Review Article

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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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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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

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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 I^2-test.[18] If significant heterogeneity was identified ($P < 0.05$, or $I^2 > 50\%$), the random-effect model was performed. Otherwise, the fixed-effect model was used for homogeneous outcomes ($P > 0.05$, $I^2 \leq 50\%$).[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[9,11-15,20-26] 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[15,23,26] 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, I^2 = 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.

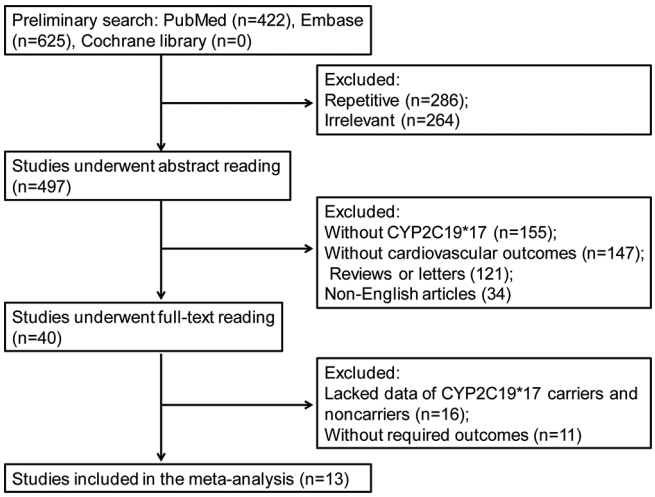

Figure 1: Flowchart of the study selection in the meta-analysis

For the two studies including patients with IHD, there also lacked heterogeneity (P = 0.87, I^2 = 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, I^2 = 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 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, I^2 = 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, I^2 = 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	PCR and the TaqMan assay	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 (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 chin reaction-restriction fragment length polymorphism; PCI = Percutaneous coronary intervention; CAD = Coronary artery disease; SNP = Single nucleotide polymorphisms, HPR = High platelet reactivity

