



It's time to use an age-based approach to D-dimer

An age-adjusted D-dimer cutoff—rather than the conventional 500 mcg/L value—is a better way to rule out VTE in patients over 50.

PRACTICE CHANGER

Use an age-adjusted D-dimer cutoff (patient's age in years \times 10 mcg/L) for patients over age 50 years when evaluating for venous thromboembolism (VTE); it reduces false positives without substantially increasing false negatives.¹

STRENGTH OF RECOMMENDATION

A: Based on consistent and good quality patient-centered evidence from a meta-analysis of cohort studies.

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;346:f2492.

ILLUSTRATIVE CASE

A 78-year-old woman with no significant past medical history or recent immobility comes into your clinic complaining of left lower extremity pain and swelling. Her D-dimer is 650 mcg/L. What is your next step?

Although D-dimer is recognized as a reasonable screening tool for VTE, the specificity of D-dimer testing using a conventional cutoff value of 500 mcg/L is particularly poor in patients over 50 years. In low-risk patients over 80 years old, the specificity is 14.7% (95% confidence interval, 11.3%-18.6%).²⁻⁵ As a result, conventional D-dimer testing is not very helpful for ruling out VTE in older patients.²⁻⁵

Improved testing is needed for a population at heightened risk

In the United States, there are more than 600,000 cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) each year.² The incidence of PE increases from 1:1000 in younger patients to 8:1000 in older patients⁴ and the mortality rate can reach 30%.⁶ The gold standards of venography and pulmonary angiography have been replaced by less burdensome tests, primarily lower extremity duplex ultrasound and computed tomography pulmonary angiogram. However, even these tests are expensive and often present logistical challenges in elderly patients. For these reasons, it is helpful to have a simple, less-expensive tool to rule out VTE in older patients who have signs or symptoms.

STUDY SUMMARY

Using age-adjusted D-dimer cutoffs significantly reduced false positives

Schouten et al¹ performed a systematic review and meta-analysis of studies of older patients with suspected VTE who had D-dimer testing using both conventional and age-adjusted cutoff values. The authors searched Medline and Embase for studies published before June 21, 2012 that were performed in outpatient, inpatient, or emergency department settings. They excluded studies of high-risk patients, specifically perioperative patients and those who'd had VTE, cancer, or a coagulation disorder.

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TABLE

Specificity of D-dimer screening for VTE significantly improves with age-adjusted cutoff¹

Age (y)	Patients (N)	Sensitivity, % (95% CI)		Specificity, % (95% CI)	
		Conventional cutoff	Age-adjusted cutoff	Conventional cutoff	Age-adjusted cutoff
≤50	5528	97.6 (95-98.9)	N/A	66.8 (61.3-72)	N/A
51-60	2043	100 (N/A)	99.4 (97.3-99.9)	57.6 (51.4-63.6)	62.3* (56.2-68)
61-70	1815	99 (96.6-99.7)	97.3 (93.8-98.8)	39.4 (33.5-45.6)	49.5* (43.2-55.8)
71-80	1842	98.7 (96.5-99.5)	97.3 (94.3-98.8)	24.5 (20-29.7)	44.2* (38-50.5)
>80	1269	99.6 (96.9-99.9)	97 (92.9-98.8)	14.7 (11.3-18.6)	35.2* (29.4-41.5)

CI, confidence interval; N/A, not applicable; VTE, venous thromboembolism.

*P<.05 between the age-adjusted (patient's age in years x 10 mcg/L) and conventional (500 mcg/L) cutoffs.

Five high-quality studies of 13 cohorts were included in this analysis (N=12,497; 6969 patients >50 years). Each of these studies was a retrospective analysis of patients with a low clinical probability of VTE, as determined by Geneva or Wells scoring. The authors calculated the VTE prevalence and D-dimer sensitivity and specificity for patients ages ≤50, 51 to 60, 61 to 70, 71 to 80, and >80 years.

The specificity of using the conventional D-dimer cutoff value for VTE (500 mcg/L) decreased with age from 57.6% in those ages 51 to 60 to 14.7% in those older than 80. When age-adjusted cutoffs were used (age in years x 10 mcg/L), specificities improved in all age categories, particularly for older patients. For example, using age-adjusted cutoff values improved specificity to 62.3% in patients ages 51 to 60 and to 35.2% in those older than 80 (TABLE). Using a hypothetical model, Schouten et al¹ calculated that applying age-adjusted cutoff values would exclude VTE in 303/1000 patients >80 years, compared with 124/1000 when using the conventional cutoff.

The benefit of using an age-adjusted cutoff is the ability to exclude VTE in more patients (1 out of 3 in those older than age 80) while not significantly increasing the number of missed VTE. In fact, the num-

ber of missed cases in the older population using the age-adjusted cutoff (approximately 1 to 4 per 1000 patients) is comparable to the false negative rate in those ages ≤50 (3 per 1000). The advantages of an age-adjusted cutoff are most notable with the use of enzyme linked fluorescent assays because these assays have a higher sensitivity and a trend toward lower specificity compared with other assays.

WHAT'S NEW

We can now make use of the D-dimer in older patients

Up until now, it was acknowledged that the simple and less expensive D-dimer test was less useful for our older patients. In fact, in their 2007 clinical practice guideline on the diagnosis of VTE in primary care, the American Academy of Family Physicians and the American College of Physicians commented on the poor performance of the test in older patients.² A more recent guideline—released by the Institute for Clinical Systems Improvement in January 2013—provided no specific guidance for patients over age 50.⁷ The meta-analysis reported on here, however, provides that guidance: Using an age-adjusted D-dimer cutoff improves the diagnostic accuracy of D-dimer screening in older adults.

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CAVEATS

Results are not generalizable to patients at higher risk

These findings are not generalizable to all patients, particularly those at higher clinical risk who would undergo imaging regardless of D-dimer results. Not all patients included in this meta-analysis whose D-dimer was negative received imaging to confirm that they did not have VTE. As a result, the diagnostic accuracy of using an age-adjusted cutoff could have been overestimated, although this is likely not clinically important because these cases would have remained symptomatic within the 45-day to 3-month follow-up period.

CHALLENGES TO IMPLEMENTATION

You, not the lab, will need to do the calculation

One of the more valuable aspects of this study is it identifies a simple calculation that can directly improve patient care. Physicians can easily apply an age-adjusted D-dimer cutoff as they interpret lab results by multiplying the patient's age in years \times 10 mcg/L. While this does not require institutional changes by the lab, hospital, or clinic, it would be helpful if the age-adjusted D-dimer calculation was provided with the lab results. **JFP**

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