Original Article

Platelet-fibrin clot strength measured by thromboelastography could predict hypercoagulability and antiplatelet effects in patients after percutaneous coronary intervention

Xiao-Qin Yan[1,2,3#], Chi Zhang[3#], Hong-Yao Shi[4#], Ling-Cong Kong[3], Li Liu[5], Zhi-Chun Gu[3]^, Qing Zhu[1]

[1]School of Pharmacy, Nantong University, Nantong, China; [2]Department of Pharmacy, Shanghai Pudong Hospital, Shanghai, China; [3]Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [4]Department of Laboratory Medicine, Shanghai Pubin Children's Hospital, Shanghai, China; [5]Department of Emergency, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Contributions: (I) Conception and design: ZC Gu, XQ Yan, Chi Zhang; (II) Administrative support: ZC Gu, L Liu, Q Zhu; (III) Provision of study materials or patients: C Zhang, XQ Yan; (IV) Collection and assembly of data: XQ Yan, HY Shi; (V) Data analysis and interpretation: ZC Gu, HY Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work, and should be considered as co-first authors.

Correspondence to: Zhi-Chun Gu, MD. Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China. Email: guzhichun213@163.com; Li Liu, MD. Department of Emergency, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China. Email: lily_1231@126.com.

Background: It has been estimated that nearly one-fifth post-percutaneous coronary intervention (PCI) patients treated with clopidogrel continued to have recurrent thrombotic events, which implied the limitation of "one-size-fits all" strategy for antiplatelet therapy.

Methods: From July 2017 to April 2019, patients with acute coronary syndrome [ACS, including unstable angina (UA), non-ST segment elevation myocardial infraction (NSTEMI), and ST segment elevation myocardial infraction (STEMI)] or old myocardial infarction (OMI), or patients without coronary heart disease (non-CAD) were retrospectively enrolled in this study. For CAD patients undergoing PCI, standard dual antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel) was prescribed. After administration of dual antiplatelet agents for at least 5 days, whole blood samples were collected and platelet function was tested using thrombelastography (TEG). Thrombin-induced platelet-fibrin clot strength ($MA_{thrombin}$) and ADP-induced platelet-fibrin clot strength (MA_{ADP}) were measured to assess the hypercoagulability and antiplatelet effects.

Results: A total of 571 patients, including 479 ACS patients, 21 OMI patients and 71 non-CAD patients were enrolled. Highest level of $MA_{thrombin}$ was detected in STEMI patients, while lowest $MA_{thrombin}$ level was observed in non-CAD patients (P1<0.05 for OMI *vs.* non-CAD; P2<0.001 for ACS *vs.* non-CAD; P3<0.05 among ACS). Higher MA_{ADP} was also observed in STEMI and NSTEMI patients compared with UA patients (P<0.001). When MA_{ADP} was divided into trisections (MA_{ADP} <31; 31–47; >47 mm), a considerable portion of 41.8% ACS patients were in the first trisection (MA_{ADP} <31 mm), containing 50.4% of UA patients, 35.7% of NSTEMI patients and 26.5% of STEMI patients, with significant difference being observed between UA patients and other ACS patients (P<0.05 for NSTEMI *vs.* UA; P<0.001 for STEMI *vs.* UA). Meanwhile, 27.6% of NSTEMI and 31.0% of STEMI patients were in the third trisection (MA_{ADP} >47 mm), which was significantly higher than that of UA patients (12.7%) (P<0.001 for NSTEMI or STEMI *vs.* UA).

Conclusions: Considering various degrees of hypercoagulability and antiplatelet effects of clopidogrel among OMI and ACS patients post-PCI. More attention should be paid to personalized antiplatelet therapy according to individual's effects of $P2Y_{12}$ receptor inhibitors.

^ ORCID: 0000-0002-1245-9690.

