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NEW RESEARCH PAPERS

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Effect of *CYP2C19* Genotype on Ischemic Outcomes During Oral $P2Y_{12}$ Inhibitor Therapy

A Meta-Analysis

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ABSTRACT

OBJECTIVES The aim of this study was to examine the effect of *CYP2C19* genotype on clinical outcomes in patients with coronary artery disease (CAD) who predominantly underwent percutaneous coronary intervention (PCI), comparing those treated with ticagrelor or prasugrel versus clopidogrel.

BACKGROUND The effect of *CYP2C19* genotype on treatment outcomes with ticagrelor or prasugrel compared with clopidogrel is unclear.

METHODS Databases through February 19, 2020, were searched for studies reporting the effect of *CYP2C19* genotype on ischemic outcomes during ticagrelor or prasugrel versus clopidogrel treatment. Study eligibility required outcomes reported for *CYP2C19* genotype status and clopidogrel and alternative $P2Y_{12}$ inhibitors in patients with CAD with at least 50% undergoing PCI. The primary analysis consisted of randomized controlled trials (RCTs). A secondary analysis was conducted by adding non-RCTs to the primary analysis. The primary outcome was a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia. Meta-analysis was conducted to compare the 2 drug regimens and test interaction with *CYP2C19* genotype.

RESULTS Of 1,335 studies identified, 7 RCTs were included (15,949 patients, mean age 62 years; 77% had PCI, 98% had acute coronary syndromes). Statistical heterogeneity was minimal, and risk for bias was low. Ticagrelor and prasugrel compared with clopidogrel resulted in a significant reduction in ischemic events (relative risk: 0.70; 95% confidence interval: 0.59 to 0.83) in *CYP2C19* loss-of-function carriers but not in noncarriers (relative risk: 1.0; 95% confidence interval: 0.80 to 1.25). The test of interaction on the basis of *CYP2C19* genotype status was statistically significant ($p = 0.013$), suggesting that *CYP2C19* genotype modified the effect. An additional 4 observational studies were found, and adding them to the analysis provided the same conclusions (p value of the test of interaction <0.001).

CONCLUSIONS The effect of ticagrelor or prasugrel compared with clopidogrel in reducing ischemic events in patients with CAD who predominantly undergo PCI is based primarily on the presence of *CYP2C19* loss-of-function carrier status. These results support genetic testing prior to prescribing $P2Y_{12}$ inhibitor therapy.
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

CAD = coronary artery disease

CI = confidence interval

CV = cardiovascular

FDA = U.S. Food and Drug Administration

HR = hazard ratio

LOF = loss-of-function

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

RR = relative risk

Clopidogrel is a prodrug and is metabolized primarily by the cytochrome P450 enzyme *CYP2C19*, resulting in an active metabolite that blocks the platelet $P2Y_{12}$ receptor, inhibiting platelet aggregation (1). Patients with *CYP2C19* loss-of-function (LOF) genotype are unable to metabolize clopidogrel effectively and hence are at an increased risk for cardiovascular (CV) ischemic events (2). The U.S. Food and Drug Administration (FDA) therefore advises medical practitioners to prescribe alternative antiplatelet therapies that are not predominantly metabolized by *CYP2C19*, such as ticagrelor or prasugrel, for patients who are *CYP2C19* poor metabolizers (3). Ticagrelor and prasugrel have both been demonstrated in randomized controlled trials (RCTs) to be superior to clopidogrel in reducing ischemic outcomes in patients with acute coronary syndromes (ACS) (4,5). However, it is not clear whether the presence of *CYP2C19* LOF genotype influenced outcomes in these RCTs. It remains uncertain whether the benefit of alternative $P2Y_{12}$ inhibitors occurs primarily in patients who are *CYP2C19* LOF carriers and not in noncarriers. Treatment with alternative $P2Y_{12}$ inhibitors compared with clopidogrel is more expensive and results in increased bleeding complications and adverse effects such as dyspnea in the case of ticagrelor; therefore, it may be advantageous to individualize antiplatelet therapy on the basis of *CYP2C19* genotype (4). A recent study of *CYP2C19* genotype-guided $P2Y_{12}$ inhibitor therapy strategy demonstrated noninferiority in reducing a composite of ischemic and bleeding events compared with treating all patients with ticagrelor after percutaneous coronary intervention (PCI) for myocardial infarction (6). In this study, patients in the genotype-guided group who were *CYP2C19* LOF carriers received ticagrelor, and noncarriers received clopidogrel, so the results were suggestive that treating noncarriers with clopidogrel was as efficacious as treating them with ticagrelor. However, *CYP2C19* genotyping information was not available for patients receiving ticagrelor in the standard-of-care arm that if available would have allowed evaluation of the test of interaction on the basis of *CYP2C19* genotype status in our study described herein. In the recently completed TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial, the point estimate suggests a 34% reduction in ischemic events in *CYP2C19* LOF carriers receiving ticagrelor compared with clopidogrel, with a 95% confidence interval (CI) of 0.43 to 1.02 (7). The upper boundary may be due to a lack of power given that the sample size calculation for the trial was based on a 50% treatment effect.

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Considering that these RCTs may not have been conclusive, largely because of a lack of power, we conducted a systematic review and meta-analysis to examine the association of *CYP2C19* genotype and clinical outcomes in patients with coronary artery disease (CAD) who predominantly underwent PCI

TABLE 1 Inclusion and Exclusion Criteria Applied for Review of All Studies Extracted Using Initial Search Strategy

Inclusion criteria
Original research published in English language
Patients >18 yrs of age
CYP2C19 genotyping available
Presentation with ACS or stable CAD
At least 50% of patients underwent PCI
One or more components of MACE should be reported
Two-arm design: clopidogrel vs. alternative (prasugrel or ticagrelor)
Outcomes by genotype groups: *CYP2C19* loss of function vs. wild-type
Exclusion criteria
Studies published in languages other than English
Study population containing patients <18 yrs of age
Nonoriginal research papers
Studies containing duplicate analyses of previously reported datasets
CYP2C19 genotyping data not available
Study population without ACS or stable CAD
Less than 50% of study population underwent PCI
Cardiovascular outcomes not reported
No two-arm design
Outcomes not reported by genotyping groups

