Haemostatic Factors and the Risk of Cardiovascular Death in Patients With Coronary Artery Disease: The AtheroGene Study


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Haemostatic Factors and the Risk of Cardiovascular Death in Patients With Coronary Artery Disease
The AtheroGene Study

P.E. Morange, C. Bickel, V. Nicaud, R. Schnabel, H.J. Rupprecht, D. Peetz, K.J. Lackner, F. Cambien, S. Blankenberg, L. Tiret, for the AtheroGene Investigators

Objective—To get a better insight into the role of hemostasis in coronary artery disease (CAD), we assessed the impact of von Willebrand factor (vWF), fibrinogen, thrombin-antithrombin (TAT) complexes, D-dimers, and plasmin-antiplasmin (PAP) complexes on the risk of cardiovascular event in a prospective cohort of CAD patients.

Methods and Results—The prospective Atherogene cohort includes 1057 individuals with an angiographically proven coronary artery disease at baseline. After a median follow-up of 6.6 years, 135 individuals died from a cardiovascular cause and 97 had a nonfatal cardiovascular event. Higher levels of all 5 hemostatic markers at baseline were associated with an increased risk of cardiovascular death, but not of nonfatal event. Except for vWF, these associations remained significant after adjustment for conventional cardiovascular risk factors and C-reactive protein (CRP) levels (P for trend according to increasing tertiles=0.20, 0.011, 0.026, 0.019, and 0.01 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively). When including the 5 hemostatic markers in a stepwise Cox regression analysis where conventional risk factors and CRP were forced into the model, fibrinogen and D-dimers remained independently associated with the risk of cardiovascular death. Adjusted hazard ratios (95% CI) associated with one SD increase of fibrinogen and D-dimers were 1.27 (1.04 to 1.55) and 1.29 (1.09 to 1.53), respectively.

Conclusions—In patients with coronary artery disease, fibrinogen and D-dimer levels are independent predictors of subsequent cardiovascular death. Our data support a role of impaired coagulation/fibrinolysis process in the complications of coronary artery disease. (Arterioscler Thromb Vasc Biol. 2006;26:2793-2799.)

Key Words: coagulation ■ hemostasis ■ coronary disease ■ atherosclerosis ■ arterial thrombosis

Thrombosis of a disrupted atherosclerotic plaque triggers most ischemic cardiovascular events. Because thrombi are resolved through the action of the fibrinolytic system, it has been hypothesized that impaired fibrinolytic function may also be a risk factor for ischemic events. Despite this pathophysiological evidence for the involvement of hemostasis in cardiovascular disease, the predictive ability of parameters reflecting activation of the coagulation or fibrinolytic system remains uncertain, in particular because of the tight interplay observed between inflammation and coagulation. Thus, whether high levels of procoagulant proteins represent only a marker of vascular inflammation in the foam of atherosclerosis or represent a risk factor for coronary artery disease (CAD) is still a matter of debate.

To get a better insight into the role of hemostasis in CAD, we assessed the impact of five hemostatic markers on the risk of cardiovascular event in a prospective cohort of CAD patients, the AtheroGene Study. The markers selected for this study were located in different part of the coagulation/fibrinolytic pathway. vWF mediates platelet adhesion, acts as the carrier protein for coagulation factor VIII, and is considered as a reliable marker of endothelial dysfunction. Fibrinogen acts on blood viscosity, platelet aggregation, and fibrin formation. Thrombin is the key enzyme of the coagulation process, it is neutralized by its physiological inhibitor anti-thrombin and thus thrombin-antithrombin (TAT) complex is believed to be a marker of thrombin generation. D-dimer, a fibrin degradation product, is a marker not only of thrombin generation but also of cross-linked fibrin turnover. Activation of the fibrinolytic system leads to plasmin formation. Plasmin is a serine protease that cleaves fibrin into soluble fragments. This enzyme is rapidly inactivated by α2-antiplasmin. Thus, quantification of plasmin-antiplasmin (PAP) complexes could be a useful tool for studying the behavior of the fibrinolytic system but also fibrin formation. Besides evaluating the individual contribution of each of...
these hemostatic markers to future cardiovascular events, we assessed whether their association with outcome might be confounded by inflammatory markers such as C-reactive protein (CRP), that is whether their capacity to predict future cardiovascular event was independent or not of the patient’s inflammatory status.

