

## HEMOSTATIC FACTORS AND THE RISK OF MYOCARDIAL INFARCTION OR SUDDEN DEATH IN PATIENTS WITH ANGINA PECTORIS

SIMON G. THOMPSON, M.A., JOACHIM KIENAST, M.D., STEPHEN D.M. PYKE, M.Sc., FRITS HAVERKATE, Ph.D., AND JÜRGEN C.W. VAN DE LOO, M.D., FOR THE EUROPEAN CONCERTED ACTION ON THROMBOSIS AND DISABILITIES ANGINA PECTORIS STUDY GROUP\*

**Abstract Background.** Increased levels of certain hemostatic factors may play a part in the development of acute coronary syndromes and may be associated with an increased risk of coronary events in patients with angina pectoris.

**Methods.** We conducted a prospective multicenter study of 3043 patients with angina pectoris who underwent coronary angiography and were followed for two years. Base-line measurements included the concentrations of selected hemostatic factors indicative of a thrombophilic state or endothelial injury. The results were analyzed in relation to the subsequent incidence of myocardial infarction or sudden coronary death.

**Results.** After adjustment for the extent of coronary artery disease and other risk factors, an increased incidence of myocardial infarction or sudden death was associated with higher base-line concentrations of fibrinogen (mean  $\pm$ SD,  $3.28 \pm 0.74$  g per liter in patients who subsequently had coronary events, as compared with  $3.00 \pm 0.71$  g per liter in those who did not;  $P = 0.01$ ), von Willebrand factor antigen ( $138 \pm 49$  percent vs.  $125 \pm 49$

percent,  $P = 0.05$ ), and tissue plasminogen activator (t-PA) antigen ( $11.9 \pm 4.7$  ng per milliliter vs.  $10.0 \pm 4.2$  ng per milliliter,  $P = 0.02$ ). The concentration of C-reactive protein was also directly correlated with the incidence of coronary events ( $P = 0.05$ ), except when we adjusted for the fibrinogen concentration. In patients with high serum cholesterol levels, the risk of coronary events rose with increasing levels of fibrinogen and C-reactive protein, but the risk remained low even given high serum cholesterol levels in the presence of low fibrinogen concentrations.

**Conclusions.** In patients with angina pectoris, the levels of fibrinogen, von Willebrand factor antigen, and t-PA antigen are independent predictors of subsequent acute coronary syndromes. In addition, low fibrinogen concentrations characterize patients at low risk for coronary events despite increased serum cholesterol levels. Our data are consistent with a pathogenetic role of impaired fibrinolysis, endothelial-cell injury, and inflammatory activity in the progression of coronary artery disease. (N Engl J Med 1995;332:635-41.)

CORONARY thrombosis is now generally recognized as the precipitating event in the transition from stable to acute ischemic heart disease, manifested by unstable angina,<sup>1</sup> acute myocardial infarction,<sup>2</sup> and sudden death from coronary causes.<sup>3</sup> Besides local stimuli such as disruption of plaques, systemic thrombogenic factors may contribute to the occurrence, extent, and persistence of coronary thrombosis and its clinical sequelae.<sup>4</sup> These factors include abnormalities of blood flow,<sup>5</sup> platelet hyperreactivity,<sup>6,7</sup> defective fibrinolysis,<sup>8,9</sup> and increased concentrations of hemostatic proteins, specifically fibrinogen and factor VII.<sup>10</sup> Thus, with the use of appropriate laboratory tests, it may be possible to detect a thrombogenic state and thus identify patients at increased risk for cardiovascular disease.

Support for this hypothesis comes mainly from prospective studies of healthy subjects, which have demonstrated a direct and independent association between plasma fibrinogen concentrations and the risk of coronary events.<sup>5,10-14</sup> However, data on patients with known coronary artery disease are sparse and come from small cohort studies of patients with angina pectoris<sup>15,16</sup> or those who have had a first myocardial infarction.<sup>8,9,17-19</sup>

In the European Concerted Action on Thrombosis

From the Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London (S.G.T., S.D.M.P.); the Department of Internal Medicine, University of Münster, Münster, Germany (J.K., J.C.W.L.); and the Gaubius Laboratory, Leiden, the Netherlands (F.H.). Address reprint requests to Dr. van de Loo at the Department of Internal Medicine, University of Münster, Albert-Schweitzer-Str. 33, D-48129 Münster, Germany.

