Long-term effects of baseline on-treatment platelet reactivity in patients with acute coronary syndrome and thrombocytopenia undergoing percutaneous coronary intervention

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Abstract

Objective: To analyse the association between on-treatment platelet reactivity (TPR) and long-term outcomes of patients with acute coronary syndrome (ACS) and thrombocytopenia (TP) in the real world.

Methods: This prospective observational study enrolled patients with coronary artery disease (CAD) that underwent percutaneous coronary intervention (PCI). Patients with ACS and TP under dual antiplatelet therapy were selected for analysis. The 2- and 5-year clinical outcomes were evaluated among patients with high on-treatment platelet reactivity (HTPR), low on-treatment platelet reactivity (LTPR) and normal on-treatment platelet reactivity (NTPR), as tested by thromboelastogram at baseline.

Results: A total of 10 724 patients with CAD that underwent PCI were identified. Of these, 474 patients with ACS and TP met the inclusion criteria: 124 (26.2%) with HTPR, 163 (34.4%) with LTPR and 187 (39.5%) with NTPR. The 5-year rates of all-cause death, major adverse cardiovascular and cerebrovascular events, cardiac death, myocardial infarction, revascularization, stroke and bleeding were not significantly different among the three groups. Multivariate Cox

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regression analysis demonstrated that patients with HTPR were not independently associated with any of the 5-year endpoints compared with patients with NTPR.

Conclusions: TPR at baseline was not independently associated with long-term outcomes in patients with ACS and TP that underwent PCI.

Introduction

It was reported that about 5.4% of patients with coronary artery disease (CAD) and 0.9% of patients with acute coronary syndrome (ACS) were diagnosed with thrombocytopenia (TP).[1,2] In patients with ACS and TP, the management of antiplatelet therapy remains difficult. To date, evidence remains limited on how to balance the risk of ischaemia and bleeding in this special population.[3–5] 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.[6] In patients with essential thrombocythemia, approximately 9.4% were diagnosed with myocardial infarction.[7] Thrombocythemia was considered to be one of the risk factors of ACS.[7] Baseline TP was also considered as an independent risk factor of adverse outcomes in patients with ACS.[8] TP was found to be independently related to in-hospital death in those that underwent emergency percutaneous coronary intervention (PCI).[9] Meanwhile, an important role of platelet function was identified for ischaemia evaluation in patients with ACS. For example, it was reported that thrombotic risk increased when the platelet volume became larger.[10–13] Our previous research demonstrated that the mean platelet volume could predict the 2-year cardiac death in patients with stable CAD and diabetes mellitus.[14] A reasonable interpretation of these findings is that platelet dysfunction can lead to thrombosis or bleeding without a change in platelet quantity.

Platelet function testing (PFT) might be one of the solutions to help guide antiplatelet therapy in patients with ACS and TP.[15,16] It is worth noting that there are limited data on the value of undertaking PFT in patients with ACS and TP, although large clinical trials have not demonstrated the value of using PFT in individualized antiplatelet therapy.[5,17–20] This current prospective observational study applied thromboelastogram (TEG) technology to measure PFT to determine whether on-treatment platelet reactivity (TPR) was associated with long-term prognosis in a population with ACS and TP that underwent PCI in the real world. The study aimed to determine if TEG can be used in the guidance of antiplatelet therapy in this special population.

Patients and methods

Study population

This prospective observational study enrolled consecutive patients with CAD that underwent PCI in the Department of

Cardiology, Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing, China, the largest cardiovascular centre in China, between January 2013 and December 2013. Diagnosis of ST-segment elevated myocardial infarction (STEMI), non-ST-segment elevated myocardial infarction (NSTEMI), unstable angina pectoris (UAP) and stable angina pectoris was based on international guidelines.[21–23] It was an all-comer study and there were no inclusion or exclusion criteria for the whole cohort.

Ethical approval was obtained from the Research Ethics Committee of Fuwai Hospital, Academy of Medical Sciences, Beijing, China (no. 2020-1310). The Institutional Review Board approved the study protocol and all patients signed written informed consent before the intervention, including a full set of risk-informed consent and information use consent for scientific purposes. All patient details were de-identified in the database.