**Materials and Methods**

**Study Population**

The general design of the AtheroGene study has been outlined elsewhere. Briefly, the present study population included 1306 CAD patients consecutively enrolled during several successive phases of recruitment between November 1996 and June 2000. Patients who underwent coronary angiography at the Medical Department of the Johannes Gutenberg-University Mainz or the Bundeswurzentralkrankenhaus Koblenz, and who had at least 1 stenosis >30% diagnosed in a major coronary artery, were enrolled in the prospective cohort. Study participants had German nationality and were inhabitants of the Rhein-Mainz area. Patients with no evidence of CAD as defined above were excluded. We also excluded patients with concomitant diseases likely to increase the risk of cardiovascular event or death or to strongly modify biochemical parameters, in particular hemodynamically significant valvular heart disease, surgery, trauma with the prior month, known cardiomyopathy, known malignant diseases, febrile conditions, or use of oral anticoagulant therapy within the prior 4 weeks. Acute coronary syndrome (ACS) was defined as acute myocardial infarction (MI) or unstable angina (Braunwald class B or C). Baseline anthropometric and clinical and therapeutic variables were collected by a physician at enrollment. The present study included individuals who had measurement of fibrinogen, vWF, TAT, and PAP complexes (n=1068). Among these, D-dimers were measured in 796 (75%) patients.

All enrolled patients were contacted from mid 2003 to mid 2004 for follow-up information, with a median follow-up of 6.6 (range 3.0 to 7.6) years. Patients either presented at our clinic (87%) or were interviewed by phone by trained medical staff. Eleven patients were lost to follow-up and were excluded from analysis. Follow-up information was obtained on death from cardiovascular causes, death from causes not related to cardiovascular causes, nonfatal MI, and nonfatal stroke. Information about the cause of death or clinical event was obtained from hospital or general practitioner charts. When information from medical charts was insufficient, death certificates were checked. Deaths from cardiovascular causes, besides fatal MI and fatal stroke, also included heart failure as a consequence of MI and ventricular arrhythmia.

The ethics committee of the University of Mainz approved the study. Participation was voluntary, and each study subject gave written informed consent.

**Laboratory Methods**

Blood was drawn in all study subjects under standardized conditions. The blood sample was collected before coronary angiography was performed. Samples were immediately placed on ice and within 30 minutes, blood was centrifuged at 4000 g for 10 minutes and frozen at −80°C until analysis. CRP was determined by a highly sensitive (hs), latex particle-enhanced immunosassay (Roche Diagnostics, Mannheim, Germany). Serum interleukin (IL)-6 (EASIA, Biosource Europe) was measured using the ELISA technique according to the manufacturer’s instructions. Fibrinogen (Derived method; Dade Behring) and serum lipid levels (total cholesterol, HDL-cholesterol, and triglycerides) were determined immediately. vWF was determined by IL Test von Willebrand Factor (Instrumentation Laboratory), TAT by Enzygnost TAT micro (Dade Behring), D-dimers by Tina-quant D-dimer (Roche Diagnostics), PAP by Enzygnost PAP micro ELISA-Kit (Dade Behring). Interassay variation coefficients were 6%, 4%, 6%, 5%, and 11% for fibrinogen, vWF, TAT, D-dimers, and PAP, respectively.

