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Relation of Coagulation Factor XI with Incident Coronary Heart Disease and Stroke: The Cardiovascular Health Study

D Appiah¹, OE Fashanu¹, Heckbert SR², M Cushman³, BM Psaty⁴, and AR Folsom¹

¹Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN

²Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, USA

³Department of Medicine, University of Vermont, Burlington, VT, USA

⁴Departments of Medicine, Epidemiology and Health Services, University of Washington; Seattle, WA, USA; Group Health Research Institute, Group Health Cooperatives, Seattle, WA, USA

Abstract

OBJECTIVES—The role of coagulation factor XI (FXI) in the etiology of arterial thrombotic events remains uncertain. We examined the association of FXI with incident coronary heart disease (CHD), ischemic stroke (IS), and hemorrhagic stroke (HS).

METHODS—Data were from 3394 adults (mean age: 74.5 years) enrolled in the Cardiovascular Health Study who had FXI antigen from plasma samples drawn in 1992–1993 and were followed for cardiovascular events until June 30, 2013.

RESULTS—Approximately 63% of participants were women and 17% were black. FXI levels were higher in blacks and women, showed positive associations with HDL and total cholesterol, body mass index and diabetes, and negative associations with age and alcohol intake. During median follow-up of 13 years, we identified 1232 incident CHD, 473 IS, and 84 HS events. In multivariable Cox models adjusted for traditional CVD risk factors, the hazard ratio per 1 standard deviation (32.2 mg/dl) increment of FXI was 1.02 (95% CI: 0.96–1.08) for CHD; 0.94 (0.85–1.04) for IS and 0.85 (0.65–1.10) for HS.

CONCLUSIONS—In this prospective cohort of elderly adults, there was no statistically significant association of higher FXI levels with incident CHD and stroke.

Keywords

Factor XI; Coronary Artery Disease; Stroke; Thrombosis; Risk Factors

Corresponding author: Duke Appiah, Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, 1300 South 2nd Street, Suite 300, Minneapolis, Minnesota 55454, USA. Telephone: (612) 626-5458. Fax: (612) 624-0315. dappiah@umn.edu.

Conflict of interest

Psaty BM serves on the DSMB of a trial funded by Zoll LifeCor and is on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson.

INTRODUCTION

Coagulation Factor XI (FXI), a component of the intrinsic pathway of coagulation, displays both procoagulant and antifibrinolytic activities by contributing to the generation of thrombin leading to the formation of fibrin clots as well as protecting fibrin clots from rapid proteolysis. While elevated levels of FXI have been consistently positively associated with venous thromboembolism (VTE) [1–3] in epidemiologic studies, the relation of FXI to ischemic stroke (IS) [4–8], hemorrhagic stroke (HS) [7], myocardial infarction [4, 9–12], or coronary heart disease (CHD) [7, 13, 14] remains uncertain.

Investigations of the association of FXI with arterial thrombotic outcomes among the elderly, a population that bears the highest burden of cardiovascular disease (CVD) related morbidity and mortality [15] are limited. Experimental data indicate that inhibition of FXI reduces venous [16] and arterial [17] thrombosis. Owing to the considerable projected growth of the older population in the US over the next three decades [18], identifying factors that can be targeted for pharmacologic interventions could offer great health benefits.

We tested the hypothesis that FXI concentration is associated positively with the incidence of CHD and IS in the Cardiovascular Health Study (CHS), a prospective study of elderly adults. We also tested the hypothesis that FXI is inversely associated with HS, as FXI deficiency is known to result in a mild-to-moderate bleeding disorder due to reduced thrombin generation and augmented fibrinolysis related to decreased activation of the thrombin activatable fibrinolysis inhibitor [3, 8].

