European Heart Journal (1999) **20,** 1493–1502
Article No. euhj.1999.1519, available online at http://www.idealibrary.com on IDEAL®

D-dimers in relation to the severity of arteriosclerosis in patients with stable angina pectoris after myocardial infarction

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Background Plasma concentrations of D-dimers show the extent of intravascular fibrinolysis of cross-linked fibrin. Higher concentrations of D-dimers are found in the plasma of arteriosclerosis patients with increased fibrin metabolism. The present study was performed in order to investigate whether there is a relationship between the severity of arteriosclerosis and fibrinolytic activity indicated by plasma levels of D-dimer.

Methods The study populations consisted of 1112 men and 299 women with stable angina pectoris, on average $36 \pm 5{\cdot}6$ days after a myocardial infarction, as well as 326 men and 138 women with no clinical signs of cardiovascular disease. In addition to cardiological and angiological examinations, the lipid status and levels of fibrinogen, plasma viscosity, $F1+2$, plasminogen, plasminogen activator inhibitor-1, D-dimer, and C-reactive protein of the participants were determined.

Results The plasma concentration of D-dimers increases with age, both in the group with coronary artery disease and in the control group, with the female gender showing consistently higher concentrations in both groups. D-dimers correlate with other parameters of the lipid and coagulation systems, which explains 32·0% and 39·2% of the variance in D-dimer values in men and women, respectively. A significant increase in the level of D-dimers can be found in participants with generalized arteriosclerosis, with a left ventricular ejection fraction $\leq 40\%$ as well as those with left-ventricular aneurysm.

Conclusion This study indicates that there is increased fibrinolytic activity in patients with severe arteriosclerosis. This finding gives further support to the hypothesis that D-dimer concentration is dependent on the amount of fibrin associated with arteriosclerotic thrombi. However, because of the low specificity and wide overlap of D-dimer values between patients and controls, enhanced D-dimer values are of limited relevance above and beyond other lipid metabolism risk indicators for coronary artery disease or coronary artery disease and peripheral arterial occlusive disease.

(Eur Heart J 1999; 20: 1493–1502)

Key Words: D-dimer, age-dependency, myocardial infarction, fibrinolysis, left ventricular dysfunction.

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Introduction

Some studies have shown that the endogenous fibrinolytic system is activated during both the stable and the unstable stages of arteriosclerosis[1,2]. In young patients after a sustained myocardial infarction and in those patients with peripheral arterial occlusive disease increased levels of fibrinogen[3–5] as well as increased levels of plasminogen activator inhibitor-1 activity[6,7] were associated with an increased risk of further myocardial infarction or stroke. Patients with increased tissue-type plasminogen activator activity were also observed to be at an increased risk of further myocardial infarction[8].

In contrast to the aforementioned markers of haemostasis, levels of D-dimers are a direct measure of

Revision submitted 15 January 1999, and accepted 20 January 1999.

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0195-668X/99/201493+10 $18.00/0

the extent of fibrinolysis, since they are a direct by-product of cross-linked fibrin degradation. Significantly increased concentrations of D-dimers have been associated with enhanced intravascular fibrin degradation. This has been demonstrated in patients with acute venous thromboembolism, pulmonary embolism, disseminated intravascular coagulation, unstable angina pectoris and acute myocardial infarction[9–24].

The increased metabolism of cross-linked fibrin in arteriosclerotic plaques leads to an increase in D-dimer concentration in plasma[1,2]. This increase has been shown to be proportional to the development of arteriosclerosis in patients with peripheral arterial occlusive disease[1]. Since coronary thrombosis plays an important role in the pathogenesis of acute myocardial infarction in those areas already damaged by arteriosclerosis, we investigated whether increased amounts of fibrin breakdown products were detectable during the chronic stage following myocardial infarction. We further examined the question of whether there is a connection between the severity of coronary artery disease and plasma concentrations of D-dimers.

Methods

Patients

The study looked at 1112 consecutive men and 299 women (patients under oral anticoagulation were excluded) with stable angina pectoris, an average of $36 \pm 5{\cdot}6$ days after myocardial infarction, as well as a control group consisting of 326 men and 138 women of similar age, with no clinical signs of cardiovascular disease.

Duplex sonography of the carotids[25], cw-Doppler ultrasound of all four extracranial cerebral arteries[26], sonography of the abdominal aorta[27], an exercise oscillogram of the legs and an exercise ECG[28,29] were carried out in all participants. All controls reached a level of at least 80% of the age-related maximal heart rate (220 minus age). Coronary angiography was carried out in those patients with coronary artery disease[30]. It was assumed that patients had peripheral arterial occlusive disease if the resting oscillogram of the legs was pathological[31], and arteriopathy of the extracranial cerebral arteries was assumed if the cw-Doppler ultrasound diagnosis showed a stenosis >50%. An early stage of peripheral arterial occlusive disease was assumed if only the exercise oscillogram was pathological without claudication[31], early arteriopathy of the extracranial cerebral arteries was assumed if only plaques without significant stenosis could be seen in the sonogram. Coronary artery disease was defined if at least one coronary vessel was constricted by more than 50%. Controls who met any of the above mentioned criteria were not included in the evaluation. In the evaluation of the B-mode pictures, a thickening of the intima was not considered to be pathological, whereas plaque, thrombi, or aneurysms were.

