RESEARCH ARTICLE

Factor VII and incidence of myocardial infarction in a Japanese population: The Jichi Medical School Cohort Study

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Background: The role of factor VII (FVII) as a risk factor in myocardial infarction (MI) has been the subject of numerous studies. However, it remains uncertain whether the FVII levels are associated with development of MI.

Methods: The subjects were 4142 men and women whose activated FVII (FVIIa) and FVII coagulant (FVIIc) levels were measured in the Jichi Medical School Cohort Study. Subjects were divided into tertiles by FVIIa and FVIIc levels, and Cox's proportional hazard model was used to calculate hazard ratios (HRs) for MI.

Results: The multivariate-adjusted HRs (95% confidential interval [CI]) for FVIIa in men were 0.67 (0.67-1.78) in tertile 2 (T2), and 0.52 (0.17-1.60) in T3. In women, the multivariate-adjusted HRs (95% CI) were 0.18 (0.02-1.60) in T2, and 0.39 (0.07-2.20) in T3. The multivariate-adjusted HRs (95% CI) for FVIIc in men were 0.54 (0.21-1.36) in T2, and 0.20 (0.04-0.91) in T3. In women, the multivariate-adjusted HRs (95% CI) were 0.44 (0.07-2.85) in T2, and 0.35 (0.06-2.22) in T3. We used T1 as a reference for all measures.

Conclusion: Our findings revealed a significant association between low FVIIc level and incidence of MI in men. The FVIIa and FVIIc levels were inversely related to increased MI risk, but did not reach statistical significance. Future studies are needed to confirm this association.

KEYWORDS

factor VII, general population, Japanese, myocardial infarction, prospective study

1 | INTRODUCTION

Factor VII (FVII) plays a key role in the initiation of blood coagulation through the extrinsic pathway.¹ Increased levels of coagulation factors promote increased fibrin turnover and the risk of arterial thrombosis. In particular, circulating FVII with binding of tissue factor (TF) causes plaque disruption which is considered a major cause of thrombosis in myocardial infarction (MI). Therefore, it is considered that FVII levels are predictive of MI.² Moreover, several studies showed that elevated FVII levels are independent predictors of mortality and reinfarction in patients with acute MI.³ New anticoagulant drugs, which show less side effects and a better tolerability, recently are used widely. Therefore, their selected use in patients

with increased levels of coagulation factors, including FVII, may not only improve the clinical outcome after MI but also prevent the onset of MI.⁴

The role of FVII as a risk factor in MI has been the subject of numerous studies. However, several studies have reached different conclusions.²⁻⁹ It remains uncertain whether FVII levels are associated with development of MI.

Several previous studies have shown a positive association between FVII levels, including activated FVII (FVIIa) and FVII coagulant (FVIIc), and MI;^{2,5,10} however, few prospective studies have examined the association, especially in the Asian population. The purpose of the present study was to examine the association between FVIIa and FVIIc levels and the incidence of MI in a Japanese general population.

2 | MATERIALS AND METHODS

2.1 | Study population

The Jichi Medical School (JMS) Cohort Study was conducted to investigate the risk of cardiovascular disease in the Japanese population. Details of the JMS Cohort Study design and some descriptive data have been published previously.^{11,12} The baseline data of this cohort study were obtained between April 1992 and July 1995. The participants were 12 490 Japanese men and women who underwent mass screening programs in 12 communities throughout Japan. At least one JMS alumnus worked as a physician in each community, and played an important role in data collection and collaboration with the local government. Mass screening for cardiovascular disease has been conducted in Japan since 1983 in accordance with the health and medical service law for the aged, and we used this system to collect the data for this study. In each community, a municipal government office sent personal invitations to all the potential participants for the examination by mail or by using public information services. The overall participation rate was 65.4%.

FVIIa and FVIIc were measured once at the baseline between 1992 and 1995 as an optional examination that included 4586 subjects (1807 men and 2779 women).

Individuals with a past history of MI ($n=34$), whose blood samples could not be obtained ($n=26$), who did not respond to questions about past history of MI, stroke, hypertension, hyperlipidemia, diabetes mellitus, alcohol consumption, or smoking habit ($n=252$), who had no follow-up date ($n=63$), and whose data regarding physical findings were incomplete ($n=69$), were excluded from the study. The 4142 subjects (1601 men and 2541 women) that remained were included as study participants.

