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D-dimer and the Risk of Stroke and Coronary Heart Disease: The REasons for Geographic and Racial Differences in Stroke (REGARDS)

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Abstract

Background—D-dimer, a biomarker of coagulation, is higher in blacks than whites and has been associated with stroke and CHD.

Objectives—To assess the association of higher D-dimer with stroke and coronary heart disease (CHD) in blacks and whites.

Materials/Methods—REGARDS recruited 30,239 black and white participants across the contiguous US and measured baseline D-dimer in stroke (n=646) and CHD (n=654) cases and a cohort random sample (n=1,104). Cox models adjusting for cardiovascular risk factors determined the hazard ratio (HR) for increasing D-dimer for cardiovascular disease with bootstrapping to assess the difference in HR for CHD versus stroke by race.

Results—D-dimer was higher with increasing age, female sex, diabetes, hypertension, pre-baseline cardiovascular disease and higher C-reactive protein (CRP). Accounting for cardiovascular risk factors, each doubling of D-dimer was associated with increased stroke (HR 1.15; 95% CI 1.01, 1.31) and CHD (HR 1.27; 95% CI 1.11, 1.45) risk. The difference in the HR between CHD and stroke was 0.20 (95% CI >0.00, 0.58) for blacks and 0.02 (95% CI -0.30, 0.27) for whites. CRP mediated 22% (95% CI 5%, 41%) of the association between D-dimer and CHD and none of the association with stroke.

Discussion—Higher D-dimer increased the risk of stroke and CHD independent of cardiovascular risk factors and CRP, with perhaps a stronger association for CHD versus stroke in blacks than whites. These findings highlight potential different pathophysiology of vascular disease by disease site and race suggesting potential further studies targeting haemostasis in primary prevention of vascular disease.

Keywords

Continental Population Groups; Coronary Disease; D-dimer; Epidemiology Stroke

Introduction

The role haemostasis biomarkers and more specifically D-dimer play in stroke and coronary heart disease (CHD) risk is not established, and the quality of evidence for stroke is less than that available for CHD(1–3). While stroke and CHD share many risk factors, each disease is unique and inflammation and coagulation may play different roles. Fibrin fragment D-dimer is a circulating peptide degradation product of cross-linked fibrin (formed during thrombus formation). In the general population plasma levels reflect systemic fibrin formation, with higher levels reflecting more systemic fibrin formation and a tendency for increased thrombosis(4). Most but not all studies show an association of higher D-dimer with future CHD, with similar but fewer results for stroke(5–9). Further, existing studies include few non-Caucasian participants and do not compare associations of D-dimer across cardiovascular diseases. As African-Americans (blacks) have higher levels of D-dimer and other markers of haemostasis than Caucasian-Americans (whites), differences in haemostasis may potentially explain any black-white differences in cardiovascular disease risk(9–11). Further, as risk factors for stroke and CHD differ, we sought to assess whether haemostasis, as measured by plasma D-dimer levels, is differentially associated with stroke and CHD risk(2).

We used the REasons for Geographic and Racial Differences in Stroke (REGARDS) study to assess the association of D-dimer with stroke and CHD and stratifying by race (blacks and whites). Further, we evaluated whether inflammation mediates any of the association of D-dimer with cardiovascular disease and whether racial differences in D-dimer cause any of the known racial differences in stroke risk. By understanding potential mechanisms of cardiovascular disease risk in individuals, researchers can design novel preventive strategies targeting domains of risk such as haemostasis, inflammation, or platelet function.

Materials and Methods

Cohort

REGARDS recruited 30,239 individuals from the contiguous United States (US) between 2003–07. By design, the cohort was 55% female, 41% black and 56% lived in the southeast of the U.S. (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) with recruitment goal being 50% for each stratum. Potential participants were contacted by telephone, and after verbal informed consent, participated in a computer assisted telephone interview gathering basic demographic and risk factor data. Exclusion criteria were medical conditions preventing long-term participation, active cancer or treatment for cancer in the past 12 months, resident in or on the waiting list for a nursing home, inability to communicate in English, or race other than black or white (by participant self-report). Participants then underwent an in-home visit where anthropomorphic data, medication inventory, fasting phlebotomy, and written informed consent were performed

(Examination Management Systems Incorporated, Irving, Texas) with detailed methods previously published(12–14). This study was approved by the institutional review boards of all participating institutions.