Laboratory analyses

Blood samples were taken after overnight fasting. Blood samples used to test the haemostatic factors were mixed with a 3·13% sodium citrate solution in a ratio of 1:10. The blood samples were centrifuged (plasma, 15 min at 2500 ***g***; serum, 10 min at 3000 ***g***), aliquots prepared and the samples frozen at $-70\,^{\circ}C$ immediately after they were taken. Serum concentrations of triglycerides, glucose and cholesterol were measured using an auto-analyser (Hitachi/Boehringer Mannheim, Germany). HDL-cholesterol concentrations were determined after precipitation with phosphotungistic acid/$MgCl_2$ (Boehringer). LDL-cholesterol was calculated using the Friedewald formula. Plasma concentrations of fibrinogen were measured according to the Clauss method, using standards from Behring Diagnostics (Marburg, Germany). Concentrations of prothrombin fragment F1+2, plasminogen and plasminogen activator inhibitor-1 activity were measured using assay kits from Behring Diagnostics. D-dimer concentrations were measured by an enzyme linked immunosorbent assay (Boehringer). Further details of laboratory analyses have already been published[32]. The serum concentration of HDL-cholesterol containing apo A-1 but not apo A-II (LpA-I) was determined with a commercially available electroimmundiffusion essay (Sebia).

Statistical evaluation

The statistical evaluation was carried out using the *Statistical Package for the Social Sciences* — SPSS[33]. In particular the programmes NPAR-Tests, Kruskal–Wallis-test 1-way ANOVA and multiple regression were used. The spread of constant characteristics between the two groups was compared using the Mann–Whitney U-test; the correlation between constant characteristics was determined using the Spearman rank-correlation coefficient.

Results

Patients

The characteristics of the patients with coronary artery disease as well as of the controls are listed in Table 1. The women with coronary artery disease examined in this study were, on average, 6·0 years older than the men. There were also fewer smokers and more diabetics in the female patients. HDL-cholesterol, fibrinogen, D-dimer concentrations and C-reactive protein were higher in women than in men, in both patients and controls. There were more smokers, diabetics and cases of high blood pressure (defined as being measured >160/90 mmHg at least three times while in a state of rest) among the male and female patients than in the control group. Fibrinogen levels, plasma viscosity and

Table 1 Basic characteristics of controls and of patients coronary artery disease

	Controls				Patients with coronary artery disease			
	Men n=326		Women n=138		Men n=1112		Women n=299	
	mean ± SD	90% range	mean ± SD	90% range	mean ± SD	90% range	mean ± SD	90% range
Age (years)	51·7 ± 8·3	36·0–62·8	55·3 ± 7·8	42·2–67·5	50·5 ± 9·4	35·5 ± 66·0	56·5 ± 9·4	39·7–70·4
Body mass index (kg . m^{-2})	26·7 ± 3·2	22·6–33·2	25·6 ± 4·0	20·4–33·8	27·1 ± 3·30	21·9–33·0	26·9 ± 3·8	21·0–33·3
Smokers (%)	30	—	18	—	70	—	51	—
Peripheral arterial occlusive disease (%)	2	—	10	—	23	—	23	—
Cerebrovascular disease (%)	—	—	1	—	6	—	11	—
Diabetes (%)	4	—	1	—	11	—	25	—
Arterial hypertension (%)	34	—	30	—	48	—	60	—
Number of coronary arteries diseased	—	—	—	—	1·67 ± 0·76	—	1·58 ± 0·73	—
Left ventricular ejection fraction (%)	—	—	—	—	59·3 ± 13·2	37·0–78·0	62·3 ± 14·1	33·0–80·6
Lysis during acute myocardial infarction (%)	—	—	—	—	55	—	51	—
Total cholesterol (mg . dl^{-1})	232 ± 44	162–312	231 ± 44	164–309	232 ± 46	166–310	241 ± 43	173–318
HDL-cholesterol (mg . dl^{-1})	47·2 ± 10·9	31·0–67·0	59·6 ± 14·9	38·0–85·3	36·3 ± 9·1	24·0–53·0	43·7 ± 11·9	27·0–63·3
LDL-cholesterol (mg . dl^{-1})	159 ± 41	93–227	152 ± 41	91–228	165 ± 40	107–233	170 ± 38	114–236
Fibrinogen (g . l^{-1})	2·65 ± 0·51	1·91–3·65	2·68 ± 0·42	2·08–3·50	3·11 ± 0·73	2·11–4·42	3·27 ± 0·71	2·35–4·62
D-dimers (ng . ml^{-1})	354 ± 192	153–777	433 ± 223	204–995	390 ± 256	131–1047	502 ± 303	183–1130
Plasma viscosity (mPa*s)	1·113 ± 0·029	1·069–1·163	1·112 ± 0·030	1·065–1·164	1·151 ± 0·048	1·089–1·236	1·152 ± 0·048	1·089–1·241
CRP (μg . ml^{-1})	0·862 ± 1·219	0·000–3·564	1·082 ± 1·549	0·000–5·005	1·460 ± 1·62	0·800–5·15	1·626 ± 1·802	0·08–6·04