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\*The investigators and institutions participating in the European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study are listed in the Appendix.

and Disabilities (ECAT) Angina Pectoris Study,<sup>20</sup> we recruited more than 3000 patients with angina pectoris and used angiography to determine the extent of coronary artery disease. Our principal objective was to investigate the associations between base-line measurements of hemostatic factors that indicate the existence of a thrombophilic state or an alteration in the vascular endothelium, on the one hand, and the occurrence of coronary events during a two-year follow-up period, on the other.

### METHODS

#### Patients

Men and women who underwent coronary angiography because of suspected coronary artery disease were eligible for the study. Patients who had had a myocardial infarction within the preceding two months or who had severe right-heart failure or noncardiac diseases likely to cause death within one year were excluded. A total of 3043 patients from 18 European centers (listed in the Appendix) were recruited between October 1984 and June 1987.

#### Blood Sampling and Measurements of Hemostatic Factors

The conditions of blood sampling and storage and the measurement of hemostatic factors have been described in detail elsewhere.<sup>21</sup> The technicians were trained at the central laboratory, and an external quality-assessment scheme was used to monitor their performance throughout the study.<sup>22,23</sup>

The following tests were performed. The number and function of platelets were assessed by means of whole-blood platelet counts and measurements of  $\beta$ -thromboglobulin and platelet factor 4. The state of the coagulation system was assessed by measurements of the activated partial-thromboplastin time, fibrinogen, fibrinopeptide A, von Willebrand factor antigen, factor VIII activity, antithrombin III antigen and activity, and protein C antigen and activity. The fibrinolytic system was assessed by the measurement of plasminogen,  $\alpha_2$ -antiplasmin activity, histidine-rich glycoprotein, and plasminogen-activator inhibitor type 1 (PAI-1) antigen and activity. Tissue plasminogen activator (t-PA) antigen and activity, as well as the euglob-

ulin clot-lysis time, were measured before and after 10 minutes of venous occlusion.

The hematocrit, white-cell count, and ABO blood type were determined according to standard local procedures, as were the total cholesterol and triglyceride concentrations. C-reactive protein was measured by a nephelometric method.

### Coronary Angiography

Coronary angiography was performed, usually by the Judkins technique but occasionally by the Sones technique.<sup>24</sup> For the purpose of this study, the angiographic results were expressed as the number of vessels (0 to 4) with stenosis of at least 50 percent of the vessel diameter or occlusion.

### Follow-up and Ascertainment of End Points

Patients were evaluated annually for two years, and information on deaths, coronary events, hospital admissions, and current drug use was obtained at each follow-up contact. Reported clinical events were reviewed independently by an end-points committee whose members were blinded to the results of the hemostatic tests. The primary end points of the study were fatal or nonfatal myocardial infarction, defined according to standard diagnostic criteria,<sup>25</sup> and sudden death from coronary causes, defined as death within one hour of the onset of cardiac symptoms. Events occurring within 72 hours of surgery (usually coronary-artery bypass surgery) or angioplasty were considered primarily related to the intervention. Patients with such events were excluded from the analyses, as were patients with possible but unconfirmed myocardial infarction or death from other cardiac causes, other causes, or uncertain causes.

### Statistical Analysis

To investigate the association between the concentrations of hemostatic factors and the incidence of definite coronary events, we used multiple regression analysis, with the hemostatic factor as the dependent variable. Mean differences between the patients who had events and those who were event-free were calculated after adjustment for the medical center; the patient's age, sex, and ABO blood type; and any of the following base-line characteristics if they were demonstrated to be significantly related ( $P < 0.01$ ) to the incidence of events: drugs used at the time of blood sampling; previous myocardial infarction; history of diabetes or hypertension; smoking; history of chest pain, including the type of angina; extent of coronary artery disease as assessed angiographically; left ventricular ejection fraction and end-diastolic pressure; body-mass index (the weight in kilograms divided by the square of the height in meters); blood pressure; and total cholesterol and triglyceride concentrations. Hemostatic variables were analyzed on a logarithmic scale when this transformation produced a more symmetrical (gaussian) distribution.

A separate analysis was carried out of the association between other (nonhemostatic) factors and the risk of coronary events; for this analysis we used multiple logistic-regression techniques and the same variables listed above.

