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# Associations of coagulation factors IX and XI levels with incident coronary heart disease and ischemic stroke: the REGARDS study

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## Summary.

**Background:** Recent studies have suggested the importance of coagulation factor IX and FXI in cardiovascular disease (CVD) risk.

**Objectives:** To determine whether basal levels of FIX or FXI antigen were associated with the risk of incident coronary heart disease (CHD) or ischemic stroke.

**Patients/Methods:** The REasons for Geographic And Racial Differences in Stroke (REGARDS) study recruited 30 239 participants across the contiguous USA between 2003 and 2007. In a case–cohort study within REGARDS, FIX and FXI antigen were measured in participants with incident CHD ($n = 609$), in participants with incident ischemic stroke ($n = 538$), and in a cohort random sample ($n = 1038$). Hazard ratios (HRs) for CHD and ischemic stroke risk were estimated with Cox models per standard deviation higher FIX or FXI level, adjusted for CVD risk factors.

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Addendum

M. Cushman, S. E. Judd, B. M. Kissela, M. M. Safford, G. Howard, and N. A. Zakai conceived the research study design. N. C. Olson and N. A. Zakai performed statistical analyses. N. C. Olson drafted the manuscript. M. Cushman, S. E. Judd, B. M. Kissela, M. M. Safford, G. Howard, and N. A. Zakai critically revised the manuscript. M. M. Safford, G. Howard, and N. A. Zakai obtained funding.

Disclosure of Conflict of Interests

M. M. Safford reports receiving salary support for investigator-initiated research from Amgen. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Results:** In models adjusting for CHD risk factors, higher FIX levels were associated with incident CHD risk (HR 1.19; 95% confidence interval [CI] 1.01–1.40) and the relationship of higher FXI levels was slightly weaker (HR 1.15; 95% CI 0.97–1.36). When stratified by race, the HR of FIX was higher in blacks (HR 1.39; 95% CI 1.10–1.75) than in whites (HR 1.06; 95% CI 0.86–1.31). After adjustment for stroke risk factors, there was no longer an association of FIX levels with ischemic stroke, whereas the association of FXI levels with ischemic stroke was slightly attenuated.

**Conclusions:** Higher FIX antigen levels were associated with incident CHD in blacks but not in whites. FIX levels may increase CHD risk among blacks.

### Keywords

coagulation factor IX; coagulation factor XI; coronary heart disease; risk factors; stroke

## Introduction

Cardiovascular disease (CVD) is the leading cause of death in the USA, with major differences in prevalence and incidence among racial/ethnic minorities [1]. Stroke incidence among African Americans (blacks) is approximately twice that of Caucasian Americans (whites) [2]. Blacks are also at higher risk of having fatal coronary heart disease (CHD) than are whites [3]. Differences in traditional CVD risk factors such as diabetes and hypertension explain some, but not all, of the CVD incidence difference between blacks and whites [4–8].

Although thrombus formation is a key mechanism in CVD pathophysiology, the importance of circulating levels of individual hemostatic factors in CHD and stroke risk remains controversial. There is compelling evidence of associations of von Willebrand factor, coagulation factor VIII and D-dimer levels with CVD risk [9–14]; however, the relationships for several coagulation factors are uncertain. The levels of some coagulation biomarkers differ by race [15,16], and whether these differences explain any of the race/ethnic differences in CVD risk remains underevaluated.

FIX and FXI are components of the intrinsic coagulation pathway, and play roles in the initiation and propagation phases of thrombin generation [17]. The FXI zymogen is cleaved to its activated form [activated FXI (FXIa)] by activated FXII and thrombin, and activates FIX to form activated FIX (FIXa) [18]. FIX is also activated by tissue factor (TF)–activated FVII (FVIIa) [19], and activates FX to form activated FX, which converts prothrombin to thrombin.