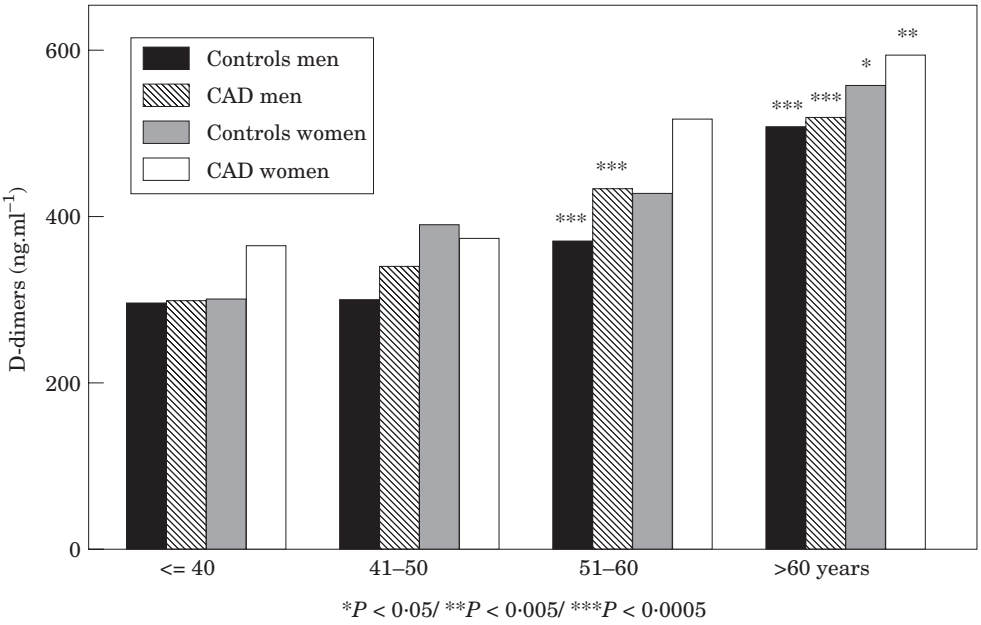


Figure 1 **Plasma concentration of D-dimers (median-values) depending on age in healthy controls and in patients with coronary artery disease (CAD). *P<0·05, **P<0·005, ***P<0·0005.**

C-reactive protein were higher, but HDL-cholesterol lower than in the corresponding control groups.

Age and sex dependence of D-dimer plasma concentrations

The concentration of D-dimers in the control group showed a strong correlation to age and sex. There was a linear increase in D-dimer concentrations with respect to age in men and women (Fig. 1). The equation of regression to compensate for age is $y = -13{\cdot}0 + 7{\cdot}1 \times$ age (equation 1) for men and $y = -34{\cdot}5 + 8{\cdot}5 \times$ age (equation 2) for women. The plasma concentration of D-dimers was higher for women in all age groups regardless of their medical status.

D-dimers and other variables

In the bivariate test model, the concentration of D-dimers not only showed the above mentioned correlation with age and sex, but also with other risk indicators of the lipid metabolism, the coagulation system and with clinical parameters (Table 2). The multiple regression analysis in men showed a positive correlation between the concentration of D-dimers and age, fibrinogen, F1+2, C-reactive protein, plasminogen, and the number of diseased coronary vessels, and a negative correlation with the ejection fraction (Table 3). These parameters accounted for 32·0% of the variance in D-dimers. Only the factors age, fibrinogen, F1+2, and the cholesterol/HDL-cholesterol ratio played a role in the concentration of D-dimers in women, accounting for 39·2% of the variance.

D-dimers in patients with arteriosclerosis

The coronary artery disease group also showed a correlation between age and plasma concentrations of D-dimers (Fig. 1). In the bivariate test model, there is a weak but significant correlation between the concentration of D-dimers and severity of coronary artery disease ($r = 0{\cdot}1452$; P<0·001). Male and female patients with three-vessel coronary artery disease had significantly higher D-dimers than those with one-vessel coronary artery disease. This difference disappears after adjustment for age (Fig. 2) and therefore in the multiple regression analysis there is only a weak correlation between D-dimer levels and severity of coronary artery disease (Table 3).

Furthermore, we observed a significant correlation between D-dimer concentrations and the left ventricular ejection fraction. D-dimer concentrations increased in patients with left ventricular dysfunction independent of age (Fig. 3). Those patients who, in addition to a left ventricular ejections $\leq$40%, also had a ventricular aneurysm, had significantly higher D-dimer concentrations than those without an aneurysm (Fig. 4).

The higher plasma concentrations of D-dimers in men with coronary artery disease and stenosis in the extracranial cerebral vessels were no longer significant once the age of the patients was taken into account. Men with

Table 2 Bivariate correlation between D-dimers and other variables

	Men		Women	
	r	*P*	r	*P*
D-dimers				
Triglycerides	−0·0784	0·006		
HDL-cholesterol	—	—	−0·1048	0·039
Cholesterol/HDL-cholesterol ratio	—	—	0·1294	0·015
Lipoprotein Al	0·0872	0·003	—	—
Glucose	0·0631	0·022	0·1368	0·011
Fibrinogen	0·3426	<0·001	0·3911	<0·001
Plasma viscosity	0·2452	<0·001	0·3164	<0·001
Plasminogen	0·0974	0·001	0·1250	0·017
PAI-1	−0·1217	<0·001	—	—
F1+2	0·2411	<0·001	0·4575	<0·001
CRP	0·3308	<0·001	0·3732	<0·001
Age	0·2905	<0·001	0·2914	<0·001
Peripheral arterial occlusive disease	0·2211	<0·001	—	—
Cerebrovascular disease	0·1667	<0·001	0·1338	0·012
Abdominal aortic aneuysm	0·2266	<0·001	—	—
RR systol.	0·0780	0·006	0·1599	0·003
Cigarettes per day	−0·0873	0·009	—	—
Physical activity	−0·0984	0·003	—	—
Left ventricular ejection fraction (%)	−0·1102	0·002	−0·1346	0·036
Number of coronary arteries diseased	0·1452	<0·001	—	—

