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Original Article

Application of thromboelastography in evaluating effects of aspirin with or without clopidogrel treatment as well as predictive factors for aspirin resistance in patients with coronary artery disease

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Abstract: The aim of this study was to apply thromboelastography (TEG) to evaluate effects of aspirin with or without clopidogrel treatment and predictive factors for aspirin resistance (AR) in coronary artery disease (CAD) patients. A total of 189 CAD patients were consecutively enrolled in this prospective cohort study and treated by aspirin, with or without clopidogrel. Venous blood was obtained and detected by TEG. Arachidonic acid (AA) inhibition rate was (61.83±26.30)% and AR occurred in 62 patients (32.8%). Additionally, adenosine diphosphate (ADP) inhibition rate was (41.83±32.07)% and clopidogrel resistance occurred in 67 patients (35.4%). Values of R time and K time were 6.75±1.82 minutes and 1.69±0.73 minutes, respectively, and α angel was 62.50±10.47°. Maximal amplitude (MA) and AA-induced and ADP-induced platelet-fibrin clot strengths were 62.85±7.39 mm, 30.81±14.93 mm, and 39.28±13.70 mm, respectively. Multivariate analysis showed that age and white blood cells (WBC) were independent factors for predicting higher risk of AR, while hemoglobin (Hb) was an independent factor for absence of AR. Furthermore, the combination of age, WBC, and Hb displayed a good predictive value for AR. TEG could assess the antithrombotic effect of aspirin, with or without clopidogrel treatment in CAD patients. Combination of age, WBC, and Hb demonstrated a good predictive value for AR risk.

Keywords: Thromboelastography, coronary artery disease, aspirin resistance, aspirin, clopidogrel, predictive factors

Introduction

Coronary artery disease (CAD), an ischemic heart disease, is characterized by coronary atherosclerosis and develops syndromes such as stable angina and asymptomatic or silent ischemia. It is a multifactorial disease that produces a world-wide health and economic burden, causing one-third of all deaths in patients over 35 years old [1, 2]. Thrombosis is the primary cause of mortality in CAD and other ischemic diseases, while platelet aggregation is the main pathogenic reason for thrombosis. Thus, antiplatelet agents such as aspirin and clopidogrel play crucial roles in the treatment of CAD [3].

Aspirin, widely used in CAD patients due to its antithrombotic effect, interdicts platelet cyclooxygenase-1 (COX-1) enzyme activity. Aspirin also inhibits the metabolic process of arachidonic acid (AA) and synthesis of thromboxane A_2 (TXA_2), which is responsible for thrombogenesis. Therefore, aspirin affects AA-induced platelet aggregation [4, 5]. A meta-analysis performed by Antiplatelet Trialists' Collaboration (ATC) revealed that antiplatelet therapy, based on aspirin, achieved a 22% reduction of recurrence in CAD patients compared to an untreated group [4]. Clopidogrel, a second generation thienopyridine, blocks adenosine diphosphate (ADP)-induced platelet aggregation and is often used with aspirin in preventing thrombosis as the standard treatment of ischemic diseases, including CAD [6]. However, patients presenting low or no response to antiplatelet agents are called resistant to antiplatelet drugs. Reported aspirin resistance occurs in 0.4% to

Table 1. Characteristics

Parameters	CAD patients (n = 189)
Age (years)	64.04±11.95
Gender (Male/female)	155/34
BMI (kg/m^2)	25.68±3.69
Treatment	
Aspirin (n/%)	55 (29.1)
Aspirin with clopidogrel (n/%)	134 (70.9)
Hypertension (n/%)	135 (71.4)
Diabetes (n/%)	56 (29.6)
Smoke (n/%)	90 (47.6)
Family history of CAD (n/%)	68 (36.0)
WBC (× 10^9/l)	7.01±3.03
Hb (g/l)	132.17±20.11
PLT (× 10^9/l)	201.45±67.05
Scr (μmol/l)	108.03±71.91
SUA (μmol/l)	373.24±133.55
TG (mmol/l)	2.01±0.82
TC (mmol/l)	4.20±1.12
HDL-C (mmol/l)	0.99±0.20
LDL-C (mmol/l)	2.58±0.83
FBG (mmol/l)	5.85±1.64
Hs-CRP (mg/l)	15.25 (12.29-20.30)
ESR (mm/h)	17.18 (13.36-21.33)
Combinations	
Nitrates (n/%)	125 (66.1)
Diuretics (n/%)	45 (23.8)
ACEI/ARB (n/%)	121 (64.0)
β receptor inhibitors (n/%)	127 (67.2)
Statins (n/%)	164 (86.8)
CCB (n/%)	67 (35.4)
LMWH (n/%)	110 (58.2)

