C19*2 loss-of-function allele (28% [n = 3,418]) displayed a significant increase in the rate of MACE compared with noncarriers (n = 331 of 3,418 [9.7%] vs. n = 672 of 8,541 [7.8%]; OR: 1.29; 95% confidence interval [CI]: 1.12 to 1.49; $p < 0.001$) (Fig. 2). There was evidence of statistical heterogeneity among the included studies (chi-square, p for heterogeneity = 0.003).

There was a 3-fold increase in the rate of definite or probable stent thrombosis in carriers of the CYP2C19*2 loss-of-function allele who underwent stent implantation compared with noncarriers (n = 41 of 1,375 [2.9%] vs. n = 30 of 3,530 [0.9%]; OR: 3.45; 95% CI: 2.14 to 5.57; $p < 0.001$; p for heterogeneity = 0.78) (Fig. 3). A similar effect (OR: 3.79; 95% CI: 1.99 to 7.22; $p < 0.001$) was observed when restricting the analysis to definite stent thrombosis only. The majority of stent thrombosis was subacute (47 of 71) and occurred within the first 30 days of stent implantation. A publication bias was observed by visual analysis of the funnel plot and by the mathematical estimate of the asymmetry of this plot provided by a linear regression

Table 1 Characteristics of the Studies Included in the Meta-Analysis

Source	No. of Participants With Available Data*	Mean Follow-Up (yrs)	Study Type	Outcomes	No. of Events for Each Outcome	Quality Score†
CYP2C19 genetic variants						
Trenk et al. (2008) (29)	797	1	Cohort	MACE (death/MI)	24	9
Simon et al. (2009) (9)	2,178	1	Cohort	MACE (death/MI/stroke)	288	8
Mega et al. (2009) (11)	1,459	1.23	Post hoc analysis of RCT	MACE (death/MI/stroke) Death	129 12	9
Collet et al. (2009) (15)	259	2.7	Cohort	MACE (death/MI/revascularization) Death	26 3	9
Giusti et al. (2009) (14)	772	0.5	Cohort	MACE (death/MI) Death	29 18	9
Sibbing et al. (2009) (10)	2,485	0.08	Cohort	MACE (death/MI/stroke) Death	177 21	9
Anderson et al. (2009) (16)	1,250	1	Cohort	MACE (death/MI) Death	137 24	8
Shuldiner et al. (2009) (13)	227	1	Cohort	MACE (death/MI)	30	9
Worrall et al. (2009) (30)	104	1	Cohort	MACE	10	7
Bhatt (2009) (31)	2,428	2.3	Post-hoc analysis of RCT	MACE (death/MI/stroke)	153	9
PPIs						
Ho et al. (2009) (32)	8,205	1.43	Cohort	MACE (death/MI) Death	2,176 1,535	9
Simon et al. (2009) (9)	2,208	1	Cohort	MACE (death/MI/stroke)	294	8
Aubert et al. (2009) (37)	16,690	1	Cohort	MACE (death/MI/stroke)	3,479	6
Collet et al. (2009) (15)	259	2.7	Cohort	MACE (death/MI/revascularization) Death	26 3	9
Dunn et al. (2008) (36)	1,053	1	Post-hoc analysis of RCT	MACE (death/MI/stroke)	89	8
Ramirez et al. (2009) (34)	535	1	Cohort	MACE (death/MI/revascularization) Death	47 27	7
Tsiaousis et al. (2009) (33)	612	1	Cohort	Death	21	6
Juurlink et al. (2009) (35)	5,546	1	Nested case-control	MACE (death/MI) Death	1,513 531	5
Banerjee et al. (2009) (39)	197	1.6	Cohort	MACE (death/MI/revascularization/stroke)	90	8
Gaspar et al. (2009) (40)	922	0.5	Cohort	MACE (death/MI/revascularization)	78	5
Sarafoff et al. (2009) (41)	2,025	0.08	Cohort	Death	20	6
O'Donoghue et al. (2009) (38)	6,795	1.23	Post-hoc analysis of RCT	MACE (death/MI/stroke) Death	781 150	9
Bhatt (2009) (42)	3,627	0.36	Post-hoc analysis of RCT	MACE (death/MI/stroke)	136	9

