A Systematic Review and Meta-analysis of D-dimer as a Rule-out Test for Suspected Acute Aortic Dissection

Stephen E. Asha, MBBS, MMed (Clin Epi)*; James W. Miers, BSc, MBBS

*Corresponding Author. E-mail: stephen.asha@sesiahs.health.nsw.gov.au.

Study objective: The aim of this systematic review and meta-analysis is to determine the diagnostic accuracy of D-dimer as a rule-out test for acute aortic dissection. Previous meta-analyses have had methodological problems with conflicting conclusions, and new diagnostic accuracy studies have been published since.

Methods: All prospective cross-sectional analytic studies of D-dimer as a diagnostic test for acute aortic dissection were included where diagnosis was confirmed by an accepted reference standard. Studies were identified with MEDLINE, EMBASE, Medion, Google Scholar, Web of Science, and bibliographies of relevant articles and previous systematic reviews. Two reviewers independently screened articles for inclusion, assessed study quality, and extracted data.

Results: Abstracts from 800 articles were reviewed, yielding 30 potentially relevant studies that were reviewed in full text. Five studies met all eligibility criteria. Data from 4 studies (1,557 participants) that used a D-dimer cutoff of 0.50 μg/mL were pooled to estimate sensitivity, specificity, and positive and negative likelihood ratios. Overall, sensitivity and negative likelihood ratio were 98.0% (95% confidence interval [CI] 96.3% to 99.1%) and 0.05 (95% CI 0.03 to 0.09), respectively. These measurements had little statistical heterogeneity. Specificity (41.9%; 95% CI 39.0% to 44.9%) and positive likelihood ratio (2.11; 95% CI 1.46 to 3.05) showed significant statistical heterogeneity. When applied to a low-risk population as defined by the American Heart Association (prevalence 6%), the posttest probability for acute aortic dissection was 0.3%.

Conclusion: This meta-analysis suggests that a negative D-dimer result may be useful to help rule out acute aortic dissection in low-risk patients. [Ann Emerg Med. 2015;66:368-378.]

Please see page 369 for the Editor's Capsule Summary of this article.

A **podcast** for this article is available at www.annemergmed.com.
Continuing Medical Education exam for this article is available at http://www.acep.org/ACEPeCME/.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2015.02.013

INTRODUCTION

Acute aortic dissection is a disorder with a high mortality rate of 1% to 2% an hour if not treated promptly.[1,2] Clinicians must have a low threshold to consider this lethal disease, but there are limited screening tools to rule it out without resorting to advanced imaging. Current guidelines recommend performing computed tomography (CT), magnetic resonance imaging (MRI), or transesophageal echocardiography to identify or exclude acute aortic dissection.[3] These diagnostic imaging techniques are expensive and time consuming, carry risks of radiation exposure and contrast reactions, and are not accessible in all hospitals. A rapid, economical, and accessible biomarker used as a screening or triage test for acute aortic dissection could reduce the number of invasive diagnostic procedures and reduce the time necessary to exclude acute aortic dissection.

During the past decade, there have been many studies published on the use of D-dimer as a rule-out test for acute aortic dissection. This literature has also been summarized and pooled in 6 systematic reviews or meta-analyses.[4-9] The conclusions have been conflicting despite largely the same literature's being evaluated in each review. However, all of these conclusions are far from robust because of the inclusion of low-quality studies. Many included studies were retrospective chart reviews, case series, and case-control studies, designs that provide unreliable estimates of diagnostic accuracy that tend to be overly optimistic.[10] There were also design flaws in these systematic reviews,[11] such as single reviewers rather than 2 independent reviewers of the literature,[5,8,9] lack of peer review,[9] lack of a formal quality assessment of included studies,[5,6,8] and overly generous assessment of study quality.[4,7] As an example, the first question in the quality assessment of diagnostic accuracy studies (QUADAS) quality assessment tool[12] was frequently answered yes by reviewers[4,7] despite the tool's directing reviewers to score studies of case-control

Editor's Capsule Summary

What is already known on this topic

Individual studies have shown various results on the diagnostic utility for D-dimer in patients with acute aortic dissection.

What question this study addressed

To determine the utility of a negative D-dimer result to rule out aortic dissection.

What this study adds to our knowledge

In this systematic review of 5 studies, with little statistical heterogeneity in sensitivity, the pooled sensitivity was 98% (95% confidence interval 96% to 99%). Results for specificity were heterogeneous; pooled specificity was 42% (95% confidence interval 39% to 45%).

How this is relevant to clinical practice

Although not definitive, this meta-analysis suggests that sensitivity may be sufficiently high to rule out aortic dissection in low-risk patients with a negative test result.

design as no. Furthermore, we are aware of several prospective diagnostic accuracy studies published in the last 5 years that were not included in these reviews.

For these reasons, an up-to-date systematic review and meta-analysis using only prospective diagnostic accuracy studies of a cross-sectional design (the ideal for the assessment of triage tests) was warranted. Our clinical question was, In patients presenting to the hospital with suspected acute aortic dissection, can a negative D-dimer result rule out this diagnosis? The aim was to determine the sensitivity, specificity, and positive and negative likelihood ratios of the D-dimer test for the diagnosis of acute aortic dissection. We also planned to discuss how the results of this meta-analysis could be used as part of an algorithm to evaluate patients with suspected acute aortic dissection.

MATERIALS AND METHODS

A computer-aided search of MEDLINE (1946 to July 2014) and EMBASE (1974 to July 2014) was conducted through the OVID SP Web site (https://ovidsp.ovid.com), using the search strategies outlined in Table 1. No limits were applied to the search strategy. A search of the Medion database (http://www.mediondatabase.nl/) was performed in July 2014. The category "Circulation" was selected for "ICPC code" and the categories "Laboratory tests" and "Medical Imaging" were selected for "Signssymp." We performed a search of Google scholar (http://scholar.google.com.au) in July 2014. We used the "advanced search" option and searched for articles that had all the words "aortic" and "dissection" and "dimer" occurring in the title. After we had identified articles from these databases that met all our inclusion and exclusion criteria, we searched forward in the Web of Science (https://apps.webofknowledge.com) for publications that had cited these articles. Finally, we hand searched the reference lists of all articles meeting the inclusion and exclusion criteria and all previous systematic reviews and meta-analyses on this topic that were identified in our searches.