Data are presented as mean value ± standard deviation, median (25th-75th value), or count (percentage). CAD, coronary artery disease; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; Scr, serum creatinine; SUA, serum uric acid; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; and LMWH, low molecular weight heparin.

83% of patients and clopidogrel resistance occurs in 15% to 30% of patients with ischemic heart diseases [5, 7]. Risk of crippling events in patients with aspirin resistance is four times higher than in patients sensitive to aspirin therapy. Therefore, precise monitoring timely reflecting platelet information during treatment and predictive factors for resistance to therapy are of great importance [8].

Thromboelastography (TEG), a viscoelastic test for blood coagulation, has been successfully applied for hemostatic therapy, transfusions, perioperative care, and hemophilia due to its point-of-care analysis and timely results [9, 10]. Moreover, TEG rapidly measures formation and dynamics of coagulation in blood. TEG has attracted increasing amounts of attention for its value in the treatment of ischemic heart and cerebrovascular diseases. Concerning aspirin resistance in CAD, we hypothesized that TEG might contribute to preventing recurrence of thrombosis due to the fact that patient platelet function is able to be monitored by TEG and antiplatelet therapy could be adjusted in time.

Hence, this present prospective cohort study was conducted to apply TEG examination to evaluate effects of aspirin, with or without clopidogrel treatment, and predictive factors for aspirin resistance in CAD patients.

Methods

Patients

A total of 189 patients with CAD, between June 2015 and May 2017, were consecutively enrolled in this prospective cohort study. Inclusion criteria were: (1) Age > 18 years; (2) Diagnosed with CAD based on clinical findings including angina pectoris, shortness of breath, positive exercise test, family history of coronary artery disease or presence of traditional coronary risk factors, and confirmed by coronary angiography which presented that one or more coronary arteries had stenosis above 50%; and (3) About to receive aspirin, with or without clopidogrel treatment. Exclusion criteria were: (1) Combination with other antiplatelet drugs; (2) Complicated with hematological malignance or solid tumors; (3) Complicated with hemorrhagic disease or gastrointestinal ulcers; (4) Severe hepatic or renal dysfunction; and (5) Known allergies to aspirin or

Table 2. Treatment efficacy evaluated by TEG

Parameters	CAD patients (n = 189)
AA inhibition rate	(61.83±26.30)%
AR rate (n/%)	62 (32.8)
ADP inhibition rate	(41.83±32.07)%
CR rate (n/%)	67 (35.4)
R time (min)	6.75±1.82
K time (min)	1.69±0.73
α angel (°)	62.50±10.47
MA (mm)	62.85±7.39
MAAA (mm)	30.81±14.93
MAADP (mm)	39.28±13.70

Data are presented as mean value ± standard deviation or count (percentage). TEG, thromboelastography, CAD, coronary artery disease; AA, arachidonic acid; AR, aspirin resistance; ADP, adenosine diphosphate; CR, clopidogrel resistance; MA, maximum amplitude; MAAA, AA-induced platelet-fibrin clot strength; and MAADP, ADP-induced platelet-fibrin clot strength.

clopidogrel. This study was approved by the Ethics Committee of Renmin Hospital of Wuhan University and each patient provided informed consent.