Keywords: Acute coronary syndrome (ACS); platelet activation; thrombelastography (TEG); percutaneous coronary intervention (PCI); clopidogrel

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Introduction

It is well understood that platelets play a pivotal role in maintaining a balance between haemostasis and bleeding in coronary artery thrombosis (1). Dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ receptor inhibitors is the current standard for acute coronary syndrome (ACS) patient or those undergoing percutaneous coronary intervention (PCI) to prevent thromboembolic events (2,3). Currently, clopidogrel is still the most widely used $P2Y_{12}$ receptor inhibitor for secondary cardiovascular disease prevention, whose beneficial effects in post-PCI patients has been demonstrated in Clopidogrel for the Reduction of Events During Observation (CREDO) and Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (PCI-CURE) studies (4,5). Nevertheless, it has been estimated that nearly one-fifth post-PCI patients treated with clopidogrel continued to have recurrent thrombotic events, which implied the obvious limitation of "one-size-fits all" strategy for antiplatelet therapy (6). High thrombin induced clot strength in whole blood now was considered associated with increased risk of recurrent thromboembolic events in patients undergoing PCI (7). ACS comprises three symptomatic manifestations, including unstable angina (UA), non-ST segment elevation myocardial infraction (NSTEMI) and ST segment elevation myocardial infraction (STEMI), and patients of each manifestation might present different degrees of hypercoagulability (8). It is speculated that different antiplatelet therapies should be given to patients according to individual's hypercoagulability and antiplatelet effects of $P2Y_{12}$ receptor inhibitors. However, scarce knowledge was understood in this field. This study therefore aims to understand the individual's hypercoagulability and antiplatelet effects of clopidogrel in ACS patients by using thrombelastography (TEG, which has been increasingly utilized to graphically illustrate overall coagulation status). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1728).

Methods

Patient selection

From July 2017 to April 2019, patients with a diagnosis of ACS or old myocardial infarction (OMI), or patients without coronary heart disease (CAD) were retrospectively enrolled in this study. ACS were further grouped according to the manifestations, including UA, NSTEMI, and STEMI. OMI was defined as the patients who suffered myocardial infarction after 2 months. Patients without CAD (control group) were healthy patients on physical examinations. The exclusion criteria were as follows: a history of serious anemia; malignant disease; serious renal or hepatic insufficiency; total platelet count $<100\times10^9$/L, hematocrit <30%, and age <18 years. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (#2018-025). Written informed consent was obtained from the patients for publication of this study.

Procedure and medication protocol

Coronary arteriography (CAG) and PCI were conducted in included ACS and OMI patients, and loading doses of aspirin (300 mg) and clopidogrel (300 mg) were given to those patients before CAG. Stent type was chosen by the operator after CAG. Standard DAPT (100 mg aspirin and 75 mg clopidogrel) was prescribed for at least 1 year. Maintenance therapy with 100 mg aspirin and 75 mg clopidogrel were already given to other patients except for control patients in this study. All interventions were performed according to the current guideline (9).

TEG and platelet aggregation analysis

After administration of DAPT for at least 5 days, whole blood samples were collected by nursing staff and drawn into a vacutainer tubes containing 3.2% trisodium citrate. Platelet rich plasma was obtained after centrifugation

at 120 ×g for 5 min. Platelet function was tested using a computerized TEG Hemostasis Analyzer system according to the manufacturer's instructions (TEG 5000; Haemoscope Corporation, Niles, IL, USA). Briefly, citrate plasma was mixed with kaolin, inverted 5 times and loaded in a heparinase-coated cup containing 20 μL of $CaCl_2$. TEG was started instantly to record for 1 hour with maximum clot amplitude ($MA_{thrombin}$), which represents maximum platelet-fibrin clot strength and is affected by changes in platelet count, fibrinogen and function. In addition, other parameters were recorded, including time to fibrin formation (R), clot formation time (K) and angle constant (α). Another sample of heparinized blood was added to a non-heparinase-coated cup in the presence of the activator F and adenosine diphosphate (ADP, 2 μmol) to generate a whole blood-crosslinked clot with platelet activation (MA_{ADP}), which represented ADP-induced platelet-fibrin clot strength. MA_{ADP} was divided into trisections (T1–T3) according to one previous study (10), which suggested that cut points between 31 and 47 mm would be the best predictive values for long-term post-PCI ischemic and bleeding events. A therapeutic range of 31 to 47 mm for MA_{ADP} could provide maximum efficacy and safety.

