Association Between Thromboelastography and Coronary Heart Disease

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Background: Thromboelastography (TEG) is a novel blood viscoelasticity detection method revealing blood coagulation status and has been reported to be helpful in predicting clinical outcomes in patients with cardiovascular diseases (CVD). In this study, we aimed to investigate the association between TEG and CVD.

Material/Methods: A single-center case-control study was performed. Individuals who took TEG tests at Tongji Hospital in Wuhan, China from 2015 to 2019 were included. The nearest-neighbor Mahalanobis matching with replacement, within propensity score calipers of 0.25 was used to control the covariate imbalance between CVD patients and controls. Logistic regression analyses were conducted to assess the relationship between TEG and CVD. Subgroup and sensitivity analyses were performed to evaluate the robustness of the association between TEG and CVD.

Results: After matching, a total of 151 participants were included in this study, with 83 patients having CVD (49 patients having coronary heart disease [CHD] and 34 patients having an ischemic stroke). By comparison, CHD patients had a significantly higher maximum amplitude (MA) (P=0.02) than controls. After multivariable adjustment, MA (OR 1.11, 95% CI 1.01-1.24, P=0.04) was independently associated with CHD. The association between MA and CHD remained robust across subgroups and in sensitivity analyses.

Conclusions: The current study suggests that MA is significantly associated with CHD. Enhanced platelet reactivity as described by high MA might be associated with risk of CHD. The exact role of MA in the measurement of CHD risk needs to be further examined in large-scale prospective cohort studies.

Keywords: Blood Coagulation • Cardiovascular Diseases • Thrombelastography

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Background

Cardiovascular diseases (CVD) are the predominant cause of mortality globally, accounting for approximately 17.9 million deaths every year [1]. Over 40% of deaths in China are attributed to CVD, and about 330 million people have CVD [2]. Driven by the expanding aging population and lifestyle changes associated with urbanization, the prevalence of CVD keeps increasing [3]. The increasing burden of CVD is one of the most important public health issues in China [4].

The primary cause of CVD, including coronary heart disease (CHD) and ischemic stroke, is atherosclerosis [5]. Atherosclerosis is an inflammatory disorder of the vascular system. It was hypothesized that atherosclerosis is "coagulation in the wrong place" [6]. Atherothrombosis is a highly procoagulant process in arteries [7], and many procoagulant factors of the coagulation system are involved in this process [8]. Researchers have investigated the association between coagulation and CVD occurrence, morbidity, and mortality [9], and higher rates of hypercoagulation were observed in patients with CVD. Assessment of blood coagulation status and using effective antiplatelet therapy in people with hypercoagulability can prevent atherosclerosis and decrease the incidence of CVD [10,11].

Blood coagulation status can be evaluated by fibrinogen level, activated partial thromboplastin time (APTT), and thromboelastography (TEG). TEG is a blood viscoelasticity detection method that dynamically monitors the whole process of blood coagulation and fibrinolysis, which was developed in 1948 and was at first used as a research tool [12,13]. TEG is now being broadly applied as a guiding tool for clotting factor replacement, platelet transfusion, and fibrinolysis treatment [14]. Some studies have noted that TEG is useful in predicting clinical outcomes in patients with CVD [15,16]. Conventional test indicators assess isolated factors of the coagulation system, but they are unable to reveal the role of these factors in the whole process of hemostasis [17]. In contrast, TEG can reveal the interaction of all components of coagulation, including platelets, fibrin, clotting factors, and thrombin, and provides an overall assessment of blood coagulation status [12]. Furthermore, the TEG test is evaluated in whole blood and can provide additional information about platelet function [18]. Given that hypercoagulability will increase the risk of CVD and TEG can assess the blood coagulation status, we hypothesized that TEG parameters were independent CVD risk factors, and hypercoagulability measured by TEG would be associated with an increased risk of CVD. We aimed to assess the association of TEG with CVD among individuals requiring routine physical examinations.

Material and Methods

Study Design

This study was a single-center retrospective case-control study and was approved with a waiver of informed consent by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20191215).