ACS = acute coronary syndrome(s); CAD = coronary artery disease; MACE = major adverse cardiovascular event(s); PCI = percutaneous coronary intervention.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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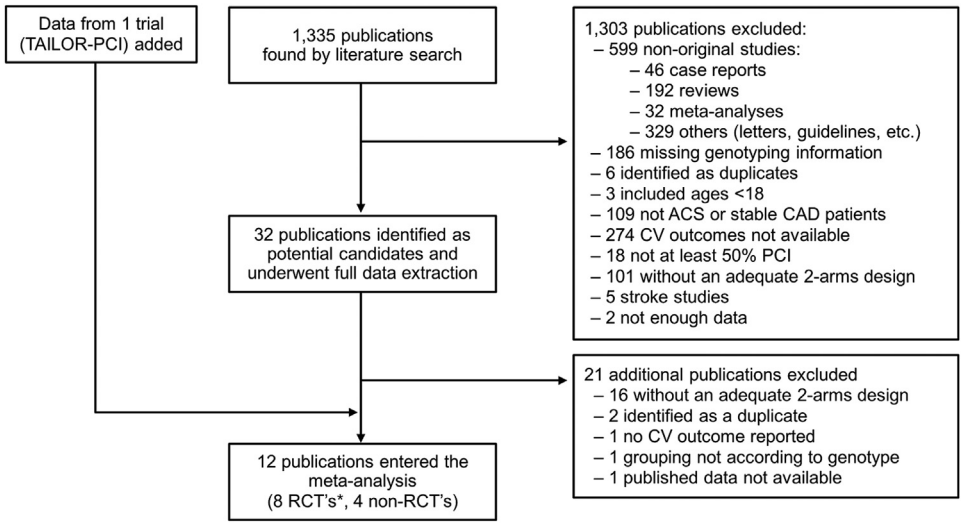
FIGURE 1 Flowchart Summary of Study Selection for Meta-Analysis According to Inclusion and Exclusion Criteria



ACS = acute coronary syndrome(s); CAD = coronary artery disease; CV = cardiovascular; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; TAILOR-PCI = Tailored Antiplatelet Therapy Following PCI.

with *CYP2C19* genotyping information available and compared outcomes of those treated with ticagrelor or prasugrel versus clopidogrel.

METHODS

The study was considered exempt by the Mayo Clinic Institutional Review Board. The inclusion and exclusion criteria of this systematic review (**Table 1**) and statistical analysis plan were defined a priori. The reporting of this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (http://www.prisma-statement.org).

SEARCH STRATEGY. A systematic search for published studies was conducted in several databases, including Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid Cochrane Central Register of Controlled Trials, and Scopus from inception to February 19, 2020. Controlled vocabulary supplemented with keywords "*CYP2C19*" and "clopidogrel," "ticagrelor," or "prasugrel" was used to search for studies in human adults. The detailed search strategy is outlined in the Supplemental Appendix.

STUDY SELECTION AND DATA EXTRACTION. The citations identified by the initial search were evaluated in 2 rounds by 2 investigators (G.M., S.S.) independently for inclusion. The first round of evaluation consisted of title and abstract review, and the second round consisted of full-text review. Any discrepancies were adjudicated by a third investigator (R.L.). The inclusion and exclusion criteria used are described in **Table 1**.

Data were extracted in duplicate (G.M., S.S.) to a standardized data collection file with pre-specified fields, including study identifiers, genotyping information, baseline characteristics, study design parameters, and clinical outcomes. The target primary efficacy endpoint was defined as the composite CV death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia. Similarly, the safety endpoint was defined as rate of major or minor bleeding on the basis of TIMI (Thrombolysis In Myocardial Infarction) criteria. If a study did not report these endpoints, the available endpoint most similar in definition was abstracted. Disagreements in data abstraction were resolved by consensus or by a third evaluator (R.L.) if consensus was not reached.

RISK FOR BIAS AND CERTAINTY IN THE EVIDENCE. The risk for bias was assessed using the Cochrane tool for assessing risk for bias in RCTs (8). The certainty in the evidence for an outcome was evaluated using the GRADE approach (9). In this approach, RCTs provide high-certainty evidence that could be rated down for risk for bias, imprecision (wide CIs), inconsistency

TABLE 2 Characteristics of Studies Included in the Meta-Analysis

First Author (Year) (Ref. #)	Type	Subgroups Reported	Ischemic Outcome	Bleeding Outcome	Alleles Genotyped	Maximum FU (months)	Clopidogrel Loading/ Maintenance Doses (mg)	Alternative Therapy	Alternative Loading/ Maintenance Doses (mg)	Mean Age (yrs)	% Men
Mega et al. (2009) (13) Mega et al. (2009) (22)	RCT	LOF and non-LOF	CVD, MI, CVA	Major or minor	*CYP2C19, CYP2C9, CYP2B6, CYP1A2, CYP3A5, CYP1A12*	15	300/75	Prasugrel	60/10	60	72
Wallentin et al. (2010) (14)	RCT	LOF and non-LOF	CVD, MI, CVA	Major	*CYP2C19* (*2, *3, *4, *5, *6, *7, *8)	12	300–600/75	Ticagrelor	180/90	63	70
Deiman et al. (2016) (15)	Non-RCT	LOF only	CVD, MI, CVA, ST, re-PCI	–	*CYP2C19* (*2, *3)	18	300/75	Prasugrel	–/10	67	74
Dong et al. (2016) (16)	RCT	LOF only	Death, MI, CVA, revasc	–	*CYP2C19* (*2, *3)	1	600/75	Ticagrelor	180/90	67	80
Ogawa et al. (2016) (17)	RCT	LOF and non-LOF	CVD, MI, CVA	Major or minor	*CYP2C19* (*2, *3)	6	300/75	Prasugrel	20/3.75	64	81
Zhang et al. (2016) (18)	RCT	LOF only	Death, MI, CVA	Major or minor	*CYP2C19* (*2, *3)	6	600/75	Ticagrelor	180/90	70	50
Chen et al. (2017) (19)	Non-RCT	LOF only	CVD, MI, CVA	Any bleeding event	*CYP2C19* (*2)	12	300/75	Ticagrelor	–/90	60	–
Cavallari et al. (2018) (20)	Non-RCT	LOF and non-LOF	Death, MI, CVA	–	*CYP2C19* (*2, *3)	12	300/75	Prasugrel, ticagrelor, high-dose clopidogrel	–/–	63	67
Lee et al. 2018 (21)	Non-RCT	LOF and non-LOF	Death, MI, CVA, TIA, ST, UA-hosp	Clinically significant	*CYP2C19* (*2, *3)	12	–	Prasugrel or ticagrelor	–/–		–
Xiong et al. (2015) (23)	RCT	LOF only	MACE	Major or minor	*CYP2C19* (*2)	1	600/150	Ticagrelor	180/90	67	71
Pereira et al. (2020) (7)	RCT	LOF only	CVD, MI, CVA, ST, SRI	Major or minor	*CYP2C19* (*2, *3)	12	300–600/75	Ticagrelor	180/90	62	76

