

# **D-dimer testing for venous thromboembolism exclusion in elderly patients**

**Age-adjusted threshold  
with Stago D-dimer reagent**

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## Learning objectives

- What is the place of D-dimer testing in VTE diagnosis strategy and its limitations?
- How can an age-adjusted threshold improve VTE diagnosis outcomes?
- What data are available on the use of the age-adjusted D-dimer threshold in clinical practice?
- What are the results of clinical studies?

## Introduction

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the third cause of cardiovascular deaths worldwide.

As clinical symptoms are not specific, VTE final diagnosis is based on specific imaging studies, such as compression ultrasound (CUS) for DVT and computed tomography pulmonary angiography (CTPA) or ventilation-perfusion (V/Q) scan for PE. The implementation of D-dimer testing combined with assessment of pre-test clinical probability allows the exclusion of the disease in numerous cases and results in subsequent reduction of imaging tests and their associated side-effects (radiation exposure, contrast-induced nephropathy), costs, potential over diagnosis and inconvenience for patients<sup>1</sup>.

D-dimer are fibrin-specific degradation products, reflecting coagulation activation and subsequent fibrinolysis<sup>2</sup>. D-dimer assay is a sensitive test for VTE and low levels of D-dimer are associated with a high negative predictive value (NPV) for VTE diagnosis. D-dimer levels below the established threshold allow for safe exclusion when performed with high-sensitivity assays in patients with non-high clinical probability<sup>3,4</sup>.

D-dimer concentration increases with age<sup>5</sup>. The specificity of the D-dimer test thus decreases as age increases, translating

into more false positive test results in older patients than in younger ones. This means that VTE will be less often excluded in older than in younger patients and older patients will need more additional imaging tests<sup>6</sup>.

In order to restore the benefits of D-dimer assays in this patient population, it has been suggested that an increased D-dimer threshold for older patients would reduce unnecessary imaging techniques without adversely affecting the high NPV of the assay and would increase the number of patients in whom imaging could safely be avoided.

Among the different proposals that have been proposed to adapt the threshold of D-dimer level for VTE exclusion, the use of a progressively increasing threshold according to age is presently the most recognized strategy. The value corresponding to the age of the patient multiplied by 10, in patients older than 50 years old, corresponds to the D-dimer age-adjusted cut-off for exclusion of VTE.

This article has been written using an exhaustive analysis of original articles present in MEDLINE/PubMed database regarding the use of the D-dimer age-adjusted threshold in the exclusion of PE, DVT or both. Twenty-eight publications were included for analysis.

## Age-adjusted D-dimer exclusion threshold, for patient over 50 years:

$$\text{Age} \times 10 \text{ (in } \mu\text{g/L)}$$

Example:

- Mr. P, 82 years old, is suspected of having pulmonary embolism.
- D-dimer level with Stago Liatest D-dimer assay is 660  $\mu\text{g/L}$ .
- If conventional threshold of 500  $\mu\text{g/L}$  is used, Mr. P would have been referred to CTPA.
- Using the age-adjusted strategy, the new exclusion threshold is  $82 \times 10 = 820 \mu\text{g/L}$ . PE is safely excluded and there is no need for CTPA.

### Available clinical data on the utility of age-adjusted threshold

The “age x 10” adjusted threshold was derived from a study conducted by Douma et al. that evaluated PE suspected patients with non-high clinical probability. The cohort was subdivided into 10-year age groups and the optimal threshold was determined for each group. It appears that the optimal threshold increases approximately by 100  $\mu\text{g/L}$  per decade (10  $\mu\text{g/L}$  per year)<sup>7</sup>.

The two initial studies which assessed the age-adjusted threshold evaluated six cohorts of patients with suspected PE (9,669 patients). Use of the age-adjusted threshold would have led to a 6% and 10% absolute increase of excluded patients based on D-dimer assay only, in the publications of Douma et al. and Penalzoza et al, respectively<sup>7,8</sup>. False negative rates when using a conventional threshold ranged from 0.0% to 0.6% and were only slightly higher with 0.3 and 0.8% of false negative rates using the age-adjusted threshold, respectively. A review and metaanalysis published by Schouten et al. analyzed 12,497 patients with non-high clinical probability and showed that the use of the age-adjusted threshold resulted in an increase of the overall test specificity, while maintaining sensitivity above 97%. Similar findings were found when patients are classified by decade (51-60, 61-70, 71-80 and > 80 years)<sup>9</sup>.