Laboratory

Laboratory methods have been described in detail previously(15). Phlebotomy was performed after a 10–12 hour fast in the morning at the in-home visit. Samples were centrifuged locally and shipped overnight on dry-ice to the study laboratory at the University of Vermont where they were recentrifuged and stored at –80°C. D-dimer was measured in plasma using an immunoturbidometric assay on the STAR analyzer and reported in ug/mL (Diagnostica Stago, Asnières sur Seine, France) with an interassay coefficient of variation of 5–17%. D-dimer was measured in incident stroke cases (n = 646, 269 blacks), incident CHD cases (n=654, 289 blacks), and in a stratified cohort random sample (CRS, n=1,104, 552 blacks). C-reactive protein (CRP) was measured using a high-sensitivity particle enhanced immunonephelometric assay on the BNII nephelometer, (N High Sensitivity CRP, Dade Behring Incorporated, Deerfield, IL) with an interassay CV 2–6%. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by colorimetric reflectance spectrophotometry using the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Rochester, NY), with low density lipoprotein cholesterol calculated by the Friedewald equation for subjects with triglycerides <400 mg/dL. Lipids and CRP were measured in the entire cohort.

Definitions

Baseline conditions were present at or before the date of the in-home visit. Prevalent stroke and peripheral arterial disease was based on participant self-report and prevalent CHD was based on participant self-report or electrocardiogram evidence of prior myocardial infarction. Prevalent cardiovascular disease was defined as stroke, peripheral arterial disease, or CHD present at enrolment. Atrial fibrillation was defined as participant report of atrial fibrillation or by electrocardiogram done at the in-home exam. Left ventricular hypertrophy was defined using the baseline electrocardiogram. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, or self-reported use of diabetes medications. Systolic blood pressure was the average of two seated measures after a 5 minute rest. Use of antihypertensive medications and cholesterol lowering medications was defined by participant self-report from a medication inventory.

Outcomes

Participants were followed for incident stroke and CHD events, with detailed methods for stroke(12) and CHD(16) event ascertainment previously published. Participants or proxies were contacted every 6 months by telephone to ascertain stroke or stroke symptoms and potential CHD hospitalizations as well as fatal CHD or stroke events. Medical records, including neuroimaging and other diagnostic reports, as well as death certificates and summaries of last hospitalizations in those who died, were retrieved and centrally reviewed by physicians to confirm endpoints. For stroke, adjudication was based on the World Health Organization's definition of stroke and/or imaging consistent with stroke. Follow-up for stroke was complete through September 1, 2011. For CHD, adjudication followed published

guidelines for major epidemiology studies for nonfatal myocardial infarction and acute CHD death(17). Myocardial infarction diagnoses were based on a rising and/or falling pattern of cardiac biomarkers to a level at least twice the upper limit of normal for the biomarker; clinical signs or symptoms consistent with ischemia; and electrocardiogram findings guided by the Minnesota Code. Acute CHD death was ascertained through interviews with proxies or next of kin about circumstances immediately prior to death, autopsy reports, hospital records, death certificates and medical history obtained at baseline. Follow-up for CHD was complete through December 31, 2009, and only definite or probable events were included in this analysis.

Statistical Analyses

We performed a stratified case-cohort analysis using methods proposed by Prentice with detailed methods in REGARDS previously published(18–21). In the CRS, correlates of D-dimer quintiles were determined accounting for sample weighting; categorical variables were compared using the Rao-Scott χ^2 statistic and means of continuous variables using weighted analysis of variance.

