

Arteriosclerosis, Thrombosis, and Vascular Biology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2002;22:353-358

doi: 10.1161/hq0202.104078

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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Hemostatic Factors as Predictors of Coronary Events and Total Mortality

The FINRISK '92 Hemostasis Study

Veikko Salomaa, Vesa Rasi, Sangita Kulathinal, Elina Vahtera, Matti Jauhiainen,
Christian Ehnholm, Juha Pekkanen

Abstract—The role of hemostatic factors as predictors of coronary heart disease (CHD) and total mortality is poorly understood. Therefore, we carried out a prospective cohort study in Finland. In 1992, a random population sample of 2378 men and women aged 45 to 64 years was investigated and then followed up until December 31, 1998. During the follow-up, 133 CHD events were observed; 73 were among participants free of CHD at baseline. The total number of deaths was 124. After adjustment for traditional risk factors and prevalent CHD at baseline and correction for regression dilution bias, a 1-SD increase in plasminogen was associated with a 1.41-fold (95% CI 1.09 to 1.81) increase in CHD risk. The predictive power of plasminogen depended significantly on the level of total cholesterol being stronger for persons with high cholesterol. A 1-SD increase in fibrinogen was associated with a 1.23-fold (95% CI 1.05 to 1.44) increase in all-cause mortality, but its association with CHD events did not reach statistical significance. Factor VII antigen or coagulant activity or lipoprotein(a) were not independent predictors of CHD risk. These findings support the role of plasminogen as a risk factor for CHD events. (*Arterioscler Thromb Vasc Biol.* 2002;22:353-358.)

Key Words: hemostatic factors ■ coronary heart disease ■ total mortality ■ fibrinogen ■ plasminogen

The central role of thrombosis of a coronary artery in the pathogenesis of coronary heart disease (CHD) is well established.¹ However, the contributions of individual hemostatic factors are less well understood. In most studies, fibrinogen has been associated with an increased risk of CHD,² but the findings regarding factor VII (FVII) have been conflicting. In the first Northwick Park Heart Study, FVII coagulant activity (FVII:c) was positively associated with CHD risk,³ whereas in the second Northwick Park Heart Study, this finding could not be repeated, and the association of activated FVII with the CHD risk was significantly negative.⁴ Also, the role of Lp(a) as a CHD risk factor has been debated. Lp(a) is assumed to impair fibrinolysis and promote thrombosis by inhibiting the binding of plasminogen to fibrin and endothelial cells.⁵ In some studies, Lp(a) has been a predictor of future CHD events or other manifestations of atherosclerotic disease,⁶ but in other studies, no such association has been found.⁷ Lp(a) is structurally similar to plasminogen, which in the recent report of the Atherosclerosis Risk in Communities (ARIC) study was a positive predictor of CHD incidence.⁸

Prospective studies on hemostatic factors are still scarce. Few of them have addressed whether hemostatic factors are useful in predicting total mortality. Because cardiovascular

causes are responsible for almost half of the total mortality in western societies and because hemostatic factors may also be related to causes of death other than cardiovascular disease, it is important to analyze their utility as predictors of total mortality.

The aim of the present prospective cohort study was to determine whether fibrinogen, FVII antigen (FVII:Ag), FVII:c, plasminogen, and Lp(a) are significant predictors of CHD events and total mortality in a Finnish population sample aged 45 to 64 years during a follow-up of almost 7 years.

Methods

The baseline investigation of the FINRISK '92 Hemostasis Study was carried out during January through March 1992. Details have been described earlier.^{9,10} In brief, random samples of men and women aged 45 to 64 years were drawn from the population register for the province of North Karelia in eastern Finland, the city of Turku and an area around the town of Loimaa in southwestern Finland, and the cities of Helsinki and Vantaa in the southern part of the country. The participation rate was 79.6%, and an adequate blood sample was obtained from 2378 people (1133 men and 1245 women). The participants were examined between 11:00 AM and 6:00 PM. They were advised to fast totally at least for 4 hours before the scheduled examination and to avoid fatty meals earlier during the

Received September 24, 2001; revision accepted October 11, 2001.

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day. Eleven participants reported the use of oral anticoagulants at baseline, and their FVII:Ag and FVII:c results have been excluded.