CVA = cerebrovascular accident; CVD = cardiovascular-related death; FU = follow-up; LOF = loss-of-function; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; re-PCI = repeat percutaneous coronary intervention; RCT = randomized controlled trial; revasc = revascularization (percutaneous coronary intervention or coronary artery bypass graft); SRI = severe recurrent ischemia; ST = stent thrombosis; TIA = transient ischemic attack; UA-hosp = hospitalization for unstable angina.

(i.e., heterogeneity), indirectness (surrogate outcomes or extrapolation from other populations), or publication bias (10).

STATISTICAL ANALYSIS. For each study, the most adjusted effect size was extracted. If unavailable, we extracted an unadjusted effect (i.e., a 2 × 2 table). Effect sizes were pooled across studies using the random-effects model (11) because of heterogeneity of study populations and settings. The pooled effect was expressed as relative risk (RR) with 95% CIs. Analysis was conducted separately for *CYP2C19* LOF carriers and noncarriers to explore the interaction between genotype and treatment effect, as well as a combined analysis that pooled both genotypes together to compare the 2 different drug regimens. The primary analysis included only RCTs. A secondary analysis was conducted by adding non-RCTs to the analysis. Heterogeneity was assessed using the I^2 statistic, which represents the percentage of heterogeneity not attributable to chance. An interaction test was conducted as described by Altman and Bland (12), with 2-tailed p values <0.05 considered to indicate statistical significance. Analysis was done using Stata version 16 (StataCorp LLC, College Station, Texas).

RESULTS

The initial search identified 1,335 potential citations, of which 1,303 (97.6%) were excluded during the initial screening, most commonly because they were not original studies (n = 599), failed to report CV outcomes (n = 274), or did not report genotyping information (n = 186). The remaining 32 publications underwent full-text review and data extraction. Of these, 21 were further excluded, most commonly because the study design did not allow assessment of outcomes on the basis of *CYP2C19* LOF carrier and noncarrier status. **Figure 1** shows the details of the search. Finally, data from the recently presented TAILOR-PCI trial were added to the systematic review, resulting in 12 studies from 7 RCTs and 4 non-RCTs (7,13–23). Two publications by Mega et al. (13,22) were subanalyses from a single RCT, as each compared *CYP2C19* LOF carriers with noncarriers

TABLE 3 Assessments of the Risk for Bias in Randomized Clinical Trials Included in the Meta-Analysis

First Author (Year) (Ref. #)	Randomization Sequence	Allocation Concealment	Blinding of Patients	Blinding of Caregivers	Blinding of Outcome Assessors	Blinding of Analysts	Percentage Lost to Follow-Up
Mega et al. (2009) (13)	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	1.2
Mega et al. (2009) (22)	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	0.75
Wallentin et al. (2010) (14)	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	0
Dong et al. (2016) (16)	Adequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	0
Ogawa et al. (2016) (17)	Adequate	Adequate	Adequate	Inadequate	Adequate	Inadequate	0
Zhang et al. (2016) (18)	Adequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	0
Xiong et al. (2015) (23)	Adequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	0
Pereira et al. (2020) (7)	Adequate	Adequate	Inadequate	Inadequate	Adequate	Inadequate	2.9

within a given $P2Y_{12}$ receptor inhibitor regimen (Figure 1). The characteristics of studies included are summarized in Table 2.

The studies reported on a total of 15,949 patients who were enrolled in RCTs (the mean age was 62 years, 71% were men, 77% underwent PCI, 98% had ACS, 25% had diabetes, and 34% were smokers) and 18,808 patients in both RCTs and non-RCTs (the mean age was 62 years, 71% were men, 80% underwent PCI, 94% had ACS, 26% had diabetes, and 34% were smokers).

RISK FOR BIAS. The details of risk for bias assessment are summarized in Table 3 for RCTs and Table 4 for non-RCTs, and definitions of indicators of risk for bias are outlined in Supplemental Table 1. Most RCTs had adequate randomization approaches and concealment of allocation, while degree of blinding varied. Most non-RCTs had appropriate selection and ascertainment approaches, while adjustment for confounding and blinded assessments were typically lacking. Overall, the global risk for bias for both ischemic and bleeding outcomes in the RCTs was low and in the non-RCTs was high.

META-ANALYSIS. Ischemic outcomes. Meta-analysis of 7 RCTs enrolling 6,409 *CYP2C19* LOF carriers demonstrated a statistically significant reduction in the risk for ischemic events (RR: 0.70; 95% CI: 0.59 to 0.83) (Figure 2A) with the use of ticagrelor or prasugrel (7.0%; 223 events in 3,172 patients) compared with clopidogrel (10.3%; 335 events in 3,237 patients). There was no similar significant reduction observed in meta-analysis of 4 studies enrolling 9,540 noncarriers (RR: 1.00; 95% CI: 0.80 to 1.25; alternative therapy 8.8% [419 of 4,781], clopidogrel 9.2% [439 of 4,759]) (Figure 2A). The test of interaction on the basis of *CYP2C19* genotype status was statistically significant ($p = 0.013$), suggesting that *CYP2C19* genotype modifies the effect. In a secondary analysis, all studies (RCTs and non-RCTs) were analyzed (Figure 2B). The results were consistent with the main analysis, demonstrating a significant reduction in the risk for ischemic events in *CYP2C19* LOF carriers treated with ticagrelor and prasugrel (11 studies) compared with clopidogrel and no difference in noncarriers (6 studies) (p value of the test of interaction <0.001).

