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Original Article

Change of tissue factor pathway ratio in Uyghur and Han patients with acute myocardial infarction in Urumqi, Xinjiang of China

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Abstract: To observe changes of tissue factor pathway (TFP) parameters and their ratios in Uyghur and Han ethnic patients with acute myocardial infarction (AMI) in Urumqi, Xinjiang of China. Plasma tissue factor (TF), tissue factor pathway inhibitor (TFPI), activated Factor VII (FVIIa), FVII antigen (FVIIAg) levels were detected by ELISA. FVII coagulant activity (FVII:C) was checked using first-stage coagulation method. TFP parameters were measured in 207 healthy middle- and old-aged people (101 Uygur, 106 Han); TFP parameters of another 90 patients with AMI (31 Uygur, 59 Han) were measured during the same time period and compared with those of the health control group. The results showed that there were significant differences in TF, total-TFPI (t-TFPI), free-TFPI (fl-TFPI), treat-TFPI (tr-TFPI), and the ratios of three TFPI parameters between AMI group and healthy control group were also statistically significant ($P<0.05$, $P<0.01$). FVII:C, FVIIa and the ratio of FVIIa/FVIIAg were significantly higher in AMI group than those in healthy controls ($P<0.05$). In AMI group, tr-TFPI/fl-TFPI and tr-TFPI/t-TFPI ratio in Uyghur patients were significantly lower than those in Han patients ($P<0.05$). In healthy control, tr-TFPI, TF/fl-TFPI and tr-TFPI/t-TFPI ratio of Uyghur group were significantly lower than those in Han healthy ($P<0.05$). In conclusion, except that tr-TFPI in healthy Uyghur was lower than that in healthy Han people, there was no significant difference in the other TFP parameters between the two ethnic healthy groups. Higher levels of TF/tr-TFPI, lower levels of tr-TFPI/fl-TFPI and tr-TFPI/t-TFPI ratio in AMI groups demonstrated the high-coagulation state during the acute stage of AMI. The ratios between the various TFP parameters are more reliable than single parameter in assessing the high-coagulation state and risk factors in cardiovascular thrombotic disease.

Keywords: Uyghur nationality, Han nationality, acute myocardial infarction, tissue factor pathway, ratio

Introduction

The Uyghur ethnic group, with the population of 9,413,796, is mainly distributed in Xinjiang, the northwestern part of China. The Uyghur group in Xinjiang accounts for 99.30% of the total Uyghur population in China and about 46% of the population of Xinjiang Uyghur Autonomous Region. Urumqi is the capital of Xinjiang Uyghur Autonomous Region, situated in the middle section of the Tianshan Mountains and the center of the Asian Continent. This high and cold area, and is mainly populated with Uyghur and Han people. Epidemiology shows that Xinjiang is an area with high incidences of cardiovascular diseases, especially coronary heart disease (CHD) whose incidence and mortality are on the rise yearly [1, 2]. Studies in recent years [3-7] have shown that tissue factor pathway (TFP) is closely associated with acute myocardial infarction (AMI) [3-7]. Knowing that AMI is associated with multiple risk factors includes race, sex and environmental factors. The present study, for the first time, analyzed the changes in various TFP parameters and their ratios in Uyghur and Han patients with AMI, and then compared with those of healthy Uyghur and Han people at the same period. The purpose of this study is to understand whether or not there is any difference in TFP between Uyghur and Han ethnic patients with AMI. Therefore provide the theoretical references for elucidating the role of TFP changes in the development and progression of AMI.

Table 1. Comparisons of general data between Han and Uyghur patients with AMI

Group	Sex (n)		Median age (range)	General data n (%)					Family history n (%)
	M	F		Smoking	Drinking	Hypertension	CHD	Diabetes	CHD
Uyghur	25	6	54.5 (38-80)	58	45.16	61.29	0	32.26	6.13
Han	42	17	60.5 (32-88)	61	52.54	58	0	23.73	23.56**

Compared with Uyghur patients with AMI, **P<0.01.

Table 2. Comparisons of blood biochemistry between Han and Uyghur patients with AMI ($\bar{x}$±s)

Group	N	Lipid and glucose (mmol/L)				
		Cholesterol	TG	HDL-C	LDL-C	Glucose
Uyghur	31	4.65±1.18	1.53±0.84	1.05±0.29	2.87±0.97	6.75±3.0
Han	59	4.13±1.0	1.60±0.86	1.20±0.43	2.26±1.10**	7.50±3.3

Compared with Uyghur patients with AMI, **P<0.01.

