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Lack of association of plasma factor XI with incident stroke and coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background and Aims—An elevated plasma concentration of intrinsic coagulation factor XI is a risk factor for venous thromboembolism, but its role in the etiology of atherothrombotic outcomes is uncertain. We examined the association of factor XI with incident stroke and coronary heart disease in the prospective Atherosclerosis Risk in Communities (ARIC) Study.

Methods—We measured factor XI on plasma samples collected in 1993–1995 from middle-aged adults (n = 11,439), who were followed through 2012 for incident cardiovascular events.

Results—Over a median of 18 years of follow-up (max = 20 years), 722 participants had incident stroke events (631 ischemic and 91 hemorrhagic) and 1,776 had incident coronary events. Although there were weak positive associations between factor XI and total, ischemic, cardioembolic, and nonlacunar stroke, when adjusted for demographics, further adjustment for other stroke risk factors eliminated the associations. Similarly, there was no independent association of factor XI with incident coronary heart disease events.

Conclusion—A higher basal factor XI concentration in the general population was not a risk marker for stroke or coronary heart disease.

Keywords

Prospective study; Factor XI; Stroke; coronary disease

1. Introduction

Factor XI is a key component of the intrinsic coagulation system. Severe factor XI deficiency leads to abnormal bleeding. Higher levels of plasma factor XI in the general

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Conflict of interest

None.

population are associated with increased risk of venous thromboembolism [1,2], and factor XI inhibition can reduce venous thrombosis [3]. Compared with venous thrombosis, factor XI levels are less clearly associated with atherothrombotic events. A recent review documented that four published studies unanimously supported a positive association between factor XI concentration and the occurrence of ischemic stroke, but only two of five studies found an association for coronary heart disease (CHD) [4]. Included in the review was our small nested case-cohort study in the prospective Atherosclerosis Risk in Communities (ARIC) Study cohort, which involved 89 incident ischemic strokes and 368 incident CHD events over 7 years, compared with a stratified random sample of 418 participants. After adjustment for other risk factors, the hazard ratio of ischemic stroke per one standard deviation higher factor XI was 1.50 (95% CI 1.10, 2.05) [5], but there was no independent association of factor XI with incident CHD [6].

Because our previous ARIC study was small and did not examine ischemic stroke subtypes, and there have been few other prospective studies of factor XI and cardiovascular disease incidence, we expanded our study to factor XI measured on the entire ARIC cohort at visit 3 (in 1993–1995). We hypothesized that there would be positive associations of factor XI with incident ischemic stroke and CHD over 20 years of follow-up of this population-based sample.

2. Methods

2.1. Study population

The ARIC investigators enrolled 15,792 men and women aged 45 to 64 years in the ARIC study cohort in 1987–1989 [7]. ARIC conducted subsequent examinations in 1990–92, 1993–95, 1996–98, and 2011–13, with regular interim telephone contact. This analysis focuses on ARIC visit 3 in 1993–95. The institutional review committees at each study center approved the methods, and participants provided written informed consent.

2.2. Plasma factor XI measurements

ARIC exhausted most baseline citrate plasma samples previously; therefore we measured factor XI concentrations on fasting citrate plasma from ARIC visit 3 in 1993–95, stored unthawed at −70°C until analysis in 2014. The Laboratory for Clinical Biochemistry Research at the University of Vermont assayed factor XI by sandwich ELISA with affinity-purified polyclonal antibodies from Affinity Biologicals (Ancaster, Ontario, CAN). The coefficient of variation for control samples during this study averaged 9.6%. Blind analysis of 74 pairs of ARIC samples split at the time of blood draw and stored until 2014 yielded a coefficient of variation of 10.8% and an intra-class reliability coefficient of 0.81.

2.3. Measurement of risk factors

We analyzed risk factors measured at ARIC visit 3, the visit in which factor XI was measured. Interviewers obtained information on cigarette smoking, medication use, alcohol intake, and education level. ARIC technicians measured seated systolic and diastolic blood pressure three times with a random-zero sphygmomanometer, and we averaged the last two for analysis. We calculated body mass index as weight (kg)/height $(m)^2$. Central laboratories

measured plasma total and HDL-cholesterol by standardized methods. We defined diabetes as a fasting serum glucose ≥126 mg/dL, nonfasting glucose ≥ 200 mg/dL, a self-reported physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. We defined history of stroke, for exclusion, as a baseline self-reported physician-diagnosed stroke or an incident stroke by ARIC criteria between baseline and visit 3. We similarly defined history of coronary heart disease at visit 3 as a myocardial infarction or a coronary revascularization.