Some evidence from epidemiologic studies has suggested the importance of higher FXI levels as a risk factor for stroke in the general population [20–22]. Higher FXI coagulant activity (FXIc) was associated with an increased risk of myocardial infarction (MI) in one case–control study of men [23], but no associations were observed in other case–control studies [21,24].

Fewer studies have evaluated relationships of FIX within the reference range with CVD risk. Higher FIX coagulant activity (FIXc) was associated with an increased CHD risk in two

case–control studies [23,24] and one prospective study [25]. Higher FIXc was associated with an increased ischemic stroke risk in one prospective study, but the relationships were not statistically significant after adjustment for risk factors [20].

We evaluated the associations of baseline FIX and FXI antigen levels with the risk of incident CHD and ischemic stroke in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a contemporary cohort with a large proportion of black participants and high geographic diversity. We hypothesized that higher FIX and FXI antigen levels would be associated with an increased risk of incident CHD and ischemic stroke. As the levels of some coagulation biomarkers may differ by race [15,16], we also hypothesized that FIX and FXI would explain some of the racial difference in stroke risk.

## Methods

### Study cohort

REGARDS is a prospective cohort study of 30 239 individuals from the contiguous USA. Participants were recruited between 2003 and 2007; the study was designed to have an equal representation of the races (42% black and 58% white) and sexes (45% men and 55% women), with oversampling of individuals living in the stroke belt in the southeastern region of the USA (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) [26]. Participants were contacted by telephone, provided verbal informed consent, and underwent a computer-assisted telephone interview in which basic demographic and CVD risk factor information was collected. An in-home visit occurred subsequently, during which written informed consent was obtained and anthropomorphic measures, blood pressure, blood samples, electrocardiograms (ECGs) and a medication inventory were assessed according to standardized protocols [26]. The telephone response rate was 33%, and the cooperation rate was 49%. Those with active cancer or undergoing cancer treatment were excluded from the study.

A stratified case–cohort study was performed within REGARDS to study associations of biomarkers with vascular outcomes [27]. The case–cohort study included all cases of CHD ($n = 654$) and ischemic and hemorrhagic stroke ($n = 645$) and a stratified cohort random sample ($n = 1104$). The cohort random sample was selected with stratification by age (45–54 years, 20%; 55–64 years, 20%; 65–74 years, 25%; 75–84 years, 25%; and ≥ 85 years, 25%), race (black, 50%; white, 50%), and sex (male, 50%; female, 50%). All REGARDS participants provided written informed consent, and the study methods were reviewed and approved by the Institutional Review Boards at the participating institutions.

### Outcomes

The methods used for CHD and stroke event ascertainment have been published previously [3,28]. Participants or their proxies were contacted by telephone every 6 months to ascertain potential CHD or stroke events, and medical records were obtained for review by adjudication committees including physicians. CHD was defined as definite or probable MI according to a standard definitions protocol [29] or as CHD death. Final adjudication of stroke was based on the World Health Organization’s definition [30] or by review of final

reports from all available neuroimaging studies that were consistent with acute ischemia. Neuroimaging reports were available for 91% of all stroke cases. In cases where imaging was not performed, imaging reports were not available, or where the patient died quickly, the stroke subtype was classified as 'unknown', and these cases were not included in this analysis. Deaths were ascertained by telephone interviews with proxies or next-of-kin, which included questions about the presence of cardiac symptoms. Causes of death, including CHD death, were adjudicated by committee. For the case–cohort study, follow-up for strokes was performed up to 1 September 2011. Ascertainment of CHD events was performed in an ancillary study within REGARDS, and follow-up was performed up to 31 December 2009.

## Definitions

Baseline CVD was defined as ECG evidence of MI or participant self-report of CHD, stroke, or peripheral artery disease. Baseline atrial fibrillation was defined as the presence of atrial fibrillation on the in-home visit ECG or by participant report. Left ventricular hypertrophy (LVH) was defined according to the ECG. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg $dL^{-1}$, a non-fasting glucose level of ≥ 200 mg $dL^{-1}$, or self-reported diabetes and the use of insulin or oral diabetes medication. Systolic blood pressure (SBP) was the average of two seated measurements.