*Participants classified as CYP2C19*2 carriers or noncarriers or as PPI users or nonusers. †The quality score was determined according to The Newcastle-Ottawa Scale for cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Each study was awarded a maximum of 1 star for each numbered item within the selection (4 items), comparability (2 items), and outcome (3 items) categories. Two independents reviewers performed the Newcastle-Ottawa Scale grading. Discrepancies were solved by a third independent reviewer.

CYP2C19 = cytochrome P450 2C19; MACE = major adverse cardiovascular event; MI = myocardial infarction; PPI = proton pump inhibitor; RCT = randomized controlled trial.

approach. The intercept of the regression line did deviate significantly from zero ($p = 0.02$).

The relative contribution of heterozygotes and homozygotes could be evaluated in 4 of the studies representing a total of 5,694 of 11,959 patients (9,10,14,15). There was a 1.59-fold (95% CI: 0.88 to 2.88) increased risk in heterozygotes and a 2.05-fold (95% CI: 1.15 to 3.63) increased risk in homozygotes for MACE. The risk for stent thrombosis was more than 3-fold higher in heterozygotes (2.94% vs. 0.87%; OR: 3.34; 95% CI: 1.84 to 5.93) and more than 4-fold higher in homozygotes (4.87% vs. 0.87%; OR: 4.68; 95% CI: 1.55 to 14.11) compared with carriers.

The pooled data for PPI coadministration showed that PPI users (42% [n = 19,614]) displayed an increased risk for MACE compared with nonusers (n = 4,285 of 19,614 [21.8%] vs. n = 4,424 of 26,423 [16.7%]; OR: 1.41; 95% CI: 1.34 to 1.48; $p < 0.001$). There was evidence of statistical heterogeneity among the included studies (chi-square, $p < 0.001$) (Fig. 2). When analyzing individual PPIs, we found that omeprazole was the most frequently prescribed PPI (50.3%), followed by pantoprazole (19.8%) and esomeprazole (19.3%). Rabeprazole and lansoprazole were prescribed in small portions of patients. In 4 studies, we were able to isolate data on the risk associated with omeprazole intake. We found that compared with PPI nonusers, omeprazole users displayed a significantly higher risk for MACE (n = 1,597 of 8,392 [19.0%] vs. n = 2,532 of 15,246 [16.6%]; OR: 1.37; 95% CI: 1.27 to 1.47; $p < 0.001$).

When combining all data (n = 55,529), we found that clopidogrel-treated patients who presented with putative CYP2C19 deficits due to carriage of the CYP2C19*2 loss-of-function allele or drug-drug interaction with PPIs had a 42% increase in the risk for MACE occurrence (OR:

