ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.04.053

Value of Plasma Fibrin D-Dimers for Detection of Acute Aortic Dissection

Holger Eggebrecht, MD,* Christoph K. Naber, MD,* Christian Bruch, MD,§ Knut Kröger, MD,† Clemens von Birgelen, MD, PHD,‖ Axel Schmermund, MD,* Marc Wichert, MD,‡ Thomas Bartel, MD,* Klaus Mann, MD,‡ Raimund Erbel, MD, FACC*

Essen and Münster, Germany; and Enschede, the Netherlands

OBJECTIVES The purpose of this research was to assess the value of systemic inflammatory biomarkers in the detection of acute aortic dissection (AD).

BACKGROUND Rapid diagnosis and initiation of treatment is pivotal for patients with acute AD. So far, there is no laboratory test to aid the diagnosis.

METHODS Plasma fibrin D-dimers, white blood cell (WBC) count, C-reactive protein (CRP), and fibrinogen were determined in 64 chest-pain (CP) patients (acute AD, n = 16; pulmonary embolism [PE], n = 16; acute myocardial infarction [AMI], n = 16; non-cardiac CP, n = 16); 32 asymptomatic patients with chronic AD served as a control group.

RESULTS All acute AD patients showed highly elevated D-dimer values that were similar to PE patients (2,238 ± 1,765 μg/l vs. 1,531 ± 837 μg/l, p = 0.15) but significantly higher than in chronic AD, AMI, or CP patients ($p < 0.001$). The WBC count was significantly increased in patients with acute AD compared with the other groups ($p < 0.001$); in addition, CRP values differed only non-significantly from PE patients (p = 0.71). There were no differences in the fibrinogen levels between the groups.

CONCLUSIONS D-dimers are highly elevated in both acute PE and acute AD. Patients with acute AD show significant systemic inflammatory reactions. Measurement of D-dimers may be a valuable addition to the current diagnostic work-up of patients with suspected AD. (J Am Coll Cardiol 2004;44:804–9) © 2004 by the American College of Cardiology Foundation

Rapid diagnosis and initiation of appropriate treatment is pivotal for patients with acute aortic dissection (AD) (1). Detection of acute AD is based on clinical presentation but mainly relies on imaging techniques (1). However, up to 30% to 40% of patients remain undiagnosed until necropsy (2). So far, there is no laboratory test—as opposed to acute coronary syndromes—to aid the diagnosis. Determination of smooth muscle myosin heavy chains or soluble elastin fragments has been shown to detect AD with high sensitivity and specificity (3,4), but these tests are not practical in a clinical emergency setting.

Previous studies suggested a role of inflammatory reactions in acute AD (5). It was the aim of the present study to evaluate the value of biochemical markers of the acute phase reaction (D-dimers, white blood cell [WBC] count, C-reactive protein [CRP], fibrinogen) in the detection of acute AD.

METHODS

Patient population. Between October 2002 and February 2004, we studied plasma fibrin D-dimers and biochemical markers of acute inflammation in 64 consecutive chest-pain (CP) patients (acute AD, n = 16; pulmonary embolism [PE], n = 16; acute myocardial infarction [AMI], n = 16; non-cardiac CP; n = 16) presenting within 48 h from onset of symptoms; 32 asymptomatic patients (28 male, age: 57.0 ± 15.1 [27.7 to 78.3] years) with previously diagnosed chronic, stable AD (mean age of the dissection: 30.4 ± 32.2 [1 to 98] months) served as a control group.

Diagnosis of AD was confirmed using standard criteria by at least two of the following examinations: transesophageal echocardiography, aortography, computed tomography (CT), or magnetic resonance imaging (1). Only patients in whom the onset of AD could be clearly determined (e.g., by symptoms) were included. Dissection was classified according to the Stanford classification, which defines any involvement of the ascending aorta as type A-AD and exclusive dissection of the descending aorta as type B-AD (6). Aortic dissection was considered to be chronic at least 14 days after onset of AD defined by the initial episode of intense pain (1).