2.2 | Measurement of baseline variables

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a fully automated sphygmomanometer BP203RV-II (Nippon Colin, Komaki, Japan) placed on the right arm of the seated subject who had rested in the sitting position for 5 minutes before the measurement. Body mass index (BMI) was calculated as weight (kg)/height (m)². Total cholesterol levels were measured using an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation [CV]=1.5%). Triglycerides (TG) were also measured using an enzymatic method (Wako, Osaka, Japan; interassay CV=1.7%). High-density lipoprotein (HDL) cholesterol was measured using the phosphotungstate precipitation method (Wako, Osaka, Japan; interassay CV=1.9%). Blood glucose (BG) was measured using an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV=1.9%). Fibrinogen levels were determined with a one-stage clotting assay kit (Data-Fi, Dade, Miami, Florida, U.S.A.; interassay CV=2.5%). Factor VII activity was measured with a chromogenic assay using a human placenta-derived calcified thromboplastic reagent (Chromoquick, Behringwerke, Marburg, Germany), human factor VII-deficient plasma (Behringwerke, Marburg, Germany), and a chromogenic

assay autoanalyzer (Behringwerke, Marburg, Germany; interassay CV=3.8%).

Information about medical history and lifestyle was obtained using a questionnaire. Hypertension, hyperlipidemia, and diabetes mellitus statuses were classified as currently undergoing treatment or no treatment. Additionally, diabetes mellitus status included fasting BG levels of more than 126 mg/dL. Smoking status was classified as current smoking, former smoking, or never smoking. Drinking status was classified as current drinking, former drinking, or never drinking.

2.3 | Ethical issues

Written informed consent for the study was obtained individually from all respondents of the mass screening. The study design and procedures were approved by each community government and the Ethical Committee of Epidemiologic Research at JMS.

2.4 | Follow-up

Repeat examinations, which are also a part of the national mass screening program, were used to follow-up with most subjects every year. Subjects were asked whether they had a history of stroke or coronary heart diseases after enrolling in the study. Those with such histories were asked the name of the hospital they had visited. Subjects who did not undergo the screening examination were contacted by mail or phone. Medical records were checked if the subjects were hospitalized for any reason. Public health nurses also visited the subjects' home to obtain further information.

If a case of MI was suspected, electrocardiograms were requested for diagnostic confirmation. We collected death certificates to ascertain the cause of death and date of death at the public health center of each community with permission from the Agency of General Affairs and the Ministry of Health, Labor, and Welfare. We were able to ascertain the endpoint of all participants who died between the date of their health examination and the end of 2002. Those who moved out of the communities during the observation period were followed until the date they left, and data on these participants were obtained by each municipal government annually.

2.5 | Diagnostic criteria

The diagnosis of MI was determined independently by the Diagnosis Committee. This included: one radiologist, one neurologist, and two cardiologists. A diagnosis of MI was determined by using the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, which was a multinational collaborative project to monitor coronary events from the mid-1980s to the mid-1990s.

2.6 | Statistical analysis

Values are expressed as the mean (standard deviation), except for TG, BG, FVIIa, and FVIIc. The distributions of TG, BG, FVIIa, and

FVIIc were highly skewed; these data were expressed as the median and interquartile range and transformed into natural logarithms for statistical analysis. Data regarding proportions were expressed as a percentage. Smoking status and drinking status were compared using the χ^2 test. Multiple group comparisons were evaluated using the Kruskal-Wallis test. To investigate the risk of MI associated with FVIIa and FVIIc, we divided the participants into three equal groups according to the tertiles of FVIIa and FVIIc levels for each sex. Cutoffs of tertiles for FVIIa were 2.3 and 3.2 in men, and 2.2 and 3.1 in women. Cutoffs of tertiles for FVIIc were 101.2 and 117.0 in men, and 105.8 and 123.2 in women. Crude incidence rates of MI were calculated per 1000 person-years. We used Cox proportional hazard model to calculate hazard ratios (HRs) and 95% confidential intervals (CIs) for MI with FVIIa and FVIIc tertiles. HRs and 95% CIs were first calculated after adjustment for age, and then for age, BMI, SBP, HDL cholesterol, hypertension, hyperlipidemia, diabetes mellitus, smoking status, and drinking status. The tertile with the lowest risk for MI was defined as the reference category in men and women. A significant difference was defined as $P < .05$. Statistical analysis was performed using SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

During a mean follow-up of 10.8 years (men, 10.7 years; women, 11.0 years), 30 of 4142 participants developed MI (men, 23 cases; women, 7 cases). Mean ages were 54.5 (13.3) years in men, and 54.8 (12.3) years in women.