Individuals requiring routine physical examinations at the physical examination center of Tongji Hospital in Wuhan, China from 2015 to 2019 were included. This is the largest physical examination center in Wuhan. TEG is always used to guide blood transfusion during cardiac surgery (such as percutaneous coronary intervention and coronary artery bypass grafting) and to monitor antiplatelet therapy. The most common indications for antiplatelet medications are cardiovascular and cerebrovascular diseases, atrial fibrillation, and peripheral arterial disease. Participants who were curious about their blood coagulation were also offered the TEG test.

The inclusion criteria were: (1) age >20 years old; (2) having TEG data. The exclusion criteria were: (1) presence of malignancy; (2) liver failure (Child-Pugh score ≥7) or kidney failure (eGFR <60 ml/[min·1.73 m^2]); (3) other heart diseases, including congenital heart disease, rheumatic heart disease, and severe cardiac arrhythmia; (4) currently on anticoagulant therapy (those receiving anticoagulants might have venous thromboembolism or atrial fibrillation and have abnormal coagulation parameters); (5) missing data; and (6) surgery in the last 3 months. Clinical data, including demographic information, results of routine laboratory tests, and TEG test results, were collected by trained doctors.

Cases were participants who had CVD (CHD or ischemic stroke). CHD included coronary artery disease, ischemic heart disease, myocardial infarction, and coronary revascularization. Ischemic stroke was defined as focal neurological deficits lasting ≥24 h and in the absence of signs of cerebral hemorrhage on computed tomography. Controls were participants who had no CVD.

Thromboelastography

Venous blood (3 ml) was collected and analyzed in the TEG 5000 device (Haemonetics® Corporation, Braintree, USA) using kaolin as the coagulation activator. TEG parameters were recorded, including reaction time (R, min), kinetic time (K, min), angle (α, degrees), and maximum amplitude (MA, mm).

Statistical Analysis

Categorical variables were presented as counts (percentage). Continuous variables were presented as means±standard
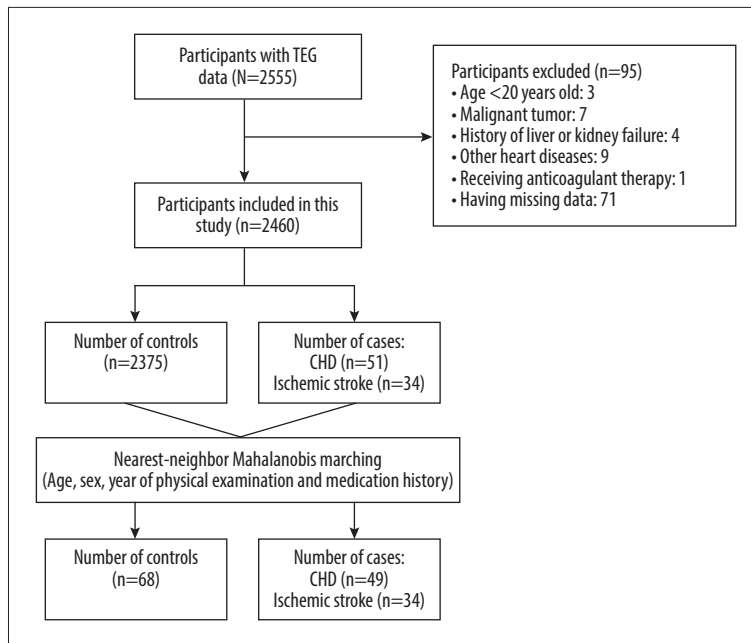
Figure 1. Study flow chart. CHD – coronary heart disease; TEG – thromboelastography. (Microsoft® PowerPoint®, 2016, Microsoft Corporation).

deviation (SD), if normally distributed; otherwise, they were presented as median (interquartile range). Statistical comparisons between case and control groups were performed using the chi-square or the Fisher exact test for categorical variables and using the *t* test or other non-parametric tests (such as Wilcoxon rank-sum test) for continuous variables, as appropriate. Correlations between continuous variables were assessed using Spearman's correlation coefficient. All statistical tests were 2-sided, and a *P* value <0.05 was considered statistically significant.

