Original Investigation

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism
The ADJUST-PE Study

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IMPORTANCE D-dimer measurement is an important step in the diagnostic strategy of clinically suspected acute pulmonary embolism (PE), but its clinical usefulness is limited in elderly patients.

OBJECTIVE To prospectively validate whether an age-adjusted D-dimer cutoff, defined as age × 10 in patients 50 years or older, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE.

DESIGN, SETTINGS, AND PATIENTS A multicenter, multinational, prospective management outcome study in 19 centers in Belgium, France, the Netherlands, and Switzerland between January 1, 2010, and February 28, 2013.

INTERVENTIONS All consecutive outpatients who presented to the emergency department with clinically suspected PE were assessed by a sequential diagnostic strategy based on the clinical probability assessed using either the simplified, revised Geneva score or the 2-level Wells score for PE; highly sensitive D-dimer measurement; and computed tomography pulmonary angiography (CTPA). Patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff did not undergo CTPA and were left untreated and formally followed-up for a 3-month period.

MAIN OUTCOMES AND MEASURES The primary outcome was the failure rate of the diagnostic strategy, defined as adjudicated thromboembolic events during the 3-month follow-up period among patients not treated with anticoagulants on the basis of a negative age-adjusted D-dimer cutoff result.

RESULTS Of the 3346 patients with suspected PE included, the prevalence of PE was 19%. Among the 2898 patients with a nonhigh or an unlikely clinical probability, 817 patients (28.2%) had a D-dimer level lower than 500 µg/L (95% CI, 26.6%-29.9%) and 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff (95% CI, 10.5%-12.9%). The 3-month failure rate in patients with a D-dimer level higher than 500 µg/L but below the age-adjusted cutoff was 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%]). Among the 766 patients 75 years or older, of whom 673 had a nonhigh clinical probability, using the age-adjusted cutoff instead of the 500 µg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%) to 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%), without any additional false-negative findings.

CONCLUSIONS AND RELEVANCE Compared with a fixed D-dimer cutoff of 500 µg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical venous thromboembolism.

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The standard diagnostic approach of patients with clinically suspected acute pulmonary embolism (PE) relies on sequential diagnostic tests, such as clinical probability assessment, plasma D-dimer measurement, compression ultrasonography, computed tomography pulmonary angiography (CTPA), or ventilation-perfusion lung scan.[1,2]

The D-dimer test has been extensively evaluated in the exclusion of PE, particularly among outpatients.[3] The enzyme-linked immunosorbent assay (ELISA) D-dimer test and second-generation latex agglutination tests (immunoturbidimetric tests) have a remarkably high sensitivity and have been proven safe first-line tests in association with clinical probability to rule out PE in outcome studies.[4,5]

Several studies have shown that D-dimer levels increase with age.[6,7] As a result, the clinical usefulness of the test, the proportion of the patients with a D-dimer level lower than the predetermined cutoff value (500 µg/L for most available commercial assays) and in whom the diagnosis of PE may be ruled out by the test, is reduced. In a previous study, the ELISA D-dimer test was able to rule out PE in 60% of patients younger than 40 years, but in only 5% of patients older than 80 years,[8] thus limiting the yield and cost-effectiveness of noninvasive diagnosis in this subgroup of older, often fragile, patients.

We retrospectively derived and validated the value of a progressive D-dimer cutoff adjusted to age in a wide sample of 1712 patients. The optimal age-adjusted cutoff was defined as patient's age multiplied by 10 in patients 50 years or older.[9] In the retrospective validation analysis, the age-adjusted D-dimer cutoff would have increased by about 20% the number of patients in whom the D-dimer test was considered negative without increasing the false-negative rate when compared with the usual 500 µg/L cutoff. The results were particularly appealing in patients older than 80 years—the age-adjusted cutoff allowed an increase in the proportion of patients with a negative D-dimer result from 9% to 21% without any false-negative test.[9]

However, prospective validation of this age-adjusted cutoff was indicated before this strategy could be implemented in clinical practice. Hence, we assessed its failure rate and usefulness in a prospective management outcome study, in which consecutive outpatients with suspected PE were left untreated on the basis of a negative age-adjusted D-dimer test result, in combination with a clinical probability assessment.

