Association of Hemostatic Variables With Prevalent Cardiovascular Disease and Asymptomatic Carotid Artery Atherosclerosis

Aaron R. Folsom, Kenneth K. Wu, Eyal Shahar, C.E. Davis, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators

The relation of hemostatic factor levels to the occurrence of cardiovascular disease is incompletely established. The Atherosclerosis Risk in Communities Study measured fibrinogen, factor VII, factor VIII, von Willebrand factor, antithrombin III, protein C, activated partial thromboplastin time, and other cardiovascular risk factors in nearly 15,000 men and women aged 45 to 64. This analysis assessed the relations of these hemostatic factors with prevalent cardiovascular disease and asymptomatic carotid artery intimal-medial thickness measured by B-mode ultrasound. Compared with participants without cardiovascular disease, those with cardiovascular disease had higher levels of fibrinogen, factor VIII, and von Willebrand factor in both sexes. The other hemostatic factors were less consistently associated with prevalent cardiovascular disease. Only fibrinogen was associated with carotid intimal-medial thickness. Adjusted for age, race, and field center, the odds ratio for carotid wall thickness in the 90th percentile or greater, compared with <50th percentile, for each SD higher fibrinogen concentration (65 mg/dL) was 1.42 (95% confidence interval, 1.25, 1.62) in men and 1.43 (1.25, 1.64) in women. This population-based study provides further evidence that fibrinogen and possibly factor VIII and von Willebrand factor are risk factors for cardiovascular disease.

(Arterioscler Thromb. 1993;13:1829-1836.)

KEY WORDS • blood coagulation factors • cerebrovascular disorders • fibrinogen • coronary disease

Evidence has accumulated that hemostatic factors may play a role in the occurrence of cardiovascular diseases. Plasma fibrinogen and factor VII have been shown in prospective epidemiological studies to be positively associated with cardiovascular disease incidence. Clinical or epidemiological evidence suggests that other factors, such as factor VIII, von Willebrand factor, protein C, and antithrombin III may also be related to cardiovascular disease occurrence. It is uncertain, however, whether hemostatic factors are associated only with the thrombotic component of cardiovascular disease or also with the atherosclerotic process.

We recently reported that 385 asymptomatic cases with increased carotid intimal-medial wall thickness (an indicator of atherosclerosis) in the Atherosclerosis Risk in Communities (ARIC) Study had higher fibrinogen levels than 385 normal control subjects. In this report we extend the ARIC analysis of hemostatic factors and carotid intimal-medial thickness to the whole cohort of 15,800 participants and also report the associations of multiple hemostatic factors with prevalent cardiovascular diseases.

Methods

The ARIC Study is a prospective investigation of atherosclerosis and clinical atherosclerotic diseases in four US communities: Forsyth Co, NC; Jackson, Miss; the northwest suburbs of Minneapolis, Minn; and Washington Co, Md. One aspect of the study includes examination and follow-up of a biracial cohort totalling 15,800 persons aged 45 to 64 years at recruitment in 1986 to 1989.

A baseline home interview assessed participants' health behaviors, sociodemographics, and disease histories. A clinic examination included measurements of cardiovascular disease risk factors, a 12-lead electrocardiogram, and a B-mode ultrasound exam of selected arterial sites. Subjects were asked to fast for 12 hours before the clinic examination. Blood was drawn from an antecubital vein of seated participants with minimal trauma (monitored by the time required to fill the first blood tube). Specimens were collected into vacuum tubes containing sodium citrate (hemostatic factors), EDTA (lipids), and a serum separator gel (glucose). The tubes were centrifuged at 3000g for 10 minutes at 4°C. After separation, aliquots were quickly frozen at −70°C until analysis within a few weeks.

