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Efficacy and safety of genotype-guided antiplatelet therapy versus standard treatment in 4,604 patients with CAD after PCI: a meta-analysis of randomized controlled trials

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Objective: To compare the efficacy and safety of genotype-guided antiplatelet strategy and standard treatment in patient with coronary artery disease (CAD) after percutaneous coronary intervention (PCI). *Methods:* Relevant studies published in Medline, Embase, CoChrane Library were searched for randomized controlled trials (RCTs) until August 2020. Studies were screened by selection criteria, quality assessed using the Cochrane Collaboration's tool. Data were extracted from the included studies and statistically analyzed by RevMan 5.3 software. *Results:* Four RCTs involving 4,604 patients were included in this meta-analysis. Compared with the standard treatment group, the pooled results showed that genotype-guided group associated with lower risk of major adverse cardiovascular events (MACE, OR=0.52, 95%CI:0.35-0.78, *P*=0.001), any bleeding (OR=0.77, 95%CI: 0.62-0.95, *P*=0.02) and myocardial infarction (MI, OR=0.48, 95%CI:0.33-0.68, *P*<0.0001). There was no significant difference in death of any cause (OR=0.53, 95%CI: 0.18-1.54, *P*=0.25), cardiovascular death (OR=0.74, 95%CI:0.48-1.14, *P*=0.17), target vessel revascularization (OR=0.66, 95%CI:0.39-1.12, *P*=0.12) and major bleeding events (OR=0.86, 95%CI: 0.58-1.28, *P*=0.47). *Conclusion:* Genotype guided antiplatelet therapy could reduce the risk of MACE, MI and any bleeding events in patients with CAD undergone PCI, compared with standard treatment. Therefore, the findings support that implementation of genotype testing to tailor antiplatelet therapy after PCI.

1. Introduction

Dual antiplatelet therapy (DAPT) is the antithrombotic cornerstone for patients undergoing percutaneous coronary intervention (PCI) (Karve et al. 2015). Clopidogrel, the second-generation thienopyridine-type P2Y12 inhibitor, along with aspirin was the most common prescription of DAPT. However, the active metabolite of clopidogrel is easily affected by CYP2C19 genetic polymorphisms, and can lead to significant interpatient variability in different levels of platelet reactivity (Gurbel et al. 2003). Of note, poor clopidogrel response can induce high platelet reactivity, which has been proved to increase ischemic events for PCI-treated patients, especially stent thrombosis (Price et al. 2008). Until now, CYP2C19*2 and/or *3 alleles carriers treated with clopidogrel show a high ischemic risk, and the *17 allele was associated with a higher bleeding risk (Mega et al. 2009; Sibbing et al. 2010). The TRITON-TIMI-38 trial (Mega et al. 2010) revealed that nearly half of the population carried loss-of-function variants of ABCB1 or CYP2C19 that confer an increased risk of major adverse cardiovascular events while being treated with standard doses of clopidogrel. Metabolic activities of ticagrelor or prasugrel are not significantly affected by genetic polymorphisms. However, the presumed high bleeding risk or socioeconomic factors may favor the use of clopidogrel in real-life scenario. Therefore, genotyping test may aid in making an optimal choice for selection of P2Y12 inhibitor. Whether genotype-guided strategy offers the favor safety and efficacy compared with standard treatment remains unclear. Thus, we conducted a meta-analysis to compare the efficacy and safety of genotype-guided strategy and standard treatment in patients with coronary artery disease (CAD) after PCI.

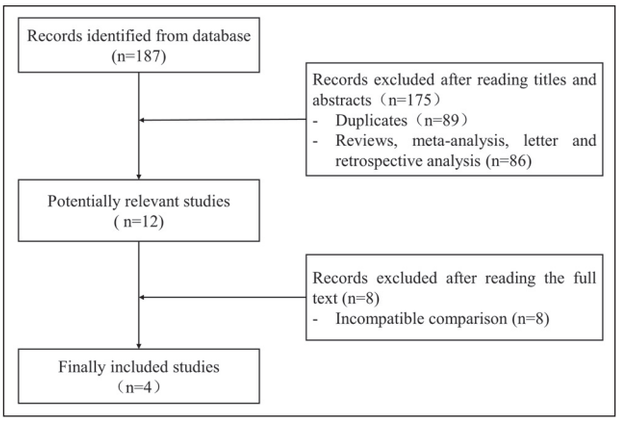

Fig. 1: Flow diagram of study selection.

