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Analysis of individualized antiplatelet therapy for patients of acute coronary syndrome after percutaneous coronary intervention under the guidance of platelet function

A one-center retrospective cohort study

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Abstract

There is controversy in clinical application of antiplatelet drugs by monitoring platelet function. Therefore, we explored whether early and dynamic medication could bring better clinical outcomes for patients under the guidance of platelet function tests (PFT).

In this retrospective cohort study, we analyzed the prognostic events of 1550 patients with acute coronary syndrome (ACS) at Tianjin People's Hospital in China. They received dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) from January 2017 to December 2018. The primary endpoint was based on the Bleeding Academic Research Consortium (BARC) 3 or 5 major bleeding. Secondary endpoints included MACCE (all-cause death, nonfatal myocardial infarction, stroke, stent thrombosis, and unplanned target vessel reconstruction) and BARC 1 to 2 minor bleeding. The endpoint events within 1 year after PCI were recorded. Patients were divided into a guided group and a control group according to the drug adjustment by PFT results. After the propensity scores matched, the end points of 2 groups were compared, and subgroup analysis was performed on major bleeding events.

After propensity score matching, there were 511 cases in the guided group and the control group, respectively. The primary endpoint events occurred in 10 patients (1.96%) in the guided group and 23 patients (4.5%) in the control group (HR: 0.45; 95% CI, 0.21–0.95; $P = .037$). After the guided group adjusted drug doses, the risk of major bleeding was lower than standard DAPT of the control group. Although some patients in the guided group reduced doses earlier, the incidence of MACCE events did not increase in the guided group compared with the control group (4.89% vs 6.07%; $P = .41$). There was no statistical difference in BARC 1 to 2 minor bleeding ($P = .22$). Subgroup analysis showed that PFT was more effective in patients with diabetes and multivessel disease.

Early observation of dynamic PFT in ACS patients after PCI can guide individualized antiplatelet therapy to reduce the risk of major bleeding without increasing the risk of ischemia.

Abbreviations: AA = arachidonic acid, ACS = acute coronary syndrome, ADP = adenosine diphosphate, BARC = Bleeding Academic Research Consortium, COPD = chronic obstructive pulmonary disease, DAPT = dual antiplatelet therapy, HPR = high platelet reactivity, LPR = low platelet reactivity, MI = myocardial infarction, NSTEMI = non-ST elevated myocardial infarction, PCI = percutaneous coronary intervention, PFT = platelet function tests, PSM = propensity score matching, STEMI = ST-elevated myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction, TxB_2 = thromboxane B_2, UA = unstable angina.

Keywords: acute coronary syndrome, dual antiplatelet therapy, percutaneous coronary intervention, platelet function tests

Editor: Ali Hosseinsabet.

This study was approved by the Ethics Committee of Tianjin People's Hospital, and all patients provided written informed consent.

The authors have no funding and conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Dang W, Wang J, Zhang Q, Liu N, Li W, Yao Z. Analysis of individualized antiplatelet therapy for patients of acute coronary syndrome after percutaneous coronary intervention under the guidance of platelet function: a one-center retrospective cohort study. Medicine 2021;100:16(e25601).

Received: 8 November 2020 / Received in final form: 23 March 2021 / Accepted: 2 April 2021

http://dx.doi.org/10.1097/MD.0000000000025601

1. Introduction

Acute coronary syndrome (ACS) describes the range of myocardial ischemic states that include unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI), or ST-elevated myocardial infarction (STEMI). The major pathology responsible for ACS involves coagulopathy such as platelet activation. Hence, sufficient platelet inhibition and (temporary) anticoagulation is essential in ACS patients, especially in those patients undergoing myocardial revascularization by percutaneous coronary intervention (PCI).[1] Dual antiplatelet therapy (DAPT) has been demonstrated to lower the risk of ischemic events such as myocardial infarction (MI) and stent thrombosis in patients with ACS undergoing PCI.[2,3] Therefore, guidelines recommend DAPT treatment for at least 12 months in patients with ACS after PCI.[1]

With the evolution of PCI technique, potent $P2Y_{12}$ receptor inhibitors, and drug-eluting stents, the risk of thromboembolism is gradually reduced, whereas bleeding has become a new challenge for ACS patients after PCI. The results of TRACER study indicated that the mortality risk after BARC 3c bleeding is much higher than that after MI.[4] The CHARISMA trial also showed that patients with bleeding have a higher incidence of bleeding-related hemodynamic damage and comorbidities.[5] These studies reveal the high risk of long-term bleeding events after PCI. Recently, several clinical trials have explored the duration of continuous DAPT administration after PCI. Such trials as GLOBAL LEADER, STOP DAPT-2, and SMAT CHOICE reveal short-term DAPT after PCI as a trend, but the optimal duration remains further exploration.[6–9] However, these trials could make more or less choices for patients when setting the inclusion and exclusion criteria, resulting in a relatively low risk for the final selected patients. Even the TWILIGHT trial for high-risk disease populations excluded patients with major bleeding and ischemic events within 3 months.[10] These have led to the difference between these clinical trials and the actual conditions of patients in the real world.

