Vascular Medicine

Diagnosis of Acute Aortic Dissection by D-Dimer
The International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) Experience

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Background—D-dimer has been reported to be elevated in acute aortic dissection. Potential use as a "rule-out" marker has been suggested, but concerns remain given that it is elevated in other acute chest diseases, including pulmonary embolism and ischemic heart disease. We evaluated the diagnostic performance of D-dimer testing in a study population of patients with suspected aortic dissection.

Methods and Results—In this prospective multicenter study, 220 patients with initial suspicion of having acute aortic dissection were enrolled, of whom 87 were diagnosed with acute aortic dissection and 133 with other final diagnoses, including myocardial infarction, angina, pulmonary embolism, and other uncertain diagnoses. D-dimer was markedly elevated in patients with acute aortic dissection. Analysis according to control disease, type of dissection, and time course showed that the widely used cutoff level of 500 ng/mL for ruling out pulmonary embolism also can reliably rule out aortic dissection, with a negative likelihood ratio of 0.07 throughout the first 24 hours.

Conclusion—D-dimer levels may be useful in risk stratifying patients with suspected aortic dissection to rule out aortic dissection if used within the first 24 hours after symptom onset. (*Circulation*. 2009;119:2702-2707.)

Key Words: aorta ■ diagnosis ■ peripheral vascular disease

Acute aortic dissection (AD) remains a potentially catastrophic cardiovascular disease.[1–6] Recent advancements in imaging methods (eg, computed tomography, magnetic resonance imaging) and the development of novel biochemical diagnostic methods (eg, smooth muscle myosin heavy chain) have made possible improved diagnosis of the disease to allow early and optimized treatment.[5–12] However, the disease at times remains overlooked or misdiagnosed because of its relatively uncommon nature. A diagnostic test that can reliably identify or exclude this disease in a cost-effective and resource-efficient manner such as a blood assay would be very useful.

Clinical Perspective on p 2707

D-dimer, a fibrin fragment seen in coagulopathic disorders and now commonly used in the diagnosis of pulmonary embolism (PE), has recently been reported to be elevated in acute AD.[13–19] D-dimer has been suggested to be useful as a "rule-out" diagnostic tool. Because most of the early studies used samples from selected patients, however, investigation of the performance of the assay in a clinically relevant population being investigated for suspected AD is necessary to accurately describe the usefulness of the assay.

The International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio study) was established to investigate and develop biomarkers of acute AD.[20] In the present study, we evaluated the diagnostic performance of D-dimer in acute AD in a population suspected of having the disease.

Methods

Patients and Samples
Fourteen centers in Europe, the United States, and Japan participated in the present study (see the Appendix in the online-only Data

Table 1. Patient Demographics and Baseline Data for Patients Presenting Within the First 24 Hours

Diagnosis	Cases (Male), n	Age, y	D-Dimer, ng/mL				
			Mean±SD	25th Percentile	50th Percentile	75th Percentile	99th Percentile
Type A AD	64 (39)	60.6±14.8	3213±1465	2083	3310	5000	5000
Type B AD	23 (14)	60.2±12.4	3574±1430	2265	3902	5000	5000
MI	46 (36)	65.2±15.0	1459±1650	325	694	2216	5000
Angina pectoris	37 (28)	61.7±13.2	760±974	250	319	250	4337
PE	5 (2)	50.0±32.0	2452±1891	776	2765	3931	4515
Other uncertain diagnoses	45 (26)	62.2±15.4	1399±1511	250	676	2252	5000

Supplement for complete list of participating centers). Institutional review board approval was obtained. Consenting patients with a suspicion of acute AD within the first 24 hours of symptom onset were enrolled in a prospective manner. The suspicion of AD had to be high enough to cause the evaluating physician to order an imaging test to identify the presence of AD on which the subjects were categorized. Standardized clinical data report forms were completed for each patient with parameters developed by IRAD.[2] Blood plasma was drawn on presentation and used for measurements in the present study.

