

A meta-analysis of cyp2c19 gene testing on the prognosis of patients aged 60 years and older with acute coronary syndrome

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Abstract: Objective Whether cyp2c19 gene testing is clinically beneficial for patients aged 60 years and older with acute coronary syndrome. Methods A computerized search of WIFANG, CNKI, CBM and Vipul databases was performed to comprehensively collect RCTs on cyp2c19 gene-guided selection of different antiplatelet regimens or placebo or blank control comparisons. Results A total of 8 RCTs were included. cyp2c19 gene-guided prognosis regarding antiplatelet regimens in the elderly was better in the ticagrelor group than in the clopidogrel group, with statistically significant differences. CONCLUSION: Current evidence suggests that in the context of acute coronary syndromes in patients, with reference to the cyp2c19 gene and age, the overall clinical benefit of ticagrelor may be much better than clopidogrel, although patients may be at greater risk of bleeding.

Keywords: Cyp2c19 gene; Genetic testing; Elderly; Ticagrelor; Clopidogrel; Acute coronary syndrome; Clinical efficacy.

1. Introduction

Coronary artery disease is a common disease with high sudden death rate and serious hazards. Standardized coronary artery disease management is the key to improve prognosis and reduce mortality, and antiplatelet therapy is the cornerstone of coronary artery disease management, regardless of whether pharmacological or interventional treatment is adopted. Percutaneous coronary intervention (PCI) is one of the most widely used procedures in the world. In addition to aspirin, the introduction of thienopyridine type P2Y₁₂ receptor inhibitors, known as dual antiplatelet therapy (DAPT) (1), has led to a substantial reduction in post-procedure thrombotic events (2). Clopidogrel became the first widely used P2Y₁₂ inhibitor to reduce the risk of post-PCI thrombotic complications with an acceptable safety profile. However, the production of active metabolites of clopidogrel is unpredictable, resulting in significant inter-patient variation in platelet response levels during treatment (3). cyp2c19 gene polymorphisms have been determined to contribute, at least in part, to the observed differences in clopidogrel response (4, 5, 6, 7). Based on the different genotypic expressions of CYP2C19, they can be classified as ultra-fast, fast, intermediate, and slow metabolizers (8). About 47.4% of the population in East Asian countries are clopidogrel intermediate metabolic type and 15% of patients are clopidogrel slow metabolic type in clinical practice, and the proportion of patients with intermediate and slow metabolic types is much higher than that in European and American countries (10). For ischemic events and stent thrombosis in patients with acute coronary syndrome (ACS), current guidelines (11, 12) recommend more effective platelet inhibitors: ticagrelor and prasugrel, as these drugs are more effective in preventing thrombotic events. However, this greater efficacy comes with a higher risk of bleeding (13,14). At the same time, these studies are consistent with advances in stent technology, with the latest generation of drug-eluting stents having a much lower risk of stent thrombosis compared

with first-generation stents, and developments in stent technology have also had a significant impact on the selection and duration of DAPT (15). The U.S. Food and Drug Administration (FDA) issued a black box warning in 2010 advising practitioners to consider alternative therapy for patients with poor CYP2C19 metabolism who may be treated with clopidogrel and to identify such patients by genotyping, although two studies based on the results of the TRITON-TIMI 38 trial and the PLATO trial both showed that prasugrel and ticagrelor were superior to clopidogrel in reducing cardiovascular death, myocardial infarction, and stroke (16,17), patients are at higher risk for bleeding and thrombotic events with increasing age, making the optimal choice of antithrombotic therapy challenging. (18)

2. Object and Method

2.1. Research materials

Computational Search Wanfang, CNKI, Vipshop database, pubmed, comprehensive collection of RCTs on cyp2c19 gene-guided selection of ticagrelor compared with clopidogrel. english search formula: " cyp2c19" OR "Clopidogrel " AND "noncarriers of CYP2C19 loss-of-function alleles" OR "ticagrelor" OR "elderly patients" AND "acute coronary syndrome" OR "P2Y₁₂ Inhibitors " OR "randomized" OR "randomly trial" AND "PCI"; Chinese search formula OR "cyp2c19" OR "clopidogrel, ticagrelor, aspirin" AND "elderly" AND "acute coronary syndrome"; Chinese search formula: "cyp2c19" OR "clopidogrel, ticagrelor, aspirin" AND "elderly" AND "acute coronary syndrome "and "PCI".