Statistical analysis

Continuous variables with normal distributions were expressed as mean ± SD and categorical variables were summarized by percentages. Categorical variables were compared using χ^2 test or Fisher's exact tests. Normal distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. Unpaired two-sides Student's *t*-test was used to compare normally distributed continuous variables between two groups and the one-way ANOVA with least significant difference (LSD) was used to compare among ACS groups (UA, NSTEMI, and STEMI). Spearman's Rho was used to calculate correlation between clot strengths and other hypercoagulability markers in ACS patients. Statistical significance was considered as P value <0.05 or P value <0.001. All statistical analyses were performed with SPSS v19.0 software (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

A total of 571 patients, with 145 female patients (25.4%) and 426 male patients (74.6%) were included in this study. Among them, 479 patients were ACS (268 of UA, 98 of NSTEMI, and 113 of STEMI), 21 patients were OMI, and 71 patients were healthy subjects in control group. The patients' demographics and characteristics of PCI procedure are described in *Tables 1*,*2*, respectively. The average age was 64.1±10.4 years. The prevalence of hypertension and hyperlipidemia were similar between groups (P>0.05 for each variable). Laboratory data including platelet counts, hemoglobin and creatinine were well balanced between groups (P>0.05 for each variable). It is worth noting that more diabetes and smoking patients were found in CAD patients than non-CAD patients regardless of ACS or OMI (P1<0.05 and P2<0.001 for diabetes; P1<0.05 and P2<0.001 for smoking). Moreover, majority of OMI and ACS patients received β-blocker, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and statins, with the proportion much higher than that in non-CAD patients (P1<0.001 and P2<0.01 for each variable). In addition, it is obvious that the levels of cardiac troponin-I (cTnI) and brain natriuretic peptide (BNP), which were biomarkers providing CAD prognostic information, were significantly higher in OMI and ACS patients compared with non-CAD patients (P2<0.001 for cTnI; P1<0.05 and P2<0.001 for BNP), especially in patients of STEMI and NSTEMI (P3<0.001 for cTnI and BNP) (*Table 1*). No significant differences were found when considering procedural characteristics among ACS patients (*Table 2*).

TEG analysis

As shown in *Table 3*, higher mean TEG-α and lower mean TEG-K were observed in ACS patients compared with non-CAD patients (P2<0.001 for TEG-α and TEG-K). Meanwhile, the mean value of TEG-α and TEG-K was significantly changed among ACS (P3<0.05 for TEG-α and TEG-K). Highest level of $MA_{thrombin}$ was detected in STEMI patients with the value of 69.4±4.7 mm, and the value was decreased in turns of NSTEMI, UA, OMI and control group (*Table 3*, *Figure 1A*). Lowest $MA_{thrombin}$ level was observed in non-CAD patients, which was significantly different from that in ACS or OMI patients (P1<0.05, P2<0.001, and P3<0.05, *Figure 1A*). Remarkably, the mean value of $MA_{thrombin}$ in STEMI patients was close to the upper normal limit (50 to 70 mm), which suggested the state of hypercoagulability after PCI (*Figure 1A*). The distribution of $MA_{thrombin}$ quartiles (Q1 to Q4) of each group in this study is presented in *Table 3* and *Figure 1B*. Hypercoagulability