The *P* values given here for differences in laboratory-test results reflect adjusted data and are two-tailed. The standardized relative risk was calculated as the relative risk of a coronary event for each increase of 1 SD in a given variable.<sup>26</sup>

## RESULTS

### Base-Line Characteristics

Of the 3043 patients enrolled in the study, 2960 (97 percent) were followed for two years. During this period 837 patients underwent coronary-artery bypass surgery, 223 underwent coronary angioplasty, and 49 underwent both interventions. A total of 106 definite coronary events were reported, 40 of which occurred in patients undergoing bypass surgery or angioplasty either just before or after the clinical event. An additional 154 major events did not fulfill the criteria for study end points (Table 1).

The base-line characteristics of the 106 patients who

Table 1. Study Population and Events during Follow-up.

PATIENT CATEGORY	No. (%)
Patients enrolled	3043
Patients with complete two-year follow-up	2960 (97.3)
Patients with definite coronary events	106 (3.6)
Sudden coronary death	31
Fatal myocardial infarction	9
Nonfatal myocardial infarction	66
Patients with other major events*	154 (5.2)
Possible myocardial infarction (not confirmed)	24
Events related to interventions†	
Death	44
Nonfatal myocardial infarction	37
Death from other cardiac causes	13
Death from cancer	7
Death from other uncertain causes	29
Patients without events	2700 (91.2)

\*These patients were excluded from subsequent analyses.

†Occurring within 72 hours of surgery or angioplasty.

had definite coronary events and the 2700 patients in the event-free group are summarized in Table 2. After adjustment for medical center, sex, and age, when appropriate, the patients who had coronary events were older, tended to have more severe angina, and were more likely to have a history of myocardial infarction than those without such events. They also had more extensive coronary artery disease and were more likely to have been treated with diuretic agents or digitalis. These differences, along with other base-line factors, were accounted for in the multiple regression analysis of the associations between the concentrations of hemostatic factors and the incidence of coronary events. A detailed analysis of base-line clinical and laboratory data was published earlier.<sup>20</sup>

### Concentrations of Hemostatic Factors and Other Test Results in Relation to Outcome

Among the various hemostatic variables measured, only the levels of fibrinogen, von Willebrand factor antigen, and t-PA antigen were significantly and directly related to the incidence of coronary events, after adjustment for other confounding factors (Table 3).

Regression analyses indicated significant positive correlations between the fibrinogen level and age ( $P < 0.001$ ), the body-mass index ( $P < 0.001$ ), the extent of coronary artery disease at enrollment ( $P < 0.001$ ), and smoking status ( $P = 0.003$ ). In addition, the mean fibrinogen concentrations were 7.6 percent, 5.8 percent, and 4.3 percent higher in patients receiving heparin, diuretics, and oral anticoagulants, respectively ( $P < 0.002$  for all comparisons). After adjustment for these confounding factors, fibrinogen concentrations in the group with coronary events were on average 6.5 percent higher than those in the event-free group ( $P = 0.01$ ).

Concentrations of von Willebrand factor antigen increased with age ( $P < 0.001$ ) and were significantly higher in the patients receiving diuretics, digitalis, heparin, or oral anticoagulants than in those not receiving these agents ( $P < 0.01$  for all comparisons). Patients

Table 2. Base-Line Characteristics of the Patients with and without Coronary Events.

CHARACTERISTIC	GROUP WITH EVENTS (N = 106)	EVENT-FREE GROUP (N = 2700)	P VALUE*
	no. (%)†		
Sex			0.18
Male	95 (90)	2296 (85)	
Female	11 (10)	404 (15)	
Age (yr)			0.02
<45	13 (12)	292 (11)	
45–69	83 (78)	2300 (85)	
>69	10 (9)	108 (4)	
Type of angina			0.06
Unstable angina‡	61 (58)	1285 (48)	
Stable angina on exertion	38 (36)	988 (37)	
Angina without typical chest pain	7 (7)	404 (15)	
Previous myocardial infarction§	71 (67)	1173 (43)	<0.001
No. of stenosed coronary arteries¶			<0.001
1 Vessel	19 (18)	706 (26)	
2 Vessels	35 (33)	652 (24)	
3 or 4 Vessels	46 (44)	668 (25)	
None	5 (5)	666 (25)	
Smoking status**			0.60
Current smoker	25 (24)	531 (20)	
Ex-smoker	57 (54)	1392 (52)	
Nonsmoker	24 (23)	774 (29)	
Medications			
Antiplatelet drugs (mainly aspirin)	34 (32)	677 (25)	0.08
Heparin	11 (10)	161 (6)	0.28
Oral anticoagulants††	16 (15)	398 (15)	0.96
β-adrenoceptor blockers	39 (37)	975 (36)	0.61
Calcium antagonists	73 (69)	1792 (66)	0.59
Nitrates	77 (73)	1742 (65)	0.11
Diuretics	34 (32)	479 (18)	<0.001
Digitalis	19 (18)	267 (10)	0.001

\*P values for the comparison of patients with events and event-free patients were obtained as follows: for sex, by the chi-square test for association, with stratification by center and age group; for age by comparison of mean ages with adjustment for medical center and sex; for type of angina, history of myocardial infarction, extent of coronary artery disease, smoking, and medications, by the chi-square test for association, with stratification by center, sex, and age group.

