

References and Article Grading

Can an Age-Adjusted D-Dimer be Used to Safely Rule Out Pulmonary Embolism in Emergency Department Patients?

Relevant Articles Chosen for Review (7)

Publication	Grade	Quality	Comments
van Es N, van der Hulle T, van Es J, et al. Wells Rule and D-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. <i>Annals of internal medicine</i> . 2016;165(4):253-261.	A	Outstanding	This systematic review and meta-analysis combined individual patient data from 6 prior studies (one of which used age-adjusted D-dimer (AADD) a priori) for a total of 7,268 pts. They had a 4.6% increase in efficiency, and a less than 3% false negative rate.
Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. <i>Cochrane database of systematic reviews (Online)</i> . 2016(8): Cd010864.	A	Outstanding	This is a Cochrane review, limited to studies conducted prior to 2013. “... no empirical evidence was available to support an increase in the diagnostic threshold of interpretation of D-dimer results for those over the age of 65 years.” Their meta-analysis included 4 studies, for a total of 1585 pts. Based on the studies they reviewed, they were unable to recommend using AADD. Although, they really didn’t have enough data to adequately address that specific question.
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. <i>BMJ (Clinical research ed)</i> . 2013;346:f2492.	A	Outstanding	Well done systematic review and meta-analysis. There is increased risk of missing VTE in patients >80. Failure rate remained below 3% in all ages. In their study 0.3% were missed in <50 population. They had 13 cohorts of over 12,000 patients. The studies were from just 3 research groups. They explain the risks of working up elderly patients in an attempt to justify the increased risk of missing PE. They also suggest that because it was such a large retrospective study, prospective studies are unnecessary.
Penaloza A, Roy PM, Kline J, et al.	A	Good	A meta-analysis of 3 databases (one US),

<p>Performance of age-adjusted D-dimer cut-off to rule out pulmonary embolism. <i>Journal of thrombosis and haemostasis</i>. 2012;10(7):1291-1296.</p>			<p>total of 4537 patients, overall PE prevalence was 10.1%. The AADD false negative rate was 0.8%(0.5-1.2%), for the >75 yo, the rate was 1.5%(0.1-7.0%).</p>
<p>Douma RA, Tan M, Schutgens RE, et al. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. <i>Haematologica</i>. 2012;97(10):1507-1513.</p>	A	Outstanding	<p>The authors used data from 5 prospective studies to retrospectively apply AADD criteria. There were a total of 2818 pts, 1884 pts were Non-High risk with DD. Cohort 1-4 were looking for PE (5 was DVT only). False negative rate was 0%(0-2.1%) in under 80, 2.0%(0.3-7.2%) in over 80; the over 80 with traditional cutoff was 2.3%(0.1-12%). Overall w/AADD was 0.8%(0.3-1.7%), although this number included pts under 50 as well.</p> <p>The test efficiency improved by 8.6%(range was 4.1 to 24%, increasing with age).</p>
<p>Han C, Zhao Y, Cheng W, et al. The performance of age-adjusted D-dimer cut-off in Chinese outpatients with suspected venous thromboembolism. <i>Thrombosis research</i>. 2015;136(4):739-743.</p>	C	Adequate	<p>They enrolled 594 patients (mixed VTE and PE, but only patients with imaging were eligible). They had a test efficiency improvement of 5.9%(3.8-8.7), with no change additional false negatives.</p>
<p>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. <i>JAMA</i>. 2014;311(11):1117-1124.</p>	C	Good	<p>Prospective study used M-Geneva or 2-step Wells and Age-adjusted Dimer. 19 hospitals in 4 countries, 3346 patients. Did not scan pts less than age-adjusted D-dimer and followed for 3 months, 1/331 pts had VTE (0.3% [0.1-1.7%]) and were able to exclude from 43/673 to 200/673 (between 26-33% increase).</p> <p>Inclusion: clinical suspicion of PE (acute onset or worsening of SOA/CP s/other obvious etiology). Exclusion: More than 24 hrs after admission, on anticoags, contrast allergy, Renal Insuf, <3mo life exp, pregnancy, or no f/u. The continued with further testing for patients with isolated subsegmental PE (they deemed that inconclusive).</p> <p>With AADD, patients over 75 yo went from 1 in 16 being r/o for PE to 1 in 3.4.</p> <p>Several financial disclosures,</p>

			governmental funding source.
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High Grade, But Not Relevant; or Relevant, But Low Grade Reviewed Articles (14)

Publication	Grade	Quality	Comments
Ann Emerg Med. 2011 Jun;57(6):628-652.e75. Doi:10.1016/j.annemergmed.2011.01.020. Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected pulmonary embolism. Fesmire FM, Brown MD, Espinosa JA, Shih RD, Silvers SM, Wolf SJ, Decker WW;	B	Good	Recommendation - No, does not address our question.
BMJ. 2009 Aug 14;339:b2990. doi: 10.1136/bmj.b2990. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. Geersing GJ(1), Janssen KJ, Oudega R, Bax L, Hoes AW, Reitsma JB, Moons KG.	B	Good	Recommendation – No, does not answer our question.
Int J Lab Hematol. 2014 Oct;36(5):541-7. doi: 10.1111/ijlh.12184. Epub 2014 Jan 16. D-dimer use for deep venous thrombosis exclusion in elderly patients: a comparative analysis of three different approaches to establish cut-off values for an assay with results expressed in D-dimer units. Cini M(1), Legnani C, Frascaro M, Sartori M, Cosmi B, Palareti G.	C	Good	Recommendation – No, looks at cut-off development.
Thromb Haemost. 2012 May;107(5):1005-7. doi: 10.1160/TH11-10-0706. Epub 2012 Mar 8. External validation of a D-dimer age-adjusted cut-off for the exclusion of	D	Good	Recommendation – No, grade D.

