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Association between *CYP3A4* gene polymorphisms and clopidogrel response in patients with cardio-cerebrovascular diseases: a systematic review and Meta-analysis

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Abstract: *CYP3A4* plays a critical role in clopidogrel activation in the liver. The polymorphism of *CYP3A4* may have an important effect on clopidogrel response in patients with cardio-cerebrovascular diseases. We conducted a systematic review and meta-analysis to evaluate the impact of *CYP3A4* polymorphism on platelet reactivity after clopidogrel treatment and the outcomes of patients. A systematic literature search (up to 7th October, 2019) was performed on the PubMed, EMBASE, Cochrane Library, clinicaltrials.gov, and Chinese databases, including China National Knowledge Infrastructure (CNKI) and Wan Fang Data. Cohort studies or case-control studies evaluated platelet reactivity and patients' outcomes in different genotype patients. The Review Manager software was used for data analysis, and the NOS scale was used to assess the quality of included studies. A total of 18 articles were included in the Meta-analysis. The results showed the platelet reactivity after clopidogrel administration had no significant difference between *CYP3A4* variant carriers and non-carriers. The occurrence of composite ischemic events or stent thrombosis had no significant difference between *CYP3A4* variant carriers and non-carriers, either. In conclusion, there was no significant association between *CYP3A4* polymorphism and clopidogrel response in patients with cardio-cerebrovascular diseases.

Keywords: Clopidogrel; *CYP3A4*; Meta-analysis

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1. Introduction

Clopidogrel is one of the most widely used P2Y12 receptor blocker to cardio-cerebrovascular diseases[1−3]. However, the effectiveness of clopidogrel is less than ticagrelor and prasugrel in the prevention of recurrent ischemic events[4−6]. According to Gallego-Fabrega et al., 16%–50% of patients treated with clopidogrel have a high on-treat platelet reactivity, which is also called clopidogrel resistance (CR) and will cause an increased risk of recurrent ischemic events[7].

As a prodrug, clopidogrel requires activation by the cytochrome P450 (CYP) family to generate an active metabolite. Clopidogrel is metabolized by the *CYP1A2*, *CYP2B6*, and *CYP2C19* to transform into an inactive intermediate, which is further metabolized by the *CYP2B6*, *CYP2C9*, *CYP2C19*, and *CYP3A4* to generate an active metabolite[8,9]. *CYP2C19* is the most evidential gene related to CR. FDA makes a black-box warning to *CYP2C19* polymorphism as the main cause of the reduced activation of clopidogrel[10]. However, *CYP2C19* polymorphism only contributes a part of CR. Besides *CYP2C19*, other genes involved in the activation of clopidogrel also have an impact on CR.

CYP3A4 is a critical hepatic enzyme to the metabolism of most drugs. The *CYP3A* isoenzymes include *CYP3A4*

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and *CYP3A5*, which contribute up to 39.8% of the active metabolite of clopidogrel[11,12]. According to Wang YQ et al., *CYP3A5* polymorphism is not related to the response of clopidogrel[13]. However, the effect of *CYP3A4* polymorphism on the platelet reactivity and the risk of recurrent ischemic events in patients treated with clopidogrel still unclear. We conducted a systematic review and Meta-analysis to investigate the impact of *CYP3A4* polymorphism on clopidogrel response in patients with cardio-cerebrovascular diseases.

2. Methods

2.1. Search strategy

A systematic literature search (up to 7th October, 2019) was performed on the PubMed, EMBASE, Cochrane Library, clinicaltrials.gov, and Chinese databases, including China National Knowledge Infrastructure (CNKI) and Wan Fang Data. The main categories were "*CYP3A4*" and "clopidogrel", which were combined by the Boolean operator "AND". The operator "OR" was used to combine the terms of each category.

2.2. Study selection

Each article was reviewed independently by two reviewers (Sibei Qin and Yu Fu). The inclusion criteria were as follows: (1) Cohort study or case-control study, (2) included patients diagnosed as cardiovascular or cerebrovascular diseases and treated with clopidogrel regularly, (3) genotyped for the *CYP3A4* gene, (4) reported the platelets reactivity or outcomes after clopidogrel treatment. The primary outcome was a composite outcome including major adverse cardiovascular events (MACE) and stent thrombosis, and secondary outcomes were the occurrence of MACE or stent thrombosis, separately, and (5) full-text publication available.