2.4. Ascertainment of incident stroke and CHD

For this report, we included stroke and CHD events occurring between ARIC visit 3 in 1993–95 and December 31, 2012. We identified participants' hospitalizations and deaths via annual follow-up calls, review of discharge lists from local hospitals, and searches of State death registries.

To identify strokes, if the list of hospital discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases, Ninth Revision, code 430 to 438), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a neuroimaging report, abstractors recorded signs and symptoms and photocopied neuroimaging and other diagnostic reports [8]. We did not ascertain transient ischemic attacks. We classified hospitalized strokes as definite or probable using a computer algorithm and an expert reviewer [8], according to criteria adapted from the National Survey of Stroke [9]. We further classified strokes into hemorrhagic stroke or ischemic stroke on the basis of neuroimaging studies or autopsies. We subclassified ischemic strokes as cardioembolic when there was either (1) medical record evidence of a possible source of embolus or (2) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain. We also subclassified definite ischemic strokes as either nonlacunar or lacunar, on the basis of the recorded neuroimaging results, with lacunar requiring: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤2 cm or unstated size.

To identify CHD events, if the hospital discharge codes included one of a broad set of codes possibly harboring CHD, ARIC abstractors recorded the patient's signs and symptoms, cardiac biomarkers, and procedures, and copied the electrocardiograms, which were then centrally coded. Likewise, if the underlying cause of death for an out-of-hospital death potentially harbored CHD, ARIC staff solicited informant interviews, coroner reports, and physician questionnaires, to obtain the patient's medical history and circumstances of death. ARIC used a standardized algorithm to classify definite or probable myocardial infarctions and definite fatal CHD, which we combined for the analysis of CHD [10].

2.5. Statistical analysis

Of the 12,887 ARIC participants who attended visit 3, we excluded those without factor XI measurement (n = 313), those with coronary heart disease or stroke prior to factor XI assessment (n = 1,063), and those who were not white or African American (n = 72). This left a maximum of 11,439 participants for the present analyses of incident stroke or CHD,

analyzed separately. We computed time at risk from the date of factor XI measurement to the earliest of the following: date of hospital admission for stroke (or CHD) event, date of death, date of last follow-up contact, or end of follow-up. We performed stroke analyses for total, hemorrhagic and ischemic strokes and then for ischemic subtypes (lacunar, nonlacunar, cardioembolic). We treated the occurrence of a hemorrhagic stroke before an ischemic stroke as a censoring event and vice versa. We used version 9.3 of SAS (SAS Institute, Cary, NC) for analyses.

We analyzed factor XI as quintiles or as a continuous variable. We first described, participants' characteristics by factor XI quintile. Our main hypothesis was that factor XI concentration would be associated positively with incidences of ischemic stroke and CHD. We plotted Kaplan-Meier curves and used Poisson regression to compute incidence rates. We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals of incident events. We performed a test for trend in event occurrence across factor XI quintiles in the Cox models using the quintile median factor XI values to represent each quintile. We verified that the proportional hazards assumption of the Cox models held for factor XI by testing a log time by factor XI interaction term. Because there was no evidence of multiplicative interactions of factor XI with race or sex ($p>0.05$), we pooled these subgroups. For stroke and CHD incidence, Model 1 adjusted for age (continuous), sex, race and ARIC field center; Model 2 additionally for systolic blood pressure (continuous), antihypertensive medication use (yes or no), diabetes status (yes or no), total and HDL cholesterol (continuous), body mass index (continuous), smoking status (never, former, current), alcohol intake (continuous), and education level (< high school, high school, > high school).

3. Results

Among the 11,439 participants free of stroke and CHD at ARIC visit 3, plasma factor XI was higher in women than men, in African Americans than whites, and associated positively with most risk factors, other than age, smoking, and HDL cholesterol [Table 1]. Over a median of 18 years of follow-up (max = 20 years), 722 participants had incident stroke events (631 ischemic and 91 hemorrhagic) and 1,776 had incident CHD events.

In Model 1 adjusted for demographic variables, there was a weak positive association between factor XI concentration and total, ischemic, cardioembolic, and nonlacunar stroke [Table 2]. However, the Model 1 analysis of factor XI by quintiles did not consistently demonstrate a step-wise increase in stroke incidence for successive quintiles. Further adjustment for other cardiovascular risk factors in Model 2 essentially eliminated the associations of factor XI with total stroke and stroke subtypes. Likewise, upon stratification by length of follow-up, there was no association of factor XI with stroke (data not shown) occurring either <10 years versus ≥ 10 years after factor XI assessment (data not shown).