Hemostatic variables were measured at the University of Texas Health Science Center at Houston. The reference material for assays was the Universal Coagu-
loration Reference Plasma (Thromboscreen, Pacific Hemostasis, Curtis Matheson Scientific, Inc, Ventura, Calif). Detailed methods have been published.10,11 In brief, fibrinogen was measured by the thrombin-time titration method12 with reagents and calibration materials (Fibriquick) obtained from General Diagnostics (Organo-Technika Co, Morris Plains, NJ). Factor VII and VIII activities were measured by determining the ability of the tested sample to correct the clotting time of human factor VII– or factor VIII–deficient plasma obtained from George King Biomedical Inc, Overland Park, Kan. The plasma factor VII and VIII levels were expressed as a percentage by relating the clotting time to a standard calibration curve constructed for each assay. von Willebrand factor antigen and protein C antigen were determined by enzyme-linked immunosorbent assay kits from American Bioproducts Co, Parsippany, NJ. AT-III activity was measured by a chromogenic substrate method and expressed as a percentage of the standard. Activated partial thromboplastin time (aPTT) was measured on an automated coagulometer (Coag-A-Mate X-2, General Diagnostics). Strict internal quality controls were instituted to ensure the accuracy and precision of these assays. Reliability coefficients (method variance plus intra-individual variance divided by total variance) obtained from repeated testing of individuals over several weeks were 0.72 for fibrinogen, 0.78 for factor VII, 0.86 for factor VIII, 0.68 for von Willebrand factor, 0.56 for protein C, 0.42 for AT-III, and 0.92 for aPTT.13

Plasma total cholesterol14 and triglycerides15 were measured by enzymatic methods, and low-density lipoprotein (LDL) cholesterol was calculated.16 High-density lipoprotein (HDL) cholesterol was measured after dextran-magnesium precipitation.17 Serum glucose was assessed by the hexokinase method. Because an oral glucose-tolerance test was not performed, prevalent diabetes mellitus was defined as a fasting glucose level ≥140 mg/dL, nonfasting glucose level ≥200 mg/dL, or a history of treatment for diabetes.

Circumferences of the waist (umbilical level) and hip (maximum buttocks) were measured to the nearest centimeter. The ratio of waist and hip circumferences was calculated as a measure of fat distribution. Three measurements of systolic and diastolic fifth-phase blood pressures were taken in the right arm of each seated participant. The mean of the last two measurements was used. Prevalent hypertension was defined as systolic pressure ≥140 mm Hg, diastolic pressure ≥90 mm Hg, or use of antihypertensive agents. Prevalent "coronary heart disease" was defined as a history of angina pectoris by the Rose questionnaire,18 a self-reported history of a physician-diagnosed heart attack, evidence of a prior myocardial infarction by electrocardiogram, or a history of cardiovascular surgery or coronary angioplasty. Prevalent "cardiovascular disease" was defined as prevalent coronary heart disease, intermittent claudication by the Rose questionnaire,19 or a self-reported history of a physician-diagnosed stroke.

Carotid artery atherosclerosis was determined by high-resolution B-mode ultrasound.19 Trained technicians in each field center scanned the extracranial carotid arteries bilaterally. The arteries were divided into three segments: the distal 1.0-cm straight portion of the common carotid artery, the carotid bifurcation, and the proximal 1.0 cm of the internal carotid artery. Thus, including both sides, six artery segments were scanned. B-mode data were recorded onto high-resolution 3/4-in. cassettes and interpreted by trained readers according to a standardized protocol.20 Using magnified images, readers recorded for each 1-cm segment as many as 11 coordinate points from each echogenic interface that identified an arterial boundary. Between-reader and within-reader coefficients of reliability for average artery wall thickness in the three segments were all 0.90 or greater.20 Because of technical difficulties, the scans of the 1858 participants examined during the first 6 months of the study have not yet been read. The unread group was approximately a random sample of the entire ARIC cohort of 15 800 because the ARIC design involved monthly probability sampling.