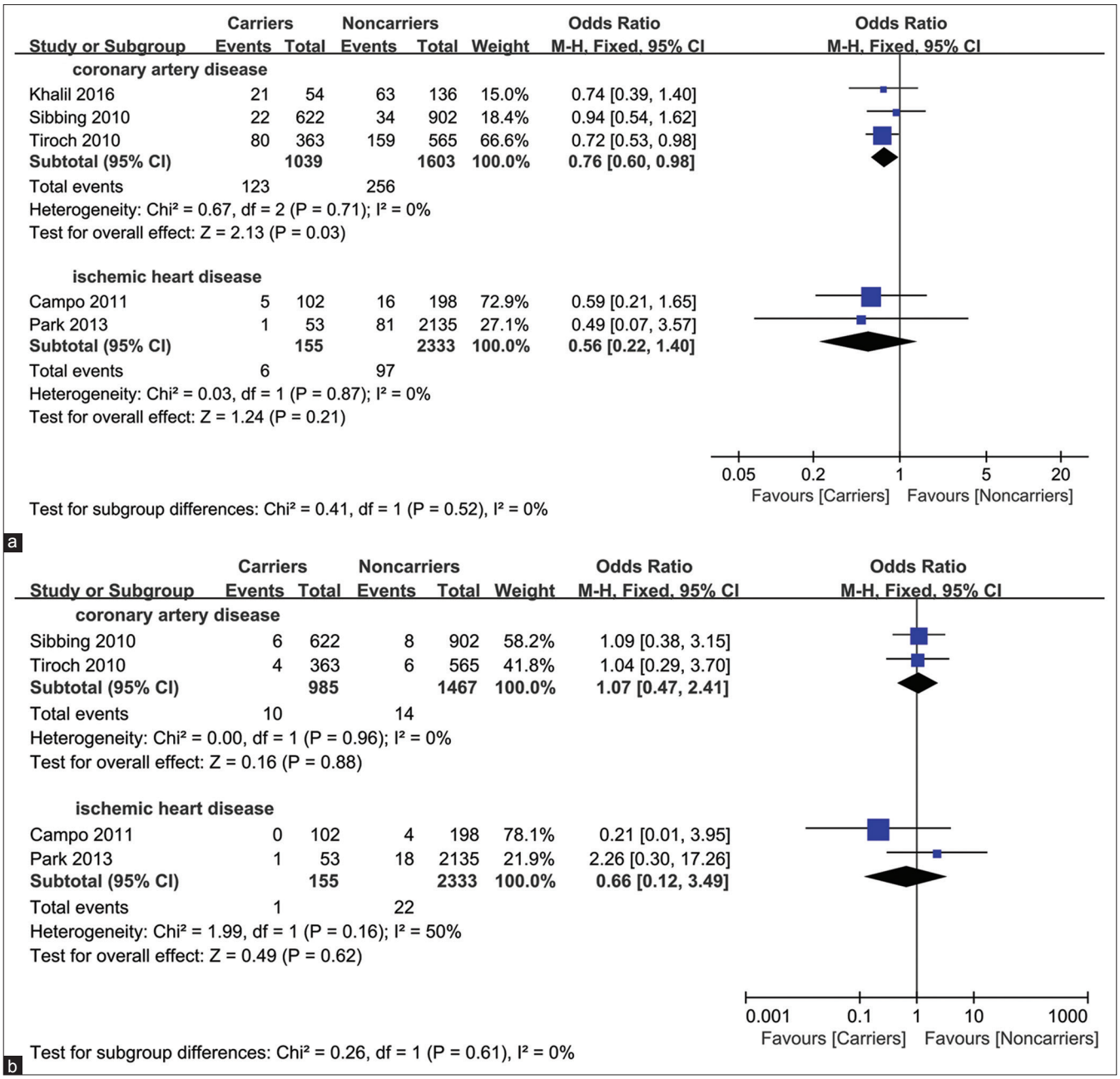

Figure 2: Results for risks of major adverse cardiovascular and cerebrovascular events (a) and stent thrombosis (b). CI = Confidence interval

risk of bleeding events in clopidogrel-treated patients. Furthermore, when stratified by different disease types: CAD[13,15] and IHD,[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[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