Large clinical trials rarely performed platelet function tests (PFT) in all patients due to methodological differences and some other reasons. Research has shown that the association between high platelet reactivity (HPR) and low platelet reactivity (LPR), using adenosine diphosphate as stimulus, with ischemic and bleeding events, respectively.[11] LPR was a strong and independent predictor of bleeding both on prasugrel and clopidogrel.[12] The balance of antiplatelet drugs between thrombosis and bleeding risk depends on the level of platelet reactivity. PFT can intuitively reflect platelet reactivity and indicate the effectiveness of antiplatelet drugs in the complex environment of human body. Despite consensus-derived cutoff values for platelet function assays have been proposed, it is uncertain whether these thresholds may differ across different populations.[13] Currently, routine measurement of platelet reactivity has not been implemented in clinical practice.

TRIGGER-PCI study showed that PFT could not be converted into clinical utility,[14] while PATROL study confirmed that for STEMI patients, drug adjustments based on PFT results can improve clinical efficacy.[15] Based on previous studies and their controversy, the present study aimed to evaluate the prognosis difference between patients receiving early individualized treatment under PFT guidance and those receiving standard DAPT without PFT guidance.

2. Patients and methods

2.1. Patients

The study protocol and informed consent form were approved by the Ethics Committee of Tianjin People's Hospital. This is a real-world study of the enrolled patients with written informed consent at Tianjin People's Hospital from January 2017 to December 2018. All works were undertaken following the provisions of the Declaration of Helsinki. The present study included ACS patients with PCI treatment and were treated with DAPT after PCI. In the initial stage, all patients were treated with aspirin and $P2Y_{12}$ receptor antagonists (clopidogrel or ticagrelor). Coronary angiography (CAG) was applied to determine the number of vascular lesions, and PCI was performed according to standard techniques. The types of implanted stent and whether to use glycoprotein IIb/IIIa inhibitor (GPI) were determined by the operator.

The inclusion and exclusion criteria are as following. Inclusion criteria:

1. Age $\geq$ 18 years old, no gender limit.
2. Inpatients clinically diagnosed with ACS, including acute STEMI, NSTEMI and UA.
3. Coronary angiography confirmed that the ACS patients who need to be underwent coronary stent placement and have successfully completed stent placement.
4. Patients treated with antiplatelet drugs after PCI, the antiplatelet drugs including aspirin and clopidogrel or ticagrelor.

Exclusion criteria:

1. Patients who allergic to antiplatelet drugs.
2. Patients who have to take anticoagulants for a long time.
3. Patients with coagulopathy.
4. Patients with malignant tumors.
5. Patients with BARC 3 or 5 bleeding or major adverse cardiac and cerebrovascular events (MACCE) during the hospitalization and before PFT.
6. Patients with incomplete or missing data.

2.2. Data collection and grouping

The data were collected from the inpatient department and the department of clinical laboratory, which recorded the patient's information and PFT results in detail. During the follow-up period, the PFT results and medical treatment were checked again. We reconfirmed that the treatment plan was made according to the PFT results, and the medication adjustment was also recorded. Based on whether the patients had valid PFT results by phototurbidimetry within 1 year after operation, they were divided into PFT guided medication group (the guided group) and standard DAPT group without PFT results (the control group). The patients in the control group received the standard-dose DAPT for 12 months according to the guideline recommendations, while those in the guided group adjusted the doses of antiplatelet drugs and shortened the duration of DAPT earlier based on PFT results. To reduce the effect of the baseline data difference on clinical outcomes, we determined the potential predictors of bleeding and thromboembolism through previous studies, and finally included 21 factors into the baseline based on clinical judgment. These indicators included demographic characteristics, past medical history, concomitant diseases, and

concomitant medications. The baseline characteristics of patients were collected from the database. The 1-year follow-up data of patients after PCI were collected through hospitalization, routine outpatient follow-up, medical questionnaire and telephone. Furthermore, we also recorded the PFT results and drug adjustment in the guided group. The baseline definition was added in Supplemental Digital Content (Table S1, http://links.lww.com/MD2/A67).

2.3. End-point events

The primary endpoint of this study was based on the BARC 3 or 5 major bleeding. Secondary endpoints include BARC1 to 2 minor bleeding and MACCE (all-cause death, nonfatal myocardial infarction, stroke, stent thrombosis, and unplanned target vessel reconstruction).

2.4. Statistical analysis

Statistical analysis was performed using SPSS 25.0 software. Since all eligible research subjects were continuously selected, and there were differences in baseline characteristics between the PFT group and the control group, we used propensity score matching to reduce the bias and confounding variables caused by baseline differences, so that the 2 groups more reasonable comparison. Multivariable logistic regression model was performed to evaluate the propensity score for comparison in each cohort. PFT was used as the dependent variable, while all the baseline characteristics listed in Table 1 were used as covariates. Propensity score analysis was performed by bootstrap method, in which 1:1 nearest neighbor matching without replacement (the caliper distance of the calculated propensity score was 0.2 SD) was used to identify well-matched units from both groups. According to the previous literatures,[16–18] the incidence of the primary endpoint in the control group was 5.2%, and after the intervention in the guided group, the expected incidence of the primary endpoint was 1.8%. While α was set to 0.05 (two-tail), and β was set to 0.20, the required sample size was finally calculated to be 458 in each group. Considering that the patients were continuously enrolled, the sample size could meet the need of statistical analysis in this study. All the patients within 2 years were finally included. After propensity score matching, there were 511 patients in each group.