**Statistical Analysis**

For continuous variables, mean levels were compared between groups by ANOVA and for categorical variables, proportions were compared by χ² test. Variables with a skewed distribution were log-transformed before analysis. Associations of hemostatic markers with anthropometric characteristics, metabolic parameters, and inflammatory markers were tested by means of Pearson’s correlation coefficient adjusted for age, sex, and outcome. For each hemostatic marker, tertiles were derived from the overall population. The frequency of fatal cardiovascular events (n=135) and nonfatal MI and stroke events (n=97) were compared across tertiles of each factor. Because the frequency of nonfatal events did not significantly differ among tertiles for any factor, further survival analyses were focused on cardiovascular deaths only. Patients who died from other causes were censored at the time of death. Survival analyses were performed using a Cox proportional hazards regression model. The effect of each hemostatic marker, treated in tertiles, was tested individually by survival analysis controlling first for age and sex (model 1). Departure from linearity of the relationship between outcome and tertiles, considered as an ordinal variable (0, 1, 2), was tested by a χ² with 1 df and was not rejected for any of the factor. The effect of each factor was then evaluated after adjustment for clinical and therapeutic covariates (presence of an ACS versus stable angina, body mass index, hypertension, diabetes, smoking status, HDL-cholesterol, statin, β-blockers, ACE-inhibitors, heparin, antiplatelet therapy; model 2). Model 3 was additionally adjusted for CRP. To further evaluate the independent effect of each hemostatic factor on cardiovascular death, they were all included in a stepwise Cox regression analysis with clinical and therapeutic covariates and CRP forced into the model. Hazard ratios (HRs) and 95% CI are reported. Analyses were performed with the SAS software, version 8.01 (SAS Institute, Inc). P<0.05 was considered to be significant.

**Results**

**Baseline Characteristics of Individuals According to Cardiovascular Outcome During Follow-Up**

Of the 1068 patients enrolled in the study, 1057 (99%) were followed up during a median interval of 6.6 (range 2.9 to 7.7) years. A total of 135 cardiovascular deaths and 97 nonfatal cardiovascular events (MI and stroke) were reported. Among the 825 patients free of cardiovascular event, 49 died from a noncardiovascular cause and were censored at the time of death. The mean age of patients was 61.5±10.2 years and 77% were males. At admission, 30.2% of patients presented with an ACS and 69.8% with a stable angina.

The baseline characteristics of the patients according to outcome are reported in Table 1. Patients who died from a cardiovascular cause were older, had a higher prevalence of diabetes and lower HDL-cholesterol levels than those who survived. They also had marked elevations of CRP and IL-6. By contrast, patients who experienced a nonfatal cardiovascular event during the follow-up did not differ from patients who remained free of event (Table 1).

**Relation Between Concentrations of Hemostatic Factors and Other Cardiovascular Risk Factors**

Interrelationships between the hemostatic factors and the conventional risk factors which might confound the relationship with cardiovascular risk were examined. vWF, D-dimer, and PAP levels increased with age, whereas fibrinogen and TAT levels did not (Table 2). PAP levels negatively correlated with body mass index and triglycerides, whereas vWF, D-dimer, and TAT levels did not (Table 2). None of the factors was associated with diabetes, hypertension, or smok-
ing status (data not shown). All five hemostatic markers strongly correlated with inflammatory markers (IL-6 and CRP; Table 2). The highest correlation was observed between fibrinogen and CRP ($r = 0.49, P = 0.001$).

Except for TAT and vWF which exhibited a weak association, the five hemostatic factors strongly correlated one with each other, with particularly strong associations of TAT and PAP complexes with D-dimer levels (Table 2). Adjustment on CRP levels only slightly reduced these correlations (data not shown).

### Hemostatic Factors and Cardiovascular Outcome During Follow-Up

The frequency of cardiovascular deaths markedly increased with increasing tertiles of each hemostatic factor measured at baseline (Figure 1). By contrast, the frequency of nonfatal cardiovascular events did not significantly vary with any of the factor (Figure 1). Further analyses were then focused on cardiovascular mortality.

Association of the five hemostatic factors with future cardiovascular death was assessed by Cox regression analysis. Each factor was introduced in tertiles in a series of models successively adjusting for potential confounders. After adjustment for age and sex, the HRs increased with increasing tertiles of all hemostatic factors (Figure 2). Linearity of the relationship across tertiles was not rejected for any factor ($P = 0.60, 0.14, 0.65, 0.32, and 0.74$ for vWF, fibrinogen, TAT, D-dimers, and PAP, respectively). The age- and sex-adjusted HR (95% CI) associated with one increasing tertile of each factor was $1.34$ (1.07 to 1.67) for vWF, $1.55$ (1.25 to 1.84) for fibrinogen, $1.32$ (1.06 to 1.63) for TAT, $1.43$ (1.11 to 1.84) for D-Dimer, and $1.46$ (1.17 to 1.82) for PAP, respectively. Adjustment on conventional risk factors and treatments, followed by further adjustment on CRP, hardly influenced these associations (Figure 2). For all factors except vWF, the association with future cardiovascular death remained significant after adjustment for conventional cardiovascular risk factors, therapeutic features, and CRP ($P$ for trend $= 0.20, 0.011, 0.026, 0.019$, and $0.01$ for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively).

