Does Baseline On-treatment Platelet Reactivity Impact Long-term Prognosis in Patients with Acute Coronary Syndrome and Thrombocytopenia Who Underwent Percutaneous Coronary Intervention?

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Research article

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Abstract

Objectives: This study analyzed the association between on-treatment platelet reactivity and long-term outcomes of patients with acute coronary syndrome (ACS) and thrombocytopenia (TP) in the real world.

Methods: A total of 10724 consecutive cases with coronary artery disease who underwent percutaneous coronary intervention (PCI) were collected from January to December 2013. Cases with ACS and TP under dual anti-platelet therapy were enrolled from the total cohort. 5-year clinical outcomes were evaluated among cases with high on-treatment platelet reactivity (HTPR), low on-treatment platelet reactivity (LTPR) and normal on-treatment platelet reactivity (NTPR), tested by thromboelastogram (TEG) at baseline.

Results: Cases with HTPR, LTPR and NTPR accounted for 26.2%, 34.4% and 39.5%, respectively. Cases with HTPR were presented with the most male sex, lowest hemoglobin level, highest erythrocyte sedimentation rate and most LM or three-vessel disease, compared with the other two groups. The rates of 5-year all-cause death, major adverse cardiovascular and cerebrovascular events (MACCE), cardiac death, myocardial infarction (MI), revascularization, stroke and bleeding were all not significantly different among three groups. Multivariable Cox regression indicated that, compared with cases with NTPR, cases with HTPR were not independently associated with all endpoints, as well as cases with LTPR (all $P>0.05$).

Conclusions: In patients with ACS and TP undergoing PCI, 5-year all-cause death, MACCE, MI, revascularization, stroke and bleeding risk were all similar between cases with HTPR and cases with NTPR, tested by TEG at baseline, in the real world. The comparison result was the same between cases with LTPR and NTPR.

Introduction

Thrombogenesis plays a crucial role throughout pathogenesis of acute coronary syndrome (ACS). Platelets are main components of thrombus. Adhesion, activation and aggregation of platelets is the core process of the thrombosis. Therefore, anti-platelet therapy has been confirmed as the cornerstone of prevention and treatment of thrombosis. Dual anti-platelet therapy (DAPT) significantly reduce the risk of both in-hospital and long-term adverse cardiovascular events. And its benefit is independent of other secondary prevention drugs and percutaneous coronary intervention (PCI). Thus, DAPT is recommended in all ACS patients [1-4]. It was reported that about 5.4% of patients with coronary artery disease (CAD), 0.9% of patients with ACS were diagnosed with thrombocytopenia (TP) [5, 6] In patients with ACS and TP, the management of anti-platelet therapy remains being difficult. Up to now evidence is still limited on how to balance the risk of ischemia and bleeding in this special population [2-4].

It was reported that research into the association between platelets and prognosis of ACS patients should take both the quantity and function of platelets into consideration [7]. In other words, the assessment of thrombotic risk, as well as anti-thrombotic therapy should think about both the quantity and function of

platelets. It was found that, in patients with essential thrombocythemia, about 9.4% of which were diagnosed with acute myocardial infarction (AMI). And thrombocythemia was considered one of the risk factors of ACS [8]. Baseline TP was also considered as an independent factor of adverse outcomes in patients with ACS. And it was found independently related to in-hospital death in those who underwent emergency PCI [9-11]. Meanwhile, an important role of platelet function was revealed for ischemia evaluation in patients with ACS. For example, it was reported that thrombotic risk increased when platelet volume became larger [12-14]. Our research team reported, in patients with stable CAD and diabetes mellitus (DM), mean platelet volume could predict the 2-year cardiac death [15]. A reasonable guess is that dysfunction of platelets in terms of enlargement of volume or enhancement of activity can lead to thrombosis or bleeding, despite of change in quantity.

Therefore, application of platelet function testing (PFT) maybe one of solutions to guide anti-platelet therapy in patients with ACS and TP [16, 17]. It is still worth noting that there is limited data on the application value of PFT in patients with ACS and TP, although large high-qualified clinical trials have not drawn out a positive result concerning on the application value of PFT in individualized anti-platelet therapy [4, 18-21]. We studied a population with ACS and TP who underwent PCI, and took thromboelastogram (TEG) as technology of PFT to find out whether on-treatment platelet reactivity (TPR) was associated with their long-term prognosis in the real world, and whether TEG has some positive meaning in guidance of anti-platelet therapy in this special population.

Methods

Ethical Statement

Ethical approvals were obtained from the Fuwai Hospital Research Ethics Committees (No. 2013-449 and No. 2020-1310). The Institutional Review Board approved the study protocol and all patients signed written informed consent before the intervention, including full set of risk-informed consent and information use consent for scientific purposes.

