



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

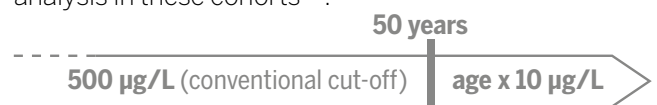
KEY POINTS

- 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⁾.



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 $\geq 500 \mu\text{g/L}$ 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 $\mu\text{g/L}$	3-mo Thromboembolism Risk		D-Dimer $\geq 500 \mu\text{g/L}$ 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	0.1 (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 outpatients, particularly in the elderly, while maintaining safety. We are now routinely using this approach in our hospital.** ”

REFERENCES

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