In 16 symptomatic PE patients (five male, age: 55.1 ± 22.2 [17.3 to 84.2] years), clinical suspicion of PE had to be confirmed by ventilation-perfusion lung scan, spiral CT scan, or pulmonary angiography before inclusion into the study. Acute myocardial infarction was defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology committee (7). Among the 16 patients with AMI (13 male, age: 62.2 ±

From the *Department of Cardiology, †Department of Angiology, and ‡Department of Clinical Chemistry, West-German Heart Center Essen, University of Duisburg-Essen, Essen, Germany; §Department of Cardiology and Angiology, University of Münster, Münster, Germany; and ‖Department of Cardiology, Medisch Spectrum Twente, Enschede, the Netherlands.

Manuscript received March 13, 2004; revised manuscript received April 13, 2004, accepted April 20, 2004.

Abbreviations and Acronyms

AD = aortic dissection
AMI = acute myocardial infarction
CP = chest pain
CRP = C-reactive protein
CT = computed tomography
FL = false lumen
PE = pulmonary embolism
WBC = white blood cell

12.6 [37.8 to 78.7] years), there were eight patients with ST-segment elevation AMI and eight patients with non–ST-segment elevation AMI. Sixteen patients (12 male, age: 50.4 ± 14.7 [23 to 67.9] years) in whom a cardiovascular origin of the symptoms could be excluded by chest X-ray, repeat electrocardiogram, and laboratory tests were considered to have non-cardiac CP.

Biochemical analysis. For the quantitative determination of D-dimers in sodium citrate plasma, a latex-enhanced turbidimetric test (D-Dimer Plus, Dade Behring, Marburg, Germany) was used on the Dade Behring BCS coagulation analyzer (upper limit of normal: 250 μg/l). Serum CRP analysis was done by an immunoturbidimetric assay (Scil Diagnostics, Martinsried, Germany) using the automated Bayer Advia 1650 clinical chemistry analyzer (upper limit of normal: 5 mg/l). The quantitative determination of fibrinogen in plasma was performed by the Multifibren U-test (Dade Behring) in modification of the Clauss method on the Dade Behring BCS coagulation analyzer (reference interval: 1.6 to 4.5 g/l). For WBC count, we used the Beckman Coulter Gen-S hematology analyzer (reference interval: 4.3 to 10×10^9/l).

Statistical analysis. All statistical analyses were performed using SPSS for Windows (version 11.0, SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean ± 1 SD and categorical variables as frequencies and percentages. Comparisons between the groups were made with the chi-square or Fisher exact test for categorical variables and analysis of variance for continuous variables using the Bonferoni correction for post hoc analysis to adjust for multiple testing (p_{adj}). The optimal cutoff points were determined by receiver operating characteristic curves, and the sensitivity and specificity of D-dimers for group distinction were determined according to: sensitivity = true positives/(true positives + false negatives) × 100%, specificity = true negatives/(true negatives + false positives) × 100%. Linear regression analysis was performed to determine the correlation between the absolute D-dimer values and the time from onset of symptoms of AD. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient characteristics. Baseline characteristics of the 16 patients with acute AD are given in Table 1. In all patients with AD (acute and chronic), the false lumen (FL) was patent without evidence of thrombus formation.

Table 1. Patient Characteristics

	Acute AD (n = 16)
Age (yrs)	65.2 ± 15.2 (36–83)
Male/female	11/5
Body mass index (kg/m^2)	27.3 ± 3.6 (23.5–35.2)
Serum creatinine (mg/l)	13 ± 5
History of hypertension	11 (70%)
Stanford type A/B	6/10
AD presumed due to hypertension	16 (100%)
Complications of AD	
(Contained) rupture	5 (31%)
Tamponade	2 (13%)
Patent false lumen	16 (100%)
Time from onset of symptoms	16 ± 15.7 h (2–48)

AD = aortic dissection.