Blood samples were drawn from an antecubital vein of the seated participant by using minimum stasis and a 20-gauge needle. The 2 citrate vacuum tubes (Vacutainer, Becton-Dickinson) used for the coagulation assays were taken as the second and third tubes of the blood sampling. The plasma samples were snap-frozen within 2 hours of venipuncture in a mixture of dry ice and alcohol. They were stored at -70°C until analyzed (within 8 months of sampling).

Persons with CHD at baseline were identified by linking the study data with computerized records of the Finnish Social Security Institute. In Finland, people with CHD get 75% of the cost of their medications reimbursed from the Social Security Institute. To obtain this benefit, a written statement has to be submitted by the subject's physician documenting the clinical and laboratory findings on which the diagnosis is based. These statements are then reviewed by the Social Security Institute's own physicians before the right to the reimbursement is granted. All positive decisions are computerized and can be traced through a social security number unique to each resident of Finland. This record linkage revealed that there were 92 male and 46 female participants receiving reimbursements for CHD medications.

To assess the intraindividual variability of hemostatic factors, the participants in North Karelia were invited for reexamination in 1995.¹¹ Complete reexamination data were obtained from 203 men and 262 women. In the analyses of the present study, these data were used to correct for the regression dilution bias.

The average follow-up time was 79 months (until December 31, 1998). The follow-up was carried out by using record linkage of the study data with the computerized National Causes-of-Death Register and the National Hospital Discharge Register. The reliability of these registers has been documented recently.^{12–14} The Hospital Discharge Register also contains additional codes for revascularization procedures. Deaths with International Classification of Diseases (ICD), 9th Revision (ICD-9) codes 410 through 414 or ICD-10 codes I20 through I25 were taken as CHD deaths, and nonfatal hospitalizations with ICD-9 codes 410 through 411 or ICD-10 codes I21, I22, and I20.0 were taken as nonfatal CHD events. In the analyses, any CHD event (ie, CHD death [$n=30$], nonfatal CHD event [$n=87$], or revascularization [$n=16$]) was used as the primary outcome of the present study. All-cause mortality ($n=124$) was used as an additional outcome. The follow-up was 100% complete regarding all-cause mortality, CHD deaths, and hospitalized nonfatal CHD events. However, the revascularization procedures are not completely covered in the Hospital Discharge Register, but the losses are very small. No attempt was made to record clinically silent myocardial infarctions.

Laboratory Methods

Fibrinogen was measured with an ACL 300R coagulometer from the light scattered by the clot during the prothrombin time assay (IL Test PT-Fibrinogen, Instrumentation Laboratories). A single lot of the IL Test Calibration Plasma from Instrumentation Laboratories was used throughout the present study. The intra-assay coefficient of variation (CV) was 3.6%, and the interassay CV was 2.3%. FVII:c was measured by a 1-stage method using rabbit brain thromboplastin (Thromboplastin-IS, Baxter Dade) and human immunodepleted FVII-deficient plasma (Behring). The assays were carried out with an ACL 300R coagulometer. A lyophilized plasma pool was used as a standard. It was calibrated with a frozen plasma pool from 44 normal donors and taken as 100%. The intra-assay and interassay CVs were 2.4% and 3.9%, respectively. FVII:Ag was measured with an ELISA technique using an Asserachrom FVII:Ag kit (Diagnostica Stago). A frozen plasma pool (as for FVII:c) was used as a standard and was taken as 100%. The intra-assay CV was 5.0%, and the interassay CV was 10.9%. Plasminogen was determined with a Coamate Plasminogen kit (Chromogenix AB). This method is independent of the fibrinogen concentration of the sample at the usual fibrinogen levels. The intra-assay and interassay CVs were 3.2% and 2.9%, respectively. The data did not show any diurnal variation in plasminogen, which is in agreement with other literature.¹⁵

Lp(a) was measured by using an immunoradiometric assay (IRMA, Pharmacia Diagnostics). Total cholesterol and triglycerides were determined by using enzymatic assays (Boehringer-Mannheim, GmbH Diagnostica). HDL cholesterol was determined after precipitation of apoB-containing lipoproteins with dextran sulfate and MgCl_2 .

