Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis

CRD summary
This generally well-conducted review concluded that D-dimer tests at the point of care for outpatients with suspected venous thromboembolism can contribute important information and guide patient management, particularly in low-risk patients. These conclusions reflect the results of the review and despite a relatively limited search appear likely to be reliable.

Authors' objectives
To assess the diagnostic accuracy of currently available point of care D-dimer tests for the exclusion of venous thromboembolism.

Searching
MEDLINE and EMBASE were searched for articles published between 1995 and September 2008. Search terms were reported. References of identified studies were checked. Experts were contacted. Only studies published in English were eligible for inclusion in the review.

Study selection
Studies that evaluated the diagnostic accuracy of point of care D-dimer tests for the exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) and reported sensitivity, specificity, negative and positive predictive values and prevalence for deep vein thrombosis or pulmonary embolism were eligible for inclusion in the review. Point of care was defined as a test performed in a near patient situation in office or emergency room, not on a routine laboratory machine. Eligible studies had a population of consecutive adult outpatients with clinical suspicion of deep vein thrombosis or pulmonary embolism in a primary or secondary care setting. Studies were required to use compression ultrasonography, venography, impedance plethysmography or uneventful follow-up for three months as a reference standard for deep vein thrombosis and computerised tomography pulmonary angiography, ventilation-perfusion lung scanning, pulmonary angiography, or uneventful follow-up as a reference standard for pulmonary embolism.

Included studies evaluated both qualitative (SimpliRED D-dimer and Clearview Simplify D-dimer) and quantitative (Cardiac D-dimer and Triage D-dimer) tests. Most studies evaluated patients with suspected deep vein thrombosis. Mean ages of patients in included studies ranged from 38 to 65 years. The percentage of males ranged from 30% to 55%. Prevalence of venous thromboembolism ranged from 3% to 51%. Most included studies used venography, compression ultrasonography or a combination of imaging and clinical follow-up as the reference test.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Studies were independently assessed for validity by two reviewers using the QUADAS tool. Disagreements were resolved by consultation with two additional reviewers.

Data extraction
Two reviewers independently extracted the data, including the number of true and false positives and negatives to permit the construction of a 2x2 table. Discrepancies were resolved through discussion and consultation with a third or fourth reviewer where necessary. Authors were contacted for missing data.

Methods of synthesis
The studies were combined in a bivariate random-effects model meta-analysis for both sensitivity and specificity. Heterogeneity was assessed using the I² statistic and explored using meta-regression analysis where a D-dimer test was
assessed in at least 10 studies; otherwise subgroup analyses based on the covariates were performed. Covariates for these planned analyses were defined a priori and were: deep vein thrombosis versus pulmonary embolism; proportion of patients with a proximal deep vein thrombosis; proportion of patients with a recurrent deep vein thrombosis; proportion of patients with active malignancy; and proportion of patients who had had surgery within four weeks. Also planned were assessments using QUADAS criteria, in particular differential verification and incorporation bias. However, only analyses based on deep vein thrombosis versus pulmonary embolism and presence of differential verification and incorporation biases for SimpliRED D-dimer and Clearview Simplify D-dimer were possible. Publication bias was assessed using a regression test on the diagnostic odds ratio (DOR).

Results of the review
Twenty-three studies (n=13,959) were included in the review. The percentages diagnosed with venous thromboembolism were 18.7% for SimpliRED D-dimer, 8.2% for Clearview Simplify D-dimer, 33.9% for Cardiac D-dimer and 13.2% for Triage D-dimer. All of the included studies were prospective and their overall quality was good, although blinding of index and reference test results was poorly reported as was the presence of uninterpretable test results. Differential verification and incorporation bias were the problems most frequently found.

The overall pooled sensitivity was 0.88 (95% CI: 0.83 to 0.92) and specificity was 0.70 (95% CI: 0.62 to 0.77). Heterogeneity was highly significant ($I^2=80\%$ for sensitivity and 96% for specificity).

SimpliRED D-dimer: Pooled sensitivity was 0.85 (95% CI: 0.78 to 0.90) and specificity was 0.74 (95% CI: 0.69 to 0.78) based on 12 studies (n=6,796).

Clearview Simplify D-dimer: Pooled sensitivity was 0.87 (95% CI: 0.81 to 0.91) and specificity was 0.62 (95% CI: 0.54 to 0.69) based on seven studies (n=5,730).

Cardiac D-dimer: Pooled sensitivity was 0.96 (95% CI: 0.91 to 0.98) and specificity was 0.57 (95% CI: 0.52 to 0.62) based on four studies (n=925).

Triage D-dimer: Pooled sensitivity was 0.93 (95% CI: 0.88 to 0.97) and specificity was 0.48 (95% CI: 0.33 to 0.62) based on a traditional analysis weighted by sample size, as a bivariate approach was not possible with only two studies (n=508).

Results of the analyses of covariates and of the impact of negative D-dimer test results on differing pre-test probabilities were also reported. The sensitivity and specificity did not vary across the covariates investigated for SimpliRED and Clearview Simplify tests. There was no evidence of publication bias.

Authors' conclusions
Point of care D-dimer tests can contribute important information and guide patient management in outpatients with suspected venous thromboembolism, particularly in low-risk patients. Quantitative tests appeared to perform better than qualitative tests, but available data remained limited. Few studies existed of these tests in patients with suspected pulmonary embolism.

CRD commentary
The review question and the inclusion criteria were clear and specific. The authors searched two relevant databases. The decision to restrict the review to published studies reported in English may have increased the likelihood of publication and language biases and the possibility that some relevant studies were not included. Publication bias was assessed and no evidence for it was found. The authors reported using methods designed to reduce reviewer bias and error in the extraction of data and the assessment of validity, but not in the selection of studies. Validity was appropriately assessed and used to inform the synthesis. The statistical synthesis appeared appropriate and reasonable steps were taken to explore sources of heterogeneity between studies. The authors' conclusions accurately reflect the results of the review and despite the relatively limited search appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that point of care D-dimer tests can safely exclude venous thromboembolism in low-risk outpatients. The choice of which point of care test to use depended on the setting, with simplicity of procedure,
accuracy and ability to concurrently test for other cardiovascular biomarkers all being relevant considerations.

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

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