3.1 | Baseline characteristics

Characteristics of the study population in accordance with tertiles of FVIIa at the baseline are shown in Table 1, and with tertiles of FVIIc at the baseline in Table 2. FVIIa levels were positively associated with current smoking, current alcohol drinking, total cholesterol, HDL cholesterol, TG, and FVIIc in men, and with age, BMI, SBP, DBP, total cholesterol, HDL cholesterol, TG, BG, fibrinogen, and FVIIc in women. FVIIc levels were positively associated with BMI, SBP, DBP, total cholesterol, HDL cholesterol, TG, and FVIIa in men, and with age, BMI, SBP, DBP, total cholesterol, TG, fibrinogen, and FVIIa in women.

3.2 | FVII (FVIIa or FVIIc) and risk of MI

Table 3 shows the crude incidence rates and HRs for MI by tertiles of FVIIa. Crude incidence rates of FVIIa tertiles 1 to 3 (T1-T3) were 1.62, 1.47, and 0.91 per 1000 person-years in men, and 0.43, 0.10, and 0.22 per 1000 person-years in women, respectively. The tertiles with the lowest risk for MI were T3 in men and T2 in women. We defined T1 as the reference category in men and women. In men, HRs for MI were 0.83 (95% CI=0.32-2.16) in T2, and 0.65 (95% CI=0.22-1.94) in T3, using T1 as the reference in age-adjusted analysis. In multivariate-adjusted analysis, HRs for MI were 0.67 (95% CI=0.67-1.78) in T2, and 0.52 (95% CI=0.17-1.60) in T3. In this analysis, HRs in T2 and

T3 were lower than in T1, but not significant. In women, HRs for MI were 0.20 (95% CI=0.02-1.83) in T2, and 0.45 (95% CI=0.08-2.44) in T3, using T1 as a reference in age-adjusted analysis. In multivariate-adjusted analysis, HRs for MI were 0.18 (95% CI=0.02-1.60) in T2, and 0.39 (95% CI=0.07-2.20) in T3. In this analysis, HRs in T2 and T3 were lower than in T1, but not significant.

Table 4 shows the crude incidence rates and HRs for MI by tertiles of FVIIc. Crude incidence rates of FVIIc T1-T3 were 2.49, 1.21, and 0.35 per 1000 person-years in men, and 0.32, 0.21, and 0.22 per 1000 person-years in women, respectively. The tertiles with the lowest risk for MI were T3 in men and T2 in women. We defined T1 as the reference category in men and women. In men, HRs for MI were 0.52 (95% CI=0.21-1.29) in T2, and 0.18 (95% CI=0.04-0.80) in T3, using T1 as the reference in age-adjusted analysis. In multivariate-adjusted analysis, HR in T3 (T3: 0.20 (95% CI=0.04-0.91) was significantly lower than in T1, but not significant in T2 (HR in T2: 0.54 (95% CI=0.21-1.36). In women, HRs for MI were 0.57 (95% CI=0.10-3.39) in T2, and 0.55 (95% CI=0.09-3.29) in T3, using T1 as a reference in age-adjusted analysis. In multivariate-adjusted analysis, HRs for MI were 0.44 (95% CI=0.07-2.85) in T2, and 0.35 (95% CI=0.06-2.22) in T3. In this analysis, HRs in T2 and T3 were lower than in T1, but not significant.

4 | DISCUSSION

We investigated the risk of MI associated with FVIIa and FVIIc levels in a Japanese general population from the Jichi Medical School Cohort Study, a population-based cardiovascular cohort study. We found a significant association between a low FVIIc level and incidence of MI in men. An association between low FVIIa and FVIIc levels and incidence of MI was observed in men and women, but not significant. Indeed, FVIIa and FVIIc levels were inversely related to increased MI risk, with the exception of FVIIa in women.