Measurements and Analysis

D-dimer levels were measured with the commercially available Triage D-Dimer Test (Biosite, San Diego, Calif). As analytical methods of diagnostic performance, sensitivity, specificity, likelihood ratios, and predictive values at designated cutoff levels and receiver-operating characteristic curve analysis with area under the curve calculations were done with Analyze-It software (version 2.03, Leeds, UK). D-dimer levels for confirmed cases of AD were compared with those of patient cohorts with other final diagnoses according to type of dissection and time course from symptom onset.

Values are presented as mean±SD, 95% confidence intervals (CIs), and percentile range as appropriate. Nonparametric Mann–Whitney tests were used for comparison between groups.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Demographics and Baseline Data

Two hundred twenty patients were enrolled in this prospective multicenter study, including 87 cases of radiographically proven acute AD and 133 control subjects with an initial suspicion of AD but a different final diagnosis, which included myocardial infarction (MI), angina, PE, or other uncertain diagnoses. Of the 87 AD cases, 53 (61%) were male, and there were 64 and 23 cases of type A and B dissections, respectively. Of the 133 non-AD cases, there were 46, 37, and 5 cases of MI, angina, and PE, respectively, and 45 cases with uncertain diagnoses. Of these control cases, 92 patients were male.

Patient demographics and baseline data are shown in Table 1. D-dimer levels were elevated in acute AD at 3213±1465 ng/mL (median, 3310 ng/mL) and 3574±1430 ng/mL (median, 3902 ng/mL) for types A and B, respectively. These were ≈4.9-fold, 10.7-fold, 1.2-fold, and 5.1-fold higher than levels for MI (1459±1650 ng/mL; median, 694 ng/mL), angina (760±974 ng/mL; median, 319 ng/mL), PE (2452±1891 ng/mL; median, 2765 ng/mL), and other uncertain diagnosis (1399±1511 ng/mL; median, 676 ng/mL), respectively.

Diagnostic Performance

The area under the curve on receiver-operating characteristics curve analysis for all 87 AD patients within 24 hours of symptom onset versus all control subjects was 0.84 (95% CI, 0.78 to 0.89) and 0.81 (95% CI, 0.72 to 0. 90), 0.93 (95% CI, 0.87 to 0.98), 0.65 (95% CI, 0.36 to 0.93), and 0.82 (95% CI, 0.73 to 0.90) versus MI, angina, PE, and other uncertain diagnosis, respectively. Thus, D-dimer showed favorable overall diagnostic performance compared with these conditions that present with chest pain with superior performance for angina but also was seemingly helpful for MI, other uncertain diagnoses, and PE (see Figure 1).

Diagnostic performance at the cutoff of 500 ng/mL was analyzed to place these findings in better perspective for potential use in the clinic or emergency department because this cutoff is commonly used for PE (see Table 2).[21,22] At this cutoff level, sensitivity was 96.6% (95% CI, 90.3 to 99.3) and specificity was 46.6% (95% CI, 37.9 to 55.5) for AD patients versus control subjects. When control subjects were subdivided according to disease, specificities ranged from 20.0% (95% CI, 0.5 to 71.6) for PE to 39.1% (95% CI, 25.1 to 54.6) for MI, 44.4% (95% CI, 29.6 to 60.0) for uncertain diagnoses, and 62.2% (95% CI, 44.8 to 77.5) for angina. Predictive values as a clinical index of likelihood and the biostatistical measure of the likelihood ratio also were analyzed. Although predictive values are widely used from a clinical perspective, their calculation depends on knowing the prevalence rate of
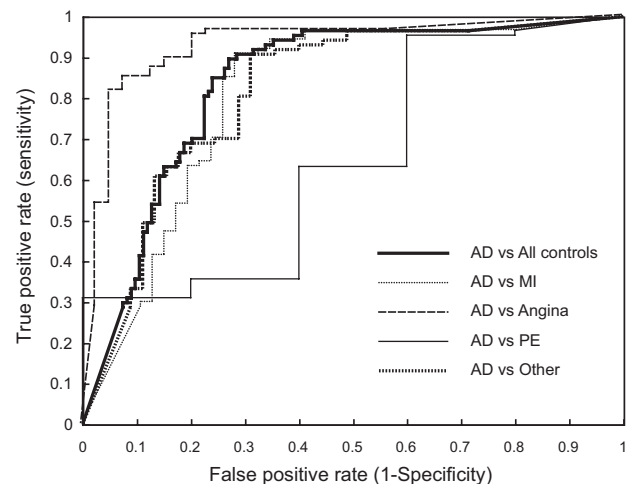