2.3. Data extraction and quality assessment

Two reviewers extracted the following data from included studies: (1) basic information, including first author name, publication year, study design, cohort size, (2) patient characters including diagnosis, gender, and age, (3) selected single nucleotide polymorphism (SNPs) of *CYP3A4*, (4) platelet reactivity and outcomes after clopidogrel treatment. Platelet reactivity included platelet maximum aggregation rate (MPR), inhibition of platelet aggregation (IPA) activated by different concentrations of adenosine diphosphate (ADP), platelet response unit (PRU) measured by VerifyNow P2Y12, and platelet residual activity index (PRI) measured by VASP protein phosphorylation. CR was defined as MPA ≥ 70% or IPA < 10%, PRU > 208 or PRI > 50% after clopidogrel treatment[8,14–16]. The Newcastle-Ottawa scale (NOS) was used to assess the data quality of observational studies. Articles with NOS scale ≥ 5 were considered as low risk of bias.

2.4. Data synthesis and analysis

Data were analyzed using Cochrane Review Manager Software 5.3, Stata 13.1. The mean difference (MD) and 95% confidence interval (CI) were calculated as the efficacy parameters using a random-effect model for the PRU of patients. The risk ratio (RR) and 95% CI were calculated as the efficacy parameters using a random-effect model for CR and stent thrombosis. A fix-effect model was used to evaluate the composite ischemic events.

The percentage of total variation across studies was determined by the I^2 metric test. The heterogeneity between studies analyzed was identified by Q test and I^2 metric results. I^2 values ≥ 50% and the *P*-value of Q test showed a significant heterogeneity[17]. The risk of publication bias was tested by the

funnel plot and further confirmed by Begg's test or Harbord test.

3. Results

3.1. Search results and study characteristics

Figure 1 shows the flow chart of the screening process. A total of 18 articles were included in the meta-analysis[18–35]. A total of 11 289 patients with CAD or cerebrovascular disease treated with clopidogrel were included in the meta-analysis. Table 1 shows the characteristics of the 18 studies included in the meta-analysis. The sample size ranged from 77 to 5714. Mean age range from 57.7 to 69.8. 7 articles reported the outcomes of patients after clopidogrel treatment. The median follow-up period was 12 months.

The SNPs included in the meta-analysis were rs2242480, rs2740574, IVS7 + 894 C > T, rs35599367, rs4646437, and rs4986910. The most studied SNP was rs2242480. Eight articles studied the impact of rs2242480 polymorphism on clopidogrel response. The NOS of each included article was all > 5 (Table 1).

3.2. Meta-analysis of the CR

A total of 13 articles reported the platelet reactivity of patients after clopidogrel treatment. The evaluation indicators of platelet reactivity included MPR, IPA, PRU, and PRI. Different indicators could not be combined easily. Moreover, 10 articles separated the participators into the CR group and non-CR (NCR) group. CR was defined as MPA ≥ 70% or IPA < 10% or PRU > 208 or PRI > 50% after clopidogrel treatment[8,14–16]. We analyzed whether *CYP3A4* polymorphism had a significant association with CR. A random-effect model was performed to analyze the CR. The results showed that *CYP3A4* polymorphism had no significant association with CR. The subgroup analysis according to SNPs did not show any significant association between different SNP polymorphisms of *CYP3A4* and CR (Fig. 2). The funnel plot of the studies included in the meta-analysis of CR was shown as Figure 3.