Elevated FVIIc levels have been reported to be a significant predictor of risk for MI in the Norhtwick Park Heart Study.² Other studies have also identified FVIIc activity as an independent risk factor for MI,⁵⁻⁷ and have shown a positive association between FVIIc levels and MI.¹³ However, several studies have found no association.^{8,9} The previously existing FVIIc assay measures an aggregate of both zymogen FVII and FVIIa levels in plasma.¹⁴ This has led to controversy about whether FVII increases the risk of MI or not. Therefore, FVIIa, FVIIc and other coagulation factors have been examined to expand our understanding of how the clotting cascade is triggered, and to understand clinical correlated FVII levels. Several studies reported that patients at high risk for MI had an increased mean level of total FVII that is not associated with an increase in FVIIa.^{10,15-17} Conversely, several studies found elevated FVIIa in patients with MI when compared with a control group,^{10,18} and FVII elevated in acute MI³ and decreased in the first hours of acute MI.¹⁹ Thus, studies linking FVIIa and FVIIc with MI have been reported, but still remain controversial. The discrepancies in various studies are a consequence of differences in study design, and of the difficulty in measuring FVII zymogen and FVIIa with functional assays. Moreover, an association had not been adequately

TABLE 1 Baseline Characteristics of the study population

		Factor VIIa (ng/mL)			
	All	T1 (<2.3)	T2 (2.3-3.1)	T3 (3.2≤)	P
Men					
Subjects, n	1601	521	560	520	
Age, years	54.5±13.3	54.6±13.9	54.6±13.3	54.3±12.7	.870 ^a
Current smoking, %	51.1	48.0	50.0	55.4	.047 ^b
Current alcohol drinking, %	76.0	71.6	75.7	80.6	.003 ^b
Body mass index, kg/m ²	22.7±2.9	22.9±2.8	22.6±2.7	22.6±3.1	.349 ^a
Systolic blood pressure, mmHg	128.4±20.5	126.4±20.1	129.5±21.6	129.2±19.7	.023 ^a
Diastolic blood pressure, mmHg	77.8±12.5	76.6±12.4	78.6±12.8	78.1±12.1	.010 ^a
Total cholesterol, mg/dL	183.5±33.6	179.8±33.1	184.0±33.3	186.7±34.0	.002 ^a
HDL cholesterol, mg/dL	48.2±13.2	46.1±12.1	47.5±13.1	51.1±13.9	<.001 ^a
Triglycerides, mg/dL	97.0 (69.0-144.0)	93.0 (67.0-133.0)	95.0 (69.0-150.0)	104.0 (72.0-149.3)	.008 ^a
Blood glucose, mg/dL	96.0(88.0-106.0)	96.0 (87.0-106.0)	96.0 (89.0-105.0)	95.0 (88.0-106.0)	.798 ^a
Fibrinogen, mg/dL	242.1±55.2	540.8±54.3	244.4±56.6	241.0±54.4	.565 ^a
Factor VIIa, ng/mL	2.6 (2.0-3.4)	1.8 (1.4-2.0)	2.6 (2.5-2.9)	3.9 (3.5-4.7)	
Factor VIIc, %	109.9 (97.0-122.1)	101.2 (89.4-113.5)	110.0 (99.2-119.8)	117.3 (104.9-129.7)	<.001 ^a
		Factor VIIa (ng/mL)			
	All	T1 (<2.2)	T2 (2.2-3.0)	T3 (3.1≤)	P
Women					
Subjects, n	2541	828	870	843	
Age, years	54.8±12.3	52.7±12.6	55.6±12.3	56.0±11.9	<.001 ^a
Current smoking, %	6.1	6.2	4.7	7.6	.046 ^b
Current alcohol drinking, %	28.7	28.9	27.1	30.0	.412 ^b
Body mass index, kg/m ²	23.0±3.2	22.6±2.9	23.1±3.3	23.3±3.5	.001 ^a
Systolic blood pressure, mmHg	126.0±21.8	122.5±21.2	127.1±21.8	128.3±22.1	<.001 ^a
Diastolic blood pressure, mmHg	75.6±12.8	73.8±12.4	76.0±12.7	76.9±13.1	<.001 ^a
Total cholesterol, mg/dL	194.7±34.8	187.2±34.3	195.6±34.5	201.3±34.1	<.001 ^a
HDL cholesterol, mg/dL	51.7±12.5	50.9±12.0	51.4±12.2	53.0±13.0	.003 ^a
Triglycerides, mg/dL	87.0 (65.0-121.0)	80.0 (59.0-111.0)	89.0 (68.0-120.0)	94.0 (67.0-134.0)	<.001 ^a
Blood glucose, mg/dL	93.0 (87.0-102.0)	92.0 (86.0-99.0)	93.0 (87.0-101.0)	94.0 (88.0-104.0)	<.001 ^a
Fibrinogen, mg/dL	249.8±55.8	242.2±53.3	249.8±55.5	257.1±57.7	<.001 ^a
Factor VIIa, ng/mL	2.6 (2.0-3.3)	1.7 (1.4-2.0)	2.6 (2.3-2.8)	3.8 (3.3-4.5)	
Factor VIIc, %	114.8 (101.0-127.9)	106.0 (94.2-117.6)	115.3 (102.2-126.2)	124.3 (110.2-138.0)	<.001 ^a