Baseline data collection

Baseline data was collected and included: (1) Demographic features: age, gender, and body mass index (BMI); (2) Complications: hypertension, diabetes, smoking, and family history of CAD; (3) Biochemical indexes: white blood cells (WBC), hemoglobin (Hb), platelet count (PLT), serum creatinine (Scr), serum uric acid (SUA), triglyceride (TG), total cholesterol (TC), fasting high-density lipoprotein cholesterol (HDL-C), fasting low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR); and (4) Combinations: nitrates, diuretics, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin Receptor Blockers (ARB), β receptor inhibitors, statins, calcium channel blockers (CCB), and low molecular weight heparin (LMWH).

Procedures

Patients were treated with aspirin, with or without clopidogrel, as follows: aspirin, 100-200 mg/d; clopidogrel, 75 mg/d. After 7-day treatment, venous blood was obtained and detected by TEG (Hemoscope (GE5000), USA). AA inhibition rate, ADP inhibition rate, R time (period to 2 mm amplitude), K time (period from 2 to 20 mm amplitude), α angel, maximum amplitude (MA), AA-induced platelet-fibrin clot strength (MAAA), and ADP-induced platelet-fibrin clot strength (MAADP) were recorded. Aspirin resistance (AR) was defined as an AA inhibition rate below 50%, while clopidogrel resistance (CR) was defined as an ADP inhibition rate below 30% [11, 12].

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM, USA). Data are mainly presented as mean value ± standard deviation, median (25th-75th value), or count (percentage). Univariate logistic regression was used to analyze factors at baseline in predicting AR occurrence. Factors with *P* values below 0.1 were subsequently determined by multivariate logistic regression. Receiver operating characteristic (ROC) curve was performed to detect the predictive value of independent factors in multivariate logistic regression for AR risk. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 189 CAD patients were enrolled in this study, with mean age of 64.04±11.95 years and mean BMI of 25.68±3.69 kg/m^2. There were 155 males and 34 females. Fifty-five (29.1%) were treated by aspirin treatment alone and 134 (70.9%) received aspirin with clopidogrel treatment (**Table 1**). Number of patients with hypertension, diabetes, smoking, and family history of CAD was 135 (71.4%), 56 (29.6%), 90 (47.6%), and 68 (36.0%), respectively. For combinations, 125 (66.1%), 45 (23.8%), 121 (64.0%), 127 (67.2%), 164 (86.8%), 67 (35.4%), and 110 (58.2%) patients were treated by nitrates, diuretics, ACEI/ARB, β receptor inhibitors, statins, CCB, and LMWH, respectively. Mean WBC, Hb, and PLT were 7.01±3.03 × 10^9/l, 132.17±20.11 g/l and 201.45±67.05 × 10^9/l, respectively. Other biochemical indexes are listed in **Table 1**.

Treatment efficacy assessed by TEG

Treatment efficacy was evaluated by TEG and displayed in **Table 2**. Mean AA inhibition rate was (61.83±26.30)% and AR occurred in 62

Table 3. Univariate logistic analysis of factors affecting AR

Total CAD patients (N = 189)	Univariate logistic regression model			
	P value	OR	95% CI	
			Lower	Higher
Age	0.007	1.038	1.010	1.066
Gender (Male)	0.235	0.641	0.299	1.375
BMI	0.307	1.044	0.961	1.135
Aspirin with clopidogrel (vs. Aspirin)	0.179	0.638	0.332	1.228
Hypertension	0.557	1.228	0.619	2.433
Diabetes	0.373	1.346	0.700	2.590
Smoking	0.091	1.697	0.920	3.131
Family history of CAD	0.585	1.191	0.636	2.233
WBC	0.040	1.114	1.005	1.235
Hb	0.005	0.977	0.961	0.993
PLT	0.907	1.000	0.996	1.005
Scr	0.111	0.996	0.992	1.001
SUA	0.143	0.998	0.996	1.001
TG	0.407	1.168	0.809	1.684
TC	0.516	1.094	0.834	1.437
HDL-C	0.810	0.825	0.172	3.949
LDL-C	0.154	1.308	0.904	1.892
FBG	0.521	1.062	0.884	1.275
Hs-CRP	0.412	1.013	0.982	1.044
ESR	0.931	1.001	0.976	1.027
Nitrates	0.328	1.388	0.720	2.678
Diuretics	0.522	0.788	0.379	1.636
ACEI/ARB	0.585	0.839	0.448	1.573
β receptor inhibitors	0.125	0.608	0.322	1.149
Statins	0.318	1.642	0.621	4.344
CCB	0.522	0.811	0.426	1.542
LMWH	0.031	2.027	1.066	3.853

Univariate logistic regression was used to analyze the factors at baseline in predicting AR occurrence. *P* value < 0.05 was considered significant. AR, aspirin resistance; CAD, coronary artery disease; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; Scr, serum creatinine; SUA, serum uric acid; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; and LMWH, low molecular weight heparin.

