Cyp2C19*2 Polymorphism Related to Clopidogrel Resistance in Patients With Coronary Heart Disease, Especially in the Asian Population: A Systematic Review and Meta-Analysis

Ying Sun1†, Qing Lu1†, Xuefei Tao1, Biao Cheng1* and Guoxing Yang2*

1Department of Geriatric Cardiology, Sichuan Provincial People’s Hospital, University of Electronic Science and Technology of China, Chengdu, China, 2Department of Operations Management, Sichuan Provincial People’s Hospital, University of Electronic Science and Technology of China, Chengdu, China

In recent years, the relationship between Cyp2C19*2 gene polymorphism and clopidogrel resistance reflected by platelet function assay has been studied extensively, but there is no clear conclusion yet. In order to evaluate the relationship between Cyp2C19*2 gene polymorphism and clopidogrel resistance more accurately, meta-analysis was conducted in this study. The I² value taking 50% as the limit, the heterogeneity is judged as high or low, and then a random effect model or a fixed effect model is selected for statistical analysis. PubMed, EMBASE, Web of Science, CNKI, and China Wanfang database were searched, and the related literatures from the establishment of the database to May 2020 were collected and analyzed by STATA 15.0 software. A total of 3,073 patients were involved in 12 studies, including 1,174 patients with clopidogrel resistance and 1,899 patients with non-clopidogrel resistance. The results of this study showed that allele model (A vs. G): OR = 2.42 (95%CI: 1.97–2.98); dominant model (AA+GA vs. GG): OR = 2.74 (95%CI: 2.09–3.59); recessive model (AA vs. GA+GG): OR = 4.07 (95%CI: 3.06–5.41); homozygote model (GA vs. GG): OR = 5.70 (95%CI: 4.22–7.71); heterozygote model (GA vs. GG): OR = 2.32 (95%CI: 1.76–3.07), the differences were statistically significant. Also, the analysis of the Ethnicity subgroup indicated that the Asian allele model and the other four gene models were statistically significant. In conclusion, Cyp2C19*2 gene polymorphism is strongly associated with clopidogrel resistance. Allele A, genotype GA, AA, and GG + GA can increase clopidogrel resistance, especially in the Asian population.

Keywords: Cyp2C19, polymorphism, clopidogrel resistance, meta-analysis, coronary heart disease
INTRODUCTION