Materials and methods

Uyghur and Han patients with AMI in Urumqi Xinjiang

Blood samples were taken from 90 AMI patients who were admitted to the Department of cardiology and emergency center of the affiliated hospital of Xinjiang Medical University between January 2007 and July 2008. Inclusion criteria were patients who (1) were admitted, less than 24 h after onset of AMI (defined as typical chest pain, ST elevation >0.1 mv in at least 2 contiguous leads and creatine kinase MB and troponin T levels of more than twice the upper limits), (2) and without using any anti-coagulants and thrombolytic therapy during the period between onset and admission. Exclusion criteria were 1) AMI patients who had underwent urgent coronary angiography for percutaneous coronary intervention therapy (PCI); 2) patients with old myocardial infarction, re-infarction and post-infarctional angina pectoris; 3) Patients with complicated infections and other inflammatory clues: hematological disease or malignancies, complicated heart failure, severe liver and kidney diseases, recent surgical trauma, and autoimmune diseases. TFP parameters and their ratios are measured from theses blood samples of 90 AMI patients as shown in **Table 1**, the 31 Uyghur AMI patients included 25 males and 6 females with the median age of 54.5 years (range 38-80 years old). The 59 Han AMI patients included 42 males and 17 females with a median age of 60.5 (range 32-88 years old). Characteristics of the Uyghur and Han patients are smoking: 58% and 61%, drinking history 45.16% and 52.54%, hypertension: 61.29% and 58%, family history of coronary heart disease (CHD): 6.13% and 23.56%, diabetes: 32.26% and 23.73%. As shown in **Table 2**, plasma levels of total cholesterol and triglycerides biochemistry were within normal range; high-density lipoprotein (HDL-C): 1.05±0.29 and 1.20±0.43 mmol/l; low-density lipoprotein LDL-C: 2.87±0.97 and 2.26±1.10 mmol/l (P<0.05); glucose was 6.75±3.0 and 7.50±3.3 mmol/l.

Healthy Uyghur and Han people in Urumqi Xinjiang

TFP parameters were measured in 207 people (101 Uyghur and 106 Han) aged ≥45 years old who underwent physical examination in physical examination centers of Urumqi with normal results. Inclusion criteria were permanent residents of Urumqi without histories of cerebrovascular disease, diabetes, renal disease, hypertension, hyperlipidemia, peripheral vascular disease, hematologic disease or tumors. No anti-coagulants and lipid-lowering drugs were used within two weeks before test. There was no blood-relationship between the participants of the study. The 101 healthy Uyghur people included 52 males and 49 females with a median age of 60.6 (range 45~76 years old), in whom three (3.0%) people have the family history of CHD. 6 people (5.94%) are smokers and 5 people (4.95%) have drinking history. The 106 Han people included 55 males and 51 females with a median age of 61.0 (range 45~78 years old), in whom five (4.7%) people have the family history of CHD. 5 people (4.7%) are smokers and 7 people (6.6%) have drinking history. According to the WHO criteria, the overweight and obesity rates in the Han group are 26.4% (30/106) and 8.5% (9/106), while overweight and obesity rates in the Uyghur group are 48.5% (49/101) and 17% (17/101), respectively (P<0.05). Blood biochemistry and

Table 3. Plasma TFAg and TFPI levels in control and AMI groups ($\bar{x}$±s)

Group	N	TFAg (ng/L)	t-TFPI (μg/L)	fl-TFPI (μg/L)	tr-TFPI (μg/L)
Control	207	199.90±99.62	84.0±17.28	31.31±8.10	52.69±17.10
AMI	90	247.45±105.41*	101.03±20.70**	56.65±20.50**	42.38±13.50*

Compared with control groups, *P<0.05, **P<0.01.

glucose were within the normal ranges in both groups. Except that LDL-C in the Uyghur group was slightly higher than that in the Han group (2.59±0.91 vs. 2.15±0.85 mol/l, P<0.05), there was no significant difference in the other parameters between the two groups.