Figure 1. Receiver-operating characteristics curves for all patients with acute AD vs all control subjects and each of the control diseases.

Table 2. Diagnostic Performance of D-Dimer for Patients Presenting Within the First 24 Hours at the Cutoff of 500 ng/ml

AD and Control	Sensitivity, %	Sensitivity 95% CI	Specificity, %	Specificity 95% CI	PLR	NLR	PPV	NPV
A and B	96.6	90.3–99.3						
All			46.6	37.9–55.5	1.81	0.07	37.6	97.6
MI only			39.1	25.1–54.6	1.59	0.09	34.6	97.1
Angina only			62.2	44.8–77.5	2.55	0.06	46.0	98.2
PE only			20.0	0.5–71.6	1.21	0.17	28.7	94.6
Other only			44.4	29.6–60.0	1.74	0.08	36.7	97.5
A only	96.9	89.2–99.6						
All			46.6	37.9–55.5	1.81	0.07	37.7	97.8
MI only			39.1	25.1–54.6	1.59	0.08	34.7	97.4
Angina only			62.2	44.8–77.5	2.56	0.05	46.0	98.4
PE only			20.0	0.5–71.6	1.21	0.16	28.8	95.0
Other only			44.4	29.6–60.0	1.74	0.07	36.8	97.7
B only	95.7	78.1–99.9						
All			46.6	37.9–55.5	1.79	0.09	37.4	97.0
MI only			39.1	25.1–54.6	1.57	0.11	34.4	96.4
Angina only			62.2	44.8–77.5	2.53	0.07	45.7	97.7
PE only			20.0	0.5–71.6	1.20	0.22	28.5	93.2
Other only			44.4	29.6–60.0	1.72	0.10	36.5	96.8

PLR indicates positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; and NPV, negative predictive value.

the disease in the tested population, in this case, patients presenting with suspicion of AD. Because this prevalence is poorly understood, we estimated that 1 in 4 patients (25%) would present with AD, which was used in our calculations as consistent with previous studies.[20] The likelihood ratio, a biostatistical measure that is not affected by prevalence, also is shown. In general, a positive likelihood ratio of >10 is suggestive of a good "rule-in" tool, and a negative likelihood ratio of <0.1 is suggestive of a good rule-out tool.[23] Because positive likelihood ratios were <3 and positive predictive values were <50%, in contrast to negative likelihood ratios of 0.07 and negative predictive values >90%, D-dimer at this cutoff value showed favorable rule-out properties.

Subanalyses According to Type of Dissection and Time Course

To further characterize diagnostic performance and association with clinical parameters, subanalyses according to type of dissection and time course relative to symptom onset were done.

According to dissection type, analysis of the 64 cases of type A dissection versus all control subjects showed areas under the curve of 0.83 (95% CI, 0.77 to 0.89) and 0.80 (95% CI, 0.71 to 0.89), 0.92 (95% CI, 0.86 to 0.98), 0.63 (95% CI, 0.33 to 0.93), and 0.81 (95% CI, 0.72 to 0.90) versus MI, angina, PE, and other uncertain diagnoses, respectively. Analysis of the 23 cases of type B dissection versus all control subjects showed areas under the curve of 0.85 (95% CI, 0.77 to 0.93) and 0.82 (95% CI, 0.72 to 0.93), 0.93 (95% CI, 0.85 to 1.00), 0.69 (95% CI, 0.42 to 0.96), and 0.83 (95% CI, 0.73 to 0.94) versus MI, angina, PE, and other uncertain diagnoses, respectively.