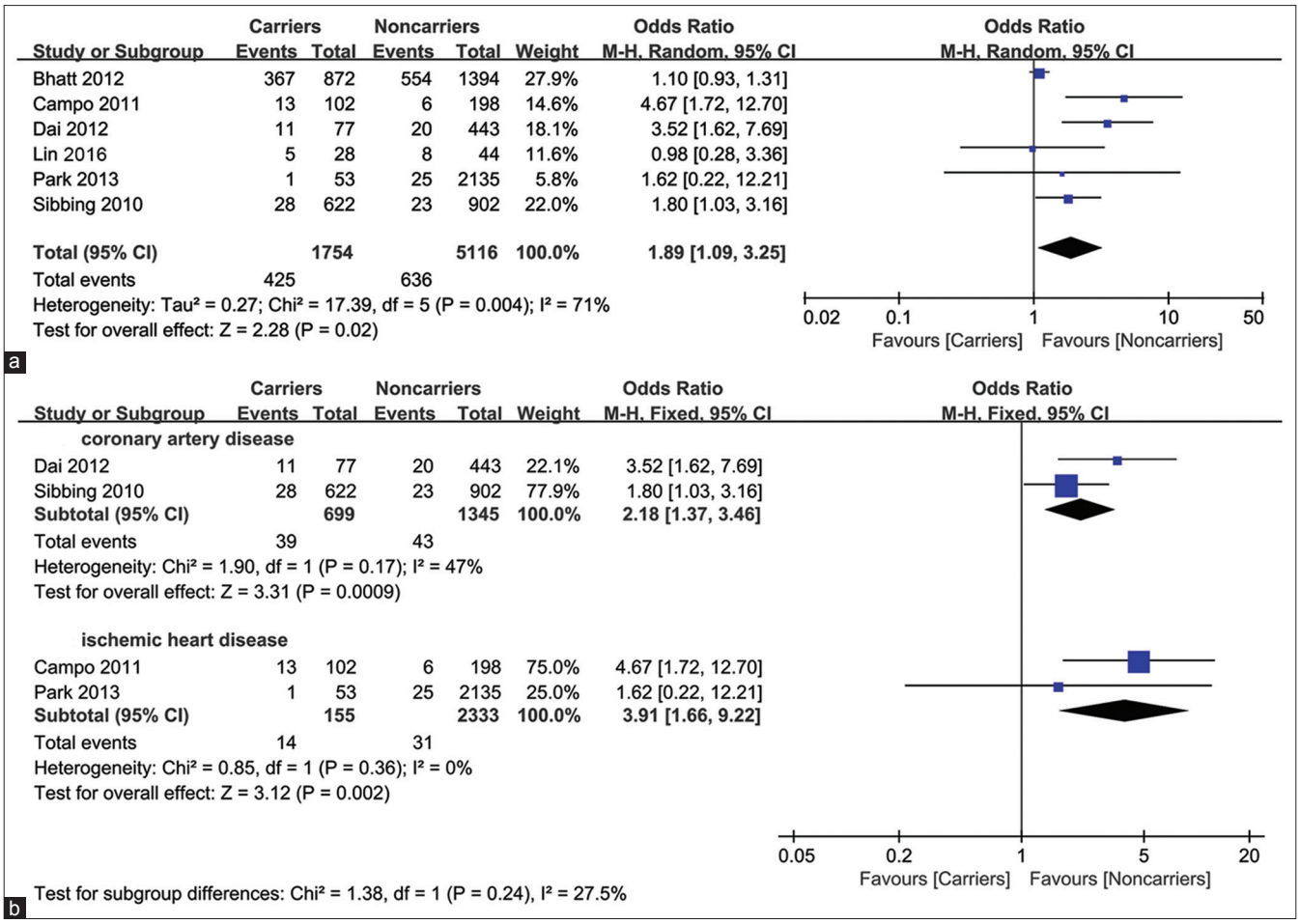

Figure 3: Results for risk of bleeding events. (a) The comprehensive analysis of six studies. (b) The subgroup analyses for patients with coronary artery disease and ischemic heart disease. CI = Confidence interval

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* = 001) [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* = 0.32, I^2 = 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 Supplementaty Figure 1-5.

DISCUSSION

Clopidogrel is an antiplatelet prodrug that requires metabolic activation by *CYP2C19* enzyme.[27] *CYP2C19**17 is