2. Investigations and results

2.1. Study identification and selection

According to the search strategy, a total of 187 records emerged, but only four of these records met the inclusion criteria for this meta-analysis (Claassens et al. 2019; Notarangelo et al. 2018; Shen et al. 2016; Xie et al. 2013). The flow diagram of study selection and the risk of bias assessment are shown in Figs. 1 and 2.

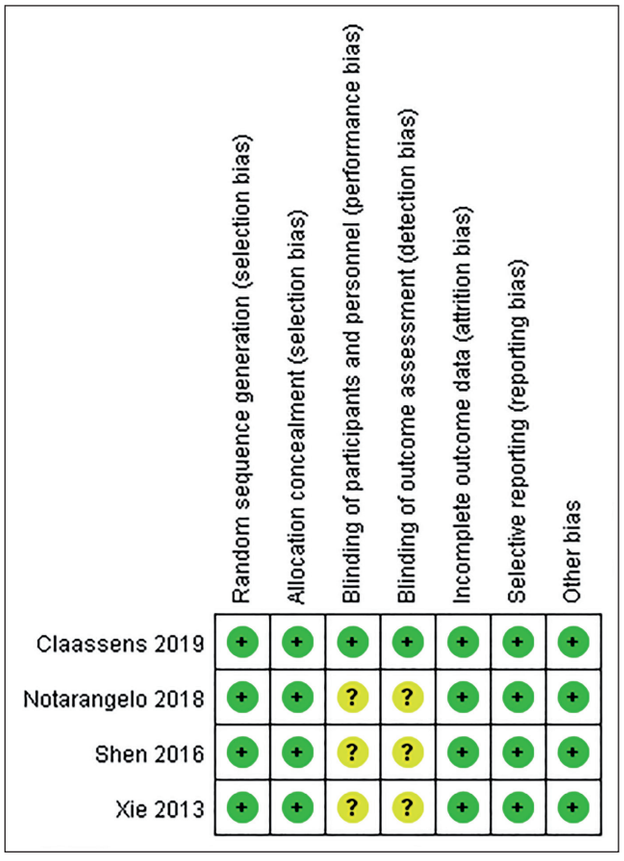

Fig. 2: The risk of bias assessment.

2.2. Characteristics of included studies

Four trials involving a total of 4,604 participants compared the genotype-guided group with the standard treatment group. Among these included studies, the median follow-up time was 12 months for three of the studies (Claassens et al. 2019; Notarangelo et al. 2018; Shen et al. 2016), while another study's follow-up time was 6 months (Xie et al. 2013). Baseline characteristics of the four included studies are shown in the Table. Notably, there are different escalation therapies of antiplatelet therapy used for poor metabolizers of clopidogrel. Three trials (Claassens et al. 2019; Notarangelo et al. 2018; Shen et al. 2016) switched from clopidogrel to ticagrelor or prasugrel for LOF alleles carriers in the genotype-guided group, but one trial (Xie et al. 2013) added cilostazol as a triple antiplatelet therapy as escalation strategy.

2.3. Primary efficacy endpoint: major adverse cardiac events (MACE)

MACE was defined as a composite of death of all cause, myocardial infarction (MI), stroke, target vessel revascularization. All included studies reported this composite endpoint, involving 4604 participants. Heterogeneity among these trials was high (I^2=53%, P=0.09), and the random model was used. The pooled analysis showed that the genotype-guided group was associated with lower risk of MACE compared with standard treatment group (OR=0.52, 95%CI: 0.35-0.78, P=0.001), as shown in Fig. 3A. Furthermore, the sensitivity analysis revealed that the outcome was not influenced by removing each trial.

