Review: negative ELISA results are best for excluding a diagnosis of deep venous thrombosis or pulmonary embolism

Stein PD, Hull RD, Patel KC, *et al.* D dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004;**140**:589–602.

Clinical impact ratings GP/FP/Primary care ★★★★★☆☆ IM/Ambulatory care ★★★★★☆☆ Internal medicine ★★★★★☆☆ Haematology ★★★★★☆☆ Respiriology ★★★★★☆☆

What are the test characteristics of various D-dimer assays for diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE)?

METHODS

Data sources: PubMed (1983 to January 2003), EMBASE/Excerpta Medica (1988 to January 2003), and bibliographies of retrieved articles.

Study selection and assessment: published prospective trials in any language that included a specific statement that DVT or PE was being diagnosed, used objective tests for diagnosis, included a broad spectrum of consecutive patients with suspected DVT or PE, included patients with and without disease, independently interpreted D-dimer and diagnostic standard results, made the decision to perform the diagnostic standard independent of D-dimer test results, included a sufficiently detailed test description, specifically stated the cutoff value for a negative D-dimer test result, and reported sensitivity and specificity or data that allowed for calculation.

Outcomes: sensitivity, specificity, and likelihood ratios.

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Test characteristics of D-dimer assays for diagnosis of deep venous thrombosis (DVT) and pulmonary embolism (PE)*

D-dimer test	Sensitivity (95% CI)	Specificity (CI)	+LR	–LR
Diagnosis of DVT				
ELISA	95% (91 to 99)	40% (32 to 49)	1.60	0.12
Quantitative rapid ELISA	96% (90 to 100)	44% (34 to 54)	1.71	0.10
Semiquantitative rapid ELISA	90% (83 to 98)	39% (29 to 50)	1.48	0.25
Qualitative rapid ELISA	93% (87 to 99)	46% (35 to 57)	1.73	0.15
Quantitative latex	86% (78 to 94)	61% (51 to 71)	2.20	0.23
Semiquantitative latex	79% (69 to 88)	66% (57 to 75)	2.33	0.32
Whole blood	86% (80 to 93)	67% (61 to 73)	2.62	0.20
Diagnosis of PE				
ELISA	96% (88 to 100)	51% (44 to 59)	1.97	0.08
Quantitative rapid ELISA	97% (87 to 100)	41% (30 to 51)	1.64	0.07
Semiquantitative rapid ELISA	93% (79 to 100)	40% (27 to 54)	1.55	0.18
Qualitative rapid ELISA	91% (68 to 100)	70% (47 to 93)	3.01	0.13
Quantitative latex	89% (80 to 99)	47% (38 to 57)	1.69	0.23
Semiquantitative latex	80% (65 to 94)	56% (42 to 70)	1.81	0.36
Whole blood	83% (74 to 92)	64% (55 to 73)	2.32	0.27

*Based on data from 69 studies of DVT and 42 studies of PE. Diagnostic terms defined in glossary.

MAIN RESULTS

31 of 78 included studies directly compared an ELISA with ≥ 1 other D-dimer assay. Overall prevalence was 36% for DVT and 25% for PE. Diagnostic standards for DVT were primarily compression ultrasonography (16 studies), venography (19 studies), and ultrasonography plus venography (11 studies); diagnostic standards for PE were primarily ventilation-perfusion lung scanning (14 studies) and lung scanning plus pulmonary angiography (12 studies). The table summarises the results.

CONCLUSIONS

For diagnosis of deep venous thrombosis, the ELISA and quantitative rapid ELISA are more sensitive than latex and whole blood agglutination assays; ELISAs have negative likelihood ratios of 0.10–0.25. For diagnosis of pulmonary embolism, the ELISA and quantitative rapid ELISA are more sensitive than semiquantitative latex and whole blood agglutination assays; ELISAs have negative likelihood ratios of 0.7–0.18.

Abstract and commentary also appear in ACP Journal Club.

Commentary

D-dimers are produced when cross linked fibrin is degraded; elevated levels therefore reflect non-specific activation of the coagulation and fibrinolytic systems. Several different assays for measuring D-dimers are available. In the systematic review, Stein *et al* applied stringent inclusion criteria to identify high quality studies that examined the accuracy of various D-dimer assays for diagnosis of acute venous thromboembolism. They convincingly show that all D-dimer assays are not equally sensitive. Specifically, they found that the ELISA and quantitative rapid ELISA are most sensitive and have the lowest negative likelihood ratios. Thus, negative results on an ELISA or quantitative rapid ELISA reliably exclude a diagnosis of venous thromboembolism, at least in patients with low to moderate pretest probability of disease ($<30\%$). Indeed, clinical outcome studies have shown that the risk of subsequent symptomatic thrombosis is very low when D-dimer results are negative in these risk groups.¹² When pretest probability is high or very high, further testing is probably warranted, even when the results of 1 of the highly sensitive assays are negative. For example, a diagnosis of pulmonary embolism was established in 68% of PLOPED participants who were thought to have a high pretest probability of disease.³ In this group, the post-test probability of PE is approximately 15% when ELISA results are negative.

Clinicians should inquire about which D-dimer assays are available in their hospitals and interpret the results accordingly. Although more costly, ELISA and quantitative rapid ELISA have been shown to be cost effective when used in combination with an assessment of pretest probability and other non-invasive tests.⁴

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1 Kruij MJ, Leclercq MG, van der Heul C, *et al.* *Ann Intern Med* 2003;**138**:941–51.

2 Bates SM, Kearon C, Crowther M, *et al.* *Ann Intern Med* 2003;**138**:787–94.

3 The PLOPED Investigators. *JAMA* 1990;**263**:2753–9.

4 Perrier A, Nendaz MR, Sarasin FP, *et al.* *Am J Respir Crit Care Med* 2003;**167**:39–4.