Table 1 Patients characteristics

Characteristics	Overall (n=571)	Control (n=71)	OMI (n=21)	ACS				P1	P2	P3
				UA (n=268)	NSTEMI (n=98)	STEMI (n=113)	Total (n=479)			
Age, years	64.1±10.4	63.1±10.6	62.6±13.6	62.8±9.2	63.7±10.4	61.5±11.6	62.7±10.0	0.682	0.754	0.675
Female, n (%)	145 (25.4)	25 (35.2)	2 (9.5)	81 (30.2)	20 (20.4)	17 (15.0)	118 (24.6)	<0.05	0.058	<0.05
Risk factors, n (%)										
Hypertension	186 (32.6)	21 (29.6)	6 (28.6)	94 (35.1)	30 (30.6)	35 (30.9)	159 (33.2)	0.930	0.125	0.245
Diabetes	227 (39.8)	19 (26.8)	11 (52.4)	119 (44.4)	39 (39.8)	48 (42.5)	206 (43.0)	<0.05	<0.001	0.274
Hyperlipidemia	139 (24.3)	21 (29.6)	7 (33.3)	58 (21.6)	23 (23.5)	30 (26.5)	111 (23.2)	0.685	0.247	0.436
Smoking	278 (48.7)	19 (26.8)	13 (61.9)	136 (50.7)	52 (53.1)	58 (51.3)	246 (51.4)	<0.05	<0.001	0.745
Medications, n (%)										
β-blockers	364 (63.7)	6 (8.5)	16 (76.2)	174 (64.9)	74 (75.5)	94 (83.2)	342 (71.4)	<0.001	<0.001	<0.001
ACEI/ARB	311 (54.5)	11 (15.5)	17 (81.0)	138 (51.5)	63 (64.3)	82 (72.6)	283 (59.1)	<0.001	<0.001	<0.05
Calcium-channel blockers	120 (21.0)	12 (16.9)	4 (19.0)	85 (31.7)	13 (13.3)	6 (5.3)	104 (21.7)	0.821	0.354	<0.05
Statins	463 (81.1)	20 (28.2)	21 (100.0)	221 (82.5)	91 (92.9)	110 (97.3)	422 (88.1)	<0.001	<0.001	<0.05
Proton-pump inhibitors	209 (36.6)	17 (23.9)	6 (28.6)	67 (25.0)	46 (46.9)	73 (64.6)	186 (38.8)	0.669	<0.05	<0.05
Laboratory data										
WBC ($\times10^9$/L)	6.9±2.1	6.2±1.4	6.0±2.0	6.9±2.0	6.7±2.2	7.5±2.4	7.0±2.1	0.845	<0.001	<0.05
Platelets ($\times10^9$/L)	201.8±55.6	203.4±47.1	202.5±51.0	197.3±50.4	206.3±66.7	207.4±62.4	201.6±57.1	0.943	0.971	0.156
Hemoglobin (g/L)	138.2±15.1	139.5±13.5	137.1±15.0	137.6±15.3	136.6±12.8	140.3±17.1	138.0±15.3	0.875	0.824	0.178
Creatinine (μmol/L)	73.5±16.4	71.9±12.1	72.0±20.7	73.7±16.9	73.4±15.9	74.2±17.0	73.8±16.7	0.897	0.574	0.942
Fibrinogen (g/L)	3.0±1.3	2.5±0.5	2.6±0.5	2.9±0.5	3.5±2.6	3.2±1.2	3.1±1.4	0.447	<0.05	<0.05
D-dimer (μg/mL)	0.2±0.2	0.2±0.4	0.1±0.1	0.2±0.2	0.2±0.1	0.2±0.2	0.2±0.2	0.374	<0.05	<0.05
cTnI (ng/mL)	3.6±13.3	0.01±0.01	0.1±0.6	0.1±0.6	6.1±14.0	13.1±24.3	4.3±14.4	0.316	<0.001	<0.001
BNP (pg/mL)	132.9±242.9	33.0±26.7	135.9±233.3	86.1±202.0	221.9±284.6	230.6±308.9	147.9±257.8	<0.05	<0.001	<0.001

P1 is the comparison between OMI and control; P2 is the comparison between ACS and control; P3 is the comparison among ACS (UA, NSTEMI and STEMI). OMI, old myocardial infarction; ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST segment elevation myocardial infraction; STEMI, ST segment elevation myocardial infraction; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; cTnI, cardiac troponin I; BNP, brain natriuretic peptide.

Table 2 Procedural characteristics

Characteristics	ACS				P
	UA (n=268)	NSTEMI (n=98)	STEMI (n=113)	Total (n=479)	
Lesion location, n (%)					
Left main coronary artery (LM)	11 (4.1)	6 (6.1)	2 (1.8)	19 (4.0)	0.417
Left anterior descending artery (LAD)	179 (66.8)	63 (64.3)	82 (72.6)	324 (67.6)	0.654
Left circumflex artery (LCX)	87 (32.5)	36 (36.7)	32 (28.3)	155 (32.4)	0.444
Right coronary artery (RCA)	105 (39.2)	42 (42.9)	52 (46.0)	199 (41.5)	0.526
Multi-vessel disease	94 (35.1)	44 (44.9)	41 (36.3)	179 (37.4)	0.086
Number of stents	1.5±0.9	1.7±1.1	1.7±1.0	1.6±1.0	0.546
Length of stents (mm)	39.6±30.2	44.1±34.2	46.6±30.3	42.2±31.2	0.248
Diameter of stents (mm)	4.2±2.6	4.8±3.1	4.7±2.9	4.5±2.8	0.657

P is the comparison among ACS (UA, NSTEMI and STEMI). ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST segment elevation myocardial infraction; STEMI, ST segment elevation myocardial infraction.

was considered as a value of $MA_{thrombin}$ in the fourth quartile (Q4 >72 mm), which might be a predictor of recurrent ischemic events. Our results found that 19.0% (91/479) of ACS patients were of hypercoagulability, among which 37 (32.7%) were STEMI patients, 25 (25.5%) were NSTEMI patients and 29 (10.8%) were UA patients (*Figure 1B*,*C*). Significant difference was detected between UA patients and other ACS patients (P<0.001 for NSTEMI or STEMI compared to UA, *Figure 1C*). Few patients in OMI (1/21, 4.8%) and non-CAD (0/71, 0%) groups showed hypercoagulable state (*Figure 1B*).