Similarly, there was no independent association of factor XI concentration with incident CHD [Table 3]. Adjustment for traditional cardiovascular risk factors in Model 2 explained entirely the Model 1 association.

4. Discussion

Procoagulative states, including elevated factor XI concentrations, increase the risk for venous thrombosis, but whether higher plasma factor XI is a risk factor for atherothrombotic events remains uncertain. This population-based prospective study found no material independent association between basal concentrations of plasma factor XI and incidences of ischemic stroke or CHD over approximately 20 years of follow-up. The lack of association of factor XI with CHD confirms the findings of our previous small nested case-control study [6] and most other epidemiologic studies for CHD [4]. However, our findings contradict our previous nested case-control study of stroke [5], as well as three other studies suggesting that higher factor XI is an independent risk factor for ischemic stroke [4].

Our previous ARIC study included only 89 incident ischemic stroke events occurring from 1987 through 1998 and observed a statistically significant 50 percent higher multivariable-adjusted ischemic stroke risk per standard deviation greater factor XI level [5]. In contrast, when analyzed by factor XI quartiles, the trend in multivariable-adjusted stroke incidence across quartiles was not statistically significant [5], suggesting the association we reported was weak and possibly a chance finding. Our current ARIC longitudinal analysis showing no association between factor XI and stroke included seven times as many ischemic stroke events from 1996 through 2012, and had the advantage of not requiring sampling of controls, which by chance might not have been representative in the previous report [5]. The analysis of different lengths of follow-up – 10 years for the first study compared with 20 years for the current study – seemingly does not explain our discordant findings, because factor XI was now not associated with ischemic stroke when follow-up was limited to <10 years. The lack of violation of the proportional hazards assumption further confirms that the absence of a factor XI association with stroke did not vary by time. Different laboratories measured factor XI antigen for the two ARIC reports, and they used different assay methods (coagulation assay versus ELISA) and frozen sample storage times. Yet, it seems unlikely that the contrasting ARIC findings for stroke were due to laboratory differences, because both methods yielded positive associations between factor XI and another endpoint – venous thromboembolism [2, and unpublished findings].

The three other studies of factor XI and ischemic stroke suggested strong positive associations [11–14] but have weaknesses. Two failed to adjust for other cardiovascular risk factors [11,14], which we showed is crucial. Yang et al studied 78 stroke or TIA patients younger than age 55 referred for evaluation for a hypercoagulable state, compared with 40 healthy age and sex-matched subjects [11]. This small study may be subject to bias because of the way that stroke/TIA patients were referred and controls were not and the failure to adjust for major stroke risk factors. A Dutch population-based study included women aged 18 to 50 years with ischemic stroke and randomly dialed controls, with blood collected from cases a median of 8 years after stroke [12,13]. Although this study controlled for confounding variables, it could not determine whether factor XI elevation preceded stroke and could generalize to only young women. An Israeli study investigated patients who had been referred for bleeding tendencies and found to have very low factor XI levels [14]. These patients self-reported whether they had a history of stroke or risk factors, and the investigators compared the observed prevalence of ischemic stroke to expected based on the

age-matched incidence rate for Israel. The comparison population not only had a higher stroke rate than the patients with low factor XI, but it also had more stroke risk factors, suggesting confounding. In addition, the study may suffer from selection bias related to the factor XI deficient patients having to have both survived their stroke and be referred for a bleeding evaluation. All in all, the evidence that elevated factor XI is a risk factor for ischemic stroke is weak, and our well designed prospective study does not support an association.

Our study was large, included a biracial sample, measured factor XI prior to stroke and CHD onset, validated its events, examined stroke subtypes, and controlled for multiple confounding variables. Limitations include, firstly, having a single measure of factor XI over a long follow-up. This prevented us from examining change in factor XI or determining whether factor XI concentration just before stroke occurrence is etiologically important. Furthermore, a single factor XI measure may have enough biological or laboratory variable to obscure true associations between factor XI and cardiovascular endpoints. However, this was not the case for venous thromboembolism in ARIC [2]. Secondly, although we validated cardiovascular endpoints based on obstructed medical records, we did not directly examine the stroke patients. Thirdly, due to often incomplete imaging data, we could not readily separate our nonlacunar ischemic stroke group into large vessel disease versus other ischemic and cryptogenic strokes. Finally, for a study finding no association, adequate statistical power is a concern. A power analysis indicated that we had high power (>80%) to detect a Model 1 hazard ratio of 1.39 for the highest factor XI quintile versus lowest quintile for total stroke. Thus, although we could not detect small, possibly clinically irrelevant, hazards ratios, we were able to detect a 39% increase in risk for contrasting quintiles.