Table 3 Multivariate regression analysis between D-dimers and the variables of Table 2 (only significant values are listed)

	Men		Women	
	r	*P*	r	*P*
D-dimers				
F1+2	0·2968	<0·0001	0·4214	<0·0001
CRP	0·1806	0·0001		
Lipoprotein Al	0·1463	0·0018		
Age	0·1297	<0·0102	0·2093	0·0025
Plasminogen	0·1127	0·0064		
Left ventricular ejection fraction	−0·1035	0·0132		
Number of coronary arteries diseased	0·0838	0·0464		
Fibrinogen	0·1793	0·0003	0·2619	0·0007
Glucose	−0·0915	0·0284		
Cholesterol/HDL-cholesterol ratio			−0·1879	0·0350
r square	0·344		0·437	
r square adjusted	0·320		0·392	

coronary artery disease and peripheral arterial occlusive disease of the upper limbs, on the other hand, had significantly higher D-dimer plasma levels even when the age factor was taken into account. A particularly large increase in the D-dimer plasma concentration was evident in the male patients who had stenosis in the extracranial cerebral vessels, as well as peripheral arterial occlusive disease of the upper limbs (Fig. 5).

There was no significant increase in D-dimer concentrations in the relatively small group of women with coronary artery disease and peripheral arterial occlusive disease of the upper limbs or stenosis in the extracranial cerebral vessels, but there was a significant increase ($P<0·05$) when all three were present together. The most significant increase of D-dimers was found in male and female patients with an aneurysm of the abdominal aorta.

Discussion

D-dimers are a primary product of cross-linked fibrin degradation and as such are a direct gauge of fibrinolysis. In the area of cholesterol-rich plaques, as well as in appositional thrombi, content of fibrin and its metabolism are enhanced[34]. There is an approximately five-fold increase in D-dimers in patients with unstable angina pectoris[35] and in those with an acute myocardial

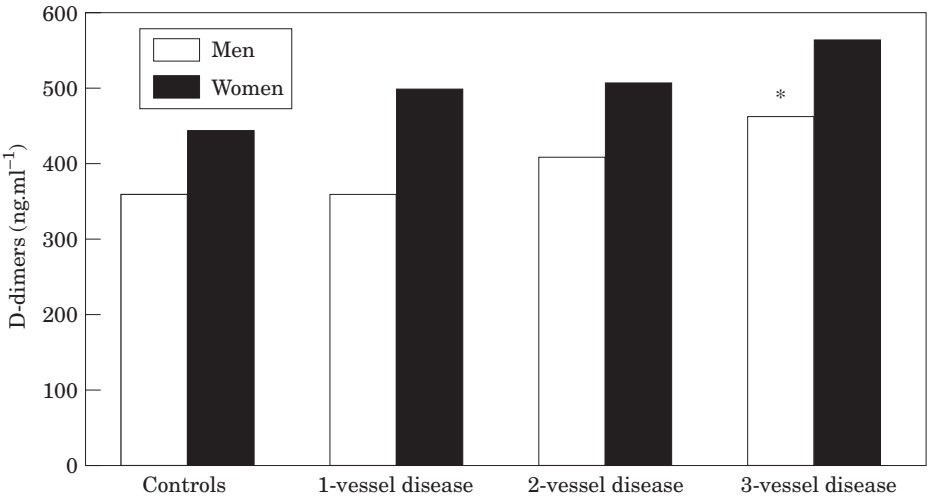


Figure 2 **Plasma concentration of D-dimers (median values) in relation to the number of diseased coronary arteries in patients with coronary artery disease after adjustment for age. Significance see Fig. 1.**

