BET 2: SHOULD WE USE AN AGE ADJUSTED D-DIMER THRESHOLD IN MANAGING LOW RISK PATIENTS WITH SUSPECTED PULMONARY EMBOLISM?

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ABSTRACT

A shortcut review was carried out to establish whether a higher age related threshold can be used when using d-dimer as a rule out test for pulmonary embolism. 29 papers were found of which 13 presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. The clinical bottom line is that in older patients suspected of having a Pulmonary Embolus (PE), with a low pretest possibility, an age-adjusted D-dimer increases specificity with minimal change in the sensitivity, thereby increasing the number of patients who can be safely discharged without further investigations

CLINICAL SCENARIO

A70-year-old man presents with pleuritic chest pain. A D-dimer taken at triage is mildly elevated from the standard positive threshold. You feel he is at low risk of pulmonary embolism based on his wells score, and proceed to CTPA. CTPA shows no evidence of pulmonary embolism. You wonder whether an age-adjusted D-dimer level would have excluded PE in this gentleman without the need for further investigations.

THREE-PART QUESTION

In (patients with signs and symptoms of pulmonary embolism who are deemed low risk) is a [age adjusted D-dimer sensitive enough) compared to a standard D-dimer to (safely exclude pulmonary embolism)?

SEARCH STRATEGY

Using Pubmed database 1966 to week 1 December 2014. ("pulmonary embolism" [MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields]) AND ("fibrin fragment D"[Supplementary Concept] OR "fibrin fragment D"[All Fields] OR "d dimer"[All Fields]) AND ("Age"[Journal] AND adjusted[All Fields])

OUTCOME

Twenty-nine unique papers of which 13 included data on patients relevant to the clinical question (12 in English and 1 in German).

Table 2 Relevant papers

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Douma *et al*,[1] 2010, Netherlands	5132 consecutive patients with suspected PE	Retrospective multicentre cohort study	Proportion of patients in the validation cohorts with a negative D-dimer test	In patients aged over 50 years, using the standard cut-off value of 500 μg/L PE could be excluded in 36% of cases and using the age adjusted D-dimer value (age×10μg/L) it could be excluded in 42% of cases	Multiple D-dimer assays Retrospective analysis
Leng *et al*,[2] 2012, UK	528 patents who underwent CTPA scanning for suspected PE	Retrospective review of notes	D-dimer and CTPA	In patients >50 years old who underwent CTPA, 22 (5.2%) of 423 had D-dimer concentrations higher than the traditional threshold but lower than the age-adjusted threshold (age in years×10), none of whom had evidence of PE on CTPA. No patient with a D-dimer concentration below the age adjusted threshold had a PE confirmed by CTPA	Retrospective study
Penaloza *et al*,[3] 2012, Belgium	4537 patients with suspected PE	Secondary analysis of three prospectively collected of patients suspected of having PE	D-dimer level	In patients over 50 years using a standard D-dimer threshold (500 μg dL-1): False negative rate 0.6% (95% CI 0.3% to1.0%). Age-adjusted D-dimer cut off (age×10 in patients over 50 years): False negative rate 0.8% (95% CI 0.5% to 1.2%). The false negative rate increased in patients over 75 years 3.9% (95% CI 1.6% to 7.9%)	Secondary analysis of prospective studies Included studies analysing DVT
Van *et al*, 2012,[4] Amsterdam	414 consecutive patients with suspected PE who were older than 50 years	Analysis of prospective cohort study	D-dimer test, Wells score, Revised Geneva Score (RGS), simplified Wells score and simplified RGS	In patients above 50 years, a normal age-adjusted D-dimer level (age×10 μg/l) substantially increased the number of patients in whom PE could be safely excluded from 13–14% to 19–22%. In patients over 70 years, the number of exclusions was nearly fourfold higher	Analysed retrospectively Small data set Wide CIs of false negative rate Different D-dimer assays
Vossen *et al*,[5] 2012, USA	237 consecutive patients with suspected PE	Retrospective review of patient records	D-dimer level and CTPA result	In patients aged over 50 years the use of a conventional D-dimer threshold (500 μg/L): Sensitivity 100% (95% CI 31% to 100%) Specificity 5% (95% CI 2% to 10%) Increasing the threshold to 2000μg/L: Sensitivity 100% (95% CI 31% to 100%) Specificity 81% (95% CI 73% to 87%)	Retrospective analysis Limited to community hospital setting
Laruelle *et al*,[6] 2013, Belgium	165 patients older than 75 with suspected PE	Retrospective chart review	Pulmonary scintigraphy and/or CTPA and D-dimer level	In patients older than 75 using a standard D-dimer threshold:-Specificity-6% Sensitivity-98% Using an age adjusted (age ×0.01 μg/mL) threshold: Specificity 23%; sensitivity 96%	Retrospective study
Rowe *et al*,[7] 2013, USA	5556 patients who had D-dimer performed for suspected VTE	Retrospective chart review	D-dimer level, CTPA	Of the total number of patients 810 had a positive D-dimer level using the traditional threshold and subsequent imaging showed only 26 had VTE. Out of these 810 patients, 130 would have tested negative with an age adjusted threshold (age×0.01 ng/mL), only 4 had VTE of this group	Retrospective study