<p>pulmonary embolism. Jaffrelot M, Le Ven F, Le Roux PY, Tissot V, Rame E, Salaun PY, Le Gal G.</p>			
<p>Blood Coagul Fibrinolysis. 2014 Jun;25(4):309-15. doi:10.1097/MBC.000000000000020. Comparison of five D-dimer reagents and application of an age-adjusted cut-off for the diagnosis of venous thromboembolism in emergency department. Mullier F(1), Vanpee D, Jamart J, Dubuc E, Bailly N, Douxfils J, Chatelain C, Dogné JM, Chatelain B.</p>	D	Good	Recommendation – No, compares performance among various tests.
<p>Chest. 2014 Dec;146(6):1444-51. doi: 10.1378/chest.13-2386. Assessment of the safety and efficiency of using an age-adjusted D-dimer threshold to exclude suspected pulmonary embolism. Woller SC, Stevens SM, Adams DM, Evans RS, Lloyd JF, Snow GL, Bledsoe JR, Gay DZ, Patten RM, Aston VT, Elliott CG.</p>	D	Adequate	Recommendation – No, Grade D.
<p>BMJ. 2010 Mar 30;340:c1475. doi: 10.1136/bmj.c1475. Potential of an age adjusted D dimer cut off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. Douma RA(1), le Gal G, Söhne M, Righini M, Kamphuisen PW, Perrier A, Kruij MJ, Bounameaux H, Büller HR, Roy PM.</p>	D	Outstanding	Recommendation – No, Grade D.
<p>Int J Lab Hematol. 2016 Feb;38(1):42-9. doi: 10.1111/ijlh.12426. Epub 2015 Sep 12. Comparison between different D Dimer cutoff values to assess the individual risk of recurrent venous thromboembolism: analysis of results obtained in the DULCIS study.</p>	D	Good	Recommendation – No, Grade D.

Palareti G(1), Legnani C(2), Cosmi B(2), Antonucci E(3), Erba N(4), Poli D(3), Testa S(5), Tosetto A(6);			
Ann Emerg Med. 2016 Feb;67(2):249-57. doi: 10.1016/j.annemergmed.2015.07.026. An Age-Adjusted D-dimer Threshold for Emergency Department Patients With Suspected Pulmonary Embolus: Accuracy and Clinical Implications. Sharp AL(1), Vinson DR(2), Alamshaw F(3), Handler J(4), Gould MK(5).	D	Good	Recommendation – No, Grade D.
Am J Emerg Med. 2014 Dec;32(12):1499-502. doi: 10.1016/j.ajem.2014.09.027. Epub 2014 Sep 28. Assessing 2 D dimer age adjustment strategies to optimize computed tomographic use in ED evaluation of pulmonary embolism. Gupta A(1), Raja AS(2), Ip IK(3), Khorasani R(4).	D	Good Outstanding	Recommendation- No, Grade D.
Acta Clin Belg. 2013 Jul Aug;68(4):298-302. D dimer cut off adjusted to age performs better for exclusion of pulmonary embolism in patients over 75 years. Laruelle M(1), Descamps OS(2), Lesage V(3).	D	Good Adequate,	Recommendation- No, Grade D.
Thromb Res. 2014 Mar;133(3):380-3. doi: 10.1016/j.thromres.2013.12.045. Epub 2014 Jan 7. A higher d dimer threshold safely rules out pulmonary embolism in very elderly emergency department patients. Polo Friz H(1), Pasciuti L(2), Meloni DF(2), Crippa M(2), Villa G(2), Molteni M(2), Primitz L(2), Del Sorbo D(2),	D	Good	Recommendation – No, Grade D.

Delgrossi G(2), Cimminiello C(2).			
<p>Eur J Haematol. 2014 Feb;92(2):147-55. doi: 10.1111/ejh.12218. Epub 2013 Nov 22.</p> <p>Influence of C reactive protein levels and age on the value of D dimer in diagnosing pulmonary embolism.</p> <p>Crop MJ(1), Siemes C, Berendes P, van der Straaten F, Willemsen S, Levin MD.</p>	D	Good	Recommendation – No, Grade D.
<p>Ann Intern Med. 2015 Nov 3;163(9):701-11. doi: 10.7326/M14-1772. Epub 2015 Sep 29.</p> <p>Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians.</p> <p>Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD; Clinical Guidelines Committee of the American College of Physicians.</p>	E	Good	Recommendation – No, more of a selected review/expert opinion.