MA_{ADP}, which could reflect antiplatelet effects of clopidogrel, was assessed after usage of DAPT for at least 5 days. MA_{ADP} was compared among ACS groups, and the results are presented in *Table 3* and *Figure 2*. There was a progressive increase of MA_{ADP} in patients with UA, NSTEMI and STEMI. Higher MA_{ADP} was observed in STEMI and NSTEMI patients when compared with UA patients (P<0.001, *Figure 2A*). Meanwhile, values of MA_{ADP} was similar between NSTEMI and STEMI patients (P=0.193, *Figure 2A*). In this study, a considerable portion of 41.8% ACS patients were in the first trisection (MA_{ADP} <31 mm), containing 50.4% of UA patients, 35.7% of NSTEMI patients and 26.5% of STEMI patients. Significant difference was observed between UA patients and other ACS patients (P<0.05 for NSTEMI *vs.* UA; P<0.001 for STEMI *vs.* UA, *Figure 2B*). Meanwhile, 27.6% of NSTEMI and 31.0% of STEMI patients were in the third trisection (MA_{ADP} >47 mm), which was significantly higher than that of UA patients (12.7%) (P<0.001 for NSTEMI or STEMI *vs.* UA, *Figure 2B*). For patients in the potential therapeutic window (MA_{ADP} 31–47 mm), there was no difference among UA, NSTEMI and STMEI patients, with the proportion of 36.9%, 36.7% and 42.5%, respectively (*Figure 2B*).

Correlations between fibrinogen and TEG variables

Weak to moderate correlations between fibrinogen and TEG variables, such as $MA_{thrombin}$, TEG-K, TEG-angle, and MA_{ADP}, were observed in ACS patients (*Table 4*). Spearman's Rho which measured the strength and direction of the relationship between two variables were 0.404, –0.349, 0.352 and 0.235 between fibrinogen and $MA_{thrombin}$, TEG-K, TEG-α, and MA_{ADP}, respectively (P<0.001 for each correlation analysis). Weak corrections between D-dimer and TEG variables were detected (*Table 4*), with Spearman's Rho being 0.219, –0.148, 0.124 and 0.115 between d-dimer and $MA_{thrombin}$, TEG-K, TEG-α, and MA_{ADP}, respectively (P<0.001 for $MA_{thrombin}$ and TEG-K; P<0.05 for TEG-α and MA_{ADP}).

Discussion

TEG now is widely used for platelet function measurement. Our study sought to describe the difference of TEG results among different manifestations of CAD after PCI. In this study, we found various degrees of hypercoagulability and

Table 3 TEG parameters

Parameters	Overall (n=571)	Control (n=71)	OMI (n=21)	ACS				P1	P2	P3
				UA (n=268)	NSTEMI (n=98)	STEMI (n=113)	Total (n=479)			
TEG-R (min)	6.9±1.7	7.2±1.2	7.0±1.6	6.9±1.9	6.9±1.4	6.6±1.3	6.8±1.7	0.604	0.064	0.287
TEG-K (min)	1.7±0.6	2.0±0.4	2.0±0.5	1.8±0.7	1.6±0.4	1.5±0.4	1.7±0.6	0.665	<0.001	<0.05
TEG-α (deg)	69.8±5.5	67.3±4.6	67.0±6.1	69.6±5.8	70.9±4.8	71.1±5.2	70.3±5.5	0.831	<0.001	<0.05
$MA_{thrombin}$ (mm)	65.0±6.8	56.6±7.0	62.1±5.8	64.6±5.7	67.5±5.6	69.4±4.7	66.4±5.8	<0.05	<0.001	<0.05
MA_{ADP} (mm)	–	–	36.2±18.1	31.1±14.0	37.7±14.8	40.4±14.8	34.6±14.9	–	–	<0.001
Quartiles of $MA_{thrombin}$, n (%)										
Q1 (<65 mm)	259 (45.4)	62 (87.3)	13 (61.9)	130 (48.5)	33 (33.7)	21 (18.6)	184 (38.4)	<0.05	<0.001	<0.05
Q2 (65–68 mm)	111 (19.4)	6 (8.5)	7 (33.3)	56 (20.9)	20 (20.4)	22 (19.5)	98 (20.5)	<0.05	<0.05	0.841
Q3 (68–72 mm)	109 (19.1)	3 (4.2)	0 (0.0)	53 (19.8)	20 (20.4)	33 (29.2)	106 (22.1)	0.254	<0.001	0.126
Q4 (>72 mm)	92 (16.1)	0 (0.0)	1 (4.8)	29 (10.8)	25 (25.5)	37 (32.7)	91 (19.0)	0.356	<0.001	<0.001
Trisections of MA_{ADP}, n (%)										
T1 (<31 mm)	–	–	9 (42.9)	135 (50.4)	35 (35.7)	30 (26.5)	200 (41.8)	–	–	<0.05
T2 (31–47 mm)	–	–	3 (14.3)	99 (36.9)	36 (36.7)	48 (42.5)	183 (38.2)	–	–	0.287
T3 (>47 mm)	–	–	9 (42.9)	34 (12.7)	27 (27.6)	35 (31.0)	96 (20.0)	–	–	<0.001