Continued

Table 2 Continued

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Schouten *et al*,[8] 2013, Netherlands	12497 patients (from 13 cohorts) with a non-high clinical probability of VTE	Systematic review and bivariate random effects meta-analysis	D-dimer level	In patients older than 80 using a standard D-dimer threshold: Specificity 14.7% (95% CI 11.3% to 18.6%). Using an age adjusted (age ×10 μg/L) threshold: Specificity 35.2% (95% CI 29.4% to 41.5%)	Multiple D-dimer assays used Multiple different reference standards Included studies looking at patients with suspected DVT
Verma *et al*,[13] 2013, Germany	1033 patients with suspected VTE	Retrospective cohort study	D-dimer	Using the conventional cut-off of 0.5 mg/dL, PE could be excluded in 68% of patients. Using the age-adjusted cut-off (age ×0.016) mg/l) PE could be ruled out in 77% of patients. In patients >70 years, the negative prediction accuracy of excluding a PE/DVT increased explicitly. The failure rate of the age-adjusted value was 0.8% (95%CI 0.3% to 1.6%)	Retrospective study Wide CI of age adjusted cut-off value 0.3–1.6%
Gupta *et al*,[9] 2014, USA	3063 patients with suspected PE	Retrospective study	CTPA and d-dimer	In patients older than 60 using a standard D-dimer threshold (500 ng/L): Sensitivity 100% (95% CI 94.2% to 100%); Specificity 7.4% (95% CI 5.8% to 9.2%); Using a decade age-adjusted D-dimer threshold (600 ng/L for 61–70, 700 ng/L for 71–80 etc): Sensitivity 98.7% (95% CI 92.1% to 99.9%). Specificity 13.5% (95% CI 12.2% to 16.8%); Using a yearly age-adjusted D-dimer threshold (age in years×10 ng/ml): Sensitivity 97.4% (95% CI 90.2% to 99.6%); specificity 16.7% (95% CI 14.4% to 19.2%)	Retrospective study
Polo Friz *et al*,[10] March 2014, Italy	481 patients with suspected PE	Retrospective cohort study	D-dimer and CTPA	In patients older than 80 using a standard D-dimer threshold (490 ng/L): Sensitivity 100% (95% CI 90.5% to 100%); Specificity 0.0% (95% CI 0.0% to 2.4%); Using an age-adjusted D-dimer threshold (age×10 ng/mL): Sensitivity 100% (95% CI 90.5% to 100%); Specificity 6.5% (95% CI 2.6% to 10.4%)	Retrospective study
Righini *et al*,[11] 2014, Switzerland	3346 patients with suspected PE	Multicentre, multinational, prospective management outcome study	RGS or the 2-level Wells score for PE; D-dimer level and CTPA result	In patients 75 years or older using conventional cut-off of 500 μg/L PE could be excluded in 43 of 673 patients (6.4% (95% CI 4.8% to 8.5%) and with the age-adjusted cutoff (age×10 μg/) 200 of 673 patients (29.7% (95% CI 26.4% to 33.3%) could be excluded without any additional false-negative findings	Multiple D-dimer assays used
Woller *et al*,[12] 2014, USA	923 patients aged older than 50 years with suspected PE	Retrospective review of patient records	RGS, D-dimer level and CTPA result	In patients aged over 50 years the use of a conventional D-dimer threshold yielded 104 negative D-dimer results (11.3%) When an age adjusted D-dimer threshold is used (age×10 ng/mL) this results in 273 negative D-dimer results (29.6%)	Retrospective study Risk of misclassification bias in calculation of RGS