2.2. Inclusion criteria

(1) Study design: domestic and foreign published RCTs, with or without blinding or allocation concealment, in English and Chinese only. (2) Study subjects: (1) patients aged 60 years and above; (2) ACS patients receiving clopidogrel or other antiplatelet therapy after PCI; (3) complete and

available medical records. (3) Interventions: ticagrelor group in the trial group and clopidogrel group in the control group. (4) Outcome indicators: observe the clinical endpoints of patients in the 2 groups. The postoperative follow-up was 12 months, and the follow-up included outpatient follow-up, readmission and telephone follow-up. Observed endpoints included 12-month all-cause death, cardiogenic death, angina pectoris, myocardial infarction, in-stent thrombosis, ischemic stroke, and bleeding events. A composite event consisting of angina, myocardial infarction, in-stent thrombosis, and ischemic stroke was defined as a combined thrombotic event. The diagnosis of myocardial infarction was referred to the new 3rd edition global definition of myocardial infarction. The diagnosis of in-stent thrombosis was based on the relevant Academic Research Consortium definition. According to the standardized definition of bleeding for cardiovascular clinical trials published by the Bleeding Academic Research Consortium (BARC), bleeding includes major bleeding (requiring transfusion) and minor bleeding (including skin petechiae, gingival bleeding, and nasal bleeding).

2.3. Exclusion criteria

Literature: descriptive literature, literature for which data could not be extracted, and duplicate publications. Subjects: (1) Patients with combined atrial fibrillation and valvular disease requiring anticoagulation; (2) Refractory hypertension with uncontrollable blood pressure; (3) Previous definite history of cerebral thrombosis, cerebral hemorrhage and other vascular accidents; (4) Combined coagulation disorders (such as nephrotic syndrome, tumors, autoimmune diseases, hematologic diseases, etc.) and long-term bedridden patients; (5) Severe renal insufficiency (5) Patients with severe renal insufficiency, abnormal thyroid function.

2.4. Literature screening and data extraction

Two investigators independently screened the literature and extracted information according to inclusion and exclusion criteria, cross-checked, and discussed and resolved differences in opinion. Information was extracted using a self-made data extraction form according to the purpose of the study, which included: general information about the study, basic information about the study population, study methods, intervention protocol, reasons for withdrawal and loss of visit, number of cases, and outcome indicators.

2.5. Quality evaluation

The risk of bias assessment tool for RCTs recommended by Cochrane Handbook 5.4 was used (28). The methodological quality of the included studies was evaluated, including random sequence generation, allocation concealment, blinding of subjects, investigators, and outcome evaluators, completeness of outcome information, selective outcome reporting, and other sources of bias. For the included literature, a "yes" (low risk of bias), "no" (high risk of bias), and "unclear" (unclear risk of bias) evaluation was made in the above six areas. The evaluation was conducted independently by two evaluators, and any disagreement was discussed and resolved.

2.6. Statistical analysis

RevMan 5.4 software (28) was used for combined statistical analysis, publication bias evaluation, funnel plot symmetry test, and sensitivity analysis. Count data were expressed using relative risk (RR) and its 95% CI. The χ^2 test was used to analyze the heterogeneity among the results of the included studies, and the magnitude of heterogeneity was also quantitatively determined by combining I^2 . If there was good homogeneity among the results of the studies ($P > 0.10$, $I^2 \leq 50\%$), Meta-analysis was performed using a fixed-effects model. If there was heterogeneity between the results of the studies [$P \leq 0.10$ and/or $I^2 > 50\%$], the source of heterogeneity was analyzed and a random-effects model was used in the absence of significant clinical heterogeneity, and subgroup analysis or descriptive analysis only was performed in the presence of significant clinical heterogeneity.

3. Results

3.1. Basic characteristics of included studies A total of 92 papers were obtained for the initial review, and 8 studies were finally included after stepwise screening

The literature screening process and results are shown in Figure 1. the basic characteristics of each included study are shown in Table 1.