P1 is the comparison between OMI and control; P2 is the comparison between ACS and control; P3 is the comparison among ACS (UA, NSTEMI and STEMI). TEG, thromboelastography; ACS, acute coronary syndrome; OMI, old myocardial infarction; UA, unstable angina; NSTEMI, non-ST segment elevation myocardial infraction; STEMI, ST segment elevation myocardial infraction; TEG-R, time to fibrin formation; TEG-K, clot formation time; $MA_{thrombin}$, platelet-fibrin clot strength; MA_{ADP}, ADP-induced clot strength.

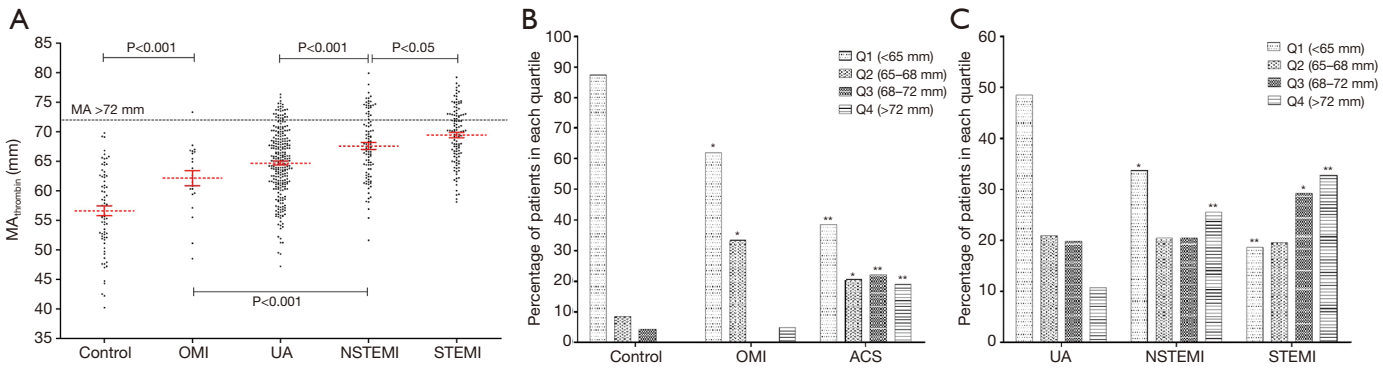

Figure 1 Levels of $MA_{thrombin}$ and $MA_{thrombin}$ quartiles. (A) $MA_{thrombin}$ among study groups; (B) $MA_{thrombin}$ quartiles among control, OMI, and ACS; (C) $MA_{thrombin}$ quartiles among UA, NSTEMI, and STEMI. Control indicates non-coronary heart disease patients; OMI indicates old myocardial infarction patients; UA indicates unstable angina patients, NSTEMI indicates non-ST segment elevation myocardial infraction; STEMI indicates ST segment elevation myocardial infraction patients; ACS indicates acute coronary syndrome patients. *, P<0.05; **, P<0.001. $MA_{thrombin}$, platelet-fibrin clot strength.