## Laboratory methods

Laboratory methods for REGARDS have been published previously [31]. FIX and FXI antigen levels were measured in stored EDTA plasma, collected at the baseline examination, by ELISA (Enzyme Research Laboratories, South Bend, IN, USA). Results were reported as a percentage of the normal concentration of pooled plasma; the coefficients of variation (CVs) ranged from 7.1% to 11.5% for FIX, and from 7.8 to 9.0% for FXI. High-sensitivity C-reactive protein (CRP) was measured by particle-enhanced immunonephelometry on a BNII nephelometer (Dade Behring, Deerfield, IL, USA) (CV 2.1–5.7%). D-dimer was measured by ELISA on the STAR analyzer (CV 5.0–14.0%) (Liatest D-DI; Diagnostica Stago, Parsippany, NJ, USA).

## Statistical analyses

All analyses included sample weighting to account for the entire REGARDS cohort. Mean differences in coagulation factors between the cohort random sample and CHD or ischemic stroke cases were assessed by the use of weighted analysis of variance. Associations of FIX and FXI with demographic variables and CVD risk factors were assessed by the use of weighted linear regression adjusted for age, sex, and race. Multivariable models with inclusion of all demographic and CVD risk factor variables were used to determine independence of the associations.

The risks of CHD or ischemic stroke by baseline FIX and FXI levels were assessed with Cox proportional hazards models. The 95% confidence intervals (CIs) were calculated with robust sandwich estimators, according to the methods proposed by Prentice [32]. FIX and FXI were analyzed per one standard deviation (SD) increase and by quintiles of the distributions. Models were adjusted for demographic variables and then for Framingham CHD Risk Score and Stroke Risk Profile Score factors. For CHD, demographic-adjusted

models included age, sex, region, and race; CVD risk factor-adjusted models included these variables plus SBP, the use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and the use of cholesterol-lowering medications [33]. For ischemic stroke, demographic-adjusted models included age, sex, race, region, and an age × race interaction term (because of a known age-by-race interaction for stroke [34]), and the fully adjusted model also included SBP, the use of antihypertensive medications, diabetes, current smoking, baseline cardiovascular disease, atrial fibrillation, and LVH [35]. Exclusion criteria included baseline CHD in CHD analyses ($n$ = 199), baseline stroke ($n$ = 87) or incident hemorrhagic stroke ($n$ = 74) in stroke analyses, and missing data for FIX or FXI antigen ($n$ = 66).

We assessed for interactions of FIX and FXI with age (< 65 years versus > 65 years), sex, and race, and assessed for an FIX-by-FXI interaction by including cross-product terms in the models, and considered an interaction $P$-value of < 0.10 to be statistically significant [36]. We planned *a priori* to present associations stratified by race.

As there are known interrelationships among inflammation, coagulation, and thrombosis [37], we evaluated whether biomarkers of inflammation or hemostatic activation that were associated with FIX or FXI modified the FIX or FXI hazard ratios (HRs) for CHD or ischemic stroke. To test this, natural logarithm (ln)-transformed CRP or D-dimer were included as covariates in CVD risk factor-adjusted Cox models. Bootstrapping with replacement (1000 replicates) was used to determine the 95% CI of the change between the HRs with and without CRP or D-dimer included in the models.

## Results

Table 1 shows the baseline characteristics of the cohort random sample, CHD cases and ischemic stroke cases among those with FIX or FXI antigen measurements. There were 609 incident CHD events over a median of 4.4 years (interquartile range [IQR] 3.1–5.3 years), and 538 incident ischemic strokes over a median of 5.8 years (IQR 4.1–7.0 years). Mean FIX levels were 103% (SD 22%) in the cohort random sample, 107% (SD 26%) in CHD cases, and 106% (SD 25%) in ischemic stroke cases. Mean FXI levels were 107% (SD 25%) in the cohort random sample, 110% (SD 33%) in CHD cases, and 110% (SD 29%) in ischemic stroke cases. The Pearson correlation coefficient for FIX and FXI was 0.39.