Study Population

A total of 10724 consecutive cases with CAD who underwent PCI were enrolled from January to December 2013 in our center, the largest cardiovascular center of China. Diagnosis of ST-segment elevated myocardial infarction (STEMI), non-ST-segment elevated myocardial infarction (NSTEMI), unstable angina pectoris (UAP) and chronic coronary syndrome (CCS) was in terms of criteria based on the “2015 ESC guidelines for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation”, “Fourth universal definition of myocardial infarction (2018)” and “2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes” [22-24].

The median platelet number was 199.0×10^9/L and the average platelet number was 203.6×10^9/L ($\pm54.4\times10^9$) in the total cohort of 10724 cases. A normal platelet count is defined as $150–350 \times 10^9$/L based on platelet number distribution and international criteria [25]. Baseline TP was defined as a platelet

count < 150 × 10^9/L. The following patients were excluded: (1) patients with CCS (n=4293); (2) patients with missing platelet count data (n=76) (3) patients with a platelet count ≧ 150 × 10^9/L (n =5537) and (4) patients without TEG data (n=344). A total of 474 cases diagnosed with ACS and TP were included in this study (Figure 1).

TEG was applied under DAPT for long-term administration (aspirin and clopidogrel) at admission or at least 6 hours after PCI. It should be better to measure it half an hour or so after the blood is taken, and then avoid bubbles in the blood drawing tube when the blood is taken, otherwise the platelets are easy to be activated and cannot be detected. On-treatment platelet reactivity tested by TEG were defined according to “2013 Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate (ADP) associated with ischemia and bleeding” [26]. High on-treatment platelet reactivity (HTPR) was defined by TEG Platelet Mapping Assay in terms of ADP-induced platelet-fibrin clot strength (mm) (MAADP)≥47 mm. Low on-treatment platelet reactivity (LTPR) was defined as MAADP ≤31 mm. Normal on-treatment platelet reactivity (NTPR) was defined as 31mm < MAADP ≤ 47mm.

Procedural Details

Before elective PCI, if not taking long-term aspirin and clopidogrel, patients received aspirin and P2Y12 inhibitor with loading dose orally. Patients with ACS scheduled for primary PCI received the same dose of aspirin and clopidogrel (loading dose 300mg or 600mg, according to bleeding risk) as soon as possible. Ticagrelor was seldom used in our center in the year of 2013 (Table 1). It was prescribed only when clopidogrel resistance was observed and patients were willing to take it on their own expense, with a loading dose of 180 mg or cumulative dose of 180 mg followed by 90 mg twice a day. Before coronary angiography (CAG), 25mg heparin sodium was administered through an arterial sheath or intravenously. Before PCI, 100 U/kg of heparin sodium was administered. The dose was lowered to 50–70 U/kg in patients over the age of seventy to reduce bleeding risk. If PCI proceeded for more than 1 h, an additional 1000 U of heparin sodium was administered. Results of CAG were read by experienced cardiologists. More than 50% stenosis of left main artery (LM), left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery (RCA), and main branch of these vessels was defined as coronary artery stenosis. More than 70% stenosis of the vessels mentioned above, along with ischemic symptoms or ischemic evidence showed by examinations, was indicated for coronary stent implantation. Three-vessel disease (TVD) was defined as angiographic stenosis of ≥50% in all three main coronary arteries, LAD, LCX, and RCA. Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (SS) and residual SNYTAX score was assessed by two of the three experienced cardiologists in an independent angiographic core laboratory, who were blinded to clinical outcomes.

Follow-Up and Definitions

The patients were visited 30 days and 6 months after PCI and every 1 year thereafter. Information of in-hospital outcome was obtained through review of medical records, and the long-term clinical outcome was collected from survey completed by telephone follow-up. A group of independent clinical physicians

oversaw checking and confirmed all adverse events carefully. Investigators training, blinded questionnaire filling, and telephone recording were performed to control the data quality.

Primary endpoint was all-cause death. Composite endpoint was defined as major adverse cardiovascular and cerebrovascular events (MACCE), including all-cause death, revascularization, MI, and stroke. Secondary endpoints were MACCE, cardiac death, revascularization, MI, stroke and bleeding. Cardiac death is identified as death caused by MI, heart failure, and/or malignant arrhythmia definitely; or death which cannot be explained clearly by other reasons. Bleeding was defined according to criteria established by Bleeding Academic Research Consortium (BARC), excluding BARC 0 and 1 type.

Statistical Analysis

Data statistics was applied using SPSS 22.0 (IBM Corp., Armonk, New York, USA). One-way ANOVA tests were used to compare continuous variables between the three groups at baseline. Student's t tests were used to compare continuous variables between the two groups. Chi-square tests were applied to compare categorical variables between the three groups at baseline and between the two groups on outcomes. Kaplan–Meier curves were drawn to compare cumulative event rates of the three groups. Multivariate Cox proportional hazard regression analyses were applied to control baseline confounders. Covariates for Cox regression were those variables with significant differences in baseline or important clinical meaning. All *P* values were two sided with a significance level of 0.05. Tendency of significant difference was judged when $0.05<P<0.1$.