Platelet analyses

A normal platelet count was defined as $150–350 \times 10^9$/l based on platelet number distribution and international criteria.[24] Baseline TP was defined as a platelet count $<150 \times 10^9$/l. The reporting of this study conforms to STROBE guidelines.[25] TEG was applied under dual antiplatelet therapy (DAPT) for long-term administration (aspirin and clopidogrel) at admission or the following morning after PCI. It was measured approximately 30 min after the blood was collected. It was essential to avoid bubbles in the blood drawing tube when the blood was taken because the platelets are easily activated and cannot be detected. The TEG Haemostasis Analyser (Model 5000; Haemoscope Corporation, Niles, IL, USA) with automated analytical software provides viscoelastic quantitative and qualitative measurements of the physical properties of a clot. Time to fibrin formation (R), angle constant (α), clot formation time (K), maximum amplitude (MA) including MA_{ADP}, MA_k and MA_f. MA_k and MA_f, were recorded, representing the maximum platelet fibrin clot strength and fibrin clot strength. The on-treatment platelet reactivity tested by TEG was defined according to the previously published 2013 consensus document.[26] High on-treatment platelet reactivity (HTPR) was defined by the TEG Platelet Mapping Assay in terms of adenosine diphosphate (ADP)-induced platelet-fibrin clot strength (mm) ($MA_{ADP}) > 47$ mm. Low on-treatment platelet reactivity (LTPR) was defined as $MA_{ADP} \leq 31$ mm. Normal on-treatment platelet reactivity (NTPR) was defined as $31\,mm < MA_{ADP} \leq 47$ mm.

PCI procedural details

Before elective PCI, the patients received standardized DAPT including aspirin and a P2Y12 inhibitor as follows: loading dose 300 mg aspirin or at least 3 days accumulation with 100 mg aspirin oral once a day, followed by 75–100 mg aspirin oral once a day for long-term; loading dose 300 mg clopidogrel or at least 5 days accumulation with 75 mg clopidogrel oral once a day, followed by 75 mg clopidogrel oral once a day for 1 year after drug-eluting stent (DES) implantation. Patients with ACS scheduled for primary PCI received DAPT as soon as possible as follows: loading dose 300 mg aspirin oral, with 75–100 mg aspirin oral once a day for long-term; loading dose 300 mg or 600 mg clopidogrel oral, with 75 mg clopidogrel oral once a day for 1 year after DES implantation. Ticagrelor was seldom used in our centre in 2013. It was prescribed only when clopidogrel resistance was observed and patients were willing to received it at their own expense. Ticagrelor was administered with a loading

dose of 180 mg or a cumulative dose of 180 mg followed by 90 mg twice a day orally for a least one year after DES implantation. The dose and duration of DAPT was also individualized according to the bleeding and ischaemic risk. Before coronary angiography (CAG), 25 mg heparin sodium was administered through an arterial sheath or intravenously. Before PCI, heparin sodium with a total dose of 100 U/kg was administered through an arterial sheath or intravenously. The dose was lowered to 50–70 U/kg in patients over the age of 70 years to reduce bleeding risk. If PCI proceeded for more than 1 h, an additional 1000 U of heparin sodium was adding. Results of CAG were read by experienced cardiologists. More than 50% stenosis of the 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 ischaemic symptoms or ischaemic evidence showed by examinations, was indicated for coronary stent implantation. Three-vessel disease (TVD) was defined as angiographic stenosis of $\geq 50\%$ in all three main coronary arteries, LAD, LCX, and RCA. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score (SS) and residual SYNTAX score were assessed in an independent angiographic core laboratory by two of the three experienced cardiologists that were blinded to the clinical outcomes.

Follow-up and definitions

Follow-up was undertaken 30 days and 6 months after PCI and every 1 year thereafter. Information regarding in-hospital outcome was obtained through a review of the medical records and the long-term clinical outcome was collected from surveys completed by telephone follow-up. A group of independent clinical physicians oversaw checking and confirmed all adverse events carefully. Training of the investigators in terms of blinded questionnaire filling and telephone recording was undertaken to control the data quality.