The variable of primary interest was the average intimal-medial thickness of the far wall of the six carotid artery segments. The rationale for intimal-medial thickness as an indicator of early atherosclerosis has been described,21 as has its strong association with major cardiovascular disease risk factors.9 Poor visualization of carotid boundaries led to missing information in part of the six segments on some scans. Where possible, values for the missing boundaries were imputed from the visualized boundaries. The first step of imputation was geometric interpolation of any of the 11 coordinate points that were missing by using a cubic splining technique. No splining was done when fewer than three coordinate points were available. If there were still insufficient data for a segment, wall thickness was imputed from sex- and race-specific multivariate linear models, employing as predictors the visualized boundaries and two variables related to poor visualization, namely body mass index and artery depth. The imputation models were fit by the EM algorithm22 using BMDP5V.23 This report is based on 13 332 scans with currently available ultrasound readings. Some imputation was required for 17% of the common carotids, about 39% of the carotid bifurcations, and 58% of the internal carotids. For analysis, we took the overall unweighted average of the mean intimal-medial wall thickness (measured or imputed) of the six arterial segments.

Although the ARIC cohort totalled 15 800 participants, this analysis was restricted to 14 904 participants who reported their race as black or white and who responded negatively to the question, "Are you taking 'blood-thinning medications'?” Participant characteristics were described as sex- and race-specific means and standard deviations or prevalence estimates. Hemostatic factor levels of those with prevalent cardiovascular disease versus no cardiovascular disease at baseline were compared by t tests. Odds ratios for prevalent cardiovascular disease per 1 SD differences in hemostatic factor levels were computed from multiple logistic regression models. Two models were examined: the first adjusted for age, race, and ARIC field center; the second adjusted for the three aforementioned factors plus LDL cholesterol, HDL cholesterol, diabetes, hypertension, cigarette-years of smoking, and waist-to-hip ratio. Adjustment for aspirin use and dietary factors was not required because they were not appreciably associated with the hemostatic factors studied. The analysis of carotid wall thickness data was restricted to those...
TABLE 1. Race- and Sex-Specific Baseline Characteristics of Participants in the ARIC Study, 1986 to 1989

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age, y</th>
<th>LDL cholesterol, mg/dL</th>
<th>HDL cholesterol, mg/dL</th>
<th>Waist/hip ratio</th>
<th>Current smoking, %</th>
<th>Hypertension, %</th>
<th>Diabetes mellitus, %</th>
<th>Fibrinogen, mg/dL</th>
<th>Factor VII, %</th>
<th>Factor VIII, %</th>
<th>von Willebrand factor, %</th>
<th>Protein C, μg/mL</th>
<th>Antithrombin III, %</th>
<th>aPTT, seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men Black</td>
<td>54±6</td>
<td>137±41</td>
<td>51±17</td>
<td>0.94±0.06</td>
<td>38</td>
<td>54</td>
<td>15</td>
<td>307±70</td>
<td>111±29</td>
<td>141±43</td>
<td>130±54</td>
<td>3.0±0.6</td>
<td>113±22</td>
<td>29.6±3.4</td>
</tr>
<tr>
<td>Men White</td>
<td>55±6</td>
<td>140±36</td>
<td>43±12</td>
<td>0.97±0.05</td>
<td>25</td>
<td>26</td>
<td>7</td>
<td>294±63</td>
<td>112±24</td>
<td>123±34</td>
<td>113±44</td>
<td>3.1±0.6</td>
<td>108±21</td>
<td>29.5±3.0</td>
</tr>
<tr>
<td>Women Black</td>
<td>53±6</td>
<td>138±44</td>
<td>58±17</td>
<td>0.91±0.08</td>
<td>25</td>
<td>56</td>
<td>6</td>
<td>298±72</td>
<td>123±31</td>
<td>150±48</td>
<td>130±54</td>
<td>3.2±0.6</td>
<td>116±23</td>
<td>28.9±3.1</td>
</tr>
<tr>
<td>Women White</td>
<td>54±6</td>
<td>135±40</td>
<td>58±17</td>
<td>0.89±0.08</td>
<td>25</td>
<td>56</td>
<td>6</td>
<td>299±60</td>
<td>126±31</td>
<td>128±35</td>
<td>111±42</td>
<td>3.3±0.6</td>
<td>28.7±2.8</td>
<td></td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and aPTT, activated partial thromboplastin time. Values are mean±SD or percent. n's (maximum available) were 1560 black men, 4928 white men, 2569 black women, and 5847 white women.

without prevalent cardiovascular disease at baseline. Age-adjusted average wall thickness values were computed according to quartiles of hemostasis variables using a weighted ANCOVA. (Weights accounted for the number of sites for which the mean wall thickness was imputed rather than measured.) The relation of carotid wall thickness to the hemostatic variables was further assessed using weighted least-squares multiple regression models. Finally, odds ratios for thickened carotid artery walls (≥90th percentile) versus <50th percentile were computed from multiple logistic regression models.

