Thrombosis of a disrupted atherosclerotic plaque triggers most ischemic cardiovascular events. Because thrombi are resolved through the action of the fibrinolytic system, researchers have hypothesized that impaired fibrinolytic function may be a risk factor for ischemic events. Fibrinolysis involves the action of tissue plasminogen activator (tPA) on plasminogen to produce plasmin, which, in turn, degrades cross-linked fibrin to D-dimer and other fibrin degradation products. Plasmin also activates matrix metalloproteinases that, in turn, degrade the extracellular matrix.1 Plasminogen activator inhibitor-1 (PAI-1) is a major plasma inhibitor of tPA.

Prospective studies have generally reported that the risk of ischemic cardiovascular events is increased in participants with coagulation activation or impaired fibrinolytic function, reflected as increased levels of tPA antigen, PAI-1, fibrin fragment D-dimer, or plasmin-antiplasmin complex or as delayed clot lysis.2-21 However, there are relatively few large prospective studies relating fibrinolytic factors to first ischemic events in population-based samples of healthy subjects.9-21 These studies (Table 1) did not always find the association between impaired fibrinolytic function and ischemic events to be independent of other cardiovascular risk factors. Furthermore, no prospective study, to our knowledge, has reported on the association of plasma plasminogen concentration with incident ischemic events. Therefore, we examined the association of several plasma markers of fibrinolytic function (tPA antigen, PAI-1 antigen, plasminogen, and D-dimer) and a marker of coagulation activation (prothrombin fragment F1.2) with the risk of incident coronary heart disease (CHD) in a cohort of middle-aged adults.

**Methods**

**Study Population and Baseline Measurements**

In 1987 through 1989, the Atherosclerosis Risk in Communities (ARIC) Study22 recruited a population-based cohort of persons aged 45 to 64 years from 4 US communities. A total of 15 792 participants completed a home interview and clinic examination. The ARIC Study reexamined the participants from 1990 to 1992 (93% return rate), 1993 to 1995 (86% return rate), and 1995 to 1997 (80% return rate).

Technicians measured resting blood pressure 3 times with a random-zero sphygmomanometer and averaged the last 2 measurements for analysis. We expressed physical activity as a sports index.
TABLE 1. Prospective Epidemiological Studies of Impaired Fibrinolytic Function and Incident Cardiovascular Disease on Initially Healthy Subjects

<table>
<thead>
<tr>
<th>Reference</th>
<th>End Point</th>
<th>Reduced Clot Lysis</th>
<th>PAI-1</th>
<th>tPA or tPA/PAI-1 Complex</th>
<th>D-Dimer</th>
<th>Plasmin-Antiplasmin</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Uni</td>
<td>Multi</td>
<td>Uni</td>
<td>Multi</td>
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<tr>
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</tr>
<tr>
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<td></td>
<td></td>
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</tr>
<tr>
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</tr>
<tr>
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<td></td>
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<td>Smith et al16</td>
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<td></td>
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<tr>
<td>Gram et al121</td>
<td>CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
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</tbody>
</table>

*Uni indicates unadjusted for risk factors other than age; Multi, multivariate adjustment for risk factors; +, positive association; and 0, no association.

*Included some participants with preexisting CHD.

-ranging from 0 (low) to 5 (high).23 Technicians measured waist (umbilical level) and hips (maximum) to compute the waist-to-hip ratio. Technicians measured average carotid intima-media thickness (IMT) by using standardized B-mode ultrasonography.24 We defined prevalent CHD at baseline as a self-reported history of a physician-diagnosed heart attack, prior myocardial infarction (MI) by ECG, prior cardiovascular surgery, or prior coronary angioplasty. The ARIC Study also measured prior stroke or transient ischemic attack through a standardized interview.25

Using a standardized protocol,26–28 ARIC technicians drew fasting blood samples into vacuum tubes containing serum-separating gel, sodium citrate, EDTA, or a combination anticoagulant solution (D-Phe-1-Pro-D-Arg chloromethyl ketone, isobutylmethylxanthine, aprotinin, and EDTA). The technicians centrifuged samples at 4°C and filtered the plasma from the combination anticoagulant tube through a 0.45-m Millipore filter. They then froze samples at −70°C until analyzed.

At baseline, ARIC laboratories measured fasting serum insulin, white blood cell count, plasma fibrinogen,29 total cholesterol,30 HDL cholesterol,31 triglycerides,32 and Lp(a) and computed LDL cholesterol.33 We defined diabetes as fasting serum glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or a physician diagnosis or pharmacological treatment for diabetes.