Methods

Study Setting

The study was designed as a multicenter, multinational, prospective diagnostic management outcome study, involving 19 hospitals in 4 European countries (Belgium, France, the Netherlands, and Switzerland). The ethics committees of all participating institutions approved the study. In Belgium, France, and Switzerland, patients provided written informed consent before enrollment. In the Netherlands, the ethics committee judged that informed consent was not necessary, but patients were in all cases informed by the treating physician about the protocol and about the 3-month phone call follow-up.

Table 1. The Simplified, Revised Geneva Score and the 2-Level Wells Score

Score	Points
Simplified, revised Geneva score[11]	
Age >65 y	1.0
Previous history of PE or DVT	1.0
Surgery or fracture within 1 mo	1.0
Active malignancy	1.0
Unilateral leg pain	1.0
Hemoptysis	1.0
Heart rate, beats/min	
75-94	1.0
≥95	2.0
Pain on lower-limb deep venous palpation and unilateral edema	1.0
Clinical probability	
Low	0-1
Intermediate	2-4
High	≥5
2-Level Wells score[12]	
Clinical signs and symptoms of DVT	3.0
Immobilization or surgery in the previous 4 wk	1.5
Heart rate greater than 100 beats/min	1.5
Previous history of PE or DVT	1.5
Hemoptysis	1.0
Malignancy	1.0
Alternative diagnosis is less likely than PE	3.0
Clinical probability	
Unlikely	≤4
Likely	>4

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Patients

Consecutive outpatients who presented to the emergency department of the participating hospitals were eligible if they had a clinical suspicion of PE defined as an acute onset or worsening shortness of breath or chest pain without another obvious etiology. Patients were excluded if a PE suspicion was raised more than 24 hours after admission to the hospital, if they were receiving anticoagulant therapy for another indication (eg, atrial fibrillation), or if they had an allergy to contrast medium, impaired renal function (creatinine clearance less than 30 mL/min as per the Cockcroft-Gault formula), life expectancy of less than 3 months, ongoing pregnancy, or inaccessibility for follow-up.

Diagnostic Strategy

Clinical probability was assessed using either the simplified, revised Geneva score[10,11] or the 2-level Wells score for PE[2,12] (**Table 1**). Patients with a high or a likely clinical probability directly proceeded to CTPA. In patients with a low/intermediate or unlikely clinical probability, a D-dimer test was performed. The D-dimer result was interpreted according to the age-adjusted cutoff: in patients younger than 50 years, PE was excluded in those with a D-dimer value lower than 500 µg/L. In patients 50 years or older, the D-dimer test result was considered negative in those with a D-dimer value lower than their

age multiplied by 10. Six different quantitative high-sensitivity D-dimer assays were used: the VIDAS D-Dimer Exclusion test (bioMérieux), second-generation Tina-quant and Cobas h 232 (Roche), STA-Liatest D-Dimer (Stago), D-Dimer HS 500 (IL Diagnostics) and Innovance D-Dimer (Siemens). Patients with a negative D-dimer test result did not undergo any further testing and were left without anticoagulant therapy. Patients with a positive D-dimer result underwent CTPA. Patients with a positive CTPA result were started on anticoagulant therapy, and patients with a negative CTPA result were left without anticoagulant treatment. Patients with inconclusive CTPA (technically inadequate for interpretation or isolated subsegmental PE) results underwent additional testing with compression ultrasonography, ventilation-perfusion lung scan, or pulmonary angiography. Given the uncertainty regarding the clinical relevance and optimal management of isolated subsegmental PE, it was decided to consider CTPA showing isolated subsegmental PE as inconclusive and to recommend further testing. The diagnostic strategy is depicted in the **Figure**.