Reagents and instruments

Main reagents and instruments used in this study were TF antigen (TFAg) and FVII antigen (FVIIAg) assay kits (Assaypro, St. Charles, America); Truncated TFPI and FVIIa assay kits (American Diagnostic Inc., America); FVII plasma (Pacific, America); ELX800 enzyme labeling instrument (Bio-Tek instruments Ins, America).

Specimen collection

Sodium citrate (0.109 mol/l) was mixed with venous blood from the subject (1:9) and centrifuged at 3000 r/min within 30 min for 10 min. Blood samples from AMI were collected right after admission before initiation of any treatment, and those from the control group were collected in a fasting state.

Determination of plasma TFP parameters

TFAg and TFPI were measured by ELISA, t-TFPI refers to total TFPI, tr-TFPI was determined as the difference between t-TFPI and fl-TFPI immunoassays. FVII:C was measured by the first-stage coagulation method, and relative activity was calculated according to the standard curve. FVIIa and FVIIAg were measured by ELISA.

Statistical analysis

The results were analyzed by ANOVA and q test. Measurement data of normal distribution are expressed as $\bar{x}$±s, and those of non-normal distribution are expressed as median and quartile. Comparisons were performed by rank-sum test. Comparison of normal distribution data between the healthy Uyghur and Han physical examinees was analyzed by t test. Count data were treated by χ^2 test. Inter-factor correlations were analyzed by correlation analysis (r), P value less than 0.05 was considered statistically significant.

Results

As shown in **Table 3**, Our study showed that TFAg, t-TFPI and fl-TFPI of AMI group were significantly higher compared with control groups, while tr-TFPI was decreased, which suggest that theses AMI patients were in a high-coagulation state, and that acute onset of AMI was related to the initiation of the coagulation process by TFP.

As shown in **Table 4**, the ratio of TFP analysis showed that although TF/t-TFPI in AMI group was higher than that in the normal control, but the difference was not statistically significant. On the other hand, TF/fl-TFPI, tr-TFPI/fl-TFPI and tr-TFPI/t-TFPI were significantly lower in AMI group which was characterized by a significant increase in TF/tr-TFPI and fl-TFPI/t-TFPI.

Our data suggest that in AMI group, FVIIa, FVII:C and ratio of FVIIa/FVIIAg were higher than control (**Table 5**). While circulating levels of TFAg, t-TFPI and fl-TFPI were found to be significantly higher in Uyghur AMI and Han AMI when compared to their control counterparts (**Table 6**). Furthermore, as shown in **Table 7**, the ratios of TF/tr-TFPI and fl-TFPI/t-TFPI were significantly increased in Uyghur AMI and Han AMI when compared to their control counterparts, but TF/fl-TFPI, tr-TFPI/fl-TFPI and tr-TFPI/t-TFPI were lower in AMI group. However, the difference of TF/t-TFPI was not statistically significant between AMI and healthy control groups. Analysis of plasma FVII:C, FVIIa, FVIIAg levels and their ratios showed that FVII:C, FVIIa and FVIIa/FVIIAg were significantly increased in AMI groups than in control of Uyghur and Han, while the differences of FVIIAg, FVIIa/FVII:C and FVII:C/FVIIAg were not statistically significant between AMI and healthy control groups (**Table 8**).

Discussion

The acute coronary thrombosis plays an important role in the mechanism of AMI. Many studies reported that activates of TFP occurs at a critical time in the occurrence and development of thrombotic process. Excessive expression of TF may initiate the thrombotic process contributing to acute clinical consequences of coronary artery disease. TF activity is controlled by tissue factor pathway inhibitor (TFPI), a kunitz-

Table 4. The ratio of plasma TF and TFPI levels in control and AMI groups ($\bar{x}$±s)

Group	N	TF/t-TFPI (%)	TF/fl-TFPI (%)	TF/tr-TFPI (%)	fl-TFPI/t-TFPI	tr-TFPI/fl-TFPI	tr-TFPI/t-TFPI
Control	207	0.24±0.09	0.64±0.24	0.38±0.16	0.37±0.09	1.68±0.49	0.63±0.17
AMI	90	0.25±0.08	0.44±0.18*	0.58±0.22**	0.56±0.22**	0.75±0.26**	0.42±0.16**

Compared with control groups, *P<0.05, **P<0.01.