### TABLE 1. Baseline Characteristics of CAD Patients According to the Outcome During Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Cardiovascular Event n=925</th>
<th>Cardiovascular Death n=135</th>
<th>Nonfatal MI or Stroke n=97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.7±10.1</td>
<td>67.1±8.6</td>
<td>61.4±10.5</td>
</tr>
<tr>
<td>Male</td>
<td>635 (77)</td>
<td>102 (76)</td>
<td>77 (77)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>253 (31)</td>
<td>40 (30)</td>
<td>25 (26)</td>
</tr>
<tr>
<td>No. of stenosed coronary arteries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel</td>
<td>220 (26)</td>
<td>27 (20)</td>
<td>23 (24)</td>
</tr>
<tr>
<td>2 vessels</td>
<td>243 (29)</td>
<td>37 (27)</td>
<td>33 (34)</td>
</tr>
<tr>
<td>≥3 vessels</td>
<td>362 (43)</td>
<td>71 (53)</td>
<td>41 (42)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0±3.6</td>
<td>26.9±4.1</td>
<td>27.2±3.9</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>120 (15)</td>
<td>24 (18)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>442 (48)</td>
<td>65 (48)</td>
<td>59 (61)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>352 (38)</td>
<td>46 (34)</td>
<td>30 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>111 (13)</td>
<td>44 (33)</td>
<td>21 (22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>584 (71)</td>
<td>106 (79)</td>
<td>66 (68)</td>
</tr>
<tr>
<td>History of previous MI</td>
<td>398 (48)</td>
<td>69 (51)</td>
<td>46 (47)</td>
</tr>
<tr>
<td>Medications at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>435 (53)</td>
<td>85 (63)</td>
<td>61 (60)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>734 (89)</td>
<td>114 (84)</td>
<td>84 (87)</td>
</tr>
<tr>
<td>Statins</td>
<td>277 (34)</td>
<td>27 (20)</td>
<td>26 (27)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>476 (58)</td>
<td>56 (41)</td>
<td>57 (59)</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>362 (44)</td>
<td>90 (67)</td>
<td>46 (47)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>147 (18)</td>
<td>26 (19)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>220±44</td>
<td>217±49</td>
<td>223±43</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>48±15</td>
<td>45±15</td>
<td>47±13</td>
</tr>
<tr>
<td>Triglycerides, mg/dl†</td>
<td>139 (103–196)</td>
<td>153 (105–207)</td>
<td>152 (108–205)</td>
</tr>
<tr>
<td>CRP (mg/l)†</td>
<td>4.2 (1.9–10.9)</td>
<td>5.9 (2.3–21.9)</td>
<td>4.6 (2.7–12.1)</td>
</tr>
<tr>
<td>IL-6 (pg/ml)†</td>
<td>9.3 (4.7–18.9)</td>
<td>14.2 (6.1–29.4)</td>
<td>11.5 (5.1–23.5)</td>
</tr>
</tbody>
</table>

CRP indicates C-reactive protein; IL-6, interleukin-6. Categorical variables are presented as n (%), and continuous variables as means±SD or median (25th/75th percentiles) for skewed variables (for these variables, test performed on log-transformed distribution).
Because of the strong clustering of all five hemostatic factors, we further evaluated which of them had an independent predictive role on outcome. When including the five hemostatic factors as continuous factors in a stepwise Cox regression analysis where all potential confounders, including CRP, were forced into the model, only D-dimers and fibrinogen remained independently associated with cardiovascular death. Adjusted HRs (95% CI) associated with one SD increase of fibrinogen and D-dimers were 1.27 (1.04 to 1.55) and 1.29 (1.09 to 1.53), respectively.