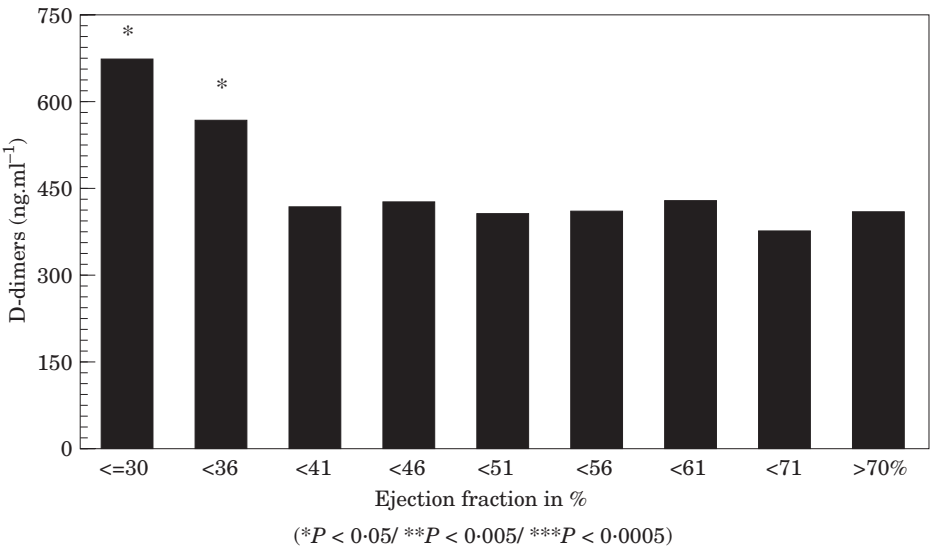
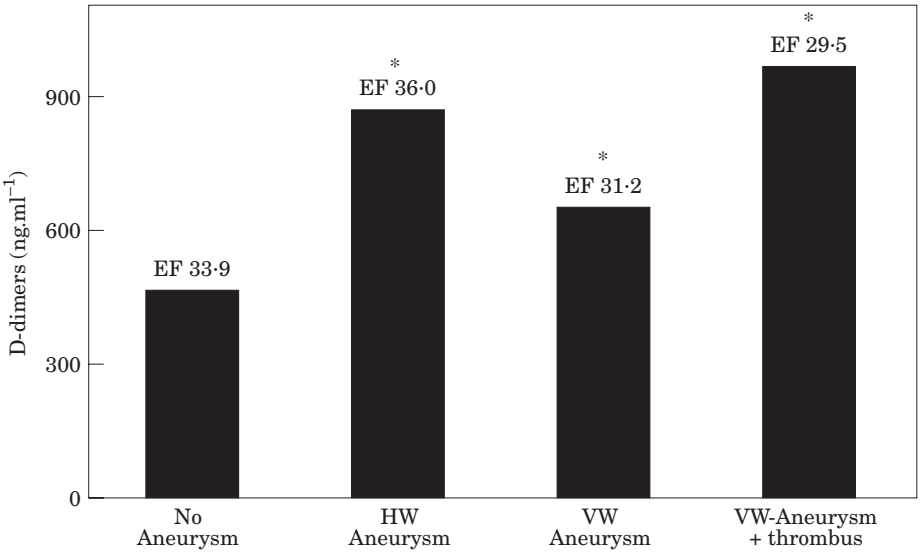


Figure 3 **Plasma concentration of D-dimers (median-values) in relation to the left ventricular ejection fraction in patients with coronary artery disease (CAD). Significance see Fig. 1.**

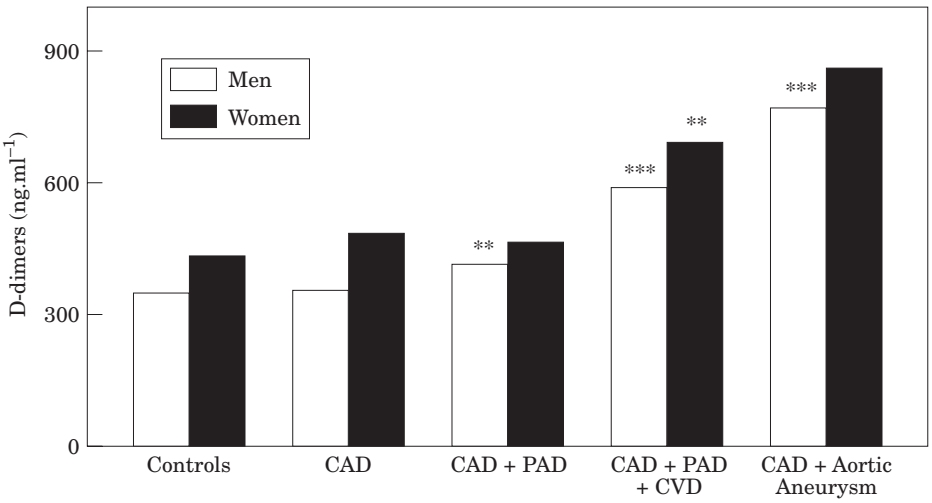
infarction[36,37]. During thrombolytic therapy the fibrinogen levels drop to 12%–20% of their original values and D-dimer plasma concentrations rise to 70–130-fold of the original values. These concentrations drop continually once thrombolytic therapy is completed, reaching normal values after approximately 1 week[22,38]. Since our patients were examined on average, 36 ± 5·6 days after acute myocardial infarction, it can be assumed that the thrombolytic treatment, which 54% of them underwent, did not affect our results. This supposition is further supported by the fact that the D-dimer concentration in our patients after myocardial infarction did not show any differences in values regardless of whether the patients underwent thrombolytic therapy or not (377 ± 242 vs 400 ± 259 ng . ml^{-1}).