†Percentages have been calculated as a proportion of those with known values. Because of rounding, percentages do not always total 100.

‡Either worsening of angina within the previous four weeks or angina at rest.

§More than two months before enrollment.

¶A reduction of at least 50 percent of the vessel diameter. Data were missing for one patient with a coronary event and for eight in the event-free group.

||Includes some patients with stenosis of the left main coronary artery.

\*\*Data were missing for three patients in the event-free group.

††Values for protein C and activated partial-thromboplastin time were considered unknown for patients receiving oral anticoagulants at the time of blood sampling.

with blood type O had substantially lower mean concentrations of von Willebrand factor antigen (107 percent) than patients in blood group A (140 percent), B (150 percent), or AB (146 percent) ( $P < 0.001$  for all comparisons). After adjustment for these variables, the concentration of von Willebrand factor antigen was on average 8.5 percent higher in the patients who subsequently had coronary events than in those who did not ( $P = 0.05$ ).

Among the fibrinolytic factors, the level of t-PA antigen, measured before venous occlusion, was significantly higher in the patients who subsequently had coronary events; the mean difference between the groups was 10.2 percent ( $P = 0.02$ ) after adjustment for the confounding influence of age, sex, medications (heparin and diuretics), smoking status, body-mass index, triglyceride concentrations, extent of coronary artery

disease, and ejection fraction. Concentrations of t-PA antigen were directly correlated with both PAI-1 activity and PAI-1 antigen ( $r = 0.40$  and  $r = 0.47$ , respectively;  $P < 0.001$  for both comparisons). However, neither PAI-1 antigen and activity nor the ratio of PAI-1 antigen to t-PA antigen differed significantly between the group with coronary events and the event-free group when all confounding factors were adjusted for ( $P > 0.2$  for all comparisons).

The concentrations of C-reactive protein were on average 20.2 percent higher in the patients who had coronary events than in those without such events ( $P = 0.05$ ), after adjustment for smoking status, body-mass index, ejection fraction, extent of coronary artery disease, triglyceride concentrations, and use of diuretics, digitalis, and heparin. The base-line measurements of C-reactive protein and fibrinogen, both of which are known to be hepatic acute-phase proteins,<sup>27-29</sup> were strongly correlated ( $r = 0.49$ ;  $P < 0.001$ ). The association of fibrinogen concentrations with the risk of coronary events remained statistically significant ( $P = 0.013$ ) after adjustment for the C-reactive protein concentration, whereas the relation of the concentration of C-reactive protein to the risk of coronary events was no longer significant after adjustment for the fibrinogen concentration ( $P = 0.48$ ).

#### Prediction of the Risk of Coronary Events

Table 4 shows the relative risk of definite coronary events in five equal subgroups of the patient population defined according to the distributions of laboratory variables that were independently related to the incidence of coronary events. Whereas fibrinogen was associated with a threefold increase in risk from the lowest to the highest quintile group, a 1.5- to 2-fold increase in risk was observed with increasing levels of each of three factors: von Willebrand factor antigen, t-PA antigen, and C-reactive protein.

A history of myocardial infarction was associated with a 1.6-fold increase in the risk of coronary events ( $P = 0.04$ ) but did not significantly influence the relation of the variables mentioned above to the incidence of coronary events. Furthermore, the standardized relative risks shown in Table 4 did not differ significantly among patients with stable angina on exertion, those with unstable angina, and those who had angina with-

Table 3. Laboratory-Test Results According to Outcome.\*

VARIABLE	GROUP WITH EVENTS (N = 106)	EVENT-FREE GROUP (N = 2700)	P VALUE
Fibrinogen (g/liter)	3.28±0.74	3.00±0.71	0.01
Von Willebrand factor antigen (%)	137.5±48.8	124.6±49.1	0.05
t-PA antigen before venous occlusion (ng/ml)	11.9±4.7	10.0±4.2	0.02
C-reactive protein (mg/liter)	2.15±1.96	1.61±1.38	0.05

\*Values are means ±SD, with adjustment for medical center, age, and sex. P values have also been adjusted for all the other risk factors for coronary disease on which we obtained data (see the Methods section). For statistical analyses of logarithmically transformed values, geometric means and approximate standard deviations are shown. Percentages have been calculated on the basis of the numbers with known values. The number of patients with definite coronary events included in the statistical analyses ranged from 89 to 106 for the various laboratory tests.

out typical chest pain (for example, acute left abdominal pain, anxiety, or dyspnea).

