MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 3824-3830
DOI: 10.12659/MSM.903054

Received: 2016.12.27
Accepted: 2017.01.05
Published: 2017.08.07

Effects of Dual-Dose Clopidogrel, Clopidogrel Combined with Tongxinluo Capsule, and Ticagrelor on Patients with Coronary Heart Disease and CYP2C19*2 Gene Mutation After Percutaneous Coronary Interventions (PCI)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Shuxia Chen
BCDEF 2 Yi Zhang
ABCDE 1 Lili Wang
BCDE 1 Yanping Geng
ABCDEFG 1 Jian Gu
BCD 1 Qingqing Hao
BF 3 Hua Wang
EF 1 Peng Qi

1 Department of Heart Center, Hebei General Hospital, Shijiazhuang, Hebei, P.R. China
2 Department of Health Care, The Third Hospital Affiliated to Hebei Medical University, Shijiazhuang, Hebei, P.R. China
3 Department of Internal Medicine, The First Hospital of Shijiazhuang, Shijiazhuang, Hebei, P.R. China

Corresponding Author: Jian Gu, e-mail: gujian_1118@163.com
Source of support: This study was funded by the Hebei Province Administration of Traditional Chinese Medicine Project (Grant No. 2013028)

Background: In recent years, genetic factors have attracted research interest as important predisposing factors for cardiovascular susceptibility. This study aimed to investigate the influences of dual-dose clopidogrel, clopidogrel combined with tongxinluo, and ticagrelor on the platelet activity and MACE events of patients with CYP2C19*2 gene function deficiency and poor clopidogrel response after PCI.

Material/Methods: We selected 458 patients with coronary heart disease undergoing PCI, and the genotype of CYP2C19*2 was detected by TaqMan real-time PCR. We finally enrolled 212 patients and divided them into 4 groups: a standard anti-platelet group of 46 patients, a clopidogrel double-dose group of 50 cases, a clopidogrel combined with tongxinluo group of 59 cases, and a ticagrelor group of 57. The platelet inhibition rate was detected by TEG. We analyzed and compared differences in platelet activity and the occurrence of MACE events in these 4 groups at different follow-up times.

Results: The results showed that inhibition of platelet aggregation was better in the double-dose clopidogrel group, the clopidogrel combined with tongxinluo group, and the ticagrelor group than in the regular-dose clopidogrel group, and ticagrelor was the best. We also found that the total incidence of MACE was much lower in the double-dose clopidogrel group, the clopidogrel combined with tongxinluo group, and the ticagrelor group, while the incidence of hemorrhage in the ticagrelor group was higher.

Conclusions: Adjusting the dose or combining with other drugs improves the efficacy of anti-platelet therapy and reduces the incidence of ischemic events after PCI.

MeSH Keywords: Antigens, Human Platelet • Cardiovascular Agents • Coronary Disease

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/903054

2393 4 3 18

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Clopidogrel, which can inhibit adenosine diphosphate (ADP)-induced platelet aggregation, has been applied to the prevention of atherothrombotic events for over 15 years [1]. The variability in clopidogrel response is associated with environmental and genetic factors [2]. Although clopidogrel has been widely used in patients with ischemic stroke, decreased metabolic activation of clopidogrel still occurs because of genetic variations in CYP2C19. The stent thrombosis risk in patients carrying a CYP2C19 loss-of-function allele appears to be similarly elevated across stable and unstable patient populations, regardless of elective or urgent PCI, or treatment with bare-metal or drug-eluting stents [3,4]. Many factors can influence the response of patients to clopidogrel therapy, including age, smoking, diabetes, drug interactions, and genetics [5,6].