METHODS

The methods and design of CHS have been previously described [19]. Briefly, the CHS is a population-based cohort of 5888 men and women aged ≥ 65 years who were recruited from a random sample of Medicare eligibility residents in four U.S. communities (Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Pittsburgh, PA) beginning in 1989. At each of the 9 annual follow-up clinic visits, standardized protocols were used to collect information on demographics, anthropometrics, lifestyle and behavioral factors, medical history, laboratory parameters, and medication use from participants. FXI antigen concentrations were measured using sandwich ELISA (Ancaster, Ontario, CAN) on fasting citrated plasma collected in 1992–1993 and stored unfrozen at –70°C until analysis in 2014. The analytical coefficient of variation was 9.6%.

Follow-up for clinical events occurred every 6 months and medical records were obtained. Incident CHD and stroke were adjudicated by the CHS Cardiac Events Committee, using standardized criteria [20, 21]. Multivariable Cox proportional hazard models were used to assess the relation of FXI with CHD, IS and HS. The occurrence of a HS before an IS was treated as a censoring event and vice versa. Person-time accrued from 1992–1993 until CHD/stroke, loss-to follow-up, death, or June 30, 2013, whichever came first.

Of the 5265 participants attending the 1992–1993 exams, we excluded those with missing FXI values (n=710), those with prevalent CHD or stroke (n=1139), and those of other races (n=22) due to small numbers, resulting in an analytic sample of 3394 participants.

RESULTS

The mean age of participants was 74.5 years with 63% and 17% being women and black, respectively. FXI levels were higher in blacks and women, showed positive associations with HDL and total cholesterol, body mass index and diabetes, and negative associations with age and alcohol intake (Table 1).

During a median follow-up of 13 years (maximum: 21 years), we identified 1232 incident CHD and 557 stroke (473 IS and 84 HS) events. In multivariable Cox models adjusted for traditional CVD risk factors (Table 2), the hazard ratio (HR) comparing the highest quintile of FXI to the lowest quintile was 1.19 (95%CI: 0.99–1.45) for CHD and 0.86 (0.65–1.15) for IS. The HR for the lowest quintile compared to the highest quintile for HS was 1.36 (0.67–2.75). Likewise, there was no statistically significant association of very high levels (>90th percentile: 154 mg/dL) of FXI with CHD or IS, nor low levels (<10th percentile: 82 mg/dL) of FXI with HS, which were also confirmed by modelling FXI concentrations using restricted cubic splines (data not shown).

DISCUSSION

In this large cohort of older adults, we found no association between FXI concentrations and the incidence of CHD or stroke events. Our findings suggest that in contrast to VTE [1–3], variation in basal concentrations of FXI may not independently influence the rate of arterial thrombotic events in the elderly.

Activated intrinsic coagulation proteins play a role in thrombosis. However, evidence for an association between FXI levels in the general population and incident arterial thrombotic diseases has been inconsistent [4–7, 9–11, 13, 14]. Possible explanations for the discrepant results may include differences in study designs and assay methodologies, small sample sizes, inadequate control of confounding factors, reverse causation, or chance. Prior case-control studies which adjusted for few covariates have consistently observed a positive association between levels of FXI and IS [4–6]. In contrast, reports from prospective studies such as the Atherosclerosis Risk in Communities (ARIC) Study [7] and the present study observed no association between FXI and IS. Case-control studies may be susceptible to survival bias, and they are also prone to reverse causation since FXI levels were measured after the incident IS among cases. Evidence for a link between FXI and HS are very limited. Similar to the findings of the present study, Folsom et al [7] observed no association between concentrations of FXI antigens and HS in the ARIC study. It is possible that limited statistical power due to the small number of HS events in both studies may have influenced the findings. Butenas et al [22] observed higher levels of activated FXI in patients with coronary artery disease than healthy controls. Doggen et al [10] reported 1.8-fold higher odds of MI among participants in the highest quintile of FXI clotting activity compared to those in the lowest quintile. Both studies only made adjustments for age. Results from the ARIC cohort [7] showed a higher HR of 1.4 for CHD among participants in the highest quartile of FXI compared with those in the lowest quartile in age, sex and race-adjusted models. However, additional control for other CHD risk factors eliminated the positive association between FXI and CHD. Consistent with this observation, results from the present

study showed that a positive association in models adjusted for demographic factors was eliminated when other traditional CHD risk factors were considered. These data demonstrate that the positive association of FXI with MI or CHD in some prior studies may reflect inadequate control of confounding factors related to CHD.