Results

Table 1 shows the characteristics of ARIC Study participants who reported that they did not take "blood-thinning medications" at baseline. Detailed differences in hemostasis variables among race- and sex-specific groups have been described fully in a previous report. Participants with prevalent cardiovascular disease had 10 to 19 mg/dL higher fibrinogen concentrations than those free of cardiovascular disease in all race- and sex-specific groups (Table 2). Factor VII was higher in women with cardiovascular disease but not in men. Factor VIII and von Willebrand factor were higher in participants with cardiovascular disease in all race- and sex-specific groups, although not always at P<.05. Protein C, AT-III, and aPTT showed no material associations with prevalent cardiovascular disease as a whole.

As Table 3 shows, after adjustment for age, race, and ARIC field center, the odds ratio of prevalent cardiovascular disease per 1 SD (65 mg/dL) higher fibrinogen
TABLE 3. Sex-Specific Odds Ratios for Prevalent Cardiovascular Disease Associated With Each 1 SD Hemostatic Factor Difference, ARIC Study, 1986 to 1989

<table>
<thead>
<tr>
<th>Factor</th>
<th>SD</th>
<th>OR₁ (95% CI)</th>
<th>OR₂</th>
<th>OR₃ (95% CI)</th>
<th>OR₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>65 mg/dL</td>
<td>1.25* (1.16, 1.34)</td>
<td>1.16*</td>
<td>1.14* (1.07, 1.22)</td>
<td>1.05</td>
</tr>
<tr>
<td>Factor VII</td>
<td>30%</td>
<td>0.99 (0.91, 1.08)</td>
<td>0.95</td>
<td>0.95* (0.90, 1.03)</td>
<td>1.09*</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>40%</td>
<td>1.15* (1.06, 1.25)</td>
<td>1.10*</td>
<td>1.14* (1.07, 1.21)</td>
<td>1.07</td>
</tr>
<tr>
<td>von Willebrand factor</td>
<td>50%</td>
<td>1.16* (1.07, 1.25)</td>
<td>1.12*</td>
<td>1.07* (1.00, 1.15)</td>
<td>1.02</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>20%</td>
<td>1.09* (1.02, 1.17)</td>
<td>1.07</td>
<td>0.97 (0.91, 1.03)</td>
<td>0.94</td>
</tr>
<tr>
<td>Protein C</td>
<td>0.6 μg/mL</td>
<td>0.97 (0.89, 1.05)</td>
<td>0.94</td>
<td>1.08* (1.02, 1.15)</td>
<td>1.04</td>
</tr>
<tr>
<td>aPTT</td>
<td>3 seconds</td>
<td>1.03 (0.96, 1.11)</td>
<td>1.03</td>
<td>0.89* (0.83, 0.96)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; OR, odds ratio; CI, confidence interval; and aPTT, activated partial thromboplastin time.

OR₁, odds ratio adjusted for age, race, and field center. OR₂, odds ratio adjusted for age, race, field center, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, hypertension, waist-to-hip ratio, and cigarette-years of smoking.

*P<.05.

value was 1.25 in men and 1.14 in women (both P<.05). Among those who had never smoked this fibrinogen odds ratio was 1.20 in men and 1.07 in women; among past or present smokers the odds ratio was 1.23 (men) and 1.21 (women). Odds ratios were also greater than 1.0 per 1 SD higher factor VII (women only), factor VIII (both sexes), von Willebrand factor (both sexes), AT-III (men only), and protein C (women only) value and less than 1.0 for 1 SD higher aPTT value (women only). Further adjustment for lifestyle and biochemical correlates of the hemostatic factors (Table 3) appreciably reduced the odds ratios.