As a pro-drug, clopidogrel requires metabolic activation by the hepatic cytochrome (CYP) P450 system, which includes CYP2C19, CYP2C9, CYP2B6, CYP3A4, and CY P3A5 [2]. Specifically, the polymorphisms of CYP2C19 are thought to play an important role in this poor clopidogrel response [7]. Individuals carrying at least 1 loss-of-function allele (either *2 or *3) of the CYP2C19 gene demonstrate reduced active clopidogrel metabolites and suppressed anti-platelet activity [8]. The 2009 Japanese Guidelines for the Management of Anticoagulant and Anti-Platelet Therapy in Cardiovascular Disease recommend the use of anti-platelet agents for preventing reinfarction following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS) [9]. The presence of at least 1 reduced-function CYP2C19 allele was associated with increased risk of major adverse cardiovascular events (MACE), particularly stent thrombosis, in clopidogrel-treated patients [10]. For this reason, CYP2C19 genetic testing has been proposed before starting clopidogrel therapy to identify patients likely to show reduced anti-platelet activity [11].

Ticagrelor (formerly developed as AZD6140) is a first-in-class anti-platelet agent chemically known as a cyclopentyl triazolopyrimidine, with distinguishing properties from that of the pyridines like ticlopidine, clopidogrel, or prasugrel. Ticagrelor, a novel oral $P2Y_{12}$ antagonist that does not undergo bio-transformation to active metabolites, has many favorable pharmacological dynamic characteristics, including rapid onset of action and reversibility, and consistent inhibition of platelet function [12]. Some studies have shown a higher prevalence of on-treatment platelet re-activity, but with a similar thrombotic event rate after PCI in East Asian patients compared with white patients [13].

Tongxinluo in capsule form is a compound prescription formulated according to the meridian theory of traditional Chinese medicine and approved in 1996 by the State Food and Drug Administration of China for treatment of angina pectoris and ischemic stroke [13]. Pharmacological research has revealed that treatment with tongxinluo capsule has a variety of therapeutic effects, such as improvement of endothelial cell function, lipid lowering, anti-inflammation, anti-apoptosis, and enhancement of angiogenesis [14].

Our study was conducted to evaluate the influences of dual-dose clopidogrel, clopidogrel combined with tongxinluo, and ticagrelor on patients with CYP2C19 gene polymorphisms after PCI at 3, 6, and 12 months.

Material and Methods

Study design and patient population

Overall, 458 patients with cardiovascular disease who received PCI treatment from June 2012 to June 2014 at Department of Cardiology, Hebei Provincial People 's Hospital were selected. Patients were included in the study according to the following criteria: (1) age >18 years; (2) diagnosis of coronary artery disease by coronary angiography in parallel PCI; (3) carry at least 1 CYP2C19 * 2 allele by genotyping assays; (4) PCI patients were treated with clopidogrel for anti-platelet therapy; (5) patients without other cardiovascular disease. Exclusion criteria were: (1) recent history of severe organ damage or surgery; (2) upper gastrointestinal ulcer or bleeding; (3) currently suffering from congenital heart disease, cardiomyopathy, myocarditis, peripheral vascular disease, or and infective endocarditis; (4) liver and kidney function was severely abnormal; (5) blood coagulation disorders; (6) cancer patients; (7) history of allergies to aspirin and clopidogrel; (8) took tongxinluo or ticagrelor before enrolment; (9) received warfarin sodium, propranolol, cimetidine, any kind of antibiotics or anti-fungal drugs, antidepressants, benzodiazepines, or anti-psychotics.

Patients were given aspirin 300 mg for the first time after admission, followed by 100 mg/day and clopidogrel 75 mg/day for routine treatment. Among the 458 patients with coronary artery disease who received successful PCI, 231 patients had at least 1 CYP2C19*2 allele. According to the inclusion and exclusion criteria and the patients, 212 patients were eventually selected and divided into the standard anti-platelet group (regular-dose clopidogrel group) (RCG) of 46 patients (75 mg/day, 12 months), the double-dose clopidogrel group (DCG) of 50 cases (150 mg/day for 1 month, then 75 mg/day), the clopidogrel combined with tongxinluo group (CTG) of 59 cases (0.26 g/tablet, 4×3/day, 3 months), and the ticagrelor group (TG) of 57 cases (90 mg×2/day, 12 months). The differences in platelet activity and the occurrence of MACE events in the 4 groups of patients at different follow-up times were analyzed and compared.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

DNA extraction

Blood samples were collected from all individuals into EDTA tubes. Genomic DNA was extracted from whole blood using the MagNA Pure automated extraction system according to the manufacturer's instructions. The quantity and purity of the extracted DNA was assessed with a Nanodrop ND-1000 device. DNA concentration was subsequently adjusted to a concentration of 5 ng/ml. The samples were stored at –80°C.