In the matched cohort, the measurement data conforming to the normal distribution were expressed as , and the independent

Table 1

Propensity score matching based on baseline characteristics.

Items	Guided group (n=511)	Control group (n=511)	*P* value
Age (year)	61.88±9.45	61.86±9.62	.97
Male	348 (68.1%)	359 (70.3%)	.45
BMI (kg/m^2)	25.54±3.22	25.43±3.08	.58
Hypertension	383 (75.0%)	378 (74.0%)	.72
Diabetes mellitus	178 (34.8%)	186 (36.4%)	.60
Dyslipidemia	306 (59.9%)	280 (54.8%)	.10
Currently smoking	210 (41.1%)	228 (44.6%)	.25
COPD	14 (2.7%)	18 (3.5%)	.47
Atrial fibrillation	22 (4.3%)	22 (4.3%)	>.99
Chronic lung disease	29 (5.7%)	30 (5.9%)	.89
Digestive system diseases	139 (27.2%)	139 (27.2%)	>.99
Peripheral vascular disease	38 (7.4%)	28 (5.7%)	.25
History of stroke	74 (14.5%)	88 (17.2%)	.23
History of major bleeding	18 (3.5%)	19 (3.7%)	.86
History of CABG	0 (0.0%)	2 (0.4%)	.50
Previous PCI	75 (14.7%)	92 (18.0%)	.15
Previous MI	79 (15.5%)	85 (16.6%)	.60
Hemoglobin (g/L)	137.56±14.79	137.68±16.88	.89
Clinical presentation			
Unstable angina	259 (50.7%)	261 (51.0%)	.90
NSTEMI	90 (17.6%)	80 (15.7%)	.40
STEMI	162 (31.7%)	170 (33.3%)	.59
Lesion vessel number			
One-vessel disease	36 (7.0%)	42 (8.2%)	.48
Two-vessel disease	126 (24.7%)	118 (23.1%)	.55
Three-vessel disease	349 (68.3%)	351 (68.7%)	.89
Concomitant mediations at hospitalization			
Ticagrelor	326 (63.8%)	308 (60.3%)	.24
Clopidogrel	185 (36.2%)	203 (39.7%)	.24
Statins	501 (98.0%)	500 (97.8%)	.82
ACEIs or ARBs	277 (54.2%)	274 (53.6%)	.85
β receptor antagonists	322 (63.0%)	317 (62.0%)	.74
Calcium channel blockers	148 (28.0%)	146 (28.6%)	.89
Diuretics	80 (15.7%)	82 (16.0%)	.86
Nitrates	283 (55.4%)	282 (55.2%)	.95

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, PCI = Percutaneous coronary intervention, STEMI = ST elevation myocardial infarction.

Table 2

Risk of primary endpoint and secondary endpoint within 1 year.

Endpoints	Guided group (n=511)	Control group (n=511)	HR (95% CI)	*P* value
BARC 3 or 5 bleeding	10 (1.96%)	23 (4.50%)	0.45 (0.21–0.95)	.037
MACCE	25 (4.89%)	31 (6.07%)	0.80 (0.47–1.36)	.41
All cause death	3 (0.59%)	10 (1.96%)	0.30 (0.08–1.08)	.066
Nonfatal myocardial infarction	2 (0.39%)	5 (0.98%)	0.40 (0.07–2.05)	.27
Stroke	5 (0.98%)	9 (1.76%)	0.56 (0.19–1.68)	.31
Stent thrombosis	2 (0.39%)	2 (0.39%)	1.00 (0.14–7.10)	>.99
Target vessel revascularization	14 (2.74%)	6 (1.17%)	2.36 (0.91–6.13)	.079
BARC 1 to 2 bleeding	68 (13.3%)	57 (11.2%)	1.25 (0.88–1.78)	.22
BARC 1, 2, 3, 5 bleeding	78 (15.3%)	80 (15.7%)	0.99 (0.72–1.34)	.93

95% CI = 95% confidence interval, BARC = Bleeding Academic Research Consortium, HR = hazard ratio, MACCE = the composite endpoint of all-cause death, nonfatal myocardial infarction, stroke, stent thrombosis, and unplanned target vessel reconstruction.

sample t test was used for comparison between the 2 groups. Data that did not conform to the normal distribution were represented by the median (lower quartile, upper quartile), and the rank sum test was used for comparison. Enumeration data was expressed as a percentage (%), and the comparison between the 2 groups was performed by χ^2 test or Fisher's exact test. A Kaplan-Meier chart was generated to visualize the incidence of end-point events between the two groups, and the Log rank test was used for comparison. When estimating the incidence of events by Kaplan–Meier method, we reviewed patients who were lost to follow-up and subsequently lost to assessment of the primary endpoints. The hazard ratio and 95% confidence interval of the clinical endpoints were determined using a univariate Cox proportional model. Multivariate Cox proportional hazards model to determine the predictors of BARC 3 or 5 major bleeding. Subgroup analysis of predictors of major bleeding and other predictors that may affect the endpoints. The P value $< .05$ is considered statistically significant.