In conclusion, a higher basal factor XI concentration in the general population was not a risk marker for stroke or CHD.

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Highlights

- Whether coagulation factor XI may be a cardiovascular risk marker.
- We assayed factor XI in a cohort of middle aged adults.
- We followed them for cardiovascular events over a median of 18 years.
- Factor XI was not a risk marker for stroke or coronary heart disease.

Table 1

Characteristics of participants according to quintiles of plasma factor XI concentration, the ARIC Study, 1993–1995.

	Factor XI quintiles (mg/dL)				
Characteristics	**Q1 (8.0–92.7)**	**Q2 (92.7–105.1)**	**Q3 (105.1–116.8)**	**Q4 (116.8–131.9)**	**Q5 (131.9–400.0)**
N	2,287	2,288	2,288	2,288	2,288
Age (years)	60.2 (5.9)	59.7 (5.7)	59.7 (5.7)	59.7 (5.6)	59.8 (5.6)
Women (%)	41.7	51.2	57.7	65.3	74.3
Race, African American (%)	21.3	21.3	22.3	23.9	27.3
Education <high school (%)	17.9	19.3	18.2	20.4	22.0
Current smoker (%)	17.2	17.3	17.6	18.4	17.4
Alcohol intake (g/w)	51 (132)	49 (135)	38 (102)	33 (79)	33 (94)
Diabetes (%)	9.5	10.8	12.3	15.4	23.3
Systolic blood pressure (mm Hg)	124 (19)	124 (19)	124 (18)	125 (19)	126 (20)
Hypertension meds (%)	30.9	32.5	32.3	35.0	42.6
Body mass index (kg/m^2)	27.6 (5.2)	27.9 (5.1)	28.6 (5.9)	28.7 (5.6)	29.6 (5.9)
Sports index	2.6 (0.8)	2.6 (0.8)	2.5 (0.8)	2.5 (0.8)	2.5 (0.8)
Total-cholesterol (mg/dl)	195 (36)	203 (35)	209 (36)	213 (36)	219 (40)
HDL-cholesterol (mg/dl)	52.2 (19.0)	52.8 (18.6)	53.1 (18.2)	53.3 (17.8)	53.5 (17.6)

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 stroke subtypes in relation to factor XI, the ARIC Study 1993–2012.

	Factor XI Quintiles, mg/dL						Continuous
Stroke subtype	**Q1 (8.0–92.7)**	**Q2 (92.7–105.1)**	**Q3 (105.1–116.8)**	**Q4 (116.8–131.9)**	**Q5 (131.9–400.0)**	**P TREND**	**Per 1-SD* increment**
Total stroke							
Events, n	134	150	125	157	156		
Incidence rate†	3.7 (3.1, 4.4)	4.1 (3.5, 4.8)	3.4 (2.9, 4.1)	4.3 (3.7, 5.0)	4.3 (3.7, 5.0)		
Model 1 HR	1 (Referent)	1.2 (0.9, 1.5)	1.0 (0.8, 1.3)	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	0.05	1.09 (1.01, 1.17)
Model 2 HR	1 (Referent)	1.1 (0.9, 1.5)	1.0 (0.7, 1.2)	1.2 (0.9, 1.5)	1.0 (0.8, 1.2)	0.84	1.00 (0.93, 1.08)
Hemorrhagic stroke							
Events, n	15	22	19	17	18		
Incidence rate†	0.4 (0.2, 0.7)	0.6 (0.4, 0.9)	0.5 (0.3, 0.8)	0.5 (0.3, 0.7)	0.5 (0.3, 0.8)		
Model 1 HR	1 (Referent)	1.4 (0.7, 2.8)	1.2 (0.6, 2.4)	1.1 (0.5, 2.2)	1.1 (0.5, 2.2)	0.84	1.02 (0.83, 1.26)
Model 2 HR	1 (Referent)	1.7 (0.8, 3.3)	1.5 (0.7, 3.0)	1.3 (0.6, 2.7)	1.3 (0.6, 2.7)	0.89	1.07 (0.87, 1.31)
Ischemic stroke							
Events, n	119	128	106	140	138		
Incidence rate†	3.3 (2.8, 3.9)	3.5 (2.9, 4.1)	2.9 (2.4, 3.5)	3.8 (3.2, 4.5)	3.8 (3.2, 4.5)		
Model 1 HR	1 (Referent)	1.1 (0.9, 1.4)	1.0 (0.7, 1.2)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	0.03	1.10 (1.02, 1.18)
Model 2 HR	1 (Referent)	1.1 (0.8, 1.4)	0.9 (0.7, 1.2)	1.1 (0.9, 1.5)	0.9 (0.7, 1.2)	0.78	0.99 (0.92, 1.08)
Cardioembolic							
Events, n	27	37	29	46	37		
Incidence rate†	0.7 (0.5, 1.1)	1.0 (0.7, 1.4)	0.8 (0.5, 1.1)	1.3 (0.9, 1.7)	1.0 (0.7, 1.4)		
Model 1 HR	1 (Referent)	1.4 (0.9, 2.4)	1.2 (0.7, 2.0)	1.9 (1.2, 3.1)	1.5 (0.9, 2.5)	0.05	1.21 (1.07, 1.37)
Model 2 HR	1 (Referent)	1.5 (0.9, 2.4)	1.1 (0.6, 1.8)	1.8 (1.1, 2.9)	1.1 (0.7, 1.9)	0.47	1.11 (0.96, 1.29)
Lacunar							
Events, n	31	17	35	31	28		
Incidence rate†	0.9 (0.6, 1.2)	0.5 (0.3, 0.7)	1.0 (0.7, 1.3)	0.8 (0.6, 1.2)	0.8 (0.5, 1.1)		
Model 1 HR	1 (Referent)	0.6 (0.3, 1.0)	1.2 (0.7, 1.9)	1.0 (0.6, 1.7)	0.9 (0.5, 1.5)	0.62	1.01 (0.86, 1.19)
Model 2 HR	1 (Referent)	0.5 (0.3, 0.9)	1.0 (0.6, 1.7)	0.8 (0.5, 1.4)	0.6 (0.3, 1.0)	0.25	0.87 (0.73, 1.04)