Plasma fibrin D-dimers. All acute AD patients showed highly elevated D-dimer values that were similar to PE patients but significantly higher than in chronic AD, AMI, or CP patients (Fig. 1, Table 2).

Among patients with acute AD, D-dimers tended to be higher in patients with type A-AD than in those with type B (2,872 ± 2,244 μg/l vs. 1,857 ± 1,401 μg/l, p = 0.28). In addition, D-dimers tended to be higher in patients presenting with complications of acute AD than in those without complications (p = 0.12) (Table 3). There was a significant negative correlation between the absolute D-dimer values and the time from onset of symptoms (r = −0.51, p = 0.045) (Fig. 2).

Serial D-dimer measurements of four patients with acute AD are presented in Figure 3. Serial D-dimer measurements of acute AD patients who died early (n = 4), who underwent emergency surgical or endovascular repair (n = 6), or who had a complicated stay on the intensive care unit (n = 2) are not presented.

Receiver operating characteristic analysis yielded an optimal cutoff value of 626 μg/l for D-dimers, with a sensi-

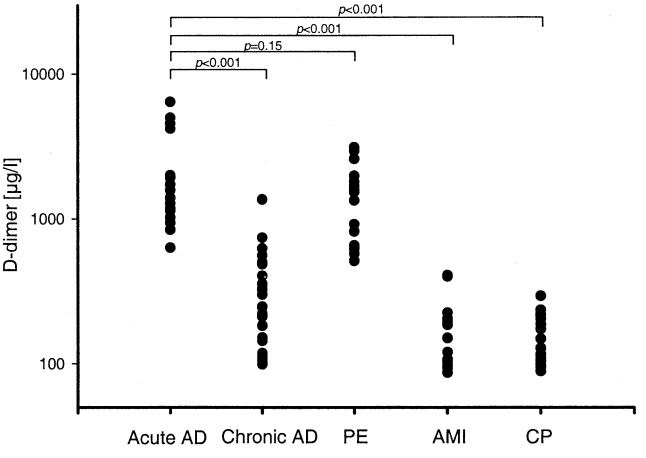

Figure 1. Comparison of D-dimer values between the different patient groups (p values adjusted according to Bonferoni). AD = aortic dissection; AMI = acute myocardial infarction; CP = chest pain; PE = pulmonary embolism.

Table 2. Biomarkers in the Different Patient Groups

	Acute AD (n = 16)	Chronic AD (n = 32)	PE (n = 16)	AMI (n = 16)	CP (n = 16)	p Value
D-dimer (μg/l)	2,238 ± 1,765 (632–6,419)	314 ± 249 (99–1,361)	1,531 ± 837 (512–3,120)	171 ± 100 (87–407)	155 ± 61 (89–293)	<0.001
WBC (× 10^9/l)	14.6 ± 5.0 (7.0–25.6)	8.3 ± 2.3 (4.5–15.1)	9.1 ± 3.4 (3.9–15.9)	8.9 ± 3.0 (4.5–14.1)	7.7 ± 2.1 (4.4–12.5)	<0.001
CRP (mg/l)	77 ± 68 (2–174)	22 ± 36 (0–156)	48 ± 42 (0–153)	34 ± 47 (2–166)	3 ± 4 (0–16)	<0.001
Fibrinogen (g/l)	4.0 ± 2.0 (1.7–8.9)	4.3 ± 1.5 (2.0–8.0)	4.2 ± 2.0 (1.2–8.3)	4.1 ± 1.2 (2.9–7.0)	3.3 ± 1.1 (2.4–5.7)	0.40

AD = aortic dissection; AMI = acute myocardial infarction; CP = chest pain; CRP = C-reactive protein; PE = pulmonary embolism; WBC = white blood cell count.