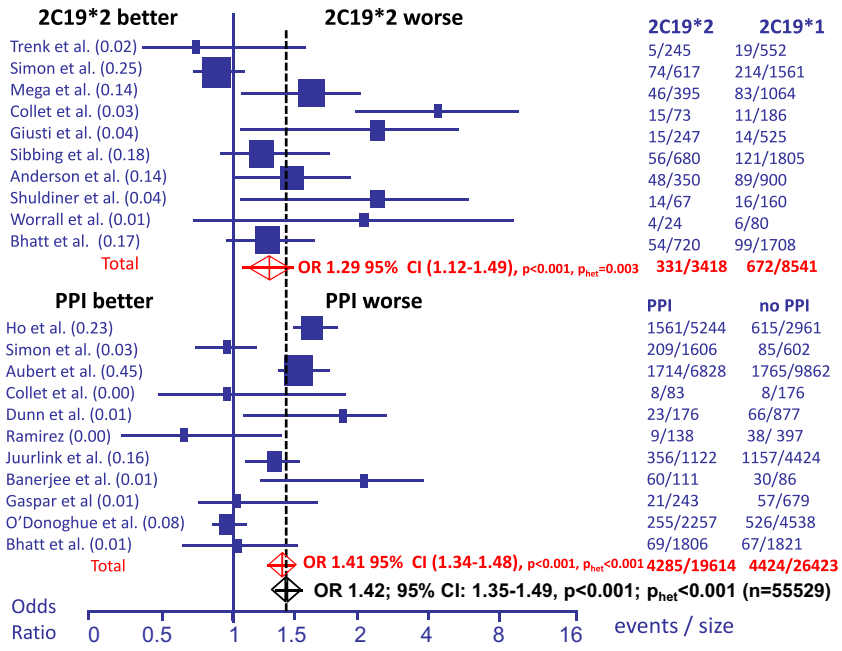

Figure 2 **ORs for MACE According to CYP2C19*2 Allele (n = 11,959) and PPI Use (n = 46,037)**

The incidence of major adverse cardiovascular events (MACE) was higher among carriers of the cytochrome P450 2C19 (CYP2C19)*2 reduced-function allele and in users of proton pump inhibitors (PPIs). The analysis for heterogeneity was significant for both analyses (p = 0.003 and p < 0.001, respectively). CI = confidence interval; OR = odds ratio.

1.42; 95% CI: 1.35 to 1.49; p < 0.001) (Fig. 2). For this pooled analysis, data from TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) were obtained from the original genetic analysis (11). Data from the PPI analysis led to a similar trend (OR: 1.43; 95% CI: 1.36 to 1.50; p < 0.001; n = 48,015) (38).

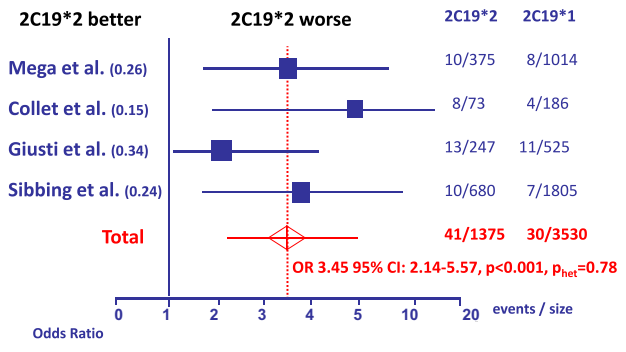

Figure 3 **ORs for Stent Thrombosis (n = 4,905) According to CYP2C19*2 Allele**

The incidence of stent thrombosis was higher among carriers of the CYP2C19*2 reduced-function allele. The analysis for heterogeneity was not significant. Data were not available in the studies of proton pump inhibitors. OR, fixed model, bilateral CI, 95% for trials, 95% for meta-analysis. Abbreviations as in Figure 2.

Mortality. Data on mortality were extracted from 5 studies evaluating the effect of the CYP2C19*2 genetic variant and from 7 studies looking at the impact of PPI coadministration. Carriage of the CYP2C19*2 gene variant was associated with an excess of all-cause mortality (n = 32 of 1,745 [1.8%] vs. n = 46 of 4,480 [1.0%]; OR: 1.79; 95% CI: 1.10 to 2.91; p = 0.019; p for heterogeneity = 0.063). Similar results were observed on cardiovascular mortality. We also observed an excess of mortality in PPI users compared with nonusers (n = 1,228 of 9,644 [12.7%] vs. n = 1,059 of 14,333 [7.4%]; OR: 1.18; 95% CI: 1.07 to 1.30; p < 0.001; p for heterogeneity = 0.13). There was no evidence of heterogeneity among the included trials. Finally, when combining all data, we also found that clopidogrel-treated patients who presented with putative CYP2C19 deficits due to carriage of the CYP2C19*2 loss-of-function allele or drug-drug interaction with PPIs had a 20% increased risk for death (OR: 1.20; 95% CI: 1.09 to 1.32; p < 0.001; p for heterogeneity = 0.021) (Fig. 4). No publication biases were observed either for carriage of CYP2C19*2 or PPI use alone or combined both on funnel plot inspection and Egger's test.