Results

Baseline Characteristics

Among 474 cases analyzed, cases with HTPR, LTPR and NTPR accounted for 26.2%, 34.4% and 39.5%, respectively. Cases with HTPR were presented with more male sex (23.4%, 8.6% and 11.8%, $P=0.001$), lower hemoglobin level (136.1 ± 16.2, 144.5 ± 15.8 and 139.9 ± 16.2, $P<0.001$), higher ESR (12.2 ± 9.9, 6.6 ± 6.9 and 9.4 ± 10.7, $P<0.001$) and more LM or three-vessel disease (8.9%, 2.5% and 4.3%, $P=0.039$), compared with cases with LTPR and cases with NTPR. And cases with HTPR had less frequent incidence of UAP, higher platelet count before PCI and hemoglobin A1c (HbA1c) level, less LAD involved, longer time of procedure and more use of PPI. These variates showed significant difference between two of the three groups, but not among the three groups respectively. (Table 1)

2-year and 5-year Clinical Outcomes

For the analyzed population, clinical follow-up was completed for 470 patients (99.2%) of 2 years, and for 435 patients (91.8%) of 5 years. The occurrence of adverse cardiovascular and cerebrovascular events in each group is listed in Table 2 and Table 3.

The rates of 2-year all-cause death, MACCE, cardiac death, myocardial infarction (MI), revascularization and bleeding were all not significantly different among three groups. However, unexpectedly, the rate of 2-

year MACCE showed a decrease tendency in cases with HTPR and cases with LTPR (8.9%, 9.2% and 16.0%, *P*=0.07), as well as the rate of 2-year MI (2.4%, 0.6% and 4.3%, *P*=0.093), compared with cases with NTPR group. Moreover, cases suffered from stroke during 2-year follow-up were zero in cases with HTPR and cases with LTPR, which made the comparison difficult among the three groups. Therefore, we applied 5-year clinical follow-up. And we found that the rates of 5-year all-cause death, MACCE, cardiac death, myocardial infarction (MI), revascularization, stroke and bleeding were all not significantly different among the three groups. Kaplan-Meier curves revealed the same finding (Figure 2).

Multivariable Cox regression models were built, including those possible confounders at baseline. It was surprised that, compared with cases with NTPR, cases with HTPR were independently associated with decreased 2-year MACCE risk (HR 0.43, 95%CI 0.21-0.88, *P*=0.019). However, cases with HTPR at baseline were not independently associated with all 5-year endpoints, compared with cases with NTPR (all *P*>0.05). The results of comparison were the same between cases with LTPR and cases with NTPR at baseline (all *P*>0.05). (Table 4, 5)

Discussion

It was identified that HTPR was associated with ischemia risk, while LTPR was associated with bleeding risk in patients who underwent DAPT. For example, ADAPT - DES (Assessment of Dual Antiplatelet Therapy With Drug - Eluting Stents) research data show that high platelet reactivity under clopidogrel treatment had significant positive correlation with stent thrombosis and myocardial infarction, while had negative correlation with hemorrhage following PCI. It prompts that the detection of platelet activity has potential value on monitoring, adjustment and individualization of antiplatelet therapy during P2Y12 inhibitor treatment [27]. Why didn't we get the results we had guessed in this study? The possible reasons are as follows.

The first is that this retrospective study reflected the situation in the real world. The TEG results analyzed were the baseline condition under DAPT during perioperative period of PCI. Subsequent individualized adjustment of antithrombotic drugs was probably applied following an unsatisfied result of TEG, which might be the main reason to correct the underlying risk of thrombus or bleeding. For example, if TEG suggested HTPR following PCI, clopidogrel was replaced with ticagrelor or a doubled dose for a least one month after discharge. On the contrary, patients with LTPR who presented with bleeding tendency might have altered DAPT plan and duration during follow-up. And this is the purpose of PFT, the individualized adjustment of anti-platelet therapy. Therefore, the negative results of this study may be instead encouraging. Despite differences in platelet reactivity at baseline, it is not surprising that there was no difference in five-year outcomes after the most likely individualized adjustment of antithrombotic strategies. If the inference holds, the value of TEG cannot be negated easily in guiding antithrombotic therapy in patients with ACS and TP.

Secondly, it is still important to acknowledge the technical advantages and limitations of TEG, as well as other PFT technologies. Currently, there are a variety of commonly used methods for PFT in clinical

practice, with different detection standards. Different experimental methods have their own advantages and disadvantages. Currently, no detection method has been found to be comprehensively superior to other methods [28-35]. Since the platelet aggregation method has a certain dependence on the platelet count, the detection results have a large deviation in patients with TP [32]. The application value of flow cytometry detection has been reported, and it has been confirmed in patients with idiopathic thrombocytopenic purpura (ITP) that the platelet longevity and protease-activated receptor-1 related activity was significantly associated with bleeding fraction in patients with ITP, independent of platelet count [33]. Due to many factors such as clinical availability and cost, optical turbidity assay and TEG detection are carried out in most domestic centers, while VerifyNow rapid analyzer, flow cytometry, PFA-100 and Plateletworks analyzer are seldom used in clinical practice [34, 35].