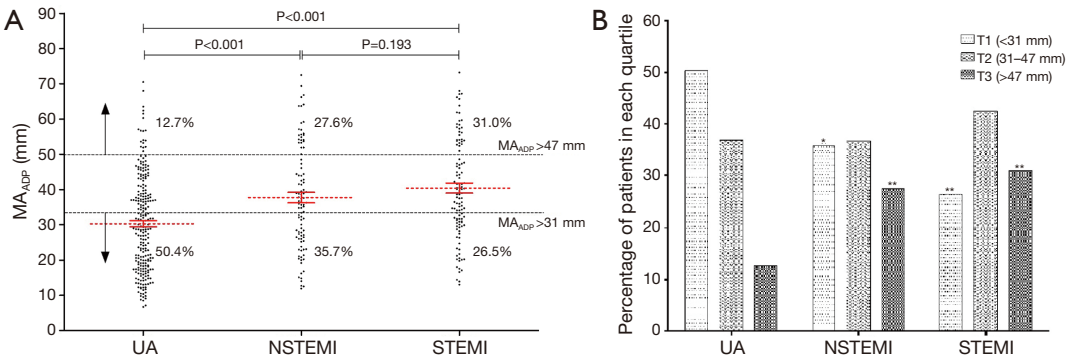

Figure 2 Levels of MA_{ADP} and MA_{ADP} trisection. (A) MA_{ADP} levels among UA, NSTEMI, and STEMI; (B) MA_{ADP} trisection among UA, NSTEMI, and STEMI. UA indicates unstable angina patients; NSTEMI indicates non-ST segment elevation myocardial infraction; STEMI indicates ST segment elevation myocardial infraction patients. *, P<0.05; **, P<0.001. MA_{ADP}, ADP-induced clot strength.

antiplatelet effects of clopidogrel among OMI, UA, and ACS (UA, NSTEMI, STEMI). Highest level of $MA_{thrombin}$ was detected in STEMI patients, while lowest $MA_{thrombin}$ level was observed in non-CAD patients. Higher MA_{ADP} was observed in STEMI and NSTEMI patients when compared with UA patients. Therefore, personalized therapy, i.e., different antiplatelet therapeutic regimens given to CAD patients according to their hypercoagulability and antiplatelet effects of clopidogrel, should be applied to achieve optimal secondary prevention.

It is well known that post-stent ischemic events are influenced by platelet activation and thrombin generation. Currently, DAPT, consisting of the combination of aspirin and a platelet $P2Y_{12}$ receptor inhibitor for ADP, is a standard care for patients after PCI. Clopidogrel is the most widely used $P2Y_{12}$ receptor inhibitor in China. The standard dose of aspirin and clopidogrel was based on the randomized clinical trial of PCI-CURE study (4), which did not assess the pharmacological effects on individuals by means of laboratory tests. Despite the proven benefits of aspirin and clopidogrel therapy, there were still nearly 20% of post-stent patients suffering recurrent ischemic or thrombotic events (9,11). Therefore, it is speculated that personalized antiplatelet therapy according to one's hypercoagulability and antiplatelet effect of clopidogrel might be appropriate for post-stent patients.

TEG, which was specially designed to assess overall clotting kinetics and strength in whole blood, was used

Table 4 Correlation analysis of white blood counts, fibrinogen, D-dimer and TEG in ACS patients

Variables	$MA_{thrombin}$	TEG-K	TEG-α	MA_{ADP}
WBC	Rho =−0.58, P=0.202	Rho =0.018, P=0.696	Rho =0.023, P=0.620	Rho =0.007, P=0.872
Fibrinogen	Rho =0.404, P<0.001	Rho =−0.349, P<0.001	Rho =0.352, P<0.001	Rho =0.235, P<0.001
D-dimer	Rho =0.219, P<0.001	Rho =−0.148, P<0.001	Rho =0.124, P<0.05	Rho =0.115, P<0.05

TEG, thromboelastography; ACS, acute coronary syndrome; WBC, white blood cell; TEG-K, clot formation time; TEG-α, angle constant; $MA_{thrombin}$, platelet-fibrin clot strength; MA_{ADP}, ADP-induced clot strength.

