Effect of cytochrome P450 2C19*17 allelic variant on cardiovascular and cerebrovascular outcomes in clopidogrel-treated patients: A systematic review and meta-analysis

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INTRODUCTION

Cardiovascular and cerebrovascular diseases (CCVDs) are the leading causes of morbidity and mortality throughout the world. However, incidence and prevalence of CCVD are varied based on different regions.[1] Clopidogrel belongs to the thienopyridine prodrug that needs complex biotransformation, and the generation of its active metabolite requires the CYP450 enzymes in the liver, such as CYP2C19 and CYP3A4.[2] Inhibition of CYP2C19 might inhibit the antiplatelet activity of clopidogrel.[3] Clopidogrel monotherapy or in combination with aspirin is widely used in the antiplatelet therapy of CCVD patients to reduce the occurrence of ischemic cardiovascular events, but it could also lead to an increased bleeding risk.[4,5] Common CYP2C19 polymorphisms are detected to influence pharmacodynamic response to clopidogrel, and loss-of-function CYP2C19 polymorphisms could result in reduced exposure to the active metabolite of clopidogrel.[6] This could decrease patient responsiveness to clopidogrel, and a low responsiveness is tied up with increased risk of ischemic events.[7] Stent thrombosis

Background: We aimed to evaluate the associations of gain-of-function allele of CYP2C19*17 and risk of clinical events in clopidogrel-treated patients with cardiovascular and cerebrovascular diseases (CCVDs). Materials and Methods: Literature search was conducted in PubMed, EMBASE, and Cochrane Library. Odds ratio (OR) combined with 95% confidence interval (CI) was the pooled statistics. Subgroup analysis was performed by disease type, bleeding events, and race. Results: Thirteen eligible studies involving 14,239 patients with CYP2C19*17 carriers or noncarriers were included in the meta-analysis. CYP2C19*17 was significantly related to decreased risk of major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with coronary artery disease (CAD) (OR = 0.76, 95% CI: 0.60–0.98, P = 0.03), however, irrelevant with stent thrombosis in neither CAD nor ischemic heart disease patients. CYP2C19*17 was also significantly linked to decreased risk of high platelet reactivity (HPR) in CCVD patients (OR = 0.61, 95% CI: 0.43–0.88, P = 0.008). Meanwhile, CYP2C19*17 was significantly associated with bleeding risk in CCVD patients (OR = 1.89, 95% CI: 1.09–3.25, P = 0.02) but not related to major bleeding risk (OR = 1.35, 95% CI: 0.87–2.08, P = 0.18). Several outcomes in Caucasian subgroup were reverse to the overall results, such as bleeding events and HPR, which lacked significance. Conclusion: CYP2C19*17 had a significant effect on the reduced risks of MACCE and HPR as well as increased bleeding risk, but not on the risks of stent thrombosis and major bleeding in clopidogrel-treated CCVD patients. Outcomes might be different in different races.

Key words: Bleeding, cardiovascular and cerebrovascular disease, clopidogrel, CYP2C19*17, high platelet reactivity, major adverse cardiovascular and cerebrovascular events, meta-analysis

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is one of such ischemic events that defined as a sudden occlusion of the stented coronary artery, and it is correlated with patients carrying CYP2C19 loss-of-function *2 or *3 allele.[2,8] Unlike CYP2C19*2 or CYP2C19*3, CYP2C19*17 could increase transcriptional activity of CYP2C19 substrates, which contributes to enhance responsiveness to clopidogrel.[7] However, gain-of-function allele CYP2C19*17 is associated with an increased risk of bleeding.[9,10] Some previous studies have found that CYP2C19*17 is associated with a set of adverse cardiovascular events, such as stent thrombosis, bleeding, and high platelet reactivity (HPR) in CCVD patients treated with clopidogrel,[11-13] whereas other studies have reported that CYP2C19*17 is irrelevant with the clinical outcomes in CCVD patients.[14,15]

Meta-analysis is an effective method to combine results in different studies within the same topic. Thus, it could enlarge samples, enhance statistic power, and provide more reliable results.[16] Therefore, we conducted a systematic review and meta-analysis to compare the cardiovascular and cerebrovascular outcomes in clopidogrel-treated CCVD patients between CYP2C19*17 carriers and noncarriers, which was expected to achieve a comprehensive understanding of the associations between the gain-of-function allele CYP2C19*17 and adverse events in clopidogrel-treated CCVD patients.