Analysis of time course was done first with box plot analysis according to time from onset (time windows of 0 to 6, 6 to 12, and 12 to 24 hours). Inspection of the box plots showed distinct temporal trends. Patients with AD demonstrated marked elevations that were 5- to 10-fold greater than in control subjects in the initial 6 hours (see Figure 2). Patient demographics and baseline data for patients presenting within the first 6 hours of onset are shown in Table 3.

Analysis of the diagnostic performance of D-dimer within the first 6 hours of symptom onset showed that the area under the curve for the 23 AD cases versus the 31 control cases was 0.94 (95% CI, 0.86 to 1.00). Subanalyses against each of the control groups, albeit limited in accuracy because of the small number of cases of each disease in this time window, was 0.96 (95% CI, 0.89 to 1.00), 0.94 (95% CI, 0.87 to 1.00), 0.97 (95% CI, 0.90 to 1.00), and 0.88 (95% CI, 0.69 to 1.00) versus MI, angina, PE, and other uncertain diagnoses, respectively. Subanalysis according to type of dissection was not done because there were only 4 cases of type B dissection in this window.

Diagnostic performance at the cutoff level of 500 ng/mL was further analyzed for this early presentation subgroup (see Table 4). At this cutoff level, D-dimer had a sensitivity of 95.7% (95% CI, 78.1 to 99.9) and a specificity of 61.3% (95% CI, 42.2 to 78.2) for identifying AD. The negative likelihood ratio during this time window was 0.07. Thus, D-dimer at this cutoff value showed consistently favorable rule-out properties. Of interest, owing to the marked difference in D-dimer levels for dissection compared with other diseases in the initial 6-hour time window, a cutoff level of >1600 ng/mL showed a positive likelihood ratio of 12.8 at 1684 ng/mL, which suggests that the test also may be used to identify patients with a high probability/likelihood of AD. Subanalyses according to control disease and dissection type also were done, but their accuracy is limited by the number of cases in each subgroup.
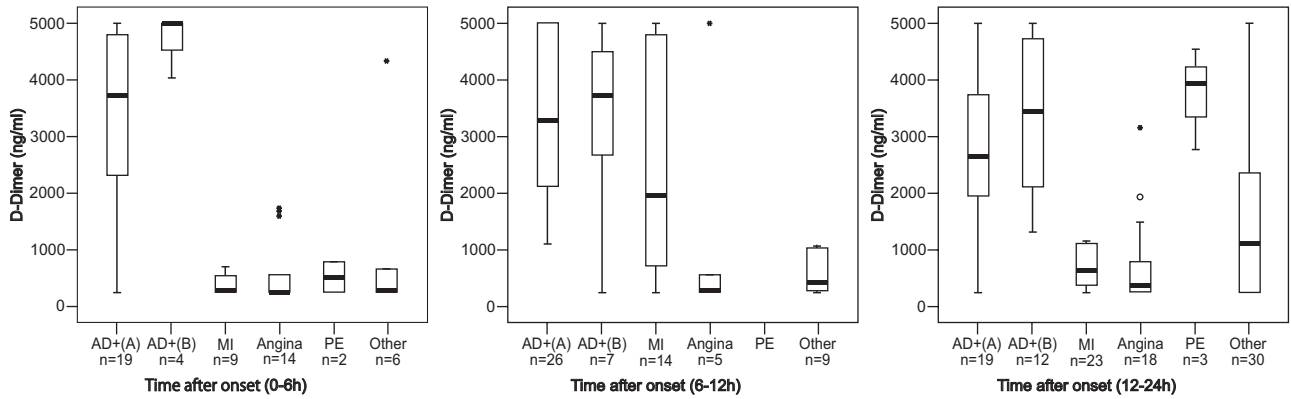
Figure 2. Time course box plots for D-dimer levels in patients according to time from onset.

