Review: Of the various D-dimer assays, negative ELISA results are most useful 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.

QUESTION

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, EMBASE/Excerpta Medica, and reference lists.

Study selection and assessment: Published prospective trials in any language that included a specific statement that DVT or PE was being diagnosed, objective tests for diagnosis, and a broad spectrum of consecutive patients with suspected DVT or PE, both with and without disease; independently interpreted D-dimer and diagnostic standard results; decided 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 (LRs).

MAIN RESULTS

78 studies met the inclusion criteria, of which 31 directly compared an ELISA with ≥ 1 other D-dimer assay. Overall prevalence of DVT was 36% and of PE was 25%. 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 test characteristics of various D-dimer tests for DVT and PE are summarized in the Table.

CONCLUSIONS

For diagnosis of DVT, the ELISA and quantitative rapid ELISA are more sensitive than latex and whole-blood agglutination assays; ELISAs have negative LRs of 0.10 to 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 LRs of 0.7 to 0.18.

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

D-dimer test for diagnosis of DVT	Sensitivity (95% CI)	Specificity (CI)	+LR	–LR
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
D-dimer test for 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.

COMMENTARY

D-dimers are produced when cross-linked fibrin is degraded; elevated levels therefore reflect nonspecific activation of the coagulation and fibrinolytic systems. In the systematic review, Stein and colleagues 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 LRs. 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 for subsequent symptomatic thrombosis is very low when D-dimer results are negative in these risk groups (1, 2). 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 PIOPED participants who were thought to have a high pretest probability of disease (3). In this group, the posttest 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 noninvasive tests (4).

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References

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