Ascertainment and Classification of Incident CHD Cases

The ARIC Study followed the cohort and ascertained CHD events.22,34 For the present study, we included CHD events occurring between ARIC visit 1 and December 31, 1993. The mean follow-up time was 4.3 years (maximum 7.1 years). We defined CHD incidence as (1) a definite or probable MI,34 (2) a silent MI between examinations by ECG, (3) a definite CHD death,34 or (4) a coronary revascularization.

Cohort Sample

We used a case-cohort design for the present study, in which information on plasma fibrinolytic factors was determined for CHD cases and a stratified random sample of the entire ARIC cohort of 15,792 participants. We first excluded participants in Forsyth County who were not white or African American (n=21) and participants in Minneapolis and Washington County who were not white (n=82), because these race-center strata were too small for meaningful sample weighting. We then excluded participants with prevalent CHD (or unknown status) at baseline (n=1112), participants with a history of stroke or transient ischemic attack at baseline (n=264), and participants with missing sampling or event information (n=7). All incident CHD cases were sampled (n=469). For the reference cohort sample (n=986), we oversampled noncases with thin average carotid IMT measurements at baseline (<30 percentile) and also stratified the sampling by age and sex. Thirty-seven participants were selected both as cases and into the reference cohort.

Laboratory Measurements

After the ARIC Study had identified the incident cases and cohort sample (total number of participants=1418), technicians attempted to retrieve these participants’ baseline samples, frozen from 1987 to 1989. However, because of an interim freezer meltdown and some other missing samples, we had complete thawed samples for only 1018 (326 cases, of which 28 were in the cohort sample, and 692 noncases). Compared with those not included in the analysis, those included were similar (within the case and noncase groups) for 13 risk characteristics (P>0.05); however, those included had a somewhat lower mean carotid IMT (0.04 mm in cases, 0.03 mm in noncases) and a higher mean sports index (cases only) and were less likely to be African American (cases only). These differences were expected to have little effect on the present study.

After the specimens were thawed (1997 to 1998), the ARIC Hemostasis Laboratory measured tPA antigen in citrated plasma with the use of an enzyme immunoassay (Asserachrom tPA kit, Diagnostica Stago).35 The laboratory measured PAI-1 antigen in citrated plasma by ELISA with use of an IMUBIND Plasma PAI-1 kit (American Diagnostica).36 This assay detects active and inactive forms of PAI-1 and complexes of tPA/PAI-1 and urokinase plasminogen activator/PAI-1, and its sensitivity level is <1 ng/mL. The laboratory measured plasminogen in citrated plasma by chromogenic
assay with the use of an Actichrome PLG kit (American Diagnostica). It measured D-dimer in citrated plasma by an enzyme immunoassay procedure (Asserachrom D-Di kit, Diagnostica Stago). The laboratory measured F1.2 with a Thrombostnika F1.2 ELISA (Organon Teknika). It measured serum C-reactive protein (CRP) by an ELISA obtained from United Biotech Magiwell. The sensitivity of the assay is <1 μg/L, and the minimal detectable concentration of CRP is 0.35 μg/L. The laboratory used an enzyme immunoassay to measure soluble thrombomodulin in citrated plasma. We tested assay reliability by using blinded duplicate specimens from different tubes of single blood drawn (n=54 to 71 pairs). Pearson correlation coefficients were 0.76 for PAI-1, 0.91 for tPA antigen, 0.70 for plasminogen, 0.27 (0.80 after excluding outliers >1000 ng/mL) for D-dimer, and 0.50 (0.66 after excluding outliers >5 mmol/L) for F1.2. An earlier ARIC study involving fresh samples taken 3 times at 1- to 2-week intervals, to assess intraindividual variability, yielded reliability coefficients of 0.81 for tPA, 0.72 for PAI-1, and 0.72 for D-dimer.

Data Analysis
The laboratory classified some samples (n=101) as lipemic, as hemolyzed, or as having microprecipitates on thawing. Statistical analyses that were run including and excluding these samples were similar, so we included them. We excluded some extreme outlying values: PAI-1≥383 ng/mL (n=2), CRP≥36.5 mg/L (n=11), F1.2≥253 nmol/L (n=3), and D-dimer≥15 000 ng/mL (n=6).