2.4. Secondary efficacy endpoints: death of any cause, cardiovascular death, MI, stroke and target vessel revascularization

The results of individual efficacy endpoints are shown in Figs. 3 and 4. Twenty-four patients receiving genotype guided therapy died of any cause compared with thirty-six patients who received standard therapy and died during the follow-up period; there was no significant difference between the two arms (OR=0.53, 95%CI: 0.18-1.54, P=0.25). In addition, the risk of cardiovascular death was similar between the genotype-guided group and the standard treatment group (OR=0.74, 95%CI: 0.48-1.14, P=0.17). Of note, genotype-guided therapy was associated with a lower risk of MI compared with standard therapy (OR=0.48, 95%CI: 0.33-0.68, P<0.0001). The two groups had comparable outcomes with stroke (OR=0.69, 95%CI: 0.35-1.38, P=0.30) and target vessel revascularization (OR=0.66, 95%CI: 0.39-1.12, P=0.12).

2.5. Primary safety endpoint: any bleeding

All studies reported any bleeding events, involving 4,604 participants (Fig. 5A). Heterogeneity among these studies was low (I^2=49%, P=0.12), and Shen's article (Shen et al. 2016) determined to be the main source of heterogeneity. Genotype-guided therapy resulted in 21.3% reduction of any bleeding (OR=0.77, 95%CI: 0.62-0.95, P=0.02), compared with standard therapy. After removing Shen's article (Shen et al. 2016), heterogeneity was significantly reduced (I^2=0%, P=0.37), and did not influence the result (OR=0.71, 95%CI: 0.57-0.89, P=0.003).

2.6. Second safety endpoint: trail-defined major bleeding

Two studies reported major bleeding according to the BARC which were defined as type 3 to 5 bleeding events (Claassens et al. 2019; Notarangelo et al. 2018). The other two studies were excluded from this comparison because one (Shen al. 2016) reported that total bleeding events were all mild bleeding, and another (Xie et al. 2013) did no distinguish between major bleeding and minor

Table: Characteristics of included studies

Study	Number of patients (n, T/C)	The average age (years, T/C)	Male (n, T/C)	Previous MI (n, T/C)	DM (n, T/C)	P2Y12 inhibitor	
						T (%)	C (%)
Claassens 2019	1242/1246	61.9/61.4	925/937	97/87	150/138	Clopidogrel (60.6) Prasugrel (1.0) Ticagrelor (38.1) None (0.2)	Clopidogrel (7.0) Prasugrel (2.3) Ticagrelo (90.5) Non (0.2)
Notarangelo 2018	448/440	71. /70.7	295/310	96/95	113/122	Clopidogrel (43.3) Prasugrel (7.6) Ticagrelor (42.6) None (6.5)	Clopidogrel (50.7) Prasugrel (8.4) Ticagrelor (32.7) None (8.2)
Shen 2016	309/319	68.0/69.61	201/214	56/65	90/102	NA	NA
Xie 2013	301/299	57.97/57.84	241/227	NA	92/97	NA	NA

T: test group; C: control group; MI: myocardial infarction; DM: diabetes mellitus; NA: data not available