The ADJUST-PE is a prospective, multicenter, management study that assessed the “age x 10” adjusted D-dimer threshold combined with clinical probability assessment. The absolute increase in PE excluded patients reached 11.6% as compared with the conventional threshold, and up to 29.7% in patients over 75 years, without compromising patient safety (false negative rate: 0.3%)<sup>10</sup>.

Over the 28 studies evaluating the age-adjusted threshold, the absolute increase in excluded patients (percentage of additional excluded patients) when the age-adjusted threshold is used compared to conventional threshold ranges from 4.2 to 24.1% (median = 8.6%). Only one study reported a limited absolute increase of excluded patients of 2%, as the initial study design excluded patients older than 80 years<sup>11</sup>, which correspond to the population who benefits the most from the application of the age-adjusted threshold (30% of absolute increase of VTE exclusion)<sup>10</sup>. The NPV ranged from 92.9 to 100% (median = 99.5%). No study reported any significant increase in false negative rate.

The evaluated clinical studies used various commercially available D-dimer assays. Different methodologies for D-dimer measurement exist (enzyme-linked immunosorbent assay, latex agglutination, whole blood point-of-care assays) and performances for VTE exclusion can vary greatly across those assays. For this reason, Goodwin and colleagues, on behalf of the American College of Physicians, recommend to consider that the age-adjusted threshold should be only applied with specific D-dimer assays adequately evaluated in clinical studies<sup>12</sup>.

### Application for Stago Liatest D-dimer assay

STA-Liatest D-Di assay was independently analyzed in 10 original studies. Nine cohorts combined a total of 9,139 patients<sup>8,10,11,13-18</sup> while another study analyzed retrospective data from US healthcare centers on 31,094 patients<sup>19</sup>.

This makes the STA Liatest D-Di assay the most extensively studied assay for D-dimer age-adjusted threshold in VTE exclusion. Reported NPV ranged from 98.8 to 99.8% (median: 99.5%) while the absolute increase of excluded patients range from 2 to 18.3% (median: 9.8%) (Figure 1). All of these studies were in favor of the use of the age-adjusted threshold as it allows exclusion of more patients from imaging techniques, while still maintaining a high degree of security.

### All of the studies published are consistent on the benefits of this strategy:

- **The performance of the assay is improved:** the proportion of false positives is significantly reduced in patients over 50 years
- **Security is maintained:** NPV remains above 98.8% in studies performing with STA-Liatest D-Di assay<sup>11, 16-19</sup>
- **The need for imaging techniques is reduced:** more rapid and efficient diagnosis, reduced costs and reduced side effects of imaging techniques