Table 2 shows the associations of FIX and FXI with CVD risk factors and coagulation biomarkers. Higher FIX levels were associated with older age, female sex, former and current smoking, the use of antihypertensive medications, the use of lipid-lowering medications, diabetes, LVH, higher SBP, total cholesterol, body mass index (BMI), CRP level, and D-dimer level, and lower HDL cholesterol. In multivariable models, the independent determinants were sex, smoking status, antihypertensive medication use, lipid-lowering medication use, diabetes, total cholesterol, HDL cholesterol, CRP, D-dimer, and FXI.

Higher FXI levels were associated with female sex, residence in non-stroke belt regions of the USA, the use of lipid-lowering medications, diabetes, and higher total cholesterol, BMI,

CRP level, and D-dimer level. In multivariable models, the independent determinants were sex, lipid-lowering medication use, diabetes, LVH, SBP, total cholesterol, CRP, D-dimer, and FIX.

Table 3 shows the associations of FIX with CHD and ischemic stroke risk. Each SD increase in FIX level (22%) was associated with an increased CHD risk in the demographic-adjusted (HR 1.34; 95% CI 1.16–1.55) and CHD risk factor-adjusted (HR 1.19; 95% CI 1.01–1.40) models. There were no differences in the relationship of FIX with CHD by age (*P*-interaction = 0.22) or sex (*P*-interaction = 0.65), and there was not an FIX-by-FXI interaction (*P* = 0.62).

Stratified by race, the CHD risk factor-adjusted association of FIX with CHD was stronger in black than in white participants (for whom there was no association) (*P*-interaction = 0.08) (Table 3). Analyzed as quintiles with adjustment for CHD risk factors, the CHD HRs for FIX in the 5th quintile versus 1st quintile were 1.81 (95% CI 0.91–3.61) among blacks and 0.91 (95% CI 0.45–1.86) among whites (Table S1).

In analyses of ischemic stroke, each SD increase in FIX level was associated with an increased ischemic stroke risk in the entire cohort after adjustment for demographic variables (HR 1.18; 95% CI 1.03–1.35) (Table 3). After adjustment for stroke risk factors, relationships were attenuated to null. There was no association of FIX quintiles with ischemic stroke (Table S2). There were no statistically significant differences in the relationship of FIX with ischemic stroke by age (*P*-interaction = 0.64), sex (*P*-interaction = 0.31), or race (*P*-interaction = 0.66).

Table 4 shows associations of FXI with CHD and ischemic stroke. Each SD increase in FXI level (25%) was associated with an increased CHD risk in demographic-adjusted models (HR 1.23; 95% CI 1.06–1.43). After adjustment for CHD risk factors the HR was attenuated to 1.15 (95% CI 0.97–1.36) and was no longer statistically significant. Similarly, there were no statistically significant associations of FXI quintiles with CHD risk after adjustment for risk factors (Table S3). Associations were not different by age (*P*-interaction = 0.89), sex (*P*-interaction = 0.13), or race (*P*-interaction = 0.18).

The HR for ischemic stroke per SD increase in FXI level was 1.11 (95% CI 0.98–1.27) in demographic-adjusted models, and there was minimal change in the HR after adjustment for stroke risk factors (Table 4). The results were similar in analyses of FXI quintiles (Table S4). Relationships of FXI with ischemic stroke were not different by age (*P*-interaction = 0.57), sex (*P*-interaction = 0.64), or race (*P*-interaction =0.80).