We determined interrelations among hemostatic factors by using Pearson correlations in the cohort random sample after appropriate weighting for the stratified case-cohort sampling design. To test the study hypotheses, we first used weighted ANCOVA to compute age-, race-, and sex-adjusted mean values of fibrinolytic factors for CHD cases versus noncases. We used geometric means for several of the hemostatic variables that were right-skewed. Reported probability values are 2-sided.

To determine the relation of fibrinolytic factors with other variables, some of which may be confounders in this analysis, we categorized the cohort sample into quintiles for each fibrinolytic factor and used ANCOVA to compute age-, race-, and sex-adjusted mean levels or percentages of the other variables for each quintile.

We computed relative risks and 95% CIs of CHD in relation to categories of study variables by a weighted proportional hazards regression, accounting for the stratified random sampling, and the case-cohort design by Barlow’s method. We analyzed each hemostatic factor separately in 2 regression models. In the first model, we adjusted for age, sex, and race (black, white). In the second multivariate model, we adjusted for sex, age, race, and other major CHD risk factors: smoking status (never, former, current), total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive medication, and diabetes. We ran additional regression models, as needed, by using continuous variables or by examining subgroups to test the independence of observed associations.

Results
Descriptive Characteristics
The final sample included 326 incident CHD cases (183 definite or probable MI, 19 silent MI, 34 definite fatal CHD, and 90 revascularization procedure) and a reference cohort sample of 720 (of whom 28 were also CHD cases). Twenty-two percent of the CHD case subjects were black, and 72% were men.

There were moderate correlations between tPA and PAI-1 (r=0.36) and between tPA and plasminogen (r=0.17) but not between PAI and plasminogen (r=-0.05). D-dimer and F1.2 were not correlated with other fibrinolytic variables.

Mean Differences in Fibrinolytic Factors
Compared with participants who remained free of CHD, those who developed CHD had higher age-, sex-, and race-adjusted mean values of tPA antigen, PAI-1 antigen, and plasminogen (all P<0.05, Table 2). However, mean D-dimer and F1.2 were not significantly different between incident cases and noncases.

Relations of Fibrinolytic Factors With Other Risk Factors
PAI-1 values were higher in diabetic than nondiabetic individuals; these values were associated positively with age, CRP, fasting insulin, plasma triglycerides, waist-to-hip ratio, fibrinogen, and soluble thrombomodulin and associated negatively with the sports index and HDL cholesterol (Table 3). tPA was similarly associated with these factors, except for the sports index and soluble thrombomodulin, and, in addition, was associated positively with systolic blood pressure and total cholesterol and associated negatively with current smoking. In contrast, plasminogen was associated positively with only triglycerides and total cholesterol and associated negatively with soluble thrombomodulin. D-dimer (not shown) was associated positively and linearly only with age (mean age was greater by 5 years across quintiles of D-dimer) and fibrinogen (mean fibrinogen was greater by 52 mg/dL across quintiles of D-dimer). F1.2 (not shown) was not materially associated with any risk factor.

Relative Risks Analyzed by Proportional Hazards Regression
As shown in Table 4 after adjustment for age, sex, and race (model 1), there were moderately strong positive associations of CHD incidence with tPA antigen, PAI-1, plasminogen, and D-dimer. The relative risk of CHD for the highest quintile, compared with the lowest quintile, was 2.05 for tPA, 2.32 for PAI-1, 2.38 for plasminogen, and 1.89 for D-dimer. There was no association of CHD with F1.2; relative to the lowest quintile, the relative risk for the highest quintile was 0.67 (Table 4) and for the highest decile was 0.47 (not shown).

After adjustment for major CHD risk factors (model 2, Table 4), plasminogen remained significantly and positively associated with CHD incidence, with a relative risk of 2.20 for the highest versus lowest quintile but little evidence of dose response. Similar adjustment for other risk factors strengthened the positive association between D-dimer and CHD, with a relative risk of 4.21 for the highest quintile (Table 4). Using stepwise regression, we determined that the adjusting covariate that most augmented the association of CHD with D-dimer was diabetes, although each covariate...
contributed to the augmentation. In contrast, multivariate adjustment completely eliminated the associations of CHD incidence with tPA and PAI-1. The covariates that had most attenuated the association of CHD with tPA and PAI-1 were diabetes, HDL cholesterol, systolic blood pressure, and anti-hypertensive medication use. With adjustment for only age, race, sex, smoking status, and total cholesterol, the relative risks of CHD for the highest versus lowest quintiles were 1.80 (95% CI 0.94 to 3.4) for tPA and 2.01 (95% CI 1.1 to 3.7) for PAI-1.

