Fibrinolytic Activation Markers Predict Myocardial Infarction in the Elderly
The Cardiovascular Health Study
Mary Cushman, Rozenn N. Lemaitre, Lewis H. Kuller, Bruce M. Psaty, Elizabeth M. Macy, A. Richey Sharrett, Russell P. Tracy

Abstract—Coagulation factor levels predict arterial thrombosis in epidemiological studies, but studies of older persons are needed. We studied 3 plasma antigenic markers of fibrinolysis, viz, plasminogen activator inhibitor-1 (PAI-1), fibrin fragment D-dimer, and plasmin-antiplasmin complex (PAP) for the prediction of arterial thrombosis in healthy elderly persons over age 65. The study was a nested case-control study in the Cardiovascular Health Study cohort of 5201 men and women ≥65 years of age who were enrolled from 1989 to 1990. Cases were 146 participants without baseline clinical vascular disease who developed myocardial infarction, angina, or coronary death during a follow-up of 2.4 years. Controls remained free of cardiovascular events and were matched 1:1 to cases with respect to sex, duration of follow-up, and baseline subclinical vascular disease status. With increasing quartile of D-dimer and PAP levels but not of PAI-1, there was an independent increased risk of myocardial infarction or coronary death, but not of angina. The relative risk for D-dimer above versus below the median value (≥120 μg/L) was 2.5 (95% confidence interval, 1.1 to 5.9) and for PAP above the median (≥5.25 nmol/L), 3.1 (1.3 to 7.7). Risks were independent of C-reactive protein and fibrinogen concentrations. There were no differences in risk by sex or presence of baseline subclinical disease. D-dimer and PAP, but not PAI-1, predicted future myocardial infarction in men and women over age 65. Relationships were independent of other risk factors, including inflammation markers. Results indicate a major role for these markers in identifying a high risk of arterial disease in this age group. (Arterioscler Thromb Vasc Biol. 1999;19:493-498.)

Key Words: blood coagulation n fibrinolysis n myocardial infarction n elderly n risk factors

Elderly persons have the highest incidence of myocardial infarction (MI). In older men and women without clinically apparent vascular disease, noninvasively assessed subclinical disease predicts subsequent clinical events. Because the endothelial damage that accompanies atherosclerosis provides a surface for cyclic thrombin production and reactive fibrinolysis, markers of fibrinolysis might predict clinical events in apparently healthy persons with subclinical disease.

D-dimer and tissue plasminogen activator (in an assay that included assessment of the tissue plasminogen activator/PAI-1 complex) predicted MI in male physicians, but these effects were not independent of lipid levels. The PAI-1 level predicted the short-term risk of recurrent MI in young men but did not predict in subjects with angina or in older men, some of whom had existing coronary disease. In the latter study D-dimer was associated with MI risk. The PAP level rose during acute MI and fibrinolytic therapy. However, to our knowledge, there are no prospective data for PAP.

Given the underlying hypotheses that hemostatic balance promotes progression of atherosclerosis and is increasingly important in the elderly, we completed a nested case-control study in the Cardiovascular Health Study (CHS). The specific hypotheses were that (1) higher baseline levels of D-dimer, PAP, and PAI-1, as indicators of fibrinolysis, would predict subsequent MI, angina, or coronary death in healthy older men and women and (2) the risks would be greatest in those with subclinical disease at baseline.

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Fibrinolytic Markers and Cardiovascular Risk

Methods

CHS Design
Subjects were selected from the CHS, a cohort study of risk factors for cardiovascular disease in 5201 free-living men and women age 65 and over. Subjects were recruited from 1989 to 1990 from random samples of Medicare eligibility lists at 4 field centers: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania. Informed consent was obtained with methods approved by institutional review committees at each center.