MATERIALS AND METHODS

Literature search
The eligible studies were retrieved by systematically searching in three databases (PubMed, EMBASE, and Cochrane Library) from their reception to February 2016. Searching keywords were “CYP2C19*17,” “clopidogrel,” and “cardiovascular.” There was no language restriction. References of the retrieved studies and reviews were scanned to obtain additional relevant articles.

Inclusion and exclusion criteria
Articles would be included in this meta-analysis if they met the following inclusion criteria: (1) participants in the studies were the CCVD patients who received clopidogrel treatment; (2) the studies compared outcomes between CYP2C19*17 carriers and noncarriers; (3) the outcomes included at least one of the following events: major adverse cardiac and cerebrovascular events (MACCEs, which were defined as death from any cause, nonfatal myocardial infarction, or stroke),[14] stent thrombosis, bleeding events, major bleeding, HPR; (4) for the repetitive studies, only that contained more outcomes and had a high quality was included; (5) all studies were English publications. Reviews, letters, conference abstracts, or comments were excluded.

Data extraction and quality assessment
After the completion of article screening, two investigators independently extracted relevant data from the eligible studies. The extracted information was as follows: the first author’s name, publication year, geographical area of study population, race and age of the participants, follow-up duration, disease characteristics, gene detection method, sample size of CYP2C19*17 carriers and noncarriers, and outcomes.

Newcastle–Ottawa Scale (NOS)[17] was utilized to assess the quality of included studies. The studies with a NOS score ≥ 5 were considered to have a high quality.

Statistical analysis
The pooled odds ratio (OR) with 95% confidence interval (CI) was used as the effect size to estimate correlations between CYP2C19*17 and cardiovascular outcomes in clopidogrel-treated patients. Heterogeneity across studies was assessed by Cochran Q- and I²-test.[18] If significant heterogeneity was identified (P < 0.05, or I² > 50%), the random-effect model was performed. Otherwise, the fixed-effect model was used for homogeneous outcomes (P > 0.05, I² ≤ 50%).[19] To better recognize the source of heterogeneity, subgroup analyses stratified by different races or disease types were performed.

To test the reliability of the meta-analysis result, we performed a sensitivity analysis by removing each study at one time. If the pooled results reversed after removing one study, it indicated that the meta-analysis was unstable and unreliable.

The pooled meta-analysis and subgroup analysis were performed using Review Manager Version 5.3 (RevMan 5.3; The Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corp, College Station, TX, USA) while the sensitivity analysis was conducted using Stata 12.0 (Stata Corp, College Station, TX, USA).

RESULTS

Eligible studies
The preliminary search yielded 1047 studies (PubMed: 422, EMBASE: 625, Cochrane Library: 0). Among them, 286 repetitive articles and 264 irrelevant studies were excluded. Then, 457 articles were further excluded by reading abstracts because 155 studies were without CYP2C19*17, 147 studies without cardiovascular outcomes, 121 reviews or letters, and 34 non-English articles. For the remaining 40 articles, they received full-text examination, and 27 were removed: 16 lacked the data regarding CYP2C19*17 carriers and noncarriers and 11 did not contain the required outcomes. Finally, 13 articles[20-26] were included in this
meta-analysis. Process of the study selection is presented in Figure 1.

Characteristics of eligible articles
Relevant data extracted from the selected articles are summarized in Table 1. Among these included articles, 12 were prospective cohort studies[9,11‑15,20‑22,24‑26] and one was a case‑control retrospective analysis.[23] Overall patient numbers sum up to 14,239. The articles were published from 2008 to 2016, and they were conducted in multiple countries (e.g., China, Germany, Korea, America, and Italy) and among different races (e.g., Caucasian and Asian). The follow‑up duration was mainly 12 months. All participants in the studies were patients who received clopidogrel treatment. Among the 13 studies, nine studies included patients with coronary artery disease (CAD).[9,12,13,15,21‑23,25,26] two studies included patients with ischemic heart disease (IHD),[11,14] and the remained two studies included patients with cerebrovascular disease.[20,24] and patients with either manifest atherothrombotic disease (coronary, cerebrovascular, peripheral artery disease) or exhibiting multiple risk factors for developing atherothrombotic disease,[20] respectively. In addition, all articles had a high quality with a NOS score from 5 to 9.