Age-, race-, and center-adjusted odds ratios per 1 SD of each hemostatic factor are shown for prevalent coronary heart disease (1616 cases), stroke (175 cases), and intermittent claudication (100 cases) separately in Figure 1. Odds ratios for coronary heart disease were nearly identical to those of model 1 in Table 3, because coronary heart disease comprised most of the prevalent cardiovascular disease. Odds ratios for stroke were ≥1.2 (P≤.05) for the following: fibrinogen (odds ratio, 1.2 in men and 1.4 in women), factor VII (1.3 in women), factor VIII (1.3 in women), von Willebrand factor (1.3 in women), and protein C (1.3 in men). For claudication, odds ratios were ≥1.4 (P<.05) for fibrinogen (1.4 in men and 1.5 in women), factor VIII (1.5 in men and 1.4 in women), and von Willebrand factor (1.7 in men).

The age-adjusted relations of carotid artery intimal-medial wall thickness to hemostatic factors were examined in subjects free of prior cardiovascular disease. The only consistent association was for fibrinogen (Figure 2); in all four race- and sex-specific groups, the association was positive with generally a dose response. The fibrinogen association was significantly stronger (P<.01) in men than women. There was no linear association for factor VII, factor VIII, or von Willebrand factor (Figure 2) nor for protein C, AT-III, or aPTT. There also was no U-shaped association with AT-III, as has been previously suggested.6

After pooling the data for both races, fibrinogen was still the only factor showing an age-, race-, and center-adjusted association with carotid wall thickness at P<.01 (Table 4, top half). Overall and in most smoking subgroups, there was about a 0.02-mm greater carotid artery

![Graphs of sex-specific and age-, race-, and center-adjusted odds ratios for prevalent cardiovascular diseases per 1 SD greater hemostasis variable level. Numbers of participants were coronary heart disease (CHD), 699 men and 917 women; stroke, 86 men and 89 women; and leg claudication, 47 men and 53 women. FIBR. indicates fibrinogen; F., factor; VWF, von Willebrand factor; AT III, antithrombin III; PR. C, protein C; and aPTT, activated partial thromboplastin time.](http://atvb.ahajournals.org/DownloadedFrom)
Fibrinogen Factor VII

QUARTILE (mg/dL)
- <259
- 259-292
- 293-334
- >334

Race-Sex Group
- WM
- BW
- Men
- Women

Factor VIII

QUARTILE (%)
- <105
- 105-125
- 126-149
- >149

Race-Sex Group
- WM
- BW
- Men
- Women

Von Willebrand Factor

QUARTILE (%)
- <83
- 83-108
- 109-140
- >140

Race-Sex Group
- WM
- BW
- Men
- Women

FIG 2. Bar graphs of age-adjusted, race- and sex-specific mean carotid intimal-medial wall thickness by quartiles of hemostasis variables among participants free of baseline cardiovascular disease. BM indicates black men; WM, white men; BW, black women; and WW, white women.

Wall thickness per each SD greater fibrinogen concentration. Adjustment for other fibrinogen correlates (Table 4, bottom half) attenuated the estimates. Adjustment for hematocrit and platelet count or tests for interactions of fibrinogen with these two factors failed to change these estimates further (data not shown).

Although factor VII was not associated with carotid wall thickness when adjusted only for age, race, and

TABLE 4. Sex- and Smoking-Status-Specific Differences in Average Carotid Artery Intimal-Medial Wall Thickness in Relation to Each 65 mg/dL Greater Fibrinogen Concentration, ARIC Study, 1986 to 1989

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Difference, mm</td>
</tr>
<tr>
<td>Adjusted for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, race, field center</td>
<td>4621</td>
<td>0.018†</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1244</td>
<td>0.023†</td>
</tr>
<tr>
<td>Former smokers</td>
<td>1967</td>
<td>0.015†</td>
</tr>
<tr>
<td>Never smokers</td>
<td>1410</td>
<td>0.022†</td>
</tr>
<tr>
<td>Age, race, field center, and others*</td>
<td>Overall</td>
<td>4501</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1205</td>
<td>0.012</td>
</tr>
<tr>
<td>Former smokers</td>
<td>1916</td>
<td>0.006</td>
</tr>
<tr>
<td>Never smokers</td>
<td>1380</td>
<td>0.013†</td>
</tr>
</tbody>
</table>

*Other covariates were low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, hypertension, and waist-to-hip ratio. Overall model also adjusted for cigarette-years of smoking.
†P<.05.