Coronary Atherosclerotic Heart Disease (CAHD), hereinafter referred to as Coronary Heart Disease (CHD), is a kind of heart disease caused by coronary atherosclerosis, which could induce vascular stenosis or obstruction, coronary circulation disturbance, myocardial ischemia, hypoxia and even necrosis. With the improvement of living standards, the incidence of coronary heart disease is increasing year by year. CHD has become one of the common diseases seriously affecting human health (Brown et al., 2016). At present, Percutaneous Coronary Intervention (PCI) is the main method for the treatment of CHD, but post-operative patients may develop stent thrombosis (ST), which is a stubborn problem of PCI. Some studies have indicated that 12 months after PCI, the incidence of ST is about 1.5% (Harne et al., 2019). Antiplatelet therapy is an important treatment for CHD to reduce ST after PCI. Dual antiplatelet therapy with clopidogrel and aspirin is the standard therapy for PCI, which can greatly reduce the incidence of subacute thrombosis after PCI (Siasos et al., 2015). The mechanism of thrombosis is so complex that thrombotic events still occur in many post-PCI patients who receive clopidogrel combined with aspirin. As the methods of evaluating platelet function and the definition of antiplatelet drug resistance are different in different studies, the incidence of antiplatelet drug response variability also varies from study to study. Currently, most studies define clopidogrel resistance (CR) as a <10% ADP-induced decrease in the maximum platelet aggregation from the baseline level (Patel et al., 2019). There are many factors affecting the antiplatelet effect of clopidogrel, including age, diabetes, smoking and proton pump inhibitors (Nakagawa et al., 2016; Desai et al., 2017). Moreover, many studies suggest that the polymorphism of genes encoding related functional proteins is also an important factor leading to clopidogrel response variability. The different genotypes lead to different clopidogrel reactivity, hence resulting in different clinical events (Hokimoto et al., 2014; Xiao et al., 2017; Wu et al., 2018). Furthermore, the research on the gene polymorphism of clopidogrel response variability mainly focuses on the coding genes of related functional proteins in absorption, metabolic transformation and binding to the P2Y12 receptor. Among the genes researched, the study of gene polymorphisms affecting the metabolic transformation of clopidogrel has attracted the most attention. The relationship between CYP2C19 gene polymorphism and clopidogrel response variability is consistent in different studies, which may suggest of the important role of CYP2C19 in the two-step metabolic transformation of clopidogrel. The metabolic transformation of clopidogrel in the liver mainly goes through two cytochrome P.450 (CYP)-dependent steps: the first step produces 2.OXO. Clopidogrel is catalyzed by cytochrome Cyp2C19, CYPLA2, and CYP286 in different proportions, and the second step produces active metabolites catalyzed by cytochrome CYP3A4/5, CYP286, Cyp2C19, and CYP2C9 (Ford, 2016). Gene polymorphism amongst different individuals would vary in changes at the level of functional proteins, which thus influence the degree of active metabolites of clopidogrel, and eventually lead to differences in clopidogrel reactions. The variation in clopidogrel response caused by altering Cyp2C19*2 site and *3 site is the most concerned. It is now agreed that clopidogrel resistance occurs when drugs fail to achieve their desired pharmacological effects, which can be analyzed in the laboratory through a variety of platelet functions. So far, some meta-analyses have been conducted to determine the relationship between Cyp2C19*2 gene polymorphism and clinical outcomes, such as thrombosis or stroke (Jin et al., 2011; Pan et al., 2017). However, the researches on the relationship between Cyp2C19*2 gene polymorphism and clopidogrel resistance reflected by platelet function measurement are ongoing, and there is no clear conclusion. Most studies tend to believe that the variant of Cyp2C19*2, allele G → A, could increase clopidogrel resistance (Chen et al., 2010; Cuisset et al., 2011), but some new studies suggest that the variant of allele G → A has nothing to do with clopidogrel resistance (Amin et al., 2017). Therefore, in this study, a meta-analysis was conducted to evaluate the association between clopidogrel resistance and Cyp2C19*2 polymorphism in patients with coronary heart disease.

MATERIALS AND METHODS

Literature Search

We performed this meta-analysis based on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Moher et al., 2009) (Supplementary Table 1). The databases of PubMed, Excerpt Medica Database (EMBASE), Web of Science, National Knowledge Infrastructure (CNKI), China Wanfang were searched to collect relevant literature up to May 2020. The retrieval strategy is as follows: (“cytochrome P450 2C19” OR “Cyp2C19”) AND (“genetic polymorphism” OR “allele” OR “genotype” OR “polymorphism”) AND clopidogrel AND (“resistance” OR “platelet reactivity” OR “platelet response”). For studies with overlapping data or the same population, only the most recent group of subjects were included. There are no language restrictions. Literature retrieval was carried out independently, cross-checked by two researchers in each database. If there were differences, they could be resolved through discussion, or decided by the third researcher.

Inclusion and Exclusion Criteria

Inclusion Criteria

(1) The relationship between Cyp2C19*2 gene polymorphism and clopidogrel resistance; (2) The study was a cohort study or a case-control study; (3) Patients were diagnosed with coronary heart disease; (4) All patients received clopidogrel antiplatelet therapy; (5) The study should provide the number of patients with clopidogrel resistance and non-resistance of each genotype; (6) Diagnostic criteria of clopidogrel resistance: percentage of adenosine diphosphate inhibition ≤ 10%, MPA induced by
adenosine diphosphate \( \geq 50\% \), angiotensin converting enzyme index \( \geq 50\% \), PRI \( \leq 50\% \), PRU > 208, IPA < 30%.