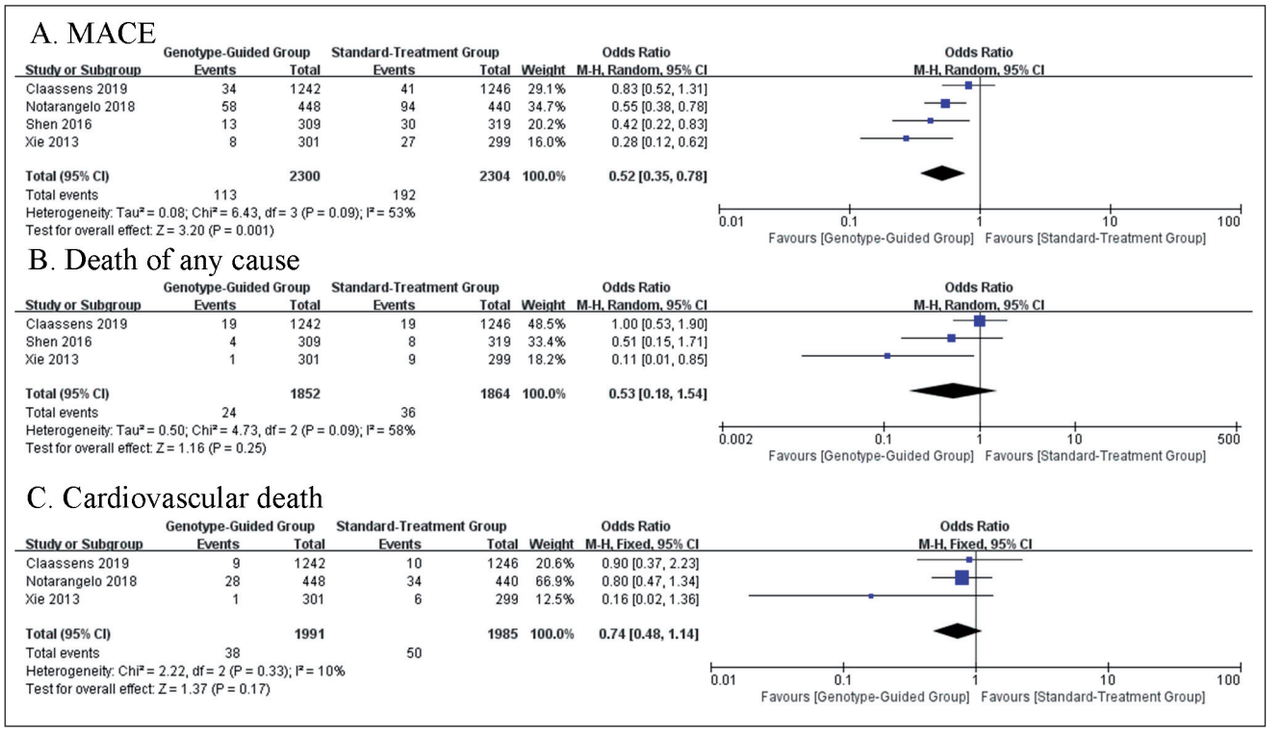

Fig. 3: Forest plot of meta-analysis for MACE, death of any cause and cardiovascular death.