Table 5. Plasma FVII:C, FVIIa and FVIIAg levels and ratios in control and AMI groups ($\bar{x}$±s)

Group	N	FVII:C (%)	FVIIa (μg/L)	FVIIAg (μg/L)	FVIIa/FVII:C (%)	FVII:C/FVIIAg	FVIIa/FVIIAg (%)
Control	207	106.72±26.62	4.61±1.62	583.41±260.86	4.32±1.30	0.18±0.06	0.79±0.32
AMI	90	122.75±30.10*	5.65±1.80*	494.6±196.0	4.60±1.33	0.25±0.10	1.14±0.41*

Compared with control groups, *P<0.05.

type inhibitor, which in its free form prevents further participation of TF in the coagulation process by forming a stable quaternary complex FXa-TFPI-FVIIa/TF. The balance between TFPI and TF most likely determines the ability of thrombus formation in AMI. Observed by Compo et al., increased TF and FVII levels were identified as independent risk factor and predictors for mortality and occurrence of AMI. FVIIa and FVIIAg are the most intensity factor to measure to identify the initiation of TFP [8].

The goal of this study is to analyze the characteristics changes of TFP parameters and their ratios in the Han and Uyghur patients with AMI in Xinjiang Urumqi. There are experiments [9, 10] demonstrating that TF-FVIIa not only facilitated the occurrence of thrombotic events but altered vascular remodeling via the promoting effect of migration in traumatic atherosclerosis. Many studies [6, 9, 11] also reported that plasma TFAg and TF activities increased markedly during AMI attacks. Moreover, high levels of TF and its specific inhibitor TFPI that are more elevated present in circulating blood of AMI patients. According to the active phase of the disease the higher concentrations of plasma TFAg in AMI, indicates a key role of TF in initiating coagulation reactions in this condition. Moreover, in circulating blood of patients with AMI, high levels of TF can't be sufficiently balanced by the high TFPI levels. Many studies demonstrated that TFPI, the specific inhibitor of TF, had a role in the pathogenesis of ischemic heart disease [12, 13]. The results of the present study are similar to those observations in the literature. Our study showed that t-TFPI and fl-TFPI increased while tr-TFPI decreased during the acute stage of AMI as compared to the normal control. (As shown in **Table 3**: total-TFPI: 101.03±20.70 *vs.* 84.0±17.28; fl-TFPI: 56.65±20.50 *vs.* 31.31±8.10; tr-TFPI: 42.38±13.50 *vs.* 52.69±17.10). TFPI is synthesized primarily in the endothelium which largely binds to, and contributes to its antithrombotic properties. In blood, it bounds predominantly to lipoproteins, where it is ineffective, while being partly bound to thrombocytes and only partly being free. TFPI is mainly produced by endothelial cells and alternative mRNA splicing, it usually generates two forms: TFPIa and TFPIβ. A portion of expressed TFPI remains associated with the cell surface through both direct (TFPIβ) and indirect (TFPIa) glycosylphosphati-dyl-inositol (GPT)-mediated anchorage. Some results demonstrate that TFPIβ is responsible for most of the anti-TF/FVIIa activity at the cell surface [14]. TFPIβ was determined as the difference between the t-TFPI and f-TFPI immunoassays.

In fact tr-TFPI (including TFPIβ) reflects the endothetial cell-associated TFPI which displays a potent anticoagulant activity. Therefore, plasma tr-TFPI level is a major force in the suppression of circulating blood TFP reaction. The TF/tr-TFPI ratio increases as tr-TFPI decrease, which indicates that tr-TFPI had a strong anticoagulation effect via over-exhaustion. It could be concluded that changes in TF/tr-TFPI levels have been related causally to the development of acute coronary thrombotic complications. As illustrated in **Table 4**, t-TFPI, fl-TFPI and tr-TFPI ratio analysis showed that the fl-TFPI/t-TFPI ratio increased, while the tr-TFPI/fl-TFPI ratios particularly decreased in AMI groups as compared to the normal control, suggesting that the tr-TFPI/fl-TFPI ratio is also an important parameter and needs to be paid a particular attention.