Follow-up

All patients underwent follow-up for 3 months. Patients were instructed to return to the clinic or to the emergency department in case of recurrent symptoms of the respiratory system or legs. At the end of follow-up, all patients included in the study were interviewed by telephone by a study coordinator using a structured questionnaire. Patients were asked to disclose all health-related events since their hospital discharge: consultations with any physician, admission to hospital, change in medication, diagnostic testing, or hemorrhagic complication. The family physician was contacted whenever a possible thromboembolic event was disclosed by the interim history, and charts were reviewed if a patient was readmitted to the hospital for any cause.

All suspected venous thromboembolic events and deaths were adjudicated by 3 independent experts who were blinded to the criteria used to rule out PE at inclusion.

Outcomes

The primary outcome was the failure rate of the diagnostic strategy, defined as the rate of adjudicated symptomatic thromboembolic events during the 3-month follow-up period among patients not treated with anticoagulants on the basis of a negative D-dimer test result according to the age-adjusted cutoff. It was computed as the number of adjudicated proximal deep vein thrombosis (DVT) or PE (involving a segmental or more proximal pulmonary artery), divided by the number of patients with a negative D-dimer result that were left without anticoagulant therapy.

Secondary outcomes included the proportion of patients with a low-intermediate or unlikely probability and a D-dimer result between 500 µg/L and their age-adjusted cutoff value. This proportion represents the additional diagnostic yield of the age-adjusted cutoff. We specifically assessed the 3-month thromboembolic risk in this subgroup of patients.

We also defined elderly patients as patients 75 years or older and we analyzed the additional diagnostic yield of the age-adjusted D-dimer cutoff in these patients.

Diagnoses of venous thromboembolic events during follow-up were established with the usual criteria: for DVT, on the basis of abnormal results on proximal compression ultrasonography; and for PE, on the basis of ventilation-perfusion lung scan showing a high-probability pattern or CTPA or angiography showing segmental or more proximal intraluminal defects. Deaths were adjudicated as surely related, probably related, possibly related, or unrelated to PE. Death was judged to be related to PE if it was confirmed by autopsy, or if death followed a clinically severe PE, either initially or after an objectively confirmed recurrent event. Death in a patient who died suddenly or unexpectedly was classified as possibly related to PE. Unrelated deaths were due to an obvious cause other than PE. Three independent experts blinded to D-dimer levels adjudicated the outcome events.