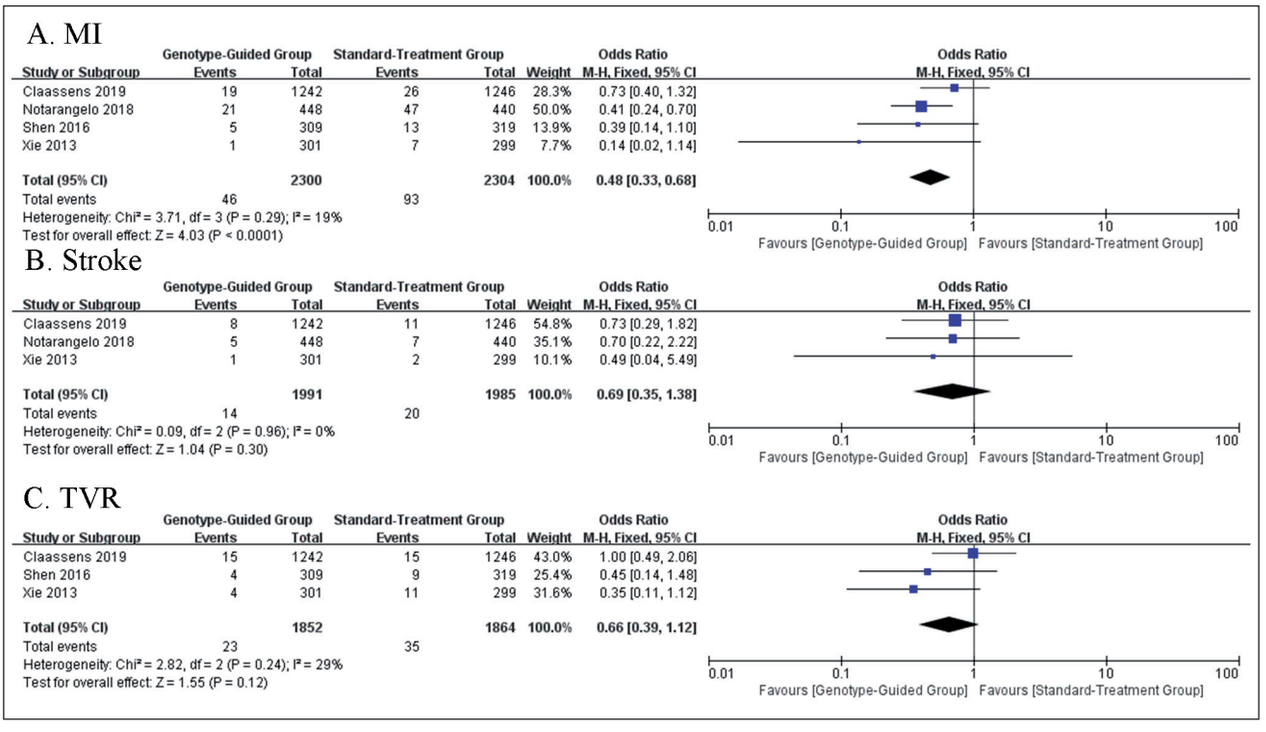

Fig. 4: Forest plot of meta-analysis for MI, stroke and TVR.

bleeding. Figure 5B shows no significant heterogeneity among the included studies (I^2=41%, P=0.19), and the pooled analysis result showed no significant difference between the two groups (OR=0.86, 95%CI: 0.58-1.28, P=0.47).

3. Discussion

The present meta-analysis assessed four eligible clinical RCTs that compared the efficacy and safety of genotype-guided antiplatelet therapy and standard therapy. The results showed that genotype guided therapy was associated with a markedly lower risk of MACE, MI, and any bleeding events than standard therapy, while other risks of ischemia and major bleeding events were noninferior to standard therapy. Therefore, genotype guided antiplatelet therapy may be a viable option in most patients with CAD undergoing PCI in need of antiplatelet therapy.

Since the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial discovered the better antithrombotic bene-

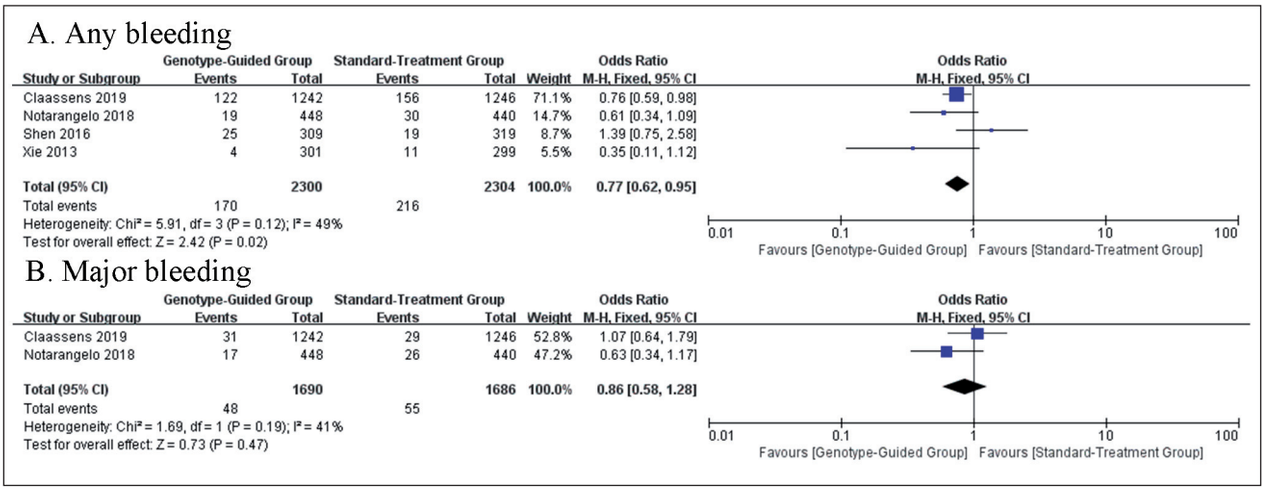

Fig. 5: Forest plot of meta-analysis for any bleeding and major bleeding.