CYP2C19*2 detection

Genomic DNA from whole blood was isolated using a QIAamp® DNA Blood Mini Kit (QIAGEN, Les Ulis, France) according to the manufacturer's instructions. CYP2C19 genotyping for rs4244285 G>A (CYP2C19*2) was carried out by Taq Man® allelic discrimination assays on an ABI PRISM 7000 Sequence Detection System (Applied Biosystems). Direct sequencing was used to validate internal quality controls corresponding to genomic DNA of each genotype.

Platelet inhibition rate and MA-ADP detection

A TEG thromboelastograph was used for platelet inhibition rate detection. TEG software automatically calculated the platelet inhibition rate and the ADP-induced maximum clot strength (MA-ADP) according to the detection results. ADP receptor inhibition rate <20% is defined as clopidogrel resistance.

Efficacy

MACE was defined as a composite of cardiovascular death, non-fatal MI, and non-fatal ischemic stroke. For the purpose of this report, efficacy outcomes included MACE occurring through 12 months, cardiovascular death, non-fatal myocardial infarction (MI), recurrence of unstable angina, target vessel reconstruction, revascularization, and stent thrombosis.

Statistical analysis

Statistical analysis was performed using SPSS 13.0. The measurement data are expressed by mean ± standard deviation (SD). Differences between 2 groups were compared by *t* test, differences between multiple groups were compared by ANOVA, and the LSD *t* test was used to compare 2 groups among multiple groups. Count data is expressed as frequency, rate of comparison using the chi-square test or Fisher exact probability method. Kaplan-Meier method was used to draw the curve of adverse cardiovascular events during follow-up.

Results

Clinicopathological characteristics of patients

The patients with CYP2C19*1*2 or CYP2C19*2*2 were enrolled, and were divided into 4 groups: (1) regular-dose clopidogrel group; (2) double-dose clopidogrel group, (3) tongxinluo capsule combined with regular anti-platelet therapy group, and (4) ticagrelor group. The baseline information and clinicopathological characteristics of the 4 groups of patients are summarized in Table 1. There were no significant differences in age, sex, BMI, smoking status, hypertension, diabetes, dyslipidemia, number of stentings, platelet count, or ejection fraction among the 4 groups ($P>0.05$). During follow-up study, the drug use among patients had no significant differences ($P>0.05$).

The platelet inhibition rate in the 4 groups of patients varied during follow-up

At 3 days after PCI, the platelet inhibition rates of the double-dose clopidogrel group, the clopidogrel combined with tongxinluo group, and the ticagrelor group were lower than that of the standard anti-platelet therapy group. The 4 groups of patients had different platelet inhibition rates during the follow-up study. Using the repeated measurement of variance analysis, we found that the platelet inhibition rates were different at different time points ($F=106.588$, $P<0.01$) (Table 2), and there was interaction between time and grouping. The inhibition rates of platelets were analyzed at different time points. The results showed that the platelet inhibition rate of the double-dose clopidogrel group, the tongxinluo group, and the ticagrelor group was higher than that of the standard anti-platelet group at 1 month after the operation ($P<0.05$). After 6 months, the platelet inhibition rate in the ticagrelor group was higher than in the other 3 groups ($P<0.05$); however, the double-dose clopidogrel group and combined with tongxinluo group were lower than the standard anti-platelet group ($P<0.05$). At 12 months after surgery, statistical results were similar to those at 6 months, and the ticagrelor group had the highest platelet inhibition rate. However, we found that although the platelet inhibition rate of patients in the ticagrelor group was always at a high level, the platelet inhibition rate was still reduced with prolonged administration (Figure 1). The combined with tongxinluo group achieved the maximum platelet inhibition rate at 3 months, while the double-dose clopidogrel group and ticagrelor group reached the maximum in the first month.