Bleeding outcome. Meta-analysis of 6 RCTs enrolling 6,309 *CYP2C19* LOF carriers showed no significant difference in the risk for major and minor bleeding (RR: 0.91; 95% CI: 0.64 to 1.30) with the use of ticagrelor or prasugrel (6.7%; 210 events in 3,132 patients) compared with clopidogrel (6.8%; 215 events in 3,177 patients) (Figure 3A). The difference was also not significant in the meta-analysis of 3 RCTs enrolling 9,466 *CYP2C19* LOF noncarriers (RR: 0.99; 95% CI: 0.86 to 1.14; alternative therapy 7.9% [376 of 4,754], clopidogrel 8.0% [375 of 4,712]) (Figure 3A). The results were also consistent with the secondary analysis that included non-RCTs (Figure 3B); that is, the reduction in the risk for the bleeding outcome was not statistically significant in meta-analysis of 9 studies with *CYP2C19* LOF carriers and in 4 studies with noncarriers. Tests of interaction on the basis of *CYP2C19* genetic status were nonsignificant in both analyses ($p = 0.67$ in RCTs, $p = 0.92$ in all studies).

HETEROGENEITY, PUBLICATION BIAS AND CERTAINTY IN THE EVIDENCE. Statistical heterogeneity of treatment effect was overall minimal ($I^2 < 50\%$ in all analyses when stratified by *CYP2C19* genotype). Publication bias could not be statistically assessed, because of the small number of studies per each stratified analysis. The certainty in the estimates of the ischemic outcome was high. The certainty in the estimates of the bleeding outcome was low, likely because of lack of power due to the smaller number of bleeding events in each genotype category, as reflected by the wide CIs.

TABLE 4 Assessments of the Risk for Bias in Non-RCT Studies Included in the Meta-Analysis

First Author (Year) (Ref. #)	Exposed Cohort Selection	Control Cohort Selection	Ascertainment of Exposure	Ascertainment of Outcome	Groups Comparable in Characteristics	Analysis Adjusted for Important Confounders	Assessment of Outcome Blinded	Follow-Up Sufficient for Outcome to Occur	Percentage Lost to Follow-Up
Deiman et al. (2016) (15)	Inadequate	Inadequate	Adequate	Adequate	Adequate	Inadequate	Inadequate	Adequate	Unknown
Chen et al. (2017) (19)	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Inadequate	Adequate	Unknown
Cavallari et al. (2018) (20)	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Inadequate	Adequate	Unknown
Lee et al. (2018) (21)	Adequate	Adequate	Adequate	Adequate	Inadequate	Inadequate	Inadequate	Adequate	Unknown

