Impact of the Age-Adjusted D-Dimer Cutoff to Exclude Pulmonary Embolism: A Multinational Prospective Real-Life Study (the RELAX-PE Study)

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RESEARCH LETTER

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A Multinational Prospective Real-Life Study (the RELAX-PE Study)

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Diagnosis of pulmonary embolism (PE) relies on the sequential use of pretest probability (PTP), plasma D-dimer, and computed tomography pulmonary angiography.[1,2] D-dimer <500 µg/L safely excludes PE in association with a low or intermediate (nonhigh) PTP in approximately one-third of outpatients. To increase the clinical usefulness of D-dimer, a cutoff adjusted to patient's age was explored. This age-adjusted D-dimer (AADD) cutoff consists of a cutoff <500 µg/L up to 50 years of age and a cutoff <(age × 10) µg/L in patients >50 years of age. After retrospective validation,[3] a large prospective multinational management outcome study proved the safety of the AADD cutoff.[4] However, the additional validation step needed was the impact analysis of its use in everyday clinical practice.

We therefore designed a multinational, prospective, real-life diagnostic outcome study involving 10 hospitals in Belgium, France, and Switzerland. The ethics committees of all participating institutions approved the study, which was registered on ClinicalTrials.gov (NCT 02601846). Patients provided informed consent. The data supporting the findings of this study are available from the corresponding author.

Outpatients in whom PE was considered to be ruled out on the basis of a nonhigh PTP and a negative ELISA D-dimer using the AADD cutoff were included and followed up for 3 months. PTP was assessed by the simplified Geneva score, and the AADD cutoff was applied in routine clinical practice to define negative D-dimer.

The main outcome was the rate of symptomatic VTE events during follow-up.[4] All suspected VTE events and deaths were adjudicated by 3 independent experts blinded to D-dimer levels. Adjudicated VTE events needed to meet objective diagnostic criteria as currently accepted in diagnostic VTE studies.[4] The secondary outcome was the proportion of patients with D-dimer between 500 µg/L and the AADD cutoff, that is, the additional diagnostic yield of the AADD cutoff compared with the standard cutoff, in the whole cohort and in patients ≥75 years of age.

Between May 2015 and March 2019, 2148 patients were screened, of whom 641 were excluded. Of the 1507 included patients, 1206 had D-dimer levels <500 µg/L and 301 had a D-dimer ≥500 µg/L but below their AADD cutoff (Figure). Twenty patients were lost to follow-up at 3 months, and 57 received anticoagulants for an indication other than a VTE event during follow-up.

Among the remaining 1430 patients, there were 9 deaths attributed to a cause other than PE. Of the 1421 patients with a nonhigh PTP and negative D-dimer using the AADD cutoff left untreated, 20 had suspected VTE. Objective testing excluded VTE in 19 and confirmed nonfatal PE in 1. The overall 3-month VTE risk was therefore very low at 1 in 1421 (0.07% [95% CI, 0.01–0.40]). The 3-month VTE risk in patients with a D-dimer ≥500 µg/L but below their AADD cutoff was 0 in 269 (0.00% [95% CI, 0.00–1.41]).

In terms of diagnostic usefulness, using the AADD cutoff resulted in a 20.0% increase in the proportion of negative D-dimer tests in the whole cohort. Among the 226 patients ≥75 years of age, the increase was 67%; only 75 had a D-dimer