Occurrence of MACE in patients from the 4 groups at 12-month follow-up

After 12 months of follow-up, the incidence of adverse cardiovascular events in the double-dose clopidogrel group, the combined tongxinluo group, and the ticagrelor group was

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Comparison of baseline data between patients from 3 groups with different metabolic syndrome.

General features	Regular dose of Clopidogrel group (n=46)	Double dose of Clopidogrel group (n=50)	Combined with Tongxinluo group (n=59)	Ticagrelor group (n=57)	*F*	*P*
Age	59.61±9.58	59.84±10.01	58.92±10.83	60.79±9.18	0.348	0.790
Gender	29	31	35	34	0.213	0.975
Smoking status	15	19	21	20	0.308	0.959
Hypertension	25	28	34	32	0.113	0.990
Diabetes	11	15	19	18	1.013	0.807
Dyslipidemia	11	13	18	16	0.630	0.889
BMI (kg/m^2)	25.31±3.27	26.16±2.94	25.75±3.19	25.83±3.57	0.441	0.648
Number of diseased blood vessels	1.68±0.58	1.61±0.64	1.66±0.72	1.67±0.65	0.281	0.839
Number of stenting	1.44±0.68	1.47±0.79	1.51±0.75	1.46±0.72	0.361	0.781
Platelet count	210.57±56.43	214.02±55.46	209.79±58.59	212.63±56.49	0.061	0.980
Ejection fraction (%)	61.84±9.21	59.94±10.68	60.92±11.06	61.02±9.48	0.529	0.663
ACEI/ARB	33	36	41	39	0.230	0.973
CCB	13	15	21	18	0.732	0.866
PPI	41	44	53	51	0.103	0.991
β-blocker	30	35	42	38	0.566	0.904

Table 2. The change of platelet inhibition rate of patients from 4 groups during follow-up.

	3 days (%)	1 month (%)	3 month (%)	6 month (%)	12 month (%)
Regular dose of Clopidogrel group (n=46)	50.16±11.21	48.15±10.35	48.27±11.45	47.58±11.34	46.76±10.61
Double dose of Clopidogrel group (n=50)	31.02±12.04*	67.02±10.04*,&	31.96±11.69*	32.24±10.31*	31.23±9.29*
Clopidogrel combined with Tongxinluo group (n=59)	29.66±11.67*	58.67±13.71*,#	64.74±19.37*,#	31.81±11.02*	30.97±10.43*
Ticagrelor group (n=57)	30.84±10.87*	71.86±20.87*,#,&	69.03±19.25*,#	62.86±16.94*,#,&	54.76±15.64*,#,&
F	35.639	74.171	83.734	81.323	57.708
P	<0.001	<0.001	<0.001	<0.001	<0.001

* $P<0.05$ compared with regular dose of clopidogrel group; # $P<0.05$ compared with double dose of clopidogrel group;
& $P<0.05$ compared with Clopidogrel combined with Tongxinluo group.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

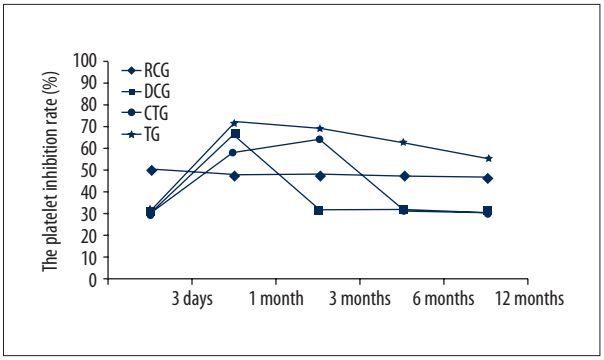

Figure 1. The change of platelet inhibition rate of patients from 4 groups during follow-up. The inhibition rates of platelets were analyzed at different time points (3 days, and 1, 3, 6, and 12 months after surgery). RCG – regular-dose clopidogrel group; DCG – double-dose clopidogrel group; CTG – clopidogrel combined with tongxinluo group; TG – ticagrelor group.