Our study agrees with those of other authors[2,39–41] who found higher D-dimer concentrations in women than in men, and a general increase in both sexes in the group older than 60 years. This finding is frequently attributed to the higher prevalence and the greater



(EF = left ventricular ejection fraction. *$P < 0{\cdot}05$/ **$P < 0{\cdot}005$/ ***$P < 0{\cdot}0005$)

Figure 4 **Plasma concentration of D-dimers (median-values) in patients with coronary artery disease and a left ventricular ejection fraction $\leq$40% without aneurysm of the left ventricle as well as with an aneurysm of the inferior wall, the anterior wall or of the anterior wall combined with a additional thrombus. Significance see Fig. 1.**



(*$P < 0{\cdot}05$/ **$P < 0{\cdot}005$/ ***$P < 0{\cdot}0005$)

Figure 5 **Plasma concentration of D-dimers (median values) in controls, in patients with coronary artery disease (CAD) and in patients with coronary artery disease associated with peripheral artery disease (CAD+PAD), with additional cerebrovascular disease (CAD+PAD+CVD) and in patients with CAD associated with an aneurysm of the abdominal aorta (CVD+AAA). Significance see Fig. 1**

extent of arteriosclerotic changes in this age group, even if there are no clinical manifestations of arteriosclerosis. To exclude the possibility of as yet unidentified arteriosclerosis as a basis of this finding we examined the patients by various non-invasive techniques. A cw-Doppler examination was carried out on all four extracranial cerebral arteries; duplex-sonography of the carotids, sonography of the abdominal aorta and an exercise oscillogram of the lower limbs arteries were performed. Controls whose examinations showed pathological changes were not included in the study. The concentration of D-dimers in men over 60 years of age in our control group was around 75% higher than the level in men under 40; for women over 60, the value was 74%

higher compared with those under 40. Even taking into account the limited sensitivity of the aforementioned angiological examinations, there is no reason to assume that the increase in D-dimers in older controls or in older patients was due to a pre-clinical arteriosclerosis. In contrast to Salomaa *et al.*[42], we found no increased D-dimer levels in patients with early arteriosclerosis.

D-dimer plasma concentrations correlate with a wide range of other parameters in the lipid metabolism and haemostatic systems (Table 2). In this study, multivariate regression analysis showed that the number of diseased vessels, the ejection fraction, F1+2, fibrinogen, plasminogen, C-reactive protein and age account for 32·0% of the variance in males with coronary artery disease (Table 3). Although Giansante *et al.*[14] observed a similar correlation in a bivariate analysis, their multivariate analysis of 571 controls with no clinical signs of cardiovascular disease was able to account for only 10% of the variance in D-dimer concentration through levels of fibrinogen, Apo AI and age.

A number of authors[1,2,41,43–46] have observed a direct correlation between D-dimer concentrations and the severity of peripheral arterial occlusive disease, when the age factor was not taken into account. In the course of a year-long study, a higher number of myocardial infarcts and strokes were observed in those patients with peripheral arterial occlusive disease, who had higher D-dimer concentrations.

The male coronary artery disease patients in our study, who also had peripheral arterial occlusive disease, had significantly higher D-dimer levels. The levels were even higher when the coronary artery disease patients had both peripheral arterial occlusive disease and cerebrovascular disease together. The highest D-dimer values were found in those patients who also had an abdominal aortic aneurysm (Fig. 5). In the smaller group of women with coronary artery disease, those with peripheral arterial occlusive disease did not have higher D-dimer concentrations, but those with peripheral arterial occlusive disease and cerebrovascular disease together, as well as an additional abdominal aortic aneurysm did.

Our findings, of a direct correlation between D-dimer plasma concentrations and extent of arteriosclerosis in a relatively large sample supports the hypothesis that the D-dimer concentration is dependent on the amount of fibrin associated with arteriosclerotic thrombi[1]. The individual deviations can be explained by the variable fibrinolytic activity in individual patients.

We observed a significant relationship between D-dimer plasma concentration and the activation peptides of prothrombin, and F1+2, in both the bivariate and multivariate tests (Table 3). This finding, taken together with the dependence of D-dimer concentrations on the severity of arteriosclerosis, must be seen as an indication of increased formation and splitting of fibrin in these patients.

We observed increased plasma concentrations of D-dimers in patients with a left ventricular ejection fraction $\leq 40\%$ (average 33·5%), independent of age and the severity of the coronary artery disease (Fig. 3). The slightly raised level for those patients with an ejection fraction between 41% and 50% was not statistically relevant. Particularly noteworthy is the fact that in the group of patients with an ejection fraction $\leq 40\%$ a particularly high concentration of D-dimers could be found among those who also had a ventricular aneurysm. This finding is an indication that the haemodynamic situation has an effect on fibrin turnover. It is to be assumed that there is a direct relationship to the greater propensity of this group towards thrombogenesis. Lip *et al.*[47,48] reported a 27% increase in the concentration of D-dimers in patients with a dysfunction of the left ventricle compared to those with a normal ejection fraction. In contrast to our study, however, the number of patients examined was too low to reach statistical significance in this study. Yasaka *et al.*[49] found, in patients with mitral stenosis, significantly higher D-dimer plasma levels in those patients with detectable left atrial thrombi. D-dimers seem to be a helpful indicator of intracardiac formation of thrombi[49].

In conclusion, in patients with coronary artery disease, and dysfunction of the left ventricle, with coronary artery disease and cerebrovascular disease, or with coronary artery disease, cerebrovascular disease and peripheral arterial occlusive disease increased fibrinolytic activity has been indicated by increased D-dimer levels. This finding gives further support to the hypothesis that the D-dimer concentration is dependent on the amount of fibrin associated with arteriosclerotic thrombi. However, because of the low specificity and the wide overlap of D-dimer values between patients and controls, enhanced D-dimer values are of limited relevance beyond the other lipid metabolism risk indicators in the assessment of risk of coronary artery disease and peripheral arterial occlusive disease.