3. Results

3.1. Enrolled patients and propensity score matching

A total of 1639 patients with ACS after PCI were consecutively included in this study from January 2017 to December 2018. Eighty nine of them were removed due to loss to follow-up (the rate was 5.43%). Eventually enrolled 1550 patients. As showed in Table 1, a total of 1022 patients were successfully matched after propensity score matching (PSM). There was no statistical difference in baseline between the guided group (n=511) and the control group (n=511).

3.2. End-point events

The 1-year incident rate of end-point events is shown in Table 2. In the cohort after PSM, there were 10 cases of guided group (1.96%) and 23 cases of control group (4.50%) had BARC 3 or 5 major bleeding, and there were statistical differences between the 2 groups (P=.037, HR: 0.45, 95% CI 0.21–0.95) (Fig. 1). However, there was no statistical difference between 2 groups in the MACCE event and its various components (P=.41) (Fig. 2). In addition, there was no statistical difference in the overall incidence of BARC 1 to 2 minor bleeding between the 2 groups (13.3% vs 11.2%, P=.22). We performed the same statistics on cohorts before and after PSM, and got similar conclusions.

3.3. Bleeding events

There were 33 people (3.23%) had major bleeding, and 125 (12.2%) had minor bleeding within 1 year. Gastrointestinal bleeding was the most common major bleeding, and the different event of major bleeding between the 2 groups was mainly the gastrointestinal bleeding (P=.038) (Table 3). Minor bleeding was most frequent in the skin, nose, and oral cavity. It is worth noting that although minor bleeding (BARC 1 to 2) in the guided group was more than that in the control group, there was no

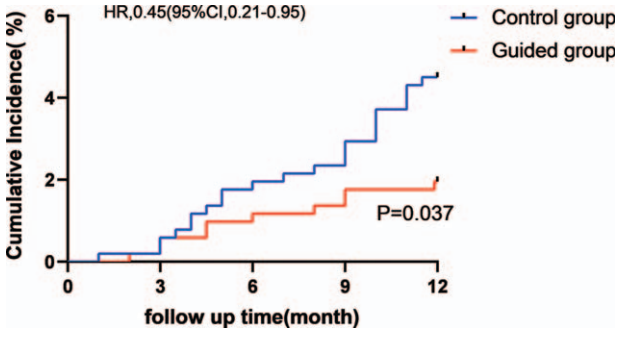

Figure 1. Cumulative risk of BARC 3 to 5 in the guided group and the control group in 1 year. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. HR and 95% CI were calculated by the Cox. 95% CI = 95% confidence interval, HR = hazard ratio.

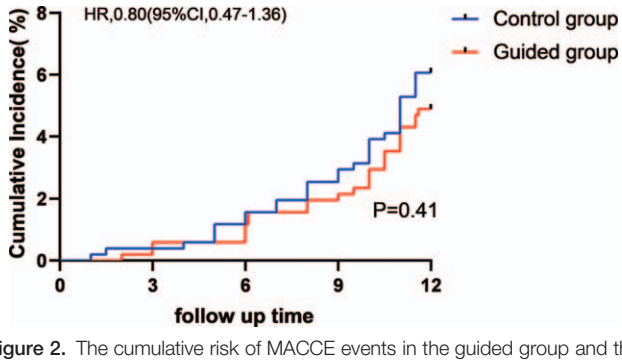

Figure 2. The cumulative risk of MACCE events in the guided group and the control group in 1 year. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. HR and 95% CI were calculated by the Cox. 95% CI = 95% confidence interval, HR = hazard ratio.

Table 3

Site of bleeding events and type of bleeding/.

Items	Guided group (n=511)	Control group (n=511)	*P* value
Site of bleeding events			
Gastrointestinal bleeding	9 (1.76%)	20 (3.91%)	.038
Intracranial bleeding	4 (0.78%)	3 (0.59%)	.67
Ecchymosis and subcutaneous bleeding	24 (4.50%)	17 (3.33%)	.25
Nasal bleeding	15 (2.94%)	9 (1.76%)	.21
Oral bleeding	9 (1.76%)	13 (2.54%)	.39
Hematoma at puncture site	4 (0.78%)	2 (0.39%)	.41
Intraocular bleeding	8 (1.57%)	8 (1.57%)	.95
Urogenital bleeding	2 (0.39%)	6 (1.17%)	.17
Other bleeding	3 (0.59%)	2 (0.39%)	.98
Type of bleeding			
BARC 1	34 (6.65%)	30 (5.87%)	.58
BARC 2	34 (6.65%)	27 (5.28%)	.55
BARC 3	9 (1.76%)	23 (4.50%)	.027
3a	1 (0.19%)	13 (2.54%)	.002
3b	5 (0.98%)	7 (1.37%)	.55
3c	3 (0.59%)	3 (0.59%)	>.99
BARC 5	1 (0.19%)	0 (0.0%)	.32
TIMI bleeding			
Major bleeding	9 (1.76%)	10 (1.95%)	.81
Minor bleeding	1 (0.19%)	13 (2.54%)	.002
Minimal bleeding	68 (13.3%)	57 (11.2%)	.22

