INCREASING THE USEFULNESS OF D-DIMER TO SAFELY RULE OUT PULMONARY EMBOLISM

by using an age-adjusted D-dimer cut-off The ADJUST-PE Study

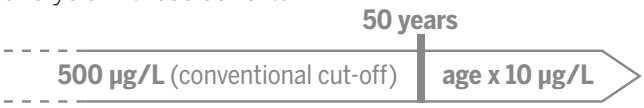
KEY POINTS

- Largest ever prospective outcome study in suspected PE (19 hospitals, 4 countries, 3324 patients).
- D-dimer tested with 6 different assays in 2898 non-high probability patients.
- In total, 12% more exclusions with age-adjusted D-dimer cut-off compared with usual cut-off.
- Most pronounced effect in elderly patients - 75 years or older (4.6-fold higher exclusion rate).
- High safety for rule-out maintained.

In association with clinical pre-test probability assessment, a quantitative sensitive D-dimer test is recommended as the first line approach in the diagnostic management of hemodynamically stable patients with suspected pulmonary embolism (PE) [1]. Many prospective outcome studies have shown that such a strategy allows safe exclusion of PE in approximately 1/3rd of suspected outpatients without the need for CT pulmonary angiography [2].

Since D-dimer levels tend to increase with age, their clinical utility for PE exclusion is reduced in the elderly [3]. In three large cohorts (n = 5132) of patients with non-high probability of PE, 59% of patients younger than 50 years had D-dimer levels below the standard cut-off value of 500 µg/L, whereas this was only 12% for patients older than 70 years [4]. Both the younger age group (< 50 years) and the older age group (> 70 years) accounted for about 1/3rd of all suspected PE patients in these cohorts.

To improve the efficiency of PE exclusion in older patients, while maintaining safety, investigators have derived and validated a **simple algorithm** for an **age-adjusted D-dimer cut-off** by retrospective data analysis in these cohorts [4]:



This algorithm achieved a relative increase of 15% in the overall exclusion rate (from 39% to 45%). In the elderly above 70 years, it more than doubled the exclusion rate (from 12% to 27%) without a significant effect on the negative predictive value (NPV) [4].

However, implementation of this age-adjusted D-dimer cut-off algorithm into clinical practice required validation in a prospective management outcome study. This was the objective of the multi-center (19 hospitals), multinational (Belgium, France, The Netherlands, and Switzerland) **ADJUST-PE study** [5].

PIONEERING DIAGNOSTICS

In the ADJUST-PE study, a total of 3324 patients (PE prevalence 19%) were prospectively recruited, making it the largest ever management outcome study in outpatients with suspected PE. D-dimer was tested with 6 different quantitative assays in a total of 2898 (87%) patients classified as non-high (simplified revised Geneva score) or unlikely (Wells score) clinical probability for PE. Patients were left untreated on the basis of a negative age-adjusted D-dimer test result. Failure rate in these patients was assessed by a 3-month follow-up period with all suspected recurrent venous thromboembolic events adjudicated by an independent committee (Table 1).

EFFICIENCY: increase of PE exclusion rate

For all 6 D-dimer assays combined, the overall PE exclusion rate was significantly increased from **28.2% to 39.8%** ($p < 0.0001$), a relative increase of 41%. The largest effect was seen in elderly patients ≥ 75 years (n = 673; 23% of total) with an almost 5-fold increase in the PE exclusion rate from 6.4% to 29.7%.

SAFETY: acceptable 3-month failure rate

This increased diagnostic yield did not affect safety because the 3-month thromboembolic failure rate in patients with D-dimer ≥ 500 µg/L but below the age-adjusted cut-off was only 0.3% (95% CI 0.1-1.7), with the upper limit of the 95% confidence interval well below the acceptable safety margin of 3%.

Table 1: Study Results According to D-Dimer Assays (adapted from Righini M., *et al.* JAMA. 2014;311:1117-24)

D-Dimer Assay	Low/Intermediate or Unlikely Clinical Probability, No. of Patients	D-Dimer <500 µg/L	3-mo Thromboembolism Risk		D-Dimer ≥500 µg/L and <Age-Adjusted Cutoff	3-mo Thromboembolism Risk	
			No. of Events/ Total Patients	% (95% CI)		No. of Events/ Total Patients	% (95% CI)
VIDAS® D-Dimer Exclusion™	1345	423	0/417	0.0 (0.0-0.9)	130	0/127	0.0 (0.0-2.9)
Innovance D-Dimer	838	202	1/202	0.5 (0.1-2.8)	103	1/103	1.0 (0.2-5.3)
STA-Liatest D-Dimer	389	132	0/132	0.0 (0.0-2.8)	49	0/47	0.0 (0.0-7.6)
D-Dimer HS 500	185	32	0/31	0.0 (0.0-11.0)	23	0/23	0.0 (0.0-14.3)
Second-generation Tina-quant	128	26	0/26	0.0 (0.0-12.9)	32	0/31	0.0 (0.0-11.0)
Cobas h 232	13	2	0/2	0.0 (0.0-65.8)	0		
Total	**2898**	**817**	**1/810**	**0 0.1 (0.0-0.7)**	**337**	**1/331**	**0.3 (0.1-1.7)**

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"The ADJUST-PE study has convincingly shown that, compared with the conventional fixed D-dimer cut-off, the age-adjusted cut-off allows exclusion of PE in a much larger number of suspected out-patients, particularly in the elderly, while maintaining safety. We are now routinely using this approach in our hospital."

REFERENCES

1. Konstantinides SV, *et al.*; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033-69, 3069a-3069k.
2. Carrier M, *et al.* VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost. 2009;101:886-92.
3. Harper PL, *et al.* D-dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. Intern Med J. 2007;37:607-13.
4. Douma RA, *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.
5. Righini M, *et al.* Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA. 2014;311:1117-24.

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