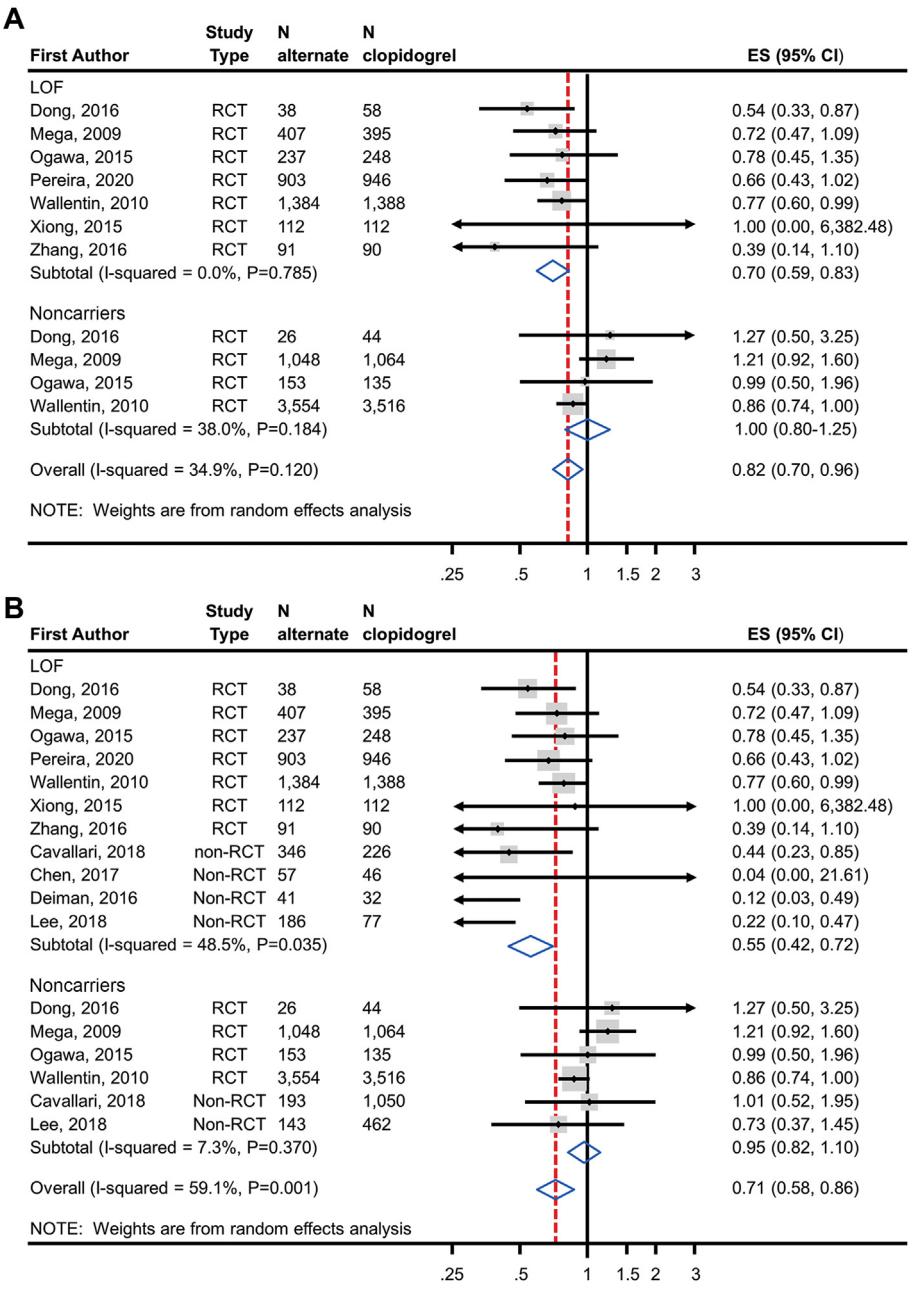
DISCUSSION

MAIN FINDINGS. In the present meta-analysis, *CYP2C19* LOF carriers with CAD who predominantly had ACS and underwent PCI had improved ischemic outcomes when treated with ticagrelor or prasugrel compared with those receiving clopidogrel. This beneficial effect was not observed in *CYP2C19* LOF noncarriers (**Central Illustration**). Our findings suggest that the reduction in ischemic events observed with alternative $P2Y_{12}$ inhibitors compared with clopidogrel in clinical trials is likely due to substantially reduced events in *CYP2C19* LOF carriers and not in noncarriers. This meta-analysis supports genetic testing for selection of $P2Y_{12}$ inhibitors in this patient population, validates the model of personalized medicine, and is proof of concept for a precision-medicine approach to adopting optimal and safe therapies for patients with CV disease (24). The increasing acceptance of genetic testing is reflected in the 2020 European Society of Cardiology guidelines for ACS that recommend as Class 2b, consideration of de-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g., with a switch from prasugrel or ticagrelor to clopidogrel) for patients with ACS deemed unsuitable for potent platelet inhibition using *CYP2C19* genotyping (25). This perspective is also reflected in a state-of-the-art expert consensus statement that advocates either de-escalation or escalation of dual-antiplatelet therapy on the basis of clinical and procedural characteristics and results of platelet function and *CYP2C19* genetic testing (26).

The use of ticagrelor compared with clopidogrel without a genotyping strategy in the PLATO (A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome) trial decreased ischemic events (hazard ratio [HR]: 0.84; 95% CI: 0.77 to 0.92) in 18,624 patients with ACS with an overall ischemic event rate that was 9.8% in the ticagrelor group and 11.7% in the clopidogrel group (5). The PLATO genetic substudy, which included 10,285 patients from the original trial, suggested a reduction in ischemic events in *CYP2C19* LOF carriers receiving ticagrelor compared with clopidogrel (HR: 0.77; 95% CI: 0.60 to 0.99) but not in noncarriers (HR: 0.86; 95% CI: 0.74 to 1.01) (14). Because of a nonsignificant interaction test ($p = 0.46$), the investigators concluded that ticagrelor was more efficacious than clopidogrel irrespective of *CYP2C19* genotype status. The investigators acknowledged that this genetic "sub-study was not prospectively powered." No similar study examining the effect of *CYP2C19* with the use of prasugrel had been performed to date.

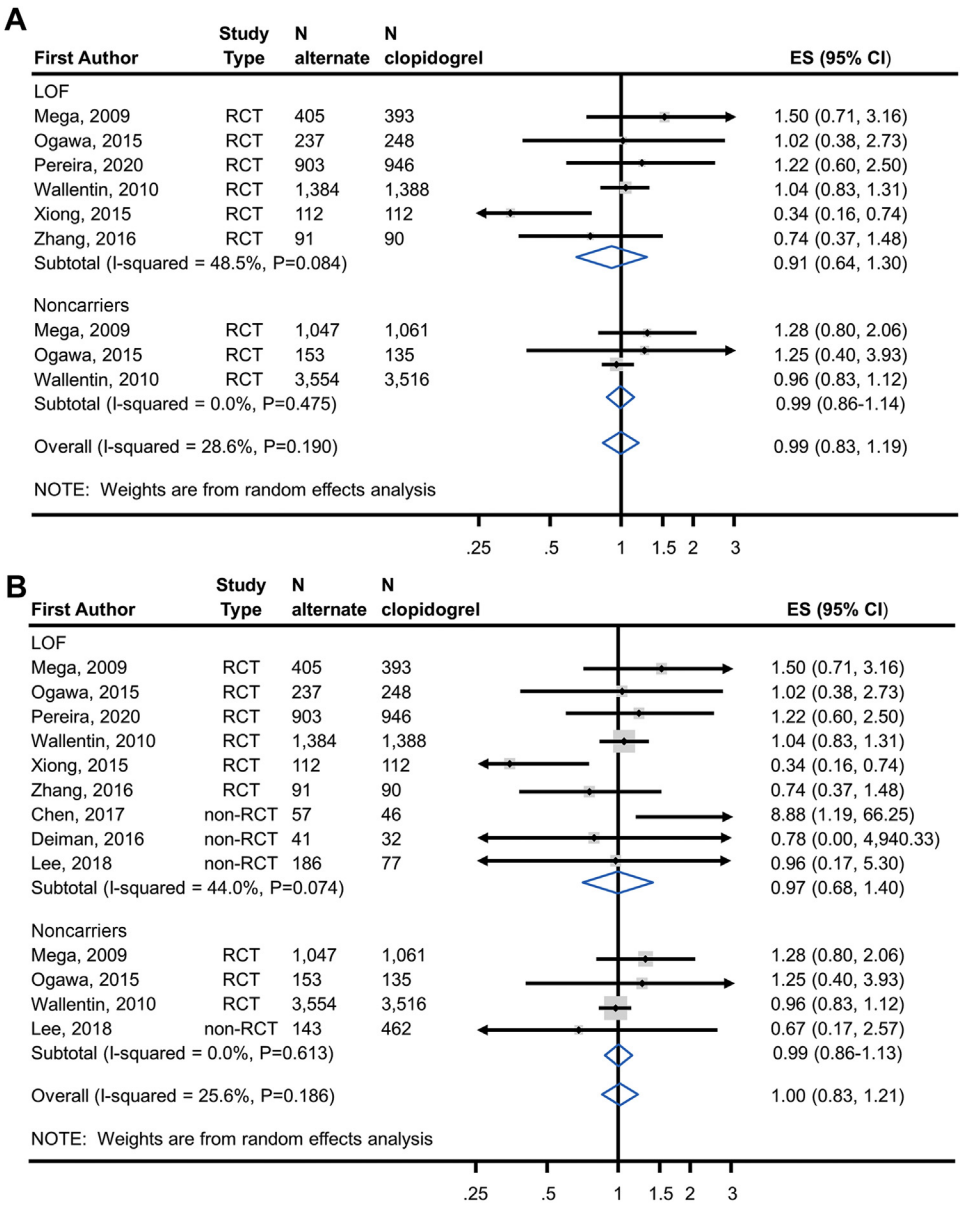
Despite an FDA black-box warning in the drug-labeling information for clopidogrel, American Heart Association and American College of Cardiology clinical expert consensus guidelines do not support the routine practice of *CYP2C19* genotyping prior to prescribing clopidogrel (3). It was unknown whether identifying *CYP2C19* LOF carriers and prescribing alternative $P2Y_{12}$ inhibitors such as ticagrelor or prasugrel on the basis of *CYP2C19* genotype reduced ischemic outcomes. The randomized trials and observational studies that followed the FDA warning were underpowered to address the question of whether to genotype and, therefore, lacked statistical significance to definitively demonstrate a role for genotyping. In the recently reported TAILOR-PCI trial, treatment with ticagrelor compared with clopidogrel in *CYP2C19* LOF carriers did not result in a significant reduction of ischemic events at 12 months on the basis of the pre-specified analysis plan and the 50% treatment effect that the study had been powered to detect (7). Despite the occurrence of 89 ischemic events observed in this trial, which exceeded the 76 events anticipated to provide adequate power, the observed RR reduction was 34% instead of the estimated 50%, hence a borderline p value of 0.056 was observed. This meta-analysis of 7 RCTs enrolling 6,409 patients overcomes this limitation and demonstrates an overall risk reduction of 30% with alternative $P2Y_{12}$ inhibitors compared with clopidogrel, consistent with the treatment effect observed in TAILOR-PCI.