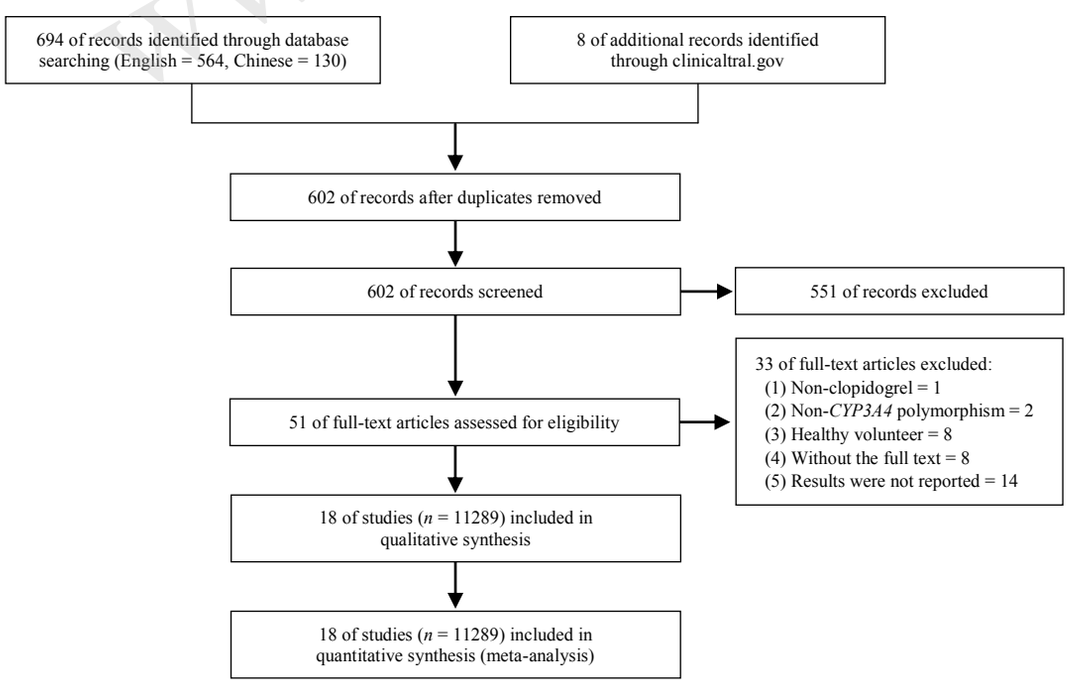

Figure 1. Flow chart of study search.

Table 1. Characteristics of the 18 studies included in the Meta−analysis.

Author (year)	Study design	Patients diagnosis	Sample size	Follow up (months)	Mean age (year, SD)	Gender (male, %)	SNPs of *CYP3A4*	NOS scales
Geisler, T (2008)	Cohort study	CAD	237	-	69.0 (13.0)	181 (76.4)	rs2740574	6
Yaling Han (2008)	Cohort study	CAD	300	-	58.0 (10.8)	202 (67.3)	IVS7 + 894 C > T	6
Harmsze, A (2010)	Cohort study	CAD	428	-	63.4 (9.6)	335 (78.3)	rs2740574	6
Harmsze, A. M (2010)	Case control study	Patient with PCI	596	12	Case: 64.1 (9.4) Control: 62.1 (9.4)	471 (79.0)	rs2740574	7
Viviani Anselmi, C (2013)	Cohort study	SCAD	1432	12	Event: 65.3 (9.8) NEvent: 64.8 (10.2)	1107 (77.7)	rs2242480 rs4986910	7
Zhang, S (2014)	Cohort study	Acute ischemic stroke	95	6	CR: 67.8 (8.2) NCR: 64.1 (11.9)	62 (65.3)	rs2242480 IVS7 + 894 C > T	7
Lin, Y. J (2014)	Cohort study	CAD	90	12	ST: 66.7 (8.0) NST: 67.3 (9.6)	74 (82.2)	IVS7 + 894 C > T	7
Chen, Y (2015)	Cohort study	ACS	336	-	CR: 69.2 (11.1) NCR: 66.6 (10.4)	223 (66.4)	rs4646437	6
Li, H (2016)	Cohort study	ACS	275	-	CR: 63.4 (10.5) NCR: 62.5 (11.3)	167 (60.7)	IVS7 + 894 C > T	6
Liu, R (2016)	Case control study	Ischemic stroke	191	-	Case: 67.0 (10.0) Control: 67.0 (10.0)	110 (57.6)	rs2242480	6
Garcia-Lagunar, M. H (2017)	Cohort study	ACS	278	-	CR: 67.3 (11.0) NCR: 61.9 (11.0)	193 (69.4)	rs2740574	6
Saydam, F (2017)	Cohort study	CAD	347	-	CR: 64.5 (median) NCR: 60 (median)	274 (79.0)	rs2242480	6
Li, C (2017)	Cohort study	ACS	5714	12	Event: 64 (median) NEvent: 59 (median)	4343 (76.0)	rs2242480	7
Al-Husein, B. A (2018)	Cohort study	CAD	280	-	CR: 57.7 (10.7) NCR: 61.3 (10.4)	195 (69.6)	rs2242480	6
Mahdieh, N (2018)	Cohort study	Patient with PCI	388	6	60.5 (10.4)	274 (70.6)	rs2242480	7
Saiz-Rodríguez Miriam (2019)	Cohort study	Patietns with percutaneous neurointervention	144	60	64.8 (11.8)	74 (51.4)	rs35599367	7
Mirzaev, K. B (2019)	Cohort study	ACS	81	-	63.9 ± 10.9	-	rs35599367	6
Zhang, Z. J (2019)	Cohort study	CAD	77	-	CR: 69.8 (12.2) NCR: 68.9 (11.0)	51 (66.2)	rs2242480	6