Higher left ventricular end-diastolic pressures measured at base line were associated with a 20 percent increase in the risk of coronary events for each additional 5 mm Hg of pressure ( $P=0.02$ ). In addition, patients who were receiving diuretics when they entered the study had a 2.5-fold risk of subsequent coronary events ( $P<0.001$ ), an increase that probably reflects the poor prognosis of patients with heart failure. Finally, patients in blood groups A and B had 1.6 times the risk of coronary events of patients with blood type O ( $P=0.05$ ). Significant associations with these base-line characteristics were taken into account in our analysis of the relation of hemostatic factors and other laboratory measurements to the risk of coronary events.

As expected, the extent of coronary artery disease was the single most powerful predictor of coronary events (Table 5). However, despite the correlation between the concentrations of fibrinogen, t-PA antigen, and C-reactive protein and the extent of coronary disease,<sup>20</sup> these variables remained independently predictive of subsequent coronary events and were valuable in identifying patients at low and at high risk of such events regardless of the severity of coronary disease.

Serum total cholesterol concentrations were not independently related to the risk of coronary events in this group of patients; the mean serum cholesterol concentration was 257 mg per deciliter (6.66 mmol per liter) in patients who subsequently had coronary events, as compared with 246 mg per deciliter (6.37 mmol per liter) in the event-free group after adjustment for other coronary risk factors ( $P=0.33$ ). However, when we analyzed the combined influence of fibrinogen, C-reactive protein, and total cholesterol on the risk of coronary events, it was clear that high fibrinogen concentrations, and particularly the combination of high fibrinogen concentrations with high concentrations of C-reactive protein, added markedly to the association of increased risk with high total cholesterol concentrations (Fig. 1). Conversely, patients with low concentrations of both fibrinogen and C-reactive protein had a

Table 4. Relative Risk of Coronary Events According to the Concentrations of Hemostatic Factors.\*

VARIABLE	QUINTILE					STANDARDIZED RELATIVE RISK (95% CI)†
	1	2	3	4	5	
Fibrinogen	1.0	1.89	2.33	2.56	2.89	1.31 (1.07–1.61)
Von Willebrand factor antigen	1.0	1.23	1.39	1.46	1.85	1.24 (1.00–1.53)
t-PA antigen	1.0	1.64	1.64	1.73	2.10	1.29 (1.04–1.60)
C-reactive protein	1.0	1.07	1.14	1.57	1.57	1.24 (1.00–1.55)

\*The relative risks are shown for each of five equal groups (quintiles) of subjects defined according to the concentrations of each factor, from 1 (the group with the lowest concentrations) to 5 (the group with the highest). Relative risks have been adjusted for all confounding factors (see the Methods section). The group of patients with the lowest values for each factor serves as the reference group.

†Defined as the relative risk for each increase of 1 SD in the variable in question. CI denotes confidence interval.

Table 5. Relative Risk of Coronary Events According to Angiographic Status at Base Line.\*

NO. OF CORONARY ARTERIES WITH $\geq 50$ PERCENT STENOSIS	RELATIVE RISK (95% CI)
0	1
1	3.44 (0.98–12.1)
2	7.55 (2.23–25.7)
3 or 4	8.14 (2.41–27.5)

\*The risk as compared with that among patients with  $<50$  percent stenosis, after adjustment for medical center, age, and other coronary risk factors (see the Methods section).  $P<0.001$  for the differences between categories. CI denotes confidence interval.

low risk of coronary events even in the presence of high total cholesterol concentrations.

## DISCUSSION

We designed this study to assess the prognostic value of the extent of coronary artery disease and of selected hemostatic variables in patients with angina pectoris who were undergoing coronary angiography. Three hemostatic variables — namely, the concentrations of fibrinogen, von Willebrand factor antigen, and t-PA antigen — proved to be directly and independently correlated with the risk of subsequent coronary events. We also found an association between the risk of coronary events and the concentration of acute-phase reactant C-reactive protein.