TEG was used to detect the changes of thrombus viscosity and elasticity during coagulation. During the detection, the oscillating cup containing the blood sample rotates at a uniform speed. When the blood clot forms, current generates due to the coupling motion of the metal needle placed in it to cut the magnetic induction line. After computer processing, it is depicted as a TEG curve. The main parameter of the curve, R time, is from the time the blood sample is put into the oscillating cup to the time the fibrin clot begins to form. MA, the maximum size of the thrombus, reflects the maximum intensity of the clot being formed. On this basis, AA and ADP were added respectively, and the MA values increased in the presence of activators, namely MAAA and MAADP, so as to calculate the inhibition degree of platelet reactivity by aspirin or P2Y12 receptor inhibitors.

TEG has many advantages over traditional coagulation function detection, such as reflecting the whole process of sample blood from clot formation to fiber dissolution, and the interaction between clotting factors and platelets. However, there are also some drawbacks. First, as an in vitro detection project, the detection environment is still different from the actual environment of the body. It can reflect the interaction between coagulation factors and platelets but cannot simulate the influence of vascular wall related factors such as vascular endothelial cells on the coagulation process. Secondly, TEG is used to detect the whole coagulation function of the body but cannot be used to distinguish one specific abnormal coagulation process. For example, abnormal MA in TEG represents abnormal platelet or fibrinogen, quality or quantity defect, which is unable to be identified respectively and still need routine coagulation function test. Thirdly, there is still a lack of standardized operation and evaluation guidelines. The quality control of TEG is not ideal. And the selection of threshold value for guiding treatment decision is not consistent, which needs to be further improved.

Therefore, one of the research directions on whether PFT can play a positive role in the individualization of antiplatelet therapy is the improvement of detection technology and quality control. On the other hand, the limitation of the study itself was also an important reason for the failure of PFT to achieve positive results in the individualization of antiplatelet therapy. A high proportion of low-risk patients were included in the Gauging Responsiveness with A VerifyNow assay-Impact on diabetes And Safety (GRAVITAS) study [18]. The Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide the alternative thErapy with pRasugrel (TRIGGER–PCI) study, only 0.4% suffered ischemic events

and it was terminated [19]. In the Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) study, 15% of patients were still in the state of high platelet reactivity after adjusting the treatment regimen according to PFT [20]. Only 4% of patients in Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC) study had an enhanced DAPT regimen [21]. Large cohort studies are still under way in the hope of producing stronger results. However, this study was carried out in a special group of patients with ACS and TP, which reflects the real-world situation. So even if the positive results of clinical studies have drawn on the PFT-directed individualized antiplatelet therapy, the existence of real-world complications cannot be negated. Clinical trials are ideal, after all.

Several limitations should be taken into consideration. Firstly, no antiplatelet drugs data was available during follow-up, as well as PFT data. Thus, we cannot analyze the change of therapy and TPR for 5 years, which likely attributes to alter their adverse events risk. Secondly, in reality, the delivery company delivered the blood to the blood transfusion department for TEG testing within two hours, more than the required optimal time, which might affect the test results to some extent. Finally, there may be additional confounders that were not controlled for within our model. Nevertheless, this is a relatively large core laboratory analysis comparing cases with baseline HTPR, LTPR and NTPR tested by TEG in patients with ACS and TP underwent PCI, a less common interdisciplinary situation, in terms of both long-term outcomes and angiographic data, and we believe that we have accounted for the most clinically relevant variables in our model.

Conclusions

In patients with ACS and TP undergoing PCI, 5-year all-cause death, MACCE, MI, revascularization, stroke and bleeding risk were all similar between cases with HTPR and cases with NTPR, tested by TEG at baseline, in the real world. The comparison result was the same between cases with LTPR and cases with NTPR.

Declarations

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Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Authors' contributions: RL contributed to all aspects of this study, including study concept and design, data acquisition, statistical analysis and interpretation, drafting and revising the report, and funding. TYL, DSY, YC, XFT, LJG, CZ, PZ, OX and RLG contributed to data acquisition and ethical issues. BX and JQY contributed to initial study conception and design, and funding. All authors have approved the final article.

Conflicts of interest: None

Authorship declaration

None of the article contents are under consideration for publication in any other journal or have been published in any journal. All authors have participated in the work and have reviewed and agree with the content of the article. We have no conflict of interest to disclose.

