Critical Review Form
Meta-analysis

Schouten HJ, Geersing GJ, Koek HL, et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ. 2013 May 3;346:f2492.

Objectives: "to assess the diagnostic value of D-dimer testing for excluding suspected venous thromboembolism in older patients, with a particular interest in whether increasing the threshold for test positivity using the proposed age adjusted manner is a safe and more efficient strategy than using the conventional cut-off value." (p. 2)

Methods: The authors searched Embase and MEDLINE on June 12, 2012 and included original diagnostic studies that enrolled **consecutive patients** with a suspicion of venous thromboembolism in whom quantitative D-dimer testing was performed using both conventional and age-adjusted cutoff values, and in which reference testing was applied in all patients. Studies carried exclusively in patients at high-risk of venous thromboembolism were excluded.

Using the data, 2X2 contingency tables were constructed and sensitivities and specificities were calculated for each cohort using only patients with a non-high pre-test clinical probability of disease (**revised Geneva score** ≤ 10 or **Well's score** ≤ 4 in PE cohorts; **Well's score** ≤ 2 or ≤ 1 or clinical probability < 80% in DVT cohorts). The patients were stratified by pre-defined age categories (≤ 50, 51-60, 61-70, 71-80, and > 80 years) and by different D-dimer cutoff values. A **random effects model** was used to pool the individual cohorts in the meta-analysis. Risk of bias was assessed using the **QUADAS-2 tool**.

Five publications comprising 13 different patient cohorts were selected, with a total of 22,608 patients. Of these, 12,630 had a non-high pretest clinical probability of disease. Seven of the cohorts concerned patients with suspected PE, and the other 6 concerned patients with suspected DVT.

Guide	Question	Comments
I	*Are the results valid?*	
1.	Did the review explicitly address a sensible question?	Yes. Several studies have demonstrated that the specificity of D-dimer decreases with age, and that those over 50 at especially high risk of a false positive result. The use of an

		age-adjusted cutoff for patients over 50 has the potential to reduce unnecessary additional testing in non-high risk patients with concern for PE (or DVT).
2.	Was the search for relevant studies detailed and exhaustive?	No. The authors conducted a search of Embase and MEDLINE, but did not search additional databases (The Cochrane Database, CINAHL). They do not mention searching reference lists of selected articles, conference abstracts, or the grey literature. They search strategy
3.	Were the primary studies of high methodological quality?	Mostly yes. All but one of the studies (Schouten 2012) was at high risk of differential or partial verification bias. Almost all of the studies were at low risk of selection bias as they used consecutive patients, and used an objective D-dimer test.
4.	Were the assessments of the included studies reproducible?	Yes. The authors assessed the quality of studies using the QUADAS-2 tool, a validated tool for evaluating the risk of bias and applicability of primary diagnostic accuracy studies.
II.	*What are the results?*	
1.	What are the overall results of the study?	• Using a conventional cutoff, the pooled specificity of D-dimer decreased substantially with increasing age. Use of an age-adjusted cutoff resulted in a less dramatic decrease in specificity with a small decrease in sensitivity (Table 1).

Table 1. Sensitivity and Specificity of D-dimer for all VTE (95% CI)

Age	Sensitivity		Specificity	
	Conventional	Age-adjusted	Conventional	Age-adjusted
≤ 50	97.6 (95.0-98.9)	NA	66.8 (61.3-72.0)	NA
51-60	100.0 (NA)	99.4 (97.3-99.9)	57.6 (51.4-63.6)	62.3 (56.2-68.0)
61-70	99.0 (96.6-99.7)	97.3 (93.8-98.8)	39.4 (33.5-45.6)	49.5 (43.2-55.8)
71-80	98.7 (96.5-99.5)	97.3 (94.3-98.8)	24.5 (20.0-29.7)	44.2 (38.0-50.5)
>80	99.6 (96.9-99.9)	97.0 (92.9-98.8)	14.7 (11.3-18.6)	35.2 (29.4-41.5)

• For pulmonary embolism, in patients > 50 years of age with non-high pretest clinical probability, the pooled specificity of D-dimer increased from 34.0% (95% CI 27.7-40.9) with a conventional cutoff to 45.7% (95% CI 38.5-53.1) with an age-adjusted cutoff.
• There was a small corresponding decrease in sensitivity from 99.2% (95% CI 97.9-99.7) to 97.5% (94.7-98.8).
• For the age-adjusted cutoff in patients > 50 with non-high

		clinical probability of PE, the positive likelihood ratio was 1.79, and the negative likelihood ratio was 0.05.
2.	How precise are the results?	See above. The authors do not provide sufficient information to calculate 95% CIs for the likelihood ratios provided.
3.	Were the results similar from study to study?	Uncertain. The authors provide no measurement of heterogeneity between studies (I^2 values, Cochrane's Q, p-values).
III.	*Will the results help me in caring for my patients?*	
1.	How can I best interpret the results to apply them to the care of my patients?	This study, despite its limitations, does demonstrate that an age-adjusted cutoff for D-dimer in the evaluation of venous thromboembolism, and PE specifically, results in a large increase in the specificity of the test in older age groups with only a small decrease in sensitivity. The overall negative LR for PE in patients over 50 was 0.05, indicating a substantial decrease in the probability of disease with a negative test. The use of such a cutoff in patients without a high pretest probability of disease should adequately rule out PE. Unfortunately, the authors provide no measure of heterogeneity between the included studies, and do not provide sufficient data to calculate a 95% CI for the negative LR.
2.	Were all patient important outcomes considered?	No. The authors provide pooled sensitivities and specificities, but do not provide these measures specifically for PE based on age group. They also do not provide likelihood ratios or the corresponding 95% confidence intervals. Based on the data available, the authors were unable to provide an estimate of the actual number of PE's missed in various age groups using an age-adjusted cutoff.
3.	Are the benefits worth the costs and potential risks?	Uncertain. Unfortunately, nearly all of the studies included in this meta-analysis were at high risk of verification bias as they did not apply the reference standard to all patients, but rather only to those with a high pretest clinical probability or a positive D-dimer test. Additionally, the authors do not provide measures of heterogeneity for the included studies, making it difficult to know if the resulting pooled estimates of specificity and sensitivity are valid.

Limitations:

1. **Although the authors reports that overall study quality was "good," in all but one of the included studies, patients with a negative index test did NOT undergo confirmatory testing with the "gold standard" (partial verification bias).**

2. The authors do not provide any measurement of **heterogeneity** for their pooled results (**I^2 statistic, Cochrane's Q, p-values**).

3. The authors chose to pool the results from cohorts being evaluated for DVT and for PE, introducing significant **clinical heterogeneity**.

4. The authors do not reports likelihood ratios, and do not provide sufficient information to calculate 95% CI's for likelihood ratios.

Bottom line:

This comprehensive systematic review and meta-analysis demonstrates a significant increase in the specificity of D-dimer for venous thromboembolism in older patients with only a modest decrease in sensitivity. The overall negative likelihood ratio for PE in patients over 50 was 0.05, demonstrating a significant ability to reduce the probability of disease with a negative test result. Unfortunately, the included studies were of fair quality overall, owing specifically to a high risk of verification bias.