Statistical Analysis

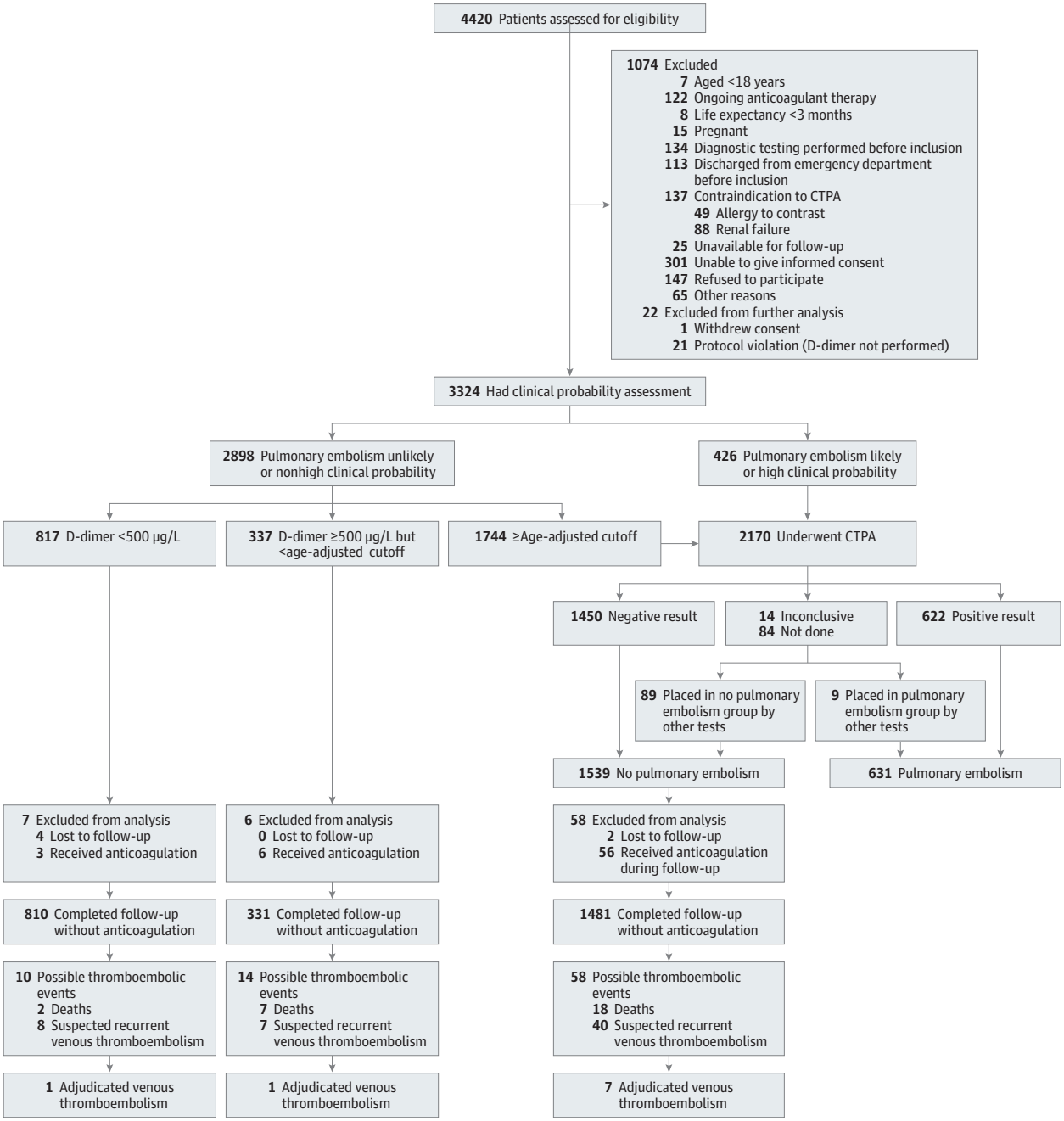
General characteristics were assessed using mean and standard deviation or median and interquartile range for continuous variables and proportions for categorical variables. We used the Wilson score method without continuity correction to compute the 95% CI around estimated proportions.[13] Sample size was estimated on the basis of our previous retrospective validation data set. We aimed at including enough patients to provide accurate estimates of our primary and secondary outcomes. To validate the safety of ruling out PE on the basis of a D-dimer level between 500 µg/L and the age-adjusted cutoff, the upper limit of the 95% CI around the 3-month thromboembolic risk (failure rate) in patients left untreated on the basis of such a D-dimer result should not be higher than 3%. This failure rate corresponds to that observed after a negative pulmonary angiography[14] and is a widely accepted criterion for the validation of diagnostic strategies for PE.[1,2,15-17] This would be obtained if no more than 2 out of 240 patients with such a D-dimer result would experience venous thromboembolism during follow-up. In our previous retrospective study, 10% of patients older than 50 years with an unlikely or a nonhigh clinical probability had a D-dimer result between 500 µg/L and their age-adjusted cutoff. Hence, to include 240 patients with a D-dimer between 500 µg/L and the age-adjusted cutoff, 2400 patients older than 50 years and with a nonhigh or unlikely clinical probability needed to be included. Because these patients represented two-thirds of all patients with suspected PE in our previous study, a total of 3200 patients with suspected PE needed to be included.

Results

Between January 1, 2010, and February 28, 2013, we screened 4420 patients. Among the 4420 screened patients, 1074 were excluded from the study for various reasons, described in the Figure. Hence, 3346 patients were included in the study.

