D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review

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CRD summary
This review assessed the sensitivity and specificity of D-dimer assays, and the variability of such measures among studies of the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism (PE). The authors appropriately concluded that, for excluding PE or DVT, a negative result on quantitative rapid enzyme-linked immunosorbent assay is as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding.

Authors' objectives
To assess the sensitivity and specificity of the D-dimer assays, and the variability of such measures among studies for the diagnosis of deep venous thrombosis (DVT) and pulmonary embolisms (PE).

Searching
PubMed (from 1983 to January 2003) and EMBASE (from 1988 to January 2003) were searched for studies published in any language; the search terms were reported. The reference lists of all original articles and review articles were checked.

Study selection
Study designs of evaluations included in the review
Prospective studies of patients recruited consecutively were eligible for inclusion. Studies that were not performed prospectively, did not recruit participants consecutively, or did not provide the cut-off value for a negative D-dimer test result (unless qualitative tests were used), were included in a sensitivity analysis.

Specific interventions included in the review
Studies that used D-dimer to exclude PE or DVT were eligible for inclusion. The cut-off value for a negative D-dimer test result needed to be stated, unless qualitative tests were used. The D-dimer assays included in the review were enzyme-linked immunosorbent assay (ELISA), quantitative rapid ELISA, semi-quantitative rapid ELISA, qualitative rapid ELISA, quantitative latex agglutination, semi-quantitative latex agglutination, and whole blood agglutination assay.

Reference standard test against which the new test was compared
The reference standards used were compression ultrasonography, venography and impedance plethysmography in the included studies of DVT, and pulmonary angiography, ventilation-perfusion lung scanning and impedance plethysmography in the included studies of PE. The studies needed to interpret the results of the D-dimer and diagnostic tests for PE and DVT independently. Test descriptions needed to be sufficiently detailed to permit replication.

Participants included in the review
Studies with populations comprising a broad spectrum of patients were eligible for inclusion. The studies needed to include participants suspected of having PE or DVT, and all studies needed to include patients with or without disease to be included in the review.

Outcomes assessed in the review
Studies that used objective tests to diagnose PE or DVT were eligible for inclusion. Studies that provided the sensitivity and specificity, or the raw data for their calculation, were included.

How were decisions on the relevance of primary studies made?
Two reviewers assessed each study for inclusion. Any disagreements were resolved by discussion.
Assessment of study quality
The authors did not state that they assessed the validity of the included studies, but topics pertaining to quality were part of the inclusion criteria and the analyses were tiered according to study quality.

Data extraction
Two reviewers extracted data for the review. The authors extracted and checked the sensitivity, specificity and likelihood ratio (LR) values of the D-dimer assay used. The cut-off value below which disease was considered to be absent was extracted, as was information on whether D-dimer was used to exclude PE or DVT.

Methods of synthesis
How were the studies combined?
Studies were categorised into three tiers. Tier 1 included studies that compared an ELISA and at least one other D-dimer assay. Tier 2 included the tier 1 studies and all other studies that met all of the inclusion criteria. Tier 3 studies did not meet one or more of the inclusion criteria. Values for the sensitivity and specificity for the different studies and test types were examined graphically using boxplots. The range between the upper and lower quartiles of the values for each assay provided a measure of between-study variability associated with the assay. By applying a restricted maximum likelihood approach, population average estimates for sensitivity and specificity were obtained and then combined to provide estimated LRs. The main exploratory term in the model was a fixed-effect, but to allow for variability in assay performance three random-effects terms were incorporated.

How were differences between studies investigated?
A linear-mixed model approach was used to assess heterogeneity. Studies that were not performed prospectively, did not recruit participants consecutively, or did not provide the cut-off value for a negative D-dimer test result (unless qualitative tests were used), were included in a sensitivity analysis.

Results of the review
Seventy-eight studies (n=15,724) were included in the review. An additional 30 studies that did not meet the inclusion criteria were used in the sensitivity analysis.

DVT.
ELISA and quantitative rapid ELISA provided the best results for DVT: the sensitivities were 0.96 (95% confidence interval, CI: 0.91, 1.00) and 0.96 (95% CI 0.90, 1.00), respectively, and the negative LRs were 0.12 (95% CI: 0.04, 0.33) and 0.09 (95% CI: 0.02, 0.41).

PE.
ELISA and quantitative rapid ELISA provided the best results for PE: the sensitivities were 0.95 (95% CI: 0.85, 1.00) and 0.95 (95% CI: 0.83, 1.00), respectively, and the negative LRs were 0.13 (95% CI: 0.03, 0.58) and 0.13 (95% CI: 0.02, 0.84).

The authors highlighted that ELISA and quantitative rapid ELISA had negative LRs that yielded a high certainty for excluding DVT or PE. The positive LRs generally ranged from 1.5 to 2.5, and did not greatly increase the certainty of diagnosis.

The sensitivity analyses did not affect the findings.

Authors' conclusions
The ELISAs generally dominated the comparative ranking among the D-dimer assays for sensitivity and negative LR. For excluding PE or DVT, a negative result on quantitative rapid ELISA was as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding.
CRD commentary
The review question was clear and used explicit inclusion criteria. A search for published studies in all languages was performed. However, it was unclear whether attempts were made to search for unpublished literature and the effect of publication bias was not assessed. Two reviews assessed studies for inclusion and extracted study data, which should reduce the chance of reviewer error and bias. The included studies were not assessed for validity, although study quality was part of the inclusion criteria and the analyses were tiered according to study quality. The authors appear to have performed appropriate analyses and their conclusions are likely to be reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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Other publications of related interest
These additional published commentaries may also be of interest. Gould MK. Review: of the various D-dimer assays, negative ELISA results are most useful for excluding a diagnosis of deep venous thrombosis or pulmonary embolism. ACP J Club 2004;141:77. Gould MK. Review: of the various D-dimer assays, negative ELISA results are most useful for excluding a diagnosis of deep venous thrombosis or pulmonary embolism. Evid Based Med 2004;9:186.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.