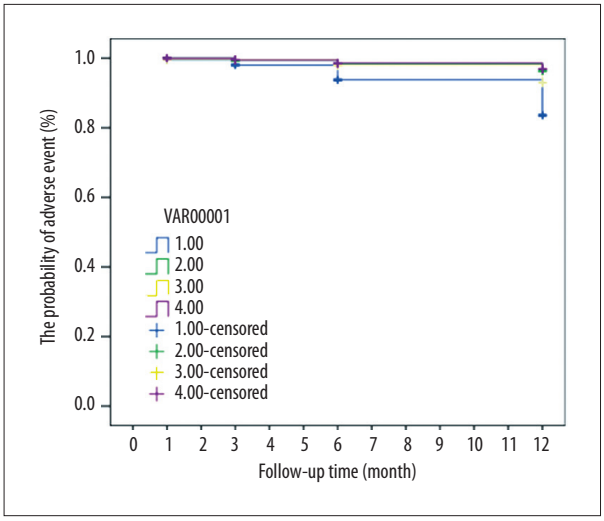

Figure 2. The incidence of non-MACE in each group during the follow-up.

Table 3. Occurrence of MACE in patients from 4 groups after followed for 12 months.

End event	Regular dose of Clopidogrel group (n=46)	Double dose of Clopidogrel group (n=50)	Combined with Tongxinluo group (n=59)	Ticagrelor group (n=57)	*F*	*P*
In-stent restenosis/ thrombosis	2	0	1	1	2.264	0.537
TVR	2	1	0	0	3.618	0.095
UA	4	2	1	1	3.732	0.285
Non-fatal myocardial infarction	2	1	1	0	2.526	0.415
Cardiac death	1	0	0	0	3.122	0.217
MACE composite endpoint	2	0	1	0	3.287	0.207
Total adverse cardiovascular events	14	4*	6*	3*	14.339	0.002

* $P<0.01$ compared with regular dose of Clopidogrel group.

significantly lower than that in the standard anti-platelet group (Figure 2, Table 3), but single occurrence of adverse cardiovascular events such as MACE composite end point, cardiac death, non-fatal myocardial infarction, and TVR were not significantly different in any group (Figure 3, Table 3).

Occurrence of bleeding events in patients from the 4 groups after 12-month follow-up

All patients were followed up for 12 months, and we found that all groups of patients had mild bleeding, but no major bleeding occurred. The incidence of bleeding in the ticagrelor group was higher than in the other 3 group, and the difference was statistically significant (Table 4).

Discussion

In this study, patients after intervention received 1 of 4 therapeutic regimens: the standard anti-platelet group, clopidogrel double-dose group, combined with tongxinluo group, and ticagrelor group. After a 12-month follow-up, we observed the platelet aggregation rate of patients at 1, 3, 6, and 12 months and MACE events at 12 months postoperatively. The results showed that the platelet inhibition rates of the clopidogrel double-dose group, combined with tongxinluo group, and ticagrelor group were all higher than in the standard anti-platelet group after using the adjustment program. This suggests that patients in the clopidogrel double-dose group, combined with tongxinluo group, and ticagrelor group had lower odds

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

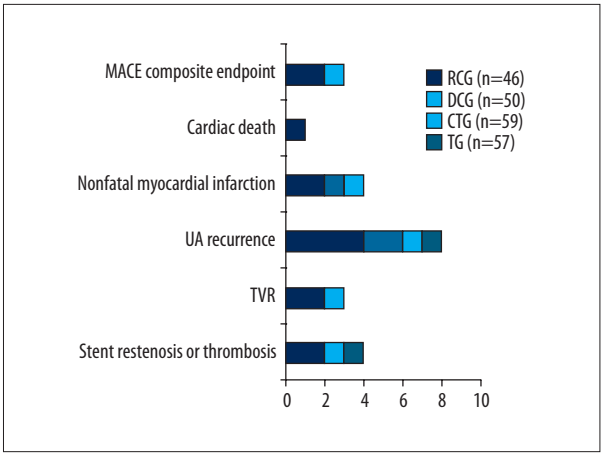

Figure 3. Occurrence of MACE in patients from the 4 groups after follow-up for 12 months. RCG – regular-dose clopidogrel group; DCG – double-dose clopidogrel group; CTG – clopidogrel combined with tongxinluo group; TG – ticagrelor group.

of adverse cardiovascular events than those in the standard anti-platelet group. Total MACE events were lower in the standard anti-platelet group than in the other 3 groups. However, any of these regimens can cause mild bleeding.