Cox proportional hazard models were used to calculate the hazard ratios (HR) with robust sandwich estimators to calculate 95% confidence intervals (CI) accounting for sample weighting. Due to skewing, D-dimer was log base 2 transformed and analysed per 1 unit log D-dimer increment when analysed as a continuous variable (which can be interpreted as a doubling of non-transformed D-dimer concentrations). Models for stroke excluded participants with prevalent stroke and models for CHD excluded participants with prevalent CHD at baseline. Three models were fitted each for stroke and CHD, the first adjusting for demographics, the second with additional adjustment for cardiovascular disease risk factors, and the third by adding C-reactive protein (CRP) to the cardiovascular disease risk factor model. For stroke, the basic model was adjusted for age, sex, region, race, and an age by race interaction term which in previous analyses was shown to be significant(12). The second model added adjustment for risk factors in the Framingham Stroke Risk Score including systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, prevalent cardiovascular disease, prevalent atrial fibrillation, and left ventricular hypertrophy(22). For CHD, the basic model was adjusted for age, sex, region and race and the cardiovascular risk factor model added systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and use of cholesterol-lowering medications. The third model added the natural log of CRP to the cardiovascular risk factor model. The difference in the HR for D-dimer between stroke and CHD was calculated by subtracting the two HR and the 95% CI for the difference was calculated by bootstrapping with 1000 replicates. The natural log of CRP was added to the second model to assess how much of the association of D-dimer with cardiovascular events was explained by D-dimer as an inflammation marker. Models were presented for the entire cohort as well as the HR for blacks and whites separately (a pre-specified analysis). Finally, we performed mediation analysis to determine whether D-dimer mediated any of the excess stroke risk in blacks using bootstrapping with 1,000 replicate samples with replacement to determine the 95% CI of the difference between the HR of race with and without D-dimer in the model. Participants with missing covariates were dropped from the analysis and

individuals were followed until the date of last follow-up, withdrawal from the study, or death.

Sensitivity analyses were done excluding haemorrhagic strokes and excluding participants with either baseline CHD or baseline stroke from analyses of either endpoint (i.e. CHD cases from the stroke models and stroke cases from the CHD models). All analyses were done using SAS 9.3 (Gary, North Carolina).

Results

During follow-up, there were 654 incidence CHD events (median follow-up 4.4 years, interquartile range 3.1 – 5.5 years) and 646 incident stroke events (median follow-up 5.8 years, interquartile range 4.1 – 7.0). Median D-dimer in the CRS was 0.40ug/mL (IQR 0.23 – 0.76), 0.52ug/mL (IQR 0.31, 0.92) in stroke cases and 0.52 ug/mL (IQR 0.32, 0.92) in CHD cases.

Presented In table 1, higher D-dimer was observed with older age, female sex, higher systolic blood pressure and use of antihypertensive medications, higher HDL cholesterol, higher CRP, and higher prevalence of baseline cardiovascular disease and left ventricular hypertrophy (all $p < 0.05$). The geometric mean D-dimer was higher in blacks (0.49ug/mL) than whites (0.39ug/mL) ($p < 0.001$). There was no association between D-dimer and total cholesterol, current smoking, or atrial fibrillation.

Higher baseline D-dimer was associated with increased risk of both incident CHD and stroke (Table 2). In the demographic model, each doubling D-dimer was associated with a 32% higher risk of CHD (HR 1.32; 95% CI 1.17, 1.50) and a 20% higher risk of stroke (HR 1.20; 95% CI 1.07, 1.35). The HR of stroke for D-dimer was similar in blacks and whites (HR 1.18 for blacks and 1.22 for whites, p -interaction = 0.80), while the HR of CHD was non-significantly higher for blacks than whites (HR 1.41 for blacks and 1.24 for whites, p -interaction = 0.30). When adjusting for cardiovascular risk factors, the HRs were slightly attenuated but statistical significance was maintained (Table 2). When D-dimer was divided into quintiles (Table 3), there was little evidence for a consistent association in blacks or whites for stroke in either the demographic or the risk factor-adjusted models. There was an association for CHD, with the highest D-dimer quintile having an HR of 1.73 (95% CI 1.02, 2.93) for CHD. While the point-estimate was greater for blacks (HR 2.41; 95% CI 1.08, 5.29) than whites (HR 1.50; 95% CI 0.73, 3.08) in the risk factor adjusted model, the interaction between D-dimer and race was not significant ($p_{\text{interaction}} = 0.24$). There was no sex by D-dimer interaction (continuous analysis) in the risk factor adjusted model for stroke or CHD.