**Exclusion Criteria**

1. Studies belong to reviews, letters, or case reports; 2. Studies involve other definitions of clopidogrel resistance; 3. Repeatedly published data from the same study; 4. Non-coronary heart disease studies, such as ischemic stroke; 5. The control group does not meet the Hardy-Weinberg equilibrium (HWE); 6. NOS (Newcastle-Ottawa Scale) score is < 6.

**Data Extraction**

The information was extracted as follows: first author, publication years, age, country, diagnostic criteria of clopidogrel resistance, clopidogrel load, genotype, and number of patients with clopidogrel resistance. The data were extracted independently by two researchers and discussed and solved by the third researcher when there was disagreement. When the included research information was insufficient, contacting author if possible.

**Literature Quality Evaluation**

After reading the literature carefully, the quality of the literature was evaluated according to The NOS (Stang, 2010). The literature with < 6 stars was of low quality, and those with 6 stars or more were high quality literature. Only those with an evaluation of 6 stars and above were included in this study.

**Statistical Analysis**

Meta-analysis was performed with Stata 15.0 statistical software. Q-test was used to test the heterogeneity of the research results. If \( I^2 \geq 50\% \), or \( P \leq 0.05 \) were considered heterogeneity, Random-effects model (REM) was used (Welton et al., 2007). If \( I^2 < 50\% \) and \( P > 0.05 \) were considered no heterogeneity, fixed-effects model (FEM) should be used for data merging (Leonard and Duffy, 2010). The significance of OR value was performed by Z test. We also made a subgroup analysis of Ethnicity, the year of publication, and the definition of clopidogrel resistance. This Meta-analysis included the evaluation of publication bias, using the funnel plot to determine whether it was symmetrical or not. If the funnel chart was asymmetric, publication bias may exist. Egger's Test was used to test the publication bias. Finally, sensitivity analysis was performed for the robust of results.

**RESULTS**

**Basic Information of Research Data**

A total of 12 trials were selected according to the criteria (Chen et al., 2010; Cuisset et al., 2011; Hwang et al., 2011; Li et al., 2013, 2018; Zhang et al., 2013; Amin et al., 2017; Liang et al., 2017; Saydam et al., 2017; Shen et al., 2017; Wang et al., 2018; Zhuo et al., 2018), including 10 from Asian population and 2 from Caucasian population. A total of 3,073 subjects were involved, including 1,174 patients with clopidogrel resistance and 1,899 patients with non-clopidogrel resistance. The specific screening process can be found in Figure 1. The characteristics of each study and the genotype distribution reported in the study can be found in Table 1. The results of NOS quality evaluation of the literature were shown in Supplementary Table 2. Thus, it can be seen that the NOS scores of the studies included in this study were all above 6, which belonged to high-quality research.
The main results of meta-analysis were shown in Table 2 and Figure 2. Compared A allele with G allele, I² = 64.8%, P < 0.05, which indicated that the heterogeneity among studies was statistically significant, and random effect model was used. The final results showed that OR = 2.42 (95%CI: 1.97–2.98, P < 0.01), the difference was statistically significant. According to the Ethnicity subgroup analysis, the results showed that there was a significant difference in Asian population with OR = 2.37 (95%CI: 1.86–3.02, P < 0.05), which showed that there was no statistical significance in the heterogeneity among the studies, and the fixed effect model was used. The results showed that there was a significant difference with OR = 4.07 (95%CI: 3.06–5.41, P < 0.05). The ethnic subgroup analysis indicated the same results, the comparison of Caucasian and Asian recessive genetic models was statistically significant, and was shown in Figure 2C. The symmetry of funnel plot showed bias (Figure 3C), Egger’s Test showed P < 0.05, which indicated that there was a certain bias.