In observational studies, imbalance in covariates is an inevitable problem and is likely to introduce bias. The nearest-neighbor Mahalanobis matching with replacement, within propensity score calipers of 0.25 was used to control the covariate imbalance between cases and controls [19]. Variables that might affect the outcome of interest and that were unbalanced between cases and controls were chosen as matched factors. These covariates included age, sex, year of physical examination, and medication history (antiplatelet drugs and lipid-lowering drugs).

Four logistic regression models were performed to examine the association between TEG and CVD. Model 1 only included TEG values that were significantly different between cases and controls. Model 2 additionally included matched factors (age, sex, year of physical examination, and medication history), and model 3 additionally adjusted for laboratory indicators (low-density lipoprotein cholesterol [LDL-C] and platelet count). Model 4 included variables with a *P* value <0.10 in univariate analysis.

To investigate whether the association between TEG and CVD were influenced by participants' basic characteristics, we conducted subgroup analyses. Subgroups were defined according to age (<60 years or 60 years or older), sex, medication with an antiplatelet drug, and medication with a lipid-lowering drug.

To evaluate the robustness of our results, several sensitivity analyses were performed based on different matching methods. Firstly, the nearest-neighbor Mahalanobis matching with replacement, within propensity score calipers of 0.20, 0.25, and without a caliper were performed. Secondly, the 1: 1 nearest-neighbor matching, within propensity score calipers of 0.20, 0.25, and without a caliper were performed.

Results

Basic Characteristics and TEG Parameters

The study flow chart is shown in **Figure 1**. Altogether, 2555 participants met the inclusion criteria and 95 participants met the exclusion criteria, leaving 2460 participants enrolled in this study. After matching, we have had 68 controls and 83 cases (49 having CHD and 34 having an ischemic stroke). The basic characteristics of the 3 groups (control group, CHD group, and ischemic stroke group) are summarized in **Table 1**. Data before matching are summarized in **Supplementary Table 1**. Demographic background, routine laboratory data, and platelet parameters of the CHD group and the ischemic stroke group were compared with controls. Patients with CHD had lower LDL-C (*P*=0.02), lower total cholesterol (TC) (*P*<0.01), and lower triglyceride (*P*=0.03).

Table 1. Basic characteristics of study participants.

	Controls (n=68)	CHD (n=49)	Ischemic stroke (n=34)
Age (years)	61.4±9.4	60.5±9.6	63.2±9.8
Male (%)	51 (75.0%)	36 (73.5%)	27 (79.4%)
Current smoker (%)	15 (22.1%)	15 (30.6%)	12 (35.3%)
BMI (kg/m^2)	25.0±3.3	25.6±3.3	25.2±2.5
Medical history			
Diabetes mellitus (%)	18 (26.5%)	8 (16.3%)	11 (32.4%)
Hypertension (%)	46 (67.6%)	32 (65.3%)	21 (61.8%)
Medication history			
Antiplatelet drug (%)	15 (22.1%)	19 (38.8%)	4 (11.8%)
Lipid-lowering drug (%)	26 (38.2%)	25 (51.0%)	11 (32.4%)
Routine laboratory test			
ESR (mm/h)	5.0 (2.0, 7.2)	4.0 (2.0, 7.0)	4.5 (2.0, 10.0)
Hemoglobin (g/L)	150.5 (142.0, 156.2)	148.0 (138.0, 157.0)	147.5 (140.2, 157.5)
WBC count (10^9/L)	5.5 (4.8, 6.3)	6.0 (4.9, 6.7)	5.7 (4.7, 6.9)
HDL-C (mmol/L)	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)	1.2 (1.0, 1.4)
LDL-C (mmol/L)	2.6±0.8	2.3±0.8*	2.9±1.3
Total cholesterol (mmol/L)	4.4±0.9	3.8±0.9*	4.5±1.4
Triglyceride (mmol/L)	1.5 (1.2, 2.2)	1.2 (0.9, 1.7)*	1.4 (1.0, 2.2)
Platelet parameters			
Platelet count (10^9/L)	212.2±54.6	213.2±49.2	207.1±49.7
Mean platelet volume (fL)	11.0±0.9	10.9±0.9	10.8±1.0
Platelet volume distribution width (fL)	13.5±2.1	13.3±2.0	13.2±2.5
Platelet hematocrit (%)	0.2±0.1	0.2±0.0	0.2±0.0

Continuous variables were described as mean±standard deviation or median (interquartile range) and categorical variables were presented as *n* (percentages). BMI – body mass index; CHD – coronary heart disease; ESR – erythrocyte sedimentation rate; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; WBC – white blood cell. * *P*<0.05 compared to the control group.