We performed a mediation analysis to evaluate whether the biomarkers of inflammation or hemostatic activation, i.e. CRP or D-dimer, associated with FIX (Table 2) attenuated the associations of FIX with CHD. When CRP was included as a covariate in CHD risk factor-adjusted models among black participants, the HR of CHD per SD increase in FIX level decreased from 1.39 (95% CI 1.10–1.75) to 1.27 (95% CI 0.99–1.69) (Table 5). Among whites, this HR was completely attenuated. D-dimer did not attenuate the association between FIX and CHD (Table 5).

## Discussion

In this prospective study of black and white adults aged ≥ 45 years from across the contiguous USA, higher FIX antigen levels were associated with an increased risk of incident CHD in blacks but not in whites. There were no associations of FIX or FXI with ischemic stroke in either racial group after adjustment for risk factors.

FIX and FXI are components of the intrinsic coagulation pathway, and are thought to be important in the initiation and propagation phases of thrombin generation. Deficiencies of FIX or FXI cause bleeding disorders (hemophilia B and C), and FIXa was implicated as being thrombogenic after infusion of prothrombin complex concentrates [38]. Our results are consistent with a role of FIX in coronary thrombosis, particularly among blacks.

Few population-based studies have evaluated relationships of FIX with CHD. In a prospective case–cohort study from the Atherosclerosis Risk in Communities (ARIC) cohort, which included whites and African Americans, higher FIXc was associated with increased CHD risk in models adjusted for demographic variables. Relationships were attenuated after adjustment for CVD risk factors, and race-stratified associations were not assessed [25]. In the Study of Myocardial Infarctions Leiden (SMILE), which was a case–control study of men born in the Netherlands, higher FIXc was associated with increased risk of a first MI among men aged < 70 years, with the highest risk being seen among men aged < 55 years [23]. FIXc was also associated with higher MI risk in a case–control study of young women from the Netherlands [24]. Although almost all participants in these two studies were white [23,24], coagulation biomarkers were not measured prior to the MI events. The long-term impact of MI or treatments for MI on coagulation biomarkers are unknown, and associations could reflect changes induced by MI or its treatment.

Our findings that higher FIX antigen levels were associated with an increased CHD risk in blacks but not in whites is novel. FIX levels were similar between blacks and whites, and we do not hypothesize that FIX functions differently by race/ethnic group. Instead, our results may be explained by interactions of FIX with other CHD risk factors that differ by race. For example, blacks had a higher risk than whites of fatal CHD in REGARDS, despite similar CHD rates [3]. The findings may also reflect different CHD phenotypes, as suggested for small versus major ischemic events [39], that vary between blacks and whites. We also cannot exclude a type I statistical error. Further study is needed to validate our findings and to examine potential differences in the pathophysiology of CHD by race.

The FIX association with CHD was attenuated by adjustment for CRP but not by adjustment for D-dimer. These results suggest a role for inflammation, and not hemostatic activation, in the relationship between FIX and CHD risk. Although CRP itself is unlikely to be in the causal pathway and FIX is not an acute-phase reactant, the results are generally consistent with known relationships between inflammation and coagulation [40]. As blacks have higher CRP levels [41], attenuation of the relationship between FIX and CHD by CRP may also explain the different relationships between FIX and CHD by race.

After adjustment for risk factors, FXI was not associated with CHD in our study, which is consistent with several [21,24,25,42,43], but not all [23], previous studies. Associations of

FIX and not FXI with CHD may reflect the importance of FIXa generation by the TF-FVIIa pathway.

Our null results for stroke contrast with several prior studies suggesting the importance of FXI in ischemic stroke risk [20–22,43–45]. The differences in results may be attributable to our use of antigenic assays rather than the coagulant activity or complexed activated protease inhibitor assays used in previous studies. The differences may also be attributable to regional or racial considerations, as only one previous study was USA-based with inclusion of African Americans [20].