Table 6. Plasma TFP parameters between the Han and Uyghur patients within AMI and healthy control groups ($\bar{x}$±s)

Group		N	TFAg (ng/L)	t-TFPI (μg/L)	fl-TFPI (μg/L)	tr-TFPI (μg/L)
Uyghur	Control	101	201.70±99.80	82.70±12.65	34.32±7.45	48.38±13.60★
	AMI	31	246.10±104.38$^{\Delta}$	102.76±20.12$^{\Delta\Delta}$	63.60±19.80$^{\Delta\Delta}$	39.16±13.10$^{\Delta}$
Han	Control	106	198.10±99.45	85.30±21.75	28.30±8.66	57.00±20.18
	AMI	59	248.8±106.45$^{\Delta}$	99.30±21.17$^{\Delta\Delta}$	53.70±21.10$^{\Delta\Delta}$	45.60±13.82$^{\Delta}$

Compared between AMI and healthy control groups, $^{\Delta}P$<0.05, $^{\Delta\Delta}P$<0.01; Comparison with Han healthy control groups, ★P<0.05.

Table 7. The ratio of Plasma TFP parameters between the Han and Uyghur patients within AMI and healthy control groups ($\bar{x}$±s)

Group		N	TF/t-TFPI (%)	TF/fl-TFPI (%)	TF/tr-TFPI (%)	fl-TFPI/t-TFPI	tr-TFPI/fl-TFPI	tr-TFPI/t-TFPI
Uyghur	Control	101	0.25±0.09	0.58±0.210★	0.42±0.16	0.42±0.08	1.40±0.35	0.58±0.13★
	AMI	31	0.24±0.08	0.39±0.16$^{\Delta}$	0.63±0.24$^{\Delta}$	0.63±0.16$^{\Delta\Delta}$	0.62±0.20$^{\Delta\Delta}$	0.38±0.10$^{*,\Delta\Delta}$
Han	Control	106	0.23±0.08	0.70±0.28	0.35±0.15	0.33±0.09	2.01±0.66	0.67±0.20
	AMI	59	0.25±0.08	0.46±0.19$^{\Delta}$	0.55±0.20$^{\Delta\Delta}$	0.54±0.16$^{\Delta\Delta}$	0.85±0.30$^{\Delta\Delta}$	0.46±0.12$^{\Delta\Delta}$

Compared between AMI and healthy control groups, $^{\Delta}P$<0.05, $^{\Delta\Delta}P$<0.01; Comparison with Han AMI patients, $^{*}P$<0.05; Comparison with Han healthy control groups, ★P<0.05.

Table 8. Plasma FVII:C, FVIIa and FVIIAg levels and ratios in Han and Uyghur ethnic group ($\bar{x}$±s)

Group		N	FVII:C (%)	FVIIa (μg/L)	FVIIAg (μg/L)	FVIIa/FVII:C (%)	FVII:C/FVIIAg	FVIIa/FVIIAg (%)
Uyghur	Control	101	109.60±27.30	4.60±1.50	565.20±221.92	4.20±1.21	0.19±0.06	0.81±0.29
	AMI	31	124.50±31.00$^{\Delta}$	5.70±1.90$^{\Delta}$	491.30±191.20	4.58±1.33	0.25±0.08	1.16±0.42$^{\Delta\Delta}$
Han	Control	106	103.84±25.93	4.61±1.75	601.62±299.81	4.40±1.40	0.17±0.06	0.77±0.34
	AMI	59	121.0±29.0$^{\Delta}$	5.60±1.60$^{\Delta}$	497.90±199.80	4.63±1.22	0.24±0.08	1.12±0.63$^{\Delta\Delta}$

Compared between AMI and healthy control groups, $^{\Delta}P$<0.05, $^{\Delta\Delta}P$<0.01.

Whether TFP can be initiated effectively also depends on how much FVII is activated into FVIIa. There are also studies in China reporting that plasma FVII:C did not change significantly while FVIIa increased markedly in AMI [15]. Some other studies reported that only FVIIa and FVII:C increased in AMI patients [16, 17]. Our data suggest that in AMI group, FVIIa, FVII:C and ratio of FVIIa/FVIIAg were higher than control (**Table 5**, P<0.05). The FVIIa increase is more important than FVII:C increase in judging TFP activity. Analysis of these ratios showed that FVIIa/FVIIAg increase is more significant than FVII:C/FVIIAg increase during the onset period of AMI and therefore should warrant special attention. The FVIIa/FVIIAg ratio mainly reflects the degree of FVII activation in vivo, while the FVII:C/FVIIAg ratio mainly indicates the coagulation-promoting potential of FVII in plasma. The result of our study suggests that detection of the ratio is more clinically meaningful than detection of TF, TFPI and FVII alone, and the former also is more reliable than the latter in assessing the high-coagulation state.