Twenty-two patients were excluded from further analysis: the D-dimer test was not performed in 21 patients, and 1 patient withdrew his consent during the study period. General characteristics of the remaining 3324 patients are depicted in **Table 2**.

Figure. Flow of Patients Through the Study



Abbreviation: CTPA, computed tomographic pulmonary angiography.

Diagnostic Work-up at Initial Presentation

The study flowchart is summarized in the Figure. The clinical probability was nonhigh (ie, low or intermediate) using the simplified, revised Geneva score or unlikely using the 2-level Wells score for PE in 2898 (87.2%) patients. Among these 2898 patients with a nonhigh or unlikely clinical probability, 1154 (39.8%) patients had a negative D-dimer result according to the age-adjusted cutoff (95% CI, 38.1%-41.6%): 817 (28.2%) patients had a D-dimer level lower than 500 µg/L (95% CI, 26.6%-29.9%) and 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff (95% CI, 10.5%-12.9%). Therefore, the use of the age-adjusted cutoff resulted in an 11.6% absolute increase (95% CI, 10.5%-12.9%) or a 41.2% relative increase (95% CI, 31.3%-52.0%) in the proportion of negative D-dimer results. The breakdown for the 6 D-dimer tests used is depicted in **Table 3**.

Further testing was performed in the remaining 1744 patients with a D-dimer level higher than the age-adjusted cut-

off and in the 426 patients with a likely or a high clinical probability of PE. Computed tomography pulmonary angiography results were positive in 622 patients and negative in 1450 patients. Computed tomography pulmonary angiography was inconclusive (n = 14) or not performed (n = 84, protocol violations) in 98 patients. Nine of the 98 patients had PE confirmed on the basis of a high-probability ventilation-perfusion lung scan (n = 2) or a proximal DVT on compression ultrasound (n = 7). Pulmonary embolism was ruled out in the remaining 89 patients on the basis of a negative result from a pulmonary angiogram (n = 1), ventilation-perfusion lung scan (n = 12), compression ultrasound (n = 26), D-dimer test result (despite likely/high clinical probability; n = 8), or without any further additional testing (n = 42). Therefore, PE was diagnosed in 631 patients, and the overall prevalence of PE in our study was 19.0% (95% CI, 17.7%-20.4%).

Three-Month Follow-up

D-Dimer Level Lower Than 500 µg/L

During the 3-month follow-up period, of the 817 patients with a D-dimer level lower than 500 µg/L, 3 patients received anticoagulants for another reason than PE, and 4 (0.5%) patients were lost to follow-up. Among the 810 remaining patients, there were 2 deaths and 8 suspected VTE during follow-up. Of these 10 events, 1 was adjudicated as having a confirmed nonfatal PE. Therefore, the 3-month thromboembolic risk was of 1 of 810 patients (0.1% [95% CI, 0.0%-0.7%]).

D-Dimer Level Between 500 µg/L and the Age-Adjusted Cutoff

Of the 337 patients with a D-dimer level between 500 µg/L and their age-adjusted cutoff, no patient was lost to follow-up and 6 patients received anticoagulation for another indication than PE. Of the remaining 331 patients, 7 died and 7 underwent testing for suspected venous thromboembolism. One of these 14 events was adjudicated as a confirmed nonfatal PE. Adjudicated causes of death were as follows: 3 were due to end-stage chronic obstructive pulmonary disease, 1 was from refractory idiopathic thrombopenic purpura with severe thrombocytopenia complicated by intestinal hemorrhage, 1 was due to a metastatic melanoma, 1 was due to terminal cachexia in the context of a psychiatric illness, and 1 was due to a hypovolemic shock after a massive hemorrhage associated with over-anticoagulation for atrial fibrillation (anticoagulation was initiated during follow-up).

Therefore, the failure rate of the age-adjusted cutoff was 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%).