CAD: coronary artery disease, SCAD: stable coronary artery disease, ACS: acute coronary syndrome, PCI: percutaneous coronary intervention, CR: clopidogrel resistance, NCR: non clopidogrel resistance, NEvent: Non-event.

Four articles reported the impact of *CYP3A4* polymorphism on PRU after clopidogrel treatment. A random-effect model was used to evaluate the association between *CYP3A4* polymorphism and platelet reactivity. Results showed that neither rs2740574 nor rs35599367 polymorphism would affect platelet reactivity after clopidogrel treatment (Fig. 4).

3.3. Meta-analysis of the outcomes of patients

Seven articles reported the outcomes of patients after clopidogrel treatment. A fixed-effect model was used to evaluate the impact of *CYP3A4* polymorphism on primary outcomes. Results showed that *CYP3A4* polymorphism did not have a significant effect on composite ischemic events (Fig. 5). The funnel plot of the studies included in the meta-analysis of composite ischemic outcomes was shown in Figure 6.

Two articles reported the outcomes of stent thrombosis separately. Results showed that there was no significant association between *CYP3A4* polymorphism and stent thrombosis (Fig. 7).

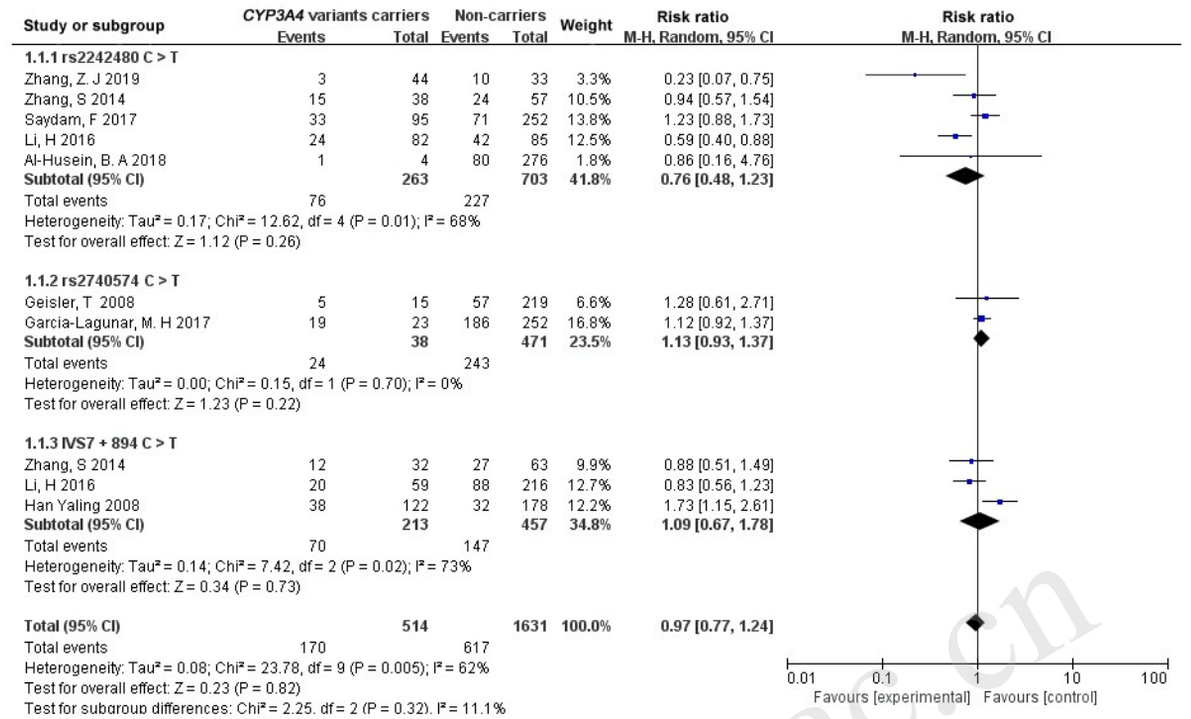

Figure 2. Forest plot demonstrating trough CR.

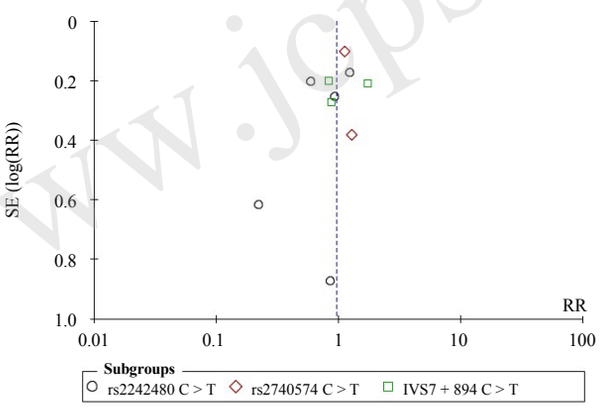

Figure 3. The funnel plot demonstrating the bias of meta-analysis to CR.

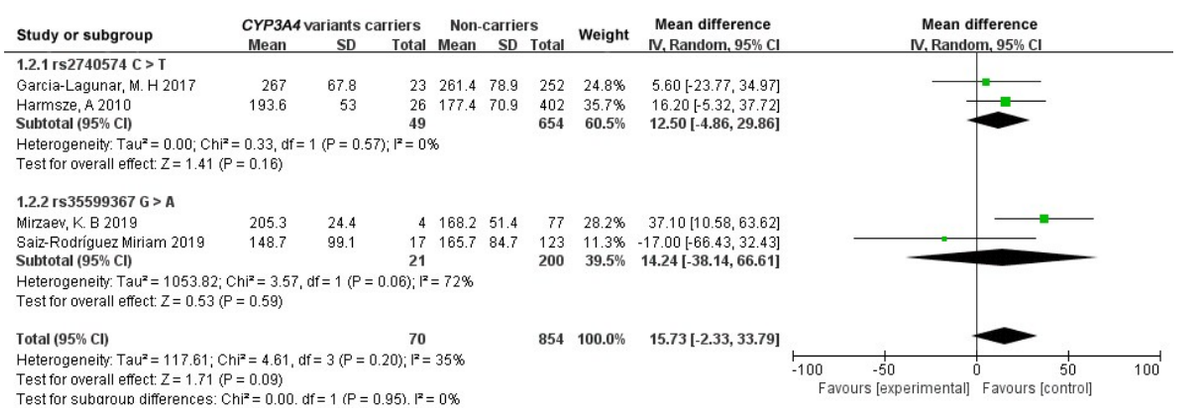

Figure 4. Forest plot demonstrating trough PRU.