The baseline examination included an interview, physical examination, phlebotomy, and assessment of clinical and subclinical vascular disease. To assess subclinical disease, subjects underwent duplex ultrasonography of the carotid arteries, echocardiography, measurement of ankle-brachial blood pressure index, and a resting 12-lead ECG, and they completed the Rose questionnaires for angina and claudication.

Definition of Variables
Hypertension was defined as absent, borderline, or present. Diabetes was evaluated as absent, impaired glucose tolerance, or diabetes by using data from the medical history and glucose challenge. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Smoking was categorized as never, former, or current use. Alcohol use was the reported number of drinks consumed per week.

Participants were classified as having subclinical disease if they possessed any 1 of the following: internal carotid wall thickness >80th percentile, common carotid wall thickness >80th percentile, carotid stenosis >25%, major ECG changes, abnormal ejection fraction or wall motion on the echocardiogram, Rose questionnaire—positive, or an ankle-brachial index <0.9.

Identification of Cases and Controls
Participants with cardiac, cerebral, or peripheral arterial disease at baseline were excluded from the study. To identify cases of MI, angina pectoris, and coronary heart disease death, participants were evaluated twice annually by clinic visits and telephone calls. Hospital and outpatient records were reviewed by committee for International Classification of Disease codes 410 through 414, 427.4, 427.5, and 428 and any discharge summary when there was a question of a cardiovascular event.

Of those remaining free of events, 1 control was matched to each case on the basis of sex, baseline subclinical disease status, and duration of follow-up. We previously reported the association of C-reactive protein level with incident disease in the same case-control group.

Laboratory Analyses
The fibrinolytic markers were measured on plasma drawn at baseline and stored at ~70°C. Blood was collected in the morning, with minimal stasis after an 8- to 12-hour fast, into tubes containing either sodium citrate or 4.5 mmol/L EDTA, 0.15 KIU/L aprotinin, and 20 μmol/L d-Phe-Pro-Arg-chloromethylketone (SCAT-1 tube, Haematologic Technologies, Inc). D-dimer was measured in SCAT-1 plasma by ELISA using 2 monoclonal antibodies directed against nonoverlapping antigenic determinants. The assay detects D-dimer from cross-linked fibrin but not D-monomer. The interassay coefficient of variation (CV) was 7.0%. PAP was measured in SCAT-1 plasma by using a 2-site ELISA with murine monoclonal antibodies specific for PAP complex. The CV was 3.6%. PAI-1 antigen was measured in citrated plasma by a sandwich-type ELISA that detects latent and active free PAI-1 but not PAI-1 complexed with tissue plasminogen activator. The CV was 10.5%. Lipids, fibrinogen, and C-reactive protein were measured as described.

Statistical Analyses
The SPSS version 6.1 was used for data analysis on an updated CHS database with minor corrections through June 1993. EGERET was used for conditional logistic regression. Means or proportions for baseline characteristics were determined in cases and controls. The distributions of the fibrinolytic markers were divided into quartiles based on the control distributions. The odds ratio (estimating relative risk) of incident MI, angina pectoris, or coronary death was determined by conditional logistic regression for each of the upper 3 quartiles compared with the first quartile. Because angina is less likely to be associated with acute thrombosis, risk of MI or coronary death was evaluated separately. The following risk factors were assessed in multivariable models and were not included in the final models in the absence of confounding: body mass index, race (white, nonwhite), smoking status, total cholesterol, LDL and HDL cholesterol, triglycerides, diabetes, hypertension, and alcohol use. Subgroup analyses were done based on the matching factors, with each hemostatic variable dichotomized at the median and using conditional logistic regression models with interaction terms.