Comparison of major adverse cardiovascular and cerebrovascular events risk between CYP2C19*17 carriers and noncarriers
Among the included studies, five studies[11,14,15,23,26] compared MACCE risk between CYP2C19*17 carriers and noncarriers. Here, patients were divided into two subgroups: patients with CAD[15,25,26] and IHD.[11,14]

For the three studies including patients with CAD, the test for heterogeneity showed that there was no significant heterogeneity among them (P = 0.71, I² = 0%), so the fixed‑effect model was used for pooling estimates of effect size. The overall effect size (OR = 0.76, 95% CI: 0.60‑0.98, P = 0.03) revealed that there were significant differences on MACCE risk between CYP2C19*17 carriers and noncarriers [Figure 2a], indicating that CYP2C19*17 was associated with reduced MACCE risk in clopidogrel‑treated patients with CAD.

For the two studies including patients with IHD, there also lacked heterogeneity (P = 0.87, I² = 0%); thus, the fixed‑effect model was used to calculate the pooled results. The overall effect size (OR = 0.56, 95% CI: 0.22‑1.40, P = 0.21) showed that there were no significant differences on MACCE risk between CYP2C19*17 carriers and noncarriers [Figure 2a], suggesting that CYP2C19*17 was irrelevant with MACCE risk in clopidogrel‑treated patients with IHD.

Comparison of stent thrombosis risk between CYP2C19*17 carriers and noncarriers
There were four articles[11,14,15,26] that reported risk of stent thrombosis between CYP2C19*17 carriers and noncarriers. Patients were divided into two subgroups: patients with CAD[15,26] and IHD.[11,14]

For studies in CAD subgroup, there were no significant heterogeneities (P = 0.96, I² = 0%); thus, the fixed‑effect model was used for pooling estimates of effect size. The overall effect size (OR = 1.07, 95% CI: 0.47‑2.41, P = 0.88) revealed that there were no significant differences on the risk of stent thrombosis between CYP2C19*17 carriers and noncarriers [Figure 2b], indicating that CYP2C19*17 was irrelevant to the increased risk of stent thrombosis in clopidogrel‑treated patients with CAD.

For the two studies including patients with IHD, heterogeneity was also not significant (P = 0.16, I² = 50%); thus, the fixed‑effect model was used for pooling estimates of effect size. According to the overall effect size (OR = 0.66, 95% CI: 0.12‑3.49, P = 0.62), there were no significant differences in the risk of stent thrombosis between CYP2C19*17 carriers and noncarriers [Figure 2b], suggesting that CYP2C19*17 was not correlated with the risk of stent thrombosis in clopidogrel‑treated patients with IHD.

Comparison of bleeding events risk between CYP2C19*17 carriers and noncarriers
Among the included studies, six studies[11,13‑15,20,24] reported the risk of bleeding events between CYP2C19*17 carriers and noncarriers. There were significant heterogeneities among them (P = 0.004, I² = 71%); therefore, the random‑effect model was used to measure the pooled results. The overall effect size (OR = 1.89, 95% CI: 1.09‑3.25, P = 0.02) revealed that there were significant differences on the risk of bleeding events between CYP2C19*17 carriers and noncarriers [Figure 3a], indicating that CYP2C19*17 was relevant to the increased
### Table 1: Characteristics of the 13 included studies