Not surprisingly, the extent of coronary artery disease assessed by angiography at study entry was the single most important indicator of outcome. It was positively related to the plasma concentrations of fibrinogen, t-PA antigen, and C-reactive protein, but even after adjustment for the extent of coronary artery disease, these variables remained independently associated with the risk of coronary events, and they were valuable in identifying patients at low and at high risk within each category of disease severity. Moreover, the predictive value of these factors did not seem to depend on the type of angina at the base-line examination. Indeed, in this study,<sup>20</sup> although not in others,<sup>30–33</sup> the type of angina was unrelated to the results of hemostatic tests and measurements of C-reactive protein. Hence, these variables appear to be independent markers of coronary atherosclerosis that is likely to progress to atherothrombotic vessel occlusion in patients with symptomatic angina pectoris.

A strong association with the risk of subsequent coronary events was observed for the fibrinogen concentration; the risk tripled from that for the patients in the bottom fifth of the sample in terms of fibrinogen levels to that for those in the top fifth. The strength of this association in our patients with angina pectoris is similar in magnitude to that in healthy subjects.<sup>10–14</sup> Thus, on the basis of the available evidence, an increased fibrinogen concentration — even within the normal range — can be regarded as a strong and independent predictor of cardiovascular risk not only in apparently healthy people, but also in patients with manifest coronary artery disease.

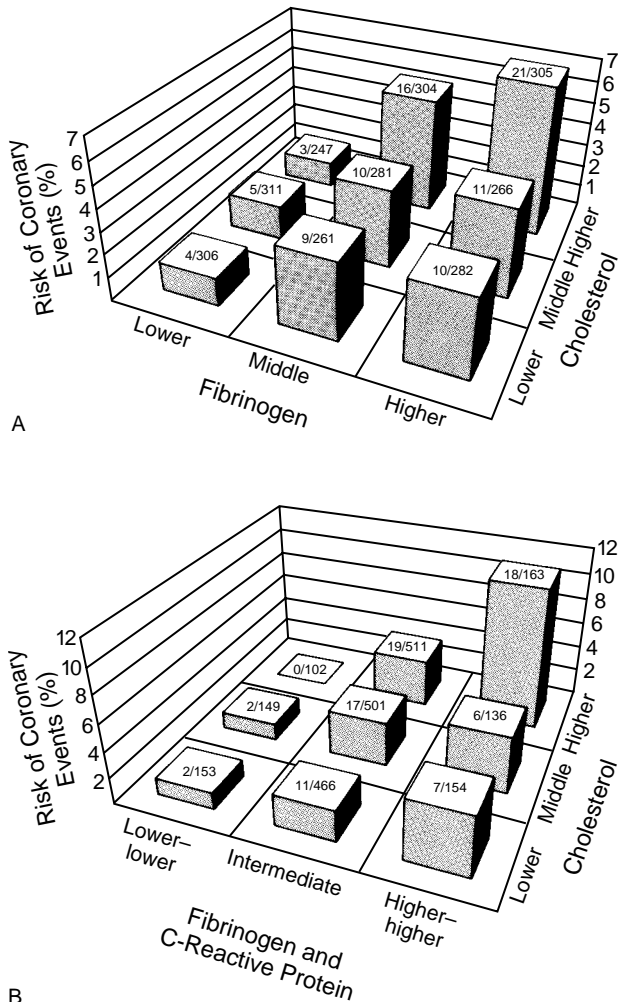


Figure 1. Incidence of Coronary Events during Two Years of Follow-up, According to Concentrations of Fibrinogen, C-Reactive Protein, and Total Cholesterol.

Panel A shows the risk of coronary events according to fibrinogen and total cholesterol concentrations. Panel B shows the risk according to fibrinogen and C-reactive protein concentrations combined, as compared with total cholesterol concentrations. The concentrations of these variables are divided into three categories (lower, middle, and higher), each containing a third of the sample, according to their respective distributions. In Panel B, "intermediate" refers to all combinations of fibrinogen and C-reactive protein concentrations other than lower-lower or higher-higher. The values used to divide the sample into thirds were 2.71 and 3.31 g per liter for fibrinogen, 5.79 and 6.80 mmol per liter (224 and 263 mg per deciliter) for cholesterol, and 0.88 and 2.17 mg per liter for C-reactive protein. The number of coronary events and the number of patients at risk are shown for each group. Only patients for whom data on both fibrinogen and total cholesterol concentrations were available are included in the analysis.