fits of DAPT, it led to a drastic decrease in the risk of ischemic events (Yusuf et al. 2001). In this era, development of secondary generation drug-eluting stents and the wide use of potent P2Y12 inhibitors has had important implications for the further reduction of ischemic events. Naturally, it follows that reducing bleeding complications becomes another goal. To date, de-escalation therapy, including switching DAPT regimen (i.e., switching from ticagrelor or prasugrel to clopidogrel) (Cuisset et al. 2017), shortening the duration of DAPT (i.e., administration with P2Y12 inhibitor monotherapy after a minimum period of DAPT) (Mehran et al. 2019), and reducing the dose of potent P2Y12 inhibitors (Bonaca et al. 2017) has been proven to decrease bleeding risks without increasing ischemic risks. However, these therapies cannot ensure that individuals will receive the most appropriate antithrombotic treatment because the CYP2C19 genetic polymorphisms could lead to significant interpatient variability in clopidogrel-treated platelet reactivity. Furthermore, multiple reasons, including clinical and socioeconomic factors, may play a role in the choice of P2Y12 inhibitor therapy in clinical practice. Until now, clopidogrel remains the most commonly used P2Y12 inhibitor for patients who need antiplatelet treatment. Thus, a tailored therapy to aid in making the optimal choice of P2Y12 inhibitor may be a proposed strategy for better clinical outcomes.

Platelet function testing (PFT) and CYP2C19 genotype testing were optional tools to predict both thrombotic and bleeding events. TROPICAL-ACS trial (Sibbing et al. 2017) proved that PFT guided early de-escalation of DATP from prasugrel to clopidogrel was noninferior to standard treatment after PCI in terms of net clinical benefit, but it was not powered suggested for ischemic or bleeding events alone. However, there are still some problems that need to be clarified through further study, and therefore, limits the application of PFT in real-world scenarios. First, the optimal timing of PFT remains a topic of debate. In addition, people of East Asian descent have a higher frequency of the CYP2C19 LoF allele than Caucasia populations (about 60% vs. 30%), but have similar or even lower risks of ischemic events (Jeong 2014). It should be considered that the therapeutic window of platelet reactivity may be different for people of European descent than for people of East Asian descent. Thus, PFT may be useful in identifying especially high-risk patients on clopidogrel who are treated in specific settings. However, the predictive value of PFT may not be better than genotype testing due to the aforementioned problems.

Recently, the POPULAR trial (Claassens et al. 2019) suggested that CYP2C19 genotype guided strategy for personalized P2Y12 inhibitor therapy was noninferior to standard treatment with respect to thrombotic events and resulted in a lower risk of bleeding. Another prospective real-world study in involving 1,445 participants, assessed the clinical benefits of routine CYP2C19 genotype testing in patients with STEMI (Hulot et al. 2020). The results of a thienopyridine resistant subgroup showed that LoF allele carriers who received adjustment of P2Y12 inhibitor treatment conferred significantly lower risks of ischemic events and bleeding events were noninferior compared to the non-adjustment treatment groups. These results suggest that genotype guided therapy could contribute to a reduction of ischemic or bleeding events. To add to this perspective, our meta-analysis included four RCTs that collectively reveal that genotype guided antiplatelet therapy could reduce the risks of MACE, MI, and any bleeding, compared with standard treatment. In line with the non-randomized study, reported that CYP2C19/ABCB1 genotype guided strategy could reduce the rate of composite cardiovascular and bleeding events after PCI compared to a non-genotype guided strategy (Sánchez-Ramos et al. 2016). In contrast to the TAILOR-PCI trial (Pereira et al. 2020), which involved 1849 CYP2C19 LOF carriers after percutaneous coronary intervention (PCI), showing neutral results both in the primary efficacy endpoint (4.0% vs 5.9%, *P*=.06) and in the safety endpoint (1.9% vs 1.6%, *P*=.58). This may be interpreted that the TAILOR-PCI trial focused on the primary analysis in only those who carry CYP2C19 LOF alleles, while the included studies in our meta-analysis focused on both LOF carriers and non-LOF carries. Therefore, more evidence from randomized controlled clinical trials was needed.