| Study          | Study period       | Country   | Race       | Follow-up duration | Participants                                                                 | Gene detection method | Outcomes                                                                 | Number of participants (carriers/noncarriers) | Age (years) | Score of quality assessment |
|----------------|--------------------|-----------|------------|-------------------|-----------------------------------------------------------------------------|-----------------------|---------------------------------------------------------------------------|-----------------------------------------------|-------------|----------------------------|
| Geisler, 2008  | 2006.07–2007.03    | Germany   | Caucasian  | -                 | Patients undergoing PCI for CAD                                            | -                     | Low and high residual platelet activity                                   | 237 (100/137)                                | 69.0±13.0   | 6                          |
| Sibbing, 2010  | 2007.02–2008.04    | Germany   | Caucasian  | 1 month          | Patients undergoing PCI for CAD                                            | TaqMan assay          | Platelet aggregation, bleeding, and stent thrombosis                      | 1524 (622/902)                               | 67.4         | 7                          |
| Tiroch, 2010   | 2005-2008          | Germany   | Caucasian  | 12 months        | Patients with acute myocardial infarction belonging to CAD                 | TaqMan assay and PCR  | Major adverse cardiovascular events, stent thrombosis                     | 928 (363/565)                                | 64.8         | 8                          |
| Wallentin, 2010| -                  | Sweden    | Caucasian  | 12 months        | Patients with or without ST-elevation acute coronary syndrome             | TaqMan assays         | Major bleeding                                                             | 5148                                         | 62.5±11.4    | 8                          |
| Campo, 2011    | 2008.12–2009.05    | Italy     | Caucasian  | 12 months        | Patients undergoing PCI for ischemic heart disease                        | Allelic discrimination assay | Platelet reactivity, ischemic and bleeding events                        | 300 (102/198)                                | 66±13        | 7                          |
| Gurbel, 2011   | -                  | America   | Mix        | 1 months         | Patients with CAD                                                         | TaqMan® SNP genotyping assays | HPR                                                                       | 118 (45/73)                                  | -            | 7                          |
| Bhatt, 2012    | -                  | Mix       | Caucasian  | 800 days         | Patients with clinically evident atherothrombotic disease or multiple risk factors for developing atherothrombotic disease | RFLP                 | Ischemic and bleeding events                                              | 2226 (872/1394)                              | 64.0±9.5     | 7                          |
| Dai, 2012      | 2009.07–2011.04    | China     | Asian      | 1 months         | Patients with blood stasis syndrome belonging to CAD who were going to have stent placement | PCR-RFLP             | Platelet aggregation, bleeding risk                                       | 520 (77/443)                                 | 61.5±10.2    | 5                          |
| Park, 2013     | 2005.01–2009.12    | Korea     | Asian      | 12 months        | Patients undergoing PCI for ischemic heart disease (stable angina or acute coronary syndrome) | Single-base extension methods | Bleeding, stent thrombosis, major adverse cardiac and cerebrovascular events | 2188 (53/2135)                              | -            | 6                          |
| Siller-Matula, 2014 | 2007.03–2008.09  | Austria   | Caucasian  | 12 months        | Patients with CAD undergoing PCI                                          | TaqMan SNP genotyping assays | Platelet reactivity                                                        | 416 (140/276)                                | 64±12        | 7                          |
| Chen, 2015     | 2012.01–2013.03    | China     | Asian      | 6 months         | Patients undergoing PCI for acute coronary syndrome                       | Sequenom MassARRAY platform | Ischemic events, HPR                                                        | 336 (6/330)                                  | 66.5±10.5    | 9                          |
| Lin, 2015      | -                  | Australia | Mix        | 3 months         | Patients undergoing endovascular treatment for intracranial aneurysms or intracranial stenosis | PCR-RFLP             | Ischemic events, hemorrhagic events                                       | 108 (56/52)                                  | 56 (48.8–65.0) | 7                          |
| Khalil, 2016   | 2012.07–2013.06    | Egypt     | Caucasian  | 12 months        | Patients with CAD                                                         | PCR followed by pyrosequencing | Major adverse cardiac events                                              | 190 (54/136)                                 | 55.9         | 8                          |

PCR-RFLP = Polymerase chain reaction-restriction fragment length polymorphism; PCI = Percutaneous coronary intervention; CAD = Coronary artery disease; SNP = Single nucleotide polymorphisms, HPR = High platelet reactivity
risk of bleeding events in clopidogrel-treated patients. Furthermore, when stratified by different disease types: CAD\cite{13,15} and IHD\cite{11,14}, significant difference was found in both CAD subgroup [OR = 2.18, 95% CI: 1.37–3.46, \( P = 0.0009 \), Figure 3b] and IHD subgroup [OR = 3.91, 95% CI: 1.66–9.22, \( P = 0.002 \), Figure 3b], suggesting that CYP2C19*17 was linked to increased risk of bleeding events in clopidogrel-treated patients, regardless of disease type.