Sensitivity analyses. The random-effect analyses of MACE and mortality yielded effect sizes that were similar in magnitude and direction to those obtained with the fixed-effect analyses (Online Table 1). The results of the sensitivity analyses to assess the influence of the status of publication, sample size, and study quality on the impact of CYP2C19*2

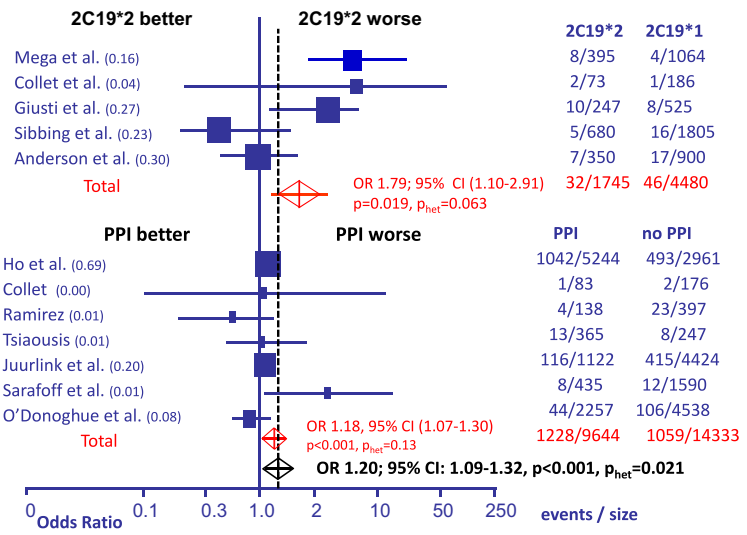

Figure 4 **ORs for Death According to CYP2C19*2 Allele (n = 6,225) and PPI Use (n = 23,977)**

The incidence of death was higher among carriers of the CYP2C19*2 reduced-function allele and in users of PPIs.
The analyses for heterogeneity were not significant. OR, fixed model, bilateral CI, 95% for trials, 95% for meta-analysis. Abbreviations as in Figure 2.

genetic variant or PPI coadministration on MACE occurrence are reported in Tables 2 and 3, respectively. After exclusion of the studies with the lowest quality score or the smallest numbers of patients, the magnitudes and directions of the effects of either the CYP2C19*2 allele or the use of PPIs in clopidogrel-treated patients remained similar. Large sample sizes and high-quality studies yielded similar conclusions on the detrimental impact of inherited or acquired CYP2C19 reduced function in clopidogrel-treated patients.

To investigate whether the effect of PPIs in clopidogrel-treated patients could be related to the incidence of MACE in the studied population, we thus performed an effect model analysis with the use of Walter's weighted regression model, testing the relationship between the annual MACE rate in PPI nonusers versus PPI users in each study. The slope of the regression line was different from 1 (1.59; 95% CI: 1.42 to 1.76; $p < 0.001$), and the 95% CI of the intercept did not include the origin (−0.047; 95% CI: −0.074 to −0.022; $p < 0.006$), demonstrating that the effect model was mixed (Fig. 5). The regression line intersected with the bisector (the reference line indicating the lack of difference between groups) at an annual MACE rate of 8%, suggesting that the impact of PPIs depends on the incidence of events in the PPI nonusers and that the impact of PPIs per se should be seen only in patients with the highest baseline risk for MACE.