(32.8%) patients. Additionally, mean ADP inhibition rate was (41.83±32.07)% and CR occurred in 67 (35.4%) patients. Mean values of R time and K time were 6.75±1.82 minutes and 1.69±0.73 minutes, respectively, and α angel was 62.50±10.47°. For maximal amplitude representing fibrin clot strength, mean MA, MAAA, and MAADP were 62.85±7.39 mm, 30.81±14.93 mm, and 39.28±13.70 mm, respectively.

Analysis of factors affecting AR

As presented in **Table 3**, factors affecting AR were analyzed by univariate logistic regression and revealed that clopidogrel combination didn't affect AR (*P* = 0.179). Age (*P* = 0.007), WBC (*P* = 0.040), and LMWH (*P* = 0.031) were verified to be factors associated with higher risk of AR, while Hb (*P* = 0.005) was correlated with less possibility of AR. In addition, smoking showed a trend in predicting AR but no significant difference was observed (*P* = 0.091).

Factors with *P* values below 0.1 in univariate analysis were subsequently analyzed in a multivariate model. As displayed in **Table 4**, age (*P* = 0.005) and WBC (*P* = 0.036) were independent factors predicting higher risk of AR, while Hb (*P* = 0.008) was an independent factor for absence of AR.

Predictive values of combination of age, WBC, and Hb for AR

ROC curves were drawn to investigate the value of age, WBC, and Hb in predicting AR (**Figure 1**). Age (AUC: 0.619, 95% CI = 0.535-0.703), WBC (AUC: 0.602, 95% = CI 0.519-0.683), and Hb (AUC: 0.602, 95% CI = 0.537-0.703) disclosed good predictive value for AR. When combining these factors together, age, WBC, and Hb displayed better predictive value for AR (AUC: 0.701, 95% CI = 0.625-0.778). Sensitivity and specificity were 75.8% and 59.1%, respectively, at the best cut-off point.

Discussion

In this study, TEG was applied to assess the effects of aspirin, with or without clopidogrel

Table 4. Multivariate logistic analysis of factors affecting AR

Total CAD patients (N = 189)	Multivariate logistic regression model			
	P value	OR	95% CI	
			Lower	Higher
Age	0.005	1.043	1.013	1.073
Smoke	0.201	1.540	0.795	2.985
WBC	0.036	1.127	1.008	1.260
Hb	0.008	0.977	0.960	0.994
LMWH	0.076	1.868	0.937	3.724

Multivariate logistic regression was used to analyze the factors with *p* value below 0.1 in univariate analysis for AR occurrence. *P* value < 0.05 was considered significant. AR, aspirin resistance; CAD, coronary artery disease; WBC, white blood cell; Hb, hemoglobin; LMWH, low molecular weight heparin.