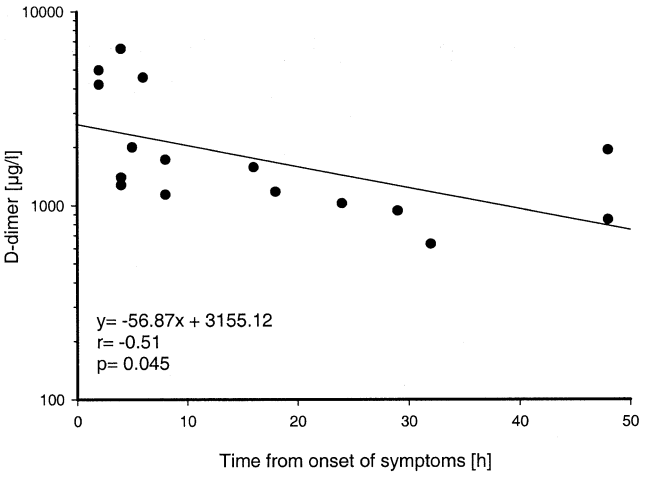

Figure 2. Correlation between D-dimers and time from symptom onset in acute aortic dissection.

tivity of 100% and a specificity of 73% for detection of acute AD (Fig. 4). At a cutoff value of 500 μg/l, sensitivity was 100% with a specificity of 67%.

Biochemical markers of systemic inflammation. White blood cell count was significantly increased in acute AD patients compared with all other groups ($p_{adj} < 0.001$) (Fig. 5); in addition, CRP values differed only non-significantly from PE patients (77 ± 68 [2 to 174] mg/l vs. 48 ± 42 [0 to 153] g/l, $p_{adj} = 0.71$) (Fig. 6, Table 2). There were no differences in the fibrinogen levels between the groups (Fig. 7).

There was a trend toward higher WBC count and CRP levels in patients with complications of acute AD than in those without complications (p = 0.550 and p = 0.185, respectively) (Table 3).

In-hospital outcome. Eight of 16 (50%) acute AD patients died during the in-hospital course. There was no difference in mortality between type A-AD and type B-AD.

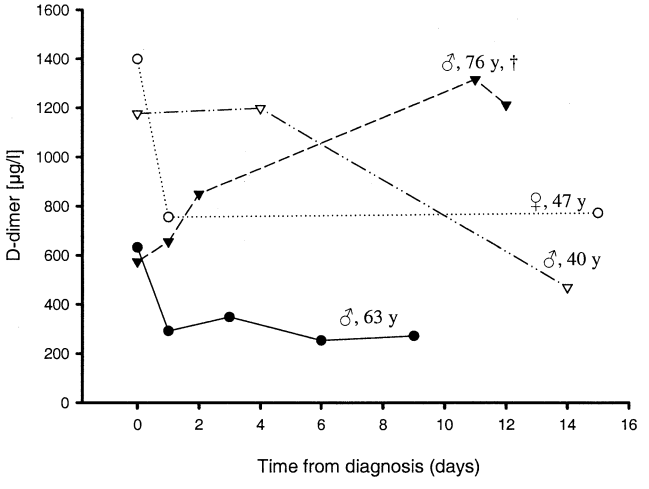

Figure 3. Serial D-dimer measurements of four acute aortic dissection patients. In the three surviving patients, serial D-dimer measurements demonstrate a decline over time, while in one patient who died (♂, 76 years old, †), steady increase was found.

Table 3. Laboratory Findings in Acute AD Patients With Versus Without Complications

	No Complications (n = 9)	Complications (n = 7)	p Value
D-dimers (μg/l)	1,634 ± 1,041 (632–4,199)	3,014 ± 2,257 (842–6,419)	0.124
WBC (× 10^9/l)	13.9 ± 5.2 (8.6–25.6)	15.5 ± 5.1 (7.0–21.0)	0.550
CRP (mg/l)	71 ± 62 (2–160)	84 ± 79 (2–174)	0.185
Fibrinogen (g/l)	4.6 ± 2.2 (1.9–8.9)	3.3 ± 1.5 (1.7–5.2)	0.718

AD = aortic dissection; CRP = c-reactive protein; WBC = white blood cell count.