Stroke subtype	Factor XI Quintiles, mg/dL						Continuous
	Q1 (8.0–92.7)	Q2 (92.7–105.1)	Q3 (105.1–116.8)	Q4 (116.8–131.9)	Q5 (131.9–400.0)	P TREND	Per 1-SD* increment
Nonlacunar							
Events, n	61	74	42	63	73		
Incidence rate†	1.7 (1.3, 2.2)	2.0 (1.6, 2.5)	1.1 (0.8, 1.5)	1.7 (1.3, 2.2)	2.0 (1.6, 2.5)		
Model 1 HR	1 (Referent)	1.3 (0.9, 1.8)	0.8 (0.5, 1.1)	1.2 (0.8, 1.7)	1.4 (1.0, 2.0)	0.18	1.07 (0.96, 1.20)
Model 2 HR	1 (Referent)	1.2 (0.9, 1.8)	0.7 (0.5, 1.1)	1.0 (0.7, 1.5)	1.1 (0.7, 1.5)	0.91	0.99 (0.88, 1.11)

Model 1: Hazard ratio (HR) with 95% confidence interval from Cox proportional hazards model adjusted for age (continuous), sex, and race–field center.
Model 2: Model 1 additionally adjusted for education level (< high school, high school, > high school), 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).

*1 standard deviation (SD) = 26.5 mg/dL.

†Unadjusted incidence rate per 1,000 person-years with 95% confidence interval.

Table 3

Incidence rates (95% CI) and hazard ratios (95% CI) of coronary heart disease in relation to factor XI, the ARIC study 1993–2012.

	Factor XI quintiles, mg/dL						Continuous
	Q1 (8.0–92.7)	**Q2 (92.7–105.1)**	**Q3 (105.1–116.8)**	**Q4 (116.8–131.9)**	**Q5 (131.9–400.0)**	**P TREND**	**Per 1−SD increment***
CHD							
Events, n	370	334	329	364	379		
Incidence rate†	10.8 (9.8, 12.0)	9.5 (8.6, 10.6)	9.4 (8.4, 10.4)	10.4 (9.4, 11.6)	10.9 (9.9, 12.1)		
Model 1 HR	1 (Referent)	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)	1.2 (1.1, 1.4)	1.4 (1.2, 1.6)	<0.0001	1.15 (1.10, 1.20)
Model 2 HR	1 (Referent)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)	0.98	1.01 (0.96, 1.06)

Model 1: Hazard ratio (HR) with 95% confidence interval from Cox proportional hazards model adjusted for age, sex and race–field center.
Model 2: Model 1 additionally adjusted for education level (< high school, high school, > high school), 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).

*1 standard deviation (SD) = 26.5 mg/dL.

†Unadjusted incidence rate per 1,000 person-years with 95% confidence interval.