Statistical Methods

Comparison of the means between participants with and without CHD was performed by using t tests. Logarithmic transformation was used for variables with skewed distributions. Each hemostatic factor was analyzed separately in 3 Cox proportional hazards regression models, and the hazard ratio (HR) and 95% CIs were computed. In the first model (model A), we adjusted for age and sex. The second model (model B) adjusted for total cholesterol, systolic blood pressure, smoking, and diabetes in addition to the first model. The third model (model C) is the same as the second model, but it is corrected for regression dilution bias by using the 1995 reexamination data. Correction for regression dilution bias in the Cox proportional hazards model was performed by using the regression calibration approach of Prentice et al.¹⁶ The reexamination data were used to obtain a variance-covariance matrix of the covariates under the nested random-effects model, and then the true covariates were estimated by using the conditional expectation of the true covariate, given the observed covariate. The standard analysis of the Cox proportional hazards model was carried out by using the estimated covariate values.

We analyzed the data separately for participants with and without CHD at baseline but also carried out analyses of the pooled data adjusting for the baseline CHD status. Additional models were analyzed to test for relevant interactions. The proportional hazards assumption for plasminogen was checked by drawing the survival curves for persons with plasminogen above and below the median. Inspection of the survival curves did not suggest violation of the proportional hazards assumption. Statistical computations were carried out by using SAS.¹⁷

Results

At baseline, there were 138 participants with CHD. Persons with CHD had higher plasma fibrinogen and Lp(a) concentrations (both $P<0.001$) than did those without CHD, but no difference was observed in FVII:c, FVII:Ag, or plasminogen (Table 1). The product moment correlation coefficient between plasminogen and fibrinogen was 0.297.

During the follow-up, 133 CHD events occurred; 73 were among participants free of CHD, and 60 were among participants with CHD at baseline. Among persons free of CHD at baseline, the conventional risk factors differed in an expected manner between those who developed a CHD event during the follow-up and those who remained free of CHD events (Table 2). Of the hemostatic factors, plasminogen ($P=0.06$), fibrinogen ($P=0.06$) and FVII:Ag ($P=0.07$) tended to be higher among persons who had experienced a CHD event than among those who had not experienced an event. Among persons with CHD at baseline, the only significant differences were lower HDL cholesterol, a higher proportion of males, and a higher proportion of diabetics among persons who had an event during the follow-up than among those who did not have an event (Table 2).

Altogether, 124 participants died during the follow-up. Most of the conventional risk factors were higher and HDL cholesterol was lower among persons who died during the follow-up than among those who survived (Table 3). Of the hemostatic factors, fibrinogen was higher among persons who died than among those who survived ($P<0.0001$). When broken down by cause of death, fibrinogen was higher among all those who

TABLE 1. Characteristics (Mean±SD or Proportion) of Participants by Baseline CHD Status

Characteristics	No CHD at Baseline		CHD at Baseline		All Participants		P*
	n	Mean±SD or Proportion	n	Mean±SD or Proportion	n	Mean±SD or Proportion	
Age, y	2240	54.1±6.0	138	58.7±4.2	2378	54.3±6.0	0.0001
Male,† %	2240	46.5	138	66.7	2378	47.7	<0.0001
Total cholesterol, mmol/L	2226	5.97±1.06	138	6.08±1.22	2364	5.97±1.07	0.28
HDL cholesterol, mmol/L	2226	1.40±0.36	138	1.22±0.34	2364	1.39±0.36	<0.0001
Triglycerides,‡ mmol/L	2225	1.40	138	1.73	2363	1.42	<0.0001
Systolic blood pressure, mm Hg	2240	142.1±19.8	138	143.7±20.6	2378	142.2±19.8	0.36
Diastolic blood pressure, mm Hg	2240	85.7±11.2	138	85.1±11.3	2378	85.7±11.2	0.56
Hypertensive,† %	2198	39.0	131	61.1	2329	40.3	<0.0001
Current smokers,† %	2233	22.7	137	26.3	2370	22.9	0.35
Body mass index, kg/m ²	2240	27.3±4.4	138	29.0±4.6	2378	27.4±4.5	<0.0001
Fibrinogen, g/L	2144	3.45±0.78	133	3.84±1.06	2277	3.47±0.81	0.0001
FVII:c, %	2161	126.2±24.9	128	127.9±32.0	2289	126.3±25.4	0.56
FVII:Ag, %	2162	106.5±23.7	126	106.6±27.4	2288	106.5±23.9	0.95
Plasminogen, %	2141	114.1±14.4	129	115.0±14.8	2270	114.2±14.4	0.51
Lp(a),‡ mg/L	2191	117.4	135	164.8	2326	119.7	0.002
Diabetic†	2229	5.1%	137	16.1%	2366	5.7%	0.0005