**Comparison of major bleeding risk between CYP2C19*17 carriers and noncarriers**

For the risk of major bleeding, there were significant heterogeneities among the four studies\cite{9,13,15,20} (\( I^2 = 59\% \)); thus, the random-effect model was used for pooling estimates of effect size. The overall effect size (OR = 1.35, 95% CI: 0.87–2.08, \( P = 0.18 \)) showed that the risk of major bleeding was not significant between CYP2C19*17 carriers and noncarriers [Figure 4a], suggesting that CYP2C19*17 was irrelevant with the risk of major bleeding in clopidogrel-treated patients. When stratified by disease type, CYP2C19*17 was not significantly correlated with risk of major bleeding in clopidogrel-treated patients with CAD [OR = 1.87, 95% CI: 0.86–4.07, \( P = 0.11 \), Figure 4b], either.

Moreover, we extracted the studies focusing on thrombolysis in myocardial infarction (TIMI) bleeding events: TIMI
bleeding and TIMI major bleeding. As a result, CYP2C19*17 was associated with increased risk of both of them (TIMI bleeding: OR = 2.15, 95% CI: 1.37, 3.38, P = 0.0008; TIMI major bleeding: OR = 2.81, 95% CI: 1.26, 6.26, P = 0.01) [Table 2], suggesting that CYP2C19*17 was more tied up with increased risk about TIMI.\[9,13,15\]

**Comparison of high platelet reactivity risk between CYP2C19*17 carriers and noncarriers**

The data of HPR risk were reported in four articles.\[12,21,22,25\] As no significant heterogeneities among the four studies were detected (P = 0.93, P = 14%), the fixed-effect model was used for pooling estimates of effect size. The overall effect size [OR = 0.61, 95% CI: 0.43–0.88, P = 0.008, Figure 5] showed that the risk of HPR was significantly different between CYP2C19*17 carriers and noncarriers, suggesting that CYP2C19*17 was related to the decreased risk of HPR in clopidogrel-treated patients.

**Subgroup analysis stratified by race**

All outcomes were undergone subgroup analysis by different races including Caucasian, Asia, or the Mix of them. However, as several outcomes had only one or two studies, especially in subgroups of Asia or the Mix, we only pooled outcomes in the subgroup of Caucasian. As presented in Table 2, we found several outcomes in Caucasian subgroup were reverse to the overall results, such as bleeding events (OR = 1.62, 95% CI: 0.92, 2.88, P = 0.10) and HPR (OR = 0.70, 95% CI: 0.48, 1.04, P = 0.08), which lacked significance. Therefore, we still need more studies with large samples to reveal correlations between CYP2C19*17 and risk of the above outcomes.

**Sensitivity analysis**

Based on sensitive analysis, not any reverse result was detected after removing any study, indicating result of this meta-analysis was stable and reliable. Sensitivity analysis results for five outcomes (MACCE, stent thrombosis, bleeding events, major bleeding and HPR) are presented in Supplementary Figure 1-5.

**DISCUSSION**

Clopidogrel is an antiplatelet prodrug that requires metabolic activation by CYP2C19 enzyme.\[27\] CYP2C19*17 is
the polymorphism that has two SNPs in the 5-flanking region of CYP2C19 gene, and it is proven to enhance CYP2C19 activity and improve antiplatelet action of clopidogrel.[28,29] A previous study has reported that clopidogrel-treated patients with CYP2C19*1/*17 and *17/*17 diplotype have a lower magnitude of platelet reactivity the *1/*1 genotype in clopidogrel-treated patients after elective coronary stenting.[7,30,31] Other studies have found that CYP2C19*17 allele is not related to the occurrence of stent thrombosis in clopidogrel-treated patients undergoing percutaneous
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Consistent with these results, based on our meta-analysis, it was found that CYP2C19*17 was significantly associated with reduced risk of HPR, but irrelevant to the risk of stent thrombosis, in neither CAD subgroup nor IHD subgroup. Moreover, CYP2C19*17 T-allele is correlated with reduced MACCE rates,[28] which is also in accordance with the overall results in our study. However, when stratified by disease type in our study, CYP2C19*17 was irrelevant with MACCE risk in patients with IHD, suggesting that clinical influence of CYP2C19*17 might be varied based on different CCVD types. These collectively suggest that CYP2C19*17 might be a protective indicator for patients treated with clopidogrel. On the other hand, our results revealed that CYP2C19*17 was significantly related to increased bleeding risk, but not major bleeding risk. A previous study has reported a similar result that there was not significant association between any gain-of-function CYP2C19 allele and a higher frequency of major bleeding.[9] However, several conflicting studies showed that CYP2C19*17 is responsible for a significantly higher risk of major bleeding events in clopidogrel-treated patients.[31,32] The incompatible results may be due to the fact that they did not specify the bleeding events, as in our meta-analysis; when we extracted the TIMI bleeding events, it was found CYP2C19*17 was significantly correlated with increased risk of TIMI bleeding and TIMI major bleeding.