Results
There were 150 study events, with a mean follow-up of 2.4 years: 61% men, 74% with baseline subclinical disease. There were 146 cases with baseline plasma samples: 64 with MI, 73 with angina, and 9 coronary deaths. In cases and controls, the range of values for the analytes were as follows: D-dimer, 21 μg/L to 4578 μg/L; PAP, 2.20 nmol/L to 24.06 nmol/L; and PAI-1, 6 μg/L to 293 μg/L. No phlebotomy or processing difficulties were reported for participants with the highest values. Baseline characteristics are shown in Table 1. Except for D-dimer and PAI-1, hemostasis variables and C-reactive protein were intercorrelated, as shown in Table 2. There were no relationships between PAI-1 and the occurrence of any event (Table 3). After event types were combined, the relative risk of any event increased with increasing quartile of D-dimer, but not of PAP (Tables 4 and 5). Adjustment for cardiovascular risk factors did not appreciably change the results. When event types were separated, there were no relationships between either analyte and the risk of angina. However, there was a graded increase in the risk of MI or coronary death with increasing D-dimer and PAP, with crude risks greater than 2-fold for D-dimer or PAP above their respective median values (Table 6). Relative risks were higher in adjusted models. To provide additional control for residual confounding by subclinical disease beyond that afforded by the matched design, there was no effect of further adjustment by ankle-arm index.

Risks of MI or coronary death associated with D-dimer or PAP above the median were unchanged by adjustment for PAI-1, fibrinogen, C-reactive protein, or the effect of each variable.
marker for the other (Table 6). Compared with participants with levels of D-dimer and PAP below the median, those with both values above the median had a crude risk of MI or coronary death of 2.7 (95% confidence interval, 1.1 to 6.7), with no effect of adjustment for other risk factors. In subgroup analyses, there were no differences in risk for D-dimer or PAP by the matching factors of sex or subclinical disease status at baseline (data not shown). However, the markers appeared to be better predictors of MI or coronary death earlier in the follow-up period (Table 7).

Discussion

The primary finding of this study was that levels of D-dimer and PAP, but not of PAI-1, predicted the first MI or coronary death, but not angina, in healthy persons over age 65. Estimated relative risks for D-dimer and PAP were substantially, with a 2.5-fold increased risk for D-dimer above the median (≥120 µg/L) and a 3.1-fold increased risk for PAP above the median (≥5.25 nmol/L). Relationships were independent of traditional risk factors, PAI-1, and a recently studied inflammation marker, C-reactive protein. D-dimer was strongly related to the procoagulant marker fibrinogen than it is to PAI-1, whereas PAI-1 is more strongly related to insulin resistance syndrome components in the study by Juhan-Vague and colleagues. Our null findings for PAI-1 antigen agree with a recent study of PAI-1 activity level in middle-aged men. Taken together, studies to date suggest that PAI-1 concentration may assess different aspects of risk, such as those associated with the insulin resistance syndrome, depending on the presence of baseline disease and characteristics of the population studied. Because PAI-1 is the major fibrinolytic inhibitor and downregulates PAP, the observed association between PAP and cardiovascular events suggests that the PAP assay reflects ongoing fibrin formation better than it reflects regulation by PAI-1 in this healthy, older population. To support this concept, in the CHS PAP is more strongly related to the procoagulant marker fibrinogen than it is to PAI-1, whereas PAI-1 is more strongly related to insulin level than it is to inflammation and procoagulation markers.

Several factors might underlie the lack of relationships of the fibrinolysis markers to angina. Misclassification of angina may have occurred, because angina is largely a clinical diagnosis. Also, angina events included both stable (which are most likely not thrombosis related) and unstable (may consist of either spasm or thrombosis) angina. All of these factors would bias results toward the null hypothesis.

Table 2: Spearman Correlations Between Selected Study Variables in Cases and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasminogen Activator Inhibitor-1, µg/L</th>
<th>D-Dimer, µg/L</th>
<th>Plasmin-Antiplasmin, nmol/L</th>
<th>C-Reactive Protein, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer, µg/L</td>
<td>−0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmin-antiplasmin, nmol/L</td>
<td>−0.31*</td>
<td>0.47*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>0.19*</td>
<td>0.17*</td>
<td>0.15*</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>0.15*</td>
<td>0.19*</td>
<td>0.41*</td>
<td>0.40*</td>
</tr>
</tbody>
</table>

*P < 0.01.