BARC = Bleeding Academic Research Consortium, TIMI = Thrombolysis in Myocardial Infarction.

statistical difference (ecchymosis and subcutaneous bleeding $P=.25$; Nasal bleeding $P=.21$; Oral bleeding $P=.39$). In addition, most patients in the guided group had minor bleeding before PFT. These patients were driven to undergo PFT due to minor bleeding, who showed higher compliance. As shown in Table 3, the results of Thrombolysis in Myocardial Infarction (TIMI) bleeding score suggested that minor bleeding (a hemoglobin drop of 3–5 g/dL) in the guided group was significantly lower than that in the control group ($P=.22$), which was consistent with the results of BARC bleeding.

3.4. Subgroup analysis

We further performed a subgroup analysis of the primary endpoint of BARC 3 and 5 bleeding to better understand the advantages of PFT in different populations (Fig. 3). Through multivariate cox analysis, we found that age greater than 75

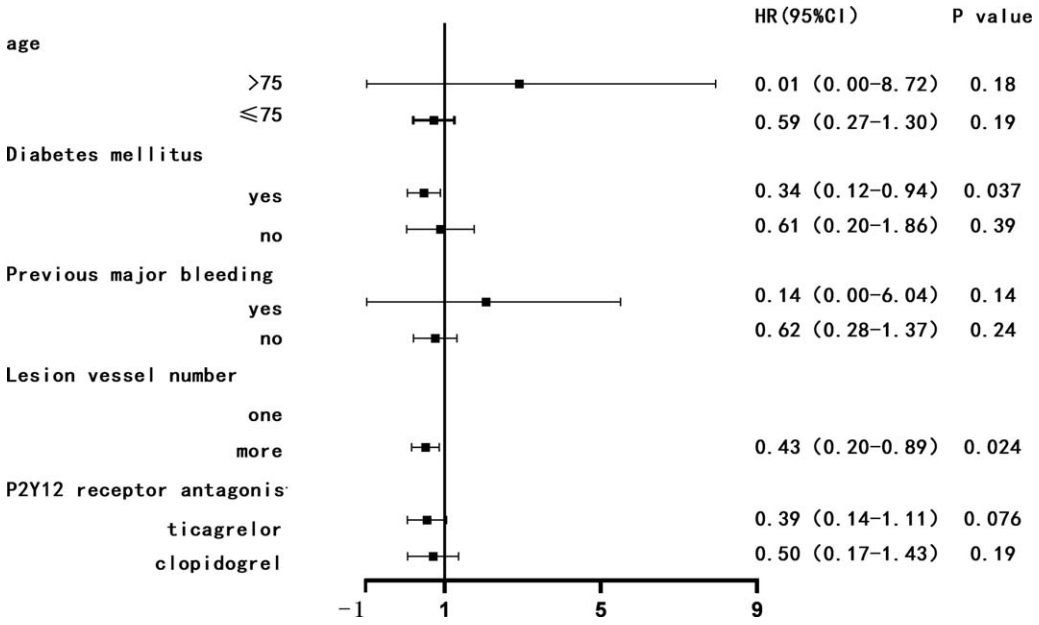

Figure 3. Subgroup analysis of major bleeding at 1 year. HR and 95% CI were calculated by the Cox. *P*-values were calculated by the log-rank test. No patients in the one-vessel disease group had BARC 3 or 5 major bleeding, so it is not shown in the figure. 95% CI = 95% confidence interval, HR = hazard ratio.

Table 4

Antiplatelet medication 1 month after PCI.

Medication	Dosage	Number of people
Aspirin	100 mg	193 (37.8%)
	75 mg	231 (45.2%)
	50 mg	69 (13.5%)
	25 mg	12 (2.34%)
	None	6 (1.17%)
Ticagrelor	90 mg bid	301 (58.9%)
	90 mg qd–45 mg qn	14 (2.74%)
	45 mg bid	57 (11.6%)
Clopidogrel	75 mg	139 (27.2%)

bid = twice a day, PCI = percutaneous coronary intervention, qd = every day, qn = every night.

years, diabetes, and previous major bleeding are predictors of major bleeding. In the subgroup analysis, we found that in patients with diabetes and multivessel coronary artery disease, the risk of major bleeding was reduced after the drug dosage was adjusted in time based on the PFT. This indicated that it was more efficient to conduct PFT to guide medication in these populations.