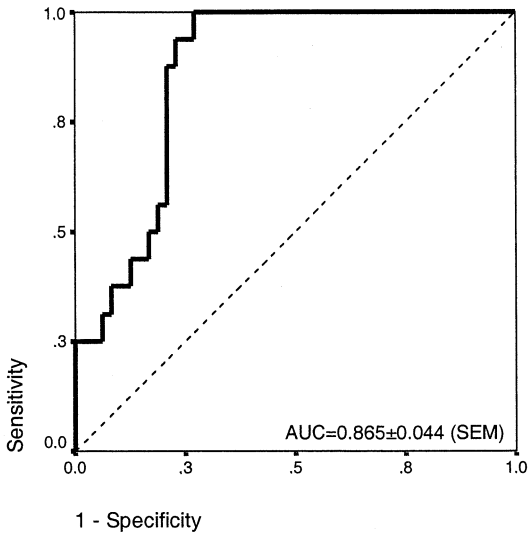

Figure 4. Calculation of optimal cutoff value between acute aortic dissection and other chest-pain syndromes, including pulmonary embolism, by receiver operator characteristic curve analysis with respect to D-dimers. **Dotted line** shows a random distribution. AUC = area under the receiver operator characteristic curve.

D-dimer levels and CRP tended to be higher in patients who died during the in-hospital period (p = 0.204 and p = 0.365, respectively) (Table 4).

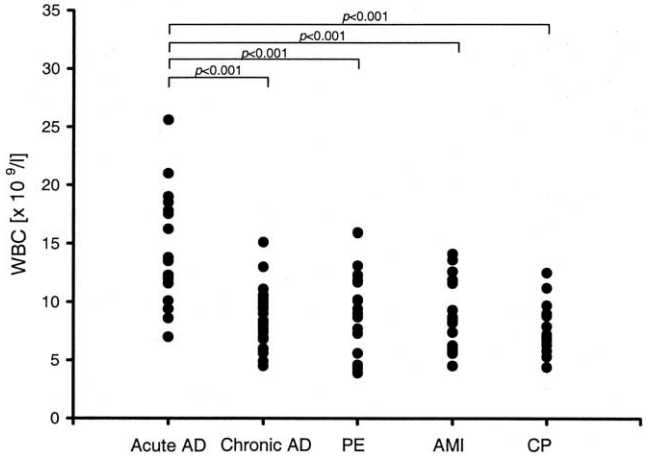

Figure 5. Comparison of white blood cell (WBC) count between the different patient groups (p values adjusted according to Bonferoni). AD = aortic dissection; AMI = acute myocardial infarction; CP = chest pain; PE = pulmonary embolism.

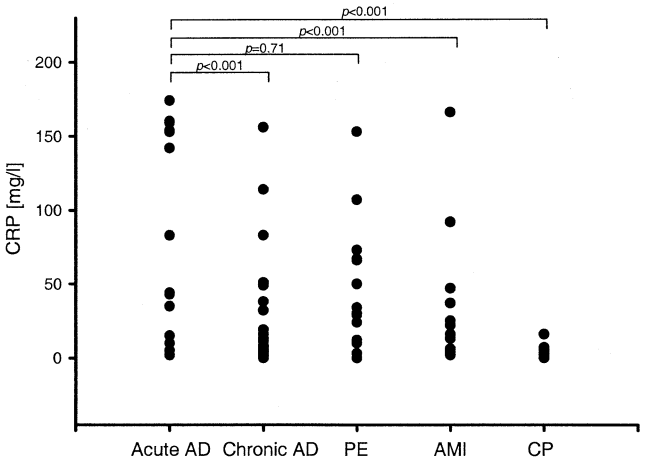

Figure 6. Comparison of C-reactive protein (CRP) values between the different patient groups (p values adjusted according to Bonferoni). AD = aortic dissection; AMI = acute myocardial infarction; CP = chest pain; PE = pulmonary embolism.