Patients With a D-Dimer Level Above the Age-Adjusted Cutoff and Patients With a Likely or High Clinical Probability

Of the 1539 patients with a D-dimer level above the age-adjusted cutoff or with a high or likely clinical probability in whom the diagnosis of PE was ruled out, 2 patients were lost to follow-up and 56 patients were given anticoagulants for another reason than PE. Of the remaining 1481 patients, 18 died and 40 presented with a suspicion of a thromboembolic event. Seven of these 58 suspected events were adjudicated as confirmed or possible events: PE (n = 4), DVT (n = 1), indeterminate (n = 2). Therefore, the failure rate in the patients with a negative CTPA result was 7 of 1481 patients (0.5% [95% CI, 0.2%-1.0%]).

Elderly Patients

Overall, 766 patients were 75 years or older. Of these patients, 673 patients (87.9%) had a nonhigh clinical probability. The proportion of patients with D-dimer level lower

Table 2. Characteristics of Included Patients

Characteristics	No. (%) (n = 3324)
Women	1887 (56.8)
Age, median (IQR), y	63 (53-74)
Personal history of VTE	466 (14.0)
Active malignancy	429 (12.9)
Surgery within 1 month	392 (11.8)
Estrogen use	183 (5.5)
Chest pain	1608 (48.3)
Dyspnea	2092 (62.9)
Syncope	263 (7.9)
Hemoptysis	134 (4.1)
Heart rate, mean (SD), beats/min	87.1 (19.6)
Respiratory rate, mean (SD), beats/min	19.2 (6.2)

Abbreviations: IQR, interquartile range; VTE, venous thromboembolism.

Table 3. Study Results According to D-Dimer Assays

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	1/8	0 0.1 (0.0-0.7)	337	1/331	0.3 (0.1-1.7)

than 500 µg/L was 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%]). Another 157 patients (23.3%) had a D-dimer level lower than their age-adjusted cutoff. Therefore, the proportion of patients older than 75 years with a nonhigh or unlikely clinical probability and a negative D-dimer result using the age-adjusted cutoff was 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%]). Of these patients, 5 received anticoagulant therapy for another indication than venous thromboembolism. None of the remaining 195 patients had a confirmed venous thromboembolism during follow-up: 0 of 195 patients (0.0% [95% CI, 0.0%-1.9%]).

Discussion

In this prospective study, using an age-adjusted D-dimer cutoff in emergency department patients with suspected PE increased the diagnostic yield of D-dimer testing. A D-dimer level higher than 500 µg/L but below the age-adjusted cutoff ruled out the diagnosis of PE, with a 3-month risk of venous thromboembolism in line with that observed in patients with a D-dimer level lower than 500 µg/L or after a negative pulmonary angiography result, the gold-standard test for PE. In patients 75 years or older, the age-adjusted cutoff increased 5-fold the proportion of patients in whom PE could be ruled out without further imaging.

These results are in line with those obtained in the initial derivation and retrospective external validation study.[9] After the publication of this initial report, other retrospective validation analyses were published, including more than 10 000 patients with suspected venous thromboembolism, using various D-dimer assays in various clinical settings (suspected DVT, suspected PE) in many different countries, which all indicated a potential clinical usefulness of the age-adjusted cutoff, particularly for elderly patients.[18,19] However, a prospective management outcome study, in which patients with suspected PE would be managed without anticoagulants on the basis of a negative D-dimer test result using the age-adjusted cutoff, was missing. In our study, the diagnostic conclusion and therapeutic management was decided on the basis of the age-adjusted cutoff. Another proposed approach in the literature was to use fixed increased cutoff values in elderly patients (eg, 750 µg/L in patients 60 years or older).[20] However, this cutoff value was never prospectively validated. Moreover, the strength of the age-adjusted cutoff is that it was derived using receiver operating characteristics (ROC) curve analysis in each age group and linear regression analysis. Another strength is that the age-adjusted cutoff is easy to memorize (patient's age multiplied by 10) and is tailored to each individual patient.