ARIC indicates Atherosclerosis Risk in Communities and CI, confidence interval.
Table 5. Sex-Specific Odds Ratios for Carotid Artery Atherosclerosis in Relation to Each 65 mg/dL Greater Fibrinogen Concentration, ARIC Study, 1986 to 1989

<table>
<thead>
<tr>
<th>Adjustment for</th>
<th>Odds Ratio (95% CI) Men</th>
<th>Odds Ratio (95% CI) Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, race, field center</td>
<td>1.42 (1.25, 1.62)</td>
<td>1.43 (1.25, 1.64)</td>
</tr>
<tr>
<td>Age, race, field center, and others*</td>
<td>1.15 (1.00, 1.33)</td>
<td>1.11 (0.95, 1.31)</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities and CI, confidence interval.

*Other covariates were low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, hypertension, waist-to-hip ratio, and cigarette-years of smoking.

center, it surprisingly became inversely associated with wall thickness after adjustment for the larger group of covariates. In this multivariable model (not shown), each 1 SD higher factor VII value (30%) predicted a lower wall thickness by 0.006 mm in men ($P=.11$) and 0.009 mm in women ($P<.001$).

The carotid wall thickness data were used to further stratify participants into a group with clearly thickened arteries ($\geq 90$th percentile) and one with little thickening ($<50$th percentile). From a logistic regression model, the estimated age-, race-, and field center-adjusted odds ratio (95% confidence interval) for thickened walls in relation to a 1 SD greater fibrinogen concentration was 1.42 (1.25, 1.62) in men and 1.43 (1.25, 1.64) in women (Table 5). The odds ratios were smaller after adjustment for other risk factors.

Discussion

The major drawback of clinical, cross-sectional studies of acute cardiovascular disease and hemostatic factors is that they cannot distinguish adequately whether alterations of hemostasis are causal or consequent. In ARIC as well, hemostatic factors could have been altered as a result of chronic atherosclerotic lesion fissuring and stimulation of hemostasis. Yet, ARIC has several advantages: it is population-based, its measurements have been carefully standardized, and it has assessed prevalent cardiovascular disease under non-acute circumstances. Furthermore, associations with asymptomatic carotid atherosclerosis should be less subject to such problems of temporality than those based on symptomatic disease. The validity of carotid intimal-medial wall thickness as a measure of atherosclerosis has been demonstrated, and in the ARIC Study wall thickness was also strongly associated with the major cardiovascular disease risk factors, namely hypertension, hypercholesterolemia, and cigarette smoking.

Fibrinogen

The finding that fibrinogen is positively related to prevalent cardiovascular disease is consistent with abundant evidence that it is an important cardiovascular risk factor. Meade identifies several mechanisms by which fibrinogen may act to produce cardiovascular disease: its plasma concentration is (1) an important determinant of the amount of fibrin formed during thrombosis, (2) an important determinant of blood viscosity, and (3) a mediator of platelet aggregation. While there is no universally accepted standard for fibrinogen assays and absolute levels vary from study to study, higher fibrinogen concentrations have been associated with a greater occurrence of coronary heart disease, peripheral artery disease, transient ischemic attack, stroke, and cardiovascular events in stroke survivors. In ARIC fibrinogen was associated with coronary heart disease, stroke, and intermittent claudication, consistent for blacks and whites and men and women. Associations were weaker after adjustment for other risk factors; however, this is expected, given that many of these may directly cause perturbations in fibrinogen and thus does not diminish the likely importance of fibrinogen as a marker for cardiovascular disease.