Contrasting results for the positive relation of FXI with VTE [1–3] and no relation for CHD [7, 13, 14] or IS [4–7] may reflect the underlying mechanistic differences between arterial and venous thrombosis, despite some shared common risk factors. Venous thrombi are characterized by red blood cells enmeshed in fibrin while arterial thrombi are mainly composed of platelets with little fibrin or red cells [23, 24]. This suggests that activation of intrinsic coagulation factors may play more important roles in the etiology of venous thrombosis than arterial thrombosis as these factors are likely to be removed by the high flow in the arterial system [25].

Potential limitations of this analysis include the use of a single measure of FXI antigen in samples that were stored for almost 20 years. FXI has been reported to be stable in plasma samples frozen for at least 18 months [26]. It is possible that biological and laboratory variation in a single measure of FXI may have masked a true association between FXI and arterial thrombotic events but this seems unlikely since this was not the case in CHS for VTE [1, 2]. The null findings for CHD, IS and HS may be due to inadequate statistical power to detect small effects. However, our study had high power (>0.8) to detect HRs of 1.25 for CHD; 1.43 for IS; and 0.54 for HS, comparing the highest quintile to the lowest quintile of FXI. Even if the study had been adequately powered to detect the small HR observed in the present study for CHD and IS, that HR may be too small to be clinically meaningful.

In conclusion, we found no statistically significant association between FXI concentrations and the incidence of CHD, IS, or HS in this large elderly cohort.

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Table 1
 Characteristics of participants according to quintiles of plasma factor XI concentration, the CHS Study

Characteristics	Factor XI quintiles, mg/dl				
	Q1 (8.0 – 92.4)	Q2 (92.5 – 107.1)	Q3 (107.1 – 120.3)	Q4 (120.3 – 138.9)	Q5 (139.0 – 400.0)
N	678	679	679	679	679
Age (years)	75.6 (5.4)	74.7 (5.3)	74.2 (5.3)	74.2 (4.7)	73.8 (5.1)
Women (%)	43.4	55.7	64.8	69.1	79.1
Race, Black (%)	13.3	16.5	15.3	18.7	18.6
Years of education	14.7 (4.7)	13.9 (4.6)	14.0 (4.8)	14.2 (4.7)	14.0 (4.5)
Current smoker (%)	8.6	8.5	9.7	12.1	11.3
Alcohol intake (g/w)	43.4 (106.5)	33.7 (80.8)	31.2 (80.8)	31.7 (77.4)	30.0 (145.2)
Diabetes (%)	12.8	10.9	12.5	14.3	16.5
Systolic blood pressure (mmHg)	135 (22)	136 (21)	135 (21)	136 (21)	135 (21)
Hypertension meds (%)	37.9	42.1	44.8	42.4	43.2
Body mass index (kg/m ²)	26.3 (4.4)	26.7 (4.6)	26.9 (4.9)	26.9 (4.6)	27.3 (5.2)
Leisure-time physical activity (kcal)	1475 (1753)	1460 (1668)	1514 (1814)	1496 (1743)	1369 (1667)
Total-cholesterol (mmol/l)	5.0 (0.91)	5.3 (0.88)	5.5 (0.93)	5.5 (0.93)	5.8 (0.98)
HDL-cholesterol (mmol/l)	1.3 (0.31)	1.4 (0.39)	1.4 (0.39)	1.4 (0.36)	1.4 (0.36)

Values are mean (standard deviation) for continuous variables and percentages for categorical variables.