FIGURE 2 **Effect of *CYP2C19* Genotype on Ischemic Outcomes in Patients Treated With Ticagrelor or Prasugrel Versus Clopidogrel**



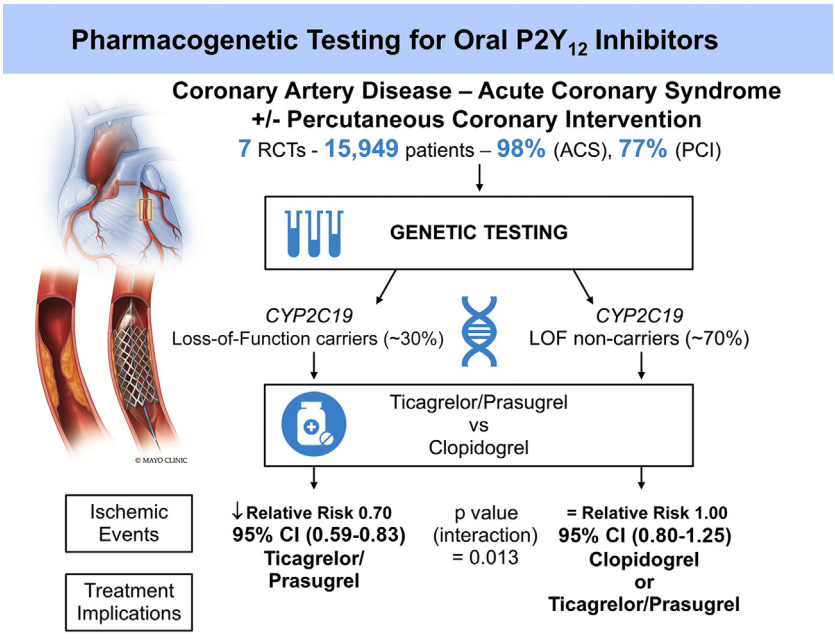
(A) Analysis of ischemic events in RCTs comparing alternative P2Y$_{12}$ inhibitors with clopidogrel treatment according to *CYP2C19* genotype status. Meta-analysis of ischemic event risk in patients with CAD predominantly after PCI treated with alternative P2Y$_{12}$ inhibitors or clopidogrel. The **top panel** analyzes patients identified as *CYP2C19* loss-of-function (LOF) carriers, and the **bottom panel** analyzes those identified as noncarriers. Risk ratios $<$ 1 indicate better outcomes for alternative therapy, and risk ratios $>$ 1 indicate better outcomes for clopidogrel. The test for interaction between genotype status and treatment effect was significant ($p = 0.013$), indicating a statistically significant difference in effect on the basis of genotype. **(B)** Analysis of ischemic events in RCTs and non-RCTs comparing alternative P2Y$_{12}$ inhibitors with clopidogrel treatment according to *CYP2C19* genotype status. Meta-analysis of ischemic event risk in patients with CAD predominantly after PCI treated with alternative P2Y$_{12}$ inhibitors or clopidogrel. The **top panel** analyzes patients identified as *CYP2C19* LOF carriers, and the **bottom panel** analyzes those identified as noncarriers. Risk ratios $<$ 1 indicate better outcomes for alternative therapy; risk ratios $>$ 1 indicate better outcomes for clopidogrel. The test for interaction between *CYP2C19* genotype status and treatment effect was significant ($p < 0.001$), indicating a statistically significant difference in effect on the basis of genotype. CI = confidence interval; ES = effect size; other abbreviations as in Figure 1.

FIGURE 3 Effect of *CYP2C19* Genotype on Bleeding Outcomes in Patients Treated With Ticagrelor or Prasugrel Versus Clopidogrel



(A) Analysis of bleeding events in RCTs comparing alternative $P2Y_{12}$ inhibitors with clopidogrel treatment according to *CYP2C19* genotype. Meta-analysis of bleeding event risk in patients with CAD predominantly after PCI treated with alternative $P2Y_{12}$ inhibitor or clopidogrel. The **top panel** analyzes patients identified as *CYP2C19* LOF carriers, and the **bottom panel** analyzes those identified as noncarriers. Risk ratios < 1 indicate better outcomes for alternative therapy, risk ratios > 1 indicate better outcomes for clopidogrel. The test for interaction between metabolizer type and treatment effect was nonsignificant ($p = 0.67$), indicating no statistically significant evidence for a differential effect of alternative therapies on the basis of genotype. **(B)** Analysis of bleeding events in RCTs and non-RCTs comparing alternative $P2Y_{12}$ inhibitors with clopidogrel treatment according to *CYP2C19* genotype. Meta-analysis of bleeding event risk in patients with CAD predominantly after PCI treated with alternative $P2Y_{12}$ inhibitors or clopidogrel. The **top panel** analyzes subjects identified as *CYP2C19* LOF carriers, and the **bottom panel** analyzes those identified as noncarriers. Risk ratios < 1 indicate better outcomes for alternative therapy, and risk ratios > 1 indicate better outcomes for clopidogrel. The test for interaction between metabolizer type and treatment effect was nonsignificant ($p = 0.92$), indicating no statistically significant evidence for a differential effect of alternative therapies based on genotype. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **A Proposed Algorithm Using *CYP2C19* Pharmacogenetic Testing to Individualize Oral $P2Y_{12}$ Inhibitor Therapy in Patients With Coronary Artery Disease on the Basis of the Meta-Analysis Results**



Pereira, N.L. et al. J Am Coll Cardiol Intv. 2021;14(7):739–50.