Elderly patients may have the greatest potential benefit of the use of the age-adjusted cutoff. In patients 75 years or older, the proportion of patients with a D-dimer level lower than 500 µg/L was 43 of 673 patients (6.4%). The proportion of patients with negative D-dimer result was 29.7% when using the age-adjusted cutoff. In other words, although only 1 in 16 patients could have the diagnosis of PE ruled out on the basis of the D-dimer as a sole test when using the conventional cutoff, this proportion increased to 1 in 3.4 patients when using the age-adjusted cutoff. Previous studies have shown that in all patients, irrespective of age, the number needed to test with a D-dimer test to rule out 1 PE is approximately 3,[4] but in elderly patients, this number could be as high as 20 after 80 years.[8] Thus, the use of the age-adjusted cutoff allows to "restore" the yield of the D-dimer test in elderly patients. This is particularly important in clinical practice. Indeed, elderly patients are more likely to present with renal impairment and to develop contrast-induced nephropathy,[21] limiting the use of CTPA in this age group. The use of the ventilation-perfusion lung scan is limited by the higher number of inconclusive results obtained in this age group.[22] The possibility of ruling out PE on the basis of a simple blood test could allow shortening a patient's stay in the ermergency department and limiting the unnecessary exposure to radiation, contrast agents of the CTPA, and anticoagulant therapy. On the other hand, it was important to ensure that the increased yield of the D-dimer test would not compromise patient safety, given the risks of untreated PE in this patient population.

This study has several strengths. This was a large international collaboration. All consecutive patients seen at participating centers were approached for inclusion, and all suspected thromboembolic events and deaths during follow-up were adjudicated by an independent committee. Our sample size was calculated to enable assessment of the age-adjusted cutoff failure rate in the subgroup of patients with a D-dimer level higher than 500 µg/L but below the age-adjusted cutoff.

This study also has several limitations. First, 2 different pretest probability assessment tools and 6 different commercial D-dimer assays were used. Therefore, not all included patients were managed using the exact same diagnostic tests. However, the 2 probability assessment tools and the high-sensitive D-dimer tests used have been demonstrated to be equivalent.[23,24] As shown in Table 3, results were homogeneous across the different D-dimer assays. Therefore, this could increase the generalizability of our finding to a wide number of settings with different practices. Second, this study was not designed as a randomized clinical study. Therefore, we could not compare the 3-month thromboembolic risk with that of a control group that would have been managed using the conventional 500 µg/L cutoff. However, the low rate of venous thromboembolic events renders a significant difference between the 2 strategies unlikely. Moreover, the use of the 3-month thromboembolic risk is widely used as the standard reference for the validation of PE diagnostic strategies.[1,2] Third, although all suspected events during follow-up were adjudicated by an independent committee, only 1 of the 7 deceased patients with D-dimer levels higher than 500 µg/L and below the age adjusted D-dimer cutoff had an autopsy (1 of the 3 patients with end-stage chronic obstructive pulmonary disease). Therefore, it is impossible to formally exclude PE as the cause of death in the 6 remaining patients. However, all the 7 deaths were adjudicated as

unrelated to PE (obvious cause other than PE). Fourth, in patients with suspected recurrences during follow-up, considering CTPA showing isolated subsegmental pulmonary embolism as inconclusive might be regarded as a potential limitation. However, this scenario did not occur during follow-up of patients with D-dimer levels lower than 500 µg/L or below the age-adjusted cutoff. Therefore, our inferences regarding the failure rate in patients having D-dimer levels between the usual cutoff and the age-adjusted cutoff are likely to be robust. Fifth, the prevalence of PE was somewhat higher than that usually observed in North American studies.[25-27] However, it is in line with previous studies in Europe.[1,2] Moreover, a lower prevalence would have likely resulted in an even lower failure rate of the age-adjusted D-dimer cutoff.