As heterogeneity was significant in several outcomes, we performed subgroup analysis stratified by different races. In the subgroup of Caucasian, several outcomes were reverse to the overall results, such as bleeding events and HPR. This reminds us that the clinical effects of CYP2C19*17 on clopidogrel-treated patients were varied based on different populations and race might be a factor causing heterogeneity. However, more studies with larger samples should be performed to support these findings. Based on sensitive analysis, not any reverse result was detected, which indicated that results of the meta-analysis were stable and reliable.

Study limitations
There are several limitations to the study. First, the patients with different symptoms should be classified into different groups for further analysis, which may generate more precise results. However, as not all the included studies involved these detailed information, we could not perform subgroup analysis stratified by this factor. Second, more indexes should be evaluated, such as ischemic stroke, myocardial infarction, mortality, and repeat revascularization. Third, although subgroup analyses stratified by CCVD type, race, and bleeding events were conducted, other confounders might exist, which might cause deviation of the results. Fourth, as there were only 2–6 studies in each subgroup, we did not perform publication bias among them. In our future study, based on the enough published studies, we will make a more accurate systematic evaluation that includes more detailed categories of patients and more clinical indexes.

CONCLUSIONS
This meta-analysis demonstrated that CYP2C19*17 was significantly associated with reduced risks of MACCE and HPR, but irrelevant with the risk of stent thrombosis in clopidogrel-treated CCVD patients, suggesting that CYP2C19*17 might be a protective indicator for these patients. However, CYP2C19*17 was also linked to increased risk of bleeding risk. Race might be a factor causing heterogeneity.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Cutter G, et al. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult Scler 2015;21:318-31.
2. Nazgul K, VaciS T, Vilius S, Gaziza S, Nazgul S, Audrone V, et al. Gene polymorphism of CYP2C19*2, *3 and CYP3A4*1B and early stent thrombosis: Case reports and literature review. Per Med 2017;13:423-8.
3. Palleria C, Di Paolo A, Girofre C, Caglioti C, Leuzzi G, Siniscalchi A, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. J Res Med Sci 2013;18:601-10.
4. Campo G, Miccoli M, Teguio M, Marchesini J, Fileti L, Monti M, et al. Genetic determinants of on-clopidogrel high platelet reactivity. Platelets 2011;22:399-407.
5. Haririhan S, Southworth MR, Madabushi R. Clopidogrel, CYP2C19 and proton pump inhibitors: What we know and what it means. J Clin Pharmacol 2014;54:884-8.
6. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429-36.
7. Sibbing D, Gebhard D, Koch W, Braun S, Stegherr J, Morath T, et al. Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy. J Thromb Haemost 2010;8:1685-93.
8. Shuldiner AR, O’Connell JR, Belden KP, Gandhi A, Ryan K, Horenstein RB, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849-57.
9. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, 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.
10. Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J,
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.

11. Campo G, Parrinello G, Ferraresi P, Lunghi B, Tebaldi M, Miccoli M, et al. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. J Am Coll Cardiol 2011;57:2474-83.

12. Gurbel PA, Shuldiner AR, Blijden JP, Ryan K, Panyak RE, Tantry US. The relationship between CYP2C19 genotype and phenotype in stented patients on maintenance dual antiplatelet therapy. Am Heart J 2011;161:598-604.

13. Dai ZL, Chen H, Wu XY. Relationship between cytochrome P450 2C19*17 genotype distribution, platelet aggregation and bleeding risk in patients with blood stasis syndrome of coronary artery disease treated with clopidogrel. Zhong Xi Yi Jie He Xue Bao 2010;10:647-54.