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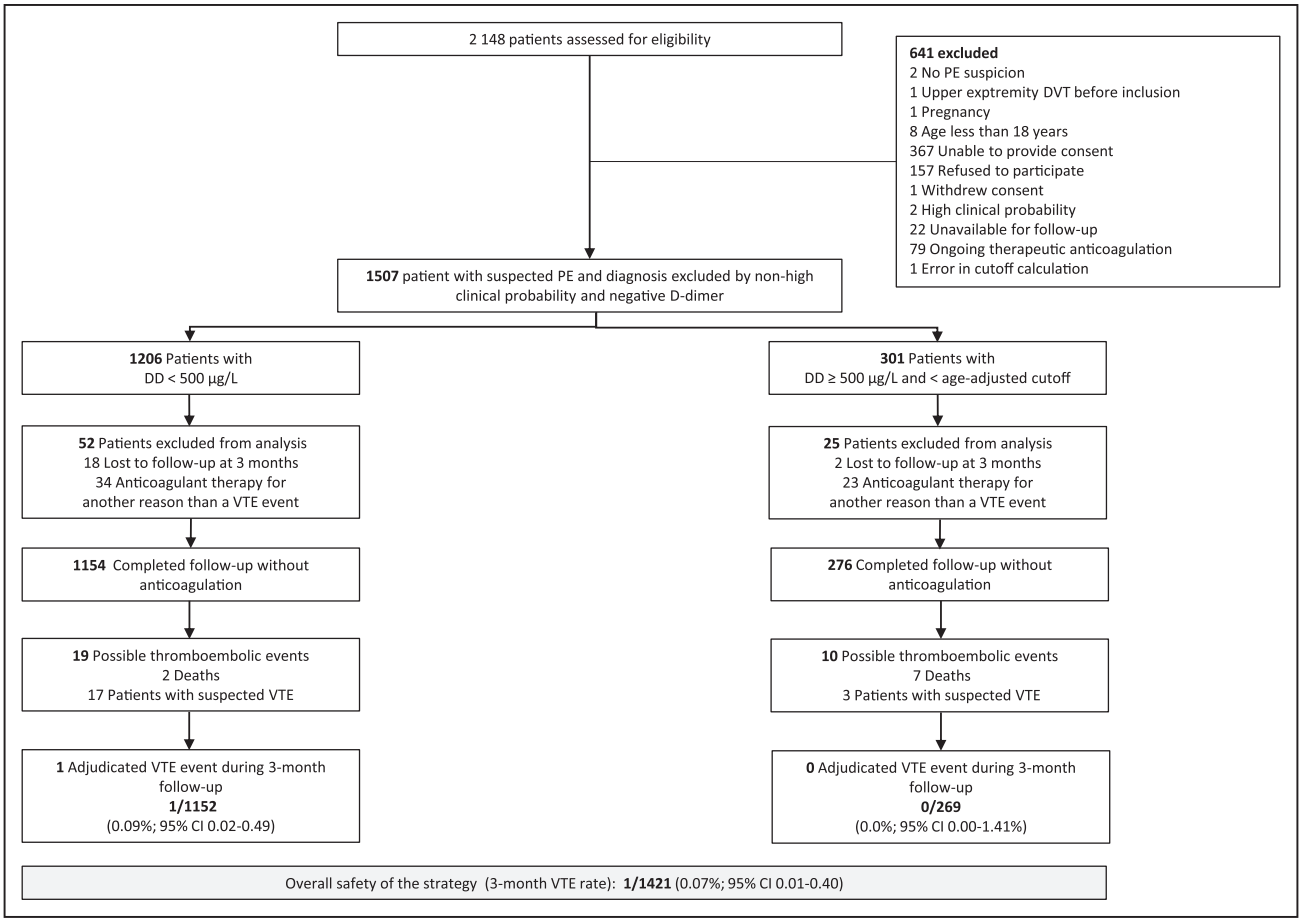

Figure. RELAX-PE (Age-Adjusted D-Dimer Cutoff to Rule Out Pulmonary Embolism in the Emergency Department: A Real Life Impact Study) study flowchart.
DD indicates D-dimer; DVT, deep vein thrombosis; PE, pulmonary embolism; and VTE, venous thromboembolism.

<500 µg/L, and 151 had a D-dimer between 500 µg/L and their AADD cutoff.

Regarding the 20 patients (1.3%) lost to follow-up, 18 of 20 (90%) were in the group of patients with D-dimer <500 µg/L. Even with the very unlikely hypothesis that 50% of patients lost to follow-up had VTE, our results remain valid.

This is the first prospective study since the publication of the ADJUST-PE study (Age-Adjusted D-dimer Cut-Off Levels to Rule out Pulmonary Embolism).[4] Whereas multiple retrospective analyses have been reported, no additional prospective data have been published. This study provides further evidence and confirmation of the safety of the AADD cutoff and represents the final validation step of this strategy.

Previous studies had shown that the incremental diagnostic yield of the AADD cutoff increased with age.[3,4] Our study confirms this observation. Indeed, in our whole cohort, using an AADD cutoff instead of a standard cutoff conferred a 20% increase in the number of negative D-dimer tests. In patients ≥50 years of age, the observed increase was 35%, and in patients ≥75 years of age, the incremental benefit was even more pronounced (67%). Significant cost reductions without a significant decrease in quality-adjusted life-years have been demonstrated in a recent cost-effectiveness analysis.[5] Applied to US data, the potential cost savings is estimated to be >$80 million/y.[5]

In terms of prospective data in patients with D-dimer ≥500 µg/L but below their AADD cutoff, the RELAX-PE (Age-Adjusted D-Dimer Cutoff to Rule Out Pulmonary Embolism in the Emergency Department: A Real Life Impact Study) doubles the number of patients in whom the safety of this strategy is confirmed. Indeed, combining the results of the ADJUST-PE and RELAX-PE studies shows a 3-month VTE risk of 1 in 600 (0.17% [95% CI, 0.03–0.94]).

In conclusion, our study demonstrates in a prospective real-life setting the safety and increased diagnostic yield of the AADD cutoff. The AADD cutoff is now the most widely validated D-dimer–adjusting strategy to minimize thoracic imaging. With these final validation data, the AADD cutoff can safely be used on a large-scale basis.

ARTICLE INFORMATION

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02601846.

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The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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