The TEG results are demonstrated in **Table 2**. In the comparison of TEG parameters, CHD patients had a significantly higher MA (*P*=0.02) than controls. However, other TEG parameters (including R, K, and angle) of patients were not significantly different from controls.

Correlation Between Basic Characteristics and TEG Parameters

Spearman's correlation analysis was performed to assess the association between basic characteristics and TEG parameters. The results of correlation analysis are displayed in **Table 3**. Our results show that both R and K values were positively correlated with hemoglobin (*P*<0.01) but negatively correlated with

age (*P*<0.01). Angle and MA were negatively correlated with hemoglobin (*P*<0.01), but positively correlated with erythrocyte sedimentation rate (ESR) (*P*<0.01). Regarding the platelet parameters, our results show that MA was positively correlated with platelet count (*P*<0.01) and platelet hematocrit (*P*<0.01).

Logistic Regression

Logistic regression analysis was performed to examine the association between MA and CHD. In model 1, MA was positively associated with CHD (OR 1.14, 95% CI 1.04-1.26, *P*<0.01). After adjusting for matched factors (age, sex, year of physical examination, and medication history), the results were similar (MA: OR 1.17, 95% CI 1.04-1.32, *P*<0.01). After additionally adjusting

Table 2. TEG parameters of study participants.

	Controls (n=68)	CHD (n=49)	Ischemic stroke (n=34)
R (min)	5.4 (4.8, 6.4)	5.5 (5.0, 6.6)	5.5 (4.8, 6.0)
K (min)	1.5 (1.2, 1.8)	1.5 (1.2, 1.7)	1.4 (1.2, 1.7)
Angle (degree)	74.0 (71.2, 75.8)	73.1 (71.6, 75.6)	74.2 (72.5, 75.6)
MA (mm)	59.9±4.5	61.8±4.0 *	60.6±4.0

Continuous variables were described as mean±standard deviation or median (interquartile range). CHD – coronary heart disease; K – kinetic time; MA – maximum amplitude; R – reaction time. * $P<0.05$ compared to the control group.

Table 3. The correlation between basic characteristics and TEG parameters.

	R (min)	K (min)	Angle (degree)	MA (mm)
Age (years)	-0.373**	-0.415**	0.426**	0.127
BMI (kg/m^2)	0.108	-0.026	-0.003	0.156
ESR (mm/h)	-0.134	-0.566**	0.511**	0.550**
Hemoglobin (g/L)	0.333**	0.596**	-0.583**	-0.316**
WBC count (10^9/L)	0.107	-0.005	-0.033	0.201
HDL-C (mmol/L)	-0.123	-0.134	0.163	-0.067
LDL-C (mmol/L)	0.019	0.073	-0.070	-0.058
Total cholesterol (mmol/L)	-0.010	0.096	-0.083	-0.084
Triglyceride (mmol/L)	0.060	0.115	-0.108	-0.035
Platelet count (10^9/L)	0.059	-0.181	0.143	0.338**
Mean platelet volume (fL)	0.095	0.124	-0.132	0.129
Platelet volume distribution width (fL)	0.102	0.122	-0.129	0.118
Platelet hematocrit (%)	0.090	-0.165	0.117	0.432**

BMI – body mass index; ESR – erythrocyte sedimentation rate; HDL-C – high-density lipoprotein cholesterol; K – kinetic time; LDL-C – low-density lipoprotein cholesterol; MA – maximum amplitude; R – reaction time; WBC – white blood cell. * $P<0.05$, ** $P<0.01$.

Table 4. Univariate and multivariate logistic regression of CVD.

