Diagnostic accuracy of conventional or age-adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis

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CRD summary
This review found that the use of age-adjusted cut-offs in D-dimer tests for venous thromboembolism increased specificity without affecting sensitivity when compared with conventional cut-offs. This was a large and well-conducted review and its results are likely to be reliable.

Authors' objectives
To review the diagnostic accuracy of D-dimer testing in older patients with suspected venous thromboembolism.

Searching
MEDLINE and EMBASE were searched in June 2012 without language restriction. The search strategy was presented in an appendix.

Study selection
Diagnostic accuracy studies in consecutive patients with clinical suspicion of venous thromboembolism were eligible. Studies had to assess quantitative D-dimer testing using both age-adjusted and conventional cut-off values. Studies in patients at high risk of thrombosis were excluded.

Mean ages in the cohorts ranged from 49 to 66. The proportion of men ranged from 27% to 52%. Both enzyme linked fluorescent assays and quantitative latex agglutination D-dimer assays were used. Patients generally had a Geneva score of less than 10 or a Wells score of less than 4 when assessing risk of thrombosis. Six cohorts concerned patients with deep vein thrombosis and seven concerned patients with pulmonary embolism. One study was conducted in primary care, the rest used patients attending hospital.

Study selection was performed by two reviewers and referred to a third to resolve discrepancies.

Assessment of study quality
Study quality was assessed using the QUADAS-2 tool for diagnostic accuracy studies. The number of reviewers that performed quality assessment was not stated.

Data extraction
True and false positive and negative rates were extracted from each study, stratified by age and by D-dimer cut-off values. Data extraction was performed by two reviewers. Study authors were contacted for additional information if data were incomplete.

Methods of synthesis
Sensitivity and specificity of D-dimer testing were calculated for both standard and age-adjusted cut-offs, stratified by age. A random-effects bivariate model was used to meta-analyse sensitivity and specificity values. Covariates were added to the model to assess the effect on diagnostic accuracy of: prevalence of venous thromboembolism, type of D-dimer assay and whether patients were suspected of having deep vein thrombosis or pulmonary embolism.

Results of the review
Five studies were included, with 22,608 patients, of which 12,630 were not at high risk, made up of 13 cohorts (sample size range: 359 to 7,940). Study quality was judged to be good, although different reference tests were often used in patients with positive and negative test results.

The sensitivity of D-dimer testing was similar at all ages. For conventional cut-off it was 99.6% (95% CI 96.9 to 99.9) in patients aged over 80, and 100% in those aged 51-60. For age-adjusted cut-offs sensitivities ranged from 97.0% (95% CI 92.9 to 98.8) in patients aged over 80, to 99.4% (95% CI 97.3 to 99.9) in those aged 51-60.
Specificity varied between ages and between conventional and age-adjusted cut-offs. For conventional cut-offs it ranged from 14.7% (95% CI 11.3 to 18.6) in patients aged over 80, to 57.6% (95% CI 51.4 to 63.6) in those aged 51-60. For age-adjusted cut-offs specificities were greater, ranging from 35.2% (95% CI 29.4 to 41.5) in patients aged over 80, to 62.3% (95% CI 56.2 to 68.0) in those aged 51-60.

There was no association between the accuracy of D-dimer testing and the prevalence of thromboembolism, or whether patients were suspected of having deep vein thrombosis or pulmonary embolism. There was a significantly higher sensitivity and higher specificity (but not statistically significant) where both enzyme linked fluorescent assays and quantitative latex agglutination D-dimer assays were used rather than only enzyme linked fluorescent assays.

**Authors’ conclusions**
The use of age-adjusted cut-offs in D-dimer tests increased specificity without affecting sensitivity when compared with conventional cut-offs in patients aged 50 or over without high risk of thrombosis. The specificity of this test was poor in patients aged over 80.

**CRD commentary**
This was a well-conducted review, with appropriate inclusion criteria. A suitable search was performed and a substantial number of cohorts and patients were included. Action was taken to reduce reviewer error and bias in the study selection and data extraction processes. Study quality was assessed and judged to be good, but the authors noted that different reference standards were used in test-positive and test-negative patients, which may have led to bias in the results. A suitable meta-analysis was conducted to synthesise the studies. Given the large size of this review, the results and authors’ conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors suggested that age-adjusted cut-offs should be used in D-dimer testing for venous thromboembolism.

**Research:** The authors suggested that cost-effectiveness and prospective impact studies were needed to confirm the value of this diagnostic strategy.

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