*P value for the differences between 2 groups.

†Proportion of a particular category is given.

‡Geometric means.

died (4.00 g/L among CHD deaths, n=39; 5.32 g/L among stroke deaths, n=5; 3.65 g/L among cancer deaths, n=41; and 3.76 g/L among other deaths, n=35) than among survivors (3.45 g/L, n=2157).

In Cox proportional hazards regression analysis, plasminogen was a significant predictor of CHD events (Table 4). In the model adjusted for age, sex, and baseline CHD status, the HR (per 1-SD increase) was 1.43 (95% CI 1.20 to 1.70). After

TABLE 2. Characteristics (Mean±SD or Proportion) of Participants Who Had and Who Did Not Have a CHD Event During Follow-Up by Baseline CHD Status

Characteristics	No CHD at Baseline					CHD at Baseline				
	Follow-Up Event +		Follow-Up Event –		P	Follow-Up Event +		Follow-Up Event –		P*
	n	Mean±SD or Proportion	n	Mean±SD or Proportion		n	Mean±SD or Proportion	n	Mean±SD or Proportion	
Age, y	73	57.6±4.9	2167	54.0±6.02	0.0001	60	58.7±4.0	78	58.5±4.7	0.51
Male,† %	73	75.0	2167	45.5	<0.0001	60	78.3	78	57.7	0.008
Total cholesterol, mmol/L	73	6.36±1.23	2153	5.95±1.06	0.0005	60	6.2±1.34	78	6.0±1.12	0.48
HDL cholesterol, mmol/L	73	1.19±0.35	2153	1.40±0.36	0.0001	60	1.11±0.31	78	1.31±0.35	0.001
Triglycerides,‡ mmol/L	73	2.05	2152	1.38	<0.0001	60	1.95	78	1.59	0.03
Systolic blood pressure, mm Hg	73	151.25±19.3	2167	141.8±19.7	0.0001	60	145.2±20.6	78	142.6±20.7	0.48
Diastolic blood pressure, mm Hg	73	88.7±11.9	2167	85.6±11.2	0.03	60	85.4±11.8	78	84.8±11.0	0.74
Hypertensive,† %	70	70.0	2128	38.02	<0.0001	56	62.5	75	60.0	0.77
Current smokers,† %	73	41.1%	2160	22.04%	0.0011	59	32.2%	78	21.8%	0.18
Body mass index, kg/m ²	73	28.7±4.08	2167	27.2±4.4	0.006	60	29.1±4.2	78	30.0±4.9	0.85
Fibrinogen, g/L	72	3.6±0.8	2072	3.44±0.78	0.06	58	4.0±1.2	75	3.7±1.0	0.16
FVII:c, %	71	127.8±23.6	2090	126.2±25.0	0.6	57	131.3±33.2	71	125.2±31.0	0.28
FVII:Ag, %	72	111.3±23.0	2090	106.3±23.6	0.07	56	109.0±29.4	70	104.7±25.7	0.38
Plasminogen, %	71	117.3±14.9	2070	114.0±14.4	0.06	58	117.3±15.7	71	113.1±13.8	0.11
Lp(a),‡ mg/L	67	105.6	2121	117.8	0.4	58	179.3	77	154.7	0.49
Diabetic,† %	72	13.9	2157	4.8	0.027	59	27.1	78	7.7	0.003

*P for the differences between 2 groups.

†Proportion of a particular category is given.

‡Geometric means.