We further explored the independence of the associations of CHD with plasminogen and D-dimer by adding to model 2 (Table 4) other variables associated with these fibrinolytic factors. After adjustments for the waist-to-hip ratio and plasma triglycerides were also made, the relative risk of CHD for the highest versus lowest quintile of plasminogen was 2.20 (95% CI 1.2 to 4.2); further adjustment for fibrinogen, white blood cell count, and thrombomodulin attenuated this relative risk to 1.25 (95% CI 0.6 to 2.7). Alternatively, adding CRP to model 2 attenuated the plasminogen relative risk, 10%. Adding fibrinogen to model 2 (Table 4) for D-dimer changed the relative risk of CHD for the highest versus lowest quintile of D-dimer to 2.79 (95% CI 1.2 to 6.8). Finally, when we put plasminogen and D-dimer in model 2 simultaneously, both were significant predictors of CHD incidence; the relative risks for highest versus lowest quintiles were 3.77 (95% CI 1.6 to 8.7) for D-dimer and 2.15 (95% CI 1.1 to 4.3) for plasminogen.

Subgroup analyses for plasminogen and D-dimer are shown in Table 5. Elevated plasminogen was associated with increased CHD in men and women, in participants with high and low carotid IMT, and in participants with high but not low CRP. D-dimer was associated positively with CHD in all strata, although not always statistically significantly, given the reduced sample sizes.

Because some researchers have reported that fibrinolytic factors may be associated more strongly with earlier compared with later cardiovascular events,19 we repeated the regression analyses with follow-up stratified according to the median (4.7 years). For plasminogen, the model 2 relative risk for the highest versus lowest quintile was higher (relative risk 2.40) for earlier than for later (relative risk 1.20) follow-up. For D-dimer, the respective relative risks were 3.91 and 3.95, suggesting no diminution in association with longer follow-up. Sixty-one events occurred in the first year. When we instead calculated relative risks of CHD for 1 year versus 1 year of follow-up, the estimates were elevated more in the first year for plasminogen (relative risk 5.16 versus 1.85, respectively) and D-dimer (relative risk 4.28 versus 3.84, respectively).

**Discussion**

The main findings of the present prospective study were that increased levels of several markers of fibrinolytic function were associated positively with the incidence of CHD. Specifically, tPA antigen, PAI antigen, plasminogen, and D-dimer were moderately strong risk factors for CHD. However, only the associations for plasminogen and D-dimer were statistically significant after adjustment for other major risk factors. We also found that F1.2 was not associated with incident CHD.

PAI-1 is associated particularly strongly with markers of the insulin resistance syndrome (Table 3), and not all previous studies have determined whether PAI-1 is associated with CHD independently of these markers. Our finding of no association for PAI-1 after multivariate adjustment is never-
Nevertheless consistent with most previous studies of healthy subjects (Table 1). In contrast to PAI-1, a number of studies have suggested that tPA antigen may be an independent risk factor for CHD (Table 1). Nevertheless, we found tPA antigen to be moderately correlated with many CHD risk factors and PAI antigen; therefore, it was not an independent risk factor for CHD. Yet, even the univariate associations of PAI-1 or tPA antigen with CHD should not be dismissed, because they still could reflect an important role of these factors in the pathogenesis of CHD events. An earlier ARIC publication

TABLE 4. Adjusted RRs of Incident CHD in Relation to Quintiles of Baseline Fibrinolytic Factors and F1.2, ARIC Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model</th>
<th>Analysis</th>
<th>Quintile</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
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<td>95% CI</td>
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<td>0.4–1.8</td>
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<td>Plasminogen</td>
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<td></td>
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<td>95% CI</td>
<td>0.8–2.3</td>
<td>0.9–2.7</td>
<td>1.3–3.8</td>
<td>1.3–4.0</td>
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<tr>
<td>D-dimer</td>
<td>1</td>
<td>RR</td>
<td>1.0</td>
<td>1.13</td>
<td>0.84</td>
<td>1.20</td>
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<td>95% CI</td>
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<td>95% CI</td>
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<td>0.7–2.2</td>
<td>0.7–2.0</td>
<td>1.4–4.1</td>
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RR indicates relative risk. Model 1 was adjusted for age, sex, and race. Model 2 was also adjusted for smoking status (current, former, never), total cholesterol, HDL cholesterol, diabetes (yes, no), systolic BP and use of antihypertensive drugs (yes, no).