3.5. PFT and individualized treatment

In the guided group, there were 423 cases (82.8%) underwent PFT within 1 month after PCI, and 156 cases (30.5%) underwent PFT several times. According to the PFT results, from 2 weeks to 1 month after PCI there were 106 cases (20.7%) adjusted the aspirin dose. There were 56 cases (30.3%) switched to ticagrelor due to HPR among the 185 cases initially taking clopidogrel. There were 10 cases (3.07%) de-escalation ticagrelor to clopidogrel, and 59 cases (18.1%) adjusted the dose of ticagrelor among the 326 cases taking ticagrelor. A total of 35 cases (11.0%) of these patients were adjusted for aspirin and ticagrelor at the same time. Therefore, the treatment of 36.4% of patients was adjusted according to PFT. The specific medications at 1 month after PCI are shown in Table 4. The adjustment of the dose of aspirin and ticagrelor is mainly manifested in the active and passive reduction of patients due to LPR and minor bleeding. Table 5 is shown the changes in the values of arachidonic acid (AA) and adenosine diphosphate (ADP) after the adjustment of DAPT drugs guided by the PFT results. It has been shown that the changes of AA and ADP were statistically different after adjusting the dose ($P = .041$, $P < .001$). Whereas the change interval does not exceed the HPR threshold even if the values of AA and ADP change. For patients with bleeding, after adjusted the dose, there was no statistical difference in AA and ADP ($P = .21$, $P = .22$). Table 6 shows the results of PFT when taking different $P2Y_{12}$ receptor antagonists, with or without bleeding. There were statistical differences in AA and ADP values between patients taking ticagrelor and clopidogrel ($P = .005$, $P < .001$). In addition, there were statistical differences in the AA and ADP values between the bleeding group and the nonbleed group ($P < .001$).

4. Discussion

Our observational cohort study in the real world presents several important findings. First of all, guiding the use of antiplatelet drugs under PFT can improve the prognosis of PCI patients. Lower the dose for patients with LPR in the early stage, while reducing the incidence of major bleeding without increasing the risk of ischemia. Secondly, for patients with high bleeding risk and small bleeding, DAPT lower than the standard dose can also achieve antithrombotic purpose. In this study, we chose the case deletion method to deal with the missing values, which may be simple and effective. The first reason is that the missing data was 44 cases (2.6%), which was limited to a small number of observations. The second is that the type of missing values was Missing Completely at Random.

Some studies have shown no significant improvements in clinical outcomes with platelet-function monitoring (on-treatment platelet reactivity) and treatment adjustment for ACS patients after PCI, as compared with standard antiplatelet therapy without monitoring.[19,20] However, patients recruited in these studies were generally low-risk, and the main medication was clopidogrel, and the definition of the best target for platelet reactivity was not clear. The ANTARCTIC study which was a multicenter, randomized controlled superiority study, included patients aged 75 years or older who had undergone coronary stenting for ACS.[17] These patients received oral prasugrel 5 mg daily with dose or drug adjustment under PFT monitoring. The conclusion also shows platelet function monitoring with treatment adjustment did not improve the clinical outcome of

Table 5

Comparison of platelet function testing results before and after the adjustment of medication regimen in the guided group.

	Bleeding patients before being instructed	Bleeding patients after being instructed	*P* value	All patients before being instructed	All patients after being instructed	*P* value
AA	5 (3.00, 8.00)	6 (3.00, 7.00)	.21	8 (5.00, 11.00)	7 (5.00, 10.00)	.014
ADP	10 (5.00, 14.00)	10 (6.00, 15.00)	.22	16 (9.00, 26.00)	12 (7.00, 20.00)	<.001

AA = arachidonic acid, ADP = adenosine diphosphate.

AA and ADP are non-normally distributed measurement data, expressed as median (lower quartile, upper quartile), and rank sum test was used for comparison between the 2 groups.

Table 6

Comparison of platelet function testing results of different populations.

	Ticagrelor	Clopidogrel	*P* value	Bleeding	Non-bleed	*P* value
AA	8 (5.00, 10.25)	9 (6.00, 11.50)	.005	5 (4.00, 8.00)	9 (5.00, 11.00)	<.001
ADP	12 (7.75, 19.00)	27 (17.50, 39.00)	<.001	10 (4.75, 15.00)	18 (10.00, 28.00)	<.001

AA = arachidonic acid, ADP = adenosine diphosphate.