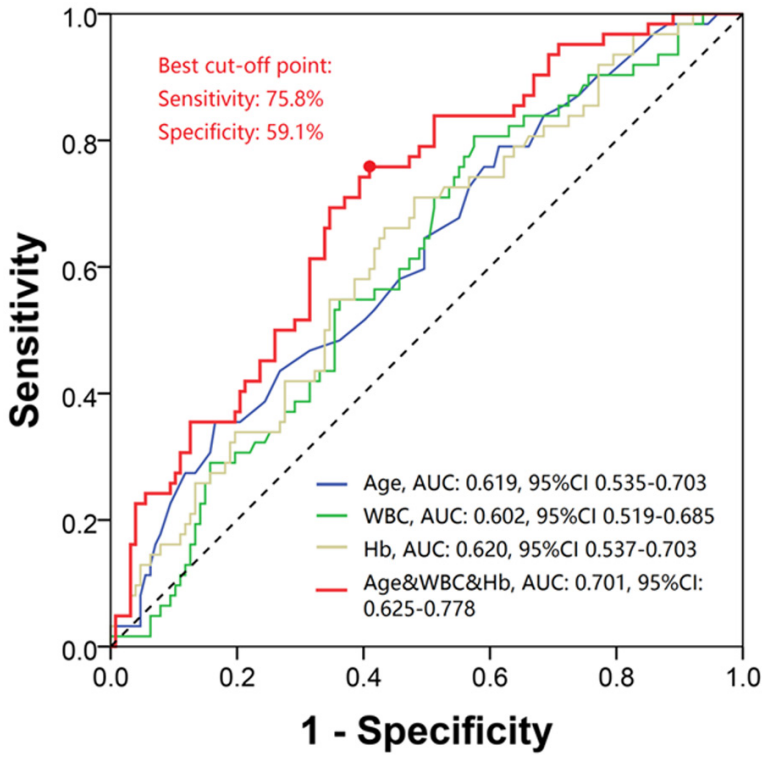

Figure 1. ROC curve analysis for AR risk. ROC curves revealed that age (AUC: 0.619, 95% CI 0.535-0.703), WBC (AUC: 0.602, 95% CI 0.519-0.683), and Hb (AUC: 0.602, 95% CI 0.537-0.703) presented good predictive values of AR risk and combination of age, WBC, and Hb displayed superior predictive value of occurrence of AR. Sensitivity and specificity were 75.8% and 59.1% at the best cut-off point.

therapy, in CAD patients. Predictive factors for AR were analyzed, attaining the following results: (1) TEG showed AA inhibition rate was (61.83±26.30)%, AR rate was 32.8%, ADP inhibition rate was (41.83±32.07)%, and CR rate was 35.4%; (2) Multivariate logistic regression revealed that age and WBC were independent factors associated with occurrence of AR, while Hb was an independent factor predicting lower risk of AR. Furthermore, ROC curve disclosed that the combination of age, WBC, and Hb presented good predictive value for AR risk.

Thrombosis is a problem that disturbs many people, resulting in various ischemic heart diseases, including CAD. Thus, antithrombosis agents play crucial roles in these diseases [13, 14]. Aspirin is able to acetylate a serine residue of the cyclooxygenase 1 (COX-1) isoform responsible for catalyzing synthesis of TXA_2 in platelets. TXA_2 originates from arachidonic acid (AA) and the combination of TXA_2 and its G-protein coupled receptor contributes to activation of phospholipase C and aggregation of platelets. Hence, aspirin, as a nonselective inhibitor of COX, affects the production of TXA_2 and prevents platelet aggregation, contributing to inhibition of AA-induced clotting [15]. Clopidogrel is a thienopyridine which has been widely applied to decrease incidence of thrombosis [16]. Once clopidogrel enters into liver cells, it is oxidized to form its active metabolite by cytochrome P450. The metabolite of clopidogrel binds to P2Y12, the receptor of ADP, and then blocks the process of platelet aggregation, subsequently inhibiting ADP-induced clotting [17, 18]. While recurrent thrombotic events or non-responsiveness during antiplatelet therapy have been reported, resistance to therapy may be due to the following: (1) It is disclosed that most events of aspirin resistance are associated with non-specific approaches, insufficient compliance, and dose in treated patients [19]; (2) Genetic polymorphisms may appear in COX-1 gene which con-

sists of A842G and C50T and receptors of platelet glycoprotein genes including Leu33Pro and P1A1/A2. Along with growing platelet turnover, particularly after surgery, all of these lead to aspirin resistance [19-21]; (3) Reactivity of platelets may be augmented by factors such as smoking, diabetes, and hyperlipidemia, thus, a uniform dose of antiplatelet agents may be threatened by unexpected events [22]. At present, a standard treatment for resistance of antiplatelet agents has not been established, therefore, monitoring platelet reactivity is of great need.