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TABLE 3. Characteristics (Mean±SD or Proportion) of Participants by Survival Status During Follow-Up

Characteristics	Deceased		Survived		<i>P</i> *
	n	Mean±SD or Proportion	n	Mean±SD or Proportion	
Age, y	124	57.7±5.2	2254	54.2±6.0	<0.0001
Male,† %	124	71.0	2254	46.4	<0.0001
Total cholesterol, mmol/L	123	5.99±1.24	2241	5.97±1.06	0.90
HDL cholesterol, mmol/L	123	1.29±0.40	2241	1.39±0.36	0.003
Triglycerides,‡ mmol/L	123	1.65	2240	1.41	0.001
Systolic blood pressure, mm Hg	124	147.8±22.7	2254	141.9±19.6	0.001
Diastolic blood pressure, mm Hg	124	85.7±13.6	2254	85.7±11.1	0.99
Hypertensive,† %	118	53.4	2211	39.6	0.003
Current smokers,† %	123	42.3	2247	21.8	<0.0001
Body mass index, kg/m ²	124	27.8±4.4	2254	27.4±4.5	0.34
Fibrinogen, g/L	120	3.87±1.05	2157	3.45±0.78	<0.0001
FVII:c, %	122	122.9±30.7	2167	126.5±25.0	0.21
FVII:Ag, %	122	104.7±26.9	2166	106.6±23.7	0.45
Plasminogen, %	118	113.4±14.9	2152	114.2±14.4	0.53
Lp(a),‡ mg/L	118	124.5	2208	119.5	0.72
Diabetic,† %	122	16.4	2244	5.1	<0.0001

**P* for the differences between 2 groups.

†Proportion of a particular category is given.

‡Geometric means.

further adjustment for the main conventional CHD risk factors, plasminogen remained significant, and after correction for the regression dilution bias, the HR was 1.41 (95% CI 1.09 to 1.81). Among persons free of CHD at baseline, the HR for plasminogen was 1.41 (95% CI 1.11 to 1.79) when adjusted for age and sex but declined to 1.16 (95% CI 0.81 to 1.66) after adjustment for traditional risk factors and correction for the regression dilution bias. Among persons with CHD at baseline, the adjusted HR for plasminogen was 1.48 (95% CI 1.03 to 2.14).

A positive interaction was observed between plasminogen and total cholesterol (*P*=0.007 among all participants, model B). Among participants with total cholesterol above the median, the HR for plasminogen was 1.55 (95% CI 1.22 to 1.97), and among those with total cholesterol below the median, it was 1.11 (95% CI 0.82 to 1.51).

Among all participants, FVII:Ag and FVII:c were marginally associated with CHD risk in models adjusted for age, sex, and baseline CHD status only (Table 4). After adjustment for conventional risk factors, however, both HRs became nonsignificant. Fibrinogen and Lp(a) were not significant predictors of CHD risk in any of the models.

Fibrinogen was a significant predictor of all-cause mortality (HR 1.23, 95% CI 1.04 to 1.46; Table 5). Neither FVII:c, FVII:Ag, plasminogen, nor Lp(a) was associated with all-cause mortality. However, plasminogen and cholesterol had a similar interaction (*P*=0.008) regarding all-cause mortality than regarding CHD events.

Discussion

The main finding of the present study was the positive association of plasminogen with the risk of CHD events. A similar result was recently reported from the ARIC study.⁸ To

our knowledge, no other prospective studies have been published on plasminogen. Thus, the present study confirms the unexpected finding of the ARIC study. Because plasminogen is a precursor of the main fibrinolytic enzyme, plasmin, one would expect a negative rather than a positive association between plasminogen and the incidence of CHD events. However, plasminogen has several nonfibrinolytic functions, the most important of which are related to inflammation.^{18–20} It has been shown that plasminogen is directly involved in monocyte recruitment during the inflammatory response.²⁰ There is also evidence that interleukin-6 can increase the expression of the plasminogen gene.^{21,22} Thus, it is possible that the increased plasminogen concentration is secondary to the inflammation present in subclinical atherosclerotic lesions. However, plasminogen was not elevated in participants with CHD at baseline compared with those without CHD. Furthermore, the correlation between plasminogen and fibrinogen was not very strong, which is consistent with the lack of correlation between plasminogen and C-reactive protein in the ARIC study.⁸ Together, these observations suggest that mechanisms other than a simple acute-phase response may be involved. The effect of plasminogen on cell migratory processes could be such a mechanism.