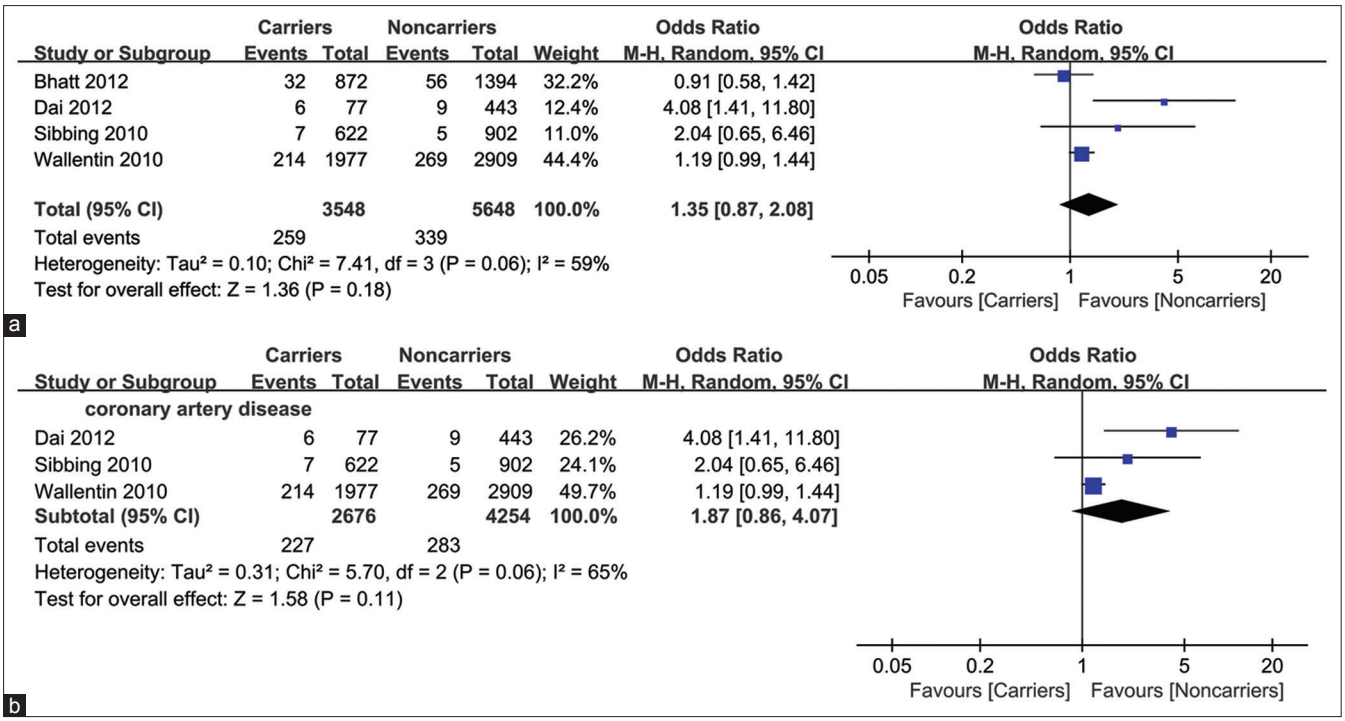

Figure 4: Results for risk of major bleeding. (a) The comprehensive analysis of four studies. (b) The subgroup analyses for patients with coronary artery disease. CI = Confidence interval

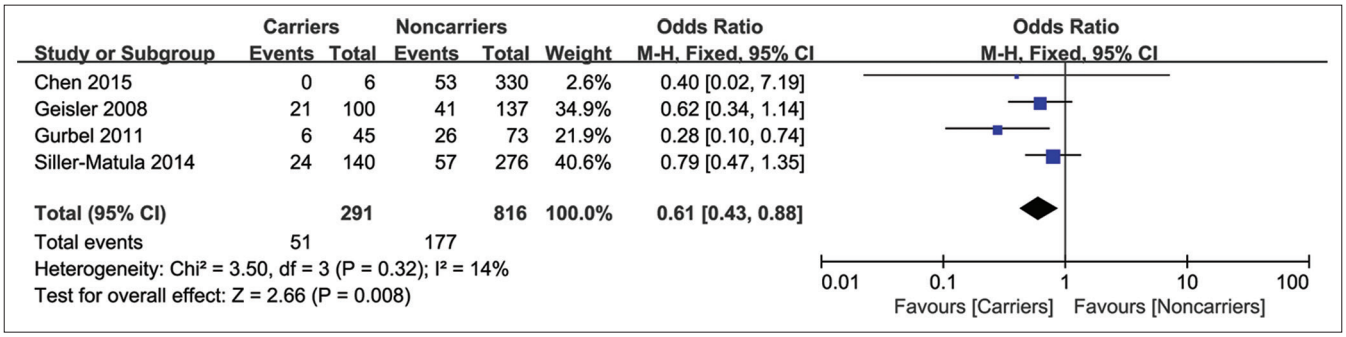

Figure 5: Result for high platelet reactivity risk. CI = Confidence interval

Table 2: Subgroup analyses stratified by type of bleeding events and race

Category	Outcomes	Number of study	Heterogeneity		OR	95% CI	*P*
			P_H	I^2 (%)			
Type of bleeding events (TIMI)	TIMI bleeding	3	0.37	0	2.15	1.37-3.38	0.0008
	TIMI major bleeding	2	0.38	0	2.81	1.26-6.26	0.01
Race (Caucasian)	MACCE	4	0.82	0	0.75	0.59-0.96	0.02
	Ischemic events	3	0.57	0	0.88	0.41-1.90	0.75
	Bleeding events	4	0.02	70	1.62	0.92-2.88	0.10
	Major bleeding	3	0.34	7	1.16	0.97-1.37	0.10
	HPR	3	0.77	0	0.70	0.48-1.04	0.08

TIMI = Thrombolysis in myocardial infarction; HPR = High platelet reactivity; MACCE = Major adverse cardiovascular and cerebrovascular events; OR = Odds ratio; CI = Confidence interval

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

coronary intervention.[7,10] 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,[26] 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.