Table 1. Search strategy used in MEDLINE and EMBASE (through OVID SP).

MEDLINE	EMBASE
1. exp Aneurysm, Dissecting/	1. exp aorta dissection/
2. exp Aorta/	2. exp aorta/
3. Aort$.tw.	3. Aort$.tw.
4. 2 or 3	4. 2 or 3
5. dissecti$.tw.	5. dissecti$.tw.
6. 4 and 5	6. 4 and 5
7. 1 or 6	7. 1 or 6
8. d dimer.tw.	8. exp fibrin degradation product/ or exp D dimer/
9. exp Fibrin Fibrinogen Degradation Products/	9. d dimer.tw.
10. 8 or 9	10. 8 or 9
11. 7 and 10	11. 7 and 10

Studies were included in the systematic review if they were (1) original research that addressed the use of D-dimer as a diagnostic test for acute aortic dissection; (2) the study design was a cross-sectional study to evaluate a diagnostic test; (3) there was prospective enrollment of participants with clinically suspected acute aortic dissection; (4) enrollment occurred before confirmation of the diagnosis by a reference standard; (5) D-dimer level was measured; (6) participants had the diagnosis confirmed or refuted with an acceptable reference standard; and (7) absolute numbers of true positive, true negative, false positive, and false negative were reported or could be derived. Studies were excluded if enrollment was retrospective, the design was case-control or case series, they were nonhuman studies, or research was published only in the form of a conference abstract. Conference abstracts were excluded because they have not undergone a peer-review process, the results may not be final, and there is not enough detail in an abstract to assess study quality.

Aortic dissection was defined as acute if the duration of symptoms was less than 14 days.[2,13] An acceptable reference standard was aortic angiography, CT aortic angiography, MRI, or transesophageal echocardiography,

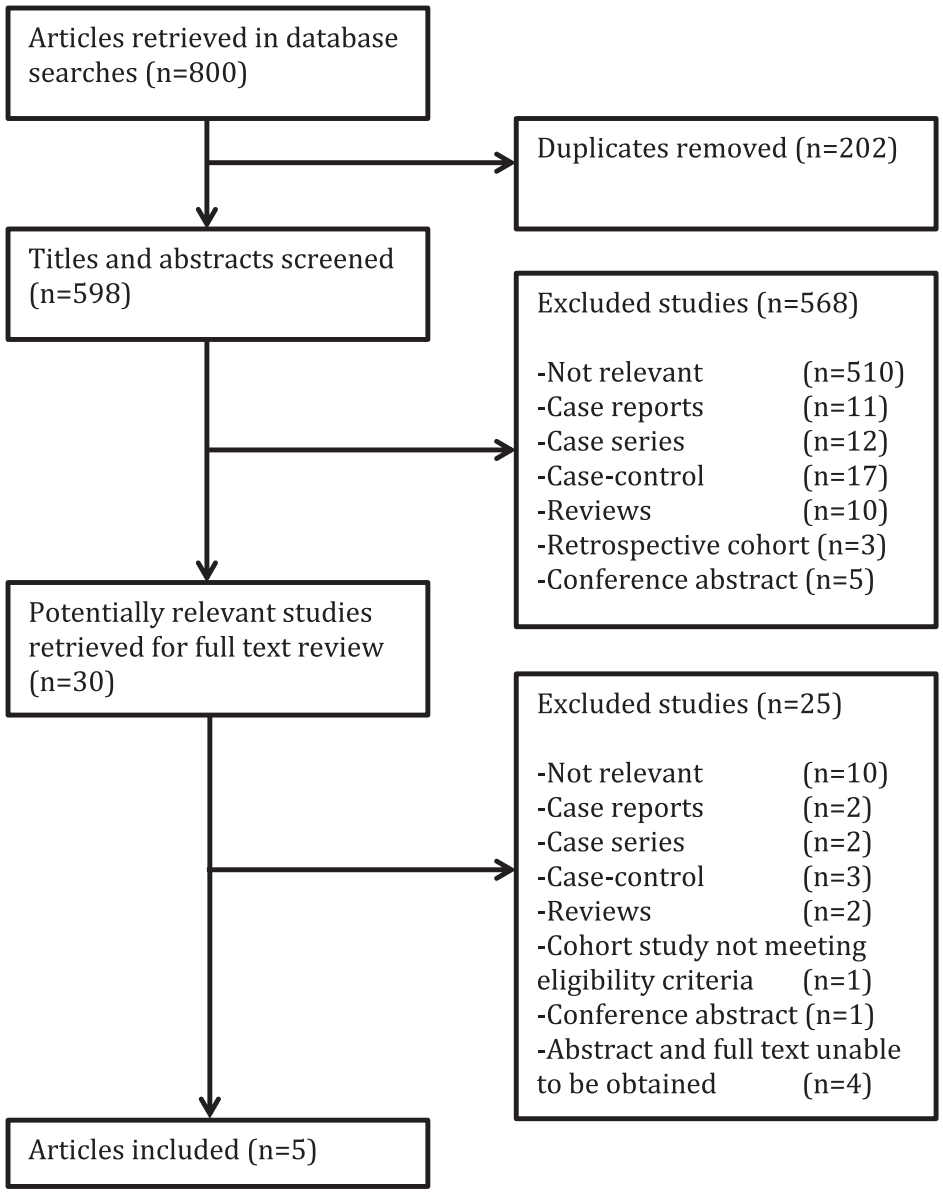

Figure 1. Flowchart describing systematic literature search and study selection process.

as recommended by the American Heart Association guidelines.[3]

Two reviewers (S.E.A., J.W.M.) independently screened the titles and abstracts of all identified citations for inclusion and exclusion criteria. The full-text article was then obtained for all potentially eligible articles that did not clearly meet an exclusion criterion or when there was disagreement about inclusion at this screening stage. Full-text articles were independently screened by each reviewer for inclusion and exclusion criteria. Any disagreements were resolved by consensus.