The primary endpoint was all-cause death. The 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 was identified as death caused by clinically-confirmed MI, heart failure and/or malignant arrhythmia; or death that cannot be explained clearly by other reasons. Bleeding was defined according to criteria established by the Bleeding Academic Research Consortium (BARC),[27] excluding BARC 0 and 1 type.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). One-way analysis of variance tests were used to compare continuous variables between the three groups at baseline. Student's *t*-test was used to compare continuous variables between two groups. χ^2-test was used to compare categorical variables between the three groups at baseline and between two groups for outcomes. Kaplan–Meier curves compared the 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 at baseline or those with an important clinical meaning. A *P*-value <0.05 was considered statistically significant.

Results

A total of 10 724 consecutive patients with CAD underwent PCI (Figure 1). The median platelet count was 199.0×10^9/l and the mean $\pm$ SD platelet count was $203.6 \pm 54.4 \times 10^9$/l in the total cohort of 10 724 patients. The following patients were excluded: (i) patients with chronic coronary syndromes (CCS; $n = 4293$); (ii) patients with missing platelet count data ($n = 76$); (iii) patients with a platelet count $\geq 150 \times 10^9$/l ($n = 5537$); and (iv) patients without TEG data ($n = 344$). A total of 474 patients diagnosed with ACS and TP were included in this study. Of these 474 patients, 124 (26.2%) patients had HTPR, 163 (34.4%) patients had LTPR and 187 (39.5%) patients had NTPR. The baseline clinical and demographic characteristics are shown in Table 1. Patients with HTPR presented with a significantly greater proportion of males, a lower haemoglobin level, a higher ESR and a greater proportion of LM or three-vessel disease compared with patients with LTPR and NTPR ($P < 0.05$ for all comparisons). Patients with HTPR had a lower prevalence of UAP, a higher platelet count before PCI, a higher glycosylated haemoglobin (HbA$_{1c}$) level, less frequent involvement of LAD, a longer procedure duration and more frequent use of proton pump inhibitors. These variates showed significant differences between two of the three groups, but not among all three groups.

Of the 474 patients included in the analysis, clinical follow-up was completed for 470 (99.2%) patients at 2 years and for 435 (91.8%) patients at 5 years. The occurrence of adverse cardiovascular and cerebrovascular events in each group at 2 and 5 years is listed in Table 2 and Table 3, respectively. The rates of 2-year all-cause death, MACCE, cardiac death, myocardial infarction (MI), revascularization and bleeding were not significantly different among the three groups. The 2-year rates of MACCE and MI were lower in patients
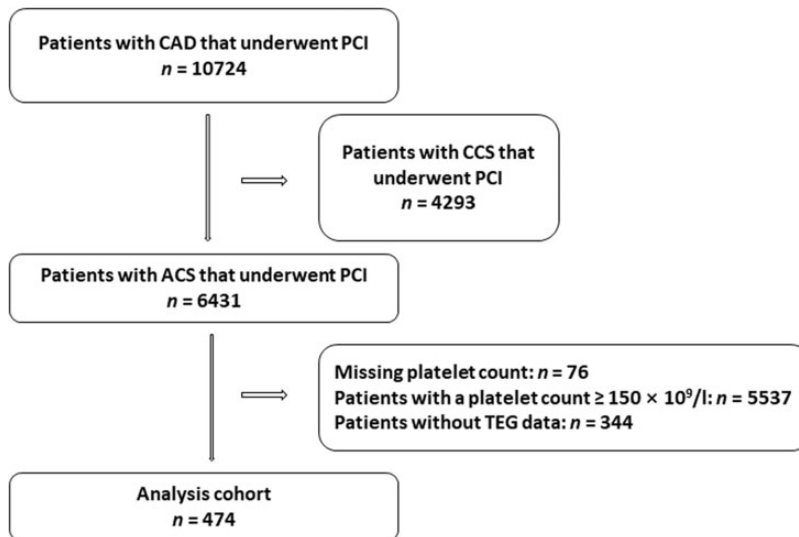
Figure 1. Flow diagram showing the progress of patients ($n = 10\ 724$) with acute coronary syndrome (ACS) and thrombocytopenia that underwent percutaneous coronary intervention (PCI) through a study to determine whether on-treatment platelet reactivity was associated with long-term prognosis. CAD, coronary artery disease; CCS, chronic coronary syndromes; TEG, thromboelastogram.

Table 1. Demographic and clinical characteristics of patients ($n = 474$) with acute coronary syndrome and thrombocytopenia that underwent percutaneous coronary intervention (PCI) and were included in a study to determine whether on-treatment platelet reactivity was associated with long-term prognosis.