Conclusions

In this study, an age-adjusted D-dimer cutoff combined with probability assessment ruled out the diagnosis of PE in emergency department patients with suspected PE and was associated with a low likelihood of subsequent symptomatic VTE, and with an increased proportion of patients in whom the diagnosis could be excluded. This was particularly true in elderly patients, with a 5-fold increase in the proportion of negative D-dimer test results in patients 75 years or older. Future studies should assess the clinical usefulness of the age-adjusted D-dimer cutoff in clinical practice. Whether the age-adjusted cutoff can result in improved cost-effectiveness or quality of care remains to be demonstrated.

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REFERENCES

1. Righini M, Le Gal G, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet*. 2008;371(9621):1343-1352.

2. van Belle A, Büller HR, Huisman MV, et al; Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*. 2006;295(2):172-179.

3. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-Dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost*. 2008;6(7):1059-1071.

4. Carrier M, Righini M, Djurabi RK, 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(5):886-892.

5. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med*. 2004;140(8):589-602.

6. Righini M, Goehring C, Bounameaux H, Perrier A. Effects of age on the performance of common diagnostic tests for pulmonary embolism. *Am J Med*. 2000;109(5):357-361.

7. Tardy B, Tardy-Poncet B, Viallon A, et al. Evaluation of D-dimer ELISA test in elderly patients with suspected pulmonary embolism. *Thromb Haemost*. 1998;79(1):38-41.

8. Righini M, Nendaz M, Le Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. *J Thromb Haemost*. 2007;5(9):1869-1877.

9. 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 3 large cohorts. *BMJ*. 2010;340:c1475.

10. Le Gal G, Righini M, Roy P-M, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med*. 2006;144(3):165-171.

11. Klok FA, Mos IC, Nijkeuter M, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. *Arch Intern Med*. 2008;168(19):2131-2136.

12. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83(3):416-420.

13. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of 7 methods. *Stat Med*. 1998;17(8):857-872.

14. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism—a critical review. *Clin Radiol*. 2001;56(10):838-842.

15. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Büller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies: a systematic review. *Ann Intern Med*. 2003;138(12):941-951.

16. Moores LK. Diagnosis and management of pulmonary embolism: are we moving toward an outcome standard? *Arch Intern Med*. 2006;166(2):147-148.

17. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med*. 2005;352(17):1760-1768.

18. Kriegel I, Desruennes E, Douard MC, et al. Standards, options: recommandations 2008: traitement curatif de la maladie thromboembolique veineuse, prévention et traitement des thromboses veineuses sur cathéter chez les patients atteints de cancer. *Ann Fr Anesth Reanim*. 2008;27(6):521-533.

19. Pernod G, Biron-Andreani C, Morange PE, et al; French group on haemostasis and thrombosis; French Society of vascular medicine. Recommendations on testing for thrombophilia in venous thromboembolic disease: a French consensus guideline. *J Mal Vasc*. 2009;34(3):156-203.

20. Schouten HJ, Koek HL, Oudega R, et al. Validation of 2 age dependent D-dimer cut-off values for exclusion of deep vein thrombosis in suspected elderly patients in primary care: retrospective, cross sectional, diagnostic analysis. *BMJ*. 2012;344:e2985.

21. Salaun PY, Couturaud F, Lacut K, et al. Management of suspected venous thromboembolism: the impact of a multifaceted intervention. *Int J Qual Health Care*. 2005;17(5):433-438.

22. Righini M, Le Gal G, Perrier A, Bounameaux H. The challenge of diagnosing pulmonary embolism in elderly patients: influence of age on commonly used diagnostic tests and strategies. *J Am Geriatr Soc*. 2005;53(6):1039-1045.

23. Douma RA, Mos IC, Erkens PM, et al; Prometheus Study Group. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. *Ann Intern Med*. 2011;154(11):709-718.

24. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J Thromb Haemost*. 2007;5(2):296-304.

25. Dunn KL, Wolf JP, Dorfman DM, Fitzpatrick P, Baker JL, Goldhaber SZ. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. *J Am Coll Cardiol*. 2002;40(8):1475-1478.

26. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *JAMA*. 2007;298(23):2743-2753.

27. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost*. 2008;6(5):772-780.