Uyghur and Han ethnics have different genetic backgrounds. According to the record of the Uyghur history, both Uyghur and Turk were from the Huns. They have their unique dietary habits and reside permanently in Xinjiang area. The local Han residents are descendants of immigrants from mainland China, and their dietary and living habits are different from those of Uyghur. According to **Tables 6**-**8**, the results of the present study showed that no significant difference in plasma TF, fl-TFPI, t-TFPI and FVII levels between health Uyghur and Han control groups. The normal range of TF, TFPI is consistent with the findings of other researchers [15, 16]. As there are few studies reporting FVIIAg and FVIIa as well as test methods are also different, their reference values need to be corrected by multi-center research in larger samples of healthy subjects.

While circulating levels of tr-TFPI, tr-TFPI/fl-TFPI and tr-TFPI/t-TFPI were found to be significantly lower in Uyghur AMI and Uyghur healthy control subjects when compared to their Han counter-

parts (as shown in the **Table 6**: in AMI groups: tr-TFPI: 39.16±13.10 *vs.* 45.60±13.82, *P*<0.05; tr-TFPI/fl-TFPI: 0.62±0.20 *vs.* 0.85±0.30, *P*< 0.05; tr-TFPI/t-TFPI: 0.38±0.10 *vs.* 0.46±0.12, *P*<0.05). Adama MJ et al. discussed that whether this discrepancy is due to ethnic difference remains unclear at present [18]. Mitchell CT et al. [19] reported that TFPI was related to age, sex, hyperlipidemia, smoking and diabetes but not related to ethnic difference. It was found in the present study that the levels of low-density lipoprotein (LDL) cholestero (2.59±0.91 *vs.* 2.15±0.85 mol/l, *P*<0.05), and tr-TFPI (48.38± 13.60 *vs.* 57.00±20.18, *P*<0.05) in health Uyghur and Han groups differed significantly. Considering that the overweight rate, obesity rate and abdominal girth in Uygru were significantly higher than those in Han, the higher LDL-C level was attributed to the dietary difference. Han residents mainly eat carbohydrates including vegetables and fruits, while Uyghur residents mainly have meats and milk with high protein and fat, and therefore the total calorie that they take is higher than that taken by Han residents. As a result, there are more overweight, belly-type and obese Uyghur residents [20], indicating that overweight and obesity in Uyghur are related to their dietary structure and high-calorie intake other than genetics. Large-amounts of animal fat consumption increases blood lipid levels, especially LDL-C. Low-density lipoprotein (LDL) cholesterol has been known to promote the development of atherosclerotic disease and consequently has been clearly identified as a risk factor for atherosclerosis and cardiovascular disease. LDL is also an important factor contributing to atherosclerosis, hypertension, hyperglycemia and metabolic disturbance, can be a reason why tr-TFPI, tr-TFPI/fl-TFPI and tr-TFPI/t-TFPI in Uyghur were significantly lower than those in Han. The fact that LDL-C was high and tr-TFPI was low in AMI Uyghur patients as compared to the Han patients suggests that the difference in tr-TFPI can also be related to blood lipid levels (especially LDL-C: 2.87±0.97 and 2.26±1.10 mmol/l, *P*<0.05) and blood lipid profiles other than genetic differences between the different ethnic groups.

The potential link between LDL and tr-TFPI in circulating blood in health Uyghur and AMI patients strengthens the close relationship between oxidant stress, lipids and thrombosis and consequently may contribute to understanding the mechanism of the pathogenesis of CAD through ox-LDL and TFPT.

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Disclosure of conflict of interest

None.

Abbreviations

TF, tissue factor; TFP, tissue factor pathway; AMI, acute myocardial infarction; TFPI, tissue factor pathway inhibitor; FVIIa, activated FVII; FVIIAg, FVII antigen; t-TFPI, total-TFPI; fl-TFPI, free-TFPI; tr-TFPI, treat-TFPI; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; CHD, coronary heart disease.

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