14. Park MW, Her SH, Kim HS, Choi YS, Park CS, Koh YS, et al. Impact of the CYP2C19*17 polymorphism on the clinical outcome of clopidogrel therapy in Asian patients undergoing percutaneous coronary intervention. Pharmacogenet Genomics 2013;23:558-62.

15. Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation 2020;159:512-8.

16. Chen SS, Song J, Tu XY, Zhao JH, Ye XQ. The association between MMP-12 82 A/G polymorphism and susceptibility to various malignant tumors: A meta-analysis. Int J Clin Exp Med 2015;8:10645-54.

17. Flohil SC, van der Leest RJ, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: A systematic review and meta-analysis. Eur J Cancer 2013;49:2365-75.

18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

19. Wang Y. Oral contraceptive use and risk of breast cancer: A meta-analysis of prospective cohort studies. Eur J Contracept Reprod Health Care 2021;27:402-14.

20. Bhatt DL, Pare G, Eikelboom JW, Simonsson KL, Emson ES, Fox KA, et al. The relationship between CYP2C19 polymorphisms and ischaemic and bleeding outcomes in stable outpatients: The CHARISMA genetics study. Eur Heart J 2012;33:2143-50.

21. Chen Y, Huang X, Tang Y, Xie Y, Zhang Y. Both PON1 Q192R and CYP2C19*2 influence platelet response to clopidogrel and ischemic events in Chinese patients undergoing percutaneous coronary intervention. Int J Clin Exp Med 2015;8:9266-74.

22. Geisler T, Schaeffer E, Dippon J, Winter S, Buse V, Bischofs C, et al. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. Pharmacogenomics 2008;9:1251-9.

23. Khalil BM, Shainin MH, Solayman MH, Langae T, Schaalan MF, Gong Y, et al. Genetic and nongenetic factors affecting clopidogrel response in the Egyptian population. Clin Transl Sci 2016;9:23-8.

24. Lin M, Todaro M, Chan J, Churilov L, Zhu WS, Ramdave S, et al. Association between CYP2C19 polymorphisms and outcomes in cerebral endovascular therapy. AJNR Am J Neuroradiol 2016;37:108-13.

25. Siller-Matula JM, Lang IM, Neunteufl T, Kozinski M, Maurer G, Linkowska K, et al. Interplay between genetic and clinical variables affecting platelet reactivity and cardiac adverse events in patients undergoing percutaneous coronary intervention. PLoS One 2014;9:e102701.

26. Tiroch KA, Sibbing D, Koch W, Roosen-Runge T, Mehilli J, Schömig A, et al. Protective effect of the CYP2C19*17 polymorphism with increased activation of clopidogrel on cardiovascular events. Am Heart J 2010;160:506-12.

27. Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of CYP2C19: Functional and clinical implications of a new variant CYP2C19*17. Br J Clin Pharmacol 2010;69:222-30.

28. Sim SC, Risinger C, Dahl ML, Akilulu E, Christensen M, Bertilsson L, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther 2006;79:103-13.

29. Gawronska-Szklarz B, Adamiak-Giera U, Wyska E, Kurzwinski M, Gornik W, Kaldonska M, et al. CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. Eur J Clin Pharmacol 2012;68:1267-74.

30. Frère 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.

31. Harmsze AM, van Werkum JW, Hackeng CM, Ruven HJ, Kelder JC, Bouman HJ, et al. The influence of CYP2C19*2 and *17 on on-treatment platelet reactivity and bleeding events in patients undergoing elective coronary stenting. Pharmacogenet Genomics 2012;22:169-75.

32. Zabalza M, Subirana I, Sala J, Lluis-Ganella C, Lucas G, Tomás M, et al. Meta-analyses of the association between cytochrome CYP2C19 loss-and gain-of-function polymorphisms and cardiovascular outcomes in patients with coronary artery disease treated with clopidogrel. Heart 2012;98:100-8.
Supplementary Figure 1: Sensitive analysis of major adverse cardiovascular and cerebrovascular event

Supplementary Figure 2: Sensitive analysis of stent thrombosis

Supplementary Figure 3: Sensitive analysis of bleeding events

Supplementary Figure 4: Sensitive analysis of major bleeding

Supplementary Figure 5: Sensitive analysis of high platelet reactivity risk