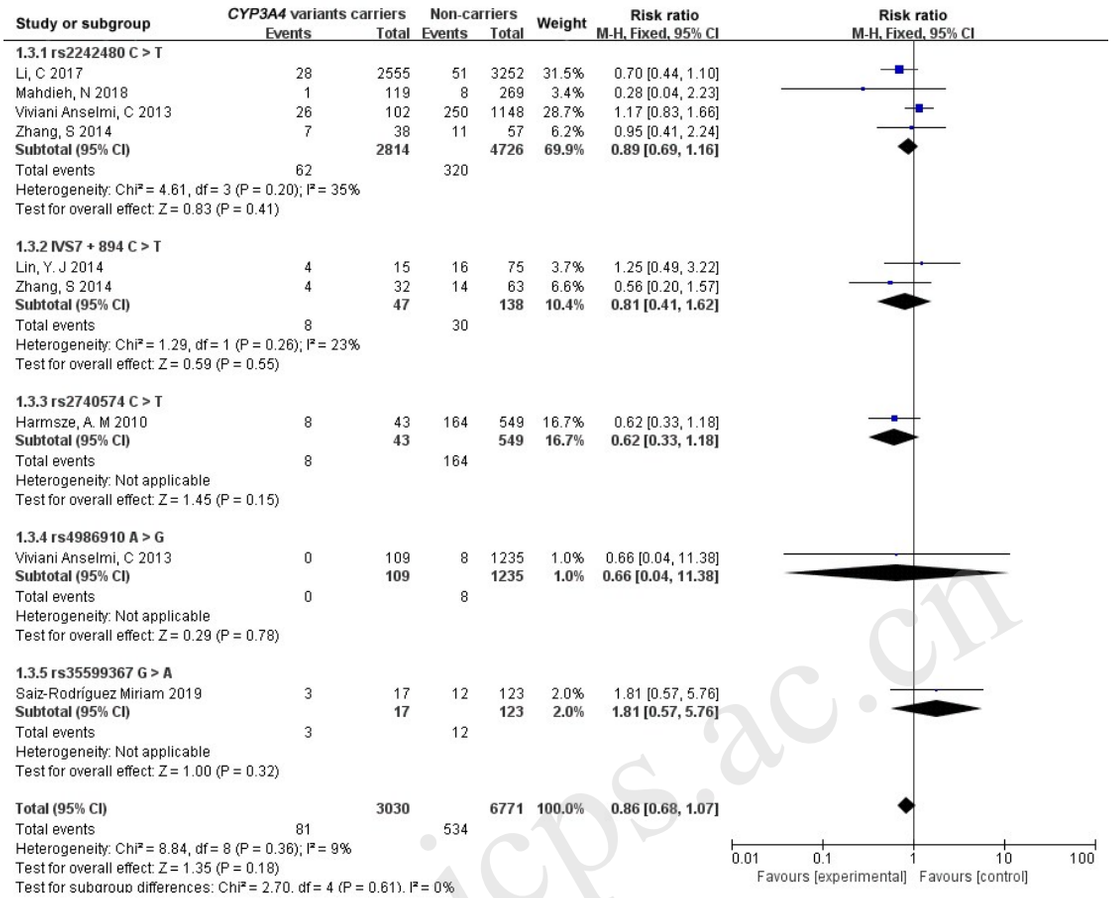

Figure 5. Forest plot demonstrating trough composite ischemic events.

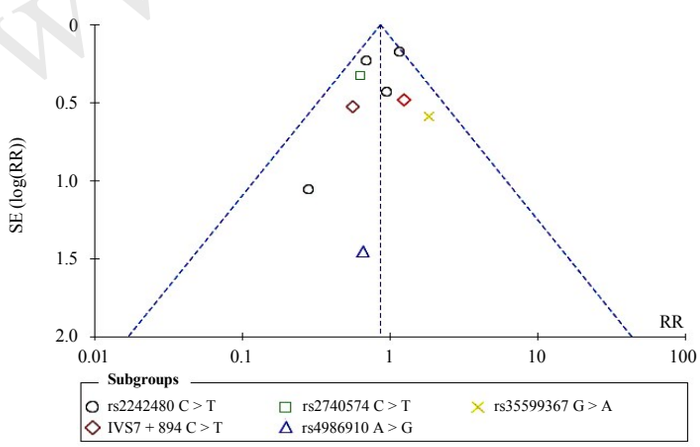

Figure 6. The funnel plot demonstrating the bias of meta-analysis to composite ischemic events.

Figure 7. Forest plot demonstrating trough recurrent stent thrombosis.

3.4. Evaluation of heterogeneity and sensitivity analysis of the analyzed studies

The results of the composite ischemic events were 9% for I^2. The *P*-value of the Q test was 0.36, indicating that there was no significant heterogeneity between the studies analyzed. The results showed that there was low heterogeneity between the studies included in the analysis of PRU and stent thrombosis (I^2 = 35%, P = 0.2 and I^2 = 32%, P = 0.23, respectively). However, the results of I^2 and Q tests showed that there was significant heterogeneity between the studies included in the analysis of CR (I^2 = 62%, P = 0.005). When two articles were deleted (Han, Y.L. 2008 and Li, H. 2016), the heterogeneity was low (I^2 = 34%, P = 0.15), indicating that these two articles might be a reason for the high heterogeneity.