**Discussion**

Results from the present study showed that markers reflecting activation of the coagulation/fibrinolytic pathway predict the risk of cardiovascular death in individuals with angiographically proven CAD. This predictive ability is independent of
inflammation markers such as CRP. Among the 5 hemostatic parameters studied, fibrinogen, and D-dimers appeared as independent predictors of cardiovascular death in CAD patients. By contrast, none of the five hemostatic factor was related to the occurrence of nonfatal cardiovascular events. However, because nonfatal events were not validated by an expert clinical panel, it is possible that some of them were misclassified, possibly biasing the effect toward the null.

One limitation of the study was that D-dimer levels were not measured in 25% of subjects. The patients with missing determination corresponded to the last series of patients included in the cohort. These patients were younger than those who had a D-dimer determination (59.5 versus 62.1 years, \( P<0.001 \)), were less often of female gender (18.4% versus 24.7%, \( P=0.04 \)) but did not differ with respect to smoking status, and prevalence of hypertension or diabetes. Because analyses were adjusted for all conventional cardiovascular factors, including age and sex, this should not introduce a substantial bias. Moreover, analyses comparing the respective predictive ability of the five hemostatic factors were conducted in the subset of subjects having all five determinations. Another limitation of the study was that nearly half of the patients reported an history of previous MI, which might bias the population study toward strong survivors of MI.

In the present study, vWF, D-dimers, and PAP complexes, but not fibrinogen and TAT complexes, correlated positively with age as observed in other epidemiological studies.\textsuperscript{7,10,11} PAP complexes negatively correlated with parameters belonging to the metabolic syndrome (body mass index, HDL-cholesterol, hypertension, diabetes, smoking status, heparin, \( \beta \)-blockers, statins, ACE-inhibitor, and antiplatelet agents) \( P \) for trend 0.10, 0.0013, 0.012, 0.01, and 0.003 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively; gray squares (model 2) indicate HRs additionally adjusted for cardiovascular risk factors (ACS versus stable angina, body mass index, HDL-cholesterol, hypertension, diabetes, smoking status, heparin, \( \beta \)-blockers, statins, ACE-inhibitor, and antiplatelet agents) \( P \) for trend 0.10, 0.0013, 0.012, 0.01, and 0.003 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively; black squares (model 3) indicate HRs adjusted for covariates of model 2 and additionally adjusted for CRP \( P \) for trend 0.20, 0.011, 0.026, 0.019, and 0.01 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively).

Figure 2. HRs (95% CI) for cardiovascular death according to increasing tertiles of vWF, fibrinogen, thrombin-antithrombin complex (TAT), D-dimer, and plasmin-antiplasmin complex (PAP). White circles indicate the lowest tertile which serves as the reference group. White squares (model 1) indicate HRs adjusted for age and sex \( P \) for trend 0.01, <0.0001, 0.012, 0.006, and 0.0008 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively; gray squares (model 2) indicate HRs additionally adjusted for cardiovascular risk factors (ACS versus stable angina, body mass index, HDL-cholesterol, hypertension, diabetes, smoking status, heparin, \( \beta \)-blockers, statins, ACE-inhibitor, and antiplatelet agents) \( P \) for trend 0.10, 0.0013, 0.012, 0.01, and 0.003 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively; black squares (model 3) indicate HRs adjusted for covariates of model 2 and additionally adjusted for CRP \( P \) for trend 0.20, 0.011, 0.026, 0.019, and 0.01 for vWF, fibrinogen, TAT, D-Dimer, and PAP, respectively.

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of ischemic heart disease independently of inflammation has been reported in the general population, but has not been assessed in patients with CAD.

By contrast to vWF, fibrinogen, and D-dimers, the relation of TAT complexes with cardiovascular risk has been less extensively studied. In a prospective study including individuals from the general population, no relation was found between TAT complexes and the risk of cardiovascular event. In a small prospective study of individuals with unstable angina, a trend toward higher risk of death was observed in individuals in the top tertile of TAT complexes compared with the bottom tertile. In a small group of patients with acute coronary syndrome, both high and low levels of prothrombin fragment 1+2, another marker of thrombin generation, were predictors of an increased risk of unfavorable outcome. Although we did not observe such a U-shaped relationship between TAT complexes and the risk of cardiovascular death, the present study confirmed that high levels of thrombin generation were associated with unfavorable outcome independently of acute-phase reactants such as CRP.