We further tested the association of D-dimer levels with status of the false lumen because ongoing communication of the dissection with systemic blood flow may be important for elevated levels and because false lumen patency has been shown to be associated with outcome.[24] Fifty-seven patients had information on false lumen patency (46 patent: median, 3477 ng/mL; 11 not patent: median, 2351 ng/mL). All dissections ($P=0.18$) and type A dissections (n=46; 39 patent: median, 3504 ng/mL; 7 not patent: median, 2351 ng/mL; $P=0.14$), but not type B dissections (n=11; 7 patent: median, 3011 ng/mL; 4 not patent: median, 3101 ng/mL; $P=0.93$), showed a slight trend for false lumen patency to be associated with higher levels of D-dimer, but this was not statistically significant.

Discussion

AD, although uncommon, can rapidly evolve into a cardiovascular catastrophe if overlooked or misdiagnosed given its high morbidity and mortality within the initial hours after onset. Because of its relative rarity but high lethality, it remains a highly litigated disease with accusations of malpractice against treating physicians and hospitals.[25] A cost-effective and technically simple method such as a blood test to rule out the disease would thus be welcomed by patients and caregivers alike.

Although past studies have described the possibility of using D-dimer as a candidate biomarker in excluding AD, they have often used selected samples, especially for controls.[13–19] The present prospective multicenter study was unique in that the entry criterion for all patients, including control subjects, was suspicion of AD, which allowed better

estimation of assay performance in the clinical setting. In addition, cases and controls were enrolled concurrently.

We found a favorable negative likelihood ratio of 0.07 and negative predictive value of 95% in patients within the first 24 hours of onset at the widely used cutoff level of 500 ng/mL, suggesting that the D-dimer assay may be useful for ruling out AD in this time window with a diagnostic performance similar to that reported for PE. Time course analysis showed that for patients presenting within the initial 6 hours of symptom onset, a rule-in cutoff level of 1600 ng/mL in this time window identifies patients with a high probability/likelihood of AD. However, we urge caution in interpreting these results because the present study examined only patients with suspected AD, not patients with chest pain in general. Additionally, we enrolled only a limited number of cases for the initial 6-hour time window (eg, PE). Comparably high D-dimer levels have been reported in PE (although the time course was not shown), so it is important not to exclude the possibility of this disease.[26] Thus, D-dimer may be useful for ruling out AD, similar to PE, in the first 24 hours after symptom onset and for ruling in these acute conditions with high rates of coagulation activation (AD and PE) in the first 6 hours from symptom onset compared with other conditions such as ischemic heart disease as evaluated in the present study.

The major limitation of our study lies in the sample size. Although this present work represents one of the largest studies to examine AD to date, the subanalyses resulted in categorical groups which contained few cases (eg, for PE), which limits the accuracy of the analysis. Furthermore, because participating institutions were centers that routinely

Table 3. Patient Demographics and Baseline Data for Patients Presenting Within the First 6 Hours

Diagnosis	Cases (Male), n	Age, y	D-Dimer, ng/mL				
			Mean±SD	25th Percentile	50th Percentile	75th Percentile	99th Percentile
Type A AD	19 (13)	58.7±13.6	3282±1606	2322	3722	4800	5000
Type B AD	4 (2)	66.6±12.3	4760±480	4760	5000	5000	5000
MI	9 (7)	59.0±23.7	402±181	250	264	560	687
Angina pectoris	14 (12)	56.0±14.8	606±584	250	250	250	1715
PE	2 (1)	41.9±59.3	513±372	382	513	645	771
Other uncertain diagnoses	6 (6)	47.4±16.5	1011±1628	250	287	588	4136

Table 4. Diagnostic Performance of D-Dimer for Patients Presenting Within the First 6 Hours at a Cutoff of 500 ng/ml