DISCUSSION

D-dimers—the degradation product of cross-linked fibrin—have been shown to play an important role in the diagnosis of acute PE (8). The present study demonstrates that highly elevated D-dimer values are also found in patients with acute AD. At a cutoff value of 500 μg/l, which has been previously proposed for the detection of PE (8), we found a sensitivity of 100% with a specificity of 67% for the presence of acute AD. In patients with acute CP and

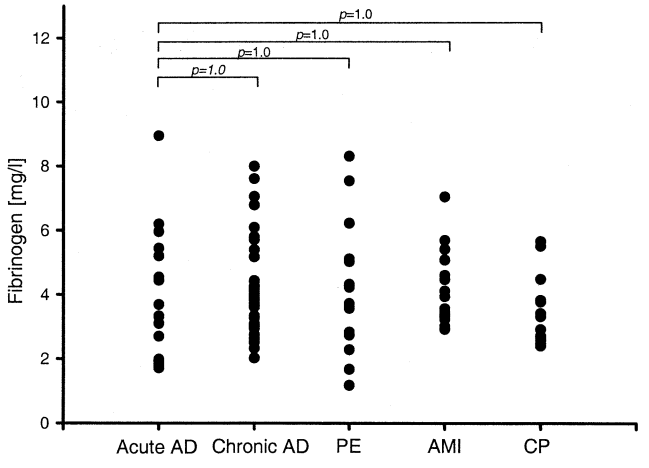

Figure 7. Comparison of fibrinogen values between the different patient groups (p values adjusted according to Bonferoni). AD = aortic dissection; AMI = acute myocardial infarction; CP = chest pain; PE = pulmonary embolism.

Table 4. Laboratory Findings in Acute AD Patients With Fatal In-Hospital Course Versus Survivors

	Survived (n = 8)	Death (n = 8)	p Value
D-dimers (μg/l)	1,665 ± 1,089 (632–4,199)	2,811 ± 2,177 (842–6,419)	0.204
WBC (× 10^9/l)	14.2 ± 5.5 (8.6–25.6)	15.1 ± 4.8 (7.0–21.0)	0.731
CRP (mg/l)	61 ± 58 (0–160)	92 ± 77 (0–170)	0.342
Fibrinogen (g/l)	4.5 ± 2.3 (1.9–8.9)	3.5 ± 1.6 (1.7–5.4)	0.365

AD = aortic dissection; CRP = C-reactive protein; WBC = white blood cell count.

elevated D-dimers, acute AD should, thus, also be taken into account. This is of particular clinical importance because precipitate thrombolysis for misdiagnosed PE may have disastrous consequences in these patients (9).

So far, there has been only one report on D-dimers in acute AD. In 10 patients, Weber et al. (10) found similar levels of D-dimers as in the present study. It may be hypothesized that the elevation of D-dimers in acute AD is due to activation of the extrinsic pathway of the coagulation cascade by tissue factor, which is largely exposed at the site of the injured aortic wall (i.e., within the whole FL) (10). The elevation of D-dimers would then reflect a profound fibrinolytic activity, which prevents thrombosis of the FL during the acute phase of AD. This is supported by clinical observations demonstrating that spontaneous FL thrombosis is only rarely observed (≤4% of patients) (11). On the other hand, elevated D-dimer values may reflect systemic inflammatory reactions, which have been previously described in patients with acute AD (4). Up to now it is unclear whether these inflammatory reactions occur due to underlying vascular inflammatory processes in the development of acute AD or as an accompanying phenomenon due to a profound systemic acute phase reaction. Most interestingly, however, Schillinger et al. (5) demonstrated that CRP is an independent predictor of mortality in patients with acute aortic disease. In our study, CRP values as well as D-dimers tended to be higher in acute AD patients who presented with complications or died during the in-hospital period; however, this difference did not reach statistical significance due to a small number of patients.