Our findings regarding the prognostic value of the concentrations of von Willebrand factor antigen extend recent observations in smaller cohorts of patients with stable angina or those who had had myocardial infarctions.<sup>15,18</sup> Increased plasma concentrations of von Willebrand factor derived from endothelial cells have been reported in various vascular disorders.<sup>34</sup> Thus, increases in the concentration of this factor in patients at high

risk for coronary thrombotic occlusion may reflect endothelial perturbation.

The association we found between the concentration of t-PA antigen and the risk of coronary events accords with the results of recent prospective studies in patients with severe angina pectoris<sup>16</sup> and in healthy men<sup>35</sup>; these studies also identified t-PA antigen as a marker of cardiovascular risk. The significant positive correlations between t-PA antigen and plasma PAI-1 antigen and activity in our study and that of others<sup>36</sup> suggest that increased concentrations of t-PA antigen in large part reflect circulating t-PA-PAI-1 complex and thus indicate reduced rather than enhanced fibrinolytic activity. Irrespective of these considerations, increased synthesis of t-PA antigen by endothelial cells may indicate dysfunction of these cells.

Increased concentrations of C-reactive protein have been reported in patients with acute coronary syndromes<sup>33,37,38</sup> and predict poor outcomes in patients with severe unstable angina.<sup>39</sup> Their relevance in patients with other types of angina and their long-term prognostic value with respect to cardiovascular risk have been unclear, however. The positive association of increasing concentrations of C-reactive protein with increases in the risk of coronary events in our study suggests a possible role of inflammation in the progression of coronary artery disease. This process may account, in part, for the association of risk with the concentration of fibrinogen, which is also known to act as a hepatic acute-phase protein.<sup>29</sup>

An interesting new aspect of our results is the effect of fibrinogen concentrations, either alone or in combination with those of C-reactive protein, on the risk of coronary events even within subgroups of patients defined by serum cholesterol level. High concentrations of fibrinogen and C-reactive protein could be used to identify patients with hypercholesterolemia who are at particularly high risk for coronary events. In contrast, low fibrinogen concentrations were associated with a low risk of new coronary events even in patients with high serum cholesterol levels. Similarly, healthy subjects with high serum levels of low-density lipoprotein cholesterol and low fibrinogen concentrations have a lower risk of coronary events than similar subjects with high fibrinogen concentrations.<sup>14</sup> These findings have implications for risk-factor control and should be considered in the design of future interventional trials.

Our results highlight the role of the concentrations of fibrinogen, t-PA antigen, and von Willebrand factor antigen as independent predictors of cardiovascular risk in patients with coronary artery disease. The association of higher concentrations of both fibrinogen and C-reactive protein with increased coronary risk suggests that the fibrinogen concentration becomes elevated, at least in part, as a consequence of inflammatory reactions that occur in progressive atherosclerosis. The positive association of the risk of coronary events with the concentrations of t-PA antigen and von Willebrand factor antigen, both of which are released by endothelial cells, points to possible endothelial perturbation in patients prone to coronary atherothrombosis.