Characteristic	All patients $n = 474$	HTPR $n = 124$	LTPR $n = 163$	NTPR $n = 187$	Statistical analyses[a]
Demographic characteristics					
Sex, male	65 (13.7)	29 (23.4)	14 (8.6)	22 (11.8)	$P = 0.001$
Age, years	60.8 ± 10.0	61.1 ± 9.8	60.4 ± 9.5	60.9 ± 10.7	NS
BMI, kg/m^2	25.7 ± 3.1	25.6 ± 3.5	25.6 ± 2.8	25.9 ± 3.2	NS
Coexisting conditions					
Smoking history	296 (62.4)	70 (56.5)	107 (65.6)	119 (63.6)	NS
Hypertension	293 (61.8)	81 (65.3)	103 (63.2)	109 (58.3)	NS
Diabetes mellitus	153 (32.3)	45 (36.3)	45 (27.6)	63 (33.7)	NS
Hyperlipidaemia	322 (67.9)	79 (63.7)	115 (70.6)	128 (68.4)	NS
Previous MI	98 (20.7)	27 (21.8)	32 (19.6)	39 (20.9)	NS
Prior PCI or CABG	139 (29.3)	40 (32.3)	46 (28.2)	53 (28.3)	NS
Family history of CAD	117 (24.7)	38 (30.6)	33 (20.2)	46 (24.6)	NS
CVD	54 (11.4)	18 (14.5)	17 (10.4)	19 (10.2)	NS
PVD	19 (4.0)	6 (4.8)	6 (3.7)	7 (3.7)	NS
COPD	18 (3.8)	6 (4.8)	4 (2.5)	8 (4.3)	NS
LVEF	61.6 ± 7.4	62.0 ± 8.1	61.2 ± 7.6	61.7 ± 6.8	NS
Clinical presentation					
Unstable angina pectoris	376 (79.3)	90 (72.6)	135 (82.8)	151 (80.7)	NS
AMI	98 (20.7)	34 (27.4)	28 (17.2)	36 (19.3)	NS
STEMI	68 (14.3)	23 (18.5)	21 (12.9)	24 (12.8)	NS
NSTEMI	30 (6.3)	11 (8.9)	7 (4.3)	12 (6.4)	NS
Laboratory examination					
eGFR before PCI, ml/min/1.73m^2	89.1 ± 15.6	88.5 ± 16.7	89.7 ± 15.4	88.9 ± 15.2	NS
HGB before PCI, g/l	140.5 ± 16.4	136.1 ± 16.2	144.5 ± 15.8	139.9 ± 16.2	$P < 0.001$
PLT before PCI, 10^9/l	130.4 ± 17.4	133.2 ± 15.3	129.9 ± 19.7	128.9 ± 16.3	NS
Uric acid, μmol/l	337.0 ± 84.7	330.8 ± 96.9	341.6 ± 79.6	337.1 ± 80.5	NS
HbA$_{1c}$, %	6.6 ± 1.3	6.8 ± 1.5	6.4 ± 1.1	6.6 ± 1.2	NS
LDL-C, mmol/l	2.25 ± 0.86	2.36 ± 0.85	2.21 ± 0.93	2.22 ± 0.81	NS
ESR, mm/h	9.2 ± 9.6	12.2 ± 9.9	6.6 ± 6.9	9.4 ± 10.7	$P < 0.001$
Angiographic and procedural characteristics					
SYNTAX score	11.6 ± 8.0	11.6 ± 8.4	11.6 ± 7.7	11.7 ± 8.1	NS
Residual SYNTAX	3.1 ± 5.3	2.7 ± 4.7	2.9 ± 5.0	3.4 ± 5.8	NS
LM or three-vessel disease	23 (4.9)	11 (8.9)	4 (2.5)	8 (4.3)	$P = 0.039$
LAD involved	432 (91.1)	109 (87.9)	146 (89.6)	177 (94.7)	NS
No. of target lesions	1.4 ± 0.7	1.5 ± 0.7	1.4 ± 0.6	1.4 ± 0.8	NS
No. of stents per patient	1.8 ± 1.1	1.9 ± 1.1	1.8 ± 1.0	1.8 ± 1.1	NS
Time of procedure, min	36.3 ± 25.8	39.7 ± 27.8	33.0 ± 21.5	36.8 ± 27.7	NS
Procedure and stent type					NS
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)	
	265 (55.9)	67 (54.0)	89 (54.6)	109 (58.3)	

(continued)

Table 1. Continued.