3.5. Risk of bias

The meta-analysis of the CR and composite ischemic events included 10 and 7 articles, respectively. The funnel plot suggested a possible bias (Fig. 3, 6).

4. Discussion

According to the 2017 ESC/EACTS Guidelines for the management of valvular heart disease, dual antiplatelet therapy (DAPT) which means the aspirin in combination with P2Y12 receptor blockers, still is an effective prevention for stent thrombosis in patients with valvular heart disease, and can reduce the risk of myocardial infarction and stroke in these patients[36]. Clopidogrel is one of the most widely used P2Y12 receptor blockers in the world. However, because of the variable individual reactions to clopidogrel, part of the patients still have recurrent ischemic events even receiving clopidogrel regularly.

Since clopidogrel is a prodrug, gene polymorphism regulated to its biotransformation process can explain part of the individual variation of clopidogrel response. *CYP3A4* and *CYP3A5* contribute up to 39.8% of the active metabolite during the second metabolic process of clopidogrel in the liver. Previous studies have shown that inhibition of *CYP3A4* activity can reduce the antiplatelet activity of clopidogrel during DAPT[37–39]. Our meta-analysis showed that the *CYP3A4* polymorphism did not have a significant association with CR. Meta-analysis to PRU also showed that the *CYP3A4* polymorphism did not have a significant association with platelet reactivity after clopidogrel treatment. Six SNPs were included in our Meta-analysis. Rs2242480, rs35599367, and rs4646437 were located in the intron, which might not affect protein structure directly. Rs2740574 was located in the upstream of *CYP3A4* gene. The polymorphism of rs2740574 is related to the drug response, such as tacrolimus[40]. However, our results showed that rs2740574 polymorphism was not related to platelet reactivity after clopidogrel administration, indicating that rs2740574 polymorphism might not affect clopidogrel activation. Our results did not find the association between IVS7 + 894 C > T, rs4986910 polymorphism and clopidogrel response, either.

The Meta-analysis of outcomes showed that there was no significant association between *CYP3A4* polymorphism and ischemic events in patients treated with clopidogrel. The results were coincident with our meta-analysis results of CR. Our results showed that *CYP3A4* polymorphism might not affect clopidogrel response in patients with cardio-cerebrovascular diseases.

However, there were some limitations in the present study. First of all, some articles were excluded because they did not report the available data. These data might affect the results. Moreover, fewer articles reported patients' outcomes. More quality studies are need in further study.

5. Conclusions

In this meta-analysis, (1) there was no significant association between *CYP3A4* polymorphism and platelet reactivity after clopidogrel administration. (2) There was no significant association between *CYP3A4* polymorphism and composite ischemic events or stent thrombosis in patients with CAD or cerebrovascular disease.

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*CYP3A4*基因多态性对心脑血管疾病患者氯吡格雷响应影响的Meta分析

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摘要: 氯吡格雷是目前使用最广泛的P2Y12受体抑制剂之一。*CYP3A4*在氯吡格雷肝脏代谢中起重要作用。因此, *CYP3A4*基因多态性或许对服用氯吡格雷治疗的心脑血管疾病患者预测氯吡格雷疗效起重要作用。本研究对*CYP3A4*基因多态性对心脑血管疾病患者氯吡格雷响应的影响进行meta分析。对2019年10月7日之前发表在Pubmed、Embase、Cochrane Library、clinicaltrail.gov、中国知网(CNKI)、万方数据库上的文献进行系统性检索, 纳入评价*CYP3A4*不同突变型患者的血小板反应性与临床结局的队列研究或病例对照研究。使用Review Manager软件进行数据分析, 使用NOS量表评价纳入文献的质量。总共纳入18篇文献进行Meta分析。Meta分析结果显示, *CYP3A4*基因多态性对心脑血管疾病患者服用氯吡格雷后的血小板反应性无显著影响。同时, *CYP3A4*基因多态性对心脑血管疾病患者长期服用氯吡格雷后的结局无显著影响。

关键词: 氯吡格雷; *CYP3A4*; Meta分析