The 2 reviewers extracted data independently from the articles selected for inclusion. The data extracted included first author, date of publication, number of study sites, study setting, study design, study period, participant sampling method (consecutive/convenience), D-dimer assay used, blinding of individuals enrolling participants to the D-dimer result, timing of blood test, D-dimer reference range, and the reference standard used. We extracted the study population characteristics sex, age, duration of symptoms before presentation, D-dimer levels, acute aortic dissection classification according to Stanford or DeBakey classification systems, and final diagnoses made for patients without acute aortic dissection. We extracted absolute numbers of true-positive, true-negative, false-positive, and false-negative results.

Table 2. Characteristics of included studies.

	Akutsu, 2005[16]	Xue, 2007[20]	Suzuki, 2009[19]	Fan, 2010[17]	Nazerian, 2014[18]
Study period	Nov 2002 to June 2004	March 2002 to April 2006	NR	Jan 2007 to Sept 2008	Jan 2008 to March 2013
Number of study sites	1	1	14	1	2
Participants enrolled	78	43	220	224*	1,455
Participants analyzed	78	43	220	224*	1,035
Participants excluded because of missing index test, No. (%)	0	0	0	0	420 (29)
Participants with AAD, No. (%)	30 (38)	16 (37)	87 (40)	107 (48)*	233 (23)
Study design	Cross-sectional analytic	Cross-sectional analytic	Cross-sectional analytic	Cross-sectional analytic	Cross-sectional analytic study, prospective enrollment, retrospective analysis
Setting, country	Japan	China	USA, Japan, Europe	China	Italy
Type of hospital	NR	NR	Tertiary referral†	Probably large referral hospital	Large referral
Department	CCU	ED and CCU	NR	NR	ED
Eligibility criteria	Clinical suspicion of AAD (sudden-onset chest/back pain); no ECG findings of myocardial ischemia; AAD not already ruled out	Patients with chest pain in whom AAD suspected; AAD not already ruled out	Clinical suspicion of AAD high enough to cause evaluating physician to order an imaging test for AAD	Clinical suspicion of AAD (chest pain, back pain, abdominal pain, myocardial ischemia). Excluded if alternate diagnosis apparent.*	Chest/back/abdominal pain, or CNS/mesenteric/myocardial/limb ischemia, or syncope; clinical suspicion of AAD high enough to order imaging test; excluded if alternate diagnosis apparent
Definition of "acute"	NR	Symptom duration <48 h	Symptom duration < 24 h	Symptom duration <14 days	NR
Patient sampling	Consecutive	Consecutive	Consecutive‡	Consecutive	NR
Enrollers blind to D-dimer	NR	NR	Yes‡	NR	NR
D-dimer assay name	Roche cardiac D-dimer system, Roche Diagnostics	Sta-Liatest D-DI (Diagnostica Stago, France)	Triage D-Dimer Test (Biosite, San Diego, CA)	Tina-quant@D-dimer, Roche Di-agnostics, Mannheim, Germany	Hemosil D-dimer, HS, Bedford or STA LIATEST D-DI, Diagnostica Stago, Mannheim
D-dimer assay method	Whole blood immunoassay	Immunoturbidimetric	Whole blood immunoassay	Immunoturbidimetric	Latex enhanced immunoassay/ immunoturbidimetric
Time blood drawn for D-dimer	On arrival	NR	On arrival	On arrival	At initial ED assessment
Negative D-dimer result, μg/mL	≤0.50	≤0.40	0.50 (not specified if < or ≤)	<0.50	<0.50
Reference standard	CT angiography	TOE, MRI, or CT	"An imaging study for AAD"	TOE/CT/MRI	CT angiography
Male, %	59	56§	66	72‖	66
Age, y	Median 68 (IQR 61, 75)§	Mean 58 (SD 17)§	Mean 61.8 (SD 14.8)	Mean 58 (SD 12)‖	Mean 67.4 (SD 14.1)
Duration of symptoms	Median 4.5 h (IQR 3.0, 8.6)	NR	NR	Median 2 days (95% CI 1–3)*	Mean 1.4 days (SD 0.2)¶
D-dimer level, μg/mL					
AAD group	Median 1.80 (IQR 1.07, 2.73)	Mean 7.9 (SD 5.5)	Mean 3.3 (SD 1.5)	Median 3.47 (IQR NR)	NR
Non-AAD group	Median 0.42 (IQR 0.20, 1.38)	Mean 1.6 (SD 1.2)	Mean 1.3 (SD 1.4)	Median 0.18–2.56# (IQR NR)	NR

NR, Not reported; *AAD*, acute aortic dissection; *CCU*, coronary care unit; *ECG*, electrocardiogram; *ED*, emergency department; *CNS*, central nervous system; *CT,* computed tomography; *TOE*, transesophageal echo; IQR interquartile range, *SD,* standard deviation; *PE*, pulmonary embolism; *AMI*, acute myocardial infarction; *UA*, unstable angina.

*The study included patients with both acute and chronic symptoms; we contacted the author and obtained data for participants with acute symptoms only.

†Data obtained from an associated article.[33]

‡Data obtained from an associated article.[32]

§Data available only for AAD group.

‖Data available only for entire study group, which included a mix of patients with acute and chronic symptoms.

¶Data obtained from an associated article.[24]

#Median reported separately for each diagnostic subgroup (PE, AMI, UA).

Table 3. Final diagnoses of patients with and without acute aortic dissection.