T, tertile; HDL, high-density lipoprotein; VIIa, activated VII; VIIc, VII coagulant.

Values represent the mean percentage± standard deviation, except triglycerides, blood glucose, factor VIIa, and factor FVIIc, where median and interquartile ranges are shown.

^aKruskal-Wallis test.

^b χ^2 test (degree of freedom=2).

demonstrated because the majority of studies were not prospective studies, and FVIIa and FVIIc levels are influenced by dietary fat intake and genetic factors.²⁰⁻²⁴

We found a significant association between a low FVIIc level and incidence of MI in men. The relation between the low FVIIa and FVIIc levels and incidence of MI was observed in a Japanese general population. A previous prospective study also found that the association

between low FVIIa and FVIIc levels and incidence of MI in men was significant.^{25,26} Additionally, a further prospective study also found the association between low FVIIc levels and incidence of MI,²⁷ as in the present study. Low FVII levels may be predictive of MI and helpful for risk assessment.

FVIIa and FVIIc levels were inversely related to increased MI risk, except for FVIIa in women. A previous prospective study showed the

TABLE 2 Baseline characteristics of the study population

		Factor VIIc (%)			
	All	T1 (<101.2)	T2 (101.2-116.9)	T3 (117≤)	P
Men					
Subjects, n	1601	534	535	532	
Age, years	54.5±13.3	54.2±14.5	55.4±13.4	53.9±11.8	.074 ^a
Current smoking, %	51.1	52.6	51.8	48.9	.438 ^b
Current alcohol drinking, %	76.0	73.2	76.6	78.0	.170 ^b
Body mass index, kg/m ²	22.7±2.9	22.4±2.7	22.6±2.9	23.1±3.0	<.001 ^a
Systolic blood pressure, mmHg	128.4±20.5	127.1±20.6	127.7±21.4	130.4±19.4	.004 ^a
Diastolic blood pressure, mmHg	77.8±12.5	76.3±12.4	77.7±12.7	79.5±12.1	<.001 ^a
Total cholesterol, mg/dL	183.5±33.6	173.2±30.9	184.1±32.2	193.3±34.6	<.001 ^a
HDL cholesterol, mg/dL	48.2±13.2	47.0±12.8	48.2±13.0	49.4±13.8	.035 ^a
Triglycerides, mg/dL	97.0 (69.0-144.0)	83.0 (63.0-118.8)	96.0 (70.0-146.0)	116.0 (79.8-162.0)	<.001 ^a
Blood glucose, mg/dL	96.0 (88.0-106.0)	95.5 (87.0-107.0)	95.0 (88.0-105.0)	96.0 (89.0-105.0)	.535 ^a
Fibrinogen, mg/dL	242.1±55.2	235.5±51.8	244.4±56.6	242.1±55.2	.002 ^a
Factor VIIa, ng/mL	2.6 (2.0-3.4)	2.3 (1.7-2.9)	2.6 (2.1-3.3)	3.1 (2.5-4.0)	<.001 ^a
Factor VIIc, %	109.9 (97.0-122.1)	91.2 (84.1-97.0)	109.9 (105.7-113.5)	127.7 (122.1-135.6)	
		Factor VIIc (%)			
	All	T1 (<105.8)	T2 (105.8-123.1)	T3 (123.2≤)	P
Women					
Subjects, n	2541	846	845	850	
Age, years	54.8±12.3	51.8±13.3	55.4±12.0	57.2±11.0	<.001 ^a
Current smoking, %	6.1	7.0	5.9	5.5	.440 ^b
Current alcohol drinking, %	28.7	31.3	27.5	27.2	.108 ^b
Body mass index, kg/m ²	23.0±3.2	22.6±3.1	23.0±3.4	23.4±3.2	<.001 ^a