AD and Control	Sensitivity, %	Sensitivity 95% CI	Specificity, %	Specificity 95% CI	PLR	NLR	PPV	NPV
A and B	95.7	78.1–99.9						
All			61.3	42.2–78.2	2.47	0.07	45.2	97.7
MI only			55.6	21.2–86.3	2.15	0.08	41.8	97.5
Angina only			64.3	35.1–87.2	2.68	0.07	47.2	97.8
PE only			50.0	1.3–98.7	1.91	0.09	38.9	97.2
Other only			66.7	22.3–95.7	2.87	0.07	48.9	97.9

Abbreviations as in Table 2.

care for AD, the diagnostic rate and prevalence of the disease as described are likely higher than seen in general clinical practice. Another limitation of the present study is that our entry criterion was suspicion of AD (which is reflected in the high prevalence) and not chest pain per se, which limits the generality of our findings in attempts to extend the interpretations to patients with chest pain in general. We also provided subgroup analysis according to type of disease (types A and B) and control disease (MI, angina, and PE), which are categorical populations for analytical purposes that would not exist separately in practice but were thought important to address given that the dissection types have consistently been analyzed separately (ie, past IRAD analyses[2,5,6,24,27]) because of their different clinical presentation, management, and outcomes and the subgroup analysis according to control disease to better place our present analysis into perspective for comparison with past findings such as for PE.[15,19]

Issues specific for AD should also be taken into account in interpretations of D-dimer levels. Lack of false lumen patency will likely result in lower levels, as our data suggest. Intramural hematoma, a distinct subentity that shows bleeding limited to the vessel wall with lack of communication with the aortic lumen but also shows an outcome similar to AD, may not show elevations.[27] D-dimer levels may be elevated in chronic stages of AD in which the coagulatory response is activated because of the thrombotic process in the false lumen. Thus, elevated levels may be seen in patients with underlying chronic dissection but unrelated chest pain. The role of D-dimer in these specific pathologies remains to be addressed in future studies.

D-dimer is currently the only commercially available test that can be used for the biochemical diagnosis of AD.[28] The assay is widely used in the evaluation of patients with suspected PE, which also may present with sudden onset of chest pain and/or dyspnea, clinical symptoms also seen in patients with AD. A D-dimer blood test could assist the clinician when stratifying patients presenting with chest pain within 24 hours of onset to rule out both PE and AD to decide whether to subject the patient to further diagnostic testing such as an imaging procedure or to refer to a tertiary center when imaging (eg, computed tomography, magnetic resonance imaging) is not readily available. We believe that patients with levels greater than this cutoff level should undergo further diagnostic testing.

We believe that the accumulated evidence is now sufficient to suggest that routine use of D-dimer testing is helpful in risk stratifying patients with suspected acute AD. Sensitivity, specificity, and predictive values will undoubtedly vary according to the type, extent, and time from presentation among patients with AD. Thus, further studies are needed to clarify the best way to integrate D-dimer testing in patients with various prior probabilities of acute AD.

Appendix

The International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) Investigators

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References

1. DeBakey ME, Cooley DA, Creech O Jr. Surgical considerations of dissecting aneurysm of the aorta. *Ann Surg.* 1955;142:586–612.

2. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, Evangelista A, Fattori R, Suzuki T, Oh JK, Moore AG, Malouf JF, Pape LA, Gaca C, Sechtem U, Lenferink S, Deutsch HJ, Diedrichs H, Marcos y Robles J, Llovet A, Gilon D, Das SK, Armstrong WF, Deeb GM, Eagle KA. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA.* 2000;283:897–903.

3. Wheat MW Jr, Palmer RF, Bartley TD, Seelman RC. Treatment of dissecting aneurysms of aorta without surgery. *J Thorac Cardiovasc Surg.* 1965;50:364–373.

4. Spittell PC, Spittell JA Jr, Joyce JW, Tajik AJ, Edwards WD, Schaff HV, Stanson AW. Clinical features and differential diagnosis of aortic dissection: experience with 236 cases (1980 through 1990). *Mayo Clin Proc.* 1993;68:642–651.