Our meta-analysis had several limitations. First, there are few trials available to be included, thus our results should be verified by more large-scale RCTs. Second, our study population was a mix cohort of ACS and non-ACS, and we could not perform subgroup analyses in stable CAD and ACS due to our lack of direct access to patients' data. Therefore, our results are more inclined to provide evidence for patients with CAD. Finally, it was not possible to assess publication bias by funnel plots because of the insufficient number of eligible studies (n<10).

In conclusion, our findings showed that genotype guided antiplatelet therapy could reduce the risk of MACE, MI, and bleeding events in patients with CAD who have undergone PCI, compared with standard treatment strategies. Therefore, these findings support that implementation of genotype testing in an effort to tailor patient-specific antiplatelet therapy after PCI.

4. Experimental

4.1. Data search

This meta-analysis was conducted according to the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Two independent investigators (Liu and Li) performed the literature search using the PubMed, Cochrane library and Embase databases until June 2020. Search terms were used as follow: (CYP2C19 genotyping test OR genotype guided strategy) AND (personal antiplatelet therapy OR selective antiplatelet therapy OR alternative antiplatelet therapy) AND (oral P2Y12 inhibitor OR clopidogrel OR ticagrelor OR prasugrel).

4.2. Study selection and screening criteria

We removed the irrelevant publications and duplicates, and screened the leftover articles by reading title, abstract and full text. The inclusion criteria were: (1) randomized control trial (RCT) compared genotype guided therapy with standard therapy in patients with CAD undergoing PCI; (2) reporting on outcomes about ischemic and bleeding events; (3) studies published in English. The exclusion criteria were: (1) other types of articles including reviews, meta-analysis, letter and retrospective analysis; (2) incompatible comparison; (3) no data available.

4.3. Data extraction and quality assessment

The following data were extracted by two investigators (Liu and Li): (1) baseline characteristics of the trials and participants; (2) number of patients per arms; (3) study design; (4) allele of genotype testing; (5) treatment strategy in the two groups; (6) follow-up duration; (7) primary and secondary endpoints. According the study design, the risk of bias assessment was performed using the Cochrane Risk of Bias Tool.

4.4. Endpoint definitions

The primary efficacy endpoint was major adverse cardiovascular events (MACE) that composite of death of all cause, myocardial infarction (MI), stroke, and target vessel revascularization. The secondary efficacy endpoints were death of any cause, cardiovascular death, MI, stroke, and target vessel revascularization. The primary safety endpoint was any bleeding and secondary safety endpoints were trial-defined major bleeding. We preferred to choose the Bleeding Academic Research Consortium (BARC) criteria when available, otherwise we would choose Thrombolysis in Myocardial Infarction (TIMI) or Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria.

4.5. Statistical analysis

Data analysis was performed by Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). Odds ratio (OR) with 95% confidence intervals (CI) were used to count the effects of each studies. The Q test and I^2 statistics was used to determine heterogeneity among included studies. A cut-off of I^2<50% and P>0.1 indicates low heterogeneity, and the Mantel-Haenszel fixed-effect model should be used to pool OR value of each study. Otherwise the random model should be adopted in case of higher heterogeneity. To evaluate the consistency of our findings, the sensitivity analysis by removing each single trial in order from pooled analysis. P <0.05 were considered significant.

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Conflict of interests: All authors had access to the data and played a role in writing this manuscript. There are no conflicts of interest need to declare.

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