	Univariate model		Multivariate-adjusted model	
	OR (95% CI)	p value	OR (95% CI)	p value
MA (mm)	1.14 (1.04-1.26)	<0.01	1.11 (1.01-1.24)	0.04
WBC count (10^9/L)	1.34 (1.01-1.81)	0.05	1.26 (0.90-1.79)	0.19
LDL-C (mmol/L)	0.56 (0.33-0.91)	0.02	1.61 (0.37-7.64)	0.54
Total cholesterol (mmol/L)	0.44 (0.27-0.69)	<0.01	0.34 (0.08-1.26)	0.12
Triglyceride (mmol/L)	0.59 (0.36-0.90)	0.02	0.78 (0.39-1.49)	0.45

CI – confidence interval; CVD – cardiovascular diseases; MA – maximum amplitude; OR – odds ratio; WBC – white blood cell.

for LDL-C and platelet count, the positive association between MA and CHD remained (OR 1.19, 95% CI 1.05-1.37, *P*=0.01). The results of model 4 are shown in **Table 4**. After adjusting for other factors (WBC count, LDL-C, TC, and triglyceride), MA was still associated with CHD (OR 1.11, 95% CI 1.01-1.24, *P*=0.04). Logistic regression results for ischemic stroke are shown in **Supplementary Table 2**. No significant association was found between TEG and ischemic stroke.

Subgroup Analyses and Sensitivity Analyses

Subgroup analyses were conducted after stratification for age, sex, medication with an antiplatelet drug, and medication with a lipid-lowering drug. No significant interaction was observed for CHD in any subgroups (*P* value for interaction >0.05; **Supplementary Table 3**). Sensitivity analyses was performed to evaluate the robustness of our results, showing that the association between MA and CHD was been broadly consistent in sensitivity analyses (**Supplementary Table 4**).

Discussion

Our study demonstrates that MA was significantly higher in patients with CHD. Higher MA was associated with increased risk of CHD in different models. Furthermore, the association of MA with CHD remained robust across subgroups and in sensitivity analyses.

Several previous publications showed the good efficacy of TEG parameters in assessing the risk of CVD. For example, Yao et al [15] found that a higher MA level was related to the severity of acute stroke (r=0.205, *P*<0.01). Kreutz et al [20] suggested that a higher plasma fibrin clot strength measured by TEG (MA) accounted for a higher rate of recurrent CVD. Yuan et al [21] showed that compared to controls, the R value increased significantly while the MA value decreased significantly in patients with acute cerebral infarction (*P*<0.05). In agreement with previous studies [22,23], our study suggests that MA was significantly associated with CHD. MA represented the maximal clot strength and revealed the reactivity of platelets, which is critical in the generation of thrombus [24]. Application of proper antiplatelet medication and adjustment of MA value within a normal range might reduce the risk of CHD in people with hypercoagulability. However, the association between other TEG parameters (including R, K, and angle) and CHD appeared to be non-significant. A possible explanation of our contrasting results compared with other studies might be the different study settings. In contrast to most of the studies that included patients in the acute or severe phase of the disease, the current study included patients at the physical examination center who were probably in stable condition. It should be noted that the blood coagulation condition of patients who have experienced or who are experiencing an acute ischemic stroke varied widely [25]. Furthermore, the small sample size and few CVD events in the present study reduce the statistical power.

The present study also evaluated the relationship between TEG parameters and blood composition, including hemoglobin and platelets. A previous study suggested that when hemoglobin decreased, the plasma protein content increased and subsequently lead to an increase in the strength of blood clots [26]. Consistent with these findings, our results showed that both R and K values were positively correlated with hemoglobin, while angle and MA were negatively correlated with hemoglobin. Platelet aggregation is a critical step in the formation of clots [27]. Thus, it is reasonable to find a positive correlation between MA and platelet component (platelet count and platelet hematocrit).