Table 3: Relative Risk of Events by Quartile of PAI-1

<table>
<thead>
<tr>
<th>Quartile†</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>0.5 (0.2–1.0)</td>
<td>0.5 (0.2–1.0)</td>
<td>0.3 (0.1–0.9)</td>
<td>0.3 (0.1–1.1)</td>
<td>0.6 (0.2–1.6)</td>
<td>0.6 (0.2–2.1)</td>
</tr>
<tr>
<td>3</td>
<td>0.9 (0.5–1.7)</td>
<td>0.9 (0.4–1.8)</td>
<td>1.4 (0.6–3.7)</td>
<td>1.5 (0.5–4.2)</td>
<td>0.6 (0.2–1.4)</td>
<td>0.6 (0.2–1.9)</td>
</tr>
<tr>
<td>4</td>
<td>0.7 (0.4–1.3)</td>
<td>0.6 (0.3–1.3)</td>
<td>0.9 (0.4–2.2)</td>
<td>0.9 (0.3–2.9)</td>
<td>0.5 (0.2–1.2)</td>
<td>0.4 (0.1–1.2)</td>
</tr>
<tr>
<td>P (trend)</td>
<td>0.65</td>
<td>0.59</td>
<td>0.47</td>
<td>0.40</td>
<td>0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>No.</td>
<td>146</td>
<td>138</td>
<td>73</td>
<td>69</td>
<td>73</td>
<td>69</td>
</tr>
</tbody>
</table>

RR indicates relative risk; ref, referent quartile.

*RRadj indicates relative risk adjusted for hypertension, smoking status, race (white or nonwhite), diabetes, and body mass index.

The following risk factors were assessed but not included in the final models owing to an absence of confounding: total, LDL, and HDL cholesterol; triglycerides; and alcohol use.

†Range of values of PAI-1 for each quartile: 1, 6 to 22 µg/L; 2, 23 to 37 µg/L; 3, 38 to 62 µg/L; and 4, 63 to 293 µg/L.
There were differences between our results and others. First, D-dimer appears to be a more sensitive indicator of risk in an aged or atherosclerotic population. D-dimer levels over the median predicted MI in our study, whereas in male physicians this association was observed for levels above the 95th percentile only.7 Our findings were similar to 2 studies that included younger subjects with vascular diagnoses at baseline.11,26 The differences may be related to age; D-dimer increases with age,30 and older persons may be similar to younger subjects with diffuse atherosclerosis. Second, associations in our study and in 2 other studies11,26 were not attenuated by adjustment for lipid levels, in contrast to findings in male physicians.7 Third, because our results were similar in elderly men and women, inclusion of women does not explain the differences between our study and others composed largely of men.

Levels of C-reactive protein or fibrinogen did not confound the associations of D-dimer and PAP with MI and coronary death. Because these analytes have cross-sectional and biochemical associations with each other, our prospective results suggest that (1) the inflammatory response and fibrinolytic activation may have independent roles in atherogenesis; (2) because their predictive capacities are independent of each other, D-dimer and PAP appear to measure different aspects of fibrinolysis; and (3) measurement of inflammation and fibrinolysis might yield additive information in predicting a high risk for MI.

A mechanistic explanation for our findings related to D-dimer and PAP cannot be provided with the current study design. However, we suggest the following hypothesis. Although the findings seem to be independent of a single determination of subclinical atherosclerosis (cases and controls were matched on subclinical disease), because the markers predicted early events better than they did later events, it is possible that higher concentrations of PAP reflect ongoing cyclic subclinical atherothrombosis (plaque destabilization) occurring in proximity to arterial occlusive events in this elderly population. To test this hypothesis, we are currently studying longitudinal changes in D-dimer and PAP in relation to changes in subclinical disease and risk prediction of clinical events.