The excellent technical assistance of Ruth Bäumer, Margit Käse, and Renate Kokott is gratefully acknowledged. This study was supported by the Landesversicherungsanstalt Westfalen and Landesversicherungsanstalt Rheinprovinz.

References

[1] Lassila R, Peltonen S, Lepantalo M, Saarinen O, Kauhanen P, Manninen V. Severity of peripheral atherosclerosis is associated with fibrinogen and degradation of cross-linked fibrin. Arterioscler Thromb 1993; 13: 1738–42.

[2] Lee AJ, Fowkes FGR, Lowe GDO, Rumley A. Fibrin D-dimer, haemostatic factors and peripheral arterial disease. Thromb Haemost 1995; 74: 828–32.

[3] Bolibar I, Kienast J, Thompson SG,. Matthias R, Niessner H, Fechtrup C. Relation of fibrinogen to presence and severity of coronary artery disease is independent of other coexisting heart disease. Am Heart J 1993; 125: 1601–5.

[4] ECAT Angina pectoris Study Group. ECAT angina pectoris study: baseline associations of haemostatic factors with extent of coronary arteriosclerosis and other coronary risk factors in 3000 patients with angina pectoris undergoing coronary angiography. Eur Heart J 1993; 14: 8–17.

[5] Eichner JE, Moore WE, McKee PA. *et al*. Fibrinogen levels in women having coronary angiography. Am J Cardiol 1996; 78: 15–18.
[6] Hamsten A, Wiman B, De Faire U, Blombäck M. Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. N Engl J Med 1985; 313: 1557–63.
[7] Hamsten A, de Faire U, Walldius G. *et al*. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. Lancet 1987.
[8] Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Hennekens CH. Endogenous tissue-type plasminogen activator and risk of myocardial infarction. Lancet 1993; 341: 1165—8.
[9] Becker DM, Philbrick JT, Bachhuber TL, Humphries JE. D-dimer testing and acute venous thromboembolism. A shortcut to accurate diagnosis? Arch Intern Med 1996; 156: 939–46.
[10] Beek van EJ, Schenk BE, Michel BC *et al*. The role of plasma D-dimers concentration in the exclusion of pulmonary embolism. Br J Haematol 1996; 92: 725–32.
[11] Boisclair MD, Lane DA, Wilde JT Ireland H, Preston FE, Ofosu FA. A comparative evaluation of assays for markers of activated coagulation and/or fibrinolysis: thrombin-antithrombin complex, D-dimer and fibrinogen/fibrin fragment E antigen. Br J Haematol 1990; 74: 471–9.
[12] Brenner B, Francis CW, Fitzpatrick PG *et al*. Relation of plasma D-dimer concentrations coronary artery reperfusion before and after thrombolytic treatment in patients with acute myocardial infarction. Am J Cardiol 1989; 63: 1179–84.
[13] Brenner B, Francis CW, Totterman S *et al*. Quantitation of venous clot lysis with the D-dimer immunoassay during fibrinolytic therapy requires correction for soluble fibrin degradation. Circulation 1990; 81: 1818–25.
[14] Giansante C, Fiotti N, Cattin L, Da-Col PG, Calabrese S. Fibrinogen, D-dimer and thrombin-antithrombin complexes in a random population sample: relationships with other cardiovascular risk factors. Thromb Haemost 1994; 71: 581–6.
[15] Gurfinkel E, Bozovich G, Cerda M, Mejail I, Oxilia A, Mautner B. Time significance of acute thrombotic reactant markers in patients with and without silent myocardial ischemia and overt unstable angina pectoris. Am J Cardiol 1995; 76: 121–4.
[16] Gurfinkel E, Altman R, Scazziota A, Rouvier J, Mautner B. Importance of thrombosis and thrombolysis in silent ischaemia: comparison of patients with acute myocardial infarction and unstable angina. Br Heart J 1994; 71: 151–5.
[17] Koh SC, Chew CY, Viegas OA, Choo M, Ratnam SS. Influence of circulating D-dimer levels on assays of fibrinogen. Ann Acad Med Singapore 1994; 23: 856–60.
[18] Koppensteiner R, Speiser W, Minar E, Ahmadi R, Ehringer H. D-dimer in local thrombolytic therapy with low doses of recombinant human tissue-type plasminogen activator (rt-PA) in patients with peripheral arterial occlusive disease. Thromb Haemost 1990; 64: 192–5.
[19] Kornberg A, Francis CW, Marder VJ. Plasma crosslinked fibrin polymers: quantitation based on tissue plasminogen activator conversion to D-dimer and measurement in normal and patients with acute thrombotic disorders. Blood 1992; 80: 709–17.
[20] Lawler CM, Bovill EG, Stump DC, Collen DJ, Mann KG, Tracy RP. Fibrin fragment D-dimer and fibrinogen B beta peptides in plasma as markers of clot lysis during thrombolytic therapy in acute myocardial infarction. Blood 1990; 76: 1341–8.
[21] Raimondi P, Bongard O, de Moerloose P, Reber G, Waldvogel F, Bounameaux H. D-dimer plasma concentration in various clinical conditions: implication for the use of this test in the diagnostic approach of venous thromboembolism. Thromb Res 1993; 69: 125–30.