Numerous studies have shown that lipid profile, including LDL-C, TC, and triglyceride, was a major risk factor for CVD. Higher levels of LDL-C may contribute to most clinical CVD events. The Chinese guidelines for the management of dyslipidemia recommend that the desirable level of LDL-C for primary prevention of CVD is <2.6 mmol/L [28]. Although LDL-C is a well-studied traditional risk factor for CVD, patients with normal blood lipid levels can also have CVD. In the current study, a majority of patients with CVD (66.3%) had LDL <2.6 mmol/L and 54.4% of controls had LDL <2.6 mmol/L. In addition, we observed that patients with CHD, even those not taking lipid-lowering medication, had lower LDL-C, TC, and triglyceride levels than controls, which was concordant with the findings described by Sachdeva et al [29]. The reason why people with lower lipid levels still have CVD might be changes in the prevalence of other CVD risk factors, such as smoking, diabetes, and hypertension [30]. Our study suggests that hypercoagulability as described by high MA might be one of the fundamental reasons. In a previous study, researchers also demonstrated in atherosclerosis animal models that platelet aggregation and activation preceded the occurrence of atherosclerosis and might play a dominant role in the development of CVD [31]. Alternatively, stronger platelet reactivity may contribute to the formation of atherosclerosis and eventually lead to CVD. Deeper understanding of biomarkers other than traditional risk factors may prompt development of more rapid and accurate interventions for CVD.

Our study showed that MA was significantly higher in patients with CHD. It is likely that CHD patients have higher platelet reactivity and have an increased risk of thrombosis. If these findings are verified in large-scale studies, the adjustment of MA to a proper level with personalized antiplatelet therapy in individuals with CHD might be able to improve their prognosis and reduce the risk of unfavorable outcomes.

There were some limitations in our study. First, it was a single-center, retrospective study. Second, the number of CVD patients (n=83) included in this study was relatively small. The study population did not include anyone with acute illness. Therefore, the patients in this study might not be representative of other populations. It should be noted that we also enrolled participants taking antiplatelet drugs, which might affect the TEG test, so these findings must be interpreted with caution. Third, a selection bias was possible because of the inclusion criteria (participants who underwent TEG). Fourth, a lack of traditional coagulation analysis, such as fibrinogen level and APTT, was a major limitation of the present study.

Conclusions

The results of the present study suggest that MA is significantly associated with CHD. Stronger platelet reactivity as described by high MA may be associated with the risk of CHD. Further large-scale studies are warranted to investigate the exact role of MA in the measurement of CHD risk.

Ethics Statement

The study was approved with a waiver of informed consent by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20191215).

Supplementary Material

The data of controls, CHD patients, and ischemic stroke patients before propensity score matching and results of logistic regression of MA for ischemic stroke and subgroup and sensitivity analyses are provided in the supplementary material.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Tables

Supplementary Table 1. Basic characteristics and TEG parameters of study participants before matching.

	Controls (n=2375)	CHD (n=51)	Ischemic stroke (n=34)
Age (years)	49.6±10.5	61.5±10.7*	63.2±9.8*
Male (%)	1571 (66.1%)	38 (74.5%)	27 (79.4%)
Current smoker (%)	697 (29.3%)	16 (31.4%)	12 (35.3%)
BMI (kg/m²)	24.5±3.2	25.6±3.2*	25.2±2.5
Medical history			
Diabetes mellitus (%)	194 (8.2%)	10 (19.6%)*	11 (32.4%)*
Hypertension (%)	793 (33.4%)	34 (66.7%)*	21 (61.8%)*
Medication history			
Antiplatelet drug (%)	33 (1.4%)	21 (41.2%)*	4 (11.8%)*
Lipid-lowering drug (%)	105 (4.4%)	27 (52.9%)*	11 (32.4%)*
Routine laboratory test			
ESR (mm/h)	4.0 (2.0, 7.0)	4.0 (2.0, 7.5)	4.5 (2.0, 10.0)
Hemoglobin (g/L)	149.0 (137.0, 158.0)	146.0 (138.0, 156.5)	147.5 (140.2, 157.5)
WBC count (10⁹/L)	5.6 (4.8, 6.5)	5.9 (4.9, 6.6)	5.7 (4.7, 6.9)
HDL-C (mmol/L)	1.2 (1.0, 1.4)	1.1 (1.0, 1.2)*	1.2 (1.0, 1.4)
LDL-C (mmol/L)	2.9±0.8	2.3±0.7*	2.9±1.3
Total cholesterol (mmol/L)	4.6±0.9	3.8±0.9*	4.5±1.4
Triglyceride (mmol/L)	1.3 (0.9, 1.9)	1.2 (0.9, 1.8)	1.4 (1.0, 2.2)

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Supplementary Table 1 continued. Basic characteristics and TEG parameters of study participants before matching.