The strengths of our study were prospective follow-up, reliable event ascertainment, ability to determine independence of relationships, and matched design, allowing efficient control for important confounders, particularly subclinical disease. Inclusion of persons over age 65 allowed study of the highest-risk population.

The main limitation of the study was the relatively small number of events; estimates of relative risk require confirmation. Owing to the entry criteria, the CHS represented a healthy portion of the older population, so findings may not

### Table 4. Relative Risk of Events by Quartile of D-Dimer

<table>
<thead>
<tr>
<th>Quartile†</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>1.0 (0.5–1.9)</td>
<td>1.0 (0.5–2.1)</td>
<td>0.5 (0.2–1.6)</td>
<td>0.4 (0.1–1.2)</td>
<td>1.5 (0.6–3.8)</td>
<td>2.7 (0.9–8.1)</td>
</tr>
<tr>
<td>3</td>
<td>1.7 (0.9–3.3)</td>
<td>2.2 (1.1–4.7)</td>
<td>1.2 (0.5–3.1)</td>
<td>1.2 (0.4–3.3)</td>
<td>2.4 (0.9–6.4)</td>
<td>5.1 (1.4–18.1)</td>
</tr>
<tr>
<td>4</td>
<td>1.8 (0.9–3.5)</td>
<td>2.1 (1.0–4.4)</td>
<td>1.0 (0.4–2.6)</td>
<td>1.0 (0.3–2.9)</td>
<td>3.1 (1.1–8.6)</td>
<td>4.1 (1.2–14.5)</td>
</tr>
</tbody>
</table>

P (trend): 0.04 0.02 0.47 0.49 0.02 0.02

No. 145 138 72 68 73 70

*RRadj indicates relative risk adjusted for hypertension, smoking status, race (white or nonwhite), and diabetes. The following risk factors were assessed but not included in the final models due to absence of confounding: body mass index; total, HDL, and LDL cholesterol; triglycerides; and alcohol use.

†Range of values of D-dimer for each quartile: 1, 21 to 74 μg/L; 2, 75 to 123 μg/L; 3, 124 to 191 μg/L; 4, 192 to 4578 μg/L

### Table 5. Relative Risk of Events by Quartile of PAP

<table>
<thead>
<tr>
<th>Quartile†</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
<th>RR (95% CI)</th>
<th>RRadj* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>1.6 (0.8–3.0)</td>
<td>1.8 (0.9–3.7)</td>
<td>1.8 (0.7–4.6)</td>
<td>2.4 (0.8–7.1)</td>
<td>1.5 (0.6–4.1)</td>
<td>1.7 (0.6–4.9)</td>
</tr>
<tr>
<td>3</td>
<td>2.0 (1.0–3.7)</td>
<td>2.1 (1.1–4.1)</td>
<td>1.6 (0.7–3.6)</td>
<td>1.4 (0.6–3.4)</td>
<td>2.6 (1.0–7.2)</td>
<td>4.2 (1.3–13.8)</td>
</tr>
<tr>
<td>4</td>
<td>1.2 (0.6–2.5)</td>
<td>1.6 (0.7–3.8)</td>
<td>0.7 (0.3–2.0)</td>
<td>0.9 (0.3–3.0)</td>
<td>2.1 (0.7–6.3)</td>
<td>3.6 (0.9–14.2)</td>
</tr>
</tbody>
</table>

P (trend): 0.44 0.16 0.06 0.82 0.10 0.02

No. 146 138 73 69 73 69

*RRadj indicates relative risk adjusted for hypertension, smoking status, race (white or nonwhite), and body mass index. The following risk factors were assessed but not included in the final models due to absence of confounding: total, LDL, and HDL cholesterol; triglycerides; diabetes; and alcohol use.