Systolic blood pressure, mmHg	126.0±21.8	122.3±21.4	125.9±21.5	129.8±22.0	<.001 ^a
Diastolic blood pressure, mmHg	75.6±12.8	73.7±12.7	75.4±13.0	77.7±12.3	<.001 ^a
Total cholesterol, mg/dL	194.7±34.8	183.3±33.3	195.1±33.3	205.7±34.1	<.001 ^a
HDL cholesterol, mg/dL	51.7±12.5	51.2±11.9	51.8±12.3	52.2±13.1	.389 ^a
Triglycerides, mg/dL	87.0 (65.0-121.0)	76.5 (58.0-104.0)	88.0 (66.0-123.0)	100.0 (73.0-136.0)	<.001 ^a
Blood glucose, mg/dL	93.0 (87.0-102.0)	92.0 (86.0-101.0)	93.0 (87.0-101.0)	94.0 (87.0-102.0)	.065 ^a
Fibrinogen, mg/dL	249.8±55.8	234.3±50.8	250.3±53.3	264.7±58.9	<.001 ^a
Factor VIIa, ng/mL	2.6 (2.0-3.3)	2.2 (1.7-2.9)	2.5 (1.9-3.2)	3.1 (2.4-4.0)	<.001 ^a
Factor VIIc, %	114.8 (101.0-127.9)	95.6 (88.0-101.0)	114.8 (110.5-118.6)	133.6 (127.7-144.1)	

T, tertile; HDL, high-density lipoprotein; VIIa, activated VII; VIIc, VII coagulant.

Value represent mean±standard division or percentage except triglycerides, blood glucose, factor VIIa, and factor FVIIc, where median and interquartile ranges are shown.

^aKruskal-Wallis test.

^b χ^2 test (degree of freedom=2).

association between low FVIIa and FVIIc levels and incidence of MI,²⁰ but the trend was not reported. This study speculated that this result may be caused by proteolytic activity of inflammatory origin on plasma proteins.²⁵ Atherosclerotic plaques, which cause MI by plaques disruption, are degraded by matrix metalloproteinases and attacked by neutrophil elastase,^{28,29} thereby increasing the likelihood occlusive thrombosis. The proteolytic enzymes also attack clotting factors,³⁰⁻³³

and neutrophil elastase is reported to block the activation of FVII both directly and indirectly.^{30,31} Additionally, atherosclerotic plaques induce a high content of TF bound to FVII, giving a reduction in free circulating FVII.²⁶ The FVII-TF complex plays a role in the migration and proliferation of vascular smooth muscle cells,³⁴ in vascular remodeling, and in plaque neovascularization,³⁵ and thereby in promoting plaque destabilization.³ As increasing risk of MI due to atherosclerotic

TABLE 3 Risk of myocardial infarction and homeostasis model assessment of factor VIIa level

		Factor VIIa (ng/mL)		
	All	T1 (<2.3)	T2 (2.3-3.1)	T3 (3.2≤)
Men				
Number of events	23	9	9	5
Crude incidence rate ^a	1.34	1.62	1.47	0.91
Age-adjusted HR		1.00	0.83 (0.32-2.16)	0.65 (0.22-1.94)
Multivariate-adjusted HR ^b		1.00	0.67 (0.25-1.78)	0.52 (0.17-1.60)
		Factor VIIa (ng/mL)		
	All	T1 (<2.2)	T2 (2.2-3.1)	T3 (3.1≤)
Women				
Number of events	7	4	1	2
Crude incidence rate	0.25	0.43	0.10	0.22
Age-adjusted HR		1.00	0.20 (0.02-1.83)	0.45 (0.08-2.44)
Multivariate-adjusted HR		1.00	0.18 (0.02-1.60)	0.39 (0.07-2.20)

VIIa, activated VII; T, tertile; HR, hazard ratio.