## Clinical usefulness of D-dimer assay according to conventional and age-adjusted thresholds

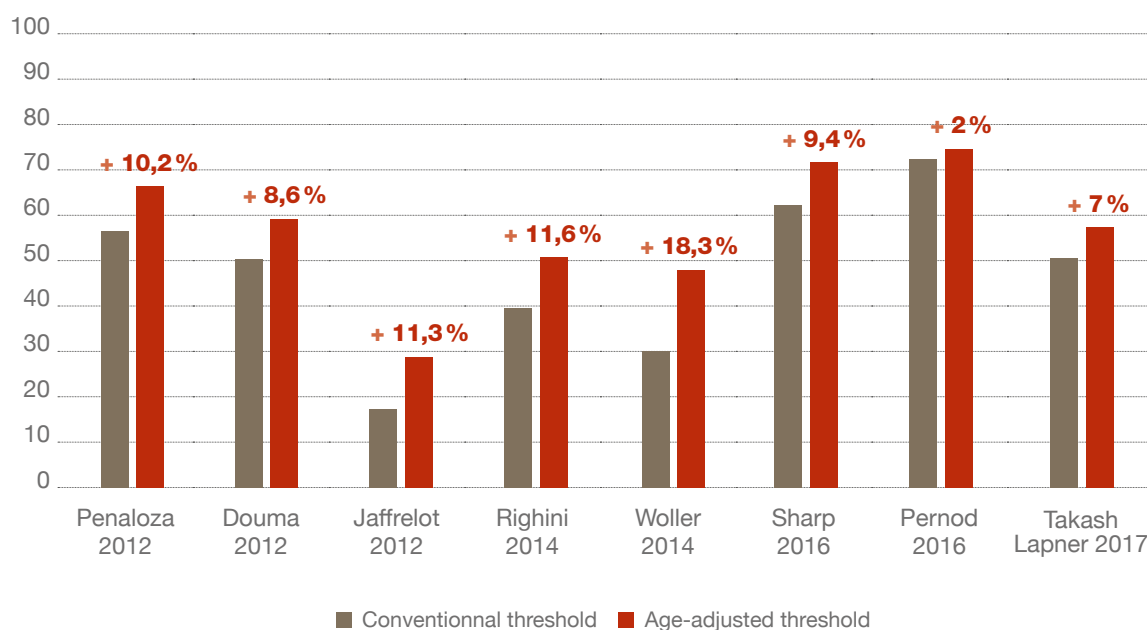


Figure 1. Percentage of VTE excluded patients on the basis of a negative D-dimer assay using the conventional and the age-adjusted thresholds. Represented data are extracted from studies which used STA Liatest D-Di assay<sup>8, 10, 11, 13-15, 17, 19</sup>.

### Commentary

D-dimer assay has shown its clinical usefulness in reducing the overall amount of imaging techniques, but suffers from limited specificity, notably in populations in whom D-dimer is frequently elevated, e.g. in elderly patients. In order to restore its performances in older patients, an age-adjusted threshold has been proposed in patients over 50 years, resulting in a decrease of the number of patients referred to imaging techniques, while maintaining adequate safety.

At present, many clinical studies have assessed the efficacy and security of the use of this modified threshold adapted to patients over 50 years. Although these studies are consistent in their conclusions, methodologies vary greatly regarding study design, assay used, number of patients, inclusion/exclusion criteria, and the suspected pathology (PE, DVT or both) and its prevalence. Most of studies are retrospective. Only one prospective management study has been performed and extrapolation of results to other health care settings or population should be taken with care<sup>10</sup>. However, the diversity in the material and methods should be considered as a strength, since all of these studies were consistent in their conclusions, thus contributing to demonstration of robustness of the strategy.

CTPA or V/Q scan are still warranted to exclude or confirm PE diagnosis when clinical probability is high, when D-dimer result is above the threshold, or when the D-dimer assay is not performed. Nevertheless imaging techniques are not devoid of risks. Patients who escape exposure to imaging techniques

on the basis of a negative D-dimer assay thus avoid the approximately 2% probability of false-positive diagnosis and its associated risk of unnecessary anticoagulation, the cost of the imaging study, radiation exposure, the 1% risk of immediate complication (such as allergy) and the 15% probability of developing contrast-induced nephropathy<sup>20-22</sup>.

To date, there is accumulating evidence on the benefits of the use of the D-dimer age-adjusted threshold. This results in its spreading use in clinical practice, and this strategy has now been implemented in recognized guidelines such as the American College of Physician Guidelines for PE diagnosis<sup>23</sup>.

### Conclusion

Compared with the standard threshold, the use of an age-adjusted threshold has shown to improve D-dimer value in elderly patients by decreasing further testing without significantly increasing the rate of missed thromboembolic events.

Stago Liatest D-dimer assay is presently validated and cleared by regulatory agencies for DVT and PE exclusion only using the conventional threshold (i.e. 500 µg/L), following the results obtained in an international multicenter management study<sup>24</sup>. The choice of the threshold used by clinical laboratory for VTE exclusion has to be made in the light of the available literature, their local experience and discussion with clinicians.

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