## APPENDIX

The following institutions and investigators participated in the ECAT study of the Commission of the European Communities. Participating centers are listed in descending order of the number of patients enrolled, with the number of patients and the responsible investigators in parentheses: *Bordeaux, France* (341) — Hôpital Cardiologique, Clinique Médicale Cardiologique (H. Bricaud) and Laboratoire d'Hémobiologie (M.R. Boisseau); *Lyon, France* (325) — Hôpital Cardiovasculaire et Pneumologique Louis Pradel (J.B. Delahaye) and Faculté de Médecine Alexis Carrel, Laboratoire d'Hémobiologie (M. Dechavanne); *Münster, Germany* (319) — University Departments of Cardiology (U.S. Müller) and Haematology (U. Schmitz-Huebner); *Bad Rothenfelde, Germany* (288) — Schüchtermann-Klinik, Department of Cardiology (R. Buchwalsky and J. Kienast, Münster); *Basel, Switzerland* (235) — Kantonsspital, University Department of Cardiology (F. Burkart) and Haemostasis Laboratory (F. Duckert); *Vienna, Austria* (208) — I. University Department of Medicine (G. Kronik and H. Niessner); *Athens, Greece* (162) — NIMTS Hospital, Department of Cardiology (C.D. Michalopoulos), Alexandra Hospital, Department of Clinical Therapeutics (S.D. Mouloupoulos), and Laikon General Hospital, Blood Transfusion Center (T. Mandalaki); *Frankfurt, Germany* (156) — University Center for Internal Medicine, Departments of Cardiology (W.D. Bussmann) and Angiology (K. Breddin); *Giessen, Germany* (144) — University Department for Internal Medicine (B. Wüsten and F.R. Matthias); *Paris* (132) — Hôpital Broussais, Clinique Cardiologique (L. Guize), and Hôtel-Dieu, Laboratoire Central d'Hématologie (M.M. Samama); *Bern, Switzerland* (128) — Inselspital, University Department of Medicine (H.P. Gurtner and P.W. Straub); *Pisa, Italy* (118) — Centro Nazionale di Ricerca Institute of Clinical Physiology (A. L'Abbate and R. de Catarina); *Brussels, Belgium* (114) — Clinique Universitaire St. Luc, Department of Cardiology (F. Lavenne), and University of Louvain, Laboratory for Haemostasis and Thrombosis Research (R. Masure); *Leeds, United Kingdom* (84) — General Infirmary, Departments of Cardiology (D.R. Smith) and Medicine (C.R.M. Prentice); *Nauheim, Germany* (82) — Kerckhoff-Clinic (M. Schlepper) and Max Planck Gesellschaft Research Group for Blood Coagulation and Thrombosis (G. Müller-Berghaus); *Mannheim, Germany* (80) — I. University Department of Medicine (B. Stegaru and W. Kirschstein); *Marseille, France* (67) — C.H.U. Timone, Department of Cardiology (A. Serradimigni), and Laboratoire d'Hématologie (I. Juhan-Vague); and *Eindhoven, the Netherlands* (60) — Catharina Hospital, Departments of Cardiology (J.J.R.M. Bonnier and H.R. Michels) and Haematology (J.J.M.L. Hoffmann).

The members of the study committees and the principal investigators of the reference laboratories were as follows: *ECAT Advisory Board*: E.F. Lüscher (chairman), Bern; J.P. Boissel, Lyon; P. Brakman, Leiden, the Netherlands; D.G. Julian, London; C.R.M. Prentice, Leeds; M. Verstraete, Leuven, Belgium; *ECAT project leader*: F. Haverkate, Leiden; *Protocol Advisory Board*: H. Bricaud, Bordeaux; F. Duckert, Basel; P.G. Hugenholtz, Rotterdam, the Netherlands; D. Julian, London; J. Lubsen, Rotterdam; U.S. Müller, Münster; C.R.M. Prentice, Leeds; S.G. Thompson, London; and J. van de Loo, Münster; *Statistical Center*: S.G. Thompson and S.D.M. Pyke, London; *End Point Committee*: G. Breithardt, Münster; M. Brochier, Tours, France; and H. Tunstall-Pedoe, Dundee, United Kingdom; *Reference Laboratories*: R.M. Bertina, Leiden (protein C); J. Conard, Paris (histidine-rich glycoprotein); F. Duckert, Basel (antithrombin III, factor VIII, von Willebrand factor, fibrinogen); P.J. Gaffney, London (plasminogen); D.S. Pepper, Edinburgh, United Kingdom (platelet factor 4 and  $\beta$ -thromboglobulin); L. Petersen, Hvidovre, Denmark ( $\alpha_2$ -antiplasmin); L. Poller, Manchester, United Kingdom (activated partial-thromboplastin time); F.E. Preston, Sheffield, United Kingdom (euglobulin clot-lysis time); P.W. Straub, Bern (fibrinopeptide A); J. Verheijen, Leiden (t-PA activity); I. Juhan-Vague, Marseille (t-PA antigen); E. Kruihof, Lausanne, Switzerland (PAI-1); *Laboratory Assay Committee*: F. Duckert, Basel (chairman); J.J. Sixma, Utrecht, the Netherlands; J. Jespersen, Esbjerg, Denmark; R.M. Bertina, Leiden; D.S. Pepper, Edinburgh; L. Poller, Manchester; D.C. Rijken, Leiden; *Central Analysis*: R.M. Bertina, Leiden (protein C activity); J. Jespersen, Esbjerg (PAI-1); I. Juhan-Vague, Marseille (t-PA antigen, C-reactive protein); and *Executive Committee*: F. Duckert, Basel; F. Haverkate, Leiden; J. van de Loo, Münster (chairman); S.G. Thompson, London.

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