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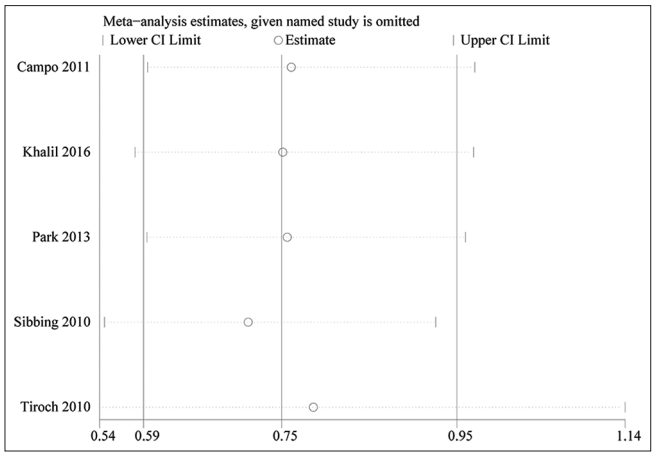
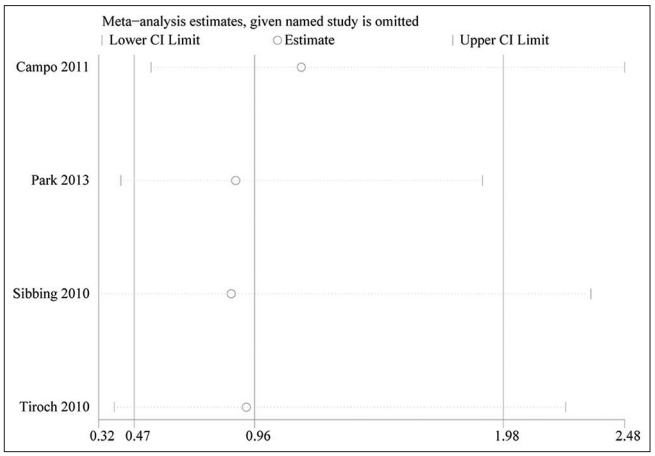
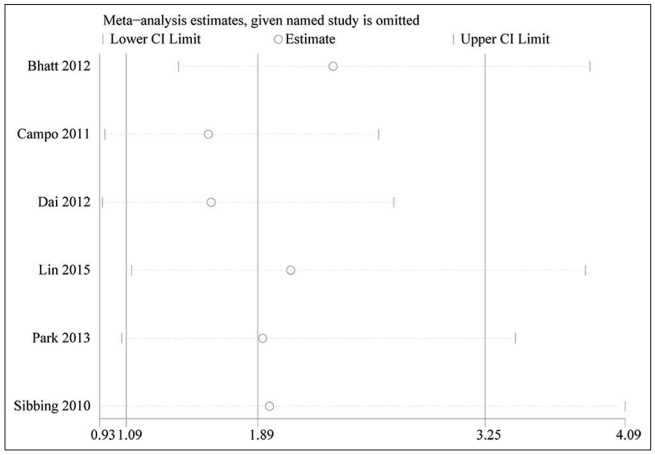


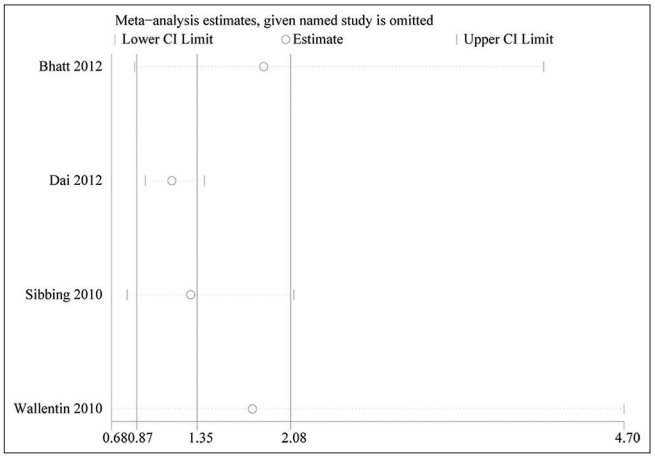
Supplementary Figure 1: Sensitive analysis of major adverse cardiovascular and cerebrovascular event



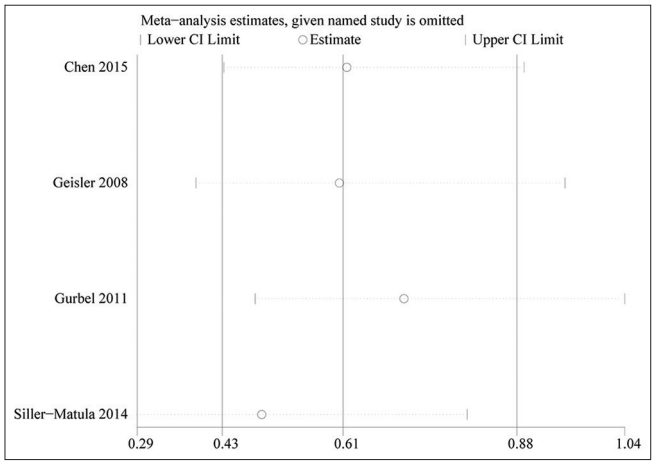
Supplementary Figure 2: Sensitive analysis of stent thrombosis



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