in this study to detect hypercoagulable states of post-stent patients (12). Various degrees of hypercoagulability and antiplatelet effects of clopidogrel were found among OMI and ACS patients with different manifestations (UA, NSTEMI and STEMI). $MA_{thrombin}$, one of the characteristics in TEG, could represent the maximal clot strength. An abrupt elevation of $MA_{thrombin}$ was found in ACS patients, and the highest level of $MA_{thrombin}$ was reported in STEMI patients, which indicated notable hypercoagulability of STEMI patients. It was worth noting that a progressive increase was exist in OMI, UA, NSTEMI and STEMI patients, suggesting that increased $MA_{thrombin}$ was associated with the stages of CAD. Similar trend was also found in the values of MA_{ADP}. MA_{ADP} could reflect platelet reactivity to ADP and assess the individual patient's response to clopidogrel therapy in this study. Cut points of MA_{ADP} were defined as 31 and 47 mm according to the previous studies, which introduced that MA_{ADP} >47 mm had the best predictive value of long-term ischemic events regardless of how high the $MA_{thrombin}$ might be, and MA_{ADP} <31 mm was a predictive value for bleeding (10). Therefore, a therapeutic range of MA_{ADP} being 31 to 47 mm was proposed to provide ideal efficacy and safety (10). In this study, 50.4% of UA patients, 35.7% of NSTEMI patients and 26.5% of STEMI patients were in the first trisection (MA_{ADP} <31 mm), indicating that UA patients might be in a higher risk of bleeding compared with NSTEMI and STEMI patients. About 31% of STEMI patients and 27.6% of NSTEMI patients were in the third trisection (MA_{ADP} >47 mm). The proportion was higher than that of UA patients (12.7%), suggesting that higher risk of thrombotic events could be predictable in STEMI and NSTEMI patients compared with UA patients. The probable mechanisms could explain these phenomena, of which the exact biologic mechanisms might not be fully understood. UA and NSTEMI are caused by severe coronary lesions and repeated plague ruptures, inducing platelet activation, and enhancing platelet aggregating function in a relative long term. In comparison, coronary plaque rupture leads to platelet aggregating immediately in STEMI, leading to the formation of coronary thrombus (13).

Considering the above factors, "one-size-fits all" strategy has obvious limitations for post-PCI patients, and more attention should be paid to personalized antiplatelet therapy according to individual's hypercoagulability and antiplatelet effects of $P2Y_{12}$ receptor inhibitors.

It is well known that many factors could affect the on-treatment platelet reactivity, including modifiable factors, such as smoking, high body mass index, drug interactions, as well as non-modifiable factors, such as genetic polymorphisms, age, sex, and chronic kidney disease (14). Besides, both ischemic risk and bleeding risk should also be taken into consideration when choosing antiplatelet drugs for CAD patients. All these factors could contribute to contemplate strategies of tailored antiplatelet regimens that included the use of more potent $P2Y_{12}$ inhibitors (14). According to our results, strengthened antiplatelet therapy should be considered in patients with higher ischemic risk and relatively lower bleeding risk. Prasugrel and ticagrelor, as newer $P2Y_{12}$ receptor inhibitors, could reduce the thrombotic events without significantly increased bleeding events compared with clopidogrel (15,16). Studies also confirmed that few ACS patients (about 3.98%) using ticagrelor were in MA_{ADP} >47 mm (17). Accordingly, current clinical guidelines recommended a potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) as a preference to clopidogrel for ACS patients (18). Nevertheless, high on-treatment platelet reactivity also observed in patients with prasugrel and ticagrelor, which correlated with the occurrence of ischemic events (19). Therefore, more exploration is needed in the individualized antiplatelet medication.

Inevitably, there are some limitations in this study. First, this is a single-center observational study. Nevertheless, this study was the first to explore different hypercoagulability and antiplatelet effects of clopidogrel among different manifestations of post-stent patients using TEG. Second,

the incidence of thrombotic events and bleeding events were not reported, as the long-term follow-up was not conducted in this study. Moreover, the risk factors associated with hypercoagulability and antiplatelet effects of clopidogrel in ACS patients were not evaluated, and the corresponding stratified analysis was not performed. Therefore, a large prospective multicenter, randomized controlled trial is necessary to further validate the present results.

Conclusions

This study suggested that various degrees of hypercoagulability and antiplatelet effects of clopidogrel existed among OMI, UA, NSTEMI and STEMI patients undergoing PCI. Highest level of $MA_{thrombin}$ and MA_{ADP} was observed in STEMI patients. Therefore, more attention should be paid to personalized antiplatelet therapy according to individual's hypercoagulability and antiplatelet effects of $P2Y_{12}$ receptor inhibitors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (No.: 2018-025). Written informed consent was obtained from the patients for publication of this study.

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