^aPer 1000 person-years of follow-up.

^bAdjusted for age, body mass index, systolic blood pressure, serum high-density lipoprotein (HDL) cholesterol, hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, and alcohol intake categories.

TABLE 4 Risk of myocardial infarction and homeostasis model assessment of factor VIIc level

		Factor VIIc (%)		
		T1 (<101.2)	T2 (101.2-116.9)	T3 (117≤)
Men				
Number of events	23	14	7	2
Crude incidence rate ^a	1.34	2.49	1.21	0.35
Age-adjusted HR		1.00	0.52 (0.21-1.29)	0.18 (0.04-0.80)
Multivariate-adjusted HR ^b		1.00	0.54 (0.21-1.36)	0.20 (0.04-0.91)
		Factor VIIc (%)		
		T1 (<105.8)	T2 (105.8-123.1)	T3 (123.2≤)
Women				
Number of events	7	3	2	2
Crude incidence rate	0.25	0.32	0.21	0.22
Age-adjusted HR		1.00	0.57 (0.10-3.39)	0.55 (0.09-3.29)
Multivariate-adjusted HR		1.00	0.44 (0.07-2.85)	0.35 (0.06-2.22)

VIIc, VII coagulant; T, tertile; HR, hazard ratio.

^aPer 1000 person-years of follow-up.

^bAdjusted for age, body mass index, systolic blood pressure, serum high-density lipoprotein (HDL) cholesterol, hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, and alcohol intake categories.

plaques, FVIIa and FVIIc levels become lower. As a result, FVIIa and FVIIc levels may be relatively low in high MI risk patients. In the present study, there was a gradual trend toward decreased HRs from T2 to T3, especially in men, with T1 serving as the reference. In men, HRs increased inversely with FVIIa and FVIIc. In women, HRs increased inversely with FVIIc. We found that the FVII levels were inversely related to increased MI risk, but not significant. However, the results

of the present study were based on a small number of incidences of MI because the MONICA criteria used here include only definite cases of MI. Further studies including a greater number of subjects and incidence of MI are warranted to confirm this trend.

FVII levels were positively associated with common risk factors, such as current smoking, alcohol drinking, and total cholesterol. However, HDL cholesterol is also positively associated with FVII

levels. FVII activity is influenced by the efficiency of the metabolism of triglyceride-rich lipoproteins.^{36,37} High plasma concentrations of triglyceride-rich lipoproteins increase FVII only in the presence of lipoprotein lipase.³⁸ Therefore, FVII may be associated with lipolytic activity. HDL cholesterol is expected to reflect lipolytic activity, and a previous study found that a positive association between FVII levels and HDL cholesterol,¹⁷ as in the present study.

The strengths of our study are as follows. First, our subjects included both men and women, who were analyzed separately. Second, we adjusted for possible confounding factors, including age, BMI, SBP, HDL cholesterol, smoking habits, alcohol drinking habits, history of hypertension, hyperlipidemia, and diabetes mellitus. Third, the blood samples were analyzed at a single laboratory using the same method of measurement, so we believe that the reliability of the data is high.

There are several limitations of the present study. First, the study subjects were not selected at random because they were selected from a population-based health checkup system. Thus, the data may not be generalizable to other urban populations. Second, single point data collection may have affected the results. We excluded 444 subjects because of inadequate past history or incomplete physical findings and this may have resulted in some selection bias. Third, the results of the present study were based on small number of incidence of MI, especially women. More cases may produce a statistical significant result. Finally, we did not investigate TF levels and gene polymorphisms influencing FVII levels. Several previous studies showed that TF levels interact with FVII in MI generation⁴ and FVII levels are related to genetic determinants.^{22–24} These data are necessary to interpretate our finding clearly. However, we could not investigate further due to the limits of the data.

In conclusion, our data indicated a significant association between a low FVIIc level and incidence of MI in men. The FVIIa and FVIIc levels were inversely related to increased MI risk, but were not significant. Future studies are needed to confirm the association between progress of atherosclerosis and levels of coagulation factors.

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