Only few and discordant data are available on the association between CAD and plasma levels of PAP complexes. An increase in PAP levels appeared to be a risk factor for MI and coronary death in a healthy elderly population. By contrast, in a small population of survivors of a first MI followed for 2 years, low PAP levels were found associated with an increased risk of re-events (fatal or non-fatal MI, coronary angioplasty, coronary artery bypass grafting). In the present study, higher levels of PAP were associated with increased risk of cardiovascular death, and this association persisted after adjustment for clinical and inflammatory confounders.

The five hemostatic parameters strongly correlated one with each other, even after adjustment for CRP, indicating that these strong relationships were not the simple consequence of an ongoing inflammatory process. These findings underline that despite their involvement in different parts of the coagulation/fibrinolysis pathway, they all reflect ongoing clot formation and degradation. When including the five hemostatic factors in a stepwise regression analysis adjusting for all potential confounders, only fibrinogen and D-dimers remained independently associated with the risk of cardiovascular death. The lack of independent effect of TAT and PAP complexes might be explained by their strong correlation with D-dimers. Recently, the population-based Caerphilly Study examined the contribution of a range of hemostatic markers (including vWF, TAT complexes, D-dimers, but not PAP complexes) on the risk of first cardiovascular event after a median follow-up of 13 years. Among the 11 studied markers, D-dimers and fibrinogen, along with plasminogen activator inhibitor (PAI)-1 and factor VIIc, were the only factors independently associated with cardiovascular risk. The present study confirms the findings of the Caerphilly Study and extend them by showing that the predictive ability of D-dimers and fibrinogen is independent of the inflammatory status reflected by the level of CRP. However, our results are drawn from a cohort of patients with overt CAD and may not be generalized to the general population in primary prevention. Moreover, the association was restricted to cardiovascular deaths. The Caerphilly study included fatal and nonfatal events, but because both type of events were analyzed together, it is not possible to know whether the association was stronger in fatal cases, as observed in our study.

Cardiovascular death in individuals with coronary disease has been mostly attributed to the development of acute thrombosis at the site of a ruptured atherosclerotic plaque. The independent association between cardiovascular death and levels of D-dimers indicates that an hypercoagulable state is involved in this process. The independent association observed between fibrinogen and cardiovascular death could be attributed to the major role played by fibrinogen in coagulation. However, the role of fibrinogen as an inflammatory biomarker could also be responsible for this association. In this case, the fact that fibrinogen remained significantly associated with the risk of cardiovascular death after adjustment for CRP underline that fibrinogen and CRP may represent different aspects of an underlying inflammatory process as previously suggested.

In conclusion, the present study provided evidence that in individuals with CAD, activation of the coagulation process contributed to the risk of cardiovascular death. Among markers that reflect ongoing clot formation and degradation, plasma levels of fibrinogen and D-dimers appeared to be the most useful markers for cardiovascular risk assessment, independently of conventional risk factors and CRP.

Appendix

The AtheroGene Group
Stefan Blankenberg, Hans-Jürgen Rupprecht, Christoph Bickel, Christine Espinola-Klein, Jürgen Meyer (Department of Medicine II), Karl J. Lackner, Dirk Peetz (Institute of Laboratory Medicine and Clinical Chemistry): Johannes Gutenberg-University, Mainz, Germany.

Laurence Tiret, Odette Poirier, Tiphaine Godefroy, Claire Perret, Viviane Nicaud, Jean-Louis Georges, David-Alexandre Tregouet, François Cambien: INSERM U525, Faculté de Médecine Pitié-Salpêtrière, Paris, France.

AtheroGene Recruitment Centers
Department of Medicine II, Johannes Gutenberg-University Mainz; Bundeswehrzentralkrankenhaus, Koblenz, Germany.

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Disclosures
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