We then assessed whether the effect of PPIs was influenced by the baseline cardiovascular risk of patients (Table 3). Studies were considered to include high-risk patients when the rate of MACE was superior to 10% (the median value of all studies) in PPI nonusers. PPI users had a significantly higher risk for MACE when considering the 6 studies with

Table 2 **Sensitivity Analyses of CYP2C19 Genetic Variants**

Subgroup	No. of Studies	Total No. of Patients	MACE in CYP2C19*2 Carriers	MACE in Noncarriers	OR (95% CI)	p Value	p Value for Heterogeneity
Overall	10	11,959	331/3,418	672/8,541	1.29 (1.12–1.49)	<0.001	0.003
Published (full-length report)	7	8,177	225/2,324	478/5,853	1.25 (1.05–1.48)	0.01	<0.001
Unpublished	3	3,782	106/1,094	194/2,688	1.40 (1.09–1.80)	0.008	0.66
Large size (n = >1,000)	5	9,800	278/2,762	606/7,038	1.20 (1.03–1.40)	0.02	0.07
Small size (n = <1,000)	5	2,159	53/656	66/1,503	2.16 (1.46–3.21)	<0.001	0.06
High-quality study*	7	8,427	205/2,427	363/6,000	1.48 (1.23–1.77)	<0.001	0.04
Low-quality study	3	3,532	126/991	309/2,541	1.06 (0.85–1.33)	0.60	0.04
High-risk patients†	5	5,218	186/1,453	408/3,765	1.22 (1.01–1.47)	0.04	0.02
Low-risk patients	5	6,741	145/1,965	264/4,776	1.40 (1.13–1.74)	0.002	0.02

The influence of the status of publication, sample size, and study quality on the impact of inherited CYP2C19 reduced function related to CYP2C19*2 genetic variant carriage on MACE in clopidogrel-treated patients was evaluated. *A high-quality study was defined as one having a Newcastle-Ottawa Scale score ≥9 (the median value of all studies). †High-risk patients were defined as an annual rate of MACE >7% in the control group.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Table 3 Sensitivity Analyses of the Impact of PPI Coadministration

Subgroup	No. of Studies	Total No. of Patients	MACE in PPI Users	MACE in PPI Nonusers	OR (95% CI)	p Value	p Value for Heterogeneity
Overall	11	46,037	4,285/19,614	4,424/26,423	1.41 (1.34–1.48)	<0.001	<0.001
Published (full-length report)	5	23,013	2,389/10,312	2,401/12,701	1.32 (1.23–1.42)	<0.001	<0.001
Unpublished	6	23,024	1,896/9,302	2,023/13,722	1.50 (1.40–1.61)	<0.001	0.02
Large size (>2,000 patients)	6	43,071	4,164/18,863	4,215/24,208	1.41 (1.34–1.49)	<0.001	<0.001
Small size (<2,000 patients)	5	2,966	121/751	209/2,215	1.35 (1.03–1.76)	0.03	0.05
High-quality study*	7	22,344	2,185/11,283	1,407/11,061	1.33 (1.23–1.44)	<0.001	<0.001
Low-quality study	4	23,693	2,100/8,331	3,017/15,362	1.47 (1.37–1.57)	<0.001	0.02
High-risk patients†	6	33,768	3,921/15,154	3,709/18,614	1.49 (1.41–1.57)	<0.001	<0.001
Low-risk patients	7	12,269	364/4,460	715/7,809	1.01 (0.88–1.16)	0.84	0.14

The influence of the status of publication, sample size, and study quality on the impact of acquired CYP2C19 reduced function related to PPI coadministration on MACE in clopidogrel-treated patients was evaluated. *A high-quality study was defined as one having a Newcastle-Ottawa Scale score ≥8 (the median value of all studies). †High-risk patients were defined as an annual rate of MACE >10% in the control group.

Abbreviations as in Tables 1 and 2.

high-risk patients (OR: 1.49; 95% CI: 1.41 to 1.57; $p < 0.001$), while no effect was observed in the remaining 7 studies including low-risk patients (OR: 1.01; 95% CI: 0.88 to 1.16; $p = 0.84$). Of interest, the impact of the CYP2C19*2 allele was found irrespective of the cardiovascular risk level of patients using a similar approach (Table 2).