As approximately half of our ischemic stroke cases at the censoring date were of undetermined etiology, our study had limited power to detect associations with ischemic stroke subtypes (e.g. cardioembolic stroke). It is possible that coagulation factor levels are important for certain ischemic stroke etiologic subtypes, but not others. We may have also missed moderate or weak associations of FXI with ischemic stroke. We do not know the correlations of FIX/FXI antigen with FIX/FXI coagulant activity, and the translation of these measurements to clinical practice is unclear. Another limitation is that novel CVD risk factors, such as socioeconomic status (SES) or genetic variants, were not included in our models. Further research is required to determine whether the increased CHD risk in blacks with higher FIX levels is related to SES, genetics, or other factors. Our prospective study design with black and white participants from across the contiguous USA and physician-adjudicated CHD and stroke events is a strength.

In conclusion, higher FIX antigen levels were associated with an increased CHD risk in blacks but not in whites, independently of traditional CHD risk factors. These findings suggest that higher FIX levels may increase CHD risk in blacks.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Essentials

- Coagulation factors (F) IX and XI have been implicated in cardiovascular disease (CVD) risk.
- We studied associations of FIX and FXI with incident coronary heart disease (CHD) and stroke.
- Higher FIX antigen was associated with incident CHD risk in blacks but not whites.
- Higher levels of FIX antigen may be a CHD risk factor among blacks.

**Table 1**

Characteristics of the REGARDS case–cohort population at baseline

| | Cohort random sample* (*n* = 1038)† | CHD cases (*n* = 609) | Ischemic stroke cases (*n* = 538) |
|---|---|---|---|
| Age (years), mean (SD) | 65 (9.3) | 68 (9.2) | 70 (8.6) |
| Female sex, *n* (%) | 519 (55.3) | 221 (36.3) | 259 (48.1) |
| Black race, *n* (%) | 514 (41.1) | 264 (43.3) | 222 (41.3) |
| Region, stroke belt, *n* (%) | 551 (54.0) | 347 (57.0) | 297 (55.2) |
| Antihypertensive medications, *n* (%) | 624 (58.2) | 425 (70.0) | 404 (75.4) |
| Systolic BP (mmHg), mean (SD) | 127 (16) | 135 (20) | 133 (18) |
| Total cholesterol (mg $dL^{-1}$), mean (SD) | 190 (39) | 193 (42) | 190 (42) |
| HDL cholesterol (mg $dL^{-1}$), mean (SD) | 52 (17) | 48 (14) | 50 (17) |
| Lipid-lowering medications, *n* (%) | 583 (59.2) | 377 (62.5) | 346 (65.2) |
| Current smoker, *n* (%) | 149 (13.8) | 119 (19.5) | 101 (18.8) |
| Former smoker, *n* (%) | 394 (38.3) | 262 (43.0) | 216 (40.3) |
| Diabetes, *n* (%) | 210 (20.7) | 191 (31.6) | 146 (27.6) |
| CVD, *n* (%) | 245 (21.3) | 84 (13.8) | 159 (29.6) |
| Atrial fibrillation, *n* (%) | 92 (9.5) | 72 (12.0) | 77 (14.6) |
| LVH, *n* (%) | 98 (8.1) | 70 (116) | 81 (15.2) |
| CRP (mg $L^{-1}$), median (25th, 75th) | 2.2 (0.9, 4.9) | 3.0 (1.2, 5.9) | 2.8 (1.2, 6.3) |
| D-dimer (μg $mL^{-1}$), median (25th, 75th) | 0.41 (0.23, 0.77) | 0.55 (0.33, 0.92) | 0.55 (0.33, 0.92) |
| FIX antigen (%), mean (SD) | 103 (22) | 107 (26) | 106 (25) |
| FXI antigen (%), mean (SD) | 107 (25) | 110 (33) | 110 (29) |

BP, blood pressure; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; SD, standard deviation.

*The cohort random sample was selected with stratification by age, sex, and race, as described in Methods.

†Cohort random sample percentages are reported as weighted values to represent the entire REGARDS cohort.