AA and ADP are non-normally distributed measurement data, expressed as median (lower quartile, upper quartile), and rank sum test was used for comparison between the 2 groups.

elderly patients treated with coronary stenting for ACS (hazard ratio [HR], 1.003, 95% CI 0.78–1.29; $P = .98$).[17] It is worth noting that in this study, prasugrel was started with a small dose, which essentially compared the curative effect of 5 mg prasugrel with low-dose prasugrel replaced by 75 mg clopidogrel in less than half of the patients. Therefore, this conclusion had weak evidence in whether the PFT was performed. However, the TROPICAL-ACS study followed a different principle, performed early de-escalation from prasugrel to clopidogrel and PFT-guided maintenance treatment for ACS patients.[12] Results showed HPR on prasugrel was associated with increased risk of ischemic events, however, LPR was a strong and independent predictor of bleeding both on prasugrel and clopidogrel.[12] It is proved that according to the PFT, it is feasible and safe to switch to an antiplatelet individualized adjustment drug therapy adapted to the disease development stage. This is consistent with the results of the present study, indicating the feasibility of PFT. Similarly, study by András Komócsi et al showed patients receiving PFT-guided $P2Y_{12}$ receptor inhibitor therapies with a lower risk of mortality.[21] Another study combined CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines) risk score with PFT and compared individual.[22] It was found that after successful PCI in patients with ACS, combining CRUSADE score with platelet reactivity yielded more accurate predictive value for 1-year bleeding risk.[22] 2020 European Society of Cardiology guidelines list the post-interventional antiplatelet de-escalation therapy for ACS based on the results of PFT as a Class IIb/A recommendation.[1] These bring evidence for PFT to be used to individualize patients, thereby providing a novel antiplatelet strategy to reduce the risk of bleeding while maintaining antiischemic efficacy. Although the present study also converted clopidogrel into a more potent ticagrelor due to HPR, it did not account for a large proportion of this cohort. At the same time, patients who had used ticagrelor in this study did not reach the consensus HPR value which published on 2010 American College of Cardiology Foundation.[23] There is evidence revealing LPR as an independent predictor of major bleeding, and patients with LPR after PCI have a higher bleeding risk.[12] The consensus defines the treatment window based on the related PFT, which may reduce the ischemic and bleeding events as much as possible by controlling the platelet reactivity within the treatment window.[13,24] Our center also complies with the above consensus on the medication dose instructions according to the results of PFT. For patients taking clopidogrel with ADP > 46, replaced clopidogrel with ticagrelor, a more potent antiplatelet medication. Patients with ADP < 10 received the reduced doses of clopidogrel and ticagrelor, or replaced ticagrelor with clopidogrel. Patients with AA < 5 received the reduced doses of aspirin. During the follow-up period, we determined again the medication adjustment in the guided group after PFT, especially for patients with multiple PFT results, and compared the changes of AA and ADP values before and after the drug change. Different treatment plans are adopted for patients in different treatment windows, which reflects the individualized antiplatelet treatment strategy. The data collected in this study also showed lower platelet reactivity in patients with bleeding, indicating a high correlation between LPR and bleeding. Therefore, when patients' PFT results show LPR, we will reduce the doses of antiplatelet drugs to reduce the risk of bleeding. At present, it is still a hypothesis that patients may have the lowest risk of adverse events within the $P2Y_{12}$ receptor inhibitor treatment window. However, the concept of treatment window needs to be re-examined. More importantly, how adjusting the patient's treatment outside the treatment window would affect the risk of bleeding or thrombosis remains uncertain.[25] Although PFT is currently only used as a part of the reference for evaluating changes in clinical conditions, it also provides us with new ideas to implement treatment. At the same time, the results of laboratory tests such as PFT increase the compliance of patients with medical treatment, and we should not ignore it.

In this study, the dose of ticagrelor and aspirin was adjusted early under the guidance of platelet function, and the adjustment was mainly manifested as a dose reduction. Taking into account individual differences in clopidogrel medication, the European Society of Cardiology guidelines also recommend ticagrelor over clopidogrel as a category I B recommendation. Therefore, for patients with low ADP values, we reduced the dose of ticagrelor, especially in the early stage (1 month after PCI). A meta-analysis of monotherapy after PCI showed that discontinuation of aspirin therapy 1 to 3 months post PCI significantly reduced the risk of major bleeding by 40% compared to DAPT, however, with no observed in the risk of major adverse cardiovascular events (2.73% vs 3.11%; HR 0.88, 0.77–1.02).[18] The recently updated 2020 European Society of Cardiology guidelines also considers patients with high bleeding risk (PRECISE$\geq$25 or ARC-HBR) after stent implantation to discontinue $P2Y_{12}$ receptor inhibitors after 3 months as a IIa/B recommendation.[1] After considering the balance of ischemia and bleeding risk, stop using aspirin after 3 to 6 months as a recommendation for IIa/A.[1] These clinical trials have confirmed the significance of early dose reduction. In addition, results of the PEGASUS-TIMI study indicated that the overall effectiveness of the 60 mg dose of ticagrelor was similar to the 90 mg dose, and the 60 mg dose reduced the occurrence of bleeding and dyspnea.[26] Therefore, 60 mg ticagrelor was recommend. The sub-study also showed that there was no statistical difference between the 2 doses in terms of pharmacokinetics and efficacy.[27] Since our center did not have a 60 mg dose of ticagrelor during 2017 to 2018, we used 45 mg twice daily to reduce ticagrelor. There has been a study have also shown that 45 mg ticagrelor could also achieve the same efficacy as the standard dose, which is consistent with our conclusions, indicating that it is feasible to reduce aspirin and ticagrelor in the early stage of PFT monitoring.[28]