Table 1. Inclusion of article baseline information sheet

Literature	Inclusion of disease sources	Ticagrelor group	Clopidogrel group	Closing indicators	Age
Tian Feng 2021	STEMI	54	54	①③④⑥⑧⑩	Above 60
Ma Hao 2021	ACS	61	60	⑥⑦⑧⑨⑩⑫	65 or more
Chen Qi 2021	ACS	161	172	⑤⑥⑬	Above 60
Huang Lihong 2021	ACS	60	60	⑤⑫⑥	Above 60
Liang Yajun 2019	ACS	73	73	⑤⑥⑦⑧⑨⑫	Above 60
Qi Jing 2020	NSTEMI	179	374	⑤⑥⑧⑨⑩⑪	65 or more
Gao Yanyan 2020	ACS	67	79	⑤⑥⑧⑫	Above 80
Cai Lin 2018	ACS	60	60	⑤⑥⑦⑧⑨⑫	75 or more

①TIMI flow classification, ② no postoperative flow, ③ postoperative malignant arrhythmia, ④ dyspnea, ⑤ bleeding, ⑥ MACE, ⑦ recurrent myocardial infarction, ⑧ incidence of cardiogenic death, ⑨ recurrent angina, ⑩ repeat PCI, ⑪ heart failure, ⑫ cardiogenic death, ⑬ stent thrombosis

3.2. Methodological quality evaluation of the included studies

All eight included studies were RCTs with no specific

grouping method stated; there were no case withdrawals in all studies. none of the eight studies had incomplete outcome information, but none mentioned allocation concealment and blinding, and it was not possible to determine whether there

was other bias. The methodological quality of the included studies was evaluated in Table 2.

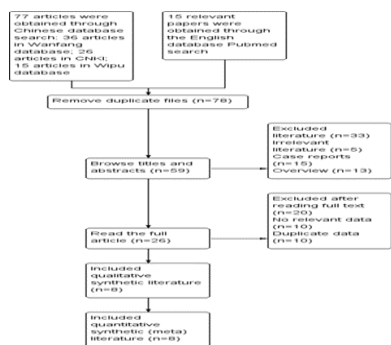
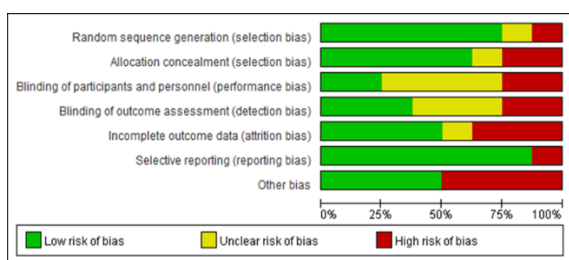


Figure 1. Literature Screening Flow Chart

Table 2. Risk Bias Summary Chart



3.3. Meta-analysis results

Four studies reported clinical endpoints in patients with cyp2c19 gene-guided antiplatelet regimens, and there was no statistical heterogeneity among the studies, so a fixed-effects model was applied for Meta-analysis, and the results are shown in Figure 2. 0.56 95% CI (0.33, 0.95), p=0.03.

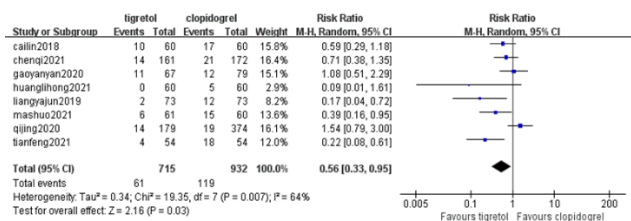


Figure 2. Comparison of total MACE incidence between Tirofiban group and clopidogrel group

4. Discussion

Clopidogrel is still the most widely used P2Y12 (purinergic receptor) P2Y12 inhibitor in China, and the percentage of patients receiving clopidogrel, prasugrel and tirofiban was 72%, 20% and 8%, respectively, in an analysis of 64,600 patients undergoing percutaneous coronary intervention in 47 Michigan hospitals in the United States and Canada for antiplatelet drugs. No specific statistics are available in China, but the Chinese guidelines for cardiovascular disease prevention (2017), the Chinese expert recommendations for antiplatelet therapy in special populations with acute coronary syndromes, and the guidelines for the diagnosis and treatment of acute ST-segment elevation myocardial infarction still prioritize clopidogrel. At present, the CYP2C19 genotype-guided strategy of choosing oral P2Y12 inhibitor therapy has been increasingly recognized, but for the physiological and metabolic peculiarities of the elderly group aged 70 years and above, whether genetic testing is necessary, and how to distinguish the definition of the testing group, we may need more in-depth and systematic research to conduct more

scientific and professional argumentation to guide clinical treatment, rather than We may need more in-depth and systematic research to conduct more scientific and professional evidence to guide clinical treatment, rather than unified standards and uniform programs. As shown in Figure 3 above, at least the current clinical trials show that we can try to give more potent antiplatelet drugs to elderly patients under genetic guidance.

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