### Recessive Genetic Model

The genotype AA was compared with genotype GA + GG, I² = 0.0%, P > 0.05, which suggested that there was no statistical significance in the heterogeneity among the studies, and the fixed effect model was used. The results showed that there was a significant difference with OR = 5.70 (95%CI: 4.22–7.71, P < 0.01). The ethnic subgroup analysis indicated the same results, the comparison of Caucasian and Asian homozygous genetic models was statistically significant, and was shown in Figure 2D. The funnel plot was basically symmetrical (Figure 3D), Egger’s Test showed P > 0.05, which suggested that the publication bias was well-controlled.

### Homozygous Model

The genotype AA vs. GG, I² = 33.9%, P > 0.05, which showed that there was no statistical significance in the heterogeneity among the studies, and the fixed effect model was used. The final results showed that there was a significant difference with OR = 3.39 (95%CI: 2.09–5.49, P < 0.01). The ethnic subgroup analysis indicated the same results, the comparison of Caucasian and Asian homozygous genetic models was statistically significant shown in Figure 2D. The funnel plot was basically symmetrical (Figure 3D), Egger’s Test showed P > 0.05, which suggested that the publication bias was well-controlled.
TABLE 2 | Results of meta-analysis for cyp2c19*2 Polymorphism and Clopidogrel resistance.