Discussion

Clopidogrel is a prodrug that requires biotransformation into its active metabolite, which binds irreversibly to the platelet adenosine diphosphate membrane receptor. In vivo generation of the active metabolite is highly variable, requiring a polymorphic hepatic CYP2C19 enzyme for clopidogrel activation. In coronary patients who carry the genetic variant associated with a loss of function of the CYP2C19 enzyme, the risk for stent thrombosis on clopidogrel treatment is 3- to 6-fold higher (9–11,14–16,29). However, the influence and magnitude of risk of the CYP2C19 genotype have been inconsistent among studies. In addition, a recent concern relates to PPIs metabolized by the same CYP2C19 enzyme (suggesting a potential interference with the conversion of clopidogrel into its active form), reducing clopidogrel's antiplatelet effect and increasing the risk for cardiovascular events (9,32–37). Our results suggest that carriers of a reduced-function CYP2C19 allele and/or users of PPIs have approximately a 40% increased risk for MACE when they are treated with clopidogrel. One of the most important contributions of our meta-analysis is the 20% higher risk for death observed in these patients. The other striking finding is that the detrimental effect of PPIs may only exist in high-risk patients as opposed to that of carriage of CYP2C19*2 allele, which was observed irrespective of patients' cardiovascular risk levels.

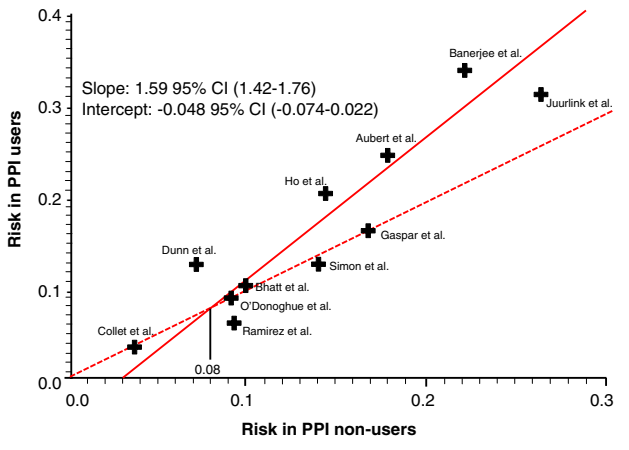

Figure 5 Effect Model Analysis of PPI Use on MACE

Weighted regression line **(solid red line)** is shown between annual incidence of major adverse cardiovascular events (MACE) in proton pump inhibitor (PPI) nonusers (x axis) and PPI users (y axis). The bisector **(dashed red line)** represents the lack of difference between groups. The regression line intersects the bisector at an annual MACE rate of 8% in PPI nonusers. Abbreviation as in Figure 2.

Several clinical studies have recently demonstrated the relationship between variants in the CYP2C19 gene and the risk for adverse cardiovascular outcome in clopidogrel-treated patients (9–11,13–16,29). However, risk estimates had wide CIs, and no significant effect on mortality was noted in most studies. We report here the impact of this single gene variant (CYP2C19*2) on mortality in patients exposed to clopidogrel. All patients who contributed to the mortality end point (6,225 of 11,959) were at high risk. All underwent stent implantation, and two-thirds presented with acute coronary syndromes. Obviously, carriage of CYP2C19*2 may have contained the effect of clopidogrel and left the patients insufficiently protected.

The hazard of reduced-function CYP2C19 allele carriage was even more striking for stent thrombosis, a serious complication of percutaneous coronary intervention (43). It is noteworthy that the magnitude of stent thrombosis excess associated with carriage of the CYP2C19*2 genetic variant was similar to the excess of risk observed with early clopidogrel discontinuation (12,44). Warnings have been delivered by scientific societies against early or inappropriate clopidogrel discontinuation in patients receiving stents (45).