	Controls (n=2375)	CHD (n=51)	Ischemic stroke (n=34)
Platelet parameters			
Platelet count (10^9/L)	228.3±55.1	213.2±49.4*	207.1±9.7*
Platelet volume (fL)	10.8±1.0	10.8±0.9	10.8±1.0
Platelet volume distribution width (fL)	13.3±2.3	13.3±2.0	13.2±2.5
Platelet hematocrit (%)	0.2±0.1	0.2±0.0*	0.2±0.0*
TEG parameters			
R (min)	5.7 (5.0, 6.3)	5.4 (4.8, 6.6)	5.5 (4.8, 6.0)
K (min)	1.5 (1.2, 1.8)	1.5 (1.2, 1.7)	1.4 (1.2, 1.7)
Angle (degree)	73.5 (71.0, 75.6)	73.1 (71.7, 75.8)	74.2 (72.5, 75.6)
MA (mm)	60.8±4.8	61.6±4.1	60.6±4.0

Continuous variables were described as mean±standard deviation or median (interquartile range) and categorical variables were presented as *n* (percentages). BMI – body mass index; CHD – coronary heart disease; ESR – erythrocyte sedimentation rate; HDL-C – high-density lipoprotein cholesterol; K – kinetic time; LDL-C – low-density lipoprotein cholesterol; MA – maximum amplitude; R – reaction time; WBC – white blood cell. * $p < 0.05$ compared to the control group.

Supplementary Table 2. Logistic regression of MA for ischemic stroke.

	OR (95% CI)	*p* value
Model 1	1.07 (0.97-1.18)	0.18
Model 2	1.10 (0.98-1.26)	0.12
Model 3	1.12 (0.98-1.28)	0.10

CI – confidence interval; MA – maximum amplitude; OR – odds ratio.

Supplementary Table 3. Results of subgroup analyses after stratification for age, sex, medication of antiplatelet drug, and medication of lipid-lowering drug.

Subgroup	No (%) of CHD patients	OR (95% CI)	*p* value for interaction
All parents	49 (41.9%)	1.11 (1.01-1.22)	
Age			0.24
<60	26 (48.1%)	1.17 (1.03-1.34)	
≥60	23 (36.5%)	1.04 (0.91-1.20)	
Sex			0.19
Male	36 (41.3%)	1.17 (1.04-1.32)	
Female	13 (43.3%)	1.01 (0.84-1.22)	
Antiplatelet drug			0.19
Yes	19 (55.9%)	1.28 (1.06-1.62)	
No	30 (36.1%)	1.09 (0.98-1.23)	
Lipid-lowering drug			0.50
Yes	25 (49.0%)	1.08 (0.96-1.24)	
No	24 (36.4%)	1.15 (1.02-1.33)	

CI – confidence interval; CHD – coronary heart disease; OR – odds ratio.

Supplementary Table 4. Results of sensitivity analyses examining association between MA and CHD.

Matching method	Caliper	No (%) of CHD patients	OR (95% CI)	p value
The nearest-neighbor Mahalanobis matching with replacement	0.20	48 (41.4%)	1.13 (1.02-1.26)	0.03
	0.25	49 (41.9%)	1.15 (1.03-1.29)	0.01
	NA	51 (43.2%)	1.15 (1.04-1.30)	0.01
The 1: 1 nearest-neighbor matching	0.20	45 (37.2%)	1.15 (1.03-1.29)	0.01
	0.25	46 (36.8%)	1.14 (1.03-1.28)	0.02
	NA	51 (37.5%)	1.13 (1.02-1.25)	0.02

NA=matching without a caliper. Matched factors included age, sex, the year of physical examination and medication history (antiplatelet drug and lipid-lowering drug). Models were adjusted for age, sex, the year of physical examination. CI – confidence interval; CHD – coronary heart disease; MA – maximum amplitude; OR – odds ratio.

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