5. Nienaber CA, Eagle KA. Aortic dissection: New frontiers in diagnosis and management, part I: from etiology to diagnostic strategies. *Circulation.* 2003;108:628–635.

6. Tsai TT, Nienaber CA, Eagle KA. Acute aortic syndromes. *Circulation.* 2005;112:3802–3813.

7. Katoh H, Suzuki T, Hiroi Y, Ohtaki E, Suzuki S, Yazaki Y, Nagai R. Diagnosis of aortic dissection by immunoassay for circulating smooth muscle myosin. *Lancet.* 1995;345:191–192.

8. Katoh H, Suzuki T, Yokomori K, Suzuki S, Ohtaki E, Watanabe M, Yazaki Y, Nagai R. A novel immunoassay of smooth muscle myosin heavy chain in serum. *J Immunol Methods.* 1995;185:57–63.

9. Suzuki T, Katoh H, Watanabe M, Kurabayashi M, Hiramori K, Hori S, Nobuyoshi M, Tanaka H, Kodama K, Sato H, Suzuki S, Tsuchio Y, Yazaki Y, Nagai R. Novel biochemical diagnostic method for aortic dissection: results of a prospective study using an immunoassay of smooth muscle myosin heavy chain. *Circulation.* 1996;93:1244–1249.

10. Suzuki T, Katoh H, Tsuchio Y, Hasegawa A, Kurabayashi M, Ohira A, Hiramori K, Sakomura Y, Kasanuki H, Hori S, Aikawa N, Abe S, Tei C, Nakagawa Y, Nobuyoshi M, Misu T, Sumiyoshi T, Nagai R. Diagnostic implications of elevated levels of smooth-muscle myosin heavy-chain protein in acute aortic dissection. *Ann Intern Med.* 2000;133:537–541.

11. Suzuki T, Katoh H, Kurabayashi M, Yazaki Y, Nagai R. Biochemical diagnosis of aortic dissection by raised concentrations of creatine kinase BB-isozyme. *Lancet.* 1997;350:784–785.

12. Suzuki T, Katoh H, Nagai R. Biochemical diagnosis of aortic dissection: from bench to bedside. *Jpn Heart J.* 1999;40:527–534.

13. Weber T, Hogler S, Auer J, Berent R, Lassnig E, Kvas E, Eber B. D-dimer in acute aortic dissection. *Chest.* 2003;123:1375–1378.

14. Perez A, Abbet P, Drescher MJ. D-dimers in the emergency department evaluation of aortic dissection. *Acad Emerg Med.* 2004;11:397–400.

15. Eggebrecht H, Naber CK, Bruch C, Kröger K, von Birgelen C, Schmermund A, Wichert M, Bartel T, Mann K, Erbel R. Value of plasma fibrin D-dimers for detection of acute aortic dissection. *J Am Coll Cardiol.* 2004;44:804–809.

16. Akutsu K, Sato N, Yamamoto T, Morita N, Takagi H, Fujita N, Tanaka K, Takano T. A rapid bedside D-dimer assay (cardiac D-dimer) for screening of clinically suspected acute aortic dissection. *Circ J.* 2005;69:397–403.

17. Hazui H, Fukumoto H, Negoro N, Hoshiga M, Muraoka H, Nishimoto M, Morita H, Hanafusa T. Simple and useful tests for discriminating between acute aortic dissection of the ascending aorta and acute myocardial infarction in the emergency setting. *Circ J.* 2005;69:677–682.

18. Ohlmann P, Faure A, Morel O, Petit H, Kabbaj H, Meyer N, Cheneau E, Jesel L, Epailly E, Desprez D, Grunebaum L, Schneider F, Roul G, Mazzucotelli JP, Eisenmann B, Bareiss P. Diagnostic and prognostic value of circulating D-dimers in patients with acute aortic dissection. *Crit Care Med.* 2006;34:1358–1364.