Our meta-analysis suggests that similar warnings could be given to carriers of the CYP2C19*2 allele treated with clopidogrel after stent implantation, and our findings support the recent changes in the labeling of clopidogrel. Indeed, the vast majority of stent thromboses were subacute, and the question arises now whether rapid genetic testing for the CYP2C19*2 variant after stent implantation has clinical relevance to adjust treatment in patients genetically exposed to a poor response to clopidogrel. This specific issue is currently investigated in the ongoing ARCTIC-GENE (Assessment With a Double Randomization of a Monitoring-Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation and Interruption Versus Continuation of Double Antiplatelet Therapy, One Year After Stenting) study (NCT00827411). Meanwhile, it appears reasonable to identify CYP2C19*2 loss of function in patients receiving stents with associated clinical features of poor functional response to clopidogrel (i.e., recurrent events while on clopidogrel, overweight, diabetes).

The relative contributions of heterozygotes and homozygotes could not be assessed in the entire cohort of studies. This information was obtained in only 4 of the studies, representing 5,694 of 11,959 patients. We found that there was an increased risk for the occurrence of MACE in heterozygotes, which however did not reach significance as opposed to homozygotes. However, because of the low frequency of homozygotes in the population (<3% of patients, about 10% of CYP2C19*2 carriers), it is likely that the detrimental impact of carriage of CYP2C19*2 observed in all carriers (heterozygotes and homozygotes) may result from increased risk in both homozygotes and heterozygotes. The relative contributions of heterozygotes and homozygotes may also vary according to clinical presentation. We were able to detect a significant gene-dose effect on the risk for stent thrombosis in patients who had undergone percutaneous coronary intervention, whereas preliminary results from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) genomic substudy indicated no reduction in drug response in CYP2C19*2 heterozygotes. This may be attributable to the characteristics of the patient population, which was composed of stable patients without recent acute coronary syndromes or stent implantation. However, inclusion of the CHARISMA results in our meta-analysis did not change the overall results, demonstrating the significant influence of the CYP2C19*2 allele.

Obviously, clinical implications are relevant. Carriers of the loss-of-function CYP2C19*2 allele represent approximately 30% of the Caucasian population and up to 50% in East Asians, and heterozygotes represent 90% of the carriers. Prospectively and adequately powered randomized studies are ongoing, and the question arises whether rapid genetic testing will play a role when new platelet adenosine diphosphate receptor inhibitors, namely prasugrel and ticagrelor, enter the market for patients with acute coronary syndromes undergoing coronary interventions. Indeed, a genomewide association study has pointed out that the polymorphic hepatic CYP2C19 enzyme accounts for only 12% of the variation in response to the thienopyridine agent clopidogrel (13). Other genetic and environmental factors may play a role and need to be clarified.

Several studies have clearly established a similar negative biological interaction between PPIs and clopidogrel (18–21). Recent clinical investigations have reported that such an interaction may lead to a significant increase in cardiovascular risk, persisting after adjustment for potential confounders (32). Although the association was not significant for mortality, several medicines regulators have issued public statements on this interaction between clopidogrel and PPIs and have recommended changes in the product information for all clopidogrel-containing medicines to discourage the concomitant use of PPIs unless absolutely necessary. These recommendations have been debated. Indeed, there are inconsistencies among these recent clinical investigations, some of them suggesting that PPI use per se rather than an interaction with clopidogrel may be a marker of hazard (36). In addition, various PPIs affect to different degrees the metabolism of clopidogrel and may have different impacts on clinical outcomes. Our meta-analysis provides evidence that the concomitant use of clopidogrel and PPIs is associated with an increased risk for MACE and mortality, supporting the recent recommendations from the regulators. The majority of patients included in the meta-analysis were treated with omeprazole, the most potent CYP2C19 inhibitor.