Von Beckerath et al. [15] showed that clopidogrel 75 mg/day at a maintenance dose of 150 mg/day was more effective in inhibiting ADP-induced platelet proliferation after PCI. Aradi et al. [16] administered clopidogrel 150 mg/day and 75 mg/day for 30 days and found that 150 mg/day of clopidogrel can effectively reduce the stability of patients with stable angina pectoris ischemic and thrombotic events. Tongxinluo capsule is a Chinese herbal compound preparation. Studies have shown that dual anti-platelet combined with the Naoxintong not only inhibits platelet aggregation and significantly reduces intracoronary microthrombosis, but also reduces the risk of bleeding. Ticagrelor is an ADP receptor antagonist that reversibly binds to the ADP receptor. Wallentin et al. [17] compared the efficacy and safety of ticagrelor and clopidogrel, and found that the incidence of combined end points was significantly lower in the tegrellozin group than in the clopidogrel group, whereas there was no significant difference between the 2 groups in total bleeding events. Gurbel et al. [18] found that in clopidogrel nonresponders, in the switch to ticagrelor, the platelet aggregation rate was significantly reduced, but when switching from ticagrelor to clopidogrel the platelet aggregation rate was significantly higher. This study is consistent with some previous non-Chinese studies, suggesting that patients with clopidogrel resistance can choose from among double-dose clopidogrel, clopidogrel combined with tongxinluo, or replacement of ticagrelor to relieve clopidogrel resistance.

The main components of tongxinluo capsule are ginseng, Quanjie, centipede, leech, soil insects, cicada skin, borneol, red peony, and other drugs. Modern pharmacological research found that tongxinluo capsules contains leeches, Quanjie, centipede, Eupolyphaga, and other insects. Its effects include hirudin effect, inhibition of extracellular matrix synthesis and secretion of inflammatory cells, and inflammatory cell aggregation. Its lumbrokinase-like effect can directly dissolve fibrin, but can also to activate plasminogen as plasmin, and thus the indirect dissolution of fibrin, with anti-platelet aggregation and antithrombotic effect. Ginseng stems and leaves, reed head, and fruit saponins can promote myocardial DNA synthesis in neonatal rats, and saponins promote prostaglandin I2 synthesis and inhibition of thromboxane formation. Red peony expands the coronary artery, inhibits platelet aggregation and smooth muscle hyperplasia, lowers blood lipids and lipid peroxidation, and protects vascular endothelial cells. Borneol can increase the plasma concentration of other drugs, promote gastrointestinal absorption, dilate the coronary artery, and slow the heart rate, thereby relieving angina. In addition, tongxinluo capsules can increase the expression of thrombin III, tissue plasminogen activator (t-PA), fibrinogen (FIB), and plasminogen activator inhibitor (Pal-1), thus regulating the balance of coagulation and fibrinolysis in patients with stent implantation, decreases the levels of ET-1, and increase NO and calcitonin gene-related peptide (CGRP). Studies have confirmed that tongxinluo capsules can reduce the incidence of clopidogrel resistance in ACS patients, but whether CYP2C19 loss-of-allele variants can slow

Table 4. Occurrence of bleeding events in patients from 4 groups after followed for 12 months.

	Regular dose of Clopidogrel group (n=46)	Double dose of Clopidogrel group (n=50)	Clopidogrel combined with Tongxinluo group (n=59)	Ticagrelor group (n=57)	*F*	*P*
Bleeding events	1#	5*	4*	11*,#	11.272	0.008
Severe bleeding	0	0	0	0	/	/
Mild bleeding	1#	5*	4*	11*,#	11.272	0.008

* $P<0.01$ compared with regular dose of Clopidogrel group; # $P<0.01$ compared with Clopidogrel combined with Tongxinluo group.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

platelet function resistance, thereby reducing the incidence of cardiovascular events, needs further study and observation.