Comparison of the Association of D-dimer with CHD and Stroke

Though the point estimate of the association of D-dimer was higher for CHD than for stroke in the risk factor model (1.27 vs 1.15), this difference was not statistically significant (difference in HR between CHD and stroke 0.12; 95% CI for the difference -0.07, 0.33). However, when stratified by race, the association of D-dimer was significantly greater in

CHD than stroke in blacks (difference in HR for CHD minus stroke 0.20; 95% CI >0.00, 0.58) but not whites (difference in HR for CHD minus stroke 0.02; 95% CI -0.30, 0.27).

Mediation Analysis

The HR of D-dimer with stroke decreased non-significantly by 13.3% (95% CI 0.0%, 40.0%) when CRP was added to the model 2 (Table 4). In contrast, the HR of D-dimer with CHD decreased significantly by 22.7% (95% CI 5.5%, 41.1%) when CRP was added to model 2 (Table 4). Figure 1 presents the association of race with stroke with and without D-dimer in the risk factor model at various ages. Consistent with prior studies, the hazard ratio for black race with stroke was highest at younger ages with a p-interaction between age and race of 0.03 in the risk factor model. Though addition of D-dimer to the risk factor model decreased the HR for the association of black race with stroke, this difference was not significant at any age (Figure 1). There was no age by race interaction for CHD (p-interaction = 0.39) in the risk factor adjusted model and there was no association of race with CHD in the main cohort.

Sensitivity analyses excluding haemorrhagic strokes (n = 73) did not change the interpretation of the results, nor did excluding participants with both prevalent stroke and CHD from all analyses (data not shown).

Discussion

Higher D-dimer was associated with stroke and CHD in blacks and whites. For blacks, the association of D-dimer was stronger for CHD than stroke, while the association was similar in whites. Higher CRP significantly decreased (but did not eliminate) the association of D-dimer with CHD but had no effect on the association of D-dimer with stroke. While D-dimer did decrease the excess risk of stroke seen in blacks at younger ages this did not reach statistical significance.

There is little doubt that there is an association of baseline elevated D-dimer with future cardiovascular disease events as most prior studies report an increased risk of cardiovascular events with higher D-dimer(5, 7–9). As seen in Table 1, higher D-dimer is correlated with adverse levels of many cardiovascular risk factors, but also with higher levels of HDL cholesterol. The pathophysiology between D-dimer and cardiovascular risk factors is not understood, however despite adjusting for these risk factors, D-dimer remained associated with cardiovascular risk. In the Cardiovascular Health Study, including 587 incident stroke and transient ischemic attack events in an elderly white population, the HR for cerebrovascular events was 1.65 (95% CI 1.19, 2.29) for the top compared to the bottom quintile of D-dimer, compared to a HR of 1.39 reported here(8). In the same analysis in CHS, with 739 CHD events, the HR of CHD for those in the 5th compared with the 1st quintile of D-dimer was 1.57 (95% CI 1.20, 2.04), compared to 1.73 reported here(8). In a meta-analysis with 1,535 CHD events, the top tertile of D-dimer was associated with an OR of 1.7 (95% CI 1.3, 2.2) for CHD, compared to the bottom tertile. In two of three studies that reported a combined CVD outcome (including stroke and CHD), higher D-dimer was associated with CVD events(7–9). In Multi-Ethnic Study of Atherosclerosis, the association of D-dimer with cardiovascular events was attenuated by adjustment for demographics and

cardiovascular risk factors, but the total number of cardiovascular disease events was less than a quarter of the number of events in the current study(9).