Diagnostic Group	Akutsu, 2005[16]	Xue, 2007[20]	Suzuki, 2009[19]	Fan, 2010[17]	Nazerian, 2014[18]
AAD group n	30	16	87	107	233
Stanford A/B, No. (%)	12 (40)/18 (60)	7 (44)/9 (56)	64 (74)/23 (26)	—	148 (74)/51 (26)*
DeBakey I/II/III, No. (%)	8 (27)/3 (10)/19 (63)	—	—	38 (35):5 (5):64 (60)	—
Non-AAD group n	48	27	133	136†	802
Acute coronary syndrome, No. (%)	15 (31)	14 (52)	83 (62)	118 (87)	94 (12)
Pulmonary embolism, No. (%)	2 (4)	2 (7)	5 (4)	18 (13)	13 (2)
Aortic aneurysm, No. (%)	7 (15)	—	—	—	—
Atrial fibrillation, No. (%)	3 (6)	—	—	—	—
Syncope, No. (%)	—	—	—	—	66 (8)
Pericarditis, No. (%)	—	4 (15)	—	—	25 (3)
Nonspecific chest pain, No. (%)	8 (17)	3 (11)	—	—	302 (38)
Gastrointestinal, No. (%)	4 (8)	4 (15)	—	—	73 (9)
Stroke, No. (%)	—	—	—	—	16 (2)
Limb/organ ischemia, No. (%)	—	—	—	—	12 (1)
Other, No. (%)	9 (19)	—	45 (34)	—	201 (25)

—, No data.
*Thirty-four cases not classified.
†Data available only for the entire non-AAD study group, which included a mix of patients with acute and chronic symptoms.

We performed this meta-analysis according to the principles outlined by Leeflang et al.[14] We assessed study quality with 2 tools: for the quality of reporting, we used the standards for reporting of diagnostic accuracy (STARD) statement for reporting studies of diagnostic accuracy,[15] and for the quality of study design and conduct, we used the QUADAS tool.[12]

We examined the study characteristics, diagnostic test characteristics, sensitivity, and specificity of each study and then, if appropriate, pooled data across studies, using the random-effects models of DerSimonian and Laird. Zero cells were handled by adding a 0.5 continuity correction. We assessed for statistical heterogeneity with Cochran's Q statistic ($P<.10$ considered statistically significant), and we calculated I^2, which describes the percentage of variation across studies that is due to heterogeneity rather than chance. Agreement between reviewers was assessed with Cohen's κ statistic. Sensitivity and subgroup analyses were not conducted because of the small number of studies. Similarly, we did not evaluate for publication bias with the use of a funnel plot because there we too few studies to enable meaningful interpretation. The analysis was performed with Meta-DiSc (version 1.4; Unidad de Biostatistica Clinica, Hospital Ramon y Cajal, Madrid, Spain) and IBM SPSS statistics (version 21; IBM Corp, Armonk, NY).

RESULTS

Eight hundred studies were identified through the database searches (Figure 1). After the exclusion of duplicates, nonrelevant studies, and other studies that met exclusion criteria on screening of the title and abstract, 30 potentially relevant studies were retrieved for full review. Four of these studies were published in Chinese journals and only the title was available. We were unable to obtain either the abstract or full text. A further 3 foreign-language studies (French, Dutch, and German) were translated into English. Five studies met all eligibility criteria.[16-20] The characteristics of these studies and the participants enrolled are outlined in Tables 2 and 3. In addition to the information presented in Tables 2 and 3, some specific points need to be highlighted. In the study by Nazerian et al,[18] data were obtained from a registry in which patients with suspected acute aortic dissection were prospectively enrolled and all participants had the diagnosis confirmed or refuted with CT angiography. The decision to use these data in a diagnostic accuracy study of D-dimer was not planned, and as a consequence, 29% of participants did not have a D-dimer result available and could not be included in this study. The authors compared the characteristics of patients included with those excluded and found that participant characteristics were similar in both groups, providing the reader with some reassurance than selection bias was not introduced by these exclusions. The study by Fan et al[17] reported on a cohort of participants with both acute and chronic symptoms (14% chronic). Data on participants with acute symptoms only could not be extracted from the article. We contacted the authors and were provided with the data set for only those participants with acute symptoms.

The quality of reporting of these studies according to the STARD statement is outlined in Table 4. Of the 25 criteria recommended to be reported, only 11 items could be found in 2 studies,[19,20] 15 items in 2 studies,[16,17] and 20 items in 1 study.[18] The quality of study design and conduct according to the QUADAS tool is outlined in Table 5. Of

Table 4. Items recommended to be reported in diagnostic accuracy studies according to the STARD statement.[15]