| Genetic models        | Subgroup       | n  | OR     | 95%CI   | P      | I² (%) | P for heterogeneity | Model | P for Publication bias |
|-----------------------|----------------|----|--------|---------|--------|--------|---------------------|-------|-----------------------|
| Allelic model (A vs. G) | Overall        | 12 | 2.42   | 1.97–2.98 | 0.000  | 64.8   | 0.001   | REM               | 0.125 |
|                             | Asian          | 10 | 2.37   | 1.86–3.02 | 0.000  | 69.3   | 0.001   | REM               | 0.178 |
|                             | Caucasian      | 2  | 2.77   | 2.03–3.79 | 0.000  | 0.0    | 0.731   | NA                | NA    |
|                             | Year ≤2013     | 5  | 1.96   | 1.68–2.30 | 0.000  | 7.2    | 0.366   | FEM               | 0.223 |
|                             | ≥2013          | 7  | 2.88   | 2.07–3.99 | 0.000  | 65.1   | 0.000   | REM               | 0.796 |
| Definition of clopidogrel resistance | Percent inhibition of ADP ≤ 10% | 2  | 1.98   | 1.53–2.57 | 0.000  | 32.4   | 0.224   | REM               | NA    |
|                             | ADP-induced MPA > 50% | 3  | 2.22   | 1.47–3.36 | 0.000  | 69.3   | 0.038   | REM               | 0.363 |
|                             | Others         | 7  | 2.76   | 2.00–3.80 | 0.000  | 64.0   | 0.011   | REM               | 0.766 |
| Dominant model (AA + AG vs. GG) | Overall       | 12 | 2.74   | 2.09–3.59 | 0.000  | 63.0   | 0.002   | REM               | 0.063 |
|                             | Asian          | 10 | 2.74   | 1.97–3.80 | 0.000  | 68.0   | 0.001   | REM               | 0.093 |
|                             | Caucasian      | 2  | 2.90   | 2.02–4.16 | 0.000  | 0.0    | 0.334   | FEM               | NA    |
|                             | Year ≤2013     | 5  | 2.12   | 1.74–2.59 | 0.000  | 0.0    | 0.780   | FEM               | 0.116 |
|                             | ≥2013          | 7  | 3.49   | 2.15–5.69 | 0.000  | 70.3   | 0.003   | REM               | 0.361 |
| Definition of clopidogrel resistance | Percent inhibition of ADP ≤ 10% | 2  | 2.19   | 1.64–2.93 | 0.000  | 0.0    | 0.516   | FEM               | NA    |
|                             | ADP-induced MPA > 50% | 3  | 2.81   | 1.44–5.50 | 0.002  | 76.8   | 0.013   | REM               | 0.296 |
|                             | Others         | 7  | 3.03   | 1.96–4.68 | 0.000  | 66.6   | 0.006   | REM               | 0.361 |
| Recessive model (AA vs. AG + GG) | Overall       | 12 | 4.07   | 3.06–5.41 | 0.000  | 63.0   | 0.595   | FEM               | 0.017 |
|                             | Asian          | 10 | 3.98   | 2.95–5.37 | 0.000  | 0.0    | 0.484   | FEM               | 0.031 |
|                             | Caucasian      | 2  | 4.96   | 1.99–12.36| 0.001  | 0.0    | 0.411   | FEM               | NA    |
|                             | Year ≤2013     | 5  | 3.25   | 2.31–4.59 | 0.000  | 0.0    | 0.721   | FEM               | 0.306 |
|                             | ≥2013          | 7  | 6.52   | 3.86–11.01| 0.000  | 0.0    | 0.856   | FEM               | 0.778 |
| Definition of clopidogrel resistance | Percent inhibition of ADP ≤ 10% | 2  | 3.34   | 2.07–5.38 | 0.000  | 0.0    | 0.578   | FEM               | NA    |
|                             | ADP-induced MPA > 50% | 3  | 3.25   | 2.00–5.29 | 0.000  | 4.0    | 0.353   | FEM               | 0.386 |
|                             | Others         | 7  | 6.53   | 3.81–11.17| 0.000  | 0.0    | 0.855   | FEM               | 0.740 |
| Homozygous model (AA vs. GG) | Overall       | 12 | 5.70   | 4.22–7.71 | 0.000  | 33.9   | 0.119   | FEM               | 0.085 |
|                             | Asian          | 10 | 5.62   | 4.09–7.73 | 0.000  | 0.0    | 0.484   | FEM               | 0.097 |
|                             | Caucasian      | 2  | 6.38   | 2.51–16.22| 0.000  | 0.0    | 0.544   | FEM               | NA    |
|                             | Year ≤2013     | 5  | 4.31   | 2.99–6.21 | 0.000  | 0.0    | 0.734   | FEM               | 0.320 |
|                             | ≥2013          | 7  | 10.52  | 6.01–18.41| 0.000  | 0.0    | 0.310   | FEM               | 0.832 |
| Definition of clopidogrel resistance | Percent inhibition of ADP ≤ 10% | 2  | 4.58   | 2.74–7.64 | 0.000  | 0.0    | 0.572   | FEM               | NA    |
|                             | ADP-induced MPA > 50% | 3  | 4.62   | 2.79–7.67 | 0.000  | 63.1   | 0.067   | REM               | 0.392 |
|                             | Others         | 7  | 9.18   | 5.18–16.26| 0.000  | 4.5    | 0.393   | FEM               | 0.854 |
| Heterozygous model (AG vs. GG) | Overall       | 12 | 2.32   | 1.76–3.07 | 0.000  | 61.4   | 0.003   | REM               | 0.085 |
|                             | Asian          | 10 | 2.29   | 1.65–3.18 | 0.000  | 65.2   | 0.002   | REM               | 0.113 |
|                             | Caucasian      | 2  | 2.56   | 1.55–4.22 | 0.000  | 42.1   | 0.189   | FEM               | NA    |
|                             | Year ≤2013     | 5  | 1.82   | 1.48–2.25 | 0.000  | 0.0    | 0.897   | FEM               | 0.095 |
|                             | ≥2013          | 7  | 2.91   | 1.75–4.85 | 0.000  | 70.4   | 0.002   | REM               | 0.443 |
| Definition of clopidogrel resistance | Percent inhibition of ADP ≤ 10% | 2  | 1.88   | 1.38–2.55 | 0.000  | 0.0    | 0.947   | FEM               | NA    |
|                             | ADP-induced MPA > 50% | 3  | 2.41   | 1.27–4.57 | 0.007  | 72.5   | 0.026   | REM               | 0.294 |
|                             | Others         | 7  | 2.52   | 1.58–4.03 | 0.000  | 68.2   | 0.004   | REM               | 0.439 |