The present study extends the earlier findings on plasminogen⁸ by noting that its predictive power for CHD events and all-cause mortality depended positively on total cholesterol level. Although the biological mechanisms underlying this interaction are far from resolved, it is conceivable that plasminogen and cholesterol have a synergistic effect on the risk of a CHD event. Cholesterol (in particular, modified LDL) initiates the atherosclerotic lesion and provokes inflammation, which, in turn, contributes to the rupture of the plaque and to the triggering

TABLE 4. HRs (95% CIs) of CHD Events During the Follow-Up

Hemostatic Factors	Model A*	Model B†	Model C‡
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Participants free of CHD at baseline (n=2240, 73 events)			
Fibrinogen, g/L	1.16 (0.93–1.46)	0.99 (0.77–1.26)	0.95 (0.74–1.22)
FVII:c, %	1.11 (0.87–1.41)	0.98 (0.77–1.26)	0.87 (0.66–1.14)
FVII:Ag, %	1.26 (1.00–1.58)	1.19 (0.93–1.51)	1.16 (0.89–1.51)
Plasminogen, %	1.41 (1.11–1.79)	1.19 (0.92–1.55)	1.16 (0.81–1.66)
Lp(a), mg/L	0.95 (0.75–1.21)	0.93 (0.73–1.18)	Not measured in 1995
Participants with CHD at baseline (n=138, 60 events)			
Fibrinogen, g/L	1.10 (0.91–1.34)	1.15 (0.92–1.43)	1.17 (0.93–1.47)
FVII:c, %	1.21 (0.98–1.51)	1.16 (0.91–1.48)	1.24 (0.93–1.66)
FVII:Ag, %	1.19 (0.95–1.50)	1.16 (0.89–1.52)	1.10 (0.82–1.49)
Plasminogen, %	1.35 (1.04–1.75)	1.36 (1.03–1.80)	1.48 (1.03–2.14)
Lp(a), mg/L	1.06 (0.81–1.40)	0.98 (0.74–1.32)	Not measured in 1995
All participants (n=2378, 133 events)§			
Fibrinogen, g/L	1.12 (0.97–1.30)	1.03 (0.88–1.22)	1.02 (0.86–1.21)
FVII:c, %	1.17 (0.99–1.38)	1.07 (0.90–1.27)	1.01 (0.83–1.23)
FVII:Ag, %	1.23 (1.05–1.44)	1.16 (0.98–1.39)	1.11 (0.92–1.34)
Plasminogen, %	1.43 (1.20–1.70)	1.35 (1.12–1.62)	1.41 (1.09–1.81)
Lp(a), mg/L	1.00 (0.83–1.19)	0.93 (0.77–1.11)	Not measured in 1995

HRs are per 1-SD increase.

*Adjusted for age and sex.

†In addition to model A, further adjusted for total cholesterol, systolic blood pressure, smoking, and diabetes.

‡In addition to model B, corrected for regression dilution bias.

§Models for all participants are adjusted for baseline CHD status also.

of the CHD event. Naturally, this interaction needs to be confirmed in other independent materials.

In the literature, fibrinogen has been fairly consistently associated with CHD risk.² In some studies, however, this has depended on the assay method, so that nephelometric but not clottable fibrinogen has been associated with increased CHD risk.²³ This may in part explain the modest association between fibrinogen and CHD risk in the present study. In cross-sectional analyses of our baseline data, fibrinogen was strongly associated with prevalent CHD. Prospectively, however, the association was modest and did not reach statistical significance in multivariate models. The pattern suggests that at least part of the association between fibrinogen and CHD may be due to the acute-phase reaction, secondary to existing atherosclerosis. In-

terestingly, fibrinogen was a significant predictor of all-cause mortality. This relationship seemed to hold for all main causes of mortality and most probably was due to unspecific acute-phase reaction. Few other studies have addressed all-cause mortality, but the Scottish Heart Health Study and, very recently, a Japanese study have also reported a positive association between fibrinogen and all-cause mortality.^{24,25}