†Range of values of PAP for each quartile: 1, 2.20 to 4.01 nmol/L; 2, 4.02 to 5.24 nmol/L; 3, 5.25 to 7.26 nmol/L; 4, 7.30 to 24.06 nmol/L.
be fully generalizable. While subclinical disease categorization is a sensitive indicator of atherosclerosis, it is not a quantitative measure, so the magnitude of subclinical disease may not have been fully assessed as a confounder or effect modifier, even with further adjustment for ankle-arm index. Finally, imprecision of the fibrinolytic assays may affect interpretation of the relationships observed; however, in our laboratory, these assays have acceptable precision, with the index of individuality for all 3 assays identical at 0.68, compared with 0.48 for cholesterol.

Measurement of PAP or D-dimer may be useful in identifying individuals at risk of MI and who might benefit from primary prevention with aspirin, lipid-lowering therapies with favorable hemostatic effects, or anticoagulants. In the CHS, the risk of cardiac disease was 2-fold in those with subclinical disease (37.2% of the cohort), 2.5-fold with C-reactive protein in the highest quartile, and 2.5-fold with D-dimer above the median. The annual incidence of coronary disease was 3.8% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5-fold with D-dimer above the median. The annual incidence of coronary disease was 3.8% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease. If one assumes independent risks with D-dimer above the median and C-reactive protein in the top quartile, these incidence rates rise to 23.8% and 1.5% for those with subclinical disease and 1.5% for those without subclinical disease.

TABLE 6. Relative Risk of Myocardial Infarction or Coronary Death for D-Dimer, PAP, or PAI-1 Levels Above Versus Below the Median and Adjusted for Other Study Variables

<table>
<thead>
<tr>
<th>Additional Covariates in Model</th>
<th>RR (95% CI)</th>
<th>D-Dimer, µg/L</th>
<th>PAP, nmol/L</th>
<th>PAI-1, µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>2.5 (1.1–5.9)</td>
<td>3.1 (1.3–7.7)</td>
<td>0.6 (0.3–1.3)</td>
</tr>
<tr>
<td>D-dimer, µg/L</td>
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<td>...</td>
<td>3.2 (1.3–8.0)</td>
<td>0.6 (0.3–1.3)</td>
</tr>
<tr>
<td>PAP, nmol/L</td>
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<td>2.4 (1.0–5.8)</td>
<td>...</td>
<td>0.7 (0.3–1.5)</td>
</tr>
<tr>
<td>PAI-1, µg/L</td>
<td></td>
<td>2.4 (1.0–5.6)</td>
<td>3.0 (1.2–7.6)</td>
<td>...</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td></td>
<td>2.4 (1.0–5.8)</td>
<td>3.1 (1.2–7.9)</td>
<td>0.6 (0.3–1.3)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td></td>
<td>2.4 (1.0–5.8)</td>
<td>3.1 (1.2–8.4)</td>
<td>0.5 (0.2–1.2)</td>
</tr>
</tbody>
</table>

*All models simultaneously adjusted for smoking status, diabetes, hypertension, and race and either D-dimer, PAP, PAI-1, C-reactive protein, or fibrinogen, entered as continuous variables.

TABLE 7. Relative Risk of Myocardial Infarction or Coronary Death for PAP or D-Dimer Level Above Versus Below the Median and by Time to Event From Enrollment

<table>
<thead>
<tr>
<th>Time to event</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Dimer, µg/L</td>
<td>PAP, nmol/L</td>
</tr>
<tr>
<td>0–12 mos (n=23)</td>
<td>5.0 (0.6–42.8)</td>
</tr>
<tr>
<td>&gt;12 mos (n=50)</td>
<td>1.8 (0.8–4.0)</td>
</tr>
</tbody>
</table>

*P value for statistical interaction between time and category of each analyte.

References

Fibrinolytic Activation Markers Predict Myocardial Infarction in the Elderly: The Cardiovascular Health Study
Mary Cushman, Rozenn N. Lemaitre, Lewis H. Kuller, Bruce M. Psaty, Elizabeth M. Macy, A. Richey Sharrett and Russell P. Tracy

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