Factor VIII and von Willebrand Factor

Factor VIII and von Willebrand factor, which bond together in the blood, were correlated ($r=.7$) in ARIC. Both were associated positively with prevalent cardiovascular disease but not with asymptomatic early carotid atherosclerosis. The odds ratios of prevalent cardiovascular disease per each SD of factor VIII and von Willebrand factor were modest: they were highest among men for intermittent claudication of the leg and among women for stroke and intermittent claudication.

Factor VIII is involved in hemostasis and thrombosis via the intrinsic coagulation system. von Willebrand factor, which plays roles in platelet adhesion to damaged vascular walls, in platelet aggregation, and in stabilizing factor VIII activity, is correlated positively with plasma levels of several atherogenic growth factors. In addition, increased levels of von Willebrand factor, particularly in unusually large multimers, may be a marker of endothelial cell dysfunction. Prospective population studies have reported factor VIII to be positively but nonsignificantly associated with coronary disease incidence and significantly associated with prevalent cerebrovascular disease. Additionally, a pro-
spective clinical investigation reported factor VII to be associated with ischemic events among vascular disease patients.\(^4\) von Willebrand factor has been associated positively with the risk of recurrent ischemic events and death in vascular disease patients.\(^4\) That factor VIII and von Willebrand factor are associated with clinical cardiovascular disease but not asymptomatic carotid atherosclerosis may indicate that they are involved more in the acute thrombotic component of cardiovascular disease than in atherogenesis. Alternatively, because factor VIII is an acute-phase reactant, it is possible that its perturbations are a consequence rather than a cause of atherosclerotic cardiovascular disease.

**Factor VII**

The finding that factor VII was associated weakly with prevalent cardiovascular disease only in women and not associated with carotid artery wall thickness was unexpected, given the positive association of factor VII with cardiovascular death in the Northwick Park Heart Study.\(^2\) The earlier ARIC case-control study of carotid atherosclerosis suggested a weak positive association that was eliminated by adjustment for covariates.\(^7\) Covariate adjustment in the full ARIC data set made the factor VII association inverse. Methods of factor VII measurement may account for discrepancies among the studies. However, this and one other population-based prevalence study,\(^8\) as well as several prospective clinical studies,\(^9\)\(^10\) have now failed to confirm a factor VII association with cardiovascular disease.

**Other Hemostatic Factors**

AT-III, protein C, and aPTT were not associated with prevalent cardiovascular disease or carotid atherosclerosis. In the Northwick Park Heart Study, AT-III was reported to have a U-shaped relation to cardiovascular disease incidence;\(^9\) in contrast, AT-III did not predict ischemic events in a prospective study of vascular disease patients.\(^4\) Both low\(^4\) and high\(^8\) protein C values have been reported in association with ischemic cardiovascular disease. Thus, evidence is weak that these factors play a role in atherosclerotic cardiovascular disease. It should be noted, however, that the intra-individual and method variability of AT-III and protein C are high enough that small but real associations may be obscured.\(^9\)

**Summary**

The current population-based study provides further evidence that fibrinogen and possibly factor VIII and von Willebrand factor are risk factors for cardiovascular disease. The prospective data of the ARIC Study will provide additional evidence for or against the role of hemostatic variables in cardiovascular disease risk.

**Acknowledgments**

Support was provided by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. The authors thank Ms Laura Kemmis for manuscript preparation, as well as the participants, investigators, and staff of ARIC for their important contributions. We especially thank Jeannette Bensen, Catherine Paton, Amy Haire, Delilah Posey, Royanne Barry, Faye Blackburn, Rajam Radhakrishnan, Sheshadri Raju, Marilyn Bowers, Bryna Lester, Gail Murton, Virginia Wyum, Carol Christman, Sonny Harrell, Joel Hill, Joan Nelling, Valerie Stinson, Pam Pifie, Hoang Pham, Teri Trevino, John Crouch, Debbie Rubin-Williams, Cynthia Stahoviak, and Yi-Hsin Yang.

**References**

A R Folsom, K K Wu, E Shahar and C E Davis

doi: 10.1161/01.ATV.13.12.1829

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/13/12/1829

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/