The influence of PPIs was, however, highly heterogeneous between studies. The question arises why the negative influence of PPIs on the antiplatelet effects of clopidogrel reported in previous studies did not translate into worse clinical outcomes in the post hoc analysis of TRITON (38) and in COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) (n = 3,627) (42), the first randomized phase 3 study testing a combination of 20-mg omeprazole and clopidogrel versus placebo and clopidogrel in patients requiring clopidogrel for at least 12 months. Our results provide evidence that the impact of PPIs in terms of clinical outcomes depends on the baseline cardiovascular risk for clopidogrel-treated patients. We did not observe any significant influence of PPIs in clopidogrel-treated patients, with an annual rate of MACE lower than 10% (OR: 1.01; 95% CI: 0.88 to 1.16; $p = 0.84$), while the PPI effect was highly significant in patients, with an annual rate of MACE higher than 10% (OR: 1.49; 95% CI: 1.41 to 1.57; $p < 0.001$). Results from TRITON and preliminary results from COGENT provide reassurance that there is probably no clinically relevant adverse cardiovascular interaction between clopidogrel and PPIs in selected low-risk patients. Evaluation of the annual rate of MACE in the PPI nonusers provides evidence that patients recruited in these trials do not resemble the higher risk patients from other studies included in the present meta-analysis. Registries may recruit more patients with reduced responses to clopidogrel that may have been further reduced by the drug–drug interac-

tion. However, a causative link between PPI use and clopidogrel response cannot be inferred from our analysis. Whether the detrimental impact of PPI use in high-risk patients is related to CYP2C19 inhibition or another mechanism remains to be determined. Our study also strongly suggests a need to further characterize particular risk factors that may promote PPI interaction in these high-risk patients.

Study limitations. First, the majority of studies were observational, coming from prospective or retrospective registries. However, the Quality of Reporting of Meta-Analyses statement checklist was rigorously applied, allowing a careful selection of studies with the systematic use of a quality score, which are key factors to control for this limitation. Second, our results are exposed to the usual limitations of meta-analyses performed on global data. Thus, we performed sensitivity analyses for both CYP2C19*2 carriage and PPI use that led to similar conclusions irrespective of the quality or the size of the studies. A fixed-effect model was chosen because the selected studies had the same population risk estimate, and the prevalence of stent thrombosis and cardiovascular mortality are low, but the results were also confirmed when we used a random-effect model.

Because the data were not available, we were also unable to evaluate differences among various PPIs according to their degrees of inhibition of the CYP2C19 isoenzyme or according to CYP2C19 polymorphism status (19–21). Subsequently, a "gene-dose effect" of the CYP2C19*2 allele on the pharmacokinetics and pharmacodynamics of PPIs, which has been previously reported (46), could not be assessed in the present meta-analysis. Finally, another bias of these selected datasets was the inadequate or incomplete information on concurrent aspirin use and the bias represented by the fact that patients treated with PPIs are likely to be at higher risk for both bleeding and ischemic events. It is thus unclear how much PPI use is a marker of more severe morbid conditions and of higher risk for adverse outcomes.

Conclusions

Our meta-analysis suggests that CYP2C19*2 carriers and/or PPI users, who represent at least 50% of patients, are at higher risk for severe cardiovascular events when they are treated with clopidogrel. Whereas the impact of the CYP2C19*2 allele is observed in all patients, the impact of PPIs might only be significant in patients with high baseline cardiovascular risk. Our findings support the recent update in clopidogrel labeling, which now considers the impact of CYP2C19 alteration on the pharmacodynamic response to clopidogrel with potential clinical consequences, especially in patients who underwent recent stent implantation. Genotype profile and PPI use deserve further attention and studies in patients exposed to clopidogrel before definitive conclusions can be drawn (47).

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Key Words: antiplatelet drugs ■ genetics ■ proton pump inhibitors.

APPENDIX

For a supplemental table, please see the online version of this article.