PRACTICAL IMPLICATIONS. These results suggest that genetic testing for identifying *CYP2C19* LOF carriers and noncarriers could be beneficial prior to prescribing antiplatelet therapy, resulting in the selection of an alternative $P2Y_{12}$ inhibitor for the former and clopidogrel for the latter patients (**Central Illustration**). If alternative $P2Y_{12}$ inhibitor therapy had reduced ischemic outcomes in noncarriers, then a ticagrelor or prasugrel for all approach, irrespective of *CYP2C19* genotype, might have been preferred to clopidogrel. On the contrary, our meta-analysis results demonstrate that there was no difference in the rates of ischemic events when noncarriers were treated either with clopidogrel or alternative $P2Y_{12}$ inhibitors. These results support the findings of the POPular Genetics trial, in which all patients in one randomized group received ticagrelor and were compared with patients receiving genotype-guided $P2Y_{12}$ inhibitors (i.e., noncarriers receiving clopidogrel and LOF carriers receiving ticagrelor). This study demonstrated that such a targeted genotyping strategy was noninferior to a ticagrelor-for-all approach, with ischemic event rates of 4.6% and 4.7%, respectively, at 12 months (6). These studies imply that a large proportion of patients could safely receive clopidogrel given that *CYP2C19* LOF noncarriers constitute approximately 50% to 70% of the population (1). *CYP2C19* genotype can be incorporated with clinical variables in the form of a composite scoring system that could be helpful in identifying high-risk patients and selecting appropriate oral $P2Y_{12}$ inhibitor therapy, as demonstrated by the recently published ABCD-GENE score (27).

In the PLATO trial, no significant difference was observed in the rates of major bleeding between ticagrelor- and clopidogrel-treated patients, although there was a higher risk for non-coronary artery bypass graft major bleeding in the ticagrelor group (HR: 1.19; 95% CI: 1.02 to 1.38) (5). In the PLATO genetic substudy, *CYP2C19* genotype was shown to have no effect on major bleeding with $P2Y_{12}$ inhibitor therapy (14), a finding that was similar to that observed in the TAILOR-PCI clinical trial (7) and our meta-analysis. It is important to note that the PLATO genetic substudy did not report TIMI minor bleeding episodes by *CYP2C19* genotype, which may have attenuated the bleeding outcomes reported in this meta-analysis. Patients treated with prasugrel have a higher risk for

major bleeding compared with clopidogrel, as demonstrated in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-TIMI 38) study (4) (HR: 1.32; 95% CI: 1.03 to 1.68). This increased risk for major bleeding was not observed in the *CYP2C19* genetic substudies of TRITON-TIMI 38 or in other studies comparing prasugrel with clopidogrel included in our meta-analysis. Although the risk for major bleeding may not be affected by *CYP2C19* genotype, multiple prior studies have demonstrated a lower incidence of minor bleeding with clopidogrel than with prasugrel or ticagrelor. For example, although Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding was reported to be lower in the genotype-guided group (9.9%) compared with ticagrelor for all (12.8%) in POPular Genetics, this effect was driven primarily by a reduction in BARC type 2 bleeding (HR: 0.69; 95% CI: 0.53 to 0.89) rather than BARC type 3 or 5 bleeding (HR: 1.23; 95% CI: 0.71 to 2.13) (6). A similar increased risk for bleeding was observed in the TAILOR-PCI trial when bleeding was assessed by the BARC classification in the *CYP2C19* LOF per-protocol genotype-guided group that primarily received ticagrelor compared with those who received clopidogrel (7). One of the potential advantages of genotype-guided $P2Y_{12}$ inhibitor therapy in which a large number of patients receive clopidogrel (given an approximate 50% to 70% prevalence of *CYP2C19* noncarriers) and the remainder receive more potent alternative $P2Y_{12}$ inhibitors is a lower risk for bleeding for this group of patients compared with all patients receiving either ticagrelor or prasugrel. This beneficial effect was observed in POPular Genetics. Similar to prior studies, our meta-analysis did not demonstrate an effect of *CYP2C19* genotype on bleeding outcomes, likely because of reporting of bleeding complications by TIMI major or minor bleeding classification, which does not result in reporting of actionable minor bleeding episodes that do not meet the drop in hemoglobin or hematocrit criteria of the TIMI classification but would be captured by BARC2 bleeding criteria, for example. Furthermore, the bleeding results of the meta-analysis need to be interpreted with caution, as the certainty in the estimates of the bleeding outcome was low.

The *CYP2C19*17* allele is considered a gain-of-function allele and has been shown, in some studies, to lead to enhanced response to clopidogrel (via platelet function testing) and perhaps a higher rate of bleeding events (28,29). However other studies have not demonstrated increased platelet inhibition or altered clinical outcomes in clopidogrel-treated patients with the *CYP2C19*17* allele (30–33). Therefore, its role in attenuating response to clopidogrel is controversial, and guidelines do not recommending altering $P2Y_{12}$ inhibitor therapy on the basis of *CYP2C19*17* genotype (34).

STUDY STRENGTHS. The strengths of this meta-analysis relate to the comprehensive search for published studies, selecting and appraising studies by independent pairs of reviewers, and evaluating the whole body of evidence of randomized and non-randomized studies with stratified analyses on the basis of study design.

STUDY LIMITATIONS. First, there was incomplete reporting across studies. Not all studies reported results in *CYP2C19* LOF noncarriers, and the ischemic endpoints varied, but most consisted of CV death, myocardial infarction, and stroke. Most studies categorized subjects on the basis of *CYP2C19*2/*3* alleles, but some had broader criteria. Nevertheless, despite such variation, we did not observe substantial statistical heterogeneity (the I^2 measure did not exceed 50% for any analysis stratified by genetic status).