The current study extends these observations as we assessed whether there was any difference by race, by cardiovascular disease type, and whether CRP, a biomarker of inflammation impacted the association of D-dimer with cardiovascular disease. While the end pathophysiology is similar in most cardiovascular disease, a thrombus blocking an artery, the underlying processes leading to tissue ischemia can differ(23). Prevention of cardiovascular disease has focused on traditional risk factor modification (namely hypertension and lipids) and to a lesser extent treatment with antiplatelet agents(24). What is lacking is a more refined approach targeting individualized underlying pathophysiology of potential cardiovascular disease rather than overall cardiovascular disease risk.

Anticoagulation therapies have been investigated for the prevention of cardiovascular disease. For stroke prevention, warfarin is superior to antiplatelet agents among patients with non-valvular atrial fibrillation(25) and may confer a slight advantage in the setting heart failure and normal sinus rhythm but at the cost of more bleeding events(26). In the primary prevention of CHD, warfarin is as efficacious as aspirin and may provide additional benefit when added to aspirin but at the cost of increased bleeding(27). While D-dimer has not been shown to improve risk stratification for cardiovascular disease(7, 8), our findings may offer insights into future individualized targeted approaches to prevent cardiovascular disease, perhaps specifically for CHD in blacks. Assuming D-dimer is a marker of activated coagulation, elevated levels may help identify a patient population who could benefit more from agents targeted at haemostasis rather than platelet function or lipids for primary prevention(28). Extreme caution and well-designed clinical trials are needed before using haemostasis biomarkers to determine the best primary prevention strategy in patients at risk for cardiovascular disease.

While REGARDS is a large national study, the design of REGARDS introduces both strengths and weaknesses over prior studies with participants centred on recruiting centres; REGARDS has a significant number of participants from rural areas which increases the generalizability of the findings, but potentially introduces a greater variation in the standards of care for stroke and CHD. Additionally, REGARDS assessed D-dimer at only at one time point. D-dimer varies depending on the acute health status of the participant, however this would tend to bias our results towards the null. Despite these weaknesses, our data demonstrate that D-dimer is associated with both stroke and CHD risk and that D-dimer may shed light onto different pathophysiologies of cardiovascular disease by cardiovascular disease type and race.

In summary, higher D-dimer was associated with an increased risk of stroke and CHD in REGARDS. The association was stronger for CHD, especially in blacks than whites suggesting coagulation may play a greater role in CHD in blacks. From a clinical standpoint, our data introduce the idea that haemostasis may play a different role in the pathogenesis of vascular disease by site (stroke versus CHD) and by race (black versus white) and that studies incorporating primary prevention strategies targeting individualized cardiovascular disease risk profiles are needed to reduce cardiovascular disease in all individuals.

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Extra Table

What is Known	Elevated D-dimer levels are associated with cardiovascular disease
	Cardiovascular disease incidence varies by race
	D-dimer levels vary by race
What this Paper Adds	Elevated D-dimer is a greater risk factor for coronary heart disease than stroke
	The increased risk for coronary heart disease is greater in American Blacks than whites
	The association of D-dimer with cardiovascular disease is not dependent on elevated biomarkers of inflammation

Figure 1.

Mediation of the Association of Black Race with Stroke by D-dimer by Age

Heavy lines represent the Hazard Ratio, dashed lines 95% CI. Percent mediation (95% CI):

Age 45: 18% (−6%, 69%), Age 55: 12% (−9%, 42%), Age 65: 3% (−17%, 24%); Age 75:

43% (−120%, 26%); Age 85: No increased risk for blacks.