19. Sodeck G, Domanovits H, Schillinger M, Ehrlich MP, Endler G, Herkner H, Laggner A. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. *Eur Heart J.* 2007;28:3067–3075.

20. Suzuki T, Distante A, Zizza A, Trimarchi S, Villani M, Salerno Uriarte JA, de Luca Tupputi Schinosa L, Renzulli A, Sabino F, Nowak R, Birkhahn R, Hollander JE, Counselman F, Bossone E, Eagle K, for the International Registry of Acute Aortic Dissection substudy on Biomarkers (IRAD-Bio) Investigators. Preliminary experience with the smooth muscle troponin-like protein, calponin, as a novel biomarker for diagnosing acute aortic dissection. *Eur Heart J.* 2008;29:1439–1445.

21. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia V, Kalra NK. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med.* 2004;140:589–602.

22. Perrier A, Roy PM, Aujesky D, Chagnon I, Howarth N, Gourdier AL, Leftheriotis G, Barghouth G, Cornuz J, Hayoz D, Bounameaux H. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. *Am J Med.* 2004;116:291–299.

23. Jaeschke R, Guyatt GH, Sackett DL Guyatt G, Bass E, Brilledwards P, Browman G, Cook D, Farkouh M, Gerstein H, Haynes B, Hayward R, Holbrook A, Juniper E, Lee H, Levine M, Moyer V, Oxman A, Patel A, Philbrick J, Richardson WS, Sauve S, Sackett D, Sinclair J, Trout KS, Tugwell P, Tunis S, Walter S, Wilson M, for the Evidence-Based Medicine Working Group. Users guides to the medical literature, III: how to use an article about a diagnostic test, B: what are the results and will they help me in caring for my patients. *JAMA.* 1994;271:703–707.

24. Tsai TT, Evangelista A, Nienaber CA, Myrmel T, Meinhardt G, Cooper JV, Smith DE, Suzuki T, Fattori R, Llovet A, Froehlich J, Hutchison S, Distante A, Sundt T, Beckman J, Januzzi JL Jr, Isselbacher EM, Eagle KA, for the International Registry of Acute Aortic Dissection. Partial thrombosis of the false lumen in patients with acute type B aortic dissection. *N Engl J Med.* 2007;357:349–359.

25. Elefteriades JA, Barrett PW, Kopf GS. Litigation in nontraumatic aortic diseases: a tempest in the malpractice maelstrom. *Cardiology.* 2007;109: 263–272.

26. Tick LW, Nijkeuter M, Kramer MH, Hovens MM, Büller HR, Leebeek FW, Huisman MV, for the Christopher Study Investigators. High D-dimer levels increase the likelihood of pulmonary embolism. *J Intern Med.* 2008;264:195–200.

27. Evangelista A, Mukherjee D, Mehta RH, O'Gara PT, Fattori R, Cooper JV, Smith DE, Oh JK, Hutchison S, Sechtem U, Isselbacher EM, Nienaber CA, Pape LA. Eagle KA, for the International Registry of Aortic Dissection (IRAD) Investigators. Acute intramural hematoma of the aorta: a mystery in evolution. *Circulation.* 2005;111:1063–1070.

28. Suzuki T, Nagai R. Molecular markers for cardiovascular disease: cardiovascular biomarkers to proteomic discovery. *Nat Clin Pract Cardiovasc Med.* 2008;5:295.

CLINICAL PERSPECTIVE

Acute aortic dissection remains a challenging disease to diagnose. This uncommon disease may be overlooked, and diagnosis typically requires imaging modalities. This prospective multicenter study evaluated 87 patients with acute aortic dissection and compared them with patients with other diseases that presented with initial suspicion of having acute aortic dissection. The data show that a D-dimer test with levels <500 ng/mL rules out acute aortic dissection (and pulmonary embolism) in patients with suspicion of having this disease if used within the first 24 hours after symptom onset. This study suggests that D-dimer could be useful in settings in which computed tomography, magnetic resonance imaging, and other imaging tests are not readily available to rule out aortic dissection.