COMMENTS

It is established knowledge that D-dimer, the fibrin degradation product, increases with age. Despite this many institutions use a fixed D-dimer level regardless of a patient's age. In patients with a low pretest probability of pulmonary embolism based on the Wells score or revised Geneva score, clinicians then proceed to a D-dimer blood test. If this is positive then imaging has to be performed, generally CTPA. This carries with it a risk of contrast-induced nephropathy and the economic impact of imaging costs and in-patient care. The above studies uniformly show that an age-adjusted D-dimer increases specificity with similar sensitivity rates in low risk patients suspected of having PE. This benefit increases with age. The threshold for the use of an age adjusted value differed between studies but were all at least above 50 years of age.

Clinical bottom line

In older patients suspected of having a PE, with a low pretest possibility, an age-adjusted D-dimer increases specificity with minimal change in the sensitivity, thereby increasing the number of patients who can be safely discharged without further investigations.

REFERENCES

1 Douma RA, le Gal G, Söhne M, *et al*. 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. *BMJ* 2010;340:c1475.

2 Leng O, Sitaraaman HB. Application of age-adjusted D-dimer threshold for exclusion thromboembolism (PTE) in older patients: a retrospective study. *Acute Med* 2012;11:129–32.

3 Penaloza A, Roy PM, Kline J, *et al*. Performance of age-adjusted D-dimer cut-off to rule out pulmonary embolism. *J Thromb Haemost* 2012;10:1291–6.

4 Van Es J, Mos I, Douma R, *et al*. The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded. *Thromb Haemost* 2012;107:167–71.

5 Vossen JA, Albrektson J, Sensarma A, *et al*. Clinical usefulness of adjusted D-dimer cut-off values to exclude pulmonary embolism in a community hospital emergency department patient population. *Acta Radiol* 2012;53:765–8.

6 Laruelle M, Descamps OS, Lesage V. D-dimer cut-off adjusted to age performs better for exclusion of pulmonary embolism in patients over 75 years. *Acta Clin Belg* 2013;68:298–302.
7 Rowe JC, Marchick MR. Evaluation of an age-adjusted D-dimer threshold in the diagnosis of acute venous thromboembolism. *Acad Emerg Med* 2013;20(Suppl 1):S104–5).
8 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.
9 Gupta A, Raja AS, Ip IK, *et al*. Assessing 2 d-dimer age-adjustment strategies to optimize computed tomographic use in ED evaluation of pulmonary embolism. *Am J Emerg Med* 2014;32:1499–502.
10 Polo Friz H, Pasciuti L, Meloni DF, *et al*. A higher d-dimer threshold safely rules-out pulmonary embolism in very elderly emergency department patients. *Thromb Res* 2014;133:380–3.
11 Righini M, Van Es J, Den Exter PL, *et al*. Haze Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA* 2014;311:1117–24. Erratum in: JAMA. 2014;311(16):1694.
12 Woller SC, Stevens SM, Adams DM, *et al*. Assessment of the safety and efficiency of using an age-adjusted d-dimer threshold to exclude suspected pulmonary embolism. *Chest* 2014;146:1444–51.
13 Verma N, Willeke P, Bicsan P, *et al*. Age-adjusted D-dimer cut-offs to diagnose thromboembolic events: validation in an emergency department. Medizinische Klinik, Intensivmedizin Und Notfallmedizin 2014; 109:121–8.

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