TABLE 5. Adjusted RRs of Incident CHD in Relation to Quintiles of Baseline Plasminogen and D-Dimer Within Subgroups of Sex, Carotid IMT, and CRP ARIC Study

<table>
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<tr>
<th>Plasminogen</th>
<th>Quintile</th>
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<th>2</th>
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<tr>
<td>Men</td>
<td>1.0</td>
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<td>0.93</td>
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<td>Carotid IMT &gt; median</td>
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<td>0.47</td>
<td>0.84</td>
<td>0.49</td>
<td>2.87</td>
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<td>Carotid IMT &lt; median</td>
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<td>7.47</td>
<td>3.93</td>
<td>4.29</td>
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<td>2.26</td>
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<td>1.19</td>
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<td>0.79</td>
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<th>4</th>
<th>5</th>
<th>( P ) for Difference</th>
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<tr>
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<td>3.10</td>
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<td>3.38</td>
<td>7.77</td>
<td>8.91</td>
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<tr>
<td>Carotid IMT &gt; median</td>
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<td>3.92</td>
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<td>4.13</td>
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<tr>
<td>Carotid IMT &lt; median</td>
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<td>5.26</td>
<td>5.31</td>
<td>14.1</td>
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<td>CRP &gt; median</td>
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<td>1.83</td>
<td>1.70</td>
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<td>3.51</td>
<td>1.68</td>
<td>2.30</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

RRs were adjusted as for model 2, Table 4. IMT median was 0.689 mm; CRP median was 3.5 mg/L.
reported PAI-1 and tPA to be associated positively and independently with carotid IMT. Yet, the present results suggest that measuring PAI-1 or tPA would have little additional benefit beyond traditional risk factors in predicting CHD.

Plasminogen level was associated negatively with soluble thrombomodulin. Soluble thrombomodulin has been shown to activate plasma thrombin-activable fibrinolysis inhibitor (TAFI), which inhibits fibrinolysis by several biochemical mechanisms. It is possible that the inverse relationship between plasminogen and soluble thrombomodulin may be related to TAFI, but the exact mechanism remains unclear and requires further investigation.

To our knowledge, there have not been previous reports on the association of plasminogen with risk of incident CHD. We found a plasminogen level in the highest quintile to be associated with increased CHD incidence even after adjustment for major CHD risk factors. This result is somewhat unexpected and seemingly contrary to our understanding of the role of fibrinolysis in arterial thrombosis. However, a positive association between plasminogen and CHD may be analagous to the positive association between tPA antigen and CHD, in which plasma tPA levels reflect tPA-PAI complexes and not free tPA levels on fibrin at the thrombotic site. Plasminogen also binds to fibrin, on which it is converted to plasmin by tPA, and the generated plasmin degrades the surrounding fibrin. It is unclear whether the quantity of plasminogen bound to fibrin is directly correlated with plasma plasminogen levels. Our results suggest that the plasma plasminogen level is not correlated with the available plasminogen on fibrin. Plasminogen activation on fibrin is reduced by TAFI. TAFI levels may be a CHD risk factor, which could explain a positive association of plasminogen and tPA with CHD. Work is underway to determine the association of TAFI with incident CHD and the correlation of TAFI with tPA and plasminogen levels.

Alternatively, elevated plasminogen could reflect the inflammation and acute-phase reaction of subclinical atherosclerosis in participants who later developed CHD, because plasminogen transcription has been shown to be increased in sclerosis in participants who later developed CHD, because inflammation and acute-phase reaction of subclinical athero-association of TAFI with incident CHD and the correlation of and tPA with CHD. Work is underway to determine the which could explain a positive association of plasminogen

Strengths of the present study were its prospective population-based design and relatively large numbers of events. Limitations included missing plasma samples for some subjects; this situation was primarily due to a freezer failure. We made only single measures of the fibrinolytic factors, and assays had only moderate precision; these measurement errors should have led to an underestimate of the strength of association between impaired fibrinolytic function and CHD. Finally, it could be that the associations observed are not causal but, instead, reflect underlying processes in the arterial wall in subclinical atherosclerosis.

In conclusion, this population-based prospective study identified for the first time that plasma plasminogen may be an independent risk factor for CHD and provides further evidence of a positive association between D-dimer and risk of CHD.

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