According to our results, most patients with BARC 1 to 2 minor bleeding occurred within 1 month after PCI. Although it has not been clearly confirmed that minor bleeding will progress to major bleeding, we should not ignore the existence of minor bleeding, which probably affects patient compliance and cause drug withdrawal. We recommend that patients undergo PFT 2 weeks to 1 month after discharge. From our experience, patients with better compliance and minor bleeding were more willing to receive PFT. In addition, the incidence of minor bleeding in the guided group was slightly higher than that in the control group, indicating that even minor bleeding could cause panic in patients and tend to seek medical treatment. The present study also found that for patients with minor bleeding, there was little change in platelet reactivity before and after dose reduction, and most minor bleeding patients had lower AA and ADP values. The underlying mechanism of bleeding is more complex, for instance, there have been remained abnormally platelet activated in patients with minor bleeding. It has been reported that LPR is an independent predictor of major bleeding, thus we will also focus on complication of minor bleeding in future work.[12] In our

study, most of the patients (82.8%) in the guided group underwent PFT from 2 weeks to 1 month after operation, while the rest (17.2%) underwent PFT 1 month after operation. ONSET/OFFSET study suggested that inhibition of platelet aggregation (IPA) remained in a relatively stable range at 6 weeks after administration of the maintenance dose of $P2Y_{12}$ receptor inhibitors,[29] while other studies chose to perform PFT 14 days after treatment.[12,17] Therefore, it may be reliable to perform platelet activity test at 2 weeks to 1 month after treatment. However, there has been no study to prove the different results that may be caused by PFT at different time points. The optimal detection time point for PFT is currently controversial. Therefore, we recommend implementing dynamic PFT due to individual differences, changes in combination medications, and epigenetics may change the platelet aggregation rate. A single PFT cannot predict the long-term prognosis of patients and improve safety.

Results of subgroup analysis showed that PFT for patients with high bleeding risk (diabetes and multivessel disease) and early intervention in their medication could improve the prognosis. Increased expression of activation-dependent platelet markers on platelet surface is an indicator of platelet activation. Abnormal platelet activation is related to many diseases, including diabetes.[30] Abnormal cell metabolism in diabetic patients may trigger cell oxidative stress and inflammation, which may cause vascular endothelial cell dysfunction. Studies have shown that diabetic patients are at greater risk of ischemia and bleeding.[31] Therefore, individualized treatment of patients with high risk of bleeding and ischemia is of particular importance. The latest consensus has improved the definition of high bleeding risk (HBR), combined with PFT can better balance bleeding and ischemia.[32] In addition, we also found that compared with patients who used clopidogrel, patients with ticagrelor had lower AA and ADP values, while patients with gastrointestinal bleeding had lower AA values than that of other bleeding patients. As a more potent $P2Y_{12}$ receptor inhibitor, ticagrelor has been verified that its ADP value induced by inhibition of platelet aggregation was lower than clopidogrel.[33] However, there is no clear conclusion about the abnormal decrease of AA values. Some studies have analyzed whether ticagrelor acted on the cox pathway of aspirin from the perspective of metabolites, but the results did not find changes in thromboxane B_2 (TxB_2), which may be due to differences in the included population and in vitro study that cannot completely simulate the metabolic activation pathway.[26,34] These reflected the complexity of platelet physiology, so more detailed and precise study may be needed to explore ticagrelor and aspirin in the future to reveal whether ticagrelor acts on the aspirin pathway or amplifies its effects. And for the combination of potent $P2Y_{12}$ receptor inhibitors, the optimal dose of aspirin is still worth exploring. In addition, a previous study compared the pharmacokinetics of ticagrelor in Caucasians and Japanese, and found that the Japanese have generally higher exposure to ticagrelor and its active metabolite AR-C124910XX.[35] Considering that East Asians have a lower risk of ischemia and a higher risk of bleeding than Europeans and Americans, it would be necessary to study the formulation of ticagrelor that probably suitable for Asian physiques. For specific populations, antiplatelet drugs with lower doses than the standard can be used as the starting dose.

The present study has some potential limitations. First of all, all patients underwent PFT at different time, and the trial ruled out that patients with pretest events may cause a reduction in related events. Although most patients were tested within 1 month after PCI and propensity score matching was applied to reduce the possible deviation caused by grouping, there was still some confusion factors cannot be avoided. Secondly, this study did not separately analyze the impact of different drug adjustment on the endpoints, and relevant subgroup analysis will be done in the future. Finally, the detection of platelet function in this study was the light transmittance aggregometry. Although it is the gold standard for platelet function detection and is inexpensive and affordable, it still to be affected by many influencing factors. Considering that the results of different detection methods may be heterogeneous, theoretically, our results cannot be generalized to other PFT.

5. Conclusion

The clinical outcomes of ACS patients after PCI may be improved using individualized antiplatelet therapy directed by early observation of dynamic PFT.

Acknowledgments

The authors would like to thank the doctors and nurses, as well as the patients for their contributions to this study.

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