Discrimination between acute and chronic AD has important prognostic and therapeutic implications, but may be difficult. The characteristic severe CP of sudden onset may be absent in 5% to 15% of patients (1,2). Our data show that D-dimers allow to reliably differentiate acute from chronic AD. At the optimal cutoff value of 626 μg/l, there were only two false positive results (sensitivity 100%, specificity 94%). The difference in D-dimers may be explained by the fact that the patent FL becomes endothelialized during the chronic course of AD; as a consequence, the coagulation cascade and fibrinolytic status is no longer activated.

Study limitations. The study is limited by the relatively small number of patients. However, AD has a low incidence. Our study analyzed biochemical markers in well-defined patient groups, and we cannot completely rule out that selection bias may have influenced the results of this study. The study design does not provide data to exclude acute AD on the basis of a normal D-dimer result. In patients with high clinical suspicion but normal D- dimers, further diagnostic testing (i.e., imaging of the aorta) should be performed. Larger, prospective multicenter studies are needed to elucidate the value of D-dimers in the screening of patients with CP and suspected acute AD. The natural course of D-dimers in acute AD would be of great interest but is difficult to obtain, as patients with acute AD may die early or may require major surgery that confounds the results of D-dimer measurements.

Proposed approach to diagnosis of acute AD. Based on our data, we believe that determination of D-dimers should be part of the current initial diagnostic work-up of patients with CP and suspected AD. Highly elevated D-dimers cannot distinguish between acute AD and PE but may prompt an urgent contrast-enhanced CT scan, which allows confirmation or exclusion of both AD and PE.

Reprint requests and correspondence: Dr. Holger Eggebrecht, Department of Cardiology, University of Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany. E-mail: holger.eggebrecht@uni-essen.de.

REFERENCES

1. Erbel R, Alfonso F, Boileau C, et al. Diagnosis and management of aortic dissection. Eur Heart J 2001;22:1642–81.
2. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. Arch Intern Med 2000;160:2977–82.
3. Suzuki T, Katoh H, Tsuchio Y, et al. Diagnostic implications of elevated levels of smooth-muscle myosin heavy-chain protein in acute aortic dissection: the smooth muscle myosin heavy chain study. Ann Intern Med 2000;133:537–41.
4. Shinohara T, Suzuki K, Okada M, et al. Soluble elastin fragments in serum are elevated in acute aortic dissection. Arterioscler Thromb Vasc Biol 2003;23:1839–44.
5. Schillinger M, Domanovits H, Bayegan K, et al. C-reactive protein and mortality in patients with acute aortic disease. Intensive Care Med 2002;28:740–5.
6. Crawford ES, Svensson LG, Coselli JS, Safi HJ, Hess KR. Surgical treatment of aneurysm and/or dissection of the ascending aorta, transverse arch, and descending aorta: factors influencing survival in 717 patients. J Thorac Cardiovasc Surg 1989;98:659–74.
7. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the

redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959–69.
8. Schutgens RE, Ackermark P, Haas FJ, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. Circulation 2003;107:593–7.
9. Khoury NE, Borzak S, Gokli A, Havstad SL, Smith ST, Jones M. "Inadvertent" thrombolytic administration in patients without myocardial infarction: clinical features and outcome. Ann Emerg Med 1996;28:553–4.
10. Weber T, Hogler S, Auer J, et al. D-dimer in acute aortic dissection. Chest 2003;123:1375–8.
11. Erbel R, Oelert H, Meyer J, et al. Effect of medical and surgical therapy on aortic dissection evaluated by transesophageal echocardiography: implications for prognosis and therapy. Circulation 1993;87:1604–15.