Table 1
Association of Baseline Cardiovascular Risk Factors with D-dimer Concentration in REGARDS

	D-dimer Quintiles (ng/mL)					P
	Q1 (0 – 0.22)	Q2 (0.23 – 0.32)	Q3 (0.33 – 0.51)	Q4 (0.52 – 0.89)	Q5 (0.90)	
Cohort Random Sample (N, weighted %)	177 (19.7%)	156 (17.9%)	212 (21.9%)	231 (20.46%)	257 (20.0%)	-
Age (years, mean, SE)	59.3 (0.5)	62.4 (0.6)	65.7 (0.6)	67.4 (0.6)	69.8 (0.61)	<0.001
Sex, Male (n, %)	105 (48.3%)	88 (52.3%)	103 (43.6%)	115 (46.1%)	105 (34.0%)	0.04
Race, Black (n, %)	73 (32.0%)	72 (39.5%)	94 (39.6%)	123 (44.9%)	148 (49.1%)	0.06
Systolic Blood Pressure (mmHg, mean, SE)	122 (1)	125 (1)	128 (1)	130 (2)	129 (1)	<0.01
Using blood pressure medications (n, %)	69 (44.1%)	72 (48.8%)	103 (50.6%)	134 (55.9%)	162 (62.5%)	0.04
Total Cholesterol (mg/dL, mean, SE)	194 (3.5)	186 (3)	188 (3)	190 (3)	190 (3)	0.74
HDL Cholesterol (mg/dL, mean, SE)	51 (1)	49 (1)	51 (1.2)	51 (1.3)	55 (1.6)	0.04
Current Smoking (n, %)	28 (12.3%)	28 (11.1%)	32 (14.0%)	32 (13.3%)	37 (17.7%)	0.56
Diabetes Mellitus (n, %)	26 (14.5%)	29 (18.1%)	47 (23.1%)	56 (25.8%)	52 (21.8%)	<0.001
Cardiovascular Disease (n, %)	27 (16.3%)	20 (12.3%)	26 (11.3%)	53 (20.9%)	71 (28.3%)	0.001
Atrial Fibrillation (n, %)	23 (12.5%)	12 (8.4%)	19 (8.5%)	15 (8.6%)	23 (9.6%)	0.80
Left Ventricular Hypertrophy (n, %)	15 (8.5%)	9 (6.0%)	12 (3.6%)	27 (12.8%)	34 (9.6%)	0.01
CRP (mg/dL, geometric mean, SE)	1.4 (1.1)	1.8 (1.1)	2.0 (1.1)	2.7 (1.4)	3.3 (2.02)	<0.001

Table 2

Association of Baseline D-dimer with Cardiovascular Disease Risk

	Per Doubling D-dimer		
	CHD HR (95% CI)	Stroke HR (95% CI)	Difference in HR (CHD – Stroke, 95% CI)
Demographic Model [*]			
Entire cohort	1.32 (1.17, 1.50)	1.20 (1.07, 1.35)	0.12 (–0.04, 0.31)
Blacks	1.41 (1.19, 1.67)	1.18 (1.00, 1.40)	0.23 (0.01, 0.56)
Whites	1.24 (1.04, 1.48)	1.22 (1.03, 1.44)	0.02 (–0.20, 0.23)
p-interaction _{race} * D-dimer	0.30	0.80	
Risk Factor Model [†]			
Entire Cohort	1.27 (1.11, 1.45)	1.15 (1.01, 1.31)	0.12 (–0.07, 0.33)
Blacks	1.33 (1.11, 1.59)	1.12 (0.92, 1.34)	0.20 (0.00, 0.58)
Whites	1.21 (1.01, 1.47)	1.19 (0.99, 1.42)	0.02 (–0.30, 0.27)
p-interaction _{race} * D-dimer	0.49	0.60	

^{*} CHD: Adjusted for age, sex, region, and race

Stroke: Adjusted for age, sex, region, race, and age*race

[†] CHD: Adjusted for age, sex, region, race, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and taking cholesterol-lowering medications

Stroke: Adjusted for age, sex, region, race, age*race, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, baseline cardiovascular disease, baseline atrial fibrillation, and baseline left ventricular hypertrophy