**Table 2**

Age-adjusted, sex-adjusted and race-adjusted associations of coagulation factor IX and coagulation factor XI antigen levels with cardiovascular disease risk factors in REGARDS at baseline

| | FIX (%) | | FXI (%) | |
|---|---|---|---|---|
| **Characteristic** | **Difference in level (95% CI)** | ***P*-value** | **Difference in level (95% CI)** | ***P*-value** |
| Age (per 9.3 years) | 1.3 (0.33–2.3) | 0.009 | − 0.4 (− 1.6 to 0.75) | 0.49 |
| Female sex | 8.2 (5.6–10.7) | < 0.0001 | 13.0 (10.1–15.8) | < 0.0001 |
| Black race | 2.0 (− 0.5 to 4.5) | 0.11 | − 1.8 (− 4.6 to 1.1) | 0.22 |
| Stroke belt region | 2.2 (−0.4, 4.7) | 0.10 | −3.1 (−6.0, −0.2) | 0.04 |
| Systolic BP (per 16 mmHg) | 3.5 (2.3–4.8) | < 0.0001 | 0.04 (− 1.3 to 1.4) | 0.95 |
| Antihypertensive medication use | 9.1 (6.4–11.8) | < 0.0001 | 3.0 (− 0.04 to 6.1) | 0.05 |
| Total cholesterol (per 39 mg $dL^{-1}$) | 3.6 (2.1–5.0) | < 0.0001 | 3.6 (1.9–5.2) | < 0.0001 |
| HDL cholesterol (per 17 mg $dL^{-1}$) | − 2.3 (− 4.0 to − 0.60) | 0.008 | − 0.62 (− 2.4 to 1.1) | 0.48 |
| Lipid-lowering medication use | 7.1 (4.4–9.8) | < 0.0001 | 9.0 (5.9–12.0) | < 0.0001 |
| Never smoked | 0.0 (Reference) | – | 0.0 (Reference) | – |
| Former smoker | 2.9 (0.11–5.6) | 0.04 | 2.5 (− 0.49 to 5.5) | 0.10 |
| Current smoker | 6.4 (2.5–10.3) | 0.001 | 3.5 (− 1.4 to 8.4) | 0.16 |
| BMI (per 5.9 kg $m^{-2}$) | 5.2 (4.0–6.4) | < 0.0001 | 3.1 (1.7–4.5) | < 0.0001 |
| Diabetes | 7.2 (4.1–10.3) | < 0.0001 | 8.7 (4.6–12.7) | < 0.0001 |
| Atrial fibrillation | − 5.0 (− 10.6 to 0.6) | 0.08 | − 0.02 (− 5.1 to 5.1) | 0.99 |
| LVH | 6.7 (2.7–10.7) | 0.001 | 0.08 (− 4.7 to 4.9) | 0.97 |
| CRP (per 1.17) | 8.5 (7.3–9.7) | < 0.0001 | 5.1 (3.7–6.6) | < 0.0001 |
| D-dimer (per 0.87) | 5.3 (3.8–6.9) | < 0.0001 | 4.6 (2.9–6.2) | < 0.0001 |
| FIX antigen (per 22%) | – | – | 9.1 (7.5–10.8) | < 0.0001 |
| FXI antigen (per 25%) | 8.1 (6.7–9.4) | < 0.0001 | – | – |

BMI, body mass index; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; LVH, left ventricular hypertrophy. Differences in coagulation factor levels were estimated by the use of $\beta$-coefficients evaluated with linear regression models per standard deviation higher value (shown in parentheses) adjusted for age, sex, and race. In models of age, sex, and race, the estimates were adjusted only for the two remaining variables. CRP and D-dimer were natural log-transformed.