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Tables

Table 1 The baseline clinical characteristics

Variables	All (n=474)	HTPR (n=124)	LTPR (n=163)	NTPR (n=187)	P value
Demographic characteristics					
Male gender, %	65 (13.7)	29 (23.4)	14 (8.6)	22 (11.8)	0.001
Age, years	60.8 ± 10.0	61.1 ± 9.8	60.4 ± 9.5	60.9 ± 10.7	0.824
BMI, kg/m^2	25.7 ± 3.1	25.6 ± 3.5	25.6 ± 2.8	25.9 ± 3.2	0.557
Coexisting conditions, %					
Smoking history	296 (62.4)	70 (56.5)	107(65.6)	119 (63.6)	0.256
Hypertension	293 (61.8)	81 (65.3)	103 (63.2)	109 (58.3)	0.414
DM	153 (32.3)	45 (36.3)	45 (27.6)	63 (33.7)	0.258
Hyperlipidemia	322 (67.9)	79 (63.7)	115 (70.6)	128 (68.4)	0.46
Previous MI	98 (20.7)	27 (21.8)	32 (19.6)	39 (20.9)	0.903
Prior PCI or CABG	139 (29.3)	40 (32.3)	46 (28.2)	53 (28.3)	0.705
Family history of CAD	117 (24.7)	38 (30.6)	33 (20.4)	46 (24.6)	0.136
CVD	54 (11.4)	18 (14.5)	17 (10.4)	19 (10.2)	0.443
PVD	19 (4.0)	6 (4.8)	6 (3.7)	7 (3.7)	0.86
COPD	18 (3.8)	6 (4.8)	4 (2.5)	8 (4.3)	0.524
LVEF (%)	61.6 ± 7.4	62.0 ± 8.1	61.2 ± 7.6	61.7 ± 6.8	0.699
Clinical presentation, %					
Unstable angina pectoris	376 (79.3)	90 (72.6)	135 (82.8)	151 (80.7)	0.087
AMI	98 (20.7)	34 (27.4)	28 (17.2)	36 (19.3)	0.087
STEMI	68 (14.3)	23 (18.5)	21 (12.9)	24 (12.8)	0.299
NSTEMI	30 (6.3)	11 (8.9)	7 (4.3)	12 (6.4)	0.288
Laboratory examination					
eGFR before PCI, mL/min/1.73m2	89.1 ±	88.5 ±	89.7 ±	88.9 ± 15.2	0.81

	15.6	16.7	15.4		
HGB before PCI, g/L	140.5 ± 16.4	136.1 ± 16.2	144.5 ± 15.8	139.9 ± 16.2	<0.001
PLT before PCI, 109/L	130.4 ± 17.4	133.2 ± 15.3	129.9 ± 19.7	128.9 ± 16.3	0.089
Uric acid, μmol/L	337.0 ± 84.7	330.8 ± 96.9	341.6 ± 79.6	337.1 ± 80.5	0.565
HbA1c, %	6.6 ± 1.3	6.8 ± 1.5	6.4 ± 1.1	6.6 ± 1.2	0.059
LDL-C, mmol/L	2.25 ± 0.86	2.36 ± 0.85	2.21 ± 0.93	2.22 ± 0.81	0.29
ESR, mm/h	9.2 ± 9.6	12.2 ± 9.9	6.6 ± 6.9	9.4 ± 10.7	<0.001
Angiographic and procedural characteristics					
SNYTAX score	11.6 ± 8.0	11.6 ± 8.4	11.6 ± 7.7	11.7 ± 8.1	0.984
Residual SNYTAX	3.1 ± 5.3	2.7 ± 4.7	2.9 ± 5.0	3.4 ± 5.8	0.405
LM or three-vessel disease, %	23 (4.9)	11 (8.9)	4 (2.5)	8 (4.3)	0.039
LAD involved, %	432 (91.1)	109 (87.9)	146 (89.6)	177 (94.7)	0.084
No. of target lesions	1.4 ± 0.7	1.5 ± 0.7	1.4 ± 0.6	1.4 ± 0.8	0.234
No. of stent per patient	1.8 ± 1.1	1.9 ± 1.1	1.8 ± 1.0	1.8 ± 1.1	0.713
Time of procedure, min	36.3 ± 25.8	39.7 ± 27.8	33.0 ± 21.5	36.8 ± 27.7	0.085
Procedure and stent type, %					0.991
PTCA	13 (2.7)	5 (4.0)	3 (1.8)	5 (2.7)	
BMS	4 (0.8)	2 (1.6)	1 (0.6)	1 (0.5)	
First-generation durable polymer DES	21 (4.4)	5 (4.0)	9 (5.5)	7 (3.7)	
Second-generation durable polymer DES	265 (55.9)	67 (54.0)	89 (54.6)	109 (58.3)	
Domestic biodegradable polymer DES	72 (15.2)	19 (15.3)	27 (16.6)	26 (13.9)	
Mixed implantation of DES	81 (17.1)	22 (17.7)	28 (17.2)	31 (16.6)	
Others (Janus, Yinyi)	8 (1.7)	2 (1.6)	2 (1.2)	4 (2.1)	
Procedure unsuccess	10 (2.1)	2 (1.6)	4 (2.5)	4 (2.1)	

Medication at discharge, %					
Aspirin	469 (98.9)	122 (98.4)	161 (98.8)	186 (99.5)	0.637
Clopidogrel	470 (99.2)	122 (98.4)	161 (98.8)	187 (100.0)	0.252
Ticagrelor	4 (0.8)	2 (1.6)	2 (1.2)	0 (0.0)	0.252
DAPT	469 (98.9)	122 (98.4)	161 (98.8)	186 (99.5)	0.637
Statin	450 (94.9)	117 (94.4)	156 (95.7)	177 (94.7)	0.852
Calcium antagonist	227 (47.9)	64 (51.6)	71 (43.6)	92 (49.2)	0.36
β-blocker	402 (84.8)	108 (87.1)	131 (80.4)	163 (87.2)	0.149
PPI	118 (24.9)	39 (31.5)	33 (20.2)	46 (24.6)	0.093

AMI, acute myocardial infarction; BMI, body mass index; BMS, bare metal stent; CAD, coronary artery disease; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cerebral vascular disease; DES, drug-eluting stent; DM, diabetes mellitus; DAPT, dual anti-platelet therapy; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; HGB, hemoglobin; HTPR, high on-treatment platelet reactivity; LAD, left anterior descending artery; LM, left main; LDL-C, low density lipoprotein cholesterol; LTPR, low on-treatment platelet reactivity; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevated myocardial infarction; NTPR, normal on-treatment platelet reactivity; PCI, percutaneous coronary intervention; PLT, platelet; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; STEMI, ST-segment elevated myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TC, total cholesterol; UAP, unstable angina pectoris

Data are expressed as mean ± standard deviation; or counts (percentage).

BMI was defined as weight in kilograms divided by height in meters squared (kg/m^2), using the Cooperative Meta- analysis Group of China Obesity Task Force BMI classification.

Table 2 2-year outcomes

Two-year Outcomes, %	All (n=474)	HTPR (n=124)	LTPR (n=163)	NTPR (n=187)	P value
MACCE	56 (11.8)	11 (8.9)	15 (9.2)	30 (16.0)	0.07
All-cause death	7 (1.5)	1 (0.8)	2 (1.2)	4 (2.1)	0.602
Cardiac death	7 (1.5)	1 (0.8)	2 (1.2)	4 (2.1)	0.602
Myocardial infarction	12 (2.5)	3 (2.4)	1 (0.6)	8 (4.3)	0.093
Revascularization	39 (8.2)	8 (6.5)	12 (7.4)	19 (10.2)	0.448
Stroke	4 (0.8)	0 (0.0)	0 (0.0)	4 (0.8)	0.045
Bleeding	34 (7.2)	6 (4.8)	15 (9.2)	13 (7.0)	0.361

HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; MACCE, major adverse cardiovascular and cerebrovascular event; NTPR, normal on-treatment platelet reactivity

Table 3 5-year outcomes

Five-year Outcomes, %	All (n=474)	HTPR (n=124)	LTPR (n=163)	NTPR (n=187)	P value
MACCE	104 (21.9)	23 (18.5)	36 (22.1)	45 (24.1)	0.515
All-cause death	15 (3.2)	3 (2.4)	6 (3.7)	6 (3.2)	0.832
Cardiac death	12 (2.5)	3 (2.4)	4 (2.5)	5 (2.7)	0.987
Myocardial infarction	35 (7.4)	7 (5.6)	12 (7.4)	16 (8.6)	0.63
Revascularization	70 (14.8)	14 (11.3)	26 (16.0)	30 (16.0)	0.446
Stroke	17 (3.6)	4 (3.2)	5 (3.1)	8 (4.3)	0.806
Bleeding	75 (15.8)	17 (13.7)	29 (17.8)	29 (15.5)	0.636

HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; MACCE, major adverse cardiovascular and cerebrovascular event; NTPR, normal on-treatment platelet reactivity

Table 4 Univariate and multivariate Cox regression analysis of 2-year outcomes

Two-year Outcomes	HTPR				LTPR			
	Univariate COX Regression		Multivariate COX Regression		Univariate COX Regression		Multivariate COX Regression	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
MACCE	0.76 (0.46, 1.26)	0.288	0.42 (0.21, 0.87)	0.019	0.91 (0.59, 1.41)	0.666	0.55 (0.29, 1.03)	0.063
All-cause death	0.38 (0.04, 3.35)	0.38	0.41 (0.03, 5.47)	0.499	0.57 (0.10, 3.10)	0.513	1.06 (0.14, 7.80)	0.956
Cardiac death	0.38 (0.04, 3.35)	0.38	0.41 (0.03, 5.47)	0.499	0.57 (0.10, 3.10)	0.513	1.06 (0.14, 7.80)	0.956
Myocardial infarction	0.56 (0.15, 2.12)	0.396	0.43 (0.11, 1.73)	0.236	0.14 (0.02, 1.14)	0.066	0.19 (0.02, 1.57)	0.122
Revascularization	0.62 (0.27, 1.42)	0.256	0.48 (0.21, 1.15)	0.099	0.71 (0.34, 1.46)	0.349	0.65 (0.31, 1.38)	0.263
Stroke	Inapplicable				Inapplicable			
Bleeding	0.70 (0.26, 1.83)	0.461	0.60 (0.22, 1.61)	0.306	1.34 (0.64, 2.82)	0.436	1.50 (0.70, 3.23)	0.299

HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; MACCE, major adverse cardiovascular and cerebrovascular event

Table 5 Univariate and multivariate Cox regression analysis of 5-year outcomes

Five-year Outcomes	HTPR				LTPR			
	Univariate COX Regression		Multivariate COX Regression		Univariate COX Regression		Multivariate COX Regression	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
MACCE	0.76 (0.46, 1.26)	0.288	0.74 (0.44, 1.25)	0.26	0.91 (0.59, 1.41)	0.666	0.95 (0.61, 1.49)	0.823
All-cause death	0.77 (0.19, 3.09)	0.717	1.00 (0.20, 4.93)	0.997	1.14 (0.37, 3.55)	0.817	2.67 (0.71, 10.12)	0.148
Cardiac death	0.93 (0.22, 3.87)	0.915	0.82 (0.14, 4.93)	0.831	0.92 (0.25, 3.41)	0.896	2.04 (0.44, 9.45)	0.362
Myocardial infarction	0.68 (0.28, 1.64)	0.387	0.67 (0.27, 1.67)	0.388	0.86 (0.41, 1.82)	0.69	0.97 (0.45, 2.08)	0.927
Revascularization	0.69 (0.37, 1.31)	0.26	0.72 (0.37, 1.38)	0.32	0.99 (0.59, 1.68)	0.976	0.98 (0.57, 1.69)	0.953
Stroke	0.77 (0.23, 2.57)	0.676	1.06 (0.31, 3.62)	0.928	0.71 (0.23, 2.18)	0.552	0.73 (0.23, 2.27)	0.582
Bleeding	0.88 (0.49, 1.61)	0.685	0.91 (0.49, 1.69)	0.769	1.16 (0.70, 1.95)	0.566	1.14 (0.67, 1.92)	0.633

HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; MACCE, major adverse cardiovascular and cerebrovascular event

Figures

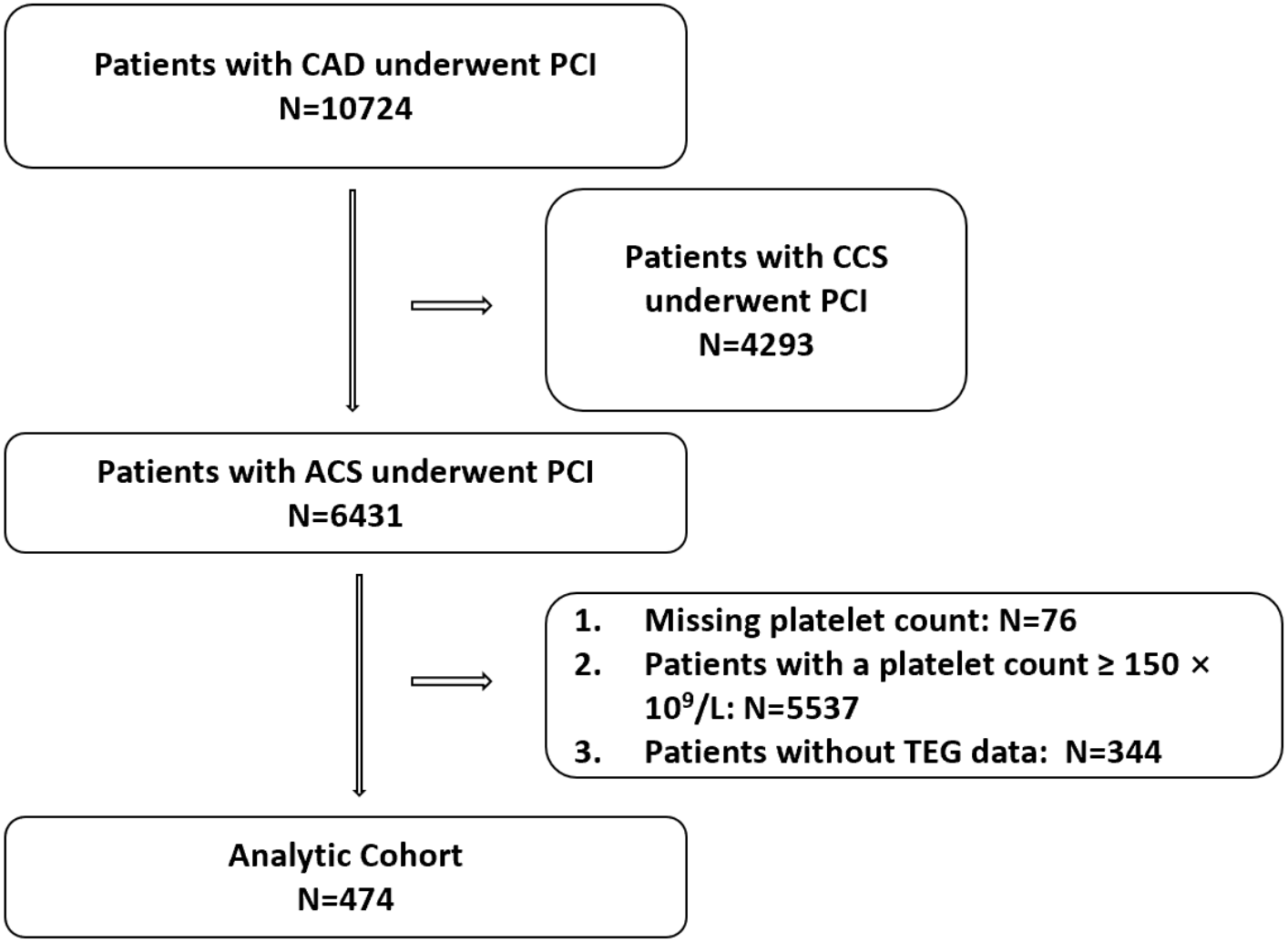

Figure 1

Flowchart

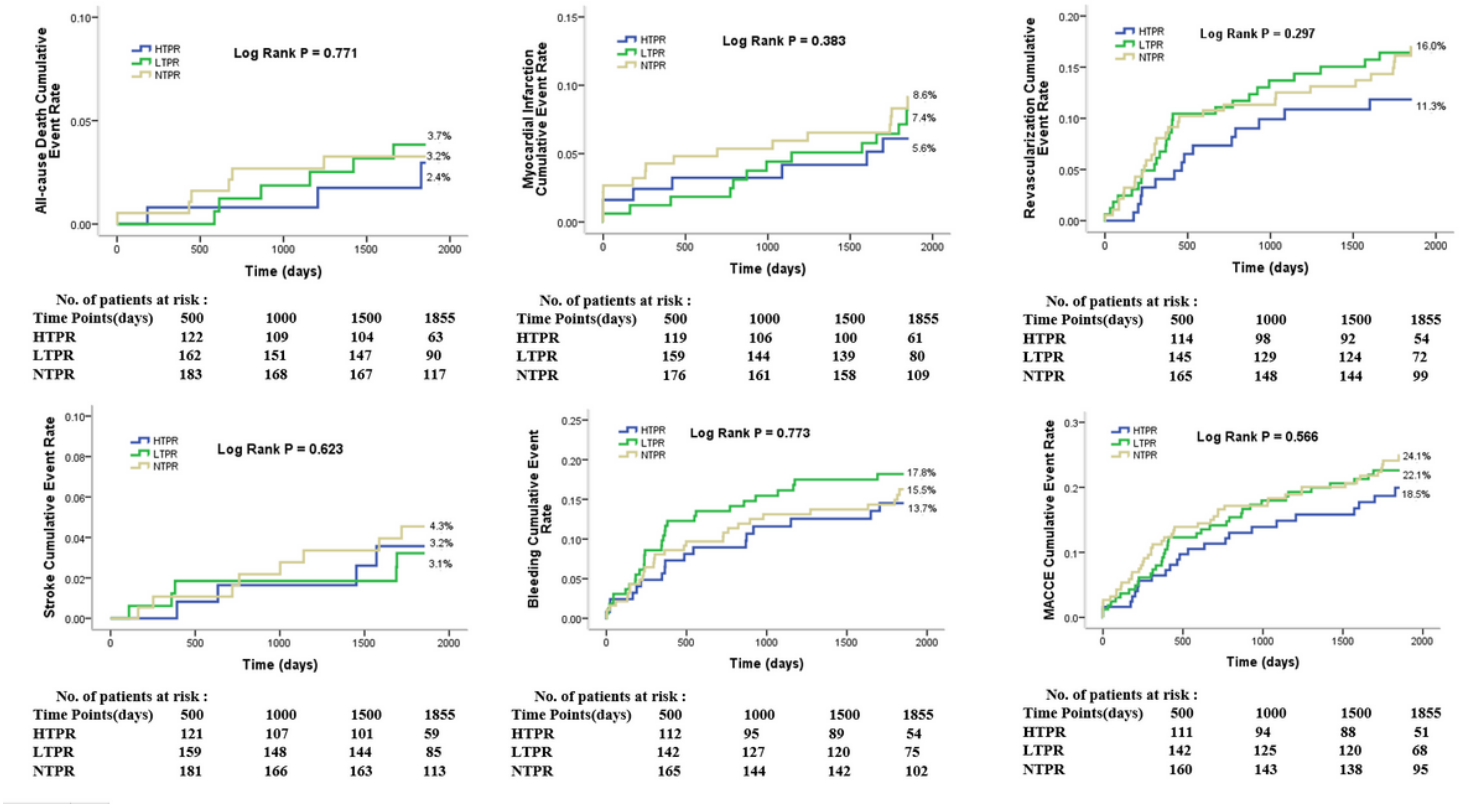

Figure 2

Kaplan-Meier survival curves among cases with baseline HTPR, LTPR and NTPR