Characteristic	All patients $n = 474$	HTPR $n = 124$	LTPR $n = 163$	NTPR $n = 187$	Statistical analyses[a]
Second-generation durable polymer DES					
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)	NS
Clopidogrel	470 (99.2)	122 (98.4)	161 (98.8)	187 (100.0)	NS
Ticagrelor	4 (0.8)	2 (1.6)	2 (1.2)	0 (0.0)	NS
DAPT	469 (98.9)	122 (98.4)	161 (98.8)	186 (99.5)	NS
Statin	450 (94.9)	117 (94.4)	156 (95.7)	177 (94.7)	NS
Calcium antagonist	227 (47.9)	64 (51.6)	71 (43.6)	92 (49.2)	NS
β-blocker	402 (84.8)	108 (87.1)	131 (80.4)	163 (87.2)	NS
PPI	118 (24.9)	39 (31.5)	33 (20.2)	46 (24.6)	NS

Data are presented as mean $\pm$ SD or n of patients (%).
[a]One-way analysis of variance tests were used to compare continuous variables between the three groups at baseline; χ^2-test was used to compare categorical variables between the three groups at baseline; NS, no significant between-group difference ($P \geq 0.05$).
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.
HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; NTPR, normal on-treatment platelet reactivity; BMI, body mass index; MI, myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cerebral vascular disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; STEMI, ST-segment elevated myocardial infarction; NSTEMI, non-ST-segment elevated myocardial infarction; eGFR, estimated glomerular filtration rate; HGB, haemoglobin; PLT, platelet; HbA_{1c}, glycosylated haemoglobin; LDL-C, low-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; LM, left main; LAD, left anterior descending artery; PTCA, percutaneous transluminal coronary angioplasty; BMS, bare metal stent; DES, drug-eluting stent; DAPT, dual antiplatelet therapy; PPI, proton pump inhibitors.

with HTPR and LTPR compared with patients with NTPR, although the differences were not significant. No patients with HTPR and LTPR experienced a stroke during the 2-year follow-up period compared with four patients with NTPR ($P = 0.045$), which made the comparison difficult among the three groups. The study then extended the follow-up to 5 years. The rates of 5-year all-cause death, MACCE, cardiac death, MI, revascularization, stroke and bleeding were not significantly different among the three

groups. Kaplan–Meier survival curves demonstrated the same findings (Figure 2).

Multivariate Cox regression models were constructed to include possible confounders at baseline ($P < 0.1$) or those having important clinical implications (Table 4 and Table 5). Compared with patients with NTPR, patients with HTPR were independently associated with decreased 2-year MACCE risk (hazard ratio 0.42, 95% confidence interval 0.21, 0.87, $P = 0.019$). Patients with HTPR at baseline were not independently associated with any of the

Table 2. Outcomes at 2 years for patients ($n = 474$) with acute coronary syndrome and thrombocytopenia that underwent percutaneous coronary intervention and were included in a study to determine whether on-treatment platelet reactivity was associated with long-term prognosis.

Outcome	All patients $n = 474$	HTPR $n = 124$	LTPR $n = 163$	NTPR $n = 187$	Statistical analyses[a]
MACCE	56 (11.8)	11 (8.9)	15 (9.2)	30 (16.0)	NS
All-cause death	7 (1.5)	1 (0.8)	2 (1.2)	4 (2.1)	NS
Cardiac death	7 (1.5)	1 (0.8)	2 (1.2)	4 (2.1)	NS
Myocardial infarction	12 (2.5)	3 (2.4)	1 (0.6)	8 (4.3)	NS
Revascularization	39 (8.2)	8 (6.5)	12 (7.4)	19 (10.2)	NS
Stroke	4 (0.8)	0 (0.0)	0 (0.0)	4 (2.1)	$P = 0.045$
Bleeding	10 (2.1)	1 (0.8)	4 (2.5)	5 (2.7)	NS

Data are presented as *n* of patients (%).
[a]χ^2-test was used to compare categorical variables between the three groups; NS, no significant between-group difference ($P \geq 0.05$).
HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; NTPR, normal on-treatment platelet reactivity; MACCE, major adverse cardiovascular and cerebrovascular event.