OR, odds ratio; FEM, fixed-effects model; REM, random-effects model.
FIGURE 2 | Forest plot for the association between cyp2c19*2 Polymorphism and Clopidogrel resistance (A: Allelic model; B: Dominant model; C: Recessive model; D: Homozygous model; E: Heterozygote model).
Heterozygote Model
The genotype GA compared with GG, $I^2 = 61.4\%$, $P < 0.05$, which showed that the heterogeneity among the studies was statistically significant, and the random effect model was used. The final results showed that there was a significant difference with OR $= 2.32$ (95%CI: 1.76–3.07, $P > 0.05$). The ethnic subgroup analysis suggested the same results, the comparison of Caucasian and Asian heterozygous genetic models was statistically significant, and the forest plot was shown in Figure 2E. The funnel plot was basically symmetrical (Figure 3E), Egger’s Test showed that $P > 0.05$, the difference was not statistically significant, which indicated that the publication bias was well-controlled.

Subgroup Analysis of Year and CR Definition
The results of subgroup analysis of the published year (Table 2) showed that the differences were statistically significant in all
According to the strict inclusion and exclusion criteria, this study included 12 high-quality literatures with a total of 3,073 subjects. The results showed that the allele model (A vs. G): OR = 2.42 (95% CI: 1.97–2.98), the difference was statistically significant. Dominant gene model, recessive gene model, homozygote model, and heterozygote model were also statistically significant. The funnel chart and Egger’s Test results of publication bias showed that there was no publication bias. The results of subgroup analysis showed that the results of the Asian population were consistent with those of the total population, while the Caucasian population was inconclusive because only two articles were included. The results of subgroup analysis of different definitions of clopidogrel resistance and the year of publication showed that the differences were statistically significant in each genetic model of each subgroup. Sensitivity analysis results indicated that after excluding a single study, the meta-analysis results of the allele model and the other four gene models did not have a statistically significant change, indicating that the results were robust. Therefore, it could be considered that there is a strong association between CYP219°2 polymorphism and clopidogrel resistance in patients with CHD, and the variant of allele G could increase clopidogrel resistance in antiplatelet therapy. This is basically consistent with the conclusion of a previous meta-analysis by Hou et al. (2014) including eight studies. Furthermore, compared with previous studies, this study is more stringent in the literature inclusion criteria, such as excluding the study that the control group does not conform to HWE, and including more latest studies. From the publication bias and stability results, the conclusions of this study are reliable and valuable.

In this study, several limitations should be noted: (1) Since there is no standard definition of clopidogrel resistance at present, multiple definitions of clopidogrel resistance were used in this study, which may weaken the comparability of the data; (2) In the subgroup analysis, the sample size is relatively small, and there are only 2 studies in the Caucasian population, so the conclusion need to be carefully adapted to the Caucasian population; (3) The lack of raw data also limits further assessment of potential gene-gene or gene-environment interactions.

In conclusion, CYP219°2 gene polymorphism is associated with clopidogrel resistance reflected by platelet function assay, and the allele (A vs. G) increases clopidogrel resistance, which is reflected in the other four models, especially in the Asian population. This conclusion can be used to guide the individualized antiplatelet therapy of clopidogrel. Due to the limitations of this study, such as multiple definitions of clopidogrel resistance, gene-gene interaction, it is necessary to do more and more in-depth studies on CYP219°2 gene polymorphism and antiplatelet therapy.

**AUTHOR CONTRIBUTIONS**

YS, GY, and QL have given substantial contributions to the conception or the design of the manuscript, GY and YS to
acquisition, analysis, and interpretation of the data. All authors have participated to drafting the manuscript, BC and GY revised it critically. All authors read and approved the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the 
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