[22] Salvioni A, Marenzi GC, Agostoni P, Grazi S, Guazzi MD. Influence of heparin on fibrinogen and D-dimer plasma levels in acute myocardial infarction treated with streptokinase. Eur Heart J 1994; 15: 654–9.
[23] Tengborn L, Palmblad S, Wojciechowski J, Peterson LE, Stigendal L. D-dimer and thrombin/antithrombin III complex-diagnostic tools in deep venous thrombosis? Haemostasis 1994; 24: 344–50.
[24] Wells PS, Brill-Edwards P, Stevens P *et al*. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. Circulation 1995; 91: 2184–7.
[25] Widder B. Doppler- und Duplex-Sonographie der hirnversorgenden Arterien. Springer-Verlag 1991.
[26] Kriessmann A, Bollinger A, Keller HM. Praxis der Doppler-Sonographie. Stuttgart-New York, Thieme 2.Aufl 1990.
[27] Lüning M, Felix R. Komplexe bildgebende Diagnostik Abdomen. Leipzig: Thieme, 1.Aufl., 1989.
[28] Kaltenbach M. Vom Belastungs-EKG zur Koronarangiographie. Berlin-Heidelberg-New York: Springer, 1980.
[29] Schamroth L. EKG bei koronarer Herzkrankheit. Stuttgart: Thieme, 1988.
[30] Lichtlen PR. Koronarangiographie. Erlangen: Perimed, 2.Aufl. 1990.
[31] Schoop W. Praktische Angiologie. Stuttgart-New York: Thieme-Verlag, 1988.
[32] Heinrich J, Schulte H, Schoenfeld R, Koehler E, Assmann G. Association of variables of coagulation, fibrinolysis and acute-phase with atherosclerosis in coronary and peripheral arteries and those arteries supplying the brain. Thromb Haemost 1995; 73: 374–9.
[33] Nie NH, Hull CH, Jenkins JG. Statistical Package for the Social Sciences (SPSS). New York: McGraw-Hill.
[34] Smith E. Fibrinogen, fibrin and fibrin degradation products in relation to atherosclerosis. Clin Haematol 1986; 15: 355–70.
[35] Kruskal JB, Commerford PJ, Franks JJ, Kirsch RE. Fibrin and fibrinogen-related antigens in patients with stable and unstable coronary artery disease. N Engl J Med 1987; 317: 1361–5.
[36] Francis CW, Connaghan DG, Scott WL, Marder V. Increased plasma concentration of cross-linked fibrin polymers in acute myocardial infarction. Circulation 1987; 75: 1170–7.
[37] Tanaka M, Suzuki A. Hemostatic abnormalities in acute myocardial infarction as detected by specific blood markers. Thromb Res 1994; 76: 289–98.
[38] Salvioni A, Perego GB, Marenzi G, Lauri G, Giraldi F, Grazi S, Guazzi MD. Late activation of the fibrinolytic system in myocardial infarction treated with thrombolytic therapy. Eur Heart J 1996; 17: 230–6.
[39] Curries MS, Rao MK, Blazer DG, Cophen HJ. Age and functional correlations of markers of coagulation and inflammation in the elderly: functional implications of elevated crosslinked fibrin degradation products (D-dimers). J Am Geriatr Soc 1994; 42: 738–42.
[40] Kario K, Matsuo T, Kobayashi H. Which factors affect high D-dimer levels in the elderly? Thromb Res 1991; 62: 501–8.
[41] Lee AJ, Fowkes GR, Lowe GD, Rumley A. Determinations of fibrin D-dimer in the Edinburgh Artery Study. Arterioscler Thromb Vasc Biol 1995; 15: 1094–7.
[42] Salomaa V, Stinson V, Kark JD, Folsom AR, Davis CE, Wu KK. Association of fibrinolytic parameters with early atherosclerosis. The ARIC Study. Circulation 1995; 91: 284–90.
[43] Al-Zahrani H, Lowe GDO, Douglas JT, Cushieri R, Pollock JG, Smith WCS. Increased fibrin turnover in peripheral arterial disease: comparison with a population study. Clin Hemorheol 1992; 12: 876–72.
[44] De Buyzere M, Philippe J, Duprez D, Baele G, Clement DL.Coagulation system activation and increase of D-dimer levels in peripheral arterial occlusive disease. Am J Hematol 1993; 43: 91–4.
[45] Fowkes FGR, Lowe GDO, Housley E *et al*. Cross-linked fibrin degradation products, progression of peripheral arterial disease, and risk of coronary heart disease. Lancet 1993; 342: 84–6.
[46] Smith FB, Lowe GDO, Fowkes FGR *et al*. Smoking, haemostatic factors and lipid peroxides in a population case control study of peripheral arterial disease. Atherosclerosis 1993; 102: 155–62.

[47] Lip GY, Lowe GD, Metcalfe MJ, Rumley A, Dunn FG. Is diastolic dysfunction associated with thrombogenesis? A study of circulating markers of a prothrombotic state in patients with coronary artery disease. Int J Cardiol 1995; 50: 31–42.
[48] Lip GYH, Lowe GDO, Metcalfe MJ, Rumley A, Dunn FG. Effects of warfarin therapy on plasma fibrinogen, von Willebrand factor, and fibrin D-dimer in left ventricular dysfunction secondary to coronary artery disease with and without aneurysms. Am J Cardiol 1995; 76: 453–8.
[49] Yasaka M, Miyatake K, Mitani M *et al*. Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis. Br Heart J 1991; 66: 22–25.