Critical Review Form
Diagnostic Test

PGY-1

Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014 Mar 19;311(11):1117-24.

Objectives: **To prospectively validate a protocol in which "in which consecutive outpatients with suspected PE were left un- treated on the basis of a negative age-adjusted D-dimer test result, in combination with a clinical probability assessment." (p. 1118)**

Methods: **This was a prospective, multicenter, multinational study conducted at 19 hospitals in 4 European countries: Belgium, France, the Netherlands, and Switzerland. Consecutive patients presenting to the emergency department (ED) with a clinical suspicion of PE were eligible for enrollment. Exclusion criteria were suspicion of PE arising more than 24 hours after hospital admission, preexisting treatment with an anticoagulant, allergy to contrast media, impaired renal function (creatinine clearance < 30 mL/min), life expectancy of less than 3 months, pregnancy, or lack of follow-up.**

Patients with a low or intermediate risk modified Geneva score or a Well's score ≤ 4 underwent D-dimer testing. All others had a CTPA performed. The D-dimer was interpreted using an age-adjusted cut-off: 500 µg/L in patients younger than 50 years, age multiplied by 10 in those over 50. Those with a d-dimer level less than their age-adjusted cut-off underwent no further testing and were discharged without anticoagulation, while patients with a value above their cut-off underwent CTPA. All patients were followed for 3 months, at the end of which they were interviewed by telephone by a study coordinator using a structured questionnaire. All thromboembolic events were adjudicated by 3 independent experts who were blinded to the criteria used to rule out PE at inclusion. Deaths were adjudicated as surely related, probably related, possibly related, or unrelated to PE.

Between January 1, 2010 and February 28, 2013, 4420 patients were screened for enrollment. Of these, 1074 were excluded, leaving 3346 total patients in the study. A further 22 were excluded from the final analysis. The median age of the remaining 3324 patients was 63 years, and 56.8% were women. A total of 2898 patients (87.2%) underwent D-dimer testing. The overall prevalence of PE in the study was 19.0%.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. These were ED patients presenting with "a clinical suspicion of PE" in whom further testing was required to exclude the diagnosis. Among included patients, 87.2% had a nonhigh probability of disease based on the modified Geneva score or a Well's score ≤ 4.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group? (Confirmation Bias)**	No. In this study, only patients with a positive D-dimer based on their age-adjusted cut-off underwent additional testing. Conceivably, this could underestimate the number of false-negative results (partial verification bias). All patients did undergo 3-month follow-up, "by telephone by a study coordinator using a structured questionnaire," (p. 1119) but the authors do not mention if this study coordinator was blinded.
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	Yes. Again, only patients felt to be high risk by either Well's score or modified Geneva score, or those with a positive D-dimer based on the age-adjusted cut-off, underwent additional testing using CTPA.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?**	• The authors do not reports likelihood ratios and do not provide enough information to calculate likelihood ratios. • Among 2898 patients in the low-intermediate risk group who underwent D-dimer testing, 817 (28.2%), had a D-dimer < 500 µg/L while an additional 337 (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff. • The use of an age-adjusted cut-off therefore resulted in an absolute increase in the proportion of negative results of 11.6% (95% CI 10.5-12.9%), or a 41.2% relative increase (95% CI 31.3-52.0%). • Of 810 patients with a D-dimer < 500 µg/L who had follow-up data, only 1 had an adjudicated venous thromboembolism. There was one additional adjuticated thromboembolism 1 one of 331 patients with a D-dimer between 500 µg/L and the age-adjusted cut-off, for an overall failure rate of 0.3% (95% CI 0.1-

		1.7%).
III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes. D-dimer is not a new test, and has been used extensively in the work-up of pulmonary embolism for over a decade. Unfortunately, the assay used at our institution is different in that our lab reports values in D-Dimer Units (DDU) rather than Fibrinogen Equivalent Units (FEU). Additionally, the reported cut-off in our system is 230 ng/mL, rather than the typically suggested 250, making it difficult to devise a formula for the calculation of an age-adjusted cut-off.
B.	**Are the results applicable to the patients in my practice?**	Yes. We frequently see older patients (>50 years of age) with a suspicion of PE, in whom D-dimer testing is employed. The ability to use an age-adjusted cut-off would be a valuable tool to reduce the use of unnecessary testing in these patients.
C.	**Will the results change my management strategy?**	Yes. Assuming we can devise a formula to allow us to accurately calculate a cut-off for patients over age 50, the low risk associated with this practice does seem to warrant its use.
D.	**Will patients be better off as a result of the test?**	Yes. The use of CT to evaluate PE is not without risks, including the risk of allergy/anaphylaxis due to IV contrast, the risk of contrast-induced nephropathy, and the risk of overdiagnosis and false positive reporting.

Limitations:

1. **This was a nonrandomized clinical outcome study with no control group for comparison, making it impossible to compare the efficacy of a protocol using an age-adjusted D-dimer cut-off to one that uses a traditional cut-off.**

2. **The authors do not specify whether or not the study coordinators conducting the 3-month telephone follow-up were blinded to D-dimer or CT results (observer bias).**

3. **Among 1154 patients with a D-dimer below the age-adjusted cutoff, 13 (1.1%) were excluded from analysis because they either received anticoagulation for a different purpose, or because they were lost to follow-up. Another 42 patients with positive D-dimer received no further testing and hence were considered to not have a PE.**

4. **Only patients with a positive D-dimer based on their age-adjusted cut-off underwent additional testing (partial verification bias).**

5. **Of the 7 patients with a D-dimer level between 500 and the age-adjusted cut-off who died, only one had an autopsy. It is possible that some (or even all) could have died as a result of a massive PE (differential verification bias).**

6. **It is likely that the racial make-up and prevalence of comorbidities is different in this European population than we see in the US (external validity).**

Bottom Line:

In this prospective diagnostic management outcome study, conducted at 19 hospitals in 4 countries in Europe, the use of an age-adjusted D-dimer resulted in a reduction in the need for CT to evaluate for PE of about 10%, with a low overall failure rate (0.3%; 95% CI 0.1-1.7%).