**Table 3**

Hazard ratios (HRs) of coronary heart disease (CHD) and ischemic stroke per standard deviation higher coagulation factor IX antigen level (22%) in REGARDS

| | CHD HR (95% CI) | Ischemic stroke HR (95% CI) |
|---|---|---|
| Demographic model * | | |
| Entire cohort | 1.34 (1.16–1.55) | 1.18 (1.03–1.35) |
| Black | 1.63 (1.31–2.04) | 1.23 (0.98–1.53) |
| White | 1.17 (0.98–1.41) | 1.15 (0.98–1.36) |
| Race × FIX | 0.02 | 0.66 |
| *P*-value | | |
| Risk factor model † | | |
| Entire cohort | 1.19 (1.01–1.40) | 1.03 (0.89–1.19) |
| Black | 1.39 (1.10–1.75) | 1.00 (0.80–1.25) |
| White | 1.06 (0.86 –1.31) | 1.05 (0.88–1.26) |
| Race × FIX | 0.08 | 0.70 |
| *P*-value | | |

CI, confidence interval.

*Adjusted for age, sex, race, and region. Stroke: adjusted for age, sex, race, region, and age × race.

†CHD: adjusted for demographic model + systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and use of cholesterol-lowering medications. Stroke: adjusted for demographic model + systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, baseline cardiovascular disease, baseline atrial fibrillation, and baseline left ventricular hypertrophy.

**Table 4**

Hazard ratios (HRs) of coronary heart disease (CHD) and ischemic stroke per standard deviation higher coagulation factor XI antigen level (25%) in REGARDS

| | CHD HR (95% CI) | Ischemic stroke HR (95% CI) |
|---|---|---|
| Demographic model * | | |
| Entire cohort | 1.23 (1.06–1.43) | 1.11 (0.98–1.27) |
| Black | 1.34 (1.07–1.68) | 1.09 (0.91–1.31) |
| White | 1.09 (0.88–1.35) | 1.13 (0.95–1.34) |
| Race × FXI *P*-value | 0.18 | 0.80 |
| Risk factor model † | | |
| Entire cohort | 1.15 (0.97–1.36) | 1.08 (0.94–1.24) |
| Black | 1.26 (1.00–1.60) | 1.01 (0.83–1.24) |
| White | 1.01 (0.78–1.30) | 1.12 (0.93–1.35) |
| Race × FXI *P*-value | 0.19 | 0.46 |

CI, confidence interval.

*CHD: adjusted for age, sex, race, and region. Stroke: adjusted for age, sex, race, region, and age × race.

†CHD: adjusted for demographic model + systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and use of cholesterol-lowering medications. Stroke: adjusted for demographic model + systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, baseline cardiovascular disease, baseline atrial fibrillation, and baseline left ventricular hypertrophy.

**Table 5**

Attenuation of the associations of factor IX antigen with coronary heart disease (CHD) by adjustment for C-reactive protein (CRP) and D-dimer

| CHD | FIX HR (95% CI) | FIX + CRP HR (95% CI) | Change in HR by CRP (95% CI) | FIX + D-dimer HR (95% CI) | Change in HR by D-dimer (95% CI) |
|---|---|---|---|---|---|
| Entire cohort | 1.19 (1.01–1.40) | 1.09 (0.92–1.30) | 0.10 (0.04–0.18) | 1.16 (0.97–1.37) | 0.03 (− 0.02 to 0.09) |
| Black | 1.39 (1.10–1.75) | 1.27 (0.99–1.64) | 0.12 (0.04–0.22) | 1.38 (1.08–1.77) | 0.01 (− 0.09 to 0.09) |
| White | 1.06 (0.86–1.31) | 0.99 (0.80–1.22) | 0.07 (0.02–0.16) | 1.03 (0.83–1.27) | 0.03 (− 0.02 to 0.10) |

CI, confidence interval; HR, hazard ratio. FIX antigen was modeled per standard deviation higher level (22%). Analyses were adjusted for: age, sex, race, region, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and cholesterol-lowering medication use. Race-stratified analyses were not adjusted for race.