	Item recommended to be reported	Akutsu, 2005[16]	Xue, 2007[20]	Suzuki, 2009[19]	Fan, 2010[17]	Nazerian, 2014[18]
1	Identify the article as a study of diagnostic accuracy	No	No	No	No	Yes
2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	Yes	Yes	Yes	Yes	Yes
3	Describe the study population: the inclusion and exclusion criteria, setting and locations where the data were collected	Yes	Yes	Yes	Yes	Yes
4	Describe participant recruitment: was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	Yes	Yes	Yes	Yes	Yes
5	Describe participant sampling: was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected.	Yes	Yes	Unclear	Yes	Unclear
6	Describe data collection: was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	Yes	Yes	Yes	Yes	Yes
7	Describe the reference standard and its rationale	Yes	Yes	Unclear	Yes	Yes
8	Describe technical specifications of material and methods involved, including how and when measurements were taken, or cite references for index tests and reference standard	No	No	No	No	Yes
9	Describe definition of and rationale for the units, cutoffs, or categories of the results of the index tests and the reference standard	Yes	Yes	Yes	Yes	Yes
10	Describe the number, training, and expertise of the persons executing and reading the index tests and the reference standard	No	No	No	No	Yes
11	Describe whether or not the readers of the index tests and reference standard were blinded to the results of the other test and describe any other clinical information available to the readers	No	No	No	No	Yes
12	Describe methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (eg, 95% CIs)	No	No	Yes	Yes	Yes
13	Describe methods for calculating test reproducibility, if done	No	No	No	No	No
14	Report when study was conducted, including beginning and ending dates of recruitment	Yes	Yes	No	Yes	Yes
15	Report clinical and demographic characteristics of the study population (eg, age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers)	Yes	Yes	Yes	Yes	Yes
16	Report the number of participants satisfying the criteria for inclusion who did or did not undergo the index tests or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended)	Yes	No	No	Yes	Yes
17	Report interval from the index tests to the reference standard, and any treatment administered between	No	No	No	No	No
18	Report distribution of severity of disease (define criteria) in patients with the target condition; other diagnoses in participants without the target condition	Yes	Yes	Yes	Yes	Yes
19	Report a cross-tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard	Yes	No	No	No	Yes
20	Report any adverse events from performing the index tests or the reference standard	No	No	No	No	No
21	Report estimates of diagnostic accuracy and measures of statistical uncertainty (eg, 95% CIs)	No	No	Yes	Yes	Yes
22	Report how indeterminate results, missing responses, and outliers of the index tests were handled	Yes	Unclear	Unclear	Unclear	Yes
23	Report estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done	Yes	No	Yes	Yes	Yes
24	Report estimates of test reproducibility, if done	No	No	No	No	No
25	Discuss the clinical applicability of the study findings	Yes	Yes	Yes	Yes	Yes

CI, Confidence intervals.

the 14 items, 9 could be answered yes in 2 studies,[19,20] 10 items in a further 2 studies,[16,17] and 14 items in 1 study.[18] The remaining items were mostly answered unclear rather than no, reflecting the relatively poor reporting quality. The agreement between the 2 reviewers for components of the STARD and QUADAS study quality assessment tools was substantial[21] (κ=0.63; 95% confidence interval [CI] 0.52 to 0.74).

The total numbers of true or false positive, true or false negatives, sensitivity, and specificity for each study are outlined in Table 6. All studies except 1 used a D-dimer cutoff value of 0.50 μg/mL.[20] This cutoff value has been validated for use in venous thromboembolic disease.[22] We therefore combined the results of the 4 studies that used 0.50 μg/mL in a meta-analysis. Individual study estimates and overall estimates of sensitivity, specificity, and positive and negative likelihood ratio are presented in Figure 2. The data of 1,557 participants were pooled across studies, yielding a sensitivity and negative likelihood ratio of 98.0% (95% CI 96.3% to 99.1%) and 0.05 (95% CI 0.03 to

Table 5. Assessment of study quality according to the QUADAS tool.[12]

	Quality Characteristic	Akutsu, 2005[16]	Xue, 2007[20]	Suzuki, 2009[19]	Fan, 2010[17]	Nazerian, 2014[18]
1	Was the spectrum of patients representative of patients who will receive the test in practice?	Unclear	Unclear	Yes	Yes	Yes
2	Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes
3	Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes
4	Is the period between the reference standard and index test short enough for one to be reasonably sure that the target condition did not change between the 2 tests?	Yes	Yes	Yes	Yes	Yes
5	Did the entire sample or a random selection of the sample receive verification with a reference standard of diagnosis?	Yes	Yes	Yes	Yes	Yes
6	Did patients receive the same reference standard regardless of index test result?	Yes	Yes	Yes	Yes	Yes
7	Was the reference standard independent of the index test (ie, index test did not form part of the reference standard)?	Yes	Yes	Yes	Yes	Yes
8	Was execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes
9	Was execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	No	Yes	Yes
10	Were index test results interpreted without knowledge of results of the reference standard?	Unclear	Unclear	Unclear	Unclear	Yes
11	Were reference standard results interpreted without knowledge of results of the index test?	Unclear	Unclear	Unclear	Unclear	Yes
12	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Unclear	Unclear	Unclear	Unclear	Yes
13	Were uninterruptible/intermediate test results reported?	Yes	Unclear	Unclear	Unclear	Yes
14	Were withdrawals from the study explained?	Yes	Yes	Yes	Yes	Yes

0.09), respectively. These measurements had little statistical heterogeneity (Q=2.1, P=.56, I^2=0.0% and Q=1.5, P=.69, I^2=0%, respectively). Specificity (41.9%; 95% CI 39.0% to 44.9%) and positive likelihood ratio (2.11; 95% CI 1.46 to 3.05) showed significant statistical heterogeneity (Q=61.5, P<.001, I^2=95.1% and Q=54.9, P<.001, I^2=94.5%, respectively).

LIMITATIONS

Several limitations should be considered when interpreting the results of this study. The accuracy of the estimates of test characteristics depended on the quality of the included studies. The main problem with the included studies was that authors failed to report important aspects of methodology that would allow the reader to determine the likelihood for bias, such as whether the D-dimer result was available to individuals enrolling participants, and timing of index and reference test. Similarly, the setting of several studies was unclear. The spectrum of disease in patients presenting to a referral hospital may be different from that of those presenting to a community emergency department (ED), which may affect test characteristics and thus generalizability.

The largest study included in this review used data from a registry that was not designed originally to answer this study question.[18] Almost a third of participants had to be excluded because of a lack of a D-dimer result. Even though the authors of this registry study found no obvious differences between those with and without D-dimer results, selection bias may still have occurred.

The high sensitivity and low negative likelihood ratio may have been weighted in favor of patients with a classic presentation, less reflective of the general population presenting to EDs for whom the diagnosis would be entertained. Most participants were included if their clinical presentation was suggestive enough of acute aortic dissection for them to undergo a diagnostic imaging test. This notion is supported by the high prevalence of acute aortic dissection in all the included studies.

Table 6. Results of included studies using D-dimer testing to rule out acute aortic dissection.

Reference	Participants n	Negative D-dimer Result, μg/mL	True Positive N	False Positive N	False Negative N	True Negative N	Sensitivity, %	Specificity, %
Akutsu, 2005[16]	78	≤0.50	30	22	0	26	100	54
Xue, 2007[20]	43	≤0.40	16	9	0	18	100	66
Suzuki, 2009[19]	220	0.50*	84	71	3	62	96.6	46.6
Fan, 2010[17,†]	224	<0.50	105	32	2	85	98.1	72.7
Nazerian, 2014[18]	1,035	<0.50	229	514	4	288	98.3	35.9

*Not specified if less than, or less than or equal to.
†The study included patients with both acute and chronic symptoms. We contacted the authors and obtained data for participants with acute symptoms only; these are the data presented in the table.

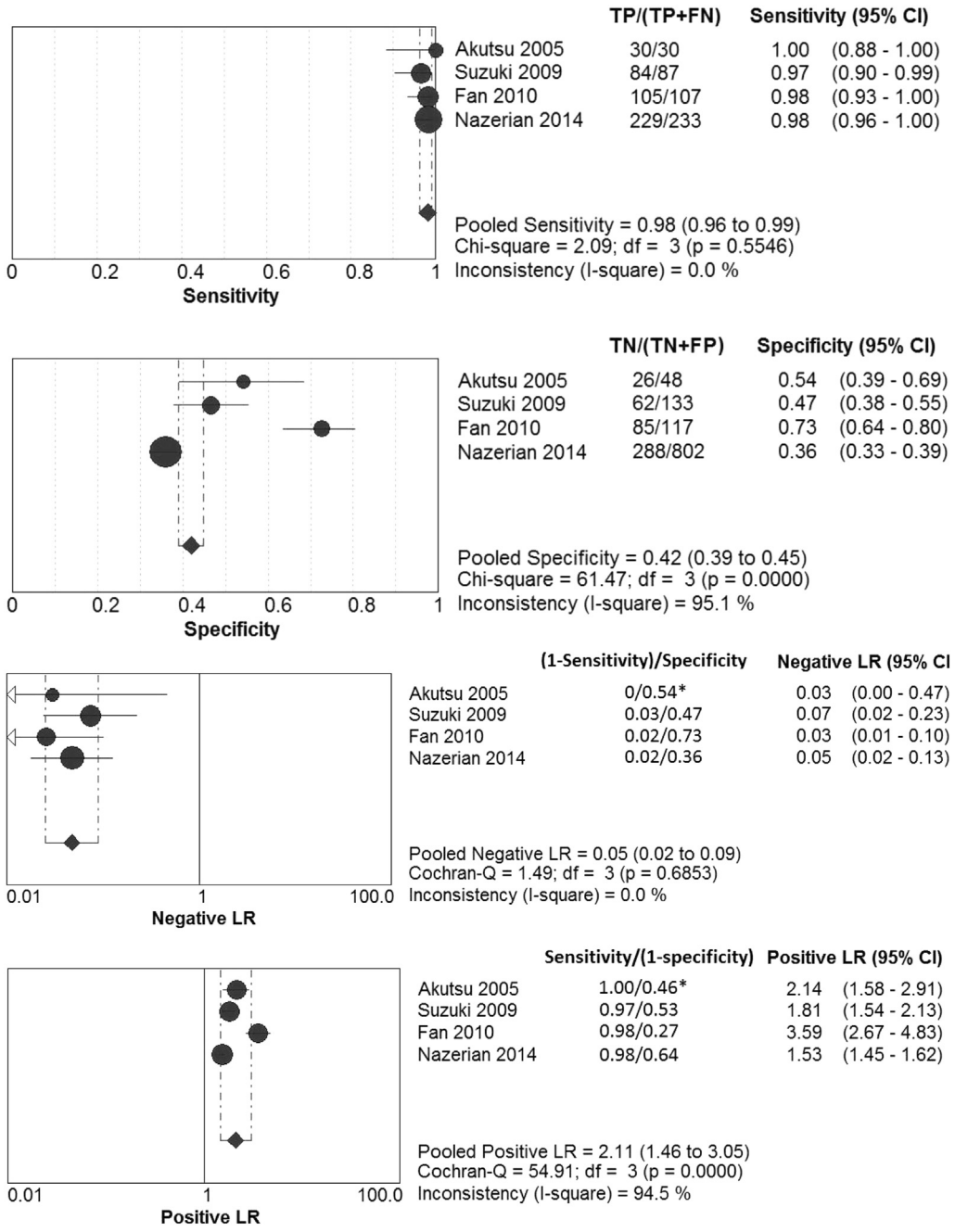

Figure 2. Individual study estimates and overall estimates of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of D-dimer for the diagnosis of acute aortic dissection. A threshold of 0.50 μg/mL was used to define a positive D-dimer result. *TP*, True positive; *FN*, false negative; *TN*, true negative; *FP*, false positive; *LR*, likelihood ratio. *The discrepancy between the ratio and the reported positive likelihood ratio is because cells in 2×2 tables with zero value were handled by adding a 0.5 continuity correction.

There was variability in the definition of *acute*. The majority of patients were enrolled within 48 hours of symptom onset; however, the study by Fan et al[17] enrolled participants up to 14 days from symptom onset.[17] Despite this, most participants in this study had symptom duration close to 48 hours (the median duration of symptoms was 2 days; interquartile range 1 to 3 days). Although the estimates of specificity and negative likelihood ratio for this study were similar to those of the other studies, the small number of patients with longer symptom duration would make generalizations of test accuracy to this subgroup questionable. We would recommend that the results of this

Predisposing conditions	Pain features	Physical findings
• Marfan Syndrome • Connective tissue disease • Family history aortic disease • Known aortic valve disease • Recent aortic manipulation • Known thoracic aortic aneurysm	Chest, back or abdominal pain described as: • Abrupt in onset/sever in intensity AND • Ripping/tearing/sharp or stabbing quality	• Evidence of perfusion deficit -Pulse deficit -Systolic BP differential -Focal neurological deficit (in conjunction with pain) • Murmur of aortic insufficiency (new or not known to be old and in conjunction with pain) • Hypotension or shock state
The acute aortic dissection risk score is calculated on the presence of risk markers in the clinical categories of predisposing conditions, pain features and physical findings. Patients lacking all risk markers (ADD risk score=0) are classified at low risk, patients with one or more risk markers in any single category (ADD risk score=1) are classified at intermediate risk, while patients with one or more risk markers in two or three categories (ADD risk score>1) are classified at high risk of acute aortic dissection.		

Figure 3. Acute aortic dissection risk score.[3,24]

study be applied only to patients with symptom duration less than 48 hours.

In addition, we did not use the summary receiver operator characteristic curve methodology to control for the fact that individual studies may not be using the same trade-off between sensitivity and specificity, and we used the STARD instrument as a tool for scoring the quality of reporting, a purpose for which it was neither developed nor validated.

DISCUSSION

Our study was designed to evaluate the diagnostic performance of D-dimer for the diagnosis of acute aortic dissection. The major strength of this meta-analysis is that we included only diagnostic accuracy studies that enrolled patients prospectively and were of a design that provided reliable estimates of test parameters. The included studies were all of moderate or higher methodological quality. This meta-analysis demonstrated the D-dimer result to be a potentially useful risk-stratification tool in acute aortic dissection, with a high sensitivity and favorable negative likelihood ratio that should enable acute aortic dissection to be ruled out in low-risk patients when the D-dimer level is less than 0.50 μg/mL. In contrast, previous reviews have included studies using designs at risk of providing overly optimistic estimates. Our results remain concordant with those of several of these previous studies.[4,5,7]

Despite variability in the assays used, study settings, patient characteristics, and years of enrollment, sensitivity and negative likelihood ratio lacked significant heterogeneity. In contrast, specificity was low with a poor positive likelihood ratio, and these pooled estimates demonstrated high statistical heterogeneity. Accordingly, D-dimer result cannot add to the certainty of acute aortic dissection diagnosis. The heterogeneity in the pooled estimates of specificity and positive likelihood ratio can largely be explained by the variability in the final diagnoses of participants who did not have acute aortic dissection. The D-dimer level would be expected to be high in patients with pulmonary embolism, whereas those with other diagnoses such as nonspecific chest pain, gastrointestinal pathology, or acute coronary syndromes would be expected to have lower levels. The varying prevalence of these alternate diagnoses between studies produced the variability in the estimates of specificity and positive likelihood ratio.

To safely exclude acute aortic dissection on the basis of a D-dimer level below a predetermined cutoff requires replication of the diagnostic strategy developed for D-dimer to rule out pulmonary embolism. This strategy relied on the following steps[23]:

1. Reliable assessment of pretest probability for acute aortic dissection, using a clinical decision rule
2. Precise and reliable estimate of the negative likelihood ratio for D-dimer, leading to a precise posttest probability for acute aortic dissection
3. Clinical outcome studies to validate the safety of this rule-out strategy

The first step was addressed by the American Heart Association in their 2010 guidelines, with the introduction of the acute aortic dissection risk score to risk-stratify patients with suspected acute aortic dissection[3] (Figure 3). This bedside risk assessment looks for high-risk features in 3 categories: predisposing conditions, pain features, and examination findings. A patient is classified as being low risk only in the absence of high-risk features in all 3 categories. The risk score has since been validated on a prospective registry of 1,328 patients with suspected acute aortic dissection who presented to EDs. The study population had a prevalence of acute aortic dissection of 22%. With an acute aortic dissection score=0 (low risk), 1 (intermediate risk), or greater than 1 (high risk), the prevalence of acute aortic dissection was 6%, 27%, and

39%, respectively.[24] A high sensitivity for identifying patients with acute aortic dissection was also confirmed in a review of 2,538 cases of acute aortic dissection. The score identified 96% of cases of acute aortic dissection classified by the score as moderate or high risk.[25] The ability of a clinical score to risk-stratify is further supported by 2 other studies that used clinical parameters to successfully identify low-risk populations.[26,27]

Evidence for the second step in the strategy to rule out acute aortic dissection with D-dimer testing is provided by this meta-analysis. With a cutoff of 0.50 μg/mL, the negative likelihood ratio was determined to be 0.05. When the D-dimer test is applied to a low-risk population determined by the American Heart Association risk-stratification tool (prevalence 6%), the posttest probability is 0.3%, or, stated another way, 1 missed case for every 333 low-risk patients evaluated. Even if the worst estimate is considered (the upper bound of the CI for the negative likelihood ratio: 0.09), the posttest probability is 0.6%, or 1 missed case for every 167 low-risk patients evaluated. Patients at moderate or high risk of acute aortic dissection would not be appropriate for D-dimer testing because the posttest probability cannot be decreased to an acceptable level of risk, and these patients should have definitive advanced imaging without D-dimer testing. One relevant article in this systematic review[20] was not included in the meta-analysis because of the slightly lower D-dimer threshold used. Despite the lower threshold, the sensitivity remained very high and supports the conclusions of the meta-analysis (Table 6).

Prospective observational studies, or randomized trials comparing outcomes of the 2 diagnostic strategies, are now needed to complete the third step in validating the safety of using this rule-out strategy.

The aim of incorporating D-dimer testing into the diagnostic algorithm for acute aortic dissection is to reduce the need for advanced imaging in low-risk patients and to increase the pretest probability of acute aortic dissection in patients undergoing such imaging. In this meta-analysis, approximately 40% of all D-dimer test results were false positive. Clinicians should be mindful that inappropriate application of a D-dimer test to patients with nonspecific symptoms for whom they would not normally consider commencing a diagnostic evaluation for acute aortic dissection could result in a paradoxic increase in the amount of CT scans performed to exclude acute aortic dissection because of false-positive D-dimer test results.[28] Rule-out testing with D-dimer should be considered only in low-risk patients whom the clinician would otherwise image if the D-dimer test were unavailable.

It would be pertinent to comment on the many case reports of patients with confirmed acute aortic dissection but a negative D-dimer result.[29-31] It should first be recognized that these cases did not have a risk-stratification applied and also that no test, no matter how good, including the reference standards for the disease, has 100% accuracy. These cases mostly represent a subgroup of patients with a thrombosed false lumen or an intramural hematoma who seem particularly likely to have a lower or negative D-dimer result. The studies in this meta-analysis included such patients, which means that the high sensitivity and excellent negative likelihood ratio were achieved with the inclusion of these problematic cases.

The D-dimer test may be a useful biomarker for use in the risk stratification of acute aortic dissection. This meta-analysis suggests that in conjunction with the American Heart Association risk-stratification tool, a negative D-dimer result may be useful to rule out acute aortic dissection in low-risk patients.

Supervising editor: Deborah B. Diercks, MD

Author affiliations: From the Emergency Department, St George Hospital, Sydney, New South Wales, Australia (Asha, Miers); and the Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia (Asha).

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Publication dates: Received for publication November 26, 2014. Revision received January 7, 2015. Accepted for publication February 17, 2015. Available online March 21, 2015.

REFERENCES

1. Mészáros I, Mórocz J, Szlávi J, et al. Epidemiology and clinicopathology of aortic dissection. *Chest*. 2000;117:1271-1278.
2. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283:897-903.
3. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation*. 2010;121:e266-e369.
4. Shimony A, Filion KB, Mottillo S, et al. Meta-analysis of usefulness of d-dimer to diagnose acute aortic dissection. *Am J Cardiol*. 2011;107:1227-1234.
5. Marill KA. Serum D-dimer is a sensitive test for the detection of acute aortic dissection: a pooled meta-analysis. *J Emerg Med*. 2008;34:367-376.
6. Sutherland A, Escano J, Coon TP. D-dimer as the sole screening test for acute aortic dissection: a review of the literature. *Ann Emerg Med*. 2008;52:339-343.

7. Sodeck G, Domanovits H, Schillinger M, et al. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. *Eur Heart J*. 2007;28:3067-3075.
8. VanderLinden C, Jones J, Brown M. Detection of acute thoracic aortic dissection with D-dimer. *Emerg Med J*. 2007;24:846-847.
9. Davies T. Can D-dimer aid the diagnosis of aortic dissection in the emergency department? Enlightenme electronic learning initiative for emergency medicine. 2012. (Cited September 6, 2014.) Updated March 15, 2012. Available at: http://www.enlightenme.org/knowledge-bank/cem-ctr/can-d-dimer-aid-diagnosis-aortic-dissection-emergency-department. Accessed July 29, 2014.
10. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA*. 1999;282:1061-1066.
11. Deville WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Med Res Methodol*. 2002;2:9.
12. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;3:25.
13. Klompas M. Does this patient have an acute thoracic aortic dissection? *JAMA*. 2002;287:2262-2272.
14. Leeflang MM, Deeks JJ, Gatsonis C, et al. Systematic reviews of diagnostic test accuracy. *Ann Intern Med*. 2008;149:889-897.
15. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med*. 2003;138:W1-12.
16. Akutsu K, Sato N, Yamamoto T, et al. A rapid bedside D-dimer assay (cardiac D-dimer) for screening of clinically suspected acute aortic dissection. *Circ J*. 2005;69:397-403.
17. Fan QK, Wang WW, Zhang ZL, et al. Evaluation of D-dimer in the diagnosis of suspected aortic dissection. *Clin Chem Lab Med*. 2010;48:1733-1737.
18. Nazerian P, Morello F, Vanni S, et al. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. *Int J Cardiol*. 2014;175:78-82.
19. Suzuki T, Distante A, Zizza A, et al. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-bio) experience. *Circulation*. 2009;119:2702-2707.
20. Xue C, Li Y. Value of d-dimers in patients with acute aortic dissection. *J Nanjing Med University*. 2007;21:86-88.
21. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37:360-363.
22. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med*. 2001;135:98-107.
23. Hugli OW. Letter by Hugli regarding article, "Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience". *Circulation*. 2010;121:e23; author reply e4.
24. Nazerian P, Giachino F, Vanni S, et al. Diagnostic performance of the aortic dissection detection risk score in patients with suspected acute aortic dissection. *Eur Heart J Acute Cardiovasc Care*. 2014;3:373-381.
25. Rogers AM, Hermann LK, Booher AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the International Registry of Acute Aortic Dissection. *Circulation*. 2011;123:2213-2218.
26. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Med*. 2000;160:2977-2982.
27. Shirakabe A, Hata N, Yokoyama S, et al. Diagnostic score to differentiate acute aortic dissection in the emergency room. *Circ J*. 2008;72:986-990.
28. Kabrhel C, Matts C, McNamara M, et al. A highly sensitive ELISA D-dimer increases testing but not diagnosis of pulmonary embolism. *Acad Emerg Med*. 2006;13:519-524.
29. Paparella D, Malvindi PG, Scrascia G, et al. D-dimers are not always elevated in patients with acute aortic dissection. *J Cardiovasc Med*. 2009;10:212-214.
30. Hazui H, Nishimoto M, Hoshiga M, et al. Young adult patients with short dissection length and thrombosed false lumen without ulcer-like projections are liable to have false-negative results of D-dimer testing for acute aortic dissection based on a study of 113 cases. *Circ J*. 2006;70:1598-1601.
31. Ohlmann P, Faure A, Morel O, et al. Lower circulating Sta-Liatest D-Di levels in patients with aortic intramural hematoma compared with classical aortic dissection. *Crit Care Med*. 2009;37:899-901.
32. Suzuki T, Distante A, Zizza A, et al. Response to letter regarding article, "Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience". *Circulation*. 2010;121:e24.
33. Suzuki T, Distante A, Zizza A, et al. 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.