TEG is used in blood monitoring and has become a novel method to evaluate changes of viscoelasticity in whole blood with a special activator of coagulation [9]. Once blood starts to aggregate, thrombin generates and then clots are formed under the effect of activated coagulation factor VIII. Movement of components in TEG is affected by the changing strength of the clot and, finally, coupling between the clot and detecting pin relieves if the clot dissolves due to fibrinolysis. During the movement, an electrical current is produced and TEG curve is drawn, reflecting the beginning and maximal strength of the clot, as well as other characteristics associated with platelet reactivity [9, 23].

A retrospective research conducted by Hyunjung Kim et al. explored resistance to aspirin and clopidogrel in patients with CAD, as well as other ischemic cerebrovascular diseases (ICD). The function of platelets was detected by VerifyNow system. They disclosed an AR rate of 13.5% (18/133) in CAD patients and 15.6% (7/45) in other ICD patients [6]. Another cohort study, which enrolled 100 consecutive patients about to undergo cardiovascular surgery, was conducted by Eli I. Lev et al. Modified TEG assay was used to evaluate platelet reactivity of all patients that had been treated by aspirin with clopidogrel. Incidence of AR in their study was 13% [20]. Inconsistent with the above studies, this present study displayed AA inhibition rate of (61.83±26.30)% and AR rate of 32.8%. Discordance of treatment efficacy between the present study and previous studies may have resulted from the following: (1) Instead of the VerifyNow system, TEG was applied in the present study to evaluate platelet function. Also, it has been reported that different assays can vary greatly. [10, 23]. (2) Criteria of AR in the Eli I. Lev et al. study (inhibition < 20%) was much lower than definition of AR (inhibition < 50%) in the present study, leading to different AR rates (13% *vs*. 32.8%).

A laboratory assessment investigated anti-thrombotic therapy in 44 CAD patients and 137 patients with other heart diseases. Among 69 patients treated by aspirin, TEG obtained R time of 5.3 (4.4-6.5) minutes, K time of 1.4 (1.2-1.8) minutes, and mean α angel of 67.1° [24]. In line with this study, R time and K time were 6.75±1.82 minutes and 1.69±0.73 minutes, respectively, and α angel was 62.50± 10.47° in aspirin (with or without clopidogrel) treated CAD patients by TEG assay. Additionally, MA, MAAA, and MAADP were 62.85±7.39 mm, 30.81±14.93 mm, and 39.28±13.70 mm, respectively.

Regarding predictive factors for AR, the retrospective study applying VerifyNow for detecting AR in CAD and ICD patients, treated by aspirin and clopidogrel, disclosed that low Hb level is a predictive factor for occurrence of AR [6]. Another prospective study investigated aspirin resistance in 200 myocardial infarction patients and used a multiplate machine to analyze platelet activity. It displayed that higher WBC and lower Hb were correlated with higher possibility of AR [5]. In line with previous studies, the present study also demonstrated that WBC predicted occurrence of AR and Hb predicted absence of AR. In addition, it was revealed that age and LMWH are predictive factors for higher risk of AR which wasn't illustrated in previous studies. These results might be due to: (1) Microinflammation and oxidative stress levels which influence antiplatelet effects of aspirin may increase with age [25]; (2) Despite the well-known anticoagulation effect of LMWH, it is also able to stimulate platelets in some circumstances and induce elevated activity of platelets, which may impair antiplatelet effects of aspirin [26]. Moreover, combined independent predictive factors were used to assess their predictive value by ROC curves. It was observed that Age, WBC, and Hb presented good predictive value for risk of AR. This was the first time that the combination of age, WBC, and Hb was applied to predict AR.

The present study has some limitations: (1) Sample size was relatively small; (2) Only CAD patients were enrolled in this study. AR in

patients with other ischemic heart diseases should be investigated further in future further studies.

In conclusion, TEG can assess antithrombosis effects of aspirin, with or without clopidogrel treatment, in CAD patients and the combination of age, WBC, and Hb discloses good predictive value for AR risk.

Disclosure of conflict of interest

None.

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