Table 3

Association of Baseline D-dimer Quintiles with Cardiovascular Disease Risk

		CHD HR (95% CI)		Stroke HR (95% CI)			
		All	Blacks	Whites	All	Blacks	Whites
Demographic Model*							
Quintile 1	Reference		Reference	Reference	Reference	Reference	Reference
Quintile 2	0.96 (0.60, 1.56)		1.00 (0.46, 2.15)	0.99 (0.53, 1.83)	1.10 (0.70, 1.73)	0.55 (0.26, 1.14)	1.67 (0.93, 2.98)
Quintile 3	1.35 (0.85, 2.14)		1.46 (0.72, 2.99)	1.34 (0.74, 2.42)	1.28 (0.83, 1.96)	1.02 (0.53, 1.96)	1.43 (0.81, 2.51)
Quintile 4	1.99 (1.25, 3.17)		2.61 (1.28, 5.34)	1.72 (0.94, 3.13)	1.49 (0.97, 2.28)	1.02 (0.52, 2.02)	1.83 (1.06, 3.18)
Quintile 5	2.17 (1.33, 3.52)		2.77 (1.34, 5.73)	1.86 (0.98, 3.93)	1.55 (0.99, 2.42)	1.15 (0.57, 2.29)	1.78 (0.99, 3.20)
Risk Factor Model†							
Quintile 1	Reference		Reference	Reference	Reference	Reference	Reference
Quintile 2	0.90 (0.54, 1.51)		0.96 (0.41, 2.24)	0.91 (0.46, 1.81)	1.14 (0.70, 1.86)	0.60 (0.27, 1.31)	1.71 (0.90, 3.25)
Quintile 3	1.14 (0.69, 1.87)		1.29 (0.58, 2.87)	1.11 (0.56, 2.19)	1.23 (0.76, 1.97)	1.09 (0.53, 2.22)	1.31 (0.69, 2.47)
Quintile 4	1.44 (0.86, 2.41)		2.31 (1.05, 5.10)	1.12 (0.55, 2.27)	1.09 (0.67, 1.78)	0.86 (0.41, 1.81)	1.21 (0.63, 2.31)
Quintile 5	1.73 (1.02, 2.93)		2.41 (1.08, 5.39)	1.50 (0.73, 3.08)	1.39 (0.85, 2.28)	1.03 (0.48, 2.20)	1.71 (0.90, 3.24)

^{*} CHD: Adjusted for age, sex, region, and race

Stroke: Adjusted for age, sex, region, race, and age*race

[†]CHD: Adjusted for age, sex, region, race, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and taking cholesterol-lowering medications

Stroke: Adjusted for age, sex, region, race, age*race, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, baseline cardiovascular disease, baseline atrial fibrillation, and baseline left ventricular hypertrophy

Table 4

Attenuation of the Association of D-dimer with Cardiovascular Disease by CRP *

	Stroke			CHD		
	Per Doubling of D-dimer		Percent Decrease in HR (Without - With CRP)	Per Doubling of D-dimer		Percent Decrease in HR (Without - With CRP)
	HR for D-dimer	HR for D-dimer adjusted for CRP		HR D-dimer	HR for D-dimer adjusted for CRP	
All	1.15 (1.01, 1.31)	1.13 (0.99, 1.29)	13.3% (0.0%, 40.0%)	1.27 (1.11, 1.45)	1.22 (1.05, 1.40)	22.7% (5.5%, 41.1%)
Blacks	1.12 (0.92, 1.34)	1.08 (0.89, 1.31)	33.3% (0.0%, 67.5.0%)	1.33 (1.11, 1.59)	1.28 (1.06, 1.55)	15.1% (0.6%, 33.0%)
Whites	1.19 (0.99, 1.42)	1.17 (0.98, 1.40)	10.5% (0.0%, 27.9%)	1.21 (1.01, 1.47)	1.15 (0.94, 1.40)	28.5% (6.7%, 61.9%)

* CHD: Adjusted for age, sex, region, race, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, total cholesterol, HDL cholesterol, and taking cholesterol-lowering medications

Stroke: Adjusted for age, sex, region, race, age* race, systolic blood pressure, use of antihypertensive medications, diabetes, current smoking, baseline cardiovascular disease, baseline atrial fibrillation, and baseline left ventricular hypertrophy