



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

Aaron R. Folsom^{*}, Kristen M. George, Duke Appiah

Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, United States

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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 1776 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.

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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 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 45–64 years in the ARIC study cohort in 1987–1989 [7]. ARIC

^{*} Corresponding author. Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, 1300 South 2nd Street, Suite 300, Minneapolis, MN 55454, United States.

E-mail address: fols001@umn.edu (A.R. Folsom).

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 unfrozen 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 ($n = 1063$), 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 1776 had incident CHD events.

In Model 1 adjusted for demographic variables, there was a weak positive association between factor XI concentration and

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