Table 2

Incidence rates (95% CI) and hazard ratios (95% CI) of coronary heart disease and strokes in relation to factor XI, the CHS Study, 1992 – 2013.

Stroke	Factor XI quintiles, mg/dL					P _{TREND}	Continuous
	Q1 (8.0–92.4)	Q2 (92.5–107.1)	Q3 (107.1–120.3)	Q4 (120.3–138.9)	Q5 (139.0–400)		Per 1-SD (32.2 mg/dL) increment
CHD							
Events, n	231	272	231	247	251		
Incidence rate [†]	32.3 (28.4–36.7)	37.3 (33.1–42.0)	29.6 (26.0–33.7)	31.7 (28.0–35.9)	33.0 (29.2–37.3)		
Model 1 HR	1 (Referent)	1.27 (1.07–1.52)	1.07 (0.89–1.28)	1.15 (0.96–1.38)	1.27 (1.05–1.53)	0.06	1.04 (0.98–1.10)
Model 2 HR	1 (Referent)	1.23 (1.03–1.48)	1.02 (0.84–1.23)	1.12 (0.93–1.35)	1.19 (0.99–1.45)	0.19	1.02 (0.96–1.08)
Total Stroke							
Events, n	112	125	108	103	109		
Incidence rate [†]	14.6 (12.1–17.6)	15.3 (12.8–18.2)	12.8 (10.6–15.5)	12.1 (10.0–14.7)	12.9 (10.7–15.5)		
Model 1 HR	1 (Referent)	1.07 (0.83–1.38)	0.91 (0.70–1.19)	0.86 (0.65–1.13)	0.94 (0.71–1.24)	0.36	0.95 (0.87–1.04)
Model 2 HR	1 (Referent)	1.08 (0.83–1.40)	0.90 (0.69–1.19)	0.83 (0.62–1.10)	0.86 (0.65–1.15)	0.11	0.93 (0.84–1.02)
Ischemic Stroke							
Events, n	91	106	93	90	93		
Incidence rate [†]	11.8 (9.6–14.6)	12.9 (10.7–15.7)	11.0 (9.0–13.5)	10.6 (8.6–13.0)	11.0 (9.0–13.5)		
Model 1 HR	1 (Referent)	1.13 (0.85–1.50)	0.98 (0.73–1.31)	0.94 (0.70–1.27)	1.01 (0.75–1.37)	0.71	0.97 (0.88–1.08)
Model 2 HR	1 (Referent)	1.13 (0.85–1.51)	0.96 (0.71–1.29)	0.89 (0.65–1.20)	0.90 (0.66–1.23)	0.22	0.94 (0.85–1.04)
Hemorrhagic Stroke							
Events, n	21	19	15	13	16		
Incidence rate [†]	2.7 (1.8–4.2)	2.3 (1.5–3.6)	1.8 (1.1–2.9)	1.5 (0.9–2.6)	1.9 (1.2–3.1)		
Model 1 HR	1 (Referent)	1.24 (0.63–2.43)	0.95 (0.47–1.93)	0.81 (0.39–1.68)	1 (Referent)	0.14	0.82 (0.64–1.06)
Model 2 HR	1 (Referent)	1.16 (0.58–2.32)	0.93 (0.45–1.91)	0.78 (0.37–1.64)	1 (Referent)	0.24	0.85 (0.65–1.10)

Model 1: Hazard ratio (HR) with 95% confidence interval from Cox proportional hazards model adjusted for age (continuous), sex, race and center.

Model 2: Model 1 additionally adjusted for years of education (continuous), smoking status (never, former, current), alcohol intake (continuous), body mass index (continuous), systolic blood pressure (continuous), antihypertensive medication use (yes or no), diabetes status (yes or no), total and HDL cholesterol (continuous).

[†]Unadjusted incidence rate per 1000 person-years with 95% confidence interval.