Second, we were unable to evaluate publication bias, which would have affected only the non-randomized studies, considering that they are not required to be registered in trial registries such as ClinicalTrials.gov.

Third, combining the use of ticagrelor and prasugrel in the alternative $P2Y_{12}$ inhibitor therapy group included in this meta-analysis may have attenuated the results of the ischemic outcomes, given findings of a recent study that demonstrated a lower incidence of death, myocardial infarction, or stroke in patients who received prasugrel compared with ticagrelor (35). However, the differences in ischemic outcomes would have been similar in both *CYP2C19* LOF patients and *CYP2C19* noncarriers without altering the overall results observed. Furthermore, *CYP2C19* LOF patients who received either ticagrelor or prasugrel have a similar degree of platelet inhibition (36).

Finally, bleeding outcomes according to the BARC definition were not reported in the RCTs included in this meta-analysis, other than TAILOR-PCI, which may limit the interpretation of bleeding risk with the use of the various $P2Y_{12}$ inhibitors according to *CYP2C19* genotype.

CONCLUSIONS

The findings of the present meta-analysis confirm the beneficial trends observed in individual studies and

support the use of genotyping to guide $P2Y_{12}$ inhibitor therapy in patients with CAD, especially with ACS and after PCI. The findings also support the concept of personalized medicine and justify the need for such studies in CV disease.

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PERSPECTIVES

WHAT IS KNOWN? Whether the benefit of alternative $P2Y_{12}$ inhibitors such as ticagrelor or prasugrel compared with clopidogrel occurs primarily in patients who are *CYP2C19* LOF carriers and not in noncarriers is unknown.

WHAT IS NEW? This meta-analysis demonstrates that ticagrelor or prasugrel compared with clopidogrel significantly reduced ischemic events in *CYP2C19* LOF carriers but not in noncarrier patients with CAD after PCI.

WHAT IS NEXT? Clopidogrel therefore can be safely used in the majority of patients, and genetic testing prior to prescribing $P2Y_{12}$ inhibitor therapy would be useful to guide selection of these agents for use after PCI.

REFERENCES

1. Pereira NL, Weinshilboum RM. Cardiovascular pharmacogenomics and individualized drug therapy. Nat Rev Cardiol 2009;6:632–8.

2. Pereira NL, Rihal CS, So DYF, et al. Clopidogrel pharmacogenetics. Circ Cardiovasc Interv 2019;12:e007811.

3. Holmes DR, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning. J Am Coll Cardiol 2010;56:321–41.

4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

5. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

6. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. N Engl J Med 2019;381:1621–31.

7. Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral $P2Y_{12}$ inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. JAMA 2020;324:761–71.

8. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

9. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.

10. Murad MH. Clinical practice guidelines: a primer on development and dissemination. Mayo Clin Proc 2017;92:423–33.

11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

12. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.

13. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354–62.

14. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320–8.

15. Deiman BALM, Tonino PAL, Kouhestani K, et al. Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Neth Heart J 2016;24:589–99.

16. Dong P, Yang X, Bian S. Genetic polymorphism of CYP2C19 and inhibitory effects of ticagrelor and clopidogrel towards post-percutaneous coronary intervention (PCI) platelet aggregation in patients with acute coronary syndromes. Med Sci Monit 2016;22:4929–36.

17. Ogawa H, Isshiki T, Kimura T, et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. J Cardiol 2016;68:29–36.

18. Zhang Y, Zhao Y, Pang M, et al. High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. Acta Cardiologica 2016;71:309–16.

19. Chen S, Zhang Y, Wang L, et al. Effects of dual-dose clopidogrel, clopidogrel combined with tongxinluo capsule, and ticagrelor on patients with coronary heart disease and CYP2C19*2 gene mutation after percutaneous coronary interventions (PCI). Med Sci Monit 2017;23:3824–30.

20. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. J Am Coll Cardiol Intv 2018;11:181–91.

21. Lee CR, Sriramoju VB, Cervantes A, et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.

22. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553–60.

23. Xiong R, Liu W, Chen L, Kang T, Ning S, Li J. A randomized controlled trial to assess the efficacy and safety of doubling dose clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes. Int J Clin Exp Med 2015;8:13310–6.

24. Pereira NL, Sargent DJ, Farkouh ME, Rihal CS. Genotype-based clinical trials in cardiovascular disease. Nat Rev Cardiol 2015;12:475–87.

25. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020 Aug 29 [E-pub ahead of print].

26. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. J Am Coll Cardiol Intv 2019;12:1521–37.

27. Angiolillo DJ, Capodanno D, Danchin N, et al. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. J Am Coll Cardiol Intv 2020;13:606–17.

28. Frére C, Cuisset T, Gaborit B, Alessi MC, Hulot JS. The CYP2C19*17 allele is associated with better platelet response to clopidogrel in patients admitted for non-ST acute coronary syndrome. J Thromb Haemost 2009;7:1409–11.

29. Sibbing D, Koch W, Gebhard D, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation 2010;121:512–8.

30. Geisler T, Schaeffeler E, Dippon J, et al. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. Pharmacogenomics 2008;9:1251–9.

31. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363–75.

32. Sorich MJ, Polasek TM, Wiese MD. Systematic review and meta-analysis of the association between cytochrome P450 2C19 genotype and bleeding. Thromb Haemost 2012;108:199–200.

33. Lewis JP, Stephens SH, Horenstein RB, et al. The CYP2C19*17 variant is not independently associated with clopidogrel response. J Thromb Haemost 2013;11:1640–6.

34. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther 2013;94:317–23.

35. Schüpke S, Neumann F-J, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381:1524–34.

36. Franchi F, Rollini F, Rivas J, et al. Prasugrel versus ticagrelor in patients with CYP2C19 loss-of-function genotypes. J Am Coll Cardiol Basic Trans Science 2020;5:419–28.

KEY WORDS clopidogrel, *CYP2C19* genotype, ischemic outcomes, meta-analysis, prasugrel, systematic review, ticagrelor

APPENDIX For data sources and search strategies and a supplemental table, please see the online version of this paper.