The relation of FVII with CHD is controversial. The Northwick Park Heart Study³ and the Prospective Cardiovascular Münster (PROCAM) study²⁶ reported that FVII:c was a significant predictor of fatal but not nonfatal CHD events. The ARIC Study and the Second Northwick Park Heart Study failed to replicate these findings, and in the latter study, activated FVII was inversely associated with CHD risk.^{4,27} On the other hand, an Italian case-control study reported that FVII:c and FVII:Ag were higher in cases with familial myocardial infarction than in controls.²⁸ Furthermore, polymorphisms of the FVII gene, which were associated with lower levels of FVII:c and FVII:Ag, provided protection from myocardial infarction.²⁸ We have demonstrated earlier that the level of FVII:c⁹ and the prevalence of the Arg353 allele of the FVII gene are high in North Karelia,²⁹ eastern Finland, an area that is notorious for its high CHD mortality and morbidity. In the present study, FVII:c was not associated and FVII:Ag was only marginally associated with CHD risk. However, the small size of the present study did not allow separate analyses for fatal events only. Although we cannot exclude the possibility that FVII may play a role as a risk factor for fatal CHD events or in some genetically defined subgroups, it seems that in the Finnish population as a whole, it is not a strong predictor of CHD events.

TABLE 5. HRs (95% CIs) of Total Mortality (n=124) During the Follow-Up (n=2378)

Hemostatic Factors	Model A*	Model B†	Model C‡
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Fibrinogen, g/L	1.39 (1.19–1.61)	1.24 (1.06–1.46)	1.23 (1.04–1.46)
FVII:c, %	0.88 (0.74–1.05)	0.85 (0.70–1.02)	0.86 (0.70–1.06)
FVII:Ag, %	0.94 (0.78–1.12)	0.92 (0.76–1.12)	0.90 (0.74–1.11)
Plasminogen, %	1.00 (0.83–1.20)	0.94 (0.77–1.13)	1.00 (0.73–1.24)
Lp(a), mg/L	1.04 (0.87–1.25)	1.03 (0.86–1.24)	Not measured in 1995

HRs are per 1-SD increase.

*Adjusted for age, sex, and baseline CHD status.

†In addition to model A, further adjusted for total cholesterol, systolic blood pressure, smoking, and diabetes.

‡In addition to model B, corrected for regression dilution bias.

Another controversial marker of cardiovascular risk is Lp(a). There is quite a lot of biochemical and experimental evidence suggesting that high levels of Lp(a) could be related to high CHD risk.⁵ However, prospective studies have been inconsistent.^{6,7,30} The present study does not support the idea of Lp(a) being a risk factor, although in cross-sectional analyses of the baseline data, Lp(a) was higher among persons with prevalent CHD than among those without CHD. It is likely that this finding results from an acute-phase reaction due to existing atherosclerosis, because the HR of future CHD events was not at all elevated.

The strengths of the present study include its population-based design, high participation rate, and prospective nature with a comprehensive follow-up. Also, the reexamination of part of the study cohort in 1995 gave us a possibility to adjust for the regression dilution bias. An obvious limitation was the study size, which did not allow for the examination of fatal and nonfatal CHD events separately. It should also be noted that a prospective study can establish a time sequence between the elevation of a risk factor and the disease event, but it cannot establish causality. Subclinical atherosclerosis can increase the levels of many hemostatic factors, and it also increases the risk of a future CHD event.

In conclusion, plasminogen was positively and significantly associated with CHD risk. After adjustment for the main traditional risk factors and correction for the regression dilution bias, a 1-SD increase in plasminogen was associated with a 41% increase in CHD risk. A 1-SD increase in fibrinogen was associated with a 23% increase in all-cause mortality, but its association with CHD events did not reach statistical significance. FVII:c, FVII:Ag, and Lp(a) were not independent predictors of CHD risk. These findings support the role of plasminogen in the risk of CHD events. However, the complex links between inflammation and the hemostatic system deserve further study.

Acknowledgments

The FINRISK '92 Hemostasis Study was supported by the Finnish Heart Association (the Fund of February 19th) and the Academy of Finland.

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