CRD summary
This review assessed the ability of rapid D-dimer testing, in combination with an estimation of clinical probability, to safely rule out deep vein thrombosis (DVT) in symptomatic out-patients.

The authors concluded that 'highly sensitive', quantitative testing could be used to rule out DVT in patients with low or moderate clinical probability, and qualitative testing could safely rule out DVT in patients with low clinical probability. Limited searches, a small number of included studies, and some problems with the analyses, mean that the authors' conclusions should be viewed with caution.

Authors' objectives
To evaluate the use of D-dimer testing, in combination with clinical assessment, to exclude the diagnosis of deep vein thrombosis (DVT) in out-patients.

Searching
MEDLINE (from June 1993 to December 2003) and DARE (31 December 2003) were searched for English language publications; the search terms were reported. The reference lists of the included studies were reviewed to identify additional articles. Editorials, letters and reviews were excluded.

Study selection
Study designs of evaluations included in the review
Prospective diagnostic cohort studies of consecutive patients, with at least 3 months' follow-up by telephone or record review, were eligible for inclusion.

Specific interventions included in the review
The included studies were required to use a rapid D-dimer assay on at least a subgroup of cases, and to estimate the risk of DVT using a validated clinical probability tool which categorised patients into those at low risk, at moderate or intermediate risk, and at high risk for DVT. Only studies of D-dimer assays that provided results within 1 hour were eligible for inclusion.

Five of the 6 included accuracy studies used a qualitative assay (SimpliRED), with 'any agglutination' as the cut-off threshold for a positive test; the remaining study used a quantitative assay (STA-LIA) with a cut-off of 0.5 microg/mL. Two of the 6 included management studies used SimpliRED, and four used different quantitative assays with a range of cut-off values. All but one of the included studies assessed clinical probability using the Wells tool (see Other Publications of Related Interest nos.1-2).

Reference standard test against which the new test was compared
Studies using an objective method of confirming DVT (venous compression ultrasound, venography, or impedance plethysmography), were eligible for inclusion. Eleven of the included studies used venous ultrasound as the reference standard, either alone or in combination with venography or impedance plethysmography. The remaining study used impedance plethysmography.

Participants included in the review
Studies of consecutive out-patients presenting with features of DVT were eligible for inclusion. Studies including in-and out-patients were eligible if the data were evaluated separately. Studies that included patients with pulmonary embolism were also eligible if the data on DVT were evaluated separately.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported sufficient data to calculate the sensitivity and specificity of the D-
dimer assay, stratified by the clinical probability level. The studies were also required to report data that allowed the calculation of prevalence of DVT for each probability level.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed the titles and abstracts of the references identified to determine suitability for inclusion. Any disagreements were resolved by consensus between all three authors. The reviewers were not blinded to the authors, institutions, or journal.

Assessment of study quality
Study quality was assessed using a method adapted from the Cochrane Methods Group on systematic review of screening and diagnostic tests (see Other Publications of Related Interest no.3). The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Two authors independently extracted the data. Any disagreements were resolved by consensus between all three authors. When relevant data were incomplete, an attempt was made to retrieve these data by contacting the primary author. The 3-month cumulative incidence of DVT, with 95% confidence intervals (CIs), was calculated for all groups in each study.

Methods of synthesis
How were the studies combined?
Data from diagnostic accuracy studies were used to derive pooled estimates. Data from the management studies were not pooled on account of small sample sizes. The pooled cumulative incidence was estimated using a random-effects logistic meta-regression model. The model included indicator terms for clinical probability and the presence of prior DVT as variables at study level.

Pooled estimates of sensitivity, specificity, and negative likelihood ratios, with 95% CI, were calculated using a random-effects logistic meta-regression model. The model included an indicator term for use of the SimpliRED D-dimer assay.

How were differences between studies investigated?
No formal assessment of between-study heterogeneity was reported. The data were stratified for analysis according to testing strategy. Separate pooled estimates were calculated for participants with and without prior DVT.

Results of the review
Twelve studies were included in the review: 6 diagnostic accuracy studies (2,199 participants) and 6 management studies (3,242 participants).

Qualitative (SimpliRED) D-dimer assay.

The 3-month incidence of DVT was 0.5% (95% CI: 0.07, 1.1) among patients with low clinical probability and a negative test result, 3.4% (95% CI: 1.3, 6.9) among patients with moderate clinical probability and a negative test result, and 21.0% (95% CI: 8.0, 37.0) among patients with high clinical probability and a negative test result. For low clinical probability, the inclusion of patients with a prior history of DVT resulted in a higher rate of DVT (P=0.04); there was no significant difference between the groups for patients with moderate or high clinical probability. The estimated pooled sensitivity was 87.5% (95% CI: 82.4, 91.7) and the specificity was 76.9% (95% CI: 65.4, 86.2), with a negative likelihood ratio of 0.16.

Quantitative D-dimer assays.

The 3-month incidence of DVT among patients with low or moderate clinical probability and a negative test result was 0.4% (95% CI: 0.04, 1.1). The estimated pooled sensitivity was 97.7% (95% CI: 96.1, 99.0) and the specificity was 45.7% (95% CI: 28.0, 66.6), with a negative likelihood ratio of 0.05.
Authors’ conclusions
For patients with a low clinical probability, a normal result from the qualitative SimpliRED D-dimer test safely excludes a diagnosis of DVT. A normal result from a quantitative D-dimer test safely excludes DVT among patients classified as having low or moderate clinical probability.

CRD commentary
The review addressed a clear research question and used appropriate and well-defined inclusion criteria. The review methodology incorporated methods designed to minimise the introduction of bias and was well reported. Details of the included studies were reported in full. The search was limited to English language publications identified from two databases and this might have resulted in the loss of relevant data. In addition, no attempt to identify unpublished studies was reported and publication bias was not assessed.

The methods used to pool the studies were clearly reported. However, a formal assessment of heterogeneity was lacking, making it difficult to judge the appropriateness of pooling. It was also unclear which studies were used to derive the pooled estimates for quantitative D-dimer assays (the authors stated that management studies were not pooled, and only one diagnostic accuracy study examined a quantitative assay). The authors stated that diagnostic accuracy parameters were calculated from a logistic meta-regression model. However, the likelihood ratios appear to have been calculated from pooled estimates of sensitivity and specificity. Given the small number of included studies and the limitations outlined, the authors’ conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors stated that among out-patients with suspected DVT, in whom the clinical probability of DVT is judged to be low or moderate, a normal quantitative D-dimer test result excludes DVT and makes ultrasound unnecessary. Among patients classified as having low clinical probability of DVT, using the original Wells criteria, a normal qualitative (SimpliRED) D-dimer test result safely excludes the presence of DVT.

Research: The authors did not state any implications for further research.

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**Record Status**
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.