In addition to genetic factors, patient compliance, drug interactions, left ventricular function, increases in other platelet activation pathways, and increased ADP release all can contribute to the recurrence of adverse cardiovascular events in patients after PCI. Therefore, we should look for more patients with PCI after the recurrence of adverse cardiovascular events, and, through the early identification of CYP2C19*2 carriers, adjust the dose, combined with other anti-platelet drugs or replacement of ticagrelor to improve the efficacy of anti-platelet therapy and reduce the incidence of ischemic events after PCI.

Conclusions

Our data suggest that the effects of double-dose clopidogrel, clopidogrel combined with tongxinluo, and ticagrelor in inhibiting platelet aggregation was better than the regular-dose standard anti-platelet therapy, and ticagrelor was the best. The total incidence of MACE was much lower in the double-dose clopidogrel group, clopidogrel combined with tongxinluo group, and ticagrelor group, while the incidence of hemorrhage in the ticagrelor group was higher. Adjusting the dose or combining other drugs could improve the efficacy of anti-platelet therapy and reduce the incidence of ischemic events after PCI.

Disclosures

All authors declare no financial competing interests. All authors declare no non-financial competing interests.

References:

1. Wang Y, Cai H, Zhou G et al: Effect of CYP2C19*2 and *3 on clinical outcome in ischemic stroke patients treated with clopidogrel. J Neurol Sci, 2016; 369: 216–19
2. Campo G, Miccoli M, Tebaldi M et al: Genetic determinants of on-clopidogrel high platelet reactivity. Platelets, 2011; 22: 399–407
3. Chikata Y, Iwata H, Osborn EA et al: Simultaneous subacute coronary artery stent thrombosis in a carrier of two CYP2C19 loss-of function polymorphisms (*2/*3). Int J Cardiol, 2016; 212: 148–50
4. Collet JP, Hulot JS, Pena A et al: Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: A cohort study. Lancet, 2009; 373: 309–17
5. Matetzky S, Shenkman B, Guetta V et al: Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation, 2004; 109: 3171–75
6. Wiviott SD, Antman EM: Clopidogrel resistance: A new chapter in a fast-moving story. Circulation, 2004; 109: 3064–67
7. Campo G, Fileti L, Valgimigli M et al: Poor response to clopidogrel: Current and future options for its management. J Thromb Thrombolysis, 2010; 30: 319–31
8. Hulot JS, Bura A, Villard E et al: Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood, 2006; 108: 2244–47
9. Ogawa H, Isshiki T, Kimura T et al: Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. J Cardiol, 2016; 68: 29–36
10. Mega JL, Simon T, Collet JP et al: Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: A meta-analysis. JAMA, 2010; 304: 1821–30
11. Desai NR, Canestaro WJ, Kyrychenko P et al: Impact of CYP2C19 genetic testing on provider prescribing patterns for antiplatelet therapy after acute coronary syndromes and percutaneous coronary intervention. Circulation, 2013; 6: 694–99
12. Storey RF, Husted S, Harrington RA et al: Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol, 2007; 50: 1852–56
13. Levine GN, Jeong YH, Goto S et al: World heart federation expert consensus statement on antiplatelet therapy in east asian patients with ACS or undergoing PCI. Glob Heart, 2014; 9: 457–67
14. Wang X, Mu C, Mu T et al: Effects of Tongxinluo on myocardial fibrosis in diabetic rats. J Chin Med Assoc, 2016; 79: 130–36
15. von Beckerath N, Kastrati A, Wieczorek A et al: A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. Eur Heart J, 2007; 28: 1814–19
16. Aradi D, Rideg O, Vorobcsuk A et al: Justification of 150 mg clopidogrel in patients with high on-clopidogrel platelet reactivity. Eur J Clin Invest, 2012; 42: 384–92
17. Wallentin L, Becker RC, Budaj A et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med, 2009; 361: 1045–57
18. Gurbel PA, Bliden KP, Butler K et al: Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: The RESPOND study. Circulation, 2010; 121: 1188–99

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]