Authors' objectives
To review the evidence of how and when D-dimer testing should be used in the diagnostic evaluation of deep venous thrombosis (DVT) or pulmonary embolism (PE).

Searching
MEDLINE and Current Contents were searched from January 1985 to February 1995 for English language articles, and pertinent references from retrieved articles were examined.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to study design were specified.

Specific interventions included in the review
Studies of D-dimer tests for the diagnosis of DVT or PE were eligible for inclusion. No details relating to the assay method or cut-off point were specified in the inclusion criteria. The D-dimer test is used to detect the presence of plasmin-mediated degradation products of fibrin that contain cross-linked D fragments. The D-dimer test methodologies used in the 13 studies which formed the basis of the primary analysis in this review were: latex agglutination tests (cut-off values, where specified, 200 to 1,500 ng/mL); enzyme-linked immunosorbent assays (ELISA; cut-off values 25 to 550 ng/mL); and immunofiltration (cut-off point 500 ng/mL); whole blood agglutination (no cut-off point specified).

Reference standard test against which the new test was compared
The included studies were required to compare D-dimer test results with those of objective diagnostic tests for DVT or PE; no specific reference standard was described in the inclusion criteria. However, the assessment of the methodological standard of the primary studies included three elements requisite for a study to be included in the review's primary analysis. One of these elements specified that the reference standard should be venography, pulmonary angiography, V/Q lung scanning with clinical correlation, or lower extremity ultrasonography with clinical correlation.

Participants included in the review
No inclusion criteria were specified in relation to the patient characteristics. However, the assessment of the methodological standard of the primary studies included three elements requisite for a study to be included in the review's primary analysis. One of these elements specified that the study participants should represent the complete spectrum of patients with suspected DVT or PE, including those with and without disease.

Outcomes assessed in the review
No inclusion criteria were specified with respect to the outcome measures. Test sensitivity and specificity were the outcome measures reported in the review, and these were illustrated using receiver operating characteristic (ROC) curves.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for review, or how many of the reviewers performed the selection.

Assessment of study quality
The methodological strength of each study was assessed according to a list of 10 standards. These evaluated: the appropriateness of the reference standard; independent interpretation of test results; patient selection; patient characteristics; stratification of results by disease severity; appropriateness of patient spectrum; whether or not the
decision to perform the reference standard test was dependent on the result of the D-dimer test; whether sufficient
details of the reference standard and index tests were reported to permit replication; whether or not sensitivity and
specificity, or the raw data to allow their calculation, were reported; and whether test reproducibility and interpretation
were evaluated in an appropriate setting. ‘Level-1’ studies were defined as those that met the standards relating to
reference standard, patient selection and patient spectrum. Three reviewers assessed each study independently, and
consensus on each study was achieved through discussions involving all four reviewers.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data
extraction.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative summary.

How were differences between studies investigated?
A narrative description of the heterogeneity of study patients, the type of assay and the designated cut-off value, was
presented.

Results of the review
Twenty-nine studies were included in the review; the number of patients included in each study was, on average, 145
(range: 32 to 401). Thirteen ‘level 1’ studies formed the basis on which the review sought to assess the performance of
D-dimer tests; only sensitivity and specificity values from these studies were presented. Almost all of the ‘level 1’
 studies evaluated latex agglutination and ELISAs.

The results of 13 level-1 studies were used to estimate the sensitivity and specificity of the D-dimer tests. The reported
sensitivity ranged from 48 to 96% for the latex agglutination tests, and from 88 to 100% for the ELISAs. The
specificity ranged from 21 to 100% and from 10 to 68% for the latex agglutination tests and ELISAs, respectively.
Overall, the ELISAs had greater sensitivities but lower specificities than latex agglutination assays. The range of
sensitivity and specificity values were illustrated, by cut-off point, on separate ROC curves for latex agglutination tests
and ELISAs.

Authors’ conclusions
The results of studies with one manufacturer’s test cannot be extrapolated to another because of the differences in D-
dimer assays. No single D-dimer assay has emerged as the best. The generalisability of the published estimates of D-
dimer accuracy for DVT or PE is limited because of many methodological problems, e.g. wide variability in assay
performance, heterogeneity among patients, and failure to define the absence or presence of venous thromboembolism
by a comprehensive reference standard for diagnosis. The clinical utility of this potentially-important test remains
unproven.

CRD commentary
The review addressed a clear research question. While no specific inclusion criteria were defined, this issue was
partially addressed by the use of some elements of the methodological quality assessment to define included studies.
The assessment of methodological quality was comprehensive and well conducted, but is of limited value since its
findings were only sparsely reported. The search strategy was poorly described and extremely limited, leaving open the
possibility that relevant studies were not identified. There was little description of the review methodology; this makes
it difficult to assess the rigour of the review process and the extent to which it may have been open to bias. Limited
detail of the included studies was reported. Aspects of the heterogeneity of the included studies were discussed in
detail, and the use of a narrative synthesis in this context seems appropriate. The illustration of the results of included
primary studies on ROC curves increased clarity. The authors’ conclusions were appropriately cautious given the
limitations of the available data.

**Implications of the review for practice and research**

**Practice:** The authors state that, until the above issues have been addressed, D-dimer should not be used as a diagnostic test for venous thromboembolism.

**Research:** The authors state that research is needed to standardise results from various D-dimer assays in a manner similar to the use of the international normalised ratio for comparing prothrombin times obtained from different thromboplastins.

Further research is required to evaluate newer immunofiltration techniques.

Future research should use a comprehensive reference standard for venous thromboembolism, including the determination of the presence or absence of DVT and PE. In addition, more attention should be paid to issues of patient spectrum; the impact on test performance of variables such as extent and type of thrombosis, duration of symptoms, clinical setting, age and co-morbidity should be investigated.

Prospective assessments of the consequences of clinical decisions based on D-dimer test results is required.

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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.