Table 3. Outcomes at 5 years for patients ($n = 474$) with acute coronary syndrome and thrombocytopenia that underwent percutaneous coronary intervention and were included in a study to determine whether on-treatment platelet reactivity was associated with long-term prognosis.

Outcome	All patients $n = 474$	HTPR $n = 124$	LTPR $n = 163$	NTPR $n = 187$
MACCE	106 (22.4)	26 (21.0)	33 (20.2)	47 (25.1)
All-cause death	16 (3.4)	4 (3.2)	6 (3.7)	6 (3.2)
Cardiac death	13 (2.7)	4 (3.2)	4 (2.5)	5 (2.7)
Myocardial infarction	33 (7.0)	8 (6.5)	10 (6.1)	15 (8.0)
Revascularization	66 (13.9)	13 (10.5)	23 (14.1)	30 (16.0)
Stroke	17 (3.6)	5 (4.0)	3 (1.8)	9 (4.8)
Bleeding	78 (16.5)	18 (14.5)	30 (18.4)	30 (16.0)

Data are presented as *n* of patients (%).
There were no significant between-group differences ($P \geq 0.05$); χ^2-test.
HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; NTPR, normal on-treatment platelet reactivity; MACCE, major adverse cardiovascular and cerebrovascular event.

5-year endpoints compared with patients with NTPR. The results of the statistical comparisons were the same between patients with LTPR and NTPR at baseline.

Discussion

The main results of this current analysis were not consistent with those previously reported, such as those from the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) study, which suggested the potential value of PFT on monitoring, adjustment and individualization of antiplatelet therapy during DAPT.[28] There are several potential explanations for this disparity.

First, this prospective observational study reflected the situation in the real world. The TEG results analysed the
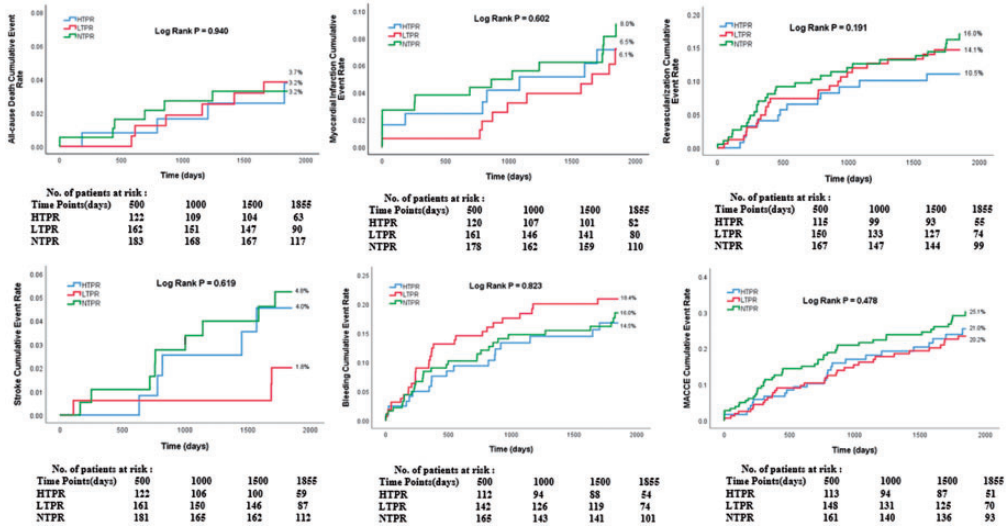
Figure 2. The 5-year Kaplan–Meier survival curves among patients ($n = 474$) stratified at baseline as having high on-treatment platelet reactivity (HTPR), low on-treatment platelet reactivity (LTPR) and normal on-treatment platelet reactivity (NTPR). MACCE, major adverse cardiovascular and cerebrovascular events. The colour version of this figure is available at: http://imr.sagepub.com.

baseline condition under DAPT during the perioperative period of PCI. Compared with patients with NTPR, patients with HTPR were independently associated with a decreased 2-year MACCE risk. This may be due to the positive effect of baseline monitoring. Subsequent individualized adjustment of antithrombotic drugs during the follow-up after an unsatisfactory baseline TEG result or a sudden ischaemic event might in part correct the underlying risk of thrombus. Indeed, PFT is supposed to provide the individualized adjustment of anti-platelet therapy. It also makes sense that the 'warning effect' of the baseline TEG results disappeared after 5 years of follow-up. During such a long follow-up duration, the antithrombotic drug regimen would have been adjusted more than once due to repeated follow-up and review. Therefore, the value of TEG cannot be negated easily in guiding antithrombotic therapy in patients with ACS and TP despite the negative results at the 5-year follow-up in this current study.

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.[29–36] Since the platelet aggregation method has a certain dependence on the platelet count, the detection results have a large deviation in patients with TP.[33] Flow cytometry detection has confirmed that platelet longevity and protease-activated receptor-1 related activity was significantly associated with bleeding fraction in patients with idiopathic thrombocytopenic purpura, independent of platelet count.[34] Due to many factors such as clinical availability and cost, optical turbidity assay and TEG detection are carried out in most domestic centres, while VerifyNow rapid analyser, flow cytometry, PFA-100

Table 4. Univariate and multivariate Cox regression analysis of the 2-year outcomes for patients (n = 474) with acute coronary syndrome and thrombocytopenia that underwent percutaneous coronary intervention and were included in a study to determine whether on-treatment platelet reactivity was associated with long-term prognosis.

	HTPR				LTPR			
	Univariate Cox Regression		Multivariate Cox Regression		Univariate Cox Regression		Multivariate Cox Regression	
Outcome	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)	P = 0.288	0.42 (0.21, 0.87)	P = 0.019	0.91 (0.59, 1.41)	P = 0.666	0.55 (0.29, 1.03)	P = 0.063
All-cause death	0.38 (0.04, 3.35)	P = 0.38	0.41 (0.03, 5.47)	P = 0.499	0.57 (0.10, 3.10)	P = 0.513	1.06 (0.14, 7.80)	P = 0.956
Cardiac death	0.38 (0.04, 3.35)	P = 0.38	0.41 (0.03, 5.47)	P = 0.499	0.57 (0.10, 3.10)	P = 0.513	1.06 (0.14, 7.80)	P = 0.956
Myocardial infarction	0.56 (0.15, 2.12)	P = 0.396	0.43 (0.11, 1.73)	P = 0.236	0.14 (0.02, 1.14)	P = 0.066	0.19 (0.02, 1.57)	P = 0.122
Revascularization	0.62 (0.27, 1.42)	P = 0.256	0.48 (0.21, 1.15)	P = 0.099	0.71 (0.34, 1.46)	P = 0.349	0.65 (0.31, 1.38)	P = 0.263
Stroke	Inapplicable				Inapplicable			
Bleeding	0.30 (0.04, 2.57)	P = 0.273	0.38 (0.04, 3.40)	P = 0.387	0.92 (0.25, 3.42)	P = 0.899	0.88 (0.23, 3.37)	P = 0.854

HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular event.

Variables adjusted in the model included: age, sex, acute myocardial infarction, haemoglobin before percutaneous coronary intervention (PCI), platelet count before PCI, erythrocyte sedimentation rate, time of procedure, left anterior descending artery involved, left main or three-vessel disease, glycosylated haemoglobin, proton pump inhibitors.

Table 5. Univariate and multivariate Cox regression analysis of the 5-year outcomes for patients (n = 474) with acute coronary syndrome and thrombocytopenia that underwent percutaneous coronary intervention and were included in a study to determine whether on-treatment platelet reactivity was associated with long-term prognosis.

Outcome	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	0.82 (0.51, 1.33)	P = 0.426	0.79 (0.48, 1.30)	P = 0.359	0.77 (0.49, 1.20)	P = 0.251	0.82 (0.52, 1.29)	P = 0.389
All-cause death	1.03 (0.29, 3.65)	P = 0.963	1.33 (0.31, 5.65)	P = 0.704	1.14 (0.37, 3.54)	P = 0.820	2.49 (0.68, 9.18)	P = 0.169
Cardiac death	1.23 (0.33, 4.59)	P = 0.755	1.21 (0.24, 6.01)	P = 0.815	0.92 (0.25, 3.41)	P = 0.895	1.92 (0.43, 8.59)	P = 0.396
Myocardial infarction	0.83 (0.35, 1.95)	P = 0.660	0.78 (0.32, 1.90)	P = 0.584	0.76 (0.34, 1.69)	P = 0.502	0.91 (0.40, 2.08)	P = 0.830
Revascularization	0.65 (0.34, 1.24)	P = 0.190	0.63 (0.32, 1.24)	P = 0.185	0.86 (0.50, 1.48)	P = 0.592	0.86 (0.49, 1.51)	P = 0.604
Stroke	0.86 (0.29, 2.57)	P = 0.787	1.03 (0.33, 3.21)	P = 0.955	0.37 (0.10, 1.38)	P = 0.140	0.39 (0.10, 1.47)	P = 0.163
Bleeding	0.91 (0.50, 1.62)	P = 0.738	0.93 (0.51, 1.69)	P = 0.809	1.16 (0.70, 1.93)	P = 0.558	1.15 (0.69, 1.92)	P = 0.603

HTPR, high on-treatment platelet reactivity; LTPR, low on-treatment platelet reactivity; HR, hazard ratio; CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular event.

Variables adjusted in the model included: age, sex, acute myocardial infarction, haemoglobin before percutaneous coronary intervention (PCI), platelet count before PCI, erythrocyte sedimentation rate, time of procedure, left anterior descending artery involved, left main or three-vessel disease, glycosylated haemoglobin, proton pump inhibitors.

and Plateletworks analyser are seldom used in clinical practice.[35,36]

Thromboelastogram has many advantages over traditional coagulation function detection, such as reflecting the whole process of sample blood from clot formation to fibre dissolution and the interaction between clotting factors and platelets.[35] However, there are also some disadvantages. First, as an *in vitro* detection method, the detection environment is still different from the actual environment of the body. It can reflect the interaction between coagulation factors and platelets, but it 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 it cannot be used to distinguish one specific abnormal coagulation process. For example, abnormal MA cannot determine if platelets or fibrinogen have abnormalities; or whether it is a quality or quantity defect. A routine coagulation function test is still needed to identify the abnormal step. Thirdly, there is still a lack of standardized operating procedures and evaluation guidelines. The quality control of TEG is not ideal and the selection of a threshold value for guiding treatment decisions is not consistent, which needs to be further improved.

Therefore, one of the research directions in terms of determining if PFT can play a positive role in the individualization of antiplatelet therapy is the improvement of the detection technology and quality control. The limitation of the technology itself was also an important reason for the failure of PFT to achieve positive results in the individualization of antiplatelet therapy. Moreover, previous large-sample clinical studies have had their own shortcomings. For example, a high proportion of low-risk patients were included in the Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety (GRAVITAS) study.[17] In the Testing platelet Reactivity In patients under Going elective stent placement on clopidogrel to Guide the alternative thErapy with pRasugrel (TRIGGER–PCI) trial, only 0.4% suffered ischaemic events and it was terminated.[18] 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.[19] Only 4% of patients in the Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC) study had an enhanced DAPT regimen.[20] 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.

This current study had several limitations. First, no antiplatelet drug or PFT data were available during follow-up, so it was not possible to analyse the change in therapy and TPR over the 5-year follow-up period, which likely contributed the risk of adverse outcomes. Secondly, the data in this study only reflected the real situation in 2013 when ticagrelor was not widely used. Moreover, as a specialist hospital, data on the aetiology of TP was missing. Meanwhile, global clotting indicators had not been collected in this database. The number of adverse events was small and consequently statistical analysis was not particularly robust. The incidence of severe bleeding (BARC3 and above) at the

2-year follow-up was too low to be used in the analysis. However, it is very difficult to accumulate a large patient sample for rare diseases, so this study has some reference value. Finally, there may be additional confounders that were not controlled for within this current model. Nevertheless, this was a relatively large core laboratory analysis of patients with ACS and TP that underwent PCI, a rare interdisciplinary situation in terms of both long-term outcomes and angiographic data, which compared patients with baseline HTPR, LTPR and NTPR tested by TEG. In our opinion, most clinically relevant variables were accounted for in the current model.

In conclusion, patients with ACS and TP undergoing PCI with HTPR at baseline were independently associated with a decreased 2-year MACCE risk compared with patients with NTPR. The 5-year all-cause death, MACCE, MI